Design of Small-Molecule Inhibitors of Sulfatase 2 and ERK5

This thesis is submitted to Newcastle University for the degree of Doctor of Philosophy

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Declaration

The work carried out contributing to this thesis was conducted between October 2010 and August 2014 in the Medicinal Chemistry laboratories, Bedson Building, Northern Institute for Cancer Research at the Newcastle Cancer Centre, Newcastle University, Newcastle upon Tyne, NE1 7RU. The research was conducted in collaboration with scientists at the Paul O'Gorman Building, Newcastle Cancer Centre, and at Cancer Research Technology Discovery Laboratories, The Cruciform Building, Gower Street, London, WC1E 6BT, the Beatson Institute for Cancer Research, Garscube Estate, Switchback Road, Bearsden, Glasgow, G61 1BD and the Babraham Institute, Babraham Research Campus, Cambridge, CB22 3AT.

All of the research presented in this thesis is original in context, and does not include any material or ideas previously published or presented by other authors except where due reference is given in the text.

No part of this thesis has been previously submitted for a degree, diploma or any qualification at any other university.

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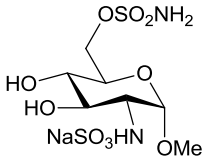
This thesis is dedicated to my dad François and my supervisor Roger, who were both diagnosed with cancer during my PhD.

Abstract

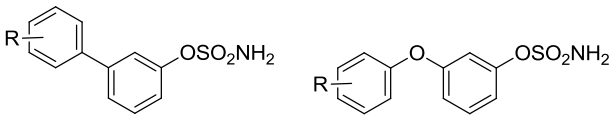
Modern targeted cancer therapeutics are directed against components of cell signalling pathways, responsible for driving tumour progression. In this thesis, chemical tools and inhibitors of two enzymes involved in cell signalling, namely sulfatase 2 (Sulf-2) and extracellular signal-regulated kinase 5 (ERK5), have been investigated.

Sulfatase 2 is a heparan sulfate (HS) processing enzyme, which has been implicated in the progression of several cancers including hepatocellular carcinoma (HCC). In HCC patients, high Sulf-2 mRNA expression correlates with a poor prognosis. The first published small-molecule Sulf-2 inhibitors were monosaccharide glucosamine derivatives, bearing a sulfamate at the O^6-position. The most potent analogue from this series, was **5**, having a reported IC_{50} against Sulf-2 of 130 μM. Although **5** was not sufficiently potent for use in target validation studies, its discovery provided encouragement that viable Sulf-2 inhibition was possible with low molecular weight compounds.



5

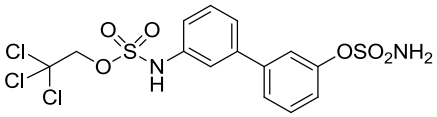
In the absence of a published crystal structure and of a biological assay suitable for a high-throughput screening campaign, the structure of the endogenous substrate was considered as a potential starting point for identification of probe compounds, for use in target validation studies. Biphenyl **A** and biphenyl ether **B** sulfamates were designed in an attempt to identify a non-saccharide scaffold, which could mimic the spatial arrangements of groups believed to be important for binding of the endogenous substrate to Sulf-2. Access to these targets was facilitated by the development of a sulfamate protecting group strategy, which enabled a more flexible approach to the synthesis of phenolic *O*-sulfamates.



A **B**

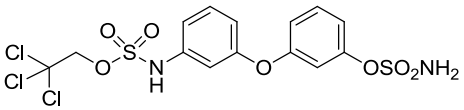
R = NH_2, NHAc, $NHSO_3Na$, CO_2H

Preliminary sulfatase inhibition data have been generated, indicating that biphenyl **162** and biphenyl ether sulfamates **197** exhibited better potency against Sulf-2 than monosaccharide glucosamine **5** in our assay format.



162

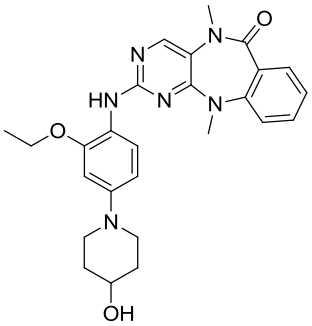
Sulf-2 IC_{50} = 156 μM



197

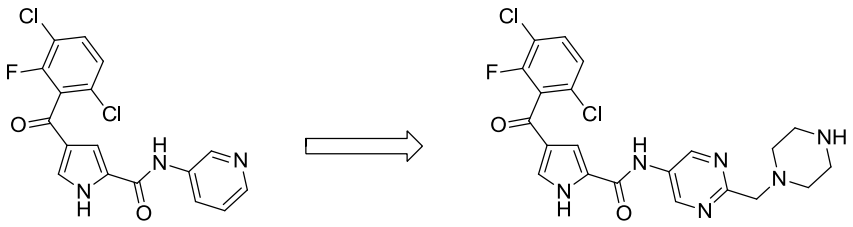
Sulf-2 IC_{50} = 409 μM

Extracellular signal-regulated kinase 5 (ERK5) is a member of the protein kinase superfamily, which plays an essential role in the transduction of extracellular signals to intracellular effectors. Activation of the ERK5 signalling pathway is associated with cell survival, proliferation, and differentiation, and ERK5 over-expression has been implicated in tumour development. An ERK5 inhibitor, XMD8-92 **218**, which was reported in the literature, displayed selectivity for ERK5 when tested against a panel of 402 kinases in an ATP-site competition binding assay (ERK5 IC_{50} = 300 nM) and showed reasonable activity in HeLa cells (GI_{50} = 1.5 μM). This compound also inhibited the growth of two human tumour xenograft models (HeLa cells and Lewis lung cells), highlighting that ERK5 is a valid target for anti-cancer therapy.



218, XMD8-92

A pyrrole carboxamide series of ERK5 inhibitors was optimised from lead compounds such as **318**, which had good absorption in the Caco-2 assay but suffered from low solubility and medium clearance in mouse liver microsomes *in vitro*, and translated to poor oral bioavailability *in vivo*. The objective of the optimisation studies was to improve ERK5 inhibitory activity, both in the biochemical and cellular assays, and improve pharmacokinetic parameters to deliver compounds suitable for *in vivo* efficacy studies. Three areas were identified for investigation i.e. alkylation of the amide nitrogen; replacement of the *meta*-chloro on the aroyl ring; and substitution on the heteroaromatic amide ring at the *ortho* and *para* positions.



318

ERK5 IC_{50} = 66 nM
Cell IC_{50} = 0.2 µM

406

ERK5 IC_{50} = 8 nM
Cell IC_{50} = 0.06 µM

Docking of compounds into a recently published co-crystal structure of an analogue of XMD8-92 bound to ERK5 has provided information on the possible binding mode of the pyrrole carboxamide series and was used to guide the design of inhibitors (Figure 1). Extension of the carboxamide heteroaromatic amine at the *para* position, with aliphatic and cyclic aliphatic side-chains bearing a basic centre, resulted in significantly improved ERK5 inhibitory activity (IC_{50} < 30 nM) as exemplified by **406**, which achieved a 3-fold improvement in cellular inhibitory activity, and combined excellent microsomal stability with high solubility. However all the compounds with a basic centre suffered from a high efflux ratio and low membrane permeability in the Caco-2 assay, and as a result, had poor *in vivo* oral bioavailability in mouse PK studies. The work presented in this thesis has extended the SARs around the pyrrole carboxamide core but did not allow to deliver a new *in vivo* tool.

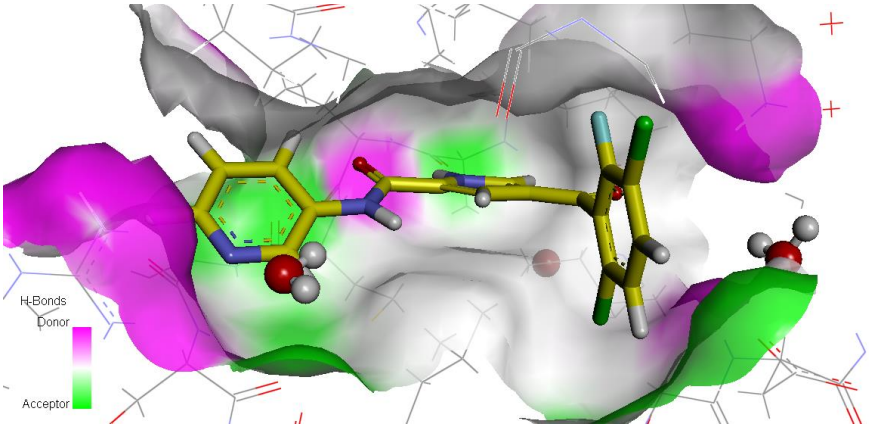


Figure 1: Possible binding pose of **318** modelled in the active site of ERK5 (PDB code 4b99)

Table of Contents

Abbreviations

ADME(T)	Absorption, distribution, metabolism, excretion, (toxicology)
Akt	Protein kinase B
ALK	Anaplastic lymphoma kinase
ALL	Acute lymphoblastic leukaemia
APCI	Atmospheric-pressure chemical ionisation
ARS	Aryl sulfatase
ARSC	Aryl sulfatase C
ATP	Adenosine triphosphate
BCRP	Breast cancer resistance protein
BLAST	Basic Local Alignment Search Tool
BMK-1	Big Map Kinase-1
Boc	*tert*-Butyloxycarbonyl
c-Abl	Abelson murine leukaemia viral oncogene homolog 1
CDI	Carbonyldiimidazole
CDK	Cyclin-dependent kinase
c-Kit	Mast/stem cell growth factor receptor
Cl	Clearance
Cl_{int}	Intrinsic clearance
CLL	Chronic lymphocytic leukaemia
Cl_u	Unbound clearance
CML	Chronic myeloid leukaemia
CRT-DL	Cancer Research Technology Discovery Laboratories

CYP	Cytrochrome P450
DABCO	1,4-Diazabicyclo[2.2.2]octane
DEAD	Diethyl azodicarboxylate
DFS	Disease-free survival
DMA	*N*,*N*-Dimethylacetamide
DMAP	4-(Dimethylamino)pyridine
dmb	2,4-Dimethoxybenzyl
DMF	*N*,*N*-Dimethylformamide
ECM	Extracellular matrix
EDCI	*N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
EMATE	Estrone sulfamate
ER	Endoplasmic reticulum
ER	Efflux ratio in the Caco-2 permeability assay
ERK	Extracellular signal-related kinase
ES^+	Electrospray ionisation positive mode
ES^-	Electrospray ionisation negative mode
F	Oral bioavailability
FAK	Focal adhesion kinase
FDA	Food and drug administration
FGE	Formylglycine-generating enzyme
FGF	Fibroblast growth factor
FGFR	Fibroblast growth factor receptor

FGly	Formylglycine
F_u	Fraction unbound in plasma
GI_{50}	Concentration required to inhibit cell growth by 50%
GIST	Gastrointestinal stromal tumour
GlcN	Glucosamine
GlcNAc	Glucosamine-2-acetate
GlcNS	Glucosamine-2-sulfate
GlcNS(6S)	Glucosamine-2,6-disulfate
HBA	Hydrogen bond acceptor
HBD	Hydrogen bond donor
HCC	Hepatocellular carcinoma
Her2	Receptor tyrosine-protein kinase erbB-2
hERG	Human ether-a-go-go-related gene
HFGly	Hydroxyformylglycine
HLM	Human liver microsomes
HPLC	High-performance liquid chromatography
HRMS	High-resolution mass spectrum
HS	Heparan sulfate
HSPG	Heparan sulfate proteoglycan
HTS	High-throughput screening
IC_{50}	Concentration for inhibition of 50% of the maximal response
IdoA	Iduronic acid
IdoA(2S)	Iduronic acid 2-sulfate

Id1	Inhibitor of differentiation 1
IL	Interleukin
IMAP	Immobilised Metal Affinity Polarisation
^{i}Pr	*iso*propyl
IR	Infrared
JAK	Janus kinase
JNK	c-Jun amino (*N*)-terminal kinase
kDa	Kilodalton
LC-MS	Liquid chromatography-mass spectrometry
L.E.	Ligand efficiency
LEF	Lymphoid enhancer-binding factor
LiHMDS	Lithium bis(trimethylsilyl)amide
LipE	Lipophilic efficiency
LOD	Limit of Detection
MAPK	Mitogen-activated protein kinase
m-CPBA	3-Chloroperbenzoic acid
MEF	Myocyte enhancer factor
MLM	Mouse liver microsomes
mol equiv.	Molar equivalent
mRNA	Messenger ribonucleic acid
MRP1	Multidrug resistance-associated protein 1
MS	Mass spectrum
4-MU	4-Methylumbelliferone
4-MUS	4-Methylumbelliferyl sulfate

Mukaiyama reagent	2-Chloro-1-methylpyridinium iodide
MW	Molecular weight
μW	Microwave irradiation
m/z	Mass charge ratio
NGF	Nerve growth factor
NLK	Nemo-like kinase
NLS	Nuclear localisation signal
NSCLC	Non-small cell lung cancer
PAMPA	Parallel artificial membrane permeability assay
P_{app}	Apparent permeability rate in Caco-2 cell assay
PDB	Protein databank
PDGF	Platelet-derived growth factor
PDGFR	Platelet-derived growth factor receptor
PG	Protecting group
P-gp	P-glycoprotein
PK	Pharmacokinetic
PLK	Polo-like kinase
PMB	*para*-Methoxybenzyl
PML	Promyelocytic leukaemia protein
Ppb	Plasma protein binding
ppm	Parts per million
PR	Proline-rich domain
R_f	Retention factor
RNAi	Ribonucleic acid interference

RSK	Ribosomal S6 kinase
RT	Room temperature
SAR	Structure-activity relationship
shRNA	Short hairpin ribonucleic acid
siRNA	Short interfering ribonucleic acid
S_N1	Nucleophilic substitution 1
S_N2	Nucleophilic substitution 2
STS	Steroid sulfatase
Sulf	Sulfatase
$t_{1/2}$	Half-life
TBDMS	*tert*-Butyldimethylsilyl
TCE	2,2,2-Trichloroethyl
TFA	Trifluoroacetic acid
TFE	2,2,2-Trifluoroethanol
TFC	Transcription factor
TLC	Thin layer chromatography
tPSA	Topological polar surface area
UA	Uronic acid
V_d	Volume of distribution
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular endothelial growth factor receptor
Wnt	Wingless/int protein

Chapter 1. Introduction to Cancer and Modern Drug Discovery

1.1. The Genetic Origin of Cancer

Cancer is a genetic disease at the cellular level that results from alterations in DNA, and is responsible of one in eight deaths worldwide.[1, 2] Each cancer is the consequence of a process of a Darwinian selective evolution at a cellular level: the continuous acquisition of genetic mutations in a cell confers the capability to proliferate and survive more efficiently than its neighbours.[2] Normal cells evolve progressively into cancer cells and acquire, in a multistep process, characteristics that guide their tumorigenic and malignant phenotype.[3] In 2000, following an analysis of different cancer types, Hanahan and Weinberg defined six hallmarks of cancers that normal cells acquire from accumulated genetic damage as they become cancerous (Figure 1.1).[4] In a recent update, two further emerging hallmarks were suggested: the avoidance of immune destruction and the reprogramming of energy metabolism.[3]

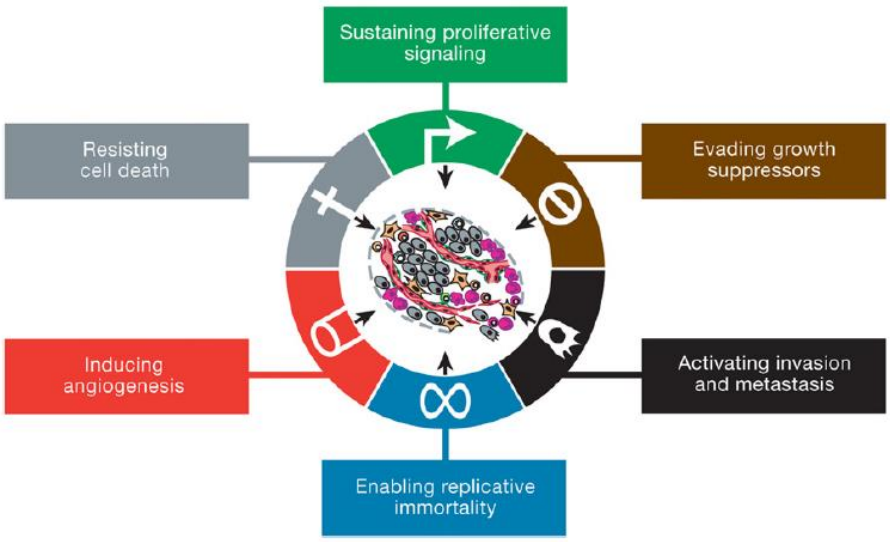


Figure 1.1: The six hallmark of cancers[4]

It is estimated that each cell of a human organism typically undergoes more than twenty thousands DNA damaging events and more than ten thousands replication errors per day.[5] Under normal circumstances, DNA repair mechanisms act on the mutated cells before the beginning of cellular replication. However, damaged DNA that escapes repair processes can lead to incorporation of altered genetic material, which is passed on to subsequent generations of cells. Genetic defects may be further accumulated with age following prolonged exposure to mutagens such as ultra-violet radiation or tobacco smoke.[1]

Endogenous DNA damage is mainly caused by reactive oxygen species and related reactive molecules.[5] The nature of DNA alteration of tumour cells has been shown to be diverse, ranging from subtle mutations such as a single DNA base pair change (transitions, transversions, insertions or deletions) to more significant mutations such as chromosomal translocation.[1] Chromosome rearrangement and gene deletions are less common than single-base substitution but may have a more profound effect by inactivating multiple contiguous genes.[5]

Examination of The Cancer Genome Atlas indicates that each tumour is unique and contains tens to hundreds of thousands of mutations, supporting the hypothesis of a mutator phenotype of cancer cells.[5] Each mutation in a cancer cell genome can be classified according to its consequences for cancer development.[6] Mutations conferring a growth advantage are classified as 'drivers' and located in a subset of genes known as 'cancer genes'. Mutations that confer little phenotypic advantage are named 'passengers'.[6] Most somatic mutations in cancer genomes are passengers.[2] The number of driver mutations required for a cell to display a cancer phenotype varies. Tumours are complex tissues, composed of largely heterogeneous cells, suggesting that they may derive from different mutations in the cancer genome.

Specific and recurrent genomic abnormalities are associated with particular cancer types.[2] The presence of abnormal cancer genes now dictates the classification and treatment protocols for some cancers.[2]

1.2. Targeted Therapies

Most cancers are treated with a combination of surgery, radiation therapy and/or chemotherapy. While surgery and radiation are used to treat cancer locally, chemotherapy also treats distant sites in the body.[7] Until the end of the twentieth century, chemotherapy consisted mainly of cytotoxic drugs that kill rapidly dividing cells, both carcinogenic and healthy, resulting in significant non-tumour toxicity.[7, 8] In order to achieve their effect, these drugs, which work by interfering with essential cellular events such as DNA replication, require high doses, resulting in narrow therapeutic windows where efficacy is maximised and adverse toxicity minimised.[9, 10]

In the 1960s, a research program studying genes identified oncogenes, suppressor oncogenes, and signalling pathways essential for cancer development, marking the

transition to the age of 'targeted therapy'.[11] This work also contributed to the development of new technologies which facilitated the sequencing of the human genome.[12] Analogous to antimicrobial drug discovery, identification and modulation of targets uniquely present in cancer cells should reduce adverse effects in healthy tissues and produce anticancer agents with enhanced therapeutic index.[13] Targeted therapeutic agents, composed of small-molecule drugs and monoclonal antibodies, alter the function of cancer-specific proteins, that play a critical role in tumour growth, progression and survival.[10, 14] In cells where the target is a 'driver', these therapies have similar efficacy to classical chemotherapy and radiotherapy, but are less harmful to normal cells, inducing fewer undesired side-effects.[15] Although cancer cells typically contain multiple mutations, some develop dependence on a single mutation for growth and survival, rendering them susceptible to targeted inhibition.[16]

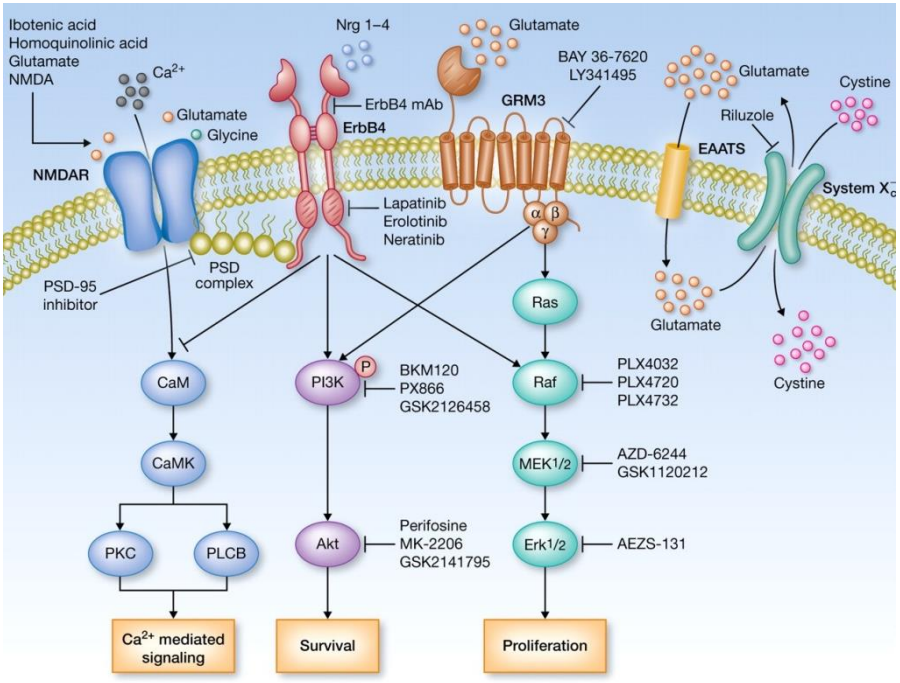
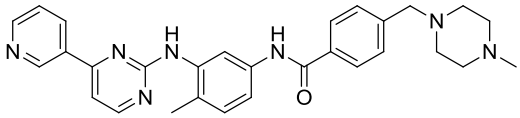


Figure 1.2: Representation of some complex signalling networks[17]

The genomic era and progress in molecular biology have led to an improved understanding of cancer cell biology, and discovery of entirely new signalling networks responsible for the regulation of cellular processes such as cell proliferation and survival.[18] More than two hundred cell signalling pathways have been identified (Figure 1.2).[17] These cascades transduce extracellular signals through the cell membrane and cytosol and cause an intracellular response.[19] Dysregulation of signalling pathways, leading to uncontrolled cell growth, proliferation and survival, is a common feature in tumours and modulation of these

cascades with small-molecules has expanded the scope for possible targeted therapies.[10] Specific components of these signalling networks, such as growth factors and their receptors or cell cycle modulators, have been recognised as promising biological targets. Dependence of a cancer to the targeted signalling pathway is decisive to the success of a treatment.[20] Selection of the pathway component to target with a small-molecule inhibitor is a complex decision. Targeting a protein early in a pathway, such as an extracellular receptor, may lead to enhanced efficacy by affecting multiple downstream outcomes, but may also cause unwanted side-effects.[21] Although safer, inhibition of a downstream protein may have limited efficacy with cell developing alternative mechanisms to bypass the inhibition.[21]



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The first targeted chemotherapeutic agent to reach the market was imatinib **1** (Glivec®), an inhibitor of the Bcr-Abl fusion protein kinase, used for the treatment of chronic myeloid leukaemia (CML).[13] Imatinib was designed to block sustained proliferative signalling in CML caused by a gene translocation, also known as the Philadelphia chromosome.[22] This genetic defect produces the Bcr-Abl fusion protein, which is only present in tumour cells and provides an opportunity for selective inhibition. Imatinib induces complete hematologic and cytogenetic remissions in most CML patients.[20] The clinical success of imatinib has established a paradigm for cancer targeted therapies. In 2014, over 30 targeted agents have been approved for clinical use in the treatment of a broad range of human cancers.[15]

1.3. Resistance to Targeted Therapies

The emergence of drug resistance prevents molecular targeted therapies from eliciting lasting clinical benefit.[16, 23] Resistance to chemotherapy can be caused by primary unresponsiveness of a small number of cells prior to drug treatment, which is called intrinsic resistance, or can be acquired over time by the tumour in response to the treatment (acquired resistance).[14, 24] Existing unresponsiveness generally results from the presence of pre-existing redundant signalling pathways. These resistant clones, originally present in a small proportion, become predominant over time under the selective pressure of

chemotherapy.[15] There are many mechanisms whereby tumours may acquire resistance to targeted therapies. Alterations in the driving pathway have been observed in several patients and include constitutive activation of downstream effectors.[25] Bypass mechanisms such as activation and up-regulation of parallel signalling pathways or gain of stem cell-like functions can also drive acquired resistance (Figure 1.3).[7]

The development of additional mutations is another resistance mechanism, common for kinase targeted therapies (Figure 1.3).[23] This includes single-point mutation, gene deletion and amplification of genomic areas.[25] Mutation of the gatekeeper residue in a kinase target may confer resistance, by abrogating drug binding while maintaining high catalytic activity.[7] For instance, 40% of patients treated with imatinib have developed resistance through point mutations that change the conformation of the c-Abl kinase.[25] The genomic pressure of selective inhibition can lead to amplification of the target gene and reduce the efficacy of drug treatment.[26] Similarly, protein expression can be upregulated to overcome inhibition.

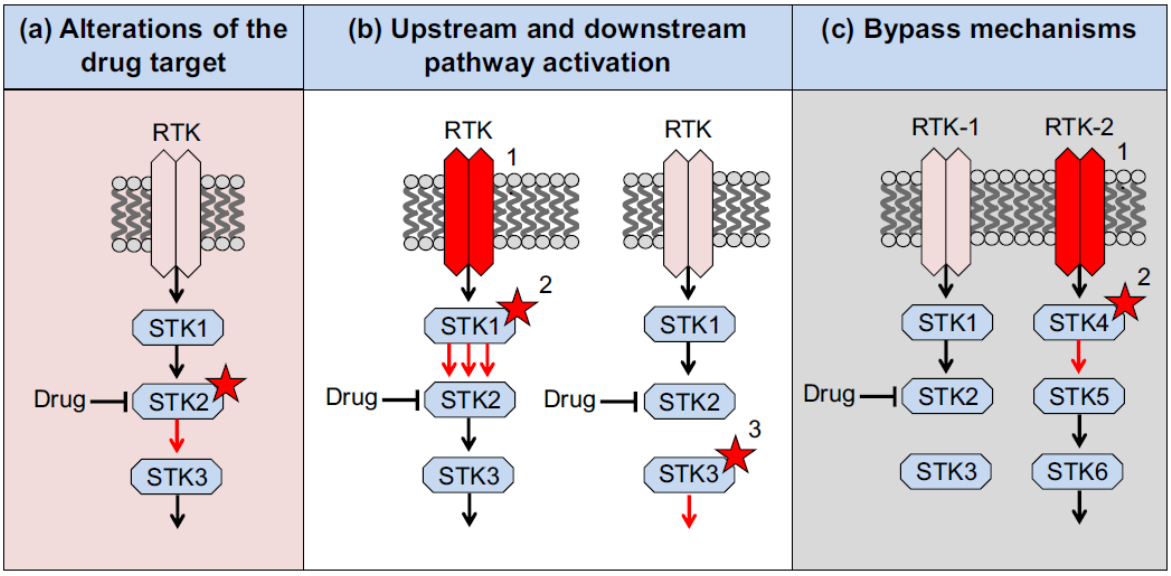


Figure 1.3: Schematic representation of three mechanisms of resistance to targeted therapies. RTK: receptor tyrosine kinase. STK: serine/threonine kinase. Red star: mutation.[23]

Overexpression of transporter efflux pumps, such as P-gp, MRP1 or BCRP, may prevent drugs from getting into cells, leading to low intracellular drug concentrations and resulting in chemoresistance.[16, 25] Altered expression of active uptake transporters can have a similar effect. Drug sequestration away from the intended intracellular site of action *via* pH variation is another mechanism leading to reduced efficacy.[16] Acquired resistance can also be mediated by pharmacokinetic and pharmacodynamics factors, such as enhanced

metabolism of the drug and high protein binding of the inhibitor.[24] An increased understanding of the biological processes underlying intrinsic and acquired resistance is required to guide subsequent treatment selection.[24]

The full potential from molecularly targeted cancer agents might arise from the use of intelligent drug combinations, which should allow the problems of intertumour genetic heterogeneity and drug resistance in cancers to be tackled.[7] Recently, heterogeneity in the tumour microenvironment has also been associated with variable responses to targeted therapy, introducing a more complex level of intertumour heterogeneity.[15] New technologies and methods are still required to evaluate and prioritise the best potential combinations.[7] Drug combinations of cytotoxic agents, which work by different molecular mechanisms, have been defined and proved more effective than single agent therapy, by achieving additive or synergistic effects. The major limitation of this strategy is the high level of induced undesired side-effects.[7] Combinations of molecularly targeted therapeutics with cytotoxic chemotherapy or radiation are already used in the clinic but without compelling biology rationale supporting them. For instance, paclitaxel (Taxol®) is used in combination with trastuzumab (Herceptin®), a monoclonal antibody, for the treatment of breast cancer.[7] Different strategies for the combination of molecular targeted agents can be envisaged, including inhibition of parallel signalling pathways. Targeting a single signalling pathway at different levels using two agents is another combinatorial option.[7] Both approaches are expected to increase activity and overcome resistance.

1.4. Personalised Medicine

The clinical benefit achieved with targeted therapies varies greatly.[16, 27] Indeed, such therapies are highly effective in patients where the targeted mutation drives tumour growth but their effect can be modest and transient when the carcinogenicity is driven by multiple mutations.[27] The average response rate to targeted therapy across an unselected patient population is between 10 and 20%. This has emphasised the importance of identifying molecular signatures, also called predictive biomarkers for patient selection.[24] Biomarkers are also used to define the best treatment regimen and identify patients with high risks for adverse effects.[28] This approach of proactively selecting populations for specific treatments is called ‘personalised’ or ‘stratified’ medicine.[29] Personalised medicine adds a step to traditional diagnosis, with a biomarker-assessment required to associate a patient with a specific therapy (Figure 1.4). Personalised medicine aims to eliminate the “one size fit all”

model of medicine.[30] A different set of biomarkers, 'response' biomarkers enable the response to be monitored during the course of treatment and can be used to guide further decision-making.[15]

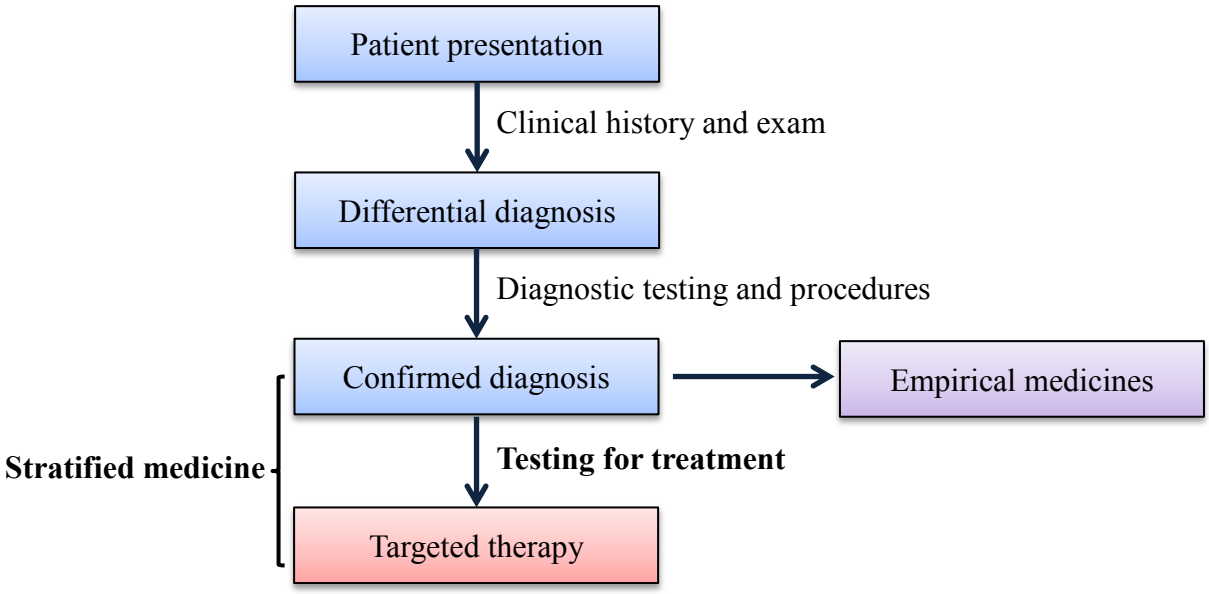


Figure 1.4: Stratified medicine in the clinical context (adapted from ref 29)

Molecular analyses at the protein, DNA, RNA or micro RNA levels have contributed to the identification of novel tumour subclasses, each with unique prognosis outcome or response to treatment.[30] These classifications are expected to significantly improve patient management. Incorporation of new, advanced technologies, that will provide detailed prognosis for each individual, will have a significant cost.

Predictive biomarkers, for defining potentially responsive patients, are also increasingly integrated into early clinical development of targeted therapies and guide clinical trial design. This has significantly accelerated drug development and approval.[15] For instance, clinical studies with crizotinib (Xalkori®) lasted just 4 years before the drug was approved by the FDA.

1.5. The Drug Discovery Process

'Omic' technologies are used during the initiation of a drug discovery program to identify novel molecular targets, whose modulation is likely to be beneficial in a given disease.[31] Validation of the target follows and is an essential step in the drug discovery process to ensure low attrition rate.[32] Complementary approaches, such as biochemical, genetic, *in*

vivo and bioinformatics studies are used to provide functional information on the target in the disease phenotype.[31, 33] Modulating target expression at the protein and mRNA levels is frequently used in cellular validation studies to examine the effects on the phenotype of cells.[32] In complement of these biological studies, identification of chemical probes for use in experiments *in vitro* is essential for rigorous preclinical target validation.[34] These molecules support the interpretation of biological experiments and give an understanding of the function of proteins and their role in physiology and pathology.[35] Molecular probes provide a proof of concept for the druggability of a target by small-molecule inhibitors.[35] Once evidence for the role of a target in a disease has been established *in vitro*, chemical tools are optimised for *in vivo* evaluation. Several recent reviews provide interesting discussions on the design of efficient tool compounds for *in vivo* studies (Figure 1.5).[34-37]

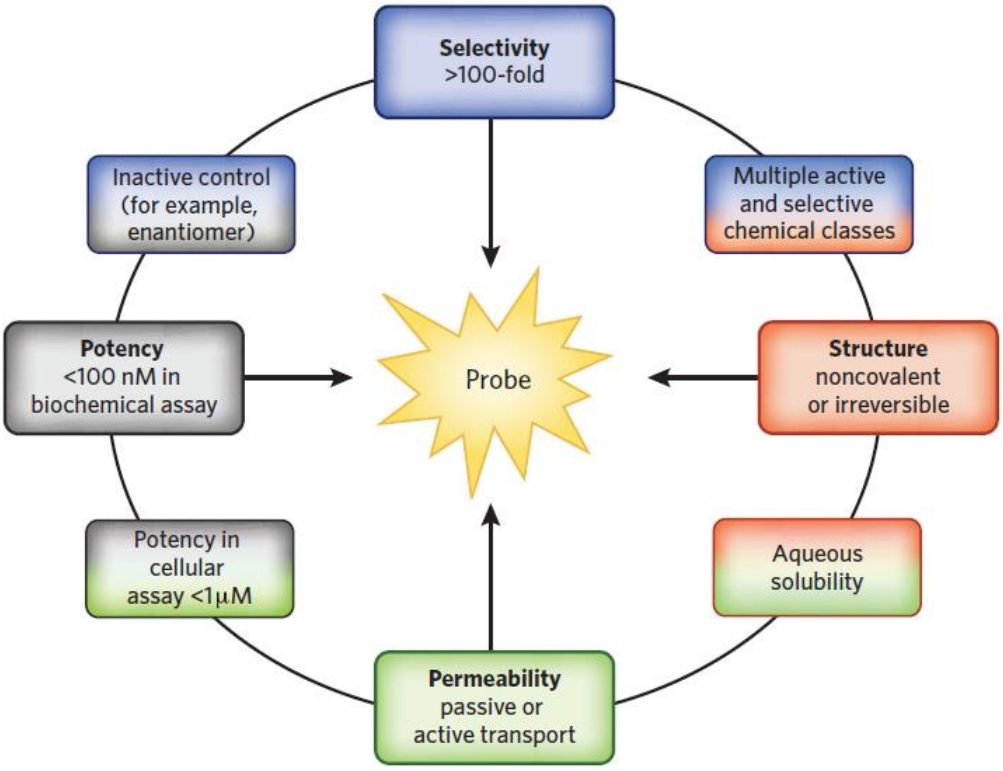


Figure 1.5: Important criteria for quality chemical probes[34]

A full drug discovery program is initiated when biological experiments have demonstrated that modulation of the target in the treatment of the disease is likely to be beneficial (Figure 1.6).[38] Hit identification is the first stage of a project and followed by a hit-to-lead phase which may use chemical tools from the target validation studies or alternative chemical hits.[39] High-throughput screening (HTS) of large libraries of chemically diverse templates is the most widely applicable technology for the identification of hits.[40, 41] However, it is now recognised that the high molecular weight and poor physicochemical

properties of compounds identified by HTS can render them unsuitable for further medicinal chemistry exploration.[42, 43] Alternative strategies, such as fragment-based approaches, *de novo* design or virtual screening may be employed.[44-47]

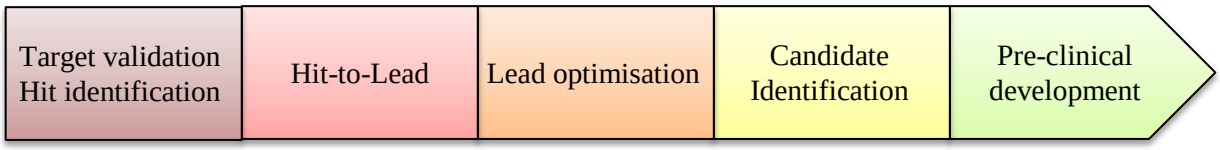


Figure 1.6: Phases in the pre-clinical drug discovery process (adapted from ref 43)

In the hit-to-lead phase, the structure-activity relationships of initial hits are explored to identify functional groups required for activity, and those that may be varied to improve potency. *In vitro* surrogate assays are also used for evaluation of pharmacokinetics parameters (plasma protein binding, microsomal stability, permeability) and off-target pharmacology properties (hERG inhibition, CYP inhibition). The lead optimisation process involves combining all of the desired properties into a single agent suitable for progression into clinical trials. A candidate molecule must achieve good potency against the primary target and selectivity over relevant secondary targets. In addition, the selected compound must demonstrate *in vivo* pharmacokinetics, safety, and pharmaceutical properties suitable for entering clinical evaluation studies.[43]

Despite increased investments in research and development activities, attrition rates for small-molecule drug candidates have remained high, leading to the perception that the pharmaceutical industry has low productivity.[38, 48, 49] In recent years, high molecular weight and lipophilicity, also termed "molecular obesity", have caused the failure of many drug candidates.[49] Defining physicochemical properties that predict long-term viability of drug candidates has been of interest for the medicinal chemistry community and was achieved *via* retrospective analysis of the physicochemical properties of marketed drugs. The pioneering study of Christopher Lipinski, regarding the physicochemical properties required to achieve good solubility and absorption, established a set of guidelines known as the "rule of 5".[50] Additional examinations of compound collections have since been conducted, with the objective to provide deeper and broader perspectives on this landmark assessment.[51, 52] These studies have raised the awareness of the importance of controlling physicochemical properties in the design of drug candidates and parametric guidelines have now been established to facilitate decision making.[48] Several binding indexes, including ligand efficiency (L.E.) and lipophilic ligand efficiency (LLE or LipE), relating

properties of a compound to potency, have been introduced to guide medicinal chemists during lead optimisation.[53, 54]

1.6. The Sulfatase-2 and ERK5 Projects

The advent of targeted therapies has provided novel efficacious treatment but only for a limited number of cancer types. A continuing effort is still required for the identification of new cancer treatments. Modulation of components of cell signalling pathways is currently an area of focus for novel anti-cancer drug discovery therapies.

The two projects described in this thesis concentrate on the development of small-molecules that modulate oncogenic signalling cascades. However, the approaches taken are significantly different. Inhibition of sulfatase-2 (Sulf-2) occurs early in the signalling sequence and is likely to affect multiple signalling pathways *via* reduction in the availability of several growth factors. In contrast, inhibition of ERK5 affects a single non-classical MAP kinase pathway at a late point in the signalling cascade.

The two projects cover different stages of the drug discovery process. The Sulf-2 project is at the target validation stage and focuses on the design of chemical tools for *in vitro* and *in vivo* model experiments. The ERK5 project is in the lead optimisation stage and focus on the optimisation of ADMET properties and pharmacology.

Chapter 2. Sulfatase-2 and Reported Small-Molecule Inhibitors

2.1. The Sulfatase Enzyme Family

The sulfation state of many physiological molecules has been associated with the regulation of important processes, including embryogenesis, inflammation, blood coagulation and drug metabolism.[55] Protein phosphorylation within cells is crucial for the regulation of most intracellular events. Sulfation of carbohydrates plays a similar role outside the cell and mediates a variety of extracellular communication events.

Two classes of enzyme modulate the degree of sulfation of proteins, lipids and saccharides: the sulfotransferases and the sulfatases.[55] Whereas sulfotransferases have been intensively studied and were thought for a long time to be the only regulators of the sulfation state of biomolecules, the sulfatases only became a subject of interest in the last 20 years when it was discovered that they were associated with lysosomal disorders.[56]

The human sulfatase family is a large protein family which comprises seventeen members (Table 2.1).[57] These proteins hydrolyse sulfate esters from diverse sulfated substrates, ranging from steroids to carbohydrates and lipids.[58] Regardless of their substrate, the sulfatases have highly conserved amino acid sequences and are structurally and mechanistically closely related. A number of sulfatases were discovered for their ability to hydrolyse phenolic sulfate esters, and have therefore been named aryl sulfatase. The endogenous physiological substrates were identified retrospectively and are in some cases still unknown (Table 2.1).[59]

Table 2.1: Substrate and subcellular location of human sulfatases[57]

Enzyme	Abbreviation	Subcellular location	Endogenous substrate
Aryl sulfatase A	ARSA	Lysosome	Sulfatide
Aryl sulfatase B	ARSB	Lysosome	Dermatan sulfate, chondroitin sulfate
Aryl sulfatase C or Steroid sulfatase	ARSC STS	ER	Steroid sulfates
Aryl sulfatase D	ARSD	ER	Unknown
Aryl sulfatase E	ARSE	Golgi apparatus	Unknown
Aryl sulfatase F	ARSF	ER	Unknown
Aryl sulfatase G	ARSG	ER	Unknown
Aryl sulfatase H	ARSH	Unknown	Unknown
Aryl sulfatase I	ARSI	ER	Unknown
Aryl sulfatase J	ARSJ	ER	Unknown
Aryl sulfatase K	ARSK	Unknown	Unknown
Galactosamine-6-sulfatase	GalN6S	Lysosome	Chondroitin sulfate, keratin sulfate
Glucosamine-6-sulfatase	GlcN6S	Lysosome	Heparin sulfate, keratin sulfate
Iduronate-2-sulfatase	IdoA2S	Lysosome	Heparan sulfate, dermatan sulfate
Heparin-*N*-sulfatase	GlcNS	Lysosome	Heparan sulfate
Sulfatase 1	Sulf-1	ECM	Heparan sulfate
Sulfatase 2	Sulf-2	ECM	Heparan sulfate

ER = endoplasmic reticulum; ECM = extracellular matrix

In human, sulfatases are part of the secretory pathway and can be found either in subcellular compartments - lysosome, Golgi network, endoplasmic reticulum (ER) - or in the extracellular matrix (ECM). Owing to these different localisations, the optimum pH for activity varies between members of the family, with lysosomal sulfatases active at acidic pH, whereas ER, Golgi apparatus and ECM sulfatases are active at neutral pH.[57]

Lysosomal sulfatases have been well characterised and play an important role in the catabolism of sulfated metabolites.[56] For instance, ARSB, GalN6S, GlcN6S, GlcNS and

IdoA2S participate in the degradation of glycosaminoglycans, which consist of long chains of unbranched repeating disaccharide units. The lysosomal sulfatases are exoenzymes that act at the non-reducing end of polysaccharides.[56] The other sulfatase to have been widely studied is ARSC, also known as steroid sulfatase (STS), which is an endoplasmic reticulum-bound protein. ARSC hydrolyses sulfate esters from steroid precursors such as oestrone, cholesterol, pregnenolone and dehydroepiandrosterone sulfates (Figure 2.1).[59] This enzyme has been associated with hormone-dependent diseases. Less is known about the recently discovered extracellular sulfatases, Sulfatase 1 and Sulfatase 2 which hydrolyse the O^6-sulfate of glucosamine residues in heparan sulfate proteoglycan (HSPG) chains.[56]

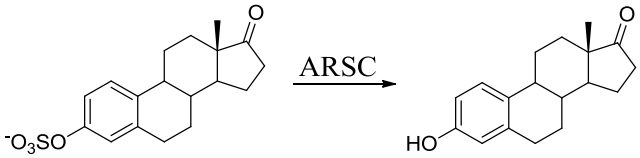


Figure 2.1: Hydrolysis of oestrone sulfate by ARSC

Several human disorders, such as mucopolysaccharidose, X-linked ichthyosis or chondrodysplacia, have been associated with a single sulfatase deficiency. Deficiency in all human sulfatases has also been observed, resulting in a rare and severe genetic disease, termed multiple sulfatase deficiency.[58]

2.2. Structure of Sulfatases

All sulfatases have a similar size ranging from 500 to 800 amino acids. The sequence homology among the seventeen members of the family ranges between 20% and 60%. The degree of similarity is higher in the *N*-terminal region which contains the catalytic site. The high degree of similarity suggests that sulfatases may result from the evolution of a common ancestral gene.[56]

The X-ray crystal structures of three human sulfatases (ARSA, ARSB and ARSC) and one bacterial sulfatase have been solved. The four structures are very similar and exhibit a globular domain composed of α-helices and β-sheets. In addition to this spherical domain, ARSC has a unique membrane-anchoring domain (Figure 2.2).[60] An overlay of the four crystal structures has revealed that the polar catalytic domains superimpose on each other,

with only minor spatial differences. No crystal structures of a sulfatase bound to its substrate has been published to date.

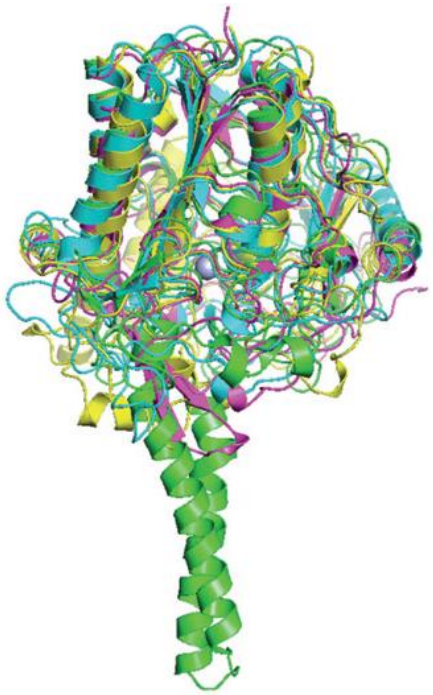


Figure 2.2: Overlay of the four sulfatase crystal structures: ARSA (blue), ARSB (magenta), ARSC (green) and Pseudomonas Aeruginosas Sulfatase (yellow)[60]

All sulfatases possess within their catalytic site a conserved cysteine residue which is post-translationally modified into a formylglycine (FGly), residue essential for the enzymatic activity of sulfatases (Figure 2.3).[58] The post-translational modification is performed by an enzyme named formylglycine-generating enzyme (FGE), which is encoded by the sulfatase modifying factor 1 gene.[57] The cysteine oxidation occurs within the ER when the polypeptide is still unfolded. A peptide segment of 11 amino acid residues, starting with the cysteine to be modified, is required to direct the FGly modification.[61] A core motif, C(X/T)P(X/S)R was revealed to be essential to obtain modest amounts of oxidation.[62] This motif is conserved across all human sulfatases. The molecular mechanism by which the FGE oxidises the cysteine residue is still unknown.[56, 57] Hydration of the aldehyde gives an activated hydroxyformylglycine (HFGly) (Figure 2.3).

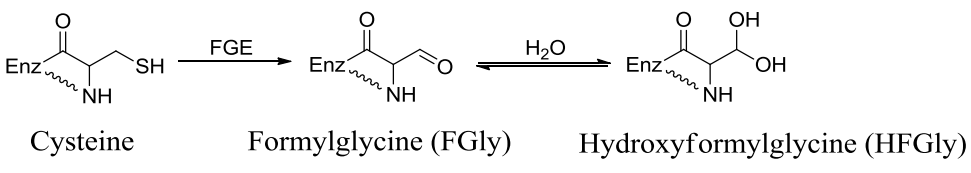


Figure 2.3: The post-translational modification mediated by FGE

The active site of sulfatases is situated in the *N*-terminal region and comprises ten polar residues and a divalent metal cation, identified as a calcium or magnesium ion by structural biology studies. The HFGly residue is located at the bottom of the catalytic cleft (Figure 2.4). The members of the sulfatase family share a common catalytic mechanism, highlighted by the conserved sequence of residues in the catalytic domain.[60] The proposed function of each residue is detailed in Table 2.2.

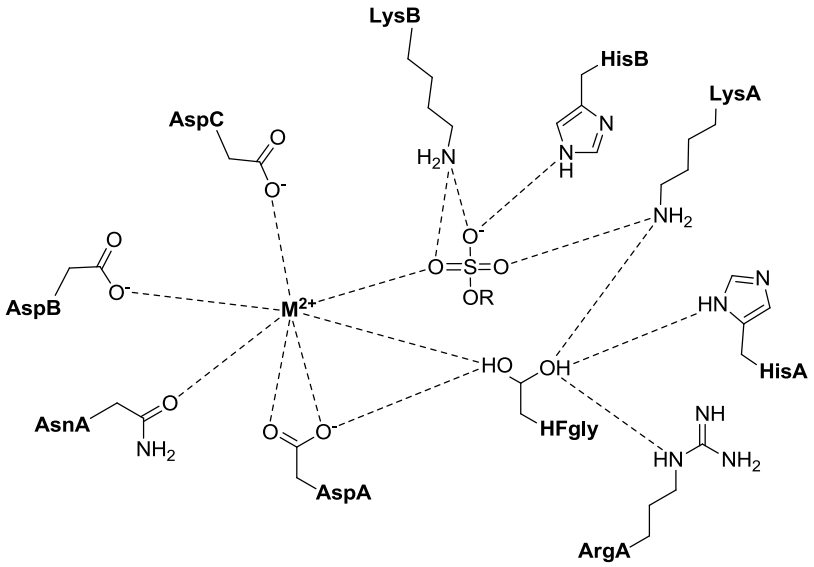


Figure 2.4: Schematic representation of the active site of the sulfatase enzymes (adapted from ref 56)

Table 2.2: Proposed function of amino acids and metal cation in the active site[56]

Residue	Proposed function
HFGly	Catalytic nucleophile
M	Substrate binding and activation, stabilisation of HFGly
AsnA	Metal coordination, activation of HFGly
AspA	Metal coordination
AspB	Metal coordination
AspC	Metal coordination
ArgA	Stabilisation of HFGly
HisA	Stabilisation of HFGly, elimination of HFGly sulfate
HisB	Substrate binding and activation, alcohol protonation
LysA	Substrate binding and activation, stabilisation of HFGly
LysB	Substrate binding and activation, alcohol protonation

Although the residues acting on substrate recognition have not been identified, it is assumed that recognition must occur outside the narrow cleft containing the highly-conserved active site. The *C*-terminal region, which is less conserved among the sulfatases, may act as a substrate discerning unit.[56, 60]

2.3. The Mechanism of Desulfation by Sulfatase Enzymes

Until the identification of the post-translational modification of the cysteine residue in 1995, the mechanism of sulfate ester hydrolysis remained unknown. The original proposed mechanism was an addition-hydrolysis mechanism based on the electrophilic nature of the formylglycine residue (Figure 2.5).[56] Nucleophilic attack of the negatively charged sulfate oxygen on the FGly moiety gives a sulfate diester. A water molecule then releases the alcohol conjugate and the formylglycine is regenerated *via* sulfate α-elimination.

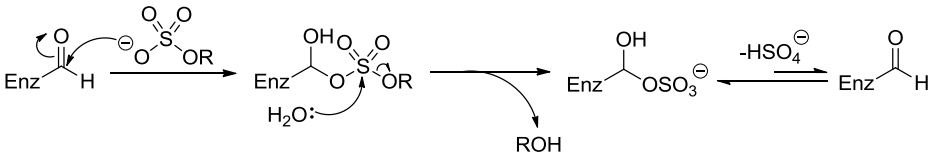


Figure 2.5: Addition-hydrolysis mechanism[56]

The crystal structure of ARSA provided the first piece of evidence, suggesting that the FGly residue may exist in its hydrated form in the resting state of the enzyme. A second potential mechanism is a transesterification-elimination mechanism, and was proposed following this discovery (Figure 2.6).[56, 63] In this instance, nucleophilic attack of the hydroxylformylglycine (HFGly) on the sulfate sulfur atom releases the alcohol conjugate. Geminal elimination of the sulfate group is followed by hydration of the FGly moiety intermediate.

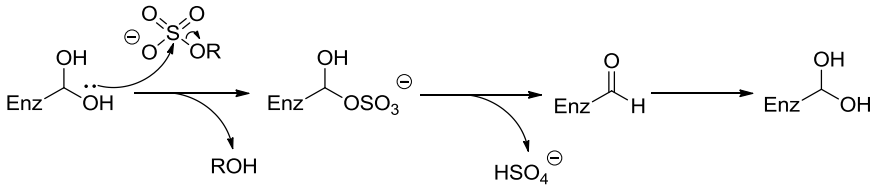


Figure 2.6: Transesterification-elimination mechanism[56]

A number of pieces of evidence supporting the transesterification-elimination mechanism have accumulated. However, the nature of sulfate ester hydrolysis is still unclear and could be either associative (S_N2 like) or dissociative (S_N1 like).[56]

2.4. Sulf-1 and Sulf-2: the Endosulfatases

Sulfatase 1 was discovered serendipitously during a study of the quail embryo.[64] The mammalian versions of the enzyme were identified shortly after in rat, mouse and human.[65, 66] During the course of a study aiming to clone a full-length Sulf-1 c-DNA, a closely related protein was identified and designated as sulfatase 2.[65]

Sulf-1 and Sulf-2 are the largest proteins of the sulfatase family, around 870 amino acids in length, and are the only two localised in the extracellular matrix. The Sulfs have a high degree of similarity (63-65%) and display the same conserved catalytic residues as the other members of the family.[67] A cysteine residue, present in the catalytic domain, needs to be oxidized into a FGly for the enzyme to be active.[57]

The Sulfs are divided into four domains. Starting from the *N*-terminal domain, there is first a promoter region, followed by the catalytic domain of 374 amino acids, then a basic hydrophilic domain of 346/366 amino acids, and finally a *C*-terminal domain of 109/127 amino acids (Figure 2.7) .[68] The central hydrophilic domain is a feature of the Sulfs which does not exist in other members of the family.[69]

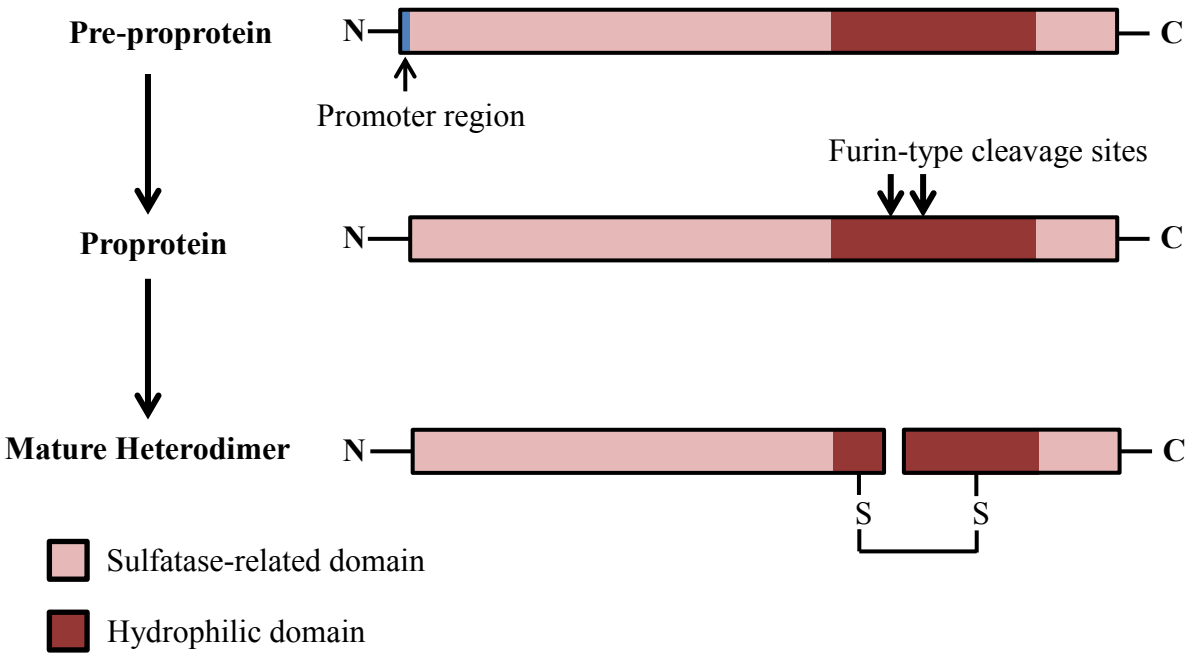


Figure 2.7: Post-translational processing of the Sulfs (adapted from ref 67)

Sulf-1 and Sulf-2 consist of a heterodimer of 75 and 50 kDa subunits, linked *via* disulfide bonds (Figure 2.7). The cleavage of the pro-protein is believed to occur in the Golgi apparatus under the action of a furin type protease. Although, the catalytic domain is

located in the *N*-terminal 75 kDa subunit, the *C*-terminal fragment is important since its deletion induces the loss of both endosulfatase and arylsulfatase activity.[69] The unique hydrophilic domain of about 320 amino acids is largely positively charged. Its deletion prevents endosulfatase activity but not hydrolysis of phenolic sulfates, suggesting that the hydrophobic domain might be involved in the binding of the Sulfs to their natural substrates, heparin and heparan sulfate proteoglycan.[68] In addition, this domain is also involved in the binding of the Sulfs to the cell surface.[67]

HSPGs are major components of the extracellular matrix and the cell surface. These macromolecules are a subtype of proteoglycans, where heparan sulfate chains are attached to a restricted set of core proteins. The heparan sulfate chains are linear polysaccharides composed of repeating and alternating disaccharide units of *N*-acetylated or *N*-sulfated glucosamines and uronic acids (glucuronic acid or iduronic acid).[70] The polysaccharides are heterogenous in terms of length, space between modified segments and extent of sulfation and epimerization.[71] The extent of sulfation of heparan sulfate is crucial for its biological functions.[72] Four different sites of sulfation exits in heparan sulfate: the N^2-, O^3-, and O^6-positions of glucosamine and the O^2-position of iduronic acid (Figure 2.8).[73]

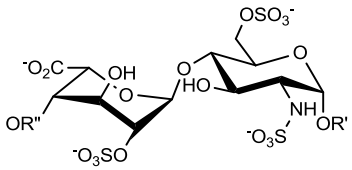


Figure 2.8: A trisulfated disaccharide unit (IdoA2S-GlcNS6S) of heparan sulfate

Heparan sulfate chains are heterogenous in their sulfation pattern, with region of high sulfation separated by regions of lower sulfation.[67] As one of the body's most negatively charged macromolecules, HSPGs bind to a variety of different proteins, such as morphogens and growth factors, and regulate important physiological processes including cell proliferation, cell migration and coagulation (Figure 2.9).[69, 71] An additional function attributed to HSPGs is to act as co-receptors for cell surface receptor tyrosine kinases. The sulfation and epimerisation of heparan sulfate chains are dynamically and strictly regulated under normal philological conditions.

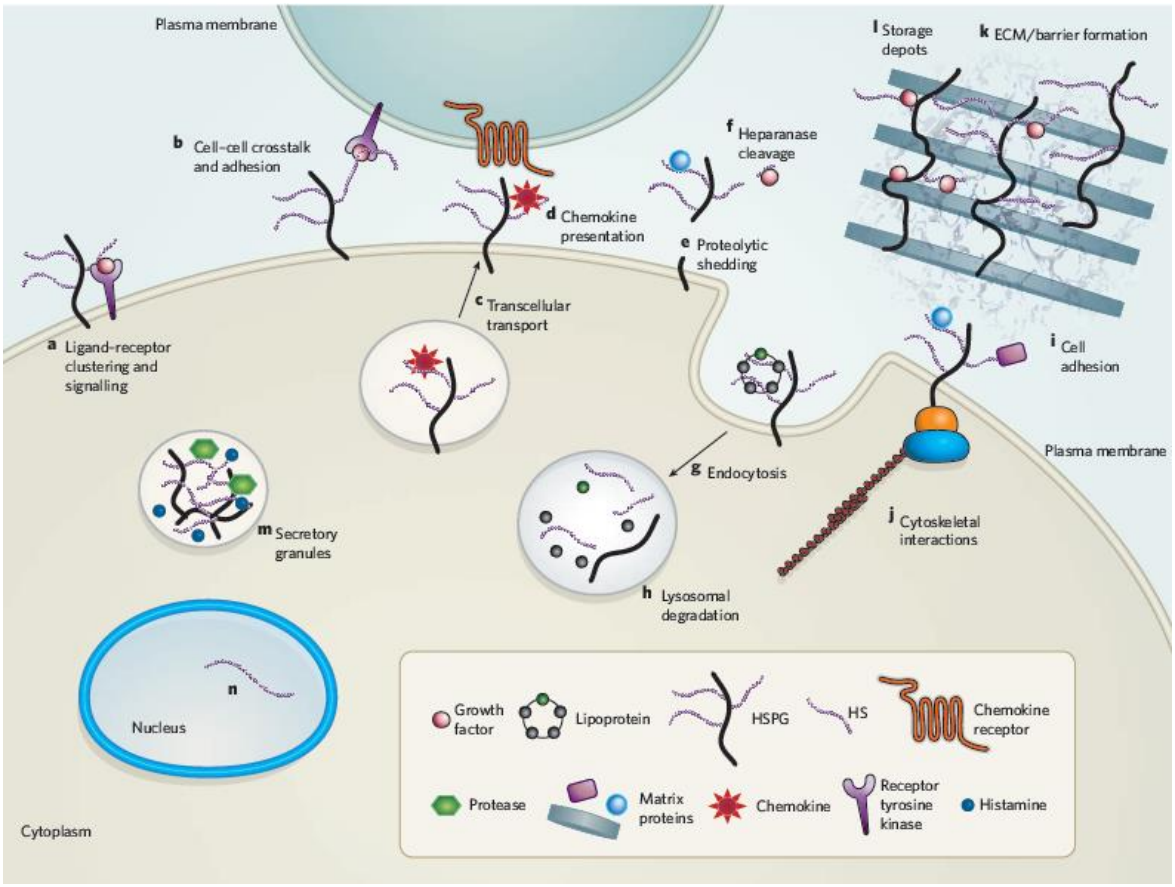


Figure 2.9: Roles of heparan sulfate proteoglycan in cell physiology[71]

The Sulfs hydrolyse O^6-sulfate from glucosamine in highly sulfated regions of HSPG and preferably on trisulfated disaccharide units (IdoA2-GlcNS6S).[65, 72, 74, 75] The O^6-sulfation of glucosamine has been identified as a key regulator of HSPG interactions with growth factors, morphogens and chemokines.[70] Therefore, the Sulfs can reverse ligand interaction with HSPG and increase ligand concentration in the extracellular matrix.[73] Although the Sulfs have some functional redundancy, biological studies have demonstrated that their effects on heparan sulfate structure are different. In addition to their endosulfatase activity, it has now been established that Sulf-1 and Sulf-2 also hydrolyse intra-chain sulfates.[65, 76]

2.5. Sulf-2: An Attractive Target for Cancer Therapy

Depending on their activating or inhibitory effects upon cell signalling, deregulation of the Sulfs has been associated with either tumour progression or suppression.[68] Sulf-1 and Sulf-2 are overexpressed in a number of cancers including breast, central nervous system, colon, lung, hepatocellular carcinoma and pancreatic cancer.[77-84] To understand the significance of upregulated Sulfs expression, a case-by-case analysis needs to be performed.

Sulf-2 expression has been correlated with aggressive tumour phenotype and poorer patient survival in HCC.[81] An analysis of 139 resected HCC tissues revealed that Sulf-2 expression was increased in 57% of the samples. Sulf-2 is also highly expressed in 73% of HCC cell lines.[81] *In vitro* overexpression of Sulf-2 promoted HCC cell growth and migration, whereas Sulf-2 knockdown abrogated HCC cell proliferation[81]. *In vivo* experiments have proven that Sulf-2 knockdown using shRNA resulted in reduced growth of HCC tumour xenograft models.[67, 80] Similarly, *in vivo* silencing of Sulf-2 in pancreatic adenocarcinoma inhibited tumour growth.[77]

Sulf-2 has been demonstrated to promote carcinogenesis through activation of the Wnt pathway.[77, 78, 85] Overexpression of Sulf-2 liberates Wnt ligands such as Wnt1, Wnt3, Wnt3a and Wnt4 from HSPG.[77] These free ligands then bind to the Frizzled receptor and activate signal transduction pathways resulting in accumulation of non-phosphorylated β-catenin in the cytoplasm. After its translocation to the nucleus, β-catenin binds to members of the TFC/LEF family of transcription factors, and activates target genes promoting cell growth.[77, 86] For instance in pancreatic adenocarcinoma cell lines, expression of Sulf-2 contributes to *in vitro* cell growth and tumourigenicity *via* promoting autocrine Wnt signaling.[87] The Wnt/Frizzled/β-catenin pathway is activated in approximately half of HCCs, a cancer type where Sulf-2 is overexpressed.[78]

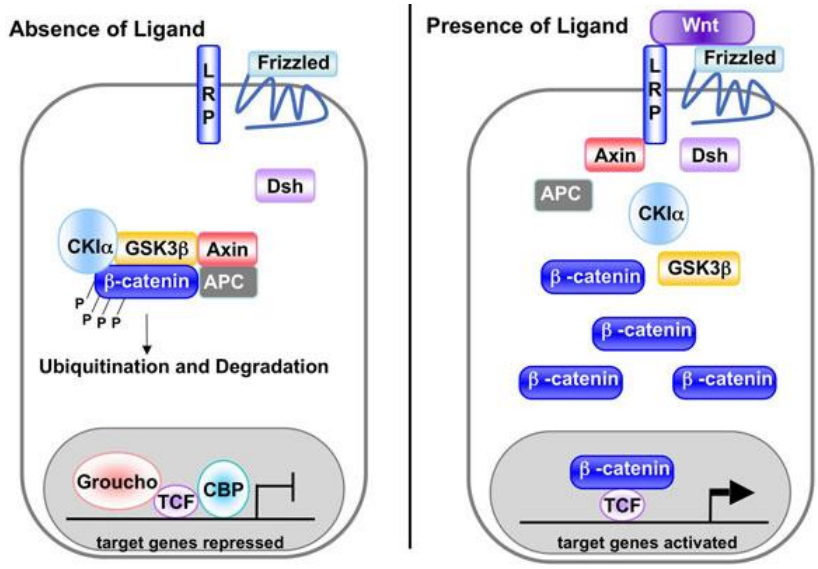


Figure 2.10: The canonical Wnt signalling pathway[88]

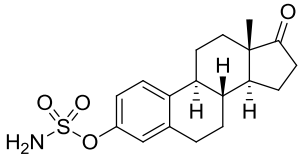
Sulf-2 has been shown to possess pro-angiogenic activity and could therefore contribute to tumourigenesis.[79] The pro-angiogenic effects could be explained by the release of VEGF ligands sequestration by HSPGs.

The release of binding proteins from HSPGs by the action of Sulf-2 increases the availability of HSPGs to interact with tyrosine kinase receptors, such as the FGF receptor. Interactions between HSPGs and the FGF receptor induce dimerization of the receptor into its active form, increasing affinity of the receptor for its FGF ligand. However, controversial data have been reported, showing that Sulf-2 could have an inhibitory effect on the FGF pathway. [67] It now appears that the effect of Sulf-2 on the classical MAP kinase pathway could be cancer-type specific.[75, 80, 81, 89]

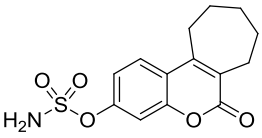
Despite their structural similarity, Sulf-1 and Sulf-2 have been shown to have opposite effects on liver cancer cells *in vitro* and *in vivo*. Sulf-1 acts as a tumour suppressor through inhibition of receptor tyrosine kinase signalling whereas Sulf-2 has been shown to exert an oncogenic effect through activation of diverse signalling pathways such APK, Akt and Wnt.[80] The contradictory findings on the effect of the Sulfs come from distinct cellular contexts, and it can be hypothesised that their effect will differ depending on cancer-types and the signalling pathways driving carcinogenesis.

2.6. Reported Sulfatases Small-Molecule Inhibitors

Among the seventeen human sulfatases, ARSC is the only member which has been the target of some drug discovery programs. ARSC inhibitors have been developed to provide novel therapies for the treatment of hormone-dependent breast cancer.[90] ARSC expression is upregulated in a large number of breast cancer patients and is a source of active oestrogens.[91] EMATE **2** was the first potent ARSC inhibitor to be developed.[92] This steroid derivative inhibits ARSC irreversibly with an IC_{50} value of 80 nM. The development of EMATE as a drug was stopped at the preclinical stage, since the inhibitor was found to exert a strong oestrogenic effect.[93] To develop xenobiotics deprived of oestrogenic effects, non-steroidal sulfamate inhibitors have been investigated, leading to the identification of 667COUMATE **3**.[91] This potent irreversible inhibitor of ARSC was found to be 3-fold more active than EMATE **2** *in vitro* and is currently in phase II clinical trial for the treatment of hormone-dependent breast cancer.[93-95]



EMATE, **2**



667COUMATE, **3**

The majority of agents modulating ARSC activity possess a sulfamate warhead which was found to be critical for their pharmacological effect.[90] Replacement of the oxygen atom of the sulfamate by a nitrogen, a sulfur or a carbon completely abolished ARSC inhibition.[56, 87, 96] Primary sulfamates have also been used for the irreversible inhibition of other sulfatases. Unlike their primary counterparts, secondary and tertiary sulfamates are reversible inhibitors and usually possess a less pronounced pharmacological effect.[97]

Four possible mechanisms have been proposed for the irreversible inhibition of sulfatases by primary sulfamates (Figure 2.11).[98, 99] The first mechanism (Figure 2.11, a)) involves nucleophilic attack of the HFGly on the sulfamate sulfur atom. Following elimination of sulfamic acid, a FGly moiety is obtained. The electrophilic FGly then reacts with sulfamic acid to form an imine, which irreversibly inhibits the enzyme activity. The second mechanism (Figure 2.11, b)) proceeds in a similar fashion up to generation of the FGly unit. In this instance a lysine residue, activated by the eliminated sulfamic acid, reacts with the FGly residue to form an imine. In the third and fourth proposed mechanisms (Figure 2.11, c) and d)) irreversible sulfatase inhibition is caused by the formation of a sulfamide. These mechanisms are hypothetical and only limited evidence have been identified in support of each.

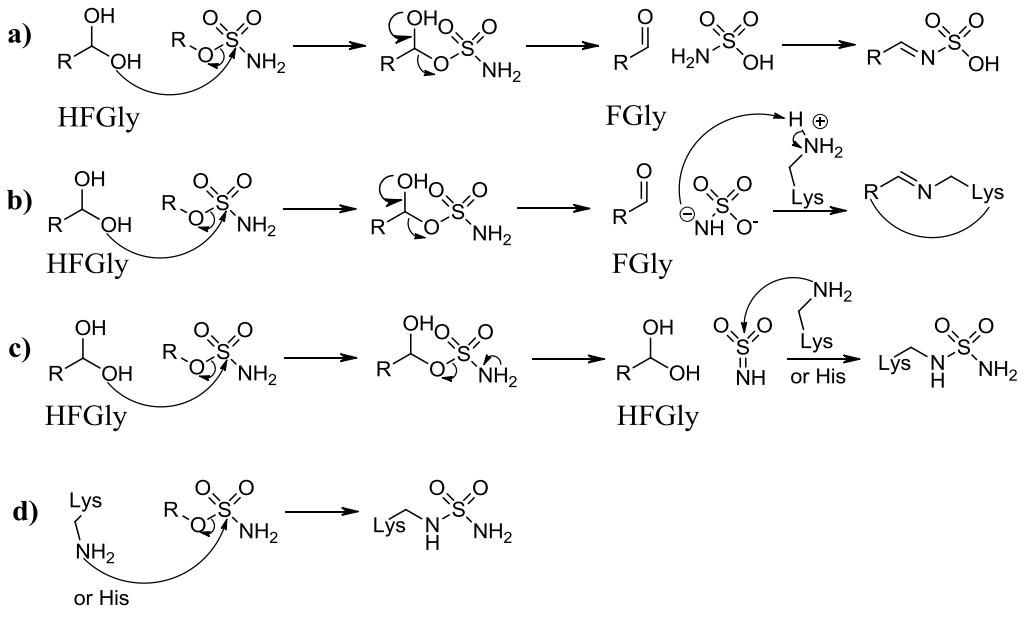


Figure 2.11: Postulated mechanisms for the irreversible inhibition of sulfatase enzymes by primary sulfamates[56, 99]

The accumulation of evidence demonstrating that Sulf-2 is contributing to carcinogenesis makes it an attractive target for the development of new anticancer drugs. In 2010, Hossain *et al.* reported the sulfated oligosaccharide PI-88 (Figure 2.12) to be a dual Sulf-1 and

Sulf-2 inhibitor.[100] This heparin mimic, derived from yeast, is under evaluation in several clinical trials as an inhibitor of the heparin sulfate-degrading enzyme heparanase.[101] PI-88 has also been shown to block the interactions of heparin sulfate with different growth factors, reducing the downstream activities of the affected pathways. The measured Sulf-2 inhibition by PI-88 was 1.6 µg/mL, an IC_{50} value very close to that reported for heparanase (2.0 µg/mL).[100]

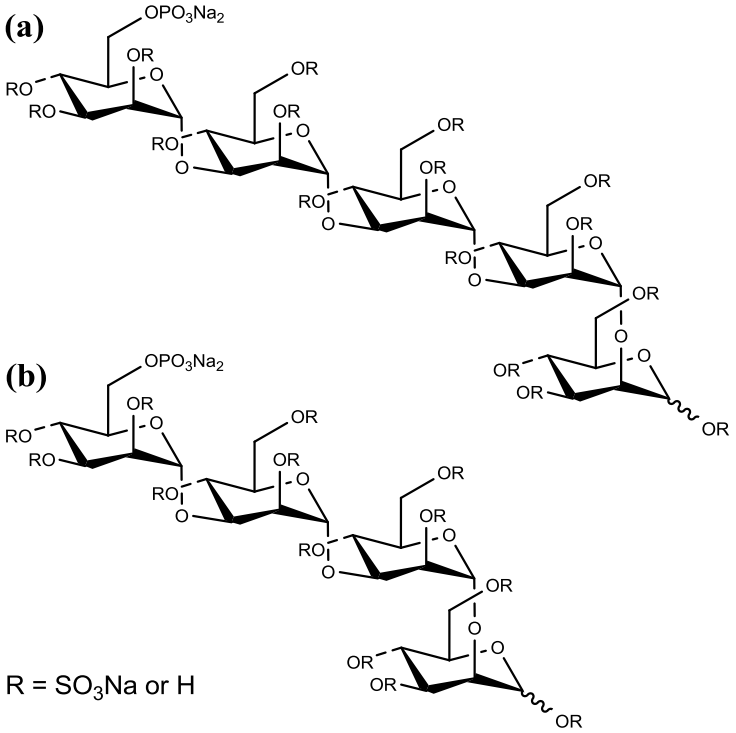
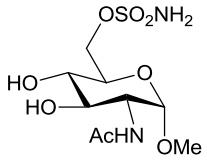


Figure 2.12: Chemical structure of PI-88. PI-88 is composed predominantly (≈ 90%) of (a) phosphomonopentaose and (b) phosphomonotetraose sulfates (adapted from ref 101)

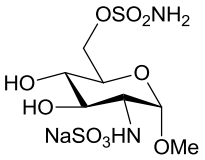
More recently Wong *et al.* reported monosaccharide sulfamate inhibitors of Sulf-1 and Sulf-2 (Figure 2.13).[102] These compounds were derived from the monosaccharide glucosamine substrate, bearing a sulfamate at the O^6-position. Two of these monosaccharide inhibitors (**5** and **8**) had activity in the micromolar range and were equipotent for Sulf-1 and Sulf-2.[102] Primary and tertiary sulfamate derivatives were assessed and both were found to be reversible inhibitors. Sulfation of the amino group of glucosamine significantly improved Sulf-2 inhibition, suggesting that polar functionalities might be required to enhance the interaction between the inhibitor and the enzyme.[102] Although these compounds were not sufficiently potent for use in target validation studies, their discovery provided encouragement that viable Sulf-2 inhibition was possible with low molecular weight compounds. In the same paper, Sulf-1 and Sulf-2 inhibition by two

simple phenyl sulfamates was found to be significantly weaker than with monosaccharides **5** and **8**.[102]



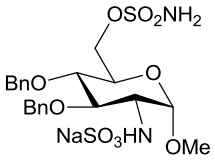
4

Sulf-2: 30% inhibition at 5 mM



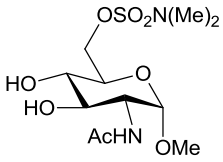
5

IC_{50} = 128-140 μM



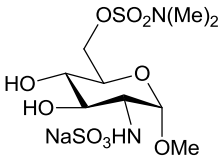
6

65% inhibition at 5 mM



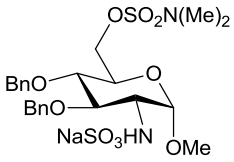
7

Sulf-2: 60% inhibition at 5 mM



8

IC_{50} = 214-258 μM

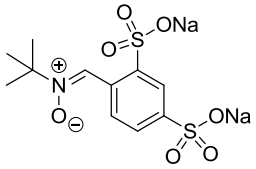


9

80% inhibition at 5 mM

Figure 2.13: Monosaccharide sulfamate inhibitors of Sulf-1 and Sulf-2 and their reported Sulf-2 inhibitory activity.[102]

In 2013, Roberts *et al.* reported 2,4-disulfonylphenyl-tert-butylnitrone (OKN-007 **10**) as a Sulf-2 inhibitor.[103] OKN-007 promoted tumour cell apoptosis and inhibited cell proliferation, viability, and migration of Huh7 cells overexpressing Sulf-2. However, no inhibition data against isolated Sulf-2 have been reported, suggesting that the cellular effects observed might be caused by alternative mechanisms than Sulf-2 modulation. OKN-007, also known as NXY-059, was originally developed as a free radical neuroprotectant for the treatment of acute ischemic stroke.[104]



OKN-007, **10**

Chapter 3. Development of Novel *O*-Aryl Sulfamate Protecting Groups for the Synthesis of Potential Non-Saccharide Sulf-2 Inhibitors

3.1. Design of Potential Chemical Probes for Sulf-2 Inhibition

3.1.1. Rationale

Chemical probes or tools are used to establish the relationship between a specific target and broader biological mechanisms, allowing a link between target perturbation and disease-related pharmacology to be established.[34, 37] Probe compounds are essential to support cell-based preclinical target validation, and in identification of molecular targets involved in disease modulation. A good chemical probe should have high potency and selectivity for the assigned primary target, to confidently associate biological response with target modulation.[36]

The initial aim of the Sulf-2 project was to identify chemical tools for use in experiments *in vitro* with the objective to determine whether IC_{50} values against Sulf-2 below 100 μM were achievable with small-molecule inhibitors, whether selectivity over other members of the human sulfatase family was achievable and whether Sulf-2 perturbation with a small-molecule inhibits cancer cell growth *in vitro*. In parallel, the reported Sulf-1/Sulf-2 dual inhibitors **5** and **8**, were resynthesised by a colleague and used for the development of a Sulf-2 primary pharmacology assay.[105]

In the absence of a published crystal structure and of a biological assay suitable for a high-throughput screening campaign, the structure of the endogenous HSPG substrate was considered as a potential starting point for identification of probe compounds. Although no crystal structure of an HSPG was available, modelled structures of the related macromolecule heparin, which is likely to reflect the structure of the highly sulfated regions of HSPGs, were utilised to gain an understanding of the structural features governing interactions between heparin and its protein binding partners.[106] Negatively charged sulfate and carboxylate groups cover most of the accessible surface of the polymer, and have been shown to regulate the binding of heparin to the enzyme 3-*O*-sulfotransferase.[106, 107] X-ray crystal structures of FGF-1 and FGF-2 in complex with heparin oligosaccharides also revealed the importance of the sulfate and carboxylate groups for binding.[108]

These studies demonstrated that interactions of the charged sulfate and carboxylate groups on the heparin oligosaccharide with basic amino acids on protein binding partners are often key contributors to tight and specific binding. Mimicking these ionic interactions was considered important for *de novo* design of potential non-saccharide based Sulf-2 inhibitors.

Several approaches were pursued in parallel for the identification of improved tool compounds, relative to **5**. Analogues of monosaccharide **5** and simplified cyclic aliphatic scaffolds were synthesised by a colleague working on the project to generate Sulf-1 and Sulf-2 SARs, and to understand structural changes affecting selectivity.[105] Since phenyl sulfamate has been reported to be a weak Sulf-2 inhibitor, a set of phenol-derived primary and dimethyl sulfamates was also prepared to examine the electronic and steric effect of substituents on Sulf-2 inhibition.[102, 105]

A second generation of aromatic sulfamate inhibitors was subsequently designed, to attempt to position the sulfamate and a second polar moiety in similar regions of space to those occupied by sulfate and carboxylate groups in heparin. This series could provide hit compounds with improved physicochemical properties compared with the monosaccharide scaffold and is more amenable to large scale and rapid analogue synthesis.

The first template designed using this strategy was based on a biphenyl sulfamate core, with polar groups on the second aromatic ring (B-ring). The biphenyl targets were energy minimised in the gas phase and overlaid onto a trisaccharide heparin fragment taken from the reducing end of the modelled heparin structure (Figure 3.1). A primary sulfamate group at the 3-position of the first phenyl ring (A-ring) was overlaid with the 6-*O* sulfate of glucosamine, enabling substituents on the second phenyl ring to overlay the *N*-sulfate of glucosamine or the *O*-sulfate of iduronic acid in the heparin-derived template structure.

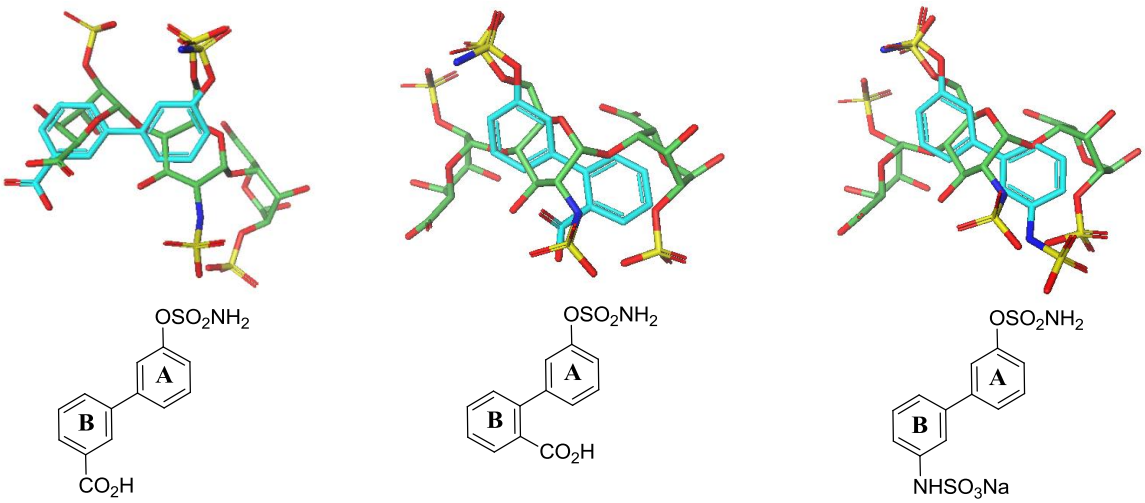


Figure 3.1: Representative overlays of biphenyl targets (cyan) with a heparin-derived trisaccharide template (green)

In addition to the rationally designed derivatives, the biphenyl core was used to probe additional polar and ionic interactions through incorporation of polar functional groups into the *ortho*, *meta* and *para* position of the B-ring.

A biphenyl ether sulfamate scaffold was the second template designed using a similar strategy (Figure 3.2). This template incorporates an oxygen linker which may mimic that found in polysaccharides and has lower energy barriers to conformational changes.

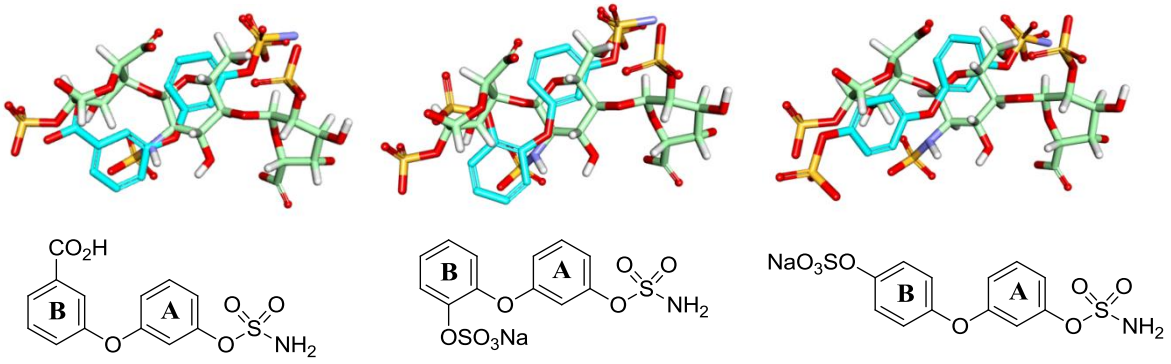


Figure 3.2: Representative overlays of biphenyl ether targets (cyan) with a heparin-derived trisaccharide template (green)

3.1.2. Requirements for a Novel Sulfamate Protecting Group

In order to explore the effect of substitution on the B-ring of a biphenyl template efficiently, it was necessary to introduce the primary sulfamate moiety early in the synthesis. Initial retrosynthetic analysis suggested that 3-bromophenylsulfamate (**11**) could be a versatile coupling partner in Suzuki-Miyaura cross-coupling reactions to access

biphenyl sulfamates, which could then undergo further chemical modifications (R^1 to R^2) to provide the desired targets (Figure 3.3).

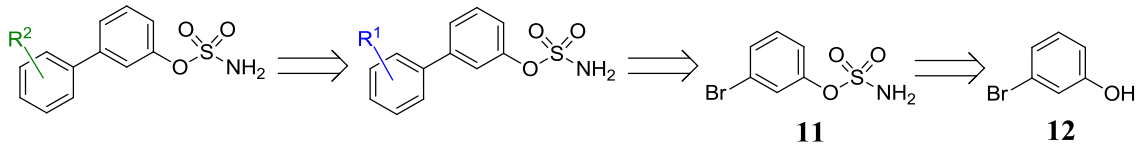
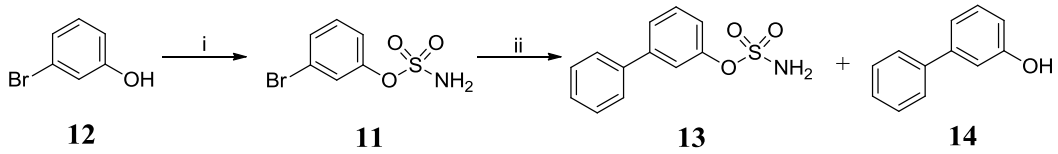


Figure 3.3: Initial retrosynthetic analysis for the biphenyl sulfamate series

However, the sensitivity of primary sulfamates to basic conditions limited the efficiency of Suzuki cross-couplings on 3-bromophenyl sulfamate (**11**), with low product yields and a mixture of desulfamoylated product and starting material obtained (Scheme 3.1). An array of conditions was explored in which the base component was varied, the best results being obtained with weak bases such as sodium carbonate and $Pd(dppf)Cl_2$ as catalyst. However, despite extensive optimisation efforts, the highest product yield was only 22%.[109] The instability of primary phenol *O*-sulfamates under basic conditions is due to an E1Cb mechanism in which deprotonation of one of the primary sulfamate protons precedes elimination of the phenol.[110, 111] Thus a protecting group was required for the synthesis of these primary sulfamate targets.



Scheme 3.1: *Reagents and conditions:* (i) NH_2SO_2Cl, DMA/toluene, 0 °C to RT, 24 h, 87%; (ii) $PhB(OH)_2$, 2 M aq. Na_2CO_3, $Pd(dppf)Cl_2$, DME, 80 °C, μW, 20 min, 22%.

Reported protecting groups for sulfamates include *N*-alkyloxycarbonyl (alkyl = *t*-butyl-[112], benzyl-[113] or methyl-[114]) and the *N*-*t*-butyl group.[115] However, these groups all retain one proton on the sulfamate nitrogen and the sulfamate is therefore still vulnerable to E1Cb degradation. A protecting group that masks both NH_2 protons would be expected to confer the sulfamate with improved base stability. Bis-benzyl protection of the NH_2 group of sulfonamides has been reported, but this protecting group can be difficult to remove.[116] Electron-releasing groups on the aryl ring of benzyl protecting groups allow the stability and deprotection conditions to be tuned.[117] Thus, bis-(benzyl) (reference standard), bis-(4-methoxybenzyl), bis-(2,4-dimethoxybenzyl) and bis-(3,4-dimethoxybenzyl) were selected for investigation as potential dual protecting groups for sulfamates. Bis-protection

of the sulfamate would be carried out early in the synthesis of the biphenyl inhibitors while the deprotection would be the final step (Figure 3.4).

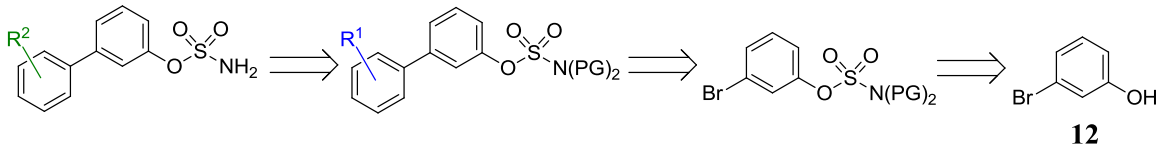
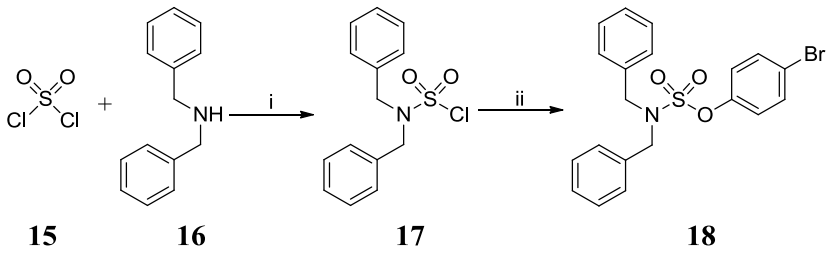


Figure 3.4: Second retrosynthetic analysis for the biphenyl sulfamate series (PG = protecting group)

3.2. Development of Novel Sulfamate Protecting Groups

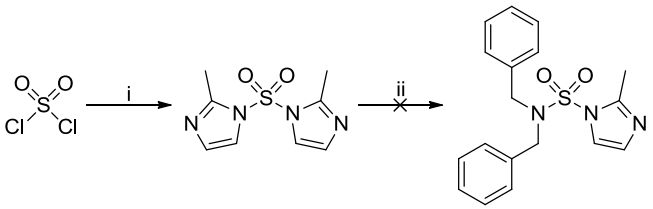
3.2.1. Identification of a Synthetic Route for the Incorporation of bis-Benzyl Sulfamates

Initially, the reaction of dibenzylamine (**16**) with sulfuryl chloride (**15**) in the presence of pyridine or triethylamine was investigated, but gave a complex mixture of products and afforded *N*,*N*-bis-benzylsulfamoyl chloride (**17**) in poor yield (Scheme 3.2). The subsequent reaction of **17** with 4-bromophenol also proceeded in disappointing yield**.**



Scheme 3.2: *Reagents and conditions:* (i) NEt_3 or pyridine, Et_2O, -78 °C to RT, 4 h, 10%; (ii) 4-bromophenol, Cs_2CO_3, THF, 67 °C, 40%.

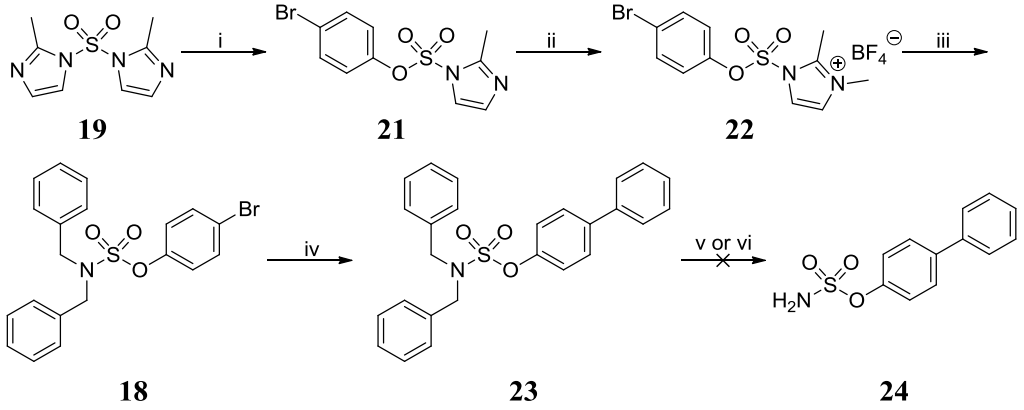
An alternative synthetic route utilising a sulfonyl-diimidazole derivative **19** was designed. Sulfonyl-diimidazoles have been used as sulfonyl transfer reagents for the preparation of sulfonates, sulfonamides and sterically congested unsymmetrical sulfonyl ureas.[118-120] Compound **19** has recently been identified as the optimal reagent of this class, and was selected for investigation.[119, 121] This compound was obtained by reacting an excess of 2-methylimidazole with sulfuryl chloride (**15**) (Scheme 3.3).[119] Reaction of **19** with dibenzylamine under a range of reaction conditions failed to displace the imidazole and attempts to activate sulfonyl-diimidazole **19** by methylation using Meerwein's salt (trimethyloxonium tetrafluoroborate) were unsuccessful.



15 **19** **20**

Scheme 3.3: *Reagents and conditions:* (i) 2-methylimidazole, DCM, 0 °C to RT, 24 h, 73%; (ii) Several conditions investigated – all failed.

The reported preparation of phenyl imidazolylsulfonates entailed the reaction of commercially available 1,1'-sulfonyldiimidazole with a phenoxide in THF at room temperature.[122, 123] As an alternative approach, this method was applied to the preparation of 4-bromophenyl 2-methyl-1*H*-imidazole-1-sulfonate (**21**), resulting in slow conversion, with heating being required to complete the reaction (67 °C, 24 h) (Scheme 3.4). This confirmed the hypothesis made by Shirbin *et al.* that this procedure had limited efficacy with electron deficient phenols.[123] To accelerate this reaction, a microwave assisted procedure was developed and afforded 4-bromophenyl 2-methyl-1*H*-imidazole-1-sulfonate (**21**) in 92% yield in 30 min.



19 **21** **22**

18 **23** **24**

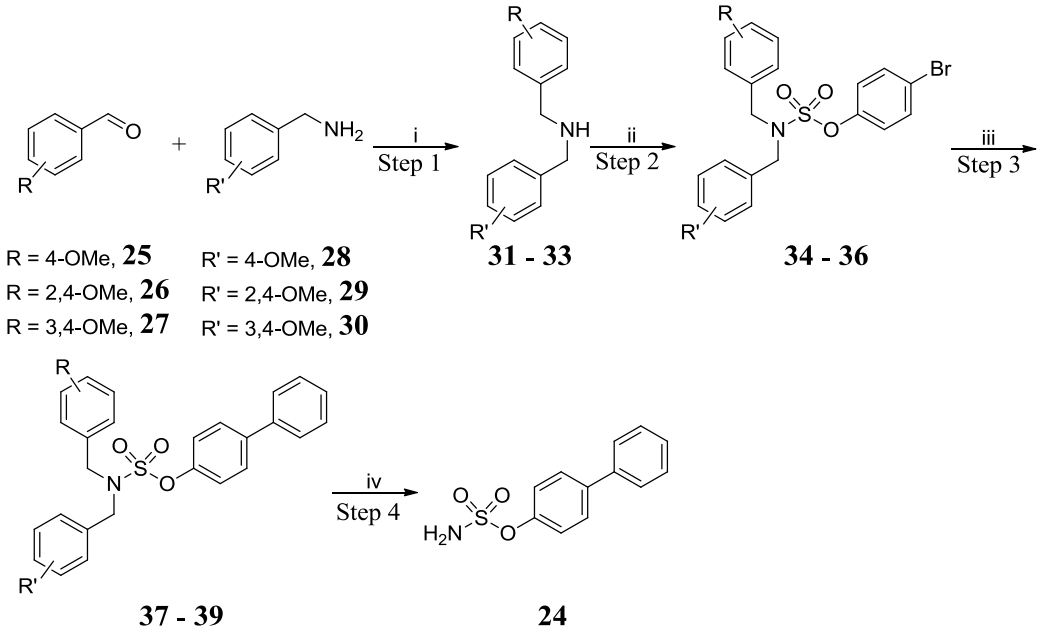
Scheme 3.4: *Reagents and conditions:* (i) 4-bromophenol, Cs_2CO_3, THF, 80 °C, μW, 30 min, 92%; (ii) $Me_3O{\cdot}BF_4$, DCM, 0 °C to RT, 8 h, 90%; (iii) Bn_2NH (**16**), MeCN, RT, 16 h, 77%; (iv) K_2CO_3, $PhB(OH)_2$, $Pd(PPh_3)_4$, MeCN, 120 °C, μW, 20 min, 72%; (v) conc. H_2SO_4, 200 °C, μW, 30 min; (vi) TFA, 100 °C, μW, 30 min.

Attempted reaction of imidazolylsulfonate **21** directly with dibenzylamine (**16**) under various conditions failed to displace the imidazole moiety. Activation of imidazole-sulfonates to nucleophilic attack by methylation with methyl triflate has been utilised for the synthesis of protected sulfates.[124-126] Owing to the extremely hazardous nature of methyl triflate, Meerwein's salt was used to effect the methylation of **21** in high yield to give tetrafluoroborate salt **22** (Scheme 3.4).

Reaction of **22** with dibenzylamine (**16**) at room temperature now proceeded in high yields to give fully protected sulfamate **18**. This compound was subjected to Suzuki cross-coupling conditions in the presence of potassium carbonate, to afford the desired biphenyl **23**, with no desulfamoylation being observed. Deprotection of bis-benzylsulfonamides is precedented under strongly acidic conditions.[127, 128] However, subjecting bis-benzylsulfamate **23** to concentrated sulfuric acid (200 °C, μW, 30 min) or neat trifluoroacetic acid (100 °C, μW, 30 min) resulted in exclusive recovery of starting material. Palladium-catalysed hydrogenation of the benzyl groups was also unsuccessful (Scheme 3.4).

The effect of electron-donating groups on the aryl ring of the benzyl moiety was then investigated. Methoxy-substituted dibenzylamines **31** - **33** were readily obtained by reductive amination (Table 3.1).[129] Substituted bis-benzylsulfamates **37** - **39** were prepared using a similar reaction sequence to that described for analogue **23** above.

Table 3.1: Summary of yields for the four step synthesis of **24**; *Reagents and conditions:* (i) a) EtOH, 78 °C, 4 h; b) $NaBH_4$, RT 16 h; (ii) **22**, MeCN, RT, 16 h; (iii) K_2CO_3, $PhB(OH)_2$, $Pd(PPh_3)_4$, MeCN, 120 °C, μW, 20 min; (iv) TFA, DCM, for ratio, time and temp. see Table 3.4.



R	R’	Step 1	Step 2	Step 3
4-OMe	4-OMe	**31**, 75%	**34**, 84%	**37**, 83%
2,4-OMe	2,4-OMe	**32**, 85%	**35**, 86%	**38**, 83%
3,4-OMe	3,4-OMe	**33**, 70%	**36**, 85%	**39**, 86%

As expected, incorporation of the methoxy functionality at the 4-, 2,4- and 3,4-positions of the benzyl groups facilitated deprotection to [1,1'-biphenyl]-4-yl sulfamate (**24**) (Tables 3.1 and 3.2), resulting in high yields of **24** under mild to moderate acidic conditions. As the conditions required for removing 3,4-dimethoxybenzyl were similar to those employed for 4-methoxybenzyl, but the reaction proceeded in poorer yield, 3,4-dimethoxybenzyl protection was not studied further.

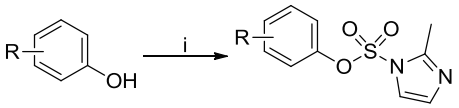
Table 3.2: Reaction conditions and yields for deprotection of *N*-protected [1,1'-biphenyl]-4-yl sulfamates **37**, **38** and **39**

Compound	TFA:DCM ratio	Temperature (°C)	Time (h)	Yield of 24
37	1:0	50	12	85%
37	1:1	42	24	90%
38	1:1	RT	0.2	95%
38	1:9	RT	2	95%
38	1:19	RT	7	90%
39	1:0	50	24	50%
39	4:1	42	30	63%

3.2.2. Scope and Limitations of the bis-(2,4-Dimethoxybenzyl) and bis-(4-Methoxybenzyl) Protecting Groups

To investigate the scope and limitations of this methodology, a range of phenols with diverse steric and electronic properties was progressed through the synthetic sequence. For the reaction of phenols with **19**, the time required for completion of the reaction for phenols with no *ortho*-substituent was found to be consistent with the pK_a value of the phenol, electron-poor phenols requiring extended reaction times (Table 3.3). Sterically hindered phenols such as 2,6-dimethylphenol also required prolonged reaction times. However, very electron poor (4-nitrophenol) and/or sterically hindered phenols (2,6-dichlorophenol), failed to yield any product (Table 3.3).

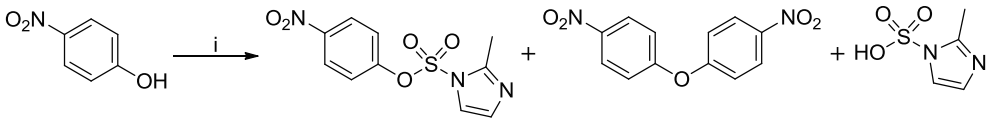
Table 3.3: Summary of reaction time for the preparation of substituted phenyl 2-methyl-1*H*-imidazole-1-sulfonate **21** and **48** - **54**; *Reagents and conditions:* (i) **19**, Cs_2CO_3, THF, 80 °C, μW.



40 - 47 **21**, **48 - 54**

Compound	R	Time for completion (min)	pK_a[130]
48	4-OMe	15	10.4
21	4-Br	30	9.7
49	4-Cl	50	9.5
50	3-Cl	65	9.3
51	2,6-Me	75	10.2
52	2-Cl	240	7.7
53	2,6-Cl	*No reaction*	7.1
54	4-NO_2	*No reaction*	6.8

To determine conditions of general applicability for diverse phenols, the two least reactive phenols, 4-nitrophenol and 2,6-dichlorophenol, were selected for further optimisation. Four parameters were investigated: time, temperature (microwave heating), solvent and the stoichiometry of **19**.



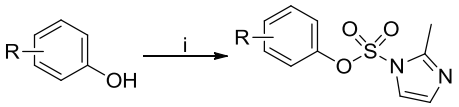
47 **54** **55** **56**

Scheme 3.5: *Reagents and conditions:* (i) **19** (1.05 mol equiv.), Cs_2CO_3, MeCN or DMF, 150 °C, μW, 10 min.

Employing THF as solvent and increasing the temperature of the reaction to 150 °C did not significantly improve conversion for these phenols. For 4-nitrophenol (**47**), the use of either DMF or acetonitrile in place of THF greatly enhanced the rate of the reaction, and after 10 min at 150 °C no starting material remained. However, a major by-product was 4,4'-oxybis(nitrobenzene) (**55**), presumably resulting from S_NAr attack of the unreacted phenol **47** on the desired product **54**, with subsequent elimination of 2-methyl-1*H*-imidazole-1-sulfonic acid (**56**) which may decompose to sulfur trioxide and 2-methylimidazole (Scheme 3.5). The conversion was also improved for 2,6-dichlorophenol (**46**) in these solvents, although unreacted 2,6-dichlorophenol was the

major component after heating for 10 min. Raising the reaction temperature to 180 °C did not improve conversion to the product. However, increasing the molar equivalents of **19** led to reduced formation of **55**, and gave excellent yields of the substituted phenyl 2-methyl-1*H*-imidazole-1-sulfonates **53** and **54** (Table 3.4).

Table 3.4: Effect of molar equivalent of **19** on the formation of **53** and **54**; *Reagents and conditions:* (i) **19**, Cs_2CO_3, MeCN, 180 °C, μW, 10 min.



R = 4-NO_2, **47**
R = 2,6-Cl, **46**

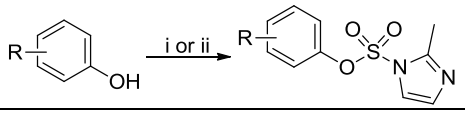
R = 4-NO_2, **54**
R = 2,6-Cl, **53**

Starting material	Molar equiv. of 19	% of product observed by LC-MS
47	1.05	22
47	5	35
47	10	75
46	1.05	20
46	5	59
46	10	80 *

* Reaction complete after 15 min

Additional optimisation studies were performed for phenols with pK_a > 7.1 and/or sterically demanding phenols. It was determined that high conversions could routinely be achieved under relatively mild conditions (15 min, microwave heating at 120 °C, 2 mol equiv. of **19**, MeCN) (Table 3.5). Thus, two methods have been identified, which allow reactive phenols (Method 1) and less reactive phenols (Method 2) to be utilised.

Table 3.5: Optimised conditions for microwave heating of substituted phenols with 1,1'-sulfonylbis(2-methyl-1*H*-imidazole) (**19**); *Reagents and conditions:* ***Method 1*** (i) **19** (2 mol equiv.), Cs_2CO_3, MeCN, 120 °C, μW, 15 min; ***Method 2*** (ii) **19** (10 mol equiv.), Cs_2CO_3, MeCN, 180 °C, μW, 15 min.

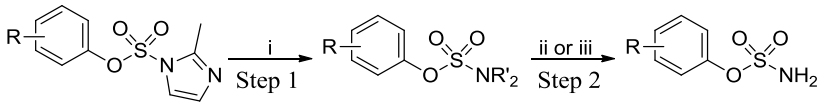


R	pK_a	Method 1 (isolated yield)	Method 2 (isolated yield)
4-OMe	10.4	**48**, 97%	*n.d.*
4-Br	9.7	**21**, 93%	*n.d.*
4-Cl	9.5	**49**, 93%	*n.d.*
3-Cl	9.3	**50**, 83%	*n.d.*
2-Cl	7.7	**52**, 90%	*n.d.*
2,6-Me	10.2	**51**, 92%	*n.d.*
2,6-Cl	7.1	**53**, 0%	**53**, 84%
4-NO_2	6.8	**54**, 0%	**54**, 82%
3-NO_2	9.3	**57**, 72%	*n.d.*
2-NO_2	6.9	**58**, 0%	**58**, 70%
4-CN	7.7	**59**, 59%	**59**, 80%
2-CN	7.0	**60**, 0%	**60**, 72%
4-CF_3	8.5	**61**, 80%	*n.d.*

n.d. = not determined

One-pot methylation of imidazolylsulfonates **21**, **48** - **54** and **57** - **61** followed by substitution with **32** to give the bis-(2,4-dimethoxybenzyl) sulfamates proceeded in similar yield for all phenols studied and deprotection with 10% TFA in DCM was also clean and high yielding (Table 3.6). The optimised conditions were applied to the protection of a set of phenol *O*-sulfamates, bis-*N*-protected by 4-methoxybenzyl. For these compounds, deprotection with 50% TFA in dichloromethane proceeded in high yield to the corresponding phenol *O*-sulfamate (Table 3.6). These results demonstrated that the sulfamate protection methodology was applicable to a range of phenols with diverse steric and electronic properties.

Table 3.6: Summary of yields for methylation/substitution with bis-(4-methoxybenzyl) amine (**31**) or bis-(2,4-dimethoxybenzyl)amine (**32**) of aryl 2-methyl-1*H*-imidazole-1-sulfamates followed by deprotection; *Reagents and conditions:* (i) a) $Me_3O{\cdot}BF_4$, DCM, 0 °C to RT, 8 h; b) **31** or **32**, MeCN, 42 °C, 24 h; (ii) 10% TFA/DCM, RT, 2 h (for R = dmb); (iii) 50% TFA/DCM, 42 °C, 24 h (for R = PMB).



48 - 54, **57 - 61** **62 - 78** **79 - 90**

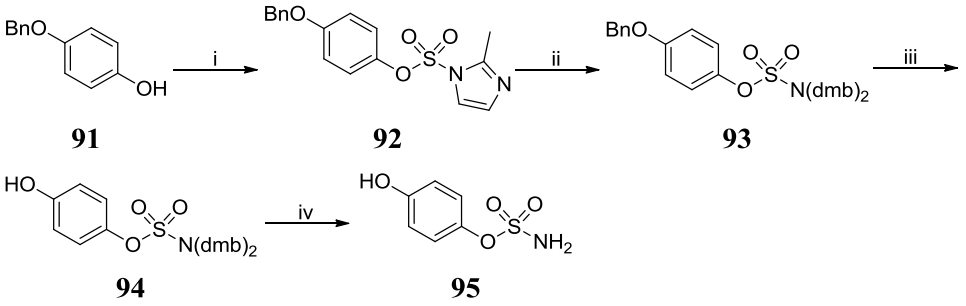
Step 1			Step 2	
R	**R'**	**Yield**	**R**	**Yield**
4-MeO	dmb	**62**, 65%	4-MeO	**79**, 90%
2,6-Me	dmb	**63**, 61%	2,6-Me	**80**, 90%
4-Cl	dmb	**64**, 63%	4-Cl	**81**, 84%
3-Cl	dmb	**65**, 61%	3-Cl	**82**, 90%
2-Cl	dmb	**66**, 68%	2-Cl	**83**, 81%
2,6-Cl	dmb	**67**, 63%	2,6-Cl	**84**, 89%
4-NO_2	dmb	**68**, 62%	4-NO_2	**85**, 80%
3-NO_2	dmb	**69**, 57%	3-NO_2	**86**, 87%
2-NO_2	dmb	**70**, 61%	2-NO_2	**87**, 40%
4-CN	dmb	**71**, 63%	4-CN	**88**, 92%
2-CN	dmb	**72**, 60%	2-CN	**89**, 86%
4-CF_3	dmb	**73**, 66%	4-CF_3	**90**, 90%
4-MeO	PMB	**74**, 80%	4-MeO	**79**, 93%
2,6-Me	PMB	**75**, 62%	2,6-Me	**80**, 92%
4-Cl	PMB	**76**, 81%	4-Cl	**81**, 90%
3-Cl	PMB	**77**, 72%	3-Cl	**82**, 86%
2-Cl	PMB	**78**, 78%	2-Cl	**83**, 92%

dmb = 2,4-dimethoxybenzyl; PMB = 4-methoxybenzyl

3.2.3. Chemical Stability of Sulfamates N-Protected with bis-(2,4-Dimethoxybenzyl)

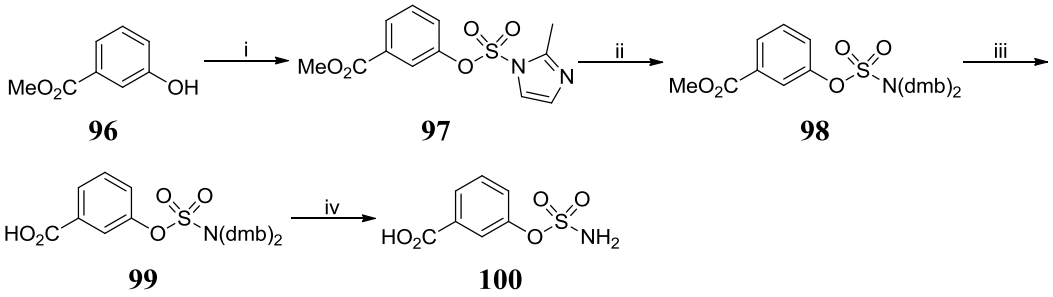
To assess the chemical stability of bis-(2,4-dimethoxybenzyl) protected sulfamates, a set of compounds was prepared to determine the robustness of this group to some common transformations. Compound **93**, synthesised following the reaction sequence optimised in section 3.2.2., was subjected to palladium-catalysed hydrogenation, resulting in cleavage

of the *O*-benzyl group while the *N*-2,4-dimethoxybenzyl groups were retained (Scheme 3.6). Deprotection of **94** with dilute trifluoroacetic acid provided **95** in 86% yield.



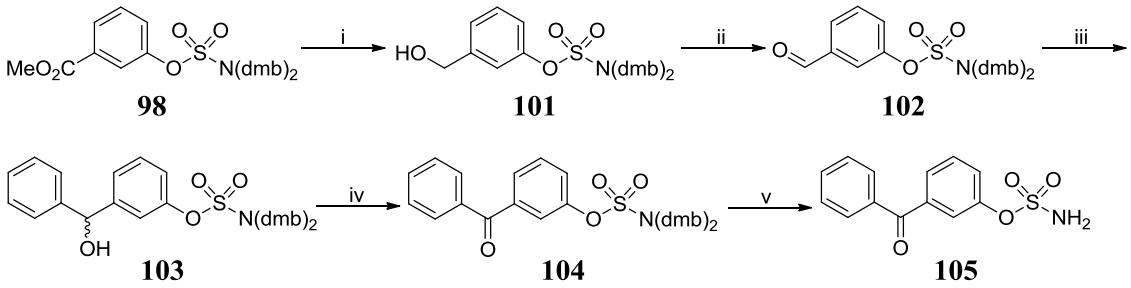
Scheme 3.6: *Reagents and conditions:* (i) **19**, Cs_2CO_3, MeCN, 120 °C, μW, 15 min, 96%; (ii) a) $Me_3O{\cdot}BF_4$, DCM, 0 °C to RT, 8 h; b) **32**, MeCN, 42 °C, 24 h, 61%; (iii) H_2, 10% Pd/C, MeOH, 50 °C, 24 h, 85%; (iv) 10% TFA/DCM, RT, 2 h, 86%.

Analogous reactions to those described above were utilised for the preparation of compound **98** (Scheme 3.7). Basic hydrolysis of methyl ester **98** was achieved in high yield without affecting the bis-*N*-protected sulfamate. Mild acidic cleavage of the 2,4-dimethoxybenzyl groups afforded **100** in 89% yield.



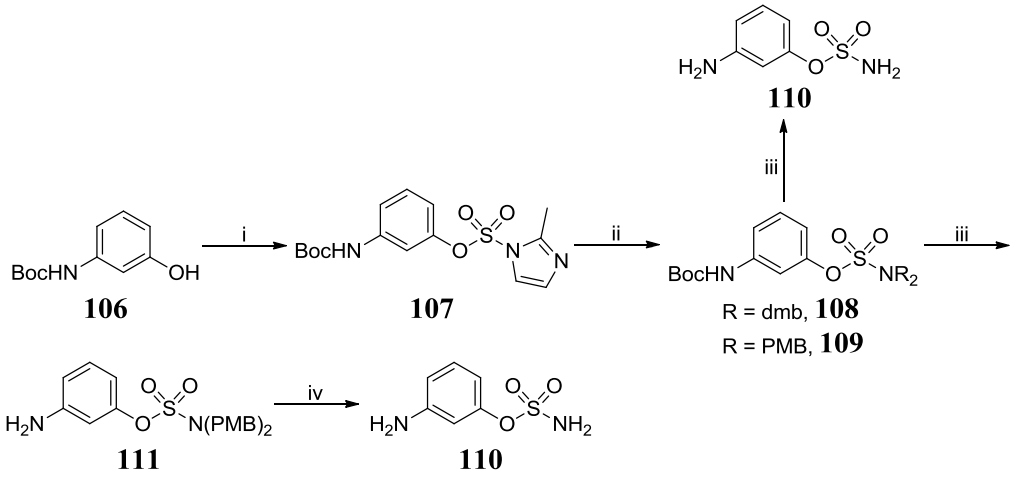
Scheme 3.7: *Reagents and conditions:* (i) **19**, Cs_2CO_3, MeCN, 120 °C, μW, 15 min, 92%; (ii) a) $Me_3O{\cdot}BF_4$, DCM, 0 °C to RT, 8 h; b) **32**, MeCN, 42 °C, 24 h, 64%; (iii) LiOH, H_2O/THF, 60 °C, 24 h, 85%; (iv) 10% TFA/DCM, RT, 2 h, 89%.

Template **98** was further elaborated to investigate stability to reduction, oxidation and anionic nucleophilic conditions. Lithium aluminium hydride reduction of methyl ester **98** gave benzyl alcohol **101**, which was oxidised with manganese dioxide (Scheme 3.8). Nucleophilic attack of phenylmagnesium bromide on the carbonyl group of **102** led to isolation of **103** in 88% yield. A second manganese dioxide oxidation followed by TFA deprotection of the sulfamate functionality of **104** were employed to access **105**.



Scheme 3.8: *Reagents and conditions:* (i) $LiAlH_4$ (2 M in THF), THF, 0 °C, 2 h , 84%; (ii) MnO_2, DCM, RT, 16 h, 89%; (iii) PhMgBr (1 M in THF), THF, 0 °C to RT, 2 h , 88%; (iv) MnO_2, DCM, RT, 16 h, 84%; (v) 10% TFA/DCM, RT, 2 h, 87%.

To investigate orthogonality with the Boc protecting group, intermediates **108** and **109** were prepared according to a similar reaction sequence to that descripted in section 3.2.2. (Scheme 3.9). Deprotection of the *N*-*t*-butyloxycarbonyl (Boc)-aniline **108** occurred with simultaneous removal of bis-*N*-2,4-dimethoxybenzyl from the sulfamate group to afford 3-aminophenyl sulfamate **110**. However, when 4-methoxybenzyl was used to protect the sulfamate moiety in **109**, the Boc group could be removed without affecting the sulfamate protecting group and afforded **111** (Scheme 3.9).

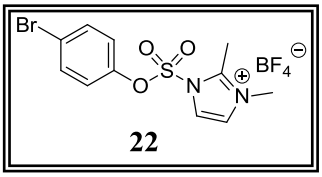


Scheme 3.9: *Reagents and conditions:* (i) **19**, Cs_2CO_3, MeCN, 120 °C, μW, 15 min, 84%; (ii) a) $Me_3O{\cdot}BF_4$, DCM, 0 °C to RT, 8 h; b) **32**, MeCN, 42 °C, 24 h (R = dmb, 57%; R = PMB, 70%); (iii) 10% TFA/DCM, RT, 2 h, (**110** from **108**, 70%; **111** from **109**, 94%); (iv) 50% TFA/DCM, 42 °C, 24 h, 88%.

In summary, it has been demonstrated that sulfamates bis-*N*-protected with 2,4-dimethoxybenzyl were stable to hydrogen/palladium catalyst, aqueous lithium hydroxide, lithium aluminium hydride, manganese dioxide and phenylmagnesium bromide. The bis-(4-methoxybenzyl) protection also enabled selective deprotection of a Boc group over the sulfamate.

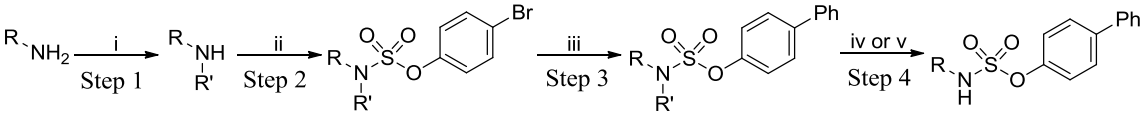
3.2.4. Extension to the Protection of Secondary O-Aryl Sulfamates

The methodology was extended to the protection of secondary aryl sulfamates. Secondary benzyl amines **115** - **118** were obtained *via* reductive amination in moderate to good yields (Table 3.7). Nucleophilic displacement of the imidazolium of **22** proceeded in high yields and was followed by Suzuki-Miyaura cross-coupling with phenylboronic acid to afford fully protected biphenyl secondary sulfamates **123** - **126**. Deprotection of secondary sulfamates occurred under similar conditions to those employed for the deprotection of primary sulfamates (Table 3.7).



22

Table 3.7: Summary of yields for the four step synthesis of secondary sulfamates; *Reagents and conditions:* (i) a) EtOH, 78 °C, 4 h; b) $NaBH_4$, RT 16 h; (ii) **22**, MeCN, RT, 16 h; (iii) K_2CO_3, $PhB(OH)_2$, $Pd(PPh_3)_4$, MeCN, 120 °C, μW, 20 min; (iv) 10% TFA/DCM, RT, 2 h; (v) 50% TFA/DCM, 42 °C, 24 h.



R = Me, **112** **115 - 118** **119 - 122** **123 - 126** **127 - 129**
R = ^{i}Bu, **113**
R = Bn, **114**

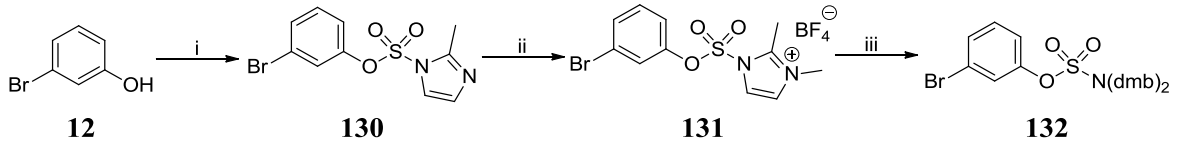
R	R'	Step 1	Step 2	Step 3	Step 4
Me	dmb	**115**, 25%	**119**, 95%	**123**, 90%	**127**, 95%
	PMB	**116**, 24%	**120**, 96%	**124**, 87%	**127**, 96%
^{i}Bu	dmb	**117**, 69%	**121**, 85%	**125**, 85%	**128**, 93%
Bn	dmb	**118**, 67%	**122**, 89%	**126**, 87%	**129**, 96%

3.2.5. Summary

Two new protecting groups for primary and secondary sulfamates have been developed and shown to be stable to a wide range of conditions used in standard functional group interconversions. These protecting groups are easily removed under mild acidic conditions.

3.3. The Biphenyl Sulfamate Series

The protecting group methodology was applied to the synthesis of a library of 13 biphenyl sulfamates. In order to explore the substitution of the B-ring efficiently, a synthetic route based on the retrosynthetic analysis presented in section 3.1.2. was established (Scheme 3.10). Key intermediate **132** was prepared on a large scale following the reaction sequence previously described.

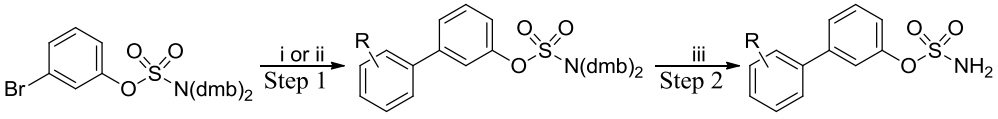


12 **130** **131** **132**

Scheme 3.10: *Reagents and conditions:* (i) **19**, Cs_2CO_3, MeCN, 120 °C, μW, 15 min, 76%; (ii) $Me_3O{\cdot}BF_4$, DCM, 0 °C to RT, 8 h, 85%; (iii) **32**, MeCN, RT, 16 h, 71%.

Microwave-assisted Suzuki-Miyaura cross-coupling of **132** in presence of potassium carbonate and $Pd(PPh_3)_4$ afforded **133** in 75% yield (Table 3.8). These conditions were unsuccessful for the preparation of **134** and **135**, but alternative Suzuki conditions, which had previously been used successfully on other substrates in the Sulf-2 project, provided these compounds in good yields. The same conditions were utilised for the synthesis of aniline derivatives **136** - **138**. All deprotections proceeded at room temperature in dilute TFA, resulting in high yields of the desired primary sulfamates **139** - **144**.

Table 3.8: Summary of yields for the two step synthesis of biphenyl sulfamate derivatives; *Reagents and conditions:* (i) K_2CO_3, R-PhB$(OH)_2$, $Pd(PPh_3)_4$, MeCN, 120 °C, μW, 20 min; (ii) R-PhB(pin), 2 M aq. Na_2CO_3, $Pd(dppf)Cl_2$, dioxane, 80 °C, μW, 20 min; (iii) 10% TFA/DCM, RT, 2 h.

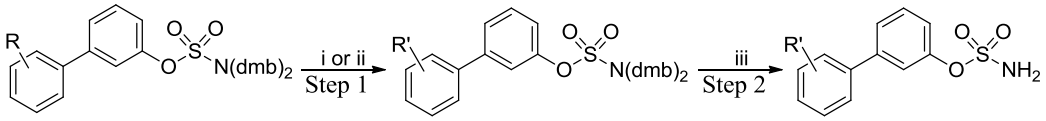


132 **133 - 138** **139 - 144**

R	Step 1		Step 2
	Method	**Yield**	**Yield**
2'-CO_2Me	i	**133**, 75%	**139**, 88%
3'-CO_2H	ii	**134**, 79%	**140**, 82%
4'-CO_2H	ii	**135**, 77%	**141**, 90%
2'-NH_2	ii	**136**, 82%	**142**, 83%
3'-NH_2	ii	**137**, 77%	**143**, 82%
4'-NH_2	ii	**138**, 72%	**144**, 82%

Methyl ester **133** was hydrolysed under basic conditions and the resulting carboxylic acid **145** was deprotected to give **149** (Table 3.9). Acetylation of aniline derivatives **136 - 138** with acetic anhydride in presence of triethylamine afforded acetamidobiphenyls **146 - 148**. Acid-mediated cleavage of 2-4-dimethoxybenzyl groups resulted in isolation of **150 - 152** in high yields.

Table 3.9: Summary of yields for the two step functionalisation/deprotection of protected biphenyl sulfamates; *Reagents and conditions:* (i) LiOH, H_2O/THF, 60 °C, 24 h, 80%; (ii) Ac_2O, NEt_3, DCM, RT, 24 h; (iii) 10% TFA/DCM, RT, 2 h.



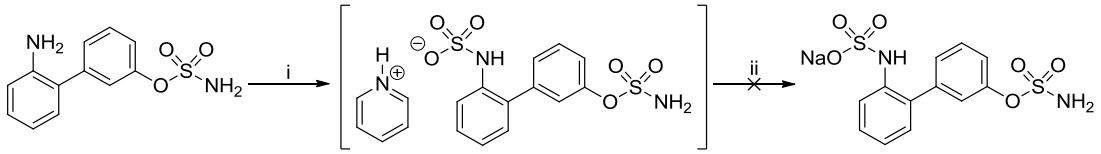
R = 2'-CO_2Me, **133**
R = 2'-NH_2, **136**
R = 3'-NH_2, **137**
R = 4'-NH_2, **138**

145 - 148

149 - 152

R'	Step 1		Step 2
	Method	**Yield**	**Yield**
2'-CO_2H	i	**145**, 80%	**149**, 89%
2'-NHAc	ii	**146**, 87%	**150**, 86%
3'-NHAc	ii	**147**, 89%	**151**, 91%
4'-NHAc	ii	**148**, 88%	**152**, 84%

Preparation of amino-sulfate derivative **154** by reaction of aniline **152** with sulfur trioxide pyridine complex was unsuccessful (Scheme 3.11). This methodology is a two-step process, whereby the initial pyridinium salt **153** is converted into a stable sodium derivative **154** under basic conditions. A range of mild bases were explored but were either incompatible with the sulfamate moiety or ineffective at displacing the pyridinium ion. Ion exchange chromatography was also attempted but resulted in exclusive recovery of **142**.



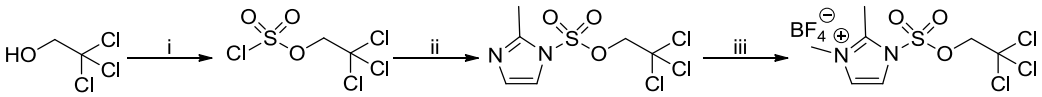
142 **153** **154**

Scheme 3.11: *Reagents and conditions:* (i) Sulfur trioxide pyridine complex, pyridine, DMF, RT, 3 h; (ii) 1 M aq. NaOH, RT, 1 h.

In 2004, Taylor *et al.* reported the 2,2,2-trichloroethyl (TCE) group as an effective protection of arylsulfate esters.[131] The protecting group is introduced by reacting a phenol

with 2,2,2-trichloroethyl chlorosulfate (**156**) in the presence of triethylamine and DMAP, and is cleaved under mild conditions using zinc or palladium.[131] Although ammonium formate was originally reported as an important component for the deprotection, recent reports have indicated that it could be replaced by alternative reagents, such as a phosphate buffer at pH = 7.4.[131-134] These neutral conditions were of interest, since they would allow deprotection of the sulfate after deprotection of the sulfamate. The imidazolium salt derivative of **156** was reported in a subsequent paper and found to be a superior reagent for the synthesis of TCE-protected sulfate esters.[126] This reagent has since been used for the sulfation of a variety of phenols and carbohydrates, but also been successfully utilised for the synthesis of aliphatic protected amino-sulfates.[121, 124, 125, 135] For these reasons, imidazolium salt **158** was selected for investigation.

TCE chlorosulfate (**156**) was obtained by reacting one equivalent of 2,2,2-trichloroethanol (**155**) with sulfuryl chloride (Scheme 3.12). Displacement of the chloride of **156** with 2-methylimidazole gave alkyl imidazole-1-sulfonate **157**, which was methylated with Meerwein's salt to give **158** in excellent yields.



155 **156** **157** **158**

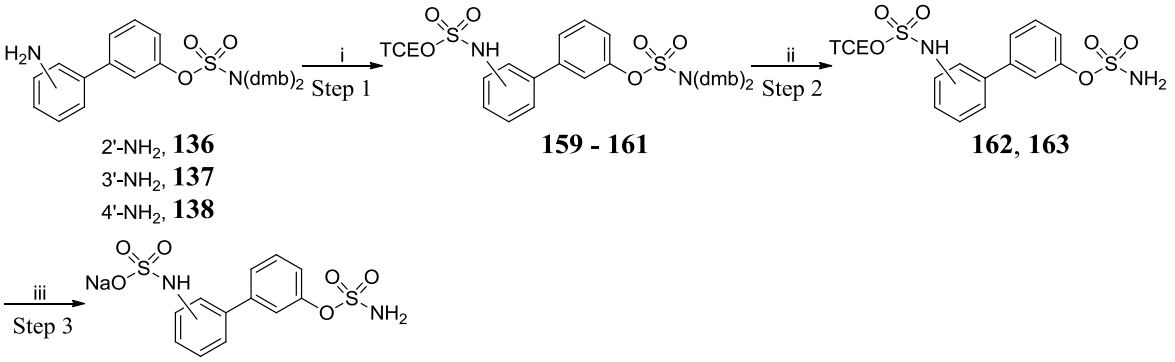
Scheme 3.12: *Reagents and conditions:* (i) SO_2Cl_2, pyridine, Et_2O, -78 °C, 4 h, 83%; (ii) 2-methylimidazole, THF, 0 °C to RT, 16 h, 95 %; (iii) $Me_3O{\cdot}BF_4$, DCM, 0 °C to RT, 20 h, 86%.

As there was no literature precedent for reaction of imidazolium salt **158** with anilines, a model system was used for the optimisation of their reaction. It was found that high conversion could be achieved using 3 molar equivalents of **158** at reflux in THF over 30 h. In an attempt to shorten the reaction time, it was determined that microwave irradiation in acetonitrile at 120 °C for 20 min provided similar results. Interestingly, the use of a base was detrimental to the sulfation and led to the formation of several by-products.

These conditions were successfully applied to the synthesis of *para*- and *meta*-derivatives **160** and **161**, but no conversion was observed for *ortho*-aniline **136**, suggesting that steric hindrance might limit the applicability of the reaction (Table 3.10). The trichloroethyl group was stable under the acidic conditions used for sulfamate deprotection. Cleavage of the trichloroethyl group was achieved using zinc in a mixture of methanol and acetate buffer (pH = 4.65) with no desulfamoylation. The resulting sulfamic acids were converted

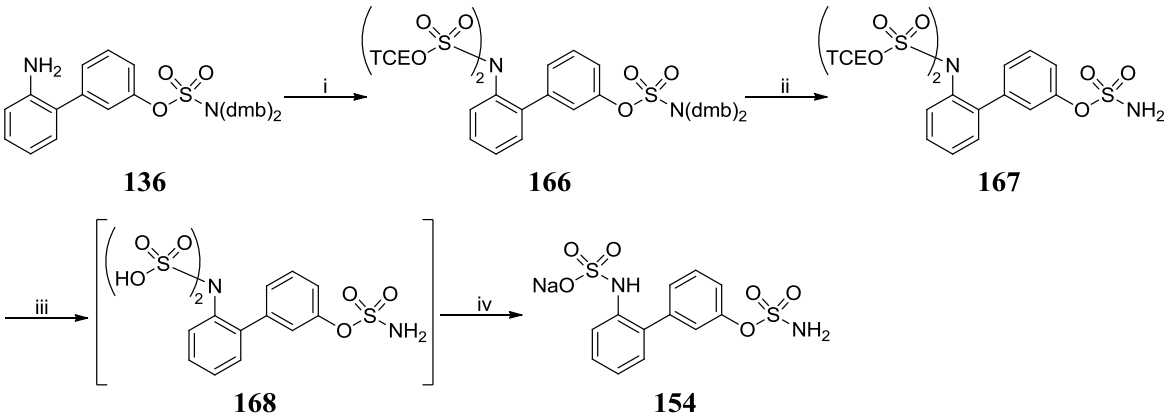
to sodium salts using ion exchange chromatography, affording targets **164** and **165** in high yields.

Table 3.10: Summary of yields for the three step synthesis of amino-sulfate derivatives; *Reagents and conditions:* (i) **158**, THF, 67 °C, 30 h; (ii) 10% TFA/DCM, RT, 2 h; (iii) a) Zn powder, MeOH, acetate buffer pH = 4.65, 60 °C, 2 h; b) Dowex 50W8X2 Na^+ form, H_2O.



Position	Step 1	Step 2	Step 3
2'-	**159**, 0%	-	-
3'-	**160**, 75%	**162**, 86%	**164**, 84%
4'-	**161**, 82%	**163**, 91%	**165**, 80%

Protection of 2-aminobiphenyl **136** with TCE chlorosulfate (**156**) was not found to be affected by steric hindrance but produced bis-*N*,*N*-sulfated aminobiphenyl **166** (Scheme 3.13). In an attempt to prevent double addition of the TCE chlorosulfate group, a variety of conditions was explored in which the base component was varied. The best results were obtained with 2,6-lutidine, but despite extensive optimisation efforts, the major product was always bis-*N*-sulfated aminobiphenyl **166**. As a result, **166** was taken forward in the synthesis. Acidic deprotection of the sulfamate protecting group afforded **167** in 90% yield. Deprotection of the sulfate groups of **167** following the procedure used for the synthesis of **164** and **165** afforded bis-*N*,*N*-sulfamic acid **168**. Interestingly, under mild acidic conditions one of the two sulfate groups could be hydrolysed leading to isolation of **154**. Using a model system for the optimisation of this reaction sequence, it was found that a one-pot deprotection/mono-sulfate hydrolysis could be achieved by addition of acetic acid to the reaction mixture. Applying these conditions to the synthesis of **154** led to isolation of the desired target in moderate yield (Scheme 3.13).



Scheme 3.13: *Reagents and conditions:* (i) **156**, NEt_3, DMAP, THF, 0 °C to RT, 24 h, 70%; (ii) 10% TFA/DCM, RT, 2 h, 90%; (iii) Zn powder, MeOH, acetate buffer pH = 4.65, AcOH, RT, 24 h; (iv) Dowex 50W8X2 Na^+ form, H_2O, 50%.

3.4. The Biphenyl Ether Sulfamate Series

Retrosynthetic analysis for the biphenyl ether series indicated that the use of the bis-(2,4-dimethoxylbenzyl) protecting group would again be beneficial (Figure 3.5). Protected sulfamate **B** would be a key intermediate in the synthesis and could be engaged in S_NAr reactions with a variety of activated fluorobenzenes. This would afford biphenyl ether scaffold **C**, which could then be further modified (R^1 to R^2), before deprotection of the sulfamate moiety at the last step to give the desired biphenyl targets **D**.

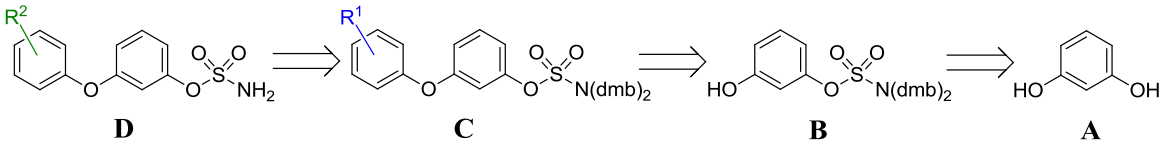
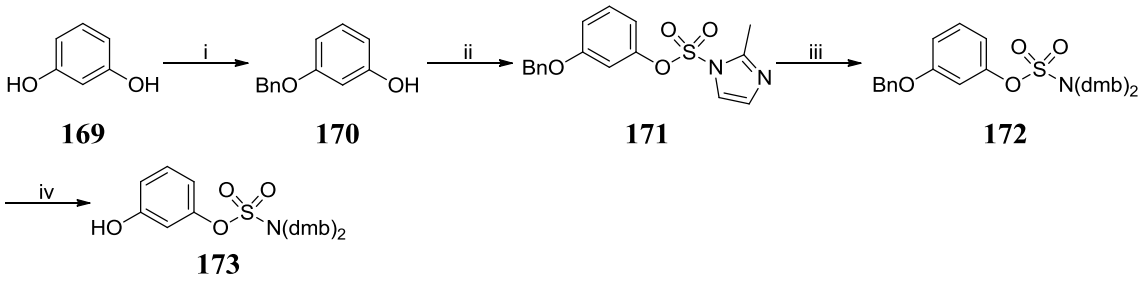


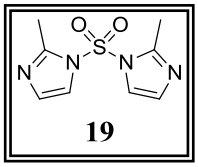
Figure 3.5: Retrosynthetic analysis for the biphenyl ether series

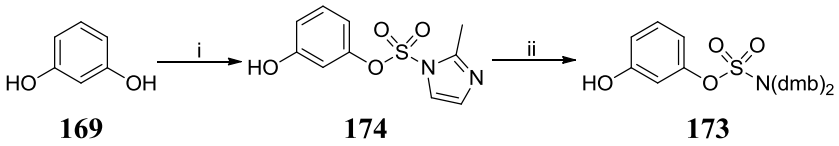
Key intermediate **173** was initially prepared following a four step synthesis starting with mono-benzylation of resorcinol (**169**) (Scheme 3.14).[136] Compound **170** was converted into bis-protected sulfamate **172** by applying the reaction sequence developed in section 3.2.2. The final step involved palladium-catalysed hydrogenation of the *O*-benzyl protecting group. All the reactions proceeded in good yield and **173** was isolated in 27% overall yield.



Scheme 3.14: *Reagents and conditions:* (i) BnBr, K_2CO_3, MeCN, 80 °C , 24 h, 72%; (ii) **19**, Cs_2CO_3, MeCN, 120 °C, μW, 15 min, 95%; (iii) a) $Me_3O{\cdot}BF_4$, DCM, 0 °C to RT, 8 h; b) **32**, MeCN, 42 °C, 24 h, 55%; (iv) H_2, 10% Pd/C, MeOH:THF (4:1), 50 °C, 24 h, 75%.

Concurrently, a shorter reaction sequence to access **173** was developed and optimised (Scheme 3.15). The use of an excess of resorcinol (**169**) and an equimolar ratio of caesium carbonate and sulfonyl-diimidazole **19** allowed isolation of **174** in 80% yield. Excess resorcinol was removed by repeated aqueous washes. The use of low temperature and a dilute reaction mixture (0.08 M) prevented side-reactions during the methylation/imidazolium displacement step. This shorter synthetic scheme provided key intermediate **173** in 48% overall yield.

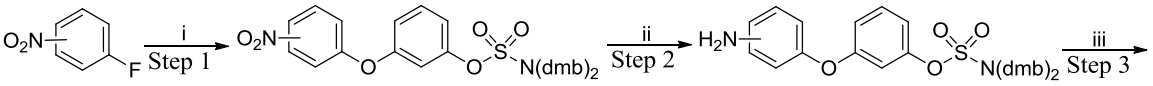




Scheme 3.15: *Reagents and conditions:* (i) **19**, Cs_2CO_3, MeCN, 120 °C, μW, 15 min, 80%; (ii) a) $Me_3O{\cdot}BF_4$, DCM:THF (8:1), 0 °C to RT, 9 h; b) **32**, MeCN, 42 °C, 24 h, 60%.

S_NAr reaction of fluoronitrobenzenes **175** - **177** with **173** in the presence of potassium carbonate gave biphenyl ether intermediates **178** - **180**, which were cleanly reduced *via* palladium-catalysed flow hydrogenation (Table 3.11). Deprotection of **181** - **183** was achieved in a 10% TFA solution in DCM, resulting in high yields of the desired primary sulfamates **184** - **186**.

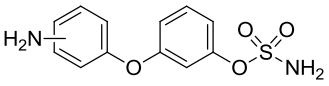
Table 3.11: Summary of yields for the three step synthesis of aminobiphenyl ether derivatives; *Reagents and conditions:* (i) **173**, K_2CO_3, DMF, 150 °C, μW, 20 min; (ii) H_2, 10% Pd/C, MeOH:THF (3:1), RT, 24 h; (iii) 10% TFA/DCM, RT, 2 h.



2-NO_2, **175**
3-NO_2, **176**
4-NO_2, **177**

178 - 180

181 - 183

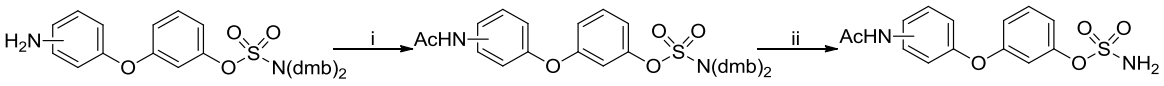


184 - 186

Position	Step 1	Step 2	Step 3
2'-	**178**, 80%	**181**, 85%	**184**, 90%
3'-	**179**, 75%	**182**, 87%	**185**, 82%
4'-	**180**, 85%	**183**, 86%	**186**, 65%

The acetamido-targets **190** - **192** were prepared in an analogous manner to the biphenyl derivatives discussed in the previous section (Table 3.12).

Table 3.12: Summary of yields for the two step synthesis of acetamidobiphenyl ether derivatives; *Reagents and conditions:* (i) Ac_2O, NEt_3, DCM, RT, 24 h; (ii) 10% TFA/DCM, RT, 2 h.



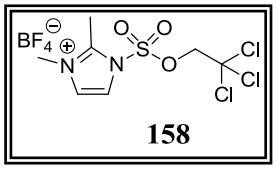
2'-NH_2, **181**
3'-NH_2, **182**
4'-NH_2, **183**

187 - 189

190 - 192

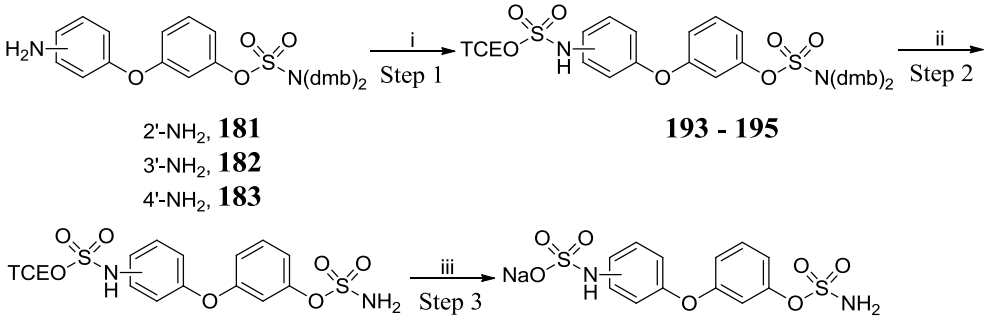
Position	Step 1	Step 2
2'-	**187**, 87%	**190**, 85%
3'-	**188**, 88%	**191**, 94%
4'-	**189**, 86%	**192**, 92%

Sulfation of aniline intermediates **181** - **183** with imidazolium salt **158** proceeded in high yields for *para*- and *meta*-derivatives **194** and **195**, but *ortho*-substitution resulted in a disappointing 15% yield of **193** (Table 3.13). Deprotection of the sulfamate and sulfate groups was achieved following the procedure previously described in section 3.3.



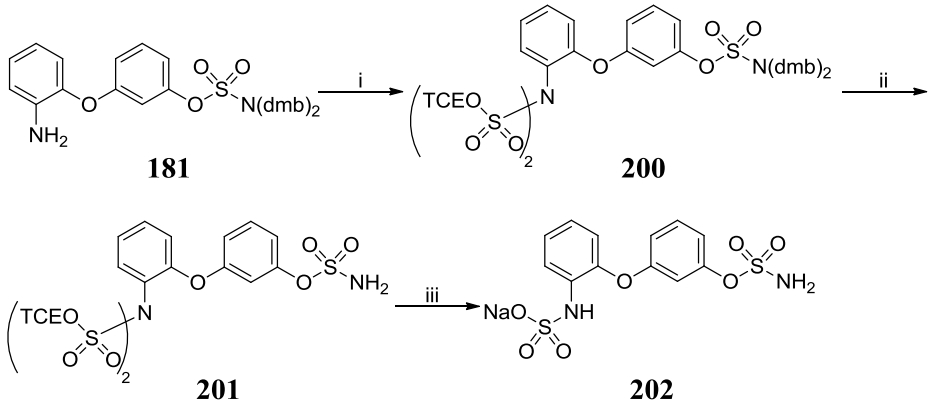
158

Table 3.13: Summary of yields for the three step synthesis of amino-sulfate derivatives; *Reagents and conditions:* (i) **158**, THF, 67 °C, 30 h; (ii) 10% TFA/DCM, RT, 2 h; (iii) a) Zn powder, MeOH, acetate buffer pH = 4.65, 60 °C, 2 h; b) Dowex 50W8X2 Na^+ form, H_2O.



Position	Step 1	Step 2	Step 3
2'-	**193**, 15%	-	-
3'-	**194**, 78%	**196**, 86%	**198**, 75%
4'-	**195**, 90%	**197**, 89%	**199**, 70%

Ortho-aminosulfate target **202** was therefore synthesised using analogous synthetic transformations to those employed for the preparation of **154** (Scheme 3.16). Noticeably, the sulfation and deprotection steps proceeded in lower yield with the biphenyl ether scaffold.

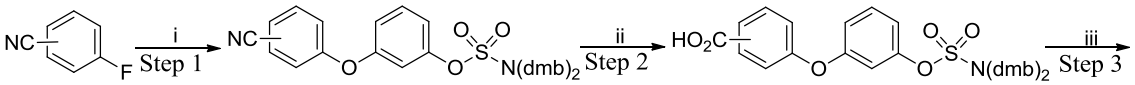


Scheme 3.16: *Reagents and conditions:* (i) **156**, NEt_3, DMAP, THF, 0 °C to RT, 24 h, 55%; (ii) 10% TFA/DCM, RT, 2 h, 86%; (iii) a) Zn powder, MeOH, acetate buffer pH = 4.65, AcOH, RT, 24 h; b) Dowex 50W8X2 Na^+ form, H_2O 33%.

S_NAr reactions of **173** with 2-fluorobenzoic acid or methyl 2-fluorobenzoate, under a variety of conditions, resulted in exclusive recovery of starting material. Due to this lack of success, the S_NAr reaction was conducted on fluorobenzonitriles **203** - **205** (Table 3.14). The resulting cyanobiphenyl ethers **206** - **208** were hydrolysed to the corresponding

benzoic acids **209 - 211** under basic conditions with prolonged microwave heating. Acidic deprotection of the sulfamate moiety afforded targets **212 - 214** in excellent yields.

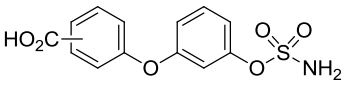
Table 3.14: Summary of yields for the three step synthesis of benzoic acid derivatives; *Reagents and conditions:* (i) **173**, K_2CO_3, DMF, 150 °C, μW, 20 min; (ii) 2 M aq. NaOH, dioxane, 130 °C, μW, 2 h; (iii) 10% TFA/DCM, RT, 2 h.



2-CN, **203**
3-CN, **204**
4-CN, **205**

206 - 208

209 - 211



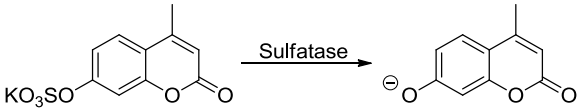
212 - 214

Position	Step 1	Step 2	Step 3
2'-	**206**, 81%	**209**, 45%	**212**, 90%
3'-	**207**, 61%	**210**, 80%	**213**, 94%
4'-	**208**, 72%	**211**, 65%	**214**, 92%

Thus, a set of 13 substituted biphenyl and 12 biphenyl ether sulfamates were prepared.

3.5. Biological Evaluation of the Biphenyl and Biphenyl Ether Sulfamate Series

In parallel with the synthesis of potential Sulf-2 inhibitors, Dr Gary Beale and Dr Sari Alhasan worked on the development of a Sulf-2 primary pharmacology assay. Isolation of active Sulf-2 enzyme was challenging and preliminary sulfatase inhibitory activity data have only recently been generated for these compounds. To determine the selectivity of the compounds, aryl sulfatases A (ARSA) and B (ARSB) inhibition was also assessed. Compounds were assayed for their ability to inhibit the desulfation of 4-methylumbelliferyl sulfate (4-MUS) (Figure 3.6) to the fluorescent phenol, 4-methylumbelliferone (MU), at a single concentration of 1 mM.



4-MUS **4-MU**

Figure 3.6: The action of sulfatases in converting 4-MUS to 4-MU

In this assay format, the reported Sulf-1/Sulf-2 inhibitors **5** and **8** exhibited no inhibition of Sulf-2, ARSA or ARSB. The measured Sulf-2 inhibition of **5** was considerably different to the reported literature value (IC_{50} = 130 μM).[102] This can be rationalised by a significant difference with the reported assay protocol, where Sulf-2 was incubated with the inhibitors at concentrations ranging from 3.75 mM to 1 mM for 10 min and then diluted into assay buffer. Hence, it would be expected that the IC_{50} values of **5** and **8** would be greater than the reported ones (i.e. compound **5** IC_{50} = 128-140 μM; compound **8** IC_{50} = 214-258 μM).

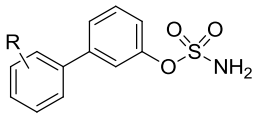
The Sulf-2 inhibitory activity of a set of simple monocyclic phenol-derived primary sulfamates, prepared by a colleague, was determined (data not included in this thesis). Although, these compounds did not inhibit Sulf-2, introduction of a phenyl ring at the 3-position started to show some inhibition. This was encouraging since this template had been selected for further elaboration.

The Sulf-2 inhibitory activity data for biphenyl inhibitors are presented in Table 3.15 and should be compared to compound **13**, which showed moderate Sulf-2 inhibition at 1 mM and was not selective over ARSB. Carboxylic acid **140**, **141**, **149** and methyl ester **139** derivatives retained Sulf-2 inhibition. The amino and aminosulfate functionalities were tolerated at the *ortho* and *meta* positions (**142**, **143**, **154**, **164**) but not at the *para* position (**144**, **165**). These polar groups appear to be tolerated in certain positions of the B-ring but do not appear to be making significant interactions to improve potency. Alternatively, it can be hypothesised that any advantages that are gained, are offset by other factors, such as desolvation penalty.

Introduction of the aminoacetate group (**150** - **152**) induced a reduction in Sulf-2 inhibitory activity. Trichloroethyl protected sulfates derivatives **162** and **163** were also assayed and showed a significant improvement in potency against Sulf-2, with more than 90% inhibition at 1 mM. Unfortunately these compounds were also potent inhibitors of ARSA and ARSB. The increased inhibitory activity of derivatives **162** and **163**, which have the highest clogP in this series, might suggest the presence of a lipophilic pocket in the enzyme active site.

With the exception of three compounds (**142**, **143**, **164**), the biphenyl sulfamate inhibitors had superior or similar potency against ARSA than Sulf-2. Interestingly, these three compounds were also selective over ARSB. Unlike biphenyl sulfamate **13**, the majority of substituted biphenyl sulfamates did not inhibit ARSB at 1 mM.

Table 3.14: Preliminary sulfatase inhibition data for the biphenyl sulfamates inhibitors. The % inhibition are the mean of two independent determinations.



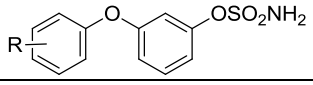
Compound	R	Sulf-2 % inhibition @ 1 mM	ARSA % inhibition @ 1 mM	ARSB % inhibition @ 1 mM
13	H	38	14	65
139	2'-CO_2Me	20	86	0
149	2'-CO_2H	31	98	0
140	3'-CO_2H	12	59	0
141	4'-CO_2H	22	85	0
142	2'-NH_2	21	0	0
143	3'-NH_2	20	0	0
144	4'-NH_2	6	61	0
150	2'-NHAc	4	33	0
151	3'-NHAc	8	52	33
152	4'-NHAc	3	0	0
154	2'-$NHSO_3Na$	37	26	0
164	3'-$NHSO_3Na$	31	0	0
165	4'-$NHSO_3Na$	4	0	0
167	2'-$N(SO_3CH_2CCl_3)_2$	10	63	0
162	3'-$NHSO_3CH_2CCl_3$	98	87	59
163	4'-$NHSO_3CH_2CCl_3$	92	100	71

The Sulf-2 inhibitory activity data for biphenyl ether inhibitors are presented in Table 3.15. Compound **215** is the reference compound, with no substituent on the B-ring, which similarly to biphenyl sulfamate **13** showed moderate Sulf-2 inhibition at 1 mM. Interestingly, the Sulf-2 SAR of the biphenyl ether series was very similar to the SAR of the biphenyl series (Table 3.14) i.e. the carboxylate, the *ortho*- and *meta*-amino and aminosulfate functionalities are tolerated, whereas the aminoacetate, the *para*-amino and aminosulfate groups induced a reduction in potency. The trichoethyl protected sulfate derivatives **196** and **197** were again the most potent derivatives of the series. These two molecules were also potent inhibitors of ARSA and ARSB.

All the biphenyl ether derivatives were moderate to good inhibitors of ARSA. Introduction of amino and substituted amino groups at the *ortho* position of the B-ring increased

inhibition of ARSB. This trend was not observed in the biphenyl series. Interestingly, incorporation of aminosulfate or trichloroethyl aminosulfate groups also induced a significant increase in ARSB inhibition. In general, the biphenyl ether derivatives were less selective for Sulf-2 over ARSB than the biphenyl series.

Table 3.15: Preliminary sulfatase inhibition data for the biphenyl sulfamates inhibitors. The % inhibition are the mean of two independent determinations.



Compound	R	**Sulf-2** % inhibition @ 1 mM	**ARSA** % inhibition @ 1 mM	**ARSB** % inhibition @ 1 mM
215	H	32	*n.d.*	*n.d.*
212	2'-CO_2H	10	44	0
213	3'-CO_2H	30	49	0
214	4'-CO_2H	23	33	0
184	2'-NH_2	28	75	13
185	3'-NH_2	31	75	0
186	4'-NH_2	14	75	0
187	2'-NHAc	11	29	47
188	3'-NHAc	10	57	0
189	4'-NHAc	14	45	0
202	2'-$NHSO_3Na$	56	54	93
198	3'-$NHSO_3Na$	58	95	85
199	4'-$NHSO_3Na$	13	34	76
201	2'-$N(SO_3CH_2CCl_3)_2$	18	82	39
196	3'-$NHSO_3CH_2CCl_3$	96	100	97
197	4'-$NHSO_3CH_2CCl_3$	95	99	87

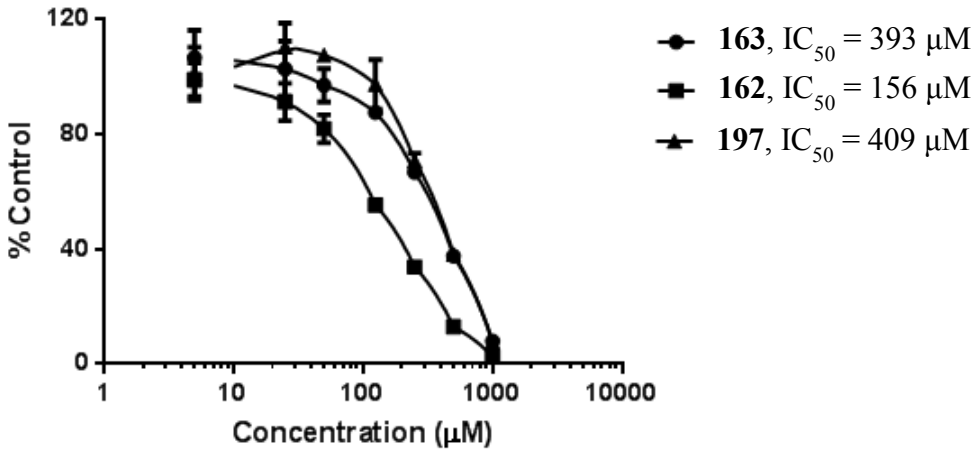


Figure 3.7: IC_{50} curves for inhibitor **162**, **163** and **197**

Sulf-2 IC_{50} values were determined for three of the most potent inhibitors (**162**, **163** and **197**) (Figure 3.7). Compound **163** had the highest Sulf-2 inhibitory activity with an IC_{50} value of 156 μM. ARSA and ARSB IC_{50} values were also determined for these three compounds, which were not selective for Sulf-2 over ARSA or ARSB (Table 3.16).

Table 3.16: ARSA and ARSB potency of inhibitors **162**, **163** and **197**

Compound	ARSA IC_{50} (μM)	ARSB IC_{50} (μM)
162	76	239
163	84	222
197	94	123

3.6. Summary

In order to attempt to identify tool compounds for use in biological target validation studies, a *de novo* design strategy was employed, based on an analysis of functional groups in the endogenous substrate HSPGs, which may be important for binding of Sulf-2. Biphenyl and biphenyl ether scaffolds were selected and a set of 31 inhibitors was prepared. The aim was to identify a non-saccharide template, with improved physicochemical properties compared with **5** and more amenable to large scale and rapid analogue synthesis. Preliminary sulfatase inhibition data indicated that biphenyl and biphenyl ether sulfamates had superior potency against Sulf-2 compared with monosaccharide **5**. Incorporation of polar functionalities around the B-ring did not improve inhibitory activity. Unexpectedly, trichloroethyl protected sulfates had improved Sulf-2 inhibition, with compound **162** having an IC_{50} value of 156 μM. This derivative is the most potent Sulf-2 inhibitor identified to date. However, **162** was also a potent inhibitor of ARSA and ARSB.

Chapter 4. The Extracellular Signal-Regulated Kinase 5 (ERK5) and Reported Small-Molecule Inhibitors

4.1. Protein Kinases: Attractive Targets for Cancer Therapy

Protein phosphorylation, a very common post-translational modification with 500,000 potential phosphorylation sites in the human proteome, is a central mechanism for biological regulation of most eukaryotic cellular processes and cell signalling pathways.[137, 138] Upon phosphorylation, the special characteristics of the dianionic phosphate group induce critical and distinct biological effects, such as enzyme activation, enzyme inhibition, protein localisation, protein degradation, protein-protein interactions and transitions in protein state.[137]

Protein kinases are enzymes that catalyse the transfer of a terminal γ-phosphoryl group of adenosine triphosphate (ATP) to the hydroxyl group of a serine, threonine or tyrosine residue in a protein. Phosphorylation on serine, threonine and tyrosine is approximately 86.4, 11.8 and 1.8% respectively.[139] Since they account for almost all protein phosphorylation, protein kinases mediate most important biological processes, including signal transduction but also metabolism, transcription, cell cycle progression, cytoskeletal rearrangement and cell movement, apoptosis and differentiation.[140] The conserved sequence of protein kinases has allowed the identification of over five hundred human protein kinases by analysis of the human genome.[140, 141] These represent approximately 2% of all human genes and constitute the third largest protein family. Typical protein kinases are classified by the residues that they phosphorylate and divided into two families, namely serine/threonine kinases and tyrosine kinases.

The catalytic domain of protein kinases consists of approximately 290 amino acid residues. In 1991, the first crystal structure of a protein kinase catalytic domain was solved.[142] There is now over 1,500 structures of approximately 200 kinases in the PDB. The conserved secondary structure of the catalytic domain is arranged into twelve subdomains which fold into a bi-lobed catalytic core structure.[143] The small *N*-terminal lobe is composed of five β-strands and a single α-helix (the regulatory αC-helix). The large *C*-terminal lobe has a predominant α-helical character and includes the activation loop, located between a conserved DFG motif and an APE motif (Figure 4.1).[138] The cleft formed between the two sub-domains, which are connected by the hinge segment, constitutes the active site.[137] ATP binds in the active site and makes the kinase catalytically active.

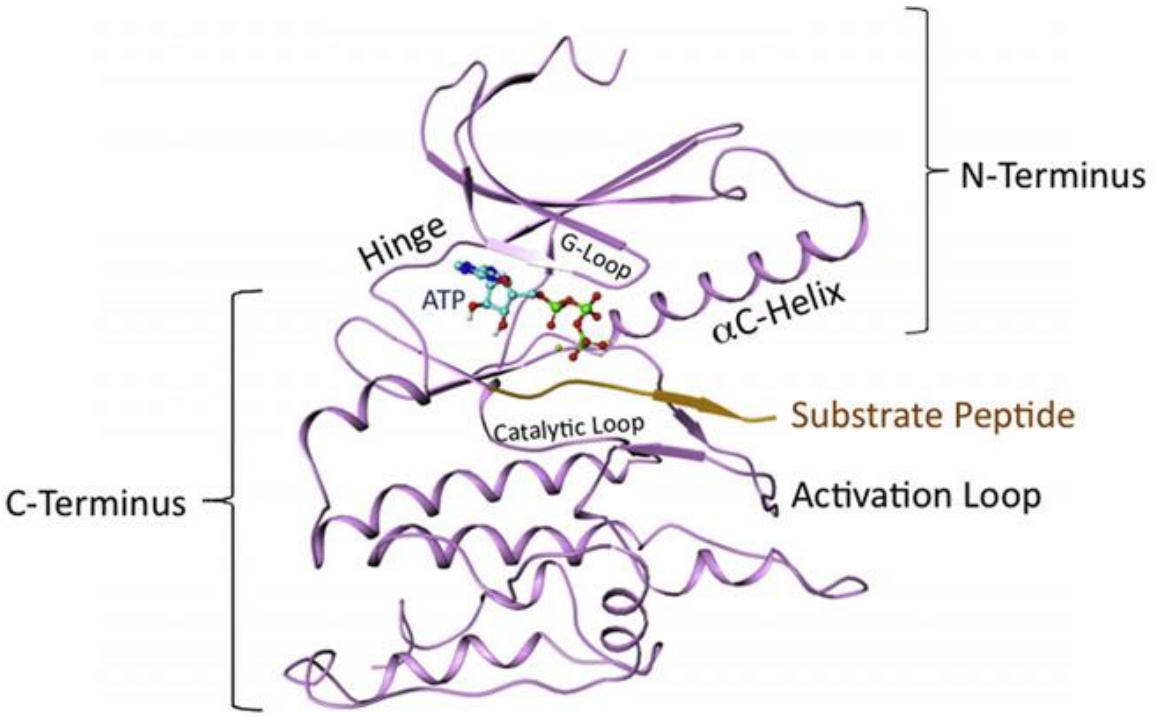


Figure 4.1: Ribbon representation of phosphorylase kinase (PDB code 2phk) showing the main features of a kinase catalytic domain[137]

Protein kinases can adopt an active or an inactive state, which have different structural conformations.[138] Whereas a common catalytically competent conformation has been established with active kinases, structural diversity is observed with inactive kinases.[138] In the inactive form, the activation segment blocks the active site, preventing ATP from binding. Different regularity mechanisms, such as phosphorylation on the activation segment or at other sites, removal of inhibitory sequences, or association of other domains induce a conformational change, which enables ATP to access the active site, resulting in the enzyme to be catalytically active.[139] The mode of ATP binding is largely consistent across kinase families, with the N^1- and N^6-positions of the adenine ring system forming hydrogen bonds with the peptide backbone of the kinase hinge region.[138] Van der Vaals interactions between the purine heterocycle and apolar aliphatic groups enhance the binding affinity. The triphosphate group points out of the adenosine pocket in direction of the peptide substrate. The non-transferable α- and β-phosphate groups form ionic interactions with three conserved glycine residues from a flexible *N*-terminal loop.[137] A second network of interactions mediated by a magnesium ion cofactor ensure correct positioning of the γ-phosphate for transfer (Figure 4.2). The substrate has a low affinity for the kinase and its binding is mediated by residues in the vicinity of the phosphorylation site. The hydroxyl group to be phosphorylated is oriented toward an aspartate residue on the catalytic loop.

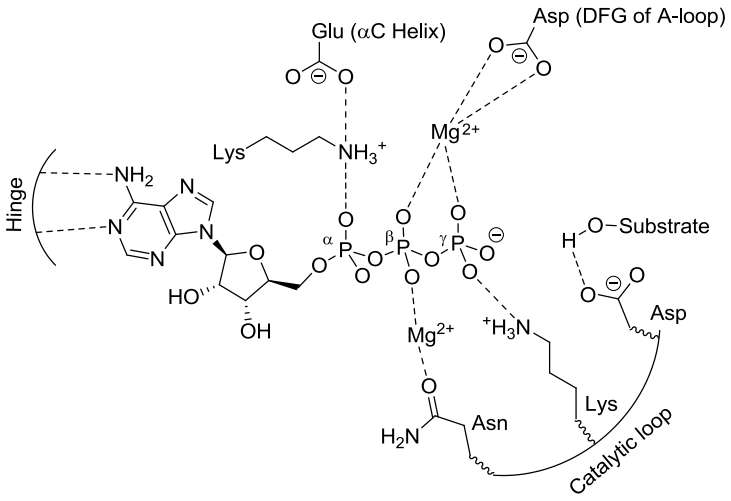


Figure 4.2: Simplified illustration of the molecular contacts between ATP and conserved active site residues and cofactors involved in catalysis of phosphate transfer (adapted from ref 137)

Most protein kinases are organised in a network of kinases, regulated by autophosphorylation and phosphorylation by other kinases. Receptor tyrosine kinases are cell-surface receptors integrated into the cell membrane which are activated by binding of growth factors and transduce extracellular signals.[144] Non-receptor tyrosine kinases are found in the cytoplasm and generally function downstream of receptor tyrosine kinases.[145]

Commensurate with their prominent role in normal physiology, protein kinase mutations and dysregulations play an important role in disease state.[137] Indeed, approximately half of all kinases map with genes associated with major diseases, including cancer, diabetes, inflammation and neurodegeneration.[140] Accordingly, the development of agonists and antagonists for this class of enzyme has been a major focus of drug development in the past two decades and has afforded new therapeutic opportunities.[146] In a disease state, deregulation of protein kinases occurs through mutation to constitutively active or inactive forms, loss of negative regulators or chromosomal rearrangements, leading to the formation of active fusion proteins.[138] This leads to aberrantly regulated signalling pathways which in cancer promote tumourigenesis.[147] The development of large scale ribonucleic acid interference (RNAi) screens and phosphoproteomic analyses has accelerated the identification of disease-associated kinase targets.[147]

4.2. Kinase Inhibitors in Clinical Use

Since the primary sequence and three-dimensional structures of kinases share a high degree of similarity, the discovery of selective inhibitors with minimum off-target activity has been and is still a real challenge.[148] In 2014, the early scepticism in the drug discovery community about kinases as drug targets has now disappeared with the original problems being solved or found to be less problematic. In the past 15 years, 27 drugs targeting kinases have been approved for clinical use and close to two hundreds are being evaluated in clinical trials (Table 4.1).[149] The most recently approved small-molecule kinase inhibitor (Ceritinib) was registered in April 2014 after a Phase I clinical trial for the treatment of lung cancer.[150] Protein kinases are estimated to represent more than 25% of all pharmaceutical drug targets.[151]

Imatinib was the first kinase inhibitor approved for clinical use in 2001.[152] Imatinib is a tyrosine kinase inhibitor originally developed for the treatment of chronic myelogenous leukaemia (CML). A reciprocal translocation of genetic material from chromosomes 9 and 22 results the generation the Bcr-Abl protein kinase, which leads the unregulated proliferation of white blood cells.[1] Imatinib binds to the ATP-binding pocket of the Bcr-Abl protein in its inactive form, resulting in a decreased activity of the tyrosine kinase. Imatinib demonstrated impressive results in the clinic and validated the targeted therapy paradigm.[22]

Most kinase targeted drug discovery programs are for application in the oncology area, where a lack of specificity has not proved to be a barrier to clinical approval.[146] Due to the simultaneous inhibition of several kinases, the majority of approved small-molecule kinase inhibitors is used to treat one or more cancer.[149] Protein kinase inhibitors constitute the most important drug class in cancer with 50 to 70% of current cancer drug discovery programmes focussing on the development of protein kinase inhibitors.[149] However, the number of kinase inhibitors undergoing clinical trials for the treatment of other diseases, such as hypertension, Parkinson's disease or autoimmune diseases, is rising, and the first protein kinase inhibitor for the treatment of inflammatory diseases has recently been approved.[149]

Protein kinase structural studies have guided drug design and explained the mechanism of inhibition by identification of the interactions of kinase inhibitor with the kinase ATP-binding site.[145] Kinase inhibitors are classified according to the kinase state they inhibit and their binding mode. They have been classified into four categories (Types I, II, III and

IV) (Figure 4.3).[148] Type I are ATP-competitive inhibitors targeting the kinase in its active conformation and comprise the majority of reported kinase inhibitors. Although the ATP-binding domain is common to all protein kinases, potent ATP-competitive inhibitors with high selectivity for a few kinases have been developed by targeting adjacent hydrophobic pockets which are less conserved.[139] Type II inhibitors target the inactive conformation of the kinase and do not compete directly with ATP binding. Targeting the inactive conformation of a kinase, which is more diverse, allowed the design of more selective inhibitors with an improved therapeutic window. In the inactive state, the DFG motif has an 'out' conformation which opens a large allosteric binding pocket which has been exploited for the tight binding of inhibitors.[146] Type III inhibitors bind to a site adjacent to the ATP-binding site known as the 'back pocket' and don't make any interaction with the hinge segment of the kinase. Type IV kinase inhibitors bind to a site remote from the ATP-binding pocket.[151] These inhibitors are known as allosteric inhibitors and act by inducing a conformational change that make the kinase inactive.[148] Since they exploit binding sites and regulatory mechanisms which are unique to a particular kinase, Type III and IV inhibitors exhibit the highest degree of kinase selectivity.[146] The first allosteric inhibitor, Trametinib, was approved for the treatment of melanoma in May 2013.[153, 154]

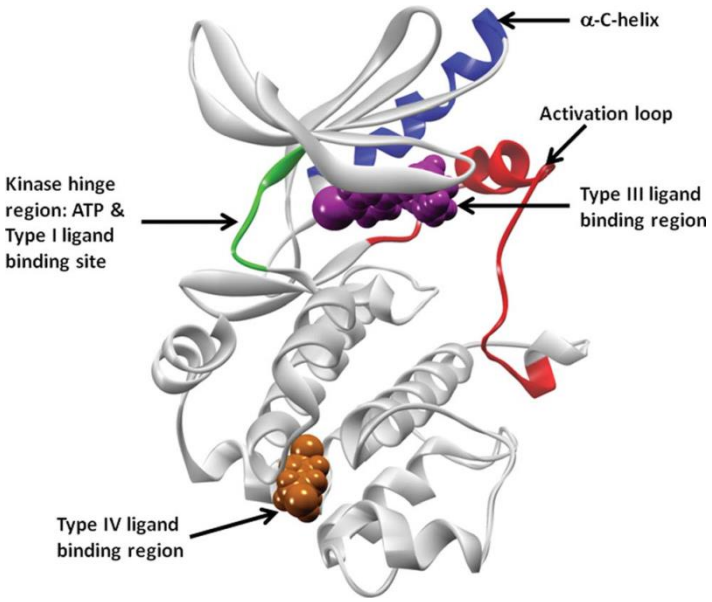
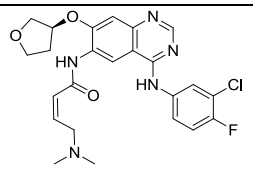
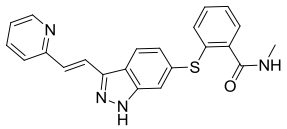
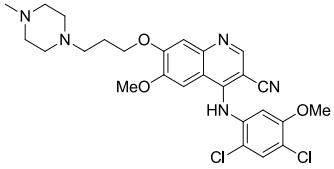
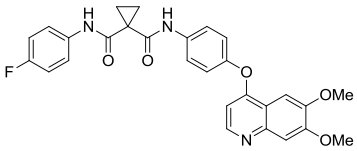
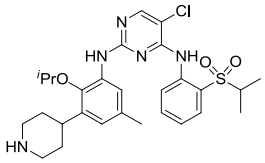
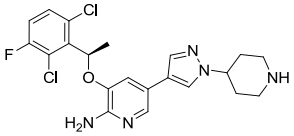
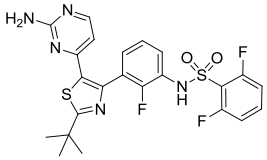
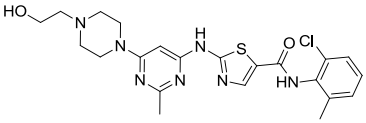
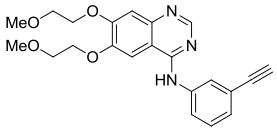
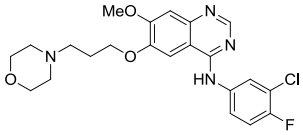
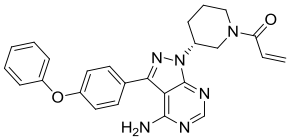
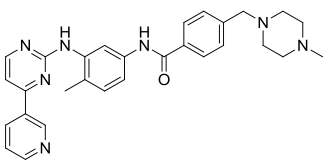
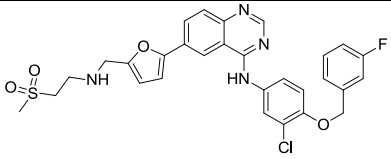
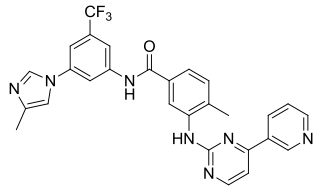
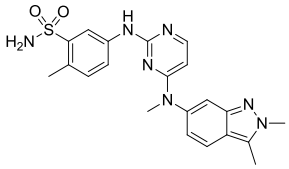
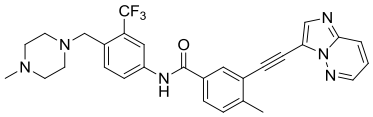
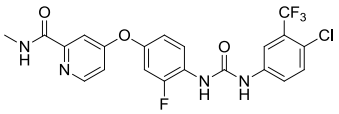
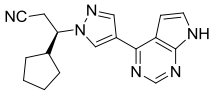
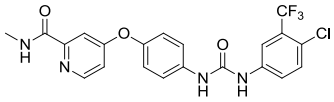
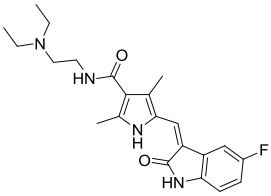
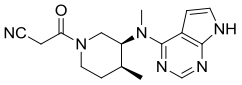
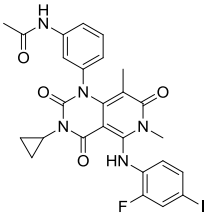
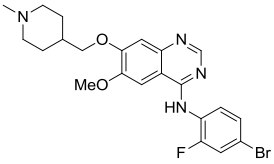
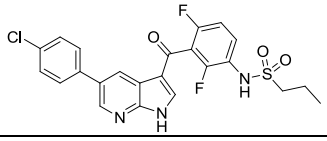


Figure 4.3: Examples of type III and IV kinase inhibitor binding sites. The cMET crystal structure in DFG-in, α-C-helix-out conformation (PDB code 3eqg) is to used highlight these pockets. The protein kinase is shown in grey, with the hinge region connecting the *N*- and the C-loops in green. Type III inhibitor (PD-325089) binding at the allosteric pocket, adjacent to the ATP pocket, is represented by magenta van der Waals surface. The region where the Type IV inhibitor GNF-2 binds, the myristoyl pocket in cAbl, is shown in this cartoon representation using a russet surface. The activation loop between the DFG and PE sequences are colored in red, and the α-C-helix is represented in blue.[151]

Table 4.1: Small-molecule kinase inhibitors approved for clinical use by the FDA

Name	Structure	Reported target	Approved for clinical use
Afatinib		Her2; EGFR	*2013*; NSCLC
Axitinib		VEGFRs; PDGFRB; c-Kit	*2012*; Renal cell carcinoma
Bosutinib		Bcr-Abl; Src; Lyn; Hck	*2012*; CML
Cabozantinib		VEGFRs; Kit; Axl; Met; TrkB; Flt3; Tie2	*2012*; Metastatic medullary thyroid cancer
Ceritinib		ALK; IGF-1R; InsR; ROS1	*2014*; NSCLC
Crizotinib		ALK; c-Met; Ros	*2011*; NSCLC
Dabrafenib		B-Raf	*2013*; Metastatic melanoma
Dasatinib		Multiple tyrosine kinases	*2006*; CML, ALL
Erlotinib		ErbB1	*2004*; NSCLC, pancreatic cancer
Gefitinib		EGFR	*2003*; NSCLC
Ibrutinib		Bruton's kinase	*2013*; Mantle cell lymphoma, CLL
Imatinib		Bcr-Abl c-Kit PDGFR	*2001*; CML, ALL, GIST

Name	Structure	Reported target	Approved for clinical use
Lapatinib		ErbB2 EGFR	*2007*; Breast cancer
Nilotinib		Bcr-Abl PDGFR	*2007*; CML
Pazopanib		VEGFR2 PDGFR c-Kit	*2009*; Renal cell carcinoma, soft tissue sarcomas
Ponatinib		Multiple tyrosine kinases	*2012*; CML, ALL
Regorafenib		Multiple tyrosine kinases	*2012*; Colorectal cancer
Ruxolitinib		JAKs	*2011*; Myelofibrosis
Sorafenib		Multiple tyrosine kinases	*2005*; HCC, renal cell carcinoma
Sunitinib		Multiple tyrosine kinases	*2006*; Renal cell carcinoma, GIST
Tofacitinib		JAKs	*2012*; Rheumatoid arthritis
Trametinib		MEK1/2	*2013*; Metastatic melanoma
Vandetanib		Multiple tyrosine kinases	*2011*; Thyroid cancer
Vemurafenib		B-Raf	*2011*; Melanoma

An emerging field in kinase drug discovery is the development of ATP-competitive irreversible inhibitors, which covalently bind to a nucleophilic cysteine residue in the active site. This irreversible binding allows to overcome competition with the high millimolar concentration of ATP.[151] Initially pharmaceutical companies were concerned with the high reactivity of these covalent inhibitors that could irreversibly modify undesired targets and lead to potential toxicities.[143] The first irreversible kinase inhibitor, Afatinib, was recently approved by the FDA for the treatment of metastatic non-small cell lung cancer in July 2013.[155, 156] A second irreversible kinase inhibitor, Ibrutinib, was approved a short time after in November 2013 for the treatment of mantle cell lymphoma and chronic lymphocytic leukaemia.[157, 158] These recent approvals highlight the emergence of this type of inhibitor.

Because kinases have essential roles in cell metabolism, survival and function, their inhibition induces a loss of function which cell compensates using extrinsic and intrinsic mechanisms leading to drug-resistance.[159] The development of acquired resistance to kinase inhibitors has limited the duration of treatment with kinase inhibitor drugs. Resistance occurs through mutations in the targeted kinase gene, reducing drug binding affinity. Mutation of the gate-keeper residue which controls the access to the hydrophobic pocket located adjacent to the ATP-binding site is the most common mutation. Non-mutation mediated resistance mechanisms have also been identified and include upregulation of alternative kinase pathways or cross-talks between signalling pathways.[137, 143] An understanding of acquired resistance to kinase inhibitors will help to overcome the problem. One strategy under investigation is to inhibit the resistant kinase with an inhibitor that binds at an alternative binding site. Combination of therapeutic agents is currently used to overcome resistance in the clinic.

Despite the recent success of novel kinase inhibitors, the scope of the therapeutic area needs to be extended. Basic kinase research is focussed on less than 10% of the human kinome, with only 50 protein kinases having been studied in detail. There are still 100 kinases with unknown functions and half of all kinases are largely uncharacterised.[137]

4.3. The MAP Kinase Signalling Pathways

The mitogen-activated protein kinase (MAPK) pathways are important cell signalling pathways in which alteration of constituent proteins has been implicated in many human diseases, including Alzheimer's disease, Parkinson's disease and various types of cancers.[160] The MAP kinases are a family of serine/threonine kinases organised in a signalling sequence that transduces mainly extracellular signals, leading to changes in the cellular environment which modulate gene transcription.[161] In eukaryotes, 14 MAP kinases have been identified and are categorised as conventional MAP kinases or atypical MAP kinases.[162] Extracellular signal-related kinase (ERK) 1/2/5, c-Jun amino (*N*)-terminal kinase (JNK) 1/2/3, and the p38 isoforms (α, β, γ and δ) are classified as conventional MAP kinases, whereas ERK3/4/7 and Nemo-like kinase (NLK) are classified as atypical. The conventional MAP kinases are characterised by having a conserved tripeptide motif T-X-Y in their activation loop, which is not conserved in the atypical MAP kinases. Dual phosphorylation of the conserved threonine and tyrosine residues is required for their full activation.[163]

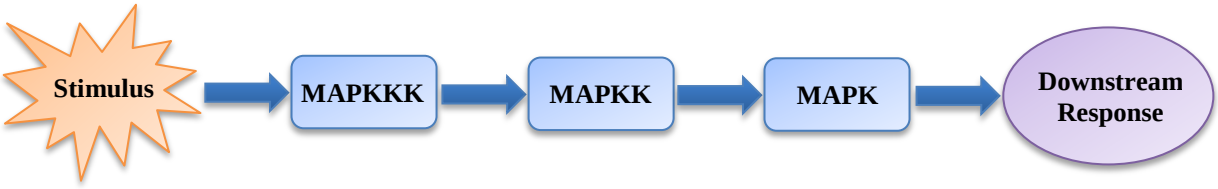


Figure 4.4: General representation of a MAP kinase signalling pathway

A conventional MAP kinase pathway involves three sequentially activated protein kinases (Figure 4.4).[164] The MAP kinase is activated by phosphorylation by a MAP kinase kinase (MAPKK), which in turn is activated by a MAP kinase kinase kinase (MAPKKK). The MAPKKK is itself activated in response to an extracellular or intracellular stimulus such as an increase in growth factor levels, cytokines, or as a stress response.[160] The MAP kinases phosphorylate key cytoplasmic and nuclear regulatory proteins such as transcription factors, co-activators and repressors, and chromatin-remodelling molecules.[165] The specificity of each MAP kinase is controlled by docking sites on the targeted substrate.[166] MAP kinases control fundamental cellular processes, including growth, proliferation, angiogenesis, differentiation, migration and apoptosis.[164] MAP kinase signalling is relatively complex and diverse since one MAPKKK can phosphorylate more than one MAPKK and current studies suggest there may be some redundancies and cross-talk among members of the MAP kinase family.[166, 167] Efficient signal transduction in the MAP

kinase pathways is maintained by adaptor/scaffold proteins through formation of multi-enzyme complexes.[166] These adaptor/scaffold proteins temporally bring at close proximity multiple members of a MAP kinase pathway to facilitate efficient phosphorylation and signal transduction.

Four MAP kinase pathways have been identified (Figure 4.5).[160] The pathway involving Raf, MEK1/2 and ERK1/2 was the first to be discovered and is referred to as the classical MAPK pathway.[162] Of the MAP kinase pathways, the classical pathway has received the most attention as a target for modulation in cancer chemotherapy as it is deregulated in approximately one-third of all human cancers and particularly in pancreatic cancers (90%), melanoma (63%) and colon cancers (50%).[164, 168]

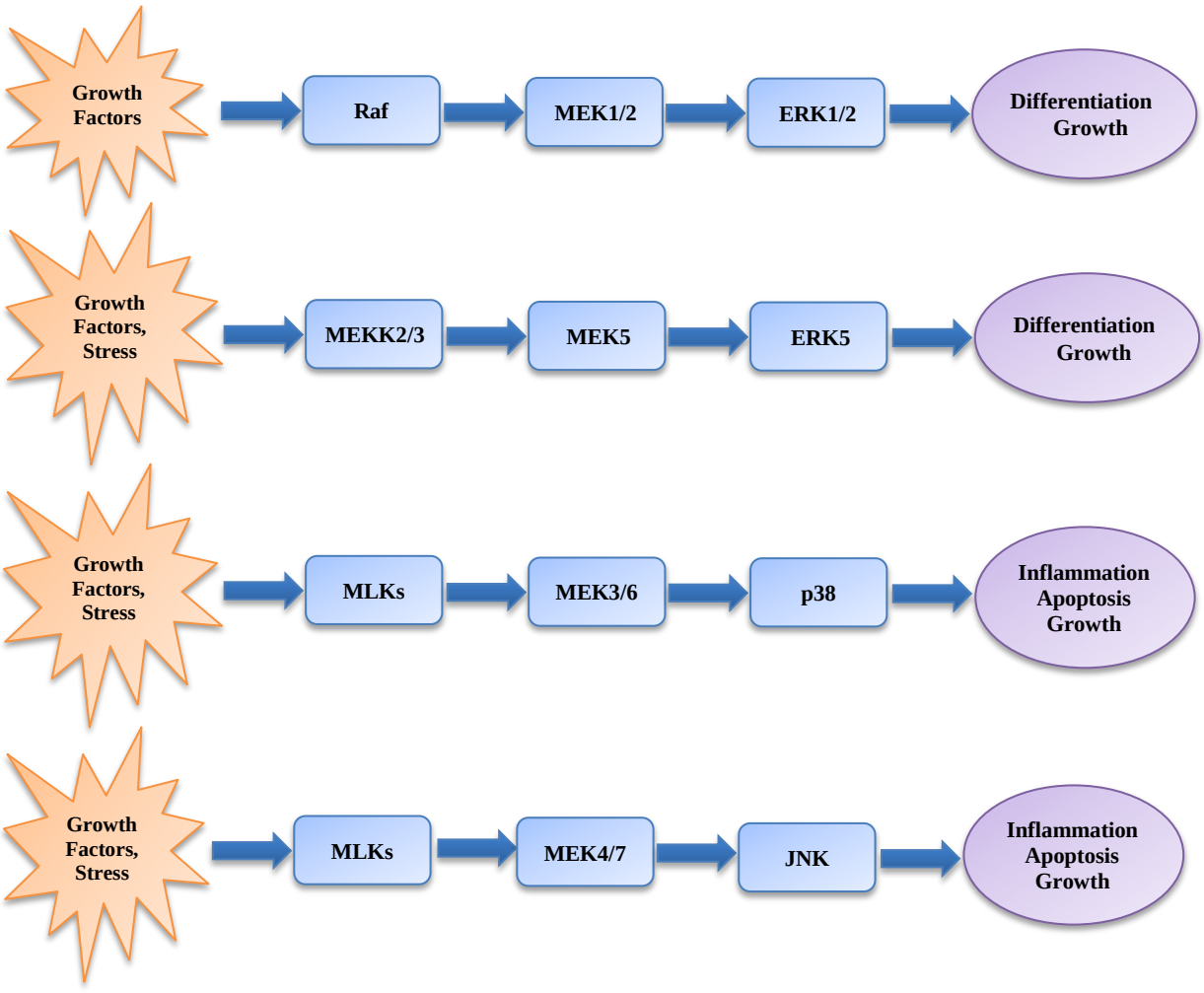


Figure 4.5: Schematic representation of the classical and non-classical MAP kinase pathways

The classical MAP kinase pathway is activated by growth factor binding to a receptor tyrosine kinase in the plasma membrane such as the fibroblast growth factor receptor (FGFR), the platelet-derived growth factor receptor (PDGFR) or the nerve growth factor

receptor (NGFR).[162] The phosphorylated receptor tyrosine kinase, in combination with co-factors, activates a member of the Ras family of proteins (H-Ras, K-Ras or N-Ras) (Figure 4.6). The Ras protein then recruits and activates a MAPKKK of the Raf kinase family (A-Raf, B-Raf or C-Raf), which in turn phosphorylates one of the MAPKK proteins, MEK1 or MEK2, which themselves phosphorylate the MAP kinase ERK1/2 proteins.[162] MEK1/2 phosphorylate ERK1/2 on threonine and tyrosine residues in a conserved TEY amino acid motif of the activation loop. This dual phosphorylation results in activation of ERK1/2, leading to phosphorylation of downstream substrates such as protein kinases, including ribosomal S6 kinase (RSK), and transcription factors, including Elk-1 and c-Myc.[169] This ultimately leads to changes in gene expression. The ERK1/2 cascade plays a central role in the control of cell proliferation and a sustained activation of this pathway is required in normal cells.[164] The ERK1/2 signalling sequence also plays important roles in regulating cell shape and motility.[170]

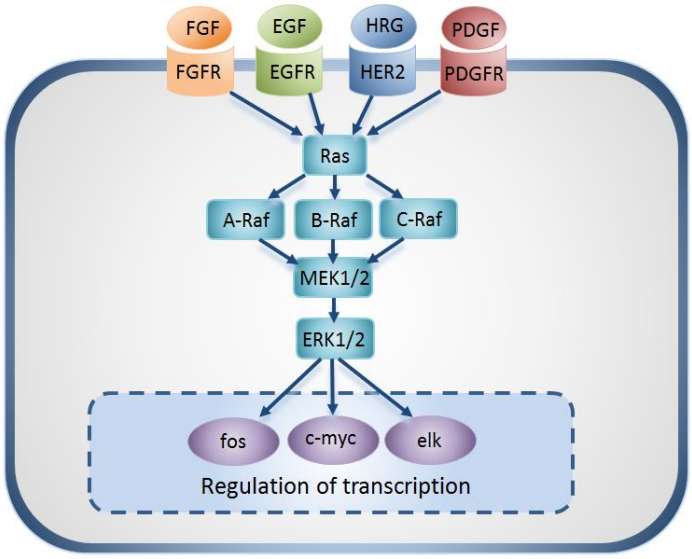


Figure 4.6: The classical MAP kinase pathway[105]

Constitutive activation of this pathway can occur through several mechanisms, including overexpression of receptor tyrosine kinases, sustained production of growth factor ligands, or mutations conferring increased constitutive activity of a member of the pathway, allowing signalling to occur in the absence of growth factors.[164] The ERK1/2 signalling pathway is also a key downstream effector of the Ras small GTPase which is the most frequently mutated oncogene in human cancers.[171] The significant contribution of this pathway in oncogenic cells development is emphasised by the fact that deregulation can occur at several levels. In cancer cells, this pathway promotes cell proliferation, cell survival and metastasis. This has triggered intensive research by the pharmaceutical

industry to develop inhibitors of the classical MAP kinase pathway for the treatment of cancer.[171] Several inhibitors of this signalling pathway have now been approved for clinical use.[143] This encompasses the B-Raf inhibitors Sorafenib and Vemurafenib, and the MEK1/2 inhibitor Trametinib. To date no inhibitors of ERK1 or ERK2 have entered clinical trials.

4.4. ERK5 and the ERK5 MAP Kinase Signalling Pathway

While the conventional MAP kinase pathway is one of the most studied signal transduction sequence, less is known about the ERK5 signalling pathway.[166] ERK5 was simultaneously discovered by two independent research groups in 1995.[172, 173] ERK5 is ubiquitously expressed in many tissues but more significantly in the heart, skeletal muscle, placenta, lungs and kidneys.[167] ERK5 double knock-out mice suffered from defects in normal cardiac development, maturation of vasculature and angiogenesis, resulting in embryonic lethality after 10 days. ERK5 deletion in adult mice leads to lethality within 2-4 weeks. ERK5 has also been shown to be a facilitator of neuronal cell survival.[167] These findings demonstrate that ERK5 plays a critical role in normal cell growth cycles, survival and differentiations.

The ERK5 protein kinase is composed of 816 amino acids and has a molecular weight of approximately 102 kDa, which is more than double that of the other MAP kinases (Figure 4.7). Because of its large size, ERK5 is also known as Big Map Kinase-1 (BMK-1).[172] The kinase domain (a.a. 78-406) shares 66% sequence identity to the kinase domain of ERK2 and resides in the *N*-terminal domain.

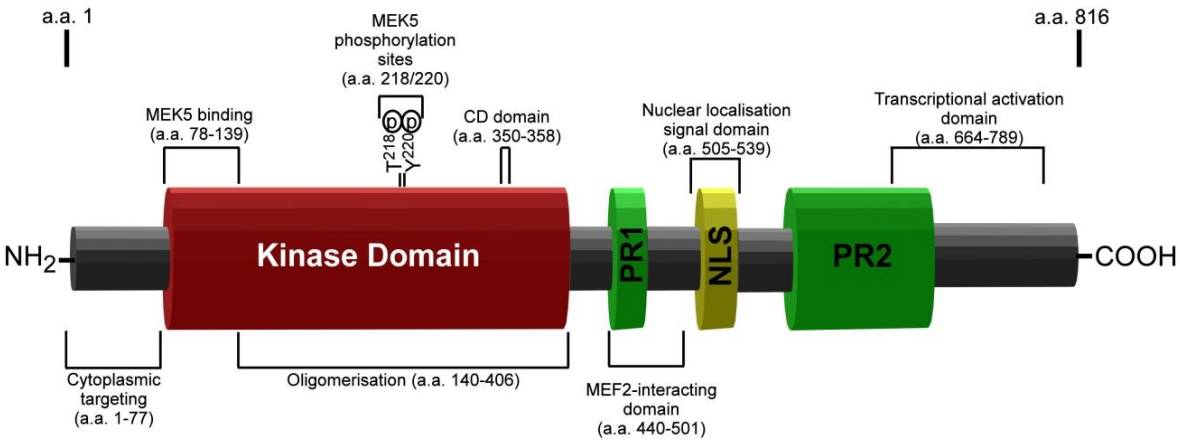


Figure 4.7: Structure of ERK5 and functional domains[167]

The large carboxy-terminal tail of ERK5 makes it distinct from the other typical MAP kinases. The *C*-terminus has an auto-inhibitory function, as truncation leads to increased kinase activity. A nuclear localisation signal (NLS) domain (a.a. 505-539), two proline-rich domains (PR1, 434-465 and PR2, 578-701), a myocyte enhancer factor 2 (MEF2) interacting region (a.a. 440-501) and a transcriptional activation domain (a.a. 664-789) are localised within the *C*-terminal domain.[167] The transcriptional activation domain is believed to undergo autophosphorylation which allows it to directly regulate gene transcription. This property of ERK5 is unique among the typical MAP kinases.[167]

In its unphosphorylated state, ERK5 is considered to exist in a folded conformation where the *N*- and *C*-terminals are interacting (Figure 4.8). The folded conformation leads to ERK5 sequestering in the cytoplasm. Dual phosphorylation by MEK5 on Thr218 and Tyr220 in the conserved TEY motif of the activation loop triggers a conformational change and translocation to the nucleus.[167] Upon dephosphorylation ERK5 reverts to a folded conformation and relocates to the cytoplasm.

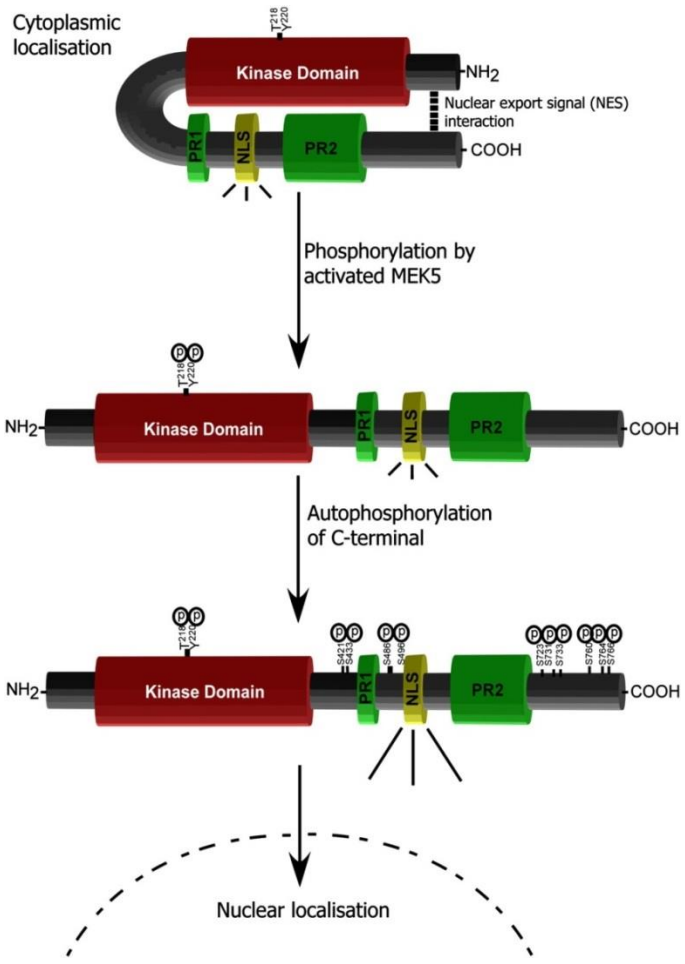


Figure 4.8: Schematic representation of the process of ERK5 activation for nuclear localisation[167]

The ERK5 MAP kinase pathway is the most recently identified MAP kinase module and has been associated with cellular proliferation, migration, survival and angiogenesis. This pathway can be stimulated by a wide range of signals, including vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), fibroblast growth factor (FGF2), platelet derived growth factor (PDGF), nerve growth factor (NGF), inflammatory cytokines such as interleukin 6 (IL6) and osmotic and hypoxic stress.[167] Upon activation by the extracellular stimuli, the closely related MEKK2 and MEKK3 phosphorylate MEK5 at Ser^{311} and Thr^{315}. The activator of MEK5 varies depending on the stimuli and the cell type.[166] In turn, MEK5, the sole MAPKK of this signalling cascade, phosphorylates ERK5 on Thr218 and Tyr220 leading to activation of the protein kinase. Activated ERK5 translocates to the nucleus where it undergoes autophosphorylation of numerous residues on its *C*-terminal domain, resulting in enhanced transcriptional activity.[167]

Phosphorylated ERK5 associates with, phosphorylates and activates a number of downstream transcription factors, such as the myocyte enhancer factor (MEF) family, c-Myc, RSK, c-Fos, c-Jun and Sap1a. Members of the MEF family of transcription factors are involved in the modulation of apoptosis. MEF2A and MEF2C are activated by both ERK5 and p38 MAP kinases, whereas MEF2D appears to be a specific substrate of ERK5.[167] The MEF2-interaction region and the transcriptional activation domain of the *C*-terminus are crucial for regulating MEF2 activity. In addition, ERK5 is able to phosphorylate MEK5 at different Serine residues. All the transcription factors activated by ERK5 have been implicated in tumour development.[174]

4.5. ERK5 and Cancer

A complete understanding of the role of ERK5 in cancer, and the effect of its inhibition on tumourigenesis has still to be established. However some key data support the inhibition of ERK5 as a potential cancer therapeutic strategy.

The ERK5 Pathway and Prognosis

ERK5 is overexpressed in tumour cells of a number of breast cancer patients. Patients with high levels of ERK5 have a lower median disease-free survival (DFS) time of 14 months compared with 34 months for patients with low ERK5 levels (Figure 4.9).[175] A similar correlation of high MEK5 expression and poor prognosis is also detected in prostate cancer patients.[176] Elevated cytoplasmic and nuclear levels of ERK5 serve as an independent

prognostic marker for advanced prostate cancer, with nuclear ERK5 expression present only in malignant cells.[177]

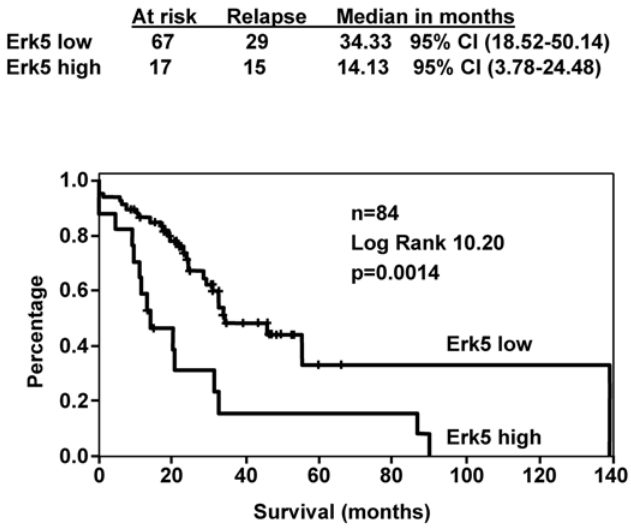


Figure 4.9: Kaplan-Meier plot of disease-free survival (DFS) with respect to ERK5 levels in 84 early stage breast cancer patients. Patients with high levels of ERK5 (n = 17) had a worse disease-free survival time (14.13 months; 95% CI: 3.78-24.48) compared with patients (n = 67) with low levels (34.33 months; 95% CI: 18.52-50.14).[175]

ERK5 Amplification and Overexpression

Amplification of the MAPK7 gene encoding for ERK5 is observed in approximately 50% of HCC tumours.[178] ERK5 expression was also found to be significantly upregulated in breast and prostate cancer patients.[175, 177]

ERK5 and In Vitro Cell Proliferation

HeLa cells proliferation has been shown to be ERK5-dependent, with dysfunctional ERK5 blocking entry into S-phase.[179] Proliferation of MCF7 and BT474 breast cancer cell lines is controlled by ERK5 activity.[174] The expression of the p21 proliferation modulator is controlled by ERK5 *via* suppression of the promyelocytic leukaemia protein (PML).[180] PML acts as a tumour suppressor by activating p21 expression leading to tumour suppression. Upon phosphorylation by ERK5, PML is inactivated and p21 expression ceased (Figure 4.10). ERK5 knockdown *via* siRNA resulted in increased p21 levels and tumour regression.[181] A recent study has also demonstrated that high ERK5 levels reduce p53 expression, increasing cell proliferation.[182]

Proliferation of the prostate cancer cell line LNCap and the T24 bladder cancer cells is affected by RNAi knockdown.[183, 184] However RNAi techniques have not confirmed the

requirement for ERK5 in cell proliferation of the prostate cancer cell line PC3, where overexpression of ERK5 increased proliferation. It demonstrates that ERK5 might only sustain proliferation in some specific cancer cell lines.[174]

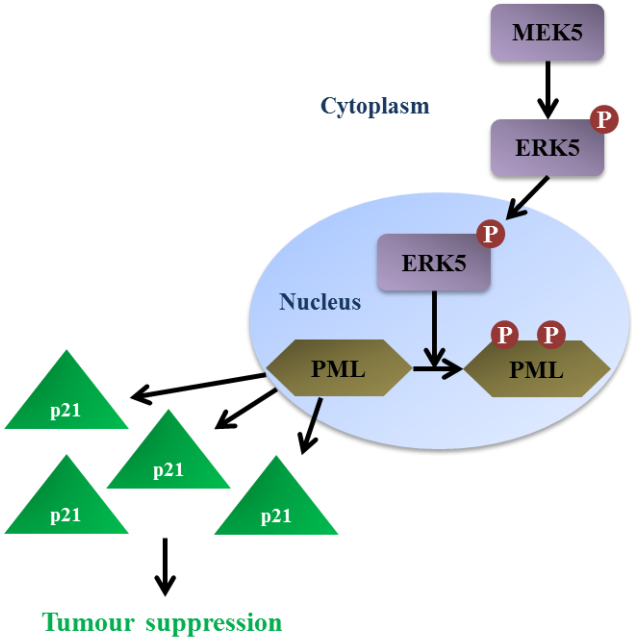


Figure 4.10: Regulation of p21 expression *via* phosphorylation of PML by ERK5

ERK5 and Apoptosis

Overexpression of wild type ERK5 protects multiple myeloma cells from induced apoptosis, whereas overexpression of a catalytically inactive mutant of ERK5 leads to increased sensitivity to induced apoptosis.[185] ERK5 also has a pro-survival role in T-lymphocytes which were sensitised to induced apoptosis by ERK5 small hairpin RNA knockdown.[186]

The ERK5 Pathway and Metastatic Potential

ERK5 has been shown to play a role in cellular invasion and metastatic spread, affecting cell migration, and attachment to the extracellular matrix, through interactions with the $\alpha_v\beta_3$ integrin and focal adhesion kinase (FAK) in breast cancer cells.[167] FAK signalling plays an important role in the regulation of cell adhesion and motility. Overexpression of MEK5 in prostate cancer induces expression of matrix metalloproteases-2 and -9 through induction of expression of activator protein-1.[176] The matrix metalloproteases assist the migration of cancer cells *via* degradation of the extracellular matrix. High ERK5 expression correlates with high levels of bone metastases and poor prognosis in prostate

cancer patients. In prostate cancer patients, MEK5 overexpression also correlates with higher metastatic potential (Figure 4.11).[177]

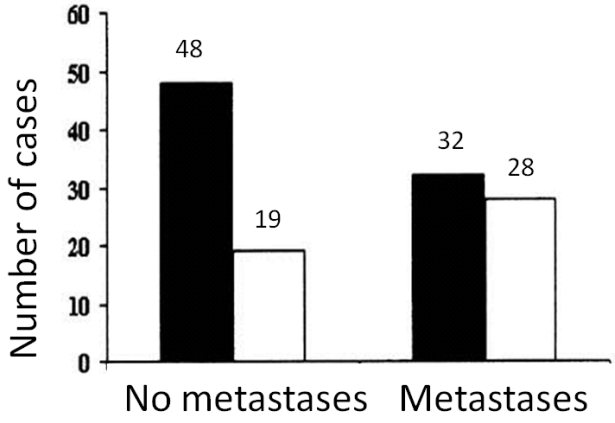


Figure 4.11: MEK5 expression level and presence of metastases[177]; White bars - high/moderate MEK5 expression, Black bars - low MEK5 expression

The ERK5 Pathway and Angiogenesis

In human xenograft models, ERK5 deletion reduced tumour growth in mice and inhibited development of tumour blood vessels.[187] VEGF-stimulated tubular morphogenesis in endothelial cells is mediated by ERK5, and VEGF and FGF pro-angiogenic factors have been shown to stimulate ERK5 activation in HUVEC cells.[188, 189] Activation of Id1 (inhibitor of differentiation 1) is triggered under specific conditions by ERK5. Id1 is a negative regulator of TSP1 (thrombospondin-1), an angiogenesis inhibitor. Hence, ERK5 might induce angiogenesis by constitutional activation of Id1.[169]

Constitutive Activation of ERK5

Out of 900 samples sequenced, only one somatic mutation of ERK5 has been reported, suggesting that mutation of ERK5 into a constitutively active form is rare in cancer. Deregulation of this pathway is therefore likely to occur through altered protein levels, as seen in HCC, with the 17p11 amplification being present in 50% of cases.[174] Sustained activation of upstream signalling, such as Src, may also result in dysregulation of ERK5 signalling.[174]

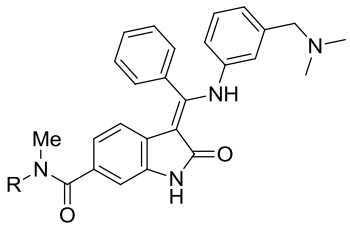
4.6. Published ERK5 Inhibitors

Two classes of inhibitors of the MEK5/ERK5 pathway have been described in the literature; an oxindole series and a diazepinone series.[190, 191] Both classes are selective for the MEK5/ERK5 pathway over the classical MAP kinase pathway.

4.6.1. The Oxindole Series

The oxindole inhibitors **216** and **217** were developed by Boehringer Ingelheim Pharmaceuticals and reported in 2008.[191] Compounds **216** and **217** inhibit both ERK5 and MEK5, with 40- to 200-fold greater activity against MEK5 than ERK5 (Table 4.2). Significant selectivity for MEK5 over MEK1, MEK2 and ERK1 (IC_{50} > 6 μM) was measured, and both compounds were over 100-fold selective for MEK5 against a panel of 85 kinases.[191]

Table 4.2: Published MEK5 and ERK5 inhibitory potency of oxindole inhibitors

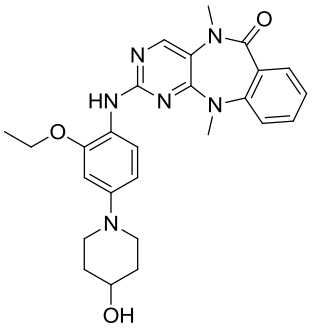


Compound	R	MEK5 IC_{50} (nM)	ERK5 IC_{50} (nM)
216	H	4.3	810
217	M	1.5	59

In Hela cells, the phosphorylation of ERK1/2, p38 or Jnk1/2 MAP kinases was not affected by **216** and **217**. Cell proliferation was reduced through inhibition of the transcriptional activity of MEF2C, a downstream substrate of the MEK5/ERK5 pathway, supporting the hypothesis that the oxindole inhibitors affect this pathway.

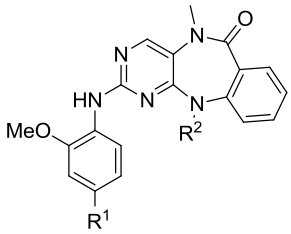
4.6.2. The Diazepinone Series

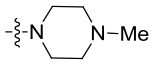
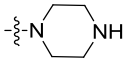
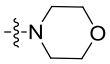
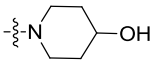
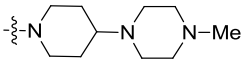
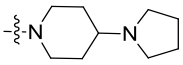
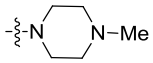
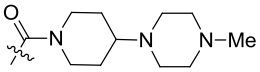
In 2010, the Scripps Research Institute reported XMD8-92 **218** as a selective ERK5 inhibitor.[181] This compound was discovered serendipitously, following screening of a library of compounds initially designed as polo-like kinase (PLK) inhibitors. SARs around the polar aliphatic heterocycle of this series was reported in a follow-up communication, showing that variation at this position had little effect on activity (Table 4.3).[190]



218, XMD8-92

Table 4.3: Selected ERK5 inhibition data for the diazepinone series[190, 192]



Compound	R^1	R^2	ERK5 IC_{50} (nM)
219		Me	190
220		Me	230
222		Me	260
223		Me	240
224		Me	200
225		Me	130
226		*c*-Pent	200
227		*c*-Pent	82

A co-crystal structure of **227** bound to ERK5, determined at a resolution of 2.8 Å, was later published (Figure 4.12).[193] Crystals were obtained from a kinase domain construct (residues 1-397), which was not phosphorylated on the activation loop. The structure confirms the key binding interaction between the 2-aminopyrimidine of **227** and the hinge region of the kinase, as previously observed with this inhibitor scaffold. The core has a non-planar shape with the *N*-cyclopentyl group pointing towards the glycine-rich loop and the carbonyl of the diazepinone forming a hydrogen bond *via* a water molecule to the backbone nitrogen of the DFG motif Asp200 and the αC helix Glu102 (Figure 4.12 B).[193] The aliphatic heterocycle ring system points out of the ATP-binding site towards the solvent exposed surface of the kinase and lies adjacent to the glycine-rich loop. This position is consistent with the flat SARs reported for analogues incorporating diverse water-solubilising groups in this region of the template.[190]

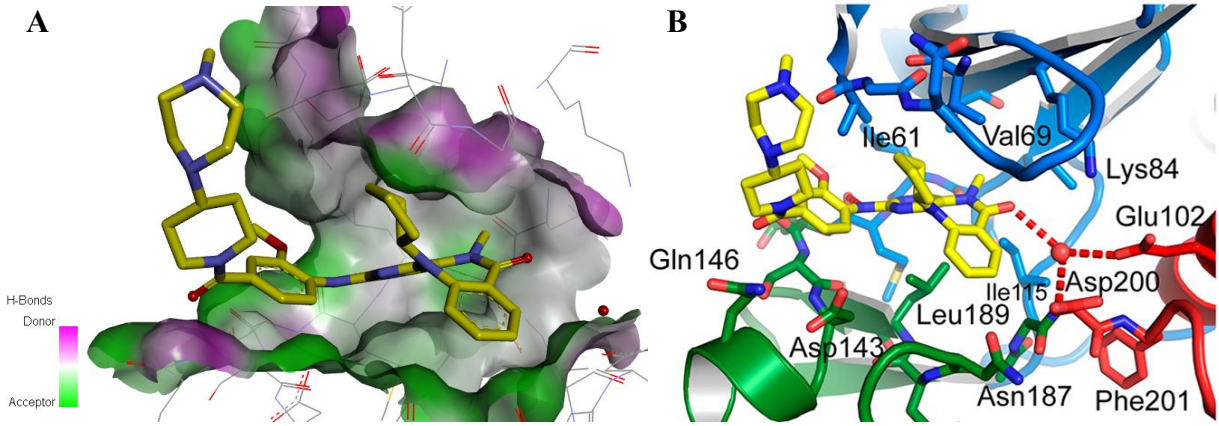


Figure 4.12: Co-crystal structure of compound **227** bound to ERK5 (PDB code 4b99).[193, 194] The *N*-terminal is colored blue. The *C*-terminal is colored green. The activation loop and αC helix are colored red, and compound **227** is colored yellow.

XMD8-92 **218** displayed high selectivity for ERK5 over a panel of 402 kinases in an *in vitro* ATP-site competition binding assay. In an enzymatic assay, the dissociation constant of **218** for ERK5 was 80 nM and no significant MEK5 inhibition was detected with doses of up to 50 μM. Compound **218** has been profiled in an *in vivo* rat pharmacokinetic study, demonstrating acceptable half-life, moderate clearance and good bioavailability (Table 4.4). XMD8-92 had an anti-proliferative effect in HeLa cells and exhibited *in vivo* growth inhibitory activity in tumour xenograft models, demonstrating the efficacy and tolerability of ERK5-targeted cancer treatment in animals.[181] In a separate *in vivo* study, XMD8-92 prevented the formation of new vasculature.

Table 4.4: *In vivo* pharmacokinetic parameters for XMD8-92 **218**. Dose 1 mg/kg *i.v.* and 2 mg/kg *p.o.*[181]

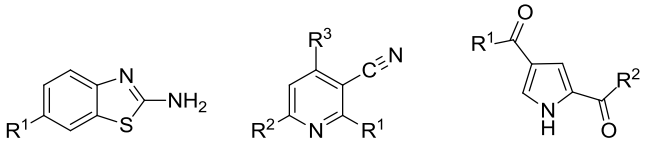
Cl mL/min/kg	**V_d** L/kg	**$t_{1/2}$** h	**F** %
37.0	3.4	3.4	69

The discovery of diazepinone inhibitor **218** provided further evidence that inhibition of the MEK5/ERK5 pathway may be a valid cancer therapy. This compound was used as a benchmark in diverse 'in house' biological assays and assisted the development of novel ERK5 inhibitors in Newcastle.

Chapter 5. Development of Novel ERK5 Inhibitors: the Pyrrole Carboxamide Series

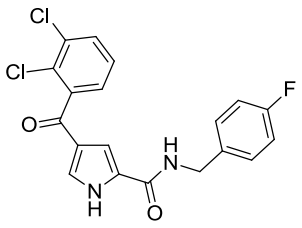
5.1. Identification of the Pyrrole Carboxamide Series by HTS

The pyrrole carboxamide chemotype was identified from a HTS of 48,500 compounds from a diverse library and 9,000 compounds from a kinase focussed library using an Immobilised Metal Affinity Polarisation (IMAP^{TM}) assay.[195] Three distinct chemical series were identified from this screening as having moderate to good ERK5 inhibitory activity: the benzothiazoles **A**, the cyanopyridines **B** and the pyrrole carboxamides **C**.



A **B** **C**

Seventeen members of the pyrrole carboxamide series demonstrated moderate to good ERK5 inhibition (IC_{50} < 33 μM), with seven compounds having an IC_{50} of less than 10 μM and the most potent hit **228** having an IC_{50} of 0.7 μM. To validate this series, the four most potent compounds were re-synthesised and re-tested against ERK5. Two of the resynthesised compounds failed to inhibit ERK5, while compound **228** only showed a low reduction in potency, having an IC_{50} of 3.7 μM.



228

5.2. Preliminary SARs in the Pyrrole Carboxamide Series

Initial SARs were conducted by Dr Sandrine Vidot, Dr Ruth Bawn, Dr Stephanie Myers and Dr Lauren Molyneux and led to the identification of functionalities required for activity.[196-198] The key SARs which had been generated at the commencement of the work described in this thesis are summarised in Figure 5.1.

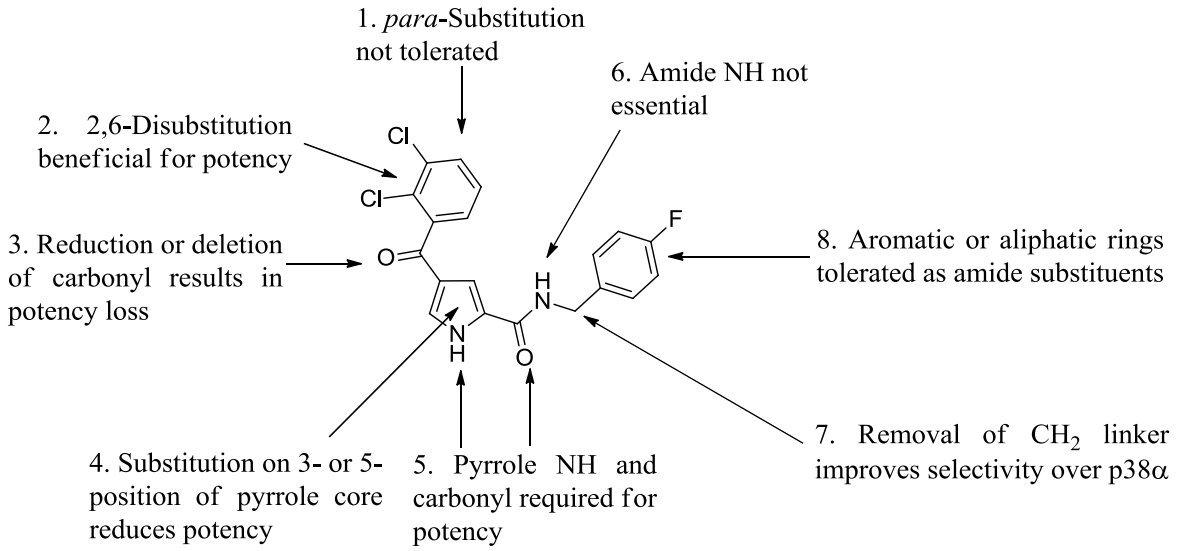
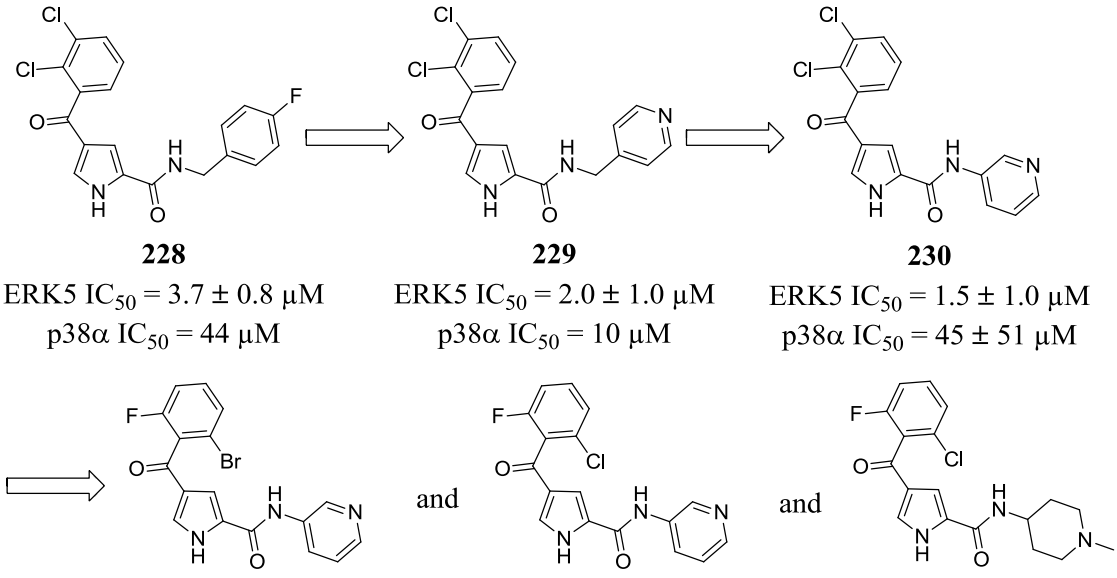


Figure 5.1: Summary of key SARs for ERK5 inhibition

The pyrrole NH and the amide carbonyl are essential for activity and it is assumed that these might interact with key residues in the hinge region of the kinase.

Introduction of a heteroatom in the benzylic amide side-chain afforded equipotent inhibitors, such as compound **229**. Truncation of the benzylic amide to heteroaryl amides and aliphatic heterocyclic amides conferred a significant and consistent improvement in selectivity over p38α (Figure 5.2).



228
ERK5 IC_{50} = 3.7 ± 0.8 μM
p38α IC_{50} = 44 μM

229
ERK5 IC_{50} = 2.0 ± 1.0 μM
p38α IC_{50} = 10 μM

230
ERK5 IC_{50} = 1.5 ± 1.0 μM
p38α IC_{50} = 45 ± 51 μM

231
ERK5 IC_{50} = 0.82 ± 0.07 μM
p38α IC_{50} >120 μM

and

232
ERK5 IC_{50} = 0.58 ± 0.24 μM
p38α IC_{50} = 93 ± 12 μM

and

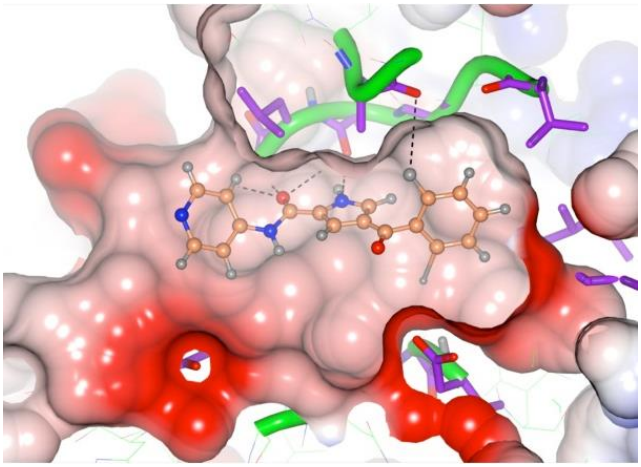
233
ERK5 IC_{50} = 0.20 ± 0.07 μM
p38α IC_{50} = 8.5 ± 0.2 μM

Figure 5.2: Hit-to-lead optimisation in the pyrrole carboxamide series

Deletion of the aryl ketone resulted in ERK5 IC_{50} of over 120 μM, demonstrating that this fragment is required for ERK5 inhibition. Replacing the benzoyl by a benzyl and reduction of the ketone to the corresponding alcohol both resulted in loss of inhibitory activity (ERK5 IC_{50} > 120 μM), suggesting that the carbonyl is crucial for activity and could be acting as a hydrogen bond acceptor. Replacement of the 2,3-dichlorophenyl ring with heteroaromatic and saturated rings was not tolerated. Incorporation of *para*-substituents, including Me, F, Cl, OMe, O^iPr, OCF_3 and NO_2, gave inactive compounds. Double *ortho*-substitution with halogens, such as 2-bromo-6-fluorophenyl **231** or 2-chloro-6-fluorophenyl **232**, was optimal and provided a significant gain of activity. Substitution at both *meta* positions was still an area under investigation.

5.3. Structure-Guided Drug Design

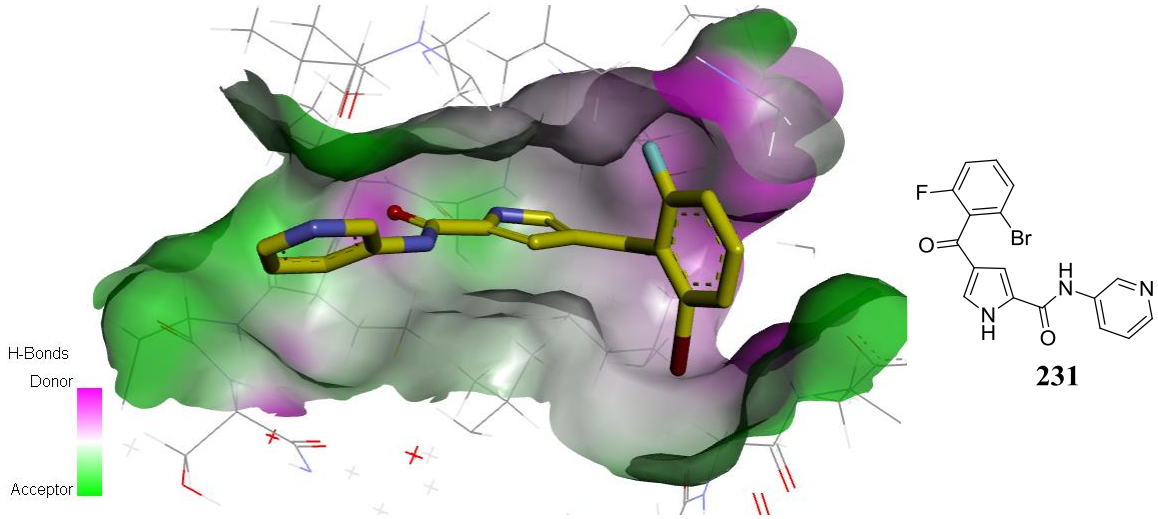
At the start of the project in 2008, no ERK5 crystal structure had been released in the public domain. As a result, homology models were developed and used to guide design. Dr Suzan Boyd, on behalf of CRT-DL, developed a first generation homology model based on the crystal structure of ERK2 which was identified by BLAST (Basic Local Alignment Search Tool) as the closest homologue of ERK5, with 51% sequence similarity in the kinase domain region and 78% in the ATP-binding domain. In 2010, a second generation homology model of ERK5, based on the crystal structure of the second closest homologue of ERK5, namely p38α, was developed at Newcastle University by Prof Martin Noble. The p38α crystal structure was retrieved from the protein data bank (PDB code 3mpt)[199, 200] and computationally mutated using MODELLER software to express the amino acid residues present in ERK5. Pyrrole carboxamide inhibitors were then built into the ERK5 model using GROMACS software (Figure 5.3).



234

Figure 5.3: Docking model of **234** in the p38α-derived homology model

More recently, the co-crystal structure of ERK5 bound to an analogue of competitor compound XMD8-92 was deposited in the protein data bank (PDB code 4b99).[193, 194] This crystal structure was used by Dr Susan Boyd to model some pyrrole carboxamide compounds in the ATP-binding site of ERK5 using the GOLD docking program (Figure 5.4).



231

Figure 5.4: Putative binding mode of compound **231** in the ATP-binding site of ERK5 (PDB code 4b99)

The pyrrole carboxamide series is assumed to inhibit ERK5 in an ATP-competitive manner, with the pyrrole NH and the amide carbonyl binding to the hinge region of the kinase (Figure 5.5). The ketone and the amide carbonyl are coplanar with the pyrrole ring, with the 2-bromo-6-fluorophenyl ring orthogonal to this plane and located in a hydrophobic pocket with limited amount of space around it. This phenyl ring could be making a π-stacking interaction with Lys62. The pyridyl side-chain is pointing towards the

outside of the binding pocket, probably into solvent. The orientation of the phenyl and pyridyl rings was difficult to predict accurately.

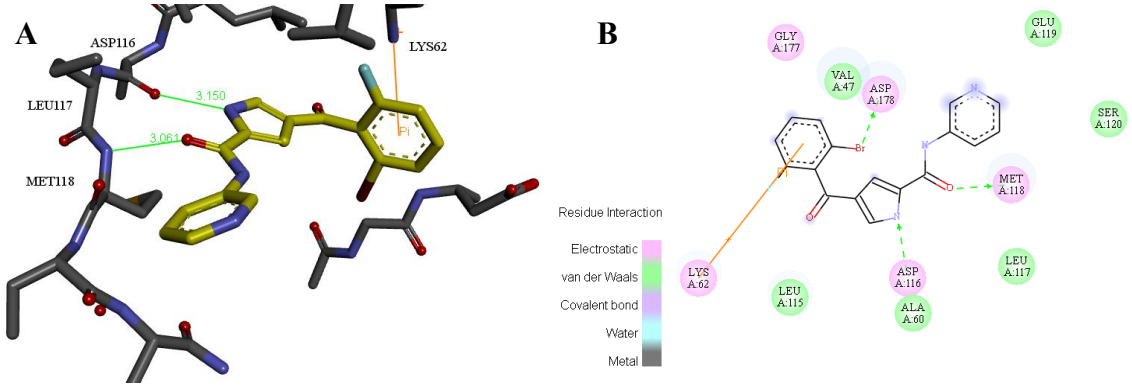


Figure 5.5: Proposed binding mode of inhibitor **231** in the ERK5 binding site

5.4. Screening Cascade in the ERK5 Project

The screening sequence starts with the generation of cell free IC_{50} data for ERK5 using an IMAP^{TM} format assay (Figure 5.6).[195] This assay assesses the potency of compounds by measuring fluorescence polarisation. A fluorescent labelled peptide, substrate for ERK5, is phosphorylated by the kinase in presence of ATP. The phosphorylation results in the formation of a complex between the phospho-group of the peptide and metal-containing nanoparticles within the IMAP^{TM} binding agent. This binding leads to a detectable increase fluorescence polarisation. In presence of a potent inhibitor, phosphorylation of the labelled substrate is impeded and the polarisation readout is reduced. This biochemical assay was performed by Ms Ai Ching Wong at Cancer Research Technology Discovery research Laboratories (London).

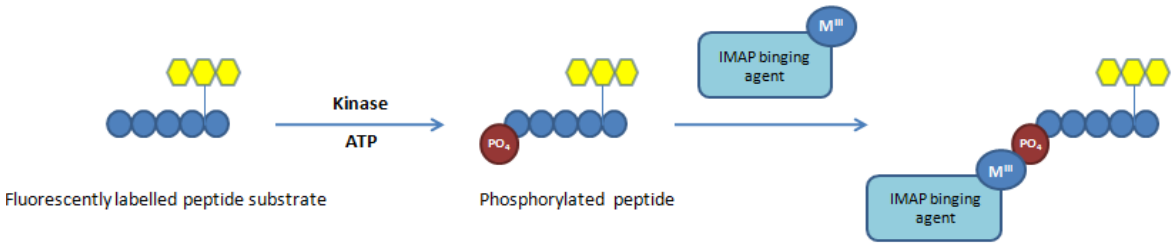


Figure 5.6: IMAP^{TM} assay format

Compounds with encouraging primary potency data (IC_{50} < 100 nM) were progressed to ERK5 cellular activity assays and counter-screened against the closely related p38α MAPK (Figure 5.7). The ERK5 cellular activity was measured in a MEF2D reporter gene

assay in HEK293 cells. In parallel ERK5 inhibition in an EGF-stimulated HeLa cell-line was determined by assessing ERK5 autophosphorylation using Western blotting. These preliminary cell-based studies were conducted by Lan-Zhen Wang, Dr Noel Edwards and Dr Pamela Lochhead.

Compounds with encouraging cellular potencies and selectivity data were progressed to a panel of *in vitro* pharmacokinetic screens (plasma protein binding, mouse liver microsomes, Caco-2 permeability and solubility) that would inform the selection of compounds for studies in mouse. Human liver microsomal (HLM) clearance, inhibition of the hERG ion channel and inhibition of cytochrome P450 (Cyp) were not considered to be critical for selection of a compound for *in vivo* studies. The *in vitro* assays used to assess the pharmacokinetics and physicochemical properties in the pyrrole carboxamide series were outsourced to Cyprotex, and are summarised in Table 5.1.

The *in vivo* pharmacokinetic profile of promising compounds was studied in mice and performed by Huw Thomas at the Paul O-Gorman Building, Newcastle Cancer Centre.

Details of the protocols for ERK5 biochemical and cell-based assays, and for the p38α selectivity assay are provided in Chapter 10.

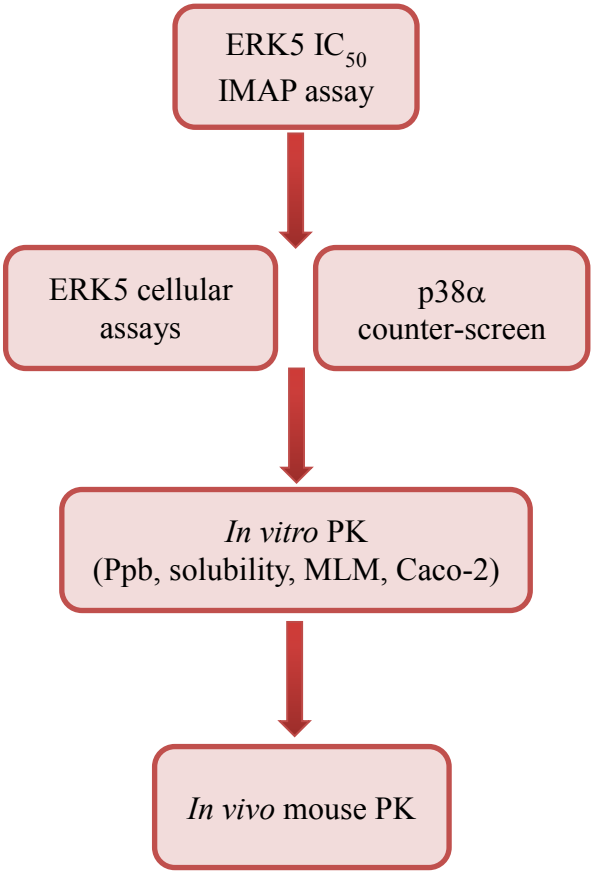


Figure 5.7: Screening sequence for the evaluation of ERK5 inhibitors

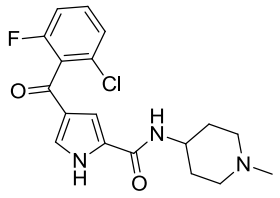
Table 5.1: Summary of Cyprotex physicochemical and *in vitro* ADMET assays used for the ERK5 inhibitor optimisation

Assay	Explanation
Solubility	Assessment of kinetic solubility was performed using a turbidimetric method, which entails diluting a test compound solution prepared in DMSO with aqueous buffer, and determining precipitation as the end-point by measuring absorbance at 620 nm. An estimated precipitation range in μM is reported, and when this value is less than 1 μM, a compound is considered highly insoluble. In cases where the lower solubility limit is between 1 and 100 μM, a compound can be considered to be moderately soluble, and above 100 μM denotes high solubility.
Ppb	Ppb represents the extent of binding to plasma proteins in blood. It is reported as fraction unbound (F_u) and is a value between 0 and 1. An F_u of 0.1 indicates that, in the blood, 90% of the compound is bound to proteins with 10% free.
HLM and MLM	A measure of the vulnerability of a compound to metabolism by cytochrome P_{450} in human or mouse. Figures are quoted as intrinsic clearance (Cl_{int}) in units of μL/min/mg protein, with lower figures representing low liability to cyp-mediated metabolism.
Caco-2	A measure of the rate of permeation of a compound across a monolayer of a Caco-2 cancer cell line, which contain efflux pumps. Intrinsic flux is measured by the B2A measurement, with recognition by efflux transporters being implied from the ratio of B2A over A2B. Two figures are quoted: apparent permeability (P_{app}) is quoted as a rate in units of 10^{-6} cm/s; efflux ratio (ER) is a ratio with no units. A high B2A figure and low ER reflect that a compound is highly permeable with low propensity for efflux.
Cyp inhibition	Inhibition of cytochrome P_{450}s can lead to drug-drug interactions, or a compound inhibiting its own metabolism leading to unpredictable accumulation. Inhibition of four isoforms of cytochrome P_{450} (2D6, 3A4, 2C9 and 2C19) were assessed, initially at a single concentration with results presented as per cent inhibition (% inh.). K_i values are generated on compounds showing evidence of Cyp inhibition.
hERG inhibition	The hERG (human ether-a-go-go-related gene product) ion channel is linked to cardiac arrhythmias leading to life-threatening Torsades de Pointes. A significant therapeutic window over hERG inhibition is required.

5.5. Lead Compounds in the Pyrrole Carboxamide Series

The most promising compounds in this series prior to the work described in this thesis can be classified in two categories according to the amide substituent.

5.5.1. Class 1: Aliphatic Heterocyclic Amides



233

The most potent analogue in this class of compounds was aminopiperidyl amide **233**, prepared by Dr Stephanie Myers (ERK5 IC_{50} = 0.20 ± 0.07 μM, LE = 0.37; p38α IC_{50} = 8.5 ± 0.2 μM). The basic centre of the amide substituent has an estimated pK_a of 9.5 and is expected to be protonated under physiological conditions.

Table 5.2: Physicochemical and *in vitro* ADME properties of **233**

MW	clogP	clogD	HLM Cl_{int}[a]	MLM Cl_{int}[a]	Caco-2 AB[b] (ER)
363	2.6	1.3	< 5	8	3.8 (9)

[a] μL/min/mg protein; [b] P_{app} 10^{-6} cm.s^{-1}

Surprisingly compound **233** had high metabolic stability in human and mouse liver microsomes but exhibited low apical to basolateral permeability and a high efflux ratio (ER) in the Caco-2 assay (Table 5.2). This suggests that the compound might be recognised by an efflux transporter, such as P-glycoproteins.

Table 5.3: *In vivo* pharmacokinetic parameters for **233**. Dose 10 mg/kg *i.v.* and *p.o.*

F_u	Cl mL/min/kg	Cl_u mL/min/kg	V_d L/kg	$t_{1/2}$ min	F %
0.32	91	284	3.4	61	< 10

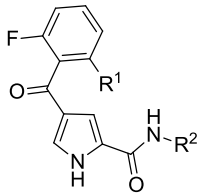
The *in vivo* pharmacokinetic parameters for compound **233** in mouse are summarised in Table 5.3. The compound had low plasma protein binding and a very high total plasma clearance, likely caused by metabolism of the high unbound fraction in plasma. The unbound clearance was moderate, consistent with low *in vitro* mouse microsomal

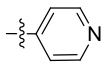
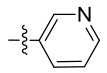
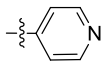
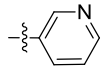
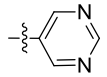
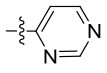
clearance. The low bioavailability was consistent with the high total plasma clearance and the problems of absorption indicated by the high efflux in the Caco-2 assay.

The objective for this class of target was to improve potency against ERK5 (IC_{50} < 10 nM), decrease *in vivo* plasma clearance, and reduce efflux in the Caco-2 assay.[105] Optimisation of leads with cyclic aliphatic amide substituent was not part of the work described in this thesis.

5.5.2. Class 2: Heteroaromatic Amides

Table 5.4: Biochemical inhibitory activity and Cyp inhibition profiles for key compounds in the second class of leads



Compound	R^1	R^2	ERK5 IC_{50} (μM)[a]	p38α IC_{50} (μM)[b]	Cyp inhibition
234	Br		0.67 ± 0.15	> 120	Strong (IC_{50} < 2 μM)
231	Br		0.82 ± 0.07	> 120	No Cyp inhibition
235	Cl		0.60 ± 0.27	> 120	Strong (IC_{50} < 2 μM)
232	Cl		0.58 ± 0.24	93 ± 12	Weak (IC_{50} > 6 μM)
236	Cl		0.40 ± 0.09	> 120	Weak (IC_{50} > 11 μM)
237	Cl		1.1 ± 0.8[c]	111 ± 1	Strong (IC_{50} < 1 μM)

[a] Determinations ± standard deviation (mean of n = 4 unless otherwise stated); [b] n = 2; [c] n = 6

In this class of compounds, similar potencies had been obtained with different heteroaromatic amide substituents (4-aminopyridyl, 3-aminopyridyl and 5-aminopyrimidyl). Compounds had been prioritised for *in vitro* pharmacokinetic studies depending on their cytochrome P_{450} enzyme inhibition profile (Table 5.4). Unflanked 4-aminopyridyl analogues **234** and **235** were found to be potent Cyp inhibitors. The pyrimidyl ring of compound **236** was an alternative to the pyridyl substituent with no inhibition of cytochrome P_{450s} but with a low flux and moderate efflux in the Caco-2 assay.

Introduction of methyl groups in *ortho* position of the pyridyl nitrogen reduced Cyp inhibition but significantly decreased the solubility. Replacement of the 4-aminopyridyl substituent by the 3-aminopyridyl group afforded compounds with retained ERK5 inhibitory activity and no cytochrome P_{450s} inhibition.

Table 5.5: Physicochemical and *in vitro* ADME properties of **231**

MW	**clogP**	**HLM Cl_{int}**[a]	**MLM Cl_{int}**[a]	**Caco-2 AB**[b] **(ER)**	**hERG inhibition** (μM)
388	3.1	< 5	26	34 (0.82)	> 25

[a] μL/min/mg protein; [b] P_{app} 10^{-6} cm.s^{-1}

In the EGF-stimulated HeLa cellular assay, compound **231** showed only a 3-fold reduction in potency, having an IC_{50} of 1.9 μM. This inhibitor was then selected for *in vitro* ADME studies and showed low clearance in mouse and human liver microsomes, high flux and no efflux in the Caco-2 assay, and no hERG inhibition (Table 5.5). It was progressed to an *in vivo* pharmacokinetic study in mouse to provide information on leads with heteroaromatic amide substituents and study whether the compound could be used in target validation studies *in vivo*. The compound had moderate plasma protein binding and total plasma clearance (Table 5.6). The volume of distribution is moderate and the half-life acceptable. The good bioavailability of the compound is consistent with the high absorption predicted in the Caco-2 assay and the moderate total plasma clearance.

Table 5.6: *In vivo* pharmacokinetic parameters for **231**. Dose 10 mg/kg *i.v.* and *p.o.*

F_u	**Cl** mL/min/kg	**Cl_u** mL/min/kg	**V_d** L/kg	**$t_{1/2}$** min	**F** %
0.06	27	459	1.2	65	68

The selectivity profile of inhibitor **231** was determined at the International Center for Kinase Profiling in Dundee against a panel of 130 diverse protein kinases. The compound was found to be a selective ERK5 kinase inhibitor, with CDK2 being the only kinase with over 50% inhibition at 1 μM. Independently, **231** was found to inhibit MEK5, the upstream activator of ERK5, with an IC_{50} of 3.4 μM.

Efficacy of compound **231** was assessed in an *in vivo* tumour xenograft model in CD1 mice transplanted with A2780 human ovarian carcinoma cells, and compared to the efficacy of competitor compound XMD8-92 (**218**). Following subcutaneous inoculation,

the tumours were allowed to grow for 7 days to an average volume of 72 mm^3. The mice were then randomised to receive either vehicle, compound **231** (100 mg/kg *p.o.*) or XMD8-92 **218** (50 mg/kg *i.p.*) twice daily for 11 days. Tumour volumes were measured at days 0, 2, 4, 7, 9 and 11, and body weight was also assessed as an indicator for toxicity. No weight loss was observed in animals dosed with pyrrole carboxamide inhibitor **231**. Similar tumour growth regression was observed in mouse treated with **231** or XMD8-92, compared with the vehicle control group (Figure 5.8). The results of this study were encouraging and demonstrated that an ERK5 inhibitor could be used as an anti-proliferative agent.

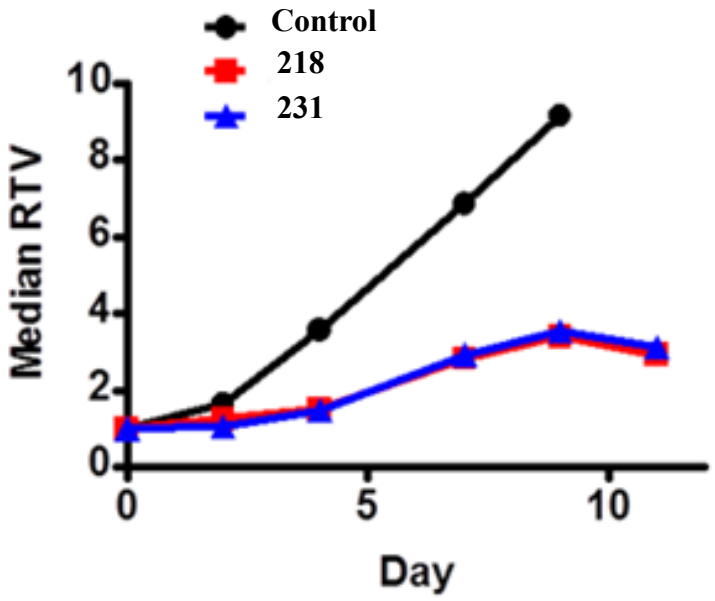


Figure 5.8: Treatment of CD1 mice bearing A280 xenograft with **231** (100 mg/kg *p.o.*) or XMD8-92 **218** (50 mg/kg *i.p.*)

With this class of leads, the target for the optimisation program was to improve ERK5 inhibitory activity, both in the biochemical and cellular assays, whist maintaining the attractive pharmacokinetic profile.

The overall objective in this drug discovery program was to identify *in vivo* tool compounds with improved potency relative to **231** and to identify compounds with the potential for pre-clinical development, having sub-ten nanomolar potency against ERK5, selectivity over p38α and a suitable ADMET profile.

5.6. Development Criteria for Pyrrole Carboxamide Inhibitors Optimisation

The desired criteria identified for an orally available ERK5 inhibitor pre-clinical candidate are outlined in Table 5.7.

Table 5.7: Desired development criteria for a pre-clinical candidate in the ERK5 pyrrole carboxamide series.

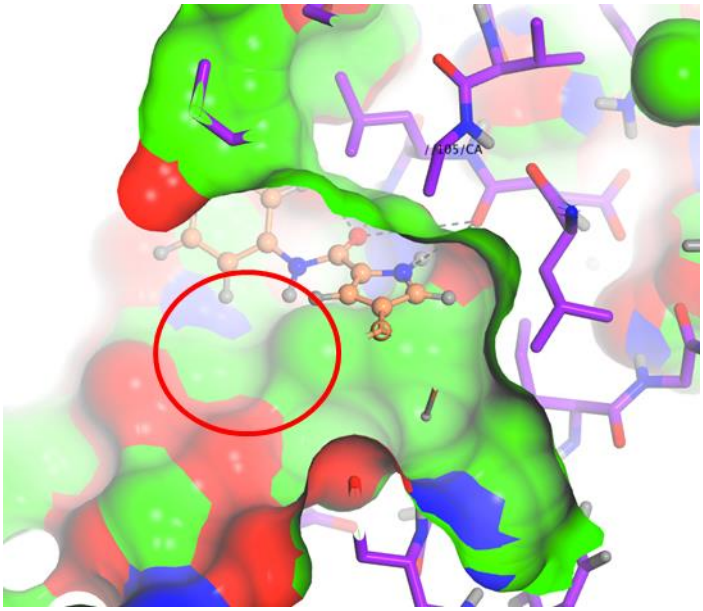
Category	Parameter	Pre-clinical candidate
Physicochemical properties	Molecular weight (MW)	< 500
	sLogP	< 5
	TPSA ($Å^2$)	75-100
	H bond donors	< 5
	H bond acceptors	< 10
***In Vitro* pharmacology**	ERK5; IC_{50} (nM)	< 10
	LE *	> 0.3
	Selectivity	> 100-fold
	Cellular ERK5; IC_{50} (nM)	< 100
	hERG; IC_{50} (µM)	> 25
***In Vitro* ADME**	Solubility L/U (µM) **	> 50/50
	PPB (%) ***	< 99
	Mouse liver microsomal (MLM) clearance (µL/min/mg)	< 48
	Human liver microsomal (HLM) clearance (µL/min/mg)	< 48
	Caco-2 A2B Papp (x 10^{-6} cm/s) / Efflux Ratio	> 10 /< 2
	CYP1A, CYP2C19, CYP2C9, CYP2D6, CYP3A4; IC_{50} (µM)	All >10
***In Vivo* DMPK**	Clearance (mL/mg/kg)	< 30
	Vdss (L/kg)	> 1
	Bioavailability (F) (%)	> 30
	$t_{1/2}$ Mouse (h)	> 1

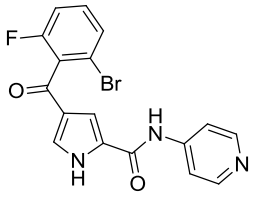
* LE = ΔG/HAC (where ΔG = -1.4 logIC_{50}); ** L/U = Lower bound/Upper bound solubility range; *** PPB in human

Chapter 6. Accessing a Lipophilic Pocket Identified from the p38α-Derived Homology Model

6.1. Rationale

A small lipophilic pocket, close to the ribose pocket, was identified in the p38α-derived homology model (Figure 6.1). Small alkyl substituents have been used in other drug discovery projects to exploit pockets located in a similar region of space.[201, 202]





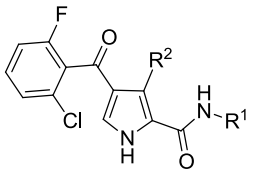
234

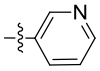
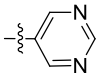
Figure 6.1: Potential lipophilic pocket circled in red, in the p38α-derived homology model

In the pyrrole carboxamide series, it was postulated that alkyl substituents at the 3-position of the pyrrole core could access this pocket and confer increased inhibitory activity. However, substitution at this position was not tolerated and resulted in complete loss of ERK5 inhibition and selectivity over p38α (Table 6.1), indicating that the binding site of ERK5 could not accommodate substituent at this position.[198] This 70-fold reduction of activity could also be explained by a conformational change of the inhibitor caused by the alkyl groups at the 3-position.

The model suggested that this pocket could also be accessed by two alternative modifications, namely alkylation of the amide nitrogen and appending *ortho*-substituents on the heteroaromatic amide side-chain. Exploration of these regions of the template had not previously been undertaken.

Table 6.1: ERK5 and p38α inhibitory activities of 3-substituted pyrroles



Compound	R^1	R^2	ERK5 IC_{50} (μM)[a]	p38α IC_{50} (μM)[a]
232		H	0.58 ± 0.24[b]	93 ± 12
238		Me	40 ± 1	43 ± 2
239		Et	38 ± 1	50 ± 1
236		H	0.40 ± 0.09[b]	> 120
240		Me	69 ± 1	13 ± 2

[a] Determinations ± standard deviation (mean of n = 2 unless otherwise stated); [b] n = 4

Initially small alkyl substituted amides were selected for investigation in order to determine whether tertiary amides would be tolerated and retain ERK5 inhibition. The *N*-methylpiperidine and 3-aminopyridine amide substituents which adopt a different spatial orientation when docked in the ERK5 active site were chosen for investigation. The 2-bromo-6-fluorobenzoyl and the 2-chloro-6-fluorobenzoyl which provide good ERK5 inhibitory activity and selectivity over p38α were incorporated in the target molecules (Figure 6.2). In parallel with this work, Dr Lauren Molyneux identified 3,6-dichloro-2-fluorobenzoyl as an alternative substituent at the pyrrole 4-position which conferred improved ERK5 inhibition relative to the 2,6-dihalogenatedbenzoyl group. A small set of compounds with this new aroyl moiety was then added to the initial list of targets.

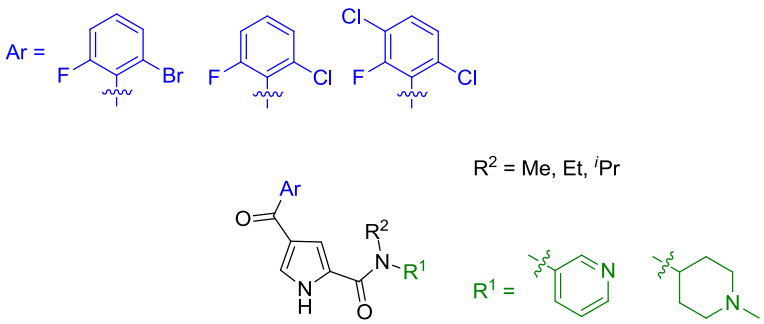


Figure 6.2: Tertiary amides to be synthesised

The orientation of the pyridyl amide ring in the ERK5 binding site being uncertain, substitution of this ring was envisaged at both *ortho* positions. Alkyl, alkoxy and alkylamine substituents were selected for investigation. The variation of the linker should

introduce different flexibility and orientation for these substituents, resulting in a slightly different occupation of space. This should maximise the chance to access the lipophilic pocket. The 2-chloro-6-fluoro and 3,6-dichloro-2-fluoroaroyl rings were incorporated in the target molecules (Figure 6.3).

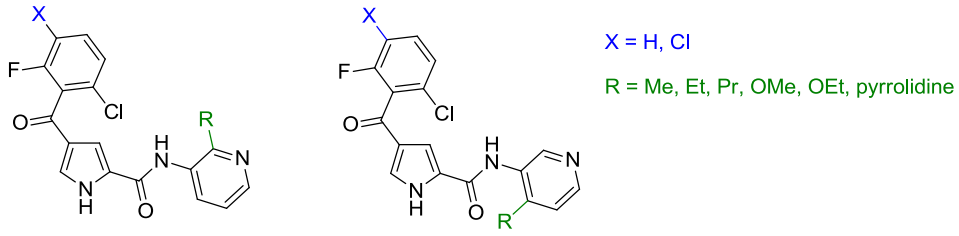
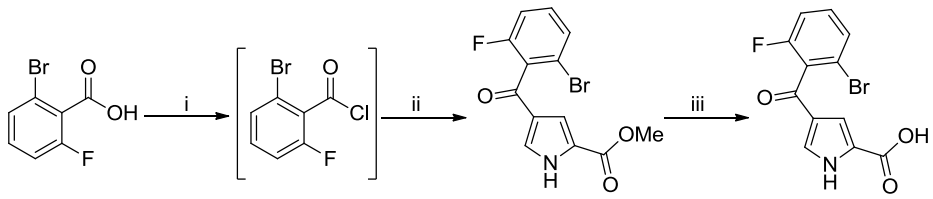


Figure 6.3: *Ortho*-substituted heteroaromatic amides to be synthesised

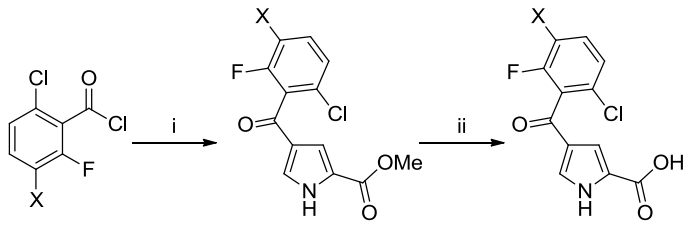
6.2. Synthesis of *N*-alkylated 4-Amino-1-methylpiperidyl and 3-Aminopyridyl Amides

Carboxylic acids **244**, **249** and **250** were key building blocks for the synthesis of amide derivatives. These were prepared in excellent yields following a two step procedure, starting with a Friedel-Crafts acylation of commercially available reagents, followed by basic hydrolysis of the methyl ester (Scheme 6.1 and 6.2). This two step procedure, which had been previously developed within the ERK5 project, was carried out on a large scale.



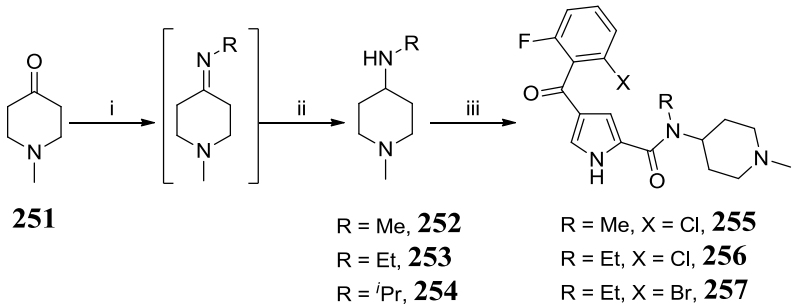
241 **242** **243** **244**

Scheme 6.1: *Reagents and conditions:* (i) $SOCl_2$, DMF, THF, 0 °C to RT, 5 h; (ii) $AlCl_3$, methyl 1*H*-pyrrole-2-carboxylate, 0 °C to RT, 20 h, 96%, (iii) LiOH, H_2O/THF, 67 °C, 18 h, 98%.



Scheme 6.2: *Reagents and conditions:* (i) $AlCl_3$, methyl 1*H*-pyrrole-2-carboxylate, 0 °C to RT, 20 h (**247**, X = H, 96%; **248**, X = Cl, 97%); (ii) LiOH, H_2O/THF, 67 °C, 18 h (**249**, X = H, 93%; **250**, X = Cl, 95%).

Exploration of the amide substitution was achieved through the preparation of secondary 4-aminopiperidine and 3-aminopyridine. *N*-Alkylated 1-methylpiperidines-4-amine can be synthesised by reductive amination from 1-methyl-4-piperidone (**251**).[203] This literature procedure, which uses sodium cyanoborohydride as reducing agent, was implemented (Scheme 6.3). Although the reactions were proceeding well when monitored by LC-MS, the desired amines were only obtained in low to moderate yields. The difficult isolation was caused by the high aqueous solubility and high volatility of these small secondary aliphatic amines.



Scheme 6.3: *Reagents and conditions:* (i) AcOH, $MgSO_4$, methyl-, ethyl-, or *iso*propyl-amine, MeOH, 30 min, RT; (ii) sodium cyanoborohydride, MeOH, 0 °C to RT, 24 h (**252**, R = Me, 9%; **253**, R = Et, 24%, **254**, R = ^{i}Pr, 40%); (iii) **244** or **249**, EDCI.HCl, DMAP, DCM, 0 °C to RT, 24 h (**255**, R = Me, X = Cl, 18%; **256**, R = Et, X = Cl, 20%; **257**, R = Et, X = Br, 22%).

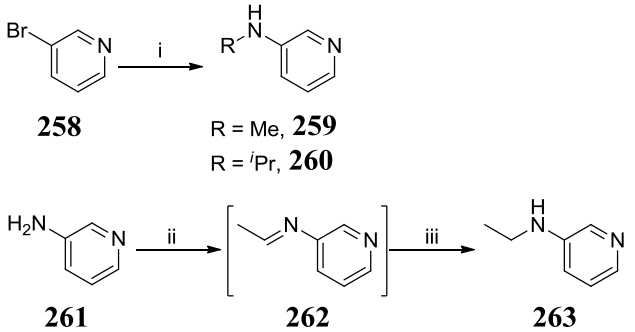
Coupling of 4-amino-1-methylpiperidine has routinely been achieved in the ERK5 project using carbonyldiimidazole (CDI) as the coupling reagent.[197, 198] However, these conditions were unsuccessful with *N*-alkylated 1-methylpipepirines-4-amine **252** - **254** and an array of different coupling conditions had to be investigated (Table 6.2). Among these conditions, only the EDCI-mediated coupling in presence of catalytic DMAP afforded the desired amide targets in high purity.[204] This coupling was low yielding and limited to small alkyl

groups. Indeed, no desired product was isolated using *N-iso*propyl-1-methylpiperidin-4-amine **254**, suggesting that alternative conditions will have to be employed with bulky amines. At this point, biological evaluation of the first set of compounds **255** - **257** indicated that ERK5 inhibitory activity was not retained with tertiary piperidine amides, and, as a result, the synthesis of the remaining targets was ceased.

Table 6.2: Exploration of conditions for the coupling of *N*-alkylated 1-methylpipepirines-4-amine **252** - **254**

#	Conditions	Observation
1	Microwave-assisted PCl_3 coupling	5% of product detected by LC-MS in complex mixture
2	Cyanuric fluoride	Acyl fluoride was formed but did not react with the amine
3	T3P	No reaction
4	EDCI and 2-hydroxypyridine *N*-oxide	No reaction
5	EDCI and HOBt	Complex mixture of products
6	EDCI and DMAP	40% of product detected by LC-MS

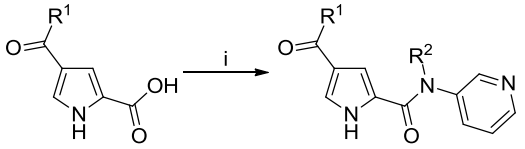
Ullman coupling of 3-bromopyridine (**258**) with methylamine, following literature conditions, afforded *N*-methylpyridin-3-amine (**259**) in a good 80% yield.[205] The same reaction conditions produced *N-iso*propylpyridin-3-amine (**260**) only in 22% yield, emphasising the limitation of this 'green' Ullman coupling methodology developed by Jiao *et al.* (Scheme 6.4).[205] Synthesis of *N*-ethylpyridin-3-amine (**263**) was achieved *via* reductive amination of 3-aminopyridine (**261**) with acetaldehyde in trifluoroethanol (Scheme 6.4).[206]



Scheme 6.4: *Reagents and conditions:* (i) methyl- or *iso*propyl-amine, H_2O, Cu, 100 °C, 24 h (**259**, R = Me, 80%; **260**, R = ^{i}Pr, 22%); (ii) acetaldehyde, $MgSO_4$, trifluoroethanol, 1 h, RT; (iii) $NaBH_4$, trifluoroethanol, 0 °C to RT, 1 h, 67%.

A previous investigation of amide coupling conditions of aromatic heterocyclic amines to carboxylic acids **244** and **249** conducted in the ERK5 project led to the identification of a PCl_3 microwave-assisted coupling as optimal.[198] This methodology was originally developed by Colombo *et al.* for the coupling of electron-poor amines.[207] The PCl_3-mediated coupling was successfully implemented with *N*-alkylated 3-aminopyridines **259**, **260**, **263** and afforded the target compounds in good yields (Table 6.3).

Table 6.3: Summary of yields for the PCl_3-mediated amide coupling; *Reagents and conditions:* (i) *N*-alkylated 3-aminopyridine, PCl_3, MeCN, 150 °C, µW, 7 min.

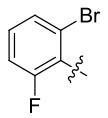
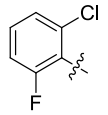
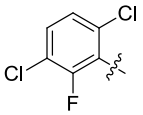


R^1 =  , **244**

R^1 =  , **249**

R^1 =  , **250**

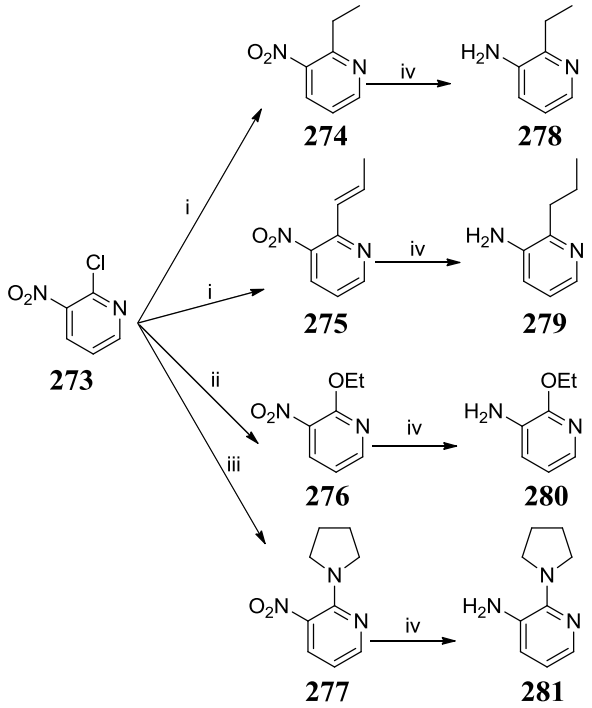
264 - 272

R^1	R^2	Yield
	Me	**264**, 62%
	Et	**265**, 50%
	^{i}Pr	**266**, 55%
	Me	**267**, 60%
	Et	**268**, 40%
	^{i}Pr	**269**, 50%
	Me	**270**, 42%
	Et	**271**, 60%
	^{i}Pr	**272**, 62%

6.3. Synthesis of 3-Aminopyridyl Amides Bearing Substituent at the 2- or 4-Position

The strategy employed for the synthesis of *ortho*-substituted amides was to prepare the requisite aminopyridines from 2-chloro-3-nitropyridine (**273**) or 4-chloro-3-nitropyridine (**293**). When the desired 3-aminopyridine was commercially available at an acceptable price, the reagent was purchased and directly coupled to pyrrole carboxylate **249** and **250**. Suzuki-Miyaura cross-coupling was used to introduce alkyl substituents at the 2-position

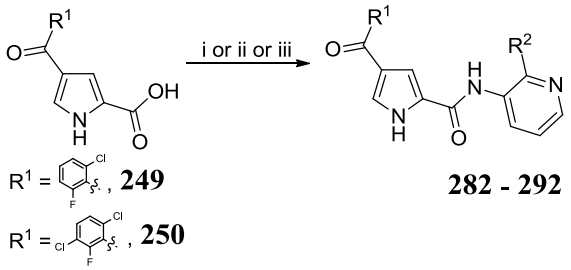
of the pyridyl ring (Scheme 6.5).[208] Interestingly, the allyl group isomerised during the reaction to form the more substituted and conjugated alkene (*E*)-bond of compound **275**. S_NAr reactions were performed to obtain **276** and **277** in high yields.[209] The 2-substituted-3-nitropyridines **274** - **277** were cleanly reduced *via* palladium-catalysed flow hydrogenation (Scheme 6.5).

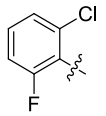
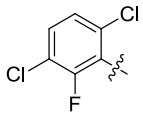


Scheme 6.5: *Reagents and conditions:* (i) K_2CO_3, ethylboronic acid or allylboronic acid pinacol ester, tetrakis(triphenylphosphine)palladium(0), dioxane, 100 °C, 48 h (**274**, 56%; **275**, 53%); (ii) sodium ethoxide, EtOH, RT, 17 h, 62%; (iii) K_2CO_3, pyrrolidine, RT, 17 h, 83%; (iv) H_2, 10% Pd/C, MeOH, 40 °C, 8 h (**278**, 93%; **279**, 90%; **280**, 76%; **281**, 92%).

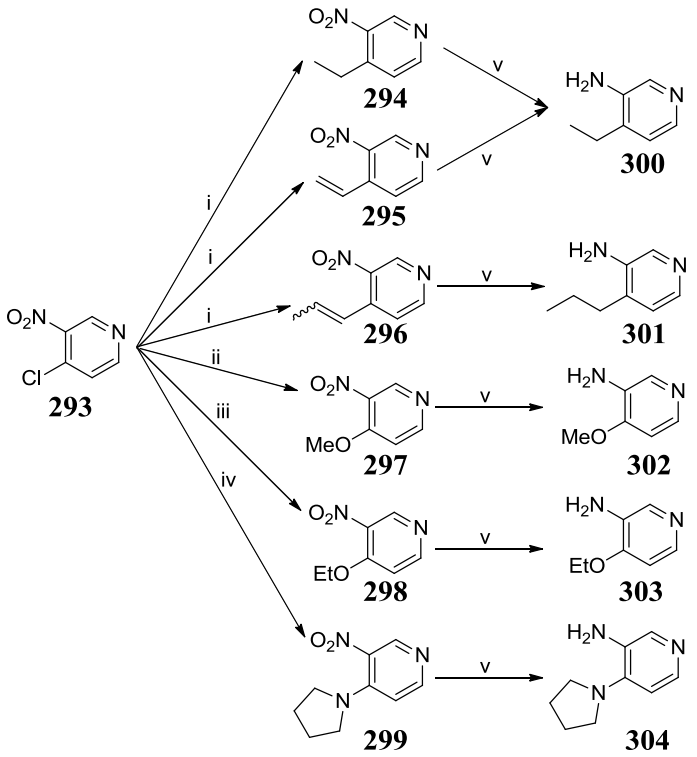
Coupling of the aminopyridines to pyrrole carboxylate **249** and **250** was achieved using three different methodologies (Table 6.4). The PCl_3-mediated amide coupling was optimal for alkyl substituted 3-aminopyridines but resulted in oxygen dealkylation when employed for the coupling of 2-ethoxy- and 2-methoxypyridine-3-amines. For these amines, coupling using cyanuric fluoride allowed isolation of the desired product in moderate to good yields.[210] Coupling of 2-(pyrrolidine-1-yl)pyridine-3-amine (**281**) proved challenging with the acidic PCl_3 and cyanuric fluoride coupling, producing a complex mixture of products. Non acidic conditions using the Mukaiyama pyridinium coupling reagent to activate the acid were applied and led to the isolation of **286** and **292** in moderate yields (Table 6.4).[211]

Table 6.4: Summary of yields for the amide coupling; *Reagents and conditions:* (i) amine, PCl_3, MeCN, 150 °C, µW, 7 min; (ii) pyridine, cyanuric fluoride, MeCN, RT, 30 min then amine, 40 °C, 24 h; (iii) 2-chloro-1-methylpyridinium, NEt_3, side-chain, DCM, 42 °C, 24 h.



R^1	R^2	Coupling conditions	Yield
	Et	PCl_3	**282**, 35%
	^{n}Pr	PCl_3	**283**, 24%
	OMe	Cyanuric fluoride	**284**, 62%
	OEt	Cyanuric fluoride	**285**, 41%
		Mukaiyama	**286**, 31%
	Me	PCl_3	**287**, 63%
	Et	PCl_3	**288**, 41%
	^{n}Pr	PCl_3	**289**, 32%
	OMe	Cyanuric fluoride	**290**, 27%
	OEt	Cyanuric fluoride	**291**, 62%
		Mukaiyama	**292**, 30%

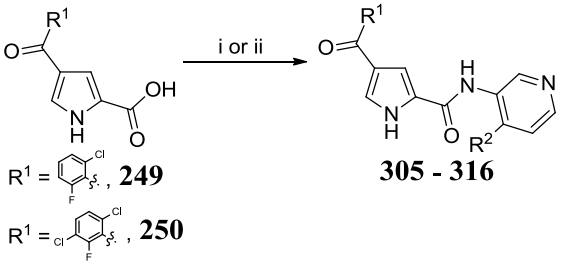
Compounds incorporating the same substituents at 4-position of the pyridyl ring were also prepared. A similar reaction sequence to that described for the preparation of 2-substituted-3-aminopyridine was employed (Scheme 6.6). Suzuki-Miyaura cross-couplings on 4-chloro-3-nitropyridine (**293**) produced more complicated mixtures of products with dehalogenation being observed. However, this did not prevent the isolation of the target products in high purity and moderate yields. Displacement of the 4-chloro group with sodium methoxide, sodium ethoxide and pyrrolidine proceeded at room temperature to give **297**, **298** and **299**. Hydrogenation was achieved in an analogous manner as previously described. Reduction of the nitro group and the alkene bound of **295** and **296** was achieved in a single process (Scheme 6.6).

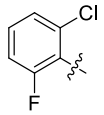
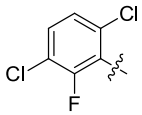


Scheme 6.6: *Reagents and conditions:* (i) K_2CO_3, ethylboronic acid, vinyl boronic acid or allylboronic acid pinacol ester, tetrakis(triphenylphosphine)palladium(0), dioxane, 100 °C, 48 h (**294**, 50%; **295**, 41%; **296**, 35%); (ii) NaOMe, MeOH, RT, 17 h, 84%; (iii) NaOEt, EtOH, RT, 17 h, 76%; (iv) K_2CO_3, pyrrolidine, RT, 17 h, 91%; (v) H_2, 10% Pd/C, MeOH, 40 °C, 8 h (**300**, 80 - 82%; **301**, 87%; **302**, 91%; **303**, 93%; **304**, 97%).

To complete the synthesis of the *ortho*-substituted pyridyl amide targets, aminopyridine intermediates **300** - **304** were coupled to pyrrole carboxylic acids **249** and **250**. The PCl_3-mediated protocol was employed for the alkyl substituted aminopyridines whereas an amended Mukaiyama procedure, free of base, was required for the other amines (Table 6.5). This alternative procedure significantly reduced the amount of side reactions detected under a range of other coupling conditions. It is assumed that electron-donating groups at the 4-position of the pyridyl ring increased the reactivity of the pyridyl nitrogen, which competed with the amino group in the coupling. In the absence of base, the pyridyl nitrogen gets protonated and the coupling takes place *via* the amino group.

Table 6.5: Summary of yields for the coupling step; *Reagents and conditions:* (i) amine, PCl_3, MeCN, 150 °C, µW, 7 min; (ii) 2-chloro-1-methylpyridinium, amine, DCM, 42 °C, 24 h.



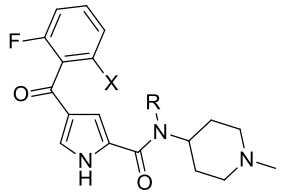
R^1	R^2	Coupling conditions	Yield
	Me	PCl_3	**305**, 65%
	Et	PCl_3	**306**, 61%
	^{n}Pr	PCl_3	**307**, 48%
	OMe	Amended Mukaiyama	**308**, 14%
	OEt	Amended Mukaiyama	**309**, 21%
		Amended Mukaiyama	**310**, 23%
	Me	PCl_3	**311**, 62%
	Et	PCl_3	**312**, 48%
	^{n}Pr	PCl_3	**313**, 41%
	OMe	Amended Mukaiyama	**314**, 5%
	OEt	Amended Mukaiyama	**315**, 13%
		Amended Mukaiyama	**316**, 34%

6.4. SARs and Biological Evaluation of *N*-Alkylated Amides and 3-Aminopyridyl Amides with Substituent at the 2- or 4-Position

The ERK5 inhibitory activity and p38α counterscreening data for compounds **255 - 257** are presented in Table 6.6 and should be compared to the secondary amide derivatives **233** and **317**. In each case, ERK5 inhibition was reduced by at least 10-fold, with the largest alkyled amides being the least active. Substitution of the amide NH in this series did not produce compounds with improved selectivity for ERK5 over p38α (Table 6.6).

In the pyridyl series, alkylation of the amide NH also reduced ERK5 binding affinity, independently of the aroyl substituents (Table 6.7). Interestingly, compounds **266** and **269** retained good ERK5 inhibitory activity, suggesting that inhibitors with large amide substituents maintain good affinity for ERK5 with a possible alternative binding mode. However, compound **269** inhibited p38α with an IC_{50} value of 5.5 μM, demonstrating that ERK5 selectivity would be difficult to achieve with such tertiary amides.

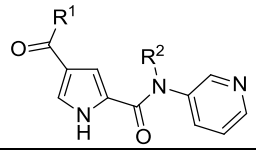
Table 6.6: ERK5 and p38α inhibitory activities of *N*-alkylated 1-methylpiperidyl amides

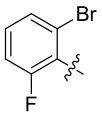
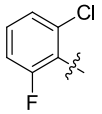
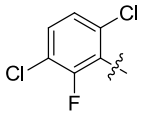


Compound	X	R	ERK5 IC_{50} (μM)[a]	p38α IC_{50} (μM)[a]
233 *	Cl	H	0.19 ± 0.07[b]	8.5 ± 0.2
255		Me	2.5 ± 0.4	*n.d.*
256		Et	3.7 ± 0.8	22.0 ± 1.4
317 *	Br	H	0.29 ± 0.12[c]	11.2 ± 0.2
257		Et	4.9 ± 0.9	38.5 ± 5.2

[a] Determinations ± standard deviation (mean of n = 2 unless otherwise stated); [b] n = 4; [c] n = 8;
* compound prepared by Dr Stephanie Myers; *n.d.* = not determined

Table 6.7: ERK5 and p38α inhibitory activities of *N*-alkylated 3-aminopyridyl amides

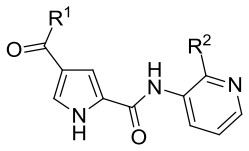


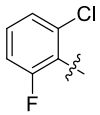
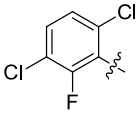
Compound	R^1	R^2	ERK5 IC_{50} (μM)[a]	p38α IC_{50} (μM)[a]
231 *		H	0.82 ± 0.01[b]	> 120
264		Me	4.5 ± 1.0	> 120
265		Et	2.1 ± 0.1	34.2 ± 0.1
266		^{i}Pr	1.1 ± 0.5[d]	*n.d.*
232 *		H	0.58 ± 0.24[b]	93.2 ± 12.5
267		Me	3.3 ± 1.0	54.7 ± 3.3
268		Et	1.3 ± 0.4	17.0 ± 1.1
269		^{i}Pr	0.98 ± 0.25[b]	5.5 ± 0.2
318 **		H	0.066 ± 0.033[c]	>120
270		Me	4.4 ± 0.1	*n.d.*
271		Et	1.8 ± 0.1	*n.d.*
272		^{i}Pr	2.2 ± 0.1	*n.d.*

[a] Determinations ± standard deviation (mean of n = 2 unless otherwise stated); [b] n = 4; [c] n = 7; [d] n = 8; * compound prepared by Dr Stephanie Myers; ** compound prepared by Dr Lauren Molyneux; *n.d.* = not determined

In both series, independently of the aroyl substitution pattern, the best results were always obtained with a non-alkylated amide. These results demonstrate that alkyl groups on the amide nitrogen might not access the pocket identified in the p38α-derived homology model. These groups probably clash with the protein ATP-binding domain wall, leading to a significant loss of inhibitory activity. These alkyl groups might also induce a twist of the amide-pyrrole bond and lead to a reduced interaction between the amide carbonyl and the hinge region of the kinase.

Table 6.8: ERK5 inhibitory activity of 2-substituted 3-aminopyridyl amides

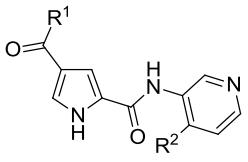


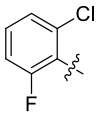
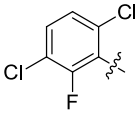
Compound	R^1	R^2	ERK5 IC_{50} (μM)[a]
232 *		H	0.58 ± 0.24[b]
319		Me	0.96 ± 0.16[b]
282		Et	1.6 ± 0.2
283		^{n}Pr	5.3 ± 1.5
284		OMe	2.8 ± 0.7
285		OEt	5.9 ± 0.1
286			8.0 ± 1.4
318 **		H	0.066 ± 0.033[c]
287		Me	0.39 ± 0.20[d]
288		Et	1.0 ± 0.2
289		^{n}Pr	3.5 ± 1.6
290		OMe	1.2 ± 0.1
291		OEt	6.1 ± 1.8
292			12.2 ± 2.7

[a] Determinations ± standard deviation (mean of n = 2 unless otherwise stated); [b] n = 4; [c] n = 7; [d] n = 6; * compound prepared by Dr Stephanie Myers; ** compound prepared by Dr Lauren Molyneux

The ERK5 inhibitory activity data for compounds **282 - 292** and **300 - 316** are presented in Table 6.8 and 6.9, and should be compared to the unsubstituted pyridyl amides **232** and **318**. All the substituents introduced at the *ortho* positions of the pyridyl ring induced a significant reduction of ERK5 inhibition. In the 2-chloro-6-fluorobenzoyl series, although the methyl group was tolerated, any larger substituent led to a significant reduction of ERK5 binding affinity. Inhibitory activity data are similar for compounds with identical substituents at the 2- or the 4-position of the pyridyl ring.

Table 6.9: ERK5 inhibitory activity of 4-substituted 3-aminopyridyl amides



Compound	R^1	R^2	ERK5 IC_{50} (μM)[a]
232 *		H	0.58 ± 0.24[b]
305		Me	1.3 ± 0.5[d]
306		Et	2.1 ± 0.5
307		^{n}Pr	3.3 ± 0.6
308		OMe	2.2 ± 0.1
309		OEt	2.3 ± 0.5
310			16.5 ± 6.6
318 **		H	0.066 ± 0.033[c]
311		Me	0.41 ± 0.22[d]
312		Et	1.2 ± 0.8
313		^{n}Pr	2.8 ± 0.8
314		OMe	1.0 ± 0.1
315		OEt	1.4 ± 0.4
316			8.7 ± 2.9

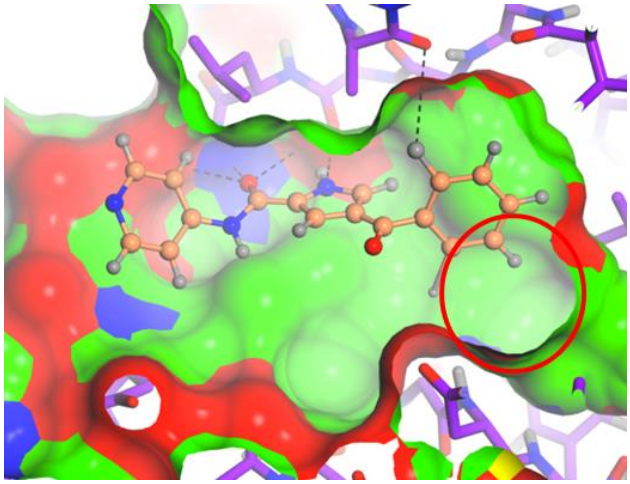
[a] Determinations ± standard deviation (mean of n = 2 unless otherwise stated); [b] n = 4; [c] n = 7; [d] n = 6; * compound prepared by Dr Stephanie Myers; ** compound prepared by Dr Lauren Molyneux

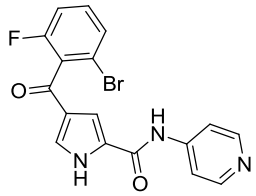
Independently of the aroyl substitution pattern, the best ERK5 inhibition values were observed with an unsubstituted pyridyl ring. These results demonstrate that substituents at the *ortho* position of the heteroaromatic ring might not access the pocket identified in the p38α-derived homology model. *Ortho*-substituents probably clash with the protein ATP-binding cleft wall, leading to a significant loss of inhibitory activity. The relatively modest potency of compounds **282** - **292** and **300** - **316** compared with the parent unsubstituted ERK5 inhibitors **232** and **318** militate against further optimisation at these positions of the pyrrole carboxamide scaffold.

Chapter 7. Structure-Activity Relationship Studies around the *Meta* Position of the Benzoyl Ring

7.1. Rationale

Examination of compound **234** modelled in the ERK5 ATP-binding site from the p38α-derived homology model led to the identification of a putative pocket highlighted in Figure 7.1. This resulted in the design of a new set of potential ERK5 inhibitors, incorporating a third substituent at the 3-position of the aroyl ring, which could improve binding interactions with the ATP-binding domain of ERK5.



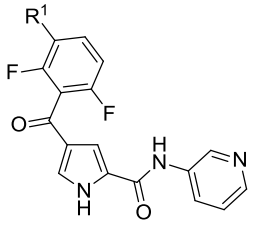


234

Figure 7.1: Docking of compound **234** in the p38α-derived homology model with potential pocket to be exploited in red.

Exploration of this area of the template had been previously explored by other members of the ERK5 project (Dr Stephanie Myers, Dr Lauren Molyneux and Amy Heptinstall).[197, 198] To initially test the hypothesis, a variety of small *meta*-substituents (F, Cl, Me, Et and vinyl) were introduced on a 2,6-difluoroaroyl motif to target the putative hydrophobic pocket. The preliminary results indicated that addition of a substituent at the 3-position of the benzoyl ring was tolerated and in most cases improved potency (Table 7.1).[197, 198] For instance, introduction of a *meta*-chlorine resulted in a 3.5-fold inhibition improvement, with compound **322** having an IC_{50} of 0.29 μM. These positive results suggested that further SARs around the 3-position of the aroyl ring could be beneficial.

Table 7.1: ERK5 inhibitory activity of *meta*-substituted difluoroaroyl pyrroles

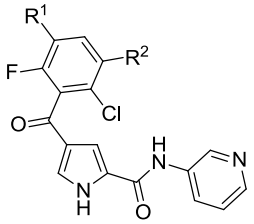


Compound	R^1	ERK5 IC_{50} (μM)[a]
320	H	1.1 ± 0.27[b]
321	F	0.40 ± 0.11
322	Cl	0.29 ± 0.11
323	Me	0.66 ± 0.27[b]
324	Et	1.3 ± 0.15
325	vinyl	1.6 ± 0.34[c]

[a] Determinations ± standard deviation (mean of n = 4 unless otherwise stated); [b] n = 6; [c] n = 2

With the hypothesis validated, it was then decided to incorporate the best *meta*-substituents identified from the initial study on the 2-chloro-6-fluorobenzoyl motif, which exhibited improved potency relative to the 2,6-difluorobenzoyl moiety, as discussed in section 5.2. Since the position of the two halogens on the aroyl ring was difficult to predict using docking software, two series of analogues were prepared for each *meta*-substituent (Table 7.2). Direct matched pair analysis of these inhibitors was expected to reveal whether the group at the 3-position had to be introduced adjacent to the fluorine or to the chlorine.

Table 7.2: ERK5 inhibitory activity of *meta*-substituted 2-chloro-6-fluoroaroyl pyrroles



Compound	R^1	R^2	ERK5 IC_{50} (μM)[a]
232	H	H	0.58 ± 0.24
326	F	H	0.71 ± 0.31
318	Cl	H	0.066 ± 0.033[b]
327	Me	H	0.51 ± 0.28[c]
328	Br	H	0.066 ± 0.026
329	H	F	1.0 ± 0.28
330	H	Cl	0.26 ± 0.10[d]
331	H	Me	0.65 ± 0.37[e]

[a] Determinations ± standard deviation (mean of n = 4 unless otherwise stated); [b] n = 7; [c] n = 8; [d] n = 9; [e] n = 6

Interestingly, modification of the *meta* position of inhibitor **232** mainly produced compounds with similar activities, with the exception of compounds **318** and **330** which

incorporate a *meta*-chlorine (Table 7.2). Inhibitor **318** exhibited a sharp increase in ERK5 inhibitory activity with an almost 9-fold improvement relative to **232**. It was the first pyrrole carboxamide inhibitor with an IC_{50} value below 100 nM. Comparison of the inhibitory activities of **318** and **330** suggested that the *meta*-substitution was more beneficial when introduced adjacent to the fluorine.

To explain the increase in ERK5 inhibition, Dr Susan Boyd at Cancer Research Technology Discovery Laboratories docked compound **318** in the ATP-binding site of ERK5 from the published protein co-crystal structure (PDB code 4b99) using the GOLD docking program (Figure 7.2 A). The model shows that the trihalogenated ring fits nicely in the back pocket of the ATP-binding domain and that the pyrrole NH and the amide carbonyl form two hydrogen bonds with the hinge region of the kinase (Figure 7.2 B). The *meta*-chlorine is positioned ideally to make a halogen bond with the backbone carbonyl oxygen of Asn189 (Figure 7.2 B). The chlorine-oxygen distance is 3.6 Å with the two atoms positioned in a "head on" fashion, which could lead to a low affinity halogen bond. Optimal halogen-oxygen distance in classical halogen bonds is about 3.0 Å and deviations from it reduce the attractive overlap of the electron-deficient σ-hole with the lone-pair of the carbonyl.[212]

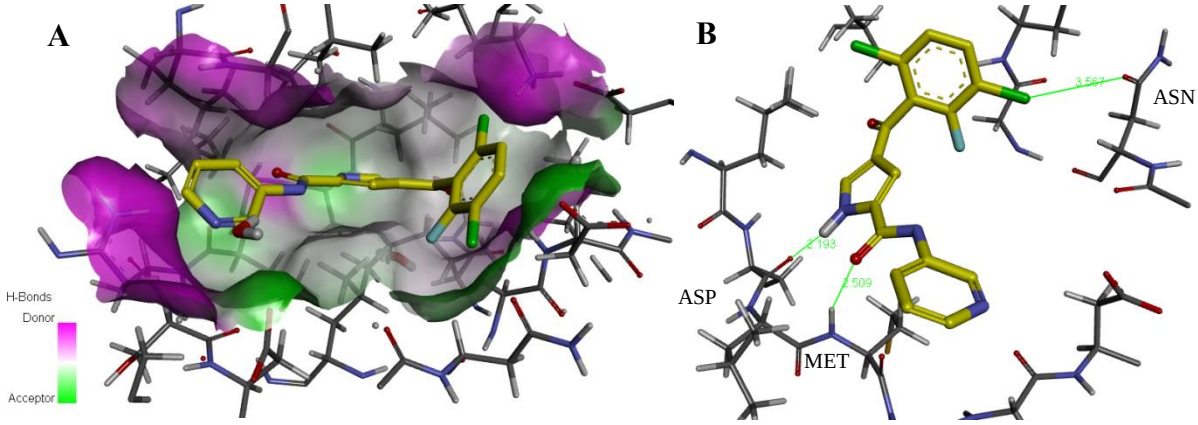


Figure 7.2: A) Modelling of **318** in the ATP-binding site of ERK5 (PDB code 4b99); B) Potential interactions between the inhibitor and the kinase.

To confirm the hypothesis that the *meta*-chlorine could form a halogen bonding interaction with a backbone carbonyl, the matched pair analogue of **318** incorporating a bromine at the 3-position of the benzoyl moiety was synthesised. Bromines have a larger σ-hole and classically lead to an increase in halogen bond strength.[213] Compound **328** retained ERK5 inhibition with an IC_{50} of 66 nM. The identical ERK5 inhibition of **328** relative to **318** did not allow to conclude whether the *meta*-halogen was involved in halogen bonding

interactions with the protein. A co-crystal structure of inhibitor **318** and ERK5 will be required to answer this question.

In the EGF-stimulated HeLa cellular assay, compound **318** showed only a 3-fold reduction in potency, having a mean IC_{50} value of 0.19 μM from three independent experiments. This inhibitor was then selected for *in vitro* ADME assessment and showed medium clearance in mouse and human liver microsomes, high flux and no efflux in the Caco-2 assay, and poor solubility (Table 7.3). Incorporation of the *meta*-chlorine increased the clogP and reduced the topological polar surface area (tPSA), resulting in lower solubility.[214] Oxidative dehalogenation by cytochrome P450s might cause the medium metabolic turnover of compound **318**.[215]

Table 7.3: Physicochemical and *in vitro* ADME data for **318**

MW	**clogP**	**tPSA** Å^2	**Sol** (μM)	**HLM** **Cl_{int}**[a]	**MLM** **Cl_{int}**[a]	**Caco-2 AB**[b] **(ER)**
378	3.8	75	10-65	32	47	25 (0.7)

[a] μL/min/mg protein; [b] P_{app} 10^{-6} cm.s^{-1}

Despite these non-optimal ADMET properties, **318** was progressed to an *in vivo* pharmacokinetic study in mouse (Table 7.4). The compound had high plasma protein binding and low total plasma clearance, with a hepatic extraction ratio of approximately 10%. The unbound clearance was high, consistent with the metabolic instability detected in mouse liver microsomes. The volume of distribution was low for a compound with a weakly basic centre, and the half-life was acceptable. The moderate oral bioavailability of the compound is not consistent with the good absorption predicted in the Caco-2 assay and the low total plasma clearance. This implies that **318** suffered impairment of absorption ($F_{abs} \approx 30\%$) probably due to the poor solubility of the compound.

Table 7.4: *In vivo* pharmacokinetic parameters for **318**. Dose 10 mg/kg *i.v.* and *p.o.*

F_u	**Cl** mL/min/kg	**Cl_u** mL/min/kg	**V_d** L/kg	**$t_{1/2}$** min	**F** %
0.02	11	550	0.3	103	24

The data presented in Table 7.3 and 7.4 demonstrated the necessity to identify an alternative *meta*-substituent which could retain the high biochemical and cellular inhibitory activities of **318**, and improve the physicochemical and pharmacokinetic properties of the compound.

7.2. Introduction of a Methoxy Group at the *Meta* Positions of the 2-Chloro-6-fluorobenzoyl Moiety

7.2.1. Rationale

Introduction of the ethyl group on the difluoro benzoyl moiety did not lead to any potency gain. Simple ethylbenzene favours a conformation where the ethyl group is twisted at 90 degrees to the plane of the ring.[216] For this group to twist out of this orientation by more than 30 degrees, there is a calculated 2 kcal/mol energy penalty which could equate to a significant potency loss and might offset any gain from lipophilic binding. Small-molecule crystal structures in the Cambridge Structural Database also support the out of plane arylethyl conformation as being favoured. The methoxy group of anisole has a strong preference for sitting in the plane of the ring, positioning the methyl group in a different region of space to the methyl in ethylbenzene.[217] The preferred conformation of *ortho*-substituted anisoles is a planar anti form, whereas the minor conformation is a non-planar form with the methyl group rotated toward the *ortho*-substituent.[218-220] This alternative minor conformer is only formed under UV irradiation and only small amount of it is expected to exist under normal conditions. Incorporation of a *meta*-methoxy group would therefore allow exploration of a different direction to that explored with the ethyl analogue and would provide further information regarding the torsion angle and the size of groups tolerated at this position.

It was decided to incorporate the 3-methoxy substituent on the 2-chloro-6-fluoroaroyl moiety with 3-aminopyridyl, 5-aminopyrimidyl and 4-amino-*N*-methylpiperidyl amide side-chains (Figure 7.3). At the time of synthesis, these side-chains combined optimal properties in terms of potency, aqueous solubility and reduced CYP450 inhibitory activity.

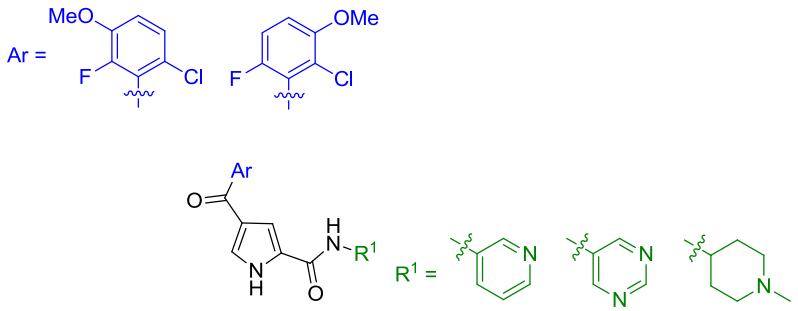
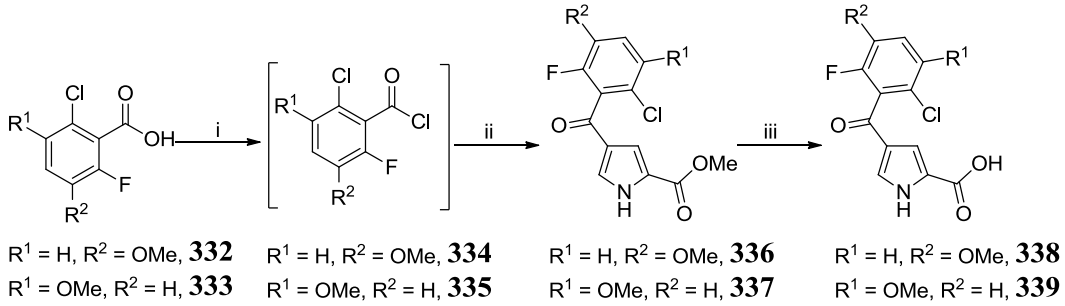


Figure 7.3: 3-Methoxy-substituted aroyl targets to be synthesised

7.2.2. Synthesis

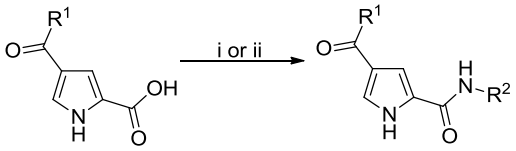
Preparation of the *meta*-methoxyaroyl carboxylic acid intermediates was achieved using procedures previously developed and optimised in the ERK5 project. The synthesis started with the thionyl chloride mediated conversion of commercially available carboxylic acids **332** and **333** to the corresponding acyl chlorides **334** and **335**, which were engaged in a Friedel-Crafts acylation with methyl pyrrole-2-carboxylate to give **336** and **337** in good yields, with minimum demethylation observed. Methyl ester hydrolysis was achieved under basic conditions and afforded pure carboxylic acids **338** and **339** in excellent yields (Scheme 7.1).



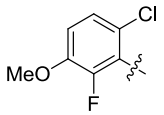
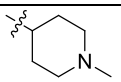
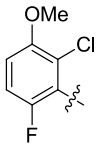
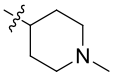
Scheme 7.1: *Reagents and conditions:* (i) $SOCl_2$, DMF, THF, 0 °C to RT, 5 h; (ii) $AlCl_3$, methyl 1*H*-pyrrole-2-carboxylate, 0 °C to RT, 20 h (**336**, R^1 = H, R^2 = OMe, 81%; **337**, R^1 = OMe, R^2 = H, 60%), (iii) LiOH, H_2O/THF, 67 °C, 18 h (**338**, R^1 = H, R^2 = OMe, 97%; **339**, R^1 = OMe, R^2 = H, 93%).

Coupling of 4-amino-1-methylpiperidine has routinely been achieved in the ERK5 project using carbonyldiimidazole (CDI) as the coupling reagent and was successfully employed in this instance (Table 7.5).[197, 198] PCl_3-mediated coupling was used with electron-poor heteroaromatic amines and afforded compounds **341**, **342**, **344** and **345** in low to good yield (17 - 72%). The yields were relatively low for the pyrimidyl amides due to difficulties in isolating the product from close-running impurities.

Table 7.5: Summary of yields for the amide coupling; *Reagents and conditions:* (i) CDI, 4-amino-1-methylpiperidine, THF, 70 °C, 3 h; (ii) 3-aminopyridine or 5-aminopyrimidine, PCl_3, MeCN, 150 °C, µW, 7 min.



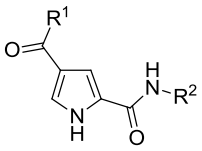
338, **339** **340 - 345**

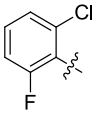
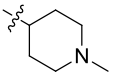
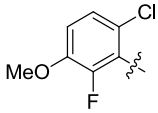
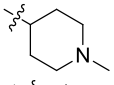
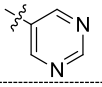
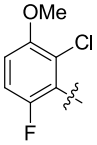
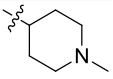
R^1	R^2	Yield
		**340**, 64%
		**341**, 56%
		**342**, 17%
		**343**, 51%
		**344**, 72%
		**345**, 22%

7.2.3. SARs and Biological Evaluation

The ERK5 inhibitory activity data for compounds **340** - **345** are presented in Table 7.6 and should be compared to the 2-chloro-6-fluoroaroyl inhibitors **232**, **233** and **236**.

Table 7.6: ERK5 inhibitory activity of *meta*-methoxyaroyl inhibitors



Compound	R^1	R^2	ERK5 IC_{50} (µM)[a]
233			0.20 ± 0.07
232			0.58 ± 0.24
236			0.40 ± 0.09
340			0.058 ± 0.019[b]
341			0.091 ± 0.037[c]
342			0.20 ± 0.07[b]
343			0.17 ± 0.05
344			0.25 ± 0.05
345			0.43 ± 0.14[b]

[a] Determinations ± standard deviation (mean of n = 4 unless otherwise stated); [b] n = 6; [c] n = 8

Compounds with the methoxy adjacent to fluorine atom exhibited a sharp increase in ERK5 inhibition, with compounds **340** and **341** having sub-100 nM ERK5 IC_{50} values. Introduction of the methoxy next to the chlorine seemed to be less effective and mainly gave compounds with activities similar to their unsubstituted matched pair. Importantly, all of the compounds in this series retained selectivity for ERK5 over p38α. These results suggested that the conformation of the *meta*-substituent was crucial to observe a potency gain. The difference of activity of **340** vs. **343**, and **341** vs. **344** also confirmed the trend observed with the *meta*-chlorine group, i.e. the *meta*-substitution was more beneficial when introduced adjacent to the fluorine.

Despite **340** being the most active of this subset of compounds, it was anticipated that this inhibitor would suffer from high efflux, as previously observed with inhibitors incorporating the *N*-methylpiperidine side-chain. As a result, the second most active compound, inhibitor **341** was selected for *in vitro* ADME studies and showed excellent solubility, low clearance in human liver microsomes, and high flux with no efflux in the Caco-2 assay (Table 7.7). Reduction of the clogP by 0.7 units compared with trihalogenated inhibitor **318** and an increased tPSA contributed to enhance the solubility. However, the *meta*-methoxy introduced another metabolic liability, namely oxygen-demethylation, and compound **341** was very highly cleared in mouse liver microsomes.[221] Interestingly, the microsomal stability of **341** was species-dependent. Owing to its high metabolic turnover, **341** was not progressed to an *in vivo* pharmacokinetic study.

Table 7.7: Physicochemical and *in vitro* ADME data for **341**

MW	**clogP**	**Sol** (μM)	**tPSA** Å^2	**HLM Cl_{int}**[a]	**MLM Cl_{int}**[a]	**Caco-2 AB**[b] **(ER)**
374	3.1	> 100	84	19	137	18 (1.5)

[a] μL/min/mg protein; [b] P_{app} 10^{-6} cm.s^{-1}

The positive results obtained with the 6-chloro-2-fluoro-3-methoxyaroyl pattern provided encouragement, that further elaboration at this position could be beneficial. The objective was to incorporate groups on the oxygen linker with reduced metabolic liability, which could maintain the favourable pharmacokinetic properties of compound **318**. Introduction of larger groups should determine the size of the optimal substituent to fill the lipophilic pocket.

A small set of 3-alkoxy-6-chloro-2-fluoroaroyl targets was proposed (Figure 7.4). Groups of different polarity bearing various spatial conformations were selected. During the course

of the program to optimise the aroyl *meta*-substituent, work in the research group was also being undertaken to investigate the SARs of the amide substituent. A colleague identified 4-amino-1-methylpyrazole as an alternative amide substituent which conferred improved ERK5 inhibition relative to 5-aminopyrimidine and improved ADME properties relative to 4-amino-1-methylpiperidine.[105] This improved amide substituent was therefore selected to be incorporated in the target compounds.

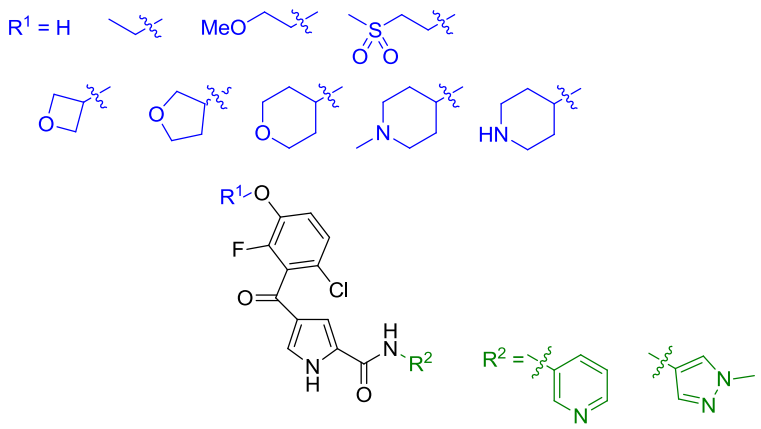
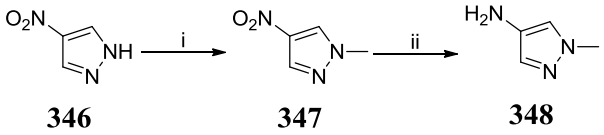


Figure 7.4: 3-Alkoxysubstituted aroyl targets to be synthesised

7.3. Synthesis of Inhibitors Incorporating 3-Alkoxy-6-chloro-2-fluorobenzoyl at the Pyrrole 4-Position

4-Amino-1-methylpyrazole (**348**) was a key building block in the synthesis of this series of compounds. It was prepared on a large scale following a two-step procedure, starting with methylation of commercially available 4-nitropyrazole **346** using dimethyl oxalate under basic conditions as the methylating reagent (Scheme 7.2).[222] This high yielding alkylation procedure prevented the use of classical carcinogenic methylating reagents. Amine **348** was then obtained by catalytic flow hydrogenation of 1-methyl-4-nitropyrazole (**347**).



Scheme 7.2: *Reagents and conditions:* (i) Dimethyl oxalate, KOtBu, DMF, 140 °C, 4 h, 85%; (ii) H_2, 10% Pd/C, MeOH, 40 °C, 8 h, 99%.

In order to explore the *meta* position efficiently, a synthetic route, which would allow late-stage diversification of the *meta* position, was established. Retrosynthetic analysis

suggested that compound **C** was a versatile intermediate, which could be utilised in alkylations or Mitsunobu reactions with alkyl alcohols, giving access to the desired alkoxyaroyl **B** (Figure 7.5). Intermediate **B** could then be converted to the target molecule in two steps, namely ester hydrolysis and amide coupling. This synthetic strategy was expected to be relatively high-throughput and give access to the library of targets in a minimum number of steps.

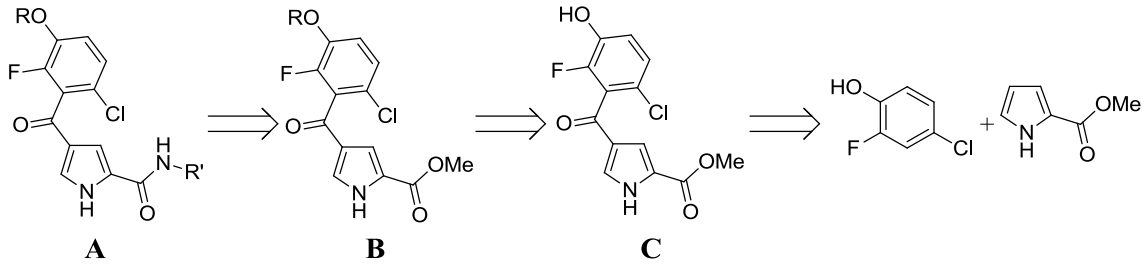
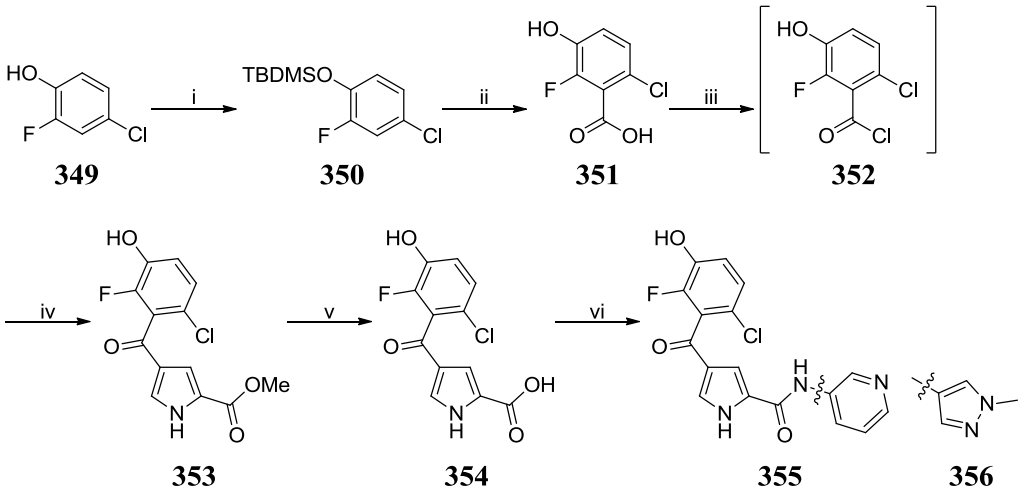


Figure 7.5: Retrosynthetic analysis for the alkoxyaroyl series

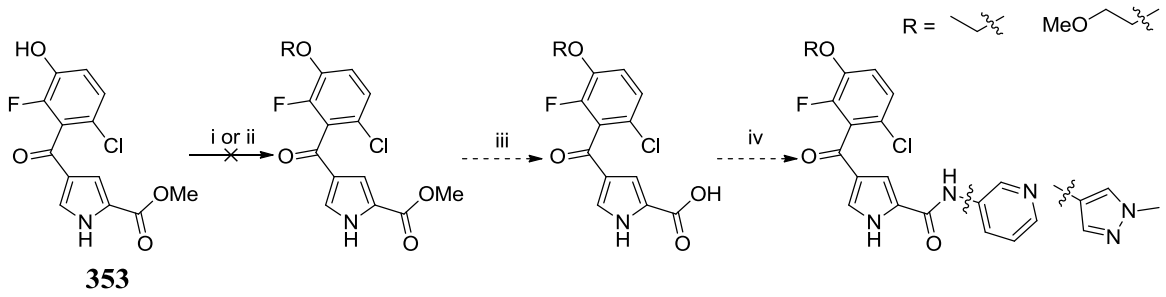
Key intermediate **C** was prepared in 4 steps (Scheme 7.3). Protection of 4-chloro-2-fluorophenol (**349**) with a *tert*-butyldimethylsilyl group was achieved in a very high yield and followed by a lithium-mediated carbonylation.[223] Unexpectedly, during the basic work-up of the reaction, the silyl protecting group was cleaved and compound **351** was isolated in 92% yield. Transformation of carboxylic acid **351** to the corresponding acyl chloride **352** was carried out under dilute conditions to prevent side-reactions. An excess of aluminium trichloride was required for the Friedel-Crafts acylation to occur and **353** was isolated in a moderate 45% yield. Ester hydrolysis was followed by PCl_3-mediated coupling to afford **355** and **356** in moderate yields.



Scheme 7.3: *Reagents and conditions:* (i) TBDMSCl, imidazole, DMF, 0 °C to RT, 18 h, 92%; (ii) a) *n*BuLi (2.4 M in hexane), THF, -78 °C, 30 min; b) CO_2 (dry ice), -78 °C to RT, 1 h; c) 2 M aq. NaOH, RT, 30 min, 92%; (iii) $SOCl_2$, DMF, THF, 0 °C to RT, 5 h; (iv) $AlCl_3$, methyl 1*H*-pyrrole-2-carboxylate, 0 °C to RT, 20 h, 45%; (v) LiOH, H_2O/THF, 67 °C, 18 h, 93%; (vi) 3-aminopyridine or 4-amino-1-methylpyrazole, PCl_3, MeCN, 150 °C, µW, 7 min (**355**, 55%; **356**, 45%).

Ethylation of the hydroxyl group of compound **353** was attempted using iodoethane and potassium carbonate as a base (Scheme 7.4).[224] Unfortunately, these conditions exclusively led to the formation of a dialkylated product, suggesting that the pK_a of the pyrrole NH was lower than predicted. The pK_a of an unsubstituted pyrrole is close to 17.[225] Addition of electron withdrawing groups at the 2- and 4-position of the ring might have reduced the pK_a by 4 or 5 units, allowing partial deprotonation by potassium carbonate. Selective dealkylation of the pyrrole nitrogen was attempted following a literature procedure but proved unsuccessful.[226] When the oxygen alkylation was attempted using milder bases, such as DABCO and pyridine, no conversion was observed.

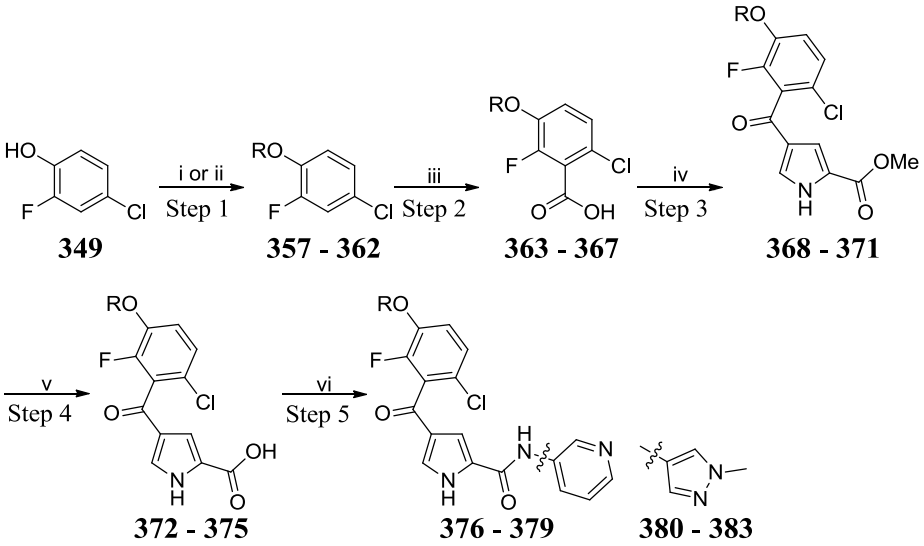
Attempted Mitsunobu reaction of **353** with 2-methoxyethanol led to a complex mixture of products, with evidence by LC-MS analysis of unprotected pyrrole participating in undesired side-reactions (Scheme 7.4).[227] Owing to the lack of success with this initial strategy, an alternative approach had to be considered.



Scheme 7.4: *Reagents and conditions:* (i) K_2CO_3, iodoethane, MeCN, 65 °C, 18 h; (ii) PPh_3, DEAD, 2-methoxyethanol, THF, 0 °C to RT, 24 h; (iii) LiOH, H_2O/THF, 67 °C, 18 h; (iv) 3-aminopyridine or 4-amino-1-methylpyrazole, PCl_3, MeCN, 150 °C, µW, 7 min.

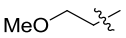
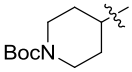
One possible strategy was to repeat the scheme with the pyrrole nitrogen protected. This implied a long synthetic route, with orthogonal protecting groups manipulation and introduction of the diversification after six steps. Mitsunobu reactions are known to be unpredictable on large substrates and its success was still uncertain in this case. A second strategy was to introduce diversification at the first step on 4-chloro-2-fluorophenol (**349**), and then use a 4-steps sequence of previously optimised reactions to access the desired targets (Table 7.8). Although this second approach would have a lower throughput, it appeared to be more robust and reliable, and was subsequently selected for the synthesis of a first set of derivatives. The five steps scheme was applied to the synthesis of a small library of analogues. The yields for each step are summarised in Table 7.8.

Table 7.8: Summary of yields for the five steps synthesis of *meta*-alkoxy derivatives; *Reagents and conditions:* (i) K_2CO_3, iodoethane, MeCN, 65 °C, 18 h; (ii) PPh_3, DEAD, R-OH, THF, 0 °C to RT, 24 h; (iii) a) *n*BuLi (2.4 M in hexane), THF, -78 °C, 30 min; b) CO_2 (dry ice), -78 °C to RT, 1 h; (iv) a) $SOCl_2$, DMF, THF, 0 °C to RT, 5 h; b) $AlCl_3$, methyl 1*H*-pyrrole-2-carboxylate, 0 °C to RT, 20 h; (v) LiOH, H_2O/THF, 67 °C, 18 h; (vi) 3-aminopyridine or 4-amino-1-methylpyrazole, PCl_3, MeCN, 150 °C, µW, 7 min.



349 **357 - 362** **363 - 367** **368 - 371**

372 - 375 **376 - 379** **380 - 383**

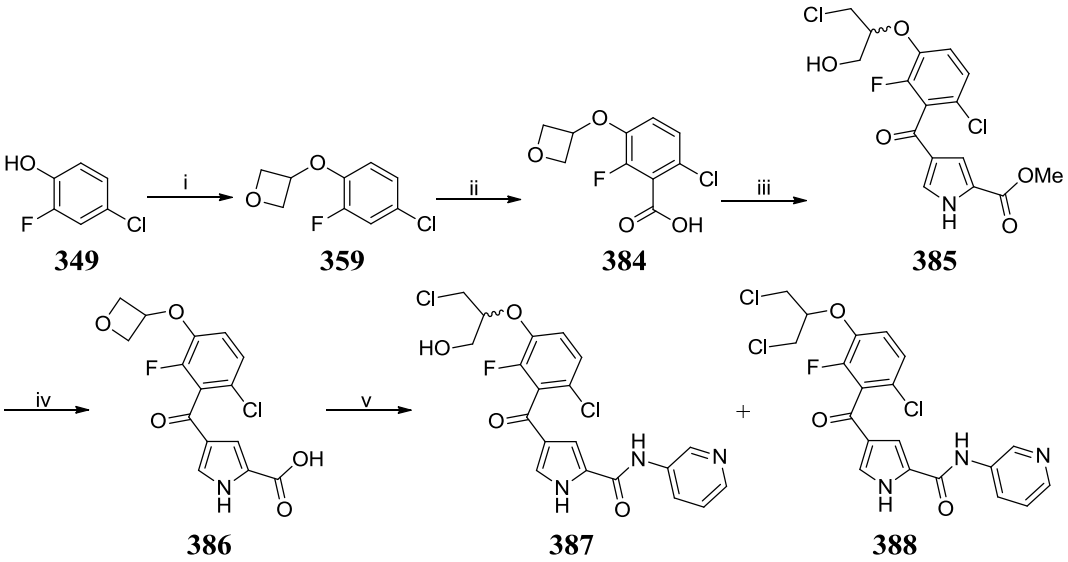
R	Step 1	Step 2	Step 3	Step 4	Step 5
	**357**, 82%	**363**, 97%	**368**, 78%	**372**, 96%	**376**, 60% **380**, 62%
	**358**, 96%	**364**, 84%	**369**, 72%	**373**, 95%	**377**, 66% **381**, 62%
	**359**, 0%	-	-	-	-
	**360**, 96%	**365**, 86%	**370**, 82%	**374**, 96%	**378**, 62% **382**, 38%
	**361**, 95%	**366**, 94%	**371**, 81%	**375**, 96%	**379**, 70% **383**, 59%
	**362**, 83%	**367**, 92%	0%	-	-

As expected, the five step scheme enabled rapid preparation of eight analogues. Mitsunobu reaction of **349** with a range of commercially available alcohols proceeded in very high yields. An array of synthetic transformations was then employed to obtain the desired products, including: carbonylation, Friedel-Crafts acylation, basic ester hydrolysis and PCl_3 coupling with microwave irradiation. All reactions proceeded in good to excellent yields (Table 7.8).

Friedel-Crafts acylation failed with benzoic acid **367**. The *t*-butyl carbamate protecting group was cleaved under the reaction conditions, leading to the formation of multiple by-

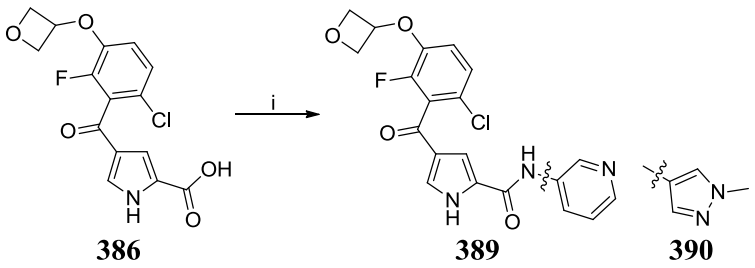
products. Targets incorporating a basic heterocycle will have to be prepared *via* an alternative route.

Reaction of 4-chloro-2-fluorophenol (**349**) with 3-hydroxyoxetane, using the standard Mitsunobu conditions, failed to produce **359**, but intermediate **359** was successfully obtained by increasing the temperature to 67 °C (Scheme 7.5). The oxetane ring of **384** opened in presence of aluminum trichloride during the Friedel-Crafts acylation, leading to the formation of **385** in 68% yield. Interestingly, partial ring closing of the 1-chloro-3-hydroxypropane moiety of **385** was observed under the basic conditions used for the methyl ester hydrolysis. A prolonged reaction time allowed complete conversion to the oxetane ring, resulting in a 74% isolated yield of **386**. Coupling of **386** with 3-aminopyridine using PCl_3 with microwave irradiation led to the formation of two major by-products **387** and **388**, which were isolated in sufficient high purity for biological evaluation (Scheme 7.5).



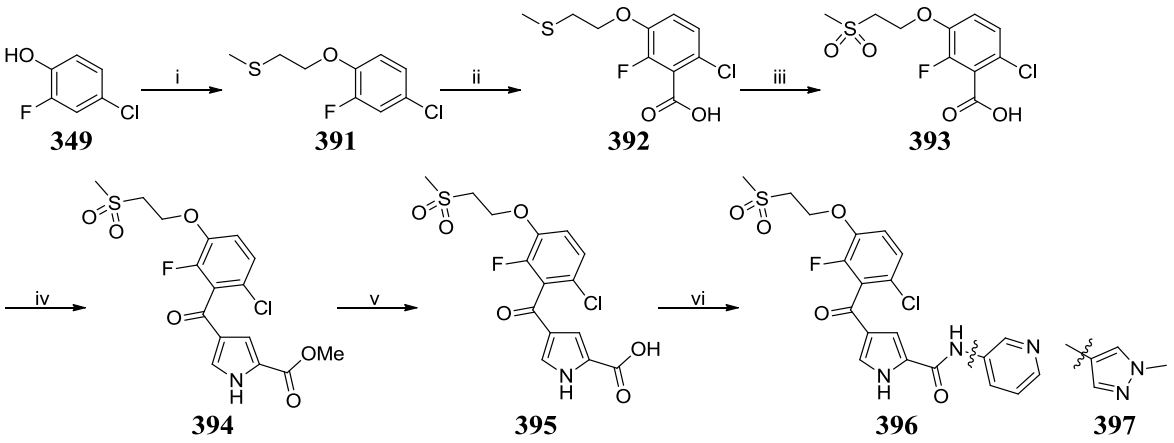
Scheme 7.5: *Reagents and conditions:* (i) PPh_3, DEAD, 3-hydroxyoxetane, THF, 0 °C to reflux, 24 h, 97%; (ii) a) *n*BuLi (2.4 M in hexane), THF, -78 °C, 30 min; b) CO_2 (dry ice), -78 °C to RT, 1 h, 94%; (iii) a) $SOCl_2$, DMF, THF, 0 °C to RT, 5 h; b) $AlCl_3$, methyl 1*H*-pyrrole-2-carboxylate, 0 °C to RT, 20 h, 68%; (iv) LiOH, H_2O/THF, 67 °C, 72 h, 74%; (v) 3-aminopyridine, PCl_3, MeCN, 150 °C, µW, 7 min (**387**, 23%; **388**, 25%).

The milder Mukaiyama coupling conditions allowed isolation of **389** and **390** (Scheme 7.6). However, the overall yield was relatively low due to difficulties in isolating the product from close-running impurities.



Scheme 7.6: *Reagents and conditions:* (i) 2-chloro-1-methylpyridinium, NEt_3, 3-aminopyridine or 4-amino-1-methylpyrazole, DCM, 42 °C, 24 h (**389**, 21%; **390**, 27%).

Synthesis of the targets incorporating the (methylsulfonyl)ethane moiety was achieved using a similar reaction sequence to that described for the synthesis of compounds **376** - **383** (Scheme 7.7). To prevent side-reactions during the carbonylation step, the side-chain was introduced as a thioether, which was subsequently oxidised using Oxone® to give **393** in 89% yield. Friedel-Crafts acylation was followed by acidic hydrolysis of methyl ester **394**. These conditions prevented a retro-Michael addition, observed under the classical basic hydrolysis conditions. PCl_3-mediated coupling led to isolation in moderate yield of the desired products **396** and **397** (Scheme 7.7).

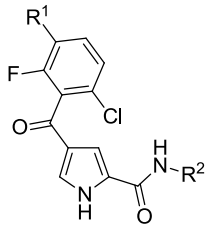


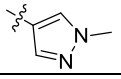
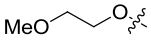
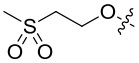
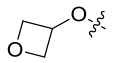
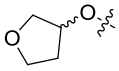
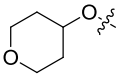
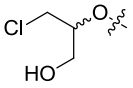
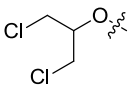
Scheme 7.7: *Reagents and conditions:* (i) PPh_3, DEAD, 2-(methylthio)ethanol, THF, 0 °C to RT, 24 h, 95%; (ii) a) *n*BuLi (2.4 M in hexane), THF, -78 °C, 30 min; b) CO_2 (dry ice), -78 °C to RT, 1 h, 88%; (iii) Oxone®, MeOH, H_2O, RT, 24 h, 89%; (iv) a) $SOCl_2$, DMF, THF, 0 °C to RT, 5 h; b) $AlCl_3$, methyl 1*H*-pyrrole-2-carboxylate, 0 °C to RT, 20 h, 69%; (v) dioxane, 4 M aq. HCl, 65 °C, 70 h, 83%; (vi) 3-aminopyridine or 4-amino-1-methylpyrazole, PCl_3, MeCN, 150 °C, µW, 7 min (**396**, 40%; **397**, 35%).

7.4. SARs and Biological Evaluation of 4-(3-Alkoxy-6-chloro-2-fluorobenzoyl)pyrrole Carboxamide Derivatives

The ERK5 inhibitory activity data of 4-(3-alkoxy-6-chloro-2-fluorobenzoyl)pyrrole carboxamide derivatives are presented in Table 7.9 and should be compared to the 2-chloro-6-fluoroaroyl inhibitors **232** and **398**. The results confirmed that the 4-amino-1-methylpyrazole and 3-aminopyridine amide substituent endowed similar ERK5 activity. Diverse substitution of the aroyl hydroxyl group was found to have little effect on ERK5 inhibitory potency, with the majority of *O*-substituted derivatives having an IC_{50} within 3-fold of **232** and **398**. The (methylsulfonyl)ethoxy moiety (**396** and **397**) was not tolerated and completely abolished binding affinity for ERK5. Smaller groups, such as ethyl (**376** and **380**) or oxetane (**389** and **390**) exhibited improved ERK5 inhibition, similar to the potency of *meta*-methoxy derivatives **340** and **399**. However, these compounds had reduced ligand efficiency relative to **340** and **399**, and did not achieve the IC_{50} threshold of 100 nM, required to trigger generating *in vitro* ADME assessment.

Table 7.9: ERK5 inhibitory activity of *meta*-alkoxyaroyl inhibitors



R^1	ERK5 IC_{50} (μM)[a]	
	R^2 = 	R^2 = 
H	**232**, 0.58 ± 0.24	**398**, 1.0 ± 0.3
OH	**355**, 1.2 ± 0.4[c]	**356**, 0.74 ± 0.33[c]
	**340**, 0.091 ± 0.037[e]	**399**, 0.11 ± 0.03
	**376**, 0.12 ± 0.01[c]	**380**, 0.20 ± 0.07[c]
	**377**, 1.5 ± 0.9[d]	**381**, 1.9 ± 1.1[e]
	**396**, > 30	**397**, > 30
	**389**, 0.12 ± 0.06	**390**, 0.19 ± 0.11[b]
	**378**, 0.48 ± 0.16[c]	**382**, 0.55 ± 0.18[c]
	**379**, 1.7 ± 0.1	**383**, 3.6 ± 1.4
	**387**, 0.67 ± 0.25	-
	**388**, 1.3 ± 0.3	-

[a] Determinations ± standard deviation (mean of n = 4 unless otherwise stated); [b] n = 6; [c] n = 3; [d] n = 7; [e] n = 8

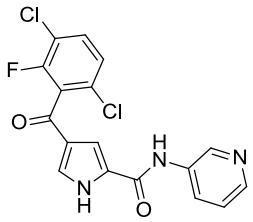
A significant reduction of ERK5 inhibitory activity was apparent for compounds **379** and **383**, suggesting that large *meta*-substituents might not be tolerated. Future work in this series should investigate small basic *meta*-substituents, such as methylazitidine or dimethylethylamine. These groups have a different polarity and could be involved in other types of binding interactions. The *meta*-methoxy group (**340** and **399**) remains the most potent substituent in this series and close analogues, such as $OCHF_2$ or OCF_3, are of interest. Indeed, in addition to an increased metabolic stability, these groups also have low energy barriers to rotation and can therefore access a wide range of conformations.[228, 229] This would allow exploration of different directions to those explored by the methoxy and ethoxy analogues.

A co-crystal structure of ERK5 with key inhibitors (**318**, **340** and **399**) will be required to get a better understanding of the binding interactions involved and guide the next round of SARs.

Chapter 8. Structure-Activity Relationship Studies Around the 2-Position of 5-Aminoheteroaromatic Amides

The results presented in this chapter have been focusing on the optimisation of the physicochemical properties of the inhibitors whilst maintaining low nanomolar potencies. Throughout this investigation, the SARs of an initial set of targets have guided the design of the following generation of analogues. Hence, to facilitate the reading and avoid several subdivisions, the SARs and biological evaluation sections will precede the synthesis of the compounds.

8.1. Rationale

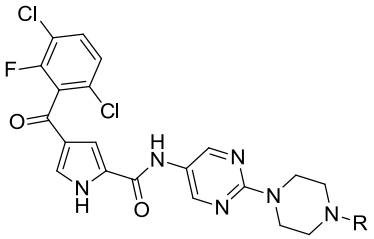


318

ERK5 IC_{50} = 66 nM
MW = 378
clogP = 3.8
tPSA = 75 $Å^2$
Sol = 10 - 65 μM
MLM Cl_{int} = 47 μL/min/mg

As discussed in section 7.1. introduction of the 3,6-dichloro-2-fluorobenzoyl moiety at the pyrrole 4-position conferred improved ERK5 inhibition relative to the 2-chloro-6-fluorobenzoylbenzoyl group. Incorporation of a third halogen on the scaffold increased the lipophilicity and decreased the tPSA, resulting in reduced solubility and low bioavailability.[198] Examination of **318** modelled in the ERK5 ATP-binding site from the literature co-crystal structure suggested that substituents at the *para* position of the pyridyl amide may project towards the solvent-exposed surface of ERK5. Introduction of water-solubilising groups at this position should be tolerated and improve the solubility of the inhibitors. These substituents would also hinder the pyridyl nitrogen and might therefore reduce the moderate metabolic liability observed with compound **318** in mouse liver microsomes. Extensive SARs were conducted at this position by Dr Duncan Miller and resulted in the identification of **400** and **401**, two compounds with sub-40 nM ERK5 inhibitory activity (Table 8.1).[105]

Table 8.1: ERK5 inhibitory activity and *in vitro* ADME properties of **400** and **401**



Compound	R	ERK5 IC_{50} (nM)[a]	Sol (µM)	HLM Cl_{int}[b]	MLM Cl_{int}[b]	Caco-2 AB[c] (ER)	hERG IC_{50} (µM)
400	H	13 ± 5	> 100	31	13	0.6 (35)	> 25
401	Me	37 ± 17	30-100	252	75	*n.d.*	2.63

[a] Determinations ± standard deviation (mean of n = 4) ; [b] µL/min/mg protein; [c] P_{app} 10^{-6} $cm.s^{-1}$; *n.d.* = not determined

The SAR studies revealed that the low potency observed for **400** and **401** was due to the basic nature of the terminal piperazine nitrogen. The solubility was increased for both compounds relative to **318** (Table 8.1). *In vitro* human and mouse liver microsomal data for **400** and **401** were dissimilar with the *NH*-piperazine analogue being five times more stable, supporting the possibility of *N*-demethylation as a major route of metabolism for **401** (Table 8.1). Compound **401** was found to inhibit hERG with an IC_{50} value of 2.63 µM whereas the hERG IC_{50} value for **400** was greater than 25 µM, indicating the presence of subtle hERG SAR in this series. In the Caco-2 membrane permeability assay, **400** was found to exhibit high efflux and low permeability, suggesting significant recognition by active transporters (Table 8.1).

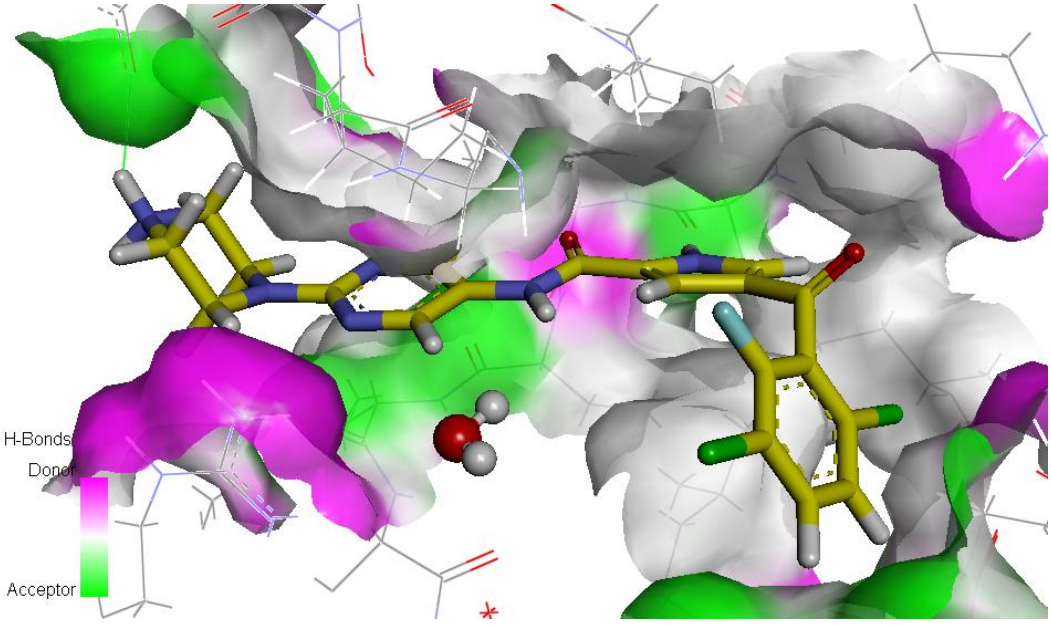
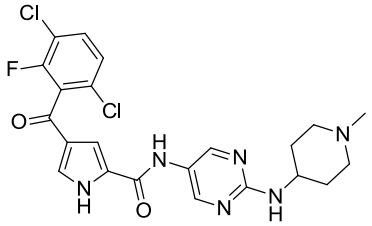


Figure 8.1: Docking of **400** in the ATP-binding site of ERK5 (PDB code 4b99)[194]

Modelling of **400** in the ATP-binding site of ERK5 from the literature co-crystal structure suggested that the piperazine could adopt a conformation that would allow the protonated basic centre to participate in an ionic interaction with a glutamate residue on the exit of the binding-site (Figure 8.1).

To investigate tolerance to variation of the position of the basic centre, an analogue of **400**, displaying an amino spacer between the pyrimidyl and the piperidinyl rings, was prepared by a colleague.[105] Compound **402** retained good ERK5 potency (Table 8.2). The metabolic stability of **402** was significantly improved relative to **401**, indicating that *N*-dealkylation was a slower metabolic process in this template. Compound **402** did not inhibit the hERG cardiac ion channel with concentration of up to 25 μM. In the Caco-2 assay, **402** had a similar high efflux and low flux relative to **400**. The focus for further investigation thus turned to reducing efflux liability while maintaining ERK5 inhibitory potency.

Table 8.2: ERK5 inhibitory activity and *in vitro* ADME properties of **402**



Compound	ERK5 IC_{50} (nM)[a]	Sol (μM)	HLM Cl_{int}[b]	MLM Cl_{int}[b]	Caco-2 AB[c] (ER)	hERG IC_{50} (μM)
402	14 ± 3	10 - 100	6	19	0.3 (99)	> 25

[a] Determinations ± standard deviation (mean of n = 4) ; [b] μL/min/mg protein; [c] P_{app} 10^{-6} cm.s^{-1}

8.2. Intestinal Absorption of Xenobiotics

8.2.1. The Caco-2 in vitro Assay

Oral delivery is the most convenient form of drug administration for patients. For this reason, the majority of drug discovery programs aims at designing pharmaceutical agents for oral administration.[230] Intestinal absorption restricts the oral bioavailability of compounds and a variety of *in vitro* assays, including the Caco-2 assay, have been developed to evaluate intestinal permeability.[230] Originally, lipophilicity was used to predict membrane permeability but was later found to be too simplistic and not always predictable.

Caco-2 cells are a human colon epithelial cancer cell line and are cultured as a monolayer to be used as a model of human intestinal absorption of drugs.[231] The Caco-2 cell monolayer mimics the human intestinal epithelium of the small intestine by expressing uptake carriers, efflux transporters and Phase II conjugation enzymes.[230] This model enables to study both paracellular and transcellular absorptions.[232] Three pathways mediating the intestinal absorption of orally administered pharmaceutical agents have been identified and are covered by the Caco-2 assay: passive diffusion, carrier-mediated or -limited transport, and vesicular transport.[230] Influx transporters, such as PEPT1 or OATP, and efflux transporters, such as P-gp or BCRP, are expressed on the apical or basolateral membrane of Caco-2 cells and play a crucial role in the transport of compounds across the monolayer.[233]

The apical and basolateral chambers represent the luminal and blood/mesenteric lymph sides of the gastrointestinal tract (Figure 8.2).[230] The xenobiotic to be assessed is added to either the apical or basolateral side of the Caco-2 monolayer. The concentration of the compound in the recipient compartment is measured at various time points and a transport rate determined. It is expressed as the apparent permeability coefficient P_{app}.[231] In the absence of active transport involvement, the apical to basolateral and basolateral to apical apparent permeability are similar.[231] Carrier-mediated efflux on the apical membrane enhances drug transport in the basolateral to apical direction, while attenuation the apical to basolateral absorption.[231]

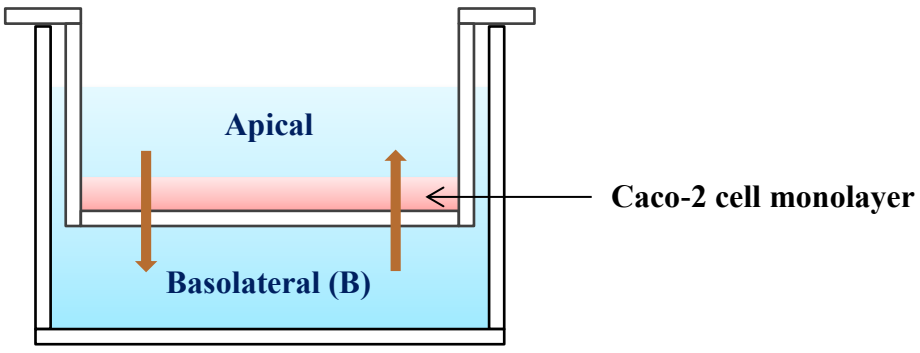


Figure 8.2: Schematic depiction of the Cacco-2 cell transporter system (adapted from ref 231)

In summary, the Caco-2 monolayer assay is a standard tool for the prediction of intestinal drug absorption and for mechanistic studies of drug transport.[231, 232] It provides valuable information for drug development in an efficient and reproducible manner and is widely used in pharmaceutical companies.[230, 233]

8.2.2. Molecular Properties Controlling Membrane Permeability

Although many biological processes regulate the absorption of pharmaceutical agents through the intestine, passive transport and active efflux have been identified as the key impeding mechanisms.

A range of molecular properties facilitating passive transport by the transcellular route through the intestinal epithelial cells has been identified.[234] A molecular weight below 500 and a tPSA below 140 have been associated with good passive absorption.[214, 235] The molecular rigidity of compounds influences the intestinal permeability. An increased molecular rigidity often results in superior bioavailability.[236] Its impact can be assessed by looking at the number of rotatable bonds, and it has been observed that for compounds with a molecular weight in the range 400 to 500, less than 10 rotatable bonds are associated with good passive absorption.[235, 236] A decrease in hydrogen bond count also improves passive permeability. A recent study from AstraZeneca has advised to maintain clogD values above 3.4 for compounds with a molecular weight in the range 450 to 500, in order to achieve high apical to basolateral P_{app} in the Caco-2 assay.[237] The ionisation state of a drug influences its rate of absorption from the small intestine. Basic compounds tend to be protonated in the gastrointestinal tract, resulting in high polarity and reduced lipophilicity. Such properties limit passive absorption across biomembranes. Reduction of an amine pK_a can lead to improved absorption.[238]

P-gp and BCPR are the most impactful efflux transporters and display a considerable overlap in their substrates.[234] Their involvement in drug absorption is more pronounced if the drug has a poor passive permeability.[231, 239] An understanding of transport mechanisms and structural activity relationship responsible for the influx and efflux of a pharmaceutical agent often allows medicinal chemists to take advantage of these processes. However, the molecular properties that confer P-gp efflux remain poorly understood.[240] P-gp transports structurally unrelated agents out of the cell, such as anthracyclines, alkaloids or steroid hormones.[241] Several tyrosine kinase inhibitors have also been identified as P-gp substrates.[242] There is little correlation between clogP and P-gp efflux liability, with a large range of clogP being tolerated to avoid P-gp efflux.[240]

Relatively modest structural changes have been successfully utilised in diverse medicinal chemistry programs to modulate P-gp recognition.[240] Consideration of tPSA and HBA/HBD values is important. Indeed, maintaining tPSA below 90 Å^2 and hydrogen bound donor count below 2 usually maximizes the chance of evading P-gp efflux.[240]

Masking HBD groups *via* intramolecular hydrogen bonding has enabled to reduce P-gp substrate recognition. Replacement of a *NH* with a methylene unit was successfully employed to reduce P-gp affinity of an GPR139 antagonist.[243] Repositioning of HBD groups in a scaffold can also diminish P-gp recognition. This strategy is valuable for compounds with low tPSA where a lower tPSA might introduce off-target activity and undesired safety profile.[240] The presence of a strongly basic amine can often induce P-gp efflux and tend to lower the threshold for tPSA tolerance. [241] Removal of the basic centre or reduction of its pK_a is a proven strategy to reduce P-gp affinity.[240]

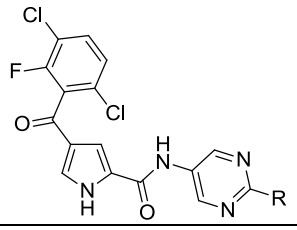
Drugs substrate of active transporters, with moderate to high passive permeability, can still have high oral bioavailability. The high drug concentration in the gastrointestinal lumen saturates efflux transporters, enabling absorption through passive diffusion.[235] Parallel artificial membrane permeability assay (PAMPA) can be used as a filter to select compounds with sufficient passive permeability to test in P-gp efflux assays, such as the Caco-2 assay.[240] In the field of central nervous system drug discovery, the MDR-MDCK cell monolayer assay is employed to detect P-gp substrate.[244]

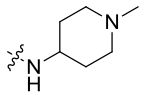
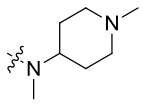
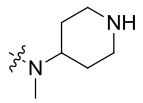
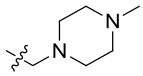
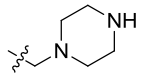
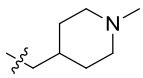
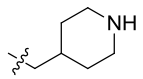
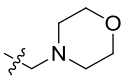
8.3. Investigation of 5-Aminoheteroaromatic Amides Introducing Piperidine and Piperazine Side-Chains *via* a Variety of Spacers at the 2-Position

8.3.1. SARs and Biological Evaluation of Pyrimidyl-Amide Linked Analogues

Pyrrole carboxamide **402** has a high tPSA (103 Å) and contains three hydrogen bond donors (Table 8.3). The pyrrole NH is essential for ERK5 activity and the amide NH cannot easily be replaced, since methylation of the amide nitrogen of **318** resulted in a 65-fold reduction of ERK5 potency (see section 6.4). Replacement of the NH-spacer had not previously been investigated and variations of this part of the template could favourably modulate the molecular properties of the inhibitors.

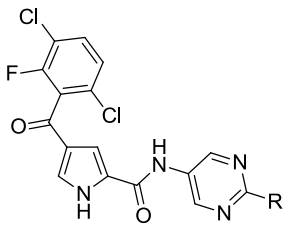
Table 8.3: Structure and molecular properties of 2-substituted 5-pyrimidyl amides **403 - 409**

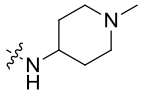
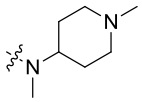
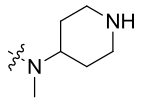
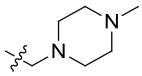
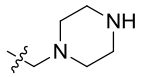
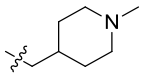
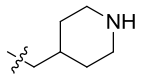
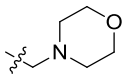


Compound	R	MW	clogP	clogD	tPSA (Å^2)	HBA	HBD
402		491	3.8	2.4	103	8	3
403		505	4.2	2.5	94	8	2
404		491	3.7	2.1	103	8	3
405		491	3.3	2.3	94	8	2
406		477	3.0	1.9	103	8	3
407		490	4.8	2.5	91	7	2
408		476	4.2	2.1	100	7	3
409		478	3.5	2.4	100	8	2

The compounds in table 8.3 were designed and synthesised with the aim of addressing the issues of membrane permeability. Methylation of the NH-spacer (**403** and **404**) or its replacement by a methylene group (**407** and **408**) removed one hydrogen bond donor and reduced the tPSA. The nitrogen spacer was also moved in the piperidine ring to give a piperazine (**405** and **406**). Although this modification was not modulating the number of HBAs or the tPSA, it would reduce the basicity of the terminal basic centre by a minimum of 1 unit and would introduce a second basic centre closer to the pyrimidyl ring. The basic centre in compound **409** was moved closer to the heteroaromatic ring and had a significantly lower pK_a (≈ 8). All these structural modifications were made to establish further SARs and to change the pattern of HBDs and HBAs in the inhibitors, with the objective to reduce transporter recognition.

Table 8.4: ERK5 inhibitory activity of 2-substituted 5-pyrimidyl amides **403 - 409**



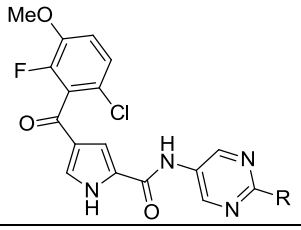
Compound	R	ERK5 IC_{50} (nM)[a]	L.E.	LipE
402		14 ± 3	0.33	5.5
403		21 ± 7	0.31	5.2
404		20 ± 5	0.32	5.6
405		7 ± 4	0.34	5.9
406		8 ± 2	0.35	6.2
407		7 ± 3	0.34	5.7
408		7 ± 3	0.35	6.0
409		53 ± 16	0.31	4.9

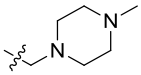
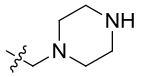
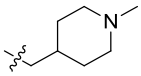
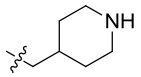
[a] Determinations ± standard deviation (mean of n = 4)

Methylation of the NH-spacer (**403** and **404**) retained ERK5 binding affinity (Table 8.4). Replacement of the amino spacer with a methylene group (**407** and **408**) resulted in a 2-fold increase in potency relative to **402**. Replacement of the piperidine (**407** and **408**) with a piperazine (**405** and **406**) was tolerated and gave equipotent compounds. For each matched pair, methylated and non-methylated compounds had comparable potency (Table 8.4). Interestingly the ERK5 inhibitory activity of morpholine analogue **409** was

only reduced by 4-fold, suggesting that an alternative position of the basic centre might be tolerated and that a HBA at this position might interact with a HBD in the protein. All the compounds had good ligand and lipophilic ligand efficiency.

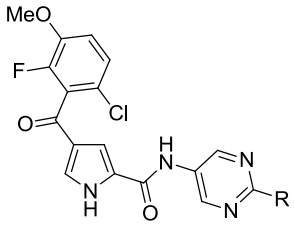
Table 8.5: Structure and molecular properties of 2-substituted 5-pyrimidyl amides **410 - 413**

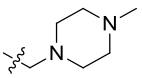
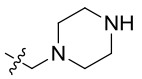
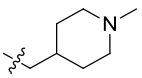
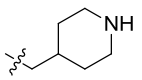


Compound	R	MW	clogP	clogD	tPSA (Å^2)	HBA	HBD
410		487	2.7	1.6	103	9	2
411		473	2.4	1.3	112	9	3
412		486	4.1	1.9	100	8	2
413		472	3.7	1.5	109	8	3

In parallel of this work, the 6-chloro-2-fluoro-3-methoxybenzoyl group was identified as an alternative substituent at the pyrrole 4-position conferring similar ERK5 inhibition relative to the 3,6-dichloro-2-fluorobenzoyl group (see section 7.2). A selection of the best amide substituent was therefore prepared in combination with the 6-chloro-2-fluoro-3-methoxybenzoyl group (Table 8.5). This alternative substitution pattern lowered the logD relative to the trihalogenated aroyl and gave compounds with similar molecular weight and higher tPSA.

Table 8.6: ERK5 inhibitory activity of 2-substituted 5-pyrimidyl amides **410 - 413**



Compound	R	ERK5 IC_{50} (nM)[a]	L.E.	LipE
410		13 ± 4	0.32	6.2
411		16 ± 2	0.32	6.5
412		18 ± 8	0.31	5.8
413		12 ± 5	0.33	6.4

[a] Determinations ± standard deviation (mean of n = 4)

Analogues **410 - 413** incorporating the *meta*-methoxybenzoyl group maintained excellent sub-20 nM potency against ERK5 (Table 8.6). Although the ERK5 inhibitory activity was slightly reduced compared with the trihalogenated matched pairs **405 - 408**, these inhibitors **410 - 413** had similar ligand efficiency and superior lipophilic ligand efficiency (Table 8.6 and Figure 8.3).

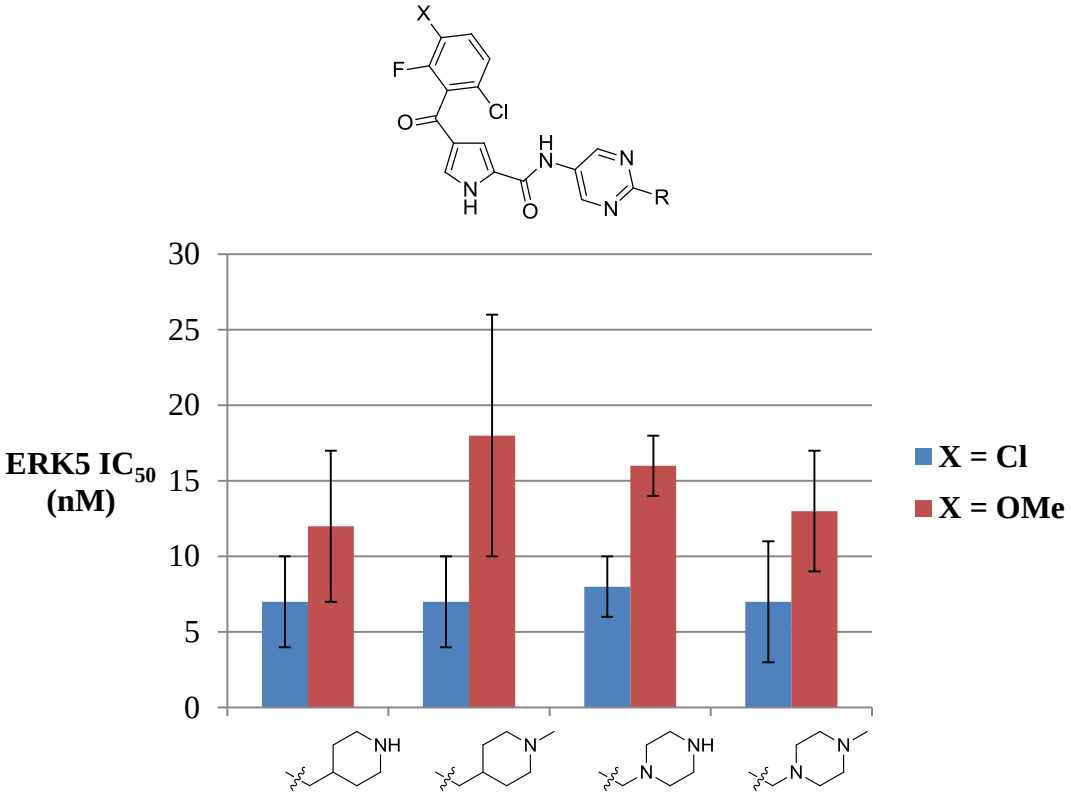
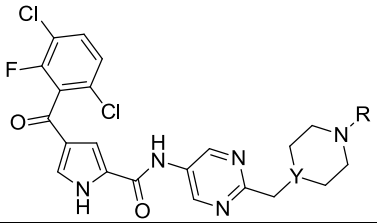


Figure 8.3: Bar diagram displaying the ERK5 inhibitory activity of the *meta*-methoxy *vs* the *meta*-chloro derivatives

The most potent compounds with the fewest HBAs and HBDs, and the lowest tPSA were selected for *in vitro* ADME studies (Table 8.7). All compounds showed excellent solubility and moderate plasma protein binding consistent with the presence of a basic centre in the molecules. In mouse liver microsomes *in vitro*, **406** and **408** had excellent stability with no metabolism being observed. Derivatives **405** and **407** suffered from moderate metabolic turnover, possibility through *N*-demethylation. All the compounds exhibited low apical to basolateral apparent permeability and high efflux in the Caco-2 assay, suggesting that they are slow to cross the intestine membrane and are likely to be recognised by efflux transporters. Methylated compounds **405** and **407** had significantly higher basolateral to apical apparent permeability than the non-methylated derivatives **406** and **408**.

Table 8.7: ERK5 inhibitory activity and *in vitro* ADME properties for **405 - 408**



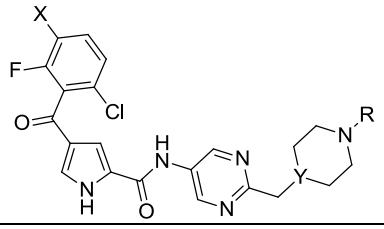
Compound	Y	R	ERK5 IC_{50} (nM)[a]	Sol (μM)	Ppb F_u	MLM Cl_{int}[b]	Caco-2 AB[c] (ER)
405	N	Me	7 ± 4	> 100	0.167	28	0.9 (20)
406	N	H	8 ± 2	> 100	0.143	< LOD	0.3 (3.7)
407	C	Me	7 ± 3	> 100	0.141	31	0.4 (40)
408	C	H	7 ± 3	> 100	0.116	< LOD	0.2 (8.7)

[a] Determinations ± standard deviation (mean of n = 4) ; [b] μL/min/mg protein; [c] P_{app} 10^{-6} cm.s^{-1}

The cellular activity of the most active compounds was measured in HeLa cells. An IC_{50} value was generated from a seven point concentration response curve, using a densitometry measurement of the phospho-ERK5 band. As Western blotting is a semi-quantitative technique and the experiment was only conducted once, a high degree of experimental variation might have impacted on the IC_{50} values generated using this assay. All the compounds with the trihalogenated aroyl at the pyrrole 4-position (**405** - **408**) had IC_{50} values close to or below 100 nM, independently of their efflux ratio in the Caco-2 assay (Table 8.8). The *meta*-methoxybenzoyl compounds **410** - **413** were less active relative to their *meta*-chloro matched pairs **405** - **408**. The low logD and high tPSA of the non-methylated compounds **411** and **413** might have impaired their cellular permeability and resulted in lower ERK5 inhibitory activities close to 1 μM.

The cellular activity of some compounds was also assessed using a MEF2D reporter gene assay in HEK293 cells (Table 8.8). Measurement of MEF2D phosphorylation, a downstream substrate of ERK5, allows determination of ERK5 IC_{50} values. The ERK5 inhibitory activities of the trihalogenated compounds were consistent with the activities measured in HeLa cells. Although the compounds were slightly less active in the HEK293T assay, **405** was still the most potent with an IC_{50} value of 100 nM. Interestingly, the *meta*-methoxybenzoyl compounds **410**, **411** and **413** were again less active than their *meta*-chloro matched pairs. The consistency observed between the two assays conferred confidence in the semi-quantitative HeLa densitometry assay and provided confirmation that this series of compounds is able to inhibit ERK5 in cells.

Table 8.8: Comparison of ERK5 inhibitory activity in the IMAP cell-free assay with ERK5 inhibition in the HeLa and HEK293T cellular assays



Compound	X	Y	R	ERK5 IC_{50} (nM)*[a]	Caco-2 AB[d] (ER)	HeLa IC_{50} (µM)[b]	HEK293T IC_{50} (µM)[c]
405	Cl	N	Me	7 ± 4	0.9 (20)	0.02	0.10 ± 0.02
406	Cl	N	H	8 ± 2	0.35 (3.7)	0.06	0.24 ± 0.05
407	Cl	C	Me	7 ± 3	0.4 (40)	0.11	*n.d.*
408	Cl	C	H	7 ± 3	0.2 (8.7)	0.05	0.24 ± 0.04
410	OMe	N	Me	13 ± 4	*n.d.*	0.10	0.46 ± 0.10
411	OMe	N	H	16 ± 2	*n.d.*	1.1	0.57 ± 0.39
412	OMe	C	Me	18 ± 8	*n.d.*	0.19	*n.d.*
413	OMe	C	H	12 ± 5	*n.d.*	0.74	0.62 ± 0.28

* ERK5 inhibitory activity in the cell-free IMAP assay; [a] Determinations ± standard deviation (mean of n = 4) ; [b] Data from a single determination; [c] n = 2; [d] P_{app} 10^{-6} $cm.s^{-1}$; *n.d.* = not determined

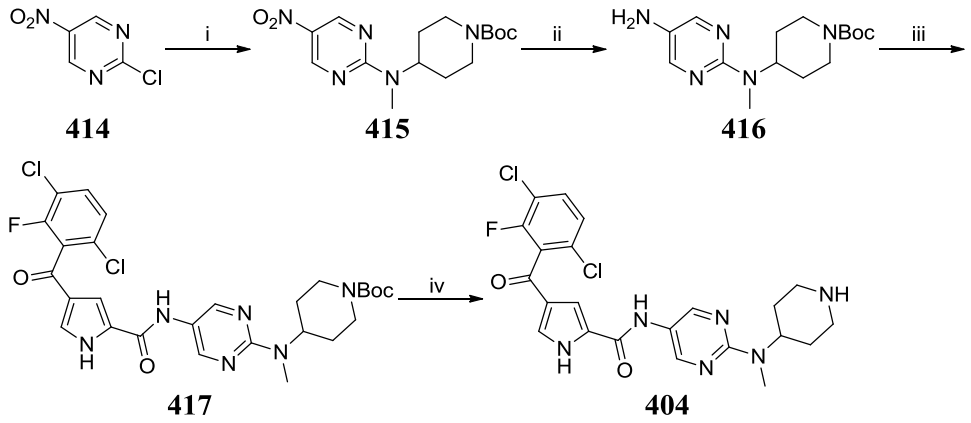
Compound **406** which had the lowest efflux ratio in the Caco-2 assay, excellent metabolic stability in MLM, high ligand and lipophilic efficiency, and was potent in both cellular assays, was selected for *in vivo* pharmacokinetic evaluation in mouse. The compound had low total plasma clearance and unbound clearance, consistent with the low *in vitro* mouse microsomal clearance (Table 8.9). However, **406** had no oral bioavailability indicating that the oral dose was not absorbed. This is consistent with the low membrane permeability and moderate efflux observed in the Caco-2 assay. The low volume of distribution was unexpected for a compound with a basic centre.

Table 8.9: *In vivo* pharmacokinetic parameters for **406**. Dose 10 mg/kg *i.v.* and *p.o.*

Cl mL/min/kg	**Cl_u** mL/min/kg	**V_d** L/kg	**$t_{1/2}$** min	**F** %
17	119	0.5	61	0

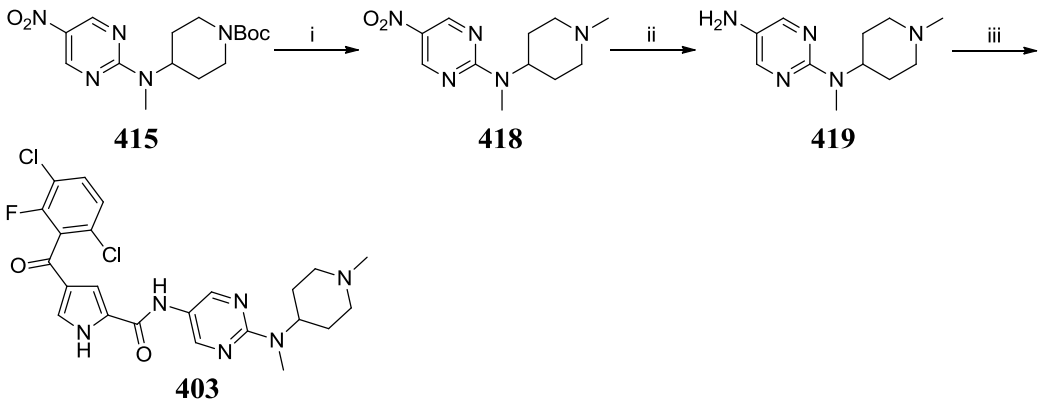
8.3.2. Synthesis of the Pyrimidyl-Amide Linked Analogues

Exploration of the pyrimidyl 2-position was achieved through preparation of 2-substituted 5-aminopyrimidines *via* various synthetic routes. S_NAr displacement of the chlorine of 2-chloro-5-nitropyrimidine (**414**) afforded **415**, which was cleanly reduced using palladium-catalysed flow hydrogenation to give *t*-butyl 4-((5-aminopyrimidin-2-yl)(methyl)amino) piperidine-1-carboxylate (**416**) in high yields (Scheme 8.1). The Mukaiyama coupling conditions, which only require a low number of equivalents of the amine coupling component (1.25 equivalents), were utilised for the coupling of **416** with **250**, and led to the isolation of **417** in 48% yield. *t*-Butyl carbamate **417** was deprotected using TFA in DCM in the presence of triethylsilane, which acted as a scavenger for the liberated *t*-butyl cation, preventing side-reactions with this reactive intermediate such as alkylation of the pyrrole ring.[245] Secondary amine target **404** was obtained in a good 75% yield (Scheme 8.1).



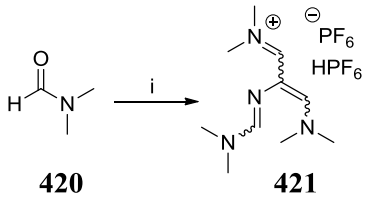
Scheme 8.1: *Reagents and conditions:* (i) *tert*-butyl 4-(methylamino)piperidine-1-carboxylate, NEt_3, THF, 0 °C to RT, 3 h, 94%; (ii) H_2, 10% Pd/C, MeOH:THF (1:1), 40 °C, 8 h, 96%; (iii) 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**), 2-chloro-1-methylpyridinium iodide, NEt_3, DCM, 42 °C, 24 h, 48%; (iv) DCM, TFA, Et_3SiH, RT, 2 h, 75%.

Intermediate **415** was converted to **418** in high yield using an *in situ* deprotection/Eschweiler-Clarke methylation procedure (Scheme 8.2).[246] A similar reaction sequence to that described for the preparation of **404** was then employed, leading to *N*-methylated piperidine target **403**.



Scheme 8.2: *Reagents and conditions:* (i) formic acid, formaldehyde (37 % wt. in water), 95 °C, 3 h, 94%; (ii) H_2, 10% Pd/C, MeOH:THF (1:1), 40 °C, 8 h, 96%; (iii) 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**), 2-chloro-1-methyl pyridinium iodide, NEt_3, DCM, RT, 24 h, 45%.

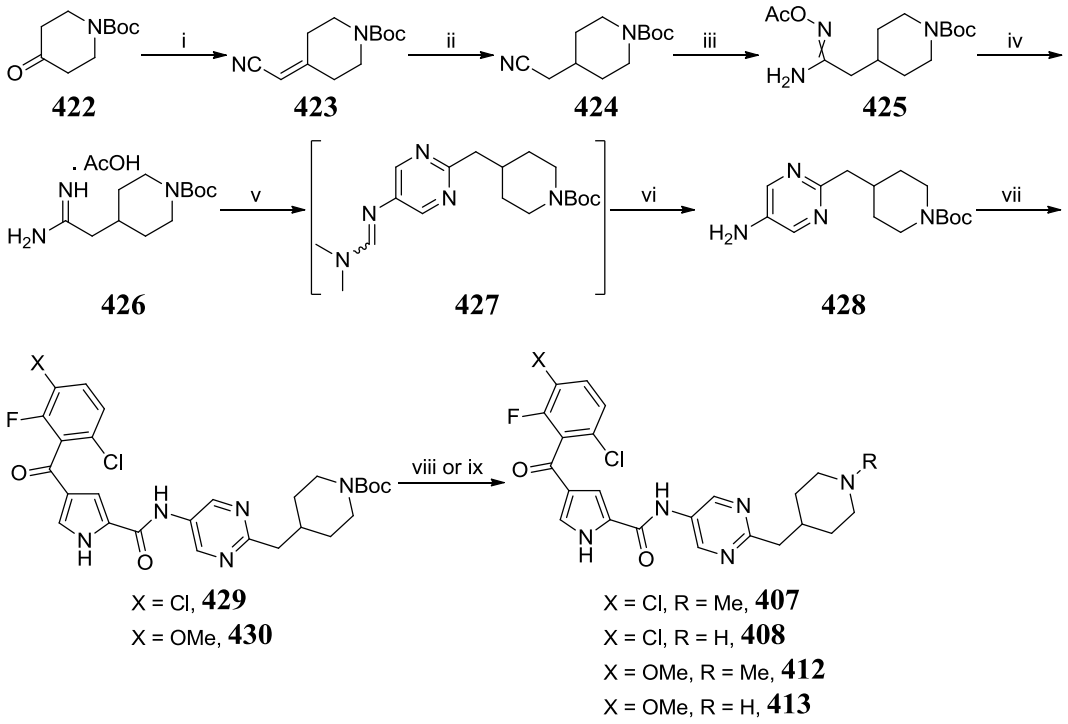
Dihexafluorophosphate salt **421** is a versatile intermediate towards the synthesis of 2-functionalised 5-aminopyrimidines. It reacts readily with functionalised amidines in presence of sodium methoxide to give dimethylaminomethylene protected 5-aminopyrimidines. It was easily prepared on a large scale following a literature procedure (Scheme 8.3).[247]



Scheme 8.3: *Reagents and conditions:* (i) a) $POCl_3$, 10 °C to RT, 20 min; b) glycine hydrochloride, 5 °C to 80 °C, 4 h; c) H_2O, 5 °C, 5 min; d) 60% aq. HPF_6, -5 °C, 40%.

The synthesis of the targets **405** and **406** displaying a piperidine side-chain began with a Horner-Wadsworth-Emmons reaction between diethyl(cyanomethyl)phosphonate and piperidone **422** (Scheme 8.4).[248] Subsequent hydrogenation of cyanoacrylate **423** provided **424**, which was converted into an amidoxime using aqueous hydroxylamine. Acetylation followed by hydrogenation of the resulting *O*-acetylamidoxime afforded amidine **426** in an excellent yield.[249] Condensation of **426** with dihexafluorophosphate salt **421** followed by basic hydrolysis of the resulting amino protecting group were utilised for the synthesis of 2-substituted 5-aminopyrimidine **428**. Amine **428** was coupled to pyrrole carboxylic acids **250** and **338** using the Mukaiyama coupling protocol. The Boc-protected amines **429** and **430** were deprotected to give secondary amine targets **408** and **413** in good yields. The

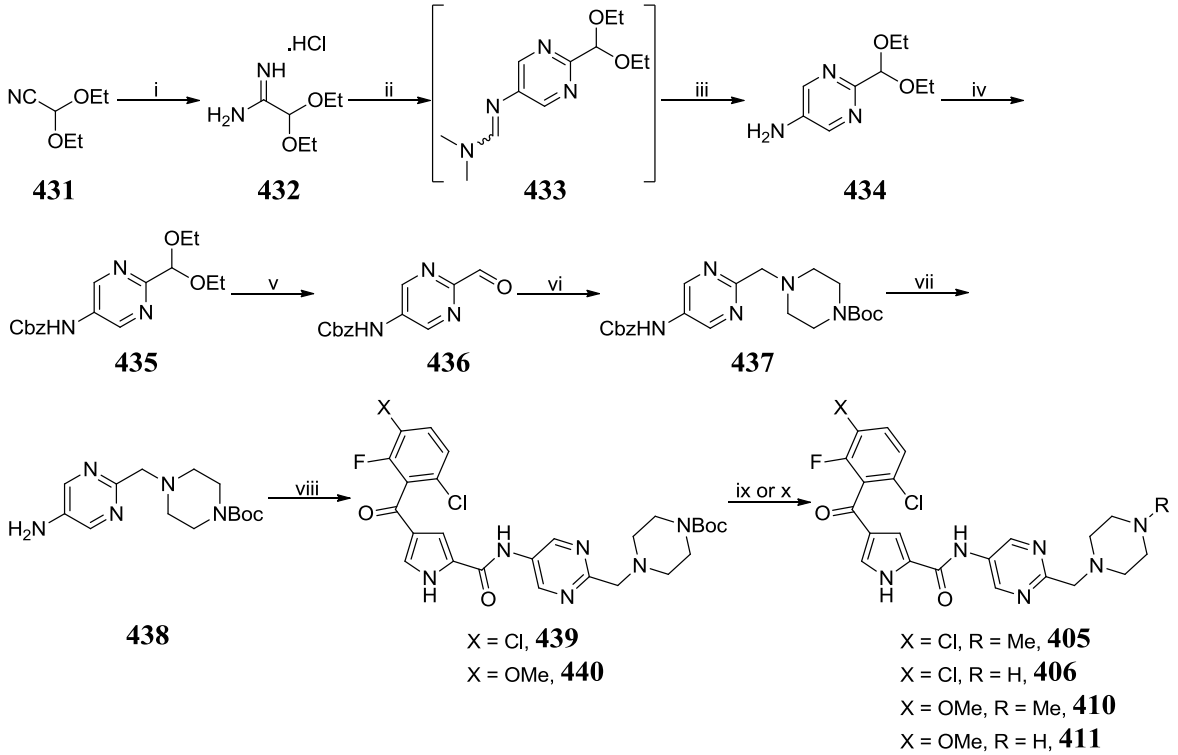
Eschweiler-Clarke methylation procedure was also employed as the final step to access the *N*-methylated targets **407** and **412** (Scheme 8.4).



Scheme 8.4: *Reagents and conditions:* (i) diethyl cyanomethylphosphonate, LiHMDS (1 M in THF), THF, -78 °C, 1 h, 92%; (ii) H_2, 10% Pd/C, EtOAc, RT, 24 h, quantitative; (iii) a) 50% aq. hydroxylamine, EtOH, 80 °C, 5 h; b) Ac_2O, NEt_3, dioxane, RT, 18 h, 79% (over 2 steps); (iv) H_2, 10% Pd/C, EtOAc:DCM (5:1), RT, 16 h, 95%; (v) hydrogen dihexafluorophosphate salt **421**, NaOMe (1 M in MeOH), EtOH, 78 °C, 2.5 h; (vi) 5% aq. K_2CO_3, dioxane, 100 °C, 18 h, 79% (over 2 steps); (vii) 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**) or 4-(6-chloro-2-fluoro-3-methoxybenzoyl)-1*H*-pyrrole-2-carboxylic acid (**338**), 2-chloro-1-methylpyridinium iodide, NEt_3, DCM, 42 °C, 24 h, (**429**, X = Cl, 51%; **430**, X = OMe, 37%); (viii) DCM, TFA, Et_3SiH, RT, 2 h, (**408**, X = Cl, R = H, 63%; **413**, X = OMe, R = H, 65%); (ix) formic acid, formaldehyde (37 % wt. in water), 95 °C, 3 h, (**407**, X = Cl, R = Me, 72%; **412**, X = OMe, R = Me, 72%).

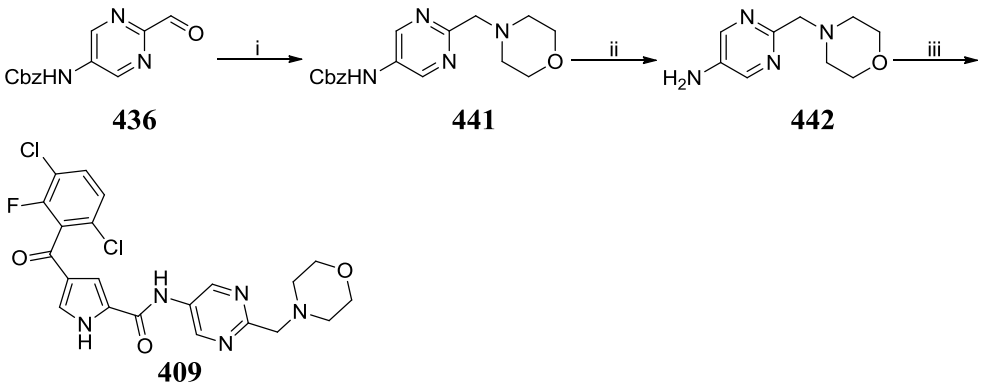
Nucleophilic addition of methoxide on diethoxyacetonitrile **431** gave methyl diethoxyacetimidate which was converted to amidine **432** by treatment with ammonium chloride (Scheme 8.5).[250] Condensation of dihexafluorophosphate salt **421** with **432**, followed by basic hydrolysis of the dimethylaminomethylene protecting group afforded 2-substituted 5-aminopyrimidine **434** in 49% yield.[247] The amino group of **434** was subsequently protected as a benzyl carbamate and the acetal hydrolysed under dilute acidic conditions, providing **436**.[251] Compound **437** was prepared *via* reductive amination of **436** with Boc-protected piperazine in trifluoroethanol.[206] The Cbz protecting group was removed in excellent yield using flow hydrogenation over 10% palladium on carbon to

afford **438**, which was engaged in a sequence of reactions analogous to those used for the synthesis of piperidine targets **405** and **406**, and provided final derivatives **405**, **406**, **410** and **411** in good yields (Scheme 8.5).



Scheme 8.5: *Reagents and conditions:* (i) a) NaOMe, MeOH, RT, 16 h; b) NH_4Cl, MeOH, RT, 18 h, 89%; (ii) hydrogen dihexafluorophosphate salt **421**, NaOMe (1 M in MeOH), EtOH, 78 °C, 2.5 h; (iii) 5% aq. K_2CO_3, dioxane, 100 °C, 18 h, 49% (over 2 steps); (iv) benzyl chloroformate, K_2CO_3, THF:H_2O (1:1), RT, 24 h, 80%; (v) 1 M aq. HCl, MeCN, RT, 8 h, 89%; (vi) a) *tert*-butyl piperazine-1-carboxylate, $MgSO_4$, trifluoroethanol, 1 h, RT; b) $NaBH_4$, trifluoroethanol, 0 °C to RT, 1 h, 42%; (vii) H_2, 10% Pd/C, EtOAc, RT, 24 h, 99%; (viii) 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**) or 4-(6-chloro-2-fluoro-3-methoxybenzoyl)-1*H*-pyrrole-2-carboxylic acid (**338**), 2-chloro-1-methylpyridinium iodide, NEt_3, DCM, 42 °C, 24 h, (**439**, X = Cl, 42%; **440**, X = OMe, 31%); (ix) DCM, TFA, Et_3SiH, RT, 2 h, (**406**, X = Cl, R = H, 70%; **411**, X = OMe, R = H, 73%); (x) formic acid, formaldehyde (37 % wt. in water), 95 °C, 3 h, (**405**, X = Cl, R = Me, 71%; **410**, X = OMe, R = Me, 76%).

Intermediate **436** was amenable to functionalisation *via* reductive amination. It enabled the introduction of the morpholine side-chain to give **441**, which was converted to final derivative **409**, using a two-step sequence (Scheme 8.6). Final derivative **409** was isolated in only 16% yield due to difficulties in isolating the product from close-running impurities.

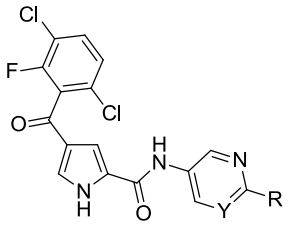


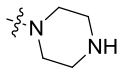
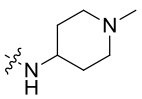
Scheme 8.6: *Reagents and conditions:* (i) a) morpholine, $MgSO_4$, trifluoroethanol, 1 h, RT; b) $NaBH_4$, trifluoroethanol, 0 °C to RT, 1 h, 68%; (ii) H_2, 10% Pd/C, EtOAc, RT, 24 h, 97%; (iii) 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**), 2-chloro-1-methylpyridinium iodide, NEt_3, DCM, 42 °C, 24 h, 16%.

8.3.3. SARs and Biological Evaluation of Pyridyl-Amide Linked Analogues

During the course of the optimisation of the pyrimidyl spacer, Dr Duncan Miller demonstrated that ERK5 inhibitory potency for 2-substituted 5-pyridyl and 5-pyrimidyl amides was broadly similar (Table 8.10).[105]

Table 8.10: Comparison of ERK5 inhibitory activity of 2-substituted 5-pyridyl and 2-substituted 5-pyrimidyl amides



Compound	Y	R	ERK5 IC_{50} (nM)[a]
400	N		13 ± 5
443	C		13 ± 6[b]
402	N		14 ± 3
444	C		24 ± 20[b]

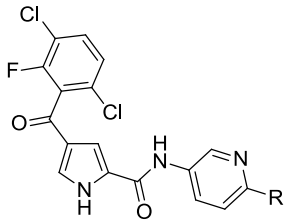
[a] Determinations ± standard deviation (mean of n = 4); [b] n = 6

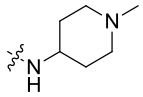
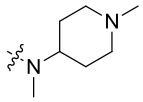
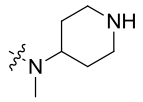
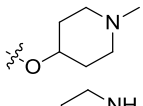
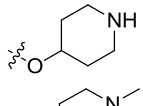
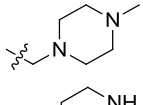
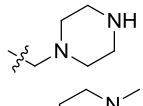
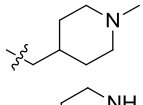
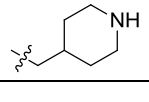
Incorporation of a pyridyl ring in place of the pyrimidyl removes a hydrogen bond acceptor, inducing a reduction in the tPSA which could be beneficial to increase membrane permeability. This modification was investigated in combination with different spacers and the trihalogenated pyrrole 4-substituent.

The compounds in Table 8.11 were designed and synthesised with the aim of reducing efflux liability and building further SARs in this position. The oxygen spacer which was

synthetically more accessible with a pyridyl linker was added to the list of spacers used in the pyrimidyl series (see section 8.3.1.).

Table 8.11: Structure and molecular properties of 2-substituted 5-pyridyl amides **445** - **452**

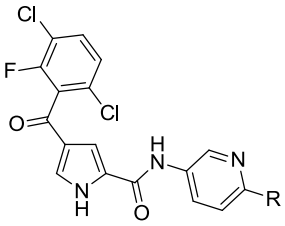


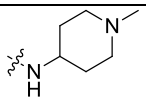
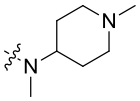
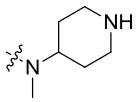
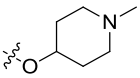
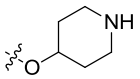
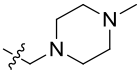
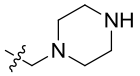
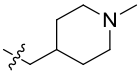
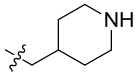
Compound	R	MW	clogP	clogD	tPSA (Å^2)	HBA	HBD
444		490	3.6	2.6	90	7	3
445		504	4.0	2.7	81	7	2
446		490	3.5	2.3	90	7	3
447		491	4.0	2.7	87	7	2
448		477	3.5	2.3	96	7	3
449		490	3.1	2.5	81	7	2
450		476	2.7	2.2	90	7	3
451		489	4.5	2.8	78	6	2
452		475	4.0	2.3	87	6	3

The ERK5 inhibitory activity of the pyridyl-amide linked analogues are presented in Table 8.12. The modifications of the spacer all yielded compounds with similar or superior potency against ERK5, relative to **444**. Independently of the terminal aliphatic heterocycle and the nature of the spacer, the methylated and non-methylated matched pairs had identical ERK5 inhibition (Figure 8.4). Methylation of the NH-spacer in compounds **445** and **446** had little effect on ERK5 inhibitory activity whereas replacement with an oxygen (**447** and **448**) conferred a 2-fold improvement in potency. Introduction of a methylene group in place of the amino spacer resulted in a significant improvement in the binding interaction, with **449**, **450**, **451** and **452** having a 4-fold increase in potency compared with **444**. ERK5 inhibition was found to be comparable for the pyridyl and pyrimidyl matched

pair analogues (see section 8.3.1.), confirming that these heterocycles were interchangeable. All compounds retained good ligand and lipophilic efficiencies (Table 8.12).

Table 8.12: ERK5 inhibitory activity of 2-substituted 5-pyridyl amides **445 - 452**



Compound	R	ERK5 IC_{50} (nM)[a]	L.E.	LipE
444		24 ± 20[b]	0.32	5.0
445		22 ± 9[b]	0.31	4.9
446		25 ± 7[b]	0.32	5.3
447		14 ±1	0.33	5.2
448		11 ± 1	0.34	5.7
449		5 ±2	0.34	5.7
450		5 ± 1[b]	0.35	6.1
451		6 ± 1	0.34	5.5
452		5 ± 1	0.35	6.0

[a] Determinations ± standard deviation (mean of n = 4); [b] n = 6

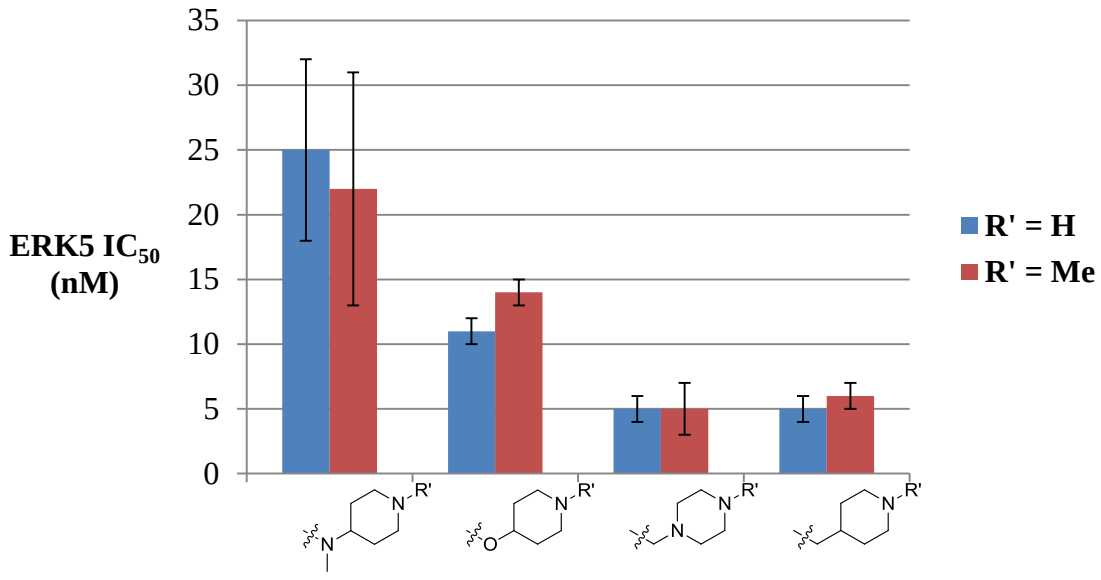
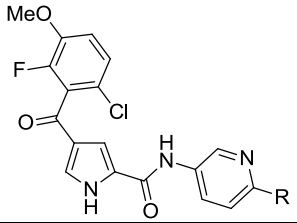
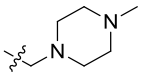
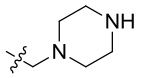
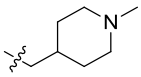
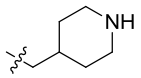


Figure 8.4: Bar diagram showing ERK5 inhibitory activity of 2-substituted 5-pyridyl amides **445 - 452**

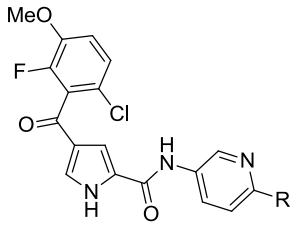
Table 8.13: Structure and molecular properties of 2-substituted 5-pyridyl amides **453 - 456**

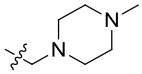
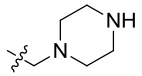
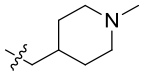
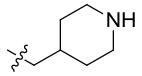


Compound	R	MW	clogP	clogD	tPSA (Å^2)	HBA	HBD
453		486	2.6	2.0	91	8	2
454		472	2.2	1.7	99	8	3
455		485	3.9	2.2	87	7	2
456		471	3.4	1.8	96	7	3

Compounds with ERK5 inhibitory potencies below 10 nM were also prepared with the *meta*-methoxy benzoyl pyrrole 4-substituent, leading to inhibitors with reduced logD but increased tPSA (Table 8.13). The *meta*-methoxybenzoyl analogues **453 - 456** retained sub-10 nM potencies comparable with the trihalogenated inhibitors (Table 8.14). These compounds had improved lipophilic efficiency.

Table 8.14: ERK5 inhibitory activity of 2-substituted 5-pyrimidyl amides **453 - 456**

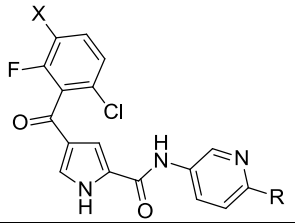


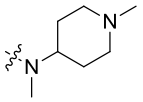
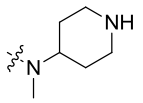
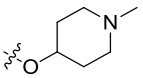
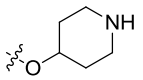
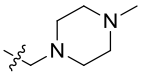
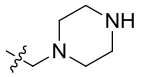
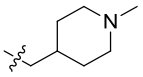
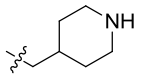
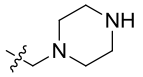
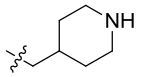
Compound	R	ERK5 IC_{50} (nM)[a]	L.E.	LipE
453		8 ± 3[b]	0.33	6.1
454		8 ± 2	0.34	6.4
455		10 ± 3	0.32	5.8
456		9 ± 1	0.33	6.2

[a] Determinations ± standard deviation (mean of n = 4); [b] n = 5

Most of the pyridyl derivatives were progressed to *in vitro* ADME profiling (Table 8.15) with a view to establish an efflux SAR around the template. All compounds had excellent solubility. Plasma protein binding of the trihalogenated compounds **447** and **449 - 452** was moderate. Replacement of the *meta*-chlorine with the methoxy (**454**, **456**) notably increased the free fraction of the drug. All of the methylated piperidines **445**, **447** and **451** or piperazine **449** had moderate to high turnover in mouse liver microsomes *in vitro*. Their non-methylated matched pairs **446**, **448**, **450** and **452** had much improved metabolic stability, indicating that *N*-demethylation may take place. Interestingly, the microsomal turnover of **447** and **451** was species-dependent, with higher stability observed in human than in mouse liver microsomes. All compounds retained undesirable high efflux ratios and apical to basolateral apparent permeability in the Caco-2 assay, suggesting that the pyridyl amides were still substrates for transporter pumps and that variation of the spacer had little influence on the permeability. The Caco-2 efflux ratio of **456** (ER = 2.5) was significantly reduced compared to **402** (ER = 99). However the apical to basolateral permeability across the Caco-2 monolayer was still low (P_{app} = 0.5 × 10^{-6} cm/s). Although **447** had a moderate Caco-2 efflux (ER = 8) some apical to basolateral permeability was observed (P_{app} = 2.5 × 10^{-6} cm/s). In the carbon spacer series, all compounds had a similar apical to basolateral P_{app}, comprised between 0.5 and 1 × 10^{-6} cm/s. However the basolateral to apical P_{app} was significantly different between methylated and non-methylated derivatives (**449** vs. **450**, **451** vs. **452**), with higher apparent permeability for the methylated inhibitors. This could be rationalised by the increased lipophilicity of the alkylated compounds **449** and **451**, which could also be substrates for an active uptake transporter on the basolateral membrane. Overall the results indicate that disappointingly reduction of the tPSA and the number of HBA and HBD had not abrogated transporter recognition.

Table 8.15: ERK5 inhibitory activity and *in vitro* ADME properties for **445** - **456**

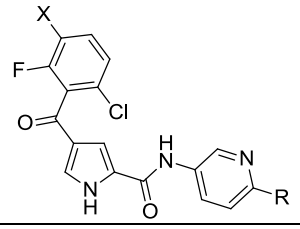


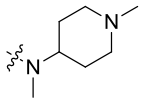
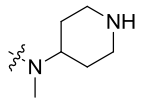
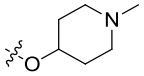
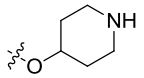
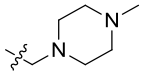
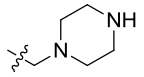
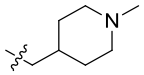
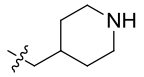
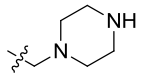
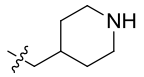
Cmpd	X	R	ERK5 IC_{50} (nM)[a]	Sol (µM)	Ppb F_u	MLM Cl_{int}[c]	HLM Cl_{int}[c]	Caco-2 AB[d] (ER)
445	Cl		22 ± 9[b]	> 100	*n.d.*	110	*n.d.*	2.0 (14)
446	Cl		25 ± 7[b]	> 100	*n.d.*	20	*n.d.*	0.2 (38)
447	Cl		14 ± 1	> 100	0.048	50	16	2.5 (8)
448	Cl		11 ± 1	> 100	*n.d.*	1	*n.d.*	0.2 (74)
449	Cl		5 ± 2	> 100	0.099	59	*n.d.*	1.0 (30)
450	Cl		5 ± 1[b]	> 100	0.091	7	*n.d.*	0.6 (6)
451	Cl		6 ± 1	> 100	0.083	34	8	0.7 (28)
452	Cl		5 ± 1	> 100	0.062	4	3	0.6 (5)
454	OMe		8 ± 2	> 100	0.182	7	*n.d.*	0.6 (4)
456	OMe		9 ± 1	> 100	0.115	14	*n.d.*	0.5 (2.5)

[a] Determinations ± standard deviation (mean of n = 4) ; [b] n = 6; [c] µL/min/mg protein; [d] P_{app} 10^{-6} $cm.s^{-1}$; *n.d.* = not determined

The cellular activity of the compounds whose ADME properties had been determined, was assessed in HeLa cells (Table 8.16). Compounds with the *N*-methyl spacer were moderately potent. Introduction of the oxygen and methylene spacer in the trihalogenated series (**447** - **452**), resulted in sub-100 nM cellular ERK5 inhibitory activity with the exception of **450** for whom a second IC_{50} value determination would be required to confirm the low potency initially measured. Similarly to the SARs observed with the pyrimidyl linker (see section 8.3.1.), compounds **454** and **456** with the *meta*-methoxybenzoyl pyrrole 4-substituent were less active compared with their *meta*-chloro matched pairs **450** and **452**.

Table 8.16: Comparison of ERK5 inhibitory activity in the IMAP cell-free assay, with ERK5 inhibition in the HeLa cellular assay



Compound	X	R	ERK5 IC_{50} (nM)*[a]	Caco-2 AB[c] (ER)	HeLa IC_{50} (µM)[d]
445	Cl		22 ± 9[b]	2.0 (14)	0.48
446	Cl		25 ± 7[b]	0.2 (38)	0.44 ± 0.32[e]
447	Cl		14 ± 1	2.5 (8)	0.06 ± 0.04[f]
448	Cl		11 ± 1	0.2 (74)	0.05
449	Cl		5 ± 2	1.0 (30)	0.07
450	Cl		5 ± 1[b]	0.6 (6)	1.5
451	Cl		6 ± 1	0.7 (28)	0.03 ± 0.02[f]
452	Cl		5 ± 1	0.6 (5)	0.04 ± 0.03[e]
454	OMe		8 ± 2	0.6 (4)	0.18
456	OMe		9 ± 1	0.5 (2.5)	0.44

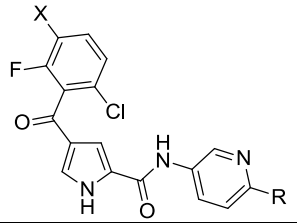
* ERK5 inhibitory activity in the cell-free IMAP assay; [a] Determinations ± standard deviation (mean of n = 4); [b] n = 6; [c] P_{app} 10^{-6} cm.s^{-1}; [d] n = 1; [e] n = 2; [f] n = 3

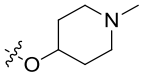
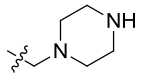
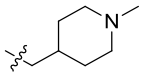
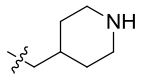
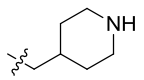
Compounds with the best combination of *in vitro* ADME properties and good cellular potencies were progressed to an *in vivo* pharmacokinetic study in mouse (Table 8.17). Compounds with a methylated terminal aliphatic heterocycle, such as **447** and **451** had moderate total plasma clearance and high unbound clearance, in agreement with the high turnover observed in *in vitro* mouse liver microsomes. These compounds had a moderate volume of distribution and low bioavailability, reflecting the poor absorption predicted in the Caco-2 assay (**447**, ER = 8; **451**, ER = 28).

Although compounds **450**, **452** and **456** had low total plasma clearance and unbound clearance, they had no bioavailability. This suggests that the oral dose was not absorbed

and that all compounds in this chemical series with an efflux ratio above 2 in the Caco-2 assay are unlikely to achieve good oral bioavailability. Surprisingly, these secondary aliphatic amines had a low volume of distribution despite their basic nature. Overall the high efflux in the Caco-2 assay translated to poor *in vivo* bioavailability. However, methylated compounds **447** and **451**, which had the higher efflux ratio, showed some bioavailability, suggesting that an increased lipophilicity might improve absorption of this chemical class.

Table 8.17: *In vivo* pharmacokinetic parameters for selected compounds. Dose 10 mg/kg *i.v.* and *p.o.*



Compound	X	R	Cl mL/min/kg	Cl_u mL/min/kg	V_d L/kg	$t_{1/2}$ min	F %
447	Cl		25	521	1.1	80	13
450	Cl		11	121	0.2	99	0
451	Cl		20	241	1	263	9
452	Cl		6	97	0.4	80	0
456	OMe		4	38	0.2	74	0

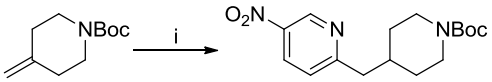
8.3.4. Synthesis of the Pyridyl-Amide Linked Analogues

Exploration of the pyridyl 2-position was achieved through preparation of 2-substituted 5-aminopyridines from 2-chloro-5-nitropyridine (**459**).

A four step strategy, where diversification of the pyridyl 2-substituent was introduced at the first step, was applied to the synthesis of a small library of eight derivatives, incorporating nitrogen-, oxygen- and carbon-linked piperidines (Table 8.19). S_NAr reactions on 2-chloro-5-nitropyridine (**459**) were utilised for the synthesis of heteroatom-linked piperidines **460** and **461**.

Hydroboration of 1-Boc-4-methylidenepiperidine (**457**) followed by Suzuki-Miyaura cross-coupling with 2-chloro-5-nitropyridine (**459**), using a literature procedure developed for the synthesis of 4-benzyl piperidines, led to isolation of **458** in only 10% yield (Table 8.18, entry 1).[252] To improve the outcome of this transformation, alternative palladium catalysts, bases and solvents were investigated but all produced **458** in disappointing yields. Use of 2-bromo-5-nitropyridine as coupling partner was also unsuccessfully attempted. Isolation of **458** in a low yield was primarily due to the formation of 5-nitropyridin-2-ol as a major by-product. Thus, increasing the number of equivalents of 2-chloro-5-nitropyridine improved conversion, with 2 equivalents proving optimal (Table 8.18, entry 3). Although the yield of the reaction was still moderate, it was deemed sufficient for the first step of a short synthetic route.

Table 8.18: Investigation of the effect of 2-chloro-5-nitropyridine equivalents on the conversion of **457** into **458**; *Reagents and conditions:* (i) a) 9-BBN (0.5 M in THF), 67 °C, 3 h; b) 2-chloro-5-nitropyridine (**459**), K_2CO_3, $PdCl_2$dppf, DMF:H_2O (10:1), 60 °C, 18 h.

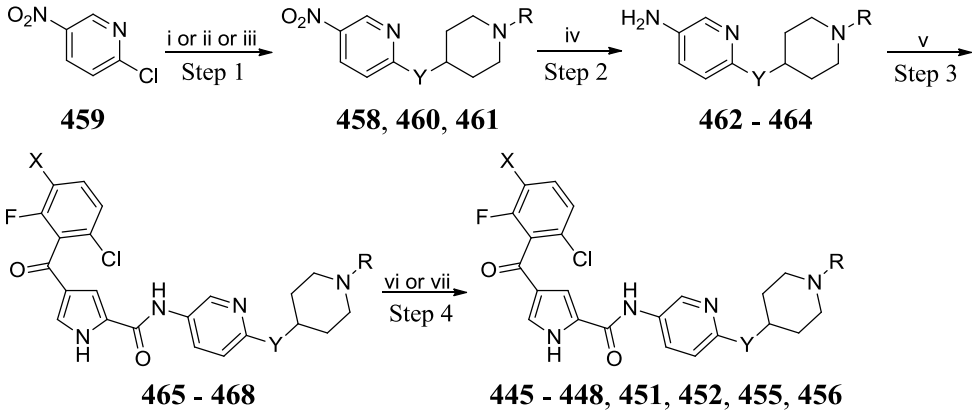


457 **458**

#	2-Chloro-5-nitropyridine Equiv.	Yield
1	1	10%
2	1.5	30%
3	2	40%
4	2.5	35%

The 2-substituted 5-nitropyridines **458**, **460** and **461** were subsequently reduced using palladium-catalysed hydrogenation to give aminopyridines **462**, **463** and **464**, which were converted into the desired final products following a similar reaction sequence to that described for the pyrimidyl analogues in section 8.3.2., namely Mukaiyama amide coupling, acid mediated-Boc deprotection and *in situ* deprotection/Eschweiler-Clarke methylation (Table 8.19). All target compounds were isolated in good yields and high purity.

Table 8.19: Summary of yields for the four steps synthesis of 2-sustituted 5-pyridyl-amides; *Reagents and conditions:* (i) *tert*-butyl 4-(methylamino)piperidine-1-carboxylate, NEt_3, THF, RT to 67 °C, 18 h, 75%; (ii) a) NaH (60% dispersion in mineral oil), 1-Boc-4-hydroxypiperidine, THF, 0 °C to RT, 1 h; b) 2-chloro-5-nitropyridine (**459**), 0 °C to RT, 20 h, 78%; (iii) a) *tert*-butyl 4-methylidenepiperidine-1-carboxylate, 9-BBN (0.5 M in THF), 67 °C, 3 h; b) 2-chloro-5-nitropyridine (**459**), K_2CO_3, $PdCl_2$dppf, DMF:H_2O (10:1), 60 °C, 18 h, 40%; (iv) H_2, 10% Pd/C, MeOH:THF (1:1), 40 °C, 8 h; (v) 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**) or 4-(6-chloro-2-fluoro-3-methoxybenzoyl)-1*H*-pyrrole-2-carboxylic acid (**338**), 2-chloro-1-methylpyridinium iodide, NEt_3, DCM, 42 °C, 24 h; (vi) DCM, TFA, Et_3SiH, RT, 2 h; (vii) formic acid, formaldehyde (37 % wt. in water), 95 °C, 3 h.



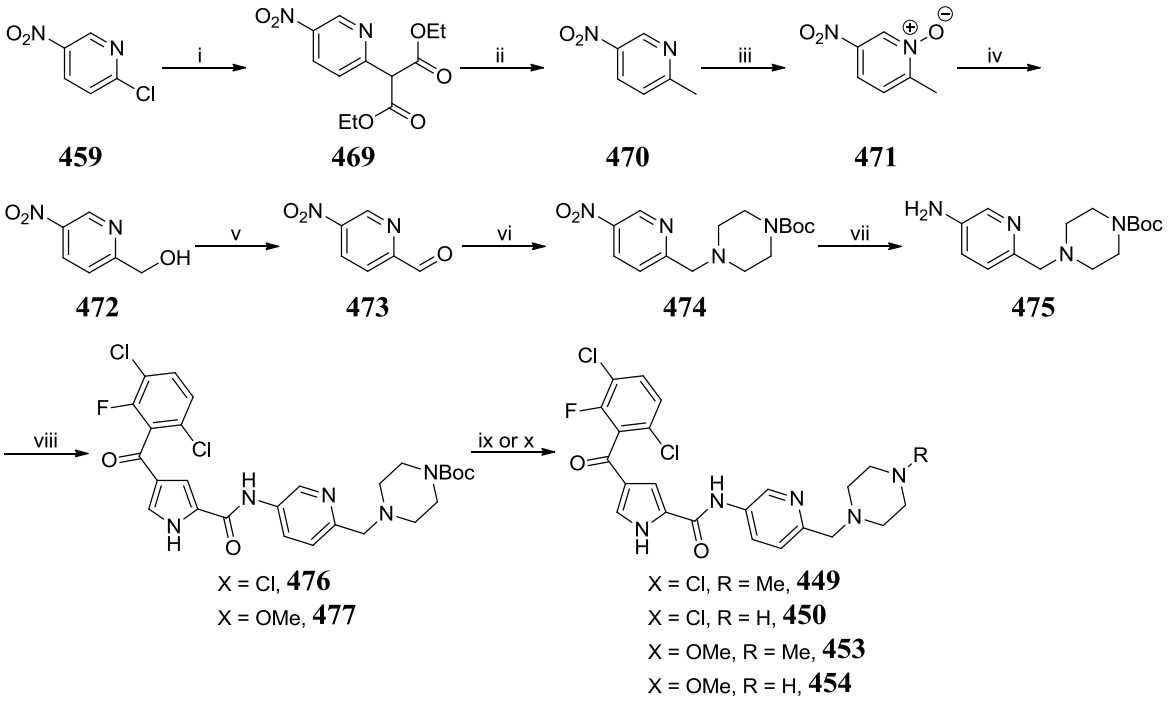
459 **458**, **460**, **461** **462 - 464**

465 - 468 **445 - 448**, **451**, **452**, **455**, **456**

Y	Step 1		Step 2		Step 3			Step 4		
	R	Yield	R	Yield	X	R	Yield	X	R	Yield
NMe	Boc	**460**, 75%	Boc	**462**, 95%	Cl	Boc	**465**, 49%	Cl	H	**446**, 77%
									Me	**445**, 74%
O	Boc	**461**, 78%	Boc	**463**, 96%	Cl	Boc	**466**, 48%	Cl	H	**448**, 77%
									Me	**447**, 71%
C	Boc	**458**, 40%	Boc	**464**, 96%	Cl	Boc	**467**, 42%	Cl	H	**452**, 70%
									Me	**451**, 75%
					OMe	Boc	**468**, 39%	OMe	H	**456**, 76%
									Me	**455**, 71%

The synthesis of the targets incorporating a piperazine side-chain (**449**, **450**, **453** and **454**) began with displacement of the 2-chloro group of **459** with the anion of diethyl malonate to give **469** in 64% yield (Scheme 8.7).[253] A tandem ester hydrolysis/decarboxylation was then carried out in boiling aqueous sulphuric acid to provide 2-methyl-5-nitropyridine

(**470**), which was subsequently *N*-oxidised using *m*-CPBA.[254] A Polonovki reaction was utilised to convert *N*-oxide **471** to pyridylmethanol **472**, which was oxidised to aldehyde **473** by manganese dioxide.[255] Intermediate **474** was prepared *via* reductive amination of **473** with Boc-protected piperazine in trifluoroethanol.[206] Hydrogenation of **474** followed by amide coupling and Boc cleavage/methylation were achieved as described for the pyrimidyl analogues. The yields of all these reactions were consistent with previous observations (Scheme 8.7).



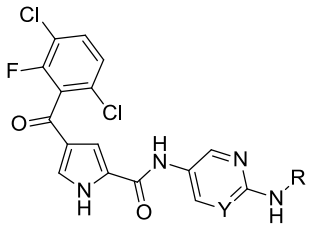
Scheme 8.7: *Reagents and conditions:* (i) a) NaH (60% dispersion in mineral oil), diethyl malonate, THF, 0 °C to RT, 1 h; b) 2-chloro-5-nitropyridine (**459**), 0 °C to RT, 20 h, 64%; (ii) 20% aq. H_2SO_4, 100 °C, 2 h, 95%; (iii) *m*-CPBA (74%), DCM, 0 °C to RT, 16 h, 96%; (iv) a) TFAA, DCM, 0 °C to RT, 16 h; b) MeOH, 0 °C to RT, 8 h, 50%; (v) MnO_2, DCM, RT, 16 h, 61%; (vi) a) *tert*-butyl piperazine-1-carboxylate, $MgSO_4$, trifluoroethanol, 1 h, 38 °C; b) $NaBH_4$, trifluoroethanol, 0 °C to RT, 1 h, 51%; (vii) H_2, 10% Pd/C, MeOH:THF (1:1), 40 °C, 8 h, 95%; (viii) 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**) or 4-(6-chloro-2-fluoro-3-methoxybenzoyl)-1*H*-pyrrole-2-carboxylic acid (**338**), 2-chloro-1-methylpyridinium iodide, NEt_3, DCM, 42 °C, 24 h, (**476**, X = Cl, 28%; **477**, X = OMe, 33%); (ix) DCM, TFA, Et_3SiH, RT, 2 h, (**450**, X = Cl, R = H, 73%; **454**, X = OMe, R = H, 71%); (x) formic acid, formaldehyde (37 % wt. in water), 95 °C, 3 h, (**449**, X = Cl, R = Me, 66%; **453**, X = OMe, R = Me, 76%).

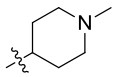
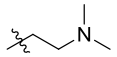
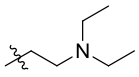
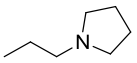
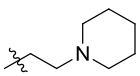
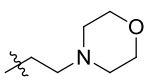
8.4. Investigation of 2-Substituents with a Different Spatial Conformation

8.4.1. SARs and Biological Evaluation of Inhibitors Bearing Basic Substituents

Subtle modifications of the molecular properties of **402** did not allow to access ERK5 inhibitors with low efflux and high permeability in the *in vitro* Caco-2 assay, suggesting that introduction of a basic aliphatic heterocycle at the 2-position of the heteroaromatic conferred affinity for one or more efflux transporters. To address the efflux liability, another approach investigated, was to append alternative 2-substituents with significant structural diversity which might reduce transporter recognition, whilst maintaining low ERK5 inhibitory activity.

Table 8.20: Structure and molecular properties of 5-pyridyl/pyrimidyl amides bearing alternative basic amines at the 2-position (**478 - 486**)

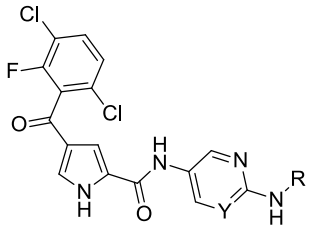


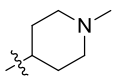
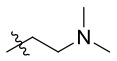
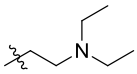
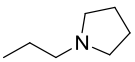
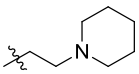
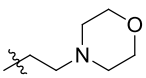
Compound	R	Y	MW	clogP	clogD	tPSA (Å^2)	HBA	HBD
444		C	490	3.6	2.6	90	7	3
402		N	491	3.8	2.4	103	8	3
478		N	465	3.6	1.9	103	8	3
479		C	492	4.1	2.6	90	7	3
480		N	493	4.3	2.4	103	8	3
481		C	490	3.7	2.7	90	7	3
482		N	491	3.9	2.5	103	8	3
483		C	504	4.2	2.9	90	7	3
484		N	505	4.5	2.7	103	8	3
485		C	506	3.0	2.7	99	8	3
486		N	507	3.3	2.5	112	9	3

A set of structurally diverse derivatives, incorporating basic side-chains at the 2-position of the 5-pyridyl/pyrimidyl amide, was therefore prepared (Table 8.20). This library of compounds, which place the basic centre at a different position relative to **402** and **444**, would allow further SARs to be established. All compounds retained high tPSA and a similar number of HBA and HBD compared with **402** and **444** (Table 8.20).

ERK5 inhibitory activity for these pyridyl- and pyrimidyl-linked analogues was comparable with **402** and **444** (Table 8.21), indicating that a broad range of substituents incorporating a basic amine was tolerated in this position. Interestingly, the increased conformational flexibility of the side-chains did not lead to an entropic penalty for binding. Modulation of the basicity of the basic centre appeared to affect ERK5 inhibition with analogues **485** and **486**, suffering from a 3- to 4-fold reduction in potency.

Table 8.21: ERK5 inhibitory activity of 5-pyridyl/pyrimidyl amides bearing alternative basic amines at the 2-position (**478** - **486**)



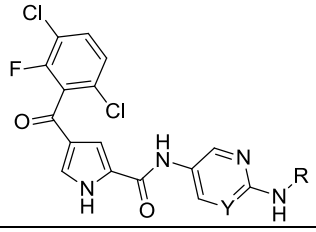
Compound	R	Y	ERK5 IC_{50} (nM)[a]	L.E.	LipE
444		C	24 ± 20[b]	0.32	5.0
402		N	14 ± 3	0.33	5.5
478		N	17 ± 3	0.34	5.9
479		C	24 ± 15[c]	0.32	5.0
480		N	19 ± 2	0.32	5.3
481		C	24 ± 13[b]	0.32	4.9
482		N	18 ± 2	0.32	5.3
483		C	11 ± 3[b]	0.32	5.1
484		N	12 ± 2	0.32	5.3
485		C	108 ± 60	0.28	4.2
486		N	49 ± 15	0.29	4.8

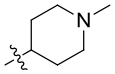
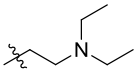
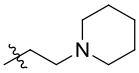
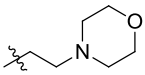
[a] Determinations ± standard deviation (mean of n = 4); [b] n = 6; [c] n = 8

Compounds **480**, **483**, **484** and **486** were progressed to *in vitro* ADME profiling (Table 8.22). The diethylamine and morpholine moieties improved solubility relative to **402**. All the compounds had moderate plasma protein binding and moderate to high metabolic instability in mouse liver microsomes *in vitro*, indicating that long aliphatic

chains at the heteroaromatic 2-position might introduce a metabolic liability. Interestingly, the clearance of pyrimidyl derivative **484** was twice lower than the clearance of its pyridyl matched pair **483**. The Caco-2 efflux ratio of these inhibitors was still very high, with low apical to basolateral apparent permeability, indicating that variation in the structure of the inhibitors did not abrogate transporter recognition.

Table 8.22: ERK5 inhibitory activity and *in vitro* ADME properties for selected inhibitors

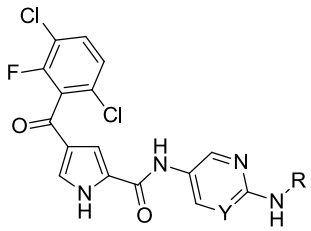


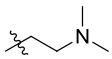
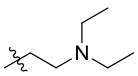
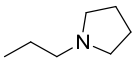
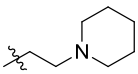
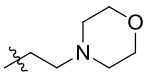
Compound	R	Y	ERK5 IC_{50} (nM)[a]	Sol (μM)	Ppb F_u	MLM Cl_{int}[c]	Caco-2 AB[d] (ER)
402		N	14 ± 3	10 - 100	0.067	19	0.3 (99)
480		N	19 ± 2	> 100	*n.d.*	41	0.4 (88)
483		C	11 ± 3[b]	30 - 100	0.058	62	0.5 (64)
484		N	12 ± 2	30 - 100	0.113	32	0.5 (60)
486		N	49 ± 15	> 100	0.039	129	0.5 (97)

[a] Determinations ± standard deviation (mean of n = 4); [b] n = 6; [c] μL/min/mg protein; [d] P_{app} 10^{-6} $cm.s^{-1}$; *n.d.* = not determined

The cellular activity of this series of compounds was also determined in HEK293 cells (Table 8.23). All the compounds had IC_{50} value between 80 and 150 nM, with derivative **482** being the most active. Compounds **485** and **486,** which were slightly less active in the enzymatic assay retained similar activity in cells relative to the other compounds of the series. The pyridyl and pyrimidyl matched pair had similar activity.

Table 8.23: Comparison of ERK5 inhibitory activity in the IMAP cell-free assay, with ERK5 inhibition in the HeLa and HEK293T cellular assays



Compound	R	Y	ERK5 IC_{50} (nM)*[a]	HeLa IC_{50} (μM)[b]	HEK293T IC_{50} (μM)[c]
478		N	17 ± 3	*n.d.*	0.12 ± 0.03
479		C	24 ± 15[e]	*n.d.*	0.15 ± 0.10
480		N	19 ± 2	0.49	0.15 ± 0.02
481		C	24 ± 13[d]	*n.d.*	0.12 ± 0.02
482		N	18 ± 2	*n.d.*	0.08 ± 0.03
483		C	11 ± 3[d]	*n.d.*	0.14 ± 0.01
484		N	12 ± 2	0.07	0.09 ± 0.02
485		C	108 ± 60	*n.d.*	0.13 ± 0.01
486		N	49 ± 15	0.35	0.14 ± 0.02

* ERK5 inhibitory activity in the cell-free IMAP assay; [a] Determinations ± standard deviation (mean of n = 4); [b] Data from a single determination; [c] n = 2; [d] n = 6; [e] n = 8; *n.d.* = not determined

8.4.2. SARs and Biological Evaluation of Inhibitors Bearing Neutral Substituents

The high efflux ratio and low permeability of all the compounds incorporating a basic amine in the pyridyl/pyrimidyl 2-position suggested that the basicity of the side-chain was driving transporter recognition. Previous SAR had established that the basic centre was providing a potency advantage and molecular modelling suggested that it might be interacting with a glutamate residue on the exit of the active site (Figure 8.5).

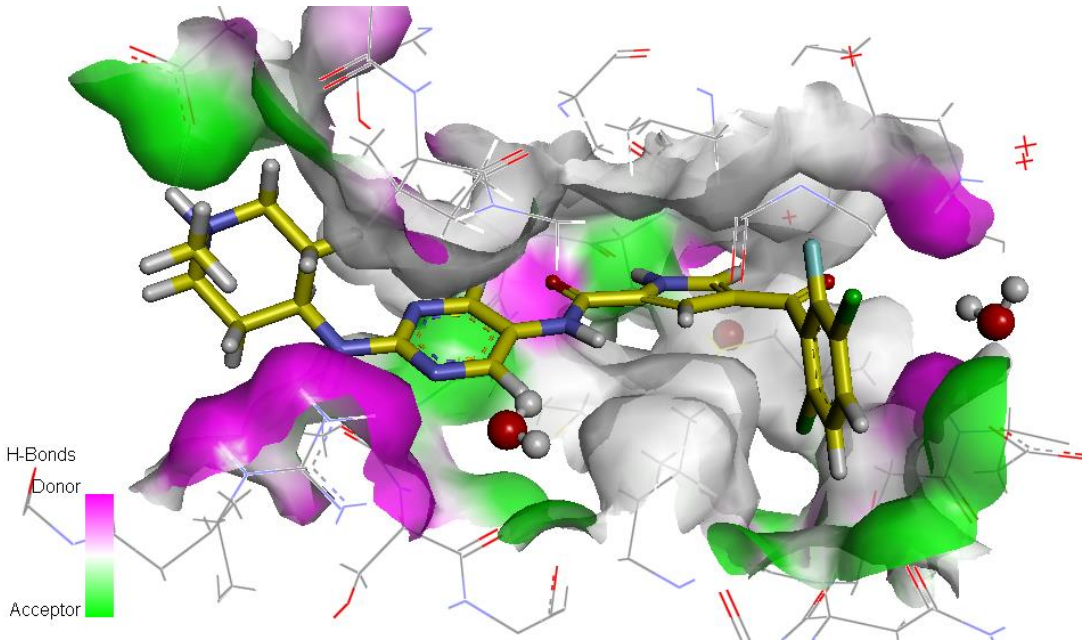
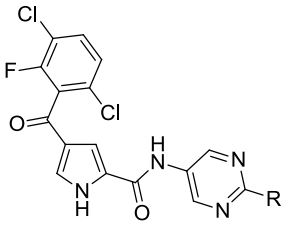
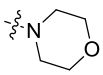
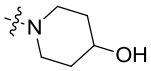
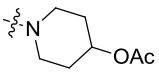


Figure 8.5: Docking of **402** in the ATP-binding site of ERK5 (PDB code 4b99) [194]

Only a small set of alternative non-basic pyrimidine 2-substituents had previously been investigated and resulted in a significant reduction of ERK5 potency for **488** and **490** (Table 8.24).[105] The 4-hydroxypiperidine moiety in inhibitor **489**, which places a hydrogen bond donor group in the vicinity of the glutamate residue, was tolerated, and **489** was equipotent with **487**. This encouraging result suggested that incorporation of neutral aliphatic substituents, which could mimic the interaction of the basic nitrogen or participate in alternative binding interactions, might improve ERK5 binding affinity.

Table 8.24: ERK5 inhibitory activity of 2-substituted 5-pyrimidyl amides



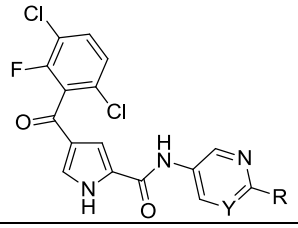
Compound	R	ERK5 IC_{50} (μM)[a]
487	H	0.32 ± 37[b]
488		1.5 ± 0.2
489		0.53 ± 0.09[c]
490		9.7 ± 7.3

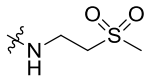
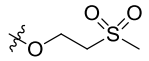
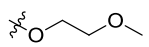
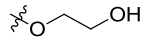
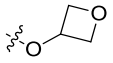
[a] Determinations ± standard deviation (mean of n = 2); [b] n = 9; [c] n = 4

A small library of compounds introducing (methylsulfonyl)ethyl, methoxyethyl, oxetane or hydroxyethyl groups at the 2-position of pyridyl or pyrimidyl amides was synthesised. These side-chains were linked to the pyridyl/pyrimidyl ring *via* an amine or an ether group.

These compounds retained high tPSA and a similar number of HBD and HBA compared with the basic analogues (Table 8.25).

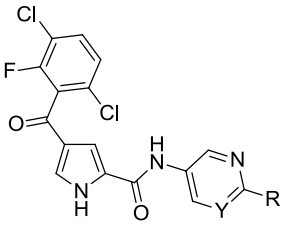
Table 8.25: Structure and molecular properties of 5-pyridyl/pyrimidyl amides bearing a neutral side-chain at the 2-position (**491 - 496**)

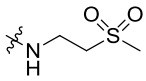
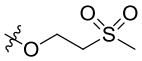
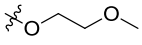
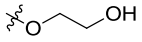
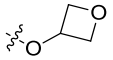


Compound	R	Y	MW	clogP	clogD	tPSA (Å^2)	HBA	HBD
318	H	C	378	3.8	3.8	75	5	2
487		N	379	4.0	4.0	88	6	2
491		C	499	2.6	2.0	121	8	3
492		N	500	3.0	1.8	134	9	3
493		C	500	2.8	2.8	118	8	2
494		C	452	3.7	3.7	93	7	2
495		C	438	3.1	3.1	104	7	3
496		C	450	3.6	3.6	93	7	2

A significant reduction in ERK5 inhibitory activity was apparent in the pyridyl series, indicating that introduction of neutral flexible substituents might induce an entropic penalty for binding (Table 8.26). Compound **495** which displays a terminal hydrogen bond donor was the most potent compound of the pyridyl series. Introduction of the (methylsulfonyl)ethyl group in pyrimidyl amide **492** conferred a 2-fold improvement in ERK5 inhibition compared with **487**, suggesting that incorporation of neutral substituents might have an opposite effect in the pyridyl and pyrimidyl series. None of these compounds achieved the IC_{50} threshold of 100 nM, required to be progressed in the cascade and submitted for *in vitro* ADME evaluation.

Table 8.26: ERK5 inhibitory activity of 5-pyridyl/pyrimidyl amides bearing a neutral side-chain at the 2-position (**491 - 496**)



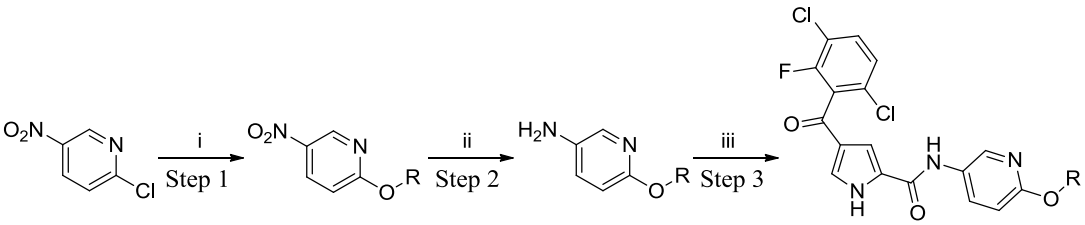
Compound	R	Y	ERK5 IC_{50} (μM)[a]	L.E.	LipE
318	H	C	0.066 ± 0.033[c]	0.39	3.4
487		N	0.32 ± 37[d]	0.36	2.5
491		C	0.21 ± 0.04[b]	0.28	4.6
492		N	0.15 ± 0.04	0.29	5.0
493		C	0.43 ± 0.17	0.27	3.5
494		C	1.2 ± 0.4	0.27	2.2
495		C	0.32 ± 0.09	0.31	3.4
496		C	1.1 ± 0.3	0.27	2.4

[a] Determinations ± standard deviation (mean of n = 4); [b] n = 6; [c] n = 7; [d] n = 9

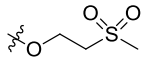
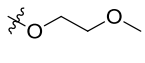
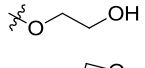
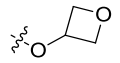
8.4.3. Synthesis

Pyridyl derivatives with oxygen-linked substituents were prepared following a three step sequence of previously optimised reactions (Table 8.27). Sodium hydride was utilised to generate alkoxides from commercially available alcohols, which were engaged in S_NAr reactions with 2-chloro-5-nitropyridine (**459**). The resulting 2-alkoxy-5-nitropyridines **498 - 500** were reduced using palladium-catalysed flow hydrogenation and coupled to pyrrole carboxylic acid **250** using the Mukaiyama procedure. All reactions proceeded in moderate to excellent yields (Table 8.27).

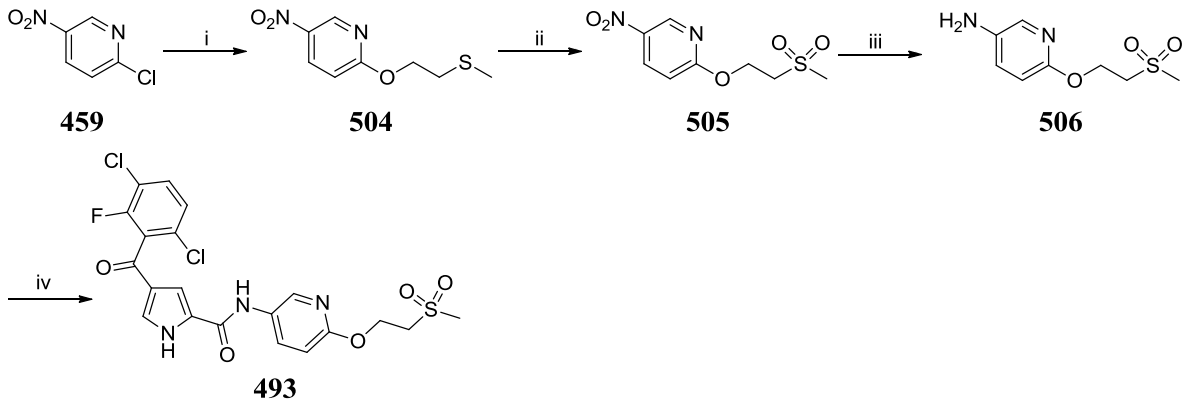
Table 8.27: Summary of yields for the three step synthesis of 2-alkoxy 5-pyridyl-amides; *Reagents and conditions:* (i) a) NaH (60% dispersion in mineral oil), R-OH, THF, 0 °C to RT, 1 h; b) 2-chloro-5-nitropyridine (**459**), 0 °C to RT, 20 h; (ii) H_2, 10% Pd/C, MeOH:THF (1:1), 40 °C, 8 h; (iii) 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**), 2-chloro-1-methylpyridinium iodide, NEt_3, DCM, 42 °C, 24 h.



459 **497 - 500** **501 - 503** **494 - 496**

R	Step 1	Step 2	Step 3
	**497**, 0%	/	/
	**498**, 69%	**501**, 96%	**494**, 51%
	**499**, 41%	**502**, 95%	**495**, 20%
	**500**, 86%	**503**, 93%	**496**, 28%

The first step of this reaction sequence failed with 2-(methylsulfonyl)ethanol due to a retro-Michael reaction taking place and leading exclusively to the formation of 5-nitro-pyridin-2-ol. To prevent this side-reaction, the S_NAr was conducted with the anion of 2-(methylthio)ethanol to form **504**, which was subsequently oxidised using Oxone® to give **505** in 57% yield (Scheme 8.8). The nitro reduction and amide coupling were conducted as previously described.



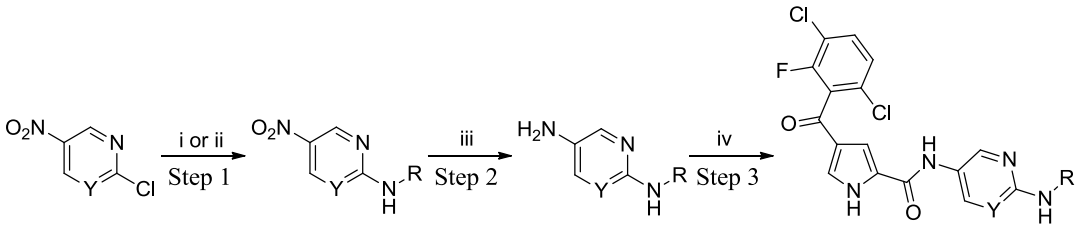
459 **504** **505** **506**

493

Scheme 8.8: (i) a) NaH (60% dispersion in mineral oil), 2-(methylthio)ethanol, THF, 0 °C to RT, 1 h; b) 2-chloro-5-nitropyridine, 0 °C to RT, 20 h, 88%; (ii) Oxone®, MeOH, H_2O, RT, 24 h, 57%; (iii) H_2, 10% Pd/C, MeOH, 40 °C, 8 h, 95%; (iv) 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**), 2-chloro-1-methylpyridinium iodide, NEt_3, DCM, 42 °C, 24 h, 24%.

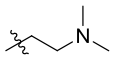
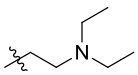
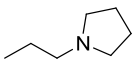
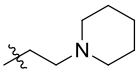
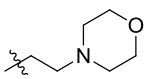
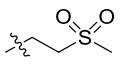
Derivatives with NH-linked side-chains were also prepared following a three step reaction sequence using a similar array of synthetic transformations, namely S_NAr reaction, palladium-catalysed nitro hydrogenation and Mukaiyama amide coupling (Table 8.28). A complex mixture of tertiary and secondary amides was obtained for the final coupling step, resulting in low to moderate yields.

Table 8.28: Summary of yields for the three step synthesis of 2-alkylamine 5-pyridyl/pyrimidyl-amides; *Reagents and conditions:* (i) R-NH_2, NEt_3, THF, 0 °C to RT, 3 h; (ii) R-NH_2, NEt_3, THF, 67 °C, 16 h; (iii) H_2, 10% Pd/C, MeOH:THF (1:1), 40 °C, 8 h; (iv) 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**), 2-chloro-1-methylpyridinium iodide, NEt_3, DCM, 42 °C, 24 h.



459; Y = C
414; Y = N

507 - 517 **518 - 528** **478 - 492**

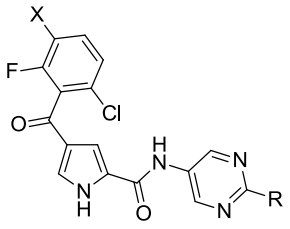
R	Y	Step 1	Step 2	Step 3
	N	**507**, 74%	**518**, 96%	**478**, 11%
	C	**508**, 59%	**519**, 98%	**479**, 27%
	N	**509**, 93%	**520**, 95%	**480**, 34%
	C	**510**, 63%	**521**, 93%	**481**, 20%
	N	**511**, 87%	**522**, 92%	**482**, 29%
	C	**512**, 96%	**523**, 97%	**483**, 22%
	N	**513**, 93%	**524**, 91%	**484**, 41%
	C	**514**, 65%	**525**, 95%	**485**, 14%
	N	**515**, 91%	**526**, 93%	**486**, 36%
	C	**516**, 63%	**527**, 95%	**491**, 17%
	N	**517**, 46%	**528**, 55%	**492**, 45%

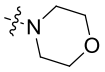
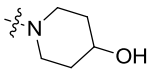
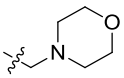
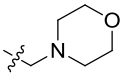
8.5. Investigation of Alternative Methylene Linked Amines at the 2-Position of 5-Aminopyridyl Amides

8.5.1. SARs and Biological Evaluation

During the course of the optimisation of the pyrimidyl spacer (see section 8.3.1.), compound **409** was identified as a sub-100 nM ERK5 inhibitor (Table 8.29). This positive result was really unexpected since all previously synthesised inhibitors missing the terminal basic nitrogen had failed to achieve low nanomolar potency. Introduction of the methylene spacer resulted in a 28-fold increase in potency relative to **488**. The significant improvement in ERK5 inhibition, emerging from the addition of the methylene group, was confirmed by the 0.13 μM IC_{50} value of **529**, the *meta*-methoxybenzoyl matched pair of **409**.

Table 8.29: ERK5 inhibitory activity of 2-substituted 5-pyrimidyl amides

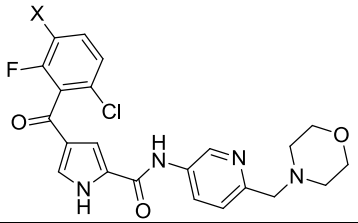


Compound	X	R	ERK5 IC_{50} (μM)[a]
487	Cl	H	0.32 ± 37[b]
488	Cl		1.5 ± 0.2
489	Cl		0.53 ± 0.09[c]
409	Cl		0.053 ± 0.016
529	OMe		0.13 ± 0.03

[a] Determinations ± standard deviation (mean of n = 2); [b] n = 9; [c] n = 4

The pyridyl amide analogues of **409** and **529** were also synthesised. Compounds **530** and **531** retained low nanomolar ERK5 inhibitory activity (Table 8.30). Inhibitor **530** had high protein plasma binding and moderate solubility, despite the presence of the water-solubilising morpholine moiety. Inhibitor **530** was subject to rapid metabolism in mouse liver microsomes *in vitro*. The Caco-2 efflux for this compound was high, but moderate apparent permeability (P_{app} = 3.7 × 10^{-6} cm/s) across the Caco-2 monolayer was observed. This result was encouraging since several kinase inhibitors approved for clinical use are substrates of efflux transporters but retained good oral bioavailability owing to their moderate to high permeability.[256]

Table 8.30: ERK5 inhibitory activity and *in vitro* ADME properties of **530** and **531**



Compound	X	ERK5 IC_{50} (nM)[a]	Ppb F_u	Sol (μM)	MLM Cl_{int}[b]	Caco-2 AB[c] (ER)
530	Cl	31 ± 6	0.047	30-100	92	3.7 (9)
531	OMe	43 ± 21	*n.d.*	*n.d.*	*n.d.*	*n.d.*

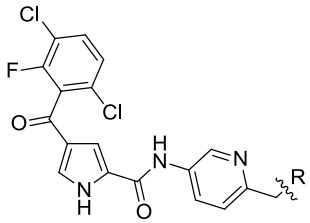
[a] Determinations ± standard deviation (mean of n = 4); [b] μL/min/mg protein; [c] P_{app} 10^{-6} $cm.s^{-1}$; *n.d.* = not determined

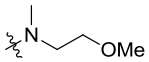
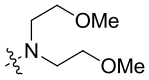
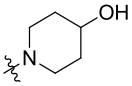
In order to determine the origin of potency gain, a small set of inhibitors incorporating methylene-linked amines was prepared (Table 8.31). Dimethylamine analogue **532** retained low nanomolar ERK5 inhibitory activity and achieved a high ligand efficiency of 0.36. Replacement of the dimethyl amine with a piperidine in inhibitor **533** led to a 2-fold improvement in potency. These data demonstrate that the morpholine oxygen of **530** was not contributing to potency. Ring opening of the morpholine to an aliphatic side-chain was tolerated, with **534** having similar potency to **530**. A slight reduction in ERK5 inhibition was apparent for compound **535**, suggesting that the flexibility of the aliphatic chains might lead to an entropic penalty for binding. The morpholine oxygen was also moved outside of the ring to give 4-hydroxypiperidine derivative **536**, which had sub-10 nM ERK5 inhibitory activity. Overall, these results demonstrated that the basicity of the benzylic nitrogen is driving potency. Indeed, compounds with higher basicity relative to **530**, all had superior ERK5 binding affinity, whereas compounds **534** and **535** had a marginal decrease in activity (Table 8.31).

Inhibitors **532** and **536** had excellent solubility and moderate plasma protein binding (Table 8.31). Unsurprisingly, **532** had high metabolic instability in mouse liver microsomes, with *N*-demethylation suspected to be the major route of metabolism. Compound **536** had good *in vitro* microsomal stability. Derivative **532** retained undesired high efflux in the Caco-2 assay and similar apparent permeability relative to **530**, indicating that reduction of the molecular weight had not abrogated efflux pump recognition. Inhibitor **536** had the lowest apical to basolateral apparent permeability observed in the pyrrole carboxamide series and a very high efflux ratio (ER = 132) compared with **530**, suggesting that incorporation of an additional HBD increases affinity for efflux transporters. These results demonstrate that substitution at the 2-position of

5-pyridyl/pyrimidyl amides with basic side-chains leads to low permeability and high efflux independently of the position, the shape or the size of the basic substituent.

Table 8.31: ERK5 inhibitory activity and *in vitro* ADME properties of **532 - 536**

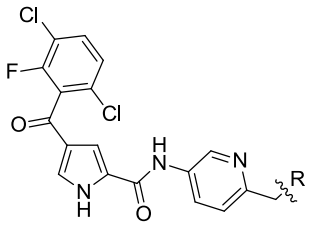


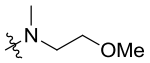
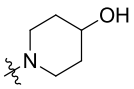
Compound	R	ERK5 IC_{50} (nM)[a]	Ppb F_u	Sol (µM)	MLM Cl_{int}[b]	Caco-2 AB[c] (ER)
532		21 ± 2	0.0132	> 100	52	2.7 (17)
533		9 ± 1	*n.d.*	*n.d.*	*n.d.*	*n.d.*
534		38 ± 6	*n.d.*	*n.d.*	*n.d.*	*n.d.*
535		115 ± 18	*n.d.*	*n.d.*	*n.d.*	*n.d.*
536		8 ± 2	0.099	> 100	17	0.2 (132)

[a] Determinations ± standard deviation (mean of n = 4); [b] µL/min/mg protein; [c] P_{app} 10^{-6} cm.s^{-1}; *n.d.* = not determined

The cellular activity of the compounds with IC_{50} values below 100 nM in the biochemical assay was determined in HEK293 cells (Table 8.32). With the exception of compound **536**, all compounds had low nanomolar activity in cells similar to the activity determined in the biochemical assay. The difference of potency for inhibitor **536** could be explained by its poor cellular permeability as determined in the Caco-2 assay. It appears the introduction of methylene linked amine at the 2-position of 5-pyridyl amide conferred improved cellular activity relative to all the side-chains previously investigated. Indeed, all the other inhibitors tested in the HEK293 assay suffered from a significant reduction of potency compared with their biochemical activity (see section 8.3.1. Table 8.8 and section 8.4.1. Table 8.23).

Table 8.32: Comparison of ERK5 inhibitory activity in the IMAP cell-free assay, with ERK5 inhibition in the HEK293T cellular assay

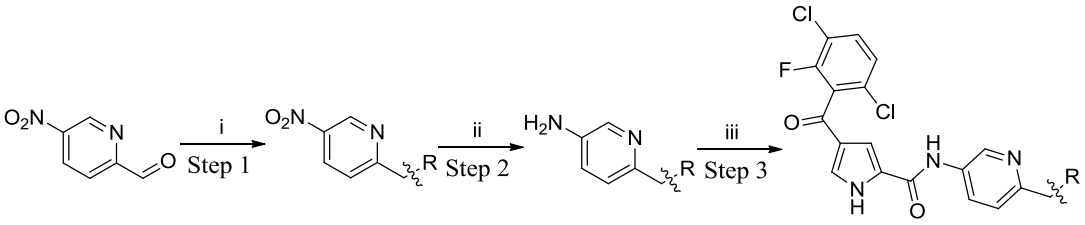


Compound	R	ERK5 IC_{50} (nM)*[a]	HEK293T IC_{50} (nM)[b]
530		31 ± 6	31 ± 9
532		21 ± 2	25 ± 10
533		9 ± 1	13 ± 2
534		38 ± 6	40 ± 14
536		8 ± 2	44 ± 7

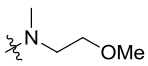
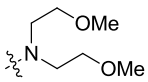
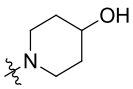
* ERK5 inhibitory activity in the cell-free IMAP assay; [a] Determinations ± standard deviation (mean of n = 4); [b] n = 3

8.5.2. Synthesis

Table 8.33: Summary of yields for the three step synthesis of 2-methylamine 5-pyridyl-amides; *Reagents and conditions:* (i) R-NH_2, $NaBH(OAc)_3$, DCE, RT, 16 h; (ii) H_2, 10% Pd/C, MeOH:THF (1:1), 40 °C, 8 h; (iii) 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**), 2-chloro-1-methylpyridinium iodide, NEt_3, DCM, 42 °C, 24 h.



473 **537 - 542** **543 - 548** **530 - 536**

R	Step 1	Step 2	Step 3
	**537**, 68%	**543**, 90%	**530**, 44%
	**538**, 63%	**544**, 93%	**532**, 8%
	**539**, 59%	**545**, 95%	**533**, 27%
	**540**, 69%	**546**, 95%	**534**, 18%
	**541**, 79%	**547**, 95%	**535**, 20%
	**542**, 75%	**548**, 96%	**536**, 23%

Compound **473** was a versatile intermediate in the synthesis of methylene-linked amines. It was prepared following the synthetic route described in section 8.3.4. Reductive amination of **473** with a range of commercially available amines was achieved in 1,2-dichloroethane using sodium triacetoxyborohydride as reducing reagent (Table 8.33). Nitro reduction and amide coupling were performed using the standard methodology previously described.

8.6. Summary

Exploration of the SAR around the *para* position of the heteroaromatic amide substituent has led to the identification of compounds with improved potency against ERK5 relative to **402**, in both biochemical and cellular assays. Incorporation of a methylene spacer between the heteroaromatic and the basic aliphatic heterocycle has provided a set of compounds with sub-10 nM ERK5 inhibitory activities. Replacement of the basic side-chain with neutral substituents was not tolerated with respect to ERK5 potency.

All ERK5 inhibitors, containing a basic centre, suffered from high efflux and low permeability in the Caco-2 assay, translating to poor *in vivo* bioavailability for several compounds. It is assumed that the basic centre increases their propensity for recognition by efflux transporters, such as P-gp or BCRP. A range of strategies to address the efflux liability has been investigated without success. This work illustrates the challenge in balancing potency and permeability.

A co-crystal structure of ERK5 with inhibitors **318** and **406** will be required to identify potential binding interactions *via* substituents at the 2-position of 5-aminoheteroaromatic amides and guide the next round of SARs.

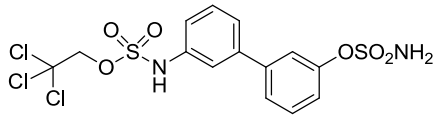
Chapter 9. Conclusions and Future Directions

The two medicinal chemistry programs described in this thesis encompassed diverse chemistry, biology and stages of the drug discovery process.

9.1. Design of Small-Molecule Inhibitors of Sulfatase-2

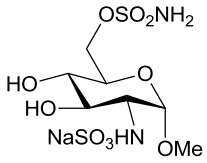
Sulf-2 has been implicated in the progression of several cancers including hepatocellular carcinoma (HCC). The aim of the Sulf-2 project was to identify chemical tools for use in experiments *in vitro* to determine whether low micromolar Sulf-2 inhibitors could be selective over other members of the human sulfatase family and block cancer cell growth. The Sulf-2 project was in the early target validation phase and the only known series of inhibitors were monosaccharide sulfamate mimics of the endogenous substrate HSPGs.

In an attempt to identify non-saccharide Sulf-2 inhibitors, a *de novo* design strategy was employed, based on an analysis of functional groups in the endogenous substrate HSPGs believed to be important for binding of Sulf-2. Biphenyl and biphenyl ether sulfamates, positioning a polar moiety in similar regions of space to those occupied by sulfate and carboxylate groups in heparin were prepared. Novel sulfamate protecting groups were developed to enable a more flexible approach to the synthesis of biphenyl and biphenyl ether *O*-sulfamates.



162

Sulf-2 IC_{50} = 156 μM



5

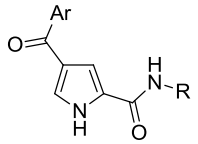
No Sulf-2 inhibition @ 1 mM

Preliminary sulfatase inhibition data have been generated, indicating that biphenyl and biphenyl ether sulfamates exhibit superior potency against Sulf-2 than monosaccharide glucosamine **5**. Incorporation of polar functionalities around the B-ring did not improve inhibitory activity, challenging the initial design hypothesis. Unexpectedly, the non-polar trichloroethyl protected sulfates had improved Sulf-2 inhibition, with compound **162** having an IC_{50} value of 156 μM. This compound was significantly more active than monosaccharide **5**, which did not inhibit Sulf-2 in our biochemical assay. Selectivity over other members of the sulfatase family was not achieved with these aromatic sulfamates.

Potential future design options include replacement of trichloroethyl protected sulfates with sulfonamides. Libraries of such derivatives could easily be prepared and would provide further SARs in this region of the scaffold. Isolation of Sulf-2 is very challenging and a more robust isolation/biochemical assay will be required for this project to become a full drug discovery program. The limitations of the *de novo* design strategy suggested that alternative methods for hit identification might need to be employed.

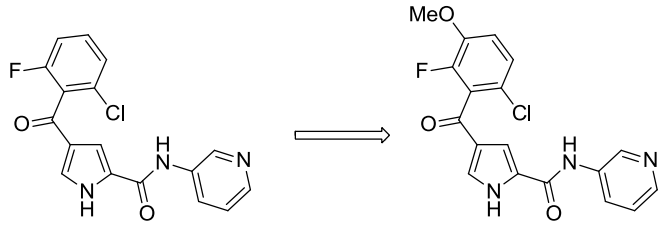
9.2. Design of Small-Molecule Inhibitors of ERK5

The ERK5 project was a more advanced program, in the lead optimisation phase. Extensive ERK5 potency SARs around the pyrrole carboxamide core **A** had previously been established. In this thesis, optimisations of the aroyl and the amide substituents were attempted, with the aim to improve both potency and ADMET properties.



A

Introduction of *meta*-alkoxy substituents on the aroyl ring was investigated with the objective to improve the binding affinity *via* interaction with residues of a lipophilic pocket identified in the p38α-derived homology model. The *meta*-methoxy group in **341** led to a 6-fold improvement in potency against ERK5, and provided inhibitors equipotent with those incorporating the trihalogenated aroyl pattern.

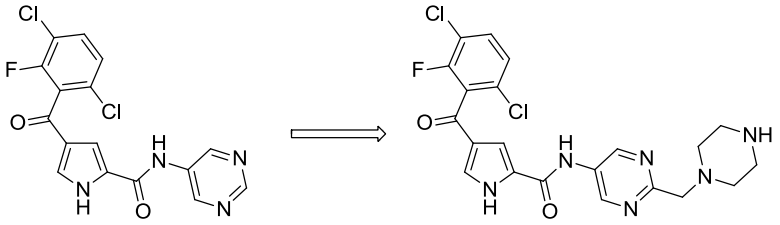


232, ERK5 IC_{50} = 0.58 μM **341**, ERK5 IC_{50} = 0.091 μM

Obtaining a co-crystal structure of ERK5 with selected pyrrole carboxamide inhibitors, such as **341**, will guide the future work around the benzoyl substituents. The SAR studies presented in this thesis have shown that groups larger than methoxy were detrimental to the ERK5 inhibition. Preparation of close analogues, incorporating a *meta*-$OCHF_2$ or OCF_3 group would be of interest.

Attempts to access a lipophilic pocket in the ERK5 binding site *via* alkylation of the amide was attempted. All tertiary amides suffered from a significant decrease in ERK5 inhibitory activity (ERK5 IC_{50} > 1 μM) and reduced selectivity over p38α. Substitution at the 2- or 4-position of 3-aminopyridine amides also failed to improve potency against ERK5 through interaction with this putative lipophilic pocket.

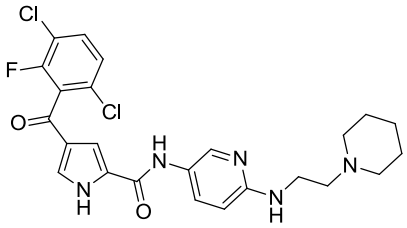
Introduction of substituents bearing a basic centre at the 2-position of 5-aminopyrimidyl amides resulted in significant improvement of ERK5 inhibition, leading to the identification of compounds with sub-20 nanomolar IC_{50} values, such as piperazine derivative **406**. Although, this compound had good cellular activity, it suffered from a high efflux ratio and low membrane permeability in the Caco-2 assay, and as a result, suffered from poor oral bioavailability in an *in vivo* mouse PK study.



487, ERK5 IC_{50} = 316 nM

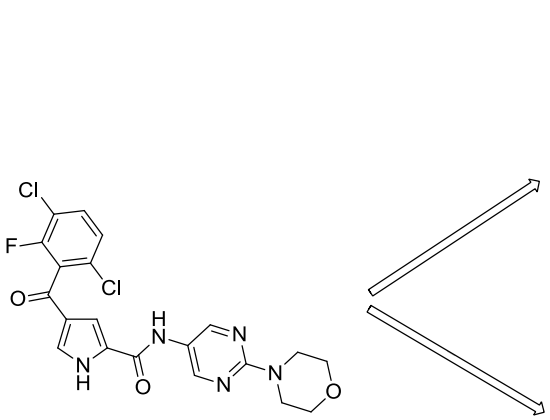
406, ERK5 IC_{50} = 8 nM
Cell IC_{50} = 240 nM
Caco-2 ER = 3.7

Reducing the tPSA and minimising the number of hydrogen bond donor and acceptor groups in the molecule through replacement of the pyrimidine with a pyridine led to compounds with similar pharmacological and *in vitro* ADME profiles. All compounds with an efflux ratio above 2 in the Caco-2 assay had poor *in vivo* oral bioavailability. Introduction of basic side-chains with a different spatial conformation provided compounds, such as **483**, which retained low nanomolar ERK5 inhibitory activity. However, all of these derivatives had very high efflux ratio and poor apical to basolateral permeability in the Caco-2 assay. Inhibitors bearing a neutral substituent at the 2-position had reduced potency against ERK5.

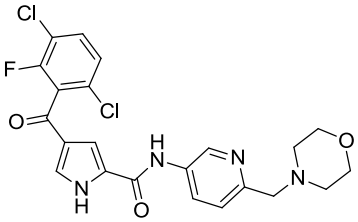


483, ERK5 IC_{50} = 11 nM
Cell IC_{50} = 140 nM
Caco-2 ER = 64

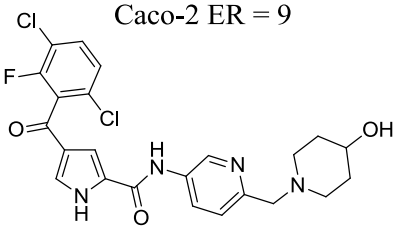
Introduction of a methylene spacer in **488**, resulted in a 28-fold increase in potency and provided compound with a basic centre in a different position. Related analogue **530** retained low nanomolar ERK5 inhibition and had improved permeability in the Caco-2 assay despite a high efflux ratio. A small library of derivatives was prepared, leading to the identification of compound **536** which had improved ERK5 inhibitory activity but a higher efflux ratio and reduced permeability relative to **530**.



488, ERK5 IC_{50} = 1.5 μM



530, ERK5 IC_{50} = 31 nM
Cell IC_{50} = 31 nM
Caco-2 ER = 9



536, ERK5 IC_{50} = 8 nM
Cell IC_{50} = 44 nM
Caco-2 ER = 132

The work presented in this thesis has extended the SARs around the pyrrole carboxamide core, and has highlighted structural modifications which improve potency against ERK5 and affect ADMET properties. Principally, introduction of basic substituents at the 2-position of 5-aminoheteroaromatic amides significantly improved ERK5 binding affinity but was detrimental to the permeability of the compounds, leading to inhibitors with poor oral bioavailability. Past SAR studies have demonstrated the limitations of the different homology models used to guide compound design in the pyrrole carboxamide series. A

co-crystal structure of ERK5 with key inhibitors is now required to guide the next round of SARs.

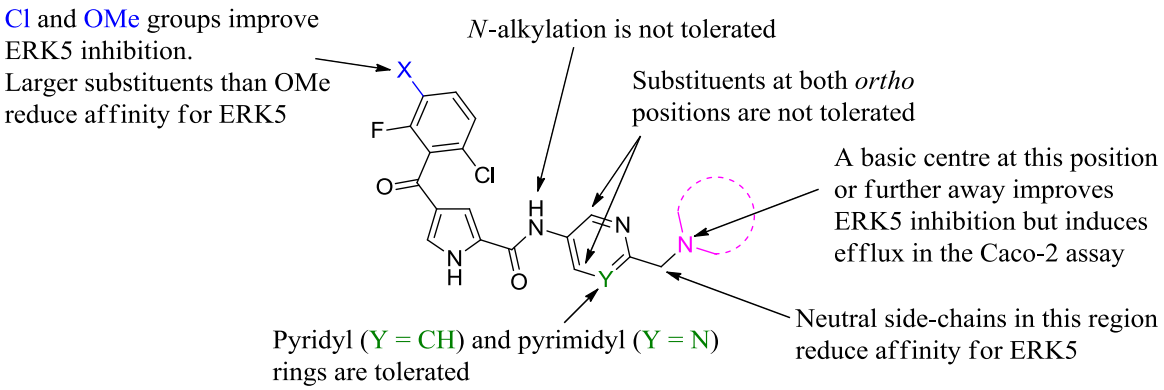


Figure 9.1: Summary of SARs for the pyrrole carboxamide series developed or confirmed by the work contained in this thesis

Chapter 10. Experimental

10.1. Summary of Generic Reactions, Analytical and Chromatographic Conditions

10.1.1. Chemicals and Solvents

All commercial reagents were purchased from Sigma-Aldrich Chemical Company, Alfa Aesar, Apollo Scientific or Tokyo Chemical Industry UK Ltd. The chemicals were of the highest available purity. Unless otherwise stated, chemicals were used as supplied without further purification. Anhydrous solvents were obtained from AcroSeal™ or Aldrich SureSeal™ bottles and were stored under nitrogen. Petrol refers to the fraction with a boiling point between 40 and 60 °C.

10.1.2. Chromatography

Thin layer chromatography utilised to monitor reaction progress was conducted on plates pre-coated with silica gel Merck $60F_{254}$ or Merck NH_2F_{254S}. The eluent was as stated (where this consisted of more than one solvent, the ratio is stated as volume:volume) and visualisation was either by short wave (254 nm) ultraviolet light, or by treatment with the visualisation reagent stated followed by heating. 'Flash' medium pressure liquid chromatography (MPLC) was carried out either on a Biotage SP4 automated purification system or a Varian 971-FP automated purification system, using pre-packed Varian or Grace silica or amino-bonded silica cartridges.

10.1.3. Microwave Reactions

All reactions carried out in a microwave were performed in a Biotage Initiator with Sixty robot.

10.1.4. Analytical Techniques

Melting points were determined using a VWR Stuart SMP40 apparatus and are uncorrected.

^{1}H, ^{13}C and ^{19}F nuclear magnetic resonance (NMR) spectra were obtained as either $CDCl_3$, CD_3OD or DMSO-d_6 solutions and recorded at 500 MHz, 126 MHz and 471 MHz, respectively, on a Bruker Avance III 500 spectrometer. Where ^{13}C NMR data are not

quoted, insufficient material was available or problems obtaining high resolution spectra were encountered. Chemical shifts are quoted in parts per million (δ) referenced to the appropriate deuterated solvent employed. Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), m (multiplet), br (broad) or combinations thereof. Coupling constant values are given in Hz. Homonuclear and heteronuclear two dimensional NMR experiments were used where appropriate to facilitate assignment of chemical shifts.

LC-MS was carried out on a Waters Acquity UPLC system with PDA and ELSD employing positive or negative electrospray modes as appropriate to the individual compound. Where LRMS data is not quoted, the mass was not recognised for that compound. High resolution mass spectrometry was performed by the EPSRC UK National Mass Spectrometry Facility, University of Wales Swansea, Singleton Park, Swansea, SA2 8PP.

FTIR spectra were recorded on either a Bio-Rad FTS 3000MX diamond ATR or an Agilent Cary 630 FTIR as a neat sample.

UV spectra were obtained using a U-2001 Hitachi Spectrophotometer with the sample dissolved in ethanol.

Data were compared with literature data for compounds which had been previously reported.

10.2. Sulf-2 Inhibitors - Experimental Procedures

10.2.1. Sulfatase Biological Assay Protocols

The sulfatase biological assays were performed by Dr Gary Beale and Dr Sari Alhasan.

Sulf-2 assay protocol

Compounds were screened using 4-MUS as a substrate for Sulf-2 according to a protocol described by Morimoto-Tomita *et al.*[65] Briefly 293T cells were transiently transfected with pcDNA3.1/Myc-His(-)-HSulf-2 DNA (Addgene) and TransIT-LT1 Transfection Reagent (Mirus) using a transfection mixture at the ratio 1:3 (µg DNA: µL transfection reagent) in Opti-MEM I reduced serum medium (Gibco). Conditioned medium containing Sulf-2 was collected after 3 days and bound to HIS-Select Nickel affinity gel (Sigma) overnight at 4 °C. Beads were washed three times with washing buffer containing 50 mM HEPES (pH 7.5), 300 mM NaCl, 0.05% Tween 20, followed by washing once with washing buffer

containing no tween. Beads were suspended in 50 mM Hepes (pH 7.5) and used in inhibition assays. 20 μL of bead slurry was incubated with 1 mM compound (in DMSO) plus 10X reaction buffer (500 mM HEPES pH 7.5, 100 mM CaCl2) for 1 h at 37 °C. The reaction was started by the addition of 20 μL of 20 mM 4-MUS (final concentration of 8 mM) and incubated at 37 °C for 1 h. The reaction was stopped with 100 μL 1 M Tris buffer (pH 10.4) and read at 460 nm following excitation at 355 nm in FLUOstar Omega plate reader (BMG Labtech) using Omega data analysis software.

ARSA and ARSB assay protocols

Compounds were screened in a 96-well black plate (Sterilin) using 4-MUS as a substrate, using 50 μL reaction mixture containing 40 ng of the commercially available enzymes (ARSA or ARSB from R & D Systems), 50 mM HEPES (pH = 4.5), 10 mM $CaCl_2$, 1 mM test compound (dissolved in DMSO; final concentration of DMSO in reaction = 2%), and H_2O (45 μL). The assay mixture was incubated for 1 h at 37 °C, followed by addition of 5 μL of 4-MUS (Km = 1.6 mM for ARSA and 612 μM for ARSB), and incubation for a further 1 h at 37 °C. The reaction was stopped with 100 μL of 1 M Tris (pH = 10.5) and read at 460 nm following excitation at 355 nm in FLUOstar Omega plate reader (BMG Labtech) using Omega data analysis software.

10.2.2. Synthesis of Sulf-2 Inhibitors: General Procedures

Except where water was included in the reaction mixture, all reactions were carried out under strict anhydrous conditions with glassware oven-dried and cooled under nitrogen. Temperatures quoted refer to bath temperatures.

General procedure A: To the appropriate 1-((phenoxy)sulfonyl)-2,3-dimethyl-1*H*-imidazol-3-ium tetrafluoroborate (1 mol equiv.) in acetonitrile (8 mL/mmol of tetrafluoroborate salt) was added the appropriate benzylamine (1 mol equiv.). The reaction mixture was stirred for 16 h. Upon completion, the solvent was removed *in vacuo* to yield a crude product. The crude product was purified by column chromatography.

General procedure B: To 1,1'-sulfonylbis(2-methyl-1*H*-imidazole) (**19**) (2 mol equiv.) and caesium carbonate (1.1 mol equiv.) in acetonitrile was added the appropriate phenol (1 mol equiv.). The resulting mixture was heated at 120 °C for 15 min under microwave irradiation. After cooling, the mixture was concentrated *in vacuo*. The resulting residue

was dissolved in saturated aq. NH_4Cl (15 mL) and the mixture extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography.

General procedure C: A solution of the appropriate protected bromophenyl sulfamate (1 mol equiv.) in acetonitrile (20 mL/mmol of 4-bromophenyl sulfamate) was sparged with nitrogen for 15 min. To this solution, potassium carbonate (3 mol equiv.), phenyl boronic acid (1.5 mol equiv.) and tetrakis(triphenylphosphine)palladium(0) (0.1 mol equiv.) were added. The resulting mixture was heated at 120 °C for 20 min under microwave irradiation. Upon completion, the solvent was removed *in vacuo*. The crude residue was dissolved in a mixture of EtOAc and water (20 mL, respectively), and extracted with EtOAc (3 × 25 mL). The pooled organic extracts were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography.

General procedure D: The appropriate 2,4-dimethoxybenzyl protected sulfamate (1 mol equiv.) was solubilised in a 10% TFA/DCM mixture (10 mL/mmol of sulfamate). The resulting solution was stirred at RT for 2 h. Upon completion, the solvent was removed *in vacuo*. The crude residue was dissolved in EtOAc (20 mL), washed with 10% aq. $NaHCO_3$ (20 mL) and extracted with EtOAc (3 × 25 mL). The combined organic extracts were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography.

General procedure E: The appropriate 4-methoxybenzyl protected sulfamate (1 mol equiv.) was solubilised in a 50% TFA/DCM mixture (10 mL/mmol of sulfamate). The resulting solution was heated at 42 °C for 24 h. Upon completion, the solvent was removed *in vacuo*. The crude residue was dissolved in EtOAc (20 mL), washed with 10% aq. $NaHCO_3$ (20 mL) and extracted with EtOAc (3 × 25 mL). The pooled organic extracts were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography.

General procedure F: To the appropriate amine (1 mol equiv.) in ethanol (0.5 mL/mmol of benzylamine) were added the appropriate benzaldehyde (1 mol equiv.) and $MgSO_4$ (300 mg). The resulting mixture was stirred at 78 °C for 4 h. Once cooled to RT, sodium

borohydride (1.1 mol equiv.) was carefully added to the reaction mixture. The resulting mixture was then stirred overnight at RT. Upon completion, the solvent was removed *in vacuo*. The crude residue was dissolved in EtOAc (60 mL), neutralised by washing with saturated aq. NH_4Cl (30 mL), washed with water and brine (30 mL, respectively), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography.

General procedure G: To 1,1'-sulfonylbis(2-methyl-1*H*-imidazole) (**19**) (10 mol equiv.) and caesium carbonate (1.1 mol equiv.) in acetonitrile was added the appropriate phenol (1 mol equiv.). The resulting mixture was heated at 180 °C for 15 min under microwave irradiation. After cooling, the mixture was concentrated *in vacuo*. The resulting residue was dissolved in saturated aq. NH_4Cl (15 mL) and the mixture extracted with EtOAc (3 × 15 mL). The pooled organic extracts were washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography.

General procedure H: To the appropriate phenyl 2-methyl-1*H*-imidazole-1-sulfonate (1 mol equiv.) in DCM (10 mL/mmol of sulfonate), cooled at 0 °C, was added trimethyloxonium tetrafluoroborate (1 mol equiv.). The resulting solution was stirred at 0 °C for 1 h and allowed to warm to RT. After 8 h, the reaction was diluted with acetonitrile (5 mL/mmol of sulfonate) and the appropriate benzylamine (1 mol equiv.) was added. The resulting reaction mixture was heated at 42 °C for 24 h. Upon completion, the solvent was removed *in vacuo* to yield a crude product. The crude product was purified by column chromatography.

General procedure I: To 3-bromophenyl bis(2,4-dimethoxybenzyl)sulfamate (**132**) in dimethoxyethane (7 mL/mmol of 3-bromophenyl sulfamate) was added a 2 M aq. solution of sodium bicarbonate (2 mol equiv.). The resulting solution was sparged with nitrogen for 15 min. The appropriate phenylboronic acid (1.2 mol equiv.) and [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with DCM (0.05 mol equiv.) were then added. The resulting mixture was heated at 80 °C for 20 min under microwave irradiation. Upon completion, the reaction mixture was diluted with water and EtOAc (10 mL, respectively), filtered through Celite and extracted with EtOAc (3 × 25 mL). The pooled organic extracts were washed with water and brine (30 mL,

respectively), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography.

General procedure J: To the appropriate aniline (1 mol equiv.) in DCM (10 mL/mmol of aniline) were added triethylamine (2 mol equiv.) and acetic anhydride (1.2 mol equiv.). The resulting solution was stirred at RT overnight. Upon completion, the reaction mixture was diluted with DCM (10 mL), washed with saturated aq. $NaHCO_3$ (20 mL) and extracted with DCM (3 × 20 mL). The combined organic extracts were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography.

General procedure K: To the appropriate aniline (1 mol equiv.) in THF (10 mL/mmol of aniline) was added 2,3-dimethyl-1-((2,2,2-trichloroethoxy)sulfonyl)-1*H*-imidazol-3-ium tetrafluoroborate (**158**) (3 mol equiv.). The resulting reaction mixture was heated at 67 °C for 30 h. Upon completion, the solvent was removed *in vacuo* to yield a crude product. The crude product was purified by column chromatography.

General procedure L: To the appropriate aniline (1 mol equiv.) in THF (10 mL/mmol of aniline), cooled in an ice bath, were added 4-(dimethylamino)pyridine (2.2 mol equiv.) and triethylamine (4 mol equiv.). The resulting solution was stirred at 0 °C for 10 min, and then a solution 2,2,2-trichloroethyl chlorosulfate (**156**) (4 mol equiv.) in THF (5 mL/mmol of aniline) was added dropwise over 15 min. The resulting solution was stirred in an ice bath for 1 h and allowed to warm to RT. The reaction mixture was left stirring for an additional 24 h. Upon completion, the mixture was diluted with EtOAc (20 mL), quenched by the cautious addition of saturated aq. $NaHCO_3$ (20 mL) and extracted with EtOAc (3 × 20 mL). The pooled organic extracts were washed with water and brine (40 mL, respectively), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was subjected to column chromatography.

General procedure M: To the appropriate 2,2,2-trichloroethylsulfamoyloxyphenyl in MeOH (10 mL/mmol of phenyl) were added acetate buffer pH 4.65 (10 mL/mmol of protected aminophenyl) and zinc (10 mol equiv.). The resulting reaction mixture was heated at 60 °C for 2 h. Upon completion, the heterogeneous mixture was filtered through Celite and washed with MeOH (10 mL). The filtrate was concentrated *in vacuo* to give a crude oil, which was dissolved in water (10 mL) and washed with ether (10 mL). The

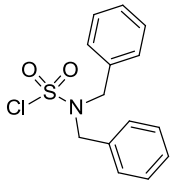
crude product was converted to the sodium salt by ion-exchange chromatography (DOWEX 50WX2 - Na^+ form). The crude product was then subjected to column chromatography.

General procedure N: To 3-hydroxyphenyl bis(2,4-dimethoxybenzyl)sulfamate (**173**) (1 mol equiv.) and potassium carbonate (1.2 mol equiv.) in *N*,*N*-dimethylformamide was added the appropriate fluorobenzene (2 mol equiv.). The resulting mixture was heated at 180 °C for 30 min under microwave irradiation. After cooling, the mixture was concentrated *in vacuo*. The resulting residue was dissolved in saturated aq. $NaHCO_3$ (20 mL) and extracted with EtOAc (3 × 20 mL). The pooled organic extracts were washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography.

General procedure O: The appropriate nitrobenzene in MeOH (15 mL/mmol of nitrobenzene) and THF (5 mL/mmol of nitrobenzene) was subjected to palladium-catalysed hydrogenation using an H-Cube® reactor and a 10% Pd/C CatCart under a full pressure of hydrogen. The reaction was conducted at RT for 24 h. Upon completion, the solvents were removed *in vacuo* and the crude product was purified by column chromatography.

10.2.3. Sulf-2 Inhibitors Synthetic Procedures

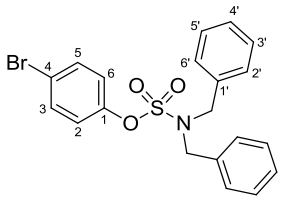
Dibenzylsulfamoyl chloride, (17)



To sulfuryl chloride (**15**) (0.41 mL, 0.68 g, 5.06 mmol) in Et_2O (10 mL), cooled at -78 °C, was added dropwise over 35 min a solution of dibenzylamine (**16**) (0.97 mL, 1.0 g, 5.06 mmol) and pyridine (0.41 mL, 0.40 g, 5.06 mmol) in Et_2O (10 mL). The resulting mixture was stirred at -78 °C for 3 h and for an additional 2 h at RT. The mixture was then filtered through Celite and concentrated *in vacuo*. The crude solid was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 98:2) to yield the *title compound* as a white solid (150 mg, 10%); R_f = 0.58 (petrol:EtOAc, 97:3; $KMnO_4$); m.p. 65.5-67.5 °C; No λ_{max} (EtOH)/nm; IR (neat) ν_{max}/cm^{-1} 1494, 1451, 1383, 1173, 1039; ^1H NMR (500 MHz, $CDCl_3$) δ 4.40 (4H, s, 2 × ArCH_2), 7.23 – 7.16 (4H, m, 4 × Ar*H*), 7.30 – 7.24

(6H, m, 6 × Ar*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 53.1 (Ar*C*H_2), 128.7 (CH Ar), 128.9 (CH Ar), 129.4 (CH Ar), 133.15 (C_q Ar).

4-Bromophenyl dibenzylsulfamate, (18)

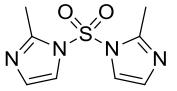


Compound **18** was synthesised following two different procedures.

1st procedure: To 4-bromophenol (**41**) (29 mg, 0.17 mmol) and caesium carbonate (60 mg, 0.18 mmol) in THF was added dibenzylsulfamoyl chloride (**17**) (54 mg, 0.18 mmol). The resulting mixture was heated at 67 °C for 16 h. After cooling, the mixture was concentrated *in vacuo*. The resulting residue was dissolved in saturated aq. NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The pooled organic extracts were washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 97:3) to yield the *title compound* as a white solid (29 mg, 40%).

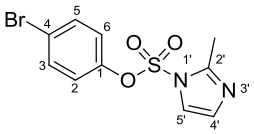
2nd procedure: Compound **18** was synthesised according to general procedure A, using the following reagents: 1-((4-bromophenoxy)sulfonyl)-2,3-dimethyl-1*H*-imidazol-3-ium tetrafluoroborate (**22**) (400 mg, 0.96 mmol), dibenzylamine (**16**) (184 µL, 189 mg, 0.96 mmol) and acetonitrile (7.7 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 97:3) to yield the *title compound* as a white solid (320 mg, 77%); R_f = 0.34 (petrol:EtOAc, 96:4); m.p. 86.5-88.5 °C; λ_{max} (EtOH)/nm 258.0; IR (neat) ν_{max}/cm^{-1} 1481, 1452, 1369, 1154, 1061; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.39 (4H, s, 2 × ArC*H*$_2$), 6.99 (2H, d, *J* = 8.8 Hz, H-2, 6), 7.31 – 7.27 (4H, m, 4 × Ar*H*), 7.39 – 7.32 (6H, m, 6 × Ar*H*), 7.44 (2H, d, *J* = 8.8 Hz, H-3, 5); ^{13}C NMR (126 MHz, $CDCl_3$) δ 51.3 (Ar*C*H_2), 120.2 (C-4), 123.8 (C-2, 6), 128.5 (CH Ar), 128.9 (CH Ar), 129.2 (CH Ar), 132.9 (C-3, 5), 134.7 (C-1'), 149.4 (C-1); HRMS (ESI) calcd for $C_{20}H_{19}BrNO_3S$ [M(^{79}Br)+H]$^+$ 432.0264, found 432.0272.

1,1'-sulfonylbis(2-methyl-1*H*-imidazole), (19)



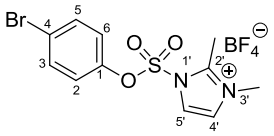
To 2-methylimidazole (20.3 g, 247 mmol) in DCM (100 mL), cooled at 0 °C, was added dropwise over 30 min sulfuryl chloride (**15**) (5 mL, 8.32 g, 61.7 mmol) in DCM (40 mL). The resulting solution was stirred at 0 °C for 1 h and allowed to warm to RT. After 24 h, the reaction was quenched by the cautious addition of water (100 mL) and extracted with DCM (2 × 50 mL). The pooled organic extracts were washed with brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude yellow solid was purified by column chromatography (silica gel, DCM:MeOH, 1:0 → 93:7) to yield the *title compound* as an off-white solid (10.2 g, 73%); R_f = 0.32 (DCM:MeOH, 93:7; $KMnO_4$); m.p. 86.0-88.0 °C (lit. 90.0-91.0 °C)[119]; No λ_{max} (EtOH)/nm; IR (neat) ν_{max}/cm^{-1} 3116, 1553, 1419, 1147, 1052; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.52 (6H, s, 2 × CH_3), 6.95 (2H, d, *J* = 1.7 Hz, H-4 or H-5), 7.37 (2H, d, *J* = 1.7 Hz, H-4 or H-5); ^{13}C NMR (126 MHz, $CDCl_3$) δ 15.1 (CH_3), 120.2 (C-4 or C-5), 128.6 (C-4 or C-5), 146.1 (C-2); LRMS (ES^+) *m/z* 227.2 $[M+H]^+$; HRMS (ESI) calcd for $C_8H_{11}N_4O_2S$ $[M+H]^+$ 227.0597, found 227.0597; ^{1}H NMR and IR data were identical to literature data.[119]

4-Bromophenyl 2-methyl-1*H*-imidazole-1-sulfonate, (21)



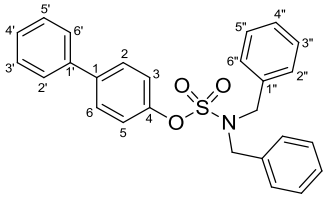
Compound **21** was synthesised according to general procedure B, using the following reagents: 1,1'-sulfonylbis(2-methyl-1*H*-imidazole) (**19**) (262 mg, 1.16 mmol), caesium carbonate (207 mg, 0.64 mmol), 4-bromophenol (**41**) (100 mg, 0.58 mmol) and acetonitrile (5 mL). The crude yellow oil was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 8:2) to yield the *title compound* as a clear oil (169 mg, 93%); R_f = 0.35 (petrol:EtOAc, 8:2; $KMnO_4$); No λ_{max} (EtOH)/nm; IR (neat) ν_{max}/cm^{-1} 1553, 1480, 1422, 1207, 1147, 1043, 1012; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.50 (3H, s, CH_3), 6.81 (2H, d, *J* = 8.9 Hz, H-2, 6), 6.89 (1H, d, *J* = 1.7 Hz, H-4' or H-5'), 7.12 (1H, d, *J* = 1.7 Hz, H-4' or H-5'), 7.49 (2H, d, *J* = 8.9 Hz, H-3, 5); ^{13}C NMR (126 MHz, $CDCl_3$) δ 15.1 (CH_3), 120.5 (C-4' or C-5'), 122.4 (C-4), 123.4 (C-2, 6), 128.2 (C-4' or C-5'), 133.6 (C-3, 5), 146.8 (C-1 or C-2'), 148.0 (C-1 or C-2'); LRMS (ES^+) *m/z* 317.1 $[M(^{79}Br)+H]^+$, 319.1 $[M(^{81}Br)+H]^+$; HRMS (ESI) calcd for $C_{10}H_{10}BrN_2O_3S$ $[M(^{79}Br)+H]^+$ 316.9590, found 316.9598.

1-((4-Bromophenoxy)sulfonyl)-2,3-dimethyl-1*H*-imidazol-3-ium tetrafluoroborate, (22)



To 4-bromophenyl 2-methyl-1*H*-imidazole-1-sulfonate (**21**) (4.18 g, 13.2 mmol) in DCM (60 mL), cooled at 0 °C, was added trimethyloxonium tetrafluoroborate (1.96 g, 13.2 mmol). The resulting solution was stirred at 0 °C for 1 h and allowed to warm to RT. After 8 h, the reaction was cooled in an ice bath and petrol (120 mL) was added to the mixture. A white precipitate formed and was filtered off, washed with cold petrol (60 mL) and dry under high vacuum. The white fluffy solid (4.97 g, 90%) was used in the next step without further purification; m.p. 131.0-133.0 °C; No λ_{max} (EtOH)/nm; IR (neat) ν_{max}/cm^{-1} 3139, 1605, 1479, 1449, 1235, 1212 1149, 1023; ^{1}H NMR (500 MHz, MeOD) δ 2.90 (3H, s, CH_3), 3.96 (3H, s, NC*H*$_3$), 7.26 (2H, d, *J* = 9.1 Hz, H-2, 6), 7.68 (2H, d, *J* = 9.1 Hz, H-3, 5), 7.70 (1H, d, *J* = 2.4 Hz, H-4' or H-5'), 7.83 (1H, d, *J* = 2.4 Hz, H-4' or H-5'); ^{13}C NMR (126 MHz, MeOD) δ 11.9 (CH_3), 36.9 (N*C*H$_3$), 122.4 (C-4' or C-5'), 124.2 (C-4), 124.6 (C-2, 6), 125.1 (C-4' or C-5'), 135.2 (C-3, 5), 149.6 (C-1 or C-2'), 150.2 (C-1 or C-2'); LRMS (ES$^+$) *m/z* 331.1 [M(^{79}Br)-BF_4]$^+$, 333.2 [M(^{81}Br)-BF_4]$^+$; HRMS (ESI) calcd for $C_{11}H_{12}BrN_2O_3S$ [M(^{79}Br)-BF_4]$^+$ 330.9747, found 330.9749.

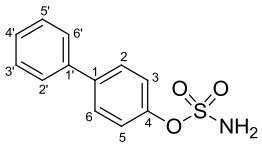
[1,1'-Biphenyl]-4-yl dibenzylsulfamate, (23)



Compound **23** was synthesised according to general procedure C, using the following reagents: 4-bromophenyl dibenzylsulfamate (**18**) (250 mg, 0.58 mmol), potassium carbonate (240 mg, 1.73 mmol), phenyl boronic acid (106 mg, 0.87 mmol), tetrakis(triphenylphosphine)palladium(0) (67 mg, 0.06 mmol) and acetonitrile (11.5 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 97:3) to yield the *title compound* as a white solid (320 mg, 72%); R_f = 0.42 (petrol:EtOAc, 96:4); m.p. 131.5-133.5 °C; λ_{max} (EtOH)/nm 251.0; IR (neat) ν_{max}/cm^{-1} 1483, 1455, 1363, 1187, 1149, 1051; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.43 (4H, s, 2 × ArC*H*$_2$), 7.21 (2H, d, *J* = 8.7 Hz, H-3, 5), 7.39 – 7.27 (11H, m, 11 × Ar*H*), 7.45 (2H, t, *J* = 7.6 Hz, H-4'), 7.58 – 7.52 (4H, m, 4 × Ar*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 51.3

(Ar*C*H_2), 122.3 (C-3, 5), 127.3 (CH Ar), 127.7 (CH Ar), 128.4 (CH Ar), 128.5 (CH Ar), 128.8 (CH Ar), 129.0 (CH Ar), 129.2 (CH Ar), 134.9 (C-1"), 140.0 (C-1 or C-1'), 140.2 (C-1 or C-1'), 149.8 (C-4); HRMS (ESI) calcd for $C_{26}H_{24}NO_3S$ $[M+H]^+$ 430.1471, found 430.1478.

[1,1'-Biphenyl]-4-yl sulfamate, (24)

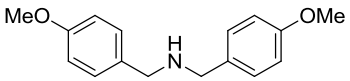


Compound **24** was synthesised following two different procedures.

1st procedure: Compound **24** was synthesised according to general procedure D, using the following reagents: [1,1'-biphenyl]-4-yl bis(2,4-dimethoxybenzyl)sulfamate (**38**) (180 mg, 0.33 mmol), DCM (3.0 mL) and TFA (0.33 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 7:3) to yield the *title compound* as an off-white solid (77 mg, 95%).

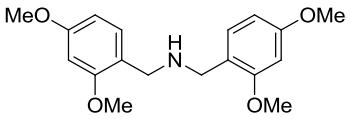
2nd procedure: Compound **24** was synthesised according to general procedure E, using the following reagents: [1,1'-biphenyl]-4-yl bis(4-methoxybenzyl)sulfamate (**37**) (100 mg, 0.20 mmol), DCM (1.0 mL) and TFA (1.0 mL). The crude product was purified by column chromatography (silica gel, petrol:DCM, 1:0 → 0:1) to yield the *title compound* as an off-white solid (45 mg, 90%); R_f = 0.34 (petrol:EtOAc, 7:3); m.p. 156.5-158.5 °C (lit. 146.0-149.0 °C)[257]; λ_{max} (EtOH)/nm 250.0; IR (neat) ν_{max}/cm^{-1} 3421, 3301, 1545, 1516, 1484, 1363, 1176, 1155; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.42 – 7.34 (3H, m, H-3, 5 and H-4'), 7.48 (2H, dd, *J* = 7.7, 7.7 Hz, H-3', 5'), 7.66 (2H, dd, *J* = 7.7, 1.1 Hz, H-2', 6'), 7.75 (2H, d, *J* = 8.7 Hz, H-2, 6), 8.04 (2H, s, ArOSO$_2$N*H*$_2$); ^{13}C NMR (126 MHz, DMSO-d_6) δ 122.6 (C-3, 5), 126.7 (C-2', 6'), 127.6 (C-4'), 128.0 (C-2, 6), 129.0 (C-3, 5), 138.5 (C-1 or C-1'), 139.2 (C-1 or C-1'), 149.6 (C-4); LRMS (ES$^-$) *m/z* 248.2 $[M-H]^-$; HRMS (ESI) calcd for $C_{12}H_{10}NO_3S$ $[M-H]^-$ 248.0387, found 248.0376; ^{1}H NMR, ^{13}C NMR and IR data were identical to literature data.[257, 258]

bis(4-Methoxybenzyl)amine, (31)



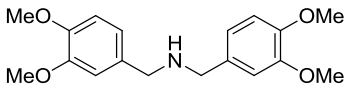
Compound **31** was synthesised according to general procedure F, using the following reagents: 4-methoxybenzylamine (3.22 mL, 3.38 g, 24.6 mmol), 4-methoxybenzaldehyde (3.0 mL, 3.36 g, 24.6 mmol), sodium borohydride (1.03 g, 27.1 mmol) and ethanol (12.3 mL). The crude product was purified by column chromatography (silica gel, DCM:MeOH, 1:0 → 94:6) to yield the *title compound* as an orange solid (4.81 g, 75%); R_f = 0.28 (DCM:MeOH, 94:6; ninhydrin); m.p. 33.0-35.0 °C (lit. 35.0-37.0°C)[259]; λ_{max} (EtOH)/nm 275.0; IR (neat) ν_{max}/cm^{-1} 1611, 1509, 1463, 1239, 1171, 1031; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.73 (4H, s, 2 × ArC*H*$_2$), 3.81 (6H, s, 2 × ArOC*H*$_3$), 6.87 (4H, d, *J* = 8.7 Hz, H-3, 5), 7.25 (4H, d, *J* = 8.7 Hz, H-2, 6); ^{13}C NMR (126 MHz, $CDCl_3$) δ 52.6 (Ar*C*H$_2$), 55.4 (ArO*C*H$_3$), 113.9 (C-3, 5), 129.4 (C-2, 6), 132.7 (C-1), 158.7 (C-4); LRMS (ES$^+$) *m/z* 258.4 [M+H]$^+$; IR, ^{1}H NMR, ^{13}C NMR and LRMS data were identical to literature data.[260, 261]

bis(2,4-Dimethoxybenzyl)amine, (32)



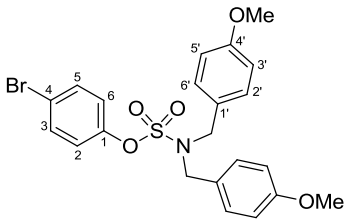
Compound **32** was synthesised according to general procedure F, using the following reagents: 2,4-dimethoxybenzylamine (2.72 mL, 3.03 g, 18.0 mmol), 2,4-dimethoxy benzaldehyde (3.0 g, 18.0 mmol), sodium borohydride (0.75 g, 19.9 mmol) and ethanol (9 mL). The crude product was purified by column chromatography (silica gel, DCM:MeOH, 1:0 → 9:1) to yield the *title compound* as a pale yellow oil (4.91 g, 85%); R_f = 0.34 (DCM:MeOH, 9:1; ninhydrin); λ_{max} (EtOH)/nm 276.5; IR (neat) ν_{max}/cm^{-1} 1611, 1586, 1505, 1454, 1287, 1205, 1154, 1031; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.73 (4H, s, 2 × ArC*H*$_2$), 3.79 (6H, s, 2 × ArOC*H*$_3$), 3.79 (6H, s, 2 × ArOC*H*$_3$), 6.46 – 6.41 (4H, m, H-3 and 5), 7.17 (2H, d, *J* = 8.6 Hz, H-6); ^{13}C NMR (126 MHz, $CDCl_3$) δ 48.2 (Ar*C*H$_2$), 55.4 (ArO*C*H$_3$), 55.5 (ArO*C*H$_3$), 98.5 (C-3), 103.7 (C-5), 120.6 (C-1), 130.6 (C-6), 158.7 (C-2 or C-4), 160.2 (C-2 or C-4); LRMS (ES$^+$) *m/z* 318.4 [M+H]$^+$; HRMS (ESI) calcd for $C_{18}H_{24}NO_4$ [M+H]$^+$ 318.1700, found 318.1703; ^{1}H NMR and ^{13}C NMR data were identical to literature data.[262, 263]

bis(3,4-Dimethoxybenzyl)amine, (33)



Compound **33** was synthesised according to general procedure F, using the following reagents: 3,4-dimethoxybenzylamine (2.72 mL, 3.02 g, 18.0 mmol), 3,4-dimethoxy benzaldehyde (3.0 g, 18.0 mmol), sodium borohydride (0.75 g, 19.9 mmol) and ethanol (9 mL). The crude product was purified by column chromatography (silica gel, DCM:MeOH, 1:0 → 9:1) to yield the *title compound* as a pale yellow solid (3.91 g, 68%); R_f = 0.33 (DCM:MeOH, 9:1; ninhydrin); m.p. 68.5-70.5 °C (lit. 69.0-71.0 °C)[129]; λ_{max} (EtOH)/nm 278.5; IR (neat) ν_{max}/cm^{-1} 1589, 1513, 1464, 1448, 1232, 1134, 1021; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.74 (4H, s, 2 × ArC*H*$_2$), 3.87 (6H, s, 2 × ArOC*H*$_3$), 3.89 (6H, s, 2 × ArOC*H*$_3$), 6.82 (2H, d, *J* = 8.2 Hz, H-5), 6.86 (2H, dd, *J* = 8.2, 1.8 Hz, H-6), 6.90 (2H, d, *J* = 1.8 Hz, H-2); ^{13}C NMR (126 MHz, $CDCl_3$) δ 53.0 (Ar*C*H$_2$), 56.0 (ArOC*H*$_3$), 56.0 (ArO*C*H$_3$), 111.0 (C-5), 111.4 (C-2), 120.3 (C-6), 133.0 (C-1), 148.1 (C-3 or C-4), 149.0 (C-3 or C-4); LRMS (ES$^+$) *m/z* 318.4 [M+H]$^+$; HRMS (ESI) calcd for $C_{18}H_{24}NO_4$ [M+H]$^+$ 318.1700, found 318.1699; ^{1}H NMR and IR data were identical to literature data.[129]

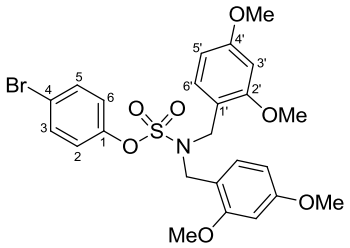
4-Bromophenyl bis(4-methoxybenzyl)sulfamate, (34)



Compound **34** was synthesised according to general procedure A, using the following reagents: 1-((4-bromophenoxy)sulfonyl)-2,3-dimethyl-1*H*-imidazol-3-ium tetrafluoroborate (**22**) (600 mg, 1.43 mmol), bis(4-methoxybenzyl)amine (**31**) (370 mg, 1.43 mmol) and acetonitrile (11.5 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 95:5) to yield the *title compound* as a pale orange solid (595 mg, 84%); R_f = 0.34 (petrol:EtOAc, 95:5); m.p. 61.5-63.5 °C; λ_{max} (EtOH)/nm 274.5; IR (neat) ν_{max}/cm^{-1} 1614, 1513, 1479, 1456, 1361, 1249, 1169, 1033; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.82 (6H, s, 2 × ArOC*H*$_3$), 4.30 (4H, s, 2 × ArC*H*$_2$), 6.88 (4H, d, *J* = 8.7 Hz, H-3', 5'), 7.00 (2H, d, *J* = 8.9 Hz, H-2, 6), 7.20 (4H, d, *J* = 8.7 Hz, H-2', 6'), 7.45 (2H, d, *J* = 8.9 Hz, H-3, 5); ^{13}C NMR (126 MHz, $CDCl_3$) δ 50.4 (Ar*C*H$_2$), 55.5 (ArO*C*H$_3$), 114.2 (C-3', 5'), 120.1 (C-4 or C-1'), 123.9 (C-2, 6), 126.8 (C-4 or C-1'),

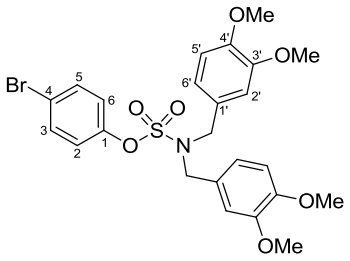
130.5 (C-2', 6'), 132.9 (C-3, 5), 149.5 (C-1), 159.7 (C-4'); HRMS (ESI) calcd for $C_{22}H_{26}BrN_2O_5S$ $[M(^{79}Br)+NH_4]^+$ 509.0740, found 509.0740.

4-Bromophenyl bis(2,4-dimethoxybenzyl)sulfamate, (35)



Compound **35** was synthesised according to general procedure A, using the following reagents: 1-((4-bromophenoxy)sulfonyl)-2,3-dimethyl-1*H*-imidazol-3-ium tetrafluoroborate (**22**) (600 mg, 1.43 mmol), bis(2,4-dimethoxybenzyl)amine (**32**) (456 mg, 1.43 mmol) and acetonitrile (11.5 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 85:15) to yield the *title compound* as a clear oil (680 mg, 86%); R_f = 0.30 (petrol:EtOAc, 85:15); λ_{max} (EtOH)/nm 277.0; IR (neat) ν_{max}/cm^{-1} 1613, 1588, 1507, 1481, 1370, 1208, 1156, 1035; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.73 (6H, s, 2 × ArOC*H*$_3$), 3.80 (6H, s, 2 × ArOC*H*$_3$), 4.44 (4H, s, 2 × ArC*H*$_2$), 6.39 (2H, d, *J* = 2.4 Hz, H-3'), 6.43 (2H, dd, *J* = 8.4, 2.4 Hz, H-5'), 6.92 (2H, d, *J* = 8.9 Hz, H-2, 6), 7.24 (2H, d, *J* = 8.4 Hz, H-6'), 7.39 (2H, d, *J* = 8.9 Hz, H-3, 5); ^{13}C NMR (126 MHz, $CDCl_3$) δ 47.1 (Ar*C*H$_2$), 55.2 (ArO*C*H$_3$), 55.5 (ArO*C*H$_3$), 98.3 (C-3'), 104.1 (C-5'), 116.6 (C-4 or C-1'), 119.7 (C-4 or C-1'), 123.8 (C-2, 6), 131.1 (C-6'), 132.6 (C-3, 5), 149.5 (C-1), 158.6 (C-2'or C-4'), 160.8 (C-2'or C-4'); HRMS (ESI) calcd for $C_{24}H_{27}BrNO_7S$ $[M(^{79}Br)+H]^+$ 552.0686, found 552.0676.

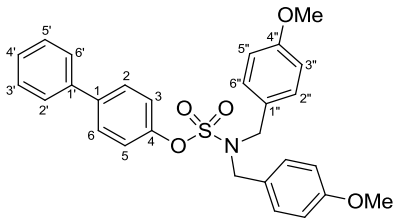
4-Bromophenyl bis(3,4-dimethoxybenzyl)sulfamate, (36)



Compound **36** was synthesised according to general procedure A, using the following reagents: 1-((4-bromophenoxy)sulfonyl)-2,3-dimethyl-1*H*-imidazol-3-ium tetrafluoroborate (**22**) (600 mg, 1.43 mmol), bis(3,4-dimethoxybenzyl)amine (**33**) (456 mg, 1.43 mmol) and acetonitrile (11.5 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 65:35) to yield the *title compound* as an

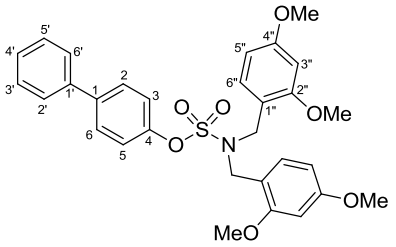
off-white solid (675 mg, 85%); R_f = 0.32 (petrol:EtOAc, 65:35); m.p. 99.5-101.5 °C; λ_{max} (EtOH)/nm 278.0; IR (neat) ν_{max}/cm^{-1} 1595, 1518, 1464, 1358, 1259, 1238, 1141, 1024; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.82 (6H, s, 2 × ArOC*H*$_3$), 3.89 (6H, s, 2 × ArOC*H*$_3$), 4.33 (4H, s, 2 × ArC*H*$_2$), 6.77 (2H, dd, *J* = 8.1, 1.9 Hz, H-6'), 6.82 (2H, d, *J* = 8.1 Hz, H-5'), 6.84 (2H, d, *J* = 1.9 Hz, H-2'), 7.05 (2H, d, *J* = 8.9 Hz, H-2, 6), 7.47 (2H, d, *J* = 8.9 Hz, H-3, 5); ^{13}C NMR (126 MHz, $CDCl_3$) δ 51.1 (Ar*C*H$_2$), 56.0 (ArO*C*H$_3$), 56.1 (ArO*C*H$_3$), 111.0 (C-5'), 112.2 (C-2'), 120.2 (C-4 or C-1'), 121.7 (C-6'), 123.7 (C-2, 6), 127.2 (C-4 or C-1'), 133.0 (C-3, 5), 149.3 (C_q Ar), 149.4 (C_q Ar), 149.5 (C_q Ar); HRMS (ESI) calcd for $C_{24}H_{30}BrN_2O_7S$ [M(^{79}Br)+NH_4]$^+$ 569.0952, found 569.0947.

[1,1'-Biphenyl]-4-yl bis(4-methoxybenzyl)sulfamate, (37)



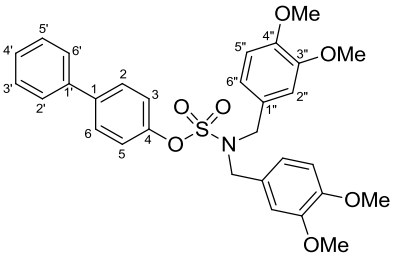
Compound **37** was synthesised according to general procedure C, using the following reagents: 4-bromophenyl bis(4-methoxybenzyl)sulfamate (**34**) (400 mg, 0.81 mmol), potassium carbonate (337 mg, 2.44 mmol), phenyl boronic acid (149 mg, 1.22 mmol), tetrakis(triphenylphosphine)palladium(0) (94 mg, 0.08 mmol) and acetonitrile (16 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 95:5) to yield the *title compound* as a pale yellow oil (330 mg, 83%); R_f = 0.38 (petrol:EtOAc, 95:5); λ_{max} (EtOH)/nm 251.0; IR (neat) ν_{max}/cm^{-1} 1610, 1511, 1484, 1379, 1248, 1178, 1153, 1052, 1031; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.81 (6H, s, 2 × ArOC*H*$_3$), 4.34 (4H, s, 2 × ArC*H*$_2$), 6.87 (4H, d, *J* = 8.7 Hz, H-3", 5"), 7.24 – 7.19 (6H, m, H-3, 5 and H-2", 6"), 7.39 – 7.34 (1H, m, H-4'), 7.45 (2H, dd, *J* = 7.6, 7.6 Hz, H-3', 5'), 7.58 – 7.52 (4H, m, H-2, 6 and H-2', 6'); ^{13}C NMR (126 MHz, $CDCl_3$) δ 50.4 (Ar*C*H$_2$), 55.4 (ArO*C*H$_3$), 114.2 (C-3", 5"), 122.3 (C-3, 5), 126.9 (C-1"), 127.2 (C-2, 6 or C-2', 6'), 127.7 (C-4'), 128.5 (C-2, 6 or C-2', 6'), 129.0 (C-3', 5'), 130.6 (C-2", 6"), 140.0 (C-1 or C-1'), 140.2 (C-1 or C-1'), 149.9 (C-4), 159.7 (C-4"); HRMS (ESI) calcd for $C_{28}H_{31}N_2O_5S$ [M+NH_4]$^+$ 507.1948, found 507.1945.

[1,1'-Biphenyl]-4-yl bis(2,4-dimethoxybenzyl)sulfamate, (38)



Compound **38** was synthesised according to general procedure C, using the following reagents: 4-bromophenyl bis(2,4-dimethoxybenzyl)sulfamate (**35**) (450 mg, 0.81 mmol), potassium carbonate (337 mg, 2.44 mmol), phenyl boronic acid (149 mg, 1.22 mmol), tetrakis(triphenylphosphine)palladium(0) (94 mg, 0.08 mmol) and acetonitrile (16 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 85:15) to yield the *title compound* as a yellow oil (375 mg, 83%); R_f = 0.32 (petrol:EtOAc, 85:15); λ_{max} (EtOH)/nm 250.5; IR (neat) ν_{max}/cm^{-1} 1612, 1590, 1507, 1469, 1369, 1206, 1154, 1042, 1034; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.73 (6H, s, 2 × ArOC*H*$_3$), 3.78 (6H, s, 2 × OC*H*$_3$), 4.48 (4H, s, 2 × ArC*H*$_2$), 6.39 (2H, d, *J* = 2.4 Hz, H-3"), 6.43 (2H, dd, *J* = 8.4, 2.4 Hz, H-5"), 7.15 (2H, d, *J* = 8.7 Hz, H-3, 5), 7.27 (2H, d, *J* = 8.4 Hz, H-6"), 7.38 – 7.33 (1H, m, H-4'), 7.44 (2H, dd, *J* = 7.6, 7.6 Hz, H-3', 5'), 7.51 (2H, d, *J* = 8.7 Hz, H-2, 6), 7.55 (2H, dd, *J* = 7.6, 1.2 Hz, H-2', 6'); ^{13}C NMR (126 MHz, $CDCl_3$) δ 47.0 (Ar*C*H$_2$), 55.2 (ArO*C*H$_3$), 55.5 (ArO*C*H$_3$), 98.3 (C-3"), 104.1 (C-5"), 116.8 (C-1"), 122.3 (C-3, 5), 127.2 (C-2', 6'), 127.6 (C-4'), 128.3 (C-2, 6), 129.0 (C-3', 5'), 131.1 (C-6"), 139.6 (C-1 or C-1'), 140.3 (C-1 or C-1'), 150.0 (C-4), 158.6 (C-2" or C-4"), 160.7 (C-2" or C-4"); HRMS (ESI) calcd for $C_{30}H_{32}NO_7S$ $[M+H]^+$ 550.1894, found 550.1887.

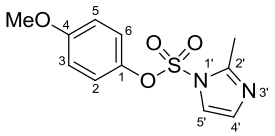
[1,1'-Biphenyl]-4-yl bis(3,4-dimethoxybenzyl)sulfamate, (39)



Compound **39** was synthesised according to general procedure C, using the following reagents: 4-bromophenyl bis(3,4-dimethoxybenzyl)sulfamate (**36**) (450 mg, 0.81 mmol), potassium carbonate (337 mg, 2.44 mmol), phenyl boronic acid (149 mg, 1.22 mmol), tetrakis(triphenylphosphine)palladium(0) (94 mg, 0.08 mmol) and acetonitrile (16 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 65:35) to yield the *title compound* as a yellow solid (385 mg, 86%); R_f = 0.35

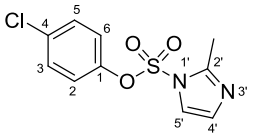
(petrol:EtOAc, 65:35); m.p. 120.5-122.5 °C; λ_{max} (EtOH)/nm 237.5; IR (neat) ν_{max}/cm^{-1} 1593, 1518, 1450, 1370, 1261, 1237, 1140, 1019; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.82 (6H, s, 2 × ArOCH_3), 3.87 (6H, s, 2 × ArOCH_3), 4.36 (4H, s, 2 × ArCH_2), 6.78 (2H, dd, *J* = 8.2, 1.8 Hz, H-6"), 6.81 (2H, d, *J* = 8.2 Hz, H-5"), 6.87 (2H, d, *J* = 1.8 Hz, H-2"), 7.25 (2H, d, *J* = 8.6 Hz, H-3, 5), 7.39 – 7.32 (1H, m, H-4'), 7.44 (2H, dd, *J* = 7.6 , 7.6 Hz, H-3', 5'), 7.59 – 7.51 (4H, m, H-2, 6 and H-2', 6'); ^{13}C NMR (126 MHz, $CDCl_3$) δ 51.1 (ArCH_2), 56.0 (ArOCH_3), 56.1 (ArOCH_3), 111.0 (C-5"), 112.2 (C-2"), 121.7 (C-6"), 122.1 (C-3, 5), 127.2 (C-2, 6 or C-2', 6'), 127.4 (C-1"), 127.8 (C-4'), 128.6 (C-2, 6 or C-2', 6'), 129.0 (C-3', 5'), 140.0 (C-1 and C-1'), 149.2 (C_q Ar), 149.4 (C_q Ar), 149.9 (C_q Ar); HRMS (ESI) calcd for $C_{30}H_{35}N_2O_7S$ $[M+NH_4]^+$ 567.2159, found 567.2155.

4-Methoxyphenyl 2-methyl-1*H*-imidazole-1-sulfonate, (48)



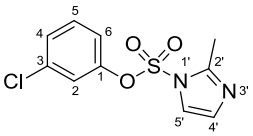
Compound **48** was synthesised according to general procedure B, using the following reagents: 1,1'-sulfonylbis(2-methyl-1*H*-imidazole) (**19**) (364 mg, 1.61 mmol), caesium carbonate (289 mg, 0.89 mmol), 4-methoxyphenol (100 mg, 0.81 mmol) and acetonitrile (5 mL). The crude yellow oil was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 8:2) to yield the *title compound* as a clear oil (210 mg, 97%); R_f = 0.26 (petrol:EtOAc, 8:2; $KMnO_4$); λ_{max} (EtOH)/nm 273.5; IR (neat) ν_{max}/cm^{-1} 1595, 1552, 1500, 1416, 1206, 1141, 1029; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.44 (3H, s, CH_3), 3.78 (3H, s, ArOCH_3), 6.82 (4H, s, H-2, 3, 4, 5), 6.88 (1H, d, *J* = 1.7 Hz, H-4' or H-5'), 7.13 (1H, d, *J* = 1.7 Hz, H-4' or H-5'); ^{13}C NMR (126 MHz, $CDCl_3$) δ 15.0 (CH_3), 55.8 (ArOCH_3), 115.1 (C-2, 6 or C-3, 5), 120.5 (C-4' or C-5'), 122.7 (C-2, 6 or C-3, 5), 128.0 (C-4' or C-5'), 142.4 (C-1 or C-2'), 147.0 (C-1 or C-2'), 159.3 (C-4); LRMS (ES^+) *m/z* 269.2 $[M+H]^+$; HRMS (ESI) calcd for $C_{11}H_{13}N_2O_4S$ $[M+H]^+$ 269.0591, found 269.0591.

4-Chlorophenyl 2-methyl-1*H*-imidazole-1-sulfonate, (49)



Compound **49** was synthesised according to general procedure B, using the following reagents: 1,1'-sulfonylbis(2-methyl-1*H*-imidazole) (**19**) (218 mg, 0.96 mmol), caesium carbonate (173 mg, 0.53 mmol), 4-chlorophenol (62 mg, 0.48 mmol) and acetonitrile (5 mL). The crude yellow oil was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 8:2) to yield the *title compound* as a clear oil (123 mg, 93%); R_f = 0.35 (petrol:EtOAc, 8:2; $KMnO_4$); λ_{max} (EtOH)/nm 264.5; IR (neat) ν_{max}/cm^{-1} 1553, 1483, 1422, 1207, 1145, 1044, 1014; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.49 (3H, s, CH_3), 6.87 (2H, d, *J* = 9.0 Hz, H-2, 6), 6.89 (1H, d, *J* = 1.7 Hz, H-4' or H-5'), 7.12 (1H, d, *J* = 1.7 Hz, H-4' or H-5'), 7.33 (2H, d, *J* = 9.0 Hz, H-3, 5); ^{13}C NMR (126 MHz, $CDCl_3$) δ 15.1 (CH_3), 120.5 (C-4' or C-5'), 123.1 (C-2, 6), 128.2 (C-4' or C-5'), 130.5 (C-3, 5), 134.6 (C-4), 146.8 (C-1 or C-2'), 147.4 (C-1 or C-2'); LRMS (ES$^+$) *m/z* 272.9 [M(^{35}Cl)+H]$^+$, 275.1 [M(^{37}Cl)+H]$^+$; HRMS (ESI) calcd for $C_{10}H_{10}ClN_2O_3S$ [M(^{35}Cl)+H]$^+$ 273.0095, found 273.0101.

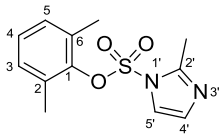
3-Chlorophenyl 2-methyl-1*H*-imidazole-1-sulfonate, (50)



Compound **50** was synthesised according to general procedure B, using the following reagents: 1,1'-sulfonylbis(2-methyl-1*H*-imidazole) (**19**) (429 mg, 1.89 mmol), caesium carbonate (340 mg, 1.04 mmol), 3-chlorophenol (100 µL, 122 mg, 0.48 mmol) and acetonitrile (5 mL). The crude yellow oil was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 8:2) to yield the *title compound* as a clear oil (214 mg, 83%); R_f = 0.33 (petrol:EtOAc, 8:2; $KMnO_4$); λ_{max} (EtOH)/nm 265.0; IR (neat) ν_{max}/cm^{-1} 1583, 1554, 1423, 1207, 1152, 1044; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.51 (3H, s, CH_3), 6.79 (1H, ddd, *J* = 8.1, 2.3 and 1.0 Hz, H-6), 6.90 (1H, d, *J* = 1.7 Hz, H-4' or H-5'), 7.03 (1H, dd, *J* = 2.3, 2.1 Hz, H-2), 7.14 (1H, d, *J* = 1.7 Hz, H-4' or H-5'), 7.29 (1H, dd, *J* = 8.1, 8.1 Hz, H-5), 7.38 – 7.32 (1H, m, H-4); ^{13}C NMR (126 MHz, $CDCl_3$) δ 15.1 (CH_3), 119.8 (C-6), 120.5 (C-4' or C-5'), 122.5 (C-2), 128.2 (C-4' or C-5'), 129.1 (C-4), 131.1 (C-5), 135.8 (C-3), 146.8 (C-1 or C-2'), 149.2 (C-1 or C-2'); LRMS (ES$^+$) *m/z* 273.4 [M(^{35}Cl)+H]$^+$,

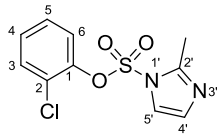
275.1 [M(^{37}Cl)+H]$^+$; HRMS (ESI) calcd for $C_{10}H_{10}ClN_2O_3S$ [M(^{35}Cl)+H]$^+$ 273.0095, found 273.0101.

2,6-Dimethylphenyl 2-methyl-1*H*-imidazole-1-sulfonate, (51)



Compound **51** was synthesised according to general procedure B, using the following reagents: 1,1'-sulfonylbis(2-methyl-1*H*-imidazole) (**19**) (370 mg, 1.64 mmol), caesium carbonate (293 mg, 0.90 mmol), 2,6-dimethylphenol (100 mg, 0.82 mmol) and acetonitrile (5 mL). The crude yellow oil was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 8:2) to yield the *title compound* as a white solid (203 mg, 93%); R_f = 0.30 (petrol:EtOAc, 8:2; $KMnO_4$); m.p. 55.0-57.0 °C; λ_{max} (EtOH)/nm 262.5; IR (neat) ν_{max}/cm^{-1} 1551, 1473, 1419, 1205, 1046; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.07 (6H, s, 2 × ArC*H*$_3$), 2.55 (3H, s, $CH_{3\ imidazole}$), 6.93 (1H, d, *J* = 1.6 Hz, H-4' or H-5'), 7.06 (2H, d, *J* = 7.4 Hz, H-3, 5), 7.16 – 7.10 (1H, m, H-4), 7.21 (1H, d, *J* = 1.6 Hz, H-4' or H-5'); ^{13}C NMR (126 MHz, $CDCl_3$) δ 15.2 (Ar*C*H$_3$), 16.3 ($CH_{3\ imidazole}$), 120.1 (C-4' or C-5'), 127.9 (C-4), 128.1 (C-4' or C-5'), 129.8 (C-3, 5), 131.7 (C-2, 6), 146.6 (C-1 or C-2'), 147.9 (C-1 or C-2'); LRMS (ES$^+$) *m/z* 267.2 [M+H]$^+$; HRMS (ESI) calcd for $C_{12}H_{15}N_2O_3S$ [M+H]$^+$ 267.0798, found 267.0803.

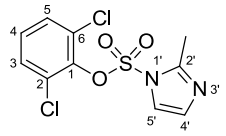
2-Chlorophenyl 2-methyl-1*H*-imidazole-1-sulfonate, (52)



Compound **52** was synthesised according to general procedure B, using the following reagents: 1,1'-sulfonylbis(2-methyl-1*H*-imidazole) (**19**) (218 mg, 0.96 mmol), caesium carbonate (173 mg, 0.53 mmol), 2-chlorophenol (50 µL, 62 mg, 0.48 mmol) and acetonitrile (5 mL). The crude yellow oil was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 8:2) to yield the *title compound* as a clear oil (119 mg, 90%); R_f = 0.33 (petrol:EtOAc, 8:2; $KMnO_4$); λ_{max} (EtOH)/nm 264.5; IR (neat) ν_{max}/cm^{-1} 1555, 1474, 1424, 1193, 1170, 1043; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.56 (3H, s, CH_3), 6.89 (1H, d, *J* = 1.9 Hz, H-4' or H-5'), 7.09 – 7.07 (1H, m, Ar*H*), 7.10 (1H, d, *J* = 1.9 Hz, H-4' or H-5'), 7.36 – 7.26 (2H, m, 2 × Ar*H*), 7.52 – 7.40 (1H, m, Ar*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 15.3 (CH_3), 120.4 (C-4' or C-5'), 123.8 (CH Ar), 127.5 (C-2), 128.2 (C-4' or

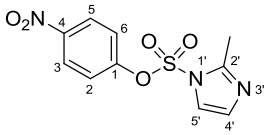
C-5'), 128.4 (CH Ar), 129.3 (CH Ar), 131.4 (CH Ar), 145.3 (C-1 or C-2'), 147.0 (C-1 or C-2'); LRMS (ES^+) *m/z* 272.9 $[M(^{35}Cl)+H]^+$, 275.2 $[M(^{37}Cl)+H]^+$; HRMS (ESI) calcd for $C_{10}H_{10}ClN_2O_3S$ $[M(^{35}Cl)+H]^+$ 273.0095, found 273.0101.

2,6-Dichlorophenyl 2-methyl-1*H*-imidazole-1-sulfonate, (53)



Compound **53** was synthesised according to general procedure G, using the following reagents: 1,1'-sulfonylbis(2-methyl-1*H*-imidazole) (**19**) (3.47 g, 15.3 mmol), caesium carbonate (550 mg, 1.69 mmol), 2,6-dichlorophenol (250 mg, 1.53 mmol) and acetonitrile (20 mL). The crude yellow oil was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 85:15) to yield the *title compound* as a clear oil (396 mg, 84%); R_f = 0.34 (petrol:EtOAc, 8:2; $KMnO_4$); λ_{max} (EtOH)/nm 271.0, 278.0; IR (neat) ν_{max}/cm^{-1} 1573, 1556, 1429, 1201, 1177, 1044; ^1H NMR (500 MHz, $CDCl_3$) δ 2.68 (3H, s, CH_3), 6.92 (1H, d, *J* = 1.8 Hz, H-4' or H-5'), 7.19 (1H, d, *J* = 1.9 Hz, H-4' or H-5'), 7.26 – 7.20 (1H, m, H-4), 7.39 (2H, d, *J* = 8.1 Hz, H-3, 5); ^{13}C NMR (126 MHz, $CDCl_3$) δ 15.3 (CH_3), 120.2 (C-4' or C-5'), 128.1 (C-4' or C-5'), 129.2 (C-4), 129.7 (C-3, 5), 129.8 (C-2, 6), 143.1 (C-1 or C-2'), 146.8 (C-1 or C-2'); LRMS (ES^+) *m/z* 307.1 $[M(^{35}Cl^{35}Cl)+H]^+$, 309.1 $[M(^{35}Cl^{37}Cl)+H]^+$; HRMS (ESI) calcd for $C_{10}H_9Cl_2N_2O_3S$ $[M(^{35}Cl^{35}Cl)+H]^+$ 306.9705, found 306.9709.

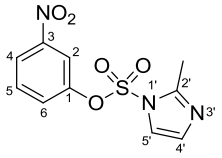
4-Nitrophenyl 2-methyl-1*H*-imidazole-1-sulfonate, (54)



Compound **54** was synthesised according to general procedure G, using the following reagents: 1,1'-sulfonylbis(2-methyl-1*H*-imidazole) (**19**) (4.07 g, 18.0 mmol), caesium carbonate (644 mg, 1.98 mmol), 4-nitrophenol (250 mg, 1.80 mmol) and acetonitrile (20 mL). The crude brawn oil was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 8:2) to yield the *title compound* as an off-white solid (418 mg, 82%); R_f = 0.29 (petrol:EtOAc, 3:1; $KMnO_4$); m.p. 113.0-115.0 °C; λ_{max} (EtOH)/nm 253.5; IR (neat) ν_{max}/cm^{-1} 1618, 1588, 1553, 1525, 1424, 1346, 1208, 1145, 1045; ^1H NMR (500 MHz, $CDCl_3$) δ 2.57 (3H, s, CH_3), 6.92 (1H, d, *J* = 1.7 Hz, H-4' or H-5'), 7.13 (1H, d, *J* = 1.7 Hz, H-4' or H-5'), 7.16 (2H, d, *J* = 9.2 Hz, H-2, 6), 8.27 (2H, d, *J* = 9.2 Hz, H-3,

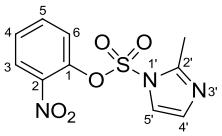
5); ^{13}C NMR (126 MHz, $CDCl_3$) δ 15.2 (CH_3), 120.5 (C-4' or C-5'), 122.9 (C-2, 6), 126.1 (C-3, 5), 128.5 (C-4' or C-5'), 146.8 (C_q Ar), 147.3 (C_q Ar), 152.8 (C_q Ar); LRMS (ES^+) *m/z* 284.4 $[M+H]^+$; HRMS (ESI) calcd for $C_{10}H_{10}N_3O_5S$ $[M+H]^+$ 284.0336, found 284.0341.

3-Nitrophenyl 2-methyl-1*H*-imidazole-1-sulfonate, (57)



Compound **57** was synthesised according to general procedure B, using the following reagents: 1,1'-sulfonylbis(2-methyl-1*H*-imidazole) (**19**) (651 mg, 2.87 mmol), caesium carbonate (515 mg, 1.58 mmol), 3-nitrophenol (200 mg, 1.44 mmol) and acetonitrile (20 mL). The crude yellow oil was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 3:1) to yield the *title compound* as a yellow solid (294 mg, 72%); R_f = 0.27 (petrol:EtOAc, 3:1; $KMnO_4$); m.p. 70.5-72.5 °C; λ_{max} (EtOH)/nm 249.0; IR (neat) ν_{max}/cm^{-1} 1557, 1522, 1418, 1351, 1193, 1160, 1045; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.57 (3H, s, CH_3), 6.93 (1H, d, *J* = 1.8 Hz, H-4' or H-5'), 7.14 (1H, d, *J* = 1.8 Hz, H-4' or H-5'), 7.26 (1H, ddd, *J* = 8.3, 2.3 and 0.9 Hz, H-6), 7.60 (1H, dd, *J* = 8.3, 8.3 Hz, H-5), 7.92 (1H, dd, *J* = 2.3, 2.3 Hz, H-2), 8.26 (1H, ddd, *J* = 8.3, 2.3 and 0.9 Hz, H-4); ^{13}C NMR (126 MHz, $CDCl_3$) δ 15.2 (CH_3), 117.8 (C-2), 120.4 (C-4' or C-5'), 123.5 (C-4), 127.7 (C-6), 128.6 (C-4' or C-5'), 131.3 (C-5), 146.8 (C_q Ar), 149.0 (C_q Ar), 149.1 (C_q Ar); LRMS (ES^+) *m/z* 284.4 $[M+H]^+$; HRMS (ESI) calcd for $C_{10}H_{10}N_3O_5S$ $[M+H]^+$ 284.0336, found 284.0337.

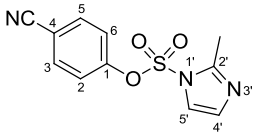
2-Nitrophenyl 2-methyl-1*H*-imidazole-1-sulfonate, (58)



Compound **58** was synthesised according to general procedure G, using the following reagents: 1,1'-sulfonylbis(2-methyl-1*H*-imidazole) (**19**) (4.88 g, 21.6 mmol), caesium carbonate (773 mg, 2.37 mmol), 2-nitrophenol (300 mg, 2.16 mmol) and acetonitrile (20 mL). The crude brawn oil was purified by column chromatography (silica gel, DCM:MeOH, 1:0 → 99:1) to yield the *title compound* as a yellow solid (428 mg, 70%); R_f = 0.20 (DCM:MeOH, 99:1; $KMnO_4$); m.p. 55.5-57.5 °C; λ_{max} (EtOH)/nm 245.0; IR (neat) ν_{max}/cm^{-1} 1600, 1532, 1425, 1339, 1208, 1151, 1045; ^{1}H NMR (500 MHz,

$CDCl_3$) δ 2.56 (3H, s, CH_3), 6.93 (1H, d, *J* = 1.8 Hz, H-4' or H-5'), 7.11 (1H, dd, *J* = 8.2, 1.3 Hz, H-6), 7.12 (1H, d, *J* = 1.8 Hz, H-4' or H-5'), 7.59 – 7.51 (1H, m, H-4), 7.66 (1H, ddd, *J* = 8.2, 7.5 and 1.7 Hz, H-5), 8.08 (1H, dd, *J* = 8.2, 1.7 Hz, H-3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 15.2 (CH_3), 120.3 (C-4' or C-5'), 124.4 (C-6), 126.8 (C-3), 128.6 (C-4' or C-5'), 129.2 (C-4), 135.0 (C-5), 141.2 (C_q Ar), 142.4 (C_q Ar), 147.1 (C_q Ar); LRMS (ES^+) *m/z* 284.1 $[M+H]^+$; HRMS (ESI) calcd for $C_{10}H_{10}N_3O_5S$ $[M+H]^+$ 284.0336, found 284.0340.

4-Cyanophenyl 2-methyl-1*H*-imidazole-1-sulfonate, (59)

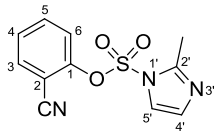


Compound **59** was synthesised following two different procedures.

1st procedure: Compound **59** was synthesised according to general procedure B, using the following reagents: 1,1'-sulfonylbis(2-methyl-1*H*-imidazole) (**19**) (760 mg, 3.36 mmol), caesium carbonate (602 mg, 1.85 mmol), 4-cyanophenol (200 mg, 1.68 mmol) and acetonitrile (20 mL). The crude yellow solid was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 7:3) to yield the *title compound* as a white solid (261 mg, 59%).

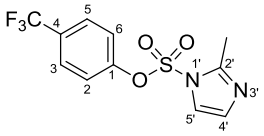
2nd procedure: Compound **59** was synthesised according to general procedure G, using the following reagents: 1,1'-sulfonylbis(2-methyl-1*H*-imidazole) (**19**) (950 mg, 4.20 mmol), caesium carbonate (150 mg, 0.46 mmol), 4-cyanophenol (50 mg, 042 mmol) and acetonitrile (5 mL). The crude yellow solid was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 7:3) to yield the *title compound* as a white solid (88 mg, 80%); R_f = 0.28 (petrol:EtOAc, 7:3; $KMnO_4$); m.p. 102.5-104.5 °C; λ_{max} (EtOH)/nm 268.5; IR (neat) ν_{max}/cm^{-1} 2239, 1601, 1555, 1498, 1417, 1206, 1144, 1048; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.54 (3H, s, CH_3), 6.91 (1H, d, *J* = 1.8 Hz, H-4' or H-5'), 7.09 (2H, d, *J* = 8.7 Hz, H-2, 6), 7.12 (1H, d, *J* = 1.8 Hz, H-4' or H-5'), 7.70 (2H, d, *J* = 8.7 Hz, H-3, 5); ^{13}C NMR (126 MHz, $CDCl_3$) δ 15.1 (CH_3), 113.1 (Ar*C*N), 117.2 (C-4), 120.4 (C-4' or C-5'), 123.0 (C-2, 6), 128.5 (C-4' or C-5'), 134.6 (C-3, 5), 146.8 (C-1 or C-2'), 151.6 (C-1 or C-2'); LRMS (ES^+) *m/z* 264.4 $[M+H]^+$; HRMS (ESI) calcd for $C_{11}H_{10}N_3O_3S$ $[M+H]^+$ 264.0437, found 264.0442.

2-Cyanophenyl 2-methyl-1*H*-imidazole-1-sulfonate, (60)



Compound **60** was synthesised according to general procedure G, using the following reagents: 1,1'-sulfonylbis(2-methyl-1*H*-imidazole) (**19**) (4.75 g, 21.0 mmol), caesium carbonate (752 mg, 2.31 mmol), 2-cyanophenol (250 mg, 2.10 mmol) and acetonitrile (20 mL). The crude brawn oil was purified by column chromatography (silica gel, DCM:MeOH, 1:0 → 99:1) to yield the *title compound* as a yellow solid (398 mg, 72%); R_f = 0.18 (DCM:MeOH, 99:1; $KMnO_4$); m.p. 96.5-98.5 °C; λ_{max} (EtOH)/nm 271.5; IR (neat) ν_{max}/cm^{-1} 1608, 1555, 1510, 1487, 1424, 1207, 1151, 1045; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.60 (3H, s, CH_3), 6.93 (1H, d, *J* = 1.8 Hz, H-4' or H-5'), 7.14 (1H, d, *J* = 1.8 Hz, H-4' or H-5'), 7.25 (1H, dd, *J* = 8.6, 1.1 Hz, H-6), 7.49 (1H, ddd, *J* = 7.6, 7.6 and 1.1 Hz, H-4), 7.67 (1H, ddd, *J* = 8.6, 7.6 and 1.7 Hz, H-5), 7.71 (1H, dd, *J* = 7.6, 1.7 Hz, H-3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 15.3 (CH_3), 108.0 (C-2), 113.6 (Ar*C*N), 120.4 (C-4' or C-5'), 123.1 (C-6), 128.6 (C-4' or C-5'), 128.9 (C-4), 134.4 (C-3), 134.8 (C-5), 147.2 (C-1 or C-2'), 149.5 (C-1 or C-2'); LRMS (ES^+) *m/z* 264.4 $[M+H]^+$; HRMS (ESI) calcd for $C_{11}H_{10}N_3O_3S$ $[M+H]^+$ 264.0437, found 264.0442.

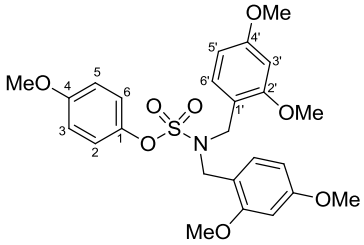
4-(Trifluoromethyl)phenyl 2-methyl-1*H*-imidazole-1-sulfonate, (61)



Compound **61** was synthesised according to general procedure B, using the following reagents: 1,1'-sulfonylbis(2-methyl-1*H*-imidazole) (**19**) (837 mg, 3.70 mmol), caesium carbonate (663 mg, 2.04 mmol), 4-(trifluoromethyl)phenol (300 mg, 1.85 mmol) and acetonitrile (20 mL). The crude orange oil was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 8:2) to yield the *title compound* as a clear oil (454 mg, 80%); R_f = 0.32 (petrol:EtOAc, 8:2; $KMnO_4$); λ_{max} (EtOH)/nm 259.5; IR (neat) ν_{max}/cm^{-1} 1613, 1555, 1508, 1427, 1323, 1211, 1173, 1127; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.52 (3H, s, CH_3), 6.91 (1H, d, *J* = 1.8 Hz, H-4' or H-5'), 7.08 (2H, d, *J* = 8.4 Hz, H-2, 6), 7.13 (1H, d, *J* = 1.8 Hz, H-4' or H-5'), 7.66 (2H, d, *J* = 8.4 Hz, H-3, 5); ^{13}C NMR (126 MHz, $CDCl_3$) δ 15.1 (CH_3), 120.5 (C-4' or C-5'), 122.4 (C-2, 6), 123.3 (d, *J* = 272.5 Hz, Ar*C*F_3), 127.9 (q, *J* = 3.7 Hz, C-3, 5), 128.4 (C-4' or C-5'), 131.1 (q, *J* = 33.4 Hz, C-4), 146.8 (C-2'),

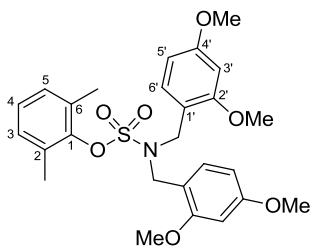
151.2 (C-1); ^{19}F NMR(471 MHz, $CDCl_3$) δ-62.6 (CF_3); LRMS (ES^+) *m/z* 308.1 $[M+H]^+$; HRMS (ESI) calcd for $C_{11}H_{10}F_3N_2O_3S$ $[M+H]^+$ 307.0359, found 307.0358.

4-Methoxyphenyl bis(2,4-dimethoxybenzyl)sulfamate, (62)



Compound **62** was synthesised according to general procedure H, using the following reagents: 4-methoxyphenyl 2-methyl-1*H*-imidazole-1-sulfonate (**48**) (350 mg, 1.30 mmol), trimethyloxonium tetrafluoroborate (193 mg, 1.30 mmol), DCM (13 mL), acetonitrile (6.5 mL) and bis(2,4-dimethoxybenzyl)amine (**32**) (414 mg, 1.30 mmol). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 3:1) to yield the *title compound* as a pale yellow oil (428 mg, 65%); R_f = 0.30 (petrol:EtOAc, 3:1; $KMnO_4$); λ_{max} (EtOH)/nm 277.0; IR (neat) ν_{max}/cm^{-1} 1613, 1589, 1502, 1463, 1367, 1208, 1156, 1032; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.72 (6H, s, 2 × ArOCH_3), 3.78 (3H, s, ArOCH_3), 3.79 (6H, s, 2 × ArOCH_3), 4.43 (4H, s, 2 × ArCH_2), 6.37 (2H, d, *J* = 2.4 Hz, H-3'), 6.42 (2H, dd, *J* = 8.4, 2.4 Hz, H-5'), 6.79 (2H, d, *J* = 9.1 Hz, H-3, 5), 7.00 (2H, d, *J* = 9.1 Hz, H-2, 6), 7.26 (2H, d, *J* = 8.4 Hz, H-6'); ^{13}C NMR (126 MHz, $CDCl_3$) δ 47.0 (Ar*C*H_2), 55.2 (ArO*C*H_3), 55.5 (ArO*C*H_3), 55.7 (ArO*C*H_3), 98.2 (C-3'), 104.1 (C-5'), 114.5 (C-3, 5), 116.8 (C-1'), 123.2 (C-2, 6), 131.0 (C-6'), 143.9 (C-1), 157.9 (C_q Ar), 158.5 (C_q Ar), 160.6 (C_q Ar); HRMS (ESI) calcd for $C_{25}H_{30}NO_8S$ $[M+H]^+$ 504.1687, found 504.1677.

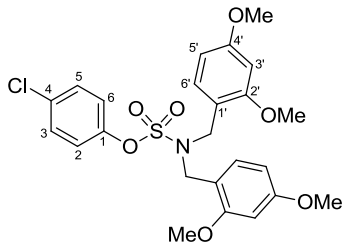
2,6-Dimethylphenyl bis(2,4-dimethoxybenzyl)sulfamate, (63)



Compound **63** was synthesised according to general procedure H, using the following reagents: 2,6-dimethylphenyl 2-methyl-1*H*-imidazole-1-sulfonate (**51**) (300 mg, 1.13 mmol), trimethyloxonium tetrafluoroborate (167 mg, 1.13 mmol), DCM (11.5 mL), acetonitrile (5.5 mL) and bis(2,4-dimethoxybenzyl)amine (**32**) (358 mg, 1,13 mmol). The

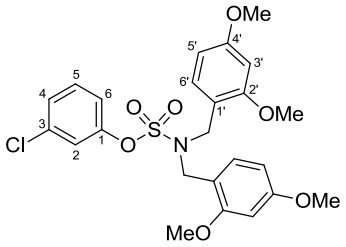
crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 85:15) to yield the *title compound* as a white solid (345 mg, 61%); R_f = 0.25 (petrol:EtOAc, 85:15; $KMnO_4$); m.p. 92.5-94.5 °C; λ_{max} (EtOH)/nm 277.0; IR (neat) ν_{max}/cm^{-1} 1612, 1608, 1510, 1466, 1364, 1289, 1204, 1027; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.35 (6H, s, 2 × ArC*H*$_3$), 3.72 (6H, s, 2 × ArOC*H*$_3$), 3.79 (6H, s, 2 × ArOC*H*$_3$), 4.60 (4H, s, 2 × ArC*H*$_2$), 6.37 (2H, d, *J* = 2.4 Hz, H-3'), 6.43 (2H, dd, *J* = 8.4, 2.4 Hz, H-5'), 7.02 (3H, s, H-3 and H-4 and H-5), 7.33 (2H, d, *J* = 8.4 Hz, H-6'); ^{13}C NMR (126 MHz, $CDCl_3$) δ 17.6 (Ar*C*H$_3$), 46.8 (Ar*C*H$_2$), 55.2 (ArO*C*H$_3$), 55.5 (ArO*C*H$_3$), 98.2 (C-3'), 104.1 (C-5'), 116.8 (C-1'), 126.4 (C-3, 5 or C-4), 129.3 (C-3, 5 or C-4), 130.7 (C-6'), 132.5 (C-2, 6), 147.9 (C-1), 158.5 (C-2' or C-4'), 160.6 (C-2' or C-4'); HRMS (ESI) calcd for $C_{26}H_{32}NO_7S$ $[M+H]^+$ 502.1894, found 502.1894.

4-Chlorophenyl bis(2,4-dimethoxybenzyl)sulfamate, (64)



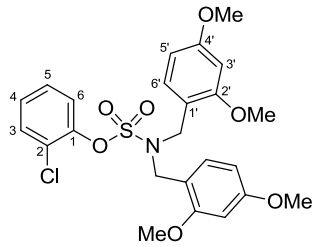
Compound **64** was synthesised according to general procedure H, using the following reagents: 4-chlorophenyl 2-methyl-1*H*-imidazole-1-sulfonate (**49**) (300 mg, 1.10 mmol), trimethyloxonium tetrafluoroborate (163 mg, 1.10 mmol), DCM (11.0 mL), acetonitrile (5.5 mL) and bis(2,4-dimethoxybenzyl)amine (**32**) (349 mg, 1,10 mmol). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 8:2) to yield the *title compound* as a clear oil (352 mg, 63%); R_f = 0.32 (petrol:EtOAc, 8:2; $KMnO_4$); λ_{max} (EtOH)/nm 277.0; IR (neat) ν_{max}/cm^{-1} 1613, 1589, 1508, 1484, 1370, 1208, 1156, 1035; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.73 (6H, s, 2 × ArOC*H*$_3$), 3.80 (6H, s, 2 × ArOC*H*$_3$), 4.44 (4H, s, 2 × ArC*H*$_2$), 6.39 (2H, d, *J* = 2.4 Hz, H-3'), 6.43 (2H, dd, *J* = 8.3, 2.4 Hz, H-5'), 6.98 (2H, d, *J* = 9.0 Hz, H-2, 6), 7.24 (4H, d, *J* = 9.0 Hz, H-3, 5 and H-6'); ^{13}C NMR (126 MHz, $CDCl_3$) δ 47.1 (Ar*C*H$_2$), 55.2 (ArO*C*H$_3$), 55.5 (ArO*C*H$_3$), 98.3 (C-3'), 104.1 (C-5'), 116.6 (C-1'), 123.5 (C-2, 6), 129.6 (C-3, 5), 131.1 (C-6'), 148.9 (C-1), 158.6 (C-2' or C-4'), 160.8 (C-2' or C-4'); HRMS (ESI) calcd for $C_{24}H_{27}ClNO_7S$ $[M+H]^+$ 508.1191, found 508.1181

3-Chlorophenyl bis(2,4-dimethoxybenzyl)sulfamate, (65)



Compound **65** was synthesised according to general procedure H, using the following reagents: 3-chlorophenyl 2-methyl-1*H*-imidazole-1-sulfonate (**50**) (300 mg, 1.10 mmol), trimethyloxonium tetrafluoroborate (163 mg, 1.10 mmol), DCM (11.0 mL), acetonitrile (5.5 mL) and bis(2,4-dimethoxybenzyl)amine (**32**) (349 mg, 1,10 mmol). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 8:2) to yield the *title compound* as a clear oil (341 mg, 61%); R_f = 0.31 (petrol:EtOAc, 8:2; $KMnO_4$); λ_{max} (EtOH)/nm 277.0; IR (neat) ν_{max}/cm^{-1} 1613, 1587, 1508, 1467, 1371, 1208, 1156, 1034; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.75 (6H, s, 2 × ArOCH_3), 3.81 (6H, s, 2 × ArOCH_3), 4.45 (4H, s, 2 × ArCH_2), 6.41 (2H, d, *J* = 2.4 Hz, H-3'), 6.45 (2H, dd, *J* = 8.4, 2.4 Hz, H-5'), 6.91 (1H, dd, *J* = 2.2, 2.0 Hz, H-2), 7.03 (1H, ddd, *J* = 7.9, 2.2 and 1.4 Hz, H-6), 7.20 – 7.16 (1H, m, H-4), 7.22 (1H, dd, *J* = 8.0, 7.9 Hz, H-5), 7.26 (2H, d, *J* = 8.4 Hz, H-6'); ^{13}C NMR (126 MHz, $CDCl_3$) δ 47.3 (Ar*C*H_2), 55.3 (ArO*C*H_3), 55.5 (ArO*C*H_3), 98.4 (C-3'), 104.1 (C-5'), 116.6 (C-1'), 120.4 (C-6), 122.6 (C-2), 126.7 (C-4), 130.3 (C-5), 131.2 (C-6'), 134.7 (C-3), 150.8 (C-1), 158.6 (C-2' or C-4'), 160.8 (C-2' or C-4'); HRMS (ESI) calcd for $C_{24}H_{27}ClNO_7S$ $[M+H]^+$ 508.1191, found 508.1187.

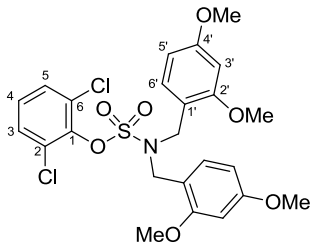
2-Chlorophenyl bis(2,4-dimethoxybenzyl)sulfamate, (66)



Compound **66** was synthesised according to general procedure H, using the following reagents: 2-chlorophenyl 2-methyl-1*H*-imidazole-1-sulfonate (**52**) (350 mg, 1.28 mmol), trimethyloxonium tetrafluoroborate (190 mg, 1.28 mmol), DCM (13 mL), acetonitrile (6.5 mL) and bis(2,4-dimethoxybenzyl)amine (**32**) (407 mg, 1,28 mmol). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 8:2) to yield the *title compound* as a clear oil (444 mg, 68%); R_f = 0.30 (petrol:EtOAc, 8:2; $KMnO_4$); λ_{max} (EtOH)/nm 276.5; IR (neat) ν_{max}/cm^{-1} 1614, 1589, 1508, 1473, 1372, 1207,

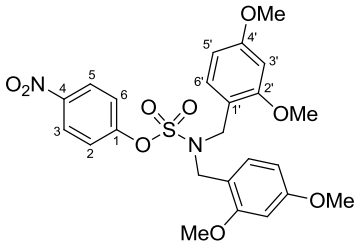
1157, 1034; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.71 (6H, s, 2 × ArOCH_3), 3.78 (6H, s, 2 × ArOCH_3), 4.56 (4H, s, 2 × ArCH_2), 6.35 (2H, d, *J* = 2.4 Hz, H-3'), 6.40 (2H, dd, *J* = 8.4, 2.4 Hz, H-5'), 7.16 (1H, ddd, *J* = 7.8, 7.8 and 1.7 Hz, H-4 or H-5), 7.23 (1H, ddd, *J* = 7.8, 7.8 and 1.7 Hz, H-4 or H-5), 7.27 (2H, d, *J* = 8.4 Hz, H-6'), 7.40 (1H, dd, *J* = 7.8, 1.7 Hz, H-3 or H-6), 7.43 (1H, dd, *J* = 7.8, 1.7 Hz, H-3 or H-6); ^{13}C NMR (126 MHz, $CDCl_3$) δ 47.1 (Ar*C*H_2), 55.2 (ArO*C*H_3), 55.5 (ArO*C*H_3), 98.2 (C-3'), 104.1 (C-5'), 116.5 (C-1'), 123.6 (C-3 or C-6), 127.2 (C-4 or C-5), 127.2 (C-2), 127.9 (C-4 or C-5), 130.8 (C-3 or C-6), 130.9 (C-6'), 146.7 (C-1), 158.5 (C-2' or C-4'), 160.6 (C-2' or C-4'); HRMS (ESI) calcd for $C_{24}H_{27}ClNO_7S$ $[M+H]^+$ 508.1191, found 508.1183.

2,6-Dichlorophenyl bis(2,4-dimethoxybenzyl)sulfamate, (67)



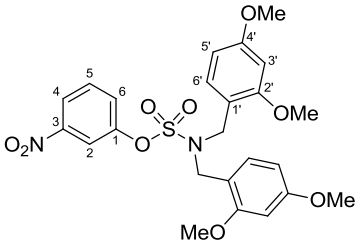
Compound **67** was synthesised according to general procedure H, using the following reagents: 2,6-dichlorophenyl 2-methyl-1*H*-imidazole-1-sulfonate (**53**) (350 mg, 1.14 mmol), trimethyloxonium tetrafluoroborate (169 mg, 1.14 mmol), DCM (11.4 mL), acetonitrile (5.7 mL) and bis(2,4-dimethoxybenzyl)amine (**32**) (362 mg, 1.14 mmol). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 8:2) to yield the *title compound* as a yellow oil (389 mg, 63%); R_f = 0.31 (petrol:EtOAc, 8:2; $KMnO_4$); λ_{max} (EtOH)/nm 277.5; IR (neat) ν_{max}/cm^{-1} 1613, 1589, 1508, 1440, 1382, 1207, 1157, 1035; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.71 (6H, s, 2 × ArOCH_3), 3.78 (6H, s, 2 × ArOCH_3), 4.60 (4H, s, 2 × ArCH_2), 6.35 (2H, d, *J* = 2.4 Hz, H-3'), 6.40 (2H, dd, *J* = 8.4, 2.4 Hz, H-5'), 7.10 (1H, dd, *J* = 8.1, 8.1 Hz, H-4), 7.30 (2H, d, *J* = 8.4 Hz, H-6'), 7.33 (2H, d, *J* = 8.1 Hz, H-3, 5); ^{13}C NMR (126 MHz, $CDCl_3$) δ 47.2 (Ar*C*H_2), 55.2 (ArO*C*H_3), 55.5 (ArO*C*H_3), 98.1 (C-3'), 104.0 (C-5'), 116.5 (C-1'), 127.3 (C-4), 129.4 (C-3, 5), 130.2 (C-2, 6), 131.0 (C-6'), 144.3 (C-1), 158.5 (C-2' or C-4'), 160.6 (C-2' or C-4'); HRMS (ESI) calcd for $C_{24}H_{26}Cl_2NO_7S$ $[M+H]^+$ 542.0802, found 542.0793.

4-Nitrophenyl bis(2,4-dimethoxybenzyl)sulfamate, (68)



Compound **68** was synthesised according to general procedure H, using the following reagents: 4-nitrophenyl 2-methyl-1*H*-imidazole-1-sulfonate (**54**) (300 mg, 1.06 mmol), trimethyloxonium tetrafluoroborate (157 mg, 1.06 mmol), DCM (10.5 mL), acetonitrile (5.3 mL) and bis(2,4-dimethoxybenzyl)amine (**32**) (337 mg, 1,06 mmol). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 8:2) to yield the *title compound* as a yellow oil (340 mg, 62%); R_f = 0.29 (petrol:EtOAc, 8:2; $KMnO_4$); λ_{max} (EtOH)/nm 275.0; IR (neat) ν_{max}/cm^{-1} 1613, 1589, 1507, 1374, 1346, 1206, 1156, 1033; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.75 (6H, s, 2 × ArOCH_3), 3.81 (6H, s, 2 × ArOCH_3), 4.48 (4H, s, 2 × ArCH_2), 6.40 (2H, d, *J* = 2.4 Hz, H-3'), 6.44 (2H, dd, *J* = 8.3, 2.4 Hz, H-5'), 7.16 (2H, d, *J* = 9.2 Hz, H-2, 6), 7.24 (2H, d, *J* = 8.3 Hz, H-6'), 8.15 (2H, d, *J* = 9.2 Hz, H-3, 5); ^{13}C NMR (126 MHz, $CDCl_3$) δ 47.4 (Ar*C*H_2), 55.3 (ArO*C*H_3), 55.6 (ArO*C*H_3), 98.4 (C-3'), 104.1 (C-5'), 116.3 (C-1'), 122.4 (C-2, 6), 125.4 (C-3, 5), 131.2 (C-6'), 145.5 (C_q Ar), 155.1 (C_q Ar), 158.6 (C-2' or C-4'), 161.0 (C-2' or C-4'); HRMS (ESI) calcd for $C_{24}H_{27}N_2O_9S$ $[M+H]^+$ 519.1432, found 519.1413.

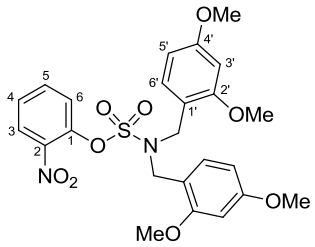
3-Nitrophenyl bis(2,4-dimethoxybenzyl)sulfamate, (69)



Compound **69** was synthesised according to general procedure H, using the following reagents: 3-nitrophenyl 2-methyl-1*H*-imidazole-1-sulfonate (**57**) (200 mg, 0.71 mmol), trimethyloxonium tetrafluoroborate (104 mg, 0.71 mmol), DCM (7.1 mL), acetonitrile (3.5 mL) and bis(2,4-dimethoxybenzyl)amine (**32**) (225 mg, 0.71 mmol). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 8:2) to yield the *title compound* as a yellow oil (208 mg, 57%); R_f = 0.27 (petrol:EtOAc, 8:2; $KMnO_4$); λ_{max} (EtOH)/nm 273.0; IR (neat) ν_{max}/cm^{-1} 1612, 1589, 1530, 1507, 1351, 1206, 1157, 1033; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.78 (6H, s, 2 × ArOCH_3), 3.82 (6H, s,

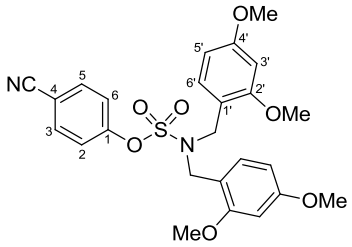
2 × ArOCH_3), 4.49 (4H, s, 2 × ArCH_2), 6.43 (2H, d, *J* = 2.3 Hz, H-3'), 6.45 (2H, dd, *J* = 8.3, 2.3 Hz, H-5'), 7.26 (2H, d, *J* = 8.3 Hz, H-6'), 7.46 (1H, dd, *J* = 8.1, 7.6 Hz, H-5), 7.51 – 7.48 (1H, m, H-6), 7.65 (1H, dd, *J* = 2.2, 2.1 Hz, H-2), 8.06 (1H, ddd, *J* = 7.7, 2.2 and 1.5 Hz, H-4); ^{13}C NMR (126 MHz, $CDCl_3$) δ 47.5 (Ar*C*H_2), 55.3 (ArO*C*H_3), 55.5 (ArO*C*H_3), 98.4 (C-3'), 104.2 (C-5'), 116.4 (C-1'), 117.7 (C-2), 121.3 (C-4), 128.6 (C-6), 130.2 (C-5), 131.3 (C-6'), 148.7 (C_q Ar), 150.6 (C_q Ar), 158.7 (C-2' or C-4'), 161.0 (C-2' or C-4'); HRMS (ESI) calcd for $C_{24}H_{27}N_2O_9S$ $[M+H]^+$ 519.1432, found 519.1409.

2-Nitrophenyl bis(2,4-dimethoxybenzyl)sulfamate, (70)



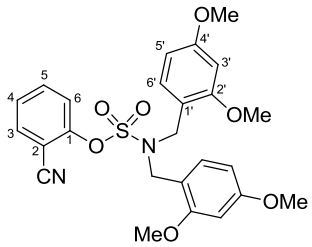
Compound **70** was synthesised according to general procedure H, using the following reagents: 2-nitrophenyl 2-methyl-1*H*-imidazole-1-sulfonate (**58**) (250 mg, 0.88 mmol), trimethyloxonium tetrafluoroborate (131 mg, 0.88 mmol), DCM (8.8 mL), acetonitrile (4.4 mL) and bis(2,4-dimethoxybenzyl)amine (**32**) (281 mg, 0.88 mmol). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 3:1) to yield the *title compound* as a yellow oil (279 mg, 61%); R_f = 0.30 (petrol:EtOAc, 3:1; $KMnO_4$); λ_{max} (EtOH)/nm 276.5; IR (neat) ν_{max}/cm^{-1} 1611, 1589, 1532, 1508, 1355, 1208, 1158, 1034; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.73 (6H, s, 2 × ArOCH_3), 3.79 (6H, s, 2 × ArOCH_3), 4.55 (4H, s, 2 × ArCH_2), 6.36 (2H, d, *J* = 2.4 Hz, H-3'), 6.40 (2H, dd, *J* = 8.4, 2.4 Hz, H-5'), 7.24 (2H, d, *J* = 8.4 Hz, H-6'), 7.34 (1H, ddd, *J* = 8.5, 7.3 and 1.5 Hz, H-4), 7.52 (1H, dd, *J* = 8.2, 1.5 Hz, H-6), 7.60 – 7.54 (1H, m, H-5), 7.92 (1H, dd, *J* = 8.5, 1.6 Hz, H-3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 47.3 (Ar*C*H_2), 55.2 (ArO*C*H_3), 55.5 (ArO*C*H_3), 98.2 (C-3'), 104.1 (C-5'), 116.2 (C-1'), 124.5 (C-4), 125.8 (C-3), 126.5 (C-6), 131.0 (C-6'), 134.2 (C-5), 142.7 (C_q Ar), 143.1 (C_q Ar), 158.6 (C-2' or C-4'), 160.7 (C-2' or C-4'); HRMS (ESI) calcd for $C_{24}H_{27}N_2O_9S$ $[M+H]^+$ 519.1432, found 519.1409.

4-Cyanophenyl bis(2,4-dimethoxybenzyl)sulfamate, (71)



Compound **71** was synthesised according to general procedure H, using the following reagents: 4-cyanophenyl 2-methyl-1*H*-imidazole-1-sulfonate (**59**) (300 mg, 1.14 mmol), trimethyloxonium tetrafluoroborate (169 mg, 1.14 mmol), DCM (11.5 mL), acetonitrile (5.7 mL) and bis(2,4-dimethoxybenzyl)amine (**32**) (362 mg, 1,14 mmol). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 3:1) to yield the *title compound* as a white solid (358 mg, 63%); R_f = 0.28 (petrol:EtOAc, 3:1; $KMnO_4$); m.p. 113.0-115.0 °C; λ_{max} (EtOH)/nm 277.0; IR (neat) ν_{max}/cm^{-1} 2229, 1606, 1509, 1367, 1303, 1204, 1156, 1030; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.74 (6H, s, 2 × ArOCH_3), 3.81 (6H, s, 2 × ArOCH_3), 4.47 (4H, s, 2 × ArCH_2), 6.41 (2H, d, *J* = 2.4 Hz, H-3'), 6.44 (2H, dd, *J* = 8.3, 2.4 Hz, H-5'), 7.13 (2H, d, *J* = 8.8 Hz, H-2, 6), 7.24 (2H, d, *J* = 8.3 Hz, H-6'), 7.59 (2H, d, *J* = 8.8 Hz, H-3, 5); ^{13}C NMR (126 MHz, $CDCl_3$) δ 47.3 (Ar*C*H_2), 55.3 (ArO*C*H_3), 55.6 (ArO*C*H_3), 98.4 (C-3'), 104.1 (C-5'), 110.1 (C-4'), 116.3 (C-1'), 118.3 (CN), 122.7 (C-2, 6), 131.2 (C-6'), 133.8 (C-3, 5), 153.7 (C-1), 158.6 (C-2' or C-4'), 160.9 (C-2' or C-4'); HRMS (ESI) calcd for $C_{25}H_{27}N_2O_7S$ $[M+H]^+$ 499.1533, found 499.1530.

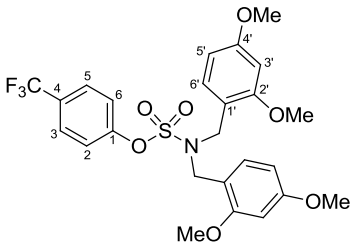
2-Cyanophenyl bis(2,4-dimethoxybenzyl)sulfamate, (72)



Compound **72** was synthesised according to general procedure H, using the following reagents: 2-cyanophenyl 2-methyl-1*H*-imidazole-1-sulfonate (**60**) (300 mg, 1.14 mmol), trimethyloxonium tetrafluoroborate (169 mg, 1.14 mmol), DCM (11.5 mL), acetonitrile (5.7 mL) and bis(2,4-dimethoxybenzyl)amine (**32**) (362 mg, 1,14 mmol). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 3:1) to yield the *title compound* as a clear oil (341 mg, 60%); R_f = 0.26 (petrol:EtOAc, 3:1; $KMnO_4$); λ_{max} (EtOH)/nm 276.5; IR (neat) ν_{max}/cm^{-1} 2236, 1613, 1592, 1508, 1450, 1374,

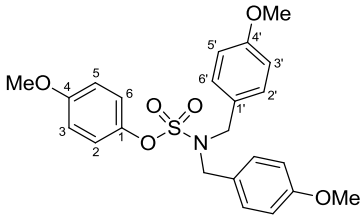
1208, 1157, 1033; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.73 (6H, s, 2 × ArOCH_3), 3.79 (6H, s, 2 × ArOCH_3), 4.61 (4H, s, 2 × ArCH_2), 6.36 (2H, d, *J* = 2.3 Hz, H-3'), 6.40 (2H, dd, *J* = 8.4, 2.3 Hz, H-5'), 7.27 (2H, d, *J* = 8.4 Hz, H-6'), 7.30 (1H, ddd, *J* = 7.6, 7.6 and 1.3 Hz, H-4), 7.53 – 7.50 (1H, m, H-6), 7.59 – 7.55 (1H, m, H-5), 7.61 (1H, dd, *J* = 7.6, 1.6 Hz, H-3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 47.4 (Ar*C*H_2), 55.2 (ArO*C*H_3), 55.5 (ArO*C*H_3), 98.2 (C-3'), 104.1 (C-5'), 107.2 (C-2), 115.3 (Ar*C*N), 116.3 (C-1'), 122.7 (C-6), 126.3 (C-4), 131.1 (C-6'), 133.7 (C-3), 134.2 (C-5), 151.8 (C-1), 158.6 (C-2' or C-4'), 160.8 (C-2' or C-4'); HRMS (ESI) calcd for $C_{25}H_{30}N_3O_7S$ $[M+NH_4]^+$ 516.1799, found 516.1796.

4-(Trifluoromethyl)phenyl bis(2,4-dimethoxybenzyl)sulfamate, (73)



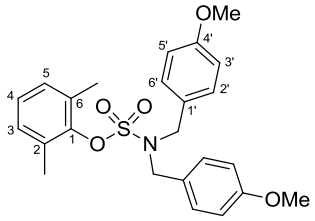
Compound **73** was synthesised according to general procedure H, using the following reagents: 4-(trifluoromethyl)phenyl 2-methyl-1*H*-imidazole-1-sulfonate (**61**) (350 mg, 1.14 mmol), trimethyloxonium tetrafluoroborate (169 mg, 1.14 mmol), DCM (11.4 mL), acetonitrile (5.7 mL) and bis(2,4-dimethoxybenzyl)amine (**32**) (362 mg, 1.14 mmol). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 8:2) to yield the *title compound* as a yellow oil (408 mg, 66%); R_f = 0.32 (petrol:EtOAc, 8:2; $KMnO_4$); λ_{max} (EtOH)/nm 277.5; IR (neat) ν_{max}/cm^{-1} 1613, 1592, 1508, 1373, 1323, 1208, 1157, 1121, 1036; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.74 (6H, s, 2 × ArOCH_3), 3.80 (6H, s, 2 × ArOCH_3), 4.47 (4H, s, 2 × ArCH_2), 6.40 (2H, d, *J* = 2.4 Hz, H-3'), 6.44 (2H, dd, *J* = 8.4, 2.4 Hz, H-5'), 7.15 (2H, d, *J* = 8.1 Hz, H-2, 6), 7.25 (2H, d, *J* = 8.4 Hz, H-6'), 7.55 (2H, d, *J* = 8.1 Hz, H-3, 5); ^{13}C NMR (126 MHz, $CDCl_3$) δ 47.2 (Ar*C*H_2), 55.2 (ArO*C*H_3), 55.5 (ArO*C*H_3), 98.3 (C-3'), 104.1 (C-5'), 116.4 (C-1'), 122.2 (C-2, 6), 123.9 (d, *J* = 272.0 Hz, Ar*C*F_3), 127.0 (q, *J* = 3.7 Hz, C-3, 5), 128.5 (d, *J* = 32.9 Hz, C-4), 131.2 (C-6'), 153.0 (C-1), 158.6 (C-2' or C-4'), 160.9 (C-2' or C-4'); ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.2 (CF_3); HRMS (ESI) calcd for $C_{25}H_{27}F_3NO_7S$ $[M+H]^+$ 542.1450, found 542.1455.

4-Methoxyphenyl bis(4-methoxybenzyl)sulfamate, (74)



Compound **74** was synthesised according to general procedure H, using the following reagents: 4-methoxyphenyl 2-methyl-1*H*-imidazole-1-sulfonate (**48**) (300 mg, 1.12 mmol), trimethyloxonium tetrafluoroborate (165 mg, 1.12 mmol), DCM (11.2 mL), acetonitrile (5.6 mL) and bis(4-methoxybenzyl)amine (**31**) (288 mg, 1.12 mmol). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 85:15) to yield the *title compound* as a clear oil (398 mg, 80%); R_f = 0.30 (petrol:EtOAc, 85:15; $KMnO_4$); λ_{max} (EtOH)/nm 274.5; IR (neat) ν_{max}/cm^{-1} 1612, 1502, 1367, 1247, 1165, 1031; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.80 (3H, s, ArOC*H*$_3$), 3.82 (6H, s, 2 × ArOC*H*$_3$), 4.29 (4H, s, 2 × ArC*H*$_2$), 6.83 (2H, d, *J* = 9.1 Hz, H-3, 5), 6.86 (4H, d, *J* = 8.7 Hz, H-3', 5'), 7.05 (2H, d, *J* = 9.1 Hz, H-2, 6), 7.20 (4H, d, *J* = 8.7 Hz, H-2', 6'); ^{13}C NMR (126 MHz, $CDCl_3$) δ 50.4 (Ar*C*H$_2$), 55.4 (ArO*C*H$_3$), 55.7 (ArO*C*H$_3$), 114.1 (C-3', 5'), 114.7 (C-3, 5), 123.2 (C-2, 6), 127.0 (C-1'), 130.5 (C-2', 6'), 143.9 (C-1), 158.1 (C-2' or C-4'), 159.6 (C-2' or C-4'); HRMS (ESI) calcd for $C_{25}H_{30}NO_8S$ $[M+H]^+$ 504.1687, found 504.1677.

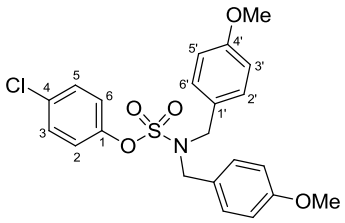
2,6-Dimethylphenyl bis(4-methoxybenzyl)sulfamate, (75)



Compound **75** was synthesised according to general procedure H, using the following reagents: 2,6-dimethylphenyl 2-methyl-1*H*-imidazole-1-sulfonate (**51**) (300 mg, 1.13 mmol), trimethyloxonium tetrafluoroborate (167 mg, 1.13 mmol), DCM (11.3 mL), acetonitrile (5.7 mL) and bis(4-methoxybenzyl)amine (**31**) (290 mg, 1.13 mmol). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 9:1) to yield the *title compound* as a clear oil (310 mg, 62%); R_f = 0.32 (petrol:EtOAc, 9:1; $KMnO_4$); λ_{max} (EtOH)/nm 274.5; IR (neat) ν_{max}/cm^{-1} 1612, 1513, 1363, 1247, 1175, 1032; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.42 (6H, s, 2 × ArC*H*$_3$), 3.82 (6H, s, 2 × ArOC*H*$_3$), 4.46 (4H, s, 2 × ArC*H*$_2$), 6.88 (4H, d, *J* = 8.7 Hz, H-3', 5'), 7.07 (3H, s, H-3 and H-4 and H-5), 7.27 (4H, d, *J* = 8.7 Hz, H-2', 6'); ^{13}C NMR (126 MHz, $CDCl_3$) δ 17.7

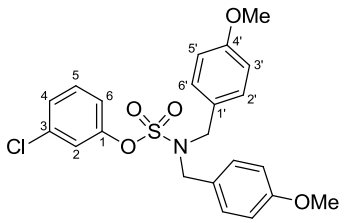
(Ar*C*H$_3$), 50.3 (Ar*C*H$_2$), 55.4 (ArO*C*H$_3$), 114.1 (C-3', 5'), 126.7 (CH Ar), 127.1 (C$_q$ Ar), 129.5 (CH Ar), 130.3 (C-2', 6'), 132.4 (C$_q$ Ar), 147.9 (C-1), 159.6 (C-4'); HRMS (ESI) calcd for $C_{24}H_{31}N_2O_5S$ $[M+NH_4]^+$ 459.1948, found 459.1949.

4-Chlorophenyl bis(4-methoxybenzyl)sulfamate, (76)



Compound **76** was synthesised according to general procedure H, using the following reagents: 4-chlorophenyl 2-methyl-1*H*-imidazole-1-sulfonate (**49**) (300 mg, 1.10 mmol), trimethyloxonium tetrafluoroborate (163 mg, 1.10 mmol), DCM (11.0 mL), acetonitrile (5.5 mL) and bis(4-methoxybenzyl)amine (**31**) (283 mg, 1.10 mmol). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 9:1) to yield the *title compound* as a clear oil (399 mg, 81%); R_f = 0.33 (petrol:EtOAc, 9:1; $KMnO_4$); λ_{max} (EtOH)/nm 274.5; IR (neat) ν_{max}/cm^{-1} 1612, 1588, 1512, 1484, 1370, 1248, 1170, 1032; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.82 (6H, s, 2 × ArOC*H*$_3$), 4.30 (4H, s, 2 × ArC*H*$_2$), 6.88 (4H, d, *J* = 8.7 Hz, H-3', 5'), 7.06 (2H, d, *J* = 8.9 Hz, H-2, 6), 7.20 (4H, d, *J* = 8.7 Hz, H-2', 6'), 7.30 (2H, d, *J* = 8.9 Hz, H-3, 5); ^{13}C NMR (126 MHz, $CDCl_3$) δ 50.4 (Ar*C*H$_2$), 55.4 (ArO*C*H$_3$), 114.2 (C-3', 5'), 123.5 (C-2, 6), 126.7 (C$_q$ Ar), 129.9 (C-3, 5), 130.5 (C-2', 6'), 132.3 (C$_q$ Ar), 148.9 (C-1), 159.7 (C-4'); HRMS (ESI) calcd for $C_{22}H_{26}ClN_2O_5S$ $[M+NH_4]^+$ 465.1245, found 465.1244.

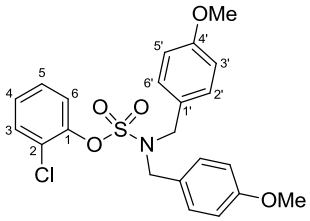
3-Chlorophenyl bis(4-methoxybenzyl)sulfamate, (77)



Compound **77** was synthesised according to general procedure H, using the following reagents: 3-chlorophenyl 2-methyl-1*H*-imidazole-1-sulfonate (**50**) (300 mg, 1.10 mmol), trimethyloxonium tetrafluoroborate (163 mg, 1.10 mmol), DCM (11.0 mL), acetonitrile (5.5 mL) and bis(4-methoxybenzyl)amine (**31**) (283 mg, 1.10 mmol). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 9:1) to yield the *title compound* as a clear oil (355 mg, 72%); R_f = 0.32 (petrol:EtOAc, 9:1; $KMnO_4$);

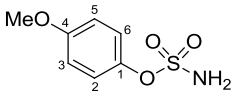
λ_{max} (EtOH)/nm 274.5; IR (neat) ν_{max}/cm^{-1} 1611, 1586, 1512, 1371, 1248, 1167, 1032; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.83 (6H, s, 2 × ArOC*H*$_3$), 4.32 (4H, s, 2 × ArC*H*$_2$), 6.89 (4H, d, *J* = 8.7 Hz, H-3', 5'), 7.06 (1H, dd, *J* = 2.3, 2.1 Hz, H-2), 7.10 (1H, ddd, *J* = 7.9, 2.3 and 1.4 Hz, H-4 or H-6), 7.22 (4H, d, *J* = 8.7 Hz, H-2', 6'), 7.26 – 7.23 (1H, m, H-4 or H-6), 7.28 (1H, dd, *J* = 7.9, 7.9 Hz, H-5); ^{13}C NMR (126 MHz, $CDCl_3$) δ 50.4 (Ar*C*H$_2$), 55.4 (ArO*C*H$_3$), 114.2 (C-3', 5'), 120.3 (C-4 or C-6), 122.6 (C-2), 126.7 (C_q Ar), 127.0 (C-4 or C-6), 130.5 (C-5), 130.5 (C-2', 6'), 135.0 (C_q Ar), 150.8 (C-1), 159.7 (C-4'); HRMS (ESI) calcd for $C_{22}H_{26}ClN_2O_5S$ $[M+NH_4]^+$ 465.1245, found 465.1244.

2-Chlorophenyl bis(4-methoxybenzyl)sulfamate, (78)



Compound **78** was synthesised according to general procedure H, using the following reagents: 2-chlorophenyl 2-methyl-1*H*-imidazole-1-sulfonate (**52**) (300 mg, 1.10 mmol), trimethyloxonium tetrafluoroborate (163 mg, 1.10 mmol), DCM (11.0 mL), acetonitrile (5.5 mL) and bis(4-methoxybenzyl)amine (**31**) (283 mg, 1.10 mmol). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 9:1) to yield the *title compound* as a clear oil (384 mg, 78%); R_f = 0.29 (petrol:EtOAc, 9:1; $KMnO_4$); λ_{max} (EtOH)/nm 274.0; IR (neat) ν_{max}/cm^{-1} 1612, 1586, 1514, 1359, 1166, 1054; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.81 (6H, s, 2 × ArOC*H*$_3$), 4.42 (4H, s, 2 × ArC*H*$_2$), 6.86 (4H, d, *J* = 8.7 Hz, H-3', 5'), 7.24 – 7.19 (5H, m, H-2', 6' and H-5), 7.30 (1H, ddd, *J* = 8.2, 8.0 and 1.6 Hz, H-4), 7.44 (1H, dd, *J* = 8.0, 1.6 Hz, H-6), 7.52 (1H, dd, *J* = 8.2, 1.6 Hz, H-3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 50.6 (Ar*C*H$_2$), 55.4 (ArO*C*H$_3$), 114.1 (C-3', 5'), 123.6 (C-6), 126.8 (C_q Ar), 127.2 (C_q Ar), 127.5 (C-4), 128.1 (C-5), 130.5 (C-2', 6'), 130.9 (C-3), 146.6 (C-1), 159.6 (C-4'); HRMS (ESI) calcd for $C_{22}H_{26}ClN_2O_5S$ $[M+NH_4]^+$ 465.1245, found 465.1244.

4-Methoxyphenyl sulfamate, (79)

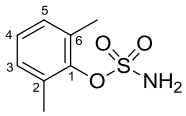


Compound **79** was synthesised following two different procedures.

1st procedure: Compound **79** was synthesised according to general procedure D, using the following reagents: 4-methoxyphenyl bis(2,4-dimethoxybenzyl)sulfamate (**62**) (250 mg, 0.50 mmol), DCM (4.5 mL) and TFA (0.5 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 65:35) to yield the *title compound* as an off-white solid (91 mg, 90%).

2nd procedure: Compound **79** was synthesised according to general procedure E, using the following reagents: 4-methoxyphenyl bis(4-methoxybenzyl)sulfamate (**74**) (250 mg, 0.56 mmol), DCM (2.8 mL) and TFA (2.8 mL). The crude product was purified by column chromatography (silica gel, petrol:DCM, 1:0 → 0:1) to yield the *title compound* as an off-white solid (107 mg, 93%); R_f = 0.33 (petrol:EtOAc, 65:35; $KMnO_4$); m.p. 68.5-70.5 °C (lit. 70-72 °C)[264]; λ_{max} (EtOH)/nm 275.0; IR (neat) ν_{max}/cm^{-1} 3376, 3275, 1595, 1542, 1499, 1356, 1242, 1149, 1027; ^{1}H NMR (500 MHz, DMSO-d_6) 3.76 (3H, s, ArOCH_3), 6.99 (2H, d, J = 9.1 Hz, H-3, 5), 7.20 (2H, d, J = 9.1 Hz, H-2, 6), 7.87 (2H, s, ArOSO$_2$NH_2); ^{13}C NMR (126 MHz, DMSO-d_6) δ 55.5 (ArO*C*H$_3$), 114.6 (C-3, 5), 123.3 (C-2, 6), 143.6 (C-1), 157.5 (C-4); LRMS (ES$^-$) *m/z* 202.1 [M-H]$^-$; IR, ^{1}H NMR, ^{13}C NMR and LRMS data were identical to literature data.[258, 264]

2,6-Dimethylphenyl sulfamate, (80)



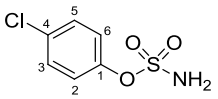
Compound **80** was synthesised following two different procedures.

1st procedure: Compound **80** was synthesised according to general procedure D, using the following reagents: 2,6-dimethylphenyl bis(2,4-dimethoxybenzyl)sulfamate (**63**) (250 mg, 0.50 mmol), DCM (4.5 mL) and TFA (0.5 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 8:2) to yield the *title compound* as a white solid (90 mg, 90%).

2nd procedure: Compound (**80**) was synthesised according to general procedure E, using the following reagents: 2,6-dimethylphenyl bis(4-methoxybenzyl)sulfamate (**75**) (200 mg,

0.45 mmol), DCM (2.3 mL) and TFA (2.3 mL). The crude product was purified by column chromatography (silica gel, petrol:DCM, 1:0 → 0:1) to yield the *title compound* as a white solid (84 mg, 92%); R_f = 0.28 (petrol:EtOAc, 8:2; $KMnO_4$); m.p. 107.5-109.5 °C (lit. 110 °C)[265]; λ_{max} (EtOH)/nm 268.5; IR (neat) ν_{max}/cm^{-1} 3355, 3269, 1547, 1470, 1339, 1188, 1143, 1090; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.32 (6H, s, 2 × CH_3), 7.13 – 7.02 (3H, m, H-3 and H-4 and H-5), 8.04 (2H, s, $ArOSO_2NH_2$); ^{13}C NMR (126 MHz, DMSO-d_6) δ 17.1 (CH_3), 126.1 (CH Ar), 129.0 (CH Ar), 131.9 (C-2, 6), 147.9 (C-1); LRMS (ES$^-$) *m/z* 200.1 [M-H]$^-$; HRMS (ESI) calcd for $C_8H_{10}NO_3S$ [M-H]$^-$ 200.0387, found 200.0383; IR, ^{1}H NMR and HRMS data were identical to literature data.[266]

4-Chlorophenyl sulfamate, (81)

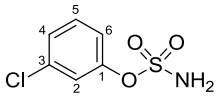


Compound **81** was synthesised following two different procedures.

1st procedure: Compound **81** was synthesised according to general procedure D, using the following reagents: 4-chlorophenyl bis(2,4-dimethoxybenzyl)sulfamate (**64**) (200 mg, 0.39 mmol), DCM (5.5 mL) and TFA (0.4 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 8:2) to yield the *title compound* as a white solid (69 mg, 84%).

2nd procedure: Compound **81** was synthesised according to general procedure E, using the following reagents: 4-chlorophenyl bis(4-methoxybenzyl)sulfamate (**76**) (250 mg, 0.56 mmol), DCM (2.8 mL) and TFA (2.8 mL). The crude product was purified by column chromatography (silica gel, petrol:DCM, 1:0 → 0:1) to yield the *title compound* as a white solid (105 mg, 90%); R_f = 0.30 (petrol:EtOAc, 8:2; $KMnO_4$); m.p. 102.0-104.0 °C (lit. 105 °C)[265]; λ_{max} (EtOH)/nm 269.0, 274.5; IR (neat) ν_{max}/cm^{-1} 3388, 3277, 1531, 1485, 1352, 1154, 1086; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.30 (2H, d, *J* = 8.8 Hz, H-2, 6), 7.53 (2H, d, *J* = 8.8 Hz, H-3, 5), 8.07 (2H, s, $ArOSO_2NH_2$); ^{13}C NMR (126 MHz, DMSO-d_6) δ 124.1 (C-2, 6), 129.7 (C-3, 5), 130.9 (C-4), 148.9 (C-1); LRMS (ES$^-$) *m/z* 206.1 [M(^{35}Cl)-H]$^-$, 208.1 [M(^{37}Cl)-H]$^-$; HRMS (ESI) calcd for $C_6H_5ClNO_3S$ [M(^{35}Cl)-H]$^-$ 205.9684, found 205.9681; IR, ^{1}H NMR and ^{13}C NMR data were identical to literature data.[258]

3-Chlorophenyl sulfamate, (82)

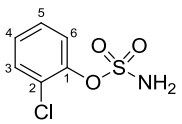


Compound **82** was synthesised following two different procedures.

1st procedure: Compound **82** was synthesised according to general procedure D, using the following reagents: 3-chlorophenyl bis(2,4-dimethoxybenzyl)sulfamate (**65**) (200 mg, 0.39 mmol), DCM (5.5 mL) and TFA (0.4 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 8:2) to yield the *title compound* as a white solid (74 mg, 90%).

2nd procedure: Compound **82** was synthesised according to general procedure E, using the following reagents: 3-chlorophenyl bis(4-methoxybenzyl)sulfamate (**77**) (250 mg, 0.56 mmol), DCM (2.8 mL) and TFA (2.8 mL). The crude product was purified by column chromatography (silica gel, petrol:DCM, 1:0 → 0:1) to yield the *title compound* as a white solid (100 mg, 86%); R_f = 0.29 (petrol:EtOAc, 8:2; $KMnO_4$); m.p. 80.5-82.5 °C (lit. 80 °C)[265]; λ_{max} (EtOH)/nm 266.0, 273.0; IR (neat) ν_{max}/cm^{-1} 3378, 3277, 1585, 1466, 1375, 1165, 1069; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.27 (1H, ddd, *J* = 8.3, 2.3 and 1.0 Hz, H-6), 7.37 (1H, dd, *J* = 2.3, 2.1 Hz, H-2), 7.42 (1H, ddd, *J* = 8.1, 2.1 and 1.1 Hz, H-4), 7.53 – 7.46 (1H, m, H-5), 8.13 (2H, s, $ArOSO_2NH_2$); ^{13}C NMR (126 MHz, DMSO-d_6) δ 121.1 (C-6), 122.3 (C-2), 126.7 (C-4), 131.2 (C-5), 133.5 (C-3), 150.7 (C-1); LRMS (ES$^-$) *m/z* 206.0 [M(^{35}Cl)-H]$^-$, 208.1 [M(^{37}Cl)-H]$^-$; HRMS (ESI) calcd for $C_6H_5ClNO_3S$ [M(^{35}Cl)-H]$^-$ 205.9684, found 205.9682; ^{1}H NMR and ^{13}C NMR data were identical to literature data.[267]

2-Chlorophenyl sulfamate, (83)

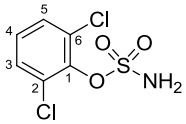


Compound **83** was synthesised following two different procedures.

1st procedure: Compound **83** was synthesised according to general procedure D, using the following reagents: 2-chlorophenyl bis(2,4-dimethoxybenzyl)sulfamate (**66**) (200 mg, 0.39 mmol), DCM (3.5 mL) and TFA (0.4 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 8:2) to yield the *title compound* as an off-white solid (66 mg, 81%).

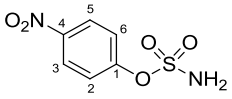
2nd procedure: Compound **83** was synthesised according to general procedure E, using the following reagents: 2-chlorophenyl bis(4-methoxybenzyl)sulfamate (**78**) (250 mg, 0.56 mmol), DCM (2.8 mL) and TFA (2.8 mL). The crude product was purified by column chromatography (silica gel, petrol:DCM, 1:0 → 0:1) to yield the *title compound* as an off-white solid (107 mg, 92%); R_f = 0.29 (petrol:EtOAc, 8:2; $KMnO_4$); m.p. 63.0-65.0 °C (lit. 62.5-63.5 °C)[268]; λ_{max} (EtOH)/nm 266.5; IR (neat) ν_{max}/cm^{-1} 3350, 3264, 1566, 1473, 1377, 1179, 1059; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.33 (1H, ddd, *J* = 8.1, 7.7 and 1.6 Hz, H-4 or H-5), 7.45 – 7.41 (1H, m, H-4 or H-5), 7.50 (1H, dd, *J* = 8.1, 1.6 Hz, H-6), 7.60 (1H, dd, *J* = 8.0, 1.6 Hz, H-3), 8.26 (2H, s, $ArOSO_2NH_2$); ^{13}C NMR (126 MHz, DMSO-d_6) δ 123.8 (C-6), 126.4 (C-2), 127.7 (C-4 or C-5), 128.4 (C-4 or C-5), 130.6 (C-3), 146.1 (C-1); LRMS (ES$^-$) *m/z* 206.1 [M(^{35}Cl)-H]$^-$, 208.0 [M(^{37}Cl)-H]$^-$; HRMS (ESI) calcd for $C_6H_5ClNO_3S$ [M(^{35}Cl)-H]$^-$ 205.9684, found 205.9684.

2,6-Dichlorophenyl sulfamate, (84)



Compound **84** was synthesised according to general procedure D, using the following reagents: 2,6-dichlorophenyl bis(2,4-dimethoxybenzyl)sulfamate (**67**) (250 mg, 0.46 mmol), DCM (4.1 mL) and TFA (0.5 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 3:1) to yield the *title compound* as an off-white solid (100 mg, 89%); R_f = 0.27 (petrol:EtOAc, 3:1; $KMnO_4$); m.p. 103.5-105.5 °C; λ_{max} (EtOH)/nm 269.5; IR (neat) ν_{max}/cm^{-1} 3352, 3280, 1576, 1544, 1441, 1373, 1227, 1173, 1066; ^{1}H NMR (500 MHz, DMSO-d_6) 7.32 (1H, dd, *J* = 8.1, 8.1 Hz, H-4), 7.57 (2H, d, *J* = 8.1 Hz, H-3, 5), 8.40 (2H, s, $ArOSO_2NH_2$); ^{13}C NMR (126 MHz, DMSO-d_6) δ 128.2 (C-2, 6), 129.4 (C-4), 129.5 (C-3, 5), 143.5 (C-1); HRMS (ESI) calcd for $C_6H_4Cl_2NO_3S$ [M-H]$^-$ 239.9294, found 239.9291.

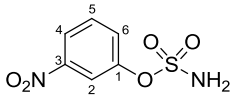
4-Nitrophenyl sulfamate, (85)



Compound **85** was synthesised according to general procedure D, using the following reagents: 4-nitrophenyl bis(2,4-dimethoxybenzyl)sulfamate (**68**) (250 mg, 0.48 mmol), DCM (4.3 mL) and TFA (0.5 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 7:3) to yield the *title compound* as a

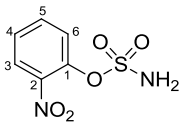
yellow solid (84 mg, 80%); R_f = 0.30 (petrol:EtOAc, 7:3; $KMnO_4$); m.p. 106.5-108.5 °C (lit. 107.2-11.8 °C)[269]; λ_{max} (EtOH)/nm 268.5; IR (neat) ν_{max}/cm^{-1} 3420, 3294, 1612, 1587, 1518, 1483, 1400, 1351, 1174, 1153, 1103; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.53 (2H, d, *J* = 9.2 Hz, H-2, 6), 8.35 (2H, d, *J* = 9.2 Hz, H-3, 5), 8.36 (s, 2H, $ArOSO_2NH_2$); ^{13}C NMR (126 MHz, DMSO-d_6) δ 122.9 (C-2, 6), 125.7 (C-3, 5), 145.3 (C-4), 154.8 (C-1); HRMS (ESI) calcd for $C_6H_7N_2O_5S$ $[M+H]^+$ 219.0070, found 219.0065; IR, ^{1}H NMR and ^{13}C NMR data were identical to literature data.[258, 267]

3-Nitrophenyl sulfamate, (86)



Compound **86** was synthesised according to general procedure D, using the following reagents: 3-nitrophenyl bis(2,4-dimethoxybenzyl)sulfamate (**69**) (150 mg, 0.29 mmol), DCM (2.6 mL) and TFA (0.3 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 7:3) to yield the *title compound* as a pale orange solid (55 mg, 87%); R_f = 0.30 (petrol:EtOAc, 7:3; $KMnO_4$); m.p. 116.0-118.0 °C; λ_{max} (EtOH)/nm 257.0; IR (neat) ν_{max}/cm^{-1} 3412, 3306, 1526, 1375, 1345, 1175, 1077; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.76 – 7.73 (1H, m, H-6), 7.78 (1H, dd, *J* = 8.0, 8.0 Hz, H-5), 8.11 (1H, dd, *J* = 2.2, 2.2 Hz, H-2), 8.22 (1H, ddd, *J* = 8.0, 2.2 and 1.3 Hz, H-4), 8.26 (s, 2H, $ArOSO_2NH_2$); ^{13}C NMR (126 MHz, DMSO-d_6) δ 117.4 (C-2), 121.6 (C-4), 129.3 (C-6), 131.3 (C-5), 148.3 (C-1 or C-3), 150.3 (C-1 or C-3); HRMS (ESI) calcd for $C_6H_7N_2O_5S$ $[M+H]^+$ 219.0070, found 219.0068; IR, ^{1}H NMR and ^{13}C NMR data were identical to literature data.[267]

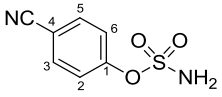
2-Nitrophenyl sulfamate, (87)



Compound **87** was synthesised according to general procedure D, using the following reagents: 2-nitrophenyl bis(2,4-dimethoxybenzyl)sulfamate (**70**) (200 mg, 0.39 mmol), DCM (3.5 mL) and TFA (0.4 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 7:3) to yield the *title compound* as a pale orange solid (34 mg, 40%); R_f = 0.28 (petrol:EtOAc, 7:3; $KMnO_4$); m.p. 98.0-100.0 °C (lit. 102-103 °C)[91]; λ_{max} (EtOH)/nm 247.5; IR (neat) ν_{max}/cm^{-1} 3404, 3264, 1601, 1512, 1380, 1356, 1176, 1087; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.58 – 7.54 (1H, m, H-4), 7.59 – 7.57

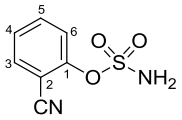
(1H, m, H-6), 7.82 (1H, ddd, *J* = 8.2, 7.4 and 1.7 Hz, H-5), 8.05 (1H, dd, *J* = 8.1, 1.7 Hz, H-3), 8.40 (2H, s, $ArOSO_2NH_2$); ^{13}C NMR (126 MHz, DMSO-d_6) δ 124.9 (C-6), 125.6 (C-3), 127.6 (C-4), 134.7 (C-5), 141.7 (C-1 or C-2), 143.3 (C-1 or C-2); HRMS (ESI) calcd for $C_6H_{10}N_3O_5S$ $[M+NH_4]^+$ 236.0336, found 236.0338; ^1H NMR data were identical to literature data.[91]

4-Cyanophenyl sulfamate, (88)



Compound **88** was synthesised according to general procedure D, using the following reagents: 4-cyanophenyl bis(2,4-dimethoxybenzyl)sulfamate (**71**) (200 mg, 0.40 mmol), DCM (3.6 mL) and TFA (0.4 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 65:35) to yield the *title compound* as a white solid (73 mg, 92%); R_f = 0.29 (petrol:EtOAc, 65:35; $KMnO_4$); m.p. No clear m.p., decomposition range 130-145 °C (lit. 155 °C)[265]; λ_{max} (EtOH)/nm 266.5; IR (neat) ν_{max}/cm^{-1} 2241, 1603, 1539, 1499, 1377, 1181, 1155; ^1H NMR (500 MHz, DMSO-d_6) δ 7.47 (2H, d, *J* = 8.7 Hz, H-2, 6), 7.98 (2H, d, *J* = 8.7 Hz, H-3, 5), 8.28 (2H, s, $ArOSO_2NH_2$); ^{13}C NMR (126 MHz, DMSO-d_6) δ 109.3 (C-4), 116.4 (Ar*C*N), 123.1 (C-2, 6), 134.4 (C-3, 5), 153.5 (C-1); LRMS (ES^+) *m/z* 199.1 $[M+H]^+$; HRMS (ESI) calcd for $C_7H_7N_2O_3S$ $[M+H]^+$ 199.0172, found 199.0169; IR, ^1H NMR and ^{13}C NMR data were identical to literature data.[258]

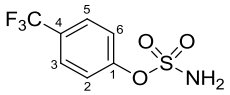
2-Cyanophenyl sulfamate, (89)



Compound **89** was synthesised according to general procedure D, using the following reagents: 2-cyanophenyl bis(2,4-dimethoxybenzyl)sulfamate (**72**) (200 mg, 0.40 mmol), DCM (3.6 mL) and TFA (0.4 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 65:35) to yield the *title compound* as an off-white solid (68 mg, 86%); R_f = 0.30 (petrol:EtOAc, 65:35; $KMnO_4$); m.p. 82.0-84.0 °C; λ_{max} (EtOH)/nm 281.0; IR (neat) ν_{max}/cm^{-1} 3366, 3243, 2247, 1602, 1558, 1487, 1450, 1385, 1162, 1098; ^1H NMR (500 MHz, DMSO-d_6) δ 7.51 (1H, ddd, *J* = 7.6, 7.6 and 1.0 Hz, H-4), 7.59 (1H, dd, *J* = 8.4, 1.0 Hz, H-6), 7.82 (1H, ddd, *J* = 8.4, 7.6 and 1.7 Hz, H-5), 7.95 (1H, dd, *J* = 7.6, 1.7 Hz, H-3), 8.50 (2H, s, $ArOSO_2NH_2$); ^{13}C NMR

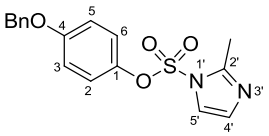
(126 MHz, DMSO-d_6) δ 106.6 (C-2), 115.3 (Ar*C*N), 122.8 (C-6), 127.1 (C-4), 134.1 (C-3), 135.0 (C-5), 151.1 (C-1); LRMS (ES^+) *m/z* 199.1 $[M+H]^+$; HRMS (ESI) calcd for $C_7H_5N_2O_3S$ $[M-H]^-$ 197.0026, found 197.0027.

4-(Trifluoromethyl)phenyl sulfamate, (90)



Compound **90** was synthesised according to general procedure D, using the following reagents: 4-(trifluoromethyl)phenyl bis(2,4-dimethoxybenzyl)sulfamate (**73**) (250 mg, 0.46 mmol), DCM (4.1 mL) and TFA (0.5 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 3:1) to yield the *title compound* as an off-white solid (100 mg, 90%); R_f = 0.28 (petrol:EtOAc, 3:1; $KMnO_4$); m.p. 102.5-104.5 °C (lit. 100-102 °C)[258]; λ_{max} (EtOH)/nm 257.0; IR (neat) ν_{max}/cm^{-1} 3381, 3278, 1614, 1534, 1510, 1351, 1320, 1158, 1126, 1066; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.50 (2H, d, *J* = 8.5 Hz, H-2, 6), 7.87 (2H, d, *J* = 8.5 Hz, H-3, 5), 8.21 (2H, s, $ArOSO_2NH_2$); ^{13}C NMR (126 MHz, DMSO-d_6) δ 123.0 (C-2, 6), 125.0 (CF_3), 126.9 (C-4), 127.3 (q, *J* = 3.7 Hz, C-3, 5), 152.9 (C-1); ^{19}F (471 MHz, DMSO) δ -60.7 (CF_3); LRMS (ES^-) *m/z* 240.1 $[M-H]^-$; HRMS (ESI) calcd for $C_7H_5F_3NO_3S$ $[M-H]^-$ 239.9948, found 239.9939; IR, ^{1}H NMR and ^{13}C NMR data were identical to literature data.[258]

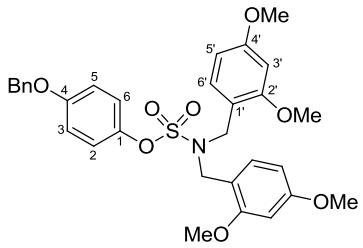
4-(Benzyloxy)phenyl 2-methyl-1*H*-imidazole-1-sulfonate, (92)



Compound **92** was synthesised according to general procedure B, using the following reagents: 1,1'-sulfonylbis(2-methyl-1*H*-imidazole) (**19**) (678 mg, 3.00 mmol), caesium carbonate (537 mg, 1.65 mmol), 4-(benzyloxy)phenol (300 mg, 1.50 mmol) and acetonitrile (20 mL). The crude yellow oil was purified by column chromatography (silica gel, petrol:EtOAc – 1:0 → 8:2) to yield the *title compound* as a clear oil (500 mg, 96%); R_f = 0.38 (petrol:EtOAc, 8:2; $KMnO_4$); λ_{max} (EtOH)/nm 273.0; IR (neat) ν_{max}/cm^{-1} 1595, 1552, 1499, 1418, 1206, 1144, 1044; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.43 (3H, s, CH_3), 5.03 (2H, s, ArCH_2), 6.86 – 6.78 (2H, m, H-2, 6 or H-3, 5), 6.88 (1H, d, *J* = 1.7 Hz, H-4' or H-5'), 6.95 – 6.87 (2H, m, H-2, 6 or H-3, 5), 7.13 (1H, d, *J* = 1.7 Hz, H-4' or H-5'), 7.37 – 7.32 (1H, m, Ar*H*), 7.39 (4H, d, *J* = 4.4 Hz, 4 × Ar*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 15.0 (CH_3), 70.6 (ArCH_2), 116.1 (C-2, 6 or C-3, 5), 120.5 (C-4' or C-5'), 122.7 (C-2, 6

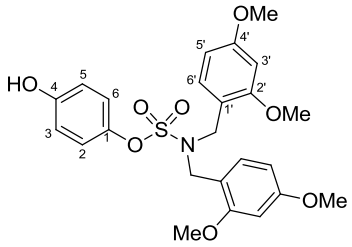
or C-3, 5), 127.6 (CH Ar), 128.0 (CH Ar), 128.4 (CH Ar), 128.8 (CH Ar), 136.2 (C_q Ar), 142.6 (C_q Ar), 147.0 (C_q Ar), 158.5 (C-4); LRMS (ES^+) *m/z* 345.2 $[M+H]^+$; HRMS (ESI) calcd for $C_{17}H_{17}N_2O_4S$ $[M+H]^+$ 345.0904, found 345.0904.

4-(Benzyloxy)phenyl bis(2,4-dimethoxybenzyl)sulfamate, (93)



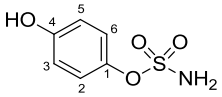
Compound **93** was synthesised according to general procedure H, using the following reagents: 4-(benzyloxy)phenyl 2-methyl-1*H*-imidazole-1-sulfonate (**92**) (450 mg, 1.31 mmol), trimethyloxonium tetrafluoroborate (193 mg, 1.31 mmol), DCM (13.0 mL), acetonitrile (6.5 mL) and bis(2,4-dimethoxybenzyl)amine (**32**) (416 mg, 1.31 mmol). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 $\rightarrow$ 8:2) to yield the *title compound* as a clear oil (461 mg, 61%); R_f = 0.30 (petrol:EtOAc, 8:2; $KMnO_4$); λ_{max} (EtOH)/nm 277.0; IR (neat) ν_{max}/cm^{-1} 1613, 1591, 1501, 1369, 1208, 1155, 1035; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.72 (6H, s, 2 × ArOCH_3), 3.79 (6H, s, 2 × ArOCH_3), 4.43 (4H, s, 2 × ArCH_2), 5.02 (2H, s, ArCH_2), 6.37 (2H, d, *J* = 2.3 Hz, H-3'), 6.42 (2H, dd, *J* = 8.4, 2.4 Hz, H-5'), 6.87 (2H, d, *J* = 9.1 Hz, H-2, 6 or H-3, 5), 7.00 (2H, d, *J* = 9.1 Hz, H-2, 6 or H-3, 5), 7.26 (2H, d, *J* = 8.4 Hz, H-6'), 7.36 – 7.31 (1H, m, Ar*H*), 7.44 – 7.36 (4H, m, 4 × Ar*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 47.0 (Ar*C*H_2), 55.2 (ArO*C*H_3), 55.5 (ArO*C*H_3), 70.5 (Ar*C*H_2), 98.2 (C-3'), 104.0 (C-5'), 115.5 (C-2, 6 or C-3, 5), 116.8 (C-1'), 123.2 (C-2, 6 or C-3, 5), 127.6 (CH Ar), 128.2 (CH Ar), 128.8 (CH Ar), 131.1 (C-6'), 136.8 (C_q Ar), 144.1 (C-1), 157.1 (C-4), 158.5 (C-2' or C-4'), 160.6 (C-2' or C-4'); HRMS (ESI) calcd for $C_{31}H_{34}NO_8S$ $[M+H]^+$ 580.2000, found 580.1991.

4-Hydroxyphenyl bis(2,4-dimethoxybenzyl)sulfamate, (94)



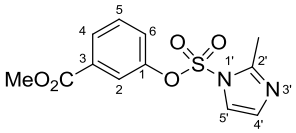
4-(Benzyloxy)phenyl bis(2,4-dimethoxybenzyl)sulfamate (**93**) (300 mg, 0.52 mmol) in MeOH (10.5 mL) was subjected to palladium-catalysed hydrogenation using an H-Cube® reactor and a 10% Pd/C CatCart. The reaction mixture was heated at 50 °C for 24 h. The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 65:35) to yield the *title compound* as a clear oil (215 mg, 85%); R_f = 0.31 (petrol:EtOAc, 65:35; $KMnO_4$); λ_{max} (EtOH)/nm 277.0; IR (neat) ν_{max}/cm^{-1} 1613, 1592, 1505, 1360, 1208, 1157, 1034; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.72 (6H, s, 2 × ArOC*H*$_3$), 3.79 (6H, s, 2 × ArOC*H*$_3$), 4.43 (4H, s, 2 × ArC*H*$_2$), 5.10 (1H, s, ArO*H*), 6.38 (2H, d, *J* = 2.4 Hz, H-3'), 6.42 (2H, dd, *J* = 8.4, 2.4 Hz, H-5'), 6.70 (2H, d, *J* = 9.0 Hz, H-3, 5), 6.93 (2H, d, *J* = 9.0 Hz, H-2, 6), 7.25 (2H, d, *J* = 8.4 Hz, H-6'); ^{13}C NMR (126 MHz, $CDCl_3$) δ 47.0 (ArC*H*$_2$), 55.2 (ArO*C*H$_3$), 55.5 (ArO*C*H$_3$), 98.2 (C-3'), 104.1 (C-5'), 116.0 (C-1'), 116.8 (C-3, 5), 123.4 (C-2, 6), 131.0 (C-6'), 143.9 (C-1), 154.0 (C-4), 158.5 (C-2' or C-4'), 160.7 (C-2' or C-4'); LRMS (ES$^-$) *m/z* 488.2 [M-H]$^-$; HRMS (ESI) calcd for $C_{24}H_{28}NO_8S$ [M+H]$^+$ 490.1530, found 490.1527.

4-Hydroxyphenyl sulfamate, (95)



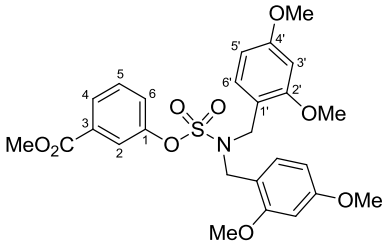
Compound **95** was synthesised according to general procedure D, using the following reagents: 4-hydroxyphenyl bis(2,4-dimethoxybenzyl)sulfamate (**94**) (150 mg, 0.31 mmol), DCM (2.8 mL) and TFA (0.3 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 1:1) to yield the *title compound* as a pale red solid (50 mg, 86%); R_f = 0.35 (petrol:EtOAc, 1:1; $KMnO_4$); m.p. 138.0-140.0 °C; λ_{max} (EtOH)/nm 277.5; IR (neat) ν_{max}/cm^{-1} 3371, 3232, 1601, 1551, 1504, 1364, 1150; ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.78 (2H, d, *J* = 9.0 Hz, H-2, 6 or H-3, 5), 7.07 (2H, d, *J* = 9.0 Hz, H-2, 6 or H-3, 5), 7.88 (2H, brs, ArOSO$_2$N*H*$_2$), 9.41 (1H, brs, ArO*H*); ^{13}C NMR (126 MHz, DMSO-d_6) δ 115.7 (C-2, 6 or C-3, 5), 123.3 (C-2, 6 or C-3, 5), 142.4 (C-1), 155.8 (C-4); LRMS (ES$^-$) *m/z* 188.1 [M-H]$^-$; HRMS (ESI) calcd for $C_6H_6NO_4S$ [M-H]$^-$ 188.0023, found 188.0023.

Methyl 3-(((2-methyl-1*H*-imidazol-1-yl)sulfonyl)oxy)benzoate, (97)



Compound **97** was synthesised according to general procedure B, using the following reagents: 1,1'-sulfonylbis(2-methyl-1*H*-imidazole) (**19**) (149 mg, 0.66 mmol), caesium carbonate (118 mg, 0.36 mmol), methyl 3-hydroxybenzoate (50 mg, 0.33 mmol) and acetonitrile (5 mL). The crude yellow oil was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 3:1) to yield the *title compound* as a clear oil (90 mg, 92%); R_f = 0.20 (petrol:EtOAc, 8:2; $KMnO_4$); λ_{max} (EtOH)/nm 272.0; IR (neat) ν_{max}/cm^{-1} 1727, 1585, 1554, 1422, 1296, 1266, 1205, 1151, 1045; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.49 (3H, s, CH_3), 3.92 (3H, s, $ArCO_2CH_3$), 6.89 (1H, d, *J* = 1.6 Hz, H-4' or H-5'), 7.08 (1H, dd, *J* = 8.2, 2.4 Hz, H-4), 7.13 (1H, d, *J* = 1.6 Hz, H-4' or H-5'), 7.45 (1H, dd, *J* = 8.2, 8.0 Hz, H-5), 7.66 (1H, dd, *J* = 2.4, 2.1 Hz, H-2), 8.04 (1H, d, *J* = 8.0 Hz, H-6); ^{13}C NMR (126 MHz, $CDCl_3$) δ 15.1 (CH_3), 52.8 ($ArCO_2CH_3$), 120.4 (C-4' or C-5'), 123.0 (C-2), 125.9 (C-4), 128.2 (C-4' or C-5'), 129.7 (C-6), 130.5 (C-5), 132.8 (C-1), 146.8 (C-3 or C-2'), 149.0 (C-3 or C-2'), 165.2 ($ArCO_2Me$); LRMS (ES$^+$) *m/z* 297.0 [M+H]$^+$; HRMS (ESI) calcd for $C_{12}H_{13}N_2O_5S$ [M+H]$^+$ 297.0540, found 297.0545.

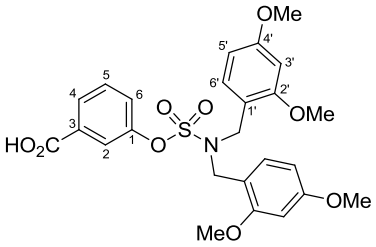
Methyl 3-((*N*,*N*-bis(2,4-dimethoxybenzyl)sulfamoyl)oxy)benzoate, (98)



Compound **98** was synthesised according to general procedure H, using the following reagents: methyl 3-(((2-methyl-1*H*-imidazol-1-yl)sulfonyl)oxy)benzoate (**97**) (750 mg, 2.53 mmol), trimethyloxonium tetrafluoroborate (374 mg, 2.53 mmol), DCM (25.3 mL), acetonitrile (12.7 mL) and bis(2,4-dimethoxybenzyl)amine (**32**) (805 mg, 2.53 mmol). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 3:1) to yield the *title compound* as a clear oil (845 mg, 64%); R_f = 0.30 (petrol:EtOAc, 8:2; $KMnO_4$); λ_{max} (EtOH)/nm 277.0; IR (neat) ν_{max}/cm^{-1} 1725, 1613, 1588, 1508, 1372, 1287, 1267, 1208, 1157, 1035; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.74 (6H, s, 2 × $ArOCH_3$), 3.80 (6H, s, 2 × $ArOCH_3$), 3.91 (3H, s, $ArCO_2CH_3$), 4.47 (4H, s, 2 × $ArCH_2$), 6.39 (2H, d, *J* = 2.4 Hz, H-3'), 6.43 (2H, dd, *J* = 8.4, 2.4 Hz, H-5'), 7.26 (2H, d, *J* = 8.4 Hz, H-6'), 7.31

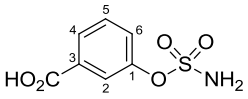
(1H, ddd, *J* = 8.1, 2.3 and 1.3 Hz, H-4), 7.37 (1H, dd, *J* = 8.1, 7.6 Hz, H-5), 7.65 (1H, dd, *J* = 2.3, 1.9 Hz, H-2), 7.89 (1H, ddd, *J* = 7.6, 1.9 and 1.3 Hz, H-6); ^{13}C NMR (126 MHz, $CDCl_3$) δ 47.1 (Ar*C*H_2), 52.4 (ArCO_2*C*H_3), 55.2 (ArO*C*H_3), 55.5 (ArO*C*H_3), 98.3 (C-3'), 104.1 (C-5'), 116.6 (C-1'), 123.2 (C-2), 126.7 (C-4), 127.6 (C-6), 129.6 (C-5), 131.1 (C-6'), 131.8 (C-1), 150.4 (C-3), 158.6 (C-2' or C-4'), 160.8 (C-2' or C-4'), 166.1 (Ar*C*O_2Me); HRMS (ESI) calcd for $C_{26}H_{30}NO_9S$ $[M+H]^+$ 532.1636, found 532.1626.

3-((*N*,*N*-bis(2,4-Dimethoxybenzyl)sulfamoyl)oxy)benzoic acid, (99)



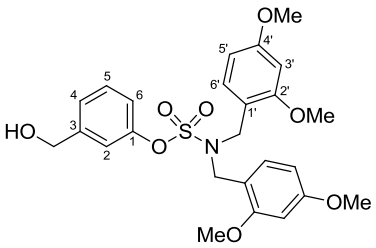
To methyl 3-((*N*,*N*-bis(2,4-dimethoxybenzyl)sulfamoyl)oxy)benzoate (**98**) in THF (5 mL) was added a 2 M aq. solution of lithium hydroxide (2.8 mL, 5.65 mmol). The resulting mixture was heated at 60 °C for 18 h. Upon completion, the mixture was acidified to pH 3 using a 4 M aq. solution of HCl. The reaction was then diluted with water (20 mL) and extracted with EtOAc (3 × 25 mL). The pooled organic extracts were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel, DCM:MeOH:AcOH, 1:0:0 → 95:4.9:0.1) to yield the *title compound* as a clear oil (249 mg, 85%); R_f = 0.32 (DCM:MeOH:AcOH, 95:4.9:0.1; $KMnO_4$); λ_{max} (EtOH)/nm 277.0; IR (neat) ν_{max}/cm^{-1} 1696, 1613, 1587, 1508, 1371, 1291, 1266, 1208, 1157, 1034; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.76 (6H, s, 2 × ArOC*H*$_3$), 3.81 (6H, s, 2 × ArOC*H*$_3$), 4.49 (4H, s, 2 × ArC*H*$_2$), 6.41 (2H, d, *J* = 2.4 Hz, H-3'), 6.44 (2H, dd, *J* = 8.4, 2.4 Hz, H-5'), 7.27 (2H, d, *J* = 8.4 Hz, H-6'), 7.45 – 7.39 (2H, m, H-4 and H-5), 7.68 (1H, dd, *J* = 1.9, 1.9 Hz, H-2), 7.98 – 7.93 (1H, m, H-6); ^{13}C NMR (126 MHz, $CDCl_3$) δ 47.2 (Ar*C*H_2), 55.3 (ArO*C*H_3), 55.5 (ArO*C*H_3), 98.4 (C-3'), 104.1 (C-5'), 116.6 (C-1'), 123.8 (C-2), 127.6 (C-4 or C-5), 128.1 (C-6), 129.8 (C-4 or C-5), 130.9 (C-1), 131.2 (C-6'), 150.5 (C-3), 158.6 (C-2' or C-4'), 160.8 (C-2' or C-4'), 170.6 (Ar*C*O_2H); HRMS (ESI) calcd for $C_{25}H_{28}NO_9S$ $[M+H]^+$ 518.1479, found 518.1474.

3-(Sulfamoyloxy)benzoic acid, (100)



Compound **100** was synthesised according to general procedure D, using the following reagents: 3-((*N*,*N*-bis(2,4-dimethoxybenzyl)sulfamoyl)oxy)benzoic acid (**99**) (200 mg, 0.39 mmol), DCM (3.5 mL) and TFA (0.4 mL). The crude product was purified by column chromatography (silica gel, DCM:MeOH:AcOH, 1:0:0 → 90:9.9:0.1) to yield the *title compound* as a white solid (75 mg, 89%); R_f = 0.28 (DCM:MeOH:AcOH, 90:9.9:0.1; $KMnO_4$); m.p. 162.0-164.0 °C; λ_{max} (EtOH)/nm 274.5; IR (neat) ν_{max}/cm^{-1} 3374, 3281, 1681, 1587, 1451, 1366, 1302, 1166, 1101; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.52 (1H, ddd, *J* = 8.1, 2.5 and 1.0 Hz, H-4), 7.60 (1H, dd, *J* = 8.1, 7.8 Hz, H-5), 7.82 (1H, dd, *J* = 2.5, 2.0 Hz, H-2), 7.90 (1H, ddd, *J* = 7.8, 2.0 and 1.0 Hz, H-6), 8.09 (2H, s, $ArOSO_2NH_2$), 13.25 (1H, brs, $ArCO_2H$); ^{13}C NMR (126 MHz, DMSO-d_6) δ 122.9 (C-2), 126.9 (C-4), 127.4 (C-6), 130.2 (C-5), 132.6 (C-1), 150.1 (C-3), 166.4 ($ArCO_2H$); LRMS (ES$^-$) *m/z* 216.1 [M-H]$^-$; HRMS (ESI) calcd for $C_7H_6NO_5S$ [M-H]$^-$ 215.9961, found 215.9962.

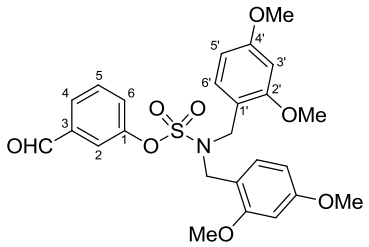
3-(Hydroxymethyl)phenyl bis(2,4-dimethoxybenzyl)sulfamate, (101)



To methyl 3-((*N*,*N*-bis(2,4-dimethoxybenzyl)sulfamoyl)oxy)benzoate (**98**) (500 mg, 0.94 mmol) in THF (8 mL), cooled at 0 °C, was added dropwise a lithium aluminium hydride solution (2.0 M in THF, 0.52 mL). The resulting solution was stirred at 0 °C for 2 h. Upon completion, the reaction was quenched by addition of saturated aq. Rochelle's salt (20 mL). The aqueous layer was extracted with EtOAc (3 × 30 mL). The pooled organic extracts were washed with water and brine (30 mL, respectively), dried over $MgSO_4$ and concentrated *in vacuo*. The crude solid was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 1:1) to yield the *title compound* as a clear oil (400 mg, 84%); R_f = 0.35 (petrol:EtOAc, 1:1; $KMnO_4$); λ_{max} (EtOH)/nm 277.0; IR (neat) ν_{max}/cm^{-1} 1613, 1588, 1508, 1367, 1208, 1158, 1034; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.77 (1H, t, *J* = 6.1 Hz, $ArCH_2OH$), 3.73 (6H, s, 2 × $ArOCH_3$), 3.80 (6H, s, 2 × $ArOCH_3$), 4.46 (4H, s, 2 × $ArCH_2$), 4.63 (2H, d, *J* = 6.1 Hz, $ArCH_2OH$), 6.39 (2H, d,

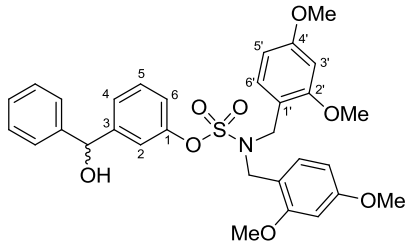
J = 2.4 Hz, H-3'), 6.43 (2H, dd, *J* = 8.4, 2.4 Hz, H-5'), 6.99 (1H, s, H-2), 7.08 – 7.02 (1H, m, H-4 or H-6), 7.21 (1H, d, *J* = 7.7 Hz, H-4 or H-6), 7.26 (2H, d, *J* = 8.4 Hz, H-6'), 7.29 (1H, dd, *J* = 7.8, 7.7 Hz, H-5); ^{13}C NMR (126 MHz, $CDCl_3$) δ 47.0 (Ar*C*H_2), 55.2 (ArO*C*H_3), 55.5 (ArO*C*H_3), 64.8 (Ar*C*H_2OH), 98.3 (C-3'), 104.1 (C-5'), 116.8 (C-1'), 120.3 (C-2), 121.1 (C-4 or C-6), 124.7 (C-4 or C-6), 129.7 (C-5), 131.1 (C-6'), 143.0 (C-3), 150.7 (C-1), 158.6 (C-2' or C-4'), 160.7 (C-2' or C-4'); HRMS (ESI) calcd for $C_{25}H_{30}NO_8S$ $[M+H]^+$ 504.1687, found 504.1684.

3-Formylphenyl bis(2,4-dimethoxybenzyl)sulfamate, (102)



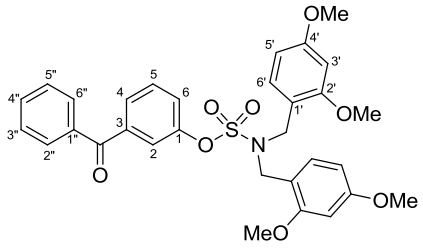
To 3-(hydroxymethyl)phenyl bis(2,4-dimethoxybenzyl)sulfamate (**101**) (300 mg, 3.60 mmol) in DCM (10 mL) was added manganese oxide (518 mg, 5.96 mmol). The resulting solution was stirred at RT for 16 h. Upon completion, the heterogeneous mixture was filtered through Celite and washed with DCM (15 mL). The filtrate was concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 7:3) to yield the *title compound* as a clear oil (266 mg, 89%); R_f = 0.30 (petrol:EtOAc, 7:3; $KMnO_4$); λ_{max} (EtOH)/nm 275.5; IR (neat) ν_{max}/cm^{-1} 1703, 1616, 1588, 1507, 1361, 1208, 1173, 1031; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.75 (6H, s, 2 × ArOC*H*$_3$), 3.81 (6H, s, 2 × ArOC*H*$_3$), 4.48 (4H, s, 2 × ArC*H*$_2$), 6.40 (2H, d, *J* = 2.3 Hz, H-3'), 6.44 (2H, dd, *J* = 8.4, 2.3 Hz, H-5'), 7.26 (2H, d, *J* = 8.4 Hz, H-6'), 7.40 – 7.37 (1H, m, H-6), 7.41 (1H, dd, *J* = 1.7, 1.7 Hz, H-2), 7.47 (1H, dd, *J* = 7.8, 7.8 Hz, H-5), 7.72 (1H, ddd, *J* = 7.8, 1.7 and 1.2 Hz, H-4), 9.91 (1H, s, ArC*H*O); ^{13}C NMR (126 MHz, $CDCl_3$) δ 47.3 (Ar*C*H_2), 55.3 (ArO*C*H_3), 55.5 (ArO*C*H_3), 98.4 (C-3'), 104.2 (C-5'), 116.6 (C-1'), 122.9 (C-2), 127.4 (C-4), 128.1 (C-6), 130.3 (C-5), 131.2 (C-6'), 137.9 (C-3), 151.1 (C-1), 158.7 (C-2' or C-4'), 160.9 (C-2' or C-4'), 191.0 (Ar*C*HO); HRMS (ESI) calcd for $C_{25}H_{28}NO_8S$ $[M+H]^+$ 502.1530, found 502.1519.

3-(Hydroxy(phenyl)methyl)phenyl bis(2,4-dimethoxybenzyl)sulfamate, (103)



To methyl 3-formylphenyl bis(2,4-dimethoxybenzyl)sulfamate (**102**) (200 mg, 0.40 mmol) in THF (10 mL), cooled at 0 °C, was added dropwise a phenyl magnesium bromide solution (1.0 M in THF, 1.2 mL, 1.20 mmol). The resulting solution was stirred at 0 °C for 3 h. Upon completion, the reaction was quenched by addition of a 1 M aq. HCl solution (4 mL) and diluted with water (10 mL). The aqueous layer was extracted with EtOAc (3 × 25 mL). The pooled organic extracts were washed with water and brine (30 mL, respectively), dried over $MgSO_4$ and concentrated *in vacuo*. The crude solid was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 7:3) to yield the *title compound* as a clear oil (203 mg, 88%); R_f = 0.25 (petrol:EtOAc – 7:3); λ_{max} (EtOH)/nm 277.0; IR (neat) ν_{max}/cm^{-1} 1613, 1588, 1508, 1368, 1208, 1157, 1034; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.25 (1H, d, *J* = 3.6 Hz, CHO*H*), 3.71 (6H, s, 2 × ArOCH_3), 3.79 (6H, s, 2 × ArOCH_3), 4.42 (4H, s, 2 × ArCH_2), 5.76 (1H, d, *J* = 3.0 Hz, C*H*OH), 6.38 (2H, d, *J* = 2.4 Hz, H-3'), 6.41 (2H, dd, *J* = 8.3, 2.4 Hz, H-5'), 7.08 – 7.02 (2H, m, 2 × Ar*H*), 7.23 – 7.19 (1H, m, Ar*H*), 7.29 – 7.23 (4H, m, 4 × Ar*H*), 7.33 (4H, d, *J* = 4.4 Hz, 4 × Ar*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 47.0 (Ar*C*H_2), 55.2 (ArO*C*H_3), 55.5 (ArO*C*H_3), 75.8 (*C*HOH), 98.3 (C-3'), 104.1 (C-5'), 116.7 (C-1'), 120.0 (CH Ar), 121.1 (CH Ar), 124.5 (CH Ar), 126.7 (CH Ar), 127.9 (CH Ar), 128.7 (CH Ar), 129.7 (CH Ar), 131.1 (C-6'), 143.4 (C_q Ar), 145.9 (C_q Ar), 150.6 (C-1), 158.6 (C-2' or C-4'), 160.7 (C-2' or C-4'); HRMS (ESI) calcd for $C_{31}H_{32}NO_8S$ $[M-H]^-$ 578.1843, found 578.1857.

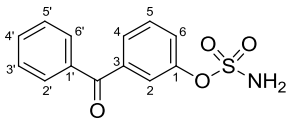
3-Benzoylphenyl bis(2,4-dimethoxybenzyl)sulfamate, (104)



To 3-(hydroxy(phenyl)methyl)phenyl bis(2,4-dimethoxybenzyl)sulfamate (**103**) (462 mg, 0.80 mmol) in DCM (15 mL) was added manganese oxide (693 mg, 7.97 mmol). The resulting solution was stirred at RT for 16 h. Upon completion, the heterogeneous mixture

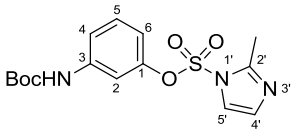
was filtered through Celite and washed with DCM (20 mL). The filtrate was concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 7:3) to yield the *title compound* as a clear oil (386 mg, 84%); R_f = 0.33 (petrol:EtOAc – 7:3); λ_{max} (EtOH)/nm 252.0; IR (neat) ν_{max}/cm^{-1} 1735, 1660, 1612, 1588, 1507, 1455, 1371, 1275, 1208, 1158, 1036; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.72 (6H, s, 2 × ArOC*H*$_3$), 3.78 (6H, s, 2 × ArOC*H*$_3$), 4.47 (4H, s, 2 × ArC*H*$_2$), 6.37 (2H, d, *J* = 2.4 Hz, H-3'), 6.40 (2H, dd, *J* = 8.3, 2.4 Hz, H-5'), 7.25 (2H, d, *J* = 8.3 Hz, H-6'), 7.39 – 7.35 (1H, m, H-4 or H-6), 7.45 – 7.41 (2H, m, H-2 and H-5), 7.53 – 7.47 (2H, m, H-3", 5"), 7.65 – 7.57 (1H, m, H-4"), 7.66 (1H, ddd, *J* = 7.7, 1.3 and 1.3 Hz, H-4 or H-6), 7.78 (2H, dd, *J* = 8.3, 1.4 Hz, H-2", 6"); ^{13}C NMR (126 MHz, $CDCl_3$) δ 47.2 (Ar*C*H$_2$), 55.2 (ArO*C*H$_3$), 55.5 (ArO*C*H$_3$), 98.4 (C-3'), 104.1 (C-5'), 116.5 (C-1'), 123.6 (C-2), 126.1 (C-4 or C-6), 128.0 (C-4 or C-6), 128.5 (C-3", 5"), 129.7 (C-5), 130.2 (C-2", 6"), 131.1 (C-6'), 132.9 (C-4"), 137.2 (C_q Ar), 139.2 (C_q Ar), 150.3 (C-1), 158.6 (C-2' or C-4'), 160.8 (C-2' or C-4'), 195.4 (CO); HRMS (ESI) calcd for $C_{31}H_{32}NO_8S$ $[M+H]^+$ 578.1843, found 578.1839.

3-Benzoylphenyl sulfamate, (105)



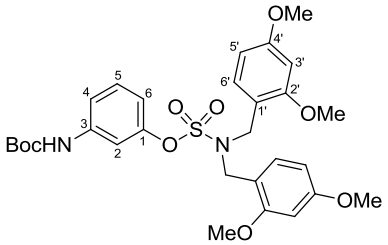
Compound **105** was synthesised according to general procedure D, using the following reagents: 3-benzoylphenyl bis(2,4-dimethoxybenzyl)sulfamate (**104**) (200 mg, 0.35 mmol), DCM (3.2 mL) and TFA (0.4 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 65:35) to yield the *title compound* as a pale orange solid (84 mg, 87%); R_f = 0.33 (petrol:EtOAc, 65:35; $KMnO_4$); m.p. 68.5-70.5 °C; λ_{max} (EtOH)/nm 252.0; IR (neat) ν_{max}/cm^{-1} 3358, 3257, 1648, 1577, 1439, 1365, 1282, 1169, 1158; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.62 – 7.55 (3H, m, 3 × Ar*H*), 7.63 (1H, dd, *J* = 2.0, 2.0 Hz, H-2), 7.67 (1H, dd, *J* = 7.8, 7.8 Hz, H-5), 7.74 – 7.69 (2H, m, 2 × Ar*H*), 7.82 – 7.75 (2H, m, 2 × Ar*H*), 8.11 (2H, s, $ArOSO_2NH_2$); ^{13}C NMR (126 MHz, DMSO-d_6) δ 123.2 (C-2), 126.7 (CH Ar), 127.8 (CH Ar), 128.7 (CH Ar), 129.7 (CH Ar), 130.3 (CH Ar), 133.0 (CH Ar), 136.5 (C_q Ar), 138.5 (C_q Ar), 149.9 (C-1), 194.6 (CO); LRMS (ES$^-$) *m/z* 276.2 $[M-H]^-$; HRMS (ESI) calcd for $C_{13}H_{12}NO_4S$ $[M+H]^+$ 278.0482, found 278.0482.

3-((*tert*-Butoxycarbonyl)amino)phenyl 2-methyl-1*H*-imidazole-1-sulfonate, (107)



Compound **107** was synthesised according to general procedure B, using the following reagents: 1,1'-sulfonylbis(2-methyl-1*H*-imidazole) (**19**) (216 mg, 0.96 mmol), caesium carbonate (171 mg, 0.53 mmol), *N*-Boc-3-aminophenol (100 mg, 0.48 mmol) and acetonitrile (5 mL). The crude yellow oil was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 8:2) to yield the *title compound* as a pale yellow solid (142 mg, 84%); R_f = 0.30 (petrol:EtOAc, 8:2; $KMnO_4$); m.p. 108.0-110.0 °C; λ_{max} (EtOH)/nm 276.0; IR (neat) ν_{max}/cm^{-1} 1724, 1601, 1556, 1494, 1425, 1204, 1152, 1049; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.51 (9H, s, C(C*H*$_3$)$_3$), 2.48 (3H, s, CH_3), 6.54 – 6.47 (1H, m, H-6), 6.57 (1H, s, ArN*H*Boc), 6.88 (1H, d, *J* = 1.7 Hz, H-4' or H-5'), 7.18 – 7.10 (2H, m, H-4' or H-5' and H-2), 7.23 (1H, dd, *J* = 8.2, 7.9 Hz, H-5), 7.32 (1H, d, *J* = 7.9 Hz, H-4); ^{13}C NMR (126 MHz, $CDCl_3$) δ 15.1 (CH_3), 28.4 (C(*C*H$_3$)$_3$), 81.5 (*C*(CH$_3$)$_3$), 111.6 (C-2), 115.3 (C-6), 118.0 (C-4), 120.5 (C-4' or C-5'), 128.0 (C-4' or C-5'), 130.5 (C-5), 140.5 (C-3), 146.9 (C-1 or C-2'), 149.5 (C-1 or C-2'), 152.2 (HN*C*O$_2$); LRMS (ES$^+$) *m/z* 354.6 [M+H]$^+$; HRMS (ESI) calcd for $C_{15}H_{20}N_3O_5S$ [M+H]$^+$ 354.1118, found 354.1124.

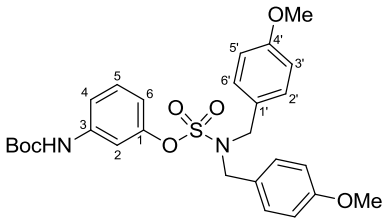
3-((*tert*-Butoxycarbonyl)amino)phenyl bis(2,4-dimethoxybenzyl)sulfamate, (108)



Compound **108** was synthesised according to general procedure H, using the following reagents: 3-((*tert*-butoxycarbonyl)amino)phenyl 2-methyl-1*H*-imidazole-1-sulfonate (**107**) (300 mg, 0.85 mmol), trimethyloxonium tetrafluoroborate (126 mg, 0.85 mmol), DCM (8.5 mL), acetonitrile (4.3 mL) and bis(2,4-dimethoxybenzyl)amine (**32**) (270 mg, 0.85 mmol). The crude product was purified by column chromatography (silica gel, petrol:EtOAc – 1:0 → 3:1) to yield the *title compound* as a pale yellow oil (290 mg, 58%); R_f = 0.28 (petrol:EtOAc, 3:1; $KMnO_4$); λ_{max} (EtOH)/nm 277.0; IR (neat) ν_{max}/cm^{-1} 1727, 1613, 1591, 1508, 1367, 1208, 1155, 1129, 1035; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.52 (9H, s, C(C*H*$_3$)$_3$), 3.71 (6H, s, 2 × ArOC*H*$_3$), 3.80 (6H, s, 2 × ArOC*H*$_3$), 4.45 (4H, s, 2 × ArC*H*$_2$), 6.37 (2H, d, *J* = 2.4 Hz, H-3'), 6.43 (2H, dd, *J* = 8.4, 2.4 Hz, H-5'), 6.79 (1H,

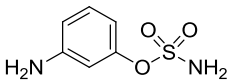
ddd, *J* = 8.1, 2.3 and 1.0 Hz, H-6), 7.03 (1H, dd, *J* = 2.4, 2.3 Hz, H-2), 7.20 (1H, dd, *J* = 8.4, 8.1 Hz, H-5), 7.26 (2H, d, *J* = 8.4 Hz, H-6'), 7.31 – 7.27 (1H, m, H-4); ^{13}C NMR (126 MHz, $CDCl_3$) δ 28.4 (C(*C*H_3)$_3$), 47.0 (Ar*C*H_2), 55.2 (ArO*C*H_3), 55.5 (ArO*C*H_3), 81.0 (*C*(CH$_3$)$_3$), 98.2 (C-3'), 104.1 (C-5'), 112.2 (C-2), 116.2 (C-4 or C-6), 116.3 (C-4 or C-6), 116.8 (C-1'), 129.9 (C-5), 131.1 (C-6'), 139.6 (C-3), 150.9 (C-1), 152.4 (HN*C*O$_2$), 158.6 (C-2' or C-4'), 160.7 (C-2' or C-4'); LRMS (ES$^-$) *m/z* 587.4 [M-H]$^-$; HRMS (ESI) calcd for $C_{29}H_{40}N_3O_9S$ [M+NH$_4$]$^+$ 606.2480, found 606.2476.

3-((*tert*-Butoxycarbonyl)amino)phenyl bis(4-methoxybenzyl)sulfamate, (109)



Compound **109** was synthesised according to general procedure H, using the following reagents: 3-((*tert*-butoxycarbonyl)amino)phenyl 2-methyl-1*H*-imidazole-1-sulfonate (**107**) (350 mg, 0.99 mmol), trimethyloxonium tetrafluoroborate (146 mg, 0.99 mmol), DCM (9.9 mL), acetonitrile (5.0 mL) and bis(4-methoxybenzyl)amine (**31**) (255 mg, 0.99 mmol). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 85:15) to yield the *title compound* as a pale yellow oil (365 mg, 70%); R_f = 0.33 (petrol:EtOAc, 85:15; $KMnO_4$); λ_{max} (EtOH)/nm 274.5; IR (neat) ν_{max}/cm^{-1} 1727, 1612, 1513, 1367, 1246, 1156, 1032; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.52 (9H, s, C(C*H*$_3$)$_3$), 3.82 (6H, s, 2 × ArOC*H*$_3$), 4.32 (4H, s, 2 × ArC*H*$_2$), 6.47 (1H, s, ArN*H*Boc), 6.86 (5H, d, *J* = 8.7 Hz, H-3', 5' and Ar*H*), 7.20 (4H, d, *J* = 8.7 Hz, H-2', 6'), 7.21 – 7.25 (3H, m, 3 × Ar*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 28.4 (C(*C*H$_3$)$_3$), 50.4 (Ar*C*H$_2$), 55.4 (ArO*C*H$_3$), 112.2 (CH Ar), 114.1 (C-3', 5'), 116.2 (CH Ar), 116.5 (CH Ar), 127.0 (C-1'), 130.0 (CH Ar), 130.6 (C-2', 6'), 139.8 (C-3), 150.8 (C-1), 152.4 (HN*C*O$_2$), 159.6 (C-4'); LRMS (ES$^-$) *m/z* 527.3 [M-H]$^-$; HRMS (ESI) calcd for $C_{27}H_{36}N_3O_7S$ [M+NH$_4$]$^+$ 546.2268, found 546.2256.

3-Aminophenyl sulfamate, (110)

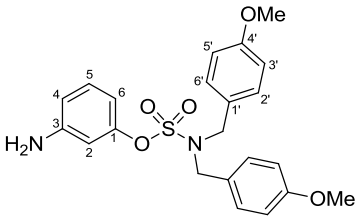


Compound **110** was synthesised following two different procedures.

1st procedure: Compound **110** was synthesised according to general procedure D, using the following reagents: 3-((*tert*-butoxycarbonyl)amino)phenyl bis(2,4-dimethoxybenzyl) sulfamate (**108**) (150 mg, 0.25 mmol), DCM (2.3 mL) and TFA (0.3 mL). The crude product was purified by column chromatography (silica gel, DCM:MeOH, 1:0 → 96:4) to yield the *title compound* as a white solid (34 mg, 70%).

2nd procedure: Compound **110** was synthesised according to general procedure E, using the following reagents: 3-aminophenyl bis(4-methoxybenzyl)sulfamate (**111**) (200 mg, 0.47 mmol), DCM (2.4 mL) and TFA (2.4 mL). The crude product was purified by column chromatography (silica gel, DCM:MeOH, 1:0 → 96:4) to yield the *title compound* as a white solid (78 mg, 88%); R_f = 0.30 (DCM:MeOH, 96:4; ninhydrin); m.p. 95.0-97.0 °C; λ_{max} (EtOH)/nm 238.5, 288.5; IR (neat) ν_{max}/cm^{-1} 3409, 3328, 1612, 1488, 1357, 1187, 1126; ^{1}H NMR (500 MHz, DMSO-d_6) δ 5.34 (2H, s, ArNH_2), 6.38 (1H, d, *J* = 8.1 Hz, H-4 or H-6), 6.57 – 6.41 (2H, m, H-2 and H-4 or H-6), 7.03 (1H, dd, *J* = 8.1, 8.0 Hz, H-5), 7.84 (2H, s, ArOSO$_2$NH_2); ^{13}C NMR (126 MHz, DMSO-d_6) δ 107.1 (CH Ar), 108.7 (CH Ar), 111.9 (CH Ar), 129.6 (C-5), 150.2 (C-1 or C-3), 151.2 (C-1 or C-3); LRMS (ES$^+$) *m/z* 189.1 [M+H]$^+$; HRMS (ESI) calcd for $C_6H_9N_2O_3S$ [M+H]$^+$ 189.0328, found 189.0328.

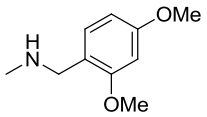
3-Aminophenyl bis(4-methoxybenzyl)sulfamate, (111)



3-((*tert*-butoxycarbonyl)amino)phenyl bis(4-methoxybenzyl)sulfamate (**109**) (300 mg, 0.57 mmol) was dissolved in a 10% TFA/DCM mixture (5 mL). The resulting solution was stirred at RT for 2 h. Upon completion, the solvent was removed *in vacuo*. The crude residue was dissolved in EtOAc (20 mL), washed with saturated aq. $NaHCO_3$ (20 mL) and extracted with EtOAc (3 × 25 mL). The pooled organic extracts were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 7:3) to yield the *title compound* as a pale yellow oil (230 mg, 94%); R_f = 0.28 (petrol:EtOAc, 7:3;

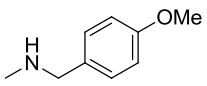
ninhydrin); λ_{max} (EtOH)/nm 275.0, 281.5; IR (neat) ν_{max}/cm^{-1} 1611, 1585, 1512, 1491, 1365, 1246, 1173, 1030; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.73 (2H, s, ArN*H*$_2$), 3.82 (6H, s, 2 × ArOC*H*$_3$), 4.30 (4H, s, 2 × ArC*H*$_2$), 6.46 (1H, dd, *J* = 2.3, 2.3 Hz, H-2), 6.53 (1H, ddd, *J* = 8.1, 2.3 and 0.8 Hz, H-4 or H-6), 6.56 (1H, ddd, *J* = 8.2, 2.3 and 0.8 Hz, H-4 or H-6), 6.87 (4H, d, *J* = 8.7 Hz, H-3', 5'), 7.09 (1H, dd, *J* = 8.2, 8.1 Hz, H-5), 7.20 (4H, d, *J* = 8.7 Hz, H-2', 6'); ^{13}C NMR (126 MHz, $CDCl_3$) δ 50.4 (Ar*C*H$_2$), 55.4 (ArO*C*H$_3$), 108.4 (C-2), 111.5 (C-4 or C-6), 113.4 (C-4 or C-6), 114.1 (C-3', 5'), 127.1 (C-1'), 130.3 (C-5), 130.5 (C-2', 6'), 148.0 (C-1 or C-3), 151.5 (C-1 or C-3), 159.6 (C-4'); LRMS (ES$^+$) *m/z* 429.4 [M+H]$^+$; HRMS (ESI) calcd for $C_{22}H_{25}N_2O_5S$ [M+H]$^+$ 429.1479, found 429.1476.

1-(2,4-Dimethoxyphenyl)-*N*-methylmethanamine, (115)



Compound **115** was synthesised according to general procedure F, using the following reagents: methylamine 8.03 M in EtOH (2.25 mL, 18.1 mmol), 2,4-dimethoxy benzaldehyde (3.0 g, 18.1 mmol), sodium borohydride (0.75 g, 19.9 mmol) and ethanol (9 mL). The crude product was purified by column chromatography (silica gel, DCM:MeOH:NH_3, 1:0:0 → 90:9:1) to yield the *title compound* as a yellow liquid (0.82 g, 25%); R_f = 0.22 (DCM:MeOH:NH_3, 90:9:1; ninhydrin); λ_{max} (EtOH)/nm 276.5; IR (neat) ν_{max}/cm^{-1} 1612, 1588, 1505, 1462, 1288, 1206, 1154, 1034; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.03 (1H, s, CH_2NHCH_3), 2.40 (3H, s, NHC*H*$_3$), 3.68 (2H, s, ArC*H*$_2$NH), 3.80 (3H, s, ArOC*H*$_3$), 3.81 (3H, s, ArOC*H*$_3$), 6.43 (1H, dd, *J* = 8.1, 2.4 Hz, H-5), 6.45 (1H, d, *J* = 2.4 Hz, H-3), 7.12 (1H, d, *J* = 8.1 Hz, H-6); ^{13}C NMR (126 MHz, $CDCl_3$) δ 35.8 (NH*C*H$_3$), 50.9 (Ar*C*H$_2$NH), 55.4 (ArO*C*H$_3$), 55.5 (ArO*C*H$_3$), 98.6 (C-3), 103.7 (C-5), 120.7 (C-1), 130.7 (C-6), 158.8 (C-2 or C-4), 160.2 (C-2 or C-4); HRMS (ESI) calcd for $C_{10}H_{16}NO_2$ [M+H]$^+$ 182.1176, found 182.1173; ^{1}H NMR data were identical to literature data.[270]

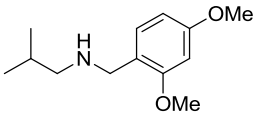
1-(4-Methoxyphenyl)-*N*-methylmethanamine, (116)



Compound **116** was synthesised according to general procedure F, using the following reagents: methylamine 8.03 M in EtOH (3.07 mL, 24.7 mmol), 4-methoxybenzaldehyde (3.0 mL, 3.36 g, 24.7 mmol), sodium borohydride (1.03 g, 27.1 mmol) and ethanol (12 mL). The crude product was purified by column chromatography (silica gel,

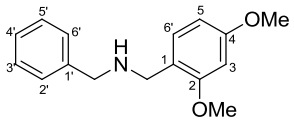
DCM:MeOH:NH_3, 1:0:0 → 90:9:1) to yield the *title compound* as a clear liquid (0.90 g, 24%); R_f = 0.24 (DCM:MeOH:NH_3, 90:9:1; ninhydrin); λ_{max} (EtOH)/nm 275.0; IR (neat) ν_{max}/cm^{-1} 1612, 1511, 1464, 1242, 1175, 1034; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.18 (1H, s, CH_2NHCH_3), 2.44 (3H, s, $NHCH_3$), 3.68 (2H, s, $ArCH_2NH$), 3.80 (3H, s, $ArOCH_3$), 6.86 (2H, d, *J* = 8.8 Hz, H-3, 5), 7.23 (2H, d, *J* = 8.8 Hz, H-2, 6); ^{13}C NMR (126 MHz, $CDCl_3$) δ 36.1 ($NHCH_3$), 55.4 ($ArOCH_3$), 55.7 ($ArCH_2NH$), 113.9 (C-3, 5), 129.4 (C-2, 6), 132.6 (C-1), 158.7 (C-4); ^{1}H NMR and ^{13}C NMR data were identical to literature data.[271]

_N_-(2,4-Dimethoxybenzyl)-2-methylpropan-1-amine, (117)



Compound **117** was synthesised according to general procedure F, using the following reagents: *iso*butylamine (1.80 mL, 1.32 g, 18.1 mmol), 2,4-dimethoxybenzaldehyde (3.0 g, 18.1 mmol), sodium borohydride (0.75 g, 19.9 mmol) and ethanol (9 mL). The crude product was purified by column chromatography (silica gel, EtOAc:MeOH, 1:0 → 95:5) to yield the *title compound* as a clear liquid (2.80 g, 69%); R_f = 0.25 (EtOAc:MeOH, 95:5; ninhydrin); λ_{max} (EtOH)/nm 276.5; IR (neat) ν_{max}/cm^{-1} 1613, 1589, 1506, 1463, 1287, 1207, 1153, 1037; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (6H, d, *J* = 6.6 Hz, $CH(CH_3)_2$), 1.49 (1H, s, CH_2NHCH_2), 1.81 – 1.72 (1H, m, $CH(CH_3)_2$), 2.38 (2H, d, *J* = 6.8 Hz, $NHCH_2CH$), 3.70 (2H, s, $ArCH_2NH$), 3.80 (3H, s, $ArOCH_3$), 3.81 (3H, s, $ArOCH_3$), 6.43 (1H, dd, *J* = 8.1, 2.4 Hz, H-5), 6.45 (1H, d, *J* = 2.4 Hz, H-3), 7.13 (1H, d, *J* = 8.1 Hz, H-6); ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.8 ($CH(CH_3)_2$), 28.4 ($CH(CH_3)_2$), 49.2 ($ArCH_2NH$), 55.4 ($ArOCH_3$), 55.5 ($ArOCH_3$), 57.4 ($CHCH_2NH$), 98.6 (C-3), 103.7 (C-5), 121.4 (C-1), 130.4 (C-6), 158.7 (C-2 or C-4), 160.0 (C-2 or C-4); HRMS (ESI) calcd for $C_{13}H_{22}NO_2$ $[M+H]^+$ 224.1645, found 224.1647.

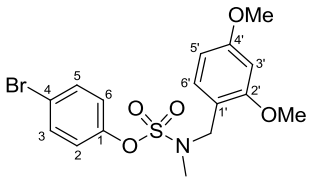
_N_-Benzyl-1-(2,4-dimethoxyphenyl)methanamine, (118)



Compound **118** was synthesised according to general procedure F, using the following reagents: benzylamine (1.97 mL, 1.93 g, 18.1 mmol), 2,4-dimethoxybenzaldehyde (3.0 g, 18.1 mmol), sodium borohydride (0.75 g, 19.9 mmol) and ethanol (9 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 1:1) to yield the *title compound* as a clear oil (3.12 g, 67%); R_f = 0.33 (petrol:EtOAc, 1:1;

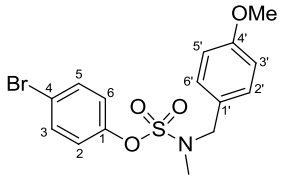
ninhydrin); λ_{max} (EtOH)/nm 276.5; IR (neat) ν_{max}/cm^{-1} 1612, 1588, 1506, 1453, 1287, 1207, 1155, 1034; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.82 (1H, s, CH_2NHCH_2), 3.75 (2H, s, $ArCH_2NH$), 3.77 (2H, s, $ArCH_2NH$), 3.81 (3H, s, $ArOCH_3$), 3.81 (3H, s, $ArOCH_3$), 6.44 (1H, dd, *J* = 8.1, 2.4 Hz, H-5), 6.47 (1H, d, *J* = 2.4 Hz, H-3), 7.14 (1H, d, *J* = 8.1 Hz, H-6), 7.26 – 7.21 (1H, m, H-4'), 7.38 – 7.29 (4H, m, 4 × Ar*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 48.5 ($ArCH_2$), 53.1 ($ArCH_2$), 55.4 ($ArOCH_3$), 55.5 ($ArOCH_3$), 98.7 (C-3), 103.7 (C-5), 121.0 (C_q Ar), 126.9 (C-4'), 128.3 (CH Ar), 128.4 (CH Ar), 130.6 (C-5), 140.8 (C_q Ar), 158.8 (C-2 or C-4), 160.2 (C-2 or C-4); HRMS (ESI) calcd for $C_{16}H_{20}NO_4$ $[M+H]^+$ 258.1489, found 258.1486.

4-Bromophenyl 2,4-dimethoxybenzyl(methyl)sulfamate, (119)



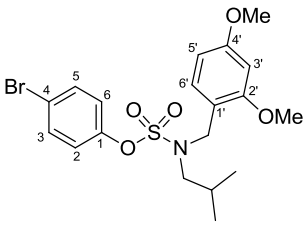
Compound **119** was synthesised according to general procedure A, using the following reagents: 1-((4-bromophenoxy)sulfonyl)-2,3-dimethyl-1*H*-imidazol-3-ium tetrafluoroborate (**22**) (600 mg, 1.43 mmol), 1-(2,4-dimethoxyphenyl)-*N*-methylmethanamine (**115**) (260 mg, 1.43 mmol) and acetonitrile (11.5 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 85:15) to yield the *title compound* as a clear oil (566 mg, 95%); R_f = 0.32 (petrol:EtOAc, 85:15; $KMnO_4$); λ_{max} (EtOH)/nm 277.0; IR (neat) ν_{max}/cm^{-1} 1613, 1589, 1509, 1481, 1372, 1197, 1155, 1034; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.87 (3H, s, NCH_3), 3.80 (3H, s, $ArOCH_3$), 3.82 (3H, s, $ArOCH_3$), 4.40 (2H, s, $ArCH_2$), 6.49 – 6.44 (2H, m, H-3' and H-5'), 7.12 (2H, d, *J* = 8.9 Hz, H-2, 6), 7.21 (1H, d, *J* = 8.2 Hz, H-6'), 7.48 (2H, d, *J* = 8.9 Hz, H-3, 5); ^{13}C NMR (126 MHz, $CDCl_3$) δ 35.8 (NCH_3), 49.3 ($ArCH_2$), 55.5 ($ArOCH_3$), 55.6 ($ArOCH_3$), 98.6 (C-3'), 104.5 (C-5'), 115.6 (C-1'), 120.0 (C-4), 123.8 (C-2, 6), 131.5 (C-6'), 132.9 (C-3, 5), 149.5 (C-1), 158.8 (C-2' or C-4'), 161.2 (C-2' or C-4'); HRMS (ESI) calcd for $C_{16}H_{22}BrN_2O_5S$ $[M+NH_4]^+$ 433.0427, found 433.0422.

4-Bromophenyl 4-methoxybenzyl(methyl)sulfamate, (120)



Compound **120** was synthesised according to general procedure A, using the following reagents: 1-((4-bromophenoxy)sulfonyl)-2,3-dimethyl-1*H*-imidazol-3-ium tetrafluoroborate (**22**) (600 mg, 1.43 mmol), 1-(4-methoxyphenyl)-*N*-methylmethanamine (**116**) (217 mg, 1.43 mmol) and acetonitrile (11.5 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 85:15) to yield the *title compound* as a white solid (532 mg, 96%); R_f = 0.34 (petrol:EtOAc, 85:15; $KMnO_4$); m.p. 65.0-67.0 °C; λ_{max} (EtOH)/nm 274.0; IR (neat) ν_{max}/cm^{-1} 1613, 1585, 1512, 1483, 1368, 1197, 1153; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.83 (3H, s, NCH_3), 3.82 (3H, s, ArOCH_3), 4.35 (2H, s, ArCH_2), 6.89 (2H, d, *J* = 8.7 Hz, H-3', 5'), 7.15 (2H, d, *J* = 8.9 Hz, H-2, 6), 7.23 (2H, d, *J* = 8.7 Hz, H-2', 6'), 7.51 (2H, d, *J* = 8.9 Hz, H-3, 5); ^{13}C NMR (126 MHz, $CDCl_3$) δ 35.2 (N*C*H$_3$), 54.8 (Ar*C*H$_2$), 55.5 (ArO*C*H$_3$), 114.3 (C-3', 5'), 120.2 (C-4 or C-1'), 123.8 (C-2, 6), 126.8 (C-4 or C-1'), 130.1 (C-2', 6'), 133.0 (C-3, 5), 149.4 (C-1), 159.8 (C-4'); HRMS (ESI) calcd for $C_{15}H_{20}BrN_2O_4S$ $[M+NH_4]^+$ 403.0322, found 403.0328.

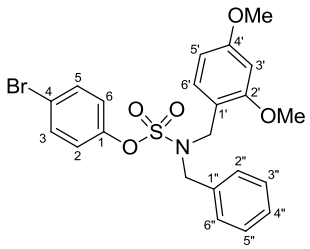
4-Bromophenyl 2,4-dimethoxybenzyl(*iso*butyl)sulfamate, (121)



Compound **121** was synthesised according to general procedure A, using the following reagents: 1-((4-bromophenoxy)sulfonyl)-2,3-dimethyl-1*H*-imidazol-3-ium tetrafluoroborate (**22**) (600 mg, 1.43 mmol), *N*-(2,4-dimethoxybenzyl)-2-methylpropan-1-amine (**117**) (321 mg, 1.43 mmol) and acetonitrile (11.5 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 9:1) to yield the *title compound* as a clear oil (560 mg, 85%); R_f = 0.27 (petrol:EtOAc, 9:1; $KMnO_4$); λ_{max} (EtOH)/nm 277.0; IR (neat) ν_{max}/cm^{-1} 1613, 1588, 1509, 1482, 1368, 1197, 1154, 1033; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (6H, d, *J* = 6.7 Hz, CH(CH_3)$_2$), 2.02 – 1.89 (1H, m, C*H*(CH$_3$)$_2$), 3.04 (2H, d, *J* = 7.5 Hz, NCH_2CH), 3.81 (3H, s, ArOCH_3), 3.82 (3H, s, ArOCH_3), 4.50 (2H, s, ArCH_2), 6.49 – 6.43 (2H, m, H-3' and H-5'), 7.01 (2H, d,

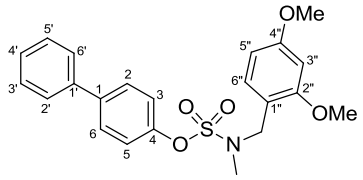
J = 8.9 Hz, H-2, 6), 7.33 (1H, d, *J* = 8.2 Hz, H-6'), 7.43 (2H, d, *J* = 8.9 Hz, H-3, 5); ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.0 (CH(*C*H_3)$_2$), 27.0 (*C*H(CH$_3$)$_2$), 47.1 (Ar*C*H$_2$), 55.4 (ArO*C*H$_3$), 55.6 (ArO*C*H$_3$), 56.5 (*C*H$_2$CH), 98.4 (C-3'), 104.4 (C-5'), 116.2 (C-1'), 119.7 (C-4), 123.7 (C-2, 6), 132.4 (C-6'), 132.7 (C-3, 5), 149.6 (C-1), 158.8 (C-2' or C-4'), 161.1 (C-2' or C-4'); HRMS (ESI) calcd for $C_{19}H_{28}BrN_2O_5S$ $[M+NH_4]^+$ 475.0897, found 475.0887.

4-Bromophenyl benzyl(2,4-dimethoxybenzyl)sulfamate, (122)



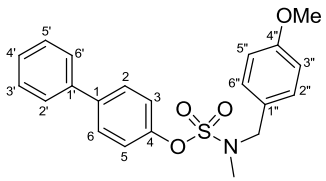
Compound **122** was synthesised according to general procedure A, using the following reagents: 1-((4-bromophenoxy)sulfonyl)-2,3-dimethyl-1*H*-imidazol-3-ium tetrafluoroborate (**22**) (600 mg, 1.43 mmol), *N*-benzyl-1-(2,4-dimethoxyphenyl)methanamine (**118**) (369 mg, 1.43 mmol) and acetonitrile (11.5 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 85:15) to yield the *title compound* as a clear oil (629 mg, 89%); R_f = 0.33 (petrol:EtOAc, 85:15; $KMnO_4$); λ_{max} (EtOH)/nm 277.0; IR (neat) ν_{max}/cm^{-1} 1613, 1588, 1509, 1481, 1370, 1196, 1155, 1039; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.77 (3H, s, ArOC*H*$_3$), 3.82 (3H, s, ArOC*H*$_3$), 4.39 (2H, s, ArC*H*$_2$), 4.41 (2H, s, ArC*H*$_2$), 6.42 (1H, d, *J* = 2.3 Hz, H-3'), 6.45 (1H, dd, *J* = 8.3, 2.3 Hz, H-5'), 6.91 (2H, d, *J* = 8.9 Hz, H-2, 6), 7.26 (1H, d, *J* = 8.3 Hz, H-6'), 7.35 – 7.28 (5H, m, 5 × Ar*H*), 7.39 (2H, d, *J* = 8.9 Hz, H-3, 5); ^{13}C NMR (126 MHz, $CDCl_3$) δ 46.1 (Ar*C*H$_2$), 52.1 (Ar*C*H$_2$), 55.3 (ArO*C*H$_3$), 55.6 (ArO*C*H$_3$), 98.4 (C-3'), 104.4 (C-5'), 115.8 (C_q Ar), 119.9 (C_q Ar), 123.9 (C-2, 6), 128.0 (CH Ar), 128.6 (CH Ar), 128.7 (CH Ar), 132.4 (C-6'), 132.7 (C-3, 5), 135.8 (C_q Ar), 149.4 (C-1), 158.8 (C-2' or C-4'), 161.2 (C-2' or C-4'); HRMS (ESI) calcd for $C_{22}H_{26}BrN_2O_5S$ $[M+NH_4]^+$ 509.0740, found 509.0739.

[1,1'-Biphenyl]-4-yl 2,4-dimethoxybenzyl(methyl)sulfamate, (123)



Compound **123** was synthesised according to general procedure C, using the following reagents: 4-bromophenyl 2,4-dimethoxybenzyl(methyl)sulfamate (**119**) (400 mg, 0.96 mmol), potassium carbonate (398 mg, 2.88 mmol), phenyl boronic acid (176 mg, 1.44 mmol), tetrakis(triphenylphosphine)palladium(0) (111 mg, 0.10 mmol) and acetonitrile (19 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 85:15) to yield the *title compound* as a yellow oil (358 mg, 90%); R_f = 0.34 (petrol:EtOAc, 85:15); λ_{max} (EtOH)/nm 251.0; IR (neat) ν_{max}/cm^{-1} 1613, 1591, 1509, 1485, 1371, 1207, 1154, 1034; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.90 (3H, s, NC*H*$_3$), 3.80 (3H, s, ArOC*H*$_3$), 3.81 (3H, s, ArOC*H*$_3$), 4.43 (2H, s, ArC*H*$_2$), 6.49 – 6.44 (2H, m, H-3" and H-5"), 7.25 (1H, d, *J* = 8.1 Hz, H-6"), 7.33 (2H, d, *J* = 8.7 Hz, H-3, 5), 7.39 – 7.35 (1H, m, H-4'), 7.45 (2H, dd, *J* = 7.6, 7.6 Hz, H-3', 5'), 7.61 – 7.54 (4H, m, H-2, 6 and H-2', 6'); ^{13}C NMR (126 MHz, $CDCl_3$) δ 35.8 (N*C*H$_3$), 49.2 (Ar*C*H$_2$), 55.5 (ArO*C*H$_3$), 55.5 (ArO*C*H$_3$), 98.6 (C-3"), 104.5 (C-5"), 115.8 (C-1"), 122.3 (C-3, 5), 127.2 (C-2, 6 or C-2', 6'), 127.7 (C-4'), 128.5 (C-2, 6 or C-2', 6'), 129.0 (C-3', 5'), 131.5 (C-6"), 139.9 (C-1 or C-1'), 140.2 (C-1 or C-1'), 149.9 (C-4), 158.9 (C-2" or C-4"), 161.1 (C-2" or C-4"); HRMS (ESI) calcd for $C_{22}H_{27}N_2O_5S$ $[M+NH_4]^+$ 431.1635, found 431.1638.

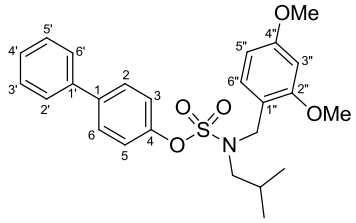
[1,1'-Biphenyl]-4-yl 4-methoxybenzyl(methyl)sulfamate, (124)



Compound **124** was synthesised according to general procedure C, using the following reagents: 4-bromophenyl 4-methoxybenzyl(methyl)sulfamate (**120**) (400 mg, 1.04 mmol), potassium carbonate (429 mg, 3.11 mmol), phenyl boronic acid (189 mg, 1.55 mmol), tetrakis(triphenylphosphine)palladium(0) (120 mg, 0.10 mmol) and acetonitrile (20 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 85:15) to yield the *title compound* as a yellow solid (345 mg, 87%); R_f = 0.35 (petrol:EtOAc, 85:15); m.p. 103.5-105.5 °C; λ_{max} (EtOH)/nm 251.0; IR (neat) ν_{max}/cm^{-1} 1609, 1594, 1512, 1485, 1460, 1373, 1180, 1151, 1032; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.86 (3H, s, NC*H*$_3$), 3.81 (3H, s, ArOC*H*$_3$), 4.38 (2H, s, ArC*H*$_2$), 6.88 (2H, d, *J* = 8.6 Hz,

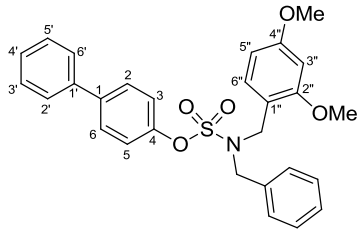
H-3”, 5”), 7.25 (2H, d, *J* = 8.6 Hz, H-2”, 6”), 7.40 – 7.33 (3H, m, H-4’ and H-3, 5), 7.45 (2H, dd, *J* = 7.6, 7.6 Hz, H-3’, 5’), 7.57 (2H, dd, *J* = 7.6, 1.2 Hz, H-2’, 6’), 7.61 (2H, d, *J* = 8.8 Hz, H-2, 6); ^{13}C NMR (126 MHz, $CDCl_3$) δ 35.2 (N*C*H$_3$), 54.8 (Ar*C*H$_2$), 55.4 (ArO*C*H$_3$), 114.2 (C-3”, 5”), 122.3 (C-3, 5), 127.0 (C-1”), 127.3 (C-2’, 6’), 127.7 (C-4’), 128.6 (C-2, 6), 129.0 (C-3’, 5’), 130.1 (C-2”, 6”), 140.1 (C-1 or C-1’), 140.1 (C-1 or C-1’), 149.8 (C-4), 159.7 (C-4”); HRMS (ESI) calcd for $C_{21}H_{25}N_2O_4S$ $[M+NH_4]^+$ 401.1530, found 401.1533.

[1,1'-Biphenyl]-4-yl 2,4-dimethoxybenzyl(*iso*butyl)sulfamate, (125)



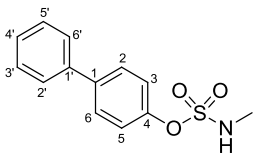
Compound **125** was synthesised according to general procedure C, using the following reagents: 4-bromophenyl 2,4-dimethoxybenzyl(*iso*butyl)sulfamate (**121**) (400 mg, 0.87 mmol), potassium carbonate (362 mg, 2.62 mmol), phenyl boronic acid (160 mg, 1.31 mmol), tetrakis(triphenylphosphine)palladium(0) (101 mg, 0.09 mmol) and acetonitrile (17 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 85:15) to yield the *title compound* as a clear oil (340 mg, 85%); R_f = 0.36 (petrol:EtOAc, 85:15); λ_{max} (EtOH)/nm 252.0; IR (neat) ν_{max}/cm^{-1} 1613, 1592, 1509, 1485, 1366, 1208, 1152, 1032; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (6H, d, *J* = 6.7 Hz, CH(C*H*$_3$)$_2$), 2.02 – 1.92 (1H, m, C*H*(CH$_3$)$_2$), 3.09 (2H, d, *J* = 7.4 Hz, NC*H*$_2$CH), 3.80 (3H, s, ArOC*H*$_3$), 3.82 (3H, s, ArOC*H*$_3$), 4.54 (2H, s, ArC*H*$_2$), 6.46 (1H, d, *J* = 2.4 Hz, H-3”), 6.48 (1H, dd, *J* = 8.3, 2.4 Hz, H-5”), 7.23 (2H, d, *J* = 8.7 Hz, H-3, 5), 7.37 – 7.32 (1H, m, H-4’), 7.39 (1H, d, *J* = 8.3 Hz, H-6”), 7.44 (2H, dd, *J* = 7.6, 7.6 Hz, H-3’, 5’), 7.58 – 7.51 (4H, m, H-2, 6 and H-2’, 6’); ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.1 (CH(*C*H$_3$)$_2$), 27.0 (*C*H(CH$_3$)$_2$), 47.1 (Ar*C*H$_2$), 55.4 (ArO*C*H$_3$), 55.5 (ArO*C*H$_3$), 56.5 (*C*H$_2$CH), 98.4 (C-3”), 104.4 (C-5”), 116.3 (C-1”), 122.2 (C-3, 5), 127.2 (C-2, 6 or C-2’, 6’), 127.6 (C-6”), 128.4 (C-2, 6 or C-2’, 6’), 129.0 (C-3’, 5’), 132.3 (C-4’), 139.6 (C-1 or C-1’), 140.2 (C-1 or C-1’), 150.0 (C-4), 158.8 (C-2” or C-4”), 161.0 (C-2” or C-4”); HRMS (ESI) calcd for $C_{25}H_{29}NO_5Na$ $[M+Na]^+$ 478.1659, found 478.1653.

[1,1'-Biphenyl]-4-yl benzyl(2,4-dimethoxybenzyl)sulfamate, (126)



Compound **126** was synthesised according to general procedure C, using the following reagents: 4-bromophenyl benzyl(2,4-dimethoxybenzyl)sulfamate (**122**) (400 mg, 0.81 mmol), potassium carbonate (337 mg, 2.44 mmol), phenyl boronic acid (149 mg, 1.22 mmol), tetrakis(triphenylphosphine)palladium(0) (94 mg, 0.08 mmol) and acetonitrile (16 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 85:15) to yield the *title compound* as a pale yellow oil (350 mg, 87%); R_f = 0.35 (petrol:EtOAc, 85:15); λ_{max} (EtOH)/nm 251.5; IR (neat) ν_{max}/cm^{-1} 1613, 1591, 1509, 1485, 1369, 1208, 1154, 1039; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.76 (3H, s, ArOC*H*$_3$), 3.79 (3H, s, ArOC*H*$_3$), 4.44 (2H, s, ArC*H*$_2$), 4.45 (2H, s, ArC*H*$_2$), 6.42 (1H, d, *J* = 2.3 Hz, H-3”), 6.45 (1H, dd, *J* = 8.4, 2.3 Hz, H-5”), 7.14 (2H, d, *J* = 8.3 Hz, H-3, 5), 7.39 – 7.27 (7H, m, 5 × Ar*H* and H-4’ and H-6”), 7.44 (2H, dd, *J* = 7.6, 7.6 Hz, H-3’, 5’), 7.51 (2H, d, *J* = 8.3 Hz, H-2, 6), 7.55 (2H, d, *J* = 7.6 Hz, H-2’, 6’); ^{13}C NMR (126 MHz, $CDCl_3$) δ 46.0 (ArO*C*H$_3$), 52.1 (ArO*C*H$_3$), 55.3 (Ar*C*H$_2$), 55.5 (Ar*C*H$_2$), 98.4 (C-3”), 104.4 (C-5”), 116.0 (C-1”), 122.3 (C-3, 5), 127.2 (C-2’, 6’), 127.6 (CH Ar), 127.9 (CH Ar), 128.4 (CH Ar), 128.5 (C-2, 6), 128.7 (CH Ar), 129.0 (C-3’, 5’), 132.4 (C-6”), 136.0 (C_q Ar), 139.7 (C-1 or C-1’), 140.2 (C-1 or C-1’), 149.8 (C-4), 158.8 (C-2” or C-4”), 161.1 (C-2” or C-4”); HRMS (ESI) calcd for $C_{28}H_{31}N_2O_5S$ $[M+NH_4]^+$ 507.1948, found 507.1947.

[1,1'-Biphenyl]-4-yl methylsulfamate, (127)

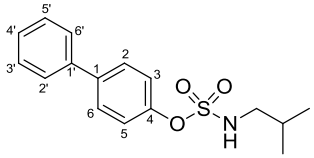


Compound **127** was synthesised following two different procedures.

1st procedure: Compound **127** was synthesised according to general procedure D, using the following reagents: [1,1'-biphenyl]-4-yl 2,4-dimethoxybenzyl(methyl)sulfamate (**123**) (250 mg, 0.60 mmol), DCM (5.4 mL) and TFA (0.6 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 8:2) to yield the *title compound* as a pale yellow solid (151 mg, 95%).

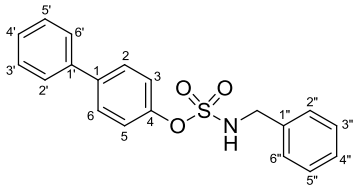
2nd procedure: Compound **127** was synthesised according to general procedure E, using the following reagents: [1,1'-biphenyl]-4-yl 4-methoxybenzyl(methyl)sulfamate (**124**) (250 mg, 0.65 mmol), DCM (3.3 mL) and TFA (3.3 mL). The crude product was purified by column chromatography (silica gel, petrol:DCM, 1:0 → 1:9) to yield the *title compound* as a pale yellow solid (165 mg, 96%); R_f = 0.30 (petrol:EtOAc, 8:2); m.p. 114.5-116.5 °C; λ_{max} (EtOH)/nm 250.0; IR (neat) ν_{max}/cm^{-1} 3299, 1599, 1516, 1484, 1351, 1171, 1134, 1085; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.75 (3H, d, *J* = 4.7 Hz, NHC*H*$_3$), 7.42 – 7.34 (3H, m, H-3, 5 and H-4'), 7.48 (2H, dd, *J* = 7.7, 7.7 Hz, H-3', 5'), 7.67 (2H, dd, *J* = 7.7, 1.1 Hz, H-2', 6'), 7.75 (2H, d, *J* = 8.7 Hz, H-2, 6), 8.28 (1H, q, *J* = 4.7 Hz, N*H*CH$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 29.2 (NH*C*H$_3$), 122.5 (C-3, 5), 126.8 (C-2', 6'), 127.7 (C-4'), 128.2 (C-2, 6), 129.0 (C-3', 5'), 138.8 (C-1 or C-1'), 139.1 (C-1 or C-1'), 149.3 (C-4); LRMS (ES$^-$) *m/z* 304.2 [M+MeCN-H]$^-$; HRMS (ESI) calcd for $C_{13}H_{12}NO_3S$ [M-H]$^-$ 262.0543, found 262.0537.

[1,1'-Biphenyl]-4-yl *iso*butylsulfamate, (128)



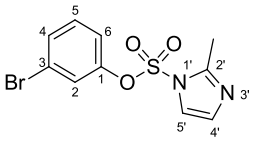
Compound **128** was synthesised according to general procedure D, using the following reagents: [1,1'-biphenyl]-4-yl 2,4-dimethoxybenzyl(*iso*butyl)sulfamate (**125**) (250 mg, 0.55 mmol), DCM (5.0 mL) and TFA (0.6 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 8:2) to yield the *title compound* as a pale orange solid (156 mg, 93%); R_f = 0.34 (petrol:EtOAc, 8:2); m.p. 98.5-100.5 °C; λ_{max} (EtOH)/nm 250.5; IR (neat) ν_{max}/cm^{-1} 3293, 1599, 1517, 1486, 1351, 1143, 1078; ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.88 (6H, d, *J* = 6.6 Hz, CH(C*H*$_3$)$_2$), 1.81 – 1.70 (1H, m, C*H*(CH$_3$)$_2$), 2.92 (2H, dd, *J* = 6.6, 5.9 Hz, NHC*H*$_2$CH), 7.41 – 7.34 (3H, m, H-3, 5 and H-4'), 7.48 (2H, dd, *J* = 7.7, 7.7 Hz, H-3', 5'), 7.67 (2H, dd, *J* = 7.7, 1.1 Hz, H-2', 6'), 7.75 (2H, d, *J* = 8.7 Hz, H-2, 6), 8.43 (1H, t, *J* = 5.8 Hz, N*H*CH$_2$); ^{13}C NMR (126 MHz, DMSO-d_6) δ 19.8 (CH(*C*H$_3$)$_2$), 28.0 (*C*H(CH$_3$)$_2$), 50.7 (Ar*C*H$_2$), 122.4 (C-3, 5), 126.7 (C-2', 6'), 127.7 (C-4'), 128.1 (C-2, 6), 129.0 (C-3', 5'), 138.6 (C-1 or C-1'), 139.1 (C-1 or C-1'), 149.4 (C-4); LRMS (ES$^-$) *m/z* 304.2 [M-H]$^-$; HRMS (ESI) calcd for $C_{16}H_{18}NO_3S$ [M-H]$^-$ 304.1013, found 304.1004.

[1,1'-Biphenyl]-4-yl benzylsulfamate, (129)



Compound **129** was synthesised according to general procedure D, using the following reagents: [1,1'-biphenyl]-4-yl benzyl(2,4-dimethoxybenzyl)sulfamate (**126**) (250 mg, 0.51 mmol), DCM (4.5 mL) and TFA (0.5 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 8:2) to yield the *title compound* as a pale yellow solid (166 mg, 96%); R_f = 0.33 (petrol:EtOAc, 8:2); m.p. 113.0-115.0 °C; λ_{max} (EtOH)/nm 251.5; IR (neat) ν_{max}/cm^{-1} 3274, 1599, 1518, 1485, 1454, 1448, 1348, 1153, 1092, 1076; ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.33 (2H, d, *J* = 6.0 Hz, ArC*H*$_2$NH), 7.31 - 7.28 (1H, m, Ar*H*), 7.32 (2H, d, *J* = 8.7 Hz, H-3, 5), 7.38 – 7.34 (4H, m, 4 × Ar*H*), 7.41 – 7.37 (1H, m, H-4'), 7.48 (2H, dd, *J* = 7.7, 7.7 Hz, H-3', 5'), 7.67 (2H, dd, *J* = 7.7, 1.1 Hz, H-2', 6'), 7.73 (2H, d, *J* = 8.8 Hz, H-2, 6), 8.98 (1H, t, *J* = 6.0 Hz, ArCH$_2$N*H*); ^{13}C NMR (126 MHz, DMSO-d_6) δ 46.7 (Ar*C*H$_2$), 122.5 (C-3, 5), 126.8 (C-2', 6'), 127.5 (CH Ar), 127.8 (CH Ar), 128.1 (CH Ar), 128.4 (CH Ar), 129.0 (C-3', 5'), 137.4 (C$_q$ Ar), 138.7 (C$_q$ Ar), 139.1 (C$_q$ Ar), 149.3 (C-4); LRMS (ES$^-$) *m/z* 338.2 [M-H]$^-$; HRMS (ESI) calcd for $C_{19}H_{16}NO_3S$ [M-H]$^-$ 338.0856, found 338.0843.

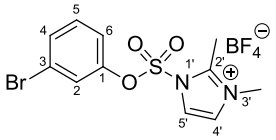
3-Bromophenyl 2-methyl-1*H*-imidazole-1-sulfonate, (130)



Compound **130** was synthesised according to general procedure B, using the following reagents: 1,1'-sulfonylbis(2-methyl-1*H*-imidazole) (**19**) (2.61 g, 11.6 mmol), caesium carbonate (2.07 g, 6.36 mmol), 3-bromophenol (**12**) (1.0 g, 5.78 mmol) and acetonitrile (20 mL). The crude yellow oil was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 8:2) to yield the *title compound* as a pale yellow oil (1.39 g, 76%); R_f = 0.32 (petrol:EtOAc, 8:2; $KMnO_4$); λ_{max} (EtOH)/nm 270.5; IR (neat) ν_{max}/cm^{-1} 1581, 1554, 1467, 1424, 1208, 1152, 890; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.51 (3H, s, CH_3), 6.83 (1H, ddd, *J* = 8.3, 2.4 and 0.9 Hz, H-6), 6.91 (1H, d, *J* = 1.8 Hz, H-4' or H-5'), 7.13 (1H, d, *J* = 1.8 Hz, H-4' or H-5'), 7.18 (1H, dd, *J* = 2.4, 1.7 Hz, H-2), 7.23 (1H, dd, *J* = 8.3, 8.0 Hz, H-5), 7.50 (1H, ddd, *J* = 8.0, 1.7 and 0.9 Hz, H-4); ^{13}C NMR (126 MHz, $CDCl_3$) δ 15.1 (CH_3), 120.3 (C-4' or C-5' or C-6), 120.5 (C-4' or C-5' or C-6), 123.2 (C-3), 125.4

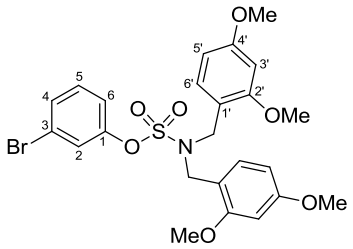
(C-2), 128.2 (C-4' or C-5'), 131.4 (C-5), 132.0 (C-4), 146.8 (C-1 or C-2'), 149.2 (C-1 or C-2'); LRMS (ES^+) *m/z* 316.9 $[M(^{79}Br)+H]^+$, 319.1 $[M(^{81}Br)+H]^+$; HRMS (ESI) calcd for $C_{10}H_{10}BrN_2O_3S$ $[M(^{79}Br)+H]^+$ 316.9590, found 316.9597.

1-((3-Bromophenoxy)sulfonyl)-2,3-dimethyl-1*H*-imidazol-3-ium tetrafluoroborate, (131)



To 3-bromophenyl 2-methyl-1*H*-imidazole-1-sulfonate (**130**) (5.5 g, 17.4 mmol) in DCM (70 mL), cooled at 0 °C, was added trimethyloxonium tetrafluoroborate (2.57 g, 17.4 mmol). The resulting solution was stirred at 0 °C for 1 h and allowed to warm to RT. Upon completion, the reaction was cooled in an ice bath. Cold petrol (120 mL) was added to the mixture, leading to the precipitation of **131**. The white precipitate was filtered off, washed with cold petrol (60 mL) and dry under high vacuum. The white fluffy solid (6.20 g, 85%) was used in the next step without further purification; m.p. 149.5-151.5 °C; λ_{max} (EtOH)/nm 265.5; IR (neat) ν_{max}/cm^{-1} 3159, 3103, 1594, 1580, 1447, 1229, 1214, 1149, 1031, 906; ^1H NMR (500 MHz, MeOD) δ 2.91 (3H, s, CH_3), 4.86 (3H, s, NCH_3), 7.29 (1H, ddd, *J* = 8.5, 2.5 and 0.9 Hz, H-6), 7.45 (1H, dd, *J* = 8.5, 8.2 Hz, H-5), 7.66 (1H, dd, *J* = 2.5, 2.1 Hz, H-2), 7.72 – 7.68 (1H, m, H-4), 7.73 (1H, d, *J* = 2.4 Hz, H-4' or H-5'), 7.87 (1H, d, *J* = 2.4 Hz, H-4' or H-5'); ^{13}C NMR (126 MHz, MeOD) δ 11.9 (CH_3), 36.8 (NCH_3), 121.5 (C-6), 122.4 (C-4' or C-5'), 124.3 (C-3), 125.0 (C-4' or C-5'), 126.2 (C-2), 133.4 (C-5), 134.0 (C-4), 150.7 (C-1); ^{19}F NMR (471 MHz, MeOD) δ -154.4 (BF_4^-); LRMS (ES^+) *m/z* 331.1 $[M(^{79}Br)-BF_4]^+$, 333.2 $[M(^{81}Br)-BF_4]^+$; HRMS (ESI) calcd for $C_{11}H_{12}BrN_2O_3S$ $[M(^{79}Br)-BF_4]^+$ 330.9747, found 330.9751.

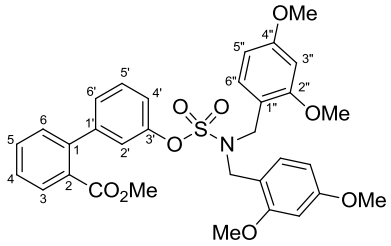
3-Bromophenyl bis(2,4-dimethoxybenzyl)sulfamate, (132)



To 1-((3-bromophenoxy)sulfonyl)-2,3-dimethyl-1*H*-imidazol-3-ium tetrafluoroborate (**131**) (3.0 g, 7.18 mmol) in acetonitrile (30 mL) was added a solution of bis(2,4-dimethoxybenzyl)amine (**32**) (2.28 g, 7.18 mmol) in acetonitrile (25 mL). The reaction

mixture was heated at 82 °C for 24 h. Upon completion, the solvent was removed *in vacuo* to yield a crude product. The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 8:2) to yield the *title compound* as a clear oil (2.81 g, 71%); R_f = 0.35 (petrol:EtOAc, 8:2; $KMnO_4$); λ_{max} (EtOH)/nm 276.5; IR (neat) ν_{max}/cm^{-1} 1612, 1584, 1508, 1466, 1372, 1208, 1157, 1038, 879; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.75 (6H, s, 2 × ArOCH_3), 3.81 (6H, s, 2 × ArOCH_3), 4.45 (4H, s, 2 × ArCH_2), 6.41 (2H, d, *J* = 2.4 Hz, H-3'), 6.45 (2H, dd, *J* = 8.4, 2.4 Hz, H-5'), 7.04 (1H, dd, *J* = 2.1, 2.1 Hz, H-2), 7.09 (1H, ddd, *J* = 8.4, 2.3 and 1.1 Hz, H-6), 7.16 (1H, dd, *J* = 8.4, 8.1 Hz, H-5), 7.26 (2H, d, *J* = 8.4 Hz, H-6'), 7.36 – 7.31 (1H, m, H-4); ^{13}C NMR (126 MHz, $CDCl_3$) δ 47.3 (Ar*C*H_2), 55.3 (ArO*C*H_3), 55.5 (ArO*C*H_3), 98.4 (C-3'), 104.2 (C-5'), 116.6 (C-1'), 120.8 (C-6), 122.4 (C-3), 125.5 (C-2), 129.6 (C-4), 130.6 (C-5), 131.2 (C-6'), 150.9 (C-1), 158.6 (C-2' or C-4'), 160.8 (C-2' or C-4'); HRMS (ESI) calcd for $C_{24}H_{27}BrNO_7S$ [M(^{79}Br)+H]$^+$ 552.0686, found 552.0675.

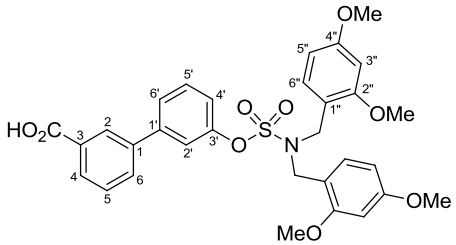
Methyl 3'-((*N*,*N*-bis(2,4-dimethoxybenzyl)sulfamoyl)oxy)-[1,1'-biphenyl]-2-carboxylate, (133)



A solution of 3-bromophenyl bis(2,4-dimethoxybenzyl)sulfamate (**132**) (750 mg, 1.36 mmol) in acetonitrile (15 mL) was sparged with nitrogen for 15 min. To this solution, potassium carbonate (563 mg, 4.07 mmol), 2-methoxycarbonylphenylboronic acid (293 mg, 1.63 mmol) and tetrakis(triphenylphosphine)palladium(0) (157 mg, 0.14 mmol) were added. The resulting mixture was heated at 120 °C for 20 min under microwave irradiation. Upon completion, the solvent was removed *in vacuo*. The crude residue was dissolved in a mixture of EtOAc and water (20 mL, respectively) and extracted with EtOAc (3 × 25 mL). The pooled organic extracts were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 7:3) to yield the *title compound* as a yellow oil (580 mg, 75%); R_f = 0.32 (petrol:EtOAc, 7:3); λ_{max} (EtOH)/nm 277.5; IR (neat) ν_{max}/cm^{-1} 1724, 1611, 1587, 1507, 1454, 1370, 1290, 1264, 1208, 1156, 1032, 886; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.61 (3H, s, ArCO_2CH_3), 3.68 (6H, s, 2 × ArOCH_3), 3.77 (6H, s, 2 × ArOCH_3), 4.45 (4H, s, 2 × ArCH_2), 6.34 (2H, d, *J* = 2.4 Hz,

H-3”), 6.43 (2H, dd, *J* = 8.4, 2.4 Hz, H-5”), 6.92 (1H, dd, *J* = 2.0, 2.0 Hz, H-2’), 7.18 - 7.12 (2H, m, H-4’ and H-6’), 7.31 – 7.27 (3H, m, H-3 and H-6”), 7.33 (1H, dd, *J* = 7.9, 7.9 Hz, H-5’), 7.44 (1H, ddd, *J* = 7.6, 7.6 and 1.3 Hz, H-4 or H-5), 7.53 (1H, ddd, *J* = 7.5, 7.5 and 1.4 Hz, H-4 or H-5), 7.85 (1H, dd, *J* = 7.7, 1.4 Hz, H-6); ^{13}C NMR (126 MHz, $CDCl_3$) δ 47.1 (Ar*C*H_2), 52.2 (ArCO_2*C*H_3), 55.2 (ArO*C*H_3), 55.5 (ArO*C*H_3), 98.3 (C-3”), 104.1 (C-5”), 116.8 (C-1”), 120.9 (C-4’ or C-6’), 122.2 (C-2’), 126.5 (C-4’ or C-6’), 127.7 (C-4 or C-5), 129.1 (C-5’), 130.1 (C-6), 130.8 (C-3), 130.9 (C-2), 131.1 (C-6”), 131.4 (C-4 or C-5), 141.4 (C-1 or C-1’), 143.1 (C-1 or C-1’), 150.2 (C-3’), 158.6 (C-2” or C-4”), 160.7 (C-2” or C-4”), 168.8 (Ar*C*O_2CH_3); HRMS (ESI) calcd for $C_{32}H_{37}N_2O_9S$ $[M+H]^+$ 625.2214, found 625.2211.

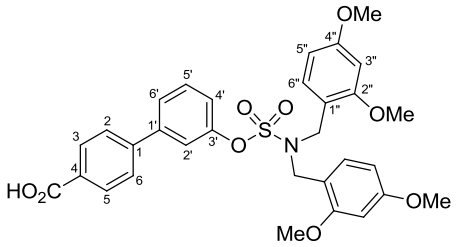
3'-((*N*,*N*-Bis(2,4-dimethoxybenzyl)sulfamoyl)oxy)-[1,1'-biphenyl]-3-carboxylic acid, (134)



Compound **134** was synthesised according to general procedure I, using the following reagents: 3-bromophenyl bis(2,4-dimethoxybenzyl)sulfamate (**132**) (750 mg, 1.36 mmol), dimethoxyethane (9.5 mL), 2 M aq. solution of sodium bicarbonate (1.36 mL, 2.72 mmol), 3-carboxyphenylboronic acid pinacol ester (404 mg, 1.63 mmol) and [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with DCM (55 mg, 0.07 mmol). The crude product was purified by column chromatography (silica gel, petrol:EtOAc:AcOH, 1:0:0 → 50:49.5:0.5) to yield the *title compound* as a pale orange oil (637 mg, 79%); R_f = 0.32 (petrol:EtOAc:AcOH, 50:49.5:0.5); No λ_{max} (EtOH)/nm; IR (neat) ν_{max}/cm^{-1} 2976, 1701, 1611, 1588, 1507, 1371, 1291, 1208, 1154, 1036, 827; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.71 (6H, s, 2 × ArOC*H*$_3$), 3.76 (6H, s, 2 × ArOC*H*$_3$), 4.48 (4H, s, 2 × ArC*H*$_2$), 6.37 (2H, d, *J* = 2.4 Hz, H-3”), 6.44 (2H, dd, *J* = 8.4, 2.4 Hz, H-5”), 7.22 – 7.14 (2H, m, H-4’ and H-2’), 7.29 (2H, d, *J* = 8.4 Hz, H-6”), 7.40 (1H, d, *J* = 8.0 Hz, H-5’), 7.52 – 7.45 (1H, m, H-6’), 7.55 (1H, dd, *J* = 7.8, 7.8 Hz, H-5), 7.73 (1H, ddd, *J* = 7.8, 1.4 and 1.4 Hz, H-6), 8.11 (1H, ddd, *J* = 7.8, 1.4 and 1.4 Hz, H-4), 8.27 (1H, dd, *J* = 1.4, 1.4 Hz, H-2); ^{13}C NMR (126 MHz, $CDCl_3$) δ 47.1 (Ar*C*H_2), 55.2 (ArO*C*H_3), 55.5 (ArO*C*H_3), 98.3 (C-3”), 104.1 (C-5”), 116.7 (C-1”), 120.8 (C-2’), 121.4 (C-4’), 125.2 (C-6’), 128.9 (C-2), 129.2 (C-5), 129.5 (C-4), 130.1 (C-5’), 131.2 (C-6”), 132.6 (C-6),

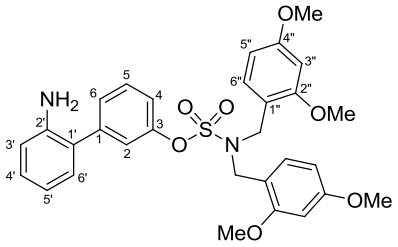
140.5 (C-1 or C-1'), 141.6 (C-1 or C-1'), 151.0 (C-3'), 158.6 (C-2" or C-4"), 160.7 (C-2" or C-4"), 177.2 (Ar*C*O_2H); LRMS (ES^-) *m/z* 592.3 $[M-H]^-$; HRMS (ESI) calcd for $C_{31}H_{30}NO_9S$ $[M-H]^-$ 592.1647, found 592.1644.

3'-((*N*,*N*-Bis(2,4-dimethoxybenzyl)sulfamoyl)oxy)-[1,1'-biphenyl]-4-carboxylic acid, (135)



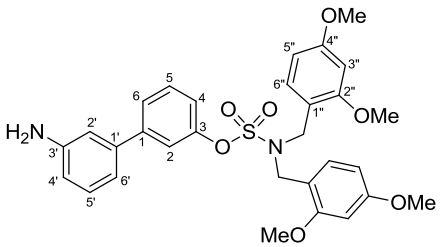
Compound **135** was synthesised according to general procedure I, using the following reagents: 3-bromophenyl bis(2,4-dimethoxybenzyl)sulfamate (**132**) (750 mg, 1.36 mmol), dimethoxyethane (9.5 mL), 2 M aq. solution of sodium bicarbonate (1.36 mL, 2.72 mmol), 4-carboxyphenylboronic acid pinacol ester (404 mg, 1.63 mmol) and [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with DCM (55 mg, 0.07 mmol). The crude product was purified by column chromatography (silica gel, petrol:EtOAc:AcOH, 1:0:0 → 50:49.5:0.5) to yield the *title compound* as a pale orange oil (620 mg, 77%); R_f = 0.28 (petrol:EtOAc:AcOH, 50:49.5:0.5); λ_{max} (EtOH)/nm 270.5; IR (neat) ν_{max}/cm^{-1} 2945, 1686, 1610, 1586, 1507, 1377, 1292, 1210, 1153; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.71 (6H, s, 2 × ArOC*H*$_3$), 3.78 (6H, s, 2 × ArOC*H*$_3$), 4.48 (4H, s, 2 × ArC*H*$_2$), 6.39 (2H, d, *J* = 2.4 Hz, H-3"), 6.45 (2H, dd, *J* = 8.4, 2.4 Hz, H-5"), 7.15 (1H, dd, *J* = 2.3, 2.0 Hz, H-2'), 7.20 (1H, ddd, *J* = 8.2, 2.3 and 1.0 Hz, H-4'), 7.30 (2H, d, *J* = 8.4 Hz, H-6"), 7.41 (1H, dd, *J* = 8.2, 7.9 Hz, H-5'), 7.50 – 7.46 (1H, m, H-6'), 7.59 (1H, d, *J* = 8.5 Hz, H-2, 6), 8.17 (2H, d, *J* = 8.5 Hz, H-3, 5); ^{13}C NMR (126 MHz, $CDCl_3$) δ 47.1 (Ar*C*H$_2$), 55.2 (ArO*C*H$_3$), 55.5 (ArO*C*H$_3$), 98.4 (C-3"), 104.1 (C-5"), 116.7 (C-1"), 120.9 (C-2'), 121.9 (C-4'), 125.3 (C-6'), 127.3 (C-2, 6), 128.6 (C-4), 130.1 (C-5'), 130.8 (C-3, 5), 131.2 (C-6"), 141.5 (C-1 or C-1'), 145.2 (C-1 or C-1'), 151.0 (C-3), 158.6 (C-2" or C-4"), 160.8 (C-2" or C-4"), 177.4 (Ar*C*O_2H); LRMS (ES^-) *m/z* 592.4 $[M-H]^-$; HRMS (ESI) calcd for $C_{31}H_{30}NO_9S$ $[M-H]^-$ 592.1647, found 592.1644.

2'-Amino-[1,1'-biphenyl]-3-yl bis(2,4-dimethoxybenzyl)sulfamate, (136)



Compound **136** was synthesised according to general procedure I, using the following reagents: 3-bromophenyl bis(2,4-dimethoxybenzyl)sulfamate (**132**) (900 mg, 1.63 mmol), dimethoxyethane (11.4 mL), 2 M aq. solution of sodium bicarbonate (1.63 mL, 3.26 mmol), 2-aminophenylboronic acid pinacol ester (428 mg, 1.95 mmol) and [1,1′ bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with DCM (67 mg, 0.08 mmol). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 7:3) to yield the *title compound* as a brown oil (755 mg, 82%); R_f = 0.31 (petrol:EtOAc, 7:3; ninhydrin); λ_{max} (EtOH)/nm 225.5; IR (neat) ν_{max}/cm^{-1} 3442, 3360, 1610, 1582, 1503, 1458, 1350, 1289, 1208, 1154; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.69 (6H, s, 2 × ArOCH_3), 3.73 (2H, s, ArNH_2), 3.77 (6H, s, 2 × ArOCH_3), 4.46 (4H, s, 2 × ArCH_2), 6.36 (2H, d, *J* = 2.4 Hz, H-3”), 6.43 (2H, dd, *J* = 8.4, 2.4 Hz, H-5”), 6.75 (1H, dd, *J* = 7.9, 1.1 Hz, H-3’), 6.81 (1H, ddd, *J* = 7.5, 7.5 and 1.2 Hz, H-5’), 7.08 – 7.04 (2H, m, H-2 and H-6’), 7.18 – 7.11 (2H, m, H-4 and H-4’), 7.28 (2H, d, *J* = 8.4 Hz, H-6”), 7.34 – 7.31 (1H, m, H-6), 7.38 (1H, dd, *J* = 7.7, 7.7 Hz, H-5); ^{13}C NMR (126 MHz, $CDCl_3$) δ 47.1 (Ar*C*H$_2$), 55.2 (ArO*C*H$_3$), 55.5 (ArO*C*H$_3$), 98.3 (C-3”), 104.1 (C-5”), 115.8 (C-3’), 116.7 (C-1”), 118.7 (C-5’), 120.8 (C-4), 122.8 (C-2), 126.3 (C-2’), 127.2 (C-6), 129.0 (C-4’), 130.0 (C-5), 130.5 (C-6’), 131.1 (C-6”), 141.2 (C-1 or C-1’), 143.6 (C-1 or C-1’), 150.8 (C-3), 158.6 (C-2” or C-4”), 160.7 (C-2” or C-4”); LRMS (ES$^+$) *m/z* 565.4 [M+H]$^+$; HRMS (ESI) calcd for $C_{30}H_{33}N_2O_7S$ [M+H]$^+$ 565.2003, found 565.1992.

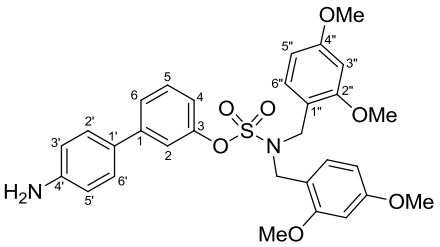
3'-Amino-[1,1'-biphenyl]-3-yl bis(2,4-dimethoxybenzyl)sulfamate, (137)



Compound **137** was synthesised according to general procedure I, using the following reagents: 3-bromophenyl bis(2,4-dimethoxybenzyl)sulfamate (**132**) (900 mg, 1.63 mmol), dimethoxyethane (11.4 mL), 2 M aq. solution of sodium bicarbonate (1.63 mL,

3.26 mmol), 3-aminophenylboronic acid pinacol ester (428 mg, 1.95 mmol) and [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with DCM (67 mg, 0.08 mmol). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 6:4) to yield the *title compound* as a brown oil (709 mg, 77%); R_f = 0.30 (petrol:EtOAc, 6:4; ninhydrin); λ_{max} (EtOH)/nm 221.5; IR (neat) ν_{max}/cm^{-1} 3465, 3379, 1610, 1588, 1507, 1464, 1367, 1291, 1207, 1156, 1132, 1034, 845; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.68 (6H, s, 2 × ArOCH_3), 3.79 (6H, s, 2 × ArOCH_3), 4.45 (4H, s, 2 × ArCH_2), 6.39 (2H, d, *J* = 2.4 Hz, H-3”), 6.45 (2H, dd, *J* = 8.4, 2.4 Hz, H-5”), 6.69 (1H, ddd, *J* = 7.9, 2.3 and 1.0 Hz, H-4’), 6.77 (1H, dd, *J* = 2.3, 1.2 Hz, H-2’), 6.90 (1H, ddd, *J* = 7.8, 1.2 and 1.2 Hz, H-6’), 7.03 (1H, dd, *J* = 2.3, 2.1 Hz, H-2), 7.13 (1H, ddd, *J* = 8.0, 2.3 and 1.1 Hz, H-4), 7.21 (1H, dd, *J* = 7.9, 7.8 Hz, H-5’), 7.30 (2H, d, *J* = 8.3 Hz, H-6”), 7.33 (1H, dd, *J* = 8.0, 7.9 Hz, H-5), 7.44 – 7.40 (1H, m, H-6); ^{13}C NMR (126 MHz, $CDCl_3$) δ 47.1 (Ar*C*H_2), 55.2 (ArO*C*H_3), 55.5 (ArO*C*H_3), 98.4 (C-3”), 104.1 (C-5”), 113.9 (C-2’), 114.6 (C-4’), 116.9 (C-1”), 117.6 (C-6’), 120.6 (C-2 or C-4), 120.8 (C-2 or C-4), 125.1 (C-6), 129.7 (C-5 or C-5’), 129.8 (C-5 or C-5’), 131.2 (C-6”), 141.1 (C-1 or C-1’), 143.0 (C-1 or C-1’), 147.0 (C-3’), 150.8 (C-3), 158.6 (C-2” or C-4”), 160.7 (C-2” or C-4”); LRMS (ES$^+$) *m/z* 565.5 [M+H]$^+$; HRMS (ESI) calcd for $C_{30}H_{33}N_2O_7S$ [M+H]$^+$ 565.2003, found 565.2000.

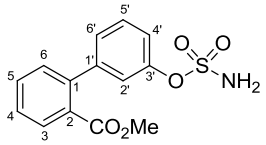
4'-Amino-[1,1'-biphenyl]-3-yl bis(2,4-dimethoxybenzyl)sulfamate, (138)



Compound **138** was synthesised according to general procedure I, using the following reagents: 3-bromophenyl bis(2,4-dimethoxybenzyl)sulfamate (**132**) (500 mg, 0.90 mmol), dimethoxyethane (6.3 mL), 2 M aq. solution of sodium bicarbonate (0.91 mL, 1.81 mmol), 4-aminobenzeneboronic acid pinacol ester (238 mg, 1.09 mmol) and [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with DCM (37 mg, 0.04 mmol). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 1:1) to yield the *title compound* as a brown oil (368 mg, 72%); R_f = 0.33 (petrol:EtOAc, 1:1; ninhydrin); λ_{max} (EtOH)/nm 283.0; IR (neat) ν_{max}/cm^{-1} 3468, 3380, 1610, 1587, 1507, 1364, 1290, 1207, 1156, 1130; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.70 (6H, s, 2 × ArOCH_3), 3.75 (2H, s, ArNH_2), 3.79 (6H, s, 2 × ArOCH_3), 4.48 (4H, s,

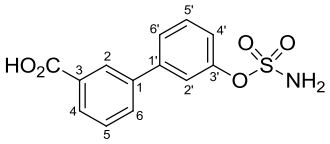
2 × ArCH_2), 6.38 (2H, d, *J* = 2.4 Hz, H-3”), 6.44 (2H, dd, *J* = 8.4, 2.4 Hz, H-5”), 6.74 (2H, d, *J* = 8.5 Hz, H-3’, 5’), 7.05 (1H, ddd, *J* = 8.3, 2.5 and 1.0 Hz, H-4), 7.14 (1H, dd, *J* = 2.5, 2.1 Hz, H-2), 7.29 (2H, d, *J* = 8.4 Hz, H-6”), 7.31 (1H, dd, *J* = 8.3, 7.7 Hz, H-5), 7.33 (2H, d, *J* = 8.5 Hz, H-2’, 6’), 7.41 – 7.36 (1H, m, H-6); ^{13}C NMR (126 MHz, $CDCl_3$) δ 47.1 (Ar*C*H_2), 55.2 (ArO*C*H_3), 55.5 (ArO*C*H_3), 98.3 (C-3”), 104.1 (C-5”), 115.4 (C-3’, 5’), 116.8 (C-1”), 119.7 (C-2 or C-4), 119.8 (C-2 or C-4), 124.3 (C-6), 128.2 (C-2’, 6’), 129.7 (C-5), 130.2 (C-4’), 131.2 (C-6”), 142.9 (C-1 or C-1’), 146.4 (C-1 or C-1’), 150.9 (C-3), 158.6 (C-2” or C-4”), 160.7 (C-2” or C-4”); LRMS (ES$^+$) *m/z* 565.4 $[M+H]^+$; HRMS (ESI) calcd for $C_{30}H_{33}N_2O_7S$ $[M+H]^+$ 565.2003, found 565.1998.

Methyl 3'-(sulfamoyloxy)-[1,1'-biphenyl]-2-carboxylate, (139)



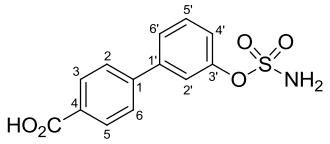
Compound **139** was synthesised according to general procedure D, using the following reagents: methyl 3'-((*N*,*N*-bis(2,4-dimethoxybenzyl)sulfamoyl)oxy)-[1,1'-biphenyl]-2-carboxylate (**133**) (250 mg, 0.41 mmol), DCM (3.7 mL) and TFA (0.4 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 6:4) to yield the *title compound* as a pale yellow oil (112 mg, 88%); R_f = 0.34 (petrol:EtOAc, 6:4); λ_{max} (EtOH)/nm 280.0; IR (neat) ν_{max}/cm^{-1} 3364, 3263, 1708, 1568, 1375, 1292, 1264, 1190; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.61 (s, 3H, $ArCO_2CH_3$), 7.19 (dd, *J* = 2.0, 2.0 Hz, 1H, H-2’), 7.31 – 7.24 (m, 2H, H-4’ and H-6’), 7.47 (dd, *J* = 7.7, 1.2 Hz, 1H, H-3), 7.51 – 7.49 (m, 1H, H-5’), 7.55 – 7.51 (m, 1H, H-4 or H-5), 7.66 (ddd, *J* = 7.6, 7.6, 1.4 Hz, 1H, H-4 or H-5), 7.77 (dd, *J* = 7.7, 1.4 Hz, 1H, H-6), 8.05 (s, 2H, $ArOSO_2NH_2$); ^{13}C NMR (126 MHz, DMSO-d_6) δ 52.1 ($ArCO_2CH_3$), 121.0 (C-4’ or C-6’), 121.8 (C-2’), 126.3 (C-4’ or C-6’), 127.9 (C-4 or C-5), 129.4 (C-6), 129.6 (C-5’), 130.6 (C-3), 130.7 (C-2), 131.6 (C-4 or C-5), 139.9 (C-1 or C-1’), 142.0 (C-1 or C-1’), 149.9 (C-3’), 168.2 ($ArCO_2CH_3$); LRMS (ES$^-$) *m/z* 306.1 $[M-H]^-$; HRMS (ESI) calcd for $C_{14}H_{12}NO_5S$ $[M-H]^-$ 306.0442, found 306.0442.

3'-(Sulfamoyloxy)-[1,1'-biphenyl]-3-carboxylic acid, (140)



Compound **140** was synthesised according to general procedure D, using the following reagents: 3'-((*N*,*N*-bis(2,4-dimethoxybenzyl)sulfamoyl)oxy)-[1,1'-biphenyl]-3-carboxylic acid (**134**) (250 mg, 0.42 mmol), DCM (3.8 mL) and TFA (0.5 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc:AcOH, 1:0:0 → 50:49.5:0.5) to yield the *title compound* as a pale pink solid (102 mg, 82%); R_f = 0.29 (petrol:EtOAc:AcOH, 50:49.5:0.5); m.p. 168.0-170.0 °C; λ_{max} (EtOH)/nm 250.0; IR (neat) ν_{max}/cm^{-1} 3368, 3274, 1677, 1606, 1577, 1459, 1362, 1312; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.37 – 7.28 (1H, m, H-4'), 7.58 (1H, dd, *J* = 7.8, 7.8 Hz, H-5 or H-5'), 7.60 (1H, dd, *J* = 2.0, 2.0 Hz, H-2'), 7.63 (1H, dd, *J* = 7.7, 7.7 Hz, H-5 or H-5'), 7.71 – 7.66 (1H, m, H-6'), 7.95 (1H, ddd, *J* = 7.8, 1.4 and 1.4 Hz, H-4 or H-6), 7.98 (1H, ddd, *J* = 7.6, 1.3 and 1.3 Hz, H-4 or H-6), 8.06 (2H, s, $ArOSO_2NH_2$), 8.21 (1H, dd, *J* = 1.8, 1.8 Hz, H-2), 13.13 (1H, s, $ArCO_2H$); ^{13}C NMR (126 MHz, DMSO-d_6) δ 120.6 (C-2'), 121.8 (C-4'), 125.0 (C-6'), 127.4 (C-2), 128.8 (C-4 or C-6), 129.5 (C-5 or C-5'), 130.5 (C-5 or C-5'), 131.3 (C-4 or C-6), 131.6 (C-3), 139.4 (C-1 or C-1'), 141.0 (C-1 or C-1'), 150.8 (C-3'), 167.1 ($ArCO_2H$); LRMS (ES$^-$) *m/z* 292.1 [M-H]$^-$; HRMS (ESI) calcd for $C_{13}H_{10}NO_5S$ [M-H]$^-$ 292.0285, found 292.0286.

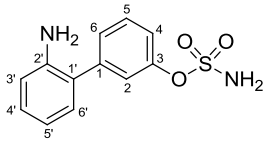
3'-(Sulfamoyloxy)-[1,1'-biphenyl]-4-carboxylic acid, (141)



Compound **141** was synthesised according to general procedure D, using the following reagents: 3'-((*N*,*N*-bis(2,4-dimethoxybenzyl)sulfamoyl)oxy)-[1,1'-biphenyl]-4-carboxylic acid (**135**) (250 mg, 0.42 mmol), DCM (3.8 mL) and TFA (0.5 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc:AcOH, 1:0:0 → 50:49.5:0.5) to yield the *title compound* as an off-white solid (112 mg, 90%); R_f = 0.26 (petrol:EtOAc:AcOH, 50:49.5:0.5); m.p. 190.0-192.0 °C; λ_{max} (EtOH)/nm 266.0; IR (neat) ν_{max}/cm^{-1} 3393, 3300, 1680, 1608, 1378, 1368, 1301, 1201, 1150, 912; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.34 (1H, ddd, *J* = 8.2, 2.3 and 1.3 Hz, H-4'), 7.59 (1H, dd, *J* = 8.2, 7.9 Hz, H-5'), 7.62 (1H, dd, *J* = 2.3, 1.3 Hz, H-2'), 7.71 (ddd, *J* = 7.7, 1.3 and 1.3 Hz, 1H, H-6'), 7.82 (2H, d, *J* = 8.3 Hz, H-2, 6), 8.05 (2H, d, *J* = 8.3 Hz, H-3, 5), 8.06

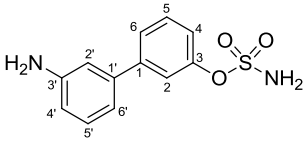
(2H, s, $ArOSO_2NH_2$), 12.98 (brs, 1H, $ArCO_2H$); ^{13}C NMR (126 MHz, DMSO-d_6) δ 120.7 (C-2'), 122.1 (C-4'), 125.2 (C-6'), 127.0 (C-2, 6), 130.0 (C-3, 5), 130.1 (C-4), 130.5 (C-5'), 140.8 (C-1 or C-1'), 143.1 (C-1 or C-1'), 150.7 (C-3'), 167.0 ($ArCO_2H$); LRMS (ES^-) *m/z* 292.1 $[M-H]^-$; HRMS (ESI) calcd for $C_{13}H_{10}NO_5S$ $[M-H]^-$ 292.0285, found 292.0277.

2'-Amino-[1,1'-biphenyl]-3-yl sulfamate, (142)



Compound **142** was synthesised according to general procedure D, using the following reagents: 2'-amino-[1,1'-biphenyl]-3-yl bis(2,4-dimethoxybenzyl)sulfamate (**136**) (330 mg, 0.58 mmol), DCM (5.3 mL) and TFA (0.6 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 6:4) to yield the *title compound* as a brown solid (128 mg, 83%); R_f = 0.29 (petrol:EtOAc, 6:4; ninhydrin); m.p. 101.5-103.5 °C; λ_{max} (EtOH)/nm 225.0; IR (neat) ν_{max}/cm^{-1} 3358, 1611, 1474, 1357, 1186, 1147; ^1H NMR (500 MHz, DMSO-d_6) δ 4.89 (2H, s, $ArNH_2$), 6.64 (1H, ddd, *J* = 7.4, 7.4 and 1.2 Hz, H-5'), 6.76 (1H, dd, *J* = 8.0, 1.2 Hz, H-3'), 7.01 (1H, dd, *J* = 7.6, 1.6 Hz, H-6'), 7.07 (1H, ddd, *J* = 8.4, 7.3 and 1.6 Hz, H-4'), 7.23 (1H, ddd, *J* = 8.2, 2.3 and 1.3 Hz, H-4), 7.40 – 7.33 (2H, m, H-2 and H-6), 7.53 (1H, dd, *J* = 8.2, 8.2 Hz, H-5), 7.98 (2H, s, $ArOSO_2NH_2$); ^{13}C NMR (126 MHz, DMSO-d_6) δ 115.3 (C-3'), 116.7 (C-5'), 120.8 (C-4), 122.4 (C-2), 124.3 (C-2'), 127.0 (C-6), 128.6 (C-4'), 130.0 (C-5 or C-6'), 130.1 (C-5 or C-6'), 141.4 (C-1 or C-1'), 145.1 (C-1 or C-1'), 150.2 (C-3); LRMS (ES^-) *m/z* 263.2 $[M-H]^-$; HRMS (ESI) calcd for $C_{12}H_{11}N_2O_3S$ $[M-H]^-$ 263.0496, found 263.0497.

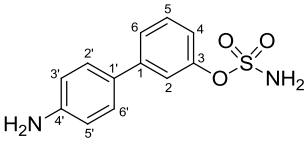
3'-Amino-[1,1'-biphenyl]-3-yl sulfamate, (143)



Compound **143** was synthesised according to general procedure D, using the following reagents: 3'-amino-[1,1'-biphenyl]-3-yl bis(2,4-dimethoxybenzyl)sulfamate (**137**) (150 mg, 0.27 mmol), DCM (2.4 mL) and TFA (0.3 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 1:1) to yield the *title compound* as a brown solid (42 mg, 82%); R_f = 0.33 (petrol:EtOAc, 1:1; ninhydrin); m.p. 106.5-108.5 °C; λ_{max} (EtOH)/nm 235.5; IR (neat) ν_{max}/cm^{-1} 3413, 3340, 3292, 3040, 1605, 1576, 1473,

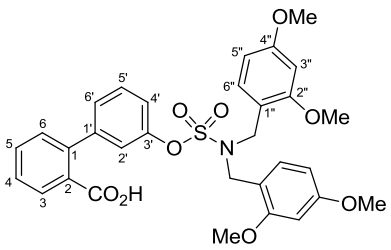
1362, 1230, 1146; ^{1}H NMR (500 MHz, DMSO-d_6) δ 5.21 (2H, s, ArNH_2), 6.59 (1H, ddd, J = 8.0, 2.3 and 1.0 Hz, H-4'), 6.81 – 6.76 (1H, m, H-6'), 6.84 (1H, dd, J = 2.0, 2.0 Hz, H-2'), 7.12 (1H, dd, J = 7.8, 7.8 Hz, H-5'), 7.28 – 7.19 (1H, m, H-4), 7.47 – 7.39 (1H, m, H-2), 7.54 – 7.47 (2H, m, H-5 and H-6), 8.02 (2H, s, ArOSO$_2$NH_2); ^{13}C NMR (126 MHz, DMSO-d_6) δ 112.0 (C-2'), 113.6 (C-4'), 114.3 (C-6), 120.1 (C-2), 120.8 (C-4), 124.6 (C-6), 129.5 (C-5'), 130.0 (C-5), 139.7 (C-1 or C-1'), 142.9 (C-1 or C-1'), 149.2 (C-3 or C-3'), 150.5 (C-3 or C-3'); LRMS (ES$^-$) *m/z* 263.2 [M-H]$^-$; HRMS (ESI) calcd for $C_{12}H_{11}N_2O_3S$ [M-H]$^-$ 263.0496, found 263.0498.

4'-Amino-[1,1'-biphenyl]-3-yl sulfamate, (144)



Compound **144** was synthesised according to general procedure D, using the following reagents: 4'-amino-[1,1'-biphenyl]-3-yl bis(2,4-dimethoxybenzyl)sulfamate (**138**) (110 mg, 0.19 mmol), DCM (1.7 mL) and TFA (0.2 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 4:6) to yield the *title compound* as a pale brown solid (42 mg, 82%); R_f = 0.29 (petrol:EtOAc, 4:6; ninhydrin); m.p. 144.5-146.5 °C; λ_{max} (EtOH)/nm 287.5; IR (neat) ν_{max}/cm^{-1} 3417, 3342, 2901, 1604, 1573, 1525, 1480, 1363, 1149, 910; ^{1}H NMR (500 MHz, DMSO-d_6) δ 5.32 (2H, s, ArNH_2), 6.65 (2H, d, J = 8.4 Hz, H-3', 5'), 7.11 (1H, ddd, J = 8.4, 2.3 and 1.0 Hz, H-4), 7.37 (2H, d, J = 8.5 Hz, H-2', 6'), 7.41 (1H, dd, J = 2.0, 2.0 Hz, H-2), 7.43 (1H, dd, J = 7.9, 7.9 Hz, H-5), 7.51 – 7.46 (1H, m, H-6), 7.98 (2H, s, ArOSO$_2$NH_2); ^{13}C NMR (126 MHz, DMSO-d_6) δ 114.2 (C-3', 5'), 118.9 (C-2), 119.2 (C-4), 123.4 (C-6), 126.1 (C_q Ar), 127.3 (C-2', 6'), 129.9 (C-5), 142.6 (C_q Ar), 148.9 (C_q Ar), 150.7 (C_q Ar); LRMS (ES$^-$) *m/z* 263.2 [M-H]$^-$; HRMS (ESI) calcd for $C_{12}H_{11}N_2O_3S$ [M-H]$^-$ 263.0496, found 263.0497

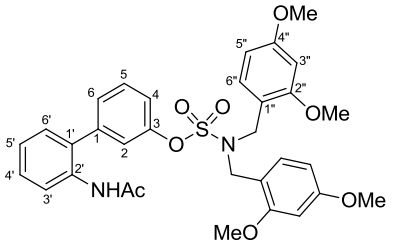
3'-((*N*,*N*-Bis(2,4-dimethoxybenzyl)sulfamoyl)oxy)-[1,1'-biphenyl]-2-carboxylic acid, (145)



To methyl 3'-((*N*,*N*-bis(2,4-dimethoxybenzyl)sulfamoyl)oxy)-[1,1'-biphenyl]-2-carboxylate (**133**) (300 mg, 0.49 mmol) in THF (5 mL) was added a 2M aq. solution of lithium

hydroxide (2.47 mL, 4.94 mmol). The resulting mixture was heated at 60 °C for 18 h. Upon completion, the mixture was acidified to pH 3 using a 4 M aq. solution of HCl. The reaction was then diluted with water (20 mL) and extracted with EtOAc (3 × 25 mL). The pooled organic extracts were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel, petrol:EtOAc:AcOH, 1:0:0 → 50:49.5:0.5) to yield the *title compound* as a yellow oil (235 mg, 80%); R_f = 0.28 (petrol:EtOAc:AcOH, 50:49.5:0.5); λ_{max} (EtOH)/nm 275.5; IR (neat) ν_{max}/cm^{-1} 2945, 1693, 1610, 1586, 1506, 1458, 1353, 1292, 1209, 1177, 1154, 1037, 890; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.68 (6H, s, 2 × ArOC*H*$_3$), 3.73 (6H, s, 2 × ArOC*H*$_3$), 4.41 (4H, s, 2 × ArC*H*$_2$), 6.33 (2H, d, *J* = 2.4 Hz, H-3”), 6.41 (2H, dd, *J* = 8.3, 2.4 Hz, H-5”), 6.79 (1H, dd, *J* = 2.3, 2.0 Hz, H-2’), 7.13 (1H, ddd, *J* = 8.1, 2.3 and 1.0 Hz, H-4’ or H-6’), 7.19 – 7.15 (1H, m, H-4’ or H-6’), 7.27 (3H, d, *J* = 8.3 Hz, H-3 and H-6”), 7.32 (1H, dd, *J* = 8.1, 7.9 Hz, H-5’), 7.44 (1H, ddd, *J* = 7.6, 7.6 and 1.3 Hz, H-4 or H-5), 7.56 (1H, ddd, *J* = 7.6, 7.5 and 1.5 Hz, H-4 or H-5), 7.94 (1H, dd, *J* = 7.8, 1.5 Hz, H-6); ^{13}C NMR (126 MHz, $CDCl_3$) δ 47.2 (Ar*C*H$_2$), 55.2 (ArO*C*H$_3$), 55.5 (ArO*C*H$_3$), 98.4 (C-3”), 104.3 (C-5”), 116.8 (C-1”), 121.2 (C-4’ or C-6’), 122.3 (C-2’), 126.7 (C-4’ or C-6’), 127.7 (C-4 or C-5), 129.2 (C-5’), 129.3 (C-2), 130.9 (C-3), 131.1 (C-6”), 131.2 (C-6), 132.1 (C-4 or C-5), 142.3 (C-1 or C-1’), 143.0 (C-1 or C-1’), 150.1 (C-3’), 158.4 (C-2” or C-4”), 160.7 (C-2” or C-4”), 171.2 (Ar*C*O$_2$H); LRMS (ES$^-$) *m/z* 592.3 [M-H]$^-$; HRMS (ESI) calcd for $C_{31}H_{30}NO_9S$ [M-H]$^-$ 592.1647, found 592.1643.

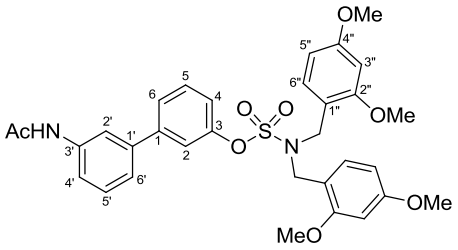
2'-Acetamido-[1,1'-biphenyl]-3-yl bis(2,4-dimethoxybenzyl)sulfamate, (146)



Compound **146** was synthesised according to general procedure J, using the following reagents: 2'-amino-[1,1'-biphenyl]-3-yl bis(2,4-dimethoxybenzyl)sulfamate (**136**) (180 mg, 0.32 mmol), triethylamine (65 mg, 89 µL, 0.64 mmol), acetic anhydride (39 mg, 36 µL, 0.38 mmol) and DCM (3.2 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 1:1) to yield the *title compound* as a pale yellow oil (168 mg, 87%); R_f = 0.32 (petrol:EtOAc, 1:1); No λ_{max} (EtOH)/nm; IR (neat) ν_{max}/cm^{-1} 1680, 1611, 1586, 1507, 1368, 1290, 1208, 1156, 1132, 1032, 887; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.03 (3H, s, C*H*$_3$CO), 3.71 (6H, s, 2 × ArOC*H*$_3$), 3.76 (6H, s,

2 × ArOCH_3), 4.49 (4H, s, 2 × ArCH_2), 6.38 (2H, d, *J* = 2.4 Hz, H-3”), 6.44 (2H, dd, *J* = 8.4, 2.4 Hz, H-5”), 7.00 (1H, dd, *J* = 2.0, 2.0 Hz, H-2), 7.25 – 7.12 (4H, m, 4 × Ar*H*), 7.28 (2H, d, *J* = 8.4 Hz, H-6”), 7.38 (1H, ddd, *J* = 8.5, 7.0 and 2.0 Hz, H-4’ or H-5’), 7.44 (1H, dd, *J* = 7.9, 7.9 Hz, H-5), 8.28 (1H, d, *J* = 8.2 Hz, H-3’); ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.7 (*C*H_3CO), 47.3 (Ar*C*H_2), 55.3 (ArO*C*H_3), 55.5 (ArO*C*H_3), 98.4 (C-3”), 104.1 (C-5”), 116.6 (C-1”), 121.7 (CH Ar), 122.0 (C-3’), 123.3 (C-2), 124.4 (CH Ar), 127.5 (CH Ar), 128.9 (C-4’ or C-5’), 130.0 (CH Ar), 130.5 (C-5), 130.9 (C_q Ar), 131.1 (C-6”), 134.9 (C_q Ar), 139.8 (C_q Ar), 150.7 (C-3), 158.6 (C-2” or C-4”), 160.8 (C-2” or C-4”), 168.8 (*C*OCH_3); LRMS (ES^-) *m/z* 605.3 $[M-H]^-$; HRMS (ESI) calcd for $C_{32}H_{33}N_2O_8S$ $[M-H]^-$ 605.1963, found 605.1965.

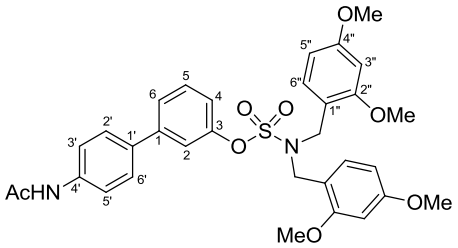
3'-Acetamido-[1,1'-biphenyl]-3-yl bis(2,4-dimethoxybenzyl)sulfamate, (147)



Compound **147** was synthesised according to general procedure J, using the following reagents: 3'-amino-[1,1'-biphenyl]-3-yl bis(2,4-dimethoxybenzyl)sulfamate (**137**) (180 mg, 0.32 mmol), triethylamine (65 mg, 89 µL, 0.64 mmol), acetic anhydride (39 mg, 36 µL, 0.38 mmol) and DCM (3.2 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 4:6) to yield the *title compound* as a pale yellow oil (172 mg, 89%); R_f = 0.29 (petrol:EtOAc, 4:6); λ_{max} (EtOH)/nm 235.0; IR (neat) ν_{max}/cm^{-1} 1669, 1610, 1589, 1507, 1368, 1207, 1156, 1133, 1035; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.24 (3H, s, C*H*$_3$CO), 3.67 (6H, s, 2 × ArOC*H*$_3$), 3.81 (6H, s, 2 × ArOC*H*$_3$), 4.43 (4H, s, 2 × ArC*H*$_2$), 6.39 (2H, d, *J* = 2.4 Hz, H-3”), 6.47 (2H, dd, *J* = 8.4, 2.4 Hz, H-5”), 6.83 (1H, dd, *J* = 2.0, 2.0 Hz, H-2), 7.17 (1H, ddd, *J* = 8.2, 2.4 and 1.1 Hz, Ar*H*), 7.25 – 7.22 (2H, m, 2 × Ar*H*), 7.32 (2H, d, *J* = 8.4 Hz, H-6”), 7.35 (1H, dd, *J* = 7.9, 7.9 Hz, H-5 or H-5’), 7.39 (1H, dd, *J* = 7.8, 7.8 Hz, H-5 or H-5’), 7.45 – 7.41 (1H, m, H-6), 7.59 (1H, s, N*H*Ac), 7.81 (1H, ddd, *J* = 8.3, 1.4 and 1.4 Hz, H-4’); ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.8 (*C*H_3CO), 47.2 (Ar*C*H_2), 55.2 (ArO*C*H_3), 55.6 (ArO*C*H_3), 98.5 (C-3”), 104.2 (C-5”), 117.0 (C-1”), 118.3 (CH Ar), 119.5 (C-4’), 120.5 (C-2), 121.3 (CH Ar), 123.0 (CH Ar), 125.1 (C-6), 129.7 (C-5 or C-5’), 129.9 (C-5 or C-5’), 131.4 (C-6”), 138.6 (C_q Ar), 140.6 (C_q Ar), 142.1 (C_q Ar), 150.9 (C-3), 158.7 (C-2” or C-4”), 160.6 (C-2” or C-4”), 168.5

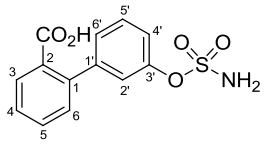
(*C*OCH$_3$); LRMS (ES$^-$) *m/z* 605.4 [M-H]$^-$; HRMS (ESI) calcd for $C_{32}H_{33}N_2O_8S$ [M-H]$^-$ 605.1963, found 605.1961.

4'-Acetamido-[1,1'-biphenyl]-3-yl bis(2,4-dimethoxybenzyl)sulfamate, (148)



Compound **148** was synthesised according to general procedure J, using the following reagents: 4'-amino-[1,1'-biphenyl]-3-yl bis(2,4-dimethoxybenzyl)sulfamate (**138**) (150 mg, 0.27 mmol), triethylamine (54 mg, 74 µL, 0.53 mmol), acetic anhydride (33 mg, 30 µL, 0.32 mmol) and DCM (2.7 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 2:8) to yield the *title compound* as an orange oil (142 mg, 88%); R_f = 0.34 (petrol:EtOAc, 2:8); λ_{max} (EtOH)/nm 277.0; IR (neat) ν_{max}/cm^{-1} 1666, 1599, 1532, 1506, 1379, 1207, 1155, 1125, 1038, 893; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.20 (3H, s, C*H*$_3$CO), 3.70 (6H, s, 2 × ArOC*H*$_3$), 3.78 (6H, s, 2 × ArOC*H*$_3$), 4.47 (4H, s, 2 × ArC*H*$_2$), 6.37 (2H, d, *J* = 2.4 Hz, H-3”), 6.43 (2H, dd, *J* = 8.4, 2.4 Hz, H-5”), 7.15 – 7.08 (2H, m, H-2 and H-4), 7.28 (2H, d, *J* = 8.4 Hz, H-6”), 7.32 (1H, s, N*H*Ac), 7.34 (1H, dd, *J* = 7.9, 7.9 Hz, H-5), 7.42 – 7.38 (1H, m, H-6), 7.44 (2H, d, *J* = 8.5 Hz, H-2’, 6’), 7.57 (2H, d, *J* = 8.5 Hz, H-3’, 5’); ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.8 (*C*H$_3$CO), 47.1 (ArC*H*$_2$), 55.2 (ArO*C*H$_3$), 55.5 (ArO*C*H$_3$), 98.3 (C-3”), 104.1 (C-5”), 116.7 (C-1”), 120.1 (C-2’, 6’), 120.3 (C-2 or C-4), 120.6 (C-2 or C-4), 124.8 (C-6), 127.8 (C-3’, 5’), 129.9 (C-5), 131.2 (C-6”), 135.8 (C_q Ar), 137.8 (C_q Ar), 142.2 (C_q Ar), 150.9 (C-3), 158.6 (C-2” or C-4”), 160.7 (C-2” or C-4”), 168.4 (*C*OCH$_3$); LRMS (ES$^-$) *m/z* 605.4 [M-H]$^-$; HRMS (ESI) calcd for $C_{32}H_{33}N_2O_8S$ [M-H]$^-$ 605.1963, found 605.1961.

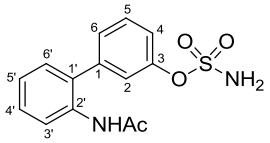
3'-(Sulfamoyloxy)-[1,1'-biphenyl]-2-carboxylic acid, (149)



Compound **149** was synthesised according to general procedure D, using the following reagents: 3'-((*N*,*N*-bis(2,4-dimethoxybenzyl)sulfamoyl)oxy)-[1,1'-biphenyl]-2-carboxylic acid (**145**) (200 mg, 0.34 mmol), DCM (3.1 mL) and TFA (0.4 mL). The crude product

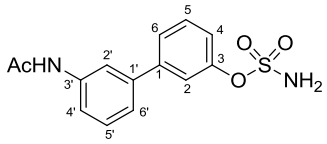
was purified by column chromatography (silica gel, petrol:EtOAc:AcOH, 1:0:0 → 50:49.5:0.5) to yield the *title compound* as a pale pink solid (88 mg, 89%); R_f = 0.26 (petrol:EtOAc:AcOH, 50:49.5:0.5); m.p. 162.0-164.0 °C; λ_{max} (EtOH)/nm 280.0; IR (neat) ν_{max}/cm^{-1} 3370, 3269, 1697, 1477, 1346, 1311, 1200, 1180; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.25 (1H, dd, *J* = 2.0, 2.0 Hz, H-2'), 7.34 – 7.26 (2H, m, H-4' and H-6'), 7.43 (1H, dd, *J* = 7.8, 1.2 Hz, H-3), 7.54 – 7.46 (2H, m, 2 × Ar*H*), 7.61 (1H, ddd, *J* = 7.6, 7.6 and 1.4 Hz, H-4), 7.77 (1H, dd, *J* = 7.8, 1.4 Hz, H-6), 8.04 (2H, s, $ArOSO_2NH_2$), 12.83 (1H, brs, $ArCO_2H$); ^{13}C NMR (126 MHz, DMSO-d_6) δ 120.9 (C-4' or C-6'), 122.0 (C-2'), 126.6 (C-4' or C-6'), 127.8 (CH Ar), 129.3 (CH Ar), 129.4 (CH Ar), 130.6 (CH Ar), 131.1 (C-3), 132.1 (C-2), 139.7 (C-1 or C-1'), 142.4 (C-1 or C-1'), 149.9 (C-3'), 169.3 ($ArCO_2H$); LRMS (ES$^-$) *m/z* 292.2 [M-H]$^-$; HRMS (ESI) calcd for $C_{13}H_{10}NO_5S$ [M-H]$^-$ 292.0285, found 292.0286.

2'-Acetamido-[1,1'-biphenyl]-3-yl sulfamate, (150)



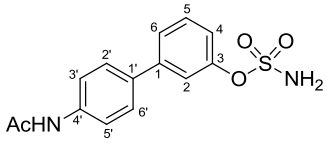
Compound **150** was synthesised according to general procedure D, using the following reagents: 2'-acetamido-[1,1'-biphenyl]-3-yl bis(2,4-dimethoxybenzyl)sulfamate (**146**) (130 mg, 0.21 mmol), DCM (1.8 mL) and TFA (0.2 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 4:6) to yield the *title compound* as a white solid (57 mg, 86%); R_f = 0.30 (petrol:EtOAc, 4:6); m.p. 164.5-166.5 °C; No λ_{max} (EtOH)/nm; IR (neat) ν_{max}/cm^{-1} 3297, 3038, 1616, 1589, 1382, 1366, 1197, 1147, 892; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.90 (3H, s, C*H*$_3$CO), 7.44 - 7.17 (6H, m, 6 × Ar*H*), 7.65 – 7.44 (2H, m, 2 × Ar*H*), 8.00 (2H, s, $ArOSO_2NH_2$), 9.26 (1H, s, ArN*H*Ac); ^{13}C NMR (126 MHz, DMSO-d_6) δ 23.1 (*C*H$_3$CO), 121.1 (CH Ar), 122.4 (CH Ar), 125.9 (CH Ar), 127.0 (CH Ar), 128.1 (CH Ar), 129.8 (CH Ar), 130.2 (CH Ar), 134.9 (C_q Ar), 135.1 (C_q Ar), 140.6 (C_q Ar), 150.0 (C-3), 168.8 (*C*OCH$_3$); LRMS (ES$^+$) *m/z* 307.2 [M+H]$^+$; HRMS (ESI) calcd for $C_{14}H_{15}N_2O_4S$ [M+H]$^+$ 307.0747, found 307.0750.

3'-Acetamido-[1,1'-biphenyl]-3-yl sulfamate, (151)



Compound **151** was synthesised according to general procedure D, using the following reagents: 3'-acetamido-[1,1'-biphenyl]-3-yl bis(2,4-dimethoxybenzyl)sulfamate (**147**) (130 mg, 0.21 mmol), DCM (1.8 mL) and TFA (0.2 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 3:7) to yield the *title compound* as a white solid (60 mg, 91%); R_f = 0.30 (petrol:EtOAc, 3:7); m.p. 152.0-154.0 °C; λ_{max} (EtOH)/nm 242.0; IR (neat) ν_{max}/cm^{-1} 3356, 3219, 1653, 1554, 1364, 1186; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.07 (3H, s, CH_3CO), 7.31 – 7.25 (1H, m, Ar*H*), 7.34 (1H, d, *J* = 7.7 Hz, Ar*H*), 7.41 (1H, dd, *J* = 7.8, 7.8 Hz, H-5), 7.51 – 7.46 (1H, m, H-2), 7.64 – 7.53 (3H, m, 3 × Ar*H*), 7.91 (1H, dd, *J* = 1.9, 1.9 Hz, H-2'), 8.05 (2H, s, ArOSO$_2$NH_2), 10.07 (1H, s, ArN*H*Ac); ^{13}C NMR (126 MHz, DMSO-d_6) δ 24.0 (*C*H$_3$CO), 117.3 (C-2'), 118.6 (CH Ar), 120.3 (C-2), 121.3 (CH Ar), 121.5 (CH Ar), 124.8 (CH Ar), 129.4 (C-5), 130.3 (CH Ar), 139.5 (C$_q$ Ar), 140.0 (C$_q$ Ar), 142.0 (C$_q$ Ar), 150.7 (C-3), 168.5 (*C*OCH$_3$); LRMS (ES$^+$) *m/z* 307.2 [M+H]$^+$; HRMS (ESI) calcd for $C_{14}H_{15}N_2O_4S$ [M+H]$^+$ 307.0747, found 307.0753.

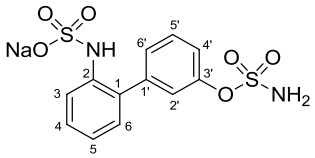
4'-Acetamido-[1,1'-biphenyl]-3-yl sulfamate, (152)



Compound **152** was synthesised according to general procedure D, using the following reagents: 4'-acetamido-[1,1'-biphenyl]-3-yl bis(2,4-dimethoxybenzyl)sulfamate (**148**) (120 mg, 0.20 mmol), DCM (1.8 mL) and TFA (0.2 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 1:9) to yield the *title compound* as a pale orange solid (51 mg, 84%); R_f = 0.32 (petrol:EtOAc, 1:9); m.p. 175.5-177.5 °C; λ_{max} (EtOH)/nm 276.5; IR (neat) ν_{max}/cm^{-1} 3362, 3291, 2976, 1656, 1595, 1528, 1358, 1182; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.07 (3H, s, CH_3CO), 7.23 (1H, dd, *J* = 7.8, 2.5 Hz, H-4), 7.56 – 7.47 (2H, m, H-2 and H-5), 7.65 – 7.58 (3H, m, H-6 and H-2', 6'), 7.69 (2H, d, *J* = 8.3 Hz, H-3', 5'), 8.02 (2H, s, ArOSO$_2$NH_2), 10.06 (1H, s, ArN*H*Ac); ^{13}C NMR (126 MHz, DMSO-d_6) δ 24.1 (*C*H$_3$CO), 119.3 (C-3', 5'), 119.9 (C-2), 120.7 (C-4), 124.4 (C-6), 127.1 (C-2', 6'), 130.2 (C-5), 133.4 (C-4'), 139.3 (C-1 or

C-1'), 141.6 (C-1 or C-1'), 150.7 (C-3), 168.4 (*C*OCH_3); LRMS (ES^+) *m/z* 307.2 $[M+H]^+$; HRMS (ESI) calcd for $C_{14}H_{13}N_2O_4S$ $[M-H]^-$ 305.0602, found 305.0593.

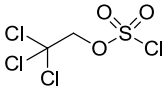
Sodium (3'-(sulfamoyloxy)-[1,1'-biphenyl]-2-yl)sulfamate, (154)



To 2,2,2-trichloroethyl (3'-(sulfamoyloxy)-[1,1'-biphenyl]-2-yl)((2,2,2-trichloroethoxy) sulfonyl)sulfamate (**167**) (110 mg, 0.16 mmol) in MeOH (3.5 mL) were added 3.5 mL of acetate buffer pH 4.65 and zinc (210 mg, 3.20 mmol). The resulting reaction mixture was stirred at RT for 24 h, until LC-MS indicated completion of the deprotection. Upon completion, the heterogeneous mixture was filtered through Celite and washed with MeOH (10 mL). The filtrate was concentrated *in vacuo* to give a crude oil, which was dissolved in a mixture of MeOH (3.5 mL) and acetate buffer pH 4.65 (3.5 mL). Acetic acid was added to acidify the reaction mixture to pH 4.0. The resulting solution was heated at 40 °C for 12 h. Upon completion, the solvents were removed *in vacuo* and the crude product was converted to the sodium salt by ion-exchange chromatography (DOWEX 50WX2 - Na^+ form). The crude product was purified by column chromatography (silica gel, EtOAc:MeOH, 1:0 → 93:7) to yield the *title compound* as a white solid (30 mg, 50%).

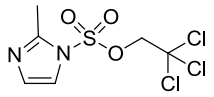
R_f = 0.25 (EtOAc:MeOH, 93:7; $KMnO_4$); m.p. 142.0-144.0 °C; λ_{max} (EtOH)/nm 275.6; IR (neat) ν_{max}/cm^{-1} 3501, 3305, 3205, 3071, 2922, 1670, 1609, 1580, 1475, 1370, 1183, 1149, 1039; ^{1}H NMR (500 MHz, MeOD) δ 7.03 (1H, ddd, *J* = 7.4, 7.4 and 1.2 Hz, H-4), 7.18 (1H, dd, *J* = 7.7, 1.7 Hz, H-3), 7.30 (1H, ddd, *J* = 8.5, 7.9 and 1.6 Hz, H-5), 7.35 (1H, ddd, *J* = 8.2, 2.3 and 1.1 Hz, H-4' or H-6'), 7.42 (1H, ddd, *J* = 7.4, 1.3 and 1.3 Hz, H-4' or H-6'), 7.46 (1H, dd, *J* = 1.9, 1.9 Hz, H-2'), 7.54 (1H, dd, *J* = 7.9, 7.9 Hz, H-5'), 7.72 (1H, dd, *J* = 8.4, 1.2 Hz, H-6); ^{13}C NMR (126 MHz, MeOD) δ 120.4 (C-6), 122.9 (C-4' or C-6'), 123.0 (C-4), 124.5 (C-2'), 128.8 (C-4' or C-6'), 129.6 (C-5), 131.0 (C-3), 131.3 (C-5'), 131.3 (C-1), 139.4 (C-2 or C-1'), 142.0 (C-2 or C-1'), 152.3 (C-3'); LRMS (ES^-) *m/z* 343.2 $[M-Na]^-$; HRMS (ESI) calcd for $C_{12}H_{11}N_2O_6S_2$ $[M-Na]^-$ 343.0064, found 343.0055

2,2,2-Trichlroethyl chlorosulfate, (156)



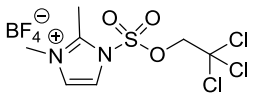
To sulfuryl chloride (6.76 mL, 83.5 mmol) in Et_2O (40 mL), cooled at -78 °C, was added dropwise over 35 min a solution of 2,2,2-trichloroethanol (**155**) (8.00 mL, 12.5 g, 83.5 mmol) and pyridine (6.76 mL, 6.61 g, 83.5 mmol) in Et_2O (40 mL). The resulting mixture was stirred at -78 °C for 1 h and for an additional 2 h at RT. The mixture was then filtered to remove the pyridinium hydrochloride salt by-product and concentrated *in vacuo*. The crude liquid was purified by distillation under reduced pressure using a Kügelrohr distillation apparatus to yield the *title compound* as a clear liquid (17.3 g, 83%); IR (neat) ν_{max}/cm^{-1} 1414, 1189, 985, 870; ^1H NMR (500 MHz, $CDCl_3$) δ 4.92 (s, 2H, CH_2OSO_3Cl); ^{13}C NMR (126 MHz, $CDCl_3$) δ 81.3 (CH_2OSO_3Cl), 91.4 (CH_2CCl_3); ^1H NMR, ^{13}C NMR and IR data were identical to literature data.[272]

2,2,2-Trichloroethyl 2-methyl-1*H*-imidazole-1-sulfonate, (157)



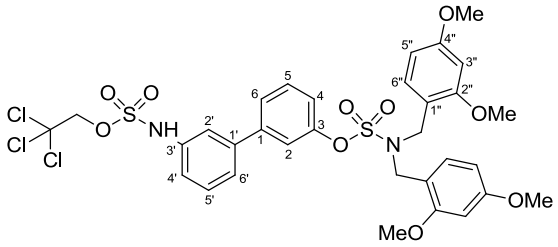
To a suspension of 2-methylimidazole (10.4 g, 126 mmol) in THF (60 mL), cooled at 0 °C, was added dropwise a solution of 2,2,2-trichloroethyl chlorosulfate (**156**) (4.68 mL, 8.7 g, 35.1 mmol) in THF (40 mL). The resulting solution was stirred at 0 °C for 1 h and allowed to warm to RT. After 16 h, the remaining 2-methylimidazole was filtered off and washed with THF (50 mL), and the filtrate was concentrated *in vacuo*. The crude residue was dissolved in EtOAc (80 mL), washed with water and brine (50 mL, respectively), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 7:3) to yield the *title compound* as a white amorphous solid (9.75 g, 95%); R_f = 0.29 (petrol:EtOAc, 7:3; $KMnO_4$); m.p. 64.5-66.5 °C (lit. 53.0-55.0 °C)[121]; IR (neat) ν_{max}/cm^{-1} 3167, 1556, 1420, 1197, 1182, 1155, 980; ^1H NMR (500 MHz, $CDCl_3$) δ 2.68 (3H, s, CH_3), 4.64 (2H, s, CH_2CCl_3), 6.95 (1H, d, *J* = 1.8 Hz, H-4 or H-5), 7.32 (1H, d, *J* = 1.8 Hz, H-4 or H-5); ^{13}C NMR (126 MHz, $CDCl_3$) δ 15.1 (CH_3), 80.1 (CH_2CCl_3), 91.9 (CH_2CCl_3), 120.3 (C-4 or C-5), 128.4 (C-4 or C-5), 146.6 (C-2); LRMS (ES^+) *m/z* 293.1 $[M(^{35}Cl^{35}Cl^{35}Cl)+H]^+$, 295.1 $[M(^{37}Cl^{35}Cl^{35}Cl)+H]^+$, 297.1 $[M(^{37}Cl^{37}Cl^{35}Cl)+H]^+$; ^1H NMR, ^{13}C NMR and LRMS data were identical to literature data.[121]

2,3-Dimethyl-1-((2,2,2-trichloroethoxy)sulfonyl)-1*H*-imidazol-3-ium tetrafluoroborate, (158)



To 2,2,2-trichloroethyl 2-methyl-1*H*-imidazole-1-sulfonate (**157**) (9.8 g, 33.4 mmol) in DCM (100 mL), cooled at 0 °C, was added trimethyloxonium tetrafluoroborate (4.94 g, 33.4 mmol). The resulting solution was stirred at 0 °C for 1 h and allowed to warm to RT. After 20 h, the reaction was cooled in an ice bath. Cold petrol (120 mL) was added to the mixture, leading to the precipitation of **158**. The white precipitate was filtered off, washed with cold petrol (60 mL) and dry under high vacuum. The white fluffy solid (11.4 g, 86%) was used in the next step without further purification; m.p. 118.5-120.5 °C; IR (neat) ν_{max}/cm^{-1} 3150, 1601, 1531, 1438, 1230, 1208, 1162, 1050, 1027, 973; ^{1}H NMR (500 MHz, MeOD) δ 2.93 (3H, s, CH_3), 3.94 (3H, s, NCH_3), 5.34 (2H, s, CH_2CCl_3), 7.74 (1H, d, *J* = 2.5 Hz, H-4 or H-5), 8.08 (1H, d, *J* = 2.5 Hz, H-4 or H-5); ^{13}C NMR (126 MHz, MeOD) δ 11.8 (CH_3), 36.6 (NCH_3), 83.3 (CH_2CCl_3), 93.0 (CH_2CCl_3), 122.1 (C-4 or C-5), 124.9 (C-4 or C-5), 150.0 (C-2); ^{19}F NMR (471 MHz, MeOD) δ -154.50 (BF_4^-); LRMS (ES^+) *m/z* 307.1 $[M(^{35}Cl^{35}Cl^{35}Cl)+H]^+$, 309.1 $[M(^{37}Cl^{35}Cl^{35}Cl)+H]^+$, 311.1 $[M(^{37}Cl^{37}Cl^{35}Cl)+H]^+$; ^{1}H NMR, ^{13}C NMR, ^{19}F NMR and LRMS data were identical to literature data.[121]

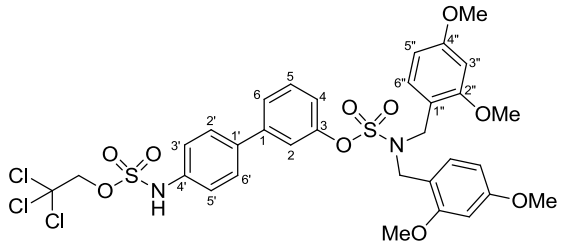
3'-(((2,2,2-Trichloroethoxy)sulfonyl)amino)-[1,1'-biphenyl]-3-yl bis(2,4-dimethoxy benzyl)sulfamate, (160)



Compound **160** was synthesised according to general procedure K, using the following reagents: 3'-amino-[1,1'-biphenyl]-3-yl bis(2,4-dimethoxybenzyl)sulfamate (**137**) (550 mg, 0.97 mmol), 2,3-dimethyl-1-((2,2,2-trichloroethoxy)sulfonyl)-1*H*-imidazol-3-ium tetrafluoroborate (**158**) (1.16 g, 2.92 mmol) and THF (9.8 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 65:35) to yield the *title compound* as a pale yellow oil (567 mg, 75%); R_f = 0.31 (petrol:EtOAc, 65:35); No λ_{max} (EtOH)/nm; IR (neat) ν_{max}/cm^{-1} 3264, 1610, 1589, 15074, 1360, 1208, 1176, 1157; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.66 (6H, s, 2 × $ArOCH_3$), 3.85 (6H, s, 2 × $ArOCH_3$), 4.42

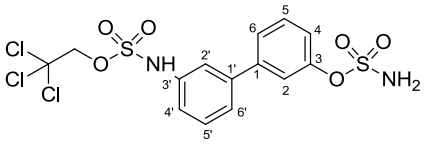
(4H, s, 2 × ArCH_2), 4.70 (2H, s, CH_2CCl_3), 6.41 (2H, d, *J* = 2.4 Hz, H-3”), 6.51 (2H, dd, *J* = 8.4, 2.4 Hz, H-5”), 6.56 (1H, dd, *J* = 2.0, 2.0 Hz, H-2’), 7.01 (1H, dd, *J* = 2.0, 2.0 Hz, H-2), 7.26 (1H, ddd, *J* = 8.0, 2.0 and 1.1 Hz, Ar*H*), 7.35 (2H, d, *J* = 8.4 Hz, H-6”), 7.39 - 7.36 (2H, m, 2 × Ar*H*), 7.46 – 7.41 (3H, m, 3 × Ar*H*), 7.71 (1H, s, ArN*H*SO_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 47.3 (Ar*C*H_2), 55.3 (ArO*C*H_3), 55.8 (ArO*C*H_3), 79.1 (*C*H_2CCl_3), 93.2 (CH_2*C*Cl_3), 98.7 (C-3”), 104.4 (C-5”), 117.3 (C-1”), 119.7 (C-2), 119.9 (CH Ar), 120.4 (C-2’), 121.7 (CH Ar), 124.3 (CH Ar), 124.9 (CH Ar), 130.1 (CH Ar), 130.2 (CH Ar), 131.6 (C-6”), 136.2 (C-3’), 141.1 (C-1 or C-1’), 141.2 (C-1 or C-1’), 150.9 (C-3), 158.8 (C-2” or C-4”), 160.5 (C-2” or C-4”); HRMS (ESI) calcd for $C_{32}H_{37}Cl_3N_3O_{10}S_2$ [M(^{35}Cl^{35}Cl^{35}Cl)+H]$^+$ 792.0980, found 792.0989.

4'-(((2,2,2-Trichloroethoxy)sulfonyl)amino)-[1,1'-biphenyl]-3-yl bis(2,4-dimethoxy benzyl)sulfamate, (161)



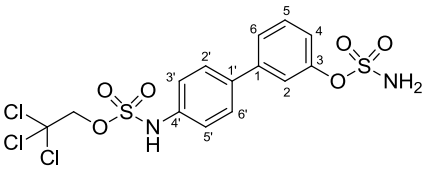
Compound **161** was synthesised according to general procedure K, using the following reagents: 4'-amino-[1,1'-biphenyl]-3-yl bis(2,4-dimethoxybenzyl)sulfamate (**138**) (550 mg, 0.97 mmol), 2,3-dimethyl-1-((2,2,2-trichloroethoxy)sulfonyl)-1*H*-imidazol-3-ium tetrafluoroborate (**158**) (1.16 g, 2.92 mmol) and THF (9.8 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 6:4) to yield the *title compound* as a yellow oil (620 mg, 82%); R_f = 0.32 (petrol:EtOAc, 6:4); λ_{max} (EtOH)/nm 272.5; IR (neat) ν_{max}/cm^{-1} 1611, 1588, 1507, 1367, 1208, 1178, 1132, 1038; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.71 (6H, s, 2 × ArOCH_3), 3.78 (6H, s, 2 × ArOCH_3), 4.47 (4H, s, 2 × ArCH_2), 4.68 (2H, s, CH_2CCl_3), 6.38 (2H, d, *J* = 2.4 Hz, H-3”), 6.44 (2H, dd, *J* = 8.4, 2.4 Hz, H-5”), 7.14 – 7.10 (2H, m, H-2 and H-4), 7.28 (2H, d, *J* = 8.4 Hz, H-6”), 7.30 (2H, d, *J* = 8.6 Hz, H-3’, 5’), 7.38 – 7.34 (1H, m, H-5), 7.41 – 7.38 (1H, m, H-6), 7.48 (2H, d, *J* = 8.6 Hz, H-2’, 6’); ^{13}C NMR (126 MHz, $CDCl_3$) δ 47.1 (Ar*C*H_2), 55.3 (ArO*C*H_3), 55.5 (ArO*C*H_3), 79.2 (*C*H_2CCl_3), 93.1 (CH_2*C*Cl_3), 98.4 (C-3”), 104.1 (C-5”), 116.7 (C-1”), 120.5 (C-2 or C-4), 121.1 (C-2 or C-4), 121.6 (C-3’, 5’), 124.9 (C-6), 128.4 (C-2’, 6’), 130.1 (C-5), 131.2 (C-6”), 135.0 (C-4’), 137.7 (C-1 or C-1’), 141.5 (C-1 or C-1’), 151.0 (C-3), 158.6 (C-2” or C-4”), 160.8 (C-2” or C-4”); HRMS (ESI) calcd for $C_{32}H_{34}Cl_3N_2O_{10}S_2$ [M(^{35}Cl^{35}Cl^{35}Cl)+H]$^+$ 775.0715, found 775.0721.

2,2,2-Trichloroethyl (3'-(sulfamoyloxy)-[1,1'-biphenyl]-3-yl)sulfamate, (162)



Compound **162** was synthesised according to general procedure D, using the following reagents: 3'-(((2,2,2-trichloroethoxy)sulfonyl)amino)-[1,1'-biphenyl]-3-yl bis(2,4-dimethoxy benzyl)sulfamate (**160**) (550 mg, 0.71 mmol), DCM (6.4 mL) and TFA (0.7 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 7:3) to yield the *title compound* as a pale orange oil (290 mg, 86%); R_f = 0.29 (petrol:EtOAc, 7:3); λ_{max} (EtOH)/nm 248.0; IR (neat) ν_{max}/cm^{-1} 3281, 1606, 1576, 1476, 1370, 1175, 1146, 1087, 1014; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.68 (2H, s, C*H*$_2$CCl$_3$), 5.12 (2H, s, ArOSO$_2$N*H*$_2$), 7.10 (1H, s, ArN*H*SO$_3$), 7.30 – 7.26 (1H, m, Ar*H*), 7.35 - 7.31 (1H, m, Ar*H*), 7.54 – 7.39 (6H, m, 6 × Ar*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 79.1 (*C*H$_2$CCl$_3$), 93.1 (CH$_2$*C*Cl$_3$), 119.8 (CH Ar), 120.5 (CH Ar), 120.9 (CH Ar), 121.5 (CH Ar), 124.8 (CH Ar), 126.1 (CH Ar), 130.4 (CH Ar), 130.5 (CH Ar), 136.1 (C-3'), 141.2 (C-1 or C-1'), 142.2 (C-1 or C-1'), 150.6 (C-3); LRMS (ES$^-$) *m/z* 473.1 [M(^{35}Cl^{35}Cl^{35}Cl)-H]$^-$, 475.1 [M(^{37}Cl^{35}Cl^{35}Cl)-H]$^-$, 477.2 [M(^{37}Cl^{37}Cl^{35}Cl)-H]$^-$; HRMS (ESI) calcd for $C_{14}H_{12}Cl_3N_2O_6S_2$ [M(^{35}Cl^{35}Cl^{35}Cl)-H]$^-$ 472.9208, found 472.9202.

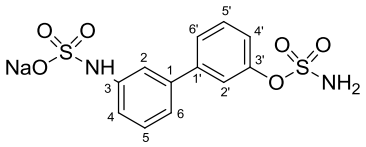
2,2,2-Trichloroethyl (3'-(sulfamoyloxy)-[1,1'-biphenyl]-4-yl)sulfamate, (163)



Compound **163** was synthesised according to general procedure D, using the following reagents: 4'-(((2,2,2-trichloroethoxy)sulfonyl)amino)-[1,1'-biphenyl]-3-yl bis(2,4-dimethoxy benzyl)sulfamate (**161**) (600 mg, 0.77 mmol), DCM (7.0 mL) and TFA (0.7 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 65:35) to yield the *title compound* as a pale yellow oil (335 mg, 91%); R_f = 0.28 (petrol:EtOAc, 65:35); λ_{max} (EtOH)/nm 264.0; IR (neat) ν_{max}/cm^{-1} 3361, 3265, 1605, 1574, 1522, 1483, 1427, 1363, 1170, 1145; ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.88 (2H, s, C*H*$_2$CCl$_3$), 7.26 (1H, ddd, *J* = 7.9, 2.3 and 1.0 Hz, H-4 or H-6), 7.34 (2H, d, *J* = 8.6 Hz, H-3', 5'), 7.57 – 7.50 (2H, m, H-2 and H-5), 7.64 – 7.58 (1H, m, H-4 or H-6), 7.70 (2H, d, *J* = 8.7 Hz, H-2', 6'), 8.03 (2H, s, ArOSO$_2$N*H*$_2$), 11.15 (1H, s, ArN*H*SO$_3$); ^{13}C NMR (126 MHz, DMSO-d_6) δ 77.8 (*C*H$_2$CCl$_3$), 93.5 (CH$_2$*C*Cl$_3$), 120.1 (C-2), 120.3

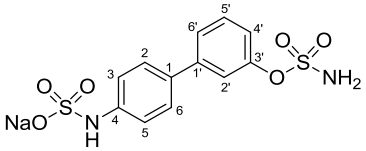
(C-3', 5'), 121.1 (C-4 or C-6), 124.6 (C-4 or C-6), 127.7 (C-2', 6'), 130.3 (C-5), 135.1 (C-1' or C-4'), 136.5 (C-1' or C-4'), 141.1 (C-1), 150.7 (C-3); LRMS (ES^-) *m/z* 473.1 [M($^{35}Cl^{35}Cl^{35}Cl$)-H]$^-$, 475.1 [M($^{37}Cl^{35}Cl^{35}Cl$)-H]$^-$, 477.1 [M($^{37}Cl^{37}Cl^{35}Cl$)-H]$^-$; HRMS (ESI) calcd for $C_{14}H_{12}Cl_3N_2O_6S_2$ [M($^{35}Cl^{35}Cl^{35}Cl$)-H]$^-$ 472.9208, found 472.9198.

Sodium (3'-(sulfamoyloxy)-[1,1'-biphenyl]-3-yl)sulfamate, (164)



Compound **164** was synthesised according to general procedure M, using the following reagents: 2,2,2-trichloroethyl (3'-(sulfamoyloxy)-[1,1'-biphenyl]-3-yl)sulfamate (**162**) (200 mg, 0.42 mmol), MeOH (4.2 mL), acetate buffer pH 4.65 (4.2 mL) and zinc (275 mg, 4.20 mmol). The crude product was converted to the sodium salt by ion-exchange chromatography (DOWEX 50WX2 - Na^+ form). The crude product was purified by column chromatography (silica gel, EtOAc:MeOH, 1:0 → 93:7) to yield the *title compound* as a white solid (128 mg, 84%); R_f = 0.21 (EtOAc:MeOH, 93:7; $KMnO_4$); m.p. 185.5-187.5 °C; λ_{max} (EtOH)/nm 235.2; IR (neat) ν_{max}/cm^{-1} 3367, 3306, 3263, 1602, 1576, 1468, 1423, 1360, 1239, 1199, 1176, 1151; ^{1}H NMR (500 MHz, MeOD) δ 7.16 (2H, dd, *J* = 8.0, 2.1 Hz, 2 × Ar*H*), 7.32 – 7.26 (2H, m, H-5 or H-5' and Ar*H*), 7.47 (1H, dd, *J* = 8.1, 8.1 Hz, H-5 or H-5'), 7.51 (1H, dd, *J* = 2.0 Hz, H-2 or H-2'), 7.60 – 7.55 (2H, m, 2 × Ar*H*); ^{13}C NMR (126 MHz, MeOD) δ 117.2 (C-2 or C-2'), 118.2 (CH Ar), 120.5 (CH Ar), 121.9 (CH Ar), 122.0 (CH Ar), 126.3 (CH Ar), 130.2 (C-5 or C-5'), 130.9 (C-5 or C-5'), 141.7 (C-3), 143.7 (C-1 or C-1'), 144.6 (C-1 or C-1'), 152.4 (C-3'); LRMS (ES^-) *m/z* 343.2 [M-Na]$^-$; HRMS (ESI) calcd for $C_{12}H_{11}N_2O_6S_2$ [M-Na]$^-$ 343.0064, found 343.0052.

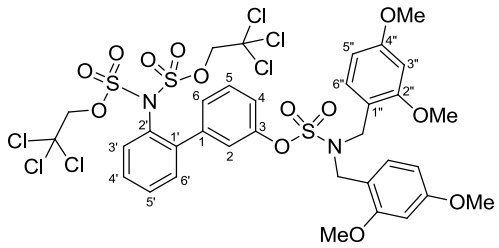
Sodium (3'-(sulfamoyloxy)-[1,1'-biphenyl]-4-yl)sulfamate, (165)



Compound **165** was synthesised according to general procedure M, using the following reagents: 2,2,2-trichloroethyl (3'-(sulfamoyloxy)-[1,1'-biphenyl]-4-yl)sulfamate (**163**) (100 mg, 0.21 mmol), MeOH (2.1 mL), acetate buffer pH 4.65 (2.1 mL) and zinc (137 mg, 2.10 mmol). The crude product was converted to the sodium salt by ion-exchange chromatography (DOWEX 50WX2 - Na^+ form). The crude product was purified by

column chromatography (silica gel, EtOAc:MeOH, 1:0 → 93:7) to yield the *title compound* as a white solid (62 mg, 80%); R_f = 0.21 (EtOAc:MeOH, 93:7; $KMnO_4$); m.p. No clear m.p., decomposition range 185-195 °C; λ_{max} (EtOH)/nm 280.5; IR (neat) ν_{max}/cm^{-1} 3362, 3254, 1607, 1586, 1573, 1523, 1480, 1365, 1195, 1183, 1154, 1064; ^{1}H NMR (500 MHz, MeOD) δ 7.26 – 7.19 (1H, m, H-4' or H-6'), 7.26 (2H, d, *J* = 8.6 Hz, H-3, 5), 7.44 (1H, dd, *J* = 8.2, 8.2 Hz, H-5'), 7.57 – 7.48 (4H, m, 4 × Ar*H*); ^{13}C NMR (126 MHz, MeOD) δ 118.8 (C-3, 5), 121.2 (CH Ar), 121.2 (CH Ar), 125.6 (CH Ar), 128.2 (C-2, 6), 130.9 (C-5'), 133.4 (C-4), 143.2 (C-1 or C-1'), 144.3 (C-1 or C-1'), 152.5 (C-3'); LRMS (ES^-) *m/z* 343.2 $[M-Na]^-$; HRMS (ESI) calcd for $C_{12}H_{11}N_2O_6S_2$ $[M-Na]^-$ 343.0064, found 343.0052.

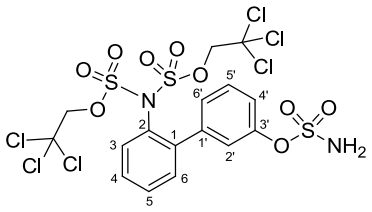
2'-(bis((2,2,2-trichloroethoxy)sulfonyl)amino)-[1,1'-biphenyl]-3-yl bis(2,4-dimethoxy benzyl)sulfamate, (166)



Compound **166** was synthesised according to general procedure L, using the following reagents: 2'-amino-[1,1'-biphenyl]-3-yl bis(2,4-dimethoxybenzyl)sulfamate (**136**) (550 mg, 0.97 mmol), 4-(dimethylamino)pyridine (262 mg, 2.14 mmol), triethylamine (543 µL, 394 mg, 3.90 mmol), 2,2,2-trichloroethyl chlorosulfate (**156**) (519 µL, 966 mg, 3.90 mmol) and THF (10 + 5 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 3:1) to yield the *title compound* as a pale yellow oil (673 mg, 70%); R_f = 0.30 (petrol:EtOAC, 3:1); λ_{max} (EtOH)/nm 276.5; IR (neat) ν_{max}/cm^{-1} 1612, 1588, 1508, 1425, 1369, 1185, 1156; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.71 (6H, s, 2 × ArOCH_3), 3.76 (6H, s, 2 × ArOCH_3), 4.45 (2H, d, *J* = 11.4 Hz, CH_2CCl_3), 4.49 (4H, s, 2 × ArCH_2), 4.66 (2H, d, *J* = 11.4 Hz, CH_2CCl_3), 6.37 (2H, d, *J* = 2.4 Hz, H-3"), 6.43 (2H, dd, *J* = 8.3, 2.4 Hz, H-5"), 7.18 (1H, dd, *J* = 1.4, 1.4 Hz, H-2), 7.24 (1H, ddd, *J* = 7.6, 2.6 and 2.6 Hz, H-4 or H-6), 7.29 (2H, d, *J* = 8.4 Hz, H-6"), 7.39 (1H, dd, *J* = 7.6, 1.7 Hz, H-3'), 7.45 - 7.40 (2H, m, H-5 and H-4 or H-6), 7.56 – 7.51 (1H, m, H-4' or H-5'), 7.62 – 7.57 (1H, m, H-4' or H-5'), 7.68 (1H, dd, *J* = 7.9, 1.3 Hz, H-6'); ^{13}C NMR (126 MHz, $CDCl_3$) δ 47.0 (Ar*C*H_2), 55.2 (ArO*C*H_3), 55.5 (ArO*C*H_3), 81.5 (*C*H_2CCl_3), 92.7 (CH_2*C*Cl_3), 98.3 (C-3"), 104.2 (C-5"), 116.6 (C-1"), 122.3 (C-4 or C-6), 123.4 (C-2), 127.4 (CH Ar), 129.6 (CH Ar), 129.7 (CH Ar), 131.1 (C-6"), 131.5 (C-4' or C-5'), 132.5 (C-3'), 132.7 (C-2'),

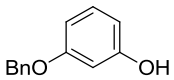
139.5 (C-1 or C-1'), 141.9 (C-1 or C-1'), 150.7 (C-3), 158.6 (C-2" or C-4"), 160.7 (C-2" or C-4"); HRMS (ESI) calcd for $C_{34}H_{38}Cl_6N_3O_{13}S_3$ $[M(6 \times {}^{35}Cl)+NH_4]^+$ 1001.9692, found 1001.9675.

2,2,2-Trichloroethyl (3'-(sulfamoyloxy)-[1,1'-biphenyl]-2-yl)((2,2,2-trichloroethoxy) sulfonyl)sulfamate, (167)



Compound **167** was synthesised according to general procedure D, using the following reagents: 2'-(bis((2,2,2-trichloroethoxy)sulfonyl)amino)-[1,1'-biphenyl]-3-yl bis(2,4-dimethoxybenzyl)sulfamate (**166**) (550 mg, 0.56 mmol), DCM (5.1 mL) and TFA (0.6 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 8:2) to yield the *title compound* as a pale orange oil (344 mg, 90%); R_f = 0.29 (petrol:EtOAc, 8:2); λ_{max} (EtOH)/nm 232.0; IR (neat) ν_{max}/cm^{-1} 3456, 3346, 1545, 1473, 1424, 1388, 1189, 1152, 1093, 990; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.53 (2H, d, *J* = 11.4 Hz, C*H*$_2$CCl$_3$), 4.72 (2H, d, *J* = 11.4 Hz, C*H*$_2$CCl$_3$), 5.10 (2H, s, ArOSO$_2$N*H*$_2$), 7.45 - 7.39 (2H, m, 2 × Ar*H*), 7.47 (1H, dd, *J* = 7.6, 1.7 Hz, H-3'), 7.59 – 7.52 (3H, m, 3 × Ar*H*), 7.65 – 7.60 (1H, m, H-4' or H-5'), 7.69 – 7.66 (1H, m, H-6'); ^{13}C NMR (126 MHz, $CDCl_3$) δ 81.6 (*C*H$_2$CCl$_3$), 92.6 (CH$_2$*C*Cl$_3$), 122.6 (CH Ar), 122.8 (CH Ar), 128.6 (CH Ar), 129.7 (C-6'), 130.0 (CH Ar), 130.5 (CH Ar), 131.8 (C-4' or C-5'), 132.3 (C-3'), 132.6 (C-2'), 139.7 (C-1 or C-1'), 141.6 (C-1 or C-1'), 150.1 (C-3); HRMS (ESI) calcd for $C_{16}H_{18}Cl_6N_3O_9S_3$ $[M(6 \times {}^{35}Cl)+NH_4]^+$ 701.8331, found 701.8334.

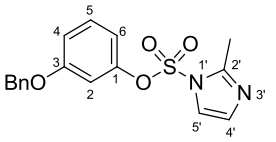
3-(Benzyloxy)phenol, (170)



To resorcinol (**169**) (7.4 g, 67.3 mmol) in acetonitrile (70 mL) were added potassium carbonate (2.32 g, 16.8 mmol) and benzyl bromide (2.0 mL, 2.88 g, 16.8 mmol). The resulting solution was heated at reflux for 24 h. Upon completion, the solvent was removed *in vacuo* to yield a crude product. The crude residue was dissolved in EtOAc (50 mL), washed with saturated aq. $NaHCO_3$ (40 mL) and water (2 × 40 mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The crude yellow solid was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 85:15) to yield the *title*

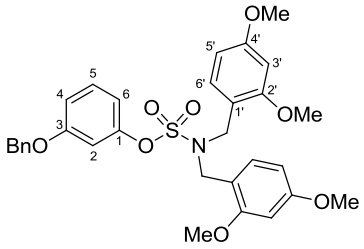
compound as a pale yellow solid (2.43 g, 72%); R_f = 0.30 (petrol:EtOAc, 85:15; $KMnO_4$); m.p. 47.5-49.5 °C (lit. 52 °C)[273]; λ_{max} (EtOH)/nm 275.0; IR (neat) ν_{max}/cm^{-1} 3292, 1592, 1497, 1487, 1462, 1451, 1378, 1277, 1142; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.74 (1H, s, ArO*H*), 5.04 (2H, s, ArCH_2), 6.44 (1H, ddd, *J* = 8.2, 2.5 and 0.8 Hz, H-4 or H-6), 6.49 (1H, dd, *J* = 2.5, 2.4 Hz, H-2), 6.58 (1H, ddd, *J* = 8.4, 2.4 and 0.8 Hz, H-4 or H-6), 7.14 (1H, dd, *J* = 8.4, 8.2 Hz, H-5), 7.35 – 7.31 (1H, m, H-4'), 7.41 – 7.36 (2H, m, H-3', 5'), 7.45 – 7.41 (2H, m, H-2', 6'); ^{13}C NMR (126 MHz, $CDCl_3$) δ 70.2 (Ar*C*H_2), 102.6 (C-2), 107.5 (C-4 or C-6), 108.2 (C-4 or C-6), 127.6 (C-3', 5'), 128.1 (C-4'), 128.7 (C-2', 6'), 130.3 (C-5), 137.0 (C-1'), 156.8 (C-1 or C-3), 160.3 (C-1 or C-3); LRMS (ES^-) *m/z* 199.1 $[M-H]^-$; HRMS (ESI) calcd for $C_{13}H_{11}O_2$ $[M-H]^-$ 199.0765, found 199.0763; ^{1}H NMR, ^{13}C NMR and IR data were identical to literature data.[273]

3-(Benzyloxy)phenyl 2-methyl-1*H*-imidazole-1-sulfonate, (171)



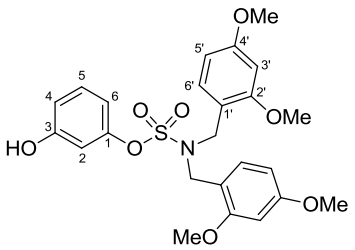
Compound **171** was synthesised according to general procedure B, using the following reagents: 1,1'-sulfonylbis(2-methyl-1*H*-imidazole) (**19**) (2.26 g, 9.99 mmol), caesium carbonate (1.79 g, 5.49 mmol), 3-(benzyloxy)phenol (**170**) (1.0 g, 4.99 mmol) and acetonitrile (20 mL). The crude yellow oil was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 3:1) to yield the *title compound* as a clear oil (1.64 g, 95%); R_f = 0.28 (petrol:EtOAc, 3:1; $KMnO_4$); λ_{max} (EtOH)/nm 271.5; IR (neat) ν_{max}/cm^{-1} 1608, 1585, 1552, 1486, 1422, 1206, 1114; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.46 (3H, s, CH_3), 4.99 (2H, s, ArCH_2), 6.52 – 6.47 (1H, m, H-4 or H-6), 6.55 (1H, dd, *J* = 2.3, 2.3 Hz, H-2), 6.88 (1H, d, *J* = 1.7 Hz, H-4' or H-5'), 6.97 – 6.93 (1H, m, H-4 or H-6), 7.13 (1H, d, *J* = 1.7 Hz, H-4' or H-5'), 7.24 (1H, dd, *J* = 8.3, 8.3 Hz, H-5), 7.41 – 7.32 (5H, m, 5 × Ar*H* (benzyl)); ^{13}C NMR (126 MHz, $CDCl_3$) δ 15.0 (CH_3), 70.6 (Ar*C*H_2), 108.4 (C-2), 113.7 (C-4 or C-6), 115.6 (C-4 or C-6), 120.5 (C-4' or C-5'), 127.6 (CH Ar (benzyl)), 128.1 (C-4' or C-5'), 128.5 (CH Ar (benzyl)), 128.9 (CH Ar (benzyl)), 130.7 (C-5), 136.0 (C_q (benzyl)), 146.9 (C-2' or C-1), 149.8 (C-2' or C-1), 160.0 (C-3); LRMS (ES^+) *m/z* 345.3 $[M+H]^+$; HRMS (ESI) calcd for $C_{17}H_{17}N_2O_4S$ $[M+H]^+$ 345.0904, found 345.0902.

3-(Benzyloxy)phenyl bis(2,4-dimethoxybenzyl)sulfamate, (172)



Compound **172** was synthesised according to general procedure H, using the following reagents: 3-(benzyloxy)phenyl 2-methyl-1*H*-imidazole-1-sulfonate (**171**) (5.0 g, 14.5 mmol), trimethyloxonium tetrafluoroborate (2.15 g, 14.5 mmol), DCM (145 mL), acetonitrile (73 mL) and bis(2,4-dimethoxybenzyl)amine (**32**) (4.62 g, 14.5 mmol). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 $\rightarrow$ 3:1) to yield the *title compound* as a clear oil (4.63 g, 55%); R_f = 0.26 (petrol:EtOAc, 3:1; $KMnO_4$); λ_{max} (EtOH)/nm 277.5; IR (neat) ν_{max}/cm^{-1} 1608, 1587, 1507, 1454, 1370, 1207, 1120; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.72 (6H, s, 2 × ArOCH_3), 3.78 (6H, s, 2 × ArOCH_3), 4.45 (4H, s, 2 × ArCH_2), 4.95 (2H, s, ArCH_2 (benzyl)), 6.39 (2H, d, *J* = 2.4 Hz, H-3'), 6.43 (2H, dd, *J* = 8.3, 2.4 Hz, H-5'), 6.67 (1H, dd, *J* = 2.5, 2.2 Hz, H-2), 6.75 (1H, ddd, *J* = 8.1, 2.2 and 0.9 Hz, H-4 or H-6), 6.84 (1H, ddd, *J* = 8.4, 2.5 and 0.9 Hz, H-4 or H-6), 7.20 (1H, dd, *J* = 8.4, 8.1 Hz, H-5), 7.27 (2H, d, *J* = 8.3 Hz, H-6'), 7.36 – 7.31 (1H, m, Ar*H* (benzyl)), 7.45 – 7.37 (4H, m, 4 × Ar*H* (benzyl)); ^{13}C NMR (126 MHz, $CDCl_3$) δ 47.0 (Ar*C*H_2), 55.2 (ArO*C*H_3), 55.5 (ArO*C*H_3), 70.3 (Ar*C*H_2 (benzyl)), 98.3 (C-3'), 104.1 (C-5'), 108.6 (C-2), 113.5 (C-4 or C-6), 114.4 (C-4 or C-6), 116.7 (C-1'), 127.7 (CH Ar (benzyl)), 128.2 (CH Ar (benzyl)), 128.7 (CH Ar (benzyl)), 130.0 (C-5), 131.1 (C-6'), 136.6 (C-1"), 151.4 (C-1), 158.6 (C-2' or C-4'), 159. 7 (C-3), 160.7 (C-2' or C-4'); HRMS (ESI) calcd for $C_{31}H_{34}NO_8S$ $[M+H]^+$ 580.2000, found 580.1987.

3-Hydroxyphenyl bis(2,4-dimethoxybenzyl)sulfamate, (173)



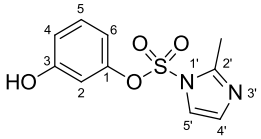
Compound **173** was synthesised following two different procedures.

1st procedure: 3-(Benzyloxy)phenyl bis(2,4-dimethoxybenzyl)sulfamate (**172**) (4.0 g, 6.90 mmol) in a mixture of MeOH (120 mL) and THF (30 mL) was subjected to palladium-catalysed hydrogenation using an H-Cube® reactor and a 10% Pd/C CatCart.

The reaction was conducted at 50 °C for 24 h in full hydrogen mode. The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 6:4) to yield the *title compound* as a pale yellow oil (2.53 g, 75%).

2nd procedure: To 3-hydroxyphenyl 2-methyl-1*H*-imidazole-1-sulfonate (**174**) (1.8 g, 7.08 mmol) in a mixture of DCM (80 mL) and THF (10 mL), cooled at 0 °C, was added trimethyloxonium tetrafluoroborate (1.05 g, 7.08 mmol). The resulting solution was stirred at 0 °C for 3 h and allowed to warm to RT. After 6 h, the reaction was diluted with acetonitrile (25 mL) and bis(2,4-dimethoxybenzyl)amine (**32**) (2.25 g, 7.08 mmol) was added. The resulting reaction mixture was heated at 42 °C for 24 h. Upon completion, the solvent was removed *in vacuo* to yield a crude product. The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 6:4) to yield the *title compound* as a clear oil (2.08 g, 60%); R_f = 0.28 (petrol:EtOAc, 6:4; $KMnO_4$); λ_{max} (EtOH)/nm 276.5; IR (neat) ν_{max}/cm^{-1} 3449, 1611, 1588, 1507, 1456, 1362, 1291, 1207, 1157, 1115, 1034; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.71 (6H, s, 2 × ArOC*H*$_3$), 3.79 (6H, s, 2 × ArOC*H*$_3$), 4.45 (4H, s, 2 × ArC*H*$_2$), 5.40 (1H, s, ArO*H*), 6.38 (2H, d, *J* = 2.4 Hz, H-3'), 6.43 (2H, dd, *J* = 8.4, 2.4 Hz, H-5'), 6.55 (1H, dd, *J* = 2.3, 2.3 Hz, H-2'), 6.71 – 6.64 (2H, m, H-4 and H-6), 7.13 (1H, dd, *J* = 8.2, 8.2 Hz, H-5), 7.26 (2H, d, *J* = 8.4 Hz, H-6'); ^{13}C NMR (126 MHz, $CDCl_3$) δ 47.1 (Ar*C*H$_2$), 55.2 (ArO*C*H$_3$), 55.5 (ArO*C*H$_3$), 98.3 (C-3'), 104.1 (C-5'), 109.5 (C-2), 113.7 (C-4 or C-6), 114.0 (C-4 or C-6), 116.7 (C-1'), 130.2 (C-5), 131.1 (C-6'), 151.3 (C-1), 156.6 (C-3), 158.6 (C-2' or C-4'), 160.7 (C-2' or C-4'); LRMS (ES^-) *m/z* 488.4 $[M-H]^-$; HRMS (ESI) calcd for $C_{24}H_{26}NO_8S$ $[M-H]^-$ 488.1385, found 488.1374.

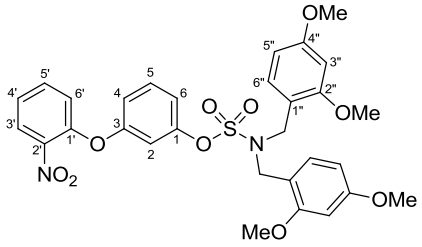
3-Hydroxyphenyl 2-methyl-1*H*-imidazole-1-sulfonate, (174)



To 1,1'-sulfonylbis(2-methyl-1*H*-imidazole) (**19**) (2.0 g, 8.84 mmol) and caesium carbonate (2.88 g, 8.84 mmol) in acetonitrile was added resorcinol (**169**) (4.87 g, 44.2 mmol). The resulting mixture was heated at 120 °C for 15 min under microwave irradiation. After cooling, the mixture was concentrated *in vacuo*. The resulting residue was dissolved in a saturated aq. NH_4Cl (20 mL) and the mixture extracted with EtOAc (3 × 20 mL). The pooled organic extracts were washed with water (2 × 20 mL) and brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude yellow solid was

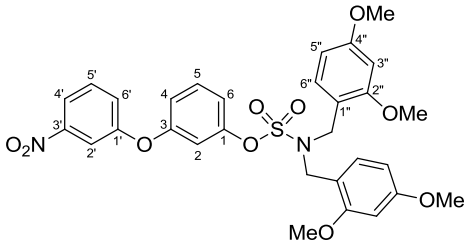
purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 6:4) to yield the *title compound* as a pale yellow solid (1.80 g, 80%); R_f = 0.30 (petrol:EtOAc, 6:4; $KMnO_4$); m.p. 122.0-124.0 °C; λ_{max} (EtOH)/nm 274.0; IR (neat) ν_{max}/cm^{-1} 1618, 1585, 1556, 1463, 1427, 1381, 1204, 1181, 1154; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.48 (3H, s, CH_3), 6.16 (1H, dd, *J* = 2.4, 2.3 Hz, H-2), 6.67 (1H, ddd, *J* = 8.2, 2.4 and 0.9 Hz, H-4 or H-6), 6.89 – 6.82 (2H, m, H-4 or H-6 and H-4' or H-5'), 7.21 (1H, d, *J* = 1.8 Hz, H-4' or H-5'), 7.26 (1H, d, *J* = 8.3 Hz, H-5), 9.43 (1H, s, ArO*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.6 (CH_3), 107.8 (C-2), 113.2 (C-4 or C-6), 116.6 (C-4 or C-6), 120.9 (C-4' or C-5'), 126.7 (C-4' or C-5'), 131.2 (C-5), 147.4 (C-1 or C-2'), 149.6 (C-1 or C-2'), 158.6 (C-3); LRMS (ES$^+$) *m/z* 255.2 [M+H]$^+$; HRMS (ESI) calcd for $C_{10}H_{11}N_2O_4S$ [M+H]$^+$ 255.0434, found 255.0439.

3-(2-Nitrophenoxy)phenyl bis(2,4-dimethoxybenzyl)sulfamate, (178)



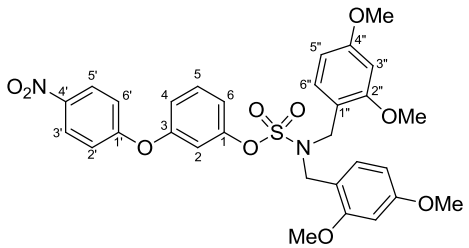
Compound **178** was synthesised according to general procedure N, using the following reagents: 3-hydroxyphenyl bis(2,4-dimethoxybenzyl)sulfamate (**173**) (1.4 g, 2.86 mmol), potassium carbonate (474 mg, 3.43 mmol), 1-fluoro-2-nitrobenzene (603 µL, 807 mg, 5.72 mmol) and *N*,*N*-dimethylformamide (20 mL). The crude brown oil was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 3:1) to yield the *title compound* as a pale orange oil (1.40 g, 80%); R_f = 0.28 (petrol:EtOAc, 3:1); λ_{max} (EtOH)/nm 276.0; IR (neat) ν_{max}/cm^{-1} 1611, 1588, 1527, 1507, 1476, 1350, 1251, 1207, 1157, 1112; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.72 (6H, s, 2 × ArOC*H*$_3$), 3.78 (6H, s, 2 × ArOC*H*$_3$), 4.43 (4H, s, 2 × ArC*H*$_2$), 6.37 (2H, d, *J* = 2.4 Hz, H-3"), 6.41 (2H, dd, *J* = 8.3, 2.4 Hz, H-5"), 6.66 (1H, dd, *J* = 2.3, 2.3 Hz, H-2), 6.90 (1H, dd, *J* = 8.0, 2.0 Hz, H-6'), 7.02 – 6.95 (2H, m, H-4 or H-6 and H-4'), 7.25 – 7.21 (3H, m, H-4 or H-6 and H-6"), 7.30 (1H, dd, *J* = 8.3, 8.3 Hz, H-5), 7.54 – 7.49 (1H, m, H-5'), 7.97 (1H, dd, *J* = 8.2, 1.6 Hz, H-3'); ^{13}C NMR (126 MHz, $CDCl_3$) δ 47.2 (Ar*C*H$_2$), 55.2 (ArO*C*H$_3$), 55.5 (ArO*C*H$_3$), 98.3 (C-3"), 104.1 (C-5"), 113.3 (C-2), 116.5 (C-1"), 117.1 (C-6'), 118.2 (C-4 or C-6 or C-4'), 120.8 (C-4 or C-6 or C-4'), 123.8 (C-4 or C-6), 126.0 (C-3'), 130.6 (C-5), 131.1 (C-6"), 134.4 (C-5'), 141.5 (C-2'), 150.2 (C-1 or C-1'), 151.5 (C-1 or C-1'), 156.4 (C-3), 158.6 (C-2" or C-4"), 160.8 (C-2" or C-4"); HRMS (ESI) calcd for $C_{30}H_{34}N_3O_{10}S$ [M+NH$_4$]$^+$ 628.1959, found 628.1957.

3-(3-Nitrophenoxy)phenyl bis(2,4-dimethoxybenzyl)sulfamate, (179)



Compound **179** was synthesised according to general procedure N, using the following reagents: 3-hydroxyphenyl bis(2,4-dimethoxybenzyl)sulfamate (**173**) (1.4 g, 2.86 mmol), potassium carbonate (474 mg, 3.43 mmol), 1-fluoro-3-nitrobenzene (609 µL, 807 mg, 5.72 mmol) and *N*,*N*-dimethylformamide (20 mL). The crude brown oil was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 3:1) to yield the *title compound* as a brown oil (1.31 g, 75%); R_f = 0.30 (petrol:EtOAc, 3:1); λ_{max} (EtOH)/nm 273.5; IR (neat) ν_{max}/cm^{-1} 1611, 1588, 1529, 1507, 1479, 1349, 1248, 1208, 1157, 1113; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.72 (6H, s, 2 × ArOC*H*$_3$), 3.78 (6H, s, 2 × ArOC*H*$_3$), 4.45 (4H, s, 2 × ArC*H*$_2$), 6.37 (2H, d, *J* = 2.4 Hz, H-3”), 6.41 (2H, dd, *J* = 8.4, 2.4 Hz, H-5”), 6.73 (1H, dd, *J* = 2.3, 2.2 Hz, H-2), 6.91 (1H, ddd, *J* = 8.3, 2.3 and 0.9 Hz, H-4 or H-6), 6.97 (1H, ddd, *J* = 8.2, 2.2 and 0.9 Hz, H-4 or H-6), 7.25 (2H, d, *J* = 8.4 Hz, H-6”), 7.30 (1H, ddd, *J* = 8.2, 2.4 and 0.9 Hz, H-6’), 7.33 (1H, dd, *J* = 8.3, 8.2 Hz, H-5), 7.50 (1H, dd, *J* = 8.2, 8.2 Hz, H-5’), 7.80 (1H, dd, *J* = 2.3, 2.3 Hz, H-2’), 7.97 (1H, ddd, *J* = 8.2, 2.1 and 0.9 Hz, H-4’); ^{13}C NMR (126 MHz, $CDCl_3$) δ 47.1 (Ar*C*H$_2$), 55.2 (ArO*C*H$_3$), 55.5 (ArO*C*H$_3$), 98.3 (C-3”), 104.1 (C-5”), 113.4 (C-2’), 113.7 (C-2), 116.5 (C-1”), 117.5 (C-4 or C-6), 118.3 (C-4 or C-6 or C-4’), 118.3 (C-4 or C-6 or C-4’), 124.4 (C-6’), 130.6 (C-5’), 130.8 (C-5), 131.1 (C-6”), 149.4 (C-3’), 151. 7 (C-1), 156.4 (C-3 or C-1’), 157.9 (C-3 or C-1’), 158.6 (C-2” or C-4”), 160.8 (C-2” or C-4”); HRMS (ESI) calcd for $C_{30}H_{34}N_3O_{10}S$ $[M+NH_4]^+$ 628.1959, found 628.1956.

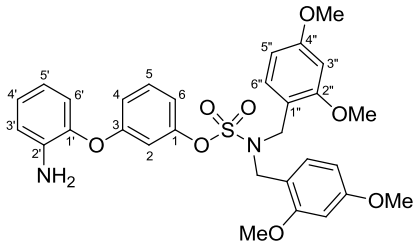
3-(4-Nitrophenoxy)phenyl bis(2,4-dimethoxybenzyl)sulfamate, (180)



Compound **180** was synthesised according to general procedure N, using the following reagents: 3-hydroxyphenyl bis(2,4-dimethoxybenzyl)sulfamate (**173**) (1.2 g, 2.45 mmol), potassium carbonate (407 mg, 2.94 mmol), 1-fluoro-4-nitrobenzene (692 mg, 4.90 mmol)

and *N*,*N*-dimethylformamide (20 mL). The crude brown oil was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 8:2) to yield the *title compound* as a yellow oil (1.28 g, 85%); R_f = 0.28 (petrol:EtOAc, 8:2); λ_{max} (EtOH)/nm 282.5; IR (neat) ν_{max}/cm^{-1} 1611, 1585, 1507, 1478, 1371, 1342, 1250, 1207, 1157, 1111; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.72 (6H, s, 2 × ArOC*H*$_3$), 3.77 (6H, s, 2 × ArOC*H*$_3$), 4.44 (4H, s, 2 × ArC*H*$_2$), 6.37 (2H, d, *J* = 2.4 Hz, H-3”), 6.41 (2H, dd, *J* = 8.4, 2.4 Hz, H-5”), 6.73 (1H, dd, *J* = 2.3, 2.2 Hz, H-2), 6.96 (1H, ddd, *J* = 8.2, 2.3 and 0.9 Hz, H-4 or H-6), 7.00 (2H, d, *J* = 9.3 Hz, H-2’, 6’), 7.03 (1H, ddd, *J* = 8.3, 2.2 and 0.9 Hz, H-4 or H-6), 7.24 (2H, d, *J* = 8.4 Hz, H-6”), 7.36 (1H, dd, *J* = 8.3, 8.2 Hz, H-5), 8.21 (2H, d, *J* = 9.3 Hz, H-3’, 5’); ^{13}C NMR (126 MHz, $CDCl_3$) δ 47.1 (Ar*C*H$_2$), 55.3 (ArO*C*H$_3$), 55.5 (ArO*C*H$_3$), 98.3 (C-3”), 104.1 (C-5”), 114.5 (C-2), 116.4 (C-1”), 117.5 (C-2’, 6’), 118.4 (C-4 or C-6), 119.1 (C-4 or C-6), 126.1 (C-3’, 5’), 130.9 (C-5), 131.1 (C-6”), 143.1 (C-4’), 151.7 (C-1), 155.4 (C-3), 158.6 (C-2” or C-4”), 160.8 (C-2” or C-4”), 162.7 (C-1’); HRMS (ESI) calcd for $C_{30}H_{31}N_2O_{10}S$ $[M+H]^+$ 611.1691, found 611.1694.

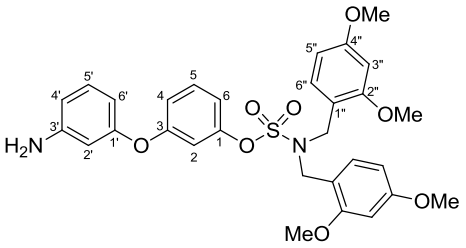
3-(2-Aminophenoxy)phenyl bis(2,4-dimethoxybenzyl)sulfamate, (181)



Compound **181** was synthesised according to general procedure O, using the following reagents: 3-(2-nitrophenoxy)phenyl bis(2,4-dimethoxybenzyl)sulfamate (**178**) (1.20 g, 1.96 mmol), MeOH (29.4 mL) and THF (9.8 mL). The crude brown oil was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 7:3) to yield the *title compound* as a yellow oil (970 mg, 85%); R_f = 0.32 (petrol:EtOAc, 7:3); λ_{max} (EtOH)/nm 277.8; IR (neat) ν_{max}/cm^{-1} 3467, 3378, 1611, 1587, 1505, 1479, 1369, 1243, 1207, 1156; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.71 (6H, s, 2 × ArOC*H*$_3$), 3.79 (6H, s, 2 × ArOC*H*$_3$), 4.44 (4H, s, 2 × ArC*H*$_2$), 6.37 (2H, d, *J* = 2.4 Hz, H-3”), 6.41 (2H, dd, *J* = 8.4, 2.4 Hz, H-5”), 6.75 - 6.70 (2H, m, 2 × Ar*H*), 6.89 – 6.79 (4H, m, 4 × Ar*H*), 7.00 (1H, ddd, *J* = 7.7, 7.7 and 1.4 Hz, H-4’), 7.22 (1H, dd, *J* = 8.3, 8.3 Hz, H-5), 7.24 (2H, d, *J* = 8.4 Hz, H-6”); ^{13}C NMR (126 MHz, $CDCl_3$) δ 47.0 (Ar*C*H$_2$), 55.2 (ArO*C*H$_3$), 55.5 (ArO*C*H$_3$), 98.3 (C-3”), 104.1 (C-5”), 111.3 (C-2), 114.9 (CH Ar), 116.2 (CH Ar), 116.6 (C-1”), 116.8 (CH Ar), 119.0 (CH Ar), 120.5 (CH Ar), 125.4 (C-4’), 130.2 (C-5), 131.0 (C-6”), 138.8 (C-1’ or C-2’), 142.6 (C-1’ or C-2’), 151.5 (C-1), 158.4 (C-3), 158.5 (C-2” or C-4”), 160.7

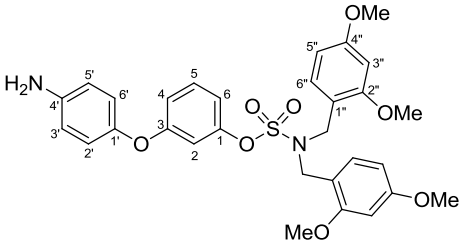
(C-2" or C-4"); LRMS (ES^+) *m/z* 581.4 $[M+H]^+$; HRMS (ESI) calcd for $C_{30}H_{33}N_2O_8S$ $[M+H]^+$ 581.1952, found 581.1947.

3-(3-Aminophenoxy)phenyl bis(2,4-dimethoxybenzyl)sulfamate, (182)



Compound **182** was synthesised according to general procedure O, using the following reagents: 3-(3-nitrophenoxy)phenyl bis(2,4-dimethoxybenzyl)sulfamate (**179**) (1.20 g, 1.96 mmol), MeOH (29.4 mL) and THF (9.8 mL). The crude brown oil was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 65:35) to yield the *title compound* as a brown oil (994 mg, 87%); R_f = 0.29 (petrol:EtOAc, 65:35); λ_{max} (EtOH)/nm 260.2; IR (neat) ν_{max}/cm^{-1} 3467, 3380, 1610, 1586, 1507, 1478, 1464, 1367, 1207, 1148, 1110; ^1H NMR (500 MHz, $CDCl_3$) δ 3.71 (6H, s, 2 × ArOCH_3), 3.78 (6H, s, 2 × ArOCH_3), 4.44 (4H, s, 2 × ArCH_2), 6.32 (1H, dd, *J* = 2.3, 2.3 Hz, H-2'), 6.37 (2H, d, *J* = 2.4 Hz, H-3"), 6.40 – 6.37 (1H, m, H-4' or H-6'), 6.41 (2H, dd, *J* = 8.4, 2.4 Hz, H-5"), 6.44 (1H, ddd, *J* = 8.1, 2.2 and 0.9 Hz, H-4' or H-6'), 6.72 (1H, dd, *J* = 2.3, 2.3 Hz, H-2), 6.91 – 6.84 (2H, m, H-4 and H-6), 7.10 (1H, dd, *J* = 8.1, 8.0 Hz, H-5'), 7.26 – 7.21 (3H, m, H-5 and H-6"); ^{13}C NMR (126 MHz, $CDCl_3$) δ 47.1 (Ar*C*H_2), 55.2 (ArO*C*H_3), 55.5 (ArO*C*H_3), 98.3 (C-3"), 104.1 (C-5"), 105.8 (C-2'), 109.2 (C-4' or C-6'), 110.7 (C-4' or C-6'), 113.0 (C-2), 116.6 (C-4 or C-6), 116.7 (C-4 or C-6), 116.9 (C-1"), 130.1 (C-5'), 130.6 (C-5), 131.1 (C-6"), 148.1 (C-3'), 151.4 (C-1), 157.9 (C-3 or C-1'), 158.1 (C-3 or C-1'), 158.5 (C-2" or C-4"), 160.7 (C-2" or C-4"); LRMS (ES^+) *m/z* 581.5 $[M+H]^+$; HRMS (ESI) calcd for $C_{30}H_{33}N_2O_8S$ $[M+H]^+$ 581.1952, found 581.1947.

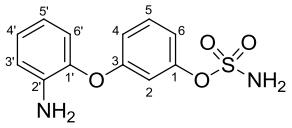
3-(4-Aminophenoxy)phenyl bis(2,4-dimethoxybenzyl)sulfamate, (183)



Compound **183** was synthesised according to general procedure O, using the following reagents: 3-(4-nitrophenoxy)phenyl bis(2,4-dimethoxybenzyl)sulfamate (**180**) (1.20 g,

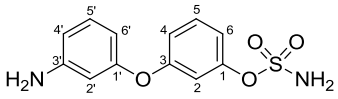
1.96 mmol), MeOH (29.4 mL) and THF (9.8 mL). The crude brown oil was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 55:45) to yield the *title compound* as a brown oil (982 mg, 86%); R_f = 0.31 (petrol:EtOAc, 55:45); λ_{max} (EtOH)/nm 264.5; IR (neat) ν_{max}/cm^{-1} 3453, 3378, 1611, 1588, 1506, 1478, 1366, 1247, 1205, 1157, 1111, 1033; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.71 (6H, s, 2 × ArOC*H*$_3$), 3.79 (6H, s, 2 × ArOC*H*$_3$), 4.43 (4H, s, 2 × ArC*H*$_2$), 6.37 (2H, d, *J* = 2.4 Hz, H-3”), 6.41 (2H, dd, *J* = 8.3, 2.4 Hz, H-5”), 6.71 – 6.66 (3H, m, H-2 and H-2’, 6’), 6.77 (1H, ddd, *J* = 8.3, 2.4 and 0.8 Hz, H-4 or H-6), 6.80 (1H, ddd, *J* = 8.2, 2.2 and 0.8 Hz, H-4 or H-6), 6.85 (2H, d, *J* = 8.7 Hz, H-3’, 5’), 7.19 (1H, dd, *J* = 8.3, 8.2 Hz, H-5), 7.23 (2H, d, *J* = 8.3 Hz, H-6”); ^{13}C NMR (126 MHz, $CDCl_3$) δ 47.0 (Ar*C*H$_2$), 55.2 (ArO*C*H$_3$), 55.5 (ArO*C*H$_3$), 98.3 (C-3”), 104.1 (C-5”), 111.3 (C-2), 115.1 (C-4 or C-6), 115.6 (C-4 or C-6), 116.6 (C-2’, 6’), 116.7 (C-1”), 121.3 (C-3’, 5’), 130.0 (C-5), 131.0 (C-6”), 142.8 (C-4’), 148.3 (C-1’), 151.4 (C-1), 158.5 (C-2” or C-4”), 159. 8 (C-3), 160.7 (C-2” or C-4”); LRMS (ES$^+$) *m/z* 581.5 [M+H]$^+$; HRMS (ESI) calcd for $C_{30}H_{33}N_2O_8S$ [M+H]$^+$ 581.1952, found 581.1945.

3-(2-Aminophenoxy)phenyl sulfamate, (184)



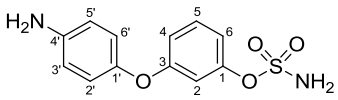
Compound **184** was synthesised according to general procedure D, using the following reagents: 3-(2-aminophenoxy)phenyl bis(2,4-dimethoxybenzyl)sulfamate (**181**) (200 mg, 0.34 mmol), DCM (3.1 mL) and TFA (0.4 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 7:3) to yield the *title compound* as a pale yellow solid (87 mg, 90%); R_f = 0.34 (petrol:EtOAc, 7:3); m.p. 91-5-93.5 °C; λ_{max} (EtOH)/nm 277.2; IR (neat) ν_{max}/cm^{-1} 3482, 3390, 3345, 3263, 1622, 1604, 1586, 1503, 1478, 1344; ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.93 (2H, s, ArN*H*$_2$), 6.57 (1H, ddd, *J* = 7.7, 7.7 and 1.6 Hz, H-5’), 6.84 – 6.78 (3H, m, 3 × Ar*H*), 6.85 (1H, dd, *J* = 8.0, 1.5 Hz, H-3’ or H-6’), 6.99 – 6.93 (2H, m, 2 × Ar*H*), 7.40 – 7.34 (1H, m, H-5), 8.02 (2H, s, ArOSO$_2$N*H*$_2$); ^{13}C NMR (126 MHz, DMSO-d_6) δ 110.4 (C-2), 114.2 (C-3’ or C-6’), 115.7 (C-4 or C-6), 116.0 (C-4 or C-6), 116.4 (C-5’), 120.9 (C-3’ or C-6’), 125.6 (C-4’), 130.4 (C-5), 140.6 (C-1’ or C-2’), 140.7 (C-1’ or C-2’), 151.0 (C-1), 158.5 (C-3); LRMS (ES$^-$) *m/z* 279.2 [M-H]$^-$; HRMS (ESI) calcd for $C_{12}H_{11}N_2O_4S$ [M-H]$^-$ 279.0445, found 279.0436.

3-(3-Aminophenoxy)phenyl sulfamate, (185)



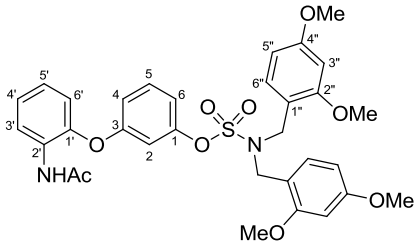
Compound **185** was synthesised according to general procedure D, using the following reagents: 3-(3-aminophenoxy)phenyl bis(2,4-dimethoxybenzyl)sulfamate (**182**) (200 mg, 0.34 mmol), DCM (3.1 mL) and TFA (0.4 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 65:35) to yield the *title compound* as a pale brown solid (80 mg, 82%); R_f = 0.31 (petrol:EtOAc, 65:35); m.p. 79.5-81.5 °C; λ_{max} (EtOH)/nm 279.2; IR (neat) ν_{max}/cm^{-1} 3438, 3357, 3321, 1607, 1586, 1478, 1363, 1250, 1181; ^{1}H NMR (500 MHz, DMSO-d_6) δ 5.26 (2H, s, ArNH_2), 6.17 (1H, dd, *J* = 8.0, 2.3 Hz, H-4' or H-6'), 6.24 (1H, dd, *J* = 2.2, 2.2 Hz, H-2'), 6.37 (1H, dd, *J* = 8.1, 1.9 Hz, H-4' or H-6'), 6.87 (1H, dd, *J* = 2.3, 2.3 Hz, H-2), 6.93 (1H, dd, *J* = 8.3, 2.3 Hz, H-4 or H-6), 7.06 – 6.97 (2H, m, H-4 or H-6 and H-5'), 7.42 (1H, dd, *J* = 8.2, 8.2 Hz, H-5'), 8.02 (2H, s, ArOSO$_2$NH_2); ^{13}C NMR (126 MHz, DMSO-d_6) δ 104.2 (C-2'), 106.1 (C-4' or C-6'), 109.9 (C-4' or C-6'), 112.0 (C-2), 116.1 (C-4 or C-6), 116.4 (C-4 or C-6), 130.2 (C-5'), 130.5 (C-5), 150.6 (C-1 or C-3'), 151.0 (C-1 or C-3'), 156.7 (C-3 or C-1'), 158.0 (C-3 or C-1'); LRMS (ES$^-$) *m/z* 279.2 [M-H]$^-$; HRMS (ESI) calcd for $C_{12}H_{11}N_2O_4S$ [M-H]$^-$ 279.0445, found 279.0438.

3-(4-Aminophenoxy)phenyl sulfamate, (186)



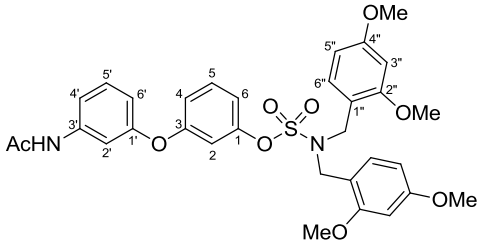
Compound **186** was synthesised according to general procedure D, using the following reagents: 3-(4-aminophenoxy)phenyl bis(2,4-dimethoxybenzyl)sulfamate (**183**) (200 mg, 0.34 mmol), DCM (3.1 mL) and TFA (0.4 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 6:4) to yield the *title compound* as a brown solid (63 mg, 65%); R_f = 0.30 (petrol:EtOAc, 6:4); m.p. 133.5-135.5 °C; λ_{max} (EtOH)/nm 242.6; IR (neat) ν_{max}/cm^{-1} 3410, 3327, 3296, 1600, 1507, 1475, 1366, 1249, 1173; ^{1}H NMR (500 MHz, DMSO-d_6) δ 5.04 (2H, s, ArNH_2), 6.60 (2H, d, *J* = 8.8 Hz, H-2', 6'), 6.74 (1H, dd, *J* = 2.3, 2.3 Hz, H-2), 6.85 – 6.76 (3H, m, H-4 or H-6 and H-3', 5'), 6.91 (1H, dd, *J* = 8.1, 2.3 Hz, H-4 or H-6), 7.36 (1H, dd, *J* = 8.2, 8.1 Hz, H-5), 7.99 (2H, s, ArOSO$_2$NH_2); ^{13}C NMR (126 MHz, DMSO-d_6) δ 110.2 (C-2), 114.3 (C-4 or C-6), 114.9 (C-3', 5'), 115.3 (C-4 or C-6), 121.1 (C-2', 6'), 130.4 (C-5), 144.7 (C-1' or C-4'), 145.9 (C-1' or C-4'), 151.0 (C-1), 159.9 (C-3); LRMS (ES$^-$) *m/z* 279.2 [M-H]$^-$; HRMS (ESI) calcd for $C_{12}H_{11}N_2O_4S$ [M-H]$^-$: 279.0445; found 279.0437.

3-(2-Acetamidophenoxy)phenyl bis(2,4-dimethoxybenzyl)sulfamate, (187)



Compound **187** was synthesised according to general procedure J, using the following reagents: 3-(2-aminophenoxy)phenyl bis(2,4-dimethoxybenzyl)sulfamate (**181**) (250 mg, 0.43 mmol), triethylamine (87 mg, 120 µL, 0.86 mmol), acetic anhydride (53 mg, 49 µL, 0.52 mmol) and DCM (4.3 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 6:4) to yield the *title compound* as a clear oil (233 mg, 87%); R_f = 0.30 (petrol:EtOAc, 6:4); λ_{max} (EtOH)/nm 277.2; IR (neat) ν_{max}/cm^{-1} 1683, 1609, 1589, 1507, 1476, 1440, 1368, 1252, 1207, 1157, 1115, 1034; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.19 (3H, s, C*H*$_3$CO), 3.71 (6H, s, 2 × ArOC*H*$_3$), 3.78 (6H, s, 2 × ArOC*H*$_3$), 4.46 (4H, s, 2 × ArC*H*$_2$), 6.38 (2H, d, *J* = 2.4 Hz, H-3”), 6.41 (2H, dd, *J* = 8.4, 2.4 Hz, H-5”), 6.75 (1H, dd, *J* = 2.5, 2.3 Hz, H-2), 6.82 (1H, dd, *J* = 8.1, 1.5 Hz, H-6’), 6.85 (1H, ddd, *J* = 8.3, 2.5 and 0.9 Hz, H-4 or H-6), 6.93 (1H, ddd, *J* = 8.2, 2.3 and 1.0 Hz, H-4 or H-6), 7.00 (1H, ddd, *J* = 7.8, 7.8 and 1.7 Hz, H-4’), 7.13 (1H, ddd, *J* = 7.7, 7.7 and 1.4 Hz, H-5’), 7.25 (2H, d, *J* = 8.4 Hz, H-6”), 7.28 (1H, dd, *J* = 8.3, 8.2 Hz, H-5), 7.69 (1H, s, ArN*H*Ac), 8.44 (1H, dd, *J* = 8.2, 1.7 Hz, H-3’); ^{13}C NMR (126 MHz, $CDCl_3$) δ 25.0 (*C*H$_3$CO), 47.1 (ArC*H*$_2$), 55.2 (ArO*C*H$_3$), 55.5 (ArO*C*H$_3$), 98.3 (C-3”), 104.1 (C-5”), 113.1 (C-2), 116.5 (C-4 or C-6), 116.6 (C-1”), 117.6 (C-4 or C-6), 117.7 (C-6’), 121.2 (C-3’), 124.2 (C-4 or C-6), 124.5 (C-4’), 129.9 (C-2’), 130.5 (C-5), 131.1 (C-6”), 145.2 (C-1’), 151.6 (C-1), 157.1 (C-3), 158.6 (C-2” or C-4”), 160.8 (C-2” or C-4”), 168.5 (*C*OCH$_3$); LRMS (ES$^-$) *m/z* 621.4 [M-H]$^-$; HRMS (ESI) calcd for $C_{32}H_{33}N_2O_9S$ [M-H]$^-$ 621.1912, found 621.1893.

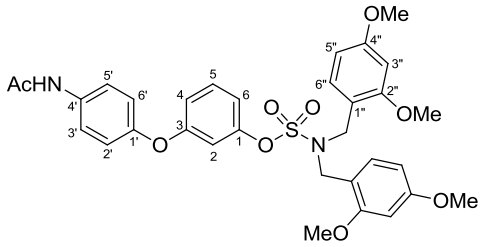
3-(3-Acetamidophenoxy)phenyl bis(2,4-dimethoxybenzyl)sulfamate, (188)



Compound **188** was synthesised according to general procedure J, using the following reagents: 3-(4-aminophenoxy)phenyl bis(2,4-dimethoxybenzyl)sulfamate (**182**) (250 mg,

0.43 mmol), triethylamine (87 mg, 120 µL, 0.86 mmol), acetic anhydride (53 mg, 49 µL, 0.52 mmol) and DCM (4.3 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 45:55) to yield the *title compound* as a clear oil (236 mg, 88%); R_f = 0.27 (petrol:EtOAc, 45:55); λ_{max} (EtOH)/nm 278.7; IR (neat) ν_{max}/cm^{-1} 1670, 1589, 1541, 1507, 1478, 1368, 1257, 1207, 1157, 1111; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.11 (3H, s, C*H*$_3$CO), 3.70 (6H, s, 2 × ArOC*H*$_3$), 3.78 (6H, s, 2 × ArOC*H*$_3$), 4.44 (4H, s, 2 × ArC*H*$_2$), 6.37 (2H, d, *J* = 2.4 Hz, H-3"), 6.41 (2H, dd, *J* = 8.4, 2.4 Hz, H-5"), 6.70 (1H, dd, *J* = 2.4, 2.3 Hz, H-2), 6.75 – 6.71 (1H, m, H-6'), 6.86 (1H, ddd, *J* = 8.2, 2.4 and 0.9 Hz, H-4 or H-6), 6.89 (1H, ddd, *J* = 8.3, 2.3 and 0.9 Hz, H-4 or H-6), 7.10 (1H, dd, *J* = 2.4, 2.3 Hz, H-2'), 7.30 – 7.21 (4H, m, H-5 and H-5' and H-6"), 7.32 (1H, s, ArN*H*Ac), 7.38 – 7.34 (1H, m, H-4'); ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.7 (*C*H$_3$CO), 47.1 (Ar*C*H$_2$), 55.3 (ArO*C*H$_3$), 55.5 (ArO*C*H$_3$), 98.3 (C-3"), 104.1 (C-5"), 110.4 (C-2'), 113.0 (C-2), 114.7 (C-6'), 115.1 (C-4'), 116.6 (C-1"), 117.0 (C-4 or C-6), 117.0 (C-4 or C-6), 130.3 (C-5 or C-5'), 130.3 (C-5 or C-5'), 131.0 (C-6"), 139.5 (C-3'), 151.4 (C-1), 157.3 (C-3 or C-1'), 157.8 (C-3 or C-1'), 158.5 (C-2" or C-4"), 160.7 (C-2" or C-4"), 168.4 (*C*OCH$_3$); LRMS (ES$^-$) *m/z* 621.4 [M-H]$^-$; HRMS (ESI) calcd for $C_{32}H_{33}N_2O_9S$ [M-H]$^-$ 621.1912, found 621.1894.

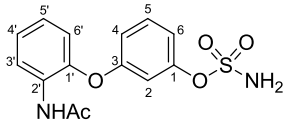
3-(4-Acetamidophenoxy)phenyl bis(2,4-dimethoxybenzyl)sulfamate, (189)



Compound **189** was synthesised according to general procedure J, using the following reagents: 3-(4-aminophenoxy)phenyl bis(2,4-dimethoxybenzyl)sulfamate (**183**) (250 mg, 0.43 mmol), triethylamine (87 mg, 120 µL, 0.86 mmol), acetic anhydride (53 mg, 49 µL, 0.52 mmol) and DCM (4.3 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 35:65) to yield the *title compound* as a white solid (231 mg, 86%); R_f = 0.30 (petrol:EtOAc, 35:65); m.p. 49.5-51.5 °C; λ_{max} (EtOH)/nm 251.0; IR (neat) ν_{max}/cm^{-1} 1667, 1611, 1589, 1505, 1478, 1368, 1249, 1206, 1157; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.16 (3H, s, C*H*$_3$CO), 3.70 (6H, s, 2 × ArOC*H*$_3$), 3.78 (6H, s, 2 × ArOC*H*$_3$), 4.44 (4H, s, 2 × ArC*H*$_2$), 6.36 (2H, d, *J* = 2.4 Hz, H-3"), 6.41 (2H, dd, *J* = 8.4, 2.4 Hz, H-5"), 6.70 (1H, dd, *J* = 2.3, 2.1 Hz, H-2), 6.82 (1H, dd, *J* = 8.3, 2.3 Hz, H-4 or H-6), 6.86 (1H, dd, *J* = 8.2, 2.1 Hz, H-4 or H-6), 6.95 (2H, d,

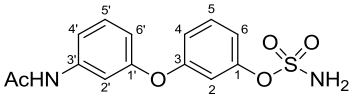
J = 8.9 Hz, H-2', 6'), 7.25 – 7.20 (3H, m, H-5 and H-6"), 7.31 (1H, s, ArN*H*Ac), 7.46 (2H, d, *J* = 8.9 Hz, H-3', 5'); ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.6 (*C*H_3CO), 47.1 (Ar*C*H_2), 55.2 (ArO*C*H_3), 55.5 (ArO*C*H_3), 98.3 (C-3"), 104.1 (C-5"), 112.3 (C-2), 116.2 (C-4 or C-6), 116.5 (C-4 or C-6), 116.6 (C-1"), 120.0 (C-2', 6'), 121.8 (C-3', 5'), 130.2 (C-5), 131.0 (C-6"), 134.0 (C-4'), 151.4 (C-1 or C-1'), 152.8 (C-1 or C-1'), 158.5 (C-3), 158.5 (C-2" or C-4"), 160.7 (C-2" or C-4"), 168.4 (*C*OCH_3); LRMS (ES^-) *m/z* 621.5 $[M-H]^-$; HRMS (ESI) calcd for $C_{32}H_{33}N_2O_9S$ $[M-H]^-$ 621.1912, found 621.1892.

3-(2-Acetamidophenoxy)phenyl sulfamate, (190)



Compound **190** was synthesised according to general procedure D, using the following reagents: 3-(2-acetamidophenoxy)phenyl bis(2,4-dimethoxybenzyl)sulfamate (**187**) (200 mg, 0.32 mmol), DCM (2.9 mL) and TFA (0.3 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 65:35) to yield the *title compound* as a white solid (88 mg, 85%); R_f = 0.29 (petrol:EtOAc, 65:35); m.p. 142.0-144.0 °C; No λ_{max} (EtOH)/nm; IR (neat) ν_{max}/cm^{-1} 3383, 3299, 1665, 1609, 1594, 1539, 1477, 1453, 1366, 1254, 1190, 1123; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.00 (3H, s, C*H*$_3$CO), 6.93 – 6.88 (2H, m, 2 × Ar*H*), 6.99 (1H, dd, *J* = 7.8, 1.8 Hz, H-6'), 7.06 – 7.02 (1H, m, Ar*H*), 7.19 – 7.08 (2H, m, 2 × Ar*H*), 7.43 (1H, dd, *J* = 8.5, 8.5 Hz, H-5), 7.94 (1H, d, *J* = 7.4 Hz, H-3'), 8.04 (2H, s, $ArOSO_2NH_2$), 9.48 (1H, s, ArN*H*Ac); ^{13}C NMR (126 MHz, DMSO-d_6) δ 23.5 (*C*H_3CO), 112.1 (CH Ar), 116.0 (CH Ar), 116.8 (CH Ar), 119.4 (C-6'), 124.2 (CH Ar), 124.3 (CH Ar), 125.0 (CH Ar), 130.1 (C-2'), 130.6 (C-5), 146.8 (C-1'), 151.0 (C-1), 157.6 (C-3), 168.7 (*C*OCH_3); LRMS (ES^-) *m/z* 321.2 $[M-H]^-$; HRMS (ESI) calcd for $C_{14}H_{13}N_2O_5S$ $[M-H]^-$ 321.0551, found 321.0539.

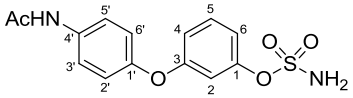
3-(3-Acetamidophenoxy)phenyl sulfamate, (191)



Compound **191** was synthesised according to general procedure D, using the following reagents: 3-(3-acetamidophenoxy)phenyl bis(2,4-dimethoxybenzyl)sulfamate (**188**) (200 mg, 0.32 mmol), DCM (2.9 mL) and TFA (0.3 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 1:1) to yield the *title compound* as a white solid (98 mg, 94%); R_f = 0.28 (petrol:EtOAc, 1:1); m.p.

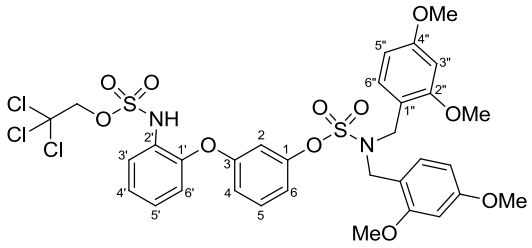
134.0-136.0 °C; λ_{max} (EtOH)/nm 275.0; IR (neat) ν_{max}/cm^{-1} 3361, 3290, 3215, 3085, 1651, 1600, 1549, 1478, 1436, 1379, 1264, 1182; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.02 (3H, s, CH_3CO), 6.76 – 6.71 (1H, m, H-6'), 6.91 (1H, dd, *J* = 2.3, 2.3 Hz, H-2), 6.96 (1H, ddd, *J* = 8.3, 2.4 and 0.9 Hz, H-4 or H-6), 7.05 (1H, ddd, *J* = 8.2, 2.2 and 0.9 Hz, H-4 or H-6), 7.35 – 7.30 (2H, m, H-5 and H-4'), 7.43 (1H, dd, *J* = 1.6, 1.6 Hz, H-2'), 7.45 (1H, dd, *J* = 8.3, 8.3 Hz, H-5'), 8.03 (2H, s, ArOSO$_2$NH_2), 10.04 (1H, s, ArN*H*Ac); ^{13}C NMR (126 MHz, DMSO-d_6) δ 24.0 (*C*H$_3$CO), 109.5 (C-2'), 112.3 (C-2), 113.5 (C-6'), 114.4 (C-4'), 116.3 (C-4 or C-6), 117.0 (C-4 or C-6), 130.2 (C-5 or C-5'), 130.8 (C-5 or C-5'), 141.0 (C-3'), 151.1 (C-1), 156.0 (C-1'), 157.5 (C-3), 168.5 (*C*OCH$_3$); LRMS (ES$^-$) *m/z* 643.3 [2M-H]$^-$; HRMS (ESI) calcd for $C_{14}H_{13}N_2O_5S$ [M-H]$^-$ 321.0551, found 321.0541.

3-(4-Acetamidophenoxy)phenyl sulfamate, (192)



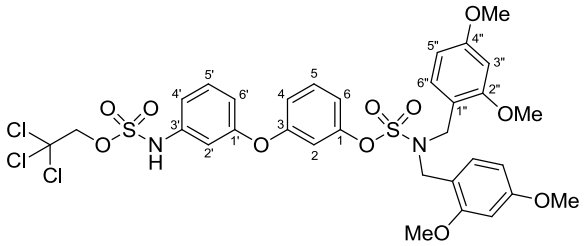
Compound **192** was synthesised according to general procedure D, using the following reagents: 3-(4-acetamidophenoxy)phenyl bis(2,4-dimethoxybenzyl)sulfamate (**189**) (200 mg, 0.32 mmol), DCM (2.9 mL) and TFA (0.3 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 45:55) to yield the *title compound* as a white solid (96 mg, 92%); R_f = 0.29 (petrol:EtOAc, 45:55); m.p. 108.0-110.0 °C; λ_{max} (EtOH)/nm 250.8; IR (neat) ν_{max}/cm^{-1} 3309, 3178, 3076, 1635, 1596, 1526, 1506, 1477, 1371, 1250, 1178, 1161; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.04 (3H, s, CH_3CO), 6.84 (1H, dd, *J* = 2.4, 2.2 Hz, H-2), 6.91 (1H, ddd, *J* = 8.3, 2.4 and 0.9 Hz, H-4 or H-6), 7.00 (1H, ddd, *J* = 8.2, 2.2 and 0.9 Hz, H-4 or H-6), 7.04 (2H, d, *J* = 9.0 Hz, H-2', 6'), 7.42 (1H, dd, *J* = 8.3, 8.2 Hz, H-5), 7.62 (2H, d, *J* = 9.0 Hz, H-3', 5'), 8.01 (2H, s, ArOSO$_2$NH_2), 9.99 (1H, s, ArN*H*Ac); ^{13}C NMR (126 MHz, DMSO-d_6) δ 23.9 (*C*H$_3$CO), 111.4 (C-2), 115.5 (C-4 or C-6), 116.4 (C-4 or C-6), 119.9 (C-2', 6'), 120.6 (C-3', 5'), 130.7 (C-5), 135.9 (C-4'), 150.5 (C-1 or C-1'), 151.0 (C-1 or C-1'), 158.4 (C-3), 168.1 (*C*OCH$_3$); LRMS (ES$^-$) *m/z* 321.2 [M-H]$^-$; HRMS (ESI) calcd for $C_{14}H_{13}N_2O_5S$ [M-H]$^-$ 321.0551, found 321.0543.

3-(2-(((2,2,2-Trichloroethoxy)sulfonyl)amino)phenoxy)phenyl bis(2,4-dimethoxy benzyl) sulfamate, (193)



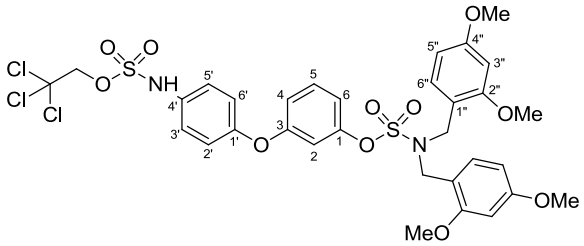
Compound **193** was synthesised according to general procedure K, using the following reagents: 3-(2-aminophenoxy)phenyl bis(2,4-dimethoxybenzyl)sulfamate (**181**) (50 mg, 0.09 mmol), 2,3-dimethyl-1-((2,2,2-trichloroethoxy)sulfonyl)-1*H*-imidazol-3-ium tetrafluoroborate (**158**) (102 mg, 0.26 mmol) and THF (1 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 3:1) to yield the *title compound* as a clear oil (10 mg, 15%); R_f = 0.31 (petrol:EtOAc, 3:1); λ_{max} (EtOH)/nm 277.2; IR (neat) ν_{max}/cm^{-1} 1611, 1589, 1507, 1368, 1255, 1208, 1174, 1157, 1116, 1036; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.72 (6H, s, 2 × ArOCH_3), 3.79 (6H, s, 2 × ArOCH_3), 4.45 (4H, s, 2 × ArCH_2), 4.68 (2H, s, CH_2CCl_3), 6.39 (2H, d, *J* = 2.4 Hz, H-3”), 6.42 (2H, dd, *J* = 8.3, 2.4 Hz, H-5”), 6.67 (1H, dd, *J* = 2.3, 2.3 Hz, H-2), 6.83 (1H, dd, *J* = 8.1, 1.5 Hz, H-6’), 6.88 (1H, ddd, *J* = 8.3, 2.4 and 0.9 Hz, H-4 or H-6), 6.97 (1H, ddd, *J* = 8.3, 2.3 and 0.9 Hz, H-4 or H-6), 7.09 (1H, ddd, *J* = 8.0, 7.6 and 1.7 Hz, H-4 or H-5), 7.14 (1H, ddd, *J* = 7.9, 1.5 and 1.5 Hz, H-4’ or H-5’), 7.24 (2H, d, *J* = 8.3 Hz, H-6”), 7.31 (1H, dd, *J* = 8.3, 8.3 Hz, H-5), 7.65 (1H, dd, *J* = 8.0, 1.6 Hz, H-3’); ^{13}C NMR (126 MHz, $CDCl_3$) δ 47.1 (Ar*C*H_2), 55.3 (ArO*C*H_3), 55.6 (ArO*C*H_3), 79.1 (*C*H_2CCl_3), 93.0 (CH_2*C*Cl_3), 98.3 (C-3”), 104.1 (C-5”), 113.3 (C-2), 116.6 (C-1”), 116.9 (C-4 or C-6), 117.6 (C-6’), 118.2 (C-4 or C-6), 121.2 (C-3’), 124.4 (C-4’ or C-5’), 126.1 (C-4’ or C-5’), 126.8 (C-2’), 130.6 (C-5), 131.1 (C-6”), 146.6 (C-1’), 151.6 (C-1), 156.1 (C-3), 158.6 (C-2” or C-4”), 160.7 (C-2” or C-4”); LRMS (ES$^-$) *m/z* 789.3 [M(^{35}Cl^{35}Cl^{35}Cl)-H]$^-$, 791.3 [M(^{37}Cl^{35}Cl^{35}Cl)-H]$^-$; HRMS (ESI) calcd for $C_{32}H_{32}Cl_3N_2O_{11}S_2$ [M(^{35}Cl^{35}Cl^{35}Cl)-H]$^-$ 789.0519, found 789.0494.

3-(3-(((2,2,2-Trichloroethoxy)sulfonyl)amino)phenoxy)phenyl bis(2,4-dimethoxy benzyl) sulfamate, (194)



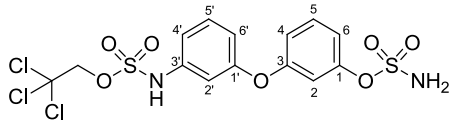
Compound **194** was synthesised according to general procedure K, using the following reagents: 3-(3-aminophenoxy)phenyl bis(2,4-dimethoxybenzyl)sulfamate (**182**) (450 mg, 0.77 mmol), 2,3-dimethyl-1-((2,2,2-trichloroethoxy)sulfonyl)-1*H*-imidazol-3-ium tetrafluoroborate (**158**) (919 mg, 2.32 mmol) and THF (7.7 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 7:3) to yield the *title compound* as a yellow oil (480 mg, 78%); R_f = 0.31 (petrol:EtOAc, 7:3); λ_{max} (EtOH)/nm 277.4; IR (neat) ν_{max}/cm^{-1} 1611, 1590, 1507, 1478, 1367, 1266, 1208, 1175, 1149, 1112; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.71 (6H, s, 2 × ArOCH_3), 3.79 (6H, s, 2 × ArOCH_3), 4.44 (4H, s, 2 × ArCH_2), 4.62 (2H, s, CH_2CCl_3), 6.38 (2H, d, *J* = 2.4 Hz, H-3”), 6.42 (2H, dd, *J* = 8.3, 2.4 Hz, H-5”), 6.69 (1H, dd, *J* = 2.3, 2.3 Hz, H-2), 6.81 (1H, dd, *J* = 2.2, 2.2 Hz, H-2’), 6.85 – 6.82 (1H, m, H-6’), 6.90 – 6.86 (1H, m, H-4 or H-6), 6.91 (1H, ddd, *J* = 8.2, 2.3 and 0.9 Hz, H-4 or H-6), 7.05 (1H, ddd, *J* = 8.2, 2.3 and 1.0 Hz, H-4’), 7.17 (1H, s, ArN*H*SO_3), 7.24 (2H, d, *J* = 8.4 Hz, H-6”), 7.27 (1H, dd, *J* = 8.2, 8.2 Hz, H-5 or H-5’), 7.32 (1H, dd, *J* = 8.1, 8.1 Hz, H-5 or H-5’); ^{13}C NMR (126 MHz, $CDCl_3$) δ 47.2 (Ar*C*H_2), 55.3 (ArO*C*H_3), 55.6 (ArO*C*H_3), 79.0 (*C*H_2CCl_3), 93.1 (CH_2*C*Cl_3), 98.4 (C-3”), 104.2 (C-5”), 111.2 (C-2’), 113.3 (C-2), 115.7 (C-4’), 116.0 (C-6’), 116.6 (C-1”), 117.3 (C-4 or C-6), 117.5 (C-4 or C-6), 130.5 (C-5 or C-5’), 131.0 (C-5 or C-5’), 131.1 (C-6”), 137.0 (C-3’), 151.4 (C-1), 157.1 (C-3 or C-1’), 157.9 (C-3 or C-1’), 158.5 (C-2” or C-4”), 160.7 (C-2” or C-4”); LRMS (ES$^-$) *m/z* 789.2 [M(^{35}Cl^{35}Cl^{35}Cl)-H]$^-$, 791.2 [M(^{37}Cl^{35}Cl^{35}Cl)-H]$^-$; HRMS (ESI) calcd for $C_{32}H_{32}Cl_3N_2O_{11}S_2$ [M(^{35}Cl^{35}Cl^{35}Cl)-H]$^-$ 789.0519, found 789.0493.

3-(4-(((2,2,2-Trichloroethoxy)sulfonyl)amino)phenoxy)phenyl bis(2,4-dimethoxy benzyl) sulfamate, (195)



Compound **195** was synthesised according to general procedure K, using the following reagents: 3-(4-aminophenoxy)phenyl bis(2,4-dimethoxybenzyl)sulfamate (**183**) (450 mg, 0.77 mmol), 2,3-dimethyl-1-((2,2,2-trichloroethoxy)sulfonyl)-1*H*-imidazol-3-ium tetrafluoroborate (**158**) (919 mg, 2.32 mmol) and THF (7.7 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 6:4) to yield the *title compound* as a yellow oil (553 mg, 90%); R_f = 0.32 (petrol:EtOAc, 65:35); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.71 (6H, s, 2 × ArOC*H*$_3$), 3.79 (6H, s, 2 × ArOC*H*$_3$), 4.44 (4H, s, 2 × ArC*H*$_2$), 4.65 (2H, s, C*H*$_2$CCl$_3$), 6.37 (2H, d, *J* = 2.4 Hz, H-3”), 6.41 (2H, dd, *J* = 8.4, 2.4 Hz, H-5”), 6.71 (1H, dd, *J* = 2.4, 2.3 Hz, H-2), 6.85 (1H, ddd, *J* = 8.3, 2.4 and 0.9 Hz, H-4 or H-6), 6.87 (1H, s, ArN*H*SO$_3$), 6.90 (1H, ddd, *J* = 8.2, 2.3 and 0.9 Hz, H-4 or H-6), 6.99 (2H, d, *J* = 8.8 Hz, H-2’, 6’), 7.30 – 7.20 (5H, m, H-5 and H-3’, 5’ and H-6”); ^{13}C NMR (126 MHz, $CDCl_3$) δ 47.1 (Ar*C*H$_2$), 55.2 (ArO*C*H$_3$), 55.5 (ArO*C*H$_3$), 79.0 (*C*H$_2$CCl$_3$), 93.2 (CH$_2$*C*Cl$_3$), 98.3 (C-3”), 104.1 (C-5”), 112.9 (C-2), 116.5 (C-1”), 116.9 (C-4 or C-6), 117.3 (C-4 or C-6), 119.9 (C-2’, 6’), 124.8 (C-3’, 5’), 130.4 (C-5), 130.6 (C-4’), 131.0 (C-5), 151.5 (C-1), 155.3 (C-1’), 157.6 (C-3), 158.6 (C-2” or C-4”), 160.7 (C-2” or C-4”); IR (neat) ν_{max}/cm^{-1} 1612, 1589, 1505, 1478, 1368, 1254, 1208, 1175, 1112, 1037; λ_{max} (EtOH)/nm 277.6; LRMS (ES$^-$) *m/z* 789.3 [M(^{35}Cl^{35}Cl^{35}Cl)-H]$^-$, 791.3 [M(^{37}Cl^{35}Cl^{35}Cl)-H]$^-$; HRMS (ESI) calcd for $C_{32}H_{32}Cl_3N_2O_{11}S_2$ [M(^{35}Cl^{35}Cl^{35}Cl)-H]$^-$ 789.0519, found 789.0497.

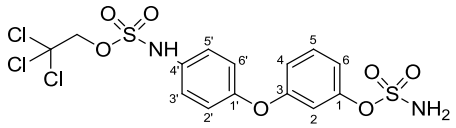
2,2,2-Trichloroethyl (3-(3-(sulfamoyloxy)phenoxy)phenyl)sulfamate, (196)



Compound **196** was synthesised according to general procedure D, using the following reagents: 3-(3-(((2,2,2-trichloroethoxy)sulfonyl)amino)phenoxy)phenyl bis(2,4-dimethoxybenzyl) sulfamate (**194**) (450 mg, 0.57 mmol), DCM (5.2 mL) and TFA (0.6 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 7:3) to yield the *title compound* as a clear brown oil (240 mg, 86%);

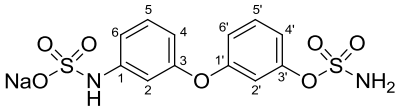
R_f = 0.33 (petrol:EtOAc, 7:3); λ_{max} (EtOH)/nm 277.4; IR (neat) ν_{max}/cm^{-1} 3285, 1593, 1478, 1363, 1257, 1181, 1146, 1112; ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.85 (2H, s, CH_2CCl$_3$), 6.84 (1H, ddd, *J* = 8.2, 2.4 and 0.9 Hz, Ar*H*), 6.94 – 6.91 (2H, m, H-2 and H-2'), 6.96 (1H, ddd, *J* = 8.2, 2.4 and 0.9 Hz, Ar*H*), 7.09 – 7.02 (2H, m, 2 × Ar*H*), 7.40 (1H, dd, *J* = 8.2, 8.2 Hz, H-5 or H-5'), 7.46 (1H, dd, *J* = 8.2, 8.2 Hz, H-5 or H-5'), 8.04 (2H, s, ArOSO$_2$NH_2), 11.16 (1H, s, ArN*H*SO$_3$); ^{13}C NMR (126 MHz, DMSO-d_6) δ 77.8 (*C*H$_2$CCl$_3$), 93.4 (CH$_2$*C*Cl$_3$), 110.1 (C-2 or C-2'), 112.6 (C-2 or C-2'), 114.7 (CH Ar), 115.0 (CH Ar), 116.4 (CH Ar), 117.4 (CH Ar), 130.9 (C-5 or C-5'), 130.9 (C-5 or C-5'), 138.3 (C-3'), 151.1 (C-1), 156.5 (C-3 or C-1'), 157.0 (C-3 or C-1'); LRMS (ES$^-$) *m/z* 489.1 [M(^{35}Cl^{35}Cl^{35}Cl)-H]$^-$, 491.2 [M(^{37}Cl^{35}Cl^{35}Cl)-H]$^-$; HRMS (ESI) calcd for $C_{14}H_{12}Cl_3N_2O_7S_2$ [M(^{35}Cl^{35}Cl^{35}Cl)-H]$^-$ 488.9157, found 488.9152.

2,2,2-Trichloroethyl (4-(3-(sulfamoyloxy)phenoxy)phenyl)sulfamate, (197)



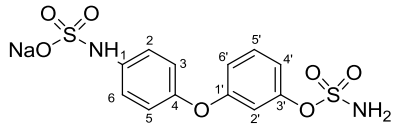
Compound **197** was synthesised according to general procedure D, using the following reagents: 3-(4-(((2,2,2-trichloroethoxy)sulfonyl)amino)phenoxy)phenyl bis(2,4-dimethoxybenzyl) sulfamate (**195**) (500 mg, 0.63 mmol), DCM (5.7 mL) and TFA (0.7 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 65:35) to yield the *title compound* as a clear brown oil (276 mg, 89%); R_f = 0.30 (petrol:EtOAc, 6:4); λ_{max} (EtOH)/nm 234.6; IR (neat) ν_{max}/cm^{-1} 3278, 1596, 1504, 1478, 1364, 1252, 1171, 1111, 1012; ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.86 (2H, s, CH_2CCl$_3$),6.89 (1H, dd, *J* = 2.4, 2.3 Hz, H-2), 6.93 (1H, ddd, *J* = 8.3, 2.4 and 1.0 Hz, H-4 or H-6), 7.04 (1H, ddd, *J* = 8.2, 2.3 and 1.0 Hz, H-4 or H-6), 7.11 (2H, d, *J* = 8.9 Hz, H-2', 6'), 7.29 (2H, d, *J* = 8.9 Hz, H-3', 5'), 7.45 (1H, dd, *J* = 8.3, 8.2 Hz, H-5), 8.03 (2H, s, ArOSO$_2$NH_2), 10.95 (1H, s, ArN*H*SO$_3$); ^{13}C NMR (126 MHz, DMSO-d_6) δ 77.7 (*C*H$_2$CCl$_3$), 93.6 (CH$_2$*C*Cl$_3$), 112.0 (C-2), 115.9 (C-4 or C-6), 117.0 (C-4 or C-6), 120.2 (C-2', 6'), 122.7 (C-3', 5'), 130.8 (C-5), 132.5 (C-4'), 151.1 (C-1), 152.7 (C-1'), 157.7 (C-3); LRMS (ES$^-$) *m/z* 489.1 [M(^{35}Cl^{35}Cl^{35}Cl)-H]$^-$, 491.2 [M(^{37}Cl^{35}Cl^{35}Cl)-H]$^-$; HRMS (ESI) calcd for $C_{14}H_{12}Cl_3N_2O_7S_2$ [M(^{35}Cl^{35}Cl^{35}Cl)-H]$^-$ 488.9157, found 488.9152.

Sodium (3-(3-(sulfamoyloxy)phenoxy)phenyl)sulfamate, (198)



Compound **198** was synthesised according to general procedure M, using the following reagents: 2,2,2-trichloroethyl (3-(3-(sulfamoyloxy)phenoxy)phenyl)sulfamate (**196**) (150 mg, 0.31 mmol), MeOH (3.1 mL), acetate buffer pH 4.65 (3.1 mL) and zinc (200 mg, 3.06 mmol). The crude product was converted to the sodium salt by ion-exchange chromatography (DOWEX 50WX2 - Na^+ form). The crude product was purified by column chromatography (silica gel, EtOAc:MeOH, 1:0 → 93:7) to yield the *title compound* as a white solid (87 mg, 75%); R_f = 0.23 (EtOAc:MeOH, 93:7; $KMnO_4$); m.p. 133.5-135.5 °C; λ_{max} (EtOH)/nm 279.2; IR (neat) ν_{max}/cm^{-1} 3472, 3346, 3093, 1592, 1478, 1368, 1185, 1150, 1045; ^{1}H NMR (500 MHz, MeOD) δ 6.55 (1H, dd, *J* = 8.4, 2.7 Hz, Ar*H*), 6.99 – 6.89 (4H, m, 4 × Ar*H*), 7.03 (1H, d, *J* = 7.7 Hz, Ar*H*), 7.20 (1H, dd, *J* = 8.0, 8.0 Hz, H-5 or H-5'), 7.35 (1H, dd, *J* = 8.1, 8.1 Hz, H-5 or H-5'); ^{13}C NMR (126 MHz, MeOD) δ 109.7 (CH Ar), 112.5 (CH Ar), 113.4 (CH Ar), 114.2 (CH Ar), 117.4 (CH Ar), 117.7 (CH Ar), 130.9 (C-5 or C-5'), 131.3 (C-5 or C-5'), 144.9 (C-1), 152.9 (C-3'), 158.1 (C-3 or C-1'), 160.0 (C-3 or C-1'); LRMS (ES^-) *m/z* 359.2 $[M-Na]^-$; HRMS (ESI) calcd for $C_{12}H_{11}N_2O_7S_2$ $[M-Na]^-$ 359.0013, found 359.0000.

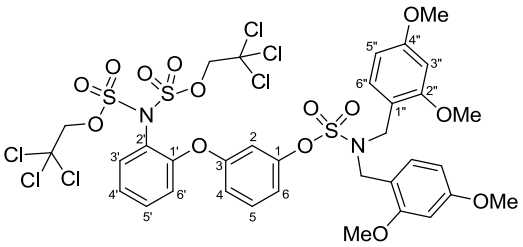
Sodium (4-(3-(sulfamoyloxy)phenoxy)phenyl)sulfamate, (199)



Compound **199** was synthesised according to general procedure M, using the following reagents: 2,2,2-trichloroethyl (4-(3-(sulfamoyloxy)phenoxy)phenyl)sulfamate (**197**) (150 mg, 0.31 mmol), MeOH (3.1 mL), acetate buffer pH 4.65 (3.1 mL) and zinc (200 mg, 3.06 mmol). The crude product was converted to the sodium salt by ion-exchange chromatography (DOWEX 50WX2 - Na^+ form). The crude product was purified by column chromatography (silica gel, EtOAc:MeOH, 1:0 → 93:7) to yield the *title compound* as a white solid (81 mg, 70%); R_f = 0.22 (EtOAc:MeOH, 93:7; $KMnO_4$); m.p. 180.0-182.0 °C; λ_{max} (EtOH)/nm 241.0; IR (neat) ν_{max}/cm^{-1} 3368, 3261, 3227, 3103, 1600, 1508, 1479, 1363, 1207, 1169, 1159; ^{1}H NMR (500 MHz, MeOD) δ 6.88 – 6.84 (2H, m, H-2' and H-4' or H-6'), 6.94 (2H, d, *J* = 8.9 Hz, H-3, 5), 6.99 (2H, ddd, *J* = 8.1, 2.0 and 1.0 Hz, H-4' or H-6'), 7.23 (2H, d, *J* = 8.9 Hz, H-2, 3), 7.33 (1H, dd, *J* = 8.6, 8.6 Hz, H-5'); ^{13}C NMR (126 MHz, MeOD) δ 112.6 (C-2'), 116.4 (C-4' or C-6'), 117.1

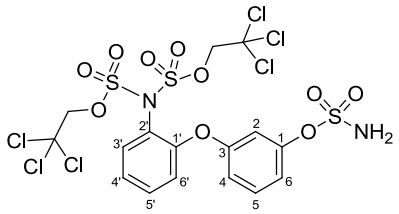
(C-4’ or C-6’), 120.9 (C-2, 6), 121.4 (C-3, 5), 131.2 (C-5), 139.7 (C-1), 151.5 (C-4 or C-3’), 152.9 (C-4 or C-3’), 161.0 (C-1’); LRMS (ES$^-$) *m/z* 359.2 [M-Na]$^-$; HRMS (ESI) calcd for $C_{12}H_{11}N_2O_7S_2$ [M-Na]$^-$ 359.0013, found 358.9998.

_O,O_-bis(2,2,2-Trichloroethyl) (2-(3-((_N,N_-bis(2,4-dimethoxybenzyl)sulfamoyl)oxy) phenoxy)phenyl)iminodisulfate, (200)



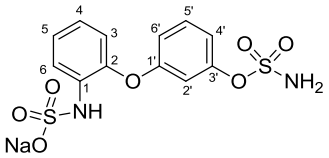
Compound (**200**) was synthesised according to general procedure L, using the following reagents: 2'-amino-[1,1'-biphenyl]-3-yl bis(2,4-dimethoxybenzyl)sulfamate (**181**) (450 mg, 0.77 mmol), 4-(dimethylamino)pyridine (208 mg, 1.70 mmol), triethylamine (432 µL, 314 mg, 3.01 mmol), 2,2,2-trichloroethyl chlorosulfate (**156**) (413 µL, 769 mg, 3.01 mmol) and THF (8 + 4 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 8:2) to yield the *title compound* as a pale yellow oil (428 mg, 55%); R_f = 0.29 (petrol:EtOAC, 8:2); λ_{max} (EtOH)/nm 277.6; IR (neat) ν_{max}/cm^{-1} 1612, 1588, 1508, 1479, 1429, 1371, 1261, 1208, 1191, 1158, 1117, 1038, 1003; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.71 (6H, s, 2 × ArOC*H*$_3$), 3.78 (6H, s, 2 × ArOC*H*$_3$), 4.46 (4H, s, 2 × ArC*H*$_2$), 4.96 (2H, d, *J* = 11.3 Hz, C*H*$_2$CCl$_3$), 5.04 (2H, d, *J* = 11.3 Hz, C*H*$_2$CCl$_3$), 6.38 (2H, d, *J* = 2.4 Hz, H-3”), 6.42 (2H, dd, *J* = 8.4, 2.4 Hz, H-5”), 6.90 (1H, dd, *J* = 8.4, 1.3 Hz, H-6’), 6.94 (1H, dd, *J* = 2.3, 2.3 Hz, H-2), 7.01 (2H, dd, *J* = 8.3, 2.3 Hz, H-4 and H-6), 7.21 (1H, ddd, *J* = 7.8, 7.8 and 1.3 Hz, H-4’), 7.25 (2H, d, *J* = 8.4 Hz, H-6”), 7.33 (1H, dd, *J* = 8.2, 8.2 Hz, H-5), 7.43 (1H, ddd, *J* = 8.5, 7.6 and 1.7 Hz, H-5’), 7.58 (1H, dd, *J* = 8.0, 1.6 Hz, H-3’); ^{13}C NMR (126 MHz, $CDCl_3$) δ 47.1 (Ar*C*H$_2$), 55.2 (ArO*C*H$_3$), 55.5 (ArO*C*H$_3$), 81.6 (*C*H$_2$CCl$_3$), 92.7 (CH$_2$*C*Cl$_3$), 98.3 (C-3”), 104.1 (C-5”), 114.4 (C-2), 116.4 (C-1”), 118.1 (C-4 or C-6), 118.3 (C-4 or C-6), 118.9 (C-6’), 124.1 (C-4’), 124.6 (C-2’), 130.9 (C-5), 131.0 (C-6”), 131.8 (C-5’), 133.0 (C-3’), 151.7 (C-1), 155.1 (C-3 or C-1’), 155.7 (C-3 or C-1’), 158.5 (C-2” or C-4”), 160.8 (C-2” or C-4”); HRMS (ESI) calcd for $C_{34}H_{38}Cl_6N_3O_{14}S_3$ [M(6 × ^{35}Cl)+NH_4]$^+$ 1017.9642, found 1017.9658.

***O,O*-bis(2,2,2-Trichloroethyl) (2-(3-(sulfamoyloxy)phenoxy)phenyl)iminodisulfate, (201)**



Compound **201** was synthesised according to general procedure D, using the following reagents: *O,O*-bis(2,2,2-trichloroethyl) (2-(3-((*N*,*N*-bis(2,4-dimethoxybenzyl)sulfamoyl) oxy) phenoxy)phenyl)iminodisulfate (**200**) (350 mg, 0.35 mmol), DCM (3.2 mL) and TFA (0.4 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 3:1) to yield the *title compound* as a clear brown oil (240 mg, 86%); R_f = 0.29 (petrol:EtOAc, 3:1); λ_{max} (EtOH)/nm 277.2; IR (neat) ν_{max}/cm^{-1} 3398, 3295, 1590, 1490, 1479, 1428, 1375, 1259, 1186, 1118; ^{1}H NMR (500 MHz, DMSO-d_6) δ 5.28 (2H, d, *J* = 11.3 Hz, CH_2CCl$_3$), 5.36 (2H, d, *J* = 11.3 Hz, CH_2CCl$_3$), 7.10 – 7.04 (3H, m, H-2 and H-4 or H-6 and H-6’), 7.17 (1H, ddd, *J* = 8.3, 2.1 and 0.9 Hz, H-4 or H-6), 7.32 (1H, ddd, *J* = 7.9, 7.9 and 1.3 Hz, H-4’), 7.61 – 7.51 (2H, m, H-5 and H-5’), 7.88 (1H, dd, *J* = 8.0, 1.6 Hz, H-3’), 8.10 (2H, s, ArOSO$_2$NH_2); ^{13}C NMR (126 MHz, DMSO-d_6) δ 80.7 (*C*H$_2$CCl$_3$), 92.8 (CH$_2$*C*Cl$_3$), 114.1 (C-2), 117.8 (C-4 or C-6 or C-6’), 118.4 (C-4 or C-6 or C-6’), 118.9 (C-4 or C-6), 124.0 (C-4’), 124.4 (C-2’), 131.2 (C-5), 132.2 (C-3’), 133.4 (C-5’), 151.1 (C-1), 154.4 (C-3 or C-1’), 155.4 (C-3 or C-1’); HRMS (ESI) calcd for $C_{16}H_{13}Cl_6N_2O_{10}S_3$ [M(6 × ^{35}Cl)-H]$^-$ 698.7869, found 698.7868.

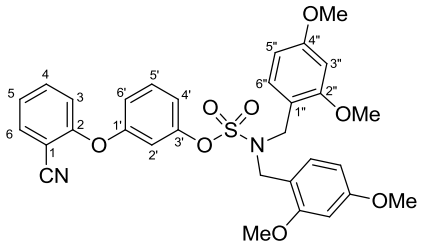
Sodium (2-(3-(sulfamoyloxy)phenoxy)phenyl)sulfamate, (202)



To *O,O*-bis(2,2,2-trichloroethyl) (2-(3-(sulfamoyloxy)phenoxy)phenyl)iminodisulfate (**201**) (140 mg, 0.20 mmol) in MeOH (3.5 mL) were added 3.5 mL of acetate buffer pH 4.65 and zinc (260 mg, 3.98 mmol). The resulting reaction mixture was stirred at RT for 24 h, until LC-MS indicated completion of the deprotection. Upon completion, the heterogeneous mixture was filtered through Celite and washed with MeOH (10 mL). The filtrate was concentrated *in vacuo* to give a crude oil, which was dissolved in a mixture of MeOH (3.5 mL) and acetate buffer pH 4.65 (3.5 mL). Acetic acid was added to acidify the reaction mixture to pH 4.0. The resulting solution was heated at 40 °C for 12 h. Upon completion, the solvents were removed *in vacuo* and the crude product was converted to

the sodium salt by ion-exchange chromatography (DOWEX 50WX2 - Na^+ form). The crude product was purified by column chromatography (silica gel, EtOAc:MeOH, 1:0 → 93:7) to yield the *title compound* as an off-white solid (25 mg, 33%); R_f = 0.24 (EtOAc:MeOH, 93:7; $KMnO_4$); m.p. No clear m.p., decomposition range 160-170 °C; λ_{max} (EtOH)/nm 270.6, 276.2; IR (neat) ν_{max}/cm^{-1} 3409, 3248, 2920, 1611, 1593, 1499, 1479, 1380, 1226, 1195, 1118, 1059; ^{1}H NMR (500 MHz, MeOD) δ 6.93 – 6.91 (2H, m, H-3 and H-4), 6.95 – 6.93 (1H, m, H-4' or H-6'), 6.96 (1H, dd, *J* = 2.3, 2.3 Hz, H-2'), 7.04 (1H, ddd, *J* = 8.2, 2.2 and 0.9 Hz, H-4' or H-6'), 7.13 (1H, ddd, *J* = 8.5, 6.2 and 2.6 Hz, H-5), 7.36 (1H, dd, *J* = 8.2, 8.2 Hz, H-5'), 7.73 – 7.69 (1H, m, H-6); ^{13}C NMR (126 MHz, MeOD) δ 112.9 (C-2'), 116.7 (C-4' or C-6'), 117.9 (C-4' or C-6'), 120.0 (C-6), 120.7 (C-3), 122.8 (C-4), 126.0 (C-5), 131.4 (C-5'), 134.9 (C-1), 145.2 (C-2), 152.9 (C-3'), 159.8 (C-1'); LRMS (ES^-) *m/z* 359.2 $[M\text{-}Na]^-$; HRMS (ESI) calcd for $C_{12}H_{11}N_2O_7S_2$ $[M\text{-}Na]^-$ 359.0013, found 358.9998.

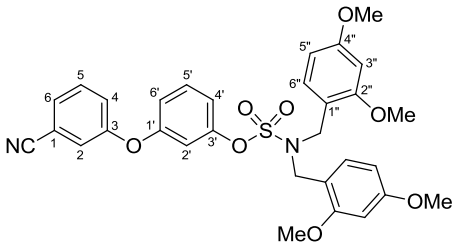
3-(2-Cyanophenoxy)phenyl bis(2,4-dimethoxybenzyl)sulfamate, (206)



Compound **206** was synthesised according to general procedure N, using the following reagents: 3-hydroxyphenyl bis(2,4-dimethoxybenzyl)sulfamate (**173**) (1.0 g, 2.04 mmol), potassium carbonate (339 mg, 2.45 mmol), 2-fluorobenzonitrile (495 mg, 443 µL, 4.08 mmol) and *N*,*N*-dimethylformamide (20 mL). The crude orange oil was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 7:3) to yield the *title compound* as a pale yellow oil (975 mg, 81%); R_f = 0.31 (petrol:EtOAc, 7:3); λ_{max} (EtOH)/nm 278.2, 283.0; IR (neat) ν_{max}/cm^{-1} 2230, 1611, 1589, 1507, 1478, 1449, 1371, 1253, 1208, 1173, 1157, 1034; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.73 (6H, s, 2 × ArOCH_3), 3.78 (6H, s, 2 × ArOCH_3), 4.44 (4H, s, 2 × ArCH_2), 6.39 (2H, d, *J* = 2.4 Hz, H-3"), 6.42 (2H, dd, *J* = 8.3, 2.4 Hz, H-5"), 6.64 (1H, dd, *J* = 2.3, 2.3 Hz, H-2), 6.84 (1H, dd, *J* = 8.5, 1.0 Hz, H-6'), 6.95 (1H, ddd, *J* = 8.2, 2.4 and 0.9 Hz, H-4 or H-6), 7.02 (1H, ddd, *J* = 8.3, 2.2 and 0.9 Hz, H-4 or H-6), 7.16 (1H, ddd, *J* = 7.6, 7.6 and 1.0 Hz, H-4'), 7.25 (2H, d, *J* = 8.5 Hz, H-6"), 7.33 (1H, dd, *J* = 8.3, 8.3 Hz, H-5), 7.48 (1H, ddd, *J* = 8.6, 7.6 and 1.7 Hz, H-5'), 7.68 (1H, dd, *J* = 7.7, 1.7 Hz, H-3'); ^{13}C NMR (126 MHz, $CDCl_3$) δ 47.2 (Ar*C*H_2), 55.3 (ArO*C*H_3), 55.5 (ArO*C*H_3), 98.3 (C-3"), 104.0 (C-5"), 104.1 (C-5"), 114.2 (C-2), 115.9

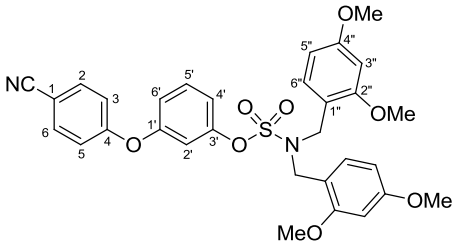
(Ar*C*N), 116.5 (C-1”), 117.1 (C-6’), 118.0 (C-4 or C-6), 118.8 (C-4 or C-6), 123.3 (C-4’), 130.7 (C-5), 131.1 (C-6”), 134.1 (C-3’), 134.4 (C-5’), 151.5 (C-1), 155.6 (C-3), 158.6 (C-2” or C-4”), 159.3 (C-1’), 160.8 (C-2” or C-4”); HRMS (ESI) calcd for $C_{31}H_{34}N_3O_8S$ $[M+NH_4]^+$ 608.2061, found 608.2056.

3-(3-Cyanophenoxy)phenyl bis(2,4-dimethoxybenzyl)sulfamate, (207)



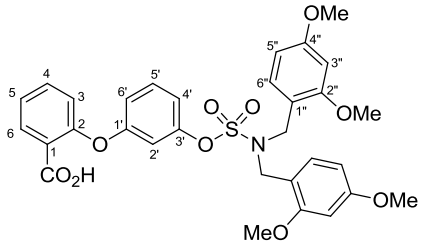
Compound **207** was synthesised according to general procedure N, using the following reagents: 3-hydroxyphenyl bis(2,4-dimethoxybenzyl)sulfamate (**173**) (1.0 g, 2.04 mmol), potassium carbonate (339 mg, 2.45 mmol), 3-fluorobenzonitrile (495 mg, 437 µL, 4.08 mmol) and *N*,*N*-dimethylformamide (20 mL). The crude orange oil was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 7:3) to yield the *title compound* as a yellow oil (740 mg, 61%); R_f = 0.30 (petrol:EtOAc, 7:3); λ_{max} (EtOH)/nm 277.8; IR (neat) ν_{max}/cm^{-1} 2232, 1611, 1588, 1507, 1478, 1370, 1255, 1207, 1175, 1157, 1111, 1033; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.72 (6H, s, 2 × ArOC*H*$_3$), 3.78 (6H, s, 2 × ArOC*H*$_3$), 4.45 (4H, s, 2 × ArC*H*$_2$), 6.38 (2H, d, *J* = 2.4 Hz, H-3”), 6.42 (2H, dd, *J* = 8.3, 2.4 Hz, H-5”), 6.72 (1H, dd, *J* = 2.3, 2.3 Hz, H-2), 6.88 (1H, ddd, *J* = 8.3, 2.3 and 0.9 Hz, H-4 or H-6), 6.96 (1H, ddd, *J* = 8.2, 2.2 and 0.9 Hz, H-4 or H-6), 7.20 (1H, ddd, *J* = 8.0, 2.5 and 1.4 Hz, H-6’), 7.26 – 7.22 (3H, m, H-2’ and H-6”), 7.31 (1H, dd, *J* = 8.2, 8.2 Hz, H-5), 7.41 – 7.38 (1H, m, H-4’), 7.45 – 7.41 (1H, m, H-5’); ^{13}C NMR (126 MHz, $CDCl_3$) δ 47.1 (Ar*C*H$_2$), 55.2 (ArO*C*H$_3$), 55.5 (ArO*C*H$_3$), 98.3 (C-3”), 104.1 (C-5”), 113.7 (C-2), 113.9 (C-3’), 116.5 (C-1”), 117.4 (C-4 or C-6), 118.1 (C-4 or C-6), 118.2 (Ar*C*N), 121.7 (C-2’), 123.1 (C-6’), 127.1 (C-4’), 130.7 (C-5 or C-5’), 130.9 (C-5 or C-5’), 131.1 (C-6”), 151.6 (C-1), 156.4 (C-3 or C-1’), 157.5 (C-3 or C-1’), 158.6 (C-2” or C-4”), 160.8 (C-2” or C-4”); HRMS (ESI) calcd for $C_{31}H_{34}N_3O_8S$ $[M+NH_4]^+$ 608.2061, found 608.2058.

3-(4-Cyanophenoxy)phenyl bis(2,4-dimethoxybenzyl)sulfamate, (208)



Compound **208** was synthesised according to general procedure N, using the following reagents: 3-hydroxyphenyl bis(2,4-dimethoxybenzyl)sulfamate (**173**) (1.0 g, 2.04 mmol), potassium carbonate (339 mg, 2.45 mmol), 4-fluorobenzonitrile (495 mg, 4.08 mmol) and *N*,*N*-dimethylformamide (20 mL). The crude orange oil was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 7:3) to yield the *title compound* as a pale yellow oil (870 mg, 72%); R_f = 0.31 (petrol:EtOAc, 7:3); λ_{max} (EtOH)/nm 272.0; IR (neat) ν_{max}/cm^{-1} 2226, 1611, 1589, 1504, 1478, 1370, 1250, 1208, 1157, 1112, 1033; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.72 (6H, s, 2 × ArOC*H*$_3$), 3.78 (6H, s, 2 × ArOC*H*$_3$), 4.44 (4H, s, 2 × ArC*H*$_2$), 6.37 (2H, d, *J* = 2.4 Hz, H-3”), 6.42 (2H, dd, *J* = 8.4, 2.4 Hz, H-5”), 6.72 (1H, dd, *J* = 2.3, 2.3 Hz, H-2), 6.93 (1H, ddd, *J* = 8.2, 2.3 and 0.9 Hz, H-4 or H-6), 7.02 – 6.97 (3H, m, H-4 or H-6 and H-2’, 6’), 7.24 (2H, d, *J* = 8.4 Hz, H-6”), 7.34 (1H, dd, *J* = 8.2, 8.2 Hz, H-5), 7.61 (2H, d, *J* = 8.8 Hz, H-3’, 5’); ^{13}C NMR (126 MHz, $CDCl_3$) δ 47.1 (Ar*C*H$_2$), 55.2 (ArO*C*H$_3$), 55.5 (ArO*C*H$_3$), 98.3 (C-3”), 104.1 (C-5”), 106.5 (C-4’), 114.4 (C-2), 116.4 (C-1”), 118.2 (C-4 or C-6), 118.3 (C-2’, 6’), 118.8 (C-4 or C-6), 118.8 (Ar*C*N), 130.8 (C-5), 131.1 (C-6”), 134.3 (C-3’, 5’), 151.6 (C-1), 155.6 (C-3), 158.6 (C-2” or C-4”), 160.8 (C-2” or C-4”), 161.0 (C-1’); HRMS (ESI) calcd for $C_{31}H_{31}N_2O_8S$ $[M+H]^+$ 591.1796, found 591.1794.

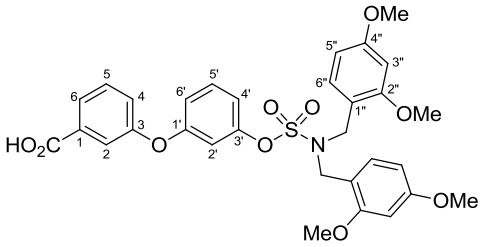
2-(3-((*N*,*N*-bis(2,4-Dimethoxybenzyl)sulfamoyl)oxy)phenoxy)benzoic acid, (209)



To 3-(2-cyanophenoxy)phenyl bis(2,4-dimethoxybenzyl)sulfamate (**206**) (600 mg, 1.02 mmol) in dioxane (5.1 mL) was added 2 M aq. solution of NaOH (5.1 mL, 10.2 mmol). The resulting mixture was heated at 130 °C for 2 h under microwave irradiation. After cooling, the mixture was acidified to pH 1-2 with using a 4 M aq. solution of HCl and stirred at RT for 30 min. The reaction was then diluted with water

(20 mL) and extracted with EtOAc (3 × 25 mL). The pooled organic extracts were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel, petrol:EtOAc:AcOH, 1:0:0 → 50:49.7:0.3) to yield the *title compound* as a yellow oil (279 mg, 45%); R_f = 0.30 (petrol:EtOAc:AcOH, 50:49.7:0.3); λ_{max} (EtOH)/nm 278.0; IR (neat) ν_{max}/cm^{-1} 1697, 1605, 1589, 1507, 1477, 1455, 1370, 1249, 1207, 1157; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.72 (6H, s, 2 × ArOCH_3), 3.77 (6H, s, 2 × ArOCH_3), 4.43 (4H, s, 2 × ArCH_2), 6.37 (2H, d, *J* = 2.4 Hz, H-3"), 6.41 (2H, dd, *J* = 8.4, 2.4 Hz, H-5"), 6.67 (1H, dd, *J* = 2.3, 2.3 Hz, H-2'), 6.92 – 6.86 (2H, m, H-3 and H-4' or H-6'), 7.00 (1H, ddd, *J* = 8.3, 2.3 and 0.9 Hz, H-4' or H-6'), 7.26 – 7.22 (m, 3H, H-5 and H-6"), 7.31 (dd, *J* = 8.2, 8.2 Hz, 1H, H-5'), 7.50 (1H, ddd, *J* = 8.3, 7.3 and 1.8 Hz, H-4), 8.15 (1H, dd, *J* = 7.9, 1.8 Hz, H-6); ^{13}C NMR (126 MHz, $CDCl_3$) δ 47.2 (Ar*C*H_2), 55.3 (ArO*C*H_3), 55.5 (ArO*C*H_3), 98.3 (C-3"), 104.2 (C-5"), 113.7 (C-2'), 116.5 (C-1"), 117.3 (C-4' or C-6'), 118.4 (C-4' or C-6'), 119.1 (C-3), 120.6 (C-1), 124.2 (C-5), 130.6 (C-5'), 131.1 (C-6"), 133.5 (C-6), 135.0 (C-4), 151.6 (C-1), 156.2 (C-2 or C-1'), 156.6 (C-2 or C-1'), 158.5 (C-2" or C-4"), 160.8 (C-2" or C-4"), 167.1 (Ar*C*O_2H); LRMS (ES^-) *m/z* 608.5 $[M-H]^-$; HRMS (ESI) calcd for $C_{31}H_{30}NO_{10}S$ $[M-H]^-$ 608.1596, found 608.1578.

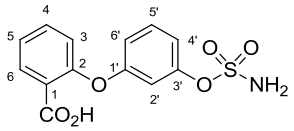
3-(3-((*N*,*N*-bis(2,4-Dimethoxybenzyl)sulfamoyl)oxy)phenoxy)benzoic acid, (210)



To 3-(3-cyanophenoxy)phenyl bis(2,4-dimethoxybenzyl)sulfamate (**210**) (600 mg, 1.02 mmol) in dioxane (5.1 mL) was added 2 M aq. solution of NaOH (5.1 mL, 10.2 mmol). The resulting mixture was heated at 130 °C for 2 h under microwave irradiation. After cooling, the mixture was acidified to pH 1-2 with using a 4 M aq. solution of HCl and stirred at RT for 30 min. The reaction was then diluted with water (20 mL) and extracted with EtOAc (3 × 25 mL). The pooled organic extracts were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel, petrol:EtOAc:AcOH, 1:0:0 → 50:49.7:0.3) to yield the *title compound* as a clear oil (495 mg, 80%); R_f = 0.31 (petrol:EtOAc:AcOH, 50:49.7:0.3); λ_{max} (EtOH)/nm 277.8; IR (neat) ν_{max}/cm^{-1} 1694, 1612, 1585, 1507, 1479, 1451, 1371, 1249, 1207; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.71 (6H, s,

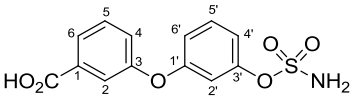
2 × ArOCH_3), 3.77 (6H, s, 2 × ArOCH_3), 4.43 (4H, s, 2 × ArCH_2), 6.36 (2H, d, *J* = 2.4 Hz, H-3”), 6.40 (2H, dd, *J* = 8.4, 2.4 Hz, H-5”), 6.69 (1H, dd, *J* = 2.3, 2.3 Hz, H-2’), 6.88 (1H, ddd, *J* = 8.2, 2.4 and 1.0 Hz, H-4’ or H-6’), 6.93 (1H, ddd, *J* = 8.3, 2.2 and 0.9 Hz, H-4’ or H-6’), 7.25 – 7.20 (3H, m, H-4 and H-6”), 7.29 (1H, dd, *J* = 8.3, 8.3 Hz, H-5), 7.45 (1H, dd, *J* = 8.0, 8.0 Hz, H-5), 7.70 (1H, dd, *J* = 2.5, 1.5 Hz, H-2), 7.86 (1H, ddd, *J* = 7.8, 1.3 and 1.3 Hz, H-6); ^{13}C NMR (126 MHz, $CDCl_3$) δ 47.1 (Ar*C*H_2), 55.2 (ArO*C*H_3), 55.5 (ArO*C*H_3), 98.3 (C-3”), 104.1 (C-5”), 113.2 (C-2’), 116.6 (C-1”), 117.0 (C-4’ or C-6’), 117.5 (C-4’ or C-6’), 120.3 (C-2), 124.3 (C-4), 125.4 (C-6), 130.2 (C-5), 130.5 (C-5’), 131.1 (C-6”), 131.3 (C-1), 151.6 (C-3’), 157.1 (C-3 or C-1’), 157.4 (C-3 or C-1’), 158.6 (C-2” or C-4”), 160.7 (C-2” or C-4”), 170.9 (Ar*C*O_2H); LRMS (ES^-) *m/z* 608.5 $[M-H]^-$; HRMS (ESI) calcd for $C_{31}H_{30}NO_{10}S$ $[M-H]^-$ 608.1596, found 608.1577.

2-(3-(Sulfamoyloxy)phenoxy)benzoic acid, (212)



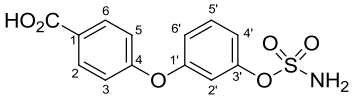
Compound **212** was synthesised according to general procedure D, using the following reagents: 2-(3-((*N*,*N*-bis(2,4-dimethoxybenzyl)sulfamoyl)oxy)phenoxy)benzoic acid (**209**) (200 mg, 0.33 mmol), DCM (3.0 mL) and TFA (0.3 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc:AcOH, 1:0:0 → 50:49.7:0.3) to yield the *title compound* as an off-white solid (91 mg, 90%); R_f = 0.30 (petrol:EtOAc:AcOH, 50:49.7:0.3); m.p. 101.5-103.5 °C; λ_{max} (EtOH)/nm 278.6; IR (neat) ν_{max}/cm^{-1} 3405, 3298, 1681, 1602, 1573, 1478, 1448, 1385, 1263, 1252, 1190, 1112; ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.82 (1H, dd, *J* = 2.4, 2.4 Hz, H-2’), 6.84 (1H, ddd, *J* = 8.3, 2.4 and 0.8 Hz, H-4’ or H-6’), 7.00 (1H, ddd, *J* = 8.3, 2.2 and 0.9 Hz, H-4’ or H-6’), 7.11 (1H, dd, *J* = 8.3, 1.1 Hz, H-3), 7.32 (1H, ddd, *J* = 7.6, 7.6 and 1.1 Hz, H-5), 7.41 (dd, *J* = 8.2, 8.2 Hz, 1H, H-5’), 7.60 (1H, ddd, *J* = 8.2, 7.3 and 1.8 Hz, H-4), 7.86 (1H, dd, *J* = 7.8, 1.8 Hz, H-6), 8.04 (2H, s, ArOSO_2NH_2), 12.85 (1H, s, ArCO_2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 111.4 (C-2’), 115.3 (C-4’ or C-6’), 116.3 (C-4’ or C-6’), 121.5 (C-3), 124.6 (C-1), 124.7 (C-5), 130.6 (C-5’), 131.5 (C-6), 133.7 (C-4), 151.0 (C-3’), 154.1 (C-2), 158.4 (C-1’), 166.3 (Ar*C*O_2H); LRMS (ES^-) *m/z* 308.2 $[M-H]^-$; HRMS (ESI) calcd for $C_{13}H_{10}NO_6S$ $[M-H]^-$ 308.0234, found 308.0222.

3-(3-(Sulfamoyloxy)phenoxy)benzoic acid, (213)



Compound **213** was synthesised according to general procedure D, using the following reagents: 3-(3-((*N*,*N*-bis(2,4-dimethoxybenzyl)sulfamoyl)oxy)phenoxy)benzoic acid (**210**) (200 mg, 0.33 mmol), DCM (3.0 mL) and TFA (0.3 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc:AcOH, 1:0:0 → 50:49.7:0.3) to yield the *title compound* as an off-white solid (95 mg, 94%); R_f = 0.32 (petrol:EtOAc:AcOH, 50:49.7:0.3); m.p. 132.0-134.0 °C; λ_{max} (EtOH)/nm 275.4; IR (neat) ν_{max}/cm^{-1} 3369, 3265, 1689, 1586, 1480, 1447, 1350, 1304, 1250, 1177, 1116; ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.97 (1H, dd, *J* = 2.3, 2.3 Hz, H-2'), 7.01 (1H, ddd, *J* = 8.3, 2.4 and 0.9 Hz, H-4' or H-6'), 7.10 (1H, ddd, *J* = 8.2, 2.3 and 0.9 Hz, H-4' or H-6'), 7.35 (1H, ddd, *J* = 8.2, 2.7 and 1.1 Hz, H-4), 7.49 (1H, dd, *J* = 8.2, 8.2 Hz, H-5 or H-5'), 7.52 (1H, dd, *J* = 2.6, 1.5 Hz, H-2), 7.55 (1H, dd, *J* = 7.9, 7.9 Hz, H-5 or H-5'), 7.76 (1H, ddd, *J* = 7.7, 1.3 and 1.3 Hz, H-6), 8.06 (2H, s, $ArOSO_2N\mathit{H}_2$), 13.09 (1H, s, $ArCO_2\mathit{H}$); ^{13}C NMR (126 MHz, DMSO-d_6) δ 112.8 (C-2'), 116.8 (C-4' or C-6'), 117.6 (C-4' or C-6'), 119.0 (C-2), 123.4 (C-4), 124.8 (C-6), 130.6 (C-5 or C-5'), 131.0 (C-5 or C-5'), 132.9 (C-1), 151.2 (C-3'), 156.2 (C-3 or C-1'), 157.1 (C-3 or C-1'), 166.6 ($ArCO_2H$); LRMS (ES$^-$) *m/z* 308.2 [M-H]$^-$; HRMS (ESI) calcd for $C_{13}H_{10}NO_6S$ [M-H]$^-$ 308.0234, found 308.0225.

4-(3-(Sulfamoyloxy)phenoxy)benzoic acid, (214)



Compound **214** was synthesised according to general procedure D, using the following reagents: 4-(3-((*N*,*N*-bis(2,4-dimethoxybenzyl)sulfamoyl)oxy)phenoxy)benzoic acid (**211**) (200 mg, 0.33 mmol), DCM (3.0 mL) and TFA (0.3 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc:AcOH, 1:0:0 → 50:49.7:0.3) to yield the *title compound* as an off-white solid (93 mg, 92%); R_f = 0.32 (petrol:EtOAc:AcOH, 50:49.7:0.3); m.p. 173.5-175.5 °C; λ_{max} (EtOH)/nm 252.2; IR (neat) ν_{max}/cm^{-1} 3368, 3286, 1669, 1593, 1485, 1429, 1366, 1248, 1181; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.02 (1H, dd, *J* = 2.3, 2.3 Hz, H-2'), 7.09 (1H, ddd, *J* = 8.2, 2.4 and 0.9 Hz, H-4' or H-6'), 7.16 - 7.10 (3H, m, H-3, 5 and H-4' or H-6'), 7.52 (1H, dd, *J* = 8.2, 8.2 Hz, H-5'), 7.97 (2H, d, *J* = 8.8 Hz, H-2, 6), 8.06 (2H, s, $ArOSO_2N\mathit{H}_2$), 12.79 (1H, s, $ArCO_2\mathit{H}$); ^{13}C NMR (126 MHz, DMSO-d_6) δ 113.7 (C-2'), 117.7 (C-4' or C-6'), 117.8 (C-3, 5), 118.3 (C-4' or C-6'), 125.9 (C-1), 131.1 (C-5'), 131.7 (C-2, 6), 151.2 (C-3'), 156.1 (C-1'), 160.2 (C-4),

166.7 (Ar*C*O_2H); LRMS (ES^-) *m/z* 308.2 $[M-H]^-$; HRMS (ESI) calcd for $C_{13}H_{10}NO_6S$ $[M-H]^-$ 308.0234, found 308.0226.

10.3. ERK5 Inhibitors - Experimental Procedures

10.3.1. ERK5 and p38α Biological Assay Protocols

The ERK5 biological assays were performed by Ms Ai Ching Wong at Cancer Research Technology Discovery research Laboratories, London, by Dr Pamela Lochhead at the Babraham Institute, Cambridge, by Ms Lan-Zhen Wang and Dr Noel Edwards at the Paul O'Gorman Building, Newcastle Cancer Centre, Newcastle upon Tyne.

ERK5 IMAP™ assay protocol

Preparation of assay buffer (1x)

The assay buffer was prepared using 0.01% Tween®-20 5x stock, supplied as part of IMAP™ FP Progressive Binding System Kit (Molecular Devices R7436) and diluted to 1x using milliQ H_2O. 1 µL of a 1 M DTT stock was added for every 1 mL of 1x assay buffer to give a final concentration of 1 mM DTT.

Preparation of ERK5 working solution

The final dilution was dependent on activity of the enzyme batches. The initial batch (08/08/08) was used at a 1 in 1 in 350 final dilution in assay buffer. A 1:175 dilution of ERK5 stock was performed in 1x assay buffer. For 1 plate, 13 µL of ERK5 stock was added to 2262 µL of 1x assay buffer. ERK5 was expressed and purified at CRT by Leon Pang and Sue Young. Aliquots were stored at -80 °C. Batch PO080808 was used at a stock concentration of 73.4 ng/µL.

Preparation of ATP/substrate working solution

For one plate, ATP disodium salt (90 µL, 20 mM) (Sigma A7699) and FAM-EGFR-derived peptide (15 µL, 100 µM) (LVEPLTPSGEAPNQ(K-5FAM)-COOH) (Molecular Devices RP7129; reconstituted in milliQ H_2O to a stock concentration of 100 µL; stored at -20 °C) was added to 2295 µL of 1x assay buffer.

Preparation of IMAP™ binding solution

For one plate, 20.5 µL of IMAP™ binding reagent stock, 1476 µL of 1x binding buffer A (60%), and 984 µL of binding buffer B (40%) (IMAP™ FP Progressive screening express kit (Molecular Devices R8127) was added to 9819.5 µL of milliQ H_2O.

Assay procedure

1 µL of inhibitor (in 60:40 H_2O/DMSO) or control/blanks (60:40 H_2O/DMSO) were dry-spotted into the relevant wells of a 384-well assay plate using the MATRIX PlateMate® Plus. 5 µL of ERK5 working solution was added to test and control wells, and 5 µL of 1x assay buffer added to blanks; 4 µL of ATP/substrate working solution was added to all wells using a Matrix multichannel pipette. The plate was sealed using DMSO resistant clear seal and incubated for 2 h at 37 °C. 1 µL of the kinase reaction mixture from the first plate was dry spotted into a second 384-well assay plate using the MATRIX PlateMate® Plus. 9 µL of assay buffer was added, followed by 30 µL of IMAP™ binding solution using a multichannel pipette. The plate was incubated at RT in darkness for 2 h. The assay plate was then read on an Analyst HT plate reader (Molecular Devices) using the settings described below:

Measurement mode = Fluorescence polarisation; Method ID = ERK5; Integration time = 100 ms; Excitation filter = Fluorescein 485-20; Emission filter = 530-25; Dichroic mirror = 505 nm; Plate definition file = Corning 384 black fb; Z-height = 5.715 mm (middle); G-factor = 1; Attenuator = out; Detector counting = Smartread+; Sensitivity = 2.

p38α LANCE assay

Preparation of assay buffer (1x)

1x assay buffer was prepared consisting of the following reagents; 250 mM tris(hydroxymethyl)aminomethane (Tris) pH 7.5, 25 mM $MgCl_2$, 2.5 mM ethylene glycol tetraacetic acid (EGTA), 10 mM DTT and 0.05% Triton X100 in milliQ H_2O (NB: 1x buffer final assay concentrations were 5x lower than stated above).

Preparation of p38α/SAPK2 working solution

The p38α/SAPK2 working solution was prepared using active N-terminal GST-tagged recombinant full length protein (Millipore 14-251) supplied as a 10 µg/4 µL stock. This was diluted to a 10 µg/40 µL (1 µM) concentration by addition of 156 µL of Tris/HCl (pH

7.5, 50 mM), NaCl (150 mM), EGTA (0.1 mM), Brij-35 surfactant (0.03%), glycerol (50%) and 0.1% 2-mercaptoethanol (0.1%). The final dilution was dependent on activity of the enzyme batches. The p38α concentration used in the assay was 1 nM. A 2x working stock solution (2 nM, 500 fold dilution of 1 µM stock) in 1x assay buffer was prepared. For one plate, 9.4 µL of p38α (1 µM) was added to 1870.6 µL of milliQ H_2O.

Preparation of ATP/substrate working solution

For one plate, ATP disodium salt (17.5 µL, 200 mM stock), (Sigma A7699) and U*light*-MBP Peptide (50 µL, 5 µM stock) (Perkin Elmer TRF0109), which were added to 400 µL of 5x assay buffer and 1532.5 µL of milliQ H_2O.

Preparation of EDTA/antibody detection reagent

For one plate, 84 µL of ethylenediaminetetraacetic acid (EDTA) (0.5 M) (Sigma E4378-100G) and 27 µL of Europium-anti-phospho-MBP antibody (0.625 µM) (Perkin Elmer) was added to 420 µL of LANCE detection buffer (1x) and 3669 of milliQ H_2O.

Assay procedure

1 µL of compound (in 80:20 H_2O/DMSO) or control/blank (80:20 H_2O/DMSO) was dry-spotted into the relevant wells of a 384-well assay plate using the MATRIX PlateMate® Plus. 5 µL of p38α working solution was added to test and control wells, and 5 µL of assay buffer added to blanks; 4 µL of ATP/substrate working solution was added to all wells using a Thermo Multidrop Combi or Matrix multichannel pipette. The plate was sealed using DMSO resistant clear seal and incubated for 1 h at 37 °C. 10 µL of the EDTA/antibody working solution was added to all wells using a Thermo Multidrop Combi or Matrix multichannel pipette. The plate was incubated at RT in darkness for 2 h. The assay plate was then read on a PheraStar microplate reader using the settings described below:

Pherastar: Measurement mode = TRF; Method ID = LANCE HTRF ERK5; Optic Module: 337, 665, 620 nm. Focal Height = 6.0, Positioning delay, 0.1 sec, Number of flashes per well = 100, Integration start = 60 µs, Integration time = 200 µs, Simultaneous dual emission, Ratio multiplicator = 1000.

Hela cell-based densitometry assay protocol

HeLa cells were serum starved overnight followed by treatment with ERK5 inhibitors for 1 h. Cells were then stimulated with 100 ng/ml EGF for 10 min. The cells were harvested and lysed at 4 °C for 5–10 min in Laemmli buffer containing Halt protease and phosphate inhibitors (Pierce). The lysates were boiled for 10 min at 100 °C. Twenty microliters sample was run on 6% Tris–glycine gels and transferred to nitrocellulose. Western blotting was done with ERK5 antibody (Cell signalling #3372S). The IC_{50} was calculated from densitometry of top bands.

Dual-luciferase reporter assay protocol

HEK293T forward transfection

HEK293T cells were seeded in 96-well luminescence (white) plates (1.68×10^4/well in 84 µL standard culture medium) and incubated overnight at 37 °C in a humidified atmosphere of 5% CO_2 in air. Next day, transfection mixtures were prepared as shown in Table 10.1. Plasmid DNA mastermix containing MEF2D-Gal4 (0.25 µg/µL), Gal4-Luc (1.25 µg/µL) and *Renilla* luciferase (0.1 µg/µL) was prepared in sterile distilled water. Constitutively-active, EGFP-tagged MEK5 (EGFP-MEK5D; 0.5 µg/µL), an EGFP-tagged construct containing no MEK5D (EGFP-C3; 0.5µg/µL), and HA-tagged ERK5 with C-terminal truncation (HA-ERK5-ΔP493; 0.5 µg/µL) were diluted separately in sterile distilled water. Plasmid DNA and Lipofectamine 2000 (Invitrogen) were separately diluted in Opti-MEM growth media (reduced serum medium, Invitrogen), and incubated at room temperature for 5min. Plasmid DNA (Tube A) and Lipofectamine 2000 (Tube B) were then combined and incubated for 20 min at room temperature to complex. Cells were then transfected by addition of 16 µL of the respective transfection mixture: 3 wells with EGFP-C3-containing (control) and 21 wells with MEK5D-containing transfection mixture (final volume, 100µL). Cells were subsequently incubated for 4 h at 37 °C prior to addition of potential ERK5-inhibitory compounds.

Table 10.1: Transfection mixture volumes for the HEK293T luciferase assay. Volumes are sufficient for the 3 control (EGFP-C3) and 21 test (MEK5D) wells required for each potential ERK5 inhibitory compound tested.

Condition	**Control**		**MEK5D-activated ERK5**	
Plasmid DNA	Tube A	Tube B	Tube A	Tube B
Mastermix	1.6 µL	-	11.0 µL	-
EGFP-C3	0.1 µL	-	-	-
EGFP-MEK5D	-	-	0.4 µL	-
HA-ERK5-ΔP493	0.5 µL	-	3.7 µL	-
Opti-MEM	27 µL	27 µL	183 µL	183 µL
Lipofectamine 2000	-	1.1 µL	-	7.3 µL

Addition of compounds to ERK5-transfected HEK293T cells

Potential ERK5-inhibitory compounds were prepared as a 2X solution by addition of 2 µL compound (or DMSO as control) to 1 mL standard culture medium. Compounds were tested in triplicate at a concentration range of 0.003 µM, 0.01 µM, 0.03 µM, 0.1 µM, 0.3 µM and 1 µM (or 0.03 µM, 0.1 µM, 0.3 µM, 1 µM, 3 µM and 10 µM for BIX02189) by addition of 100 µL 2X solution to 100 µL transfected cells (final DMSO, 0.1% v/v). Cells were incubated for 24 h at 37°C.

Cell lysis and luciferase quantification

After 24 h incubation in the absence (control) or presence of potential inhibitor, the culture medium was aspirated and cells lysed in 20 µL 1X passive lysis buffer (Dual-Luciferase Reporter Assay System, Promega) for a minimum of 15 min with agitation. Lysates were further processed immediately or stored at -80 °C. Cellular inhibition of ERK5 was quantified using the Dual-Luciferase Reporter Assay System (Promega). Luciferase assay buffer/Luciferase assay substrate and Stop and Glo assay buffer/Stop and Glo substrate were prepared according to the manufacturer's instructions. Luciferase reagent (50 µL/well) was added immediately before luminescence detection using a FLUOstar Omega plate reader (BMG Labtech). Stop and Glo reagent (50 µL/well) was subsequently added, and the *Renilla* luciferase signal (transfection efficiency control) quantified.

Data analysis

The ERK5-specific signalling activity was calculated by subtraction of the EGFP-C3 luciferase signal from the EGFP-MEK5D-induced luminescence. Luminescence in the absence of potential ERK5 inhibitor (DMSO control) was taken as 100% ERK5 activity. IC_{50} values (the concentration of compound yielding 50% inhibition of ERK5 activity) were determined from point-to-point analyses using GraphPad Prism v.6. Unless stated otherwise, data are mean ± standard deviation of three independent experiments.

10.3.2. Synthesis of ERK5 Inhibitors: General Procedures

Except where water was included in the reaction mixture, all reactions were carried out under strict anhydrous conditions with glassware oven-dried and cooled under nitrogen. Temperatures quoted refer to bath temperatures.

General procedure P: To a solution or a suspension of the appropriate carboxylic acid (1 mol equiv.) in THF (1 mL/mmol of carboxylic acid), cooled at 0 °C, were added thionyl chloride (1.5 mol equiv.) and *N*,*N*-dimethylformamide (0.1 mol equiv.). The resulting solution was stirred at 0 °C for 30 min and allowed to warm to RT. Upon completion, the solvent was removed *in vacuo* and the crude material used in the next step without further purification.

General procedure Q: To a suspension of aluminium trichloride (2.5 mol equiv.) in DCM (1 mL/mmol of aluminium trichloride), cooled at 0 °C, was added the appropriate acyl chloride (2 mol equiv.), followed by methyl 1*H*-pyrrole-2-carboxylate (1 mol equiv.). The resulting solution was stirred at 0 °C for 30 min and allowed to warm to RT. After 20 h, the reaction mixture was cooled to 0 °C and quenched by cautious addition of 1 M aq. HCl (0.5 mL/mmol of aluminium trichloride). The resulting solution was stirred at RT for 2 h. The reaction was then diluted with water (20 mL) and extracted with DCM (3 × 50 mL). The combined organic extracts were washed with saturated aq. $NaHCO_3$ and brine (50 mL, respectively), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography.

General procedure R: To the appropriate pyrrole ester (1 mol equiv.) in THF (8 mL/mmol of pyrrole ester) was added a 2 M aq. solution of lithium hydroxide (15 mol equiv.). The resulting mixture was heated at 67 °C for 18 h. Upon completion, the mixture

was acidified to pH 3 using a 4 M aq. solution of HCl. The reaction was then diluted with water (30 mL) and extracted with EtOAc (3 × 50 mL). The pooled organic extracts were washed with water and brine (50 mL, respectively), dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was used in the next step without further purification.

General procedure S: To 1-methyl-4-piperidone (**251**) (1 mol equiv.) in MeOH (1 mL/mmol of piperidone) was added acetic acid (1.1 mol equiv.), followed by a solution of the appropriate amine (2 mol equiv.) in MeOH (0.5 mL/mmol of amine). The resulting solution was stirred at RT for 30 min and then cooled to 0 °C. Sodium cyanoborohydride (1.5 mol equiv.) was added in several portions. The resulting solution was stirred at 0 °C for 30 min and allowed to warm to RT. After 24 h, the reaction mixture was poured in 1 M aq. sodium hydroxide (20 mL) and stirred for 30 min. The reaction mixture was concentrated *in vacuo*. The crude product was then dissolved in water (30 mL) and extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with water and brine (50 mL, respectively), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by Kugelröhr distillation.

General procedure T: To the appropriate carboxylic acid (1 mol equiv.) in DCM (10 mL/mmol of carboxylic acid), cooled at 0 °C, were added the appropriate amine (3 mol equiv.), 4-(dimethylamino)pyridine (0.1 mol equiv.) and *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (2 mol equiv.). The resulting solution was stirred at 0 °C for 30 min and allowed to warm to RT. After 24 h, the reaction mixture was concentrated *in vacuo*. The crude residue was then dissolved in water (20 mL) and extracted with EtOAc (3 × 30 mL). The pooled organic extracts were washed with water and brine (50 mL, respectively), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography.

General procedure U: To the appropriate carboxylic acid (1 mol equiv.) in acetonitrile (5 mL/mmol of carboxylic acid) were added the appropriate amine (2.5 mol equiv.) and phosphorus trichloride (1 mol equiv.). The resulting mixture was heated at 150 °C for 7 min under microwave irradiation. After cooling, the mixture was quenched by addition of 2 M aq. NaOH (10 mL/mmol of carboxylic acid). The resulting heterogeneous solution was stirred at RT until solubilisation of all the brown residues formed during the reaction. The mixture was extracted with EtOAc (3 × 20 mL), the pooled organic extracts were

washed with an acetate buffer pH = 4.65 (20 mL) and brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography.

General procedure V: The appropriate nitropyridine in MeOH (20 mL/mmol of nitropyridine) was subjected to palladium-catalysed hydrogenation using an H-Cube® reactor and a 10% Pd/C CatCart. The reaction mixture was conducted at 40 °C under a full pressure of hydrogen for 8 h. Upon completion, the solvent was removed *in vacuo* and the crude product was purified by column chromatography if required.

General procedure W: The appropriate chloropyridine (1 mol equiv.) in dioxane (4.9 mL/mmol of chloropyridine) was sparged with nitrogen for 15 min. To this solution, potassium carbonate (3 mol equiv.), the appropriate boronic acid (1.1 mol equiv.) and tetrakis(triphenylphosphine)palladium(0) (0.1 mol equiv.) were added. The resulting mixture was heated at 100 °C for 48 h. Upon completion, the heterogeneous mixture was filtered through Celite and the solvent removed *in vacuo*. The crude residue was dissolved in a mixture of EtOAc and water (20 mL, respectively) and extracted with EtOAc (3 × 25 mL). The pooled organic extracts were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography.

General procedure X: To the appropriate carboxylic acid (1 mol equiv.) in acetonitrile (10 mL/mmol of carboxylic acid) were added pyridine (1 mol equiv.) and cyanuric fluoride (0.4 mol equiv.). The reaction mixture was stirred at RT for 30 min before addition of the appropriate amine (2.5 mol equiv.). The resulting mixture was stirred at 40 °C for 24 h. Upon completion, the mixture was quenched by addition of saturated aq. $NaHCO_3$ (15 mL) and extracted with EtOAc (3 × 20 mL). The pooled organic extracts were washed with an acetate buffer pH = 4.65 and brine (30 mL, respectively), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography.

General procedure Y: To the appropriate 1*H*-pyrrole-2-carboxylic acid (1 mol equiv.) in DCM (10 mL/mmol of carboxylic acid) were added triethylamine (2.5 mol equiv.), 2-chloro-1-methylpyridinium iodide (1.1 mol equiv.) and the appropriate amine (1.25 mol equiv.). The resulting solution was stirred at 42 °C for 24 h. Upon completion, the solvent was removed *in vacuo*. The crude residue was dissolved in EtOAc (30 mL), washed with saturated aq. $NaHCO_3$ (20 mL) and extracted with EtOAc (3 × 20 mL). The combined

organic extracts were washed with brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography.

General procedure Z: Carbonyl diimidazole (CDI, 2 mol equiv.) was added to a solution of the relevant carboxylic acid (1 mol equiv.) in THF (2 mL/mmol) and the mixture heated to 70 °C for 3 h. The relevant amine (2.5 mol equiv.) was added and the mixture was heated at 70 °C for 2 h. The mixture was partitioned between EtOAc (20 mL) and saturated aq. $NaHCO_3$ (20 mL). The aqueous layer was extracted with EtOAc (2 × 20 mL) The organic layers were combined, washed with brine (20 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by column chromatography.

General procedure A': To the appropriate 3-alkyloxy-4-chloro-2-fluorobenzene (1 mol equiv.) in THF (3 mL/mmol of benzene), cooled at -78 °C, was added dropwise *n*-butyllithium (2.4 M in hexane, 1 mol equiv.). The resulting mixture was stirred at -78 °C for 30 min. Crushed solid carbon dioxide was added in one portion and the reaction allowed to warm to RT. After 1 h, the solvent was removed *in vacuo* and the crude residue dissolved in 2 M aq. NaOH (20 mL). The aqueous layer was washed with EtOAc (20 mL), then acidified to pH 1-2 using a 4 M aq. solution of HCl and extracted with EtOAc (3 × 25 mL). The pooled organic extracts were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography.

General procedure B': To 4-chloro-2-fluorophenol (**349**) (1 mol equiv.) in THF (5 mL/mmol of phenol), cooled at 0 °C, were added triphenylphosphine (1.5 mol equiv.) and the appropriate alcohol (1.3 mol equiv.). Diethyl azodicarboxylate (1.5 mol equiv.) was then added dropwise at 0 °C. The resulting orange solution was stirred at 0 °C for 30 min and allowed to warm to RT. The reaction was left stirring for 24 h. Upon completion, the mixture was diluted with EtOAc (30 mL), washed with saturated aq. $NaHCO_3$ and brine (20 mL, respectively), dried over $MgSO_4$ and concentrated *in vacuo*. The crude orange solid was purified by column chromatography.

General procedure C': To a solution of 2-chloro-5-nitropyrimidine (**414**) (1 mol equiv.) in THF (5.0 mL/mmol of 2-chloro-5-nitropyrimidine), cooled at 0 °C, was added triethylamine (1.1 mol equiv.), followed by the appropriate amine. The resulting solution was stirred at 0 °C for 5 min and allowed to warm to RT. Upon completion, the solvent

was removed *in vacuo*. The crude residue was dissolved in EtOAc (20 mL), washed with water (20 mL) and extracted with EtOAc (3 × 25 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography.

General procedure D': The appropriate nitro-pyrimidine/pyridine in MeOH:THF (1:1) (20 mL/mmol of nitro-pyrimidine/pyridine) was subjected to palladium-catalysed hydrogenation using an H-Cube® reactor and a 10% Pd/C CatCart. The reaction was conducted at 40 °C under a full pressure of hydrogen for 8 h. Upon completion, the solvents were removed *in vacuo* and the crude product was purified by column chromatography if required.

General procedure E': To a suspension of the appropriate Boc-protected amine in formic acid (4 mL/mmol of amine) was added a solution of formaldehyde in water (37 wt. %) (4 mol equiv.). The resulting mixture was heated at 95 °C for 3 h. Upon completion, the reaction was cooled in an ice bath and quenched by addition of 2 M aq. NaOH until the pH was alkaline and then extracted with EtOAc (3 × 20 mL). The pooled organic extracts were washed with water and brine (40 mL, respectively), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography.

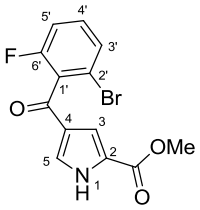
General procedure F': To the appropriate Boc-protected amine (1 mol equiv.) in DCM (5 mL/mmol of amine) were added trifluoroacetic acid (5 mL/mmol of amine) and triethylsilane (2.5 mol equiv.). The resulting mixture was stirred at RT for 2 h. Upon completion, the solvent was removed *in vacuo*. The crude residue was dissolved in EtOAc (30 mL), washed with saturated aq. $NaHCO_3$ (20 mL) and extracted with EtOAc (3 × 20 mL). The pooled organic extracts were washed with brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography.

General procedure G': To a solution of 2-chloro-5-nitropyridine (**459**) (1 mol equiv.) in THF (5.0 mL/mmol of 2-chloro-5-nitropyridine), cooled at 0 °C, was added triethylamine (1.1 mol equiv.), followed by the appropriate amine. The resulting solution was stirred at 67 °C overnight. Upon completion, the solvent was removed *in vacuo*. The crude residue was dissolved in EtOAc (20 mL), washed with water (20 mL) and extracted with EtOAc (3 × 25 mL). The combined organic extracts were washed with brine (30 mL), dried over

$MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography.

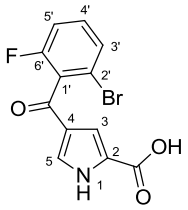
10.3.3. ERK5 Inhibitors Synthetic Procedures

Methyl 4-(2-bromo-6-fluorobenzoyl)-1*H*-pyrrole-2-carboxylate, (243)



Compound **243** was synthesised according to general procedure P and Q, using the following reagents: 2-bromo-6-fluorobenzoic acid (**241**) (10.5 g, 47.9 mmol), thionyl chloride (5.22 mL, 8.56 g, 71.9 mmol), *N*,*N*-dimethylformamide (0.37 mL, 0.35 g, 4.79 mmol), THF (48 mL), methyl 1*H*-pyrrole-2-carboxylate (3.0 g, 24.0 mmol), aluminum trichloride (8.0 g, 59.9 mmol) and DCM (60 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 7:3) to yield the *title compound* as a white solid (7.51 g, 96%); R_f = 0.29 (petrol:EtOAc, 7:3); m.p. 143.0-145.0 °C; λ_{max} (EtOH)/nm 263.0; IR (neat) ν_{max}/cm^{-1} 3233, 3140, 2996, 1731, 1639, 1599, 1564, 1442, 1393, 1283, 1230; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.79 (3H, s, CO_2CH_3), 6.99 (1H, brs, H-3), 7.44 – 7.37 (1H, m, H-5'), 7.53 – 7.46 (2H, m, , H-5 and H-4'), 7.59 (1H, d, *J* = 7.8 Hz, H-3'), 12.89 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 51.7 (CO_2CH_3), 114.7 (C-3), 115.4 (d, *J* = 21.4 Hz, C-5'), 118.9 (d, *J* = 5.1 Hz, C-2'), 124.6 (C-2 or C-4), 125.0 (C-2 or C-4), 128.8 (d, *J* = 3.2 Hz, C-3'), 129.7 (d, *J* = 22.6 Hz, C-1'), 130.1 (C-5), 132.3 (d, *J* = 8.8 Hz, C-4'), 158.4 (d, *J* = 247.8 Hz, C-6'), 160.3 (CO_2CH_3), 184.7 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -113.8 (ArF); LRMS (ES$^+$) *m/z* 326.3 [M(^{79}Br)+H]$^+$, 328.3 [M(^{81}Br)+H]$^+$; HRMS (ESI) calcd for $C_{13}H_{10}BrFNO_3$ [M(^{79}Br)+H]$^+$ 325.9823, found 325.9823.

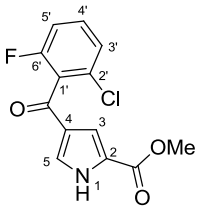
4-(2-Bromo-6-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid, (244)



Compound **244** was synthesised according to general procedure R, using the following reagents: methyl 4-(2-bromo-6-fluorobenzoyl)-1*H*-pyrrole-2-carboxylate (**243**) (7.50 g,

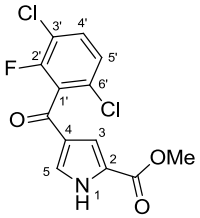
23.0 mmol), 2 M aq. lithium hydroxide (173 mL, 346 mmol) and THF (184 mL). The crude off-white solid (7.05 g, 98%) was used in the next step without further purification; R_f = 0.18 (petrol:EtOAc:AcOH, 50:49.7:0.3); m.p. 220.0-222.0 °C; λ_{max} (EtOH)/nm 263.4; IR (neat) ν_{max}/cm^{-1} 3318, 2888, 1667, 1641, 1602, 1560, 1440, 1390, 1278; ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.94 (1H, d, *J* = 2.0 Hz, H-3), 7.40 (1H, dd, *J* = 8.8, 8.8 Hz, H-5'), 7.43 (1H, d, *J* = 2.0 Hz, H-5), 7.49 (1H, ddd, *J* = 8.8, 8.0 and 6.1 Hz, H-4'), 7.58 (1H, dd, *J* = 8.0, 0.9 Hz, H-3'), 12.70 (1H, s, NH-pyrrole), 12.94 (s, 1H, CO_2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 114.3 (C-3), 115.4 (d, *J* = 21.4 Hz, C-5'), 119.0 (d, *J* = 5.2 Hz, C-2), 125.0 (C-2 or C-4), 125.9 (C-2 or C-4), 128.8 (d, *J* = 3.0 Hz, C-3'), 129.7 (C-5), 129.9 (d, *J* = 22.7 Hz, C-1'), 132.2 (d, *J* = 8.7 Hz, C-4'), 158.4 (d, *J* = 248.1 Hz, C-6'), 161.3 (CO_2H), 184.7 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -113.84 (ArF); LRMS (ES$^-$) *m/z* 310.1 [M(^{79}Br)-H]$^-$, 312.1 [M(^{81}Br)-H]$^-$; HRMS (ESI) calcd for $C_{12}H_6BrFNO_3$ [M(^{79}Br)-H]$^-$ 309.9521, found 309.9518.

Methyl 4-(2-chloro-6-fluorobenzoyl)-1*H*-pyrrole-2-carboxylate, (247)



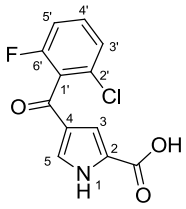
Compound **247** was synthesised according to general procedure Q, using the following reagents: 2-chloro-6-fluorobenzoyl chloride (**245**) (4.31 mL, 6.17 g, 33.0 mmol), methyl 1*H*-pyrrole-2-carboxylate (2.0 g, 16.0 mmol), aluminum trichloride (5.33 g, 40.0 mmol) and DCM (40 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 7:3) to yield the *title compound* as a white solid (4.31 g, 96%); R_f = 0.31 (petrol:EtOAc, 7:3); m.p. 145.5-147.5 °C; λ_{max} (EtOH)/nm 262.6; IR (neat) ν_{max}/cm^{-1} 3225, 3007, , 1731, 1639, 1603, 1563, 1440, 1394, 1284, 1230;^{1}H NMR (500 MHz, DMSO-d_6) δ 3.79 (3H, s, CO_2CH_3), 7.00 (1H, d, *J* = 1.8, H-3), 7.38 (1H, dd, *J* = 8.8, 8.8 Hz, H-5'), 7.45 (1H, d, *J* = 8.1 Hz, H-3'), 7.54 (1H, d, *J* = 1.8 Hz, H-5), 7.57 (1H, ddd, *J* = 8.8, 8.1 and 6.2 Hz, H-4'), 12.91 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 51.7 (CO_2CH_3), 114.6 (C-3), 115.0 (d, *J* = 21.7 Hz, C-5'), 124.6 (C-2 or C-4), 125.4 (C-2 or C-4), 125.9 (d, *J* = 3.0 Hz, C-3'), 127.8 (d, *J* = 22.9 Hz, C-1'), 130.2 (C-5), 130.3 (d, *J* = 6.2 Hz, C-2'), 132.0 (d, *J* = 9.0 Hz, C-4'), 158.5 (d, *J* = 247.1 Hz, C-6'), 160.3 (CO_2CH_3), 183.7 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -114.4 (ArF); LRMS (ES$^+$) *m/z* 282.3 [M(^{35}Cl)+H]$^+$, 284.3 [M(^{37}Cl)+H]$^+$; HRMS (ESI) calcd for $C_{13}H_{10}ClFNO_3$ [M(^{35}Cl)+H]$^+$ 282.0328, found 282.0330.

Methyl 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylate, (248)



Compound **248** was synthesised according to general procedure Q, using the following reagents: 3,6-dichloro-2-fluorobenzoyl chloride (**246**) (7.27 g, 32.0 mmol), methyl 1*H*-pyrrole-2-carboxylate (2.0 g, 16.0 mmol), aluminum trichloride (5.33 g, 40.0 mmol) and DCM (40 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 8:2) to yield the *title compound* as an off-white solid (4.91 g, 97%); R_f = 0.28 (petrol:EtOAc, 8:2); m.p. 135.5-137.5 °C; λ_{max} (EtOH)/nm 281.4; IR (neat) ν_{max}/cm^{-1} 3286, 3231, 1690, 1656, 1594, 1560, 1447, 1388, 1283; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.80 (3H, s, CO_2CH_3), 7.09 (1H, d, *J* = 1.8 Hz, H-3), 7.49 (1H, dd, *J* = 8.8, 1.4 Hz, H-5'), 7.67 (1H, d, *J* = 1.8 Hz, H-5), 7.76 (1H, dd, *J* = 8.8, 8.4 Hz, H-4'), 12.94 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 51.7 (CO_2CH_3), 114.6 (C-3), 119.4 (d, *J* = 17.8 Hz, C-3'), 124.8 (C-2 or C-4), 124.9 (C-2 or C-4), 126.8 (d, *J* = 3.7 Hz, C-5'), 128.9 (d, *J* = 22.9 Hz, C-1'), 129.1 (d, *J* = 5.1 Hz, C-6'), 131.0 (C-5), 131.9 (C-4'), 153.8 (d, *J* = 248.7 Hz, C-2'), 160.3 (CO_2CH_3), 182.5 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.7 (ArF); LRMS (ES$^-$) *m/z* 314.2 [M(^{35}Cl^{35}Cl)-H]$^-$, 316.1 [M(^{35}Cl^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{13}H_9Cl_2FNO_3$ [M(^{35}Cl)+H]$^+$ 315.9938, found 315.9944.

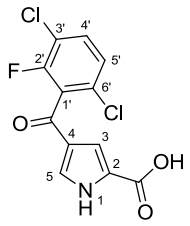
4-(2-Chloro-6-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid, (249)



Compound **249** was synthesised according to general procedure R, using the following reagents: methyl 4-(2-chloro-6-fluorobenzoyl)-1*H*-pyrrole-2-carboxylate (**247**) (2.70 g, 9.59 mmol), 2 M aq. lithium hydroxide (72 mL, 144 mmol) and THF (77 mL). The crude white solid (2.43 g, 95%) was used in the next step without further purification; R_f = 0.19 (petrol:EtOAc:AcOH, 50:49.7:0.3); m.p. 218.0-220.0 °C; λ_{max} (EtOH)/nm 280.8; IR (neat) ν_{max}/cm^{-1} 3314, 1881, 1669, 1638, 1609, 1553, 1443, 1391, 1276, 1242; ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.95 (1H, d, *J* = 2.0 Hz, H-3), 7.37 (1H, dd, *J* = 8.5, 8.5 Hz, H-5'), 7.49 – 7.42 (2H, m, H-5 and H-3'), 7.56 (1H, ddd, *J* = 8.5, 8.3 and 6.2 Hz, H-4'), 12.71 (1H, s, NH-pyrrole), 12.93 (1H, s, CO_2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 114.2 (C-3),

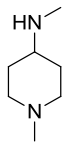
115.0 (d, *J* = 21.5 Hz, C-5'), 125.3 (C-2 or C-4), 125.9 (d, *J* = 3.2 Hz, C-3'), 125.9 (C-2 or C-4), 127.9 (d, *J* = 23.0 Hz, C-1'), 129.8 (C-5), 130.4 (d, *J* = 6.1 Hz, C-2'), 131.9 (d, *J* = 9.1 Hz, C-4'), 158.6 (d, *J* = 247.1 Hz, C-6'), 161.3 (CO_2H), 183.8 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -114.4 (ArF); LRMS (ES^-) *m/z* 266.2 [M(^{35}Cl)-H]$^-$, 268.2 [M(^{37}Cl)-H]$^-$; HRMS (ESI) calcd for $C_{12}H_6ClFNO_3$ [M(^{35}Cl)-H]$^-$ 266.0026, found 266.0022.

4-(3,6-Dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid, (250)



Compound **250** was synthesised according to general procedure R, using the following reagents: methyl 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylate (**248**) (5.0 g, 15.8 mmol), 2 M aq. lithium hydroxide (119 mL, 238 mmol) and THF (127 mL). The crude white solid (4.45 g, 93%) was used in the next step without further purification; R_f = 0.25 (petrol:EtOAc:AcOH, 50:49.7:0.3); m.p. 228.5-230.5 °C; λ_{max} (EtOH)/nm 281.6; IR (neat) ν_{max}/cm^{-1} 3268, 3144, 3092, 1698, 1648, 1565, 1501, 1452, 1420, 1390, 1239; ^1H NMR (500 MHz, DMSO-d_6) δ 7.03 (1H, d, *J* = 2.0 Hz, H-3), 7.49 (1H, dd, *J* = 8.8, 1.3 Hz, H-5'), 7.60 (1H, d, *J* = 2.0 Hz, H-5), 7.75 (1H, dd, *J* = 8.8, 8.4 Hz, H-4'), 12.75 (1H, s, NH-pyrrole), 12.93 (1H, brs, CO_2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 114.1 (C-3), 119.3 (d, *J* = 18.2 Hz, C-3'), 124.8 (C-2 or C-4), 126.1 (C-2 or C-4), 126.8 (d, *J* = 3.8 Hz, C-5'), 128.9 (d, *J* = 23.3 Hz, C-1'), 129.1 (d, *J* = 5.5 Hz, C-6'), 130.6 (C-5), 131.9 (C-4'), 153.8 (d, *J* = 248.6 Hz, C-2'), 161.3 (CO_2H), 182.47 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.7 (ArF); LRMS (ES^-) *m/z* 300.0 [M($^{35}Cl^{35}Cl$)-H]$^-$, 302.1 [M($^{35}Cl^{37}Cl$)-H]$^-$; HRMS (NSI) calcd for $C_{12}H_5Cl_2FNO_3$ [M($^{35}Cl^{35}Cl$)-H]$^-$ 299.9636, found 299.9632.

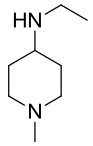
***N*,1-Dimethylpiperidin-4-amine, (252)**



Compound **252** was synthesised according to general procedure S, using the following reagents: 1-methyl-4-piperidone (1.54 mL, 1.5 g, 13.3 mmol), acetic acid (0.83 mL, 0.88 g, 14.6 mmol), 2 M methylamine in EtOH (13.3 mL, 26.6 mmol) and EtOH (13.3 mL). The

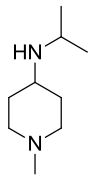
crude yellow oil was purified by Kugelröhr distillation to yield the *title compound* as a clear liquid (150 mg, 9%); R_f = 0.22 (EtOAc:MeOH, 6:4); IR (neat) ν_{max}/cm^{-1} 3283, 2938, 2851, 2791, 2738, 1659, 1467, 1450, 1370, 1277; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.40 - 1.29 (2H, m, H-3$_{axial}$ and H-5$_{axial}$), 1.89 – 1.82 (2H, m, H-3$_{equ}$ and H-5$_{equ}$), 2.00 - 1.92 (2H, m, H-2$_{axial}$ and H-6$_{axial}$), 2.24 (3H, s, NCH_3), 2.35 – 2.27 (1H, m, H-4), 2.40 (3H, s, NHCH_3), 2.83 – 2.74 (2H, m, H-2$_{equ}$ and H-6$_{equ}$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 32.5 (C-3 and C-5), 33.6 (NH*C*H_3), 46.3 (N*C*H_3), 54.7 (C-2 and C-6), 56.2 (C-4); LRMS (ES^+) *m/z* 129.3 $[M+H]^+$; HRMS (APCI) calcd for $C_7H_{17}N_2$ $[M+H]^+$ 129.1386, found 129.1385.

_N_-Ethyl-1-methylpiperidin-4-amine, (253)



Compound **253** was synthesised according to general procedure S, using the following reagents: 1-methyl-4-piperidone (**251**) (1.54 mL, 1.5 g, 13.3 mmol), acetic acid (0.83 mL, 0.88 g, 14.6 mmol), 2 M ethylamine in MeOH (13.3 mL, 26.6 mmol) and MeOH (13.3 mL). The crude yellow oil was purified by Kugelröhr distillation to yield the *title compound* as a clear liquid (450 mg, 24%); R_f = 0.20 (EtOAc:MeOH, 7:3); IR (neat) ν_{max}/cm^{-1} 3273, 2936, 2843, 2783, 2737, 2677, 1660, 1465, 1447, 1377, 1278; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.11 (3H, t, *J* = 7.1 Hz, CH_2CH_3), 1.45 – 1.33 (2H, m, H-3$_{axial}$ and H-5$_{axial}$), 1.92 – 1.82 (2H, m, H-3$_{equ}$ and H-5$_{equ}$), 2.01 – 1.91 (2H, m, H-2$_{axial}$ and H-6$_{axial}$), 2.26 (3H, s, NCH_3), 2.44 (1H, tt, *J* = 10.3, 4.0 Hz, H-4), 2.67 (2H, q, *J* = 7.1 Hz, NCH_2CH$_3$), 2.86 – 2.75 (2H, m, H-2$_{equ}$ and H-6$_{equ}$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 15.8 (NCH$_2$*C*H$_3$), 33.1 (C-3 and C-5), 41.1 (N*C*H$_2$CH$_3$), 46.4 (N*C*H$_3$), 54.6 (C-4), 54.9 (C-2 and C-6); LRMS (ES^+) *m/z* 143.3 $[M+H]^+$; HRMS (NSI) calcd for $C_8H_{19}N_2$ $[M+H]^+$ 143.1543, found 143.1539.

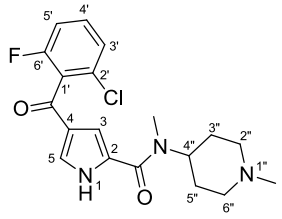
_N-Iso_propyl-1-methylpiperidin-4-amine, (254)



Compound **254** was synthesised according to general procedure S, using the following reagents: 1-methyl-4-piperidone (**251**) (1.54 mL, 1.5 g, 13.3 mmol), acetic acid (0.83 mL, 0.88 g, 14.6 mmol), 2 M *iso*propylamine in MeOH (13.3 mL, 26.6 mmol) and MeOH

(13.3 mL). The crude yellow oil was purified by Kugelröhr distillation to yield the *title compound* as a clear liquid (825 mg, 40%); R_f = 0.23 (EtOAc:MeOH, 7:3); IR (neat) ν_{max}/cm^{-1} 3258, 2961, 2937, 2845, 2790, 2739, 2676, 1466, 1449, 1379, 1278; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02 (6H, d, *J* = 6.2 Hz, NCH(C*H*$_3$)$_2$), 1.40 – 1.24 (2H, m, H-3$_{axial}$ and H-5$_{axial}$), 1.90 – 1.78 (2H, m, H-3$_{equ}$ and H-5$_{equ}$), 1.96 (2H, ddd, *J* = 11.8, 11.8 and 2.6 Hz, H-2$_{axial}$ and H-6$_{axial}$), 2.24 (3H, s, NC*H*$_3$), 2.49 (1H, tt, *J* = 10.5, 4.0 Hz, H-4), 2.80 (2H, ddd, *J* = 11.8, 3.7 and 3.7 Hz, H-2$_{equ}$ and H-6$_{equ}$), 3.01 – 2.91 (1H, m, NC*H*(CH$_3$)$_2$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 23.6 (NCH(*C*H$_3$)$_2$), 33.6 (C-3 and C-5), 44.7 (N*C*H(CH$_3$)$_2$), 46.5 (N*C*H$_3$), 51.4 (C-4), 55.2 (C-2 and C-6); LRMS (ES$^+$) *m/z* 157.3 $[M+H]^+$; HRMS (NSI) calcd for $C_9H_{21}N_2$ $[M+H]^+$ 157.1699, found 157.1696.

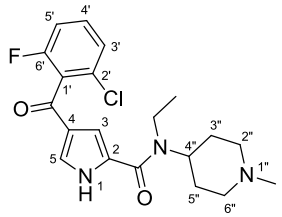
4-(2-Chloro-6-fluorobenzoyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)-1*H*-pyrrole-2-carboxamide, (255)



Compound **255** was synthesised according to general procedure T, using the following reagents: 4-(2-chloro-6-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**249**) (100 mg, 0.37 mmol), *N*,1-dimethylpiperidin-4-amine (**252**) (144 mg, 1.12 mmol), 4-(dimethylamino)pyridine (5 mg, 0.04 mmol), *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (144 mg, 0.75 mmol) and DCM (3.7 mL). The product was purified by column chromatography (silica gel, DCM:MeOH, 1:0 → 92:8) to yield the *title compound* as an off-white solid (26 mg, 18%); R_f = 0.22 (DCM:MeOH, 92:8); m.p. 226.0-228.0 °C; λ_{max} (EtOH)/nm 234.4, 285.2; IR (neat) ν_{max}/cm^{-1} 3158, 2940, 2908, 2847, 2785, 1653, 1587, 1558, 1483, 1448, 1391, 1322, 1244;^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 1.65 – 1.52 (2H, m, H-3"$_{equ}$ and H-5"$_{equ}$), 1.85 (2H, dddd, *J* = 12.1, 12.1, 12.1 and 3.8 Hz, H-3"$_{axial}$ and H-5"$_{axial}$), 1.95 (2H, ddd, *J* = 11.7, 11.7 and 2.3 Hz, H-2"$_{axial}$ and H-6"$_{axial}$), 2.19 (3H, s, NC*H*$_3$), 2.88 – 2.79 (2H, m, H-2"$_{equ}$ and H-6"$_{equ}$), 3.00 (3H, s, CONC*H*$_3$), 4.17 (1H, tt, *J* = 11.7, 4.0 Hz, H-4"), 6.74 (1H, d, *J* = 1.5 Hz, H-3), 7.26 (1H, d, *J* = 1.5 Hz, H-5), 7.30 (1H, dd, *J* = 8.7, 8.7 Hz, H-5'), 7.40 (1H, d, *J* = 8.2 Hz, H-3'), 7.53 (1H, ddd, *J* = 8.7, 8.2 and 6.2 Hz, H-4'), 11.91 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 28.2 (C-3" and C-5"), 29.4 (CON*C*H$_3$), 45.0 (N*C*H$_3$), 52.9 (C-4"), 54.2 (C-2" and C-6"), 110.1 (C-3), 114.2 (d, *J* = 22.2 Hz, C-5'), 124.5 (C-2 or C-4), 125.2 (d, *J* = 3.3 Hz, C-3'), 127.2 (C-5), 127.4 (C-2 or C-4), 128.0 (d, *J* = 23.3 Hz, C-1'), 130.4

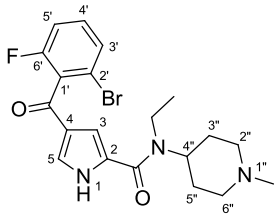
(d, *J* = 6.1 Hz, C-6'), 131.0 (d, *J* = 9.3 Hz, C-4'), 158.3 (d, *J* = 247.5 Hz, C-6'), 160.8 (CON), 183.0 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -114.4 (ArF); LRMS (ES$^-$) *m/z* 376.0 [M(^{35}Cl)-H]$^-$, 378.0 [M(^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{19}H_{20}ClFN_3O_2$ [M(^{35}Cl)-H]$^-$ 376.1234, found 376.1230.

4-(2-Chloro-6-fluorobenzoyl)-*N*-ethyl-*N*-(1-methylpiperidin-4-yl)-1*H*-pyrrole-2-carboxamide, (256)



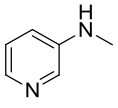
Compound **256** was synthesised according to general procedure T, using the following reagents: 4-(2-chloro-6-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**249**) (100 mg, 0.37 mmol), *N*-ethyl-1-methylpiperidin-4-amine (**253**) (160 mg, 1.12 mmol), 4-(dimethylamino)pyridine (5 mg, 0.04 mmol), *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (144 mg, 0.75 mmol) and DCM (3.7 mL). The product was purified by column chromatography (silica gel, DCM:MeOH, 1:0 → 93:7) to yield the *title compound* as an off-white solid (30 mg, 20%); R_f = 0.22 (DCM:MeOH, 93:7); m.p. 208.0-210.0 °C; λ_{max} (EtOH)/nm 285.8, 235.2; IR (neat) ν_{max}/cm^{-1} 3156, 2961, 2921, 1849, 2787, 1651, 1579, 1556, 1444, 1386, 1379, 1278; ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 1.17 (3H, t, *J* = 7.0 Hz, C*H*$_3$CH$_2$N), 1.72 – 1.58 (2H, m, CH$_{2\ piperidine}$), 1.97 - 1.83 (4H, m, CH$_{2\ piperidine}$), 2.19 (3H, s, NC*H*$_3$), 2.90 – 2.76 (2H, m, CH$_{2\ piperidine}$), 3.46 (2H, q, *J* = 7.0 Hz, CH$_3$C*H*$_2$N), 4.07 (1H, m, H-4"), 6.67 (1H, d, *J* = 1.5 Hz, H-3), 7.26 (1H, d, *J* = 1.5 Hz, H-5), 7.31 (1H, dd, *J* = 8.7, 8.7 Hz, H-5'), 7.40 (1H, d, *J* = 8.1 Hz, H-3'), 7.54 (1H, ddd, *J* = 8.7, 8.1 and 6.2 Hz, H-4'), 11.94 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 45.8 (N*C*H$_3$), 54.8 (N*C*H$_2$-piperidine), 109.6 (C-3), 114.9 (d, *J* = 21.6 Hz, C-5'), 124.7 (C-2 or C-4), 125.8 (d, *J* = 3.1 Hz, C-3'), 127.7 (C-2 or C-4), 128.0 (d, *J* = 23.0 Hz, C-1'), 128.4 (C-5), 130.4 (d, *J* = 6.2 Hz, C-2'), 131.8 (d, *J* = 9.3 Hz, C-4'), 158.6 (d, *J* = 246.7 Hz, C-6'), 160.7 (CON), 183.7 (ArCO) – C-3", 5" C-4" and the carbons of the ethyl are not visualised; ^{19}F NMR (471 MHz, DMSO-d_6) δ -114.37 (ArF); LRMS (ES$^+$) *m/z* 392.5 [M(^{35}Cl)+H]$^+$, 394.4 [M(^{37}Cl)+H]$^+$; HRMS (ESI) calcd for $C_{20}H_{24}ClFN_3O_2$ [M(^{35}Cl)+H]$^+$ 392.1536, found 392.1531.

4-(2-Bromo-6-fluorobenzoyl)-*N*-ethyl-*N*-(1-methylpiperidin-4-yl)-1*H*-pyrrole-2-carboxamide, (257)



Compound **257** was synthesised according to general procedure T, using the following reagents: 4-(2-bromo-6-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**244**) (100 mg, 0.32 mmol), *N*-ethyl-1-methylpiperidin-4-amine (**253**) (137 mg, 0.96 mmol), 4-(dimethylamino)pyridine (4 mg, 0.03 mmol), *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (123 mg, 0.64 mmol) and DCM (3.2 mL). The product was purified by column chromatography (silica gel, DCM:MeOH, 1:0 → 93:7) to yield the *title compound* as an off-white solid (31 mg, 22%); R_f = 0.25 (DCM:MeOH, 93:7); m.p. 198.0-200.0 °C; λ_{max} (EtOH)/nm 285.6, 234.6; IR (neat) ν_{max}/cm^{-1} 3162, 2959, 2922, 2849, 2785, 1651, 1579, 1555, 1442, 1379, 1278; ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 1.16 (3H, t, *J* = 7.0 Hz, NCH$_2$C*H*$_3$), 1.60 – 1.66 (2H, m, CH$_{2\ \text{piperidine}}$), 1.84 – 1.96 (4H, m, CH$_{2\ \text{piperidine}}$), 2.18 (3H, s, NC*H*$_3$), 2.82 – 2.87 (2H, m, CH$_{2\ \text{piperidine}}$), 3.45 (2H, q, *J* = 7.0 Hz, NC*H*$_2$CH$_3$), 4.01 – 4.10 (1H, m, H-4"), 6.65 (1H, d, *J* = 1.5 Hz, H-3), 7.26 (1H, d, *J* = 1.5 Hz, H-5), 7.33 (1H, dd, *J* = 8.6, 8.6 Hz, H-5'), 7.46 (1H, ddd, *J* = 8.6, 8.0 and 6.1 Hz, H-4'), 7.54 (1H, d, *J* = 8.0 Hz, H-3'), 11.88 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 15.1 (NCH$_2$*C*H$_3$), 29.5 (C-3", 5"), 37.4 (N*C*H$_2$CH$_3$), 45.1 (NCH$_3$), 54.4 (C-4"), 54.5 (C-2", 6"), 109.7 (C-3), 115.3 (d, *J* = 21.7 Hz, C-5'), 119.1 (d, *J* = 5.3 Hz, C-2'), 124.4 (C-2 or C-4), 127.7 (C-2 or C-4), 128.3 (C-5), 128.8 (d, *J* = 3.0 Hz, C-3'), 129.9 (d, *J* = 22.6 Hz, C-1'), 132.1 (d, *J* = 8.9 Hz, C-4'), 158.5 (d, *J* = 247.9 Hz, C-6'), 160.7 (CON), 184.6 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -113.8 (ArF); LRMS (ES$^+$) *m/z* 436.4 [M(^{79}Br)+H]$^+$, 438.4 [M(^{81}Br)+H]$^+$; HRMS (ESI) calcd for $C_{20}H_{24}BrFN_3O_2$ [M(^{79}Br)+H]$^+$ 436.1030, found 436.1021.

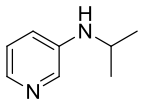
_N_-Methylpyridin-3-amine, (259)



A microwave vial was charged with 3-bromopyridine (**258**) (610 µL, 1.0 g, 6.33 mmol), copper powder (20 mg, 0.32 mmol), water (1.17 mL) and 40% aq. methylamine (3.52 mL, 31.7 mmol). The resulting solution was stirred at 100 °C for 20 h. Upon completion, the reaction mixture was diluted with water (15 mL) and extracted with EtOAc (3 × 25 mL). The pooled organic extracts were washed with brine (30 mL), dried over $MgSO_4$ and

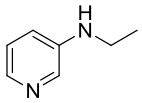
concentrated *in vacuo*. The crude green oil was purified by column chromatography (silica gel, EtOAc:MeOH, 1:0 → 97:3) to yield the *title compound* as a pale yellow liquid (548 mg, 80%); R_f = 0.32 (EtOAc:MeOH, 97:3); λ_{max} (EtOH)/nm 250.8, 314.8; IR (neat) ν_{max}/cm^{-1} 3273, 3044, 2982, 2892, 2814, 1654, 1580, 1521, 1486, 1304, 1248; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.68 (3H, d, *J* = 5.1 Hz, NHC*H*$_3$), 5.86 (1H, q, *J* = 5.1 Hz, N*H*CH$_3$), 6.84 (1H, ddd, *J* = 8.3, 2.9 and 1.4 Hz, H-4), 7.07 (1H, dd, *J* = 8.3, 4.6 Hz, H-5), 7.75 (1H, dd, *J* = 4.6, 1.4 Hz, H-6), 7.92 (1H, d, *J* = 2.9 Hz, H-2); ^{13}C NMR (126 MHz, DMSO-d_6) δ 29.3 (NH*C*H$_3$), 116.9 (C-4), 123.6 (C-5), 135.0 (C-2), 136.6 (C-6), 145.8 (C-3); LRMS (ES$^+$) *m/z* 109.1 [M+H]$^+$; HRMS (APCI) calcd for $C_6H_9N_2$ [M+H]$^+$ 109.0760, found 109.0758; ^{1}H and ^{13}C NMR data were identical to literature data.[205]

***N*-*Iso*propylpyridin-3-amine, (260)**



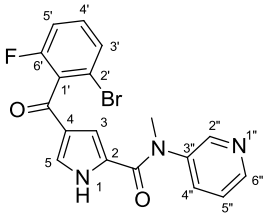
A microwave vial was charged with 3-bromopyridine (**258**) (610 µL, 1.0 g, 6.33 mmol), copper powder (20 mg, 0.32 mmol), water (6.35 mL) and *iso*propylamine (2.72 mL, 1.87 g, 31.7 mmol). The resulting solution was stirred at 100 °C for 72 h. Upon completion, the reaction mixture was diluted with water (15 mL) and extracted with EtOAc (3 × 25 mL). The pooled organic extracts were washed with brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude brawn oil was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 15:85) to yield the *title compound* as a yellow oil (190 mg, 22%); R_f = 0.29 (petrol:EtOAc, 15:85); λ_{max} (EtOH)/nm 253.6, 316.2; IR (neat) ν_{max}/cm^{-1} 3264, 3102, 3039, 2964, 2926, 2871, 1589, 1578, 1529, 1483, 1317, 1245; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.12 (6H, d, *J* = 6.3 Hz, CH(C*H*$_3$)$_2$), 3.54 (1H, dhept, *J* = 8.0, 6.3 Hz, NHC*H*(CH$_3$)$_2$), 5.63 (1H, d, *J* = 8.0 Hz, N*H*CH(CH$_3$)$_2$), 6.86 (1H, ddd, *J* = 8.3, 2.9 and 1.4 Hz, H-4), 7.04 (1H, dd, *J* = 8.3, 4.6 Hz, H-5), 7.70 (1H, dd, *J* = 4.6, 1.4 Hz, H-6), 7.92 (1H, d, *J* = 2.9 Hz, H-2); ^{13}C NMR (126 MHz, DMSO-d_6) δ 22.3 (CH(*C*H$_3$)$_2$), 42.7 (*C*H(CH$_3$)$_2$), 117.5 (C-4), 123.6 (C-5), 135.7 (C-2), 136.3 (C-6), 144.2 (C-3); LRMS (ES$^+$) *m/z* 137.2 [M+H]$^+$; HRMS (ESI) calcd for $C_8H_{13}N_2$ [M+H]$^+$ 137.1073, found 137.1070; ^{1}H and ^{13}C NMR data were identical to literature data.[274]

***N*-Ethylpyridin-3-amine, (263)**



To 3-aminopyridine (**261**) (1.0 g, 10.6 mmol) in 2,2,2-trifluoroethanol (15 mL) was added acetaldehyde (596 µL, 468 mg, 10.6 mmol). The resulting solution was stirred at RT for 1 h. Once cooled at 0 °C, sodium borohydride was carefully added. The resulting mixture was allowed to warm to RT and then stirred for 1 h. Upon completion, the solvent was removed *in vacuo*. The crude residue was dissolved in EtOAc (30 mL), neutralised by washing with saturated aq. NH_4Cl (20 mL), washed with water and brine (20 mL, respectively), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 2:8) to yield the *title compound* as a pale yellow oil (875 mg, 67%); R_f = 0.29 (petrol:EtOAc, 2:8); λ_{max} (EtOH)/nm 252.0, 315.0; IR (neat) ν_{max}/cm^{-1} 3263, 3099, 3035, 2969, 2873, 1585, 1522, 1478, 1319, 1303, 1244; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.16 (3H, t, *J* = 7.1 Hz, $NHCH_2CH_3$), 3.03 (2H, qd, *J* = 7.1, 5.5 Hz, $NHCH_2CH_3$), 5.75 (1H, t, *J* = 5.5 Hz, $ArNHCH_2$), 6.86 (1H, ddd, *J* = 8.3, 2.9 and 1.4 Hz, H-4), 7.05 (1H, dd, *J* = 8.3, 4.6 Hz, H-5), 7.73 (1H, dd, *J* = 4.6, 1.4 Hz, H-6), 7.93 (1H, d, *J* = 2.9 Hz, H-2); ^{13}C NMR (126 MHz, DMSO-d_6) δ 14.2 ($NHCH_2CH_3$), 36.9 ($NHCH_2CH_3$), 117.2 (C-4), 123.6 (C-5), 135.2 (C-2), 136.6 (C-6), 144.9 (C-3); LRMS (ES$^+$) *m/z* 123.1 [M+H]$^+$; HRMS (APCI) calcd for $C_7H_{11}N_2$ [M+H]$^+$ 123.0917, found 123.0916; ^{1}H NMR, ^{13}C NMR and IR data were identical to literature data.[275, 276]

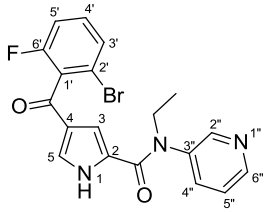
4-(2-Bromo-6-fluorobenzoyl)-*N*-methyl-*N*-(pyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (264)



Compound **264** was synthesised according to general procedure U, using the following reagents: 4-(2-bromo-6-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**244**) (100 mg, 0.32 mmol), *N*-methylpyridin-3-amine (**259**) (87 mg, 0.80 mmol), phosphorus trichloride (28 µL, 44 mg, 0.32 mmol) and acetonitrile (1.60 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 15:85) to yield the *title compound* as a white solid (80 mg, 62%); R_f = 0.29 (petrol:EtOAc, 15:85); m.p. 181.5-183.5 °C; No λ_{max} (EtOH)/nm; IR (neat) ν_{max}/cm^{-1} 3207, 1662, 1608, 1551,

1483, 1438, 1397, 1347, 1298; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.35 (3H, s, NCH_3), 5.02 (1H, brs, H-3), 7.26 (1H, brs, H-5), 7.33 (1H, dd, *J* = 8.5, 8.5 Hz, H-5'), 7.44 (1H, ddd, *J* = 8.5, 8.0 and 6.1 Hz, H-4'), 7.49 (1H, dd, *J* = 8.1, 4.7 Hz, H-5"), 7.51 (1H, d, *J* = 8.0 Hz, H-3'), 7.87 (1H, ddd, *J* = 8.1, 2.6 and 1.6 Hz, H-4"), 8.59 – 8.50 (2H, m, H-2" and H-6"), 12.51 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 38.0 (NCH_3), 113.0 (C-3), 115.2 (d, *J* = 21.5 Hz, C-5'), 118.8 (d, *J* = 5.0 Hz, C-2'), 124.3 (C-5"), 124.4 (C-2 or C-4), 127.0 (C-2 or C-4), 128.1 (C-5), 128.7 (d, *J* = 3.2 Hz, C-3'), 129.6 (d, *J* = 22.6 Hz, C-2'), 132.0 (d, *J* = 8.6 Hz, C-4'), 135.4 (C-4"), 140.3 (C-3"), 148.8 (C-2" or C-6"), 148.9 (C-2" or C-6"), 158.2 (d, *J* = 247.8 Hz, C-6'), 159.9 (CON), 184.4 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -113.8 (ArF); LRMS (ES$^+$) *m/z* 402.3 [M(^{79}Br)+H]$^+$, 404.2 [M(^{81}Br)+H]$^+$; HRMS (ESI) calcd for $C_{18}H_{14}BrFN_3O_2$ [M(^{79}Br)+H]$^+$ 402.0248, found 402.0247.

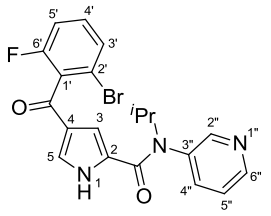
4-(2-Bromo-6-fluorobenzoyl)-*N*-ethyl-*N*-(pyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (265)



Compound **265** was synthesised according to general procedure U, using the following reagents: 4-(2-bromo-6-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**244**) (100 mg, 0.32 mmol), *N*-ethylpyridin-3-amine (**263**) (98 mg, 0.80 mmol), phosphorus trichloride (28 µL, 44 mg, 0.32 mmol) and acetonitrile (1.60 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 1:3) to yield the *title compound* as a white solid (67 mg, 50%); R_f = 0.32 (petrol:EtOAc, 1:3); m.p. 184.5-186.5 °C; No λ_{max} (EtOH)/nm; IR (neat) ν_{max}/cm^{-1} 3196, 1663, 1601, 1549, 1445, 1431, 1307; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.10 (3H, t, *J* = 7.1 Hz, CH_3CH$_2$N), 3.81 (2H, q, *J* = 7.1 Hz, CH$_3$CH_2N), 5.02 (1H, brs, H-3), 7.25 (1H, brs, H-5), 7.32 (1H, dd, *J* = 8.6, 8.6 Hz, H-5'), 7.54 – 7.40 (3H, m, H-3' and H-4' and H-5"), 7.84 (1H, d, *J* = 8.0 Hz, H-4"), 8.52 (1H, d, *J* = 2.2 Hz, H-2"), 8.59 (1H, d, *J* = 3.7 Hz, H-6"), 12.50 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 12.6 (*C*H$_3$CH$_2$N), 44.6 (CH$_3$*C*H$_2$N), 112.9 (C-3), 115.1 (d, *J* = 21.7 Hz, C-5'), 118.8 (d, *J* = 5.2 Hz, C-2'), 124.4 (C-2 or C-4 or C-5"), 124.4 (C-2 or C-4 or C-5"), 127.1 (C-2 or C-4), 128.0 (C-5), 128.7 (d, *J* = 3.2 Hz, C-3'), 129.5 (d, *J* = 22.4 Hz, C-1'), 132.0 (d, *J* = 8.7 Hz, C-4'), 136.4 (C-4"), 138.5 (C-3"), 149.1 (C-2" or C-6"), 149.7 (C-2" or C-6"), 158.2 (d, *J* = 247.9 Hz, C-6'), 159.4 (CON), 184.4

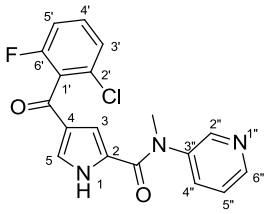
(ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -113.8 (ArF); LRMS (ES$^+$) *m/z* 416.3 [M(^{79}Br)+H]$^+$, 418.3 [M(^{81}Br)+H]$^+$; HRMS (ESI) calcd for $C_{19}H_{16}BrFN_3O_2$ [M(^{79}Br)+H]$^+$ 416.0404, found 416.0401.

4-(2-Bromo-6-fluorobenzoyl)-*N*-*iso*propyl-*N*-(pyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (266)



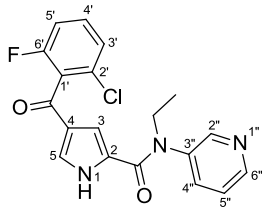
Compound **266** was synthesised according to general procedure U, using the following reagents: 4-(2-bromo-6-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**244**) (100 mg, 0.32 mmol), *N*-*iso*propylpyridin-3-amine (**260**) (109 mg, 0.80 mmol), phosphorus trichloride (28 µL, 44 mg, 0.32 mmol) and acetonitrile (1.60 mL). The crude product was purified by column chromatography (amine silica gel, petrol:EtOAc, 1:0 → 7:3) to yield the *title compound* as an off-white solid (76 mg, 55%); R_f = 0.31 (petrol:EtOAc, 35:65); m.p. 196.5-198.5 °C; λ_{max} (EtOH)/nm 236.6; IR (neat) ν_{max}/cm^{-1} 3221, 3099, 2975, 1664, 1595, 1577, 1548, 1479, 1434, 1328, 1229, 1117; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.06 (6H, d, *J* = 6.9 Hz, NCH(C*H*$_3$)$_2$), 4.58 (1H, s, H-3), 4.99 (1H, hept, *J* = 6.9 Hz, NC*H*(CH$_3$)$_2$), 7.24 (1H, s, H-5), 7.33 (1H, dd, *J* = 8.6, 8.6 Hz, H-5'), 7.55 – 7.40 (3H, m, H-3' and H-4' and H-5"), 7.80 (1H, ddd, *J* = 7.1, 2.2 and 2.2 Hz, H-4"), 8.47 (1H, d, *J* = 2.6 Hz, H-2"), 8.61 (1H, dd, *J* = 4.9, 1.6 Hz, H-6"), 12.46 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 20.5 (NCH(*C*H$_3$)$_2$), 46.5 (N*C*H(CH$_3$)$_2$), 112.7 (C-3), 115.2 (d, *J* = 21.6 Hz, C-5'), 118.8 (d, *J* = 5.1 Hz, C-2'), 124.1 (C-5"), 124.4 (C-2 or C-4), 127.3 (C-2 or C-4), 127.7 (C-5), 128.7 (d, *J* = 3.2 Hz, C-3'), 129.5 (d, *J* = 22.6 Hz, C-1'), 132.0 (d, *J* = 8.7 Hz, C-4'), 134.7 (C-3"), 138.5 (C-4"), 149.6 (C-6"), 151.3 (C-2"), 157.2 (d, *J* = 248.4 Hz, C-6'), 159.1 (CON), 184.4 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -113.9 (ArF); LRMS (ES$^+$) *m/z* 430.0 [M(^{79}Br)+H]$^+$, 432.0 [M(^{81}Br)+H]$^+$; HRMS (NSI) calcd for $C_{20}H_{16}BrFN_3O_2$ [M(^{79}Br)-H]$^-$ 428.0415, found 428.0410.

4-(2-Chloro-6-fluorobenzoyl)-*N*-methyl-*N*-(pyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (267)



Compound **267** was synthesised according to general procedure U, using the following reagents: 4-(2-chloro-6-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**249**) (100 mg, 0.37 mmol), *N*-methylpyridin-3-amine (**259**) (101 mg, 0.94 mmol), phosphorus trichloride (34 µL, 51 mg, 0.37 mmol) and acetonitrile (1.85 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 15:85) to yield the *title compound* as an off-white solid (81 mg, 60%); R_f = 0.28 (petrol:EtOAc, 15:85); m.p. 155.0-157.0 °C; λ_{max} (EtOH)/nm 234.4; IR (neat) ν_{max}/cm^{-1} 3200, 1658, 1607, 1549, 1482, 1443, 1298; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.35 (3H, s, NCH_3), 5.02 (1H, brs, H-3), 7.33 – 7.25 (2H, m, H-5 and H-5'), 7.37 (1H, d, *J* = 8.1 Hz, H-3'), 7.48 (1H, dd, *J* = 8.1, 4.8 Hz, H-5"), 7.52 (1H, ddd, *J* = 8.4, 8.1 and 6.2 Hz, H-4'), 7.87 (1H, ddd, *J* = 8.1, 2.7 and 1.6 Hz, H-4"), 8.59 – 8.53 (2H, m, H-2" and H-6"), 12.52 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 38.0 (NCH_3), 113.0 (C-3), 114.8 (d, *J* = 21.7 Hz, C-5'), 124.3 (C-5"), 124.7 (C-2 or C-4), 125.7 (d, *J* = 3.1 Hz, C-3'), 127.0 (C-2 or C-4), 127.6 (d, *J* = 23.1 Hz, C-1'), 128.0 (C-5), 130.2 (d, *J* = 6.0 Hz, C-2'), 131.7 (d, *J* = 9.2 Hz, C-4'), 135.4 (C-4"), 140.3 (C-3"), 148.8 (C-2" or C-6"), 148.9 (C-2" or C-6"), 158.3 (d, *J* = 246.9 Hz, C-6'), 159.9 (CON), 183.5 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -114.4 (ArF); LRMS (ES$^+$) *m/z* 358.3 [M(^{35}Cl)+H]$^+$, 360.4 [M(^{37}Cl)+H]$^+$; HRMS (ESI) calcd for $C_{18}H_{14}ClFN_3O_2$ [M(^{35}Cl)+H]$^+$ 358.0753, found 358.0751.

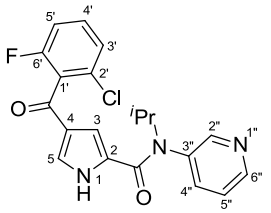
4-(2-Chloro-6-fluorobenzoyl)-*N*-ethyl-*N*-(pyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (268)



Compound **268** was synthesised according to general procedure U, using the following reagents: 4-(2-chloro-6-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**249**) (100 mg, 0.37 mmol), *N*-ethylpyridin-3-amine (**263**) (114 mg, 0.94 mmol), phosphorus trichloride (34 µL, 51 mg, 0.37 mmol) and acetonitrile (1.85 mL). The crude product was purified by

column chromatography (silica gel, petrol:EtOAc, 1:0 → 1:3) to yield the *title compound* as a white solid (56 mg, 40%); R_f = 0.30 (petrol:EtOAc, 1:3); m.p. 186.0-188.0 °C; λ_{max} (EtOH)/nm 234.6; IR (neat) ν_{max}/cm^{-1} 3197, 1664, 1603, 1581, 1575, 1549, 1448, 1432, 1308; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.10 (3H, t, *J* = 7.1 Hz, CH_3CH$_2$N), 3.81 (2H, q, *J* = 7.1 Hz, CH$_3$CH_2N), 4.88 (1H, brs, H-3), 7.34 – 7.26 (2H, m, H-5 and H-5'), 7.37 (1H, d, *J* = 8.1 Hz, H-3'), 7.60 – 7.44 (2H, m, H-4 and H-5"), 7.84 (1H, d, *J* = 7.9 Hz, H-4"), 8.51 (1H, d, *J* = 1.9 Hz, H-2"), 8.59 (1H, d, *J* = 3.9 Hz, H-6"), 12.51 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 12.6 (*C*H$_3$CH$_2$N), 44.6 (CH$_3$*C*H$_2$N), 112.9 (C-3), 114.8 (d, *J* = 21.6 Hz, C-5'), 124.4 (C-5"), 124.7 (C-2 or C-4), 125.7 (d, *J* = 3.3 Hz, C-3'), 127.1 (C-2 or C-4), 127.6 (d, *J* = 22.8 Hz, C-1'), 128.0 (C-5), 130.2 (d, *J* = 5.9 Hz, C-2'), 131.7 (d, *J* = 9.1 Hz, C-4'), 136.4 (C-4"), 138.5 (C-3"), 149.1 (C-2" or C-6"), 149.7 (C-2" or C-6"), 158.3 (d, *J* = 246.8 Hz, C-6'), 159.4 (CON), 183.5 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -114.4 (ArF); LRMS (ES$^+$) *m/z* 372.3 [M(^{35}Cl)+H]$^+$, 374.4 [M(^{37}Cl)+H]$^+$; HRMS (ESI) calcd for $C_{19}H_{16}ClFN_3O_2$ [M(^{35}Cl)+H]$^+$ 372.0910, found 372.0909.

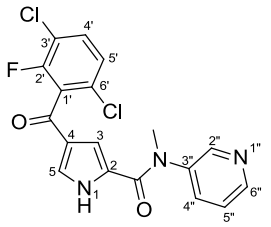
4-(2-Chloro-6-fluorobenzoyl)-*N*-isopropyl-*N*-(pyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (269)



Compound **269** was synthesised according to general procedure U, using the following reagents: 4-(2-chloro-6-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**249**) (100 mg, 0.37 mmol), *N-iso*propylpyridin-3-amine (**260**) (128 mg, 0.94 mmol), phosphorus trichloride (34 µL, 51 mg, 0.37 mmol) and acetonitrile (1.85 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 35:65) to yield the *title compound* as an off-white solid (72 mg, 50%); R_f = 0.31 (petrol:EtOAc, 35:65); m.p. 194.5-196.5 °C; λ_{max} (EtOH)/nm 236.6 nm; IR (neat) ν_{max}/cm^{-1} 3219, 1663, 1597, 1575, 1548, 1435, 1329; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.06 (6H, d, *J* = 6.9 Hz, (CH_3)$_2$CHN), 4.59 (1H, brs, H-3), 4.99 (1H, hept, *J* = 6.9 Hz, (CH$_3$)$_2$C*H*N), 7.27 (1H, brs, H-5), 7.30 (1H, dd, *J* = 9.1, 9.1 Hz, H-5'), 7.37 (1H, d, *J* = 8.1 Hz, H-3'), 7.57 – 7.45 (2H, m, H-4' and H-5"), 7.80 (1H, ddd, *J* = 7.6, 2.1 and 2.1 Hz, H-4"), 8.47 (1H, d, *J* = 2.1 Hz, H-2"), 8.61 (1H, dd, *J* = 4.9, 2.1 Hz, H-6"), 12.47 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 20.5 ((*C*H$_3$)$_2$CHN), 46.5 ((CH$_3$)$_2$*C*HN), 112.7 (C-3), 114.8 (d,

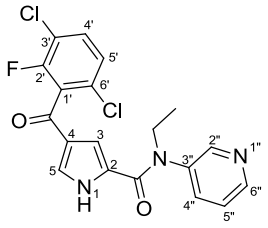
J = 21.6 Hz, C-3'), 124.1 (C-5"), 124.7 (C-2 or C-4), 125.7 (d, *J* = 3.2 Hz, C-3'), 127.3 (C-2 or C-4), 127.5 (d, *J* = 22.1 Hz, C-1'), 127.7 (C-5), 130.2 (d, *J* = 6.1 Hz, C-2'), 131.7 (d, *J* = 8.9 Hz, C-4'), 134.7 (C-3"), 138.5 (C-4"), 149.6 (C-6"), 151.3 (C-2"), 158.3 (d, *J* = 247.0 Hz, C-6'), 159.2 (CON), 183.5 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -114.5 (ArF); LRMS (ES$^+$) *m/z* 386.4 [M(^{35}Cl)+H]$^+$, 388.4 [M(^{37}Cl)+H]$^+$; HRMS (ESI) calcd for $C_{20}H_{18}ClFN_3O_2$ [M(^{35}Cl)+H]$^+$ 386.1066, found 386.1063.

4-(3,6-Dichloro-2-fluorobenzoyl)-*N*-methyl-*N*-(pyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (270)



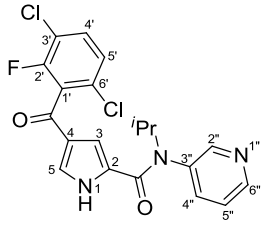
Compound **270** was synthesised according to general procedure U, using the following reagents: 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**) (100 mg, 0.33 mmol), *N*-methylpyridin-3-amine (**259**) (89 mg, 0.83 mmol), phosphorus trichloride (29 µL, 45 mg, 0.33 mmol) and acetonitrile (1.65 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 15:85) to yield the *title compound* as a pale yellow solid (55 mg, 42%); R_f = 0.28 (petrol:EtOAc, 15:85); m.p. 198.5-200.5 °C; λ_{max} (EtOH)/nm 280.4; IR (neat) ν_{max}/cm^{-1} 3214, 1667, 1614, 1584, 1557, 1448, 1385, 1298; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.35 (3H, s, NC*H*$_3$), 5.05 (1H, brs, H-3), 7.43 (1H, d, *J* = 8.9 Hz, H-5'), 7.45 (1H, brs, H-5), 7.50 (1H, dd, *J* = 8.1, 4.7 Hz, H-5"), 7.72 (1H, dd, *J* = 8.9, 8.3 Hz, H-4'), 7.88 (1H, d, *J* = 8.1 Hz, H-4"), 8.65 – 8.45 (2H, m, H-2" and H-6"), 12.60 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 38.0 (N*C*H$_3$), 112.8 (C-3), 119.2 (d, *J* = 17.9 Hz, C-3'), 124.2 (C-2 or C-4), 124.3 (C-5"), 126.7 (d, *J* = 3.8 Hz, C-5'), 127.2 (C-2 or C-4), 128.8 (d, *J* = 23.0 Hz, C-1), 128.9 (C-5), 129.0 (d, *J* = 5.0 Hz, C-6'), 131.8 (C-4'), 135.4 (C-4"), 140.3 (C-3"), 148.8 (C-2" or C-6"), 148.9 (C-2" or C-6"), 153.6 (d, *J* = 248.3 Hz, C-2'), 159.9 (Ar*C*ON), 182.2 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.7 (ArF); LRMS (ES$^-$) *m/z* 390.2 [M(^{35}Cl^{35}Cl)-H]$^-$, 392.2 [M(^{35}Cl^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{18}H_{11}Cl_2FN_3O_2$ [M(^{35}Cl^{35}Cl)-H]$^-$ 390.0218, found 390.0214.

4-(3,6-Dichloro-2-fluorobenzoyl)-*N*-ethyl-*N*-(pyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (271)



Compound **271** was synthesised according to general procedure U, using the following reagents: 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**) (100 mg, 0.33 mmol), *N*-ethylpyridin-3-amine (**263**) (101 mg, 0.83 mmol), phosphorus trichloride (29 µL, 45 mg, 0.33 mmol) and acetonitrile (1.65 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 35:65) to yield the *title compound* as a white solid (80 mg, 60%); R_f = 0.30 (petrol:EtOAc, 35:65); m.p. 169.5-171.5 °C; λ_{max} (EtOH)/nm 280.0; IR (neat) ν_{max}/cm^{-1} 3244, 2986, 2938, 1657, 1632, 1543, 1447, 1431, 1418, 1298, 1228; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.11 (3H, t, *J* = 7.3 Hz, NCH$_2$C*H*$_3$), 3.81 (2H, q, *J* = 7.1 Hz, NC*H*$_2$CH$_3$), 4.90 (1H, brs, H-3), 7.47 - 7.35 (2H, m, H-5 and H-5'), 7.51 (1H, dd, *J* = 8.2, 4.5 Hz, H-5"), 7.72 (1H, dd, *J* = 8.4, 8.4 Hz, H-4'), 7.86 (1H, d, *J* = 8.2 Hz, H-4"), 8.53 (1H, brs, H-2"), 8.60 (1H, d, *J* = 4.5 Hz, H-6"), 12.59 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 12.6 (NCH$_2$*C*H$_3$), 44.6 (NCH$_2$*C*H$_3$), 112.7 (C-3), 119.2 (d, *J* = 18.1 Hz, C-3'), 124.2 (C-2 or C-4), 124.4 (C-5"), 126.7 (d, *J* = 3.7 Hz, C-5'), 127.3 (C-2 or C-4), 128.8 (d, *J* = 22.9 Hz, C-1'), 128.8 (C-5), 129.0 (d, *J* = 5.1 Hz, C-6'), 131.7 (C-4'), 136.4 (C-4"), 138.5 (C-3"), 149.0 (C-6"), 149.7 (C-2"), 153.6 (d, *J* = 248.3 Hz, C-2'), 159.3 (Ar*C*ON), 182.2 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.8 (ArF); LRMS (ES$^-$) *m/z* 404.2 [M(^{35}Cl^{35}Cl)-H]$^-$, 406.3 [M(^{35}Cl^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{19}H_{13}Cl_2FN_3O_2$ [M(^{35}Cl^{35}Cl)-H]$^-$ 404.0374, found 404.0371.

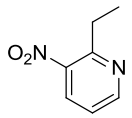
4-(3,6-Dichloro-2-fluorobenzoyl)-*N*-isopropyl-*N*-(pyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (272)



Compound **272** was synthesised according to general procedure U, using the following reagents: 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**) (100 mg,

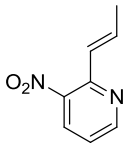
0.33 mmol), *N-iso*propylpyridin-3-amine (**260**) (113 mg, 0.83 mmol), phosphorus trichloride (29 µL, 45 mg, 0.33 mmol) and acetonitrile (1.65 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 45:55) to yield the *title compound* as an off-white solid (86 mg, 62%); R_f = 0.29 (petrol:EtOAc, 45:55); m.p. 181.5-183.5 °C; λ_{max} (EtOH)/nm 280.0; IR (neat) ν_{max}/cm^{-1} 3244, 1656, 1609, 1580, 1550, 1479, 1429, 1384, 1315, 1235; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.07 (6H, d, *J* = 6.8 Hz, NCH(CH_3)$_2$), 4.60 (1H, brs, H-3), 4.99 (1H, hept, *J* = 6.8 Hz, NC*H*(CH$_3$)$_2$), 7.46 – 7.38 (2H, m, H-5 and H-5'), 7.51 (1H, dd, *J* = 8.1, 4.8 Hz, H-5"), 7.73 (1H, dd, *J* = 8.4, 8.4 Hz, H-4'), 7.82 (1H, dd, *J* = 8.1, 1.9 Hz, H-4"), 8.49 (1H, d, *J* = 1.9 Hz, H-2"), 8.63 (1H, d, *J* = 4.8 Hz, H-6"), 12.56 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 20.4 (NCH(*C*H$_3$)$_2$), 46.5 (N*C*H(CH$_3$)$_2$), 112.5 (C-3), 119.2 (d, *J* = 18.2 Hz, C-3'), 124.1 (C-5"), 124.2 (C-2 or C-4), 126.7 (d, *J* = 3.7 Hz, C-5'), 127.6 (C-2 or C-4), 128.5 (C-5), 128.7 (d, *J* = 22.9 Hz, C-1'), 129.0 (d, *J* = 5.0 Hz, C-6'), 131.7 (C-4'), 134.8 (C-3"), 138.6 (C-4"), 149.6 (C-6"), 151.3 (C-2"), 153.5 (d, *J* = 248.5 Hz, C-2'), 159.1 (Ar*C*ON), 182.2 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.8 (ArF); LRMS (ES$^-$) *m/z* 418.3 [M(^{35}Cl^{35}Cl)-H]$^-$, 420.3 [M(^{35}Cl^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{20}H_{15}Cl_2FN_3O_2$ [M(^{35}Cl^{35}Cl)-H]$^-$ 418.0531, found 418.0526.

2-Ethyl-3-nitropyridine, (274)



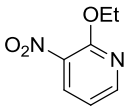
Compound **274** was synthesised according to general procedure W, using the following reagents: 2-chloro-3-nitropyridine (**273**) (650 mg, 4.10 mmol), ethylboronic acid (333 mg, 4.51 mmol), potassium carbonate (1.70 g, 12.3 mmol), tetrakis(triphenylphosphine) palladium(0) (474 mg, 0.41 mmol) and dioxane (20 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 9:1) to yield the *title compound* as a clear yellow oil (350 mg, 56%); R_f = 0.30 (petrol:EtOAc, 9:1); λ_{max} (EtOH)/nm 273.4; IR (neat) ν_{max}/cm^{-1} 3079, 2940, 2877, 1597, 1565, 1522, 1465, 1431, 1346; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.27 (3H, t, *J* = 7.5 Hz, ArCH$_2$CH_3), 3.00 (2H, q, *J* = 7.5 Hz, ArCH_2CH$_3$), 7.54 (1H, dd, *J* = 8.3, 4.7 Hz, H-5), 8.37 (1H, dd, *J* = 8.3, 1.5 Hz, H-4), 8.82 (1H, dd, *J* = 4.7, 1.5 Hz, H-6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 12.7 (ArCH$_2$*C*H$_3$), 28.0 (Ar*C*H$_2$CH$_3$), 122.4 (C-5), 132.6 (C-4), 145.7 (C-3), 152.9 (C-6), 156.1 (C-2); LRMS (ES$^+$) *m/z* 153.0 [M+H]$^+$; HRMS (APCI) calcd for $C_7H_9N_2O_2$ [M+H]$^+$ 153.0659, found 153.0658.

(*E*)-3-Nitro-2-(prop-1-en-1-yl)pyridine, (275)



Compound **275** was synthesised according to general procedure W, using the following reagents: 2-chloro-3-nitropyridine (**273**) (650 mg, 4.10 mmol), allylboronic acid pinacol ester (851 µL, 758 mg, 4.51 mmol), potassium carbonate (1.70 g, 12.3 mmol), tetrakis(triphenylphosphine)palladium(0) (474 mg, 0.41 mmol) and dioxane (20 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 9:1) to yield the *title compound* as an orange liquid (355 mg, 53%); R_f = 0.29 (petrol:EtOAc, 9:1); λ_{max} (EtOH)/nm 233.2, 272.0; IR (neat) ν_{max}/cm^{-1} 3063, 2969, 2938, 2914, 2851, 1645, 1590, 1559, 1518, 1446, 1424, 1342; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.95 (3H, dd, *J* = 6.9, 1.7 Hz, ArCH=CHCH_3), 6.85 (1H, dq, *J* = 15.2, 1.7 Hz, ArC*H*=CHCH$_3$), 7.13 (1H, dq, *J* = 15.2, 6.9 Hz, ArCH=C*H*CH$_3$), 7.50 (1H, dd, *J* = 8.3, 4.6 Hz, H-5), 8.33 (1H, dd, *J* = 8.3, 1.6 Hz, H-4), 8.79 (1H, dd, *J* = 4.6, 1.6 Hz, H-6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 18.4 (ArCH=CH*C*H$_3$), 122.6 (C-5), 124.4 (Ar*C*H=CHCH$_3$), 132.8 (C-4), 137.0 (ArCH=*C*HCH$_3$), 143.8 (C-3), 147.4 (C-2), 152.9 (C-6); LRMS (ES$^+$) *m/z* 165.2 [M+H]$^+$; HRMS (APCI) calcd for $C_8H_9N_2O_2$ [M+H]$^+$ 165.0659, found 165.0657.

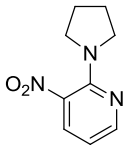
2-Ethoxy-3-nitropyridine, (276)



To a suspension of 2-chloro-3-nitropyridine (**273**) (1.0 g, 6.31 mmol) in ethanol (15 mL) was added sodium ethoxide (1.29 g 18.9 mmol). The resulting solution was stirred at RT overnight. Upon completion, the solvent was removed *in vacuo*. The crude residue was dissolved in EtOAc (40 mL), washed with water and brine (20 mL, respectively), dried over $MgSO_4$ and concentrated *in vacuo*. The crude brawn oil was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 9:1) to yield the *title compound* as an orange oil (661 mg, 62%); R_f = 0.31 (petrol:EtOAc, 9:1); λ_{max} (EtOH)/nm 242.6, 309.0; IR (neat) ν_{max}/cm^{-1} 2985, 1601, 1569, 1522, 1437, 1345, 1304, 1246; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.35 (3H, t, *J* = 7.1 Hz, ArOCH$_2$CH_3), 4.50 (2H, q, *J* = 7.1 Hz, ArOCH_2CH$_3$), 7.22 (1H, dd, *J* = 7.9, 4.9 Hz, H-5), 8.41 (1H, dd, *J* = 7.9, 1.8 Hz, H-4), 8.48 (1H, dd, *J* = 4.9, 1.8 Hz, H-6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 14.2 (ArOCH$_2$*C*H$_3$), 63.1

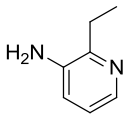
(ArO*C*H_2CH_3), 117.1 (C-5), 135.2 (C-4), 151.8 (C-6), 155.1 (C-2); LRMS (ES^+) *m/z* 169.0 $[M+H]^+$; HRMS (APCI) calcd for $C_7H_9N_2O_3$ $[M+H]^+$ 169.0608, found 169.0603.

3-Nitro-2-(pyrrolidin-1-yl)pyridine, (277)



To a suspension of 2-chloro-3-nitropyridine (**273**) (1.0 g, 6.31 mmol) in acetonitrile (15 mL) was added potassium carbonate (959 mg, 6.94 mmol) and pyrrolidine (579 µL, 493 mg, 6.94 mmol). The resulting solution was stirred at RT overnight. Upon completion, the potassium carbonate was removed by filtration and the solvent removed *in vacuo*. The crude residue was dissolved in EtOAc (40 mL), washed with water and brine (20 mL, respectively), dried over $MgSO_4$ and concentrated *in vacuo*. The crude orange oil was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 9:1) to yield the *title compound* as a yellow oil (1.11 g, 83%); R_f = 0.33 (petrol:EtOAc, 9:1); λ_{max} (EtOH)/nm 235.2, 286.2; IR (neat) ν_{max}/cm^{-1} 2970, 2953, 2874, 1592, 1552, 1501, 1476, 1455, 1435, 1347, 1335, 1322, 1247; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.90 (4H, t, *J* = 6.4 Hz, $NCH_2C\mathit{H}_2$), 3.29 (4H, t, *J* = 6.4 Hz, $NC\mathit{H}_2CH_2$), 6.78 (1H, dd, *J* = 8.2, 4.5 Hz, H-5), 8.18 (1H, d, *J* = 8.2 Hz, H-4), 8.38 (1H, d, *J* = 4.5 Hz, H-6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 24.9 ($NCH_2\mathit{C}H_2$), 49.1 ($N\mathit{C}H_2CH_2$), 111.4 (C-5), 131.2 (C-3), 134.9 (C-4), 149.7 (C-2), 152.2 (C-6); LRMS (ES^+) *m/z* 194.1 $[M+H]^+$; HRMS (NSI) calcd for $C_9H_{12}N_3O_2$ $[M+H]^+$ 194.0924, found 194.0925.

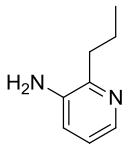
2-Ethylpyridin-3-amine, (278)



Compound **278** was synthesised according to general procedure V, using the following reagents: 2-ethyl-3-nitropyridine (**274**) (550 mg, 3.61 mmol) and methanol (73 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 15:85) to yield the *title compound* as a white solid (410 mg, 93%); R_f = 0.32 (petrol:EtOAc, 15:85); m.p. 114.5-116.5 °C; λ_{max} (EtOH)/nm 241.0, 300.0; IR (neat) ν_{max}/cm^{-1} 3657, 3393, 3150, 2981, 2889, 1647, 1580, 1448, 1380, 1238; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.16 (3H, t, *J* = 7.5 Hz, $ArCH_2C\mathit{H}_3$), 2.59 (2H, q, *J* = 7.5 Hz, $ArC\mathit{H}_2CH_3$), 4.99 (2H, brs, $ArN\mathit{H}_2$), 6.90 – 6.86 (2H, m, H-4 and H-6), 7.70 (1H, dd, *J* = 3.7, 2.4 Hz, H-5); ^{13}C NMR (126 MHz, DMSO-d_6) δ 11.4 ($ArCH_2\mathit{C}H_3$), 25.6

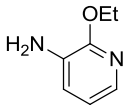
(Ar*C*$H_2$$CH_3$), 119.8 (C-4 or C-6), 121.5 (C-4 or C-6), 136.4 (C-5), 141.7 (C-3), 146.7 (C-2); LRMS (ES^+) *m/z* 123.0 $[M+H]^+$; HRMS (NSI) calcd for $C_7H_{11}N_2$ $[M+H]^+$ 123.0917, found 123.0917.

2-Propylpyridin-3-amine, (279)



Compound **279** was synthesised according to general procedure V, using the following reagents: (*E*)-3-nitro-2-(prop-1-en-1-yl)pyridine (**275**) (300 mg, 1.83 mmol) and methanol (37 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 3:7) to yield the *title compound* as a yellow oil (225 mg, 90%); R_f = 0.32 (petrol:EtOAc, 3:7); λ_{max} (EtOH)/nm 240.4, 300.4; IR (neat) ν_{max}/cm^{-1} 3335, 3202, 2959, 2932, 2871, 1621, 1583, 1451, 1305, 1236; ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.92 (3H, t, *J* = 7.4 Hz, $ArCH_2CH_2CH_3$), 1.64 (2H, tq, *J* = 7.6, 7.4 Hz, $ArCH_2CH_2CH_3$), 2.55 (2H, t, *J* = 7.6 Hz, $ArCH_2CH_2CH_3$), 4.98 (2H, brs, $ArNH_2$), 6.90 – 6.84 (2H, m, H-4 and H-5), 7.69 (1H, dd, *J* = 4.0, 2.1 Hz, H-6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 14.0 ($ArCH_2CH_2CH_3$), 20.0 ($ArCH_2CH_2CH_3$), 34.6 ($ArCH_2CH_2CH_3$), 120.0 (C-4 or C-5), 121.5 (C-4 or C-5), 136.4 (C-6), 141.9 (C-2 or C-3), 145.8 (C-2 or C-3); LRMS (ES^+) *m/z* 137.2 $[M+H]^+$; HRMS (NSI) calcd for $C_8H_{13}N_2$ $[M+H]^+$ 137.1073, found 137.1067.

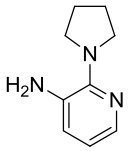
2-Ethoxypyridin-3-amine, (280)



Compound **280** was synthesised according to general procedure V, using the following reagents: 2-ethoxy-3-nitropyridine (**273**) (600 mg, 3.57 mmol) and methanol (72 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 85:15) to yield the *title compound* as a yellow oil (378 mg, 76%); R_f = 0.30 (petrol:EtOAc, 15:85); λ_{max} (EtOH)/nm 240.6, 294.4; IR (neat) ν_{max}/cm^{-1} 3464, 3332, 3217, 2978, 2934, 2896, 1612, 1596, 1452, 1386, 1347, 1233; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.31 (3H, t, *J* = 7.0 Hz, $ArOCH_2CH_3$), 4.29 (2H, q, *J* = 7.0 Hz, $ArOCH_2CH_3$), 4.83 (2H, brs, $ArNH_2$), 6.67 (1H, dd, *J* = 7.5, 4.9 Hz, H-5), 6.85 (1H, dd, *J* = 7.5, 1.7 Hz, H-4), 7.33 (1H, dd, *J* = 4.9, 1.7 Hz, H-6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 14.7 ($ArOCH_2CH_3$), 60.5 ($ArOCH_2CH_3$), 117.2 (C-5), 118.6 (C-4), 132.4 (C-3), 132.4 (C-6), 151.5 (C-2);

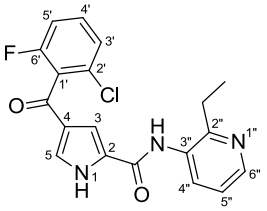
LRMS (ES^+) *m/z* 139.2 $[M+H]^+$; HRMS (APCI) calcd for $C_7H_{11}N_2O$ $[M+H]^+$ 139.0866, found 139.0864.

2-(Pyrrolidin-1-yl)pyridin-3-amine, (281)



Compound **281** was synthesised according to general procedure V, using the following reagents: 3-nitro-2-(pyrrolidin-1-yl)pyridine (**277**) (1.0 g, 5.18 mmol) and methanol (103 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 3:7) to yield the *title compound* as a purple oil (776 mg, 92%); R_f = 0.31 (petrol:EtOAc, 3:7); λ_{max} (EtOH)/nm 254.6, 312.8; IR (neat) ν_{max}/cm^{-1} 3320, 3213, 2945, 2865, 1587, 1444, 1346, 1229; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.85 – 1.77 (4H, m, NCH_2CH_2), 3.32 – 3.24 (4H, m, NCH_2CH_2), 4.60 (2H, brs, $ArNH_2$), 6.61 (1H, dd, *J* = 7.5, 4.7 Hz, H-5), 6.85 (1H, dd, *J* = 7.5, 1.6 Hz, H-4), 7.46 (1H, dd, *J* = 4.7, 1.6 Hz, H-6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 24.4 (NCH_2CH_2), 48.3 (NCH_2CH_2), 116.4 (C-5), 120.3 (C-4), 134.8 (C-6), 134.9 (C-3), 149.6 (C-2); LRMS (ES^+) *m/z* 164.2 $[M+H]^+$; HRMS (NSI) calcd for $C_9H_{14}N_3$ $[M+H]^+$ 164.1182, found 164.1182.

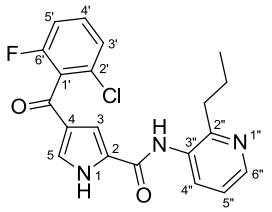
4-(2-Chloro-6-fluorobenzoyl)-*N*-(2-ethylpyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (282)



Compound **282** was synthesised according to general procedure U, using the following reagents: 4-(2-chloro-6-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**249**) (100 mg, 0.37 mmol), 2-ethylpyridin-3-amine (**278**) (114 mg, 0.94 mmol), phosphorus trichloride (34 µL, 51 mg, 0.37 mmol) and acetonitrile (1.85 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 3:7) to yield the *title compound* as a white solid (45 mg, 35%); R_f = 0.29 (petrol:EtOAc, 3:7); m.p. 125.5-127.5 °C; λ_{max} (EtOH)/nm 239.2, 286.0; IR (neat) ν_{max}/cm^{-1} 3234, 3126, 2970, 2936, 1634, 1558, 1516, 1445, 1287, 1245; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.18 (3H, t, *J* = 7.5 Hz, $ArCH_2CH_3$), 2.77 (2H, q, *J* = 7.5 Hz, $ArCH_2CH_3$), 7.27 (1H, dd, *J* = 7.9, 4.9 Hz, H-5”), 7.51 – 7.34 (4H, m, H-3, H-5, H-3’ and H-5’), 7.57 (1H, ddd, *J* = 8.3, 8.3 and 6.3 Hz,

H-4'), 7.68 (1H, d, *J* = 7.9 Hz, H-4"), 8.40 (1H, d, *J* = 4.9 Hz, H-6"), 9.90 (1H, s, CON*H*Ar), 12.65 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 12.3 (ArCH$_2$*C*H$_3$), 26.2 (Ar*C*H$_2$CH$_3$), 111.2 (C-3), 115.0 (d, *J* = 21.6 Hz, C-5'), 121.3 (C-5"), 125.3 (C-2 or C-4), 125.8 (d, *J* = 3.1 Hz, C-3'), 128.1 (d, *J* = 23.1 Hz, C-1'), 128.3 (C-2 or C-4), 129.2 (C-5), 130.5 (d, *J* = 6.0 Hz, C-2'), 131.2 (C-3"), 131.8 (d, *J* = 9.3 Hz, C-4'), 134.8 (C-4"), 146.6 (C-6"), 158.4 (*C*ONHAr or C-2"), 158.6 (d, *J* = 246.7 Hz, C-6'), 159.0 (*C*ONHAr or C-2"), 183.9 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -114.3 (ArF); LRMS (ES$^-$) *m/z* 370.3 [M(^{35}Cl)-H]$^-$, 372.2 [M(^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{19}H_{14}ClFN_3O_2$ [M(^{35}Cl)-H]$^-$ 370.0764, found 370.0762.

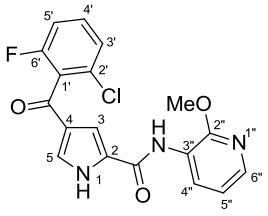
4-(2-Chloro-6-fluorobenzoyl)-*N*-(2-propylpyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (283)



Compound **283** was synthesised according to general procedure U, using the following reagents: 4-(2-chloro-6-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**249**) (100 mg, 0.37 mmol), 2-propylpyridin-3-amine (**279**) (127 mg, 0.94 mmol), phosphorus trichloride (34 µL, 51 mg, 0.37 mmol) and acetonitrile (1.85 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 4:6) to yield the *title compound* as a pale orange solid (35 mg, 24%); R_f = 0.29 (petrol:EtOAc, 4:6); m.p. 128.5-130.5 °C; λ_{max} (EtOH)/nm 239.6, 286.6; IR (neat) ν_{max}/cm^{-1} 3312, 3196, 2969, 1644, 1628, 1609, 1574, 1558, 1510, 1442, 1397, 1289, 1246; ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.86 (3H, t, *J* = 7.4 Hz, ArCH$_2$CH$_2$C*H*$_3$), 1.67 (2H, tq, *J* = 7.6, 7.4 Hz, ArCH$_2$C*H*$_2$CH$_3$), 2.73 (2H, t, *J* = 7.6 Hz, ArC*H*$_2$CH$_2$CH$_3$), 7.27 (1H, dd, *J* = 8.0, 4.7 Hz, H-5"), 7.43 – 7.36 (2H, m, H-5 and H-5'), 7.50 – 7.43 (2H, m, H-3 and H-3'), 7.58 (1H, ddd, *J* = 8.3, 8.3 and 6.1 Hz, H-4'), 7.68 (1H, dd, *J* = 8.0, 1.8 Hz, H-4"), 8.40 (1H, dd, *J* = 4.7, 1.8 Hz, H-6"), 9.90 (1H, s, CON*H*Ar), 12.64 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 13.9 (ArCH$_2$CH$_2$*C*H$_3$), 20.9 (ArCH$_2$*C*H$_2$CH$_3$), 35.1 (Ar*C*H$_2$CH$_2$CH$_3$), 111.1 (C-3), 115.0 (d, *J* = 21.6 Hz, C-5'), 121.3 (C-5"), 125.2 (C-2 or C-4), 125.8 (d, *J* = 3.1 Hz, C-3'), 128.0 (d, *J* = 23.3 Hz, C-1'), 128.3 (C-2 or C-4), 129.2 (C-5), 130.4 (d, *J* = 6.0 Hz, C-2'), 131.4 (C-3"), 131.8 (d, *J* = 9.0 Hz, C-4'), 134.8 (C-4"), 146.5 (C-6"), 157.4 (*C*ONHAr or C-2"), 158.6 (d, *J* = 246.3 Hz, C-6'), 159.0 (*C*ONHAr or C-2"), 183.9 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -114.4 (ArF); LRMS (ES$^-$) *m/z* 384.3 [M(^{35}Cl)-H]$^-$, 386.2

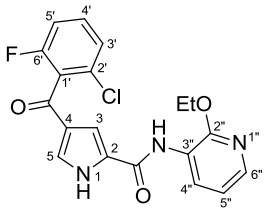
[M(^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{20}H_{18}ClFN_3O_2$ [M(^{35}Cl)+H]$^+$ 386.1066, found 386.1064.

4-(2-Chloro-6-fluorobenzoyl)-*N*-(2-methoxypyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (284)



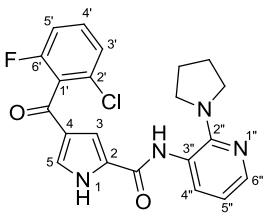
Compound **284** was synthesised according to general procedure X, using the following reagents: 4-(2-chloro-6-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**249**) (100 mg, 0.37 mmol), pyridine (31 µL, 30 mg, 0.37 mmol), cyanuric fluoride (13 µL, 20 mg, 0.15 mmol), acetonitrile (3.7 mL) and 3-amino-2-methoxypyridine (116 mg, 0.94 mmol). The crude product was purified by column chromatography (amine silica gel, petrol:EtOAc, 1:0 → 3:7) to yield the *title compound* as a white solid (87 mg, 62%); R_f = 0.30 (amine silica, petrol:EtOAc, 3:7); m.p. 226.5-228.5 °C; λ_{max} (EtOH)/nm 299.4; IR (neat) ν_{max}/cm^{-1} 3288, 1678, 1645, 1603, 1552, 1510, 1450, 1404, 1275; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.91 (3H, s, ArOCH_3), 7.03 (1H, dd, *J* = 7.7, 4.9 Hz, H-5”), 7.39 (1H, dd, *J* = 8.6, 8.6 Hz, H-5’), 7.49 – 7.42 (3H, m, H-3, H-5 and H-3’), 7.58 (1H, ddd, *J* = 8.6, 8.3 and 6.2 Hz, H-4’), 7.97 (1H, dd, *J* = 7.7, 1.8 Hz, H-4”), 8.00 (1H, dd, *J* = 4.9, 1.8 Hz, H-6”), 9.62 (1H, s, CON*H*Ar), 12.65 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 53.4 (ArO*C*H$_3$), 111.7 (C-3), 115.0 (d, *J* = 21.5 Hz, C-5’), 116.9 (C-5”), 121.2 (C-2 or C-4), 125.3 (C-2 or C-4), 125.8 (d, *J* = 3.2 Hz, C-3’), 128.1 (d, *J* = 23.1 Hz, C-1’), 128.2 (C-3”), 129.1 (C-5), 130.4 (d, *J* = 6.1 Hz, C-2’), 131.8 (d, *J* = 9.0 Hz, C-4’), 133.2 (C-4”), 142.6 (C-6”), 156.5 (*C*ONHAr or C-2”), 158.6 (d, *J* = 246.9 Hz, C-6’), 158.7 (*C*ONHAr or C-2”), 183.9 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -114.4 (ArF); LRMS (ES$^-$) *m/z* 372.2 [M(^{35}Cl)-H]$^-$, 374.2 [M(^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{18}H_{12}ClFN_3O_3$ [M(^{35}Cl)-H]$^-$ 372.0557, found 372.0556.

4-(2-Chloro-6-fluorobenzoyl)-*N*-(2-ethoxypyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (285)



Compound **285** was synthesised according to general procedure X, using the following reagents: 4-(2-chloro-6-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**249**) (100 mg, 0.37 mmol), pyridine (31 µL, 30 mg, 0.37 mmol), cyanuric fluoride (13 µL, 20 mg, 0.15 mmol), acetonitrile (3.7 mL) and 2-ethoxypyridin-3-amine (**280**) (129 mg, 0.94 mmol). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 7:3) to yield the *title compound* as a brown solid (60 mg, 41%); R_f = 0.31 (petrol:EtOAc, 7:3); m.p. 181.0-183.0 °C; λ_{max} (EtOH)/nm 299.4; IR (neat) ν_{max}/cm^{-1} 3428, 3232, 2987, 2937, 1653, 1605, 1558, 1532, 1486, 1438, 1344, 1285, 1230; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.33 (3H, t, *J* = 7.0 Hz, ArOCH$_2$C*H*$_3$), 4.38 (2H, q, *J* = 7.0 Hz, ArOC*H*$_2$CH$_3$), 7.00 (1H, dd, *J* = 7.6, 5.0 Hz, H-5”), 7.39 (1H, dd, *J* = 8.7, 8.7 Hz, H-5’), 7.48 – 7.41 (3H, m, H-3, H-5 and H-3’), 7.57 (ddd, *J* = 8.7, 8.3 and 6.1 Hz, 1H, H-4’), 8.01 – 7.90 (2H, m, H-4” and H-6”), 9.52 (1H, s, CON*H*Ar), 12.66 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 14.5 (ArOCH$_2$*C*H$_3$), 61.5 (ArO*C*H$_2$CH$_3$), 111.5 (C-3), 114.9 (d, *J* = 21.5 Hz, C-5’), 116.6 (C-5”), 121.1 (C-2 or C-4), 125.2 (C-2 or C-4), 125.8 (d, *J* = 3.2 Hz, C-3’), 128.1 (d, *J* = 23.1 Hz, C-1’), 128.3 (C-3”), 129.3 (C-5), 130.4 (d, *J* = 6.0 Hz, C-2’), 131.8 (d, *J* = 9.0 Hz, C-4’), 133.1 (C-4”), 142.6 (C-6”), 156.2 (*C*ONHAr or C-2”), 158.6 (d, *J* = 246.8 Hz, C-6’), 158.6 (*C*ONHAr or C-2”), 183.9 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -114.4 (ArF); LRMS (ES$^-$) *m/z* 386.2 [M(^{35}Cl)-H]$^-$, 388.3 [M(^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{19}H_{14}ClFN_3O_3$ [M(^{35}Cl)-H]$^-$ 386.0713, found 386.0709.

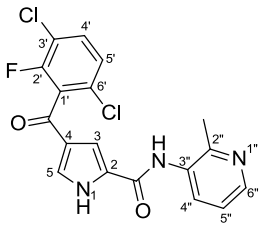
4-(2-Chloro-6-fluorobenzoyl)-*N*-(2-(pyrrolidin-1-yl)pyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (286)



Compound **286** was synthesised according to general procedure Y, using the following reagents: 4-(2-chloro-6-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**249**) (100 mg,

0.37 mmol), triethylamine (131 µL, 95 mg, 0.94 mmol), 2-chloro-1-methylpyridinium iodide (105 mg, 0.41 mmol), 2-(pyrrolidin-1-yl)pyridin-3-amine (**281**) (76 mg, 0.56 mmol) and DCM (3.7 mL). The crude yellow solid was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 3:7) to yield the *title compound* as a yellow solid (48 mg, 31%); R_f = 0.31 (petrol:EtOAc, 3:7); m.p. 239.5-241.5 °C; λ_{max} (EtOH)/nm 237.4; IR (neat) ν_{max}/cm^{-1} 3335, 3164, 3124, 2981, 2876, 1632, 1593, 1571, 1519, 1446, 1394, 1281, 1244; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.81 (4H, t, *J* = 6.4 Hz, NCH_2CH_2), 3.44 (4H, t, *J* = 6.4 Hz, NCH_2CH_2), 6.66 (2H, dd, *J* = 7.4, 4.8 Hz, H-5”), 7.41 – 7.30 (3H, m, H-5, H-5’ and H-4”), 7.42 (1H, s, H-3), 7.45 (2H, d, *J* = 8.2 Hz, H-3’), 7.57 (2H, ddd, *J* = 8.3, 8.2 and 6.0 Hz, H-4’), 8.01 (2H, dd, *J* = 4.8, 1.8 Hz, H-6”), 9.84 (1H, s, CONHAr), 12.56 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 25.1 (NCH_2CH_2), 48.4 (NCH_2CH_2), 110.7 (C-3), 112.3 (C-5”), 114.9 (d, *J* = 21.7 Hz, C-5’), 118.0 (C-2 or C-4), 125.3 (C-2 or C-4), 125.8 (d, *J* = 3.3 Hz, C-3’), 128.1 (d, *J* = 23.1 Hz, C-1’), 128.7 (C-3”), 129.1 (C-5), 130.4 (d, *J* = 6.2 Hz, C-2’), 131.8 (d, *J* = 9.0 Hz, C-4’), 137.9 (C-4”), 145.6 (C-6”), 155.3 (C-2”), 158.6 (d, *J* = 246.8 Hz, C-6’), 159.2 (CONHAr), 183.8 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -114.3 (ArF); LRMS (ES^-) *m/z* 411.3 $[M(^{35}Cl)-H]^-$, 413.4 $[M(^{37}Cl)-H]^-$; HRMS (NSI) calcd for $C_{21}H_{17}ClFN_4O_2$ $[M(^{35}Cl)-H]^-$ 411.1030, found 411.1024.

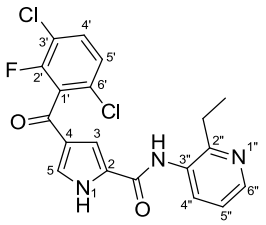
4-(3,6-Dichloro-2-fluorobenzoyl)-*N*-(2-methylpyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (287)



Compound **287** was synthesised according to general procedure U, using the following reagents: 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**) (100 mg, 0.33 mmol), 3-amino-2-methylpyridine (89 mg, 0.83 mmol), phosphorus trichloride (29 µL, 45 mg, 0.33 mmol) and acetonitrile (1.65 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 0:1) to yield the *title compound* as a white solid (82 mg, 63%); R_f = 0.31 (EtOAc, 100%); m.p. 146.0-148.0 °C; λ_{max} (EtOH)/nm 239.0, 286.2; IR (neat) ν_{max}/cm^{-1} 3127, 1636, 1594, 1558, 1518, 1447, 1290, 1223; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.44 (3H, s, $ArCH_3$), 7.27 (1H, dd, *J* = 7.9, 4.7 Hz, H-5”), 7.50 (1H, s, H-3), 7.51 (1H, d, *J* = 9.1 Hz, H-5’), 7.59 (1H, s, H-5), 7.72 (1H, dd, *J* = 7.9, 1.8 Hz, H-4”), 7.77 (1H, dd, *J* = 9.1, 8.3 Hz, H-4’), 8.34 (1H, dd, *J* = 4.7,

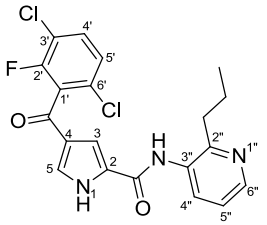
1.8 Hz, H-6”), 9.90 (1H, s, CON*H*Ar), 12.74 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 21.1 (Ar*C*H$_3$), 111.2 (C-3), 119.3 (d, *J* = 18.1 Hz, C-3’), 121.4 (C-5”), 124.8 (C-2 or C-4), 126.9 (d, *J* = 3.8 Hz, C-5’), 128.5 (C-2 or C-4), 129.1 (d, *J* = 19.4 Hz, C-1’), 129.2 (d, *J* = 8.6 Hz, C-6’), 130.1 (C-5), 131.8 (d, *J* = 8.3 Hz, C-4’), 133.9 (C-4”), 146.2 (C-6”), 153.9 (d, *J* = 248.6 Hz, C-2’), 153.9 (C-2”), 158.6 (*C*ONHAr), 182.6 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.7 (ArF); LRMS (ES$^-$) *m/z* 390.3 [M(^{35}Cl^{35}Cl)-H]$^-$, 392.2 [M(^{35}Cl^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{18}H_{11}Cl_2FN_3O_2$ [M(^{35}Cl^{35}Cl)-H]$^-$ 390.0218, found 390.0214.

4-(3,6-Dichloro-2-fluorobenzoyl)-*N*-(2-ethylpyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (288)



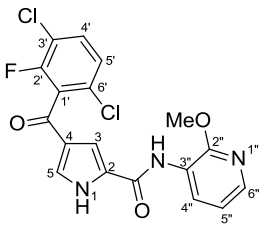
Compound **288** was synthesised according to general procedure U, using the following reagents: 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**) (100 mg, 0.33 mmol), 2-ethylpyridin-3-amine (**278**) (101 mg, 0.83 mmol), phosphorus trichloride (29 µL, 45 mg, 0.33 mmol) and acetonitrile (1.65 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 35:65) to yield the *title compound* as an off-white solid (55 mg, 41%); R_f = 0.29 (petrol:EtOAc, 35:65); m.p. 122.5-124.5 °C; λ_{max} (EtOH)/nm 238.2, 285.6; IR (neat) ν_{max}/cm^{-1} 3236, 2981, 2889, 1635, 1594, 1558, 1518, 1448, 1393, 1287, 1240, 1225; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.18 (3H, t, *J* = 7.4 Hz, ArCH$_2$C*H*$_3$), 2.77 (2H, q, *J* = 7.4 Hz, ArC*H*$_2$CH$_3$), 7.28 (1H, dd, *J* = 7.9, 5.1 Hz, H-5”), 7.55 – 7.48 (2H, m, H-3 and H-5’), 7.59 (1H, s, H-5), 7.69 (1H, d, *J* = 7.9 Hz, H-4”), 7.77 (1H, dd, *J* = 8.3, 8.3 Hz, H-4’), 8.41 (1H, d, *J* = 5.1 Hz, H-6”), 9.91 (1H, s, CON*H*Ar), 12.72 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 12.3 (ArCH$_2$*C*H$_3$), 26.2 (Ar*C*H$_2$CH$_3$), 111.1 (C-3), 119.3 (d, *J* = 18.0 Hz, C-3’), 121.4 (C-5”), 124.8 (C-2 or C-4), 126.9 (d, *J* = 3.8 Hz, C-5’), 128.5 (C-2 or C-4), 129.2 (d, *J* = 23.0 Hz, C-1’), 129.2 (d, *J* = 5.0 Hz, C-2’), 130.1 (C-5), 131.1 (C-3”), 131.8 (C-4’), 134.8 (C-4”), 146.6 (C-6”), 153.9 (d, *J* = 248.4 Hz, C-2’), 158.4 (*C*ONHAr or C-2”), 158.9 (*C*ONHAr or C-2”), 182.6 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.7 (ArF); LRMS (ES$^-$) *m/z* 404.2 [M(^{35}Cl^{35}Cl)-H]$^-$, 406.3 [M(^{35}Cl^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{19}H_{15}Cl_2FN_3O_2$ [M(^{35}Cl^{35}Cl)+H]$^+$ 406.0520, found 406.0525.

4-(3,6-Dichloro-2-fluorobenzoyl)-*N*-(2-propylpyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (289)



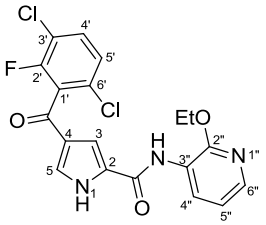
Compound **289** was synthesised according to general procedure U, using the following reagents: 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**) (100 mg, 0.33 mmol), 2-propylpyridin-3-amine (**279**) (113 mg, 0.83 mmol), phosphorus trichloride (29 µL, 45 mg, 0.33 mmol) and acetonitrile (1.65 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 45:55) to yield the *title compound* as a brown solid (45 mg, 32%); R_f = 0.30 (petrol:EtOAc, 45:55); m.p. 131.5-133.5 °C; λ_{max} (EtOH)/nm 238.8, 285.4; IR (neat) ν_{max}/cm^{-1} 3225, 3122, 2967, 2934, 2872, 1634, 1594, 1558, 1519, 1448, 1424, 1392, 1287; ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.87 (3H, t, *J* = 7.4 Hz, ArCH$_2$CH$_2$C*H*$_3$), 1.67 (2H, tq, *J* = 7.6, 7.5 Hz, ArCH$_2$C*H*$_2$CH$_3$), 2.74 (2H, t, *J* = 7.6 Hz, ArC*H*$_2$CH$_2$CH$_3$), 7.27 (1H, dd, *J* = 7.9, 4.7 Hz, H-5”), 7.49 (1H, s, H-3), 7.51 (1H, d, *J* = 9.0 Hz, H-5’), 7.58 (1H, s, H-5), 7.69 (1H, dd, *J* = 7.9, 1.7 Hz, H-4”), 7.77 (1H, dd, *J* = 8.3, 8.3 Hz, H-4’), 8.40 (1H, dd, *J* = 4.7, 1.7 Hz, H-6”), 9.90 (1H, s, CON*H*Ar), 12.72 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 13.9 (ArCH$_2$CH$_2$*C*H$_3$), 20.9 (ArCH$_2$*C*H$_2$CH$_3$), 35.1 (Ar*C*H$_2$CH$_2$CH$_3$), 111.1 (C-3), 119.3 (d, *J* = 18.1 Hz, C-3’), 121.3 (C-5”), 124.8 (C-2 or C-4), 126.9 (d, *J* = 3.8 Hz, C-5’), 128.5 (C-2 or C-4), 129.2 (d, *J* = 22.4 Hz, C-1’), 129.2 (d, *J* = 5.3 Hz, C-6’), 130.1 (C-5), 131.4 (C-3”), 131.8 (C-4’), 134.8 (C-4”), 146.6 (C-6”), 153.9 (d, *J* = 248.2 Hz, C-2’), 157.4 (*C*ONHAr or C-2”), 158.9 (*C*ONHAr or C-2”), 182.6 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.6 (ArF); LRMS (ES$^-$) *m/z* 418.2 [M(^{35}Cl^{35}Cl)-H]$^-$, 420.2 [M(^{35}Cl^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{20}H_{17}Cl_2FN_3O_2$ [M(^{35}Cl^{35}Cl)+H]$^+$ 420.0676, found 420.0673.

4-(3,6-Dichloro-2-fluorobenzoyl)-*N*-(2-methoxypyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (290)



Compound **290** was synthesised according to general procedure X, using the following reagents: 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**) (100 mg, 0.33 mmol), pyridine (27 µL, 26 mg, 0.33 mmol), cyanuric fluoride (11 µL, 18 mg, 0.13 mmol), acetonitrile (3.3 mL) and 3-amino-2-methoxypyridine (103 mg, 0.83 mmol). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 7:3) to yield the *title compound* as a pale yellow solid (36 mg, 27%); R_f = 0.32 (petrol:EtOAc, 3:7); m.p. 185.5-187.5 °C; λ_{max} (EtOH)/nm 298.6; IR (neat) ν_{max}/cm^{-1} 3213, 1642, 1594, 1556, 1520, 1465, 1448, 1405, 1223; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.92 (3H, s, ArOCH_3), 7.03 (1H, dd, *J* = 7.6, 5.0 Hz, H-5"), 7.55 – 7.47 (2H, m, H-3 and H-5'), 7.60 (1H, s, H-5), 7.78 (1H, dd, *J* = 8.4 Hz, H-4'), 7.98 (1H, dd, *J* = 7.6, 1.9 Hz, H-4"), 8.00 (1H, dd, *J* = 5.0, 1.9 Hz, H-6"), 9.61 (1H, s, CON*H*Ar), 12.72 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 53.4 (ArO*C*H$_3$), 111.6 (C-3), 116.9 (C-5"), 119.3 (d, *J* = 18.0 Hz, C-3'), 121.1 (C-2 or C-4), 124.8 (C-2 or C-4), 126.9 (d, *J* = 3.7 Hz, C-5'), 128.4 (C-3"), 129.2 (d, *J* = 22.9 Hz, C-1'), 129.2 (d, *J* = 5.2 Hz, C-6'), 129.9 (C-5), 131.8 (C-4'), 133.2 (C-4"), 142.6 (C-6"), 153.9 (d, *J* = 248.8 Hz, C-1'), 156.5 (*C*ONHAr or C-2"), 158.6 (*C*ONHAr or C-2"), 182.6 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.7 (ArF); LRMS (ES$^-$) *m/z* 406.4 [M(^{35}Cl^{35}Cl)-H]$^-$, 408.6 [M(^{35}Cl^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{18}H_{11}Cl_2FN_3O_3$ [M(^{35}Cl^{35}Cl)-H]$^-$ 406.0167, found 406.0162.

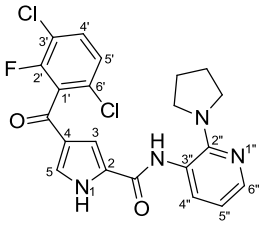
4-(3,6-Dichloro-2-fluorobenzoyl)-*N*-(2-ethoxypyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (291)



Compound **291** was synthesised according to general procedure X, using the following reagents: 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**) (100 mg, 0.33 mmol), pyridine (27 µL, 26 mg, 0.33 mmol), cyanuric fluoride (11 µL, 18 mg, 0.13 mmol), acetonitrile (3.3 mL) and 2-ethoxypyridin-3-amine (**280**) (114 mg, 0.83 mmol). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 3:1) to yield the *title compound* as a pale brown solid (87 mg, 62%); R_f = 0.28 (petrol:EtOAc, 3:1); m.p. 180.5-182.5 °C; λ_{max} (EtOH)/nm 299.4; IR (neat) ν_{max}/cm^{-1} 3661, 3423, 3239, 2981, 2889, 1656, 1531, 1444, 1379, 1275, 1229; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.34 (3H, t, *J* = 7.0 Hz, ArOCH$_2$CH_3), 4.39 (2H, q, *J* = 7.0 Hz, ArOCH_2CH$_3$), 7.00 (1H, dd, *J* = 7.5, 5.0 Hz, H-5"), 7.49 (1H, s, H-3), 7.51 (1H, dd,

J = 8.5, 1.3 Hz, H-5'), 7.59 (1H, s, H-5), 7.77 (1H, dd, *J* = 8.5, 8.4 Hz, H-4'), 8.04 – 7.89 (2H, m, H-4" and H-6"), 9.52 (1H, s, CON*H*Ar), 12.73 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 14.5 (ArOCH$_2$*C*H$_3$), 61.5 (ArO*C*H$_2$CH$_3$), 111.4 (C-3), 116.6 (C-5"), 119.3 (d, *J* = 18.0 Hz, C-3'), 121.1 (C-2 or C-4), 124.8 (C-2 or C-4), 126.9 (d, *J* = 3.8 Hz, C-5'), 128.5 (C-3"), 129.2 (d, *J* = 23.1 Hz, C-1'), 129.2 (d, *J* = 5.1 Hz, C-6'), 130.1 (C-5), 131.8 (C-4'), 133.1 (C-4"), 142.6 (C-6"), 153.9 (d, *J* = 248.6 Hz, C-2'), 156.2 (*C*ONHAr or C-2"), 158.6 (*C*ONHAr or C-2"), 182.6 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.6 (ArF); LRMS (ES$^-$) *m/z* 420.2 [M(^{35}Cl^{35}Cl)-H]$^-$, 422.2 [M(^{35}Cl^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{19}H_{13}Cl_2FN_3O_3$ [M(^{35}Cl^{35}Cl)-H]$^-$ 420.0323, found 420.0320.

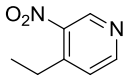
4-(3,6-Dichloro-2-fluorobenzoyl)-*N*-(2-(pyrrolidin-1-yl)pyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (292)



Compound **292** was synthesised according to general procedure Y, using the following reagents: 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**) (100 mg, 0.33 mmol), triethylamine (115 µL, 84 mg, 0.83 mmol), 2-chloro-1-methylpyridinium iodide (93 mg, 0.36 mmol), 2-(pyrrolidin-1-yl)pyridin-3-amine (**281**) (67 mg, 0.41 mmol) and DCM (3.3 mL). The crude yellow solid was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 4:6) to yield the *title compound* as a pale yellow solid (45 mg, 30%); R_f = 0.30 (petrol:EtOAc, 4:6); m.p. 236.5-238.5 °C; λ_{max} (EtOH)/nm 236.6; IR (neat) ν_{max}/cm^{-1} 3230, 2970, 2870, 1635, 1594, 1562, 1516, 1448, 1294, 1227; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.81 (4H, t, *J* = 6.5 Hz, NCH$_2$C*H*$_2$), 3.44 (4H, t, *J* = 6.5 Hz, NC*H*$_2$CH$_2$), 6.67 (1H, dd, *J* = 7.5, 4.8 Hz, H-5"), 7.38 (1H, dd, *J* = 7.5, 1.9 Hz, H-4"), 7.44 (1H, s, H-3), 7.51 (1H, d, *J* = 9.2 Hz, H-5'), 7.53 (1H, s, H-5), 7.77 (1H, dd, *J* = 9.2, 8.3 Hz, H-4'), 8.02 (1H, dd, *J* = 4.8, 1.9 Hz, H-6"), 9.84 (1H, s, CON*H*Ar), 12.64 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 25.1 (NCH$_2$*C*H$_2$), 48.4 (N*C*H$_2$CH$_2$), 110.6 (C-3), 112.3 (C-5"), 117.9 (C-2 or C-4), 119.2 (C-3'), 124.8 (C-2 or C-4), 126.8 (d, *J* = 3.4 Hz, C-5'), 128.9 (C-3"), 129.2 (d, *J* = 23.0 Hz, C-1'), 129.2 (d, *J* = 5.0 Hz, C-6'), 130.0 (C-5), 131.8 (C-4'), 137.9 (C-4"), 145.6 (C-6"), 153.9 (d, *J* = 248.3 Hz, C-2'), 155.3 (*C*ONHAr or C-2"), 159.1 (*C*ONHAr or C-2"), 182.5 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.6 (ArF); LRMS (ES$^+$) *m/z* 447.3 [M(^{35}Cl^{35}Cl)+H]$^+$, 449.3

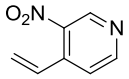
[M(^{35}Cl^{37}Cl)+H]$^+$; HRMS (NSI) calcd for $C_{21}H_{16}Cl_2FN_4O_2$ [M(^{35}Cl^{35}Cl)-H]$^-$ 445.0640, found 445.0636.

4-Ethyl-3-nitropyridine, (294)



Compound **294** was synthesised according to general procedure W, using the following reagents: 4-chloro-3-nitropyridine (**293**) (650 mg, 4.10 mmol), ethylboronic acid (333 mg, 4.51 mmol), potassium carbonate (1.70 g, 12.3 mmol), tetrakis(triphenylphosphine) palladium(0) (474 mg, 0.41 mmol) and dioxane (20 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 7:3) to yield the *title compound* as a clear yellow oil (312 mg, 50%); R_f = 0.30 (petrol:EtOAc, 7:3); λ_{max} (EtOH)/nm 241.8; IR (neat) ν_{max}/cm^{-1} 2979, 2940, 2880, 1602, 1522, 1349, 1215; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.22 (3H, t, *J* = 7.5 Hz, ArCH$_2$C*H*$_3$), 2.88 (2H, q, *J* = 7.5 Hz, ArC*H*$_2$CH$_3$), 7.61 (1H, d, *J* = 5.1 Hz, H-5), 8.76 (1H, d, *J* = 5.1 Hz, H-6), 9.08 (1H, s, H-2); ^{13}C NMR (126 MHz, DMSO-d_6) δ 13.7 (ArCH$_2$*C*H$_3$), 24.5 (Ar*C*H$_2$CH$_3$), 125.5 (C-5), 145.2 (C-2), 145.8 (C-3), 147.2 (C-4), 153.3 (C-6); LRMS (ES$^+$) *m/z* 153.2 [M+H]$^+$; HRMS (ESI) calcd for $C_7H_9N_2O_2$ [M+H]$^+$ 153.0659, found 153.0656; ^{1}H and ^{13}C NMR data were identical to literature data.[277]

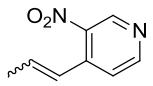
3-Nitro-4-vinylpyridine, (295)



Compound **295** was synthesised according to general procedure W, using the following reagents: 4-chloro-3-nitropyridine (**293**) (650 mg, 4.10 mmol), vinylboronic acid pinacol ester (765 µL, 695 mg, 4.51 mmol), potassium carbonate (1.70 g, 12.3 mmol), tetrakis(triphenylphosphine)palladium(0) (474 mg, 0.41 mmol) and dioxane (20 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 8:2) to yield the *title compound* as a clear yellow liquid (254 mg, 41%); R_f = 0.33 (petrol:EtOAc, 8:2); λ_{max} (EtOH)/nm 234.2; IR (neat) ν_{max}/cm^{-1} 1597, 1541, 1519, 1407, 1347, 1220; ^{1}H NMR (500 MHz, DMSO-d_6) δ 5.77 (1H, d, *J* = 11.1 Hz, ArCH=C*H*$_2$), 6.21 (1H, d, *J* = 17.3 Hz, ArCH=C*H*$_2$), 7.09 (1H, dd, *J* = 17.3, 11.1 Hz, ArC*H*=CH$_2$), 7.86 (1H, d, *J* = 5.2 Hz, H-5), 8.82 (1H, d, *J* = 5.2 Hz, H-6), 9.14 (1H, s, H-2); ^{13}C NMR (126 MHz, DMSO-d_6) δ 121.6 (C-5), 123.8 (ArCH=*C*H$_2$), 129.7 (Ar*C*H=CH$_2$), 139.4 (C-4), 143.7

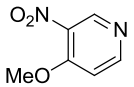
(C-3), 145.5 (C-2), 153.5 (C-6); LRMS (ES^+) *m/z* 151.1 $[M+H]^+$; HRMS (APCI) calcd for $C_7H_7N_2O_2$ $[M+H]^+$ 151.0502, found 151.0501.

3-Nitro-4-(prop-1-en-1-yl)pyridine, (296)



Compound **296** was synthesised according to general procedure W, using the following reagents: 4-chloro-3-nitropyridine (**293**) (650 mg, 4.10 mmol), allylboronic acid pinacol ester (851 µL, 758 mg, 4.51 mmol), potassium carbonate (1.70 g, 12.3 mmol), tetrakis(triphenylphosphine)palladium(0) (474 mg, 0.41 mmol) and dioxane (20 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 85:15) to yield the *title compound* as an orange solid (235 mg, 35%); R_f = 0.30 (petrol:EtOAc, 7:3); m.p. 42.0-44.0 °C; λ_{max} (EtOH)/nm 241.6; IR (neat) ν_{max}/cm^{-1} 2976, 2944, 2920, 2865, 1648, 1598, 1541, 1519, 1353, 1227; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.95 (3H, d, *J* = 5.2 Hz, ArCH=CHCH_3), 6.84 – 6.73 (2H, m, ArC*H*=C*H*CH_3), 7.81 (1H, d, *J* = 5.3 Hz, H-5), 8.72 (1H, d, *J* = 5.3 Hz, H-6), 9.06 (1H, s, H-2); ^{13}C NMR (126 MHz, DMSO-d_6) δ 18.9 (ArCH=C*H*CH_3), 121.3 (C-5), 123.0 (Ar*C*H=$CHCH_3$ or ArCH=*C*HCH_3), 137.1 (Ar*C*H=$CHCH_3$ or ArCH=*C*HCH_3), 139.2 (C-4), 143.4 (C-3), 145.5 (C-6), 152.9 (C-2); LRMS (ES^+) *m/z* 165.1 $[M+H]^+$; HRMS (APCI) calcd for $C_8H_9N_2O_2$ $[M+H]^+$ 165.0659, found 165.0658.

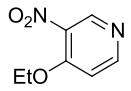
4-Methoxy-3-nitropyridine, (297)



To a suspension of 4-chloro-3-nitropyridine (**293**) (1.0 g, 6.31 mmol) in ethanol (15 mL) was added sodium methoxide (1.02 g 18.9 mmol). The resulting solution was stirred at RT overnight. Upon completion, the solvent removed *in vacuo*. The crude residue was dissolved in EtOAc (40 mL), washed with water and brine (20 mL, respectively), dried over $MgSO_4$ and concentrated *in vacuo*. The crude brawn oil was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 4:6) to yield the *title compound* as a yellow solid (815 mg, 84%); R_f = 0.28 (petrol:EtOAc, 4:6); m.p. 72.0-74.0 °C (lit. 73.0-75.0 °C)[278]; λ_{max} (EtOH)/nm 283.4; IR (neat) ν_{max}/cm^{-1} 3101, 3005, 2870, 1595, 1562, 1511, 1438, 1353, 1311, 1285, 1247, 1202; ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.02 (3H, s, ArOCH_3), 7.45 (1H, d, *J* = 5.9 Hz, H-5), 8.69 (1H, d, *J* = 5.9 Hz, H-6), 8.98 (1H, s, H-2); ^{13}C NMR (126 MHz, DMSO-d_6) δ 57.2 (ArO*C*H_3), 109.9 (C-5), 136.4 (C-3), 146.0 (C-2),

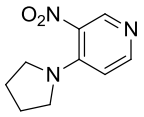
155.0 (C-6), 158.2 (C-4); LRMS (ES^+) *m/z* 155.1 $[M+H]^+$; HRMS (ESI) calcd for $C_6H_7N_2O_3$ $[M+H]^+$ 155.0451, found 155.0451; ^1H and ^{13}C NMR data were identical to literature data.[279]

4-Ethoxy-3-nitropyridine, (298)



To a suspension of 4-chloro-3-nitropyridine (**293**) (1.0 g, 6.31 mmol) in ethanol (15 mL) was added sodium ethoxide (1.29 g 18.9 mmol). The resulting solution was stirred at RT overnight. Upon completion, the solvent removed *in vacuo*. The crude residue was dissolved in EtOAc (40 mL), washed with water and brine (20 mL, respectively), dried over $MgSO_4$ and concentrated *in vacuo*. The crude brawn oil was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 4:6) to yield the *title compound* as a yellow solid (760 mg, 76%); R_f = 0.32 (petrol:EtOAc, 4:6); m.p. 46.5-48.5 °C; λ_{max} (EtOH)/nm 242.2, 286.8; IR (neat) ν_{max}/cm^{-1} 3000, 2951, 1596, 1558, 1522, 1491, 1468, 1353, 1318, 1287, 1240; ^1H NMR (500 MHz, DMSO-d_6) δ 1.37 (3H, t, *J* = 7.0 Hz, $ArOCH_2CH_3$), 4.33 (2H, q, *J* = 7.0 Hz, $ArOCH_2CH_3$), 7.43 (1H, d, *J* = 5.9 Hz, H-5), 8.66 (1H, d, *J* = 5.9 Hz, H-6), 8.96 (1H, s, H-2); ^{13}C NMR (126 MHz, DMSO-d_6) δ 14.0 ($ArOCH_2CH_3$), 65.8 ($ArOCH_2CH_3$), 110.3 (C-5), 136.6 (C-3), 146.0 (C-2), 154.8 (C-6), 157.3 (C-4); LRMS (ES^+) *m/z* 169.1 $[M+H]^+$; HRMS (NSI) calcd for $C_7H_9N_2O_3$ $[M+H]^+$ 169.0608, found 169.0608.

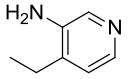
3-Nitro-4-(pyrrolidin-1-yl)pyridine, (299)



To a suspension of 4-chloro-3-nitropyridine (**293**) (1.0 g, 6.31 mmol) in acetonitrile (15 mL) was added potassium carbonate (959 mg, 6.94 mmol) and pyrrolidine (579 µL, 493 mg, 6.94 mmol). The resulting solution was stirred at RT overnight. Upon completion, the potassium carbonate was removed by filtration and the solvent removed *in vacuo*. The crude residue was dissolved in EtOAc (40 mL), washed with water and brine (20 mL, respectively), dried over $MgSO_4$ and concentrated *in vacuo*. The crude orange oil was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 1:3) to yield the *title compound* as a yellow solid (1.22 g, 91%); R_f = 0.30 (petrol:EtOAc, 1:3); m.p. 88.5-90.5 °C; λ_{max} (EtOH)/nm 244.4; IR (neat) ν_{max}/cm^{-1} 2953, 2925, 2879, 2858, 1599, 1531, 1507, 1496, 1386, 1341, 1243, 1204; ^1H NMR (500 MHz, DMSO-d_6) δ 1.98 – 1.85

(4H, m, NCH_2CH_2), 3.28 – 3.13 (4H, m, NCH_2CH_2), 6.94 (1H, d, *J* = 6.2 Hz, H-5), 8.23 (1H, d, *J* = 6.2 Hz, H-6), 8.66 (1H, s, H-2); ^{13}C NMR (126 MHz, DMSO-d_6) δ 25.0 (NCH_2CH_2), 50.0 (NCH_2CH_2), 110.8 (C-5), 134.1 (C-3), 145.1 (C-4), 146.9 (C-6), 150.8 (C-2); LRMS (ES^+) *m/z* 194.0 $[M+H]^+$; HRMS (NSI) calcd for $C_9H_{12}N_3O_2$ $[M+H]^+$ 194.0924, found 194.0925.

4-Ethylpyridin-3-amine, (300)

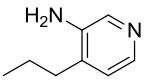


Compound **300** was synthesised following two different procedures:

1st procedure: Compound **300** was synthesised according to general procedure V, using the following reagents: 4-ethyl-3-nitropyridine (**294**) (250 mg, 1.64 mmol) and methanol (33 mL). The crude product was purified by column chromatography (amine silica gel, petrol:EtOAc, 1:0 → 3:7) to yield the *title compound* as a pale yellow solid (164 mg, 82%).

2nd procedure: Compound **300** was synthesised according to general procedure V, using the following reagents: 3-nitro-4-vinylpyridine (**295**) (200 mg, 1.33 mmol) and methanol (27 mL). The crude product was purified by column chromatography (amine silica gel, petrol:EtOAc, 1:0 → 3:7) to yield the *title compound* as a pale yellow solid (130 mg, 80%); R_f = 0.29 (amine silica, petrol:EtOAc, 3:7); m.p. 82.0-84.0 °C; λ_{max} (EtOH)/nm 242.0, 296.2; IR (neat) ν_{max}/cm^{-1} 3337, 3176, 2969, 2935, 2879, 1645, 1595, 1563, 1502, 1462, 1417, 1377, 1320, 1289; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.12 (3H, t, *J* = 7.5 Hz, $ArCH_2CH_3$), 2.43 (2H, q, *J* = 7.5 Hz, $ArCH_2CH_3$), 5.05 (2H, brs, $ArNH_2$), 6.89 (1H, d, *J* = 4.7 Hz, H-5), 7.69 (1H, d, *J* = 4.7 Hz, H-6), 7.89 (1H, s, H-2); ^{13}C NMR (126 MHz, DMSO-d_6) δ 12.1 ($ArCH_2CH_3$), 22.5 ($ArCH_2CH_3$), 122.4 (C-5), 133.8 (C-4), 136.2 (C-2), 137.6 (C-6), 142.6 (C-3); LRMS (ES^+) *m/z* 123.2 $[M+H]^+$; HRMS (ESI) calcd for $C_7H_{11}N_2$ $[M+H]^+$ 123.0917, found 123.0917.

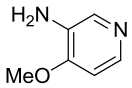
4-Propylpyridin-3-amine, (301)



Compound **301** was synthesised according to general procedure V, using the following reagents: 3-nitro-4-(prop-1-en-1-yl)pyridine (**296**) (180 mg, 1.10 mmol) and methanol (22 mL). The crude product was purified by column chromatography (amine silica gel,

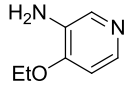
petrol:EtOAc, 1:0 → 1:1) to yield the *title compound* as a yellow oil (130 mg, 87%); R_f = 0.29 (amine silica, petrol:EtOAc, 1:1); λ_{max} (EtOH)/nm 242.2, 297.4; IR (neat) ν_{max}/cm^{-1} 3331, 3203, 2959, 2931, 2871, 1633, 1595, 1560, 1501, 1420, 1325, 1282; ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.91 (3H, t, *J* = 7.3 Hz, $ArCH_2CH_2CH_3$), 1.54 (2H, tq, *J* = 7.7, 7.3 Hz, $ArCH_2CH_2CH_3$), 2.39 (2H, t, *J* = 7.7 Hz, $ArCH_2CH_2CH_3$), 5.04 (2H, brs, $ArNH_2$), 6.86 (1H, d, *J* = 4.7 Hz, H-5), 7.67 (1H, d, *J* = 4.7 Hz, H-6), 7.89 (1H, s, H-2); ^{13}C NMR (126 MHz, DMSO-d_6) δ 13.8 ($ArCH_2CH_2CH_3$), 20.6 ($ArCH_2CH_2CH_3$), 31.5 ($ArCH_2CH_2CH_3$), 123.4 (C-5), 132.2 (C-4), 136.5 (C-2), 137.4 (C-6), 142.7 (C-3); LRMS (ES$^+$) *m/z* 137.2 [M+H]$^+$; HRMS (NSI) calcd for $C_8H_{13}N_2$ [M+H]$^+$ 137.1073, found 137.1068.

4-Methoxypyridin-3-amine, (302)



Compound **302** was synthesised according to general procedure V, using the following reagents: 4-methoxy-3-nitropyridine (**297**) (700 mg, 4.54 mmol) and methanol (91 mL). The crude product was purified by column chromatography (amine silica gel, petrol:EtOAc, 1:0 → 3:7) to yield the *title compound* as an orange solid (515 mg, 91%); R_f = 0.19 (EtOAc, 100%); m.p. 78.5-80.5 °C (lit. 83.0-85.0 °C)[280]; λ_{max} (EtOH)/nm 246.8, 285.2; IR (neat) ν_{max}/cm^{-1} 3404, 3338, 3171, 3096, 2934, 2843, 1645, 1575, 1511, 1427, 1304, 1286, 1234; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.81 (3H, s, $ArOCH_3$), 4.81 (2H, brs, $ArNH_2$), 6.80 (1H, d, *J* = 5.3 Hz, H-5), 7.73 (1H, d, *J* = 5.3 Hz, H-6), 7.85 (1H, s, H-2); ^{13}C NMR (126 MHz, DMSO-d_6) δ 55.1 ($ArOCH_3$), 105.9 (C-5), 134.2 (C-3), 135.2 (C-2), 139.0 (C-6), 151.6 (C-4); LRMS (ES$^+$) *m/z* 125.2 [M+H]$^+$; HRMS (ESI) calcd for $C_6H_9N_2O$ [M+H]$^+$ 125.0709, found 125.0710; ^{1}H NMR, ^{13}C NMR and IR data were identical to literature data.[281]

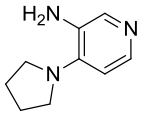
4-Ethoxypyridin-3-amine, (303)



Compound **303** was synthesised according to general procedure V, using the following reagents: 4-ethoxy-3-nitropyridine (**298**) (700 mg, 4.16 mmol) and methanol (83 mL). The crude product was purified by column chromatography (amine silica gel, petrol:EtOAc, 1:0 → 3:7) to yield the *title compound* as an orange solid (535 mg, 93%); R_f = 0.21 (EtOAc, 100%); m.p. 63.5-65.5 °C; λ_{max} (EtOH)/nm 247.0, 286.6; IR (neat) ν_{max}/cm^{-1}

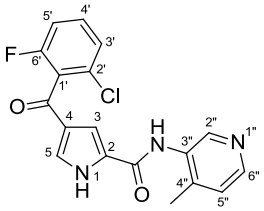
3410, 3321, 3298, 3182, 2982, 2940, 2896, 1617, 1575, 1513, 1487, 1433, 1397, 1303, 1282, 1234, 1225; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.35 (3H, t, *J* = 7.0 Hz, ArOCH$_2$C*H*$_3$), 4.07 (2H, q, *J* = 7.0 Hz, ArOC*H*$_2$CH$_3$), 4.75 (2H, brs, ArN*H*$_2$), 6.78 (1H, d, *J* = 5.4 Hz, H-5), 7.70 (1H, d, *J* = 5.4 Hz, H-6), 7.85 (1H, s, H-2); ^{13}C NMR (126 MHz, DMSO-d_6) δ 14.4 (ArOCH$_2$*C*H$_3$), 63.1 (ArO*C*H$_2$CH$_3$), 106.5 (C-5), 134.2 (C-3), 135.3 (C-2), 138.9 (C-6), 150.7 (C-4); LRMS (ES$^+$) *m/z* 139.2 [M+H]$^+$; HRMS (NSI) calcd for $C_7H_{11}N_2O$ [M+H]$^+$ 139.0866, found 139.0866.

4-(Pyrrolidin-1-yl)pyridin-3-amine, (304)



Compound **304** was synthesised according to general procedure V, using the following reagents: 3-nitro-4-(pyrrolidin-1-yl)pyridine (**299**) (1.1 g, 5.69 mmol) and methanol (114 mL). The crude product was purified by column chromatography (amine silica gel, petrol:EtOAc – 1:0 → 0:1) to yield the *title compound* as an orange oil (900 mg, 97%); R_f = 0.31 (EtOAc:MeOH – 9:1); λ_{max} (EtOH)/nm 271.0, 299.0; IR (neat) ν_{max}/cm^{-1} 3660, 3312, 3179, 2981, 2884, 1579, 1506, 1359, 1262; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.92 -1.74 (4H, m, NCH$_2$C*H*$_2$), 3.30 – 3.10 (4H, m, NC*H*$_2$CH$_2$), 4.48 (2H, brs, ArN*H*$_2$), 6.53 (1H, d, *J* = 5.3 Hz, H-5), 7.64 (1H, d, *J* = 5.3 Hz, H-6), 7.79 (1H, s, H-2); ^{13}C NMR (126 MHz, DMSO-d_6) δ 24.3 (NCH$_2$*C*H$_2$), 48.8 (N*C*H$_2$CH$_2$), 109.9 (C-5), 134.9 (C-3), 137.2 (C-2), 139.6 (C-6), 143.1 (C-4); LRMS (ES$^+$) *m/z* 164.1 [M+H]$^+$; HRMS (NSI) calcd for $C_9H_{14}N_3$ [M+H]$^+$ 164.1182, found 164.1182.

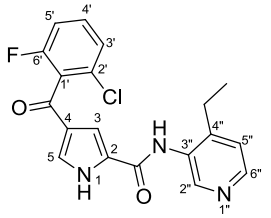
4-(2-Chloro-6-fluorobenzoyl)-*N*-(4-methylpyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (305)



Compound **305** was synthesised according to general procedure U, using the following reagents: 4-(2-chloro-6-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**249**) (100 mg, 0.37 mmol), 3-amino-4-methylpyridine (101 mg, 0.94 mmol), phosphorus trichloride (34 µL, 51 mg, 0.37 mmol) and acetonitrile (1.85 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 0:1) to yield the *title compound* as an off-white solid (87 mg, 65%); R_f = 0.30 (EtOAc, 100%); m.p. 276.5-278.5 °C;

λ_{max} (EtOH)/nm 238.6, 285.8; IR (neat) ν_{max}/cm^{-1} 3255, 1663, 1610, 1552, 1524, 1445, 1420, 1309, 1297, 1225, 1147; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.24 (3H, s, ArCH_3), 7.31 (1H, d, *J* = 4.9 Hz, H-5”), 7.39 (1H, ddd, *J* = 8.6, 8.3 and 0.9 Hz, H-5’), 7.49 – 7.42 (3H, m, H-3, H-5 and H-3’), 7.57 (1H, ddd, *J* = 8.6, 8.3 and 6.2 Hz, H-4’), 8.31 (1H, d, *J* = 4.9 Hz, H-6”), 8.45 (1H, s, H-2”), 9.95 (1H, s, CON*H*Ar), 12.67 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 17.4 (Ar*C*H$_3$), 111.3 (C-3), 115.0 (d, *J* = 21.5 Hz, C-5’), 125.3 (C-2 or C-4), 125.3 (C-5”), 125.8 (d, *J* = 3.1 Hz, C-3’), 128.0 (d, *J* = 21.9 Hz, C-1’), 128.1 (C-2 or C-4), 129.1 (C-5), 130.4 (d, *J* = 6.1 Hz, C-3’), 131.8 (d, *J* = 8.9 Hz, C-4’), 132.8 (C-4”), 142.9 (C-3”), 146.7 (C-6”), 147.4 (C-2”), 158.6 (d, *J* = 246.7 Hz, C-6’), 158.8 (*C*ONHAr), 183.9 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -114.3 (ArF); LRMS (ES$^-$) *m/z* 356.0 [M(^{35}Cl)-H]$^-$, 358.2 [M(^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{18}H_{12}ClFN_3O_2$ [M(^{35}Cl)-H]$^-$ 356.0603, found 356.0608.

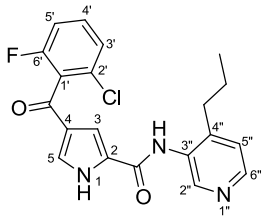
4-(2-Chloro-6-fluorobenzoyl)-*N*-(4-ethylpyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (306)



Compound **306** was synthesised according to general procedure U, using the following reagents: 4-(2-chloro-6-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**249**) (100 mg, 0.37 mmol), 4-ethylpyridin-3-amine (**300**) (114 mg, 0.94 mmol), phosphorus trichloride (34 µL, 51 mg, 0.37 mmol) and acetonitrile (1.85 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 15:85) to yield the *title compound* as an off-white solid (85 mg, 61%); R_f = 0.30 (petrol:EtOAc, 15:85); m.p. 228.0-230.0 °C; λ_{max} (EtOH)/nm 238.2, 285.8; IR (neat) ν_{max}/cm^{-1} 3278, 3122, 3092, 2970, 2881, 1659, 1643, 1607, 1573, 1522, 1454, 1418, 1390, 1316, 1256, 1235; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.14 (3H, t, *J* = 7.5 Hz, ArCH$_2$CH_3), 2.62 (2H, q, *J* = 7.5 Hz, ArCH_2CH$_3$), 7.34 (1H, d, *J* = 5.0 Hz, H-5”), 7.39 (1H, dd, *J* = 9.0, 9.0 Hz, H-5’), 7.42 (1H, s, H-5), 7.46 (2H, d, *J* = 7.7 Hz, H-3 and H-3’), 7.57 (1H, ddd, *J* = 9.0, 7.7 and 6.2 Hz, H-4’), 8.38 (1H, d, *J* = 5.0 Hz, H-6”), 8.42 (1H, s, H-2”), 9.93 (1H, s, CON*H*Ar), 12.66 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 13.0 (ArCH$_2$*C*H$_3$), 23.2 (Ar*C*H$_2$CH$_3$), 111.2 (C-3), 115.0 (d, *J* = 21.4 Hz, C-5’), 123.3 (C-5”), 125.3 (C-2 or C-4), 125.8 (d, *J* = 3.1 Hz, C-3’), 128.0 (d, *J* = 22.8 Hz, C-1’), 128.1 (C-2 or C-4), 129.2 (C-5), 130.4 (d, *J* = 6.0 Hz, C-2’), 131.8 (d, *J* = 9.1 Hz, C-4’), 132.1 (C-3”), 147.3 (C-6”), 148.2

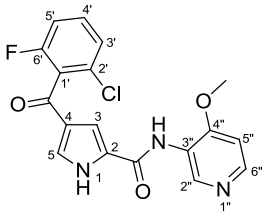
(C-2”), 148.6 (C-4”), 158.6 (d, *J* = 246.8 Hz, C-6’), 159.2 (*C*ONHAr), 183.9 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -114.4 (ArF); LRMS (ES$^-$) *m/z* 370.2 [M(^{35}Cl)-H]$^-$, 372.2 [M(^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{19}H_{16}ClFN_3O_2$ [M(^{35}Cl)+H]$^+$ 372.0910, found 372.0906.

4-(2-Chloro-6-fluorobenzoyl)-*N*-(4-propylpyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (307)



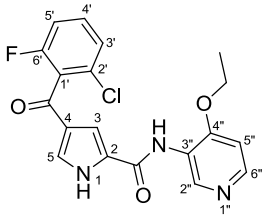
Compound **307** was synthesised according to general procedure U, using the following reagents: 4-(2-chloro-6-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**249**) (60 mg, 0.23 mmol), 4-propylpyridin-3-amine (**301**) (76 mg, 0.56 mmol), phosphorus trichloride (20 µL, 31 mg, 0.23 mmol) and acetonitrile (1.15 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 1:3) to yield the *title compound* as an off-white solid (42 mg, 48%); R_f = 0.28 (petrol:EtOAc, 1:3); m.p. 195.5-197.5 °C; λ_{max} (EtOH)/nm 238.4, 285.4; IR (neat) ν_{max}/cm^{-1} 3262, 2970, 2880, 1661, 1634, 1605, 1566, 1520, 1452, 1419, 1387, 1314, 1289, 1231; ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.86 (3H, t, *J* = 7.3 Hz, ArCH$_2$CH$_2$C*H*$_3$), 1.57 (2H, tq, *J* = 7.7, 7.3 Hz, ArCH$_2$C*H*$_2$CH$_3$), 2.58 (2H, t, *J* = 7.7 Hz, ArC*H*$_2$CH$_2$CH$_3$), 7.32 (1H, d, *J* = 5.0 Hz, H-5”), 7.39 (1H, dd, *J* = 9.0, 8.6 Hz, H-5’), 7.42 (1H, s, H-5), 7.49 – 7.44 (2H, m, H-3 and H-3’), 7.57 (1H, ddd, *J* = 9.0, 8.3 and 6.1 Hz, H-4’), 8.36 (1H, d, *J* = 5.0 Hz, H-6”), 8.43 (1H, s, H-2”), 9.93 (1H, s, CON*H*Ar), 12.66 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 13.8 (ArCH$_2$CH$_2$*C*H$_3$), 21.6 (ArCH$_2$*C*H$_2$CH$_3$), 32.1 (Ar*C*H$_2$CH$_2$CH$_3$), 111.2 (C-3), 115.0 (d, *J* = 21.6 Hz, C-5’), 124.1 (C-5”), 125.3 (C-2 or C-4), 125.8 (d, *J* = 3.2 Hz, C-3’), 128.0 (d, *J* = 23.0 Hz, C-1’), 128.2 (C-2 or C-4), 129.2 (C-5), 130.4 (d, *J* = 6.1 Hz, C-2’), 131.8 (d, *J* = 9.0 Hz, C-4’), 132.3 (C-3”), 147.1 (C-4” or C-6”), 147.1 (C-4” or C-6”), 148.4 (C-2”), 158.6 (d, *J* = 247.0 Hz, C-6’), 159.2 (*C*ONHAr), 183.9 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -114.3 (ArF); LRMS (ES$^-$) *m/z* 384.2 [M(^{35}Cl)-H]$^-$, 386.2 [M(^{37}Cl)-H]$^-$ HRMS (NSI) calcd for $C_{20}H_{18}ClFN_3O_2$ [M(^{35}Cl)+H]$^+$ 386.1066, found 386.1061.

4-(2-Chloro-6-fluorobenzoyl)-*N*-(4-methoxypyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (308)



Compound **308** was synthesised according to general procedure Y, using the following reagents: 4-(2-chloro-6-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**249**) (100 mg, 0.37 mmol), triethylamine (131 µL, 95 mg, 0.94 mmol), 2-chloro-1-methylpyridinium iodide (105 mg, 0.41 mmol), 4-methoxypyridin-3-amine (**302**) (58 mg, 0.47 mmol) and DCM (3.7 mL). The crude yellow solid was purified by column chromatography (amine silica gel, petrol:EtOAc, 1:0 → 15:85) to yield the *title compound* as an off-white solid (19 mg, 14%); R_f = 0.28 (amine silica, petrol:EtOAc, 15:85); m.p. No clear m.p., decomposition range 255-265 °C; λ_{max} (EtOH)/nm 253.0, 290.0; IR (neat) ν_{max}/cm^{-1} 3244, 2981, 2922, 2851, 1657, 1627, 1601, 1558, 1531, 1499, 1446, 1424, 1305, 1236; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.88 (3H, s, ArOCH_3), 7.15 (1H, d, *J* = 5.7 Hz, H-5”), 7.39 (1H, dd, *J* = 8.6, 8.6 Hz, H-5’), 7.44 (2H, d, *J* = 2.8 Hz, H-3 and H-5), 7.46 (1H, d, *J* = 8.3 Hz, H-3’), 7.58 (1H, ddd, *J* = 8.6, 8.3 and 6.2 Hz, H-4’), 8.33 (1H, d, *J* = 5.7 Hz, H-6”), 8.52 (1H, s, H-2”), 9.68 (1H, s, CON*H*Ar), 12.63 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 55.8 (ArO*C*H$_3$), 107.4 (C-5”), 111.6 (C-3), 115.0 (d, *J* = 21.5 Hz, C-5’), 122.9 (C-3”), 125.2 (C-2 or C-4), 125.8 (d, *J* = 3.1 Hz, C-3’), 128.1 (d, *J* = 23.2 Hz, C-1’), 128.1 (C-2 or C-4), 128.9 (C-5), 130.4 (d, *J* = 6.1 Hz, C-2’), 131.8 (d, *J* = 9.0 Hz, C-4’), 147.2 (C-2”), 148.3 (C-6”), 158.6 (d, *J* = 247.0 Hz, C-6’), 158.7 (*C*ONHAr or C-4”), 158.8 (*C*ONHAr or C-4”), 183.9 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -114.4 (ArF); LRMS (ES$^-$) *m/z* 372.2 [M(^{35}Cl)-H]$^-$, 374.2 [M(^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{18}H_{14}ClFN_3O_3$ [M(^{35}Cl)+H]$^+$ 374.0702, found 374.0705.

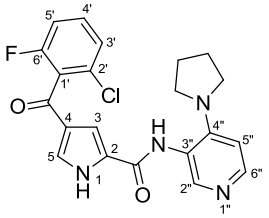
4-(2-Chloro-6-fluorobenzoyl)-*N*-(4-ethoxypyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (309)



To a solution of 4-(2-chloro-6-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**249**) (100 mg, 0.37 mmol) in DCM (3.7 mL) was added 4-ethoxypyridin-3-amine (**303**) (65 mg,

0.47 mmol) followed by 2-chloro-1-methylpyridinium iodide (105 mg, 0.41 mmol). The resulting solution was stirred at 42 °C for 72 h. Upon completion, the solvent removed *in vacuo*. The crude residue was dissolved in EtOAc (30 mL), washed with saturated aq. $NaHCO_3$ (20 mL) and extracted with EtOAc (2 × 20 mL). The pooled organic extracts were washed with brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude yellow solid was purified by column chromatography (amine silica gel, petrol:EtOAc, 1:0 → 1:9) to yield the *title compound* as a white solid (30 mg, 21%); R_f = 0.24 (amine silica, petrol:EtOAc, 1:9); m.p. 188.5-190.5 °C; λ_{max} (EtOH)/nm 250.6, 291.0; IR (neat) ν_{max}/cm^{-1} 3298, 2996, 2982, 2948, 2908, 1670, 1644, 1603, 1537, 1501, 1447, 1430, 1320, 1307, 1235, 1152; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.34 (3H, t, *J* = 7.0 Hz, $ArOCH_2CH_3$), 4.18 (2H, q, *J* = 7.0 Hz, $ArOCH_2CH_3$), 7.13 (1H, d, *J* = 5.6 Hz, H-5”), 7.39 (1H, dd, *J* = 9.0, 8.5 Hz, H-5’), 7.42 (1H, s, H-5), 7.44 (1H, s, H-3), 7.46 (1H, d, *J* = 8.2 Hz, H-3’), 7.57 (1H, ddd, *J* = 9.0, 8.2 and 6.1 Hz, H-4’), 8.30 (1H, d, *J* = 5.6 Hz, H-6”), 8.52 (1H, s, H-2”), 9.62 (1H, s, CONHAr), 12.64 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 14.2 ($ArOCH_2CH_3$), 64.0 ($ArOCH_2CH_3$), 108.0 (C-5”), 111.4 (C-3), 114.9 (d, *J* = 21.5 Hz, C-5’), 123.0 (C-2 or C-4), 125.2 (C-3”), 125.8 (d, *J* = 3.3 Hz, C-3’), 128.1 (d, *J* = 23.0 Hz, C-1’), 128.3 (C-2 or C-4), 129.1 (C-5), 130.4 (d, *J* = 6.1 Hz, C-2’), 131.8 (d, *J* = 9.0 Hz, C-4’), 147.3 (C-2”), 148.2 (C-6”), 158.0 (CONHAr or C-4”), 158.6 (d, *J* = 246.7 Hz, C-6’), 158.6 (CONHAr or C-4”), 183.9 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -114.4 (ArF); LRMS (ES^-) *m/z* 386.2 [M(^{35}Cl)-H]$^-$, 388.2 [M(^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{19}H_{14}ClFN_3O_3$ [M(^{35}Cl)-H]$^-$ 386.0713, found 386.0708.

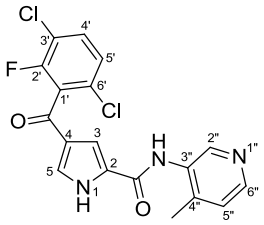
4-(2-Chloro-6-fluorobenzoyl)-*N*-(4-(pyrrolidin-1-yl)pyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (310)



To a solution of 4-(2-chloro-6-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**249**) (100 mg, 0.37 mmol) in DCM (3.7 mL) was added 4-(pyrrolidin-1-yl)pyridin-3-amine (**304**) (76 mg, 0.56 mmol) followed by 2-chloro-1-methylpyridinium iodide (105 mg, 0.41 mmol). The resulting solution was stirred at 42 °C for 72 h. Upon completion, the solvent removed *in vacuo*. The crude residue was dissolved in EtOAc (30 mL), washed with saturated aq. $NaHCO_3$ (20 mL) and extracted with EtOAc (2 × 20 mL). The pooled

organic extracts were washed with brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude yellow solid was purified by column chromatography (amine silica gel, EtOAc:MeOH, 1:0 → 95:5) to yield the *title compound* as an off-white solid (35 mg, 23%); R_f = 0.31 (amine silica, EtOAc:MeOH – 95:5); m.p. 182.0-184.0 °C; λ_{max} (EtOH)/nm 237.0; IR (neat) ν_{max}/cm^{-1} 3178, 3094, 2976, 2878, 1644, 1595, 1567, 1531, 1513, 1497, 1446, 1429, 1394, 1383, 1294, 1228; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.84 (4H, t, *J* = 6.6 Hz, NCH_2CH_2), 3.37 (4H, t, *J* = 6.6 Hz, NCH_2CH_2), 6.59 (1H, d, *J* = 5.8 Hz, H-5”), 7.35 (1H, s, H-5), 7.43 – 7.36 (2H, m, H-3 and H-5’), 7.46 (1H, d, *J* = 8.1 Hz, H-3’), 7.57 (1H, ddd, *J* = 8.3, 8.1 and 6.2 Hz, H-4’), 7.92 (1H, s, H-2”), 8.03 (1H, d, *J* = 5.8 Hz, H-6”), 9.82 (1H, s, CONHAr), 12.57 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 25.0 (NCH_2CH_2), 48.8 (NCH_2CH_2), 109.1 (C-5”), 110.7 (C-3), 114.9 (d, *J* = 21.5 Hz, C-5’), 117.8 (C-3”), 125.3 (C-2 or C-4), 125.8 (d, *J* = 3.4 Hz, C-3’), 128.0 (d, *J* = 23.2 Hz, C-1’), 128.7 (C-2 or C-4), 129.2 (C-5), 130.4 (d, *J* = 6.1 Hz, C-2’), 131.8 (d, *J* = 9.2 Hz, C-4’), 147.9 (C-6”), 149.9 (C-4”), 151.0 (C-2”), 158.6 (d, *J* = 247.0 Hz, C-6’), 159.8 (CONHAr), 183.8 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -114.3 (ArF); LRMS (ES$^+$) *m/z* 413.4 [M(^{35}Cl)+H]$^+$, 415.4 [M(^{37}Cl)+H]$^+$; HRMS (NSI) calcd for $C_{21}H_{19}ClFN_4O_2$ [M(^{35}Cl)+H]$^+$ 413.1175, found 413.1170.

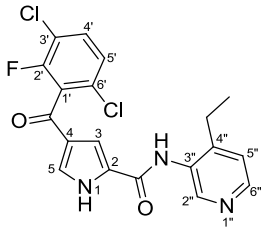
4-(3,6-Dichloro-2-fluorobenzoyl)-*N*-(4-methylpyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (311)



Compound **311** was synthesised according to general procedure U, using the following reagents: 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**) (100 mg, 0.33 mmol), 3-amino-4-methylpyridine (89 mg, 0.83 mmol), phosphorus trichloride (29 µL, 45 mg, 0.33 mmol) and acetonitrile (1.65 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 0:1) to yield the *title compound* as a pale yellow solid (81 mg, 62%); R_f = 0.33 (EtOAc, 100%); m.p. 224.0-226.0 °C; λ_{max} (EtOH)/nm 284.2; IR (neat) ν_{max}/cm^{-1} 1663, 1634, 1596, 1564, 1520, 1448, 1419, 1386, 1316, 1286; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.25 (3H, s, $ArCH_3$), 7.32 (1H, d, *J* = 4.9 Hz, H-5”), 7.49 (1H, s, H-3), 7.52 (1H, dd, *J* = 8.8, 1.3 Hz, H-5’), 7.60 (1H, s, H-5), 7.78 (1H, dd, *J* = 8.8, 8.4 Hz, H-4’), 8.32 (1H, d, *J* = 4.9 Hz, H-6”), 8.46 (1H, s, H-2”), 9.95 (1H, s, CONHAr), 12.74 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6)

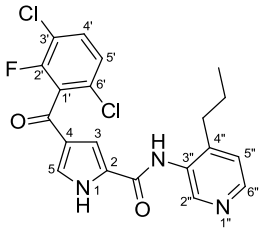
δ 17.4 (Ar*C*H$_3$), 111.2 (C-3), 119.3 (d, *J* = 18.0 Hz, C-3'), 124.8 (C-2 or C-4), 125.3 (C-5"), 126.9 (d, *J* = 3.8 Hz, C-5'), 128.4 (C-2 or C-4), 129.1 (d, *J* = 19.4 Hz, C-1'), 129.2 (d, *J* = 8.9 Hz, C-6'), 130.1 (C-5), 131.8 (C-4'), 132.8 (C-4"), 142.9 (C-3"), 146.7 (C-6"), 147.4 (C-2"), 153.9 (d, *J* = 248.5 Hz, C-2'), 158.8 (CON*H*Ar), 182.6 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.7 (ArF); LRMS (ES$^+$) *m/z* 392.1 [M(^{35}Cl^{35}Cl)+H]$^+$, 394.1 [M(^{35}Cl^{37}Cl)+H]$^+$; HRMS (NSI) calcd for $C_{18}H_{13}Cl_2FN_3O_2$ [M(^{35}Cl^{35}Cl)+H]$^+$ 392.0363, found 392.0369.

4-(3,6-Dichloro-2-fluorobenzoyl)-*N*-(4-ethylpyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (312)



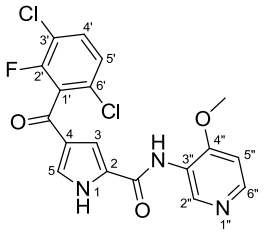
Compound **312** was synthesised according to general procedure U, using the following reagents: 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**) (100 mg, 0.33 mmol), 2-ethylpyridin-3-amine (**300**) (101 mg, 0.83 mmol), phosphorus trichloride (29 µL, 45 mg, 0.33 mmol) and acetonitrile (1.65 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 35:65) to yield the *title compound* as a white solid (65 mg, 48%); R_f = 0.30 (petrol:EtOAc, 2:8); m.p. 257.0-259.0 °C; λ_{max} (EtOH)/nm 238.4, 285.0; IR (neat) ν_{max}/cm^{-1} 3254, 3117, 2971, 2883, 1664, 1636, 1564, 1520, 1480, 1449, 1420, 1387, 1315, 1288; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.14 (3H, t, *J* = 7.5 Hz, ArCH$_2$C*H*$_3$), 2.62 (2H, q, *J* = 7.5 Hz, ArC*H*$_2$CH$_3$), 7.35 (1H, d, *J* = 5.0 Hz, H-5"), 7.49 (1H, s, H-3), 7.52 (1H, dd, *J* = 8.9, 1.3 Hz, H-5'), 7.59 (1H, s, H-5), 7.78 (1H, dd, *J* = 8.9, 8.4 Hz, H-4'), 8.38 (1H, d, *J* = 5.0 Hz, H-6"), 8.43 (1H, s, H-2"), 9.94 (1H, s, CON*H*Ar), 12.73 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 13.0 (ArCH$_2$*C*H$_3$), 23.2 (Ar*C*H$_2$CH$_3$), 111.1 (C-3), 119.3 (d, *J* = 18.1 Hz, C-3'), 123.3 (C-5"), 124.8 (C-2 or C-4), 126.9 (d, *J* = 3.7 Hz, C-5'), 128.4 (C-2 or C-4), 129.2 (d, *J* = 23.1 Hz, C-1'), 129.2 (d, *J* = 5.1 Hz, C-6'), 130.1 (C-5), 131.8 (C-4'), 132.0 (C-3"), 147.3 (C-6"), 148.2 (C-2"), 148.6 (C-4"), 153.9 (d, *J* = 248.5 Hz, C-2'), 159.1 (*C*ONHAr), 182.6 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.7 (ArF); LRMS (ES$^-$) *m/z* 404.2 [M(^{35}Cl^{35}Cl)-H]$^-$, 406.2 [M(^{35}Cl^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{19}H_{15}Cl_2FN_3O_2$ [M(^{35}Cl^{35}Cl)+H]$^+$ 406.0520, found 406.0515.

4-(3,6-Dichloro-2-fluorobenzoyl)-*N*-(4-propylpyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (313)



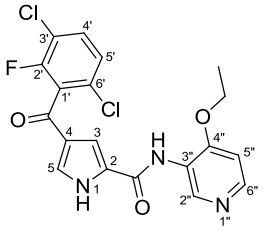
Compound **313** was synthesised according to general procedure U, using the following reagents: 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**) (60 mg, 0.20 mmol), 4-propylpyridin-3-amine (**301**) (68 mg, 0.50 mmol), phosphorus trichloride (17 µL, 27 mg, 0.20 mmol) and acetonitrile (1.0 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 3:7) to yield the *title compound* as an off-white solid (34 mg, 41%); R_f = 0.29 (petrol:EtOAc, 3:7); m.p. 250.0-252.0 °C; λ_{max} (EtOH)/nm 237.8, 280.6; IR (neat) ν_{max}/cm^{-1} 3254, 2964, 2929, 2876, 1663, 1634, 1597, 1565, 1518, 1448, 1419, 1387, 1313, 1226; ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.86 (3H, t, *J* = 7.3 Hz, ArCH$_2$CH$_2$C*H*$_3$), 1.57 (2H, tq, *J* = 7.7, 7.3 Hz, ArCH$_2$C*H*$_2$CH$_3$), 2.59 (2H, t, *J* = 7.7 Hz, ArC*H*$_2$CH$_2$CH$_3$), 7.32 (1H, d, *J* = 5.0 Hz, H-5”), 7.49 (1H, s, H-3), 7.52 (1H, dd, *J* = 8.8, 1.4 Hz, H-5’), 7.59 (1H, s, H-5), 7.78 (1H, dd, *J* = 8.8, 8.4 Hz, H-4’), 8.37 (1H, d, *J* = 5.0 Hz, H-6”), 8.44 (1H, s, H-2”), 9.93 (1H, s, CON*H*Ar), 12.73 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 13.8 (ArCH$_2$CH$_2$*C*H$_3$), 21.6 (ArCH$_2$*C*H$_2$CH$_3$), 32.1 (Ar*C*H$_2$CH$_2$CH$_3$), 111.1 (C-3), 119.3 (d, *J* = 17.9 Hz, C-3’), 124.1 (C-5”), 124.8 (C-2 or C-4), 126.9 (d, *J* = 3.8 Hz, C-5’), 128.4 (C-2 or C-4), 129.2 (d, *J* = 22.6 Hz, C-1’), 129.2 (d, *J* = 5.3 Hz, C-6’), 130.1 (C-5), 131.8 (C-4’), 132.2 (C-3”), 147.1 (C-4” or C-6”), 147.1 (C-4” or C-6”), 148.4 (C-2”), 153.9 (d, *J* = 248.5 Hz, C-2’), 159.1 (*C*ONHAr), 182.6 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.7 (ArF); LRMS (ES$^-$) *m/z* 418.3 [M(^{35}Cl^{35}Cl)-H]$^-$, 420.3 [M(^{35}Cl^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{20}H_{17}Cl_2FN_3O_2$ [M(^{35}Cl^{35}Cl)+H]$^+$ 420.0676, found 420.0671.

4-(3,6-Dichloro-2-fluorobenzoyl)-*N*-(4-methoxypyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (314)



Compound **314** was synthesised according to general procedure Y, using the following reagents: 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**) (150 mg, 0.50 mmol), triethylamine (173 µL, 126 mg, 1.24 mmol), 2-chloro-1-methylpyridinium iodide (140 mg, 0.55 mmol), 4-methoxypyridin-3-amine (**302**) (77 mg, 0.62 mmol) and DCM (5 mL). The crude yellow solid was purified by column chromatography (amine silica gel, petrol:EtOAc, 1:0 → 15:85) to yield the *title compound* as a pale yellow solid (10 mg, 5%); R_f = 0.27 (amine silica, petrol:EtOAc, 15:85); m.p. 174.0-176.0 °C; λ_{max} (EtOH)/nm 248.0, 289.0; IR (neat) ν_{max}/cm^{-1} 2981, 2889, 1649, 1595, 1558, 1530, 1490, 1448, 1422, 1392, 1301, 1239; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.89 (3H, s, ArOCH_3), 7.16 (1H, d, *J* = 5.6 Hz, H-5”), 7.48 (1H, s, H-3), 7.52 (1H, d, *J* = 8.7 Hz, H-5’), 7.59 (1H, s, H-5), 7.78 (1H, dd, *J* = 8.7, 8.3 Hz, H-4’), 8.33 (1H, d, *J* = 5.6 Hz, H-6”), 8.53 (1H, s, H-2”), 9.68 (1H, s, CON*H*Ar), 12.71 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 55.8 (ArO*C*H$_3$), 107.4 (C-5”), 111.5 (C-3), 119.3 (d, *J* = 18.0 Hz, C-3’), 122.9 (C-3”), 124.7 (C-2 or C-4), 126.9 (d, *J* = 3.7 Hz, C-5’), 128.4 (C-2 or C-4), 129.2 (d, *J* = 4.8 Hz, C-6’), 129.2 (d, *J* = 23.4 Hz, C-1’), 129.8 (C-5), 131.8 (C-4’), 147.2 (C-2”), 148.4 (C-6”), 153.8 (d, *J* = 248.3 Hz, C-2’), 158.7 (*C*ONHAr or C-4”), 158.8 (*C*ONHAr or C-4”), 182.6 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.7 (ArF); LRMS (ES$^-$) *m/z* 406.2 [M(^{35}Cl^{35}Cl)-H]$^-$, 408.2 [M(^{35}Cl^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{18}H_{13}Cl_2FN_3O_3$ [M(^{35}Cl^{35}Cl)+H]$^+$ 408.0313, found 408.0309.

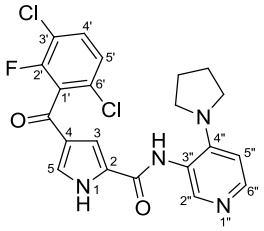
4-(3,6-Dichloro-2-fluorobenzoyl)-*N*-(4-ethoxypyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (315)



To a solution of 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**) (100 mg, 0.33 mmol) in DCM (3.3 mL) was added 4-ethoxypyridin-3-amine (**303**) (57 mg,

0.41 mmol) followed by 2-chloro-1-methylpyridinium iodide (93 mg, 0.36 mmol). The resulting solution was stirred at 42 °C for 72 h. Upon completion, the solvent removed *in vacuo*. The crude residue was dissolved in EtOAc (30 mL), washed with saturated aq. $NaHCO_3$ (20 mL) and extracted with EtOAc (2 × 20 mL). The pooled organic extracts were washed with brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude yellow solid was purified by column chromatography (amine silica gel, petrol:EtOAc, 1:0 → 85:15) to yield the *title compound* as an off-white solid (18 mg, 13%); R_f = 0.29 (amine silica, petrol:EtOAc, 1:9); m.p. 269.0-271.0 °C; λ_{max} (EtOH)/nm 247.4, 290.0; IR (neat) ν_{max}/cm^{-1} 3426, 2919, 1679, 1652, 1594, 1532, 1489, 1450, 1430, 1321, 1307, 1240; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.34 (3H, t, *J* = 6.9 Hz, $ArOCH_2CH_3$), 4.18 (2H, q, *J* = 6.9 Hz, $ArOCH_2CH_3$), 7.14 (1H, d, *J* = 5.7 Hz, H-5”), 7.47 (1H, s, H-3), 7.51 (1H, dd, *J* = 8.7, 1.3 Hz, H-5’), 7.58 (1H, s, H-5), 7.78 (1H, dd, *J* = 8.7, 8.4 Hz, H-4’), 8.30 (1H, d, *J* = 5.7 Hz, H-6”), 8.53 (1H, s, H-2”), 9.61 (1H, s, CONHAr), 12.71 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 14.2 ($ArOCH_2CH_3$), 64.0 ($ArOCH_2CH_3$), 108.0 (C-5”), 111.3 (C-3), 119.3 (d, *J* = 18.2 Hz. C-3’), 123.0 (C-3”), 124.7 (C-2 or C-4), 126.9 (d, *J* = 3.7 Hz, C-5’), 128.5 (C-2 or C-4), 129.2 (d, *J* = 23.1 Hz, C-1’), 129.2 (d, *J* = 5.3 Hz, C-6’), 130.0 (C-5), 131.8 (C-4’), 147.3 (C-2”), 148.2 (C-6”), 153.8 (d, *J* = 248.1 Hz, C-2’), 158.0 (CONHAr or C-4”), 158.6 (CONHAr or C-4”), 182.6 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.7 (ArF); LRMS (ES^-) *m/z* 420.2 $[M(^{35}Cl^{35}Cl)-H]^-$, 422.2 $[M(^{35}Cl^{37}Cl)-H]^-$; HRMS (NSI) calcd for $C_{19}H_{15}Cl_2FN_3O_3$ $[M(^{35}Cl^{35}Cl)+H]^+$ 422.0469, found 422.0465.

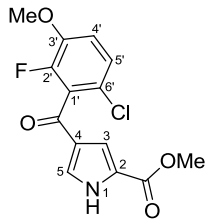
4-(3,6-Dichloro-2-fluorobenzoyl)-*N*-(4-(pyrrolidin-1-yl)pyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (316)



To a solution of 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**) (100 mg, 0.33 mmol) in DCM (3.3 mL) was added 4-(pyrrolidin-1-yl)pyridin-3-amine (**304**) (67 mg, 0.41 mmol) followed by 2-chloro-1-methylpyridinium iodide (93 mg, 0.36 mmol). The resulting solution was stirred at 42 °C overnight. Upon completion, the solvent removed *in vacuo*. The crude residue was dissolved in EtOAc (30 mL), washed with saturated aq. $NaHCO_3$ (20 mL) and extracted with EtOAc (2 × 20 mL). The pooled organic extracts were washed with brine (30 mL), dried over $MgSO_4$ and concentrated *in*

vacuo. The crude yellow solid was purified by column chromatography (amine silica gel, EtOAc:MeOH, 1:0 → 95:5) to yield the *title compound* as an off-white solid (50 mg, 34%); R_f = 0.32 (amine silica, EtOAc:MeOH, 95:5); m.p. 242.0-244.0 °C; λ_{max} (EtOH)/nm 229.4; IR (neat) ν_{max}/cm^{-1} 3227, 2981, 2964, 2883, 2837, 1659, 1634, 1603, 1505, 1485, 1428, 1386, 1320, 1245; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.84 (4H, t, *J* = 6.6 Hz, NCH_2CH_2), 3.37 (4H, t, *J* = 6.6 Hz, NCH_2CH_2), 6.59 (1H, d, *J* = 5.9 Hz, H-5”), 7.43 (1H, s, H-3), 7.51 (1H, dd, *J* = 8.7, 1.3 Hz, H-5’), 7.53 (1H, s, H-5), 7.77 (1H, dd, *J* = 8.7, 8.3 Hz, H-4’), 7.93 (1H, s, H-2”), 8.03 (1H, d, *J* = 5.9 Hz, H-6”), 9.83 (1H, s, CONHAr), 12.66 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 25.0 (NCH_2CH_2), 48.8 (NCH_2CH_2), 109.1 (C-5”), 110.6 (C-3), 117.7 (C-3”), 119.3 (d, *J* = 18.2 Hz, C-3’), 124.8 (C-2 or C-4), 126.8 (d, *J* = 3.7 Hz, C-5’), 128.9 (C-2 or C-4), 129.2 (d, *J* = 22.8 Hz, C-1’), 129.2 (d, *J* = 5.3 Hz, C-6’), 130.1 (C-5), 131.8 (C-4’), 147.9 (C-6”), 149.9 (C-4”), 151.0 (C-2”), 153.9 (d, *J* = 248.6 Hz, C-2’), 159.8 (CONHAr), 182.5 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.6 (ArF); LRMS (ES$^-$) *m/z* 445.2 [M(^{35}Cl^{35}Cl)-H]$^-$, 447.2 [M(^{35}Cl^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{21}H_{16}Cl_2FN_4O_2$ [M(^{35}Cl^{35}Cl)-H]$^-$ 445.0640, found 445.0633.

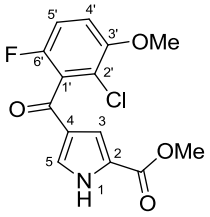
Methyl 4-(6-chloro-2-fluoro-3-methoxybenzoyl)-1*H*-pyrrole-2-carboxylate, (336)



Compound **336** was synthesised according to general procedure P and Q, using the following reagents: 6-chloro-2-fluoro-3-methoxybenzoic acid (**332**) (10.0 g, 48.9 mmol), thionyl chloride (5.32 mL, 8.73 g, 73.3 mmol), *N*,*N*-dimethylformamide (0.38 mL, 0.36 g, 4.89 mmol), THF (49 mL), methyl 1*H*-pyrrole-2-carboxylate (3.06 g, 24.4 mmol), aluminum trichloride (8.15 g, 61.1 mmol) and DCM (60 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 7:3) to yield the *title compound* as a white solid (6.15 g, 81%); R_f = 0.29 (petrol:EtOAc, 7:3); m.p. 124.0-126.0 °C; λ_{max} (EtOH)/nm 282.0; IR (neat) ν_{max}/cm^{-1} 3287, 3238, 2957, 2843, 1730, 1696, 1656, 1630, 1561, 1473, 1434, 1390, 1268; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.79 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 7.00 (1H, s, H-3), 7.31 (1H, dd, *J* = 8.9, 8.9 Hz, H-4’), 7.36 (1H, dd, *J* = 8.9, 1.3 Hz, H-5’), 7.54 (1H, s, H-5), 12.89 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 51.7 (OCH_3), 56.5 (OCH_3), 114.6 (C-3), 115.3 (d, *J* = 1.8 Hz, C-4’), 120.1 (d, *J* = 4.8 Hz, C-6’), 124.6 (C-2 or C4), 125.3 (C-2 or C4), 125.6

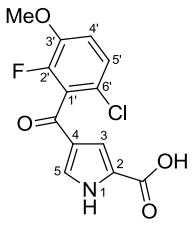
(d, *J* = 3.8 Hz, C-5')), 128.1 (d, *J* = 19.8 Hz, C-1'), 130.2 (C-5), 146.4 (d, *J* = 10.5 Hz, C-3'), 147.9 (d, *J* = 247.4 Hz, C-2'), 160.3 (*C*O_2Me), 183.4 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -136.2 (ArF); LRMS (ES$^-$) *m/z* 310.2 [M(^{35}Cl)-H]$^-$, 312.2 [M(^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{14}H_{12}ClFNO_4$ [M(^{35}Cl)+H]$^+$ 312.0433, found 312.0434.

Methyl 4-(2-chloro-6-fluoro-3-methoxybenzoyl)-1*H*-pyrrole-2-carboxylate, (337)



Compound **337** was synthesised according to general procedure P and Q, using the following reagents: 2-chloro-6-fluoro-3-methoxybenzoic acid (**333**) (2.0 g, 9.78 mmol), thionyl chloride (1.06 mL, 14.7 mmol), *N*,*N*-dimethylformamide (76 μL, 0.98 mmol), THF (9.8 mL), aluminum trichloride (1.64 g, 12.2 mmol), methyl 1*H*-pyrrole-2-carboxylate (0.61 g, 4.90 mmol) and DCM (12.2 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 7:3) to yield the *title compound* as a white solid (906 mg, 60%); R_f = 0.30 (petrol:EtOAc, 7:3); m.p. 133.5-135.5 °C; λ_{max} (EtOH)/nm 284.4; IR (neat) ν_{max}/cm^{-1} 3279, 1707, 1655, 1560; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.79 (3H, s, CO_2CH_3), 3.89 (3H, s, ArOCH_3), 6.99 (1H, d, *J* = 1.8 Hz, H-3), 7.31 – 7.24 (1H, m, H-5'), 7.39 – 7.31 (1H, m, H-4'), 7.52 (1H, d, *J* = 1.8 Hz, H-5), 12.87 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 51.7 (CO_2CH_3), 56.7 (ArOCH_3), 113.8 (d, *J* = 8.5 Hz, C-5'), 114.6 (C-2), 115.2 (C-4'), 118.0 (d, *J* = 6.5 Hz, C-2'), 124.5 (C-1), 125.3 (C-3), 128.7 (d, *J* = 24.4 Hz, C-1'), 130.1 (C-4), 151.5 (d, *J* = 2.3 Hz, C-3'), 152.0 (d, *J* = 238.5 Hz, C-6'), 160.3 (*C*O_2Me), 183.6 (ArCO); ^{19}F NMR (471 MHz, DMSO) δ -125.9 (ArF); LRMS (ES$^+$) *m/z* 312.2 [M(^{35}Cl)+H]$^+$, 314.3 [M(^{37}Cl)+H]$^+$; HRMS (NSI) calcd for $C_{14}H_{12}ClFNO_4$ [M(^{35}Cl)+H]$^+$ 312.0433, found 312.0437.

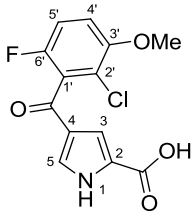
4-(6-Chloro-2-fluoro-3-methoxybenzoyl)-1*H*-pyrrole-2-carboxylic acid, (338)



Compound **338** was synthesised according to general procedure R, using the following reagents: methyl 4-(6-chloro-2-fluoro-3-methoxybenzoyl)-1*H*-pyrrole-2-carboxylate (**336**)

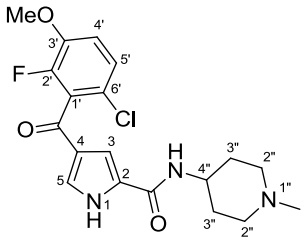
(4.50 g, 14.4 mmol), 2 M aq. lithium hydroxide (108 mL, 216 mmol) and THF (115 mL). The crude off-white solid (4.15 g, 97%) was used in the next step without further purification; R_f = 0.19 (petrol:EtOAc:AcOH, 50:49.7:0.3); m.p. 161.0-163.0 °C; λ_{max} (EtOH)/nm 230.4, 289.2; IR (neat) ν_{max}/cm^{-1} 3275, 3128, 1648, 1555, 1472, 1433, 1386, 1271, 1230; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.89 (3H, s, ArOCH_3), 6.95 (1H, s, H-3), 7.31 (1H, dd, *J* = 8.8, 8.8 Hz, H-4'), 7.36 (1H, d, *J* = 8.8 Hz, H-5'), 7.46 (1H, s, H-5), 12.69 (1H, s, NH-pyrrole), 12.85 (1H, s, CO_2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 56.5 (ArOCH_3), 114.2 (C-3), 115.2 (d, *J* = 1.8 Hz, C-4'), 120.1 (d, *J* = 4.8 Hz, C-6'), 125.2 (C-2 or C-4), 125.5 (d, *J* = 3.6 Hz, C-5'), 125.9 (C-2 or C-4), 128.3 (d, *J* = 19.7 Hz, C-1'), 129.8 (C-5), 146.4 (d, *J* = 10.5 Hz, C-3'), 147.9 (d, *J* = 247.5 Hz, C-2'), 161.3 (CO_2H), 183.4 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -136.2; LRMS (ES$^-$) *m/z* 296.1 [M(^{35}Cl)-H]$^-$, 298.1 [M(^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{13}H_{10}ClFNO_4$ [M(^{35}Cl)+H]$^+$ 298.0278, found 298.0277.

4-(2-Chloro-6-fluoro-3-methoxybenzoyl)-1*H*-pyrrole-2-carboxylic acid, (339)



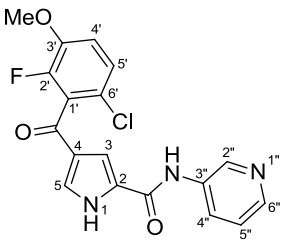
Compound **339** was synthesised according to general procedure R, using the following reagents: methyl 4-(2-chloro-6-fluoro-3-methoxybenzoyl)-1*H*-pyrrole-2-carboxylate (**337**) (333 mg, 1.07 mmol), 2 M aq. lithium hydroxide (8.0 mL, 16.0 mmol) and THF (8.6 mL). No purification required. The crude white solid (294 mg, 93 %) was used in the next step without further purification; R_f = 0.32 (petrol:EtOAc:AcOH, 50:49.7:0.3); m.p. 226.0-228.0 °C; λ_{max} (EtOH)/nm 266.8; IR (neat) ν_{max}/cm^{-1} 3250, 2360, 1676, 1648; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.88 (3H, s, ArOCH_3), 6.92 (1H, s, H-3), 7.27 (1H, dd, *J* = 9.0, 5.0 Hz, H-5'), 7.33 (1H, dd, *J* = 9.0, 9.0 Hz, H-4'), 7.40 (1H, s, H-5), 12.60 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 56.8 (ArOCH_3), 113.7 (C-5'), 113.8 (C-3), 115.0 (d, *J* = 22.7 Hz, C-4'), 118.1 (d, *J* = 6.6 Hz, C-1'), 125.1 (C-2 or C-4), 128.8 (C-2 or C-4), 129.0 (C-5), 129.4 (C-2'), 151.5 (d, *J* = 2.4 Hz, C-3'), 153.4 – 150.7 (m, C-6'), 161.9 (CO_2H), 183.7 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -141.4 (ArF); LRMS (ES$^+$) *m/z* 298.2 [M(^{35}Cl)+H]$^+$, 300.3 [M(^{37}Cl)+H]$^+$; HRMS (NSI) calcd for $C_{13}H_8ClFNO_4$ [M(^{35}Cl)-H]$^-$ 296.0131, found 296.0129.

4-(6-Chloro-2-fluoro-3-methoxybenzoyl)-*N*-(1-methylpiperidin-4-yl)-1*H*-pyrrole-2-carboxamide, (340)



Compound **340** was synthesised according to general procedure Z, using the following reagents: 4-(6-chloro-2-fluoro-3-methoxybenzoyl)-1*H*-pyrrole-2-carboxylic acid (**338**) (100 mg, 0.34 mmol), carbonyl diimidazole (109 mg, 0.67 mmol), THF (1.68 mL) and *N*-methyl-4-aminopiperidine (96 mg, 0.84 mmol). The crude product was purified by column chromatography (amine silica gel, petrol:EtOAc, 1:0 $\rightarrow$ 0:1) to yield the *title compound* as a white solid (85 mg, 64 %); R_f = 0.23 (amine silica, EtOAc, 100%); m.p. 206.0-208.0 °C; λ_{max} (EtOH)/nm 286.0; IR (neat) ν_{max}/cm^{-1} 3358, 3184, 1619, 1574, 1540; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.52 (2H, tt, *J* = 12.9, 6.5 Hz, H-3”), 1.72 (2H, d, *J* = 10.7 Hz, H-3”), 1.91 (2H, t, *J* = 11.6 Hz, H-2”), 2.14 (3H, s, NCH_3), 2.74 (2H, d, *J* = 11.0 Hz, H-2”), 3.75 – 3.54 (1H, m, H-4”), 3.89 (3H, s, ArOCH_3), 7.19 (1H, s, H-3), 7.40 – 7.26 (3H, m, H-5 and H-4’ and H-5’), 8.09 (1H, d, *J* = 8.2 Hz, CON*H*), 12.39 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 31.6 (C-3”), 45.9 (NCH_3), 46.0 (C-4”), 54.5 (C-2”), 56.4 (ArOCH_3), 110.0 (C-3), 115.0 (d, *J* = 1.8 Hz, C-4’), 120.2 (d, *J* = 4.9 Hz, C-6’), 124.9 (C-2 or C-4), 125.5 (d, *J* = 3.7 Hz, C-5’), 128.2 (C-5), 128.6 (d, *J* = 19.9 Hz, C-1’), 128.9 (C-2 or C-4), 146.4 (d, *J* = 10.6 Hz, C-3’), 147.9 (d, *J* = 246.8 Hz, C-2’), 159.1 (*C*ONH), 183.6 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -136.2 (ArF); LRMS (ES$^+$) *m/z* 394.4 [M(^{35}Cl)+H]$^+$, 396.4 [M(^{37}Cl)+H]$^+$; HRMS (NSI) calcd for $C_{19}H_{22}ClFN_3O_3$ [M(^{35}Cl)+H]$^+$ 394.1328, found 394.1322.

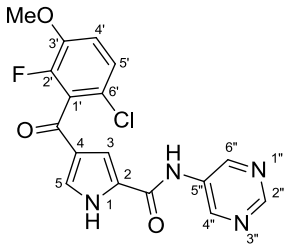
4-(6-Chloro-2-fluoro-3-methoxybenzoyl)-*N*-(pyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (341)



Compound **341** was synthesised according to general procedure U, using the following reagents: 4-(6-chloro-2-fluoro-3-methoxybenzoyl)-1*H*-pyrrole-2-carboxylic acid (**338**) (100 mg, 0.34 mmol), 3-aminopyridine (79 mg, 0.84 mmol), phosphorus trichloride

(30 μL, 0.34 mmol) and acetonitrile (1.70 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 0:1) to yield the *title compound* as a white solid (14 mg, 56%); R_f = 0.16 (EtOAc, 100%); m.p. 234.5-236.5 °C; λ_{max} (EtOH)/nm 293.2; IR (neat) ν_{max}/cm^{-1} 3294, 1661, 1639, 1603, 1555, 1537; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.90 (3H, s, ArOCH_3), 7.33 (1H, dd, *J* = 9.1, 9.1 Hz, H-4'), 7.43 – 7.36 (2H, m, H-5' and H-5"), 7.49 (2H, brs, H-3 and H-5), 8.13 (1H, d, *J* = 8.2 Hz, H-4"), 8.29 (1H, d, *J* = 4.8 Hz, H-6"), 8.89 (1H, s, H-2"), 10.24 (1H, s, CON*H*Ar), 12.71 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 56.5 (ArO*C*H$_3$), 111.6 (C-3), 115.2 (C-4'), 120.2 (d, *J* = 4.8 Hz, C-6'), 123.6 (C-5"), 125.2 (C-2 or C-4), 125.6 (d, *J* = 3.6 Hz, C-5'), 127.0 (C-4"), 128.2 (C-2 or C-4), 128.4 (d, *J* = 20.4 Hz, C-1'), 129.5 (C-5), 135.5 (C-3"), 141.6 (C-2"), 144.4 (C-6"), 146.5 (d, *J* = 10.5 Hz, C-3'), 148.0 (d, *J* = 247.1 Hz, C-2'), 158.7 (*C*ONHAr), 183.7 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -136.14 (ArF); LRMS (ES$^+$) *m/z* 374.3 [M(^{35}Cl)+H]$^+$, 376.3 [M(^{37}Cl)+H]$^+$; HRMS (NSI) calcd for $C_{18}H_{14}ClFN_3O_3$ [M(^{35}Cl)+H]$^+$ 374.0702, found 374.0701.

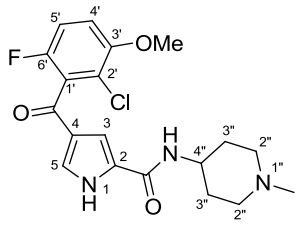
4-(6-Chloro-2-fluoro-3-methoxybenzoyl)-*N*-(pyrimidin-5-yl)-1*H*-pyrrole-2-carboxamide, (342)



Compound **342** was synthesised according to general procedure U, using the following reagents: 4-(6-chloro-2-fluoro-3-methoxybenzoyl)-1*H*-pyrrole-2-carboxylic acid (**338**) (100 mg, 0.34 mmol), 5-aminopyrimidine (80 mg, 0.84 mmol), phosphorus trichloride (30 μL, 0.34 mmol) and acetonitrile (1.70 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 2:8) to yield the *title compound* as a white solid (21 mg, 17%); R_f = 0.62 (EtOAc, 100%); m.p. 162.5-164.5 °C; λ_{max} (EtOH)/nm 290.4; IR (neat) ν_{max}/cm^{-1} 3731, 3122, 2925, 1642, 1578, 1531; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.90 (3H, s, ArOCH_3), 7.34 (1H, d, *J* = 8.7 Hz, H-4'), 7.38 (1H, s, H-5'), 7.51 (2H, brs, H-3 and H-5), 8.91 (1H, s, H-2"), 9.12 (2H, s, H-4", 6"), 10.43 (1H, s, CON*H*Ar), 12.80 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 56.5 (ArO*C*H$_3$), 112.2 (C-3), 115.2 (C-4'), 120.2 (d, *J* = 4.5 Hz, C-3'), 125.3 (C-2 or C-4), 125.6 (d, *J* = 3.7 Hz, C-5'), 127.7 (C-2 or C-4), 128.4 (d, *J* = 20.1 Hz, C-1'), 129.8 (C-5), 134.3 (C-5"), 146.5 (d, *J* = 10.0 Hz, C-6'), 147.9 (C-4" and C-6"), 146.9 – 149.1 (m, C-2'), 153.2 (C-2''),

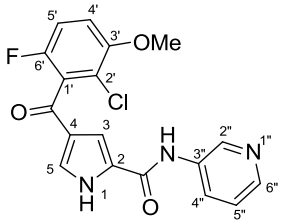
158.9 (*C*ONHAr), 183.7 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -136.1 (ArF); LRMS (ES$^+$) *m/z* 375.3 [M(^{35}Cl)+H]$^+$, 377.3 [M(^{37}Cl)+H]$^+$; HRMS (NSI) calcd for $C_{17}H_{13}ClFN_4O_3$ [M(^{35}Cl)+H]$^+$ 375.0655, found 375.0654.

4-(2-Chloro-6-fluoro-3-methoxybenzoyl)-*N*-(1-methylpiperidin-4-yl)-1*H*-pyrrole-2-carboxamide, (343)



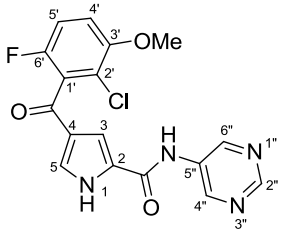
Compound **343** was synthesised according to general procedure Z, using the following reagents: 4-(2-chloro-6-fluoro-3-methoxybenzoyl)-1*H*-pyrrole-2-carboxylic acid (**339**) (60 mg, 0.20 mmol), carbonyl diimidazole (65 mg, 0.40 mmol), THF (1.0 mL) and *N*-methyl-4-aminopiperidine (58 mg, 0.50 mmol). The crude product was purified by column chromatography (silica gel, DCM:MeOH, 1:0 → 9:1) to yield the *title compound* as a white solid (40 mg, 51%); R_f = 0.10 (DCM:MeOH, 9:1); m.p. 232.0-234.0 °C; λ_{max} (EtOH)/nm 288.8; IR (neat) ν_{max}/cm^{-1} 3206, 2943, 2848, 2791, 1663, 1631, 1572, 1541; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.52 (2H, dd, *J* = 11.2, 4.3 Hz, H-3”), 1.73 (2H, d, *J* = 10.9 Hz, H-3”), 1.98 (2H, dd, *J* = 14.6, 9.0 Hz, H-2”), 2.18 (3H, s, NC*H*$_3$), 2.64 – 2.93 (2H, m, H-2”), 3.57 – 3.76 (1H, m, H-4”), 3.89 (3H, s, ArOCH$_3$), 7.18 (1H, s, H-3), 7.41 - 7.21 (3H, m, H-5 and H-4’ and H-5’), 8.10 (1H, d, *J* = 8.0 Hz, CON*H*), 12.37 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 31.4 (C-3”), 45.8 (N*C*H$_3$), 45.8 (C-4”), 54.3 (C-2”), 56.7 (ArO*C*H$_3$), 110.0 (C-3), 113.5 (d, *J* = 8.5 Hz, C-4’), 115.0 (d, *J* = 22.6 Hz, C-5’), 118.1 (d, *J* = 6.5 Hz, C-2’), 124.9 (C-2 or C-4), 128.0 (C-5), 128.9 (C-2 or C-4), 129.1 (d, *J* = 24.6 Hz, C-1’), 151.4 (d, *J* = 2.4 Hz, C-3’), 152.0 (d, *J* = 239.1 Hz, C-6’), 159.1 (*C*ONH), 183.8 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -125.82 (ArF); LRMS (ES$^+$) *m/z* 394.3 [M(^{35}Cl)+H]$^+$, 396.3 [M(^{37}Cl)+H]$^+$; HRMS (NSI) calcd for $C_{19}H_{22}ClFN_3O_3$ [M(^{35}Cl)+H]$^+$ 394.1328, found 394.1323.

4-(2-Chloro-6-fluoro-3-methoxybenzoyl)-*N*-(pyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (344)



Compound **344** was synthesised according to general procedure U, using the following reagents: 4-(2-chloro-6-fluoro-3-methoxybenzoyl)-1*H*-pyrrole-2-carboxylic acid (**339**) (100 mg, 0.34 mmol), 3-aminopyridine (79 mg, 0.84 mmol), phosphorus trichloride (30 μL, 0.34 mmol) and acetonitrile (1.70 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 0:1) to yield the *title compound* as a white solid (90 mg, 72%); R_f = 0.50 (EtOAc, 100%); m.p. 198.5-200.5 °C; λ_{max} (EtOH)/nm 293.0; IR (neat) ν_{max}/cm^{-1} 3238, 3123, 2967, 1638, 1601, 1536; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.90 (3H, s, ArOCH_3), 7.42 – 7.16 (3H, m, H-4', H-5' and H-5"), 7.48 (2H, s, H-3 and H-5), 8.13 (1H, d, *J* = 8.4 Hz, H-4"), 8.29 (1H, d, *J* = 5.0 Hz, H-6"), 8.89 (1H, s, H-2"), 10.23 (1H, s, CON*H*Ar), 12.69 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 56.7 (ArO*C*H$_3$), 111.6 (C-3), 113.6 (d, *J* = 8.5 Hz, C-4'), 115.1 (d, *J* = 23.1 Hz, C-5'), 118.1 (d, *J* = 6.3 Hz, C-2'), 123.6 (C-5"), 125.2 (C-2 or C-4), 127.0 (C-4"), 128.1 (C-2 or C-4), 129.0 (d, *J* = 24.5 Hz, C-1'), 129.4 (C-5), 135.5 (C-3"), 141.6 (C-2"), 144.4 (C-6"), 151.5 (d, *J* = 2.4 Hz, C-3'), 152.0 (d, *J* = 239.0 Hz, C-6'), 158.7 (*C*ONHAr), 183.8 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -125.7 (ArF); LRMS (ES$^+$) *m/z* 374.3 [M(^{35}Cl)+H]$^+$, 376.3 [M(^{37}Cl)+H]$^+$; HRMS (NSI) calcd for $C_{18}H_{14}ClFN_3O_3$ [M(^{35}Cl)+H]$^+$ 374.0702, found 374.0703.

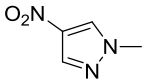
4-(2-Chloro-6-fluoro-3-methoxybenzoyl)-*N*-(pyrimidin-5-yl)-1*H*-pyrrole-2-carboxamide, (345)



Compound **345** was synthesised according to general procedure U, using the following reagents: 4-(2-chloro-6-fluoro-3-methoxybenzoyl)-1*H*-pyrrole-2-carboxylic acid (**339**) (100 mg, 0.34 mmol), 5-aminopyrimidine (80 mg, 0.84 mmol), phosphorus trichloride (30 μL, 0.34 mmol) and acetonitrile (1.70 mL). The crude product was purified by column

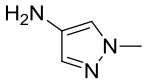
chromatography (silica gel, petrol:EtOAc, 1:0 → 2:8) to yield the *title compound* as a white solid (28 mg, 22%); Rf = 0.62 (EtOAc, 100%); m.p. 147.0-149.0 °C; λ_{max} (EtOH)/nm 291.4, IR (neat) ν_{max}/cm^{-1} 3733, 3239, 3123, 2981, 1637, 1583, 1529; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.90 (3H, s, ArOCH_3), 7.30 (1H, dd, *J* = 9.0, 4.8 Hz, H-4'), 7.37 (1H, t, *J* = 9.0 Hz, H-5'), 7.44 – 7.50 (1H, m, H-3), 7.51 – 7.57 (1H, m, H-5), 8.91 (1H, s, H-2"), 9.12 (2H, s, H-4", 6"), 10.42 (1H, s, CONHAr), 12.79 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 56.7 (ArOCH_3), 112.2 (C-3), 113.7 (d, *J* = 8.3 Hz, C-4'), 115.1 (d, *J* = 22.8 Hz, C-5'), 118.1 (d, *J* = 6.6 Hz, C-2'), 125.3 (C-2 or C-4), 127.6 (C-2 or C-4), 128.9 (d, *J* = 24.5 Hz, C-1'), 129.7 (C-5), 134.3 (C-5"), 147.9 (C-4", 6"), 151.5 (d, *J* = 2.3 Hz, C-3'), 152.0 (d, *J* = 238.9 Hz, C-6'), 153.2 (C-2"), 158.8 (CONHAr), 183.8 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -125.7 (s, ArF); LRMS (ES$^+$) *m/z* 375.3 [M(^{35}Cl)+H]$^+$, 377.3 [M(^{37}Cl)+H]$^+$; HRMS (NSI) calcd for $C_{17}H_{13}ClFN_4O_3$ [M(^{35}Cl)+H]$^+$ 375.0655, found 375.0655.

1-Methyl-4-nitro-1*H*-pyrazole, (347)



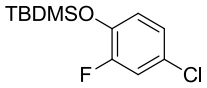
Dimethyl oxalate (10.4 g, 92.9 mmol) was added to 4-nitropyrazole (**346**) (7.0 g, 61.9 mmol) and potassium *tert*-butoxide (11.0 g, 92.9 mmol) in *N*,*N*-dimethylformamide (100 mL). The resulting solution was stirred at 140 °C for 4 h. Upon completion, the solvent was removed *in vacuo*. The dark orange residue was dissolved in saturated aq. $NaHCO_3$ (70 mL) and extracted with EtOAc (2 × 80 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 65:35) to yield the *title compound* as a pale yellow solid (6.73 g, 85%); R_f = 0.40 (petrol:EtOAc, 65:35); m.p. 91.5-93.5 °C; λ_{max} (EtOH)/nm 271.8; IR (neat) ν_{max}/cm^{-1} 3111, 1552, 1527, 1504, 1420, 1399, 1309; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.91 (3H, s, NCH_3), 8.24 (1H, s, H-3), 8.85 (1H, s, H-5); ^{13}C NMR (126 MHz, DMSO-d_6) δ 39.6 (NCH_3), 131.0 (C-5), 134.8 (C-4), 135.5 (C-3); LRMS (ES$^+$) *m/z* 128.1 [M+H]$^+$; HRMS (APCI) calcd for $C_4H_6N_3O_2$ [M+H]$^+$ 128.0455, found 128.0451; ^{1}H NMR and ^{13}C NMR data were identical to literature data.[165]

1-Methyl-1*H*-pyrazol-4-amine, (348)



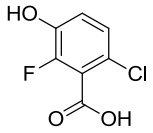
Compound **348** was synthesised according to general procedure V, using the following reagents: 1-methyl-4-nitro-1*H*-pyrazole (**347**) (6.7 g, 5.27 mmol) and methanol (200 mL). The crude orange oil (5.07 g, 99%) was used in the next step without further purification; R_f = 0.12 (amine silica, EtOAc, 100%); λ_{max} (EtOH)/nm 336.6; IR (neat) ν_{max}/cm^{-1} 3205, 3109, 2940, 1655, 1591, 1520, 1439, 1403, 1376, 1349; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.64 (3H, s, NCH_3), 3.79 (2H, brs, ArNH_2), 6.86 (1H, s, H-3), 6.97 (1H, s, H-5); ^{13}C NMR (126 MHz, DMSO-d_6) δ 38.4 (N*C*H$_3$), 117.2 (C-5), 128.9 (C-3), 131.0 (C-4); LRMS (ES$^+$) *m/z* 98.0 [M+H]$^+$; HRMS (APCI) calcd for $C_4H_8N_3$ [M+H]$^+$ 98.0713, found 98.0703.

***tert*-Butyl(4-chloro-2-fluorophenoxy)dimethylsilane, (350)**



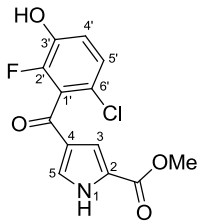
To 4-chloro-2-fluorophenol (**349**) (3.63 mL, 5.0 g, 34.1 mmol) and imidazole (2.79 g, 40.9 mmol) in *N*,*N*-dimethylformamide (50 mL), cooled in an ice bath, was added *tert*-butyldimethylsilyl chloride (6.17 g, 40.9 mmol) portionwise. Once dissolution of *tert*-butyldimethylsilyl chloride was complete, the ice bath was removed and the reaction stirred at RT for 18 h. Upon completion, saturated aq. $NaHCO_3$ (30 mL) was cautiously added and the mixture extracted with diethyl ether (3 × 50 mL). The combined organic extracts were washed with water (40 mL) and brine (40 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give the *title compound* as a clear liquid (8.21 g, 92%),which was used in the next step without further purification; R_f = 0.70 (petrol, 100%); λ_{max} (EtOH)/nm 275.0; IR (neat) ν_{max}/cm^{-1} 2955, 2931, 2888, 2859, 1605, 1580, 1494; ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.18 (6H, s, Si(CH_3)$_2$), 0.95 (9H, s, C(CH_3)$_3$), 7.04 (1H, dd, *J* = 9.0, 9.0 Hz, H-6), 7.10 – 7.18 (1H, m, H-5), 7.43 (1H, dd, *J* = 10.7, 2.5 Hz, H-3); ^{13}C NMR (126 MHz, DMSO-d_6) δ -4.9 (Si(*C*H$_3$)$_2$), 18.0 (*C*(CH$_3$)$_3$), 25.3 (C(*C*H$_3$)$_3$), 117.0 (d, *J* = 22.6 Hz, C-3), 123.2 (d, *J* = 2.3 Hz, C-6), 124.9 (d, *J* = 3.8 Hz, C-5), 125.1 (d, *J* = 9.1 Hz, C-4), 141.8 (d, *J* = 12.0 Hz, C-1), 153.3 (d, *J* = 246.3 Hz, C-2); ^{19}F NMR (471 MHz, DMSO-d_6) δ -129.2 (ArF); LRMS (ES$^+$) *m/z* 261.1 [M(^{35}Cl)+H]$^+$; HRMS (APCI) calcd for $C_{12}H_{19}ClFOSi$ [M(^{35}Cl)+H]$^+$ 260.0872, found 260.0868.

6-Chloro-2-fluoro-3-hydroxybenzoic acid, (351)



Compound **351** was synthesised according to general procedure A', using the following reagents: *tert*-butyl(4-chloro-2-fluorophenoxy)dimethylsilane (**350**) (6.0 g, 23.0 mmol), *n*-butyllithium (9.58 mL, 23.0 mmol) and THF (69 mL). The white solid (4.05 g, 92%) was used in the next step without further purification; R_f = 0.31 (petrol:EtOAc:AcOH, 50:49.7:0.3; $KMnO_4$); m.p. 134.0-136.0 °C; λ_{max} (EtOH)/nm 284.8; IR (neat) ν_{max}/cm^{-1} 3387, 1676, 1615, 1577, 1475, 1454, 1281; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.01 (1H, dd, *J* = 9.1, 8.8 Hz, H-4), 7.15 (1H, dd, *J* = 8.8, 1.5 Hz, H-5), 10.46 (1H, s, ArO*H*), 13.95 (1H, s, ArCO_2*H*); ^{13}C NMR (126 MHz, DMSO-d_6) δ 118.2 (d, *J* = 4.5 Hz, C-6), 119.0 (d, *J* = 3.7 Hz, C-4), 124.3 (d, *J* = 19.0 Hz, C-1), 125.3 (d, *J* = 3.6 Hz, C-5), 144.3 (d, *J* = 12.0 Hz, C-3), 147.4 (d, *J* = 246.5 Hz, C-2), 163.9 (Ar*CO2*H); ^{19}F NMR (471 MHz, DMSO-d_6) δ -136.4 (ArF); LRMS (ES$^-$) *m/z* 189.0 [M(^{35}Cl)-H]$^-$, 191.0 [M(^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_7H_3ClFO_3$ [M(^{35}Cl)-H]$^-$ 188.9760, found 188.9757.

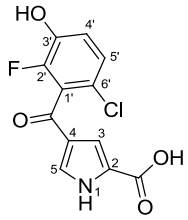
Methyl 4-(6-chloro-2-fluoro-3-hydroxybenzoyl)-1*H*-pyrrole-2-carboxylate, (353)



To a solution of 6-chloro-2-fluoro-3-hydroxybenzoic acid (**351**) (500 mg, 2.62 mmol) in THF (10 mL), cooled at 0 °C, was added thionyl chloride (286 μL, 468 mg, 3.94 mmol) and *N*,*N*-dimethylformamide (20 μL, 19 mg, 0.26 mmol). The resulting solution was stirred at 0 °C for 30 min and allowed to warm to RT. After 5 h, the solvent was removed *in vacuo* and crude residue dissolved in DCM (5 mL). The resulting solution was added to a suspension of aluminium trichloride (875 mg, 6.56 mmol) in DCM (10 mL), cooled at 0 °C, followed by methyl 1*H*-pyrrole-2-carboxylate (328 mg, 2.62 mmol). The resulting solution was stirred at 0 °C for 30 min and allowed to warm to RT. After 20 h, the reaction mixture was cooled to 0 °C and quenched by cautious addition of 1 M aq. HCl (10 mL). The resulting solution was stirred at RT for 2 h. The reaction was then diluted with water (20 mL) and extracted with DCM (3 × 40 mL). The pooled organic extracts were washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude yellow solid was purified by column chromatography (petrol:EtOAc, 1:0 → 55:45) to yield the *title*

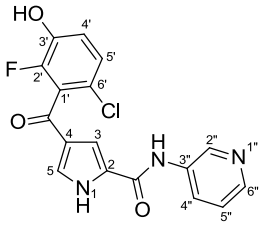
compound as a white solid (351 mg, 45%); R_f = 0.30 (petrol:EtOAc, 55:45); m.p. 160.5-162.5 °C; λ_{max} (EtOH)/nm 230.2, 282.8; IR (neat) ν_{max}/cm^{-1} 3212, 1700, 1646, 1557, 1487, 1445, 1285; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.79 (3H, s, CO_2CH_3), 6.99 (1H, s, H-3), 7.06 (1H, dd, *J* = 9.1, 8.8 Hz, H-4'), 7.19 (1H, dd, *J* = 8.8, 1.0 Hz, H-5'), 7.51 (1H, s, H-5), 10.46 (1H, s, ArO*H*), 12.86 (1H, s, pyrrole-NH); ^{13}C NMR (126 MHz, DMSO-d_6) δ 51.7 (CO_2CH_3), 114.7 (C-3), 118.3 (d, *J* = 4.5 Hz, C-6'), 119.0 (d, *J* = 3.5 Hz, C-4'), 124.5 (C-2 or C-4), 125.4 (C-2 or C-4), 125.5 (d, *J* = 3.2 Hz, C-5'), 128.4 (d, *J* = 20.0 Hz, C-1'), 130.1 (C-5), 144.4 (d, *J* = 12.3 Hz, C-3'), 147.5 (d, *J* = 244.2 Hz, C-2'), 160.3 (CO_2CH_3), 183.8 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -137.2 (ArF); LRMS (ES$^+$) *m/z* 298.2 [M(^{35}Cl)+H]$^+$, 300.2 [M(^{37}Cl)+H]$^+$; HRMS (NSI) calcd for $C_{13}H_{10}ClFNO_4$ [M(^{35}Cl)+H]$^+$ 298.0277, found 298.0279.

4-(6-Chloro-2-fluoro-3-hydroxybenzoyl)-1*H*-pyrrole-2-carboxylic acid, (354)



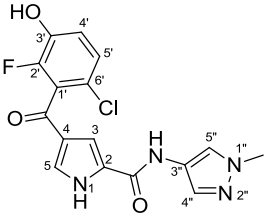
Compound **354** was synthesised according to general procedure R, using the following reagents: methyl 4-(6-chloro-2-fluoro-3-hydroxybenzoyl)-1*H*-pyrrole-2-carboxylate (**353**) (140 mg, 0.47 mmol), 2 M aq. lithium hydroxide (3.5 mL, 7.05 mmol) and THF (3.8 mL). The crude white solid (124 mg, 93%) was used in the next step without further purification; R_f = 0.15 (petrol:EtOAc:AcOH, 50:49.7:0.3); m.p. 218.5-220.5 °C; λ_{max} (EtOH)/nm 230.2, 282.8; IR (neat) ν_{max}/cm^{-1} 3346, 3113, 1689, 1627, 1578, 1558, 1280; ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.94 (1H, s, H-3), 7.06 (1H, dd, *J* = 9.1, 8.8 Hz, H-4'), 7.19 (1H, dd, *J* = 8.8, 1.2 Hz, H-5'), 7.43 (1H, s, H-5), 10.45 (1H, s, ArO*H*), 12.67 (1H, s, NH-pyrrole), 12.90 (1H, s, CO_2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 114.2 (C-3), 118.3 (d, *J* = 4.6 Hz, C-6'), 118.9 (d, *J* = 3.4 Hz, C-4'), 125.3 (C-2 or C-4), 125.5 (d, *J* = 3.3 Hz, C-5'), 125.8 (C-2 or C-4), 128.6 (d, *J* = 20.0 Hz, C-1'), 129.6 (C-3), 144.3 (d, *J* = 12.1 Hz, C-3'), 147.5 (d, *J* = 244.1 Hz, C-2'), 161.3 (CO_2H), 183.8 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -137.2 (ArF); LRMS (ES$^-$) *m/z* 282.1 [M(^{35}Cl)-H]$^-$, 284.0 [M(^{37}Cl)-H]$^-$; HRMS (ESI) calcd for $C_{12}H_8ClFNO_4$ [M(^{35}Cl)+H]$^+$ 284.0120, found 284.0123.

4-(6-Chloro-2-fluoro-3-hydroxybenzoyl)-*N*-(pyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (355)



Compound **355** was synthesised according to general procedure U, using the following reagents: 4-(6-chloro-2-fluoro-3-hydroxybenzoyl)-1*H*-pyrrole-2-carboxylic acid (**354**) (100 mg, 0.35 mmol), 3-aminopyridine (83 mg, 0.88 mmol), phosphorus trichloride (32 µL, 48 mg, 0.35 mmol) and acetonitrile (1.75 mL). The crude product was purified by column chromatography (silica gel, DCM:MeOH, 1:0 → 95:5) to yield the *title compound* as a white solid (70 mg, 55%); R_f = 0.32 (EtOAc, 100%); No clear m.p., decomposition range 300-310 °C; λ_{max} (EtOH)/nm 292.6; IR (neat) ν_{max}/cm^{-1} 3275, 1627, 1602, 1586, 1557, 1535, 1421, 1281; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.05 (1H, dd, *J* = 9.1, 8.7 Hz, H-4'), 7.16 (1H, d, *J* = 8.7 Hz, H-5'), 7.38 (1H, dd, *J* = 8.3, 4.9 Hz, H-5"), 7.46 (2H, s, H-3 and H-5), 8.11 – 8.17 (1H, m, H-4"), 8.29 (1H, dd, *J* = 4.9, 2.5 Hz, H-6"), 8.90 (1H, d, *J* = 2.5 Hz, H-2"), 10.32 (1H, s, CON*H*Ar), 12.17 (2H, s, NH-pyrrole and ArO*H*); ^{13}C NMR (126 MHz, DMSO-d_6) δ 111.9 (C-3), 117.1 (d, *J* = 7.6 Hz, C-6'), 119.1 (d, *J* = 3.8 Hz, C-4'), 123.6 (C-5"), 125.3 (d, *J* = 3.2 Hz, C-5'), 125.4 (C-2 or C-4), 127.0 (C-4"), 128.1 (C-2 or C-4), 128.6 (d, *J* = 20.0 Hz, C-1'), 129.2 (C-5), 135.6 (C-3"), 141.6 (C-2"), 144.4 (C-6"), 145.8 (d, *J* = 10.3 Hz, C-3'), 147.9 (d, *J* = 243.4 Hz, C-2'), 158.8 (*C*ONHAr), 184.4 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -137.3 (ArF); LRMS (ES$^-$) *m/z* 358.1 [M(^{35}Cl)-H]$^-$, 360.1 [M(^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{17}H_{12}ClFN_3O_3$ [M(^{35}Cl)+H]$^+$ 360.0546, found 360.0549.

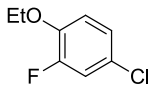
4-(6-Chloro-2-fluoro-3-hydroxybenzoyl)-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-2-carboxamide, (356)



Compound **356** was synthesised according to general procedure U, using the following reagents: 4-(6-chloro-2-fluoro-3-hydroxybenzoyl)-1*H*-pyrrole-2-carboxylic acid (**254**) (100 mg, 0.35 mmol), 1-methyl-1*H*-pyrazol-4-amine (**348**) (85 mg, 0.88 mmol), phosphorus trichloride (32 µL, 48 mg, 0.35 mmol) and acetonitrile (1.75 mL). The crude

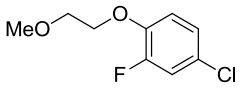
product was purified by column chromatography (silica gel, DCM:MeOH, 1:0 → 96:4) to yield the *title compound* as a off-white solid (58 mg, 45%); R_f = 0.29 (DCM:MeOH, 95:5); No clear m.p., decomposition range 280-290 °C; λ_{max} (EtOH)/nm 250.4; IR (neat) ν_{max}/cm^{-1} 3330, 3186, 3123, 1622, 1595, 1569, 1543, 1396, 1368; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.81 (3H, s, NCH_3), 7.07 (1H, dd, *J* = 9.0, 8.9 Hz, H-4'), 7.20 (1H, dd, *J* = 8.9, 1.4 Hz, H-5'), 7.27 (1H, s, H-3), 7.40 (1H, s, H-5), 7.49 (1H, s, H-5"), 7.94 (1H, s, H-3"), 10.24 (1H, s, CON*H*Ar), 10.48 (1H, s, ArO*H*), 12.54 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 38.7 (N*C*H$_3$), 110.4 (C-3), 118.3 (d, *J* = 4.6 Hz, C-6'), 118.9 (d, *J* = 3.6 Hz, C-4'), 121.2 (C-4"), 121.4 (C-3"), 125.2 (C-2 or C-4), 125.5 (d, *J* = 3.5 Hz, C-5'), 128.3 (C-2 or C-4), 128.5 (C-5), 128.8 (d, *J* = 20.2 Hz, C-1'), 129.9 (C-5"), 144.4 (d, *J* = 12.0 Hz, C-3'), 147.5 (d, *J* = 243.9 Hz, C-2'), 156.8 (*C*ONHAr), 184.1 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -137.1 (ArF); LRMS (ES$^-$) *m/z* 361.1 [M(^{35}Cl)-H]$^-$, 363.1 [M(^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{16}H_{13}ClFN_4O_3$ [M(^{35}Cl)+H]$^+$ 363.0655 found 363.0658.

4-Chloro-1-ethoxy-2-fluorobenzene, (357)



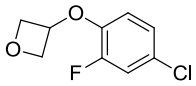
To 4-chloro-2-fluorophenol (**349**) (1.0 g, 6.82 mmol) in acetonitrile (20 mL) was added potassium carbonate (1.41 g) and iodoethane (658 μL, 1.28 g, 8.19 mmol) at RT. The resulting solution was stirred at 65 °C for 18 h. Upon completion, the potassium carbonate was filtered off and the reaction mixture concentrated *in vacuo*. The crude yellow oil was purified by column chromatography (silica gel, petrol, 100%) to yield the *title compound* as a clear liquid (980 mg, 82%); R_f = 0.28 (petrol, 100%; $KMnO_4$); λ_{max} (EtOH)/nm 277.4; IR (neat) ν_{max}/cm^{-1} 2984, 2934, 1583, 1495, 1476, 1264, 1205; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.33 (3H, t, *J* = 7.0 Hz, OCH$_2$CH_3), 4.10 (2H, q, *J* = 7.0 Hz, OCH_2CH$_3$), 7.15 – 7.22 (2H, m, H-5 and H-6), 7.38 – 7.44 (1H, m, H-3); ^{13}C NMR (126 MHz, DMSO-d_6) δ 14.5 (OCH$_2$*C*H$_3$), 64.6 (O*C*H$_2$CH$_3$), 115.9 (d, *J* = 2.5 Hz, C-6), 116.5 (d, *J* = 21.7 Hz, C-3), 123.6 (d, *J* = 9.2 Hz, C-4), 124.6 (d, *J* = 3.7 Hz, C-5), 145.6 (d, *J* = 10.4 Hz, C-1), 151.5 (d, *J* = 247.6 Hz, C-2); ^{19}F NMR (471 MHz, DMSO-d_6) δ -131.8 (ArF); HRMS (APCI) calcd for C_8H_9ClFO [M(^{35}Cl)+H]$^+$ 175.0320, found 175.0318.

4-Chloro-2-fluoro-1-(2-methoxyethoxy)benzene, (358)



Compound **358** was synthesised according to general procedure B', using the following reagents: 4-chloro-2-fluorophenol (**349**) (363 μL, 500 mg, 3.41 mmol), triphenylphosphine (1.34 g, 5.12 mmol), 2-methoxyethanol (350 μL, 337 mg, 4.44 mmol), diethyl azodicarboxylate (806 μL, 891 mg, 5.12 mmol) and THF (17 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 93:7) to yield the *title compound* as a clear liquid (670 mg, 96%); R_f = 0.29 (petrol:EtOAc, 93:7; $KMnO_4$); λ_{max} (EtOH)/nm 277.2; IR (neat) ν_{max}/cm^{-1} 2984, 2929, 2883, 2822, 1587, 1498, 1266, 1205; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.30 (3H, s, CH_2OCH_3), 3.63 – 3.69 (2H, m, OCH_2), 4.14 – 4.20 (2H, m, OCH_2), 7.17 – 7.23 (2H, m, H-5 and H-6), 7.39 – 7.46 (1H, m, H-3); ^{13}C NMR (126 MHz, DMSO-d_6) δ 58.2 (CH_2OCH_3), 68.4 (OCH_2), 70.1 (OCH_2), 116.1 (d, *J* = 2.4 Hz, C-6), 116.6 (d, *J* = 21.8 Hz, C-3), 123.9 (d, *J* = 9.1 Hz, C-4), 124.6 (d, *J* = 3.7 Hz, C-5), 145.6 (d, *J* = 10.3 Hz, C-1), 151.5 (d, *J* = 247.8 Hz, C-2); ^{19}F NMR (471 MHz, DMSO-d_6) δ -131.5 (ArF); HRMS (APCI) calcd for $C_9H_{11}ClFO_2$ $[M(^{35}Cl)+H]^+$ 205.0426 found 205.0423.

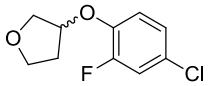
3-(4-Chloro-2-fluorophenoxy)oxetane, (359)



To 4-chloro-2-fluorophenol (**349**) (254 μL, 350 mg, 2.39 mmol) in THF (12 mL), cooled at 0 °C, was added triphenylphosphine (940 mg, 3.58) and 3-hydroxyoxetane (197 μL, 230 mg). Di*iso*propryl azodicarboxylate (705 μL, 724 mg, 3.58 mmol) was then added dropwise at 0 °C. The resulting orange solution was stirred at 0 °C for 30 min and allowed to warm to RT before being reflux for 24 h. Upon completion, the mixture was diluted with EtOAc (30 mL), washed with saturated aq. $NaHCO_3$ and brine (20 mL, respectively), dried over $MgSO_4$ and concentrated *in vacuo*. The crude orange solid was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 93:7) to yield the *title compound* as a white solid (470 mg, 97%); R_f = 0.29 (petrol:EtOAc, 93:7; $KMnO_4$); m.p. 89.0-91.0 °C; λ_{max} (EtOH)/nm 275.8; IR (neat) ν_{max}/cm^{-1} 3073, 3045, 2990, 2955, 2884, 1587, 1495, 1419, 1375, 1269; ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.57 (2H, ddd, *J* = 7.4, 4.9 and 1.0 Hz, ArOCHCH_2O), 4.91 (2H, dd, *J* = 7.1, 7.1 Hz, ArOCHCH_2O), 5.33 (1H, ddd, *J* = 10.8, 6.0 and 4.8 Hz, ArOC*H*CH_2O), 6.87 (1H, dd, *J* = 9.0, 9.0 Hz, H-6), 7.14 – 7.22 (1H, m, H-5), 7.49 (1H, dd, *J* = 11.2, 2.5 Hz, H-3); ^{13}C NMR (126 MHz, DMSO-d_6) δ 71.3

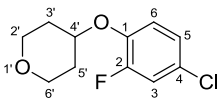
(ArO*C*HCH$_2$O), 76.5 (ArOCH*C*H$_2$O), 116.0 (d, *J* = 2.2 Hz, C-6), 117.0 (d, *J* = 21.6 Hz, C-3), 124.8 (d, *J* = 4.1 Hz, C-5), 124.8 (d, *J* = 8.7 Hz, C-4), 143.4 (d, *J* = 10.6 Hz, C-1), 151.5 (d, *J* = 248.2 Hz, C-2); ^{19}F NMR (471 MHz, DMSO-d_6) δ -131.4 (ArF); HRMS (APCI) calcd for $C_9H_9ClFO_2$ $[M(^{35}Cl)+H]^+$ 203.0270, found 203.0269.

3-(4-Chloro-2-fluorophenoxy)tetrahydrofuran, (360)



Compound **360** was synthesised according to general procedure B', using the following reagents: 4-chloro-2-fluorophenol (**349**) (508 μL, 700 mg, 4.78 mmol), triphenylphosphine (1.88 g, 7.16 mmol), 3-hydroxytetrahydrofuran (502 μL, 547 mg, 6.21 mmol), diethyl azodicarboxylate (1.13 mL, 1.25 g, 7.16 mmol) and THF (24 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 92:8) to yield the *title compound* as a clear liquid (989 mg, 96%); R_f = 0.28 (petrol:EtOAc, 92:8; $KMnO_4$); λ_{max} (EtOH)/nm 277.4; IR (neat) ν_{max}/cm^{-1} 2976, 2951, 2866, 1584, 1494, 1265, 1204; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.97 (1H, dt, *J* = 12.7, 5.7 Hz, ArOCHC*H*$_2$CH$_2$), 2.21 (1H, dtd, *J* = 12.7, 8.4 and 6.3 Hz, ArOCHC*H*$_2$CH$_2$), 3.75 (1H, td, *J* = 8.4, 4.5 Hz, OC*H*$_2$), 3.79 – 3.89 (3H, m, OC*H*$_2$), 5.08 (1H, dddd, *J* = 6.2, 4.0, 2.0 and 2.0 Hz, ArOC*H*(CH$_2$)$_2$), 7.15 – 7.23 (2H, m, H-5 and H-6), 7.40 – 7.47 (1H, m, H-3); ^{13}C NMR (126 MHz, DMSO-d_6) δ 32.3 (ArOCH*C*H$_2$CH$_2$), 66.4 (O*C*H$_2$), 72.1 (O*C*H$_2$), 78.9 (ArO*C*H), 116.8 (d, *J* = 21.8 Hz, C-3), 117.2 (d, *J* = 2.3 Hz, C-6), 124.2 (d, *J* = 9.3 Hz, C-4), 124.7 (d, *J* = 3.7 Hz, C-5), 144.2 (d, *J* = 10.3 Hz, C-1), 152.0 (d, *J* = 247.8 Hz, C-2); ^{19}F NMR (471 MHz, DMSO-d_6) δ -131.0 (ArF); HRMS (APCI) calcd for $C_{10}H_{11}ClFO_2$ $[M(^{35}Cl)+H]^+$ 217.0426, found 217.0424.

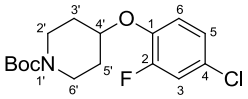
4-(4-Chloro-2-fluorophenoxy)tetrahydro-2*H*-pyran, (361)



Compound **361** was synthesised according to general procedure B', using the following reagents: 4-chloro-2-fluorophenol (**349**) (508 μL, 700 mg, 4.78 mmol), triphenylphosphine (1.88 g, 7.16 mmol), 4-hydroxytetrahydropyran (592 μL, 634 mg, 6.21 mmol), diethyl azodicarboxylate (1.13 mL, 1.25 g, 7.16 mmol) and THF (24 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 93:7) to yield the *title compound* as a clear liquid (1.05 mg, 95%); R_f = 0.29 (petrol:EtOAc, 93:7; $KMnO_4$); λ_{max} (EtOH)/nm 277.4; IR (neat) ν_{max}/cm^{-1} 2956, 2934, 2852, 1583, 1493, 1266, 1203;

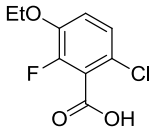
^{1}H NMR (500 MHz, DMSO-d_6) δ 1.59 (2H, dddd, *J* = 13.1, 9.1, 9.1 and 4.1 Hz, H-3', 5'$_{axial}$), 1.89 – 2.00 (2H, m, H-3', 5'$_{equ}$), 3.46 (2H, ddd, *J* = 13.1, 9.1 and 2.7 Hz, H-2', 6'$_{axial}$), 3.84 (2H, ddd, *J* = 13.1, 4.1 and 4.1 Hz, H-2', 6'$_{equ}$), 4.58 (1H, tt, *J* = 8.5, 4.1 Hz, H-4'), 7.19 (1H, ddd, *J* = 8.9, 2.4 and 1.5 Hz, H-5), 7.29 (1H, dd, *J* = 9.0, 8.9 Hz, H-6), 7.43 (1H, dd, *J* = 11.1, 2.4 Hz, H-3); ^{13}C NMR (126 MHz, DMSO-d_6) δ 31.6 (C-3', 5'), 64.4 (C-2', 6'), 73.6 (C-4'), 116.9 (d, *J* = 22.2 Hz, C-3), 118.6 (d, *J* = 2.3 Hz, C-6), 124.4 (d, *J* = 9.3 Hz, C-4), 124.7 (d, *J* = 3.7 Hz, C-5), 143.8 (d, *J* = 10.5 Hz, C-1), 152.5 (d, *J* = 247.7 Hz, C-2); ^{19}F NMR (471 MHz, DMSO-d_6) δ -130.5 (ArF); HRMS (APCI) calcd for $C_{11}H_{13}ClFO_2$ $[M(^{35}Cl)+H]^+$ 231.0583, found 231.0582.

tert-Butyl 4-(4-chloro-2-fluorophenoxy)piperidine-1-carboxylate, (362)



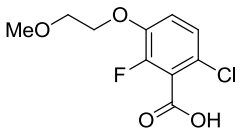
Compound **362** was synthesised according to general procedure B', using the following reagents: 4-chloro-2-fluorophenol (**349**) (508 μL, 700 mg, 4.78 mmol), triphenylphosphine (1.88 g, 7.16 mmol), 1-Boc-4-hydroxypiperidine (1.25 g, 6.21 mmol), diethyl azodicarboxylate (1.13 mL, 1.25 g, 7.16 mmol) and THF (24 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 95:5) to yield the *title compound* as an off-white solid (1.31 g, 83%); R_f = 0.31 (petrol:EtOAc, 95:5; $KMnO_4$); m.p. 78.0-100.0 °C; λ_{max} (EtOH)/nm 277.2; IR (neat) ν_{max}/cm^{-1} 3048, 2970, 2932, 2888, 1676, 1604, 1583, 1500, 1420; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.40 (9H, s, C(CH_3)$_3$), 1.52 (2H, dddd, *J* = 12.8, 8.6, 8.6 and 3.9 Hz, H-3', 5'$_{axial}$), 1.89 (2H, dddd, *J* = 12.8, 6.7, 3.9 and 3.9 Hz, H-3', 5'$_{equ}$), 3.17 (2H, brs, H-2', 6'$_{equ}$), 3.64 (2H, ddd, *J* = 12.8, 6.7 and 3.9 Hz, H-2', 6'$_{axial}$), 4.56 (1H, tt, *J* = 7.9, 3.9 Hz, H-4'), 7.19 (1H, ddd, *J* = 8.8, 2.5 and 1.4 Hz, H-5), 7.29 (1H, dd, *J* = 8.9, 8.8 Hz, H-6), 7.43 (1H, dd, *J* = 11.1, 2.5 Hz, H-3); ^{13}C NMR (126 MHz, DMSO-d_6) δ 28.0 (C(*C*H$_3$)$_3$), 30.3 (C-3', 5'), 40.1 (C-2', 6'), 74.3 (C-4'), 78.8 (O*C*(CH$_3$)$_3$), 116.9 (d, *J* = 22.2 Hz, C-3), 118.8 (d, *J* = 2.1 Hz, C-6), 124.6 (d, *J* = 9.3 Hz, C-4), 124.7 (d, *J* = 3.7 Hz, C-5), 143.8 (d, *J* = 10.4 Hz, C-1), 152.6 (d, *J* = 247.6 Hz, C-2), 153.9 (*C*O$_2$N); ^{19}F NMR (471 MHz, DMSO-d_6) δ -130.4 (ArF); LRMS (ES$^+$) *m/z* 330.2 $[M(^{35}Cl)+H]^+$, 332.2 $[M(^{37}Cl)+H]^+$; HRMS (NSI) calcd for $C_{16}H_{22}ClFNO_3$ $[M(^{35}Cl)+H]^+$ 330.1267, found 330.1269.

6-Chloro-3-ethoxy-2-fluorobenzoic acid, (363)



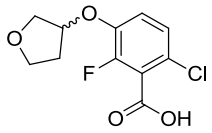
Compound **363** was synthesised according to general procedure A', using the following reagents: 4-chloro-1-ethoxy-2-fluorobenzene (**357**) (950 mg, 5.44 mmol), *n*-butyllithium (2.27 mL, 5.44 mmol) and THF (16.3 mL). The white solid (1.16 g, 97%) was used in the next step without further purification; R_f = 0.45 (petrol:EtOAc:AcOH, 50:49.7:0.3; $KMnO_4$); m.p. 153.0-155.0 °C; λ_{max} (EtOH)/nm 283.2; IR (neat) ν_{max}/cm^{-1} 2984, 2889, 1701, 1613, 1578, 1486, 1466, 1454, 1291, 1266; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.34 (3H, t, *J* = 7.0 Hz, OCH_2CH_3), 4.14 (2H, q, *J* = 7.0 Hz, OCH_2CH_3), 7.26 (1H, dd, *J* = 9.0, 8.8 Hz, H-4), 7.30 (1H, dd, *J* = 9.0, 1.0 Hz, H-5), 14.07 (1H, s, $ArCO_2H$); ^{13}C NMR (126 MHz, DMSO-d_6) δ 14.4 (OCH_2CH_3), 64.9 (OCH_2CH_3), 116.2 (d, *J* = 2.6 Hz, C-4), 119.9 (d, *J* = 4.6 Hz, C-6), 124.1 (d, *J* = 19.1 Hz, C-1), 125.4 (d, *J* = 3.9 Hz, C-5), 145.6 (d, *J* = 10.3 Hz, C-3), 148.0 (d, *J* = 249.3 Hz, C-2), 163.7 ($ArCO_2H$); ^{19}F NMR (471 MHz, DMSO-d_6) δ -135.0 (ArF); LRMS (ES$^+$) *m/z* 219.1 [M(^{35}Cl)+H]$^+$, 221.1 [M(^{37}Cl)+H]$^+$; HRMS (NSI) calcd for $C_9H_9ClFO_3$ [M(^{35}Cl)+H]$^+$ 219.0219 found 219.0219.

6-Chloro-2-fluoro-3-(2-methoxyethoxy)benzoic acid, (364)



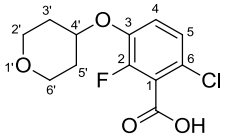
Compound **364** was synthesised according to general procedure A', using the following reagents: 4-chloro-2-fluoro-1-(2-methoxyethoxy)benzene (**358**) (1.05 g, 5.13 mmol), *n*-butyllithium (2.14 mL, 5.13 mmol) and THF (15.4 mL). The off-white solid (1.07 g, 84%) was used in the next step without further purification; R_f = 0.22 (petrol:EtOAc:AcOH, 50:49.7:0.3; $KMnO_4$); m.p. 126.0-128.0 °C; λ_{max} (EtOH)/nm 282.6; IR (neat) ν_{max}/cm^{-1} 2928, 2879, 2831, 1717, 1611, 1577, 1480, 1452, 1256; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.30 (3H, s, CH_3OCH_2), 3.62 – 3.71 (2H, m, CH_3OCH_2), 4.17 - 4.25 (2H, m, $ArOCH_2$), 7.26 – 7.33 (2H, m, H-4 and H-5), 14.12 (1H, s, $ArCO_2H$); ^{13}C NMR (126 MHz, DMSO-d_6) δ 58.2 (CH_3OCH_2), 68.7 (OCH_2), 70.1 (OCH_2), 116.4 (d, *J* = 1.9 Hz, C-4), 120.1 (d, *J* = 4.6 Hz, C-6), 124.2 (d, *J* = 19.1 Hz, C-1), 125.4 (d, *J* = 3.8 Hz, C-5), 145.6 (d, *J* = 10.4 Hz, C-3), 148.0 (d, *J* = 249.6 Hz, C-2), 163.6 ($ArCO_2H$); ^{19}F NMR (471 MHz, DMSO-d_6) δ -134.7 (ArF); LRMS (ES$^-$) *m/z* 247.1 [M(^{35}Cl)-H]$^-$, 249.1 [M(^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{10}H_{11}ClFO_4$ [M(^{35}Cl)+H]$^+$ 249.0324, found 249.0329.

6-Chloro-2-fluoro-3-((tetrahydrofuran-3-yl)oxy)benzoic acid, (365)



Compound **365** was synthesised according to general procedure A', using the following reagents: 3-(4-chloro-2-fluorophenoxy)tetrahydrofuran (**360**) (980 mg, 4.52 mmol), *n*-butyllithium (1.88 mL, 4.52 mmol) and THF (13.6 mL). The white solid (1.02 g, 86%) was used in the next step without further purification; R_f = 0.30 (petrol:EtOAc:AcOH, 50:49.7:0.3; $KMnO_4$); m.p. 11.5-113.5 °C; λ_{max} (EtOH)/nm 283.0; IR (neat) ν_{max}/cm^{-1} 2949, 2891, 1720, 1613, 1574, 1472, 1245; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.98 (1H, dt, *J* = 12.6, 5.7 Hz, ArOCHC*H*$_2$CH$_2$), 2.23 (1H, dtd, *J* = 14.2, 8.2, 6.3 Hz, ArOCHC*H*$_2$CH$_2$), 3.75 (1H, td, *J* = 8.4, 4.5 Hz, OC*H*$_2$), 3.80 – 3.90 (3H, m, OC*H*$_2$), 5.13 (1H, dddd, *J* = 5.9, 3.8, 1.8 and 1.8 Hz, ArOC*H*), 7.27 (1H, dd, *J* = 9.1, 8.7 Hz, H-4), 7.32 (1H, d, *J* = 9.1 Hz, H-5), 14.13 (1H, s, ArCO$_2$*H*); ^{13}C NMR (126 MHz, DMSO-d_6) δ 32.3 (ArOCH*C*H$_2$CH$_2$), 66.4 (O*C*H$_2$), 72.1 (O*C*H$_2$), 79.2 (ArO*C*H), 117.4 (d, *J* = 1.8 Hz, C-4), 120.4 (d, *J* = 4.7 Hz, C-6), 124.4 (d, *J* = 18.9 Hz, C-1), 125.4 (d, *J* = 3.9 Hz, C-5), 144.2 (d, *J* = 10.4 Hz, C-3), 148.5 (d, *J* = 249.5 Hz, C-2), 163.6 (ArCO$_2$*H*); ^{19}F NMR (471 MHz, DMSO-d_6) δ -134.3 (ArF); LRMS (ES$^-$) *m/z* 259.1 [M(^{35}Cl)-H]$^-$, 261.1 [M(^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{11}H_{11}ClFO_4$ [M(^{35}Cl)+H]$^+$ 261.0324, found 261.0329.

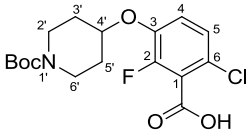
6-Chloro-2-fluoro-3-((tetrahydro-2*H*-pyran-4-yl)oxy)benzoic acid, (366)



Compound **366** was synthesised according to general procedure A', using the following reagents: 4-(4-chloro-2-fluorophenoxy)tetrahydro-2*H*-pyran (**361**) (1.05 g, 4.55 mmol), *n*-butyllithium (1.90 mL, 4.55 mmol) and THF (13.7 mL). The white solid (1.18 g, 94%) was used in the next step without further purification; R_f = 0.29 (petrol:EtOAc:AcOH, 50:49.7:0.3; $KMnO_4$); m.p. 159.5-161.5 °C; λ_{max} (EtOH)/nm 282.4; IR (neat) ν_{max}/cm^{-1} 2935, 2877, 1716, 1611, 1575, 1469, 1263; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.60 (2H, dddd, *J* = 13.0, 9.1, 9.1 and 4.0 Hz, H-3', 5'$_{axial}$), 1.90 – 2.01 (2H, m, H-3', 5'$_{equ}$), 3.46 (2H, ddd, *J* = 13.0, 9.5, 2.7 Hz, H-2', 6'$_{axial}$), 3.84 (2H, ddd, *J* = 13.0, 4.0 and 4.0 Hz, H-2', 6'$_{equ}$), 4.64 (1H, tt, *J* = 8.4, 4.0 Hz, H-4'), 7.30 (1H, dd, *J* = 9.0, 1.5 Hz, H-5), 7.38 (1H, dd, *J* = 9.0, 9.0 Hz, H-4), 14.11 (1H, s, ArCO$_2$*H*); ^{13}C NMR (126 MHz, DMSO-d_6) δ 31.5 (C-3', 5'), 64.4 (C-2', 6'), 73.8 (C-4'), 118.7 (d, *J* = 1.8 Hz, C-4), 120.6 (d, *J* = 4.7 Hz,

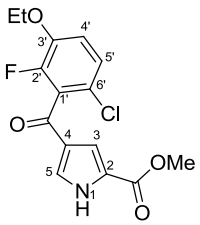
C-6), 124.5 (d, *J* = 19.4 Hz, C-1), 125.4 (d, *J* = 3.8 Hz, C-5), 143.9 (d, *J* = 10.5 Hz, C-3), 148.9 (d, *J* = 249.4 Hz, C-2), 163.6 ($ArCO_2H$); ^{19}F NMR (471 MHz, DMSO-d_6) δ -133.8 (ArF); LRMS (ES^-) *m/z* 273.1 [M(^{35}Cl)-H]$^-$, 275.1 [M(^{37}Cl)-H]$^-$; HRMS (APCI) calcd for $C_{12}H_{16}NClFO_4$ [M(^{35}Cl)+NH_4]$^+$ 292.0746, found 292.0747.

3-((1-(*tert*-Butoxycarbonyl)piperidin-4-yl)oxy)-6-chloro-2-fluorobenzoic acid, (367)



Compound **367** was synthesised according to general procedure A', using the following reagents: *tert*-butyl 4-(4-chloro-2-fluorophenoxy)piperidine-1-carboxylate (**362**) (1.25 g, 3.79 mmol), *n*-butyllithium (1.58 mL, 3.79 mmol) and THF (11.4 mL). The white solid (1.30 g, 92%) was used in the next step without further purification; R_f = 0.32 (petrol:EtOAc:AcOH, 50:49.7:0.3); m.p. 136.0-138.0 °C; λ_{max} (EtOH)/nm 281.4; IR (neat) ν_{max}/cm^{-1} 2972, 2933, 2869, 1733, 1687, 1637, 1575, 1471, 1434, 1365, 1267, 1234; ^1H NMR (500 MHz, DMSO-d_6) δ 1.40 (9H, s, C(CH_3)$_3$), 1.54 (2H, dddd, *J* = 12.5, 8.6, 8.6 and 3.9 Hz, H-3', 5'$_{axial}$), 1.86 – 1.94 (2H, m, H-3', 5'$_{equ}$), 3.08 – 3.23 (2H, m, H-2', 6'$_{equ}$), 3.64 (2H, ddd, *J* = 12.5, 3.9 and 3.9 Hz, H-2', 6'$_{axial}$), 4.62 (1H, tt, *J* = 7.9, 3.9 Hz, H-4'), 7.30 (1H, dd, *J* = 9.0, 1.3 Hz, H-5), 7.36 (1H, dd, *J* = 9.0, 8.9 Hz, H-4), 14.13 (1H, s, $ArCO_2H$); ^{13}C NMR (126 MHz, DMSO-d_6) δ 28.1 (C(*C*H_3)$_3$), 30.2 (C-3', 5'), 40.1 (C-2', 6'), 74.5 (C-4'), 78.8 (O*C*(CH$_3$)$_3$), 118.7 (C-4), 120.7 (d, *J* = 4.6 Hz, C-6), 125.4 (d, *J* = 3.9 Hz, C-5), 143.9 (d, *J* = 10.6 Hz, C-3), 149.0 (d, *J* = 249.4 Hz, C-2), 153.9 (*C*O_2N), 163.6 (Ar*C*O_2H); ^{19}F NMR (471 MHz, DMSO-d_6) δ -133.7 (ArF); LRMS (ES^-) *m/z* 372.2 [M(^{35}Cl)-H]$^-$, 374.2 [M(^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{17}H_{22}ClFNO_5$ [M(^{35}Cl)+H]$^+$ 374.1165, found 374.1161.

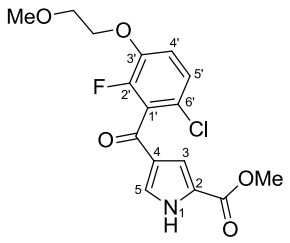
Methyl 4-(6-chloro-3-ethoxy-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylate, (368)



To a solution of 6-chloro-3-ethoxy-2-fluorobenzoic acid (**363**) (1.14 g, 5.21 mmol) in THF (10 mL), cooled at 0 °C, was added thionyl chloride (567 μL, 931 mg, 7.82 mmol) and *N*,*N*-dimethylformamide (40 μL, 38 mg, 0.52 mmol). The resulting solution was stirred at 0 °C for 30 min and allowed to warm to RT. After 5 h, the solvent was removed *in vacuo*

and the crude residue dissolved in DCM (5 mL). The resulting solution was added to a suspension of aluminium trichloride (869 mg, 6.52 mmol) in DCM (10 mL), cooled at 0 °C, followed by methyl 1*H*-pyrrole-2-carboxylate (435 mg, 3.47 mmol). The resulting solution was stirred at 0 °C for 30 min and allowed to warm to RT. After 20 h, the reaction mixture was cooled to 0 °C and quenched by cautious addition of 1 M aq. HCl (10 mL). The resulting solution was stirred at RT for 2 h. The reaction was then diluted with water (20 mL) and extracted with DCM (3 × 40 mL). The pooled organic extracts were washed with saturated aq. $NaHCO_3$ and brine (50 mL, respectively), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 7:3) to yield the *title compound* as a white solid (880 mg, 78%); R_f = 0.32 (petrol:EtOAc, 7:3); m.p. 119.0-121.0 °C; λ_{max} (EtOH)/nm 230.6, 282.2; IR (neat) ν_{max}/cm^{-1} 3292, 3103, 2989, 2950, 1712, 1639, 1562, 1467, 1438, 1272, 1234, 1196; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.35 (3H, t, *J* = 7.0 Hz, OCH_2CH_3), 3.79 (3H, s, CO_2CH_3), 4.15 (2H, q, *J* = 7.0 Hz, OCH_2CH_3), 7.00 (1H, s, H-3), 7.29 (1H, dd, *J* = 9.3, 8.8 Hz, H-4'), 7.34 (1H, d, *J* = 9.3 Hz, H-5'), 7.54 (1H, s, H-5), 12.88 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 14.4 (OCH_2CH_3), 51.7 (CO_2CH_3), 64.9 (OCH_2CH_3), 114.6 (C-3), 116.1 (d, *J* = 2.4 Hz, C-4'), 120.0 (d, *J* = 4.8 Hz, C-6'), 124.5 (C-2 or C-4), 125.3 (C-2 or C-4), 125.5 (d, *J* = 3.7 Hz, C-5'), 128.2 (d, *J* = 20.0 Hz, C-1'), 130.2 (C-5), 145.7 (d, *J* = 10.6 Hz, C-3'), 148.0 (d, *J* = 246.9 Hz, C-2'), 160.3 (CO_2CH_3), 183.5 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -135.8 (ArF); LRMS (ES^+) *m/z* 326.2 $[M(^{35}Cl)+H]^+$, 328.2 $[M(^{37}Cl)+H]^+$; HRMS (NSI) calcd for $C_{15}H_{14}ClFNO_4$ $[M(^{35}Cl)+H]^+$ 326.0590 found 326.0590.

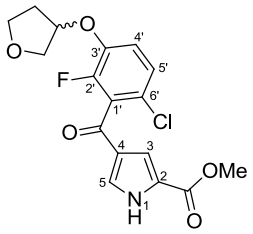
Methyl 4-(6-chloro-2-fluoro-3-(2-methoxyethoxy)benzoyl)-1*H*-pyrrole-2-carboxylate, (369)



To a solution of 6-chloro-2-fluoro-3-(2-methoxyethoxy)benzoic acid (**364**) (1.05 g, 4.22 mmol) in THF (10 mL), cooled at 0 °C, was added thionyl chloride (460 μL, 754 mg, 6.33 mmol) and *N*,*N*-dimethylformamide (33 μL, 31 mg, 0.42 mmol). The resulting solution was stirred at 0 °C for 30 min and allowed to warm to RT. After 5 h, the solvent was removed *in vacuo* and the crude residue dissolved in DCM (5 mL). The resulting solution was added to a suspension of aluminium trichloride (1.13 g, 8.44 mmol) in DCM

(10 mL), cooled at 0 °C, followed by methyl 1*H*-pyrrole-2-carboxylate (349 mg, 2.79 mmol). The resulting solution was stirred at 0 °C for 30 min and allowed to warm to RT. After 20 h, the reaction mixture was cooled to 0 °C and quenched by cautious addition of 1 M aq. HCl (10 mL). The resulting solution was stirred at RT for 2 h. The reaction was then diluted with water (20 mL) and extracted with DCM (3 × 40 mL). The pooled organic extracts were washed with saturated aq. $NaHCO_3$ and brine (50 mL, respectively), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 6:4) to yield the *title compound* as a yellow oil (718 mg, 72%); R_f = 0.29 (petrol:EtOAc, 6:4); λ_{max} (EtOH)/nm 281.8; IR (neat) ν_{max}/cm^{-1} 3262, 3128, 2987, 2935, 2883, 1710, 1651, 1558, 1469, 1441, 1269, 1229; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.30 (3H, s, CH_2OCH_3), 3.68 (2H, dd, *J* = 5.1, 3.7 Hz, CH_2O), 3.79 (3H, s, CO_2CH_3), 4.23 (2H, dd, *J* = 5.1, 3.7 Hz, CH_2O), 7.00 (1H, s, H-3), 7.27 – 7.41 (2H, m, H-4' and H-5'), 7.55 (1H, s, H-5), 12.91 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 51.7 (CO_2CH_3), 58.2 (CH_2OCH_3), 68.6 (CH_2O), 70.1 (CH_2O), 114.7 (C-3), 116.4 (C-4'), 120.3 (d, *J* = 4.8 Hz, C-6'), 124.6 (C-2 or C-4), 125.3 (C-2 or C-4), 125.5 (d, *J* = 3.7 Hz, C-5'), 128.3 (d, *J* = 19.9 Hz, C-1'), 130.2 (C-5), 145.7 (d, *J* = 10.6 Hz, C-3'), 148.1 (d, *J* = 247.2 Hz, C-2'), 160.3 (CO_2CH_3), 183.4 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -135.6 (ArF); LRMS (ES^+) *m/z* 356.3 $[M(^{35}Cl)+H]^+$, 358.3 $[M(^{37}Cl)+H]^+$; HRMS (NSI) calcd for $C_{16}H_{16}ClFNO_5$ $[M(^{35}Cl)+H]^+$ 356.0696, found 356.0697.

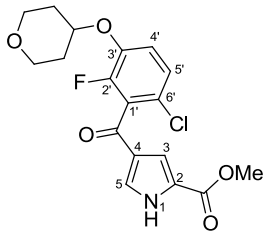
Methyl 4-(6-chloro-2-fluoro-3-((tetrahydrofuran-3-yl)oxy)benzoyl)-1*H*-pyrrole-2-carboxylate, (370)



To a solution of 6-chloro-2-fluoro-3-((tetrahydrofuran-3-yl)oxy)benzoic acid (**365**) (1.0 g, 3.84 mmol) in THF (10 mL), cooled at 0 °C, was added thionyl chloride (417 μL, 685 mg, 5.75 mmol) and *N*,*N*-dimethylformamide (30 μL, 28 mg, 0.38 mmol). The resulting solution was stirred at 0 °C for 30 min and allowed to warm to RT. After 5 h, the solvent was removed *in vacuo* and the crude residue dissolved in DCM (5 mL). The resulting solution was added to a suspension of aluminium trichloride (1.02 g, 7.67 mmol) in DCM (10 mL), cooled at 0 °C, followed by methyl 1*H*-pyrrole-2-carboxylate (317 mg, 2.53 mmol). The resulting solution was stirred at 0 °C for 30 min and allowed to warm to

RT. After 20 h, the reaction mixture was cooled to 0 °C and quenched by cautious addition of 1 M aq. HCl (10 mL). The resulting solution was stirred at RT for 2 h. The reaction was then diluted with water (20 mL) and extracted with DCM (3 × 40 mL). The pooled organic extracts were washed with saturated aq. $NaHCO_3$ and brine (50 mL, respectively), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 6:4) to yield the *title compound* as a white solid (765 mg, 82%); R_f = 0.28 (petrol:EtOAc, 6:4); m.p. 87.5-89.5 °C; λ_{max} (EtOH)/nm 230.4, 282.0; IR (neat) ν_{max}/cm^{-1} 3259, 3130, 2952, 2875, 1711, 1652, 1559, 1466, 1439, 1389, 1272, 1229, 1198; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.03 (1H, dt, *J* = 11.5, 4.3 Hz, ArOCHC*H*$_2$CH$_2$), 2.25 (1H, dtd, *J* = 14.2, 8.2, 6.1 Hz, ArOCHC*H*$_2$CH$_2$), 3.75 (1H, dt, *J* = 8.4, 4.2 Hz, OC*H*$_2$), 3.79 (3H, s, CO_2CH_3), 3.82 – 3.91 (3H, m, OC*H*$_2$), 5.14 (1H, dddd, *J* = 6.1, 3.9, 1.9 and 1.9 Hz, ArOC*H*(CH$_2$)$_2$), 7.02 (1H, s, H-3), 7.30 (1H, dd, *J* = 9.2, 8.8 Hz, H-4'), 7.35 (1H, d, *J* = 9.2 Hz, H-5'), 7.54 – 7.59 (1H, m, H-5), 12.90 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 32.3 (ArOCH*C*H$_2$CH$_2$), 51.7 (CO_2CH_3), 66.4 (O*C*H$_2$), 72.1 (O*C*H$_2$), 79.1 (ArO*C*H), 114.6 (C-3), 117.2 (d, *J* = 2.1 Hz, C-4'), 120.5 (d, *J* = 4.9 Hz, C-6'), 124.6 (C-2 or C-4), 125.3 (C-2 or C-4), 125.5 (d, *J* = 3.8 Hz, C-5'), 128.5 (d, *J* = 20.1 Hz, C-1'), 130.4 (C-5), 144.4 (d, *J* = 10.6 Hz, C-3'), 148.6 (d, *J* = 247.2 Hz, C-2'), 160.3 (*C*O$_2$CH$_3$), 183.4 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -135.21 (ArF); LRMS (ES$^+$) *m/z* 368.3 [M(^{35}Cl)+H]$^+$, 370.3 [M(^{37}Cl)+H]$^+$; HRMS (NSI) calcd for $C_{17}H_{16}ClFNO_5$ [M(^{35}Cl)+H]$^+$ 368.0696, found 368.0700.

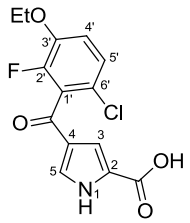
Methyl 4-(6-chloro-2-fluoro-3-((tetrahydro-2*H*-pyran-4-yl)oxy)benzoyl)-1*H*-pyrrole-2-carboxylate, (371)



To a solution 6-chloro-2-fluoro-3-((tetrahydro-2*H*-pyran-4-yl)oxy)benzoic acid (**366**) (1.15 g, 4.19 mmol) in THF (10 mL), cooled at 0 °C, was added thionyl chloride (456 μL, 747 mg, 6.28 mmol) and *N*,*N*-dimethylformamide (32 μL, 31 mg, 0.42 mmol). The resulting solution was stirred at 0 °C for 30 min and allowed to warm to RT. After 5 h, the solvent was removed *in vacuo* and the crude residue dissolved in DCM (5 mL). The resulting solution was added to a suspension of aluminium trichloride (1.12 g, 8.37 mmol) in DCM (10 mL), cooled at 0 °C, followed by methyl 1*H*-pyrrole-2-carboxylate (346 mg, 2.76 mmol). The resulting solution was stirred at 0 °C for 30 min and allowed to warm to

RT. After 20 h, the reaction mixture was cooled to 0 °C and quenched by cautious addition of 1 M aq. HCl (10 mL). The resulting solution was stirred at RT for 2 h. The reaction was then diluted with water (20 mL) and extracted with DCM (3 × 40 mL). The pooled organic extracts were washed with saturated aq. $NaHCO_3$ and brine (50 mL, respectively), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 6:4) to yield the *title compound* as a white solid (852 mg, 81%); R_f = 0.30 (petrol:EtOAc, 6:4); m.p. 113.5-115.5 °C; λ_{max} (EtOH)/nm 230.8, 282.2; IR (neat) ν_{max}/cm^{-1} 3260, 3126, 2953, 2855, 1709, 1651, 1559, 1462, 1440, 1389, 1270; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.62 (2H, dddd, *J* = 13.0, 9.1, 9.1 and 4.0 Hz, ArOCHC*H*$_{2\ axial}$), 1.99 (2H, dd, *J* = 13.0, 3.5 Hz, ArOCHC*H*$_{2\ equ}$), 3.47 (2H, ddd, *J* = 13.0, 9.7 and 2.7 Hz, ArOCHCH$_2$C*H*$_{2\ axial}$), 3.79 (3H, s, CO_2CH_3), 3.84 (2H, ddd, *J* = 13.0, 4.0, 4.0 Hz, ArOCHCH$_2$C*H*$_{2\ equ}$), 4.66 (1H, tt, *J* = 8.4, 4.0 Hz, ArOC*H*), 7.01 (1H, s, H-3), 7.33 (1H, dd, *J* = 9.0, 1.1 Hz, H-5'), 7.42 (1H, dd, *J* = 9.0, 9.0 Hz, H-4'), 7.55 (1H, s, H-5), 12.88 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 31.6 (ArOCH*C*H$_2$), 51.7 (CO_2*C*H$_3$), 64.4 (ArOCHCH$_2$*C*H$_2$), 73.8 (ArO*C*H), 114.6 (C-3), 118.6 (d, *J* = 1.7 Hz, C-4'), 120.7 (d, *J* = 4.9 Hz, C-6'), 124.6 (C-2 or C-4), 125.3 (C-2 or C-4), 125.5 (d, *J* = 3.6 Hz, C-5'), 128.6 (d, *J* = 20.2 Hz, C-1'), 130.3 (C-5), 144.0 (d, *J* = 10.7 Hz, C-3'), 149.0 (d, *J* = 246.9 Hz, C-2'), 160.3 (*C*ONHAr), 183.4 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -134.6 (ArF); LRMS (ES$^+$) *m/z* 382.3 [M(^{35}Cl)+H]$^+$, 384.2 [M(^{37}Cl)+H]$^+$; HRMS (NSI) calcd for $C_{18}H_{18}ClFNO_5$ [M(^{35}Cl)+H]$^+$ 382.0852, found 382.0850.

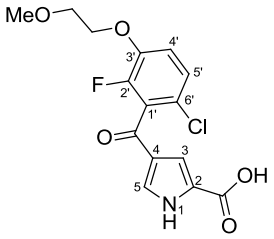
4-(6-Chloro-3-ethoxy-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid, (372)



Compound **372** was synthesised according to general procedure R, using the following reagents: methyl 4-(6-chloro-3-ethoxy-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylate (**368**) (800 mg, 2.46 mmol), 2 M aq. lithium hydroxide (18.5 mL, 36.8 mmol) and THF (19.7 mL). The crude white solid (732 mg, 96%) was used in the next step without further purification; R_f = 0.26 (petrol:EtOAc:AcOH, 50:49.7:0.3); m.p. 163.5-165.5 °C; λ_{max} (EtOH)/nm 230.8, 283.4; IR (neat) ν_{max}/cm^{-1} 3280, 3126, 2986, 2888, 1713, 1647, 1554, 1466, 1442, 1282, 1268, 1232; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.35 (3H, t, *J* = 7.0 Hz, OCH$_2$C*H*$_3$), 4.15 (2H, q, *J* = 7.0 Hz, O*CH*$_2$CH$_3$), 6.95 (1H, s, H-3), 7.29 (1H,

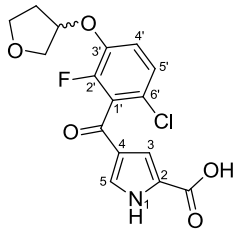
dd, *J* = 9.2, 8.8 Hz, H-4'), 7.33 (1H, d, *J* = 9.2 Hz, H-5'), 7.45 (1H, s, H-5), 12.69 (1H, s, NH-pyrrole), 12.85 (1H, s, CO_2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 14.5 (OCH_2CH_3), 64.9 (OCH_2CH_3), 114.2 (C-3), 116.0 (C-4'), 120.0 (d, *J* = 4.8 Hz, C-6'), 125.2 (C-2 or C-4), 125.5 (d, *J* = 3.7 Hz, C-5'), 125.8 (C-2 or C-4), 128.3 (d, *J* = 20.0 Hz, C-1'), 129.8 (C-5), 145.7 (d, *J* = 10.6 Hz, C-3'), 148.0 (d, *J* = 246.8 Hz, C-2'), 161.3 (CO_2H), 183.5 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -135.8 (ArF); LRMS (ES$^-$) *m/z* 310.1 [M(^{35}Cl)-H]$^-$, 312.1 [M(^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{14}H_{12}ClFNO_4$ [M(^{35}Cl)+H]$^+$ 312.0433, found 312.0436.

4-(6-Chloro-2-fluoro-3-(2-methoxyethoxy)benzoyl)-1*H*-pyrrole-2-carboxylic acid, (373)



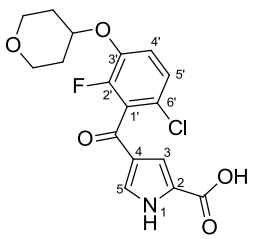
Compound **373** was synthesised according to general procedure R, using the following reagents: methyl 4-(6-chloro-2-fluoro-3-(2-methoxyethoxy)benzoyl)-1*H*-pyrrole-2-carboxylate (**369**) (650 mg, 1.83 mmol), 2 M aq. lithium hydroxide (13.8 mL, 27.6 mmol) and THF (14.6 mL). The crude pale orange solid (593 mg, 95%) was used in the next step without further purification; R_f = 0.18 (petrol:EtOAc:AcOH, 50:49.7:0.3); m.p. 100.0-102.0 °C; λ_{max} (EtOH)/nm 230.4, 282.2; IR (neat) ν_{max}/cm^{-1} 3125, 2958, 2862, 1701, 1688, 1650, 1559, 1464, 1437, 1268, 1226; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.30 (3H, s, CH_3OCH_2), 3.68 (2H, t, *J* = 4.2 Hz, OCH_2), 4.23 (2H, t, *J* = 4.2 Hz, OCH_2), 6.96 (1H, s, H-3), 7.28 – 7.37 (2H, m, H-4' and H-5'), 7.47 (1H, s, H-5), 12.72 (1H, s, NH-pyrrole), 12.95 (1H, s, CO_2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 58.2 (CH_3OCH_2), 68.7 (OCH_2), 70.1 (OCH_2), 114.2 (C-3), 116.3 (C-4'), 120.4 (d, *J* = 4.7 Hz, C-6'), 125.2 (C-2 or C-4), 125.5 (d, *J* = 3.6 Hz, C-5'), 125.9 (C-2 or C-4), 128.4 (d, *J* = 20.0 Hz, C-1'), 129.9 (C-5), 145.7 (d, *J* = 10.6 Hz, C-3'), 148.1 (d, *J* = 247.2 Hz, C-2'), 161.3 (CO_2H), 183.5 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -135.5 (ArCO); LRMS (ES$^-$) *m/z* 340.1 [M(^{35}Cl)-H]$^-$, 342.1 [M(^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{15}H_{14}ClFNO_5$ [M(^{35}Cl)+H]$^+$ 342.0539, found 342.0542.

4-(6-Chloro-2-fluoro-3-((tetrahydrofuran-3-yl)oxy)benzoyl)-1*H*-pyrrole-2-carboxylic acid, (374)



Compound **374** was synthesised according to general procedure R, using the following reagents: methyl 4-(6-chloro-2-fluoro-3-((tetrahydrofuran-3-yl)oxy)benzoyl)-1*H*-pyrrole-2-carboxylate (**370**) (650 mg, 1.77 mmol), 2 M aq. lithium hydroxide (13.3 mL, 26.6 mmol) and THF (14.2 mL). The crude pale orange solid (600 mg, 96%) was used in the next step without further purification; R_f = 0.19 (petrol:EtOAc:AcOH, 50:49.7:0.3); m.p. 111.5-113.5 °C; λ_{max} (EtOH)/nm 230.2, 282.4; IR (neat) ν_{max}/cm^{-1} 3127, 2987, 2933, 2887, 1687, 1640, 1558, 1469, 1448, 1268, 1227, 1191; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.95 – 2.08 (1H, m, ArOCHCH_2CH$_2$), 2.24 (1H, dtd, *J* = 14.3, 8.3, 6.0 Hz, ArOCHCH_2CH$_2$), 3.75 (1H, td, *J* = 8.3, 4.5 Hz, OCH_2), 3.81 – 3.91 (3H, m, OCH_2), 5.13 (1H, s, ArOC*H*), 6.98 (1H, s, H-3), 7.29 (1H, dd, *J* = 9.1, 8.8 Hz, H-4'), 7.34 (1H, d, *J* = 9.1 Hz, H-5'), 7.49 (1H, s, H-5), 12.72 (1H, s, NH-pyrrole), 12.94 (1H, s, CO_2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 32.4 (ArOCH*C*H$_2$CH$_2$), 66.4 (O*C*H$_2$), 72.1 (O*C*H$_2$), 79.2 (ArO*C*H), 114.3 (C-3), 117.2 (C-4'), 120.6 (d, *J* = 4.7 Hz, C-6'), 125.2 (C-2 or C-4), 125.5 (d, *J* = 3.6 Hz, C-5'), 125.9 (C-2 or C-4), 128.7 (d, *J* = 20.1 Hz, C-1'), 130.0 (C-5), 144.4 (d, *J* = 10.7 Hz, C-3'), 148.6 (d, *J* = 247.1 Hz, C-2'), 161.4 (*C*O$_2$H), 183.5 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -135.2 (ArF); LRMS (ES$^-$) *m/z* 352.1 [M(^{35}Cl)-H]$^-$, 354.1 [M(^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{16}H_{14}ClFNO_5$ [M(^{35}Cl)+H]$^+$ 354.0539, found 354.0543.

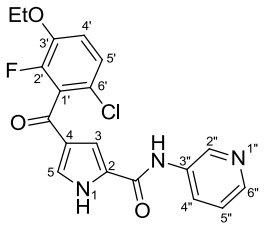
4-(6-Chloro-2-fluoro-3-((tetrahydro-2*H*-pyran-4-yl)oxy)benzoyl)-1*H*-pyrrole-2-carboxylic acid, (375)



Compound **375** was synthesised according to general procedure R, using the following reagents: methyl 4-(6-chloro-2-fluoro-3-((tetrahydro-2*H*-pyran-4-yl)oxy)benzoyl)-1*H*-pyrrole-2-carboxylate (**371**) (800 mg, 2.09 mmol), 2 M aq. lithium hydroxide (15.7 mL,

31.4 mmol) and THF (16.7 mL). The crude white solid (740 mg, 96%) was used in the next step without further purification; R_f = 0.21 (petrol:EtOAc:AcOH, 50:49.7:0.3); m.p. 111.5-113.5 °C; λ_{max} (EtOH)/nm 230.6, 282.8; IR (neat) ν_{max}/cm^{-1} 3129, 2958, 2865, 1698, 1689, 1649, 1559, 1463, 1435, 1268, 1225; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.62 (2H, dddd, *J* = 13.1, 9.0, 9.0 and 4.1 Hz, ArOCHC*H*$_2$), 1.92 – 2.03 (2H, m, ArOCHC*H*$_2$), 3.47 (2H, ddd, *J* = 13.1, 9.0 and 2.8 Hz, ArOCHCH$_2$C*H*$_2$O), 3.84 (2H, ddd, *J* = 13.1, 4.1 and 4.1 Hz, ArOCHCH$_2$C*H*$_2$O), 4.65 (1H, tt, *J* = 9.0, 4.1 Hz, ArOC*H*), 6.96 (1H, s, H-3), 7.32 (1H, dd, *J* = 9.0, 1.1 Hz, H-5'), 7.41 (1H, dd, *J* = 9.0, 9.0 Hz, H-4'), 7.47 (1H, s, H-5), 12.69 (1H, s, NH-pyrrole), 12.91 (1H, s, CO$_2$*H*); ^{13}C NMR (126 MHz, DMSO-d_6) δ 31.6 (ArOCH*C*H$_2$), 64.4 (ArOCHCH$_2$*C*H$_2$O), 73.8 (ArO*C*H), 114.2 (C-3), 118.5 (C-4'), 120.7 (d, *J* = 4.9 Hz, C-6'), 125.2 (C-2 or C-4), 125.5 (d, *J* = 2.8 Hz, C-5'), 125.9 (C-2 or C-4), 128.7 (d, *J* = 20.2 Hz, C-1'), 129.9 (C-5), 144.0 (d, *J* = 10.5 Hz, C-3'), 149.0 (d, *J* = 246.7 Hz, C-2'), 161.3 (*C*O$_2$H), 183.5 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -134.6 (ArF); LRMS (ES$^-$) *m/z* 366.1 [M(^{35}Cl)-H]$^-$, 368.1 [M(^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{17}H_{16}ClFNO_5$ [M(^{35}Cl)+H]$^+$ 368.0696, found 368.0691.

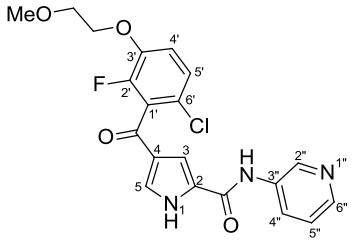
4-(6-Chloro-3-ethoxy-2-fluorobenzoyl)-*N*-(pyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (376)



Compound **376** was synthesised according to general procedure U, using the following reagents: 4-(6-chloro-3-ethoxy-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**372**) (100 mg, 0.32 mmol), 3-aminopyridine (76 mg, 0.80 mmol), phosphorus trichloride (29 µL, 44 mg, 0.32 mmol) and acetonitrile (1.6 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 1:9) to yield the *title compound* as an off-white solid (75 mg, 60%); R_f = 0.29 (petrol:EtOAc, 1:9); m.p. 146.0-148.0 °C; λ_{max} (EtOH)/nm 293.4; IR (neat) ν_{max}/cm^{-1} 3123, 2976, 2958, 2932, 1633, 1598, 1555, 1532, 1464, 1284, 1235; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.36 (3H, t, *J* = 7.0 Hz, OCH$_2$C*H*$_3$), 4.16 (2H, q, *J* = 7.0 Hz, O*C*H$_2$CH$_3$), 7.31 (1H, dd, *J* = 9.0, 8.8 Hz, H-4'), 7.33 – 7.41 (2H, m, H-5' and H-5"), 7.49 (2H, s, H-3 and H-5), 8.13 (1H, ddd, *J* = 8.5, 2.6 and 1.5 Hz, H-4"), 8.30 (1H, dd, *J* = 4.7, 1.5 Hz, H-6"), 8.89 (1H, d, *J* = 2.6 Hz, H-2"), 10.24 (1H, s, CON*H*AR), 12.71 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 14.5 (OCH$_2$*C*H$_3$), 64.9 (O*C*H$_2$CH$_3$), 111.6 (C-3), 116.0 (d, *J* = 2.4 Hz, C-4'), 120.1 (d,

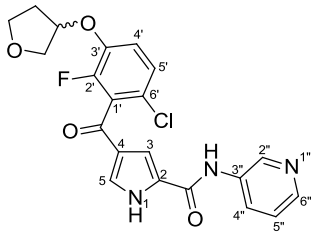
J = 4.9 Hz, C-6'), 123.6 (C-5"), 125.2 (C-2 or C-4), 125.6 (d, *J* = 3.6 Hz, C-5'), 127.0 (C-4"), 128.1 (C-2 or C-4), 128.5 (d, *J* = 20.2 Hz, C-1'), 129.5 (C-5), 135.5 (C-3"), 141.6 (C-2"), 144.4 (C-6"), 145.7 (d, *J* = 10.6 Hz, C-3'), 148.1 (d, *J* = 246.8 Hz, C-2'), 158.7 (*C*ONHAr), 183.7 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -135.7 (ArF); LRMS (ES$^-$) *m/z* 386.1 [M(^{35}Cl)-H]$^-$, 388.2 [M(^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{19}H_{16}ClFN_3O_3$ [M(^{35}Cl)+H]$^+$ 388.0859, found 388.0860.

4-(6-Chloro-2-fluoro-3-(2-methoxyethoxy)benzoyl)-*N*-(pyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (377)



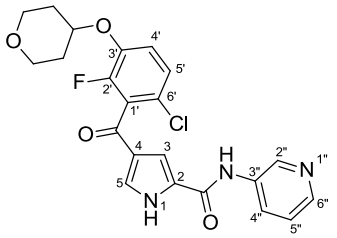
Compound **377** was synthesised according to general procedure U, using the following reagents: 4-(6-chloro-2-fluoro-3-(2-methoxyethoxy)benzoyl)-1*H*-pyrrole-2-carboxylic acid (**373**) (100 mg, 0.29 mmol), 3-aminopyridine (69 mg, 0.73 mmol), phosphorus trichloride (26 µL, 40 mg, 0.29 mmol) and acetonitrile (1.5 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 5:95) to yield the *title compound* as a pale pink solid (80 mg, 66%); R_f = 0.29 (petrol:EtOAc, 5:95); m.p. 148.0-150.0 °C; λ_{max} (EtOH)/nm 251.2, 293.4; IR (neat) ν_{max}/cm^{-1} 3122, 2933, 1637, 1598, 1554, 1534, 1471, 1451, 1422, 1272; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.31 (3H, s, C*H*$_3$OCH$_2$), 3.69 (2H, t, *J* = 4.3 Hz, CH$_3$OC*H*$_2$), 4.24 (2H, t, *J* = 4.3 Hz, C*H*$_2$OAr), 7.34 (1H, dd, *J* = 9.0, 9.0 Hz, H-4'), 7.36 (1H, d, *J* = 9.0 Hz, H-5'), 7.38 (1H, dd, *J* = 8.8, 4.4 Hz, H-5"), 7.48 (1H, s, H-3), 7.50 (1H, s, H-5), 8.13 (1H, ddd, *J* = 8.8, 2.5 and 1.4 Hz, H-4"), 8.30 (1H, dd, *J* = 4.4, 1.4 Hz, H-6"), 8.89 (1H, d, *J* = 2.5, H-2"), 10.25 (1H, s, CON*H*Ar), 12.72 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 58.2 (*C*H$_3$OCH$_2$), 68.6 (O*C*H$_2$), 70.1 (O*C*H$_2$), 111.7 (C-3), 116.2 (C-4'), 120.4 (d, *J* = 4.7 Hz, C-6'), 123.6 (C-5"), 125.2 (C-2 or C-4), 125.6 (d, *J* = 3.9 Hz, C-5'), 127.0 (C-4"), 128.1 (C-2 or C-4), 128.5 (d, *J* = 20.3 Hz, C-1'), 129.4 (C-5), 135.5 (C-3"), 141.6 (C-2"), 144.4 (C-6"), 145.7 (d, *J* = 10.8 Hz, C-3'), 148.1 (d, *J* = 247.0 Hz, C-2'), 158.7 (*C*ONHAr), 183.7 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -135.5 (ArF); LRMS (ES$^-$) *m/z* 416.2 [M(^{35}Cl)-H]$^-$, 418.2 [M(^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{20}H_{18}ClFN_3O_4$ [M(^{35}Cl)+H]$^+$ 418.0964, found 418.0953.

4-(6-Chloro-2-fluoro-3-((tetrahydrofuran-3-yl)oxy)benzoyl)-*N*-(pyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (378)



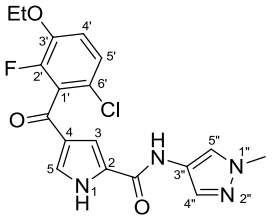
Compound **378** was synthesised according to general procedure U, using the following reagents: 4-(6-chloro-2-fluoro-3-((tetrahydrofuran-3-yl)oxy)benzoyl)-1*H*-pyrrole-2-carboxylic acid (**374**) (100 mg, 0.28 mmol), 3-aminopyridine (67 mg, 0.71 mmol), phosphorus trichloride (25 µL, 39 mg, 0.28 mmol) and acetonitrile (1.4 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 5:95) to yield the *title compound* as a white solid (76 mg, 62%); R_f = 0.30 (petrol:EtOAc, 5:95); m.p. 150.5-152.5 °C; λ_{max} (EtOH)/nm 250.8, 292.4; IR (neat) ν_{max}/cm^{-1} 3112, 2953, 2864, 1636, 1596, 1553, 1531, 1464, 1420, 1271; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.02 (1H, dt, *J* = 12.7, 5.9 Hz, ArOCHC*H*$_2$CH$_2$), 2.26 (1H, dtd, *J* = 14.2, 8.2, 6.0 Hz, ArOCHC*H*$_2$CH$_2$), 3.76 (1H, td, *J* = 8.4, 4.6 Hz, OC*H*$_2$), 3.82 – 3.92 (3H, m, OC*H*$_2$), 5.09 – 5.20 (1H, m, ArOC*H*), 7.31 (1H, dd, *J* = 9.7, 8.8 Hz, H-4'), 7.37 (1H, d, *J* = 9.7 Hz, H-5'), 7.40 (1H, dd, *J* = 8.4, 4.3 Hz, H-5"), 7.46 – 7.54 (2H, m, H-3 and H-5), 8.14 (1H, d, *J* = 8.4 Hz, H-4"), 8.30 (1H, d, *J* = 4.3 Hz, H-6"), 8.90 (1H, s, H-2"), 10.26 (1H, s, CON*H*Ar), 12.72 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 32.3 (ArOCH*C*H$_2$CH$_2$), 66.4 (O*C*H$_2$), 72.1 (O*C*H$_2$), 79.1 (ArO*C*H), 111.6 (C-3), 117.1 (C-4'), 120.7 (d, *J* = 4.9 Hz, C-6'), 123.6 (C-5"), 125.2 (C-2 or C-4), 125.5 (d, *J* = 3.7 Hz, C-5'), 127.1 (C-4"), 128.2 (C-2 or C-4), 128.8 (d, *J* = 20.2 Hz, C-1'), 129.7 (C-5), 135.5 (C-3"), 141.5 (C-2"), 144.3 (C-6"), 144.4 (d, *J* = 9.6 Hz, C-3'), 148.6 (d, *J* = 246.9 Hz, C-2'), 158.7 (*C*ONHAr), 183.6 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -135.1 (ArF); LRMS (ES$^+$) *m/z* 428.2 [M(^{35}Cl)+H]$^+$, 430.2 [M(^{37}Cl)+H]$^+$; HRMS (NSI) calcd for $C_{21}H_{18}ClFN_3O_4$ [M(^{35}Cl)+H]$^+$ 430.0964, found 430.0957.

4-(6-Chloro-2-fluoro-3-((tetrahydro-2*H*-pyran-4-yl)oxy)benzoyl)-*N*-(pyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (379)



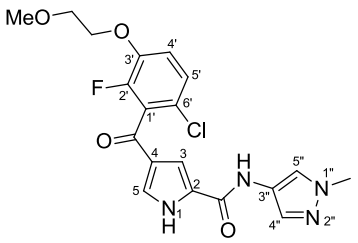
Compound **379** was synthesised according to general procedure U, using the following reagents: 4-(6-chloro-2-fluoro-3-((tetrahydro-2*H*-pyran-4-yl)oxy)benzoyl)-1*H*-pyrrole-2-carboxylic acid (**375**) (100 mg, 0.27 mmol), 3-aminopyridine (64 mg, 0.68 mmol), phosphorus trichloride (24 µL, 37 mg, 0.27 mmol) and acetonitrile (1.4 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 5:95) to yield the *title compound* as a white solid (85 mg, 70%); R_f = 0.31 (petrol:EtOAc, 5:95); m.p. 133.5-135.5 °C; λ_{max} (EtOH)/nm 251.2, 293.4; IR (neat) ν_{max}/cm^{-1} 3238, 3120, 2955, 2923, 2852, 1635, 1596, 1553, 1531, 1462, 1420, 1271, 1227; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.63 (2H, dddd, *J* = 13.2, 8.9, 8.9 and 4.0 Hz, ArOCHC*H*$_2$), 1.93 – 2.07 (2H, m, ArOCHC*H*$_2$), 3.48 (2H, ddd, *J* = 13.2, 8.9 and 2.9 Hz, ArOCHCH$_2$C*H*$_2$O), 3.85 (2H, ddd, *J* = 13.2, 4.5 and 4.5 Hz, ArOCHCH$_2$C*H*$_2$O), 4.67 (1H, tt, *J* = 8.9, 4.0 Hz, ArOC*H*), 7.35 (1H, d, *J* = 9.0 Hz, H-5'), 7.38 (1H, dd, *J* = 8.2, 4.7 Hz, H-5"), 7.43 (1H, dd, *J* = 9.0, 8.9 Hz, H-4'), 7.50 (2H, s, H-3 and H-5), 8.13 (1H, d, *J* = 8.2 Hz, H-4"), 8.30 (1H, d, *J* = 4.7 Hz, H-6"), 8.89 (1H, s, H-2"), 10.25 (1H, s, CON*H*Ar), 12.71 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 31.6 (ArOCH*C*H$_2$), 64.4 (ArOCHCH$_2$*C*H$_2$O), 73.8 (ArO*C*H), 111.6 (C-3), 118.5 (C-4'), 120.8 (d, *J* = 5.0 Hz, C-6'), 123.6 (C-5"), 125.2 (C-2 or C-4), 125.5 (d, *J* = 3.3 Hz, C-5'), 127.0 (C-4"), 128.2 (C-2 or C-4), 128.8 (d, *J* = 20.3 Hz, C-1'), 129.6 (C-5), 135.5 (C-3"), 141.6 (C-2"), 144.0 (d, *J* = 10.7 Hz, C-3'), 144.4 (C-6"), 149.0 (d, *J* = 246.8 Hz, C-2'), 158.7 (*C*ONHAr), 183.6 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -134.5 (ArF); LRMS (ES$^+$) *m/z* 444.3 [M(^{35}Cl)+H]$^+$, 446.3 [M(^{37}Cl)+H]$^+$; HRMS (NSI) calcd for $C_{22}H_{20}ClFN_3O_4$ [M(^{35}Cl)+H]$^+$ 444.1121, found 444.1115.

4-(6-Chloro-3-ethoxy-2-fluorobenzoyl)-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-2-carboxamide, (380)



Compound **380** was synthesised according to general procedure U, using the following reagents: 4-(6-chloro-3-ethoxy-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**372**) (100 mg, 0.32 mmol), 1-methyl-1*H*-pyrazol-4-amine (**348**) (78 mg, 0.80 mmol), phosphorus trichloride (29 µL, 44 mg, 0.32 mmol) and acetonitrile (1.6 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 5:95) to yield the *title compound* as a white solid (78 mg, 62%); R_f = 0.30 (petrol:EtOAc, 5:95); m.p. 152.5-154.5 °C; λ_{max} (EtOH)/nm 251.6; IR (neat) ν_{max}/cm^{-1} 3319, 3123, 2979, 2935, 1619, 1593, 1571, 1464, 1268, 1243; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.36 (3H, t, *J* = 7.0 Hz, OCH_2CH_3), 3.81 (3H, s, NCH_3), 4.16 (2H, q, *J* = 7.0 Hz, OCH_2CH_3), 7.25 - 7.32 (2H, m, H-3 and H-4'), 7.35 (1H, dd, *J* = 9.0, 1.3 Hz, H-5'), 7.42 (1H, s, H-5), 7.50 (1H, s, H-5"), 7.94 (1H, s, H-3"), 10.25 (1H, s, CONHAr), 12.57 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 14.5 (OCH_2CH_3), 38.7 (NCH_3), 64.9 (OCH_2CH_3), 110.3 (C-3), 115.9 (C-4'), 120.1 (d, *J* = 4.8 Hz, C-6'), 121.2 (C-2"), 121.4 (C-3"), 125.1 (C-2 or C-4), 125.5 (d, *J* = 3.6 Hz, C-5'), 128.4 (C-2 or C-4), 128.6 (d, *J* = 20.2 Hz, C-1'), 128.7 (C-5), 129.9 (C-5"), 145.7 (d, *J* = 10.7 Hz, C-3'), 148.0 (d, *J* = 246.7 Hz, C-2'), 156.8 (CONHAr), 183.7 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -135.8 (ArF); LRMS (ES$^-$) *m/z* 389.2 [M(^{35}Cl)-H]$^-$, 391.2 [M(^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{18}H_{17}ClFN_4O_3$ [M(^{35}Cl)+H]$^+$ 391.0968 found 391.0968.

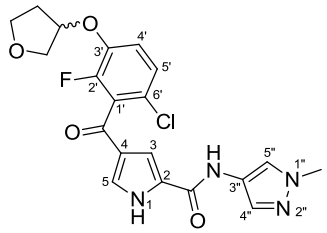
4-(6-Chloro-2-fluoro-3-(2-methoxyethoxy)benzoyl)-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-2-carboxamide, (381)



Compound **381** was synthesised according to general procedure U, using the following reagents: 4-(6-chloro-2-fluoro-3-(2-methoxyethoxy)benzoyl)-1*H*-pyrrole-2-carboxylic acid (**373**) (100 mg, 0.29 mmol), 1-methyl-1*H*-pyrazol-4-amine (**348**) (71 mg, 0.73 mmol),

phosphorus trichloride (26 µL, 40 mg, 0.29 mmol) and acetonitrile (1.5 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 5:95) to yield the *title compound* as a pale pink solid (76 mg, 62%); R_f = 0.31 (petrol:EtOAc, 5:95); m.p. 241.0-243.0 °C; λ_{max} (EtOH)/nm 251.0; IR (neat) ν_{max}/cm^{-1} 3344, 3121, 2935, 1622, 1589, 1569, 1544, 1471, 1449, 1435, 1404, 1272, 1241; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.31 (3H, s, CH_3OCH$_2$), 3.64 – 3.72 (2H, m, CH$_3$OCH_2), 3.81 (3H, s, NCH_3), 4.20 – 4.27 (2H, m, CH_2OAr), 7.28 (1H, s, H-3), 7.30 – 7.38 (2H, m, H-4', 5'), 7.43 (1H, s, H-5), 7.50 (1H, s, H-5"), 7.94 (1H, s, H-3"), 10.25 (1H, s, CON*H*Ar), 12.57 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 38.7 (N*C*H$_3$), 58.2 (*C*H$_3$OCH$_2$), 68.6 (O*C*H$_2$), 70.1 (O*C*H$_2$), 110.3 (C-3), 116.1 (d, *J* = 2.3 Hz, C-4'), 120.4 (d, *J* = 4.9 Hz, C-6'), 121.2 (C-3"), 121.4 (C-4"), 125.1 (C-2 or C-4), 125.5 (d, *J* = 3.6 Hz, C-5'), 128.4 (C-2 or C-4), 128.6 (d, *J* = 20.3 Hz, C-1'), 128.7 (C-5), 129.9 (C-5"), 145.7 (d, *J* = 10.5 Hz, C-3'), 148.1 (d, *J* = 247.0 Hz, C-2'), 156.8 (*C*ONHAr), 183.6 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -135.5 (ArF); LRMS (ES$^-$) *m/z* 419.2 [M(^{35}Cl)-H]$^-$, 421.2 [M(^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{19}H_{19}ClFN_4O_4$ [M(^{35}Cl)+H]$^+$ 421.1073, found 421.1064.

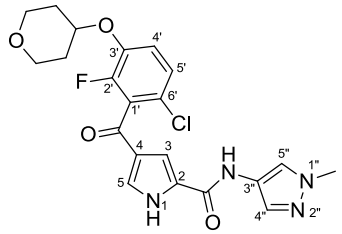
4-(6-Chloro-2-fluoro-3-((tetrahydrofuran-3-yl)oxy)benzoyl)-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1H-pyrrole-2-carboxamide, (382)



Compound **382** was synthesised according to general procedure U, using the following reagents: 4-(6-chloro-2-fluoro-3-((tetrahydrofuran-3-yl)oxy)benzoyl)-1*H*-pyrrole-2-carboxylic acid (**374**) (100 mg, 0.28 mmol), 1-methyl-1*H*-pyrazol-4-amine (**348**) (69 mg, 0.71 mmol), phosphorus trichloride (25 µL, 39 mg, 0.28 mmol) and acetonitrile (1.4 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 5:95) to yield the *title compound* as a white solid (46 mg, 38%); R_f = 0.29 (petrol:EtOAc, 5:95); m.p. 158.5-160.5 °C; λ_{max} (EtOH)/nm 251.2; IR (neat) ν_{max}/cm^{-1} 3187, 3123, 2954, 2866, 1631, 1591, 1568, 1545, 1465, 1435, 1407, 1271; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.02 (1H, dt, *J* = 12.7, 5.9 Hz, ArOCHCH_2CH$_2$), 2.26 (1H, dq, *J* = 12.7, 7.8 Hz, ArOCHCH_2CH$_2$), 3.76 (1H, td, *J* = 8.5, 4.7 Hz, OCH_2), 3.81 (3H, s, NCH_3), 3.83 – 3.93 (3H, m, OCH_2), 5.15 (1H, s, ArOC*H*), 7.25 – 7.33 (2H, m, H-3 and H-4'), 7.36 (1H, d, *J* = 9.0 Hz, H-5'), 7.44 (1H, s, H-5), 7.50 (1H, s, H-5"), 7.94 (1H, s, H-3"), 10.25 (1H, s, CON*H*Ar), 12.58 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz,

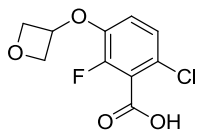
DMSO-d_6) δ 32.3 (ArOCH*C*H$_2$CH$_2$), 38.7 (N*C*H$_3$), 66.4 (O*C*H$_2$), 72.1 (O*C*H$_2$), 79.1 (ArO*C*H), 110.2 (C-3), 117.1 (C-4'), 120.7 (d, *J* = 4.9 Hz, C-6'), 121.2 (C-5"), 121.4 (C-4"), 125.0 (C-2 or C-4), 125.5 (d, *J* = 3.4 Hz, C-5'), 128.5 (C-2 or C-4), 128.9 (d, *J* = 20.4 Hz, C-2'), 129.0 (C-5), 129.9 (C-3"), 144.3 (d, *J* = 10.8 Hz, C-3'), 148.6 (d, *J* = 247.0 Hz, C-2'), 156.8 (*C*ONHAr), 183.6 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -135.1 (ArF); LRMS (ES$^-$) *m/z* 431.2 [M(^{35}Cl)-H]$^-$, 433.2 [M(^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{20}H_{19}ClFN_4O_4$ [M(^{35}Cl)+H]$^+$ 433.1073, found 433.1062.

4-(6-Chloro-2-fluoro-3-((tetrahydro-2*H*-pyran-4-yl)oxy)benzoyl)-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-2-carboxamide, (383)



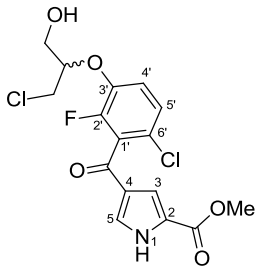
Compound **383** was synthesised according to general procedure U, using the following reagents: 4-(6-chloro-2-fluoro-3-((tetrahydro-2*H*-pyran-4-yl)oxy)benzoyl)-1*H*-pyrrole-2-carboxylic acid (**375**) (100 mg, 0.27 mmol), 1-methyl-1*H*-pyrazol-4-amine (**348**) (66 mg, 0.68 mmol), phosphorus trichloride (24 µL, 37 mg, 0.27 mmol) and acetonitrile (1.4 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 5:95) to yield the *title compound* as a white solid (71 mg, 59%); R_f = 0.29 (petrol:EtOAc, 5:95); m.p. 125.0-127.0 °C; λ_{max} (EtOH)/nm 251.2; IR (neat) ν_{max}/cm^{-1} 3192, 3122, 2955, 2924, 2853, 1630, 1590, 1567, 1544, 1462, 1433, 1407, 1270, 1232; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.63 (2H, dddd, *J* = 13.1, 9.0, 9.0 and 4.0 Hz, ArOCHC*H*$_2$), 1.94 – 2.03 (2H, m, ArOCHC*H*$_2$), 3.48 (2H, ddd, *J* = 13.1, 9.0 and 2.8 Hz, ArOCHCH$_2$C*H*$_2$O), 3.81 (3H, s, NC*H*$_3$), 3.85 (2H, ddd, *J* = 13.1, 4.2 and 4.2 Hz, ArOCHCH$_2$C*H*$_2$O), 4.66 (1H, tt, *J* = 9.0, 4.2 Hz, ArOC*H*), 7.29 (1H, s, H-3), 7.34 (1H, d, *J* = 9.3 Hz, H-5'), 7.42 (1H, dd, *J* = 9.3, 8.7 Hz, H-4'), 7.43 (1H, s, H-5), 7.50 (1H, s, H-5"), 7.94 (1H, s, H-3"), 10.25 (1H, s, CON*H*Ar), 12.56 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 31.6 (ArOCH*C*H$_2$), 64.4 (ArOCHCH$_2$*C*H$_2$O), 73.8 (ArO*C*H), 110.3 (C-3), 118.4 (C-4'), 120.8 (d, *J* = 4.8 Hz, C-6'), 121.2 (C-4"), 121.4 (C-3"), 125.1 (C-2 or C-4), 125.5 (d, *J* = 3.4 Hz, C-5'), 128.5 (C-2 or C-4), 128.8 (C-5), 128.9 (d, *J* = 20.7 Hz, C-1'), 129.9 (C-5"), 144.0 (d, *J* = 10.8 Hz, C-3'), 149.0 (d, *J* = 246.8 Hz, C-2'), 156.8 (*C*ONHAr), 183.6 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -134.5 (ArF); LRMS (ES$^+$) *m/z* 447.3 [M(^{35}Cl)+H]$^+$, 449.3 [M(^{37}Cl)+H]$^+$; HRMS (NSI) calcd for $C_{21}H_{21}ClFN_4O_4$ [M(^{35}Cl)+H]$^+$ 447.1230, found 447.1224.

6-Chloro-2-fluoro-3-(oxetan-3-yloxy)benzoic acid, (384)



Compound **384** was synthesised according to general procedure A', using the following reagents: 3-(4-chloro-2-fluorophenoxy)oxetane (**349**) (500 mg, 2.47 mmol), *n*-butyllithium (1.03 mL, 2.47 mmol) and THF (7.4 mL). The white solid (570 mg, 94%) was used in the next step without further purification; R_f = 0.29 (petrol:EtOAc:AcOH, 50:49.7:0.3); m.p. 152.0-154.0 °C; λ_{max} (EtOH)/nm 282.4; IR (neat) ν_{max}/cm^{-1} 2952, 2923, 2886, 1720, 1614, 1577, 1472, 1253; ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.58 (2H, dd, *J* = 7.4, 4.8 Hz, ArOCHC*H*$_2$O), 4.85 – 4.96 (2H, m, ArOCHC*H*$_2$O), 5.37 (1H, p, *J* = 5.4 Hz, ArOC*H*CH$_2$O), 6.95 (1H, dd, *J* = 9.0, 8.9 Hz, H-4), 7.29 (1H, dd, *J* = 8.9, 1.5 Hz, H-5), 14.17 (1H, s, ArCO$_2$*H*); ^{13}C NMR (126 MHz, DMSO-d_6) δ 71.6 (ArO*C*HCH$_2$O), 76.4 (ArOCH*C*H$_2$O), 116.3 (d, *J* = 1.9 Hz, C-4), 121.0 (d, *J* = 4.6 Hz, C-6), 124.5 (d, *J* = 19.0 Hz, C-1), 125.5 (d, *J* = 3.9 Hz, C-5), 143.5 (d, *J* = 10.7 Hz, C-3), 148.0 (d, *J* = 250.0 Hz, C-2), 163.5 (Ar*C*O$_2$H); ^{19}F NMR (471 MHz, DMSO-d_6) δ -134.6 (ArF); LRMS (ES$^-$) *m/z* 245.1 [M(^{35}Cl)-H]$^-$, 247.1 [M(^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{10}H_9ClFO_4$ [M(^{35}Cl)+H]$^+$ 245.0022, found 245.0022.

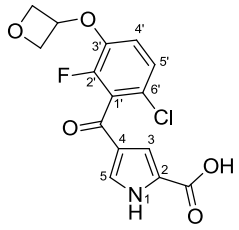
Methyl 4-(6-chloro-3-((1-chloro-3-hydroxypropan-2-yl)oxy)-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylate, (385)



To a solution 6-chloro-2-fluoro-3-(oxetan-3-yloxy)benzoic acid (**384**) (550 mg, 2.23 mmol) in THF (5 mL), cooled at 0 °C, was added thionyl chloride (243 μL, 398 mg, 3.03 mmol) and *N*,*N*-dimethylformamide (17 μL, 16 mg, 0.22 mmol). The resulting solution was stirred at 0 °C for 30 min and allowed to warm to RT. After 5 h, the solvent was removed *in vacuo* and the crude residue dissolved in DCM (3 mL). The resulting solution was added to a suspension of aluminium trichloride (594 mg, 4.46 mmol) in DCM (7 mL), cooled at 0 °C, followed by methyl 1*H*-pyrrole-2-carboxylate (184 mg, 1.47 mmol). The resulting solution was stirred at 0 °C for 30 min and allowed to warm to RT. After 20 h, the reaction mixture was cooled to 0 °C and quenched by cautious addition

of 1 M aq. HCl (10 mL). The resulting solution was stirred at RT for 2 h. The reaction was then diluted with water (15 mL) and extracted with DCM (3 × 30 mL). The pooled organic extracts were washed with saturated aq. $NaHCO_3$ and brine (40 mL, respectively), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 35:65) to yield the *title compound* as a yellow oil (390 mg, 68%); R_f = 0.30 (petrol:EtOAc, 35:65); λ_{max} (EtOH)/nm 230.2, 282.2; IR (neat) ν_{max}/cm^{-1} 3261, 3128, 2953, 2925, 2854, 1704, 1641, 1559, 1462, 1440, 1389, 1270, 1229; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.68 (2H, dd, *J* = 5.4, 5.4 Hz, ArOCHC*H*$_2$OH), 3.79 (3H, s, CO_2CH_3), 3.85 (1H, dd, *J* = 11.9, 5.6 Hz, ArOCHC*H*$_2$Cl), 3.94 (1H, dd, *J* = 11.9, 4.0 Hz, ArOCHC*H*$_2$Cl), 4.60 – 4.68 (1H, m, ArOC*H*), 5.13 (1H, t, *J* = 5.6 Hz, ArOCHCH$_2$O*H*), 7.01 (1H, s, H-3), 7.32 – 7.37 (1H, m, H-5'), 7.44 (1H, dd, *J* = 9.0, 9.0 Hz, H-4'), 7.51 – 7.58 (1H, s, H-5), 12.89 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 43.8 (ArOCH*C*H$_2$Cl), 51.7 (CO_2CH_3), 60.1 (ArOCH*C*H$_2$OH), 80.1 (ArO*C*H), 114.7 (C-3), 118.8 (C-4'), 121.2 (d, *J* = 4.8 Hz, C-6'), 124.6 (C-2 or C-4), 125.3 (C-2 or C-4), 125.6 (d, *J* = 3.7 Hz, C-5'), 128.6 (d, *J* = 20.4 Hz, C-1'), 130.3 (C-5), 144.9 (d, *J* = 10.7 Hz, C-3'), 148.9 (d, *J* = 247.6 Hz, C-2'), 160.3 (*C*O$_2$CH$_3$), 183.4 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -133.9 (ArF); LRMS (ES$^+$) *m/z* 390.2 [M(^{35}Cl)+H]$^+$, 392.2 [M(^{37}Cl)+H]$^+$; HRMS (NSI) calcd for $C_{16}H_{15}Cl_2FNO_5$ [M(^{35}Cl)+H]$^+$ 390.0306, found 390.0306.

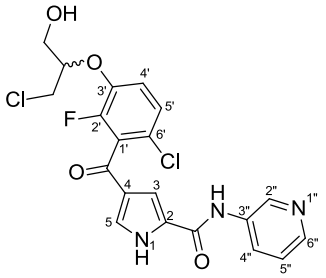
4-(6-Chloro-2-fluoro-3-(oxetan-3-yloxy)benzoyl)-1*H*-pyrrole-2-carboxylic acid, (386)



Compound **386** was synthesised according to general procedure R, using the following reagents: methyl 4-(6-chloro-3-((1-chloro-3-hydroxypropan-2-yl)oxy)-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylate (**385**) (350 mg, 0.90 mmol), 2 M aq. lithium hydroxide (6.8 mL, 13.6 mmol) and THF (7.2 mL). The reaction mixture was reflux for 72 h. The crude product was purified by column chromatography (silica gel, DCM:MeOH:AcOH, 1:0:0 → 90:9.9:0.1) to yield the *title compound* as a white solid (225 mg, 74%); R_f = 0.34 (DCM:MeOH:AcOH, 90:9.9:0.1); m.p. 94.5-96.5 °C; λ_{max} (EtOH)/nm 230.0, 283.0; IR (neat) ν_{max}/cm^{-1} 3126, 2952, 2880, 1689, 1640, 1559, 1465, 1269, 1227; ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.61 (2H, dd, *J* = 7.4, 4.9 Hz, ArOCHC*H*$_2$O), 4.93 (2H, t,

J = 6.9 Hz, ArOCHC*H*$_2$O), 5.39 (1H, p, *J* = 5.5 Hz, ArOC*H*CH$_2$O), 6.94 – 7.02 (2H, m, H-3 and H-4'), 7.31 (1H, dd, *J* = 8.9, 1.2 Hz, H-5'), 7.49 (1H, s, H-5), 12.71 (1H, s, NH-pyrrole), 12.79 (1H, s, CO$_2$*H*); ^{13}C NMR (126 MHz, DMSO-d_6) δ 71.5 (ArO*C*HCH$_2$O), 76.4 (ArOCH*C*H$_2$O), 114.2 (C-3), 116.2 (C-4'), 121.1 (d, *J* = 4.7 Hz, C-6'), 125.1 (C-2 or C-4), 125.6 (d, *J* = 3.8 Hz, C-5'), 125.9 (C-2 or C-4), 128.7 (d, *J* = 19.8 Hz, C-1'), 130.0 (C-5), 143.6 (d, *J* = 11.0 Hz, C-3'), 148.1 (d, *J* = 247.4 Hz, C-2'), 161.3 (*C*O$_2$H), 183.2 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -135.4 (ArF); LRMS (ES$^-$) *m/z* 338.0 [M(^{35}Cl)-H]$^-$, 340.0 [M(^{37}Cl)-H]$^-$; HRMS (NSI) calcd for C$_{15}$H$_{12}$ClFNO$_5$ [M(^{35}Cl)+H]$^+$ 340.0383 found 340.0385.

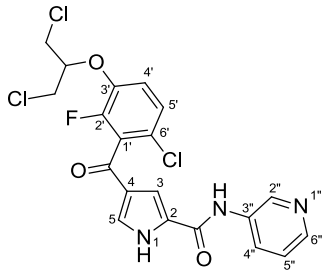
4-(6-Chloro-3-((1-chloro-3-hydroxypropan-2-yl)oxy)-2-fluorobenzoyl)-*N*-(pyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (387)



Compound **387** was synthesised according to general procedure U, using the following reagents: 4-(6-chloro-2-fluoro-3-(oxetan-3-yloxy)benzoyl)-1*H*-pyrrole-2-carboxylic acid (**386**) (50 mg, 0.15 mmol), 3-aminopyridine (35 mg, 0.37 mmol), phosphorus trichloride (13 µL, 20 mg, 0.15 mmol) and acetonitrile (0.8 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 1:9) to yield the *title compound* as an off-white solid (15 mg, 23%); R_f = 0.26 (petrol:EtOAc, 1:9); m.p. 121.5-123.5 °C; λ_{max} (EtOH)/nm 251.2, 293.2; IR (neat) ν_{max}/cm^{-1} 3225, 2956, 2922, 2852, 1635, 1600, 1553, 1534, 1462, 1422, 1274, 1233; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.68 (2H, dd, *J* = 5.4, 5.4 Hz, ArOCHC*H*$_2$OH), 3.86 (1H, dd, *J* = 11.9, 5.4 Hz, ArOCHC*H*$_2$Cl), 3.95 (1H, dd, *J* = 11.9, 4.0 Hz, ArOCHC*H*$_2$Cl), 4.65 (1H, p, *J* = 5.4 Hz, ArOC*H*), 5.14 (1H, t, *J* = 5.4 Hz, ArOCHCH$_2$O*H*), 7.35 – 7.41 (2H, m, H-5' and H-5"), 7.45 (1H, dd, *J* = 9.0, 9.0 Hz, H-4'), 7.49 (1H, s, H-3), 7.50 (1H, s, H-5), 8.13 (1H, dd, *J* = 8.5, 2.6 Hz, H-4"), 8.30 (1H, d, *J* = 4.0 Hz, H-6"), 8.89 (1H, d, *J* = 2.6 Hz, H-2"), 10.26 (1H, s, CON*H*Ar), 12.72 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 43.8 (ArOCH*C*H$_2$Cl), 60.1 (ArOCH*C*H$_2$OH), 80.1 (ArO*C*H), 111.6 (C-3), 118.7 (C-4'), 121.3 (d, *J* = 5.0 Hz, C-6'), 123.5 (C-5"), 125.1 (C-2 or C-4), 125.5 (d, *J* = 3.6 Hz, C-5'), 127.0 (C-4"), 128.2 (C-2 or C-4), 128.8 (d, *J* = 20.5 Hz, C-1'), 129.5 (C-5), 135.5 (C-3"), 141.6 (C-2"), 144.4 (C-6"), 144.9 (d, *J* = 10.8 Hz, C-3'), 148.9 (d, *J* = 247.5 Hz, C-2'), 158.7 (*C*ONHAr), 183.6

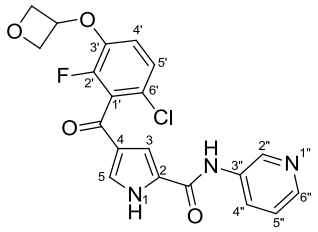
(ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -133.9 (ArF); LRMS (ES$^-$) *m/z* 450.2 [M(^{35}Cl^{35}Cl)-H]$^-$, 452.2 [M(^{37}Cl^{35}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{20}H_{17}Cl_2FN_3O_4$ [M(^{35}Cl^{35}Cl)+H]$^+$ 452.0575, found 452.0570.

4-(6-Chloro-3-((1,3-dichloropropan-2-yl)oxy)-2-fluorobenzoyl)-*N*-(pyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (388)



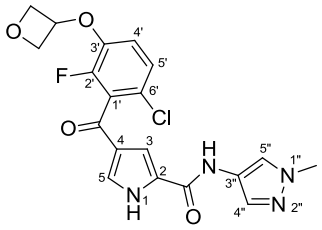
Compound **388** was synthesised according to general procedure U, using the following reagents: 4-(6-chloro-2-fluoro-3-(oxetan-3-yloxy)benzoyl)-1*H*-pyrrole-2-carboxylic acid (**386**) (50 mg, 0.15 mmol), 3-aminopyridine (35 mg, 0.37 mmol), phosphorus trichloride (13 µL, 20 mg, 0.15 mmol) and acetonitrile (0.8 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 4:6) to yield the *title compound* as a white solid (17 mg, 25%); R_f = 0.62 (petrol:EtOAc, 1:9); m.p. 182.5-184.5 °C; λ_{max} (EtOH)/nm 252.8, 293.0; IR (neat) ν_{max}/cm^{-1} 3237, 3123, 2961, 1636, 1599, 1554, 1533, 1462, 1423, 1276, 1234; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.97 (4H, qd, *J* = 12.0, 4.9 Hz, ArOCH(C*H*$_2$Cl)$_2$), 4.99 (1H, p, *J* = 4.9 Hz, ArOC*H*), 7.36 – 7.44 (2H, m, H-5' and H-5"), 7.48 – 7.56 (3H, m, H-3, H-5 and H-4'), 8.13 (1H, dd, *J* = 8.4, 1.8 Hz, H-4"), 8.30 (1H, d, *J* = 3.9 Hz, H-6"), 8.89 (1H, s, H-2"), 10.26 (1H, s, CON*H*Ar), 12.73 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 43.7 (ArOCH(*C*H$_2$Cl)$_2$), 78.4 (ArO*C*H), 111.5 (C-3), 119.3 (C-4'), 122.3 (d, *J* = 4.7 Hz, C-6'), 123.6 (C-5"), 125.1 (C-2 or C-4), 125.7 (d, *J* = 3.6 Hz, C-5'), 127.0 (C-4"), 128.2 (C-2 or C-4), 129.0 (d, *J* = 20.6 Hz, C-1'), 129.7 (C-5), 135.5 (C-3"), 141.6 (C-2"), 144.1 (d, *J* = 11.0 Hz, C-3'), 144.4 (C-6"), 149.1 (d, *J* = 248.2 Hz, C-2'), 158.7 (*C*ONHAr), 183.4 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -133.5 (ArF); LRMS (ES$^-$) *m/z* 468.2 [M(^{35}Cl^{35}Cl^{35}Cl)-H]$^-$, 470.2 [M(^{37}Cl^{35}Cl^{35}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{20}H_{16}Cl_3FN_3O_3$ [M(^{35}Cl^{35}Cl^{35}Cl)+H]$^+$ 470.0236, found 470.0230.

4-(6-Chloro-2-fluoro-3-(oxetan-3-yloxy)benzoyl)-*N*-(pyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (389)



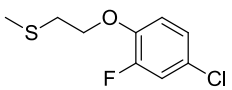
Compound **389** was synthesised according to general procedure Y, using the following reagents: 4-(6-chloro-2-fluoro-3-(oxetan-3-yloxy)benzoyl)-1*H*-pyrrole-2-carboxylic acid (**386**) (75 mg, 0.22 mmol), triethylamine (77 µL, 56 mg, 0.55 mmol), 2-chloro-1-methylpyridinium iodide (62 mg, 0.24 mmol), 3-aminopyridine (26 mg, 0.28 mmol) and DCM (2.2 mL). The crude yellow solid was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 1:9) to yield the *title compound* as a white solid (19 mg, 21%); R_f = 0.29 (petrol:EtOAc, 1:9); m.p. 148.5-150.5 °C; λ_{max} (EtOH)/nm 250.8, 293.2; IR (neat) ν_{max}/cm^{-1} 3259, 3121, 2955, 2876, 1638, 1598, 1553, 1534, 1465, 1422, 1271, 1233; ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.61 (2H, dd, *J* = 7.6, 4.8 Hz, ArOCHC*H*$_2$O), 4.95 (2H, t, *J* = 6.8 Hz, ArOCHC*H*$_2$O), 5.40 (1H, p, *J* = 5.5 Hz, ArOC*H*CH$_2$O), 7.00 (1H, dd, *J* = 9.0, 9.0 Hz, H-4'), 7.34 (1H, dd, *J* = 9.0, 1.6 Hz, H-5'), 7.39 (1H, dd, *J* = 8.3, 4.7 Hz, H-5"), 7.47 – 7.57 (2H, m, H-3 and H-5), 8.13 (1H, d, *J* = 8.3, H-4"), 8.30 (1H, d, *J* = 4.7 Hz, H-6"), 8.89 (1H, s, H-2"), 10.25 (1H, s, CON*H*Ar), 12.74 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 71.6 (ArO*C*HCH$_2$O), 76.4 (ArOCH*C*H$_2$O), 111.5 (C-3), 116.1 (C-4'), 121.3 (d, *J* = 4.9 Hz, C-6'), 123.6 (C-5"), 125.1 (C-2 or C-4), 125.7 (d, *J* = 3.5 Hz, C-5'), 127.0 (C-4"), 128.2 (C-2 or C-4), 128.9 (d, *J* = 20.0 Hz, C-1'), 129.7 (C-5), 135.5 (C-3"), 141.6 (C-2"), 143.6 (d, *J* = 11.0 Hz, C-3'), 144.4 (C-6"), 148.1 (d, *J* = 247.2 Hz, C-2'), 158.7 (*C*ONHAr), 183.4 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -135.3 (ArF); LRMS (ES$^-$) *m/z* 414.2 [M(^{35}Cl)-H]$^-$, 416.2 [M(^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{20}H_{16}ClFN_3O_4$ [M(^{35}Cl)+H]$^+$ 416.0808, found 416.0803.

4-(6-Chloro-2-fluoro-3-(oxetan-3-yloxy)benzoyl)-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-2-carboxamide, (390)



Compound **390** was synthesised according to general procedure Y, using the following reagents: 4-(6-chloro-2-fluoro-3-(oxetan-3-yloxy)benzoyl)-1*H*-pyrrole-2-carboxylic acid (**386**) (75 mg, 0.22 mmol), triethylamine (77 µL, 56 mg, 0.55 mmol), 2-chloro-1-methylpyridinium iodide (62 mg, 0.24 mmol), 1-methyl-1*H*-pyrazol-4-amine (**348**) (27 mg, 0.28 mmol) and DCM (2.2 mL). The crude yellow solid was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 1:9) to yield the *title compound* as a white solid (25 mg, 27%); R_f = 0.30 (petrol:EtOAc, 5:95); m.p. 141.5-143.5 °C; λ_{max} (EtOH)/nm 251.4; IR (neat) ν_{max}/cm^{-1} 3180, 3122, 2952, 2924, 2875, 1631, 1591, 1566, 1545, 1464, 1434, 1407, 1270, 1234; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.81 (3H, s, NCH_3), 4.61 (2H, dd, *J* = 7.4, 5.0 Hz, ArOCHCH_2O), 4.94 (2H, t, *J* = 6.9 Hz, ArOCHCH_2O), 5.40 (1H, p, *J* = 5.7 Hz, ArOC*H*CH$_2$O), 6.99 (1H, dd, *J* = 9.0, 8.9 Hz, H-4'), 7.31 (1H, s, H-3), 7.33 (1H, dd, *J* = 8.9, 1.3 Hz, H-5'), 7.45 (1H, s, H-5), 7.50 (1H, s, H-5"), 7.94 (1H, s, H-3"), 10.26 (1H, s, CON*H*Ar), 12.60 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 38.7 (N*C*H$_3$), 71.5 (ArO*C*HCH$_2$O), 76.4 (ArOCH*C*H$_2$O), 110.2 (C-3), 116.1 (C-4'), 121.2 (C-4"), 121.3 (d, *J* = 4.8 Hz, C-6'), 121.4 (C-3"), 125.0 (C-2 or C-4), 125.6 (d, *J* = 3.7 Hz, C-5'), 128.5 (C-2 or C-4), 128.9 (d, *J* = 17.2 Hz, C-1'), 129.0 (C-5), 129.9 (C-5"), 143.6 (d, *J* = 10.8 Hz, C-3'), 148.1 (d, *J* = 247.6 Hz, C-2'), 156.8 (*C*ONHAr), 183.4 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -135.3 (ArF); LRMS (ES$^-$) *m/z* 417.3 [M(^{35}Cl)-H]$^-$, 419.3 [M(^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{19}H_{17}ClFN_4O_4$ [M(^{35}Cl)+H]$^+$ 419.0917, found 419.0912.

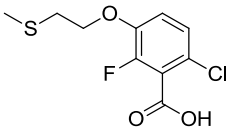
(2-(4-Chloro-2-fluorophenoxy)ethyl)(methyl)sulfane, (391)



Compound **391** was synthesised according to general procedure B', using the following reagents: 4-chloro-2-fluorophenol (**349**) (508 µL, 700 mg, 4.78 mmol), triphenylphosphine (1.88 g, 7.16 mmol), 2-(methylthio)ethanol (540 µL, 572 mg, 6.21 mmol), diethyl azodicarboxylate (1.13 mL, 1.25 g, 7.16 mmol) and THF (24 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 96:4) to yield the *title*

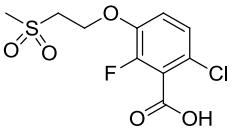
compound as a clear liquid (1.01 g, 95%); R_f = 0.40 (petrol:EtOAc, 95:5; $KMnO_4$); λ_{max} (EtOH)/nm 276.8; IR (neat) ν_{max}/cm^{-1} 2919, 1585, 1495, 1304, 1264, 1204, 1128; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.15 (3H, s, SCH_3), 2.85 (2H, t, J = 6.5 Hz, CH_2SCH$_3$), 4.22 (2H, t, J = 6.5 Hz, ArOCH_2), 7.17 – 7.27 (2H, m, H-5 and H-6), 7.41 – 7.45 (1H, m, H-3); ^{13}C NMR (126 MHz, DMSO-d_6) δ 15.3 (CH$_2$S*C*H$_3$), 32.0 (*C*H$_2$SCH$_3$), 68.5 (ArO*C*H$_2$), 116.1 (C-6), 116.6 (d, J = 21.7 Hz, C-3), 124.0 (d, J = 9.2 Hz, C-4), 124.7 (d, J = 3.8 Hz, C-5), 145.3 (d, J = 10.3 Hz, C-1), 151.4 (d, J = 247.8 Hz, C-2); ^{19}F NMR (471 MHz, DMSO-d_6) δ -131.5 (ArF); HRMS (APCI) calcd for $C_9H_{11}ClFOS$ [M(^{35}Cl)+H]$^+$ 221.0198, found 221.0198.

6-Chloro-2-fluoro-3-(2-(methylthio)ethoxy)benzoic acid, (392)



Compound **392** was synthesised according to general procedure A', using the following reagents: (2-(4-chloro-2-fluorophenoxy)ethyl)(methyl)sulfane (**391**) (1.05 g, 4.76 mmol), *n*-butyllithium (1.98 mL, 4.76 mmol) and THF (14.3 mL). The off-white solid (1.11 g, 88%) was used in the next step without further purification; R_f = 0.30 (petrol:EtOAc:AcOH, 50:49.7:0.3; $KMnO_4$); m.p. 98.0-100.0 °C; λ_{max} (EtOH)/nm 282.6; IR (neat) ν_{max}/cm^{-1} 2945, 1696, 1611, 1572, 1476, 1461, 1445, 1262; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.15 (3H, s, SCH_3), 2.86 (2H, t, J = 6.5 Hz, CH_2SCH$_3$), 4.26 (2H, t, J = 6.5 Hz, ArOCH_2), 7.28 – 7.34 (2H, m, H-4 and H-5), 14.13 (1H, s, ArCO$_2$*H*); ^{13}C NMR (126 MHz, DMSO-d_6) δ 15.3 (CH$_2$S*C*H$_3$), 31.9 (*C*H$_2$SCH$_3$), 68.7 (ArO*C*H$_2$), 116.4 (C-4), 120.2 (d, J = 4.6 Hz, C-6), 124.2 (d, J = 19.2 Hz, C-1), 125.4 (d, J = 3.9 Hz, C-5), 145.4 (d, J = 10.4 Hz, C-3), 148.0 (d, J = 249.5 Hz, C-2), 163.6 (Ar*C*O$_2$H); ^{19}F NMR (471 MHz, DMSO-d_6) δ -134.7 (ArF); LRMS (ES$^+$) *m/z* 264.9 [M(^{35}Cl)+H]$^+$, 266.9 [M(^{37}Cl)+H]$^+$; HRMS (NSI) calcd for $C_{10}H_{11}ClFO_3S$ [M(^{35}Cl)+H]$^+$ 265.0096, found 265.0099.

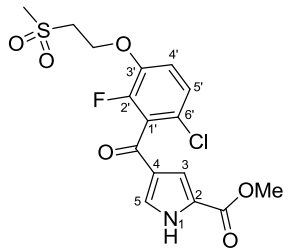
6-Chloro-2-fluoro-3-(2-(methylsulfonyl)ethoxy)benzoic acid, (393)



To 6-chloro-2-fluoro-3-(2-(methylthio)ethoxy)benzoic acid (**392**) (300 mg, 1.13 mmol) in MeOH (8 mL) was added a solution of OXONE® (monopersulfate compound) (1.04 g, 3.40 mmol) in water (4 mL). The resulting cloudy solution was stirred at RT for 24 h. The

reaction mixture was filtered through Celite and concentrated *in vacuo*. The white residue was dissolved in saturated aq. NH_4Cl (20 mL) and extracted with EtOAc (3 × 20 mL). The pooled organic extracts were washed with water and brine (30 mL, respectively), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel, DCM:MeOH:AcOH, 1:0:0 → 90:9.9:0.1) to yield the *title compound* as a white solid (300 mg, 89%); R_f = 0.25 (DCM:MeOH:AcOH, 90:9.9:0.1; $KMnO_4$); m.p. 180.0-182.0 °C; λ_{max} (EtOH)/nm 251.2, 293.4; IR (neat) ν_{max}/cm^{-1} 3150, 3100, 3040, 3011, 2983, 2927, 1744, 1618, 1579, 1482, 1468, 1267, 1235; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.08 (3H, s, CH_3SO$_2$CH$_2$), 3.68 (2H, t, *J* = 5.6 Hz, CH$_3$SO$_2$CH_2), 4.46 (2H, t, *J* = 5.6 Hz, CH_2OAr), 7.33 – 7.39 (2H, m, H-4 and H-5), 14.17 (1H, s, ArCO$_2$*H*); ^{13}C NMR (126 MHz, DMSO-d_6) δ 42.3 (*C*H$_3$SO$_2$CH$_2$), 53.1 (CH$_3$SO$_2$*C*H$_2$), 63.6 (*C*H$_2$OAr), 116.5 (C-4), 120.9 (d, *J* = 4.5 Hz, C-6), 124.3 (d, *J* = 19.1 Hz, C-1), 125.6 (d, *J* = 3.8 Hz, C-5), 144.8 (d, *J* = 10.5 Hz, C-3), 148.0 (d, *J* = 249.7 Hz, C-2), 163.5 (Ar*C*O$_2$H); ^{19}F NMR (471 MHz, DMSO-d_6) δ -134.70 (ArF); LRMS (ES$^-$) *m/z* 295.1 [M(^{35}Cl)-H]$^-$, 297.0 [M(^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{10}H_{11}ClFO_5S$ [M(^{35}Cl)+H]$^+$ 296.9994, found 296.9996.

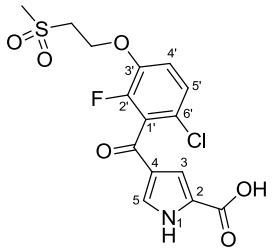
Methyl 4-(6-chloro-2-fluoro-3-(2-(methylsulfonyl)ethoxy)benzoyl)-1*H*-pyrrole-2-carboxylate, (394)



To a solution 6-chloro-2-fluoro-3-(2-(methylsulfonyl)ethoxy)benzoic acid (**393**) (600 mg, 2.02 mmol) in THF (5 mL), cooled at 0 °C, were added thionyl chloride (220 μL, 361 mg, 3.03 mmol) and *N*,*N*-dimethylformamide (16 μL, 15 mg, 0.20 mmol). The resulting solution was stirred at 0 °C for 30 min and allowed to warm to RT. After 5 h, the solvent was removed *in vacuo* and the crude residue dissolved in DCM (3 mL). The resulting solution was added to a suspension of aluminium trichloride (674 mg, 5.06 mmol) in DCM (7 mL), cooled at 0 °C, followed by methyl 1*H*-pyrrole-2-carboxylate (167 mg, 1.33 mmol). The resulting solution was stirred at 0 °C for 30 min and allowed to warm to RT. After 20 h, the reaction mixture was cooled to 0 °C and quenched by cautious addition of 1 M aq. HCl (10 mL). The resulting solution was stirred at RT for 2 h, diluted with water (15 mL) and extracted with DCM (3 × 30 mL). The pooled organic extracts were

washed with saturated aq. $NaHCO_3$ and brine (40 mL, respectively), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 4:6) to yield the *title compound* as a white solid (370 mg, 69%); R_f = 0.29 (petrol:EtOAc, 4:6); m.p. 72.0-74.0 °C; λ_{max} (EtOH)/nm 229.6, 282.0; IR (neat) ν_{max}/cm^{-1} 3274, 3126, 2952, 2929, 1708, 1651, 1559, 1461, 1441, 1390, 1272, 1230, 1199, 1125; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.06 (3H, s, CH_3SO$_2$CH$_2$), 3.68 (2H, t, *J* = 5.6 Hz, $CH_3SO_2CH_2$), 3.79 (3H, s, CO_2CH_3), 4.49 (2H, t, *J* = 5.6 Hz, CH_2OAr), 7.02 (1H, s, H-3), 7.36 – 7.43 (2H, m, H-4' and H-5'), 7.57 (1H, s, H-5), 12.89 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 42.2 ($CH_3SO_2CH_2$), 51.7 (CO_2CH_3), 53.1 ($CH_3SO_2CH_2$), 63.5 (CH_2OAr), 114.6 (C-3), 116.5 (C-4'), 121.0 (d, *J* = 4.7 Hz, C-6'), 124.6 (C-2 or C-4), 125.2 (C-2 or C-4), 125.7 (d, *J* = 3.4 Hz, C-5'), 128.4 (d, *J* = 19.8 Hz, C-1'), 130.4 (C-5), 144.8 (d, *J* = 10.8 Hz, C-3'), 148.1 (d, *J* = 247.2 Hz, C-2'), 160.3 (CO_2CH_3), 183.3 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -135.5 (ArF); LRMS (ES$^-$) *m/z* 404.2 [M(^{35}Cl)-H]$^-$, 406.2 [M(^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{16}H_{16}ClFNO_6S$ [M(^{35}Cl)+H]$^+$ 404.0365, found 404.0359.

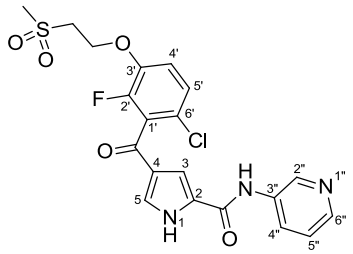
4-(6-Chloro-2-fluoro-3-(2-(methylsulfonyl)ethoxy)benzoyl)-1*H*-pyrrole-2-carboxylic acid, (395)



To methyl 4-(6-chloro-2-fluoro-3-(2-(methylsulfonyl)ethoxy)benzoyl)-1*H*-pyrrole-2-carboxylate (**394**) (300 mg, 0.74 mmol) in dioxane (6 mL) was added 4 M aq. HCl solution (6 mL) and the resulting solution was stirred for 70 h at 65 °C. Upon completion, the solvents were removed *in vacuo* to yield a yellow solid which was dissolved in saturated aq. $NaHCO_3$ (20 mL). The aqueous layer was washed with EtOAc (20 mL), then acidified to pH 1-2 using a 4 M aq. solution of HCl and extracted with EtOAc (3 × 25 mL). The pooled organic extracts were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The off-white solid (240 mg, 83%) was used in the next step without further purification; R_f = 0.28 (DCM:MeOH:AcOH, 90:9.9:0.1); m.p. 123.0-125.0 °C; λ_{max} (EtOH)/nm 229.6, 282.6; IR (neat) ν_{max}/cm^{-1} 3248, 3127, 2989, 2933, 1700, 1643, 1558, 1461, 1439, 1389, 1271, 1227; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.06 (3H, s, CH_3SO$_2$CH$_2$), 3.68 (2H, t, *J* = 5.6 Hz, $CH_3SO_2CH_2$), 4.49 (2H, t, *J* = 5.6 Hz,

C*H*$_2$OAr), 6.97 (1H, s, H-3), 7.36 – 7.43 (2H, m, H-4’ and H-5’), 7.46 – 7.51 (1H, m, H-5), 12.69 (1H, s, NH-pyrrole), 12.90 (1H, s, CO_2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 42.2 (*C*$H_3SO_2CH_2$), 53.1 ($CH_3SO_2CH_2$), 63.5 (*C*H_2OAr), 114.2 (C-3), 116.4 (C-4’), 121.1 (d, *J* = 4.8 Hz, C-6’), 125.1 (C-2 or C-4), 125.6 (d, *J* = 3.6 Hz, C-5’), 125.9 (C-2 or C-4), 128.5 (d, *J* = 19.9 Hz, C-1’), 129.9 (C-3), 144.8 (d, *J* = 10.8 Hz, C-3’), 148.1 (d, *J* = 247.2 Hz, C-2’), 161.3 (CO_2H), 183.2 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -135.5 (ArF); LRMS (ES$^+$) *m/z* 390.3 [M(^{35}Cl)+H]$^+$, 392.3 [M(^{37}Cl)+H]$^+$; HRMS (NSI) calcd for $C_{15}H_{14}ClFNO_6S$ [M(^{35}Cl)+H]$^+$ 390.0209, found 390.0212.

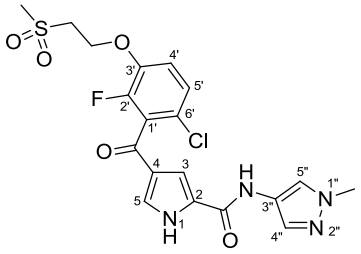
4-(6-Chloro-2-fluoro-3-(2-(methylsulfonyl)ethoxy)benzoyl)-*N*-(pyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (396)



Compound **396** was synthesised according to general procedure U, using the following reagents: 4-(6-chloro-2-fluoro-3-(2-(methylsulfonyl)ethoxy)benzoyl)-1*H*-pyrrole-2-carboxylic acid (**395**) (100 mg, 0.26 mmol), 3-aminopyridine (60 mg, 0.64 mmol), phosphorus trichloride (23 µL, 35 mg, 0.26 mmol) and acetonitrile (1.3 mL). The crude product was purified by column chromatography (silica gel, DCM:MeOH, 1:0 → 95:5) to yield the *title compound* as a white solid (48 mg, 40%); R_f = 0.32 (DCM:MeOH, 95:5); m.p. 238.0-240.0 °C; λ_{max} (EtOH)/nm 255.6, 292.2; IR (neat) ν_{max}/cm^{-1} 3349, 3116, 2922, 2852, 1639, 1589, 1571, 1537, 1426, 1397, 1304, 1286, 1231; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.97 (3H, s, C*H*$_3$SO$_2$CH$_2$), 3.67 (2H, t, *J* = 7.0 Hz, CH$_3$SO$_2$C*H*$_2$), 4.78 (2H, t, *J* = 7.0 Hz, C*H*$_2$OAr), 7.09 (1H, dd, *J* = 9.0, 8.7 Hz, H-4’), 7.22 (1H, d, *J* = 8.7 Hz, H-5’), 7.38 (1H, dd, *J* = 8.2, 4.7 Hz, H-5”), 7.54 (1H, s, H-3), 7.79 (1H, s, H-5), 8.12 (1H, d, *J* = 8.2 Hz, H-4”), 8.30 (1H, d, *J* = 4.7 Hz, H-6”), 8.86 (1H, s, H-2”), 10.30 (1H, s, CON*H*Ar), 10.51 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 40.7 (*C*$H_3SO_2CH_2$), 43.2 ($CH_3SO_2CH_2$), 54.0 (*C*H_2OAr), 114.5 (C-3), 118.4 (d, *J* = 5.0 Hz, C-6’), 119.0 (d, *J* = 3.0 Hz, C-4’), 122.9 (C-2 or C-4), 123.5 (C-5”), 125.5 (d, *J* = 3.5 Hz, C-5’), 126.8 (C-2 or C-4), 127.4 (C-4”), 128.4 (d, *J* = 19.8 Hz, C-1’), 135.1 (C-5), 135.4 (C-3”), 142.0 (C-2”), 144.4 (d, *J* = 11.9 Hz, C-3’), 144.5 (C-6”), 147.6 (d, *J* = 244.1 Hz, C-2’), 159.2 (*C*ONHAr), 183.7 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -136.9 (ArF);

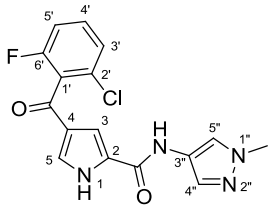
LRMS (ES^+) *m/z* 466.3 [M(^{35}Cl)+H]$^+$, 468.3 [M(^{37}Cl)+H]$^+$; HRMS (NSI) calcd for $C_{20}H_{18}ClFN_3O_5S$ [M(^{35}Cl)+H]$^+$ 466.0634, found 466.0627.

4-(6-Chloro-2-fluoro-3-(2-(methylsulfonyl)ethoxy)benzoyl)-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-2-carboxamide, (397)



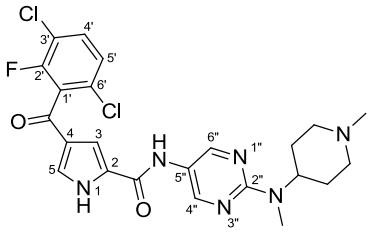
Compound **397** was synthesised according to general procedure U, using the following reagents: 4-(6-chloro-2-fluoro-3-(2-(methylsulfonyl)ethoxy)benzoyl)-1*H*-pyrrole-2-carboxylic acid (**395**) (100 mg, 0.26 mmol), 1-methyl-1*H*-pyrazol-4-amine (**348**) (66 mg, 0.68 mmol), phosphorus trichloride (23 µL, 35 mg, 0.26 mmol) and acetonitrile (1.3 mL). The crude product was purified by column chromatography (silica gel, DCM:MeOH, 1:0 → 95:5) to yield the *title compound* as a white solid (41 mg, 35%); R_f = 0.33 (DCM:MeOH, 95:5); m.p. 253.5-255.5 °C; λ_{max} (EtOH)/nm 253.4; IR (neat) ν_{max}/cm^{-1} 3373, 3119, 2923, 1657, 1619, 1555, 1539, 1492, 1393, 1374, 1303, 1254; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.98 (3H, s, CH_3SO$_2$CH$_2$), 3.66 (2H, t, *J* = 7.1 Hz, CH$_3$SO$_2$CH_2), 3.81 (3H, s, NCH_3), 4.77 (2H, t, *J* = 7.1 Hz, CH_2OAr), 7.08 (1H, dd, *J* = 9.0, 9.0 Hz, H-4'), 7.19 – 7.23 (1H, m, H-5'), 7.37 (1H, s, H-3), 7.49 (1H, s, H-5"), 7.74 (1H, s, H-5), 7.98 (1H, s, H-3"), 10.32 (1H, s, CONHAr), 10.51 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 38.6 (NCH$_3$), 40.7 (CH$_3$SO$_2$CH$_2$), 43.1 (CH$_3$SO$_2$CH$_2$), 54.1 (CH$_2$OAr), 113.3 (C-3), 118.3 (d, *J* = 4.5 Hz, C-6'), 119.0 (d, *J* = 3.4 Hz, C-4'), 121.1 (C-4"), 121.6 (C-3"), 122.9 (C-2 or C-4), 125.5 (d, *J* = 3.5 Hz, C-5'), 127.0 (C-2 or C-4), 128.4 (d, *J* = 20.0 Hz, C-1'), 130.0 (C-5"), 134.4 (C-5), 144.5 (d, *J* = 10.9 Hz, C-3'), 147.6 (d, *J* = 244.1 Hz, C-2'), 157.2 (CONHAr), 183.7 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -137.0 (ArF); LRMS (ES^+) *m/z* 469.3 [M(^{35}Cl)+H]$^+$, 471.3 [M(^{37}Cl)+H]$^+$; HRMS (NSI) calcd for $C_{19}H_{19}ClFN_4O_5S$ [M(^{35}Cl)+H]$^+$ 469.0743, found 469.0737.

4-(2-Chloro-6-fluorobenzoyl)-*N*-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrole-2-carboxamide, (398)



Compound **398** was synthesised according to general procedure U, using the following reagents: 4-(2-chloro-6-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**249**) (100 mg, 0.37 mmol), 1-methyl-1*H*-pyrazol-4-amine (**348**) (91 mg, 0.94 mmol), phosphorus trichloride (34 µL, 51 mg, 0.37 mmol) and acetonitrile (1.85 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 1:9) to yield the *title compound* as a white solid (80 mg, 62%); R_f = 0.32 (petrol:EtOAc, 1:9); m.p. 218.5-220.5 °C; λ_{max} (EtOH)/nm 257.0; IR (neat) ν_{max}/cm^{-1} 3346, 3164, 3126, 2973, 2928, 2858, 1626, 1590, 1570, 1543, 1442, 1397, 1274, 1238; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.81 (3H, s, NCH_3), 7.29 (1H, s, H-3), 7.39 (1H, dd, *J* = 8.7, 8.7 Hz, H-5'), 7.42 (1H, s, H-5), 7.46 (1H, d, *J* = 8.1 Hz, H-3'), 7.50 (1H, s, H-5"), 7.57 (1H, ddd, *J* = 8.7, 8.1 and 6.4 Hz, H-4'), 7.94 (1H, s, H-3"), 10.25 (1H, s, CON*H*Ar), 12.57 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 38.7 (N*C*H$_3$), 110.3 (C-3), 114.9 (d, *J* = 21.5 Hz, C-5'), 121.2 (C-4"), 121.4 (C-3"), 125.2 (C-2 or C-4), 125.8 (d, *J* = 3.1 Hz, C-3'), 128.1 (d, *J* = 23.1 Hz, C-1'), 128.5 (C-2 or C-4), 128.6 (C-5), 129.9 (C-5"), 130.5 (d, *J* = 6.1 Hz, C-2'), 131.8 (d, *J* = 9.0 Hz, C-4'), 156.8 (*C*ONHAr), 158.6 (d, *J* = 247.0 Hz, C-6'), 183.9 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -114.3 (ArF); LRMS (ES$^+$) *m/z* 347.3 [M(^{35}Cl)+H]$^+$, 349.3 [M(^{37}Cl)+H]$^+$; HRMS (NSI) calcd for $C_{16}H_{13}ClFN_4O_2$ [M(^{35}Cl)+H]$^+$ 347.0706, found 347.0707.

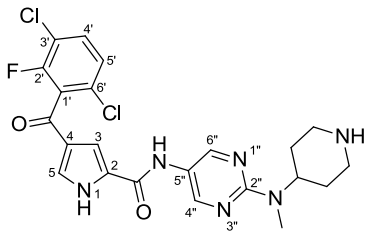
4-(3,6-Dichloro-2-fluorobenzoyl)-*N*-(2-(methyl(1-methylpiperidin-4-yl)amino) pyrimidin-5-yl)-1*H*-pyrrole-2-carboxamide, (403)



Compound **403** was synthesised according to general procedure Y, using the following reagents: 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**) (100 mg, 0.33 mmol), triethylamine (115 µL, 84 mg, 0.83 mmol), 2-chloro-1-methylpyridinium iodide (93 mg, 0.36 mmol), N^2-methyl-N^2-(1-methylpiperidin-4-yl)pyrimidine-2,5-diamine

(**419**) (92 mg, 0.41 mmol) and DCM (3.3 mL). The crude yellow solid was purified by column chromatography (amine silica gel, DCM:MeOH, 1:0 → 97:3) to yield the *title compound* as a white solid (75 mg, 45%); R_f = 0.18 (amine silica, DCM:MeOH, 97:3); m.p. 178.5-180.5 °C; λ_{max} (EtOH)/nm 284.4; IR (neat) ν_{max}/cm^{-1} 3175, 2981, 2954, 2890, 2797, 1663, 1645, 1591, 1552, 1519, 1486, 1448, 1404, 1296; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.40 – 1.63 (2H, m, CH_2CH$_2$NMe), 1.80 (2H, dddd, *J* = 12.2, 12.2, 12.2 and 3.7 Hz, CH_2CH$_2$NMe), 1.93 – 2.11 (2H, m, CH$_2$CH_2NMe), 2.21 (3H, s, NCH_3), 2.88 (2H, d, *J* = 12.2 Hz, CH$_2$CH_2NMe), 2.96 (3H, s, NCH_3), 4.52 (1H, tt, *J* = 12.3, 3.7 Hz, ArN(CH$_3$)C*H*), 7.40 (1H, s, H-3), 7.52 (2H, dd, *J* = 8.8, 1.0 Hz, H-5'), 7.60 (1H, s, H-5), 7.78 (1H, dd, *J* = 8.8, 8.4 Hz, H-4'), 8.57 (2H, s, H-4", 6"), 10.01 (1H, s, CON*H*Ar), 12.74 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 28.2 (N*C*H$_3$) , 28.8 (*C*H$_2$CH$_2$NMe), 45.7 (N*C*H$_3$), 51.7 (ArN(CH$_3$)*C*H), 54.9 (CH$_2$*C*H$_2$NMe), 111.0 (C-3), 119.3 (d, *J* = 18.1 Hz, C-3'), 122.9 (C-5"), 124.7 (C-2 or C-4), 126.9 (d, *J* = 3.8 Hz, C-5'), 128.4 (C-2 or C-4), 129.2 (d, *J* = 22.8 Hz, C-1'), 129.2 (d, *J* = 5.1 Hz, C-6'), 129.8 (C-5), 131.8 (C-4'), 151.3 (C-4", 6"), 153.8 (d, *J* = 248.4 Hz, C-2'), 158.4 (*C*ONHAr), 182.6 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.7 (ArF); LRMS (ES$^-$) *m/z* 503.3 [M(^{35}Cl^{35}Cl)-H]$^-$, 505.3 [M(^{35}Cl^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{23}H_{24}Cl_2FN_6O_2$ [M(^{35}Cl^{35}Cl)+H]$^+$ 505.1316, found 505.1304.

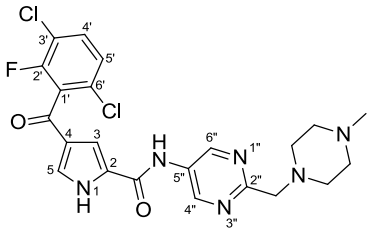
4-(3,6-Dichloro-2-fluorobenzoyl)-*N*-(2-(methyl(piperidin-4-yl)amino)pyrimidin-5-yl)-1*H*-pyrrole-2-carboxamide, (404)



Compound **404** was synthesised according to general procedure F', using the following reagents: *tert*-butyl 4-((5-(4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxamido)pyrimidin-2-yl)(methyl)amino)piperidine-1-carboxylate (**417**) (100 mg, 0.17 mmol), triethylsilane (68 µL, 49 mg, 0.42 mmol), TFA (0.85 mL) and DCM (0.85 mL). The crude yellow solid was purified by column chromatography (amine silica gel, DCM:MeOH, 1:0 → 95:5) to yield the *title compound* as a white solid (62 mg, 75%); R_f = 0.31 (amine silica, DCM:MeOH, 95:5); m.p. 182.5-184.5 °C; λ_{max} (EtOH)/nm 290.2; IR (neat) ν_{max}/cm^{-1} 3166, 3126, 2981, 2955, 1667, 1647, 1593, 1557, 1519, 1484, 1449, 1405, 1381, 1301; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.42 – 1.56 (2H, m, CH_2CH$_2$NH), 1.62 (2H, dddd, *J* = 12.1, 12.1, 12.1 and 4.2 Hz, CH_2CH$_2$NH), 2.56 (2H, ddd, *J* = 12.1,

12.1 and 2.6 Hz, CH_2CH_2NH), 2.95 (3H, s, NCH_3), 2.98 – 3.09 (2H, m, CH_2CH_2NH), 4.61 (1H, tt, *J* = 12.1, 4.2 Hz, $ArN(CH_3)CH$), 7.37 (1H, s, H-3), 7.51 (1H, dd, *J* = 8.8, 1.4 Hz, H-5'), 7.58 (1H, s, H-5), 7.77 (1H, dd, *J* = 8.8, 8.4 Hz, H-4'), 8.57 (2H, s, H-4", 6"), 9.98 (1H, s, CONHAr); ^{13}C NMR (126 MHz, DMSO-d_6) δ 28.8 (NCH_3), 29.8 (CH_2CH_2NH), 45.8 (CH_2CH_2NH), 52.4 ($ArN(CH_3)CH$), 111.0 (C-3), 119.3 (d, *J* = 17.7 Hz, C-3'), 122.9 (C-5"), 124.8 (C-2 or C-4), 126.9 (d, *J* = 3.9 Hz, C-5'), 128.7 (C-2 or C-4), 129.2 (d, *J* = 5.5 Hz, C-6'), 129.3 (d, *J* = 23.1 Hz, C-1'), 130.0 (C-5), 131.8 (C-4'), 151.3 (C-4", 6"), 153.8 (d, *J* = 248.3 Hz, C-2'), 158.3 (CONHAr or C-2"), 158.6 (CONHAr or C-2"), 182.5 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.7 (ArF); LRMS (ES^-) *m/z* 489.3 $[M(^{35}Cl^{35}Cl)-H]^-$, 491.3 $[M(^{35}Cl^{37}Cl)-H]^-$; HRMS (NSI) calcd for $C_{22}H_{22}Cl_2FN_6O_2$ $[M(^{35}Cl^{35}Cl)+H]^+$ 491.1160, found 491.1151.

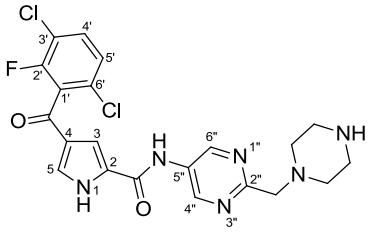
4-(3,6-Dichloro-2-fluorobenzoyl)-*N*-(2-((4-methylpiperazin-1-yl)methyl)pyrimidin-5-yl)-1*H*-pyrrole-2-carboxamide, (405)



Compound **405** was synthesised according to general procedure E', using the following reagents: *tert*-butyl 4-((5-(4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxamido)pyrimidin-2-yl)methyl)piperazine-1-carboxylate (**439**) (60 mg, 0.10 mmol), formic acid (0.5 mL) and formaldehyde (37 % wt. in water) (31 µL, 0.42 mmol). The crude yellow solid was purified by column chromatography (amine silica gel, DCM:MeOH, 1:0 → 96:4) to yield the *title compound* as a white solid (36 mg, 71%); R_f = 0.30 (amine silica, DCM:MeOH, 96:4); m.p. 183.0-185.0 °C; λ_{max} (EtOH)/nm 293.0; IR (neat) ν_{max}/cm^{-1} 2935, 2802, 1641, 1581, 1557, 1515, 1447, 1280; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.13 (3H, s, NCH_3), 2.29 (4H, brs, $NCH_{2\ piperazine}$), 2.47 (4H, brs, $NCH_{2\ piperazine}$), 3.64 (2H, s, $ArCH_2N$), 7.50 (1H, s, H-3), 7.52 (1H, dd, *J* = 8.8, 1.4 Hz, H-5'), 7.67 (1H, s, H-5), 7.79 (1H, dd, *J* = 8.8, 8.4 Hz, H-4'), 9.07 (2H, s, H-4", 6"), 10.41 (1H, s, CONHAr), 12.85 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 45.7 (NCH_3), 52.5 ($NCH_{2\ piperazine}$), 54.7 ($NCH_{2\ piperazine}$), 63.9 ($ArCH_2N$), 111.9 (C-3), 119.4 (d, *J* = 18.1 Hz, C-3'), 124.8 (C-2 or C-4), 126.9 (d, *J* = 3.8 Hz, C-5'), 128.0 (C-2 or C-4), 129.1 (d, *J* = 23.2 Hz, C-1'), 129.2 (d, *J* = 5.4 Hz, C-6'), 130.5 (C-5), 131.9 (C-4'), 132.4 (C-5"), 147.9 (C-4", 6"), 153.8 (d, *J* = 248.7 Hz, C-2'), 158.7 (CONHAr), 161.4 (C-2"), 182.6 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.7 (ArF); LRMS (ES^+) *m/z* 491.4

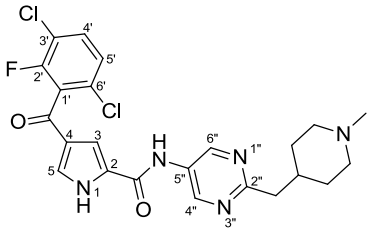
$[M(^{35}Cl^{35}Cl)+H]^+$, 493.4 $[M(^{35}Cl^{37}Cl)+H]^+$; HRMS (NSI) calcd for $C_{22}H_{22}Cl_2FN_6O_2$ $[M(^{35}Cl^{35}Cl)+H]^+$ 491.1160, found 491.1154.

4-(3,6-Dichloro-2-fluorobenzoyl)-*N*-(2-(piperazin-1-ylmethyl)pyrimidin-5-yl)-1*H*-pyrrole-2-carboxamide, (406)



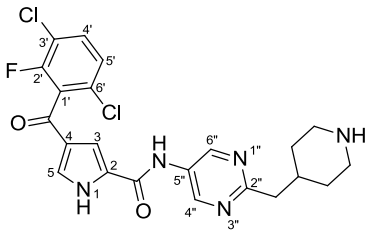
Compound **406** was synthesised according to general procedure F', using the following reagents: *tert*-butyl 4-((5-(4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxamido) pyrimidin-2-yl)methyl)piperazine-1-carboxylate (**439**) (60 mg, 0.10 mmol), triethylsilane (41 µL, 30 mg, 0.26 mmol), TFA (0.5 mL) and DCM (0.5 mL). The crude yellow solid was purified by column chromatography (amine silica gel, DCM:MeOH, 1:0 → 94:6) to yield the *title compound* as an off-white solid (35 mg, 70%); R_f = 0.29 (amine silica, DCM:MeOH, 94:6); m.p. 239.5-241.5 °C; λ_{max} (EtOH)/nm 266.0, 293.2; IR (neat) ν_{max}/cm^{-1} 3069, 2932, 2812, 1639, 1581, 1558, 1510, 1444, 1389, 1268; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.41 (4H, brs, NCH_2 $_{piperazine}$), 2.70 (4H, t, *J* = 4.9 Hz, NCH_2 $_{piperazine}$), 3.63 (2H, s, ArCH_2N), 7.48 (1H, s, H-3), 7.52 (1H, dd, *J* = 8.7, 1.4 Hz, H-5'), 7.66 (1H, s, H-5), 7.78 (1H, dd, *J* = 8.7, 8.4 Hz, H-4'), 9.08 (2H, s, H-4", 6"), 10.41 (1H, s, CON*H*Ar); ^{13}C NMR (126 MHz, DMSO-d_6) δ 45.3 (N*C*H$_2$ $_{piperazine}$), 53.6 (N*C*H$_2$ $_{piperazine}$), 64.5 (Ar*C*H$_2$N), 112.0 (C-3), 119.3 (d, *J* = 17.9 Hz, C-3'), 124.9 (C-2 or C-4), 126.9 (d, *J* = 3.8 Hz, C-5'), 128.3 (C-2 or C-4), 129.2 (d, *J* = 23.1 Hz, C-1'), 129.2 (d, *J* = 5.1 Hz, C-6'), 130.7 (C-5), 131.9 (C-4'), 132.4 (C-5"), 147.8 (C-4", 6"), 153.8 (d, *J* = 248.5 Hz, C-2'), 158.9 (*C*ONHAr), 161.3 (C-2"), 182.5 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.7 (ArF); LRMS (ES^+) *m/z* 473.3 $[M(^{35}Cl^{35}Cl)+H]^+$, 475.3 $[M(^{35}Cl^{37}Cl)+H]^+$; HRMS (NSI) calcd for $C_{21}H_{20}Cl_2FN_6O_2$ $[M(^{35}Cl^{35}Cl)+H]^+$ 477.1003, found 477.0999.

4-(3,6-Dichloro-2-fluorobenzoyl)-*N*-(2-((1-methylpiperidin-4-yl)methyl)pyrimidin-5-yl)-1*H*-pyrrole-2-carboxamide, (407)



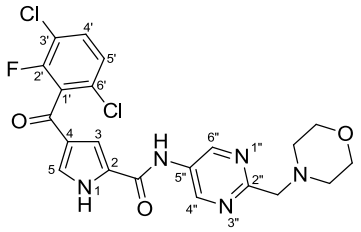
Compound **407** was synthesised according to general procedure E', using the following reagents: *tert*-butyl 4-((5-(4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxamido) pyrimidin-2-yl)methyl)piperidine-1-carboxylate (**429**) (165 mg, 0.29 mmol), formic acid (1.45 mL) and formaldehyde (37 % wt. in water) (85 µL, 1.14 mmol). The crude yellow solid was purified by column chromatography (amine silica gel, DCM:MeOH, 1:0 → 97:3) to yield the *title compound* as a white solid (100 mg, 72%); R_f = 0.30 (amine silica, DCM:MeOH, 97:3); m.p. 146.5-148.5 °C; λ_{max} (EtOH)/nm 266.0, 293.2; IR (neat) ν_{max}/cm^{-1} 2923, 2849, 2788, 1637, 1580, 1558, 1511, 1444, 1391, 1272; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.24 (2H, dddd, *J* = 12.3, 12.3, 12.3 and 3.6 Hz, C*H*$_2$CH$_2$NCH$_3$), 1.52 (2H, d, *J* = 12.3 Hz, C*H*$_2$CH$_2$NCH$_3$), 1.80 (3H, dd, *J* = 12.3, 12.3 Hz, CH$_2$C*H*$_2$NCH$_3$ and ArCH$_2$C*H*), 2.11 (3H, s, NC*H*$_3$), 2.70 (2H, d, *J* = 12.3 Hz, CH$_2$C*H*$_2$NCH$_3$), 2.75 (2H, d, *J* = 7.1 Hz, ArC*H*$_2$CH), 7.48 (1H, s, H-3), 7.52 (1H, dd, *J* = 8.7, 1.3 Hz, H-5'), 7.65 (1H, s, H-5), 7.78 (1H, dd, *J* = 8.7, 8.4 Hz, H-4'), 9.02 (2H, s, H-4", 6"), 10.35 (1H, s, CON*H*Ar), 12.79 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 31.7 (*C*H$_2$CH$_2$NCH$_3$), 34.9 (ArCH$_2$*C*H), 44.9 (Ar*C*H$_2$CH), 46.2 (N*C*H$_3$), 55.3 (CH$_2$*C*H$_2$NMe), 111.8 (C-3), 119.4 (d, *J* = 18.1 Hz, C-3'), 124.8 (C-2 or C-4), 126.9 (d, *J* = 3.9 Hz, C-5'), 128.1 (C-2 or C-4), 129.2 (d, *J* = 23.3 Hz, C-1'), 129.2 (d, *J* = 5.0 Hz, C-6'), 130.5 (C-5), 131.7 (C-4'), 131.9 (C-5"), 148.1 (C-4", 6"), 153.9 (d, *J* = 248.7 Hz, C-2'), 158.7 (*C*ONHAr), 163.9 (C-2"), 182.6 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.6 (ArF); LRMS (ES$^+$) *m/z* 477.3 [M(^{35}Cl^{35}Cl)+H]$^+$, 479.3 [M(^{35}Cl^{37}Cl)+H]$^+$; HRMS (NSI) calcd for $C_{23}H_{23}Cl_2FN_5O_2$ [M(^{35}Cl^{35}Cl)+H]$^+$ 490.1207 found 490.1201.

4-(3,6-Dichloro-2-fluorobenzoyl)-*N*-(2-(piperidin-4-ylmethyl)pyrimidin-5-yl)-1*H*-pyrrole-2-carboxamide, (408)



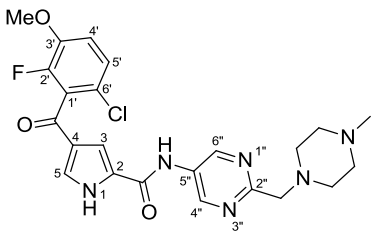
Compound **408** was synthesised according to general procedure F', using the following reagents: *tert*-butyl 4-((5-(4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxamido) pyrimidin-2-yl)methyl)piperidine-1-carboxylate (**429**) (165 mg, 0.29 mmol), triethylsilane (114 µL, 83 mg, 0.71 mmol), TFA (1.45 mL) and DCM (1.45 mL). The crude yellow solid was purified by column chromatography (amine silica gel, DCM:MeOH, 1:0 → 95:5) to yield the *title compound* as a white solid (86 mg, 63%); R_f = 0.31 (amine silica, DCM:MeOH, 95:5); m.p. No clear m.p. Decomposition range 265-275 °C; λ_{max} (EtOH)/nm 270.4, 293.0; IR (neat) ν_{max}/cm^{-1} 2919, 1639, 1588, 1561, 1509, 1495, 1443, 1390, 1270; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.14 (2H, dddd, *J* = 12.4, 12.4, 12.4 and 3.8 Hz, C*H*$_2$CH$_2$NH), 1.52 (2H, d, *J* = 11.1 Hz, C*H*$_2$CH$_2$NH), 1.96 (1H, ttt, *J* = 12.4, 7.4 and 3.8 Hz, ArCH$_2$C*H*), 2.40 – 2.49 (2H, m, CH$_2$C*H*$_2$NH), 2.74 (2H, d, *J* = 7.4 Hz, ArC*H*$_2$CH), 2.94 (2H, d, *J* = 12.4 Hz, CH$_2$C*H*$_2$NH), 7.39 (1H, s, H-3), 7.51 (1H, dd, *J* = 8.9, 1.4 Hz, H-5'), 7.60 (1H, s, H-5), 7.77 (1H, dd, *J* = 8.9, 8.4 Hz, H-4'), 9.03 (2H, s, H-4", 6"), 10.31 (1H, s, CON*H*Ar); ^{13}C NMR (126 MHz, DMSO-d_6) δ 32.2 (*C*H$_2$CH$_2$NH), 35.6 (ArCH$_2$*C*H), 45.4 (Ar*C*H$_2$CH), 45.6 (CH$_2$*C*H$_2$NH), 112.1 (C-3), 119.3 (d, *J* = 18.1 Hz, C-3'), 125.0 (C-2 or C-4), 126.8 (d, *J* = 3.8 Hz, C-5'), 129.3 (d, *J* = 5.2 Hz, C-6'), 129.3 (C-2 or C-4), 129.5 (d, *J* = 22.8 Hz, C-1'), 131.5 (C-5), 131.7 (C-4'), 131.8 (C-5"), 147.9 (C-4", 6"), 153.8 (d, *J* = 248.2 Hz, C-2'), 159.3 (CON*H*Ar), 163.6 (C-2"), 182.2 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.6 (ArF); LRMS (ES$^+$) *m/z* 476.3 [M(^{35}Cl^{35}Cl)+H]$^+$, 478.3 [M(^{35}Cl^{37}Cl)+H]$^+$; HRMS (NSI) calcd for $C_{22}H_{21}Cl_2FN_5O_2$ [M(^{35}Cl^{35}Cl)+H]$^+$ 476.1051, found 476.1045.

4-(3,6-Dichloro-2-fluorobenzoyl)-*N*-(2-(morpholinomethyl)pyrimidin-5-yl)-1*H*-pyrrole-2-carboxamide, (409)



Compound **409** was synthesised according to general procedure Y, using the following reagents: 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**) (80 mg, 0.26 mmol), triethylamine (92 µL, 67 mg, 0.66 mmol), 2-chloro-1-methylpyridinium iodide (74 mg, 0.29 mmol), 2-(morpholinomethyl)pyrimidin-5-amine (**442**) (64 mg, 0.33 mmol) and DCM (2.6 mL). The crude yellow solid was purified by column chromatography (silica gel, DCM:MeOH, 1:0 → 95:5) to yield the *title compound* as a white solid (20 mg, 16%); R_f = 0.28 (DCM:MeOH, 97:3); m.p. 158.5-160.5 °C; λ_{max} (EtOH)/nm 292.6; IR (neat) ν_{max}/cm^{-1} 3125, 2960, 2924, 2857, 2819, 1641, 1585, 1557, 1517, 1447, 1392, 1272; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.43 – 2.49 (4H, m, NCH_2 morpholine), 3.52 – 3.59 (4H, m, CH_2O morpholine), 3.66 (2H, s, ArCH_2N), 7.50 (1H, s, H-3), 7.51 – 7.55 (1H, m, H-5'), 7.68 (1H, s, H-5), 7.79 (1H, dd, *J* = 8.7, 8.4 Hz, H-4'), 9.08 (2H, s, H-4", 6"), 10.43 (1H, s, CON*H*Ar), 12.87 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 53.2 (N*C*H$_2$ morpholine), 64.2 (Ar*C*H$_2$N), 66.2 (*C*H$_2$O morpholine), 111.9 (C-3), 119.4 (d, *J* = 17.9 Hz, C-3'), 124.9 (C-2 or C-4), 126.9 (d, *J* = 3.8 Hz, C-5'), 128.0 (C-2 or C-4), 129.1 (d, *J* = 24.3 Hz, C-1'), 129.2 (d, *J* = 5.5 Hz, C-6'), 130.6 (C-5), 131.9 (C-4'), 132.5 (C-5"), 147.9 (C-4", 6"), 153.9 (d, *J* = 248.7 Hz, C-2'), 158.8 (*C*ONHAr), 161.1 (C-2"), 182.6 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.7 (ArF); LRMS (ES$^+$) *m/z* 478.3 [M(^{35}Cl^{35}Cl)+H]$^+$, 480.3 [M(^{35}Cl^{37}Cl)+H]$^+$; HRMS (NSI) calcd for $C_{21}H_{19}Cl_2FN_5O_3$ [M(^{35}Cl^{35}Cl)+H]$^+$ 478.0843, found 478.0838.

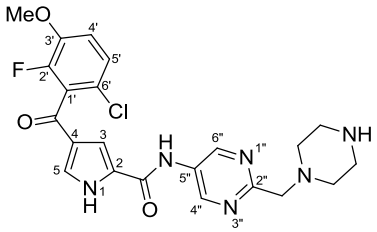
4-(6-Chloro-2-fluoro-3-methoxybenzoyl)-*N*-(2-((4-methylpiperazin-1-yl)methyl) pyrimidin-5-yl)-1*H*-pyrrole-2-carboxamide, (410)



Compound **410** was synthesised according to general procedure E', using the following reagents: *tert*-butyl 4-((5-(4-(6-chloro-2-fluoro-3-methoxybenzoyl)-1*H*-pyrrole-2-

carboxamido)pyrimidin-2-yl)methyl)piperazine-1-carboxylate (**440**) (50 mg, 0.09 mmol), formic acid (0.45 mL) and formaldehyde (37 % wt. in water) (26 µL, 0.35 mmol). The crude yellow solid was purified by column chromatography (amine silica gel, DCM:MeOH, 1:0 → 96:4) to yield the *title compound* as a white solid (31 mg, 76%); R_f = 0.26 (amine silica, DCM:MeOH, 96:4); m.p. 210.0-212.0 °C; λ_{max} (EtOH)/nm 292.6; IR (neat) ν_{max}/cm^{-1} 2936, 2803, 1641, 1577, 1555, 1517, 1472, 1438, 1271; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.13 (3H, s, NCH_3), 2.29 (4H, brs, NC$H_{2\ piperazine}$), 2.47 (4H, brs, NC$H_{2\ piperazine}$), 3.64 (2H, s, ArCH_2N), 3.90 (3H, s, ArOCH_3), 7.33 (1H, dd, *J* = 9.0, 9.0 Hz, H-4'), 7.39 (1H, dd, *J* = 9.0, 1.4 Hz, H-5'), 7.46 (1H, s, H-3), 7.54 (1H, s, H-5), 9.07 (2H, s, H-4", 6"), 10.41 (1H, s, CON*H*Ar), 12.79 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 45.7 (NCH_3), 52.5 (N*C*H$_{2\ piperazine}$), 54.7 (N*C*H$_{2\ piperazine}$), 56.5 (ArO*C*H$_3$), 63.9 (ArCH_2N), 112.1 (C-3), 115.2 (C-4'), 120.2 (d, *J* = 5.0 Hz, C-6'), 125.2 (C-2 or C-4), 125.6 (d, *J* = 3.3 Hz, C-5'), 127.7 (C-2 or C-4), 128.4 (d, *J* = 19.8 Hz, C-1'), 129.7 (C-5), 132.4 (C-5"), 146.4 (d, *J* = 10.7 Hz, C-3'), 147.9 (C-4", 6"), 147.9 (d, *J* = 247.4 Hz, C-2'), 158.7 (*C*ONHAr), 161.4 (C-2"), 183.7 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -136.1 (ArF); LRMS (ES$^+$) *m/z* 487.4 [M(^{35}Cl)+H]$^+$, 489.4 [M(^{37}Cl)+H]$^+$; HRMS (NSI) calcd for $C_{23}H_{25}ClFN_6O_3$ [M(^{35}Cl)+H]$^+$ 487.1647, found 487.1655.

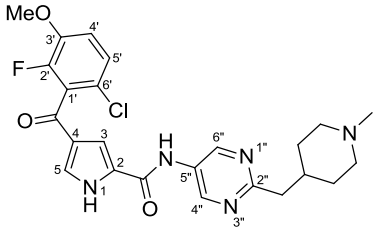
4-(6-Chloro-2-fluoro-3-methoxybenzoyl)-*N*-(2-(piperazin-1-ylmethyl)pyrimidin-5-yl)-1*H*-pyrrole-2-carboxamide, (411)



Compound **411** was synthesised according to general procedure F', using the following reagents: *tert*-butyl 4-((5-(4-(6-chloro-2-fluoro-3-methoxybenzoyl)-1*H*-pyrrole-2-carboxamido)pyrimidin-2-yl)methyl)piperazine-1-carboxylate (**440**) (50 mg, 0.09 mmol), triethylsilane (35 µL, 25 mg, 0.22 mmol), TFA (0.45 mL) and DCM (0.45 mL). The crude yellow solid was purified by column chromatography (amine silica gel, DCM:MeOH, 1:0 → 94:6) to yield the *title compound* as a white solid (30 mg, 73%); R_f = 0.27 (amine silica, DCM:MeOH, 94:6); m.p. 195.5-197.5 °C; λ_{max} (EtOH)/nm 292.8; IR (neat) ν_{max}/cm^{-1} 2935, 2815, 1639, 1576, 1556, 1512, 1471, 1435, 1268; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.40 (4H, brs, NC$H_{2\ piperazine}$), 2.68 (4H, t, *J* = 4.8 Hz, NC$H_{2\ piperazine}$), 3.62 (2H, s, ArCH_2N), 3.90 (3H, s, ArOCH_3), 7.33 (1H, dd, *J* = 9.1, 9.0 Hz, H-4'), 7.39 (1H, d, *J* = 9.1 Hz, H-5'), 7.45 (1H, s, H-3), 7.53 (1H, s, H-5), 9.07 (2H, s, H-4", 6"), 10.41 (1H, s,

CON*H*Ar); ^{13}C NMR (126 MHz, DMSO-d_6) δ 45.4 (NC$H_{2\ piperazine}$), 53.7 (NC$H_{2\ piperazine}$), 56.5 (ArOCH_3), 64.5 (ArCH_2N), 112.1 (C-3), 115.2 (C-4'), 120.2 (d, *J* = 4.8 Hz, C-6'), 125.3 (C-2 or C-4), 125.6 (C-5'), 127.9 (C-2 or C-4), 128.4 (d, *J* = 19.9 Hz, C-1'), 129.9 (C-5), 132.4 (C-5"), 146.4 (d, *J* = 10.8 Hz, C-3'), 147.8 (C-4", 6"), 147.9 (d, *J* = 246.9 Hz, C-2'), 158.9 (*C*ONHAr), 161.3 (C-2"), 183.6 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -136.1 (ArF); LRMS (ES$^+$) *m/z* 473.3 [M(^{35}Cl)+H]$^+$, 475.3 [M(^{37}Cl)+H]$^+$; HRMS (NSI) calcd for $C_{22}H_{23}ClFN_6O_3$ [M(^{35}Cl)+H]$^+$ 473.1499, found 473.1491.

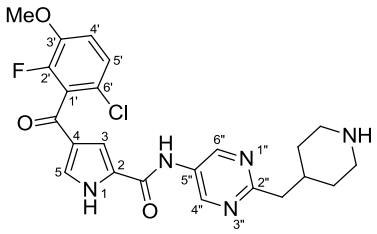
4-(6-Chloro-2-fluoro-3-methoxybenzoyl)-*N*-(2-((1-methylpiperidin-4-yl)methyl) pyrimidin-5-yl)-1*H*-pyrrole-2-carboxamide, (412)



Compound **412** was synthesised according to general procedure E', using the following reagents: *tert*-butyl 4-((5-(4-(6-chloro-2-fluoro-3-methoxybenzoyl)-1*H*-pyrrole-2-carboxamido)pyrimidin-2-yl)methyl)piperidine-1-carboxylate (**430**) (125 mg, 0.22 mmol), formic acid (1.1 mL) and formaldehyde (37 % wt. in water) (65 µL, 0.87 mmol). The crude yellow solid was purified by column chromatography (amine silica gel, DCM:MeOH, 1:0 → 97:3) to yield the *title compound* as a white solid (76 mg, 72%); R_f = 0.26 (amine silica, DCM:MeOH, 97:3); m.p. 255.0-257.0 °C; λ_{max} (EtOH)/nm 293.0; IR (neat) ν_{max}/cm^{-1} 2925, 2843, 2783, 1638, 1576, 1555, 1511, 1471, 1438, 1270; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.23 (2H, dddd, *J* = 12.4, 12.4, 12.4 and 3.6 Hz, CH_2CH$_2$NCH$_3$), 1.52 (2H, d, *J* = 12.4 Hz, CH_2CH$_2$NCH$_3$), 1.74 – 1.84 (3H, m, CH$_2$CH_2NCH$_3$ and ArCH$_2$C*H*), 2.11 (3H, s, NCH_3), 2.70 (2H, d, *J* = 12.4 Hz, CH$_2$CH_2NCH$_3$), 2.74 (2H, d, *J* = 7.1 Hz, ArCH_2CH), 3.90 (3H, s, ArOCH_3), 7.33 (1H, dd, *J* = 9.0, 8.9 Hz, H-4'), 7.39 (1H, dd, *J* = 9.0, 1.4 Hz, H-5'), 7.44 (1H, s, H-3), 7.52 (1H, s, H-5), 9.02 (2H, s, H-4", 6"), 10.35 (1H, s, CON*H*Ar), 12.75 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 31.7 (*C*H$_2$CH$_2$NCH$_3$), 34.9 (ArCH$_2$*C*H), 44.9 (Ar*C*H$_2$CH), 46.2 (N*C*H$_3$), 55.3 (CH$_2$*C*H$_2$NMe), 56.5 (ArO*C*H$_3$), 112.0 (C-3), 115.2 (C-4'), 120.2 (d, *J* = 4.8 Hz, C-6'), 125.2 (C-2 or C-4), 125.6 (d, *J* = 3.7 Hz, C-5'), 127.9 (C-2 or C-4), 128.4 (d, *J* = 19.9 Hz, C-1'), 129.7 (C-5), 131.7 (C-5"), 146.4 (d, *J* = 10.7 Hz, C-3'), 147.9 (d, *J* = 247.3 Hz, C-2'), 148.0 (C-4", 6"), 158.8 (*C*ONHAr), 163.9 (C-2"), 183.6 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -136.1 (ArF); LRMS (ES$^+$) *m/z* 486.4 [M(^{35}Cl)+H]$^+$, 488.4

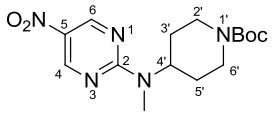
[M(^{37}Cl)+H]$^+$; HRMS (NSI) calcd for $C_{24}H_{26}ClFN_5O_3$ [M(^{35}Cl)+H]$^+$ 486.1703, found 463.1695.

4-(6-Chloro-2-fluoro-3-methoxybenzoyl)-*N*-(2-(piperidin-4-ylmethyl)pyrimidin-5-yl)-1*H*-pyrrole-2-carboxamide, (413)



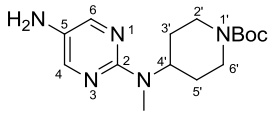
Compound **413** was synthesised according to general procedure F', using the following reagents: *tert*-butyl 4-((5-(4-(6-chloro-2-fluoro-3-methoxybenzoyl)-1*H*-pyrrole-2-carboxamido)pyrimidin-2-yl)methyl)piperidine-1-carboxylate (**430**) (125 mg, 0.22 mmol), triethylsilane (87 µL, 64 mg, 0.55 mmol), TFA (1.1 mL) and DCM (1.1 mL). The crude yellow solid was purified by column chromatography (amine silica gel, DCM:MeOH, 1:0 → 95:5) to yield the *title compound* as a white solid (67 mg, 65%); R_f = 0.30 (amine silica, DCM:MeOH, 95:5); m.p. 234.5-236.5 °C; λ_{max} (EtOH)/nm 296.0; IR (neat) ν_{max}/cm^{-1} 2924, 2842, 1640, 1576, 1510, 1471, 1439, 1390, 1270; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.13 (2H, dddd, *J* = 12.3, 12.3, 12.3 and 3.8 Hz, C*H*$_2$CH$_2$NH), 1.51 (2H, d, *J* = 12.3 Hz, C*H*$_2$CH$_2$NH), 1.96 (1H, ttt, *J* = 12.3, 7.2 and 3.9 Hz, ArCH$_2$C*H*), 2.40 – 2.48 (2H, m, CH$_2$C*H*$_2$NH), 2.73 (2H, d, *J* = 7.2 Hz, ArC*H*$_2$CH), 2.93 (2H, d, *J* = 12.3 Hz, CH$_2$C*H*$_2$NH), 3.90 (3H, s, ArOC*H*$_3$), 7.32 (1H, dd, *J* = 9.0, 9.0 Hz, H-4'), 7.35 – 7.42 (2H, m, H-3 and H-5'), 7.49 (1H, s, H-5), 9.02 (2H, s, H-4", 6"), 10.32 (1H, s, CON*H*Ar); ^{13}C NMR (126 MHz, DMSO-d_6) δ 32.3 (*C*H$_2$CH$_2$NH), 35.7 (ArCH$_2$*C*H), 45.5 (Ar*C*H$_2$CH), 45.7 (CH$_2$*C*H$_2$NH), 56.4 (ArO*C*H$_3$), 112.1 (C-3), 115.0 (C-4'), 120.3 (d, *J* = 5.0 Hz, C-6'), 125.3 (C-2 or C-4), 125.5 (C-5'), 128.6 (C-2 or C-4), 128.7 (d, *J* = 20.6 Hz, C-1'), 130.3 (C-5), 131.8 (C-5"), 146.4 (d, *J* = 10.6 Hz, C-3'), 147.9 (d, *J* = 246.8 Hz, C-2'), 148.0 (C-4", 6"), 159.1 (CON*H*Ar), 163.7 (C-2"), 183.4 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -136.13 (ArF); LRMS (ES$^+$) *m/z* 472.4 [M(^{35}Cl)+H]$^+$, 474.3 [M(^{37}Cl)+H]$^+$; HRMS (NSI) calcd for $C_{23}H_{24}ClFN_5O_3$ [M(^{35}Cl)+H]$^+$ 472.1546, found 472.1538.

***tert*-Butyl 4-(methyl(5-nitropyrimidin-2-yl)amino)piperidine-1-carboxylate, (415)**



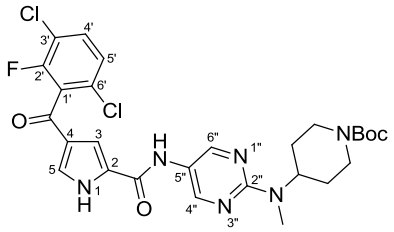
Compound **415** was synthesised according to general procedure C', using the following reagents: 2-chloro-5-nitropyrimidine (**414**) (600 mg, 3.76 mmol), triethylamine (580 µL, 421 mg, 4.14 mmol), *tert*-butyl 4-(methylamino)piperidine-1-carboxylate (883 µL, 887 mg, 4.14 mmol) and THF (18.8 mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 15:85) to yield the *title compound* as a pale yellow solid (1.20 g, 94%); R_f = 0.28 (petrol:EtOAc, 15:85); m.p. 155.0-157.0 °C; λ_{max} (EtOH)/nm 344.8; IR (neat) ν_{max}/cm^{-1} 2964, 2935, 2858, 1684, 1594, 1558, 1533, 1415, 1323, 1295, 1241; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.41 (9H, s, C(CH_3)$_3$), 1.75 - 1.60 (4H, m, H-3', 5'), 2.83 (2H, brs, H-2', 6'), 3.11 (3H, s, NCH_3), 4.08 (2H, brs, H-2', 6'), 4.85 (1H, tt, *J* = 11.6, 4.4 Hz, H-4'), 9.13 (2H, d, *J* = 3.0 Hz, H-4, 6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 28.1 (C(*C*H$_3$)$_3$), 28.2 (C-3', 5'), 29.9 (N*C*H$_3$), 42.7 (C-2', 6'), 53.5 (C-4'), 78.8 (O*C*(CH$_3$)$_3$), 133.3 (C-5), 153.7 (*C*O$_2$N), 154.7 (C-4 or C-6), 155.0 (C-4 or C-6), 161.2 (C-2); HRMS (ESI) calcd for $C_{15}H_{24}N_5O_4$ [M+H]$^+$ 338.1823, found 338.1824.

***tert*-Butyl 4-((5-aminopyrimidin-2-yl)(methyl)amino)piperidine-1-carboxylate, (416)**



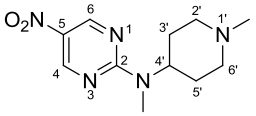
Compound **416** was synthesised according to general procedure D', using the following reagents: *tert*-butyl 4-(methyl(5-nitropyrimidin-2-yl)amino)piperidine-1-carboxylate (**415**) (400 mg, 1.19 mmol), THF (12 mL) and methanol (12 mL). The orange solid (350 mg, 96%) was used in the next step without further purification; R_f = 0.22 (EtOAc, 100%); m.p. 142.0-144.0 °C; λ_{max} (EtOH)/nm 255.0; IR (neat) ν_{max}/cm^{-1} 3392, 3336, 3232, 3003, 2970, 2951, 2864, 1669, 1543, 1475, 1427, 1408, 1364, 1244; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.40 (9H, s, C(CH_3)$_3$), 1.64 – 1.44 (4H, m, H-3', 5'), 2.81 (2H, brs, H-2', 6'), 2.82 (3H, s, NCH_3), 4.04 (2H, brs, H-2', 6'), 4.46 (2H, brs, ArNH_2), 4.54 (1H, tt, *J* = 10.4, 5.5 Hz, H-4'), 7.88 (2H, s, H-4, 6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 28.1 (C(*C*H$_3$)$_3$), 28.5 (C-3', 5'), 28.7 (N*C*H$_3$), 43.2 (C-2', 6'), 51.8 (C-4'), 78.6 (O*C*(CH$_3$)$_3$), 133.3 (C-5), 144.4 (C-4, 6), 153.8 (*C*O$_2$N), 155.7 (C-2); LRMS (ES$^+$) *m/z* 308.4 [M+H]$^+$; HRMS (NSI) calcd for $C_{15}H_{26}N_5O_2$ [M+H]$^+$ 308.2081, found 308.2080.

***tert*-Butyl 4-((5-(4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxamido) pyrimidin-2-yl)(methyl)amino)piperidine-1-carboxylate, (417)**



Compound **417** was synthesised according to general procedure Y, using the following reagents: 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**) (150 mg, 0.50 mmol), triethylamine (173 µL, 126 mg, 1.24 mmol), 2-chloro-1-methylpyridinium iodide (140 mg, 0.55 mmol), *tert*-butyl 4-((5-aminopyrimidin-2-yl)(methyl)amino)piperidine-1-carboxylate (**416**) (191 mg, 0.62 mmol) and DCM (5 mL). The crude yellow solid was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 6:4) to yield the *title compound* as a pale brawn solid (142 mg, 48%); R_f = 0.27 (petrol:EtOAc, 6:4); m.p. 228.5-230.5 °C; λ_{max} (EtOH)/nm 291.8; IR (neat) ν_{max}/cm^{-1} 3187, 2973, 2936, 2863, 1655, 1637, 1500, 1447, 1403, 1365, 1284, 1240; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.41 (9H, s, C(CH_3)$_3$), 1.55 – 1.70 (4H, m, CH_2CH$_2$NBoc), 2.81 (2H, s, CH$_2$CH_2NBoc), 2.95 (3H, s, NCH_3), 4.08 (2H, s, CH$_2$CH_2NBoc), 4.70 (1H, tt, *J* = 10.8, 5.1 Hz, ArN(CH$_3$)C*H*), 7.39 (1H, s, H-3), 7.52 (1H, dd, *J* = 8.8, 1.4 Hz, H-5'), 7.60 (1H, s, H-5), 7.78 (1H, dd, *J* = 8.8, 8.4 Hz, H-4'), 8.58 (2H, s, H-4", 6"), 10.01 (1H, s, CON*H*Ar), 12.73 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 28.1 (*C*H$_2$CH$_2$NBoc), 28.5 (C(*C*H$_3$)$_3$), 28.8 (N*C*H$_3$), 42.9 (CH$_2$*C*H$_2$NBoc), 52.0 (ArN(CH$_3$)*C*H), 78.7 (O*C*(CH$_3$)$_3$), 111.0 (C-3), 119.3 (d, *J* = 18.1 Hz, C-3'), 123.0 (C-5"), 124.7 (C-2 or C-4), 126.9 (d, *J* = 3.9 Hz, C-5'), 128.4 (C-2 or C-4), 129.2 (d, *J* = 23.1 Hz, C-1'), 129.2 (d, *J* = 5.2 Hz, C-6'), 129.8 (C-5), 131.8 (C-4'), 151.3 (C-4", 6"), 153.8 (C-2"), 153.8 (d, *J* = 248.5 Hz, C-2'), 158.3 (*C*ONHAr or *C*O$_2$N), 158.4 (*C*ONHAr or *C*O$_2$N), 182.6 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.7 (ArF); LRMS (ES$^-$) *m/z* 589.3 [M(^{35}Cl^{35}Cl)-H]$^-$, 591.3 [M(^{35}Cl^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{27}H_{30}Cl_2FN_6O_4$ [M(^{35}Cl^{35}Cl)+H]$^+$ 591.1684, found 591.1680.

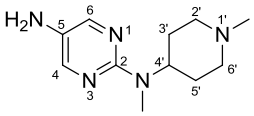
***N*-Methyl-*N*-(1-methylpiperidin-4-yl)-5-nitropyrimidin-2-amine, (418)**



Compound **418** was synthesised according to general procedure E', using the following reagents: *tert*-butyl 4-(methyl(5-nitropyrimidin-2-yl)amino)piperidine-1-carboxylate (**415**)

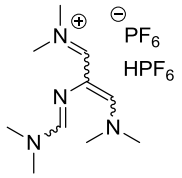
(600 mg, 1.78 mmol), formic acid (7.1 mL) and formaldehyde (37 % wt. in water) (529 µL, 7.11 mmol). The crude yellow solid (420 mg, 94%) was used in the next step without further purification; R_f = 0.31 (amine silica, petrol:EtOAc, 7:3); m.p. 179.5-181.5 °C; λ_{max} (EtOH)/nm 352.6; IR (neat) ν_{max}/cm^{-1} 2945, 2926, 2777, 2736, 1598, 1542, 1480, 1412, 1330, 1297, 1277; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.55 – 1.64 (2H, m, H-3', 5'$_{equ}$), 1.85 (2H, dddd, *J* = 12.1, 12.1, 12.1 and 4.1 Hz, H-3', 5'$_{axial}$), 1.94 – 2.03 (2H, m, H-2', 6'), 2.19 (3H, s, NC*H*$_3$), 2.82 – 2.92 (2H, m, H-2', 6'), 3.12 (3H, s, NC*H*$_3$), 4.66 (1H, tt, *J* = 12.1, 4.1 Hz, H-4'), 9.12 (2H, s, H-4, 6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 28.1 (C-3', 5'), 29.9 (N*C*H$_3$), 45.8 (N*C*H$_3$), 53.4 (C-4'), 54.6 (C-2', 6'), 133.2 (C-5), 154.7 (C-4 or C-6), 155.0 (C-4 or C-6), 161.3 (C-2); LRMS (ES$^+$) *m/z* 252.3 [M+H]$^+$; HRMS (NSI) calcd for $C_{11}H_{18}N_5O_2$ [M+H]$^+$ 252.1455, found 252.1452.

N^2-Methyl-N^2-(1-methylpiperidin-4-yl)pyrimidine-2,5-diamine, (419)



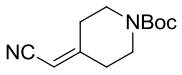
Compound **419** was synthesised according to general procedure D', using the following reagents: *N*-methyl-*N*-(1-methylpiperidin-4-yl)-5-nitropyrimidin-2-amine (**418**) (450 mg, 1.79 mmol), THF (18 mL) and methanol (18 mL). The crude yellow solid (380 mg, 96%) was used in the next step without further purification; R_f = 0.32 (amine silica, DCM:MeOH, 98:2); m.p. 150.5-152.5 °C; λ_{max} (EtOH)/nm 255.2; IR (neat) ν_{max}/cm^{-1} 3314, 3151, 2933, 2852, 2792, 2735, 1547, 1481, 1465, 1403, 1373; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.41 – 1.51 (2H, m, H-3', 5'$_{equ}$), 1.72 (2H, dddd, *J* = 12.2, 12.2, 12.2 and 3.9 Hz, H-3', 5'$_{axial}$), 1.93 (2H, ddd, *J* = 12.2, 12.2 and 2.3 Hz, H-2', 6'$_{axial}$), 2.16 (3H, s, NC*H*$_3$), 2.79 – 2.83 (2H, m, H-2', 6'$_{equ}$), 2.83 (3H, s, NC*H*$_3$), 4.34 (1H, tt, *J* = 12.3, 3.9 Hz, H-4'), 4.43 (2H, brs, ArN*H*$_2$), 7.87 (2H, s, H-4, 6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 28.4 (C-3', 5'), 28.8 (N*C*H$_3$), 46.0 (N*C*H$_3$), 51.6 (C-4'), 55.2 (C-2', 6'), 133.1 (C-5), 144.4 (C-4, 6), 155.9 (C-2); LRMS (ES$^+$) *m/z* 222.3 [M+H]$^+$; HRMS (NSI) calcd for $C_{11}H_{20}N_5$ [M+H]$^+$ 222.1713, found 222.1710.

_N_-(3-(Dimethylamino)-2-[[(dimethylamino)methylene]amino]prop-2-en-1-ylidene)-_N_-methylmethanaminium hydrogen dihexafluorophosphate, (421)



Phosphorus(V) oxychloride (7.52 mL, 12.4 g, 80.7 mmol) was added dropwise to *N*,*N*-dimethylformamide (16.1 mL), cooled to 10 °C. During the addition, the temperature of the solution was maintained between 10 and 15 °C with an ice bath. Once the addition was complete, the reaction was stirred at RT for 20 min. The resulting solution was cooled to 5 °C before powdered glycine hydrochloride (3.0 g, 26.9 mmol) was added in portions; the temperature of the reaction mixture was maintained below 10 °C during the addition. The resulting reaction mixture was heated at 80 ± 2 °C (internal temperature) for 4 h. Then the still hot, dark orange, solution was poured directly in a fine stream into water (43 mL), precooled to 5 °C. The temperature of the solution was kept below 20 °C with an acetone dry ice bath. 5 min after the transfer was complete, the reaction mixture was cooled to -5 °C and treated from a plastic vessel with 60% aq. HPF_6 (7.93 mL, 53.8 mmol). The thick precipitate, which formed upon addition of the acid, was filtered off and washed with cold EtOH (100 mL) until a pale yellow solid was obtained (5.24 g, 40%); m.p. 151.0-153.0 °C; λ_{max} (EtOH)/nm 254.6; IR (neat) ν_{max}/cm^{-1} 1701, 1611, 1402, 1291; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.19 (9H, s, 3 × NCH_3), 3.24 (3H, s, NCH_3), 3.29 (6H, s, 2 × NCH_3), 7.70 (2H, s, 2 × CH), 8.07 (1H, d, J = 10.4 Hz, CHNH$(CH_3)_2^+$), 10.74 (1H, d, J = 6.8 Hz, CHN$H$$(CH_3)_2^+$); ^{13}C NMR (126 MHz, DMSO-d_6) δ 37.0 (NCH$_3$), ca. 40 (overlapping with DMSO) (NCH$_3$), 43.6 (NCH$_3$), 48.8 (NCH$_3$), 100.8 (C_q), 158.1 (CH), 160.7 (CHNH$(CH_3)_2^+$); ^{19}F NMR (471 MHz, DMSO-d_6) δ -70.9 (PF_6^-), -69.4 (PF_6^-); LRMS (ES$^+$) *m/z* 197.3 [M-HP$_2$F$_{12}^-$]$^+$; HRMS (NSI) calcd for $C_{10}H_{21}N_4$ [M-HP$_2$F$_{12}^-$]$^+$ 197.1761, found 197.1760.

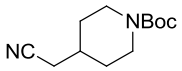
***tert*-Butyl 4-(cyanomethylene)piperidine-1-carboxylate, (423)**



To diethyl cyanomethylphosphonate (3.50 mL, 3.83 g, 21.6 mmol) in THF (60 mL), cooled at -78 °C, was added lithium bis(trimethylsilyl)amide (1.0 M solution in THF, 21.6 mL, 21.6 mmol) and 1-Boc-4-piperidone (**422**) (3.92 g, 19.7 mmol) in THF (10 mL). The resulting solution was stirred at -78 °C for 1 h. Upon completion, the reaction mixture was quenched by the cautious addition saturated aq. NH_4Cl (50 mL) and extracted with

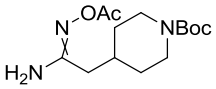
EtOAc (3 × 60 mL). The pooled organic extracts were washed with water and brine (40 mL, respectively), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 8:2) to yield the *title compound* as a white solid (4.02 g, 92%); R_f = 0.33 (petrol:EtOAc, 8:2); m.p. 118.0-120.0 °C (lit. 117.0-119.0 °C)[282]; λ_{max} (EtOH)/nm 230.4; IR (neat) ν_{max}/cm^{-1} 3053, 2976, 2872, 2215, 1674, 1631, 1425, 1360; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.41 (9H, s, C(CH_3)$_3$), 2.31 (2H, t, *J* = 5.7 Hz, CH_2CH$_2$NBoc), 2.44 (2H, t, *J* = 5.7 Hz, CH_2CH$_2$NBoc), 3.38 (2H, t, *J* = 5.9 Hz, CH$_2$CH_2NBoc), 3.43 (2H, t, *J* = 5.9 Hz, CH$_2$CH_2NBoc), 5.57 (1H, s, C*H*CN); ^{13}C NMR (126 MHz, DMSO-d_6) δ 28.0 (C(*C*H$_3$)$_3$), 32.1 (*C*H$_2$CH$_2$NBoc), 34.0 (*C*H$_2$CH$_2$NBoc), 43.5 (CH$_2$*C*H$_2$NBoc), 44.0 (CH$_2$*C*H$_2$NBoc), 79.2 (O*C*(CH$_3$)$_3$), 94.0 (*C*HCN), 116.8 (CH*C*N), 153.6 (C-4), 164.1 (*C*O$_2$N); LRMS (ES$^+$) *m/z* 223.3 [M+H]$^+$; HRMS (ESI) calcd for $C_{12}H_{19}N_2O_2$ [M+H]$^+$: 223.1441; found 223.1436; ^{1}H and ^{13}C NMR data were identical to literature data.[282]

tert-Butyl 4-(cyanomethyl)piperidine-1-carboxylate, (424)



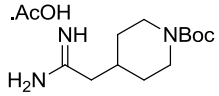
tert-Butyl 4-(cyanomethylene)piperidine-1-carboxylate (**423**) (4.0 g, 18.0 mmol) in EtOAc (360 mL) was subjected to palladium-catalysed hydrogenation using an H-Cube® reactor and a 10% Pd/C CatCart under a full pressure of hydrogen. The reaction was conducted at RT for 24 h. The reaction mixture was concentrated *in vacuo* to afford a white solid (4.04 g, quantitative) which was used in the next step without further purification; R_f = 0.32 (petrol:EtOAc, 3:1); m.p. 74.0-76.0 °C; IR (neat) ν_{max}/cm^{-1} 2985, 2968, 2952, 2935, 2922, 2853, 2240, 1684, 1419, 1365; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.07 (2H, dddd, *J* = 12.4, 12.4, 12.4 and 4.4 Hz, CH_2CH$_2$NBoc), 1.37 (9H, s, C(CH_3)$_3$), 1.65 (2H, d, *J* = 12.4 Hz, CH_2CH$_2$NBoc), 1.76 (1H, ttt, *J* = 12.4, 6.7 and 3.7 Hz, C*H*CH$_2$CN), 2.48 (2H, d, *J* = 6.7 Hz, CHCH_2CN), 2.68 (2H, brs, CH$_2$CH_2NBoc), 3.92 (2H, d, *J* = 9.8 Hz, CH$_2$CH_2NBoc); ^{13}C NMR (126 MHz, DMSO-d_6) δ 22.7 (CH*C*H$_2$CN), 28.1 (C(*C*H$_3$)$_3$), 30.6 (*C*H$_2$CH$_2$NBoc), 32.3 (*C*HCH$_2$CN), 43.0 (CH$_2$*C*H$_2$NBoc), 78.6 (O*C*(CH$_3$)$_3$), 119.4 (CHCH$_2$*C*N), 153.8 (*C*O$_2$N); LRMS (ES$^+$) *m/z* 225.2 [M+H]$^+$; HRMS (ESI) calcd for $C_{12}H_{24}N_3O_2$ [M+NH$_4$]$^+$: 242.1863; found 242.1857; ^{1}H and ^{13}C NMR data were identical to literature data.[283]

***tert*-Butyl 4-(2-(acetoxyimino)-2-aminoethyl)piperidine-1-carboxylate, (425)**



To *tert*-butyl 4-(cyanomethyl)piperidine-1-carboxylate (**424**) (3.5 g, 15.6 mmol) in EtOH (35 mL) was added aqueous hydroxylamine (50% solution, 1.91 mL, 31.2 mmol) and the resulting solution stirred at 80 °C for 5 h. Once cooled to RT, the reaction solution was concentrated *in vacuo* to give *tert*-butyl 4-(2-amino-2-(hydroxyimino)ethyl)piperidine-1-carboxylate as a white solid. To this solid, dissolved in dioxane (35 mL), were added acetic anhydride (2.95 mL, 3.19 g, 31.2 mmol) and triethylamine (2.18 mL, 1.58 g, 31.2 mmol). The resulting solution was stirred overnight at RT. Upon completion, the mixture was diluted with water (25 mL) and extracted with EtOAc (3 × 40 mL). The pooled organic extracts were washed with water and brine (50 mL, respectively), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 3:1) to yield the *title compound* as a white solid (3.67 g, 79%); R_f = 0.31 (petrol:EtOAc, 3:1); m.p. 149.5-151.5 °C; λ_{max} (EtOH)/nm 274.2; IR (neat) ν_{max}/cm^{-1} 3461, 3436, 3331, 3302, 3264, 3174, 2978, 2929, 2908, 2845, 1738, 1679, 1631, 1604, 1427; ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.99 (2H, dddd, *J* = 12.6, 12.6, 12.6 and 4.2 Hz, H-3, 5), 1.38 (9H, s, C(C*H*$_3$)$_3$), 1.62 (2H, d, *J* = 12.6 Hz, H-3, 5), 1.77 (1H, ttt, *J* = 12.6, 7.3 and 3.5 Hz, H-4), 1.95 (2H, d, *J* = 7.3 Hz, C*H*$_2$CH), 2.02 (3H, s, C*H*$_3$CO$_2$), 2.67 (2H, brs, H-2, 6), 3.90 (2H, d, *J* = 12.6 Hz, H-2, 6), 6.31 (2H, brs, NH$_2$); ^{13}C NMR (126 MHz, DMSO-d_6) δ 19.8 (*C*H$_3$CO$_2$), 28.1 (C(*C*H$_3$)$_3$), 31.3 (C-3, 5), 33.4 (C-4), 36.9 (*C*H$_2$CH), 43.3 (C-2, 6), 78.4 (O*C*(CH$_3$)$_3$), 153.8 (*C*O$_2$N), 157.4 (*C*(NH$_2$)NO$_2$CCH$_3$), 168.4 (CH$_3$*C*O$_2$); LRMS (ES$^+$) *m/z* 300.4 [M+H]$^+$; HRMS (NSI) calcd for $C_{14}H_{26}N_3O_4$ [M+H]$^+$ 300.1918, found 300.1915.

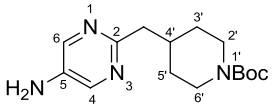
***tert*-Butyl 4-(2-amino-2-iminoethyl)piperidine-1-carboxylate acetate, (426)**



tert-Butyl 4-(2-(acetoxyimino)-2-aminoethyl)piperidine-1-carboxylate (**425**) (3.5 g, 11.7 mmol) was dissolved in a EtOH:DCM (5:1) (84 mL), followed by addition of palladium on carbon (10 wt. %) (350 mg). The resulting heterogeneous solution was stirred under a hydrogen atmosphere at RT for 16 h. Upon completion, the reaction mixture was filtered through Celite and concentrated *in vacuo* to afford the *title compound* as an off-white solid (3.32 g, 95%). The crude material was used in the next step without further purification; m.p. 176.0-178.0 °C; IR (neat) ν_{max}/cm^{-1} 2983, 2967, 2927, 2866, 1673, 1586,

1523, 1426, 1409; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.03 (2H, dddd, *J* = 12.5, 12.5, 12.5 and 4.1 Hz, H-3, 5), 1.39 (9H, s, C(C*H*$_3$)$_3$), 1.59 (2H, d, *J* = 12.5 Hz, H-3, 5), 1.64 (3H, s, C*H*$_3$CO$_2$), 1.84 (1H, ttt, *J* = 12.5, 7.5 and 3.8 Hz, H-4), 2.20 (2H, d, *J* = 7.5 Hz, C*H*$_2$CH), 2.70 (2H, brs, H-2, 6), 3.92 (2H, d, *J* = 12.5 Hz, H-2, 6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 25.0 (*C*H$_3$CO$_2^-$), 28.1 (C(*C*H$_3$)$_3$), 31.0 (C-3, 5), 33.6 (C-4), 43.0 (C-2, 6), 78.6 (O*C*(CH$_3$)$_3$), 153.8 (*C*O$_2$N), 169.7 (*C*(NH$_2$)NH$_2^+$), 176.3 (CH$_3$*C*O$_2^-$); LRMS (ES$^+$) *m/z* 242.4 [M-AcO$^-$]$^+$; HRMS (NSI) calcd for C$_{12}$H$_{23}$N$_3$O$_2$ [M-AcO$^-$]$^+$ 242.1863, found 242.1859.

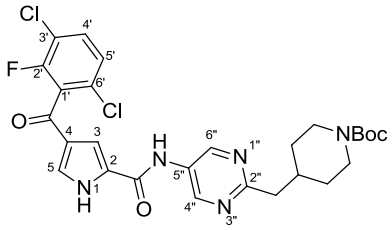
tert-Butyl 4-((5-aminopyrimidin-2-yl)methyl)piperidine-1-carboxylate, (428)



To a slurry of *N*-(3-(dimethylamino)-2-[[(dimethylamino)methylene]amino]prop-2-en-1-ylidene)-*N*-methylmethanaminium hydrogen dihexafluorophosphate (**421**) (4.05 g, 8.29 mmol) and *tert*-butyl 4-(2-amino-2-iminoethyl)piperidine-1-carboxylate acetate (**426**) (3.0 g, 9.95 mmol) in EtOH (20 mL) was added dropwise a solution of NaOMe in MeOH (1.61 g, 29.9 mmol, 25% w/v); the mixture was heated to reflux halfway through the addition. After refluxing for 150 min, the mixture was cooled to 0 °C, the inorganic precipitate was filtered off, washed with cold EtOH (2 ×20 mL) and the filtrate evaporated. The residue was dissolved in DCM (50 mL), washed with water (3 × 20 mL), dried over MgSO$_4$, and concentrated *in vacuo* to give *tert*-butyl 4-((5-(((dimethylamino)methylene) amino)pyrimidin-2-yl)methyl)piperidine-1-carboxylate (**427**) as an orange oil. The oil was dissolved in dioxane (15 mL), treated with 5% aq. potassium carbonate (21 mL) and refluxed overnight. Once cooled to RT, the reaction mixture was extracted with EtOAc (3 × 40 mL). The pooled organic extracts were washed with water and brine (50 mL, respectively), dried over MgSO$_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (amine silica gel, petrol:EtOAc, 1:0 → 4:6) to yield the *title compound* as an off-white solid (1.91 g, 79%); R$_f$ = 0.32 (amine silica, petrol:EtOAc, 4:6); m.p. 133.5-135.5 °C; λ$_{max}$ (EtOH)/nm 246.6, 318.2; IR (neat) ν$_{max}$/cm^{-1} 3457, 3342, 2970, 2944, 2916, 2863, 2842, 1663, 1618, 1547, 1443, 1424; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.02 (2H, dddd, *J* = 12.5, 12.5, 12.5 and 4.2 Hz, H-3', 5'), 1.38 (9H, s, C(C*H*$_3$)$_3$), 1.51 (2H, d, *J* = 12.5 Hz, H-3', 5'), 1.92 (1H, ttt, *J* = 12.5, 7.2 and 4.0 Hz, H-4'), 2.58 (2H, d, *J* = 7.2 Hz, ArC*H*$_2$CH), 2.69 (2H, brs, H-2', 6'), 3.88 (2H, brs, H-2', 6'), 5.31 (2H, brs, ArN*H*$_2$), 8.02 (2H, s, H-4, 6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 28.1 (C(C*H*$_3$)$_3$), 31.6 (C-3', 5'), 35.5 (C-4'), 43.5 (C-2', 6'), 44.3 (Ar*C*H$_2$), 78.4

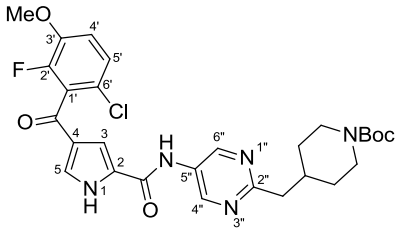
(O*C*(CH_3)$_3$), 140.4 (C-5), 141.8 (C-4, 6), 153.9 (*C*O_2N), 156.6 (C-5); LRMS (ES^+) *m/z* 293.2 $[M+H]^+$; HRMS (NSI) calcd for $C_{15}H_{25}N_4O_2$ $[M+H]^+$ 293.1972, found 293.1974.

tert-Butyl 4-((5-(4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxamido) pyrimidin-2-yl)methyl)piperidine-1-carboxylate, (429)



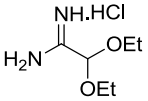
Compound **429** was synthesised according to general procedure Y, using the following reagents: 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**) (400 mg, 1.32 mmol), triethylamine (461 µL, 335 mg, 3.31 mmol), 2-chloro-1-methylpyridinium iodide (372 mg, 1.46 mmol), *tert*-butyl 4-((5-aminopyrimidin-2-yl)methyl)piperidine-1-carboxylate (**428**) (484 mg, 1.65 mmol) and DCM (13.2 mL). The crude yellow solid was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 45:55) to yield the *title compound* as a white solid (386 mg, 51%); R_f = 0.31 (petrol:EtOAc, 45:55); m.p. 217.5-219.5 °C; λ_{max} (EtOH)/nm 264.0; IR (neat) ν_{max}/cm^{-1} 3241, 2958, 2927, 2866, 1649, 1584, 1555, 1514, 1445, 1425, 1392, 1274; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.09 (2H, dddd, *J* = 12.5, 12.5, 12.5 and 4.0 Hz, C*H*$_2$CH$_2$NBoc), 1.38 (9H, s, C(C*H*$_3$)$_3$), 1.56 (2H, d, *J* = 12.5 Hz, C*H*$_2$CH$_2$NBoc), 2.04 (1H, ttt, *J* = 12.5, 7.4 and 3.4 Hz, ArCH$_2$C*H*), 2.69 (2H, brs, CH$_2$C*H*$_2$NBoc), 2.77 (2H, d, *J* = 7.4 Hz, ArC*H*$_2$CH), 3.90 (2H, d, *J* = 12.5 Hz, CH$_2$C*H*$_2$NBoc), 7.49 (1H, s, H-3), 7.52 (1H, dd, *J* = 8.6, 1.3 Hz, H-5'), 7.66 (1H, s, H-5), 7.79 (1H, dd, *J* = 8.6, 8.4 Hz, H-4'), 9.03 (2H, s, H-4", 6"), 10.36 (1H, s, CON*H*Ar), 12.84 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 28.1 (*C*(CH$_3$)$_3$), 31.5 (*C*H$_2$CH$_2$NBoc), 35.3 (ArCH$_2$*C*H), 43.2 (CH$_2$*C*H$_2$NBoc), 44.7 (Ar*C*H$_2$CH), 78.4 (O*C*(CH$_3$)$_3$), 111.8 (C-3), 119.4 (d, *J* = 18.1 Hz, C-3'), 124.8 (C-2 or C-4), 126.9 (d, *J* = 3.9 Hz, C-5'), 128.0 (C-2 or C-4), 129.1 (d, *J* = 22.3 Hz, C-1'), 129.2 (d, *J* = 4.7 Hz, C-6'), 130.5 (C-5), 131.7 (C-4'), 131.9 (C-5"), 148.1 (C-4", 6"), 153.8 (d, *J* = 248.6 Hz, C--2'), 153.9 (*C*O_2N), 158.7 (*C*ONHAr), 163.7 (C-2"), 182.6 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.7 (ArF); LRMS (ES^-) *m/z* 574.3 $[M(^{35}Cl^{35}Cl)-H]^-$, 576.3 $[M(^{35}Cl^{37}Cl)-H]^-$; HRMS (NSI) calcd for $C_{27}H_{29}Cl_2FN_5O_4$ $[M(^{35}Cl^{35}Cl)+H]^+$ 576.1575, found 576.1570.

***tert*-Butyl 4-((5-(4-(6-chloro-2-fluoro-3-methoxybenzoyl)-1*H*-pyrrole-2-carboxamido) pyrimidin-2-yl)methyl)piperidine-1-carboxylate, (430)**



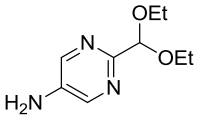
Compound **430** was synthesised according to general procedure Y, using the following reagents: 4-(6-chloro-2-fluoro-3-methoxybenzoyl)-1*H*-pyrrole-2-carboxylic acid (**338**) (400 mg, 1.34 mmol), triethylamine (468 µL, 340 mg, 3.36 mmol), 2-chloro-1-methylpyridinium iodide (378 mg, 1.48 mmol), *tert*-butyl 4-((5-aminopyrimidin-2-yl)methyl)piperidine-1-carboxylate (**428**) (491 mg, 1.68 mmol) and DCM (13.4 mL). The crude yellow solid was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 $\rightarrow$ 4:6) to yield the *title compound* as a white solid (281 mg, 37%); R_f = 0.29 (petrol:EtOAc, 4:6); m.p. 228.0-230.0 °C; λ_{max} (EtOH)/nm 292.6; IR (neat) ν_{max}/cm^{-1} 3199, 2127, 2970, 2928, 2855, 1652, 1637, 1577, 1554, 1514, 1473, 1425, 1392, 1272; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.09 (2H, dddd, *J* = 12.5, 12.5, 12.5 and 4.0 Hz, C*H*$_2$CH$_2$NBoc), 1.38 (9H, s, C(C*H*$_3$)$_3$), 1.56 (2H, d, *J* = 12.5 Hz, C*H*$_2$CH$_2$NBoc), 2.04 (1H, ttt, *J* = 12.5, 7.1 and 3.7 Hz, ArCH$_2$C*H*), 2.67 (2H, brs, CH$_2$C*H*$_2$NBoc), 2.77 (2H, d, *J* = 7.1 Hz, ArC*H*$_2$CH), 3.90 (5H, brs, CH$_2$C*H*$_2$NBoc and ArOC*H*$_3$), 7.33 (1H, dd, *J* = 9.0, 8.9 Hz, H-4'), 7.39 (1H, dd, *J* = 9.0, 1.4 Hz, H-5'), 7.45 (1H, s, H-3), 7.53 (1H, s, H-5), 9.02 (2H, s, H-4", 6"), 10.35 (1H, s, CON*H*Ar), 12.77 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 28.1 (*C*(CH$_3$)$_3$), 31.5 (*C*H$_2$CH$_2$NBoc), 35.3 (ArCH$_2$*C*H), 43.5 (Ar*C*H$_2$CH), 44.7 (CH$_2$*C*H$_2$NBoc), 56.5 (ArOCH$_3$), 78.4 (O*C*(CH$_3$)$_3$), 111.9 (C-3), 115.2 (C-4'), 120.2 (d, *J* = 4.8 Hz, C-6'), 125.2 (C-2 or C-4), 125.6 (d, *J* = 3.6 Hz, C-5'), 127.8 (C-2 or C-4), 128.4 (d, *J* = 20.0 Hz, C-1'), 129.6 (C-5), 131.8 (C-5"), 146.4 (d, *J* = 10.3 Hz, C-3'), 147.9 (d, *J* = 246.9 Hz, C-2'), 148.1 (C-4", 6"), 153.9 (*C*O$_2$N), 158.7 (*C*ONHAr), 163.6 (C-2"), 183.6 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -136.1 (ArF); LRMS (ES$^-$) *m/z* 570.4 [M(^{35}Cl)-H]$^-$, 572.4 [M(^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{28}H_{32}ClFN_5O_5$ [M(^{35}Cl)+H]$^+$ 572.2071, found 572.2063.

2,2-Diethoxyacetimidamide hydrochloride, (432)



Sodium (8 mg, 0.36 mmol) was carefully added to MeOH (5 mL) at RT. Once effervescence had ceased, diethoxyacetonitrile (**431**) (1.0 mL, 929 mg, 7.19 mmol) was added and the resulting mixture stirred at RT for 16 h. Solid carbon dioxide was added and the solvent was removed *in vacuo*. The resulting oil was dissolved in Et_2O (10 mL) and the sodium carbonate removed by filtration. The filtrate was concentrated *in vacuo* to afford methyl diethoxyacetimidate as a yellow oil which was used with no further purification. The oil was dissolved in MeOH (5 mL) and ammonium chloride (385 mg, 7.19 mmol) was added in one portion. The resulting solution was stirred at RT overnight before the solvent was concentrated *in vacuo*. The resulting oil was triturated with Et_2O to afford diethoxyacetimidamide hydrochloride as an off-white solid (1.17 g, 89%). The compound was used in the next step without further purification; m.p. 58.0-60.0 °C (lit. 81.0-82.0 °C)[284]; IR (neat) ν_{max}/cm^{-1} 3259, 3042, 2975, 1692, 1083; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.19 (6H, t, J = 7.0 Hz, OCH_2CH_3), 3.62 (4H, qd, J = 7.0, 3.0 Hz, OCH_2CH_3), 5.29 (1H, s, $CH(OEt)_2$), 9.05 (4H, s, NH_2 and NH_2^+); ^{13}C NMR (126 MHz, DMSO-d_6) δ 14.9 (OCH_2CH_3), 63.1 (OCH_2CH_3), 95.7 ($CH(OEt)_2$), 165.8 (C=NH(NH_2)); LRMS (ES^+) *m/z* 147.2 $[M\text{-}Cl]^+$; HRMS (ESI) calcd for $C_6H_{15}N_2O_2$ $[M\text{-}Cl]^+$ 147.1128, found 147.1123; ^{1}H NMR data were identical to literature data.[250]

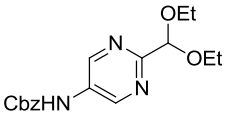
2-(Diethoxymethyl)pyrimidin-5-amine, (434)



To a slurry of *N*-(3-(dimethylamino)-2-[[(dimethylamino)methylene]amino]prop-2-en-1-ylidene)-*N*-methylmethanaminium hydrogen dihexafluorophosphate (**421**) (5.70 g, 11.7 mmol) and 2,2-diethoxyacetimidamide hydrochloride (**432**) (2.56 g, 14.0 mmol) in EtOH (25 mL) was added dropwise a solution of NaOMe in MeOH (2.27 g, 42.0 mmol, 25% w/v); the mixture was heated to reflux halfway through the addition. After refluxing for 150 min, the mixture was cooled to 0 °C, the inorganic precipitate was filtered off, washed with cold EtOH (3 × 20 mL) and the filtrate evaporated. The residue was dissolved in DCM (50 mL), washed with water (3 × 20 mL), dried over $MgSO_4$, and concentrated *in vacuo* to give *N*'-(2-(diethoxymethyl)pyrimidin-5-yl)-*N*,*N*-dimethylformimidamide (**433**) as an orange oil. The oil was dissolved in dioxane (20 mL), treated with 5% aq. potassium

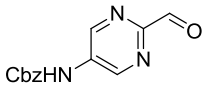
carbonate (30 mL) and refluxed overnight. Once cooled to RT, the reaction mixture was extracted with EtOAc (3 × 40 mL). The pooled organic extracts were washed with water and brine (50 mL, respectively), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel, DCM:MeOH, 1:0 → 95:5) to yield the *title compound* as an off-white solid (1.12 g, 49%); R_f = 0.25 (DCM:MeOH, 95:5); m.p. 134.0-136.0 °C; λ_{max} (EtOH)/nm 250.4, 315.4; IR (neat) ν_{max}/cm^{-1} 3358, 3324, 3202, 2977, 2929, 2877, 1646, 1583, 1555, 1452; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.09 (6H, t, *J* = 7.1 Hz, OCH_2CH_3), 3.49 (2H, dq, *J* = 9.7, 7.1 Hz, OCH_2CH_3), 3.61 (2H, dq, *J* = 9.7, 7.1 Hz, OCH_2CH_3), 5.27 (1H, s, $ArCH(OEt)_2$), 5.60 (2H, brs, $ArNH_2$), 8.07 (2H, s, H-4, 6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 15.2 (OCH_2CH_3), 61.2 (OCH_2CH_3), 102.0 ($ArCH(OEt)_2$), 141.1 (C-4, 6), 142.1 (C-5), 153.5 (C-2); LRMS (ES$^+$) *m/z* 198.2 $[M+H]^+$; HRMS (NSI) calcd for $C_9H_{15}N_3O_2Na$ $[M+Na]^+$ 220.1056, found 220.1052; ^{1}H and ^{13}C NMR data were identical to literature data.[247]

Benzyl (2-(diethoxymethyl)pyrimidin-5-yl)carbamate, (435)



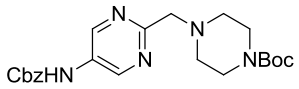
To 2-(diethoxymethyl)pyrimidin-5-amine (**434**) (1.5 g, 7.60 mmol) in THF:H_2O (1:1) (20 mL) was added potassium carbonate (2.1 g, 15.2 mmol) in one portion, followed by dropwise addition of benzyl chloroformate (2.17 mL, 2.6 g, 15.2 mmol) in THF (5 mL). The resulting reaction mixture was stirred at RT for 24 h. Upon completion, the mixture was diluted with water (20 mL) and extracted with EtOAc (3 × 40 mL). The pooled organic extracts were washed with water and brine (40 mL, respectively), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 6:4) to yield the *title compound* as a clear oil (2.03 g, 80%); R_f = 0.32 (petrol:EtOAc, 6:4); λ_{max} (EtOH)/nm 238.0; IR (neat) ν_{max}/cm^{-1} 3227, 3032, 2975, 2933, 2882, 1728, 1586, 1525, 1224; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.11 (6H, t, *J* = 7.0 Hz, 2 × OCH_2CH_3), 3.54 (2H, dq, *J* = 9.6, 7.0 Hz, OCH_2CH_3), 3.65 (2H, dq, *J* = 9.6, 7.0 Hz, OCH_2CH_3), 5.20 (2H, s, OCH_2Ph), 5.42 (1H, s, $ArCH(OEt)_2$), 7.33 – 7.47 (5H, m, 5 × Ar*H*), 8.88 (2H, s, H-4, 6), 10.26 (1H, s, ArN*H*Cbz); ^{13}C NMR (126 MHz, DMSO-d_6) δ 15.2 (OCH_2CH_3), 61.6 (OCH_2CH_3), 66.5 (OCH_2Ph), 101.7 ($ArCH(OEt)_2$), 128.2 (CH Ar), 128.5 (CH Ar), 133.7 (C_q Ar), 136.1 (C_q Ar), 146.2 (C-4, 6), 153.4 ($ArNHCO_2Bn$), 159.3 (C-2); LRMS (ES$^-$) *m/z* 330.3 $[M-H]^-$; HRMS (NSI) calcd for $C_{17}H_{21}N_3O_4$ $[M+H]^+$: 332.1605 found 332.1600.

Benzyl (2-formylpyrimidin-5-yl)carbamate, (436)



To benzyl (2-(diethoxymethyl)pyrimidin-5-yl)carbamate (**435**) (1.9 g, 5.73 mmol) in acetonitrile (20 mL) was added 1 M aq. HCl (3.5 mL) at RT. The resulting mixture was stirred at RT for 8 h. Upon completion, the solvents were removed under reduced pressure and the resulting white residue dissolved in saturated aq. $NaHCO_3$ (20 mL). The aqueous layer was extracted with EtOAc (3 × 30 mL) and the pooled organic extracts were washed with water and brine (40 mL, respectively), dried over $MgSO_4$ and concentrated *in vacuo* to afford the *title compound* as a white solid (1.31 g, 89%). The crude material was used in the next step without further purification; R_f = 0.31 (petrol:EtOAc, 1:1); m.p. 166.5-168.5 °C; λ_{max} (EtOH)/nm 283.4; IR (neat) ν_{max}/cm^{-1} 3217, 3062, 3033, 2964, 2876, 1730, 1715, 1586, 1566, 1526; ^{1}H NMR (500 MHz, DMSO-d_6) δ 5.24 (2H, s, OCH_2Ph), 7.34 – 7.49 (5H, m, 5 × Ar*H*), 9.10 (2H, s, H-4, 6), 9.89 (1H, s, ArC*H*O), 10.69 (1H, s, ArN*H*Cbz); ^{13}C NMR (126 MHz, DMSO-d_6) δ 66.9 (O*C*H$_2$Ph), 128.3 (CH Ar), 128.5 (CH Ar), 135.8 (C_q Ar), 136.2 (C_q Ar), 146.0 (C-4, 6), 153.2 (C-2 or ArNH*C*O$_2$Bn), 153.6 (C-2 or ArNH*C*O$_2$Bn), 190.4 (Ar*C*HO); LRMS (ES$^+$) *m/z* 258.2 [M+H]$^+$; HRMS (NSI) calcd for $C_{13}H_{12}N_3O_3$ [M+H]$^+$ 258.0873, found 258.0875.

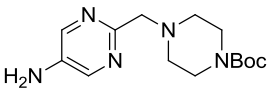
***tert*-Butyl 4-((5-(((benzyloxy)carbonyl)amino)pyrimidin-2-yl)methyl)piperazine-1-carboxylate, (437)**



To benzyl (2-formylpyrimidin-5-yl)carbamate (**436**) (900 mg, 3.50 mmol) in TFE (25 mL) was added *tert*-butyl piperazine-1-carboxylate (1.30 g, 7.00 mmol). The resulting solution was stirred at 38 °C for 1 h. Once cooled at 0 °C, sodium borohydride was carefully added. The resulting mixture was allowed to warm to RT and then stirred for 30 min. Upon completion, the solvent was removed *in vacuo*. The crude residue was dissolved in EtOAc (40 mL), neutralised by washing with saturated aq. NH_4Cl (25 mL), washed with water and brine (20 mL, respectively), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (amine silica gel, petrol:EtOAc, 1:0 → 4:6) to yield the *title compound* as a yellow solid (630 mg, 42%); R_f = 0.34 (amine silica, petrol:EtOAc, 4:6); λ_{max} (EtOH)/nm 236.8 nm; IR (neat) ν_{max}/cm^{-1} 2974, 1684, 1591, 1528, 1416; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.38 (9H, s, C(CH_3)$_3$), 2.35 – 2.45 (4H, m, $CH_{2\ piperazine}$), 3.28 (4H, s, $CH_{2\ piperazine}$), 3.65 (2H, s, ArCH_2N), 5.19 (2H, s, OCH_2Ph), 7.33

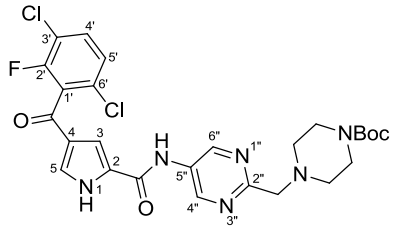
– 7.46 (5H, m, 5 × Ar*H*), 8.83 (2H, s, H-4, 6), 10.17 (1H, s, ArN*H*Cbz); ^{13}C NMR (126 MHz, DMSO-d_6) δ 28.0 (C(*C*H$_3$)$_3$), 43.1 (CH$_2$ $_{piperazine}$), 52.3 (CH$_2$ $_{piperazine}$), 63.6 (Ar*C*H$_2$N), 66.4 (O*C*H$_2$Ph), 78.7 (O*C*(CH$_3$)$_3$), 128.2 (CH Ar), 128.2 (CH Ar), 128.5 (CH Ar), 132.7 (C$_q$ Ar), 136.1 (C$_q$ Ar), 146.3 (C-4, 6), 153.4 (^{t}BuO*C*ON or ArNH*C*O$_2$Bn), 153.8 (^{t}BuO*C*ON or ArNH*C*O$_2$Bn), 160.4 (C-2); LRMS (ES$^+$) *m/z* 428.5 [M+H]$^+$; HRMS (NSI) calcd for C$_{22}$H$_{30}$N$_5$O$_4$ [M+H]$^+$ 428.2292, found 428.2288.

tert-Butyl 4-((5-aminopyrimidin-2-yl)methyl)piperazine-1-carboxylate, (438)



tert-Butyl 4-((5-(((benzyloxy)carbonyl)amino)pyrimidin-2-yl)methyl)piperazine-1-carboxylate (**437**) (600 mg, 1.40 mmol) in EtOAc (28 mL) was subjected to palladium-catalysed hydrogenation using an H-Cube® reactor and a 10% Pd/C CatCart under a full pressure of hydrogen. The reaction was conducted at RT for 24 h. The reaction mixture was concentrated *in vacuo* to afford the *title compound* as a pale yellow solid (407 mg, 99%) which was used in the next step without further purification; R_f = 0.26 (amine silica, DCM:MeOH, 97:3); m.p. 200.5-202.5 °C; λ_{max} (EtOH)/nm 249.0, 318.0; IR (neat) ν_{max}/cm^{-1} 3381, 3323, 3197, 2972, 2929, 2894, 2863, 2811, 2775, 1673, 1589, 1554, 1453; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.37 (9H, s, C(C*H*$_3$)$_3$), 2.35 (4H, t, *J* = 5.0 Hz, CH$_2$ $_{piperazine}$), 3.26 (4H, brs, CH$_2$ $_{piperazine}$), 3.50 (2H, s, ArC*H*$_2$N), 5.47 (2H, brs, ArN*H*$_2$), 8.05 (2H, s, H-4, 6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 28.1 (C(*C*H$_3$)$_3$), 43.3 (CH$_2$ $_{piperazine}$), 52.3 (CH$_2$ $_{piperazine}$), 63.8 (Ar*C*H$_2$N), 78.7 (O*C*(CH$_3$)$_3$), 141.1 (C-5), 141.5 (C-4, 6), 153.8 (C-2 or *C*O$_2$N), 154.1 (C-2 or *C*O$_2$N); LRMS (ES$^+$) *m/z* 294.3 [M+H]$^+$; HRMS (NSI) calcd for C$_{14}$H$_{24}$N$_5$O$_2$ [M+H]$^+$ 294.1925, found 294.1926.

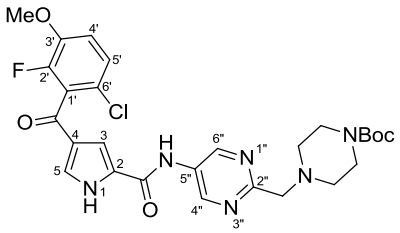
tert-Butyl 4-((5-(4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxamido) pyrimidin-2-yl)methyl)piperazine-1-carboxylate, (439)



Compound **439** was synthesised according to general procedure Y, using the following reagents: 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**) (200 mg, 0.66 mmol), triethylamine (231 µL, 167 mg, 1.65 mmol), 2-chloro-1-methylpyridinium iodide (186 mg, 0.73 mmol), *tert*-butyl 4-((5-aminopyrimidin-2-yl)methyl)piperazine-1-

carboxylate (**438**) (243 mg, 1.65 mmol) and DCM (6.6 mL). The crude yellow solid was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 15:85) to yield the *title compound* as a white solid (160 mg, 42%); R_f = 0.32 (petrol:EtOAc, 15:85); m.p. 162.5-164.5 °C; λ_{max} (EtOH)/nm 292.8; IR (neat) ν_{max}/cm^{-1} 2967, 2932, 2864, 2815, 1652, 1585, 1555, 1516, 1447, 1423, 1392; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.38 (9H, s, C(CH_3)$_3$), 2.43 (4H, t, *J* = 5.1 Hz, $CH_{2\ piperazine}$), 3.29 (4H, brs, $CH_{2\ piperazine}$), 3.69 (2H, s, ArCH_2N), 7.51 (1H, s, H-3), 7.53 (1H, dd, *J* = 8.9, 1.4 Hz, H-5'), 7.68 (1H, s, H-5), 7.79 (1H, dd, *J* = 8.9, 8.4 Hz, H-4'), 9.08 (2H, s, H-4", 6"), 10.43 (1H, s, CON*H*Ar), 12.88 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 28.1 (C(*C*H_3)$_3$), 43.2 ($CH_{2\ piperazine}$), 52.3 ($CH_{2\ piperazine}$), 63.7 (Ar*C*H_2N), 78.7 (O*C*(CH$_3$)$_3$), 111.9 (C-3), 119.4 (d, *J* = 18.2 Hz, C-3'), 124.9 (C-2 or C-4), 126.9 (d, *J* = 3.9 Hz, C-5'), 128.0 (C-2 or C-4), 129.1 (d, *J* = 23.1 Hz, C-1'), 129.2 (d, *J* = 5.1 Hz, C-6'), 130.6 (C-5), 131.9 (C-4'), 132.5 (C-5"), 147.9 (C-4", 6"), 153.8 (*C*O$_2$N), 153.9 (d, *J* = 248.5 Hz, C-2'), 158.7 (*C*ONHAr), 161.1 (C-2"), 182.6 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.7 (ArF); LRMS (ES$^-$) *m/z* 575.3 [M(^{35}Cl^{35}Cl)-H]$^-$, 577.3 [M(^{35}Cl^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{26}H_{28}Cl_2FN_6O_4$ [M(^{35}Cl^{35}Cl)+H]$^+$ 577.1528, found 577.1521.

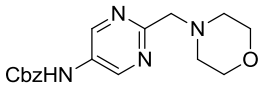
tert-Butyl 4-((5-(4-(6-chloro-2-fluoro-3-methoxybenzoyl)-1*H*-pyrrole-2-carboxamido) pyrimidin-2-yl)methyl)piperazine-1-carboxylate, (440)



Compound **440** was synthesised according to general procedure Y, using the following reagents: 4-(6-chloro-2-fluoro-3-methoxybenzoyl)-1*H*-pyrrole-2-carboxylic acid (**338**) (200 mg, 0.67 mmol), triethylamine (234 µL, 170 mg, 1.68 mmol), 2-chloro-1-methylpyridinium iodide (189 mg, 0.74 mmol), *tert*-butyl 4-((5-aminopyrimidin-2-yl)methyl)piperazine-1-carboxylate (**438**) (246 mg, 0.84 mmol) and DCM (6.7 mL). The crude yellow solid was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 1:9) to yield the *title compound* as a white solid (121 mg, 31%); R_f = 0.29 (petrol:EtOAc, 1:9); m.p. 169.0-171.0 °C; λ_{max} (EtOH)/nm 293.0; IR (neat) ν_{max}/cm^{-1} 2958, 2933, 2865, 2815, 1653, 1578, 1553, 1515, 1472, 1433, 1391; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.38 (9H, s, C(CH_3)$_3$), 2.43 (4H, t, *J* = 5.1 Hz, $CH_{2\ piperazine}$), 3.29 (4H, brs, $CH_{2\ piperazine}$), 3.68 (2H, s, ArCH_2N), 3.90 (3H, s, ArOCH_3), 7.33 (1H, dd, *J* = 9.0, 9.0 Hz, H-4'), 7.39 (1H, dd, *J* = 9.0, 1.4 Hz, H-5'), 7.46 (1H, s, H-3), 7.54 (1H, s, H-5), 9.08 (2H,

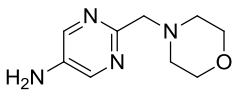
s, H-4”, 6”), 10.42 (1H, s, CON*H*Ar), 12.81 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 28.1 (C(*C*H$_3$)$_3$), 43.3 (CH$_2$ $_{piperazine}$), 52.3 (CH$_2$ $_{piperazine}$), 56.5 (ArO*C*H$_3$), 63.7 (Ar*C*H$_2$N), 78.7 (O*C*(CH$_3$)$_3$), 112.1 (C-3), 115.2 (C-4’), 120.2 (d, *J* = 4.6 Hz, C-6’), 125.3 (C-2 or C-4), 125.6 (d, *J* = 3.7 Hz, C-5’), 127.7 (C-2 or C-4), 128.4 (d, *J* = 20.0 Hz, C-1’), 129.8 (C-5), 132.5 (C-5”), 146.5 (d, *J* = 10.6 Hz, C-3’), 147.9 (C-4”, 6”), 147.9 (d, *J* = 247.1 Hz, C-2’), 153.8 (*C*O$_2$N), 158.8 (*C*ONHAr), 161.1 (C-2”), 183.7 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -136.2 (ArF); LRMS (ES$^-$) *m/z* 571.3 [M(^{35}Cl)-H]$^-$, 573.4 [M(^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{27}H_{31}ClFN_6O_5$ [M(^{35}Cl)+H]$^+$ 573.2023, found 573.2015.

Benzyl (2-(morpholinomethyl)pyrimidin-5-yl)carbamate, (441)



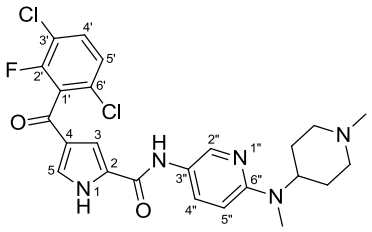
To benzyl (2-formylpyrimidin-5-yl)carbamate (**436**) (350 mg, 1.36 mmol) in TFE (10 mL) was added morpholine (238 µL, 237 mg, 2.72 mmol). The resulting solution was stirred at 38 °C for 1 h. Once cooled at 0 °C, sodium borohydride was carefully added. The resulting mixture was allowed to warm to RT and then stirred for 30 min. Upon completion, the solvent was removed *in vacuo*. The crude residue was dissolved in EtOAc (30 mL), neutralised by washing with saturated aq. NH_4Cl (20 mL), washed with water and brine (20 mL, respectively), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (amine silica gel, petrol:EtOAc, 1:0 → 3:7) to yield the *title compound* as a yellow solid (305 mg, 68%); R_f = 0.32 (amine silica, petrol:EtOAc, 3:7); m.p. 132.5-134.5 °C; λ_{max} (EtOH)/nm 237.0; IR (neat) ν_{max}/cm^{-1} 3207, 3144, 3063, 3005, 2960, 2868, 2812, 1729, 1589, 1531, 1452, 1228; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.40 – 2.47 (4H, m, NC*H*$_2$ $_{morpholine}$), 3.51 – 3.57 (4H, m, OC*H*$_2$ $_{morpholine}$), 3.62 (2H, s, ArC*H*$_2$N), 5.19 (2H, s, OC*H*$_2$Ph), 7.32 – 7.46 (5H, m, 5 × Ar*H*), 8.83 (2H, s, H-4, 6), 10.17 (1H, s, ArN*H*Cbz); ^{13}C NMR (126 MHz, DMSO-d_6) δ 53.1 (N*C*H$_2$ $_{morpholine}$), 64.1 (Ar*C*H$_2$N), 66.1 (O*C*H$_2$ $_{morpholine}$), 66.4 (O*C*H$_2$Ph), 128.2 (CH Ar), 128.2 (CH Ar), 128.5 (CH Ar), 132.7 (C$_q$ Ar), 136.1 (C$_q$ Ar), 146.3 (C-4, 6), 153.4 (ArNH*C*O$_2$Bn), 160.3 (C-2); LRMS (ES$^+$) *m/z* 329.4 [M+H]$^+$; HRMS (NSI) calcd for $C_{17}H_{21}N_4O_3$ [M+H]$^+$ 329.1608, found 329.1608.

2-(Morpholinomethyl)pyrimidin-5-amine, (442)



Benzyl (2-(morpholinomethyl)pyrimidin-5-yl)carbamate (**441**) (275 mg, 0.84 mmol) in MeOH (17 mL) was subjected to palladium-catalysed hydrogenation using an H-Cube® reactor and a 10% Pd/C CatCart under a full pressure of hydrogen. The reaction was conducted at RT for 24 h. The reaction mixture was concentrated *in vacuo* to afford the *title compound* as a brown oil (158 mg, 97%) which was used in the next step without further purification; R_f = 0.34 (amine silica, EtOAc, 100%); λ_{max} (EtOH)/nm 248.6, 317.0; IR (neat) ν_{max}/cm^{-1} 3298, 3189, 2920, 2854, 2815, 1660, 1627, 1581, 1449; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.29 – 2.45 (4H, m, NC$H_{2\ morpholine}$), 3.47 (2H, s, ArCH_2N), 3.49 - 3.62 (4H, m, OC$H_{2\ morpholine}$), 5.45 (2H, brs, ArNH_2), 8.06 (2H, s, H-4, 6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 53.1 (NC$H_{2\ morpholine}$), 64.2 (Ar*C*H_2N), 66.0 (O*C*$H_{2\ morpholine}$), 141.1 (C-5), 141.5 (C-4, 6), 154.8 (C-2); LRMS (ES$^+$) *m/z* 195.3 [M+H]$^+$; HRMS (NSI) calcd for $C_9H_{15}N_4O$ [M+H]$^+$ 195.1240, found 195.1242.

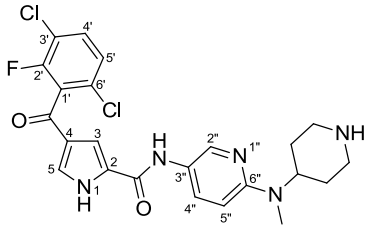
4-(3,6-Dichloro-2-fluorobenzoyl)-*N*-(6-(methyl(1-methylpiperidin-4-yl)amino)pyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (445)



Compound **445** was synthesised according to general procedure E', using the following reagents: *tert*-butyl 4-((5-(4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxamido) pyridin-2-yl)(methyl)amino)piperidine-1-carboxylate (**465**) (100 mg, 0.17 mmol), formic acid (0.85 mL) and formaldehyde (37 % wt. in water) (50 µL, 0.68 mmol). The crude yellow solid was purified by column chromatography (amine silica gel, DCM:MeOH, 1:0 → 97:3) to yield the *title compound* as a white solid (63 mg, 74%); R_f = 0.32 (amine silica, DCM:MeOH, 97:3); m.p. 217.5-219.5 °C; λ_{max} (EtOH)/nm 291.4; IR (neat) ν_{max}/cm^{-1} 3313, 2981, 2971, 2782, 1646, 1584, 1532, 1500, 1448, 1394, 1296, 1281, 1264; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.42 – 1.57 (2H, m, CH_2CH$_2$NMe), 1.75 (2H, dddd, *J* = 12.2, 12.2, 12.2 and 3.8 Hz, CH_2CH$_2$NMe), 1.99 (2H, ddd, *J* = 12.2, 12.2 and 2.5 Hz, CH$_2$CH_2NMe), 2.17 (3H, s, NCH_3), 2.81 (3H, s, NCH_3), 2.82 – 2.85 (2H, m, CH$_2$CH_2NMe), 4.34 (1H, tt, *J* = 12.2, 3.8 Hz, ArN(CH$_3$)C*H*), 6.64 (1H, d, *J* = 9.1 Hz, H-5"), 7.41 (1H, s, H-3), 7.51 (1H, dd, *J* = 8.8, 1.4 Hz, H-5'), 7.56 (1H, s, H-5), 7.75 (1H,

dd, *J* = 9.1, 2.7 Hz, H-4”), 7.77 (1H, dd, *J* = 8.8, 8.5 Hz, H-4’), 8.35 (1H, d, *J* = 2.7 Hz, H-2”), 9.89 (1H, s, CON*H*Ar), 12.66 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 28.4 (*C*H_2CH$_2$NMe), 29.6 (N*C*H$_3$), 46.0 (N*C*H$_3$), 51.8 (ArN(CH$_3$)*C*H), 55.1 (CH$_2$*C*H$_2$NMe), 105.5 (C-5”), 110.6 (C-3), 119.3 (d, *J* = 18.1 Hz, C-3’), 124.5 (C-3”), 124.7 (C-2 or C-4), 126.9 (d, *J* = 3.8 Hz, C-5’), 128.9 (C-2 or C-4), 129.2 (d, *J* = 5.5 Hz, C-6’), 129.2 (d, *J* = 23.1 Hz, C-1’), 129.7 (C-5), 131.3 (C-4’ or C-4”), 131.8 (C-4’ or C-4”), 140.4 (C-2”), 153.8 (d, *J* = 247.2 Hz, C-2’), 155.3 (C-6”), 158.2 (*C*ONHAr), 182.6 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.7 (ArF); LRMS (ES$^-$) *m/z* 502.3 [M(^{35}Cl^{35}Cl)-H]$^-$, 504.3 [M(^{35}Cl^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{24}H_{25}Cl_2FN_5O_2$ [M(^{35}Cl^{35}Cl)+H]$^+$ 504.1364, found 504.1352.

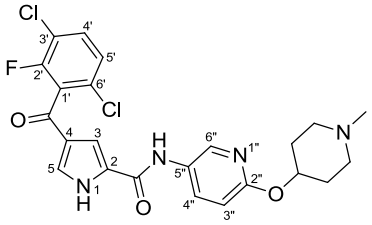
4-(3,6-Dichloro-2-fluorobenzoyl)-*N*-(6-(methyl(piperidin-4-yl)amino)pyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (446)



Compound **446** was synthesised according to general procedure F’, using the following reagents: *tert*-butyl 4-((5-(4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxamido) pyridin-2-yl)(methyl)amino)piperidine-1-carboxylate (**465**) (120 mg, 0.20 mmol), triethylsilane (81 µL, 59 mg, 0.51 mmol), TFA (1 mL) and DCM (1 mL). The crude yellow solid was purified by column chromatography (amine silica gel, DCM:MeOH, 1:0 → 96:4) to yield the *title compound* as a white solid (77 mg, 77%); R_f = 0.31 (amine silica, DCM:MeOH, 96:4); m.p. 172.0-174.0 °C; λ_{max} (EtOH)/nm 285.8; IR (neat) ν_{max}/cm^{-1} 3328, 2981, 2971, 1644, 1583, 1531, 1501, 1448, 1319, 1297, 1284; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.49 (2H, d, *J* = 9.7 Hz, C*H*$_2$CH$_2$NH), 1.59 (2H, dddd, *J* = 12.1, 12.1, 12.1 and 4.1 Hz, C*H*$_2$CH$_2$NH), 2.57 (2H, ddd, *J* = 12.1, 12.1 and 2.7 Hz, CH$_2$C*H*$_2$NH), 2.81 (3H, s, NC*H*$_3$), 3.01 (2H, d, *J* = 12.1 Hz, CH$_2$C*H*$_2$NH), 4.43 (1H, tt, *J* = 12.1, 4.1 Hz, ArN(CH$_3$)C*H*), 6.64 (1H, d, *J* = 9.1 Hz, H-5”), 7.39 (1H, s, H-3), 7.51 (1H, dd, *J* = 8.8, 1.3 Hz, H-5’), 7.55 (1H, s, H-5), 7.71 – 7.82 (2H, m, H-4’ and H-4”), 8.35 (1H, d, *J* = 2.7 Hz, H-2”), 9.89 (1H, s, CON*H*Ar); ^{13}C NMR (126 MHz, DMSO-d_6) δ 29.6 (*C*H$_2$CH$_2$NH), 29.9 (N*C*H$_3$), 45.8 (CH$_2$*C*H$_2$NH), 52.5 (ArN(CH$_3$)*C*H), 105.5 (C-5”), 110.6 (C-3), 119.3 (d, *J* = 18.1 Hz, C-3’), 124.5 (C$_q$ Ar), 124.7 (C$_q$ Ar), 126.8 (d, *J* = 3.8 Hz, C-5’), 129.2 (d, *J* = 4.9 Hz, C-6’), 129.3 (d, *J* = 27.0 Hz, C-1’), 129.9 (C-5), 131.3 (C-4’ or C-4”), 131.8 (C-4’ or C-4”), 140.4 (C-2”), 153.8 (d, *J* = 248.3 Hz, C-2’), 155.2 (C-3”),

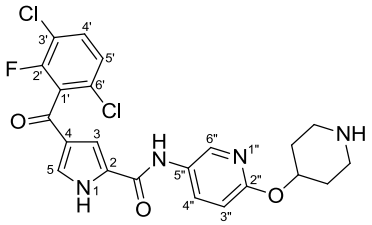
158.3 (*C*ONHAr), 182.5 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.7 (ArF); LRMS (ES$^-$) *m/z* 488.3 [M(^{35}Cl^{35}Cl)-H]$^-$, 490.3 [M(^{35}Cl^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{23}H_{23}Cl_2FN_5O_2$ [M(^{35}Cl^{35}Cl)+H]$^+$ 490.1207, found 490.1198.

4-(3,6-Dichloro-2-fluorobenzoyl)-*N*-(6-((1-methylpiperidin-4-yl)oxy)pyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (447)



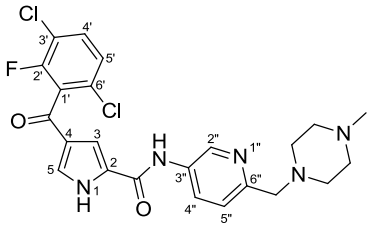
Compound **447** was synthesised according to general procedure E', using the following reagents: *tert*-butyl 4-((5-(4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxamido) pyridin-2-yl)oxy)piperidine-1-carboxylate (**466**) (100 mg, 0.17 mmol), formic acid (0.85 mL) and formaldehyde (37 % wt. in water) (52 µL, 0.69 mmol). The crude yellow solid was purified by column chromatography (amine silica gel, DCM:MeOH, 1:0 → 97:3) to yield the *title compound* as a white solid (60 mg, 71%); R_f = 0.28 (amine silica, DCM:MeOH, 97:3); m.p. 189.5-191.5 °C; λ_{max} (EtOH)/nm 263.0; IR (neat) ν_{max}/cm^{-1} 3357, 2981, 2971, 1670, 1635, 1588, 1528, 1485, 1450, 1289, 1275, 1231; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.64 (2H, dddd, *J* = 12.9, 9.3, 9.3 and 3.6 Hz, C*H*$_2$CH$_2$NMe), 1.89 – 2.00 (2H, m, C*H*$_2$CH$_2$NMe), 2.14 (2H, dd, *J* = 12.9, 12.9 Hz, CH$_2$C*H*$_2$NMe), 2.17 (3H, s, NC*H*$_3$), 2.63 (2H, ddd, *J* = 12.9, 4.5 and 4.5 Hz, CH$_2$C*H*$_2$NMe), 4.92 (1H, tt, *J* = 8.6, 3.9 Hz, ArOC*H*), 6.79 (1H, d, *J* = 8.9 Hz, H-5"), 7.45 (1H, d, *J* = 1.9 Hz, H-3), 7.52 (1H, dd, *J* = 8.8, 1.4 Hz, H-5'), 7.59 (1H, d, *J* = 1.9 Hz, H-5), 7.78 (1H, dd, *J* = 8.8, 8.4 Hz, H-4'), 7.96 (1H, dd, *J* = 8.9, 2.7 Hz, H-4"), 8.43 (1H, d, *J* = 2.7 Hz, H-2"), 10.09 (1H, s, CON*H*Ar), 12.72 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 30.7 (*C*H$_2$CH$_2$NMe), 45.8 (NC*H*$_3$), 52.8 (CH$_2$*C*H$_2$NMe), 70.2 (ArO*C*H), 110.8 (C-5"), 111.0 (C-3), 119.3 (d, *J* = 18.2 Hz, C-3'), 124.7 (C-2 or C-4), 126.9 (d, *J* = 3.8 Hz, C-5'), 128.6 (C-2 or C-4), 129.2 (d, *J* = 24.0 Hz, C-1' and C-3"), 129.2 (d, *J* = 5.2 Hz, C-6'), 130.0 (C-5), 131.8 (C-4'), 132.5 (C-4"), 138.6 (C-2"), 153.8 (d, *J* = 248.6 Hz, C-2'), 158.4 (*C*ONHAr or C-6"), 158.9 (*C*ONHAr or C-6"), 182.6 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.7 (ArF); LRMS (ES$^-$) *m/z* 489.3 [M(^{35}Cl^{35}Cl)-H]$^-$, 491.2 [M(^{35}Cl^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{23}H_{22}Cl_2FN_4O_3$ [M(^{35}Cl^{35}Cl)+H]$^+$ 491.1048, found 491.1038.

4-(3,6-Dichloro-2-fluorobenzoyl)-*N*-(6-(piperidin-4-yloxy)pyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (448)



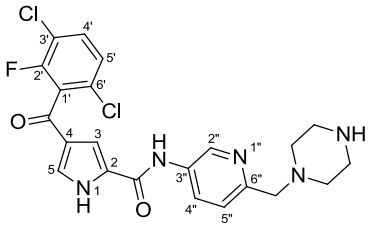
Compound **448** was synthesised according to general procedure F', using the following reagents: *tert*-butyl 4-((5-(4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxamido) pyridin-2-yl)oxy)piperidine-1-carboxylate (**466**) (120 mg, 0.21 mmol), triethylsilane (83 µL, 30 mg, 0.52 mmol), TFA (1.1 mL) and DCM (1.1 mL). The crude yellow solid was purified by column chromatography (amine silica gel, DCM:MeOH, 1:0 → 96:4) to yield the *title compound* as a white solid (77 mg, 77%); R_f = 0.25 (amine silica, DCM:MeOH, 96:4); m.p. 212.0-214.0 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.47 (2H, dddd, *J* = 12.9, 10.5, 10.2 and 4.0 Hz, C*H*$_2$CH$_2$NH), 1.84 – 2.00 (2H, m, C*H*$_2$CH$_2$NH), 2.57 (2H, ddd, *J* = 12.9, 10.5 and 2.9 Hz, CH$_2$C*H*$_2$NH), 2.95 (2H, ddd, *J* = 12.9, 4.1 and 4.1 Hz, CH$_2$C*H*$_2$NH), 4.99 (1H, tt, *J* = 9.2, 4.2 Hz, ArOC*H*), 6.78 (1H, d, *J* = 8.9 Hz, H-5"), 7.42 (1H, s, H-3), 7.51 (1H, dd, *J* = 8.8, 1.3 Hz, H-5'), 7.58 (1H, s, H-5), 7.77 (1H, dd, *J* = 8.8, 8.4 Hz, H-4'), 7.96 (1H, dd, *J* = 8.9, 2.8 Hz, H-4"), 8.42 (1H, d, *J* = 2.8 Hz, H-2"), 10.07 (1H, s, CON*H*Ar); ^{13}C NMR (126 MHz, DMSO-d_6) δ 32.3 (*C*H$_2$CH$_2$NH), 43.9 (CH$_2$*C*H$_2$NH), 71.4 (ArO*C*H), 110.7 (C-5"), 111.1 (C-3), 119.3 (d, *J* = 17.8 Hz, C-3'), 124.8 (C-2 or C-4), 126.9 (d, *J* = 3.8 Hz, C-5'), 128.9 (C-2 or C-4), 129.2 (d, *J* = 5.4 Hz, C-6'), 129.3 (C-3"), 129.3 (d, *J* = 23.0 Hz, C-1'), 130.3 (C-5), 131.8 (C-4'), 132.4 (C-4"), 138.6 (C-2"), 153.8 (d, *J* = 248.5 Hz, C-2'), 158.5 (*C*ONHAr or C-6"), 158.9 (*C*ONHAr or C-6"), 182.5 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.7 (ArF); IR (neat) ν_{max}/cm^{-1} 3364, 3301, 2933, 2857, 1643, 1532, 1485, 1447, 1289, 1271, 1228; λ_{max} (EtOH)/nm 262.4; LRMS (ES$^-$) *m/z* 473.3 [M(^{35}Cl^{35}Cl)-H]$^-$, 475.3 [M(^{35}Cl^{37}Cl)-H]$^-$; HRMS (ESI) calcd for $C_{22}H_{20}Cl_2FN_4O_3$ [M(^{35}Cl^{35}Cl)+H]$^+$ 477.0891, found 477.0885.

4-(3,6-Dichloro-2-fluorobenzoyl)-*N*-(6-((4-methylpiperazin-1-yl)methyl)pyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (449)



Compound **449** was synthesised according to general procedure E', using the following reagents: *tert*-butyl 4-((5-(4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxamido) pyridin-2-yl)methyl)piperazine-1-carboxylate (**476**) (45 mg, 0.08 mmol), formic acid (0.4 mL) and formaldehyde (37 % wt. in water) (23 µL, 0.31 mmol). The crude yellow solid was purified by column chromatography (amine silica gel, DCM:MeOH, 1:0 → 95:5) to yield the *title compound* as a white solid (25 mg, 66%); R_f = 0.28 (amine silica, DCM:MeOH, 95:5); m.p. 161.5-163.5 °C; λ_{max} (EtOH)/nm 296.0; IR (neat) ν_{max}/cm^{-1} 3215, 2933, 2802, 1639, 1590, 1527, 1491, 1446, 1391; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.16 (3H, s, NCH_3), 2.22 – 2.49 (8H, m, NC$H_{2\ piperazine}$), 3.53 (2H, s, ArCH_2N), 7.39 (1H, d, *J* = 8.5 Hz, H-5"), 7.47 – 7.55 (2H, m, H-3 and H-5'), 7.61 (1H, s, H-5), 7.78 (1H, dd, *J* = 8.8, 8.4 Hz, H-4'), 8.10 (1H, dd, *J* = 8.5, 2.5 Hz, H-4"), 8.79 (1H, d, *J* = 2.5 Hz, H-2"), 10.22 (1H, s, CON*H*Ar), 12.76 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 45.7 (N*C*H$_3$), 52.6 (N*C*H$_{2\ piperazine}$), 54.7 (N*C*H$_{2\ piperazine}$), 63.3 (Ar*C*H$_2$N), 111.4 (C-3), 119.4 (d, *J* = 18.0 Hz), 122.6 (C-5"), 124.8 (C-2 or C-4), 126.9 (d, *J* = 3.7 Hz, C-5'), 127.6 (C-4"), 128.5 (C-2 or C-4), 129.1 (d, *J* = 23.2 Hz, C-1'), 129.2 (d, *J* = 4.9 Hz, C-6'), 130.2 (C-5), 131.9 (C-4'), 134.0 (C-3"), 140.7 (C-2"), 153.2 (C-6"), 153.9 (d, *J* = 248.5 Hz, C-2'), 158.6 (*C*ONHAr), 182.6 (Ar*C*O); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.7 (ArF); LRMS (ES$^+$) *m/z* 490.4 [M(^{35}Cl^{35}Cl)+H]$^+$, 492.5 [M(^{35}Cl^{37}Cl)+H]$^+$; HRMS (NSI) calcd for $C_{23}H_{23}Cl_2FN_5O_2$ [M(^{35}Cl^{35}Cl)+H]$^+$ 490.1207, found 490.1195.

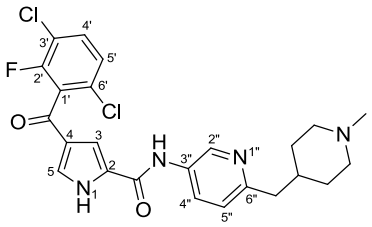
4-(3,6-Dichloro-2-fluorobenzoyl)-*N*-(6-(piperazin-1-ylmethyl)pyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (450)



Compound **450** was synthesised according to general procedure F', using the following reagents: *tert*-butyl 4-((5-(4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxamido)

pyridin-2-yl)methyl)piperazine-1-carboxylate (**476**) (50 mg, 0.09 mmol), triethylsilane (35 µL, 25 mg, 0.22 mmol), TFA (0.45 mL) and DCM (0.45 mL). The crude yellow solid was purified by column chromatography (amine silica gel, DCM:MeOH, 1:0 → 9:1) to yield the *title compound* as a white solid (30 mg, 73%); R_f = 0.25 (amine silica, DCM:MeOH, 9:1); m.p. 179.5-181.5 °C; λ_{max} (EtOH)/nm 296.0; IR (neat) ν_{max}/cm^{-1} 3105, 2921, 2812, 1637, 1589, 1525, 1490, 1445, 1389; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.33 (4H, brs, NC$H_{2\ piperazine}$), 2.70 (4H, t, *J* = 4.8 Hz, NC$H_{2\ piperazine}$), 3.51 (2H, s, ArCH_2N), 7.40 (1H, d, *J* = 8.5 Hz, H-5"), 7.49 (1H, s, H-3), 7.52 (1H, dd, *J* = 8.8, 0.6 Hz, H-5'), 7.60 (1H, s, H-5), 7.78 (1H, dd, *J* = 8.8, 8.3 Hz, H-4'), 8.09 (1H, dd, *J* = 8.5, 2.6 Hz, H-4"), 8.79 (1H, d, *J* = 2.6 Hz, H-2"), 10.20 (1H, s, CON*H*Ar); ^{13}C NMR (126 MHz, DMSO-d_6) δ 45.5 (N*C*H$_{2\ piperazine}$), 54.0 (N*C*H$_{2\ piperazine}$), 64.1 (Ar*C*H$_2$N), 111.4 (C-3), 119.3 (d, *J* = 17.9 Hz, C-3'), 122.6 (C-5"), 124.8 (C-2 or C-4), 126.9 (d, *J* = 3.7 Hz, C-5'), 127.5 (C-4"), 128.7 (C-2 or C-4), 129.2 (d, *J* = 23.0 Hz, C-1'), 129.2 (d, *J* = 5.2 Hz, C-6'), 130.4 (C-5), 131.8 (C-4'), 134.0 (C-3"), 140.6 (C-2"), 153.2 (C-6"), 154.8 (d, *J* = 248.8 Hz, C-2'), 158.7 (*C*ONHAr), 182.5 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.6 (ArF); LRMS (ES$^+$) *m/z* 476.5 [M(^{35}Cl^{35}Cl)+H]$^+$, 478.5 [M(^{35}Cl^{37}Cl)+H]$^+$; HRMS (NSI) calcd for $C_{22}H_{21}Cl_2FN_5O_2$ [M(^{35}Cl^{35}Cl)+H]$^+$ 476.1051, found 476.1040.

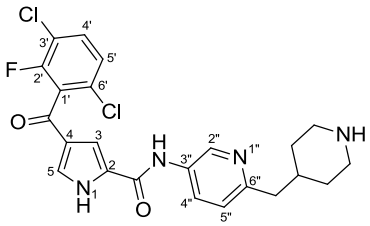
4-(3,6-Dichloro-2-fluorobenzoyl)-*N*-(6-((1-methylpiperidin-4-yl)methyl)pyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (451)



Compound **451** was synthesised according to general procedure E', using the following reagents: *tert*-butyl 4-((5-(4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxamido) pyridin-2-yl)methyl)piperidine-1-carboxylate (**467**) (100 mg, 0.17 mmol), formic acid (0.85 mL) and formaldehyde (37 % wt. in water) (52 µL, 0.69 mmol). The crude yellow solid was purified by column chromatography (amine silica gel, DCM:MeOH, 1:0 → 96:4) to yield the *title compound* as an off-white solid (64 mg, 75%); R_f = 0.26 (amine silica, DCM:MeOH, 96:4); m.p. 148.0-150.0 °C; λ_{max} (EtOH)/nm 261.4, 296.0; IR (neat) ν_{max}/cm^{-1} 3286, 2926, 2846, 2788, 1646, 1592, 1525, 1493, 1447, 1392, 1282, 1237, 1224; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.11 – 1.31 (2H, m, CH_2CH$_2$NMe), 1.50 (2H, d, *J* = 12.0 Hz, CH_2CH$_2$NMe), 1.57 – 1.70 (1H, m, ArCH$_2$C*H*), 1.77 (2H, dd, *J* = 12.0, 12.0 Hz, CH$_2$CH_2NMe), 2.11 (3H, s, NCH_3), 2.59 (2H, d, *J* = 7.0 Hz, ArCH_2CH), 2.70 (2H, d,

J = 10.9 Hz, CH_2CH_2NMe), 7.20 (1H, d, *J* = 8.4 Hz, H-5”), 7.49 (1H, s, H-3), 7.52 (1H, d, *J* = 8.8 Hz, H-5’), 7.61 (1H, s, H-5), 7.78 (1H, dd, *J* = 8.8, 8.3 Hz, H-4’), 8.02 (1H, d, *J* = 8.4 Hz, H-4”), 8.78 (1H, s, H-2”), 10.17 (1H, s, CONHAr), 12.72 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 31.7 (CH_2CH_2NMe), 35.6 ($ArCH_2CH$), 43.8 ($ArCH_2CH$), 46.2 (NCH_3), 55.3 (CH_2CH_2NMe), 111.3 (C-3), 119.3 (d, *J* = 18.1 Hz, C-3’), 123.0 (C-5”), 124.8 (C-2 or C-4), 126.9 (d, *J* = 3.7 Hz, C-5’), 127.4 (C-4”), 128.6 (C-2 or C-4), 129.2 (d, *J* = 23.0 Hz, C-1’), 129.2 (d, *J* = 5.0 Hz, C-3’), 130.2 (C-5), 131.8 (C-4’), 133.1 (C-3”), 141.0 (C-2”), 153.9 (d, *J* = 248.9 Hz, C-2’), 155.1 (CONHAr or C-6”), 158.6 (CONHAr or C-6”), 182.6 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.6 (ArF); LRMS (ES^-) *m/z* 487.3 [M($^{35}Cl^{35}Cl$)-H]$^-$, 489.3 [M($^{35}Cl^{37}Cl$)-H]$^-$; HRMS (NSI) calcd for $C_{24}H_{24}Cl_2FN_4O_2$ [M($^{35}Cl^{35}Cl$)+H]$^+$ 489.1255, found 489.1243.

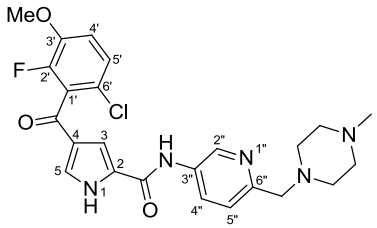
4-(3,6-Dichloro-2-fluorobenzoyl)-*N*-(6-(piperidin-4-ylmethyl)pyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (452)



Compound **452** was synthesised according to general procedure F’, using the following reagents: *tert*-butyl 4-((5-(4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxamido) pyridin-2-yl)methyl)piperidine-1-carboxylate (**467**) (120 mg, 0.21 mmol), triethylsilane (83 µL, 61 mg, 0.52 mmol), TFA (1.1 mL) and DCM (1.1 mL). The crude yellow solid was purified by column chromatography (amine silica gel, DCM:MeOH, 1:0 → 95:5) to yield the *title compound* as an off-white solid (69 mg, 70%); R_f = 0.24 (amine silica, DCM:MeOH, 95:5); m.p. 170.0-172.0 °C; λ_{max} (EtOH)/nm 261.2, 295.8; IR (neat) ν_{max}/cm^{-1} 3112, 2921, 2851, 1642, 1592, 1526, 1490, 1447, 1392, 1286, 1239, 1225; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.00 – 1.17 (2H, m, CH_2CH_2NH), 1.39 – 1.54 (2H, m, CH_2CH_2NH), 1.68 – 1.88 (1H, m, $ArCH_2CH$), 2.43 (2H, dd, *J* = 11.5, 11.5 Hz, CH_2CH_2NH), 2.58 (2H, d, *J* = 7.0 Hz, $ArCH_2CH$), 2.91 (2H, ddd, *J* = 11.5, 3.4 and 3.4 Hz, CH_2CH_2NH), 7.19 (1H, d, *J* = 8.4 Hz, H-5”), 7.42 (1H, s, H-3), 7.51 (1H, d, *J* = 8.7 Hz, H-5’), 7.57 (1H, s, H-5), 7.77 (1H, dd, *J* = 8.7, 8.3 Hz, H-4’), 8.02 (1H, dd, *J* = 8.4, 2.8 Hz, H-4”), 8.78 (1H, d, *J* = 2.8 Hz, H-2”), 10.14 (1H, s, CONHAr); ^{13}C NMR (126 MHz, DMSO-d_6) δ 32.5 (CH_2CH_2NH), 36.5 ($ArCH_2CH$), 44.4 ($ArCH_2CH$), 45.8 (CH_2CH_2NH), 111.5 (C-3), 119.3 (d, *J* = 18.3 Hz, C-3’), 123.0 (C-5”), 124.9 (C-2 or C-4), 126.8 (d, *J* = 4.1 Hz, C-5’), 127.3 (C-4”), 129.3 (d, *J* = 5.2 Hz, C-6’), 129.4 (d, *J* = 23.3 Hz, C-1’),

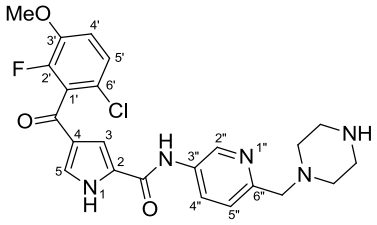
129.4 (C-2 or C-4), 130.9 (C-5), 131.7 (C-4'), 133.2 (C-3"), 141.0 (C-2"), 152.9 (d, *J* = 248.2 Hz, C-2'), 154.8 (*C*ONHAr or C-6"), 159.0 (*C*ONHAr or C-6"), 182.3 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.6 (ArF); LRMS (ES$^-$) *m/z* 473.3 [M(^{35}Cl^{35}Cl)-H]$^-$, 475.3 [M(^{35}Cl^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{23}H_{22}Cl_2FN_4O_2$ [M(^{35}Cl^{35}Cl)+H]$^+$ 475.1098, found 475.1090.

4-(6-Chloro-2-fluoro-3-methoxybenzoyl)-*N*-(6-((4-methylpiperazin-1-yl)methyl) pyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (453)



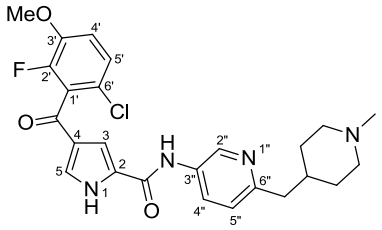
Compound **453** was synthesised according to general procedure E', using the following reagents: *tert*-butyl 4-((5-(4-(6-chloro-2-fluoro-3-methoxybenzoyl)-1*H*-pyrrole-2-carboxamido)pyridin-2-yl)methyl)piperazine-1-carboxylate (**477**) (70 mg, 0.12 mmol), formic acid (0.6 mL) and formaldehyde (37 % wt. in water) (36 µL, 0.49 mmol). The crude yellow solid was purified by column chromatography (amine silica gel, DCM:MeOH, 1:0 → 96:4) to yield the *title compound* as a white solid (45 mg, 76%); R_f = 0.27 (amine silica, DCM:MeOH, 96:4); m.p. 212.0-214.0 °C; λ_{max} (EtOH)/nm 296.2; IR (neat) ν_{max}/cm^{-1} 2938, 2802, 1641, 1607, 1555, 1528, 1491, 1472, 1437, 1277; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.14 (3H, s, NC*H*$_3$), 2.32 (4H, brs, NC*H*$_{2\ \text{piperazine}}$), 2.40 (4H, brs, NC*H*$_{2\ \text{piperazine}}$), 3.53 (2H, s, ArC*H*$_2$N), 3.90 (3H, s, ArOC*H*$_3$), 7.33 (1H, dd, *J* = 8.9, 8.9 Hz, H-4'), 7.39 (2H, d, *J* = 8.9 Hz, H-5' and H-5"), 7.47 (1H, s, H-3), 7.48 (1H, s, H-5), 8.10 (1H, dd, *J* = 8.9, 2.6 Hz, H-4"), 8.78 (1H, d, *J* = 2.6 Hz, H-2"), 10.22 (1H, s, CON*H*Ar), 12.69 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 45.7 (NC*H*$_3$), 52.7 (NC*H*$_{2\ \text{piperazine}}$), 54.7 (NC*H*$_{2\ \text{piperazine}}$), 56.5 (ArO*C*H$_3$), 63.3 (ArC*H*$_2$N), 111.5 (C-3), 115.1 (C-4'), 120.2 (d, *J* = 4.9 Hz, C-6'), 122.6 (C-5"), 125.2 (C-2 or C-4), 125.6 (d, *J* = 3.8 Hz, C-5'), 127.6 (C-4"), 128.2 (C-2 or C-4), 128.4 (d, *J* = 19.9 Hz, C-1'), 129.4 (C-5), 134.0 (C-3"), 140.6 (C-2"), 146.4 (d, *J* = 10.8 Hz, C-3'), 147.9 (d, *J* = 247.0 Hz, C-2'), 153.2 (C-6"), 158.6 (*C*ONHAr), 183.6 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -136.1 (ArF); LRMS (ES$^+$) *m/z* 486.4 [M(^{35}Cl)+H]$^+$, 488.4 [M(^{37}Cl)+H]$^+$; HRMS (NSI) calcd for $C_{24}H_{26}ClFN_5O_3$ [M(^{35}Cl)+H]$^+$ 486.1703, found 486.1695.

4-(6-Chloro-2-fluoro-3-methoxybenzoyl)-*N*-(6-(piperazin-1-ylmethyl)pyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (454)



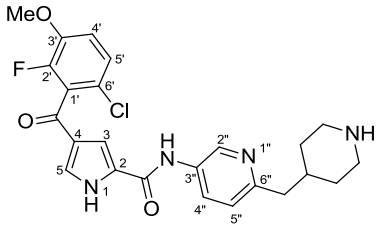
Compound **454** was synthesised according to general procedure E', using the following reagents: *tert*-butyl 4-((5-(4-(6-chloro-2-fluoro-3-methoxybenzoyl)-1*H*-pyrrole-2-carboxamido)pyridin-2-yl)methyl)piperazine-1-carboxylate (**477**) (70 mg, 0.12 mmol), triethylsilane (49 µL, 36 mg, 0.31 mmol), TFA (0.6 mL) and DCM (0.6 mL). The crude yellow solid was purified by column chromatography (amine silica gel, DCM:MeOH, 1:0 → 94:6) to yield the *title compound* as a white solid (41 mg, 71%); R_f = 0.27 (amine silica, DCM:MeOH, 94:6); m.p. 234.5-236.5 °C; λ_{max} (EtOH)/nm 296.0; IR (neat) ν_{max}/cm^{-1} 3110, 2935, 2812, 1639, 1525, 1490, 1471, 1435, 1270; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.33 (4H, brs, NC$H_{2\ piperazine}$), 2.70 (4H, t, *J* = 4.8 Hz, NC$H_{2\ piperazine}$), 3.50 (2H, s, ArCH_2N), 3.90 (3H, s, ArOCH_3), 7.32 (1H, dd, *J* = 8.9, 8.6 Hz, H-4'), 7.38 (1H, dd, *J* = 8.6, 0.8 Hz, H-5'), 7.39 (1H, d, *J* = 8.4 Hz, H-5"), 7.46 (1H, s, H-3), 7.47 (1H, s, H-5), 8.09 (1H, dd, *J* = 8.4, 2.6 Hz, H-4"), 8.79 (1H, d, *J* = 2.6 Hz, H-2"), 10.21 (1H, s, CON*H*Ar); ^{13}C NMR (126 MHz, DMSO-d_6) δ 45.5 (NC$H_{2\ piperazine}$), 54.1 (NC$H_{2\ piperazine}$), 56.5 (ArO*C*H$_3$), 64.1 (ArCH_2N), 111.5 (C-3), 115.1 (C-4'), 120.2 (d, *J* = 4.9 Hz, C-6'), 122.6 (C-5"), 125.2 (C-2 or C-4), 125.6 (d, *J* = 3.8 Hz, C-5'), 127.5 (C-4"), 128.4 (C-2 or C-4), 128.5 (d, *J* = 20.3 Hz, C-1'), 129.6 (C-5), 134.0 (C-3"), 140.6 (C-2"), 146.4 (d, *J* = 10.7 Hz, C-3'), 147.9 (d, *J* = 247.0 Hz, C-2'), 153.1 (C-6"), 158.7 (*C*ONHAr), 183.6 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -136.1 (ArF); LRMS (ES$^+$) *m/z* 472.4 [M(^{35}Cl)+H]$^+$, 474.3 [M(^{37}Cl)+H]$^+$; HRMS (NSI) calcd for $C_{23}H_{24}ClFN_5O_3$ [M(^{35}Cl)+H]$^+$ 472.1546, found 472.1538.

4-(6-Chloro-2-fluoro-3-methoxybenzoyl)-*N*-(6-((1-methylpiperidin-4-yl)methyl)pyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (455)



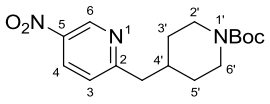
Compound **455** was synthesised according to general procedure E', using the following reagents: *tert*-butyl 4-((5-(4-(6-chloro-2-fluoro-3-methoxybenzoyl)-1*H*-pyrrole-2-carboxamido)pyridin-2-yl)methyl)piperidine-1-carboxylate (**468**) (90 mg, 0.16 mmol), formic acid (0.65 mL) and formaldehyde (37 % wt. in water) (47 µL, 0.63 mmol). The crude yellow solid was purified by column chromatography (amine silica gel, DCM:MeOH, 1:0 → 96:4) to yield the *title compound* as an off-white solid (54 mg, 71%); R_f = 0.27 (amine silica, DCM:MeOH, 96:4); m.p. 138.0-140.0 °C; λ_{max} (EtOH)/nm 295.8; IR (neat) ν_{max}/cm^{-1} 2931, 2844, 2792, 1637, 1525, 1471, 1435, 1392; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.20 (2H, dddd, *J* = 12.1, 12.1, 12.1 and 4.1 Hz, C*H*$_2$CH$_2$NMe), 1.50 (2H, d, *J* = 12.1 Hz, C*H*$_2$CH$_2$NMe), 1.58 – 1.68 (1H, m, ArCH$_2$C*H*), 1.77 (2H, dd, *J* = 10.8, 10.8 Hz, CH$_2$C*H*$_2$NMe), 2.11 (3H, s, NC*H*$_3$), 2.59 (2H, d, *J* = 7.1 Hz, ArC*H*$_2$CH), 2.70 (2H, d, *J* = 11.3 Hz, CH$_2$C*H*$_2$NMe), 3.90 (3H, s, ArOC*H*$_3$), 7.20 (1H, d, *J* = 8.4 Hz, H-5"), 7.32 (1H, dd, *J* = 9.6, 8.9 Hz, H-4'), 7.38 (1H, d, *J* = 9.6 Hz, H-5'), 7.45 (1H, s, H-3 or H-5), 7.47 (1H, s, H-3 or H-5), 8.01 (1H, dd, *J* = 8.4, 2.5 Hz, H-4"), 8.77 (1H, d, *J* = 2.5 Hz, H-2"), 10.16 (1H, s, CON*H*Ar), 12.66 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 31.8 (*C*H$_2$CH$_2$NMe), 35.7 (ArCH$_2$*C*H), 43.8 (Ar*C*H$_2$CH), 46.2 (N*C*H$_3$), 55.4 (CH$_2$*C*H$_2$NMe), 56.5 (ArO*C*H$_3$), 111.4 (C-3), 115.1 (C-4'), 120.2 (d, *J* = 4.9 Hz, C-6'), 123.0 (C-5"), 125.2 (C-2 or C-4), 125.6 (d, *J* = 3.6 Hz, C-5'), 127.4 (C-4"), 128.3 (C-2 or C-4), 128.4 (d, *J* = 20.1 Hz, C-1'), 129.4 (C-5), 133.2 (C-3"), 141.0 (C-2"), 146.4 (d, *J* = 10.5 Hz, C-3'), 148.0 (d, *J* = 247.0 Hz, C-2'), 155.1 (C-6"), 158.6 (*C*ONHAr), 183.6 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -136.1 (ArF); LRMS (ES^+) *m/z* 485.5 $[M(^{35}Cl)+H]^+$, 487.5 $[M(^{37}Cl)+H]^+$; HRMS (NSI) calcd for $C_{25}H_{27}ClFN_4O_3$ $[M(^{35}Cl)+H]^+$ 485.1750, found 485.1736.

4-(6-Chloro-2-fluoro-3-methoxybenzoyl)-*N*-(6-(piperidin-4-ylmethyl)pyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (456)



Compound **456** was synthesised according to general procedure F', using the following reagents: *tert*-butyl 4-((5-(4-(6-chloro-2-fluoro-3-methoxybenzoyl)-1*H*-pyrrole-2-carboxamido)pyridin-2-yl)methyl)piperidine-1-carboxylate (**468**) (90 mg, 0.16 mmol), triethylsilane (63 µL, 46 mg, 0.39 mmol), TFA (0.8 mL) and DCM (0.8 mL). The crude yellow solid was purified by column chromatography (amine silica gel, DCM:MeOH, 1:0 → 95:5) to yield the *title compound* as an off-white solid (56 mg, 76%); R_f = 0.29 (amine silica, DCM:MeOH, 95:5); m.p. 218.0-220.0 °C; λ_{max} (EtOH)/nm 295.8; IR (neat) ν_{max}/cm^{-1} 3101, 2919, 2841, 1638, 1586, 1522, 1469, 1434, 1389; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.02 – 1.15 (2H, m, C*H*$_2$CH$_2$NH), 1.44 – 1.52 (2H, m, C*H*$_2$CH$_2$NH), 1.71 - 1.85 (1H, m, ArCH$_2$C*H*), 2.42 (2H, ddd, *J* = 12.1, 12.1 and 2.6 Hz, CH$_2$C*H*$_2$NH), 2.58 (2H. d, *J* = 7.1 Hz, ArC*H*$_2$CH), 2.90 (2H, ddd, *J* = 12.1, 3.4 and 3.4 Hz, CH$_2$C*H*$_2$NH), 3.90 (3H, s, ArOC*H*$_3$), 7.19 (1H, d, *J* = 8.4 Hz, H-5"), 7.31 (1H, dd, *J* = 9.0, 8.9 Hz, H-4'), 7.38 (1H, dd, *J* = 9.0, 1.4 Hz, H-5'), 7.41 (1H, s, H-3 or H-5), 7.45 (1H, s, H-3 or H-5), 8.02 (1H, dd, *J* = 8.4, 2.5 Hz, H-4"), 8.77 (1H, d, *J* = 2.5 Hz, H-2"), 10.15 (1H, s, CON*H*Ar), 12.68 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 32.6 (*C*H$_2$CH$_2$NH), 36.6 (ArCH$_2$*C*H), 44.5 (Ar*C*H$_2$CH), 45.9 (CH$_2$*C*H$_2$NH), 56.5 (ArO*C*H$_3$), 111.6 (C-3), 115.0 (C-4'), 120.3 (d, *J* = 4.7 Hz, C-6'), 123.0 (C-5"), 125.3 (C-2 or C-4), 125.5 (d, *J* = 3.7 Hz, C-5'), 127.3 (C-4"), 128.6 (d, *J* = 20.0 Hz, C-1'), 128.9 (C-2 or C-4), 130.0 (C-5), 133.2 (C-3"), 141.0 (C-2"), 146.4 (d, *J* = 10.7 Hz, C-3'), 147.9 (d, *J* = 246.9 Hz, C-2'), 154.9 (C-6"), 158.9 (*C*ONHAr), 183.5 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -136.1 (ArF); LRMS (ES$^+$) *m/z* 471.5 [M(^{35}Cl)+H]$^+$, 473.5 [M(^{37}Cl)+H]$^+$; HRMS (NSI) calcd for $C_{24}H_{25}ClFN_4O_3$ [M(^{35}Cl)+H]$^+$ 471.1594, found 471.1583.

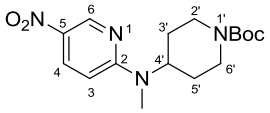
***tert*-Butyl 4-((5-nitropyridin-2-yl)methyl)piperidine-1-carboxylate, (458)**



To a degassed sample of *tert*-butyl 4-methylidenepiperidine-1-carboxylate (**457**) (750 mg, 3.80 mmol) was added 9-BBN (0.5 M in THF) (7.60 mL, 3.80 mmol). The resulting

solution was sparged with nitrogen for 15 min and then reflux for 3 h. After cooling to RT, *N*,*N*-dimethylformamide (7 mL) and water (0.7 mL) were added and the resulting solution was sparged with nitrogen for 15 min. To the degassed mixture was added 2-chloro-5-nitropyridine (1.20 g, 7.60 mmol), potassium carbonate (788 mg, 5.70 mmol) and [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with DCM (233 mg, 0.28 mmol). The resulting mixture was heated at 60 °C overnight. Upon completion, the heterogeneous mixture was filtered through Celite and the solvent was removed *in vacuo*. The crude residue was dissolved in a mixture of EtOAc and water (30 mL, respectively) and extracted with EtOAc (3 × 30 mL). The pooled organic extracts were washed with water (40 mL) and brine (40 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 3:1) to yield the *title compound* as a yellow solid (485 mg, 40%); R_f = 0.31 (petrol:EtOAc, 3:1); m.p. 80.5-82.5 °C; λ_{max} (EtOH)/nm 254.8, 278.4; IR (neat) ν_{max}/cm^{-1} 3044, 2972, 2922, 2851, 1683, 1597, 1576, 1515, 1468, 1423, 1354, 1287, 1238; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.04 – 1.15 (2H, m, H-3', 5'), 1.38 (9H, s, C(CH_3)$_3$), 1.48 – 1.56 (2H, m, H-3', 5'), 1.91 – 2.03 (1H, m, H-4'), 2.66 (2H, brs, H-2', 6'), 2.82 (2H, d, *J* = 7.1 Hz, ArCH_2), 3.89 (2H, d, *J* = 13.2 Hz, H-2', 6'), 7.56 (1H, d, *J* = 8.6 Hz, H-3), 8.50 (1H, dd, *J* = 8.6, 2.7 Hz, H-4), 9.29 (1H, d, *J* = 2.7 Hz, H-6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 28.1 (C(CH_3)$_3$), 31.3 (C-3', 5'), 35.8 (C-4'), 43.1 (C-2', 6'), 44.0 (Ar*C*H$_2$), 78.4 (O*C*(CH$_3$)$_3$), 124.2 (C-3), 131.6 (C-4), 142.6 (C-5), 144.2 (C-6), 153.8 (*C*O$_2$N), 167.0 (C-2); LRMS (ES$^+$) *m/z* 320.3 [M+H]$^+$; HRMS (NSI) calcd for $C_{16}H_{24}N_3O_4$ [M+H]$^+$ 322.1761, found 322.1763.

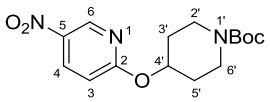
tert-Butyl 4-(methyl(5-nitropyridin-2-yl)amino)piperidine-1-carboxylate, (460)



To 2-chloro-5-nitropyridine (**459**) (672 mg, 4.24 mmol) in THF (20 mL) was added triethylamine (650 µL, 472 mg, 4.67 mmol) and *tert*-butyl 4-(methylamino)piperidine-1-carboxylate (995 µL, 1.0 g, 4.67 mmol) at RT. The resulting solution was stirred at reflux overnight. Upon completion, the solvent was removed *in vacuo*. The crude residue was dissolved in EtOAc (20 mL), washed with water (20 mL) and extracted with EtOAc (3 × 25 mL). The pooled organic extracts were washed with brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude yellow solid was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 3:1) to yield the *title compound* as a yellow solid (1.07 g, 75%); R_f = 0.31 (petrol:EtOAc, 3:1); m.p. 158.5-160.5 °C;

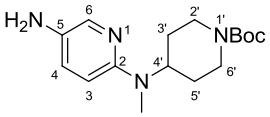
λ_{max} (EtOH)/nm 368.6; IR (neat) ν_{max}/cm^{-1} 2963, 2926, 1691, 1595, 1571, 1509, 1477, 1410, 1334, 1295, 1241; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.41 (9H, s, C(CH_3)$_3$), 1.55 - 1.74 (4H, m, H-3', 5'), 2.84 (2H, brs, H-2', 6'), 2.98 (3H, s, NCH_3), 4.06 (2H, brs, H-2', 6'), 4.79 (1H, brs, H-4'), 6.81 (1H, d, *J* = 9.7 Hz, H-3), 8.22 (1H, dd, *J* = 9.7, 2.9 Hz, H-4), 8.97 (1H, d, *J* = 2.9 Hz, H-6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 28.1 (C(*C*H$_3$)$_3$), 28.4 (C-3', 5'), 30.3 (N*C*H$_3$), 42.7 (C-2', 6'), 78.8 (O*C*(CH$_3$)$_3$), 105.6 (C-3), 132.7 (C-4), 134.1 (C-5), 146.0 (C-6), 153.7 (*C*O$_2$N), 160.1 (C-2); HRMS (NSI) calcd for $C_{16}H_{25}N_4O_4$ [M+H]$^+$ 337.1870, found 337.1871.

tert-Butyl 4-((5-nitropyridin-2-yl)oxy)piperidine-1-carboxylate, (461)



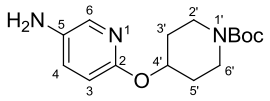
To a suspension of sodium hydride (60% dispersion in mineral oil, 246 mg, 6.15 mmol) in THF (20 mL), cooled in an ice bath, was added 1-Boc-4-hydroxypiperidine (1.24 g, 6.15 mmol). The resulting solution was stirred at 0 °C for 10 min and allowed to warm to RT. After 1 h, the reaction mixture was cooled in an ice bath and 2-chloro-5-nitropyridine (**459**) (650 mg, 4.10 mmol) added in several portions. The resulting mixture was then stirred overnight at RT. Upon completion, the mixture was diluted with EtOAc (20 mL), quenched by the cautious addition of saturated aq. $NaHCO_3$ (20 mL) and extracted with EtOAc (3 × 20 mL). The pooled organic extracts were washed with water and brine (40 mL, respectively), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 9:1) to yield the *title compound* as an off-white solid (1.03 g, 78%); R_f = 0.30 (petrol:EtOAc, 1:9); m.p. 109.5-111.5 °C; λ_{max} (EtOH)/nm 295.0; IR (neat) ν_{max}/cm^{-1} 2961, 2924, 2873, 1675, 1605, 1579, 1513, 1473, 1425, 1349, 1318, 1273; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.41 (9H, s, C(CH_3)$_3$), 1.60 (2H, dddd, *J* = 12.9, 8.8, 8.8 and 4.0 Hz, H-3', 5'$_{axial}$), 2.03 – 1.90 (2H, m, H-3', 5'$_{equ}$), 3.20 (2H, brs, H-2', 6'$_{axial}$), 3.69 (2H, ddd, *J* = 12.9, 4.6 and 4.6 Hz, H-2', 6'$_{equ}$), 5.32 (1H, tt, *J* = 8.8, 4.0 Hz, H-4'), 7.02 (1H, d, *J* = 9.1 Hz, H-3), 8.47 (1H, dd, *J* = 9.1, 2.9 Hz, H-4), 9.07 (1H, d, *J* = 2.9 Hz, H-6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 28.0 (C(*C*H$_3$)$_3$), 30.2 (C-3', 5'), 40.6 (C-2', 6') 72.3 (C-4'), 78.8 (O*C*(CH$_3$)$_3$), 111.8 (C-3), 134.9 (C-4), 139.3 (C-5), 144.6 (C-6), 153.9 (*C*O$_2$N), 165.9 (C-2); HRMS (NSI) calcd for $C_{15}H_{22}N_3O_5$ [M+H]$^+$ 324.1554, found 324.1553; ^{1}H NMR data were identical to literature data.[285]

***tert*-Butyl 4-((5-aminopyridin-2-yl)(methyl)amino)piperidine-1-carboxylate, (462)**



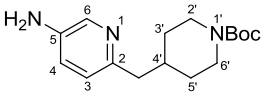
Compound **462** was synthesised according to general procedure D', using the following reagents: *tert*-butyl 4-(methyl(5-nitropyridin-2-yl)amino)piperidine-1-carboxylate (**460**) (750 mg, 2.23 mmol), THF (22.5 mL) and methanol (22.5 mL). The crude pale red solid (650 mg, 95%) was used in the next step without further purification; R_f = 0.32 (EtOAc, 100%); m.p. 108.0-110.0 °C; λ_{max} (EtOH)/nm 257.0; IR (neat) ν_{max}/cm^{-1} 3411, 3339, 3232, 3004, 2945, 1673, 1562, 1494, 1412, 1290, 1270, 1243; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.40 (9H, s, C(CH_3)$_3$), 1.46 – 1.54 (4H, m, H-3', 5'), 2.66 (3H, s, NCH_3), 2.79 (2H, brs, H-2', 6'), 4.03 (2H, brs, H-2', 6'), 4.31 – 4.46 (3H, m, ArNH_2 and H-4'), 6.46 (1H, d, *J* = 8.9 Hz, H-3), 6.91 (1H, dd, *J* = 8.9, 2.9 Hz, H-4), 7.58 (1H, d, *J* = 2.9 Hz, H-6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 28.1 (C(*C*H$_3$)$_3$), 28.4 (C-3', 5'), 29.9 (N*C*H$_3$), 43.0 (C-2', 6'), 52.4 (C-4'), 78.5 (O*C*(CH$_3$)$_3$), 106.9 (C-3), 125.1 (C-4), 133.5 (C-6), 135.6 (C-5), 151.6 (C-2), 153.8 (*C*O$_2$N); LRMS (ES$^+$) *m/z* 307.4 [M+H]$^+$; HRMS (NSI) calcd for $C_{16}H_{27}N_4O_2$ [M+H]$^+$ 307.2129, found 307.2128.

***tert*-Butyl 4-((5-aminopyridin-2-yl)oxy)piperidine-1-carboxylate, (463)**



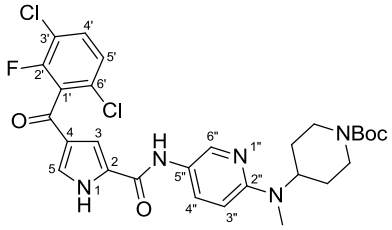
Compound **463** was synthesised according to general procedure D', using the following reagents: *tert*-butyl 4-((5-nitropyridin-2-yl)oxy)piperidine-1-carboxylate (**461**) (800 mg, 2.47 mmol), THF (24.7 mL) and methanol (24.7 mL). The crude pale yellow solid (700 mg, 96%) was used in the next step without further purification; R_f = 0.29 (EtOAc, 100%); m.p. 160.0-162.0 °C; λ_{max} (EtOH)/nm 236.6, 313.8; IR (neat) ν_{max}/cm^{-1} 3384, 3335, 2980, 2961, 2925, 2865, 1681, 1485, 1418, 1369, 1270, 1249, 1236; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.40 (9H, s, C(CH_3)$_3$), 1.46 (2H, dddd, *J* = 13.2, 9.2, 9.1 and 4.1 Hz, H-3', 5'$_{axial}$), 1.87 (2H, ddd, *J* = 13.2, 5.8 and 3.3 Hz, H-3', 5'$_{equ}$), 3.12 (2H, brs, H-2', 6'$_{axial}$), 3.66 (2H, ddd, *J* = 13.2, 4.9 and 4.9 Hz, H-2', 6'$_{equ}$), 4.74 (2H, brs, ArNH_2), 4.93 (1H, tt, *J* = 8.3, 3.8 Hz, H-4'), 6.51 (1H, d, *J* = 8.6 Hz, H-3), 6.98 (1H, dd, *J* = 8.6, 2.9 Hz, H-4), 7.48 (1H, d, *J* = 2.9 Hz, H-6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 28.1 (C(*C*H$_3$)$_3$), 30.7 (C-3', 5'), 40.6 (C-2', 6'), 69.3 (C-4'), 78.6 (O*C*(CH$_3$)$_3$), 110.9 (C-3), 126.3 (C-4), 131.1 (C-6), 139.4 (C-5), 153.9 (C-2 or *C*O$_2$N), 154.3 (C-2 or *C*O$_2$N); LRMS (ES$^+$) *m/z* 294.4 [M+H]$^+$; HRMS (ESI) calcd for $C_{15}H_{24}N_3O_3$ [M+H]$^+$ 294.1812, found 294.1811.

***tert*-Butyl 4-((5-aminopyridin-2-yl)methyl)piperidine-1-carboxylate, (464)**



Compound **464** was synthesised according to general procedure D', using the following reagents: *tert*-butyl 4-((5-nitropyridin-2-yl)methyl)piperidine-1-carboxylate (**458**) (300 mg, 0.93 mmol), THF (9.3 mL) and methanol (9.3 mL). The crude orange solid (261 mg, 96%) was used in the next step without further purification; R_f = 0.26 (amine silica, petrol:EtOAc, 1:1); m.p. 107.5-109.5 °C; λ_{max} (EtOH)/nm 243.6, 307.4; IR (neat) ν_{max}/cm^{-1} 3398, 3323, 3219, 2981, 2917, 2852, 1668, 1573, 1493, 1425, 1366; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.00 (2H, dddd, *J* = 12.3, 12.3, 12.3 and 4.3 Hz, H-3', 5'), 1.38 (9H, s, C(CH_3)$_3$), 1.47 – 1.54 (2H, m, H-3', 5'), 1.76 (1H, ttt, *J* = 12.3, 7.2 and 4.3 Hz, H-4'), 2.44 (2H, d, *J* = 7.2 Hz, ArCH_2CH), 2.64 (2H, brs, H-2', 6'), 3.88 (2H, d, *J* = 13.1 Hz, H-2', 6'), 5.03 (2H, brs, ArNH_2), 6.81 – 6.84 (2H, m, H-3 and H-4), 7.84 (1H, d, *J* = 1.7 Hz, H-6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 28.1 (C(CH_3)$_3$), 31.5 (C-3', 5'), 36.2 (C-4'), 42.9 (C-2', 6'), 43.3 (Ar*C*H$_2$), 78.3 (O*C*(CH$_3$)$_3$), 120.4 (C-3 or C-4), 123.0 (C-3 or C-4), 135.7 (C-6), 142.5 (C-5), 146.8 (C-2), 153.8 (*C*O$_2$N); LRMS (ES$^+$) *m/z* 292.4 [M+H]$^+$; HRMS (NSI) calcd for $C_{16}H_{26}N_3O_2$ [M+H]$^+$ 292.2020, found 292.2019.

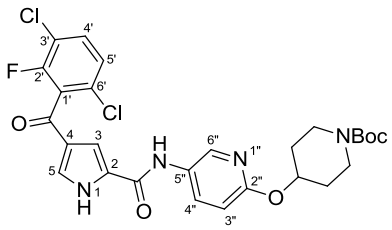
***tert*-Butyl 4-((5-(4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxamido)pyridin-2-yl)(methyl)amino)piperidine-1-carboxylate, (465)**



Compound **465** was synthesised according to general procedure Y, using the following reagents: 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**) (300 mg, 0.99 mmol), triethylamine (346 µL, 251 mg, 2.48 mmol), 2-chloro-1-methylpyridinium iodide (279 mg, 1.09 mmol), *tert*-butyl 4-((5-aminopyridin-2-yl)(methyl)amino)piperidine-1-carboxylate (**462**) (380 mg, 1.24 mmol) and DCM (9.9 mL). The crude yellow solid was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 1:1) to yield the *title compound* as a pale orange solid (285 mg, 49%); R_f = 0.31 (petrol:EtOAc, 1:1); m.p. 173.0-175.0 °C; λ_{max} (EtOH)/nm 290.0; IR (neat) ν_{max}/cm^{-1} 3223, 2958, 2931, 2865, 1656, 1638, 1527, 1494, 1448, 1421, 1393, 1365, 1291; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.41 (9H, s, C(CH_3)$_3$), 1.52 – 1.63 (4H, m, CH_2CH$_2$NBoc), 2.79 (3H, s, NCH_3), 2.81 (2H, brs, CH$_2$CH_2NBoc), 4.06 (2H, brs, CH$_2$CH_2NBoc), 4.58 (1H, tt, *J* = 10.5, 5.9 Hz,

ArN(CH_3)C*H*), 6.67 (1H, d, *J* = 9.1 Hz, H-3”), 7.41 (1H, s, H-3), 7.51 (1H, dd, *J* = 8.7, 1.4 Hz, H-5’), 7.56 (1H, s, H-5), 7.71 – 7.83 (2H, m, H-4’ and H-4”), 8.36 (1H, d, *J* = 2.7 Hz, H-6”), 9.91 (1H, s, CON*H*Ar), 12.67 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 28.1 (C(*C*H_3)$_3$), 28.6 (*C*H_2CH_2NBoc), 29.6 (N*C*H_3), 43.4 (CH_2*C*H_2NBoc), 51.9 (ArN(CH_3)*C*H), 78.6 (O*C*(CH_3)$_3$), 105.6 (C-3”), 110.6 (C-3), 119.3 (d, *J* = 18.2 Hz, C-3’), 124.7 (C-2 or C-4 and C-5”), 126.9 (d, *J* = 3.3 Hz, C-5’), 128.9 (C-2 or C-4), 129.2 (d, *J* = 5.2 Hz, C-6’), 129.2 (d, *J* = 23.0 Hz, C-1’), 129.6 (C-5), 131.4 (C-4’ or C-4”), 131.8 (C-4’ or C-4”), 140.4 (C-6”), 153.8 (*C*O_2N or C-2”), 153.8 (d, *J* = 248.4 Hz, C-2’), 155.2 (*C*O_2N or C-2”), 158.2 (*C*ONHAr), 182.6 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.7; LRMS (ES$^-$) *m/z* 588.3 [M(^{35}Cl^{35}Cl)-H]$^-$, 590.3 [M(^{35}Cl^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{28}H_{31}Cl_2FN_5O_4$ [M(^{35}Cl^{35}Cl)+H]$^+$ 590.1732, found 590.1725.

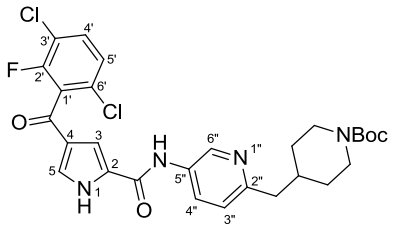
tert-Butyl 4-((5-(4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxamido)pyridin-2-yl)oxy)piperidine-1-carboxylate, (466)



Compound **466** was synthesised according to general procedure Y, using the following reagents: 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**) (300 mg, 0.99 mmol), triethylamine (346 µL, 251 mg, 2.48 mmol), 2-chloro-1-methylpyridinium iodide (279 mg, 1.09 mmol), *tert*-butyl 4-((5-aminopyridin-2-yl)oxy)piperidine-1-carboxylate (**463**) (364 mg, 1.24 mmol) and DCM (9.9 mL). The crude yellow solid was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 6:4) to yield the *title compound* as a pale orange solid (275 mg, 48%); R_f = 0.30 (petrol:EtOAc, 6:4); m.p. 226.5-228.5 °C; λ_{max} (EtOH)/nm 261.6; IR (neat) ν_{max}/cm^{-1} 3166, 2980, 2936, 2857, 1658, 1647, 1593, 1556, 1538, 1484, 1433, 1365, 1263;^{1}H NMR (500 MHz, DMSO-d_6) δ 1.41 (9H, s, C(C*H*$_3$)$_3$), 1.53 (2H, dddd, *J* = 13.0, 9.1, 9.0 and 4.0 Hz, C*H*$_2$CH$_2$NBoc), 1.94 (2H, ddd, *J* = 13.0, 5.9 and 3.4 Hz, C*H*$_2$CH$_2$NBoc), 3.16 (2H, brs, CH$_2$C*H*$_2$NBoc), 3.70 (2H, ddd, *J* = 13.0, 4.8 and 4.8 Hz, CH$_2$C*H*$_2$NBoc), 5.13 (1H, tt, *J* = 8.3, 3.8 Hz, ArOC*H*), 6.81 (1H, d, *J* = 8.9 Hz, H-3”), 7.45 (1H, s, H-3), 7.52 (1H, dd, *J* = 8.7, 1.3 Hz, H-5’), 7.59 (1H, s, H-5), 7.78 (1H, dd, *J* = 8.7, 8.5 Hz, H-4’), 7.98 (1H, dd, *J* = 8.9, 2.7 Hz, H-4”), 8.44 (1H, d, *J* = 2.7 Hz, H-6”), 10.10 (1H, s, CON*H*Ar), 12.73 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 28.1 (C(*C*H_3)$_3$), 30.6 (*C*H_2CH_2NBoc), 40.7

(CH_2CH_2NBoc), 70.0 (ArO*C*H), 78.7 (O*C*$(CH_3)_3$), 110.8 (C-3”), 111.0 (C-3), 119.3 (d, *J* = 18.1 Hz, C-3’), 124.7 (C-2 or C-4), 126.9 (d, *J* = 3.4 Hz, C-5’), 128.6 (C-2 or C-4), 129.2 (d, *J* = 23.3 Hz, C-1’), 129.2 (d, *J* = 5.3 Hz, C-6’), 129.5 (C-5”), 130.0 (C-5), 131.8 (C-4’), 132.5 (C-4”), 138.6 (C-6”), 153.8 (d, *J* = 248.3 Hz, C-2’), 153.9 (*C*O_2N), 158.4 (*C*ONHAr or C-2”), 158.7 (*C*ONHAr or C-2”), 182.6 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.7 (ArF); LRMS (ES^-) *m/z* 575.3 [M($^{35}Cl^{35}Cl$)-H]$^-$, 577.3 [M($^{35}Cl^{37}Cl$)-H]$^-$; HRMS (NSI) calcd for $C_{27}H_{28}Cl_2FN_4O_5$ [M($^{35}Cl^{35}Cl$)+H]$^+$ 577.1415, found 577.1408.

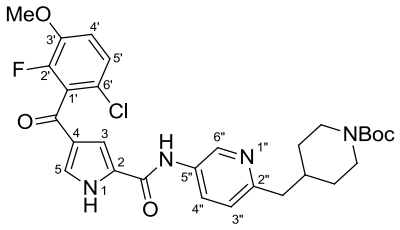
tert-Butyl 4-((5-(4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxamido)pyridin-2-yl)methyl)piperidine-1-carboxylate, (467)



Compound **467** was synthesised according to general procedure Y, using the following reagents: 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**) (250 mg, 0.83 mmol), triethylamine (288 µL, 209 mg, 2.07 mmol), 2-chloro-1-methylpyridinium iodide (233 mg, 0.91 mmol), *tert*-butyl 4-((5-aminopyridin-2-yl)methyl)piperidine-1-carboxylate (**464**) (301 mg, 1.03 mmol) and DCM (8.3 mL). The crude yellow solid was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 1:1) to yield the *title compound* as an orange solid (201 mg, 42%); R_f = 0.29 (petrol:EtOAc, 1:1); m.p. 132.0-134.0 °C; λ_{max} (EtOH)/nm 295.6; IR (neat) ν_{max}/cm^{-1} 3238, 2926, 2853, 1651, 1592, 1531, 1448, 1424, 1394, 1366; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.01 – 1.10 (2H, m, C*H*$_2$CH$_2$NBoc), 1.38 (9H, s, C(C*H*$_3$)$_3$), 1.53 (2H, dd, *J* = 12.6, 3.6 Hz, C*H*$_2$CH$_2$NBoc), 1.83 – 1.90 (1H, m, ArCH$_2$C*H*), 2.62 (2H, d, *J* = 7.1 Hz, ArC*H*$_2$CH), 2.66 (2H, brs, CH$_2$C*H*$_2$NBoc), 3.90 (2H, d, *J* = 13.1 Hz, CH$_2$C*H*$_2$NBoc), 7.21 (1H, d, *J* = 8.4 Hz, H-3”), 7.50 (1H, s, H-3), 7.52 (1H, dd, *J* = 8.8, 1.2 Hz, H-5’), 7.61 (1H, s, H-5), 7.78 (1H, dd, *J* = 8.8, 8.4 Hz, H-4’), 8.02 (1H, dd, *J* = 8.4, 2.5 Hz, H-4”), 8.78 (1H, d, *J* = 2.5 Hz, H-6”), 10.18 (1H, s, CON*H*Ar), 12.75 (1H, s, NH-pyrrole);^{13}C NMR (126 MHz, DMSO-d_6) δ 28.1 (*C*(CH$_3$)$_3$), 31.5 (*C*H$_2$CH$_2$NBoc), 36.0 (ArCH$_2$*C*H), 43.6 (Ar*C*H$_2$CH), 43.9 (CH$_2$*C*H$_2$NBoc), 78.4 (O*C*(CH$_3$)$_3$), 111.3 (C-3), 119.3 (d, *J* = 17.8 Hz, C-3’), 123.1 (C-3”), 124.8 (C-2 or C-4), 126.9 (d, *J* = 3.7 Hz, C-5’), 127.5 (C-4”), 128.5 (C-2 or C-4), 129.1 (d, *J* = 22.8 Hz, C-1’), 129.2 (d, *J* = 5.4 Hz, C-6’), 130.2 (C-5), 131.9 (C-4’), 133.2 (C-5”), 141.1 (C-6”), 153.8 (*C*O$_2$N or C-2”), 153.9 (d, *J* = 248.6 Hz, C-2’), 154.8 (*C*O$_2$N or C-2”),

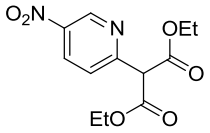
158.5 (*C*ONHAr), 182.6 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.7 (ArF); LRMS (ES$^+$) *m/z* 573.4 [M(^{35}Cl^{35}Cl)+H]$^+$, 575.4 [M(^{35}Cl^{37}Cl)+H]$^+$; HRMS (NSI) calcd for $C_{28}H_{30}Cl_2FN_4O_4$ [M(^{35}Cl^{35}Cl)+H]$^+$ 575.1623, found 575.1616.

tert-Butyl 4-((5-(4-(6-chloro-2-fluoro-3-methoxybenzoyl)-1*H*-pyrrole-2-carboxamido)pyridin-2-yl)methyl)piperidine-1-carboxylate, (468)



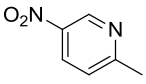
Compound **468** was synthesised according to general procedure Y, using the following reagents: 4-(6-chloro-2-fluoro-3-methoxybenzoyl)-1*H*-pyrrole-2-carboxylic acid (**338**) (300 mg, 1.01 mmol), triethylamine (351 µL, 255 mg, 2.52 mmol), 2-chloro-1-methylpyridinium iodide (283 mg, 1.11 mmol), *tert*-butyl 4-((5-aminopyridin-2-yl)methyl)piperidine-1-carboxylate (**464**) (367 mg, 1.26 mmol) and DCM (10.1 mL). The crude yellow solid was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 45:55) to yield the *title compound* as a pale pink solid (222 mg, 39%); R_f = 0.28 (petrol:EtOAc, 45:55); m.p. 227.5-229.5 °C; λ_{max} (EtOH)/nm 296.0; IR (neat) ν_{max}/cm^{-1} 3341, 3195, 2938, 2860, 1682, 1639, 1559, 1530, 1476, 1434; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.05 (2H, dddd, *J* = 12.5, 12.5, 12.5 and 4.3 Hz, C*H*$_2$CH$_2$NBoc), 1.38 (9H, s, C(C*H*$_3$)$_3$), 1.49 – 1.58 (2H, m, C*H*$_2$CH$_2$NBoc), 1.88 (1H, ttt, *J* = 12.5, 7.1 and 3.5 Hz, ArCH$_2$C*H*), 2.61 (2H, d, *J* = 7.1 Hz, ArC*H*$_2$CH), 2.65 (2H, s, CH$_2$C*H*$_2$NBoc), 3.85 (2H, s, CH$_2$C*H*$_2$NBoc), 3.90 (3H, s, ArOC*H*$_3$), 7.21 (1H, d, *J* = 8.4 Hz, H-3"), 7.33 (1H, dd, *J* = 9.0, 8.9 Hz, H-4'), 7.39 (1H, dd, *J* = 8.9, 1.4 Hz, H-5'), 7.43 – 7.50 (2H, m, H-3 and H-5), 8.02 (1H, dd, *J* = 8.4, 2.5 Hz, H-4"), 8.78 (1H, d, *J* = 2.5 Hz, H-6"), 10.17 (1H, s, CON*H*Ar), 12.68 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 28.1 (C(*C*H$_3$)$_3$), 31.5 (*C*H$_2$CH$_2$NBoc), 36.0 (ArCH$_2$*C*H), 42.9 (CH$_2$*C*H$_2$NBoc), 43.6 (Ar*C*H$_2$), 56.5 (ArO*C*H$_3$), 78.4 (O*C*(CH$_3$)$_3$), 111.4 (C-3), 115.1 (C-4'), 120.2 (d, *J* = 4.8 Hz, C-6'), 123.1 (C-3"), 125.2 (C-2 or C-4), 125.6 (d, *J* = 3.6 Hz, C-5'), 127.4 (C-4"), 128.3 (C-2 or C-4), 128.4 (d, *J* = 20.1 Hz, C-1'), 129.4 (C-5), 133.2 (C-5"), 141.1 (C-6"), 146.4 (d, *J* = 10.7 Hz, C-3'), 147.9 (d, *J* = 247.1 Hz, C-2'), 153.8 (*C*O$_2$N or C-2"), 154.7 (*C*O$_2$N or C-2"), 158.6 (*C*ONHAr), 183.6 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -136.1 (ArF); LRMS (ES$^-$) *m/z* 569.5 [M(^{35}Cl)-H]$^-$, 571.4 [M(^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{29}H_{33}ClFN_4O_5$ [M(^{35}Cl)+H]$^+$ 571.2118, found 571.2113.

Diethyl 2-(5-nitropyridin-2-yl)malonate, (469)



To a suspension of sodium hydride (60% dispersion in mineral oil, 4.04 g, 101 mmol) in THF (60 mL), cooled in an ice bath, was added diethyl malonate (8.08 g, 7.66 mL, 50.5 mmol). The resulting solution was stirred at 0 °C for 10 min and allowed to warm to RT. After 1 h, the reaction mixture was cooled in an ice bath and a solution of 2-chloro-5-nitropyridine (**459**) (8.0 g, 50.5 mmol) in THF (20 mL) added dropwise. The resulting mixture was then stirred overnight at RT. Upon completion, the mixture was diluted with EtOAc (40 mL), quenched by the cautious addition of 1 M aq. HCl (20 mL) and extracted with EtOAc (3 × 60 mL). The pooled organic extracts were washed with water and brine (40 mL, respectively), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 85:15) to yield the *title compound* as a yellow solid (9.05 g, 64%); R_f = 0.32 (petrol:EtOAc, 85:15); m.p. 86.5-88.5 °C (lit. 97.0-99.0 °C)[286]; λ_{max} (EtOH)/nm 247.6, 272.4; IR (neat) ν_{max}/cm^{-1} 3129, 3074, 2986, 2939, 1662, 1637, 1588, 1529, 1509, 1341; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.19 (6H, t, *J* = 7.1 Hz, OCH_2CH_3), 4.19 (4H, qd, *J* = 7.1, 1.9 Hz, OCH_2CH_3), 5.41 (1H, s, $ArCH(CO_2Et)_2$), 7.77 (1H, d, *J* = 8.6 Hz, H-3), 8.64 (1H, dd, *J* = 8.6, 2.7 Hz, H-4), 9.33 (1H, d, *J* = 2.7 Hz, H-6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 13.9 (OCH_2CH_3), 59.2 ($ArCH(CO_2Et)_2$), 61.8 (OCH_2CH_3), 125.0 (C-3), 132.4 (C-4), 143.7 (C-5), 144.3 (C-6), 158.9 (C-2), 166.5 ($ArCH(CO_2Et)_2$); LRMS (ES^+) *m/z* 283.3 $[M+H]^+$; HRMS (ESI) calcd for $C_{12}H_{15}N_2O_6$ $[M+H]^+$ 283.0925, found 283.0917.

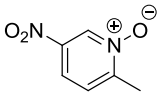
2-Methyl-5-nitropyridine, (470)



To diethyl 2-(5-nitropyridin-2-yl)malonate (**469**) (8.0 g, 28.3 mmol) was added cold 20% aq. sulphuric acid (80 mL). The resulting solution was stirred at 100 °C for 2 h. Upon completion, the mixture was cooled in an ice bath, neutralised by the cautious addition of 2 M aq. NaOH until pH 8-9 and extracted with DCM (3 × 100 mL). The pooled organic extracts were washed with water and brine (100 mL, respectively), dried over $MgSO_4$ and concentrated *in vacuo* to give the *title compound* as a pale yellow solid (3.71 g, 95%). The crude material was used in the next step without further purification; R_f = 0.32 (petrol:EtOAc, 9:1); m.p. 109.5-110.5 °C (lit. 110-111)[287]; λ_{max} (EtOH)/nm 252.8, 276.4; IR (neat) ν_{max}/cm^{-1} 3039, 3019, 2950, 2854, 1600, 1572, 1512, 1469; ^{1}H NMR (500 MHz,

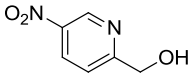
DMSO-d_6) δ 2.62 (3H, s, ArCH_3), 7.57 (1H, d, J = 8.6 Hz, H-3), 8.48 (1H, dd, J = 8.6, 2.8 Hz, H-4), 9.24 (1H, d, J = 2.8 Hz, H-6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 24.3 (ArCH$_3$), 123.8 (C-3), 131.6 (C-4), 142.5 (C-5), 144.1 (C-6), 165.2 (C-2); LRMS (ES$^+$) *m/z* 139.1 [M+H]$^+$; HRMS (APCI) calcd for $C_6H_7N_2O_2$ [M+H]$^+$ 139.0502, found 139.0500; ^{1}H NMR, ^{13}C NMR and IR data were identical to literature data.[288, 289]

2-Methyl-5-nitropyridine 1-oxide, (471)



To 2-methyl-5-nitropyridine (**470**) (2.0 g, 14.5 mmol) in DCM (50 mL), cooled in an ice bath, was added 3-chloroperbenzoic acid (74%, 5.06 g, 21.7 mmol) in portions. The resulting solution was stirred in an ice bath for 1 h and allowed to warm to RT. After 16 h, the reaction was quenched by addition of saturated aq. $NaHCO_3$ (50 mL) and stirred for 30 min. The aqueous layer was extracted with DCM (3 × 40 mL). The pooled organic extracts were washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 0:1) to yield the *title compound* as a yellow solid (2.15 g, 96%); R_f = 0.27 (EtOAc, 100%); m.p. 149.5-151.5 °C; λ_{max} (EtOH)/nm 247.8, 278.2; IR (neat) ν_{max}/cm^{-1} 3126, 3102, 3036, 2920, 1564, 1519, 1491, 1350, 1285; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.44 (3H, s, ArCH_3), 7.76 (1H, d, J = 8.7 Hz, H-3,), 8.05 (1H, dd, J = 8.7, 2.2 Hz, H-4), 9.01 (1H, d, J = 2.2 Hz, H-6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 17.4 (ArCH$_3$), 119.2 (C-4), 126.4 (C-3), 134.6 (C-6), 145.0 (C-5), 154.7 (C-2); LRMS (ES$^+$) *m/z* 155.2 [M+H]$^+$; HRMS (NSI) calcd for $C_6H_7N_2O_3$ [M+H]$^+$ 155.0451, found 155.0448.

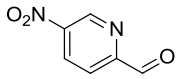
(5-Nitropyridin-2-yl)methanol, (472)



To 2-methyl-5-nitropyridine 1-oxide (**471**) (1.0 g, 6.49 mmol) in DCM (20 mL), cooled in an ice bath, was added dropwise trifluoroacetic anhydride (1.80 mL, 2.73 g, 13.0 mmol). The resulting solution was stirred in an ice bath for 1 h and allowed to warm to RT. After 16 h, the reaction was cooled in an ice bath, quenched by addition of MeOH (15 mL) and stirred for 8 h. The volatiles were concentrated *in vacuo*. The crude residue was dissolved in EtOAc (30 mL), washed with a saturated aq. $NaHCO_3$ (30 mL) and extracted with EtOAc (2 × 35 mL). The pooled organic extracts were washed with water (40 mL) and brine (40 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was

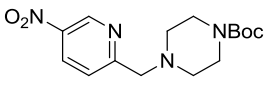
purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 55:45) to yield the *title compound* as a yellow solid (500 mg, 50%); R_f = 0.31 (petrol:EtOAc, 55:45); m.p. 95.0-97.0 °C; λ_{max} (EtOH)/nm 253.2, 276.2; IR (neat) ν_{max}/cm^{-1} 3161, 3040, 2917, 2852, 1596, 1575, 1515, 1451, 1434, 1345; ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.69 (2H, s, ArC*H*$_2$OH), 5.77 (1H, brs, ArCH$_2$O*H*), 7.75 (1H, d, *J* = 8.7 Hz, H-3), 8.61 (1H, dd, *J* = 8.7, 2.7 Hz, H-4), 9.28 (1H, d, *J* = 2.7 Hz, H-6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 64.0 (Ar*C*H$_2$OH), 120.4 (C-3), 132.1 (C-4), 143.0 (C-5), 143.9 (C-6), 168.9 (C-2); LRMS (ES$^+$) *m/z* 155.2 [M+H]$^+$; HRMS (APCI) calcd for $C_6H_7N_2O_3$ [M+H]$^+$ 155.0451, found 155.0450.

5-Nitropicolinaldehyde, (473)



To (5-nitropyridin-2-yl)methanol (**472**) (1.2 g, 7.79 mmol) in DCM (30 mL) was added manganese oxide (6.77 g, 77.9 mmol). The resulting solution was stirred at RT for 16 h. Upon completion, the heterogeneous mixture was filtered through Celite and washed with DCM (15 mL). The filtrate was concentrated *in vacuo* to give a yellow solid. The crude solid was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 8:2) to yield the *title compound* as an orange solid (720 mg, 61%); R_f = 0.28 (petrol:EtOAc, 8:2); m.p. 65.0-67.0 °C (lit. 55 °C)[288]; λ_{max} (EtOH)/nm 248.2, 273.6; IR (neat) ν_{max}/cm^{-1} 3102, 2981, 2889, 2845, 1712, 1598, 1528, 1349; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.16 (1H, dd, *J* = 8.5, 0.7 Hz, H-3), 8.80 (1H, dd, *J* = 8.5, 2.5 Hz, H-4), 9.56 (1H, d, *J* = 2.5 Hz, H-6), 10.08 (1H, d, *J* = 0.7 Hz, ArC*H*O); ^{13}C NMR (126 MHz, DMSO-d_6) δ 122.4 (C-3), 133.4 (C-4), 145.3 (C-6), 146.1 (C-5), 155.2 (C-2), 192.0 (Ar*C*HO); LRMS (ES$^+$) *m/z* 153.2 [M+H]$^+$; HRMS (APCI) calcd for C6H5N2O3 [M+H]$^+$ 153.0295, found 153.0292; ^{1}H and ^{13}C NMR data were identical to literature data.[288]

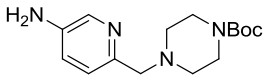
***tert*-Butyl 4-((5-nitropyridin-2-yl)methyl)piperazine-1-carboxylate, (474)**



To 5-nitropicolinaldehyde (**473**) (300 mg, 1.97 mmol) in TFE (10 mL) was added *tert*-butyl piperazine-1-carboxylate (367 mg, 1.97 mmol). The resulting solution was stirred at 38 °C for 1 h. Once cooled at 0 °C, sodium borohydride was carefully added. The resulting mixture was allowed to warm to RT and then stirred for 30 min. Upon completion, the solvent was removed *in vacuo*. The crude residue was dissolved in EtOAc (30 mL), neutralised by washing with saturated aq. NH_4Cl (20 mL), washed with water and brine

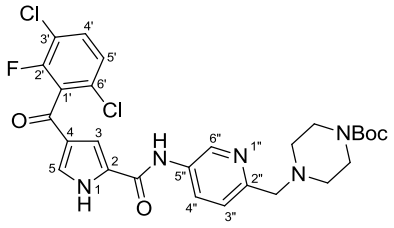
(20 mL, respectively), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 1:1) to yield the *title compound* as a white solid (325 mg, 51%); R_f = 0.34 (petrol:EtOAc, 1:1); m.p. 107.5-109.5 °C; λ_{max} (EtOH)/nm 246.4, 305.4; IR (neat) ν_{max}/cm^{-1} 2981, 2941, 2881, 2820, 1686, 1601, 1580, 1523, 1420, 1356, 1345; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.39 (9H, s, C(CH_3)$_3$), 2.40 (4H, t, *J* = 5.0 Hz, $CH_{2\ piperazine}$), 3.34 (4H, t, *J* = 5.0 Hz, $CH_{2\ piperazine}$), 3.76 (2H, brs, ArCH_2N), 7.75 (1H, d, *J* = 8.6 Hz, H-3), 8.57 (1H, dd, *J* = 8.6, 2.7 Hz, H-4), 9.29 (1H, d, *J* = 2.7 Hz, H-6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 28.1 (C(*C*H_3)$_3$), 43.0 ($CH_{2\ piperazine}$), 52.5 ($CH_{2\ piperazine}$), 63.0 (Ar*C*H_2N), 78.8 (O*C*(CH$_3$)$_3$), 123.1 (C-3), 132.0 (C-4), 143.2 (C-5), 144.1 (C-6), 153.8 (*C*O_2N), 165.2 (C-2); LRMS (ES^-) *m/z* 321.2 $[M-H]^-$; HRMS (NSI) calcd for $C_{15}H_{23}N_4O_4$ $[M+H]^+$ 323.1714, found 323.1712.

tert-Butyl 4-((5-aminopyridin-2-yl)methyl)piperazine-1-carboxylate, (475)



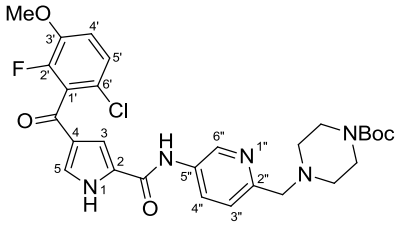
Compound **475** was synthesised according to general procedure D', using the following reagents: *tert*-butyl 4-((5-nitropyridin-2-yl)methyl)piperazine-1-carboxylate (**474**) (300 mg, 0.93 mmol), THF (9.3 mL) and methanol (9.3 mL). The crude colourless oil (258 mg, 95%) was used in the next step without further purification; R_f = 0.32 (EtOAc, 100%); λ_{max} (EtOH)/nm 246.4, 305.4; IR (neat) ν_{max}/cm^{-1} 3410, 3327, 3204, 2980, 2925, 2891, 2808, 2769, 1671, 1598, 1574, 1495, 1455, 1423; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.38 (9H, s, C(CH_3)$_3$), 2.29 (4H, t, *J* = 5.1 Hz, $CH_{2\ piperazine}$), 3.28 (4H, t, *J* = 5.1 Hz, $CH_{2\ piperazine}$), 3.39 (2H, s, ArCH_2N), 5.18 (2H, brs, ArNH_2), 6.88 (1H, dd, *J* = 8.3, 2.8 Hz, H-4), 7.03 (1H, d, *J* = 8.3 Hz, H-3), 7.83 (1H, d, *J* = 2.8 Hz, H-6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 28.0 (C(*C*H_3)$_3$), 43.5 ($CH_{2\ piperazine}$), 52.4 ($CH_{2\ piperazine}$), 63.3 (Ar*C*H_2N), 78.7 (O*C*(CH$_3$)$_3$), 120.4 (C-4), 123.1 (C-3), 135.2 (C-6), 143.5 (C-2 or C-5), 144.6 (C-2 or C-5), 153.8 (*C*O_2N); LRMS (ES^+) *m/z* 293.5 $[M+H]^+$; HRMS (NSI) calcd for $C_{15}H_{25}N_4O_2$ $[M+H]^+$ 293.1972, found 293.1971.

***tert*-Butyl 4-((5-(4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxamido)pyridin-2-yl)methyl)piperazine-1-carboxylate, (476)**



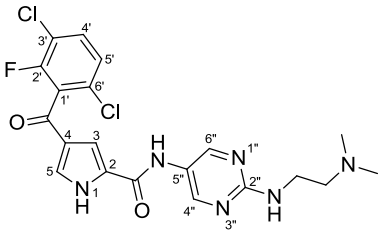
Compound **476** was synthesised according to general procedure Y, using the following reagents: 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**) (211 mg, 0.70 mmol), triethylamine (243 µL, 177 mg, 1.75 mmol), 2-chloro-1-methylpyridinium iodide (196 mg, 0.77 mmol), *tert*-butyl 4-((5-aminopyridin-2-yl)methyl)piperazine-1-carboxylate (**475**) (255 mg, 0.87 mmol) and DCM (7 mL). The crude yellow solid was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 2:8) to yield the *title compound* as a pale orange solid (113 mg, 28%); R_f = 0.28 (petrol:EtOAc, 8:2); m.p. 147.0-149.0 °C; λ_{max} (EtOH)/nm 295.8; IR (neat) ν_{max}/cm^{-1} 3238, 2964, 2932, 2871, 2819, 1652, 1531, 1448, 1423, 1393; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.39 (9H, s, C(C*H*$_3$)$_3$), 2.32 – 2.42 (4H, m, CH$_2$ $_{piperazine}$), 3.33 (4H, brs, CH$_2$ $_{piperazine}$), 3.56 (2H, s, ArC*H*$_2$N), 7.42 (1H, d, *J* = 8.5 Hz, H-3”), 7.48 – 7.54 (2H, m, H-3 and H-5’), 7.62 (1H, s, H-5), 7.78 (1H, dd, *J* = 8.7, 8.2 Hz, H-4’), 8.11 (1H, dd, *J* = 8.5, 2.6 Hz, H-4”), 8.80 (1H, d, *J* = 2.6 Hz, H-6”), 10.23 (1H, s, CON*H*Ar), 12.77 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 28.1 (C(*C*H$_3$)$_3$), 43.2 (CH$_2$ $_{piperazine}$), 52.5 (CH$_2$ $_{piperazine}$), 63.2 (Ar*C*H$_2$N), 78.7 (O*C*(CH$_3$)$_3$), 111.4 (C-5), 119.3 (d, *J* = 18.0 Hz, C-3’), 122.7 (C-3”), 124.8 (C-2 or C-4), 126.9 (d, *J* = 3.7 Hz, C-5’), 127.6 (C-4”), 128.5 (C-2 or C-4), 129.1 (d, *J* = 22.9 Hz, C-1’), 129.2 (d, *J* = 5.3 Hz, C-6’), 130.3 (C-5), 131.9 (C-4’), 134.1 (C-5”), 140.7 (C-6”), 152.8 (*C*O$_2$N or C-2”), 153.8 (*C*O$_2$N or C-2”), 153.9 (d, *J* = 248.7 Hz, C-2’), 158.6 (*C*ONHAr), 182.6 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.7 (ArF); LRMS (ES$^+$) *m/z* 576.5 [M(^{35}Cl^{35}Cl)+H]$^+$, 578.5 [M(^{35}Cl^{37}Cl)+H]$^+$; HRMS (NSI) calcd for $C_{27}H_{29}Cl_2FN_5O_4$ [M(^{35}Cl^{35}Cl)+H]$^+$ 576.1575, found 576.1568.

***tert*-Butyl 4-((5-(4-(6-chloro-2-fluoro-3-methoxybenzoyl)-1*H*-pyrrole-2-carboxamido) pyridin-2-yl)methyl)piperazine-1-carboxylate, (477)**



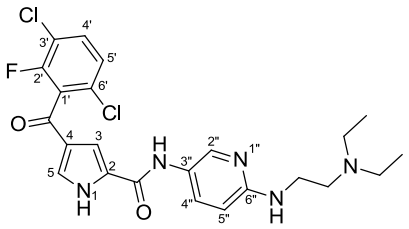
Compound **477** was synthesised according to general procedure Y, using the following reagents: 4-(6-chloro-2-fluoro-3-methoxybenzoyl)-1*H*-pyrrole-2-carboxylic acid (**338**) (300 mg, 1.01 mmol), triethylamine (351 µL, 255 mg, 2.52 mmol), 2-chloro-1-methylpyridinium iodide (283 mg, 1.11 mmol), *tert*-butyl 4-((5-aminopyridin-2-yl)methyl)piperazine-1-carboxylate (**475**) (368 mg, 1.26 mmol) and DCM (10.1 mL). The crude yellow solid was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 $\rightarrow$ 15:85) to yield the *title compound* as a white solid (189 mg, 33%); R_f = 0.30 (petrol:EtOAc, 15:85); m.p. 166.5-168.5 °C; λ_{max} (EtOH)/nm 274.8; IR (neat) ν_{max}/cm^{-1} 2956, 2933, 1653, 1553, 1527, 1472, 1432, 1391, 1271, 1240; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.38 (9H, s, C(CH_3)$_3$), 2.35 (4H, t, *J* = 4.9 Hz, $CH_{2\ piperazine}$), 3.31 (4H, brs, $CH_{2\ piperazine}$), 3.56 (2H, s, ArCH_2N), 3.90 (3H, s, ArOCH_3), 7.33 (1H, dd, *J* = 9.6, 8.9 Hz, H-4'), 7.39 (1H, d, *J* = 9.6 Hz, H-5'), 7.41 (1H, d, *J* = 8.5 Hz, H-3"), 7.47 (1H, s, H-3), 7.49 (1H, s, H-5), 8.11 (1H, dd, *J* = 8.5, 2.6 Hz, H-4"), 8.79 (1H, d, *J* = 2.6 Hz, H-6"), 10.23 (1H, s, CON*H*Ar), 12.71 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 28.1 (C(CH$_3$)$_3$), 42.9 ($CH_{2\ piperazine}$), 52.5 ($CH_{2\ piperazine}$), 56.5 (ArOCH$_3$), 63.2 (ArCH$_2$N), 78.8 (OC(CH$_3$)$_3$), 111.5 (C-3), 115.2 (C-4'), 120.2 (d, *J* = 4.7 Hz, C-6'), 122.7 (C-3"), 125.2 (C-2 or C-4), 125.6 (d, *J* = 3.8 Hz, C-5'), 127.6 (C-4"), 128.2 (C-2 or C-4), 128.4 (d, *J* = 20.1 Hz, C-1'), 129.5 (C-5), 134.1 (C-5"), 140.7 (C-6"), 146.5 (d, *J* = 10.8 Hz, C-3'), 148.0 (d, *J* = 247.1 Hz, C-2'), 152.8 (CO$_2$N or C-2"), 153.8 (CO$_2$N or C-2"), 158.6 (CONHAr), 183.7 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -136.2 (ArF); LRMS (ES$^-$) *m/z* 570.4 [M(^{35}Cl)-H]$^-$, 572.4 [M(^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{28}H_{32}ClFN_5O_5$ [M(^{35}Cl)+H]$^+$ 572.2071, found 572.2062.

4-(3,6-Dichloro-2-fluorobenzoyl)-*N*-(2-((2-(dimethylamino)ethyl)amino)pyrimidin-5-yl)-1*H*-pyrrole-2-carboxamide, (478)



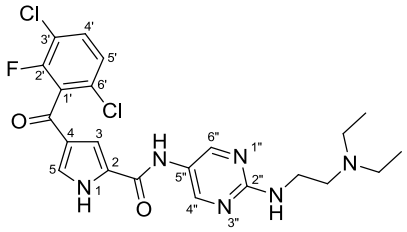
Compound **478** was synthesised according to general procedure Y, using the following reagents: 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**) (100 mg, 0.33 mmol), triethylamine (115 µL, 84 mg, 0.83 mmol), 2-chloro-1-methylpyridinium iodide (93 mg, 0.36 mmol), N^2-(2-(dimethylamino)ethyl)pyrimidine-2,5-diamine (**518**) (75 mg, 0.41 mmol) and DCM (3.3 mL). The crude yellow solid was purified by column chromatography (amine silica gel, DCM:MeOH, 1:0 → 96:4) to yield the *title compound* as a pale orange solid (17 mg, 11%); R_f = 0.26 (amine silica, DCM:MeOH, 96:4); m.p. 137.5-139.5 °C; λ_{max} (EtOH)/nm 281.6; IR (neat) ν_{max}/cm^{-1} 3237, 1633, 1582, 1535, 1510, 1445, 1423, 1390; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.16 (6H, s, $CH_2N(CH_3)_2$), 2.39 (2H, t, *J* = 6.8 Hz, $CH_2CH_2NMe_2$), 3.30 – 3.39 (2H, m, $NHCH_2CH_2$), 6.86 (1H, t, *J* = 5.8 Hz, $ArNHCH_2$), 7.39 (1H, s, H-3), 7.51 (1H, dd, *J* = 8.7, 1.2 Hz, H-5'), 7.59 (1H, s, H-5), 7.77 (1H, dd, *J* = 8.7, 8.4 Hz, H-4'), 8.49 (2H, s, H-4", 6"), 9.95 (1H, s, CONHAr), 12.71 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 39.0 ($ArNHCH_2$), 45.3 ($CH_2N(CH_3)_2$), 58.1 ($CH_2CH_2NMe_2$), 110.9 (C-3), 119.3 (d, *J* = 18.1 Hz, C-3'), 123.3 (C-5"), 124.7 (C-2 or C-4), 126.9 (d, *J* = 3.8 Hz, C-5'), 128.5 (C-2 or C-4), 129.2 (d, *J* = 23.0 Hz, C-1'), 129.2 (d, *J* = 5.2 Hz, C-6'), 129.8 (C-5), 131.8 (C-4'), 151.6 (C-4", 6"), 153.8 (d, *J* = 248.5 Hz, C-2'), 158.4 (CONHAr or C-2"), 159.4 (CONHAr or C-2"), 182.6 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.7 (ArF); LRMS (ES^+) *m/z* 465.4 $[M(^{35}Cl^{35}Cl)+H]^+$, 467.4 $[M(^{35}Cl^{37}Cl)+H]^+$; HRMS (NSI) calcd for $C_{20}H_{20}Cl_2FN_6O_2$ $[M(^{35}Cl^{35}Cl)+H]^+$ 465.1003, found 465.0995.

4-(3,6-Dichloro-2-fluorobenzoyl)-*N*-(6-((2-(diethylamino)ethyl)amino)pyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (479)



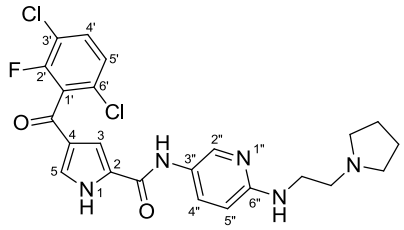
Compound **479** was synthesised according to general procedure Y, using the following reagents: 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**) (150 mg, 0.50 mmol), triethylamine (173 µL, 126 mg, 1.24 mmol), 2-chloro-1-methylpyridinium iodide (140 mg, 0.55 mmol), N^2-(2-(diethylamino)ethyl)pyridine-2,5-diamine (**519**) (129 mg, 0.62 mmol) and DCM (5 mL). The crude product was purified by column chromatography (amine silica gel, DCM:MeOH, 1:0 → 97:3) to yield the *title compound* as a pink solid (66 mg, 27%); R_f = 0.36 (amine silica, DCM:MeOH, 97:3); m.p. 200.0-202.0 °C; λ_{max} (EtOH)/nm 279.4; IR (neat) ν_{max}/cm^{-1} 3413, 3314, 3236, 3115, 2965, 2820, 1635, 1581, 1512, 1443; ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.95 (6H, t, *J* = 7.1 Hz, $CH_2N(CH_2CH_3)_2$), 2.46 – 2.51 (4H, q, *J* = 7.1 Hz, $CH_2N(CH_2CH_3)_2$), 2.53 (2H, t, *J* = 7.0 Hz, CH_2NEt_2), 3.25 (2H, td, *J* = 7.0, 5.6 Hz, $ArNHCH_2$), 6.17 (1H, t, *J* = 5.6 Hz, $ArNHCH_2$), 6.47 (1H, d, *J* = 8.9 Hz, H-5”), 7.38 (1H, s, H-3), 7.50 (1H, dd, *J* = 8.9, 1.2 Hz, H-5’), 7.54 (1H, s, H-5), 7.62 (1H, dd, *J* = 8.9, 2.7 Hz, H-4”), 7.76 (1H, dd, *J* = 8.9, 8.3 Hz, H-4’), 8.21 (1H, d, *J* = 2.7 Hz, H-2”), 9.81 (1H, s, CONHAr), 12.61 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 11.8 ($CH_2N(CH_2CH_3)_2$), 40.4 ($ArNHCH_2$), 46.6 ($CH_2N(CH_2CH_3)_2$), 51.7 (CH_2NEt_2), 107.4 (C-5”), 110.5 (C-3), 119.3 (d, *J* = 18.2 Hz, C-1’), 124.4 (C-2 or C-4), 124.7 (C-3”), 126.9 (d, *J* = 3.5 Hz, C-5’), 129.0 (C-2 or C-4), 129.2 (d, *J* = 5.0 Hz, C-6’), 129.2 (d, *J* = 22.9 Hz, C-3’), 129.6 (C-5), 131.2 (C-4”), 131.8 (C-4’), 140.6 (C-2”), 153.8 (d, *J* = 248.4 Hz, C-2’), 155.9 (C-6”), 158.1 (CONHAr), 182.6 (ArCO-pyrrole); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.7 (ArF); LRMS (ES$^+$) *m/z* 492.4 [M(^{35}Cl^{35}Cl)+H]$^+$, 494.4 [M(^{37}Cl^{35}Cl)+H]$^+$; HRMS (NSI) calcd for $C_{23}H_{25}Cl_2FN_5O_2$ [M(^{35}Cl^{35}Cl)+H]$^+$ 492.1264, found 492.1343.

4-(3,6-Dichloro-2-fluorobenzoyl)-*N*-(2-((2-(diethylamino)ethyl)amino)pyrimidin-5-yl)-1*H*-pyrrole-2-carboxamide, (480)



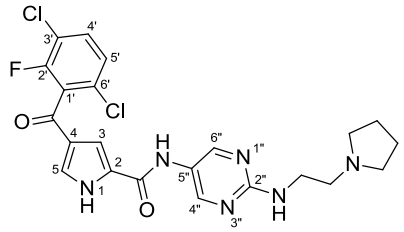
Compound **480** was synthesised according to general procedure Y, using the following reagents: 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**) (100 mg, 0.33 mmol), triethylamine (115 µL, 84 mg, 0.83 mmol), 2-chloro-1-methylpyridinium iodide (93 mg, 0.36 mmol), N^2-(2-(diethylamino)ethyl)pyrimidine-2,5-diamine (**520**) (87 mg, 0.41 mmol) and DCM (3.3 mL). The crude yellow solid was purified by column chromatography (amine silica gel, DCM:MeOH, 1:0 → 97:3) to yield the *title compound* as a pale orange solid (55 mg, 34%); R_f = 0.32 (amine silica, DCM:MeOH, 96:4); m.p. 160.0-162.0 °C; λ_{max} (EtOH)/nm 282.6; IR (neat) ν_{max}/cm^{-1} 3317, 2970, 1637, 1514, 1448, 1426, 1395, 1284; ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.95 (6H, t, *J* = 7.1 Hz, N(CH$_2$C*H*$_3$)$_2$), 2.52 – 2.47 (4H, m, N(C*H*$_2$CH$_3$)$_2$), 2.54 (2H, t, *J* = 7.1 Hz, C*H*$_2$NEt$_2$), 3.38 -3.26 (2H, m, ArNHC*H*$_2$CH$_2$), 6.81 (1H, t, *J* = 5.8 Hz, ArN*H*CH$_2$), 7.38 (1H, s, H-3), 7.51 (1H, dd, *J* = 8.8, 1.3 Hz, H-5'), 7.59 (1H, s, H-5), 7.78 (1H, dd, *J* = 8.8, 8.4 Hz, H-4'), 8.48 (2H, s, H-4", 6"), 9.94 (1H, s, CON*H*Ar), 12.69 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 11.9 (N(CH$_2$*C*H$_3$)$_2$), ca. 40 (overlapping with DMSO) (ArNH*C*H$_2$), 46.7 (N(*C*H$_2$CH$_3$)$_2$), 51.5 (*C*H$_2$NEt$_2$), 110.9 (C-3), 119.3 (d, *J* = 18.3 Hz, C-3'), 123.3 (C-5"), 124.7 (C-2 or C-4), 126.9 (d, *J* = 3.9 Hz, C-5'), 128.5 (C-2 or C-4), 129.2 (d, *J* = 23.4 Hz, C-1'), 129.2 (d, *J* = 5.0 Hz, C-6'), 129.8 (C-5), 131.8 (C-4'), 151.6 (C-4", 6"), 153.8 (d, *J* = 248.3 Hz, C-2'), 158.4 (*C*ONHAr or C-2'), 159.5 (*C*ONHAr or C-2'), 182.6 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.7 (ArF); LRMS (ES$^-$) *m/z* 491.3 [M(^{35}Cl^{35}Cl)-H]$^-$, 493.3 [M(^{35}Cl^{37}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{22}H_{24}Cl_2FN_6O_2$ [M(^{35}Cl^{35}Cl)+H]$^+$ 493.1316, found 493.1306.

4-(3,6-Dichloro-2-fluorobenzoyl)-*N*-(6-((2-(pyrrolidin-1-yl)ethyl)amino)pyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (481)



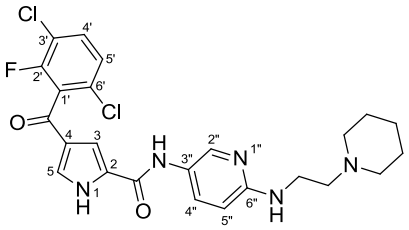
Compound **481** was synthesised according to general procedure Y, using the following reagents: 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**) (75 mg, 0.25 mmol), triethylamine (87 µL, 63 mg, 0.62 mmol), 2-chloro-1-methylpyridinium iodide (70 mg, 0.27 mmol), N^2-(2-(pyrrolidin-1-yl)ethyl)pyridine-2,5-diamine (**521**) (64 mg, 0.31 mmol) and DCM (5 mL). The crude product was purified by column chromatography (amine silica gel, DCM:MeOH, 1:0 → 97:3) to yield the *title compound* as a cream solid (24 mg, 20%); R_f = 0.18 (amine silica, DCM:MeOH, 97:3); m.p. 158.8-160.8 °C; λ_{max} (EtOH)/nm 282.8; IR (neat) ν_{max}/cm^{-1} 2923, 2853, 1731, 1608, 1534, 1511, 1483, 1405; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.68 (4H, p, *J* = 3.1 Hz, NCH$_2$C*H*$_2$ $_{\text{pyrrolidine}}$), 2.47 (4H, p, *J* = 3.1 Hz, NC*H*$_2$CH$_2$ $_{\text{pyrrolidine}}$), 2.57 (2H, t, *J* = 6.8 Hz, ArNHCH$_2$C*H*$_2$N), 3.25 – 3.38 (2H, m, ArNHC*H*$_2$CH$_2$N), 6.28 (1H, t, *J* = 5.7 Hz, ArN*H*CH$_2$), 6.49 (1H, d, *J* = 8.9 Hz, H-5"), 7.39 (1H, s, H-3), 7.51 (1H, dd, *J* = 8.8, 1.3 Hz, H-5'), 7.54 (1H, s, H-5), 7.62 (1H, dd, *J* = 8.9, 2.7 Hz, H-4"), 7.77 (1H, dd, *J* = 8.8, 8.4 Hz, H-4'), 8.21 (1H, d, *J* = 2.7 Hz, H-2"), 9.82 (1H, s, CON*H*Ar), 12.63 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 23.1 (NCH$_2$*C*H$_2$ $_{\text{pyrrolidine}}$), 40.2 (ArNH*C*H$_2$), 53.6 (N*C*H$_2$CH$_2$ $_{\text{pyrrolidine}}$), 55.0 (ArNHCH$_2$*C*H$_2$N), 107.5 (C-5"), 110.5 (C-3), 119.3 (d, *J* = 18.2 Hz, C-1'), 124.4 (C-2 or C-4), 124.7 (C-3"), 126.8 (d, *J* = 3.3 Hz, C-5'), 129.0 (C-2 or C-4), 129.2 (d, *J* = 5.4 Hz, C-6'), 129.2 (d, *J* = 23.0 Hz, C-3'), 129.6 (C-5), 131.2 (C-4"), 131.8 (C-4'), 140.5 (C-2"), 153.8 (d, *J* = 248.7 Hz, C-2'), 155.8 (C-6"), 158.1 (*C*ONHAr), 182.5 (ArCO-pyrrole); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.7 (ArF); LRMS (ES$^+$) *m/z* 490.4 [M(^{35}Cl^{35}Cl)+H]$^+$, 492.4 [M(^{37}Cl^{35}Cl)+H]$^+$; HRMS (NSI) calcd for $C_{23}H_{23}Cl_2FN_5O_2$ [M+H]$^+$ 490.1207, found 490.1193.

4-(3,6-Dichloro-2-fluorobenzoyl)-*N*-(2-((2-(pyrrolidin-1-yl)ethyl)amino)pyrimidin-5-yl)-1*H*-pyrrole-2-carboxamide, (482)



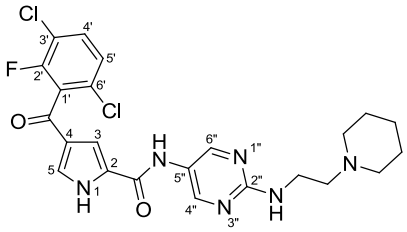
Compound **482** was synthesised according to general procedure Y, using the following reagents: 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**) (150 mg, 0.50 mmol), triethylamine (173 µL, 126 mg, 1.24 mmol), 2-chloro-1-methylpyridinium iodide (140 mg, 0.55 mmol), N^2-(2-(pyrrolidin-1-yl)ethyl)pyrimidine-2,5-diamine (**522**) (129 mg, 0.62 mmol) and DCM (5 mL). The crude yellow solid was purified by column chromatography (amine silica gel, DCM:MeOH, 1:0 → 96:4) to yield the *title compound* as an off-white solid (70 mg, 29%); R_f = 0.28 (amine silica, DCM:MeOH, 96:4); m.p. 140.0-142.0 °C; λ_{max} (EtOH)/nm 282.4; IR (neat) ν_{max}/cm^{-1} 3285, 2960, 2801, 1634, 1510, 1445, 1424, 1392; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.61 – 1.72 (4H, m, $NCH_2CH_{2\ pyrrolidine}$), 2.42 – 2.49 (4H, m, $NCH_2CH_{2\ pyrrolidine}$), 2.56 (2H, t, *J* = 6.9 Hz, $ArNHCH_2CH_2N$), 3.37 (2H, td, *J* = 6.9, 5.8 Hz, $ArNHCH_2CH_2$), 6.93 (1H, t, *J* = 5.8 Hz, $ArNHCH_2$), 7.38 (1H, s, H-3), 7.51 (1H, dd, *J* = 8.8, 1.4 Hz, H-5'), 7.59 (1H, s, H-5), 7.78 (1H, dd, *J* = 8.8, 8.4 Hz, H-4'), 8.48 (2H, s, H-4", 6"), 9.94 (1H, s, CONHAr), 12.70 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 23.1 ($NCH_2CH_{2\ pyrrolidine}$), 40.1 ($ArNHCH_2$), 53.6 ($NCH_2CH_{2\ pyrrolidine}$), 54.8 ($ArNHCH_2CH_2N$), 110.9 (C-3), 119.3 (d, *J* = 17.9 Hz, C-3'), 123.3 (C-5"), 124.7 (C-2 or C-4), 126.9 (d, *J* = 3.6 Hz, C-5'), 128.5 (C-2 or C-4), 129.2 (d, *J* = 22.8 Hz, C-1'), 129.2 (d, *J* = 5.2 Hz, C-6'), 129.8 (C-5), 131.8 (C-4'), 151.6 (C-4", 6"), 153.8 (d, *J* = 248.8 Hz, C-2'), 158.4 (CONHAr or C-2"), 159.4 (CONHAr or C-2"), 182.6 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.7 (ArF); LRMS (ES$^+$) *m/z* 491.4 [M(^{35}Cl^{35}Cl)+H]$^+$, 493.4 [M(^{35}Cl^{37}Cl)+H]$^+$; HRMS (NSI) calcd for $C_{22}H_{22}Cl_2FN_6O_2$ [M(^{35}Cl^{35}Cl)+H]$^+$ 491.1160, found 491.1149.

4-(3,6-Dichloro-2-fluorobenzoyl)-*N*-(6-((2-(piperidin-1-yl)ethyl)amino)pyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (483)



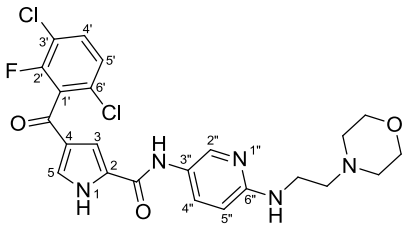
Compound **483** was synthesised according to general procedure Y, using the following reagents: 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**) (150 mg, 0.50 mmol), triethylamine (173 µL, 126 mg, 1.24 mmol), 2-chloro-1-methylpyridinium iodide (140 mg, 0.55 mmol), N^2-(2-(piperidin-1-yl)ethyl)pyridine-2,5-diamine (**523**) (137 mg, 0.62 mmol) and DCM (5mL). The crude product was purified by column chromatography (amine silica gel, DCM:MeOH, 1:0 → 97:3) to yield the *title compound* as a grey solid (56 mg, 22%); R_f = 0.30 (amine silica, DCM:MeOH, 97:3); m.p. 217.5-219.5 °C; λ_{max} (EtOH)/nm 290.8; IR (neat) ν_{max}/cm^{-1} 3333, 3225, 3122, 2927, 2850, 2768, 1632, 1583, 1516, 1445;^{1}H NMR (500 MHz, DMSO-d_6) δ 1.33 – 1.41 (2H, m, $NCH_2CH_2CH_2$ $_{piperidine}$), 1.45 – 1.53 (4H, m, $NCH_2CH_2CH_2$ $_{piperidine}$), 2.36 (4H, brs, $NCH_2CH_2CH_2$ $_{piperidine}$), 2.42 (2H, t, *J* = 6.8 Hz, $ArNHCH_2CH_2N$), 3.30 (2H, td, *J* = 6.8, 5.6 Hz, $ArNHCH_2CH_2N$), 6.20 (1H, t, *J* = 5.6 Hz, $ArNHCH_2$), 6.49 (1H, d, *J* = 8.9 Hz, H-5”), 7.40 (1H, s, H-3), 7.51 (1H, dd, *J* = 8.8, 1.3 Hz, H-5’), 7.55 (1H, s, H-5), 7.63 (1H, dd, *J* = 8.9, 2.7 Hz, H-4”), 7.77 (1H, dd, *J* = 8.8, 8.4 Hz, H-4’), 8.22 (1H, d, *J* = 2.7 Hz, H-2”), 9.82 (1H, s, CONHAr), 12.64 (1H, s, NH-pyrrole);^{13}C NMR (126 MHz, DMSO-d_6) δ 24.1 ($NCH_2CH_2CH_2$ $_{piperidine}$), 25.6 ($NCH_2CH_2CH_2$ $_{piperidine}$), 38.5 ($ArNHCH_2CH_2N$), 54.2 ($NCH_2CH_2CH_2$ $_{piperidine}$), 57.9 ($ArNHCH_2CH_2N$), 107.4 (C-5”), 110.5 (C-3), 119.3 (d, *J* = 18.0 Hz, C-1’), 124.4 (C-2 or C-4), 124.68 (C-3”), 126.9 (d, *J* = 3.9 Hz, C-5’), 129.0 (C-2 or C-4), 129.2 (d, *J* = 5.2 Hz, C-6’), 129.2 (d, *J* = 23.0 Hz, C-3’), 129.6 (C-5), 131.2 (C-4”), 131.8 (C-4’), 140.6 (C-2”), 153.8 (d, *J* = 248.6 Hz, C-2’), 155.8 (C-6”), 158.1 (CONHAr), 182.6 (ArCO-pyrrole); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116. 7 (ArF); LRMS (ES$^+$) *m/z* 504.4 [M(^{35}Cl^{35}Cl)+H]$^+$, 506.4 [M(^{37}Cl^{35}Cl)+H]$^+$; HRMS (NSI) calcd for $C_{24}H_{25}Cl_2FN_5O_2$ [M(^{35}Cl^{35}Cl)+H]$^+$ 504.1364, found 504.1347.

4-(3,6-Dichloro-2-fluorobenzoyl)-*N*-(2-((2-(piperidin-1-yl)ethyl)amino)pyrimidin-5-yl)-1*H*-pyrrole-2-carboxamide, (484)



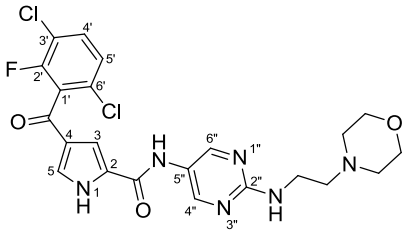
Compound **484** was synthesised according to general procedure Y, using the following reagents: 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**) (150 mg, 0.50 mmol), triethylamine (173 µL, 126 mg, 1.24 mmol), 2-chloro-1-methylpyridinium iodide (140 mg, 0.55 mmol), N^2-(2-(piperidin-1-yl)ethyl)pyrimidine-2,5-diamine (**524**) (137 mg, 0.62 mmol) and DCM (5 mL). The crude yellow solid was purified by column chromatography (amine silica gel, DCM:MeOH, 1:0 → 97:3) to yield the *title compound* as an off-white solid (102 mg, 41%); R_f = 0.32 (amine silica, DCM:MeOH, 97:3); m.p. 144.5-146.5 °C; λ_{max} (EtOH)/nm 283.0; IR (neat) ν_{max}/cm^{-1} 3315, 3123, 2933, 2855, 2806, 1636, 1510, 1445, 1429, 1394; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.32 – 1.40 (2H, m, $NCH_2CH_2CH_2$ piperidine), 1.48 (4H, p, *J* = 5.6 Hz, $NCH_2CH_2CH_2$ piperidine), 2.36 (4H, brs, $NCH_2CH_2CH_2$ piperidine), 2.42 (2H, t, *J* = 6.9 Hz, $ArNHCH_2CH_2N$), 3.36 (2H, td, *J* = 6.9, 5.7 Hz, $ArNHCH_2CH_2$), 6.83 (1H, t, *J* = 5.7 Hz, $ArNHCH_2$), 7.39 (1H, s, H-3), 7.51 (1H, dd, *J* = 8.8, 1.4 Hz, H-5'), 7.59 (1H, s, H-5), 7.78 (1H, dd, *J* = 8.8, 8.4 Hz, H-4'), 8.48 (2H, s, H-4", 6"), 9.95 (1H, s, CONHAr), 12.71 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 24.1 ($NCH_2CH_2CH_2$ piperidine), 25.6 ($NCH_2CH_2CH_2$ piperidine), 38.5 ($ArNHCH_2$), 54.1 ($NCH_2CH_2CH_2$ piperidine), 57.6 ($ArNHCH_2CH_2N$), 110.9 (C-3), 119.3 (d, *J* = 18.1 Hz, C-3'), 123.3 (C-5"), 124.7 (C-2 or C-4), 126.9 (d, *J* = 3.8 Hz, C-5'), 128.5 (C-2 or C-4), 129.2 (d, *J* = 5.2 Hz, C-6'), 129.3 (d, *J* = 23.2 Hz, C-1'), 129.8 (C-5), 131.8 (C-4'), 151.6 (C-4", 6"), 153.8 (d, *J* = 248.6 Hz, C-2'), 158.4 (CONHAr or C-2"), 159.4 (CONHAr or C-2"), 182.6 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.7 (ArF); LRMS (ES^+) *m/z* 505.4 $[M(^{35}Cl^{35}Cl)+H]^+$, 507.4 $[M(^{35}Cl^{37}Cl)+H]^+$; HRMS (NSI) calcd for $C_{23}H_{24}Cl_2FN_6O_2$ $[M(^{35}Cl^{35}Cl)+H]^+$ 505.1316, found 505.1302.

4-(3,6-Dichloro-2-fluorobenzoyl)-*N*-(6-((2-morpholinoethyl)amino)pyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (485)



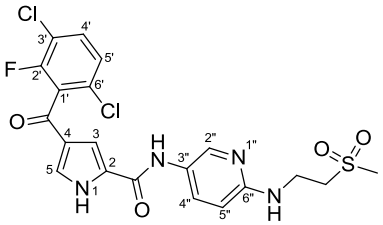
Compound **485** was synthesised according to general procedure Y, using the following reagents: 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**) (150 mg, 0.50 mmol), triethylamine (173 µL, 126 mg, 1.24 mmol), 2-chloro-1-methylpyridinium iodide (140 mg, 0.55 mmol), N^2-(2-morpholinoethyl)pyridine-2,5-diamine (**525**) (138 mg, 0.62 mmol) and DCM (5 mL). The crude product was purified by column chromatography (amine silica gel, DCM:MeOH, 1:0 → 97:3) to yield the *title compound* as a grey solid (36 mg, 14%); R_f = 0.29 (amine silica, DCM:MeOH, 97:3); m.p. 118.0-120.0°C; λ_{max} (EtOH)/nm 283.0; IR (neat) ν_{max}/cm^{-1} 2921, 2852, 1633, 1590, 1504, 1445; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.40 (4H, t, *J* = 4.6 Hz, NC*H*$_{2\ morpholine}$), 2.46 (2H, t, *J* = 6.7 Hz, ArNHCH$_2$C*H*$_2$N), 3.34 (2H, m, ArNHC*H*$_2$CH$_2$), 3.58 (4H, t, *J* = 4.6 Hz, OC*H*$_{2\ morpholine}$), 6.26 (1H, t, *J* = 5.6 Hz, ArN*H*CH$_2$), 6.50 (1H, d, *J* = 8.9 Hz, H-5”), 7.40 (1H, s, H-3), 7.51 (1H, d, *J* = 8.8 Hz, H-5’), 7.55 (1H, s, H-5), 7.63 (1H, dd, *J* = 8.9, 2.7 Hz, H-4”), 7.77 (1H, dd, *J* = 8.8, 8.4 Hz, H-4’), 8.22 (1H, d, *J* = 2.7 Hz, H-2”), 9.82 (1H, s, CON*H*Ar), 12.63 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 38.1 (ArNH*C*H$_2$), 53.4 (N*C*H$_{2\ morpholine}$), 57.5 (ArNHCH$_2$*C*H$_2$N), 66.2 (O*C*H$_{2\ morpholine}$), 107.5 (C-5”), 110.5 (C-3), 119.3 (d, *J* = 18.1 Hz, C-1’), 124.5 (C-2 or C-4), 124.7 (C-3”), 126.9 (d, *J* = 3.8 Hz, C-5’), 128.9 (C-2 or C-4), 129.2 (d, *J* = 5.2 Hz, C-6’), 129.2 (d, *J* = 23.0 Hz, C-3’), 129.6 (C-5), 131.2 (C-4”), 131.8 (C-4’), 140.5 (C-2”), 153.8 (d, *J* = 248.6 Hz, C-2’), 155.8 (C-6”), 158.1 (*C*ONHAr), 182.6 (ArCO-pyrrole); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.7 (ArF); LRMS (ES$^+$) *m/z* 506.3 [M(^{35}Cl^{35}Cl)+H]$^+$, 508.4 [M(^{37}Cl^{35}Cl)+H]$^+$; HRMS (NSI) calcd for $C_{23}H_{23}Cl_2FN_5O_3$ [M+H]$^+$ 506.1156, found 506.1146.

4-(3,6-Dichloro-2-fluorobenzoyl)-*N*-(2-((2-morpholinoethyl)amino)pyrimidin-5-yl)-1*H*-pyrrole-2-carboxamide, (486)



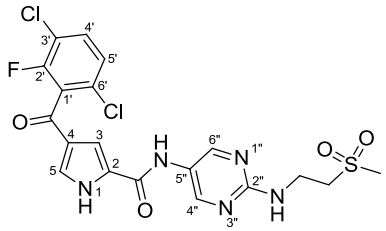
Compound **486** was synthesised according to general procedure Y, using the following reagents: 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**) (150 mg, 0.50 mmol), triethylamine (173 µL, 126 mg, 1.24 mmol), 2-chloro-1-methylpyridinium iodide (140 mg, 0.55 mmol), N^2-(2-morpholinoethyl)pyrimidine-2,5-diamine (**526**) (139 mg, 0.62 mmol) and DCM (5 mL). The crude yellow solid was purified by column chromatography (amine silica gel, DCM:MeOH, 1:0 → 97:3) to yield the *title compound* as an off-white solid (91 mg, 36%); R_f = 0.30 (amine silica, DCM:MeOH, 97:3); m.p. 140.5-142.5 °C; λ_{max} (EtOH)/nm 282.0; IR (neat) ν_{max}/cm^{-1} 3122, 2955, 2815, 1635, 1510, 1445, 1424, 1392; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.40 (4H, brs, NCH_2 morpholine), 2.46 (2H, t, *J* = 6.8 Hz, ArNHCH$_2$CH_2N), 3.38 (2H, td, *J* = 6.8, 5.8 Hz, ArNHCH_2CH$_2$), 3.56 (4H, t, *J* = 4.6 Hz, OCH_2 morpholine), 6.90 (1H, t, *J* = 5.8 Hz, ArN*H*CH$_2$), 7.39 (1H, s, H-3), 7.51 (1H, dd, *J* = 8.8, 1.4 Hz, H-5'), 7.59 (1H, s, H-5), 7.77 (1H, dd, *J* = 8.8, 8.4 Hz, H-4'), 8.49 (2H, s, H-4", 6"), 9.95 (1H, s, CON*H*Ar), 12.71 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 38.1 (ArNH*C*H$_2$), 53.4 (N*C*H$_2$ morpholine), 57.3 (ArNHCH$_2$*C*H$_2$N), 66.2 (O*C*H$_2$ morpholine), 110.9 (C-3), 119.3 (d, *J* = 18.0 Hz, C-3'), 123.4 (C-5"), 124.7 (C-2 or C-4), 126.9 (d, *J* = 4.0 Hz, C-5'), 128.4 (C-2 or C-4), 129.2 (d, *J* = 22.9 Hz, C-1'), 129.2 (d, *J* = 5.1 Hz, C-6'), 129.8 (C-5), 131.8 (C-4'), 151.6 (C-4", 6"), 153.8 (d, *J* = 248.4 Hz, C-2'), 158.4 (*C*ONHAr or C-2"), 159.4 (*C*ONHAr or C-2"), 182.6 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.7 (ArF); LRMS (ES$^+$) *m/z* 507.4 [M(^{35}Cl^{35}Cl)+H]$^+$, 509.4 [M(^{35}Cl^{37}Cl)+H]$^+$; HRMS (NSI) calcd for $C_{22}H_{22}Cl_2FN_6O_3$ [M(^{35}Cl^{35}Cl)+H]$^+$ 507.1109, found 507.1099.

4-(3,6-Dichloro-2-fluorobenzoyl)-*N*-(6-((2-(methylsulfonyl)ethyl)amino)pyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (491)



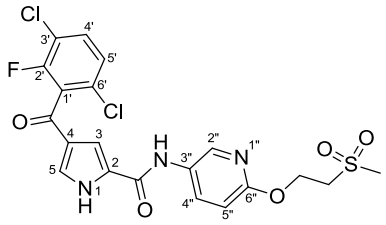
Compound **491** was synthesised according to general procedure Y, using the following reagents: 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**) (150 mg, 0.50 mmol), triethylamine (173 µL, 126 mg, 1.24 mmol), 2-chloro-1-methylpyridinium iodide (140 mg, 0.55 mmol), N^2-(2-(methylsulfonyl)ethyl)pyridine-2,5-diamine (**527**) (133 mg, 0.62 mmol) and DCM (5 mL). The crude product was purified by column chromatography (amine silica gel, DCM:MeOH, 1:0 → 97:3) to yield the *title compound* as an off-white solid (43 mg, 17%); R_f = 0.31 (amine silica, DCM:MeOH, 97:3); m.p. 182.0-184.0 °C; λ_{max} (EtOH)/nm 270.4; IR (neat) ν_{max}/cm^{-1} 3282, 3122, 2922, 2852, 1631, 1501, 1446, 1391, 1276, 1122; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.01 (3H, s, SO_2CH_3), 3.36 (2H, t, *J* = 6.5 Hz, $CH_2SO_2CH_3$), 3.66 (2H, td, *J* = 6.5, 5.9 Hz, ArNHCH_2), 6.54 (1H, d, *J* = 8.9 Hz, H-5”), 6.69 (1H, t, *J* = 5.9 Hz, ArN*H*CH$_2$), 7.41 (1H, s, H-3), 7.51 (1H, dd, *J* = 8.6, 1.5 Hz, H-5’), 7.56 (1H, s, H-5), 7.68 (1H, dd, *J* = 8.9, 2.8 Hz, H-4”), 7.77 (1H, dd, *J* = 8.6, 8.3 Hz, H-4’), 8.30 (1H, d, *J* = 2.8 Hz, H-2”), 9.87 (1H, s, CON*H*Ar), 12.65 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 35.0 (ArNH*C*H$_2$), 41.1 (SO_2CH_3), 53.2 ($CH_2SO_2CH_3$), 108.2 (C-5”), 110.6 (C-3), 119.3 (d, *J* = 18.0 Hz, C-1’), 124.7 (C-2 or C-4), 125.2 (C-3”), 126.9 (d, *J* = 3.8 Hz, C-5’), 128.9 (C-2 or C-4), 129.2 (d, *J* = 5.0 Hz, C-6’), 129.2 (d, *J* = 22.9 Hz, C-3’), 129.7 (C-5), 131.3 (C-4”), 131.8 (C-4’), 140.3 (C-2”), 153.8 (d, *J* = 248.6 Hz, C-2’), 154.9 (C-6”), 158.2 (*C*ONHAr), 182.6 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.7 (ArF); LRMS (ES$^-$) *m/z* 497.2 [M(^{35}Cl^{35}Cl)-H]$^-$, 499.2 [M(^{37}Cl^{35}Cl)-H]$^-$; HRMS (NSI) calcd for $C_{20}H_{18}Cl_2FN_4O_4S$ [M(^{35}Cl^{35}Cl)+H]$^+$ 499.0404, found 499.0389.

4-(3,6-Dichloro-2-fluorobenzoyl)-*N*-(2-((2-(methylsulfonyl)ethyl)amino)pyrimidin-5-yl)-1*H*-pyrrole-2-carboxamide, (492)



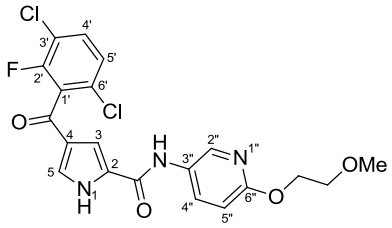
Compound **492** was synthesised according to general procedure Y, using the following reagents: 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**) (100 mg, 0.33 mmol), triethylamine (115 µL, 84 mg, 0.83 mmol), 2-chloro-1-methylpyridinium iodide (93 mg, 0.36 mmol), N^2-(2-(methylsulfonyl)ethyl)pyrimidine-2,5-diamine (**528**) (89 mg, 0.41 mmol) and DCM (3.3 mL). The crude yellow solid was purified by column chromatography (amine silica gel, DCM:MeOH, 1:0 → 97:3) to yield the *title compound* as a white solid (74 mg, 45%); R_f = 0.31 (amine silica, DCM:MeOH, 97:3); m.p. 258.5-260.5 °C; λ_{max} (EtOH)/nm 281.4; IR (neat) ν_{max}/cm^{-1} 3382, 3345, 2896, 1658, 1591, 1522, 1455, 1401; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.02 (3H, s, SO_2CH_3), 3.37 (2H, t, *J* = 6.9 Hz, $CH_2SO_2CH_3$), 3.69 (2H, td, *J* = 6.9, 5.9 Hz, ArNHCH_2CH$_2$), 7.27 (1H, t, *J* = 5.9 Hz, ArNHCH$_2$), 7.40 (1H, s, H-3), 7.52 (1H, dd, *J* = 8.7, 1.2 Hz, H-5'), 7.60 (1H, s, H-5), 7.78 (1H, dd, *J* = 8.7, 8.4 Hz, H-4'), 8.56 (2H, s, H-4", 6"), 10.01 (1H, s, CONHAr), 12.73 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 35.1 (ArNHCH_2), 41.0 (SO_2CH_3), 52.9 ($CH_2SO_2CH_3$), 111.0 (C-3), 119.3 (d, *J* = 18.1 Hz, C-3'), 124.2 (C-5"), 124.7 (C-2 or C-4), 126.9 (d, *J* = 3.7 Hz, C-5'), 128.4 (C-2 or C-4), 129.2 (d, *J* = 23.0 Hz, C-1'), 129.2 (d, *J* = 5.2 Hz, C-6'), 129.9 (C-5), 131.8 (C-4'), 151.5 (C-4", 6"), 153.8 (d, *J* = 248.6 Hz, C-2'), 158.4 (CONHAr or C-2"), 158.9 (CONHAr or C-2"), 182.6 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.7 (ArF); LRMS (ES$^+$) *m/z* 500.3 [M(^{35}Cl^{35}Cl)+H]$^+$, 502.3 [M(^{35}Cl^{37}Cl)+H]$^+$; HRMS (NSI) calcd for $C_{19}H_{17}Cl_2FN_5O_4S$ [M(^{35}Cl^{35}Cl)+H]$^+$ 500.0357, found 500.0343.

4-(3,6-Dichloro-2-fluorobenzoyl)-*N*-(6-(2-(methylsulfonyl)ethoxy)pyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (493)



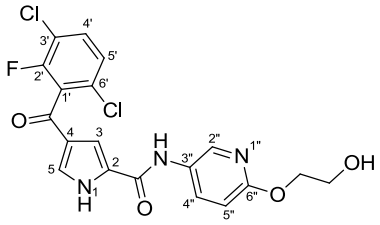
Compound **493** was synthesised according to general procedure Y, using the following reagents: 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**) (150 mg, 0.50 mmol), triethylamine (173 µL, 126 mg, 1.24 mmol), 2-chloro-1-methylpyridinium iodide (140 mg, 0.55 mmol), 6-(2-(methylsulfonyl)ethoxy)pyridin-3-amine (**506**) (134 mg, 0.62 mmol) and DCM (5mL). The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 35:65) to yield the *title compound* as an off-white solid (60 mg, 24%); R_f = 0.32; (silica, petrol:EtOAc, 35:65); m.p. 173.0-175.0 °C; λ_{max} (EtOH)/nm 261.0; IR (neat) ν_{max}/cm^{-1} 3334, 3218, 3123, 1627, 1590, 1560, 1528, 1485, 1446; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.06 (3H, s, SO_2CH_3), 3.62 (2H, t, *J* = 5.8 Hz, $CH_2SO_2CH_3$), 4.61 (2H, t, *J* = 5.8 Hz, ArOCH_2), 6.90 (1H, d, *J* = 8.9 Hz, H-5”), 7.47 (1H, s, H-3), 7.52 (1H, d, *J* = 8.7 Hz, H-5’), 7.61 (1H, s, H-5), 7.78 (1H, dd, *J* = 8.7, 8.3 Hz, H-4’), 8.03 (1H, dd, *J* = 8.9, 2.7 Hz, H-4”), 8.50 (1H, d, *J* = 2.7 Hz, H-2”), 10.14 (1H, s, CON*H*Ar), 12.74 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 42.1 (SO_2CH_3), 53.2 ($CH_2SO_2CH_3$), 59.4 (ArOCH_2), 110.4 (C-5”), 111.1 (C-3), 119.3 (d, *J* = 18.2 Hz, C-1’), 124.7 (C-2 or C-4), 126.9 (d, *J* = 3.8 Hz, C-5’), 128.5 (C-2 or C-4), 129.2 (d, *J* = 23.2 Hz, C-3’), 129.2 (d, *J* = 5.1 Hz, C-6’), 130.0 (C-5), 130.1 (C-3”), 131.8 (C-4”), 132.5 (C-4’), 138.5 (C-2”), 153.8 (d, *J* = 248.4 Hz, C-2’), 158.4 (*C*ONHAr or C-6”), 158.5 (*C*ONHAr or C-6”), 182.6 (ArCO-pyrrole); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.7 (ArF); LRMS (ES$^+$) *m/z* 500.3 [M(^{35}Cl^{35}Cl)+H]$^+$, 502.3 [M(^{37}Cl^{35}Cl)+H]$^+$; HRMS (NSI) calcd for $C_{20}H_{17}Cl_2FN_3O_5S$ [M+H]$^+$ 500.0245, found 500.0236.

4-(3,6-Dichloro-2-fluorobenzoyl)-*N*-(6-(2-methoxyethoxy)pyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (494)



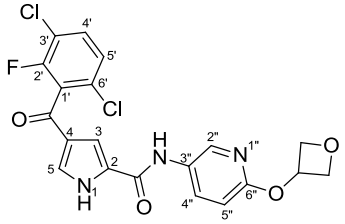
Compound **494** was synthesised according to general procedure Y, using the following reagents: 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**) (150 mg, 0.50 mmol), triethylamine (173 µL, 126 mg, 1.24 mmol), 2-chloro-1-methylpyridinium iodide (140 mg, 0.55 mmol), 6-(2-methoxyethoxy)pyridin-3-amine (**501**) (104 mg, 0.62 mmol) and DCM (5 mL). The crude yellow solid was purified by column chromatography (amine silica gel, DCM:MeOH, 1:0 → 97:3) to yield the *title compound* as an off-white solid (114 mg, 51%); R_f = 0.32 (petrol:EtOAc, 6:4); m.p. 215.0-217.0 °C; λ_{max} (EtOH)/nm 261.0; IR (neat) ν_{max}/cm^{-1} 3316, 3173, 3124, 2981, 2926, 1665, 1643, 1612, 1592, 1556, 1537, 1485, 1446, 1438; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.29 (3H, s, CH_2OCH_3), 3.60 – 3.68 (2H, m, CH_2CH_2OMe), 4.29 – 4.38 (2H, m, $ArOCH_2CH_2$), 6.85 (1H, d, *J* = 8.9 Hz, H-5”), 7.46 (1H, s, H-3), 7.49 – 7.56 (1H, m, H-5’), 7.60 (1H, s, H-5), 7.78 (1H, dd, *J* = 8.4, 8.4 Hz, H-4’), 7.99 (1H, dd, *J* = 8.9, 2.7 Hz, H-4”), 8.45 (1H, d, *J* = 2.7 Hz, H-2”), 10.10 (1H, s, CONHAr), 12.73 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 58.1 (CH_2OCH_3), 64.6 ($ArOCH_2$), 70.3 (CH_2OMe), 110.3 (C-5”), 111.0 (C-3), 119.3 (d, *J* = 17.9 Hz, C-1’), 124.7 (C-2 or C-4), 126.9 (d, *J* = 3.9 Hz, C-5’), 128.6 (C-2 or C-4), 129.2 (d, *J* = 22.9 Hz, C-3’), 129.2 (d, *J* = 5.2 Hz, C-6’), 129.6 (C-3”), 129.9 (C-5), 131.8 (C-4’), 132.4 (C-4”), 138.5 (C-2”), 153.8 (d, *J* = 248.6 Hz, C-2’), 158.4 (C-6”), 159.4 (CONHAr), 182.6 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.7 (ArF); LRMS (ES$^+$) *m/z* 452.3 [M(^{35}Cl^{35}Cl)+H]$^+$, 454.3 [M(^{35}Cl^{37}Cl)+H]$^+$; HRMS (NSI) calcd for $C_{20}H_{17}Cl_2FN_3O_4$ [M(^{35}Cl^{35}Cl)+H]$^+$ 452.0575, found 452.0574.

4-(3,6-Dichloro-2-fluorobenzoyl)-*N*-(6-(2-hydroxyethoxy)pyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (495)



Compound **495** was synthesised according to general procedure Y, using the following reagents: 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**) (150 mg, 0.50 mmol), triethylamine (173 µL, 126 mg, 1.24 mmol), 2-chloro-1-methylpyridinium iodide (140 mg, 0.55 mmol), 2-((5-aminopyridin-2-yl)oxy)ethanol (**502**) (96 mg, 0.62 mmol) and DCM (5 mL). The crude yellow solid was purified by column chromatography (amine silica gel, DCM:MeOH, 1:0 → 97:3) to yield the *title compound* as a pale orange solid (43 mg, 20%); R_f = 0.34 (petrol:EtOAc, 2:8); m.p. 127.0-129.0 °C; λ_{max} (EtOH)/nm 261.8; IR (neat) ν_{max}/cm^{-1} 3239, 3123, 2925, 1632, 1591, 1557, 1529, 1486, 1446, 1392; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.70 (2H, dt, *J* = 5.4, 5.0 Hz, CH_2CH_2OH), 4.24 (2H, t, *J* = 5.0 Hz, $ArOCH_2CH_2$), 4.81 (1H, t, *J* = 5.4 Hz, CH_2OH), 6.83 (1H, d, *J* = 8.8 Hz, H-5”), 7.45 (1H, s, H-3), 7.52 (1H, d, *J* = 8.7 Hz, H-5’), 7.60 (1H, s, H-5), 7.78 (1H, dd, *J* = 8.7, 8.3 Hz, H-4’), 7.99 (1H, dd, *J* = 8.8, 2.3 Hz, H-4”), 8.44 (1H, d, *J* = 2.3 Hz, H-2”), 10.09 (1H, s, CONHAr), 12.73 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 59.4 (CH_2OH), 67.3 ($ArOCH_2$), 110.3 (C-5”), 111.0 (C-3’), 119.3 (d, *J* = 18.1 Hz, C-1’), 124.7 (C-2 or C-4), 126.9 (d, *J* = 3.5 Hz, C-5’), 128.6 (C-2 or C-4), 129.2 (d, *J* = 23.0 Hz, C-3’), 129.2 (d, *J* = 5.2 Hz, C-6’), 129.4 (C-3”), 129.9 (C-5), 131.8 (C-4’), 132.4 (C-4”), 138.6 (C-2”), 153.8 (d, *J* = 248.3 Hz, C-2’), 158.4 (C-6”), 159.6 (CONHAr), 182.6 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.7 (ArF); LRMS (ES$^+$) *m/z* 438.3 [M(^{35}Cl^{35}Cl)+H]$^+$, 440.3 [M(^{35}Cl^{37}Cl)+H]$^+$; HRMS (NSI) calcd for $C_{19}H_{15}Cl_2FN_3O_4$ [M(^{35}Cl^{35}Cl)+H]$^+$ 438.0418, found 438.0418.

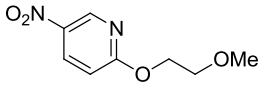
4-(3,6-Dichloro-2-fluorobenzoyl)-*N*-(6-(oxetan-3-yloxy)pyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (496)



Compound **496** was synthesised according to general procedure Y, using the following reagents: 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**) (150 mg,

0.50 mmol), triethylamine (173 µL, 126 mg, 1.24 mmol), 2-chloro-1-methylpyridinium iodide (140 mg, 0.55 mmol), 6-(oxetan-3-yloxy)pyridin-3-amine (**503**) (103 mg, 0.62 mmol) and DCM (5 mL). The crude yellow solid was purified by column chromatography (amine silica gel, DCM:MeOH, 1:0 → 97:3) to yield the *title compound* as an off-white solid (63 mg, 28%); R_f = 0.29 (petrol:EtOAc, 6:4); m.p. 248.5-250.5 °C; λ_{max} (EtOH)/nm 260.6; IR (neat) ν_{max}/cm^{-1} 3344, 3207, 3125, 3061, 2952, 2875, 1625, 1589, 1560, 1527, 1486, 1446, 1277, 1230; ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.55 (2H, dd, *J* = 7.4, 5.1 Hz, CHC*H*$_2$O), 4.89 (2H, t, *J* = 6.8 Hz, CHC*H*$_2$O), 5.53 (1H, p, *J* = 5.8 Hz, ArOC*H*), 6.92 (1H, d, *J* = 8.9 Hz, H-5"), 7.46 (1H, s, H-3), 7.49 – 7.54 (1H, m, H-5'), 7.60 (1H, s, H-5), 7.78 (1H, dd, *J* = 8.4, 8.4 Hz, H-4'), 8.02 (1H, dd, *J* = 8.9, 2.6 Hz, H-4"), 8.43 (1H, d, *J* = 2.6 Hz, H-2"), 10.12 (1H, s, CON*H*Ar), 12.74 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 68.8 (ArO*C*H), 77.0 (CH*C*H$_2$O), 110.3 (C-5"), 111.1 (C-3), 119.3 (d, *J* = 17.9 Hz, C-1'), 124.7 (C-2 or C-4), 126.9 (d, *J* = 3.8 Hz, C-5'), 128.5 (C-2 or C-4), 129.2 (d, *J* = 22.9 Hz, C-3'), 129.2 (d, *J* = 5.1 Hz, C-6'), 130.0 (C-5), 130.2 (C-3"), 131.8 (C-4'), 132.6 (C-4"), 138.5 (C-2"), 153.8 (d, *J* = 248.5 Hz, C-2'), 158.0 (C-6"), 158.4 (*C*ONHAr), 182.6 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.7 (ArF); LRMS (ES$^+$) *m/z* 450.3 [M(^{35}Cl^{35}Cl)+H]$^+$, 452.3 [M(^{35}Cl^{37}Cl)+H]$^+$; HRMS (NSI) calcd for $C_{20}H_{15}Cl_2FN_3O_4$ [M(^{35}Cl^{35}Cl)+H]$^+$ 450.0418, found 450.0418.

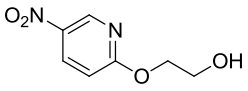
2-(2-Methoxyethoxy)-5-nitropyridine, (498)



To a suspension of sodium hydride (60% dispersion in mineral oil, 189 mg, 4.73 mmol) in THF (16 mL), cooled in an ice bath, was added 2-methoxyethanol (373 µL, 360 mg, 4.73 mmol). The resulting solution was stirred at 0 °C for 10 min and allowed to warm to RT. After 1 h, the reaction mixture was cooled in an ice bath and 2-chloro-5-nitropyridine (**459**) (500 mg, 3.15 mmol) added in portions. The resulting mixture was then stirred overnight at RT. Upon completion, the mixture was diluted with EtOAc (20 mL), quenched by the cautious addition of saturated aq. $NaHCO_3$ (20 mL) and extracted with EtOAc (3 × 20 mL). The pooled organic extracts were washed with water and brine (40 mL, respectively), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 9:1) to yield the *title compound* as a white solid (430 mg, 69%); R_f = 0.29 (petrol:EtOAc, 9:1); m.p. 65.5-67.5 °C; λ_{max} (EtOH)/nm 294.4; IR (neat) ν_{max}/cm^{-1} 3078, 3057, 2989, 2937, 2901, 2849, 2816, 1598, 1575, 1503, 1477, 1345, 1310, 1295, 1273; ^{1}H NMR (500 MHz,

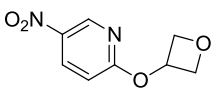
DMSO-d_6) δ 3.29 (3H, s, CH_2OCH_3), 3.65 – 3.71 (2H, m, CH_2CH_2OMe), 4.48 – 4.55 (2H, m, $ArOCH_2CH_2$), 7.06 (1H, d, *J* = 9.1 Hz, H-3), 8.47 (1H, dd, *J* = 9.1, 2.9 Hz, H-4), 9.07 (1H, d, *J* = 2.9 Hz, H-6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 58.1 ($ArOCH_2$), 66.4 (CH_2OCH_3), 69.8 (CH_2OMe), 111.4 (C-3), 134.7 (C-4), 139.5 (C-5), 144.5 (C-6), 166.5 (C-2); LRMS (ES^+) *m/z* 199.2 $[M+H]^+$; HRMS (NSI) calcd for $C_8H_{11}N_2O_4$ $[M+H]^+$ 199.0713, found 199.0714.

2-((5-Nitropyridin-2-yl)oxy)ethanol, (499)



To a suspension of sodium hydride (60% dispersion in mineral oil, 189 mg, 4.73 mmol) in THF (16 mL), cooled in an ice bath, was added ethylene glycol (264 μL, 294 mg, 4.73 mmol). The resulting solution was stirred at 0 °C for 10 min and allowed to warm to RT. After 1 h, the reaction mixture was cooled in an ice bath and 2-chloro-5-nitropyridine (**459**) (500 mg, 3.15 mmol) added in portions. The resulting mixture was then stirred overnight at RT. Upon completion, the mixture was diluted with EtOAc (20 mL), quenched by the cautious addition of saturated aq. $NaHCO_3$ (20 mL) and extracted with EtOAc (3 × 20 mL). The pooled organic extracts were washed with water and brine (40 mL, respectively), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 6:4) to yield the *title compound* as a pale yellow solid (240 mg, 41%); R_f = 0.32 (petrol:EtOAc, 6:4); m.p. 113.0-115.0 °C; λ_{max} (EtOH)/nm 294.2; IR (neat) ν_{max}/cm^{-1} 3231, 3078, 2947, 2878, 1602, 1575, 15313, 1477, 1341, 1308, 1276; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.74 (2H, td, *J* = 5.5, 5.1 Hz, CH_2CH_2OH), 4.41 (2H, t, *J* = 5.1 Hz, $ArOCH_2CH_2$), 4.92 (1H, t, *J* = 5.5 Hz, CH_2OH), 7.03 (1H, d, *J* = 9.1 Hz, H-3), 8.47 (1H, dd, *J* = 9.1, 2.9 Hz, H-4), 9.07 (1H, d, *J* = 2.9 Hz, H-6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 59.0 (CH_2OH), 69.1 ($ArOCH_2$), 111.4 (C-3), 134.6 (C-4), 139.3 (C-5), 144.6 (C-6), 166.8 (C-2); LRMS (ES^+) *m/z* 185.2 $[M+H]^+$; HRMS (NSI) calcd for $C_7H_9N_2O_4$ $[M+H]^+$ 185.0557, found 185.0556.

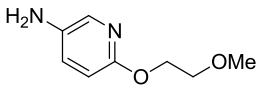
5-Nitro-2-(oxetan-3-yloxy)pyridine, (500)



To a suspension of sodium hydride (60% dispersion in mineral oil, 189 mg, 4.73 mmol) in THF (16 mL), cooled in an ice bath, was added 3-hydroxyoxetane (300 μL, 350 mg, 4.73 mmol). The resulting solution was stirred at 0 °C for 10 min and allowed to warm to

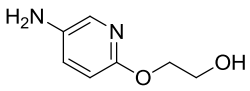
RT. After 1 h, the reaction mixture was cooled in an ice bath and 2-chloro-5-nitropyridine (**459**) (500 mg, 3.15 mmol) added in portions. The resulting mixture was then stirred overnight at RT. Upon completion, the mixture was diluted with EtOAc (20 mL), quenched by the cautious addition of saturated aq. $NaHCO_3$ (20 mL) and extracted with EtOAc (3 × 20 mL). The pooled organic extracts were washed with water and brine (40 mL, respectively), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 85:15) to yield the *title compound* as a white solid (530 mg, 86%); R_f = 0.30 (petrol:EtOAc, 85:15); m.p. 108.0-110.0 °C; λ_{max} (EtOH)/nm 290.2; IR (neat) ν_{max}/cm^{-1} 3091, 3007, 2974, 2951, 2933, 2886, 1599, 1573, 1515, 1467, 1397, 1342, 1301, 1265; ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.60 (2H, ddd, *J* = 7.6, 4.9 and 1.0 Hz, CHC*H*$_2$O), 4.92 (2H, ddd, *J* = 7.2, 6.2 and 1.0 Hz, CHC*H*$_2$O), 5.69 (1H, tt, *J* = 6.2, 4.9 Hz, ArOC*H*), 7.14 (1H, d, *J* = 9.1 Hz, H-3), 8.53 (1H, dd, *J* = 9.1, 2.9 Hz, H-4), 9.03 (1H, d, *J* = 2.9 Hz, H-6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 70.5 (ArO*C*H), 76.5 (CH*C*H$_2$O), 111.5 (C-3), 135.1 (C-4), 140.0 (C-5), 144.5 (C-6), 165.1 (C-2); LRMS (ES$^+$) *m/z* 197.2 [M+H]$^+$; HRMS (NSI) calcd for $C_8H_9N_2O_4$ [M+H]$^+$ 197.0557, found 197.0555.

6-(2-Methoxyethoxy)pyridin-3-amine, (501)



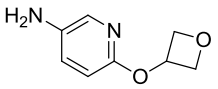
Compound **501** was synthesised according to general procedure D', using the following reagents: 2-(2-methoxyethoxy)-5-nitropyridine (**498**) (400 mg, 2.02 mmol), THF (20 mL) and methanol (20 mL). The crude brown oil (325 mg, 96%) was used in the next step without further purification; R_f = 0.28 (petrol:EtOAc, 1:1); λ_{max} (EtOH)/nm 235.8, 312.4; IR (neat) ν_{max}/cm^{-1} 3416, 3340, 3222, 2930, 2886, 2818, 1628, 1577, 1486, 1416, 1269, 1246; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.27 (3H, s, CH$_2$OC*H*$_3$), 3.56 – 3.61 (2H, m, CH$_2$C*H*$_2$OMe), 4.16 – 4.23 (2H, m, ArOC*H*$_2$CH$_2$), 4.74 (2H, brs, ArN*H*$_2$), 6.54 (1H, d, *J* = 8.7 Hz, H-3), 7.00 (1H, dd, *J* = 8.7, 2.9 Hz, H-4), 7.48 (1H, d, *J* = 2.9 Hz, H-6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 58.0 (CH$_2$O*C*H$_3$), 64.0 (ArO*C*H$_2$), 70.5 (*C*H$_2$OMe), 110.2 (C-3), 126.3 (C-4), 130.9 (C-6), 139.4 (C-5), 155.1 (C-2); LRMS (ES$^+$) *m/z* 169.2 [M+H]$^+$; HRMS (NSI) calcd for $C_8H_{13}N_2O_2$ [M+H]$^+$ 169.0972, found 169.0968.

2-((5-Aminopyridin-2-yl)oxy)ethanol, (502)



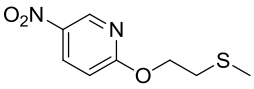
Compound **502** was synthesised according to general procedure D', using the following reagents: 2-((5-nitropyridin-2-yl)oxy)ethanol (**499**) (200 mg, 1.09 mmol), THF (10.9 mL) and methanol (10.9 mL). The crude off-white solid (159 mg, 95%) was used in the next step without further purification; R_f = 0.35 (EtOAc, 100%); m.p. 60.5-62.5 °C; λ_{max} (EtOH)/nm 236.0, 312.8; IR (neat) ν_{max}/cm^{-1} 3428, 3310, 3202, 2920, 2869, 1624, 1573, 1491, 1458, 1419, 1386, 1274, 1238; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.64 (2H, s, CH_2CH_2OH), 4.10 (2H, t, J = 5.3 Hz, $ArOCH_2CH_2$), 4.74 (3H, brs, $ArNH_2$ and CH_2OH), 6.53 (1H, d, J = 8.7 Hz, H-3), 7.00 (1H, dd, J = 8.7, 2.9 Hz, H-4), 7.48 (1H, d, J = 2.9 Hz, H-6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 59.7 (CH_2OH), 66.8 ($ArOCH_2$), 110.2 (C-3), 126.3 (C-4), 131.0 (C-6), 139.3 (C-5), 155.4 (C-2); LRMS (ES$^+$) *m/z* 155.1 $[M+H]^+$; HRMS (NSI) calcd for $C_7H_{11}N_2O_2$ $[M+H]^+$ 155.0815, found 155.0812.

6-(Oxetan-3-yloxy)pyridin-3-amine, (503)



Compound **503** was synthesised according to general procedure D', using the following reagents: 5-nitro-2-(oxetan-3-yloxy)pyridine (**500**) (500 mg, 2.55 mmol), THF (26 mL) and methanol (26 mL). The crude yellow solid (394 mg, 93%) was used in the next step without further purification; R_f = 0.28 (petrol:EtOAc, 1:1); m.p. 84.0-86.0 °C; λ_{max} (EtOH)/nm 236.4, 312.0; IR (neat) ν_{max}/cm^{-1} 3366. 3314, 2947, 2878, 1646, 1610, 1577, 1482, 1423, 1249; ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.43 – 4.54 (2H, m, $CHCH_2O$), 4.80 (2H, brs, $ArNH_2$), 4.82 (2H, t, J = 6.9 Hz, $CHCH_2O$), 5.38 (1H, p, J = 5.7 Hz, ArOC*H*), 6.60 (1H, d, J = 8.7 Hz, H-3), 7.02 (1H, dd, J = 8.7, 2.9 Hz, H-4), 7.42 (1H, d, J = 2.9 Hz, H-6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 68.2 (ArO*C*H), 77.3 ($CHCH_2O$), 110.2 (C-3), 126.4 (C-4), 131.0 (C-6), 140.0 (C-5), 153.7 (C-2); LRMS (ES$^+$) *m/z* 167.2 $[M+H]^+$; HRMS (NSI) calcd for $C_8H_{11}N_2O_2$ $[M+H]^+$ 167.0815, found 167.0812.

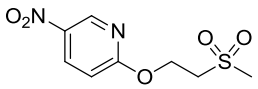
2-(2-(Methylthio)ethoxy)-5-nitropyridine, (504)



To a suspension of sodium hydride (60% dispersion in mineral oil, 136 mg, 5.68 mmol) in THF (20 mL), cooled in an ice bath, was added 2-(methylthio)ethanol (523 mg, 493 µL,

5.68 mmol). The resulting solution was stirred at 0 °C for 10 min and allowed to warm to room temperature. After 1 h, the reaction mixture was cooled in an ice bath and 2-chloro-5-nitropyridine (**459**) (600 mg, 3.78 mmol) added in portions. The resulting mixture was then stirred overnight at room temperature. Upon completion, the mixture was diluted with EtOAc (20 mL), quenched by the cautious addition of sat. aq. $NaHCO_3$ (20 mL) and extracted with EtOAc (3 × 20 mL). The pooled organic extracts were washed with water and brine (40 mL, respectively), dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 95:5) to yield the title compound as an off-white solid (715 mg, 88%); R_f = 0.45 (petrol:EtOAc, 9:1); m.p. 43.0-45.0 °C; λ_{max} (EtOH)/nm 292.2; IR (neat) ν_{max}/cm^{-1} 2976, 2916, 1604, 1576, 1506, 1482, 1451, 1400; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.14 (3H, s, CH_2SCH_3), 2.88 (2H, t, *J* = 6.7 Hz, CH_2SCH_3), 4.56 (2H, t, *J* = 6.7 Hz, $ArOCH_2$), 7.04 (1H, d, *J* = 9.2 Hz, H-3), 8.48 (1H, dd, *J* = 9.2, 2.9 Hz, H-4), 9.08 (1H, d, *J* = 2.9 Hz, H-6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 15.1 (CH_2SCH_3), 31.7 (CH_2SCH_3), 66.1 ($ArOCH_2$), 111.4 (C-3), 134.8 (C-4), 139.5 (C-5), 144.6 (C-6), 166.3 (C-2); HRMS (NSI) calcd for $C_8H_{11}N_2O_3S$ $[M+H]^+$: 215.0485; found 215.0486.

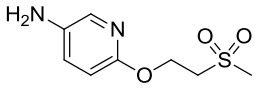
2-(2-(Methylsulfonyl)ethoxy)-5-nitropyridine, (505)



To 2-(2-(methylthio)ethoxy)-5-nitropyridine (**504**) (138 mg, 0.64 mmol) in MeOH (5 mL) was added a solution of OXONE® (monopersulfate compound) (396 mg, 1.29 mmol) in water (5 mL). The resulting cloudy solution was stirred at room temperature for 24 h. The reaction mixture was filtered through Celite and concentrated *in vacuo*. The white residue was dissolved in sat. aq. NH_4Cl (20 mL) and extracted with EtOAc (3 × 20 mL). The pooled organic extracts were washed with water and brine (30 mL, respectively), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel, DCM:MeOH, 1:0 → 97:3) to yield the *title compound* as a grey solid (91 mg, 57%); R_f = 0.75 (DCM:MeOH, 95:5); m.p. 99.5-101.5 °C; λ_{max} (EtOH)/nm 287.6; IR (neat) ν_{max}/cm^{-1} 3030, 2989, 2937, 1602, 1576, 1509, 1483, 1457, 1421; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.07 (3H, s, $CH_2SO_2CH_3$), 3.69 (2H, t, *J* = 5.8 Hz, $CH_2SO_2CH_3$), 4.77 (2H, t, *J* = 5.8 Hz, $ArOCH_2$), 7.11 (1H, d, *J* = 9.1 Hz, H-3), 8.52 (1H, dd, *J* = 9.1, 2.9 Hz, H-4), 9.11 (1H, d, *J* = 2.9 Hz, H-6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 42.0 ($CH_2SO_2CH_3$), 52.8 ($CH_2SO_2CH_3$), 61.0 ($ArOCH_2$), 111.5 (C-3), 135.0

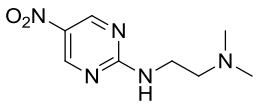
(C-4), 139.9 (C-5), 144.5 (C-6), 165.6 (C-2); LRMS (ES^+) *m/z* 247.2 $[M+H]^+$; HRMS (NSI) calcd for $C_8H_{11}N_2O_5S$ $[M+H]^+$ 247.0383, found 247.0384.

6-(2-(Methylsulfonyl)ethoxy)pyridin-3-amine, (506)



Compound **506** was synthesised according to general procedure 3, using the following reagents: 2-(2-(methylsulfonyl)ethoxy)-5-nitropyridine (**505**) (379 mg, 1.54 mmol), 10% Pd/C (38 mg) and MeOH (15 mL). The brown solid (342 mg, 95%) was used in the next step without further purification; R_f = 0.66 (amine silica, EtOAc 100%); m.p. 102.0-104.0 °C; λ_{max} (EtOH)/nm 312.4, 235.6; IR (neat) ν_{max}/cm^{-1} 3413, 3347, 3243, 3016, 2958, 2915, 1907, 1640, 1609, 1580, 1487, 1422; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.03 (3H, s, $CH_2SO_2CH_3$), 3.54 (2H, t, *J* = 5.9 Hz, $CH_2SO_2CH_3$), 4.46 (2H, t, *J* = 5.9 Hz, $ArOCH_2$), 4.82 (2H, brs, $ArNH_2$), 6.59 (1H, d, *J* = 8.7 Hz, H-3), 7.03 (1H, dd, *J* = 8.7, 3.0 Hz, H-4), 7.51 (1H, d, *J* = 3.0 Hz, H-6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 42.1 ($CH_2SO_2CH_3$), 53.4 ($CH_2SO_2CH_3$), 59.0 ($ArOCH_2$), 110.3 (C-3), 126.3 (C-4), 130.9 (C-6), 140.1 (C-5), 154.2 (C-2); LRMS (ES^+) *m/z* 217.2 $[M+H]^+$; HRMS (NSI) calcd for $C_8H_{13}N_2O_3S$ $[M+H]^+$ 217.0641; found 217.0641.

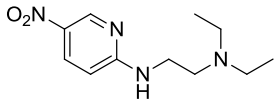
***N*^{1}, *N*^{1}-Dimethyl-*N*^{2}-(5-nitropyrimidin-2-yl)ethane-1,2-diamine, (507)**



Compound **507** was synthesised according to general procedure C', using the following reagents: 2-chloro-5-nitropyrimidine (**414**) (250 mg, 1.57 mmol), triethylamine (240 µL, 174 mg, 1.72 mmol), *N*,*N*-dimethylethylenediamine (189 µL, 152 mg, 1.72 mmol) and THF (7.9 mL). The crude product was purified by column chromatography (amine silica gel, petrol:EtOAc, 1:0 → 1:1) to yield the *title compound* as a pale yellow solid (245 mg, 74%); R_f = 0.29 (amine silica, petrol:EtOAc, 1:1); m.p. 144.5-146.5 °C; λ_{max} (EtOH)/nm 332.8; IR (neat) ν_{max}/cm^{-1} 3253, 2971, 2941, 2859, 2827, 2772, 1573, 1550, 1496, 1473, 1459, 1443, 1319, 1289, 1274, 1255; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.16 (6H, s, $CH_2N(CH_3)_2$), 2.42 (2H, t, *J* = 6.7 Hz, $CH_2CH_2NMe_2$), 3.48 (2H, td, *J* = 6.7, 5.8 Hz, $ArNHCH_2CH_2$), 8.68 (1H, t, *J* = 5.8 Hz, $ArNHCH_2$), 9.01 (1H, d, *J* = 3.4 Hz, H-4 or H-6), 9.09 (1H, d, *J* = 3.4 Hz, H-4 or H-6); ^{13}C NMR (126 MHz, DMSO-d_6) δ ca. 40 (overlapping with DMSO) ($ArNHCH_2$) 45.2 ($CH_2N(CH_3)_2$), 57.6 ($CH_2N(CH_3)_2$), 133.6

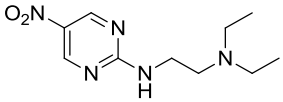
(C-5), 155.2 (C-4 or C-6), 155.4 (C-4 or C-6), 162.7 (C-2); LRMS (ES^+) *m/z* 212.2 $[M+H]^+$; HRMS (NSI) calcd for $C_8H_{14}N_5O_2$ $[M+H]^+$ 212.1142, found 212.1143.

_N_,_N_-Diethyl-_N_'-(5-nitropyridin-2-yl)ethane-1,2-diamine, (508)



Compound **508** was synthesised according to general procedure G', using the following reagents: 2-chloro-5-nitropyridine (**459**) (400 mg, 2.52 mmol), triethylamine (387 µL, 281 mg, 2.78 mmol), *N*,*N*-diethylethylenediamine (390 µL, 323 mg, 2.78 mmol) and THF (10 mL). The crude product was purified by column chromatography (amine silica gel, petrol:EtOAc, 1:0 → 3:1) to yield the *title compound* as a yellow oil (356 mg, 59%); R_f = 0.14 (amine silica, petrol:EtOAc, 8:2); λ_{max} (EtOH)/nm 360.4; IR (neat) ν_{max}/cm^{-1} 3367, 2967, 2812, 1599, 1576, 1526, 1497, 1468; ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.95 (6H, t, *J* = 7.1 Hz, $CH_2N(CH_2CH_3)_2$), 2.50 (4H, q, *J* = 7.1 Hz, $CH_2N(CH_2CH_3)_2$), 2.57 (2H, t, *J* = 6.8 Hz, CH_2NEt_2), 3.46 (2H, brs, $ArNHCH_2$), 6.58 (1H, d, *J* = 9.4 Hz, H-3), 7.95 - 8.14 (2H, m, H-4 and $ArNHCH_2$), 8.90 (1H, d, *J* = 2.9 Hz, H-6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 11.8 ($CH_2N(CH_2CH_3)_2$), 38.8 ($ArNHCH_2$), 46.6 ($CH_2N(CH_2CH_3)_2$), 51.2 (CH_2NEt_2), 108.6 (C-3), 131.5 (C-4), 134.1 (C-5), 146.9 (C-6), 161.4 (C-2); LRMS (ES^-) *m/z* 237.2 $[M-H]^-$; HRMS (NSI) calcd for $C_{11}H_{19}N_4O_2$ $[M+H]^+$ 239.1503, found 239.1498.

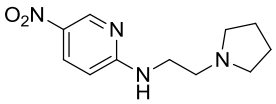
_N_^{1}, _N_^{1}-Diethyl-_N_^{2}-(5-nitropyrimidin-2-yl)ethane-1,2-diamine, (509)



Compound **509** was synthesised according to general procedure C', using the following reagents: 2-chloro-5-nitropyrimidine (**414**) (250 mg, 1.57 mmol), triethylamine (240 µL, 174 mg, 1.72 mmol), *N*,*N*-diethylethylenediamine (242 µL, 200 mg, 1.72 mmol) and THF (7.9 mL). The crude product was purified by column chromatography (amine silica gel, petrol:EtOAc, 1:0 → 8:2) to yield the *title compound* as a yellow solid (350 mg, 93%); R_f = 0.29 (amine silica, petrol:EtOAc, 8:2); m.p. 70.0-72.0 °C; λ_{max} (EtOH)/nm 334.6; IR (neat) ν_{max}/cm^{-1} 3364, 2965, 2934, 2900, 2875, 2805, 1599, 1556, 1471, 1337, 1285; ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.95 (6H, t, *J* = 7.1 Hz, $N(CH_2CH_3)_2$), 2.50 (4H, q, *J* = 7.1 Hz, $N(CH_2CH_3)_2$), 2.58 (2H, t, *J* = 7.0 Hz, CH_2NEt_2), 3.46 (2H, td, *J* = 7.0, 5.9 Hz, $ArNHCH_2CH_2$), 8.64 (1H, t, *J* = 5.9 Hz, $ArNHCH_2$), 9.02 (1H, d, *J* = 3.4 Hz, H-4 or H-6), 9.10 (1H, d, *J* = 3.4 Hz, H-4 or H-6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 11.9

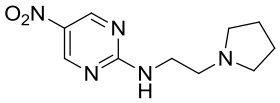
($N(CH_2CH_3)_2$), ca. 40 (overlapping with DMSO) ($ArNHCH_2$), 46.6 ($N(CH_2CH_3)_2$), 51.0 (CH_2NEt_2), 133.5 (C-5), 155.1 (C-4 or C-6), 155.4 (C-4 or C-6), 162.8 (C-2); LRMS (ES^+) *m/z* 240.3 $[M+H]^+$; HRMS (NSI) calcd for $C_{10}H_{18}N_5O_2$ $[M+H]^+$ 240.1455, found 240.1455.

5-Nitro-*N*-(2-(pyrrolidin-1-yl)ethyl)pyridin-2-amine, (510)



Compound **510** was synthesised according to general procedure G', using the following reagents: 2-chloro-5-nitropyridine (**459**) (400 mg, 2.52 mmol), triethylamine (387 µL, 281 mg, 2.78 mmol), 1-(2-aminoethyl)pyrrolidine (286 µL, 317mg, 2.78 mmol) and THF (10 mL). The crude product was purified by column chromatography (amine silica gel, petrol:EtOAc, 1:0 → 3:7) to yield the *title compound* as a yellow solid (377 mg, 63%); R_f = 0.32 (amine silica, petrol:EtOAc, 3:7); m.p. 78.5-80.5 °C; λ_{max} (EtOH)/nm 359.4; IR (neat) ν_{max}/cm^{-1} 3236, 3178, 2925, 2809, 1606, 1547, 1476, 1405; ^1H NMR (500 MHz, DMSO-d_6) δ 1.63 – 1.72 (4H, m, J = 3.7 Hz, NCH_2CH_2 pyrrolidine), 2.43 – 2.49 (4H, m, NCH_2CH_2 pyrrolidine), 2.59 (2H, t, J = 6.6 Hz, $ArNHCH_2CH_2N$), 3.51 (2H, brs, $ArNHCH_2$), 6.60 (1H, d, J = 9.4 Hz, H-3), 7.83 – 8.32 (2H, m, H-4 & ArNH), 8.90 (1H, d, J = 2.4 Hz, H-6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 23.1 (NCH_2CH_2 pyrrolidine), 40.5 ($ArNHCH_2$), 53.6 (NCH_2CH_2 pyrrolidine), 54.5 ($ArNHCH_2CH_2N$), 108.6 (C-3), 131.6 (C-4), 134.1 (C-5), 146.9 (C-6), 161.3 (C-2); LRMS (ES^+) *m/z* 257.2 $[M+H]^+$; HRMS (NSI) calcd for $C_{11}H_{17}N_4O_2$ $[M+H]^+$ 237.1346, found 237.1339.

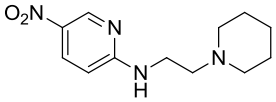
5-Nitro-*N*-(2-(pyrrolidin-1-yl)ethyl)pyrimidin-2-amine, (511)



Compound **511** was synthesised according to general procedure C', using the following reagents: 2-chloro-5-nitropyrimidine (**414**) (350 mg, 2.19 mmol), triethylamine (336 µL, 244 mg, 2.41 mmol), 1-(2-aminoethyl)pyrrolidine (306 µL, 276 mg, 2.41 mmol) and THF (11 mL). The crude product was purified by column chromatography (amine silica gel, petrol:EtOAc, 1:0 → 3:1) to yield the *title compound* as a pale yellow solid (454 mg, 87%); R_f = 0.26 (amine silica, petrol:EtOAc, 3:1); m.p. 138.5-140.5 °C; λ_{max} (EtOH)/nm 331.8; IR (neat) ν_{max}/cm^{-1} 3255, 2950, 2806, 1574, 1550, 1497, 1464, 1322; ^1H NMR (500 MHz, DMSO-d_6) δ 1.63 – 1.69 (4H, m, NCH_2CH_2 pyrrolidine), 2.44 – 2.49 (4H, m, NCH_2CH_2 pyrrolidine), 2.60 (2H, t, J = 6.8 Hz, $NHCH_2CH_2N$), 3.51 (2H, td, J = 6.8, 5.9 Hz,

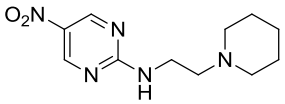
NHC*H*$_2$CH$_2$N), 8.73 (1H, t, *J* = 5.9 Hz, ArN*H*CH$_2$), 9.01 (1H, d, *J* = 3.3 Hz, H-4 or H-6), 9.09 (1H, d, *J* = 3.3 Hz, H-4 or H-6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 23.1 (NCH$_2$*C*H$_2$ pyrrolidine), 40.5 (ArNH*C*H$_2$), 53.6 (N*C*H$_2$CH$_2$ pyrrolidine), 54.2 (NHCH$_2$*C*H$_2$N), 133.6 (C-5), 155.2 (C-4 or C-6), 155.3 (C-4 or C-6), 162.7 (C-2); LRMS (ES$^+$) *m/z* 238.3 [M+H]$^+$; HRMS (NSI) calcd for $C_{10}H_{16}N_5O_2$ [M+H]$^+$ 238.1299, found 238.1298.

_N_-Piperidine-_N_'-(5-nitropyridin-2-yl)ethane-1,2-diamine, (512)



Compound **512** was synthesised according to general procedure **G'**, using the following reagents: 2-chloro-5-nitropyridine (**459**) (152 mg, 0.96 mmol), triethylamine (147 µL, 106 mg, 1.05 mmol), 1-(2-aminoethyl)piperidine (150 µL, 135 mg, 1.05 mmol) and THF (5 mL). The crude product was purified by column chromatography (amine silica gel, petrol:EtOAc, 1:0 → 3:1) to yield the *title compound* as a brown oil (230 mg, 96%); R_f = 0.15 (amine silica, petrol:EtOAc, 8:2); λ_{max} (EtOH)/nm 359.6; IR (neat) ν_{max}/cm^{-1} 3237, 3177, 3043, 2925, 2856, 2812, 2791, 2764, 1608, 1589, 1545, 1497, 1471, 1408; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.31 – 1.42 (2H, m, NCH$_2$CH$_2$C*H*$_2$ piperidine), 1.48 (4H, p, *J* = 5.6 Hz, NCH$_2$C*H*$_2$CH$_2$ piperidine), 2.30 – 2.40 (4H, m, NC*H*$_2$CH$_2$CH$_2$ piperidine), 2.44 (2H, t, *J* = 6.7 Hz, ArNHCH$_2$C*H*$_2$N), 3.49 (2H, brs, ArNHC*H*$_2$CH$_2$N), 6.59 (1H, d, *J* = 9.4 Hz, H-3), 7.95 – 8.15 (2H, m, H-4 and ArN*H*CH$_2$), 8.90 (1H, d, *J* = 2.9 Hz, H-6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 24.0 (NCH$_2$CH$_2$*C*H$_2$ piperidine), 25.5 (NCH$_2$*C*H$_2$CH$_2$ piperidine), 38.8 (ArNH*C*H$_2$CH$_2$N), 54.1 (N*C*H$_2$CH$_2$CH$_2$ piperidine), 57.4 (ArNHCH$_2$*C*H$_2$N), 108.6 (C-3), 131.5 (C-4), 134.1 (C-), 146.9 (C-6), 161.3 (C-2); LRMS (ES$^+$) *m/z* 251.2 [M+H]$^+$; HRMS (NSI) calcd for $C_{12}H_{19}N_4O_2$ [M+H]$^+$ 251.1503, found 251.1496.

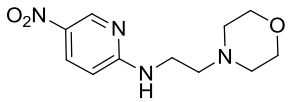
5-Nitro-_N_-(2-(piperidin-1-yl)ethyl)pyrimidin-2-amine, (513)



Compound **513** was synthesised according to general procedure C', using the following reagents: 2-chloro-5-nitropyrimidine (**414**) (350 mg, 2.19 mmol), triethylamine (336 µL, 244 mg, 2.41 mmol), 1-(2-aminoethyl)piperidine (344 µL, 309 mg, 2.41 mmol) and THF (11 mL). The crude product was purified by column chromatography (amine silica gel, petrol:EtOAc, 1:0 → 8:2) to yield the *title compound* as a pale yellow solid (510 mg, 93%); R_f = 0.29 (amine silica, petrol:EtOAc, 8:2); m.p. 97.5-99.5 °C; λ_{max} (EtOH)/nm 332.0; IR (neat) ν_{max}/cm^{-1} 3263, 2968, 2921, 2912, 1595, 1575, 1553, 1328, 1152;

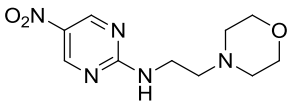
^{1}H NMR (500 MHz, DMSO-d_6) δ 1.31 – 1.40 (2H, m, $NCH_2CH_2CH_2$ $_{piperidine}$), 1.42 – 1.51 (4H, m, $NCH_2CH_2CH_2$ $_{piperidine}$), 2.36 (4H, brs, $NCH_2CH_2CH_2$ $_{piperidine}$), 2.45 (2H, t, J = 6.8 Hz, CH_2CH_2N), 3.49 (2H, td, J = 6.8, 5.5 Hz, $ArNHCH_2CH_2$), 8.65 (1H, t, J = 5.5 Hz, $ArNHCH_2$), 9.01 (1H, d, J = 3.3 Hz, H-4 or H-6), 9.08 (1H, d, J = 3.3 Hz, H-4 or H-6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 24.0 ($NCH_2CH_2CH_2$ $_{piperidine}$), 25.5 ($NCH_2CH_2CH_2$ $_{piperidine}$), 38.9 ($ArNHCH_2$), 54.0 ($NCH_2CH_2CH_2$ $_{piperidine}$), 57.1 (CH_2CH_2N), 133.6 (C-5), 155.1 (C-4 or C-6), 155.3 (C-4 or C-6), 162.7 (C-2); LRMS (ES^+) *m/z* 252.4 $[M+H]^+$; HRMS (NSI) calcd for $C_{11}H_{18}N_5O_2$ $[M+H]^+$ 252.1455, found 252.1454.

_N_-(2-Morpholinoethyl)-5-nitropyridin-2-amine, (514)



Compound **514** was synthesised according to general procedure G', using the following reagents: 2-chloro-5-nitropyridine (**459**) (400 mg, 2.52 mmol), triethylamine (387 µL, 281 mg, 2.78 mmol), 4-(2-aminoethyl)morpholine (358 µL, 361 mg, 2.78 mmol) and THF (10 mL). The crude product was purified by column chromatography (amine silica gel, petrol:EtOAc, 1:0 → 1:1) to yield the *title compound* as a yellow oil (416 mg, 65%); R_f = 0.26 (amine silica, petrol:EtOAc, 1:1); λ_{max} (EtOH)/nm 359.4; IR (neat) ν_{max}/cm^{-1} 3361, 2937, 2854, 2810, 1599, 1576, 1527, 1495, 1467; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.40 (4H, t, J = 4.7 Hz, NCH_2 $_{morpholine}$), 2.47 (2H, t, J = 6.6 Hz, $ArNHCH_2CH_2N$), 3.51 (2H, brs, $ArNHCH_2CH_2$), 3.56 (4H, t, J = 4.7 Hz, OCH_2 $_{morpholine}$), 6.59 (1H, d, J = 9.4 Hz, H-3), 8.07 (2H, brs, H-4 and $ArNHCH_2$), 8.89 (1H, d, J = 2.8 Hz, H-6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 37.9 ($ArNHCH_2$), 53.3 (NCH_2 $_{morpholine}$), 57.0 ($ArNHCH_2CH_2N$), 66.1 (OCH_2 $_{morpholine}$), 108.6 (C-3), 131.6 (C-4), 134.2 (C-5), 146.8 (C-6), 161.3 (C-2); LRMS (ES^+) *m/z* 253.2 $[M+H]^+$; HRMS (NSI) calcd for $C_{11}H_{17}N_4O_3$ $[M+H]^+$ 253.1295, found 253.1289.

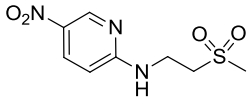
_N_-(2-Morpholinoethyl)-5-nitropyrimidin-2-amine, (515)



Compound **515** was synthesised according to general procedure C', using the following reagents: 2-chloro-5-nitropyrimidine (**414**) (350 mg, 2.19 mmol), triethylamine (336 µL, 244 mg, 2.41 mmol), 4-(2-aminoethyl)morpholine (317 µL, 314 mg, 2.41 mmol) and THF (11 mL). The crude product was purified by column chromatography (amine silica gel, petrol:EtOAc, 1:0 → 65:35) to yield the *title compound* as a pale yellow solid (504 mg,

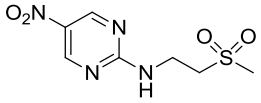
91%); R_f = 0.29 (amine silica, petrol:EtOAc, 65:35); m.p. 125.0-127.0 °C; λ_{max} (EtOH)/nm 332.2; IR (neat) ν_{max}/cm^{-1} 3220, 3066, 2926, 2876, 2863, 2831, 1593, 1556, 1495, 1327; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.36 – 2.43 (4H, m, NC$H_{2\ morpholine}$), 2.48 (2H, t, J = 6.7 Hz, NHCH$_2$CH_2N), 3.49 – 3.57 (6H, m, NHCH_2CH$_2$N and OC$H_{2\ morpholine}$), 8.68 (1H, t, J = 6.0 Hz, ArNHCH$_2$), 9.02 (1H, d, J = 3.3 Hz, H-4 or H-6), 9.08 (1H, d, J = 3.3 Hz, H-4 or H-6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 38.5 (ArNHCH$_2$), 53.3 (NCH$_{2\ morpholine}$), 56.8 (CH$_2$$CH_2$N), 66.2 (O$CH_{2\ morpholine}$), 133.6 (C-5), 155.2 (C-4 or C-6), 155.3 (C-4 or C-6), 162.8 (C-2); LRMS (ES$^+$) *m/z* 254.3 [M+H]$^+$; HRMS (NSI) calcd for $C_{10}H_{16}N_5O_3$ [M+H]$^+$ 254.1248, found 254.1246.

_N_-(2-(Methylsulfonyl)ethyl)-5-nitropyridin-2-amine, (516)



Compound **516** was synthesised according to general procedure G', using the following reagents: 2-chloro-5-nitropyridine (**459**) (400 mg, 2.52 mmol), triethylamine (915 µL, 664 mg, 6.56 mmol), 2-aminoethyl methyl sulfone hydrochloride (524 mg, 3.28 mmol) and THF (15 mL). The crude product was purified by recrystallization from DCM to yield the *title compound* as a yellow solid (391 mg, 63%); R_f = 0.5 (amine silica, EtOAc, 100%); m.p. 242.0-244.0 °C; λ_{max} (EtOH)/nm 347.0; IR (neat) ν_{max}/cm^{-1} 3359, 2993, 1599, 1578, 1522, 1492, 1463, 1410; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.03 (3H, s, SO$_2$CH_3), 3.42 (2H, t, J = 6.7 Hz, CH_2SO$_2$CH$_3$), 3.81 (2H, td, J = 6.7, 6.4 Hz, ArNHCH_2), 6.64 (1H, d, J = 8.2 Hz, H-3), 8.15 (1H, d, J = 8.2 Hz, H-4), 8.34 (1H, brs, ArNHCH$_2$), 8.95 (1H, d, J = 2.8 Hz, H-6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 34.8 (ArNHCH$_2$), 41.0 (SO$_2$$CH_3$), 52.5 ($CH_2SO_2CH_3$), 109.0 (C-4), 132.0 (C-3), 134.9 (C-5), 146.5 (C-6), 160.9 (C-2); LRMS (ES$^+$) *m/z* 246.2 [M+H]$^+$; HRMS (NSI) calcd for $C_8H_{12}N_3O_4S$ [M+H]$^+$ 246.0543, found 246.0538.

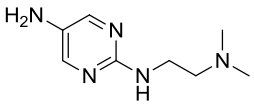
_N_-(2-(Methylsulfonyl)ethyl)-5-nitropyrimidin-2-amine, (517)



Compound **517** was synthesised according to general procedure C', using the following reagents: 2-chloro-5-nitropyrimidine (**414**) (350 mg, 2.19 mmol), triethylamine (672 µL, 488 mg, 4.82 mmol), 4-aminoethyl methylsulfone hydrochloride (385 mg, 2.41 mmol) and THF (11 mL). The crude product was purified by recrystallisation from DCM to yield the *title compound* as an off-white solid (250 mg, 46%); R_f = 0.29 (amine silica, petrol:EtOAc,

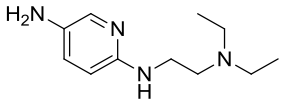
7:3); m.p. 204.0-206.0 °C; λ_{max} (EtOH)/nm 322.2; IR (neat) ν_{max}/cm^{-1} 3325, 3298, 1593, 1562, 1498, 1340, 1275; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.04 (3H, s, $CH_2SO_2CH_3$), 3.42 (2H, t, J = 6.9 Hz, $CH_2SO_2CH_3$), 3.81 (2H, td, J = 6.9, 5.9 Hz, ArNHCH_2CH$_2$), 8.90 (1H, t, J = 5.9 Hz, ArNHCH$_2$), 9.07 (1H, d, J = 3.3 Hz, H-4 or H-6), 9.15 (1H, d, J = 3.3 Hz, H-4 or H-6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 35.3 (ArNHCH_2), 40.9 (SO_2CH_3), 52.3 (CH_2SO_2), 134.3 (C-5), 155.3 (C-4 and C-6), 162.6 (C-2); LRMS (ES$^-$) *m/z* 245.2 [M-H]$^-$; HRMS (NSI) calcd for $C_7H_{11}N_4O_4S$ [M+H]$^+$ 247.0496, found 247.0495.

N^2-(2-(Dimethylamino)ethyl)pyrimidine-2,5-diamine, (518)



Compound **518** was synthesised according to general procedure D', using the following reagents: N^1,N^1-dimethyl-N^2-(5-nitropyrimidin-2-yl)ethane-1,2-diamine (**507**) (200 mg, 0.95 mmol), THF (9.5 mL) and methanol (9.5 mL). The orange solid (165 mg, 96%) was used in the next step without further purification; R_f = 0.20 (amine silica, DCM:MeOH, 8:2); m.p. 97.5-99.5 °C; λ_{max} (EtOH)/nm 249.6; IR (neat) ν_{max}/cm^{-1} 3391, 3262, 3127, 3010, 2910, 2818, 1613, 1573, 1530, 1447, 1422, 1366, 1340; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.14 (6H, s, $CH_2N(CH_3)_2$), 2.34 (2H, t, J = 6.8 Hz, $CH_2CH_2NMe_2$), 3.23 (2H, td, J = 6.8, 5.7 Hz, ArNHCH_2CH$_2$), 4.39 (2H, brs, $ArNH_2$), 5.88 (1H, t, J = 5.7 Hz, ArNHCH$_2$), 7.79 (2H, s, H-4, 6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 39.3 (ArNHCH_2), 45.3 ($CH_2N(CH_3)_2$), 58.4 ($CH_2N(CH_3)_2$), 133.6 (C-5), 144.6 (C-4, 6), 156.4 (C-2); LRMS (ES$^+$) *m/z* 182.3 [M+H]$^+$; HRMS (NSI) calcd for $C_8H_{16}N_5$ [M+H]$^+$ 182.1400, found 182.1398.

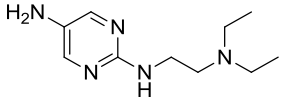
N^2-(2-(Diethylamino)ethyl)pyridine-2,5-diamine, (519)



Compound **519** was synthesised according to general procedure V, using the following reagents: *N*,*N*-diethyl-*N*'-(5-nitropyridin-2-yl)ethane-1,2-diamine (**508**) (320 mg, 1.34 mmol) and MeOH (27 mL). The crude red oil (275 mg, 98%) was used in the next step without further purification; R_f = 0.62 (amine silica, DCM:MeOH, 97:3); λ_{max} (EtOH)/nm 252.6, 336.6; IR (neat) ν_{max}/cm^{-1} 3315, 2966, 2933, 2814, 1607, 1574, 1499; ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.94 (6H, t, J = 7.1 Hz, $CH_2N(CH_2CH_3)_2$), 2.47 (4H, q, J = 7.1 Hz, $CH_2N(CH_2CH_3)_2$), 2.50 (2H, t, J = 6.8 Hz, CH_2NEt_2), 3.13 (2H, td, J = 6.8, 5.6 Hz, ArNHCH_2), 4.27 (2H, brs, ArNH_2), 5.26 (1H, t, J = 5.6 Hz, ArNHCH$_2$),

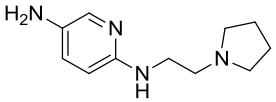
6.29 (1H, d, *J* = 8.6 Hz, H-3), 6.81 (1H, dd, *J* = 8.6, 2.8 Hz, H-4), 7.45 (1H, d, *J* = 2.8 Hz, H-6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 11.8 ($CH_2N(CH_2CH_3)_2$), 39.6 ($ArNHCH_2$), 46.6 ($CH_2N(CH_2CH_3)_2$), 51.9 (CH_2NEt_2), 108.1 (C-3), 125.3 (C-4), 133.3 (C-6), 135.3 (C-5), 151.8 (C-2); LRMS (ES^+) *m/z* 209.2 $[M+H]^+$; HRMS (NSI) calcd for $C_{11}H_{21}N_4$ $[M+H]^+$ 209.1761, found 209.1757.

N^2-(2-(Diethylamino)ethyl)pyrimidine-2,5-diamine, (520)



Compound **520** was synthesised according to general procedure D', using the following reagents: N^1,N^1-diethyl-N^2-(5-nitropyrimidin-2-yl)ethane-1,2-diamine (**509**) (300 mg, 1.25 mmol), THF (12.5 mL) and methanol (12.5 mL). The orange oil (249 mg, 95%) was used in the next step without further purification; R_f = 0.34 (amine silica, EtOAc – 100%); λ_{max} (EtOH)/nm 250.2; IR (neat) ν_{max}/cm^{-1} 3308, 3218, 2968, 2934, 2872, 2810, 1678, 1610, 1560, 1500, 1443; ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.94 (6H, t, *J* = 7.1 Hz, $N(CH_2CH_3)_2$), 2.55 – 2.41 (6H, m, $N(CH_2CH_3)_2$ and CH_2NEt_2), 3.20 (2H, td, *J* = 7.0, 5.9 Hz, $ArNHCH_2CH_2$), 4.39 (2H, brs, $ArNH_2$), 5.84 (1H, t, *J* = 5.9 Hz, $ArNHCH_2$), 7.79 (2H, s, H-4, 6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 11.9 ($N(CH_2CH_3)_2$), ca. 40 (overlapping with DMSO) ($ArNHCH_2$), 46.6 ($N(CH_2CH_3)_2$), 51.7 (CH_2NEt_2), 133.6 (C-5), 144.6 (C-4, 6), 156.5 (C-2); LRMS (ES^+) *m/z* 210.3 $[M+H]^+$; HRMS (NSI) calcd for $C_{10}H_{20}N_5$ $[M+H]^+$ 210.1713, found 210.1714.

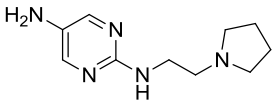
N^2-(2-(Pyrrolidin-1-yl)ethyl)pyridine-2,5-diamine, (521)



Compound **521** was synthesised according to general procedure V, using the following reagents: 5-nitro-*N*-(2-(pyrrolidin-1-yl)ethyl)pyridin-2-amine (**510**) (338 mg, 1.43 mmol), 10% Pd/C (34 mg) and MeOH (15 mL). The crude red oil (274 mg, 93%) was used in the next step without further purification; R_f = 0.69 (amine silica, DCM:MeOH, 97:3); λ_{max} (EtOH)/nm 254.6, 339.4; IR (neat) ν_{max}/cm^{-1} 3317, 2958, 2929, 2875, 2797, 1615, 1576, 1498, 1419; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.65 (4H, p, *J* = 3.1 Hz, $NCH_2CH_{2\ pyrrolidine}$), 2.41 (4H, m, $NCH_2CH_{2\ pyrrolidine}$), 2.51 (2H, t, *J* = 6.8 Hz, $ArNHCH_2CH_2N$), 3.18 (2H, td, *J* = 6.8, 5.8 Hz, $ArNHCH_2$), 4.23 (2H, brs, $ArNH_2$), 5.34 (1H, t, *J* = 5.8 Hz, $ArNHCH_2$), 6.28 (1H, d, *J* = 8.7 Hz, H-3), 6.79 (1H, dd, *J* = 8.7, 2.8 Hz, H-4), 7.43 (1H, d, *J* = 2.8 Hz, H-6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 23.1

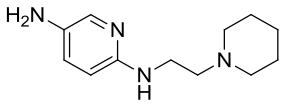
(NCH$_2$*C*H$_2$ pyrrolidine), 40.9 (ArNH*C*H$_2$), 53.7 (N*C*H$_2$CH$_2$ pyrrolidine), 55.3 (ArNHCH$_2$*C*H$_2$N), 108.1 (C-3), 125.4 (C-4), 133.2 (C-6), 135.2 (C-5), 151.8 (C-2); LRMS (ES$^+$) *m/z* 207.2 [M+H]$^+$; HRMS (NSI) calcd for $C_{11}H_{19}N_4$ [M+H]$^+$ 207.1604, found 207.1601.

N^2-(2-(Pyrrolidin-1-yl)ethyl)pyrimidine-2,5-diamine, (522)



Compound **522** was synthesised according to general procedure D', using the following reagents: 5-nitro-*N*-(2-(pyrrolidin-1-yl)ethyl)pyrimidin-2-amine (**511**) (430 mg, 1.81 mmol), THF (18.1 mL) and methanol (18.1 mL). The pale brown solid (346 mg, 92%) was used in the next step without further purification; R_f = 0.34 (amine silica, EtOAc, 100%); m.p. 113.0-115.0 °C; λ_{max} (EtOH)/nm 249.6; IR (neat) ν_{max}/cm^{-1} 3389, 3277, 3135, 2957, 2909, 2798, 1613, 1573, 1531, 1445; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.62 – 1.70 (4H, m, NCH$_2$C*H*$_2$ pyrrolidine), 2.39 – 2.46 (4H, m, NC*H*$_2$CH$_2$ pyrrolidine), 2.51 (2H, t, *J* = 6.9 Hz, NHCH$_2$C*H*$_2$N), 3.26 (2H, td, *J* = 6.9, 5.8 Hz, NHC*H*$_2$CH$_2$N), 4.38 (2H, brs, ArN*H*$_2$), 5.94 (1H, t, *J* = 5.8 Hz, ArN*H*CH$_2$), 7.79 (2H, s, H-4, 6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 23.1 (NCH$_2$*C*H$_2$ pyrrolidine), 40.4 (ArNH*C*H$_2$), 53.6 (N*C*H$_2$CH$_2$ pyrrolidine), 55.1 (NHCH$_2$*C*H$_2$N), 133.6 (C-5), 144.6 (C-4, 6), 156.4 (C-2); LRMS (ES$^+$) *m/z* 208.3 [M+H]$^+$; HRMS (NSI) calcd for $C_{10}H_{18}N_5$ [M+H]$^+$ 208.1557, found 208.1554.

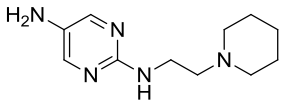
N^2-(2-(Piperidin-1-yl)ethyl)pyridine-2,5-diamine, (523)



Compound **523** was synthesised according to general procedure V, using the following reagents: *N*-piperidine-*N*'-(5-nitropyridin-2-yl)ethane-1,2-diamine (**512**) (371 mg, 1.48 mmol), 10% Pd/C (37 mg) and MeOH (15 mL). The crude brown oil (317 mg, 97%) was used in the next step without further purification; R_f = 0.53 (amine silica, DCM:MeOH, 97:3); λ_{max} (EtOH)/nm 250.6, 338.8; IR (neat) ν_{max}/cm^{-1} 3310, 2928, 2850, 1603, 1574, 1497, 1469; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.37 (2H, m, NCH$_2$CH$_2$C*H*$_2$ piperidine), 1.48 (4H, m, NCH$_2$C*H*$_2$CH$_2$ piperidine), 2.32 (4H, brs, NC*H*$_2$CH$_2$CH$_2$ piperidine), 2.37 (2H, t, *J* = 6.7 Hz, ArNHCH$_2$C*H*$_2$N), 3.17 (2H, td, *J* = 6.7, 5.5 Hz, ArNHC*H*$_2$CH$_2$N), 4.25 (2H, brs, ArN*H*$_2$), 5.27 (1H, t, *J* = 5.5 Hz, ArN*H*CH$_2$), 6.29 (1H, d, *J* = 8.6 Hz, H-3), 6.80 (1H, dd, *J* = 8.6, 2.8 Hz, H-4), 7.44 (1H, d, *J* = 2.8 Hz, H-6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 24.1 (NCH$_2$CH$_2$*C*H$_2$ piperidine), 25.6 (NCH$_2$*C*H$_2$CH$_2$ piperidine), 38.9 (ArNH*C*H$_2$CH$_2$N), 54.2 (N*C*H$_2$CH$_2$CH$_2$ piperidine), 58.0

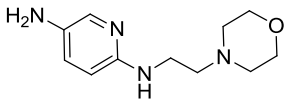
(ArNHCH$_2$*C*H$_2$N), 108.0 (C-3), 125.3 (C-4), 133.2 (C-6), 135.3 (C-5), 151.8 (C-2); LRMS (ES$^+$) *m/z* 221.3 [M+H]$^+$; HRMS (NSI) calcd for $C_{12}H_{21}N_4$ [M+H]$^+$ 221.1761, found 221.1757.

N^2-(2-(Piperidin-1-yl)ethyl)pyrimidine-2,5-diamine, (524)



Compound **524** was synthesised according to general procedure D', using the following reagents: 5-nitro-*N*-(2-(piperidin-1-yl)ethyl)pyrimidin-2-amine (**513**) (480 mg, 1.91 mmol), THF (19.1 mL) and methanol (19.1 mL). The pale yellow solid (385 mg, 91%) was used in the next step without further purification; R_f = 0.28 (amine silica, EtOAc, 100%); m.p. 125.5-127.5 °C; λ_{max} (EtOH)/nm 249.8; IR (neat) ν_{max}/cm^{-1} 3384, 3277, 3157, 2935, 2801, 1613, 1573, 1532, 1447, 1429; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.33 – 1.40 (2H, m, NCH$_2$CH$_2$C*H*$_2$ $_{piperidine}$), 1.44 – 1.51 (4H, m, NCH$_2$C*H*$_2$CH$_2$ $_{piperidine}$), 2.33 (4H, brs, NC*H*$_2$CH$_2$CH$_2$ $_{piperidine}$), 2.37 (2H, t, *J* = 6.9 Hz, CH$_2$C*H*$_2$N), 3.25 (2H, td, *J* = 6.9, 5.7 Hz, ArNHC*H*$_2$CH$_2$), 4.39 (2H, brs, ArN*H*$_2$), 5.86 (1H, t, *J* = 5.7 Hz, ArN*H*CH$_2$), 7.79 (2H, s, H-4, 6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 24.1 (NCH$_2$CH$_2$*C*H$_2$ $_{piperidine}$), 25.6 (NCH$_2$*C*H$_2$CH$_2$ $_{piperidine}$), 38.7 (ArNH*C*H$_2$), 54.1 (N*C*H$_2$CH$_2$CH$_2$ $_{piperidine}$), 57.9 (CH$_2$*C*H$_2$N), 133.6 (C-5), 144.6 (C-4, 6), 156.4 (C-2); LRMS (ES$^+$) *m/z* 222.3 [M+H]$^+$; HRMS (NSI) calcd for $C_{11}H_{20}N_5$ [M+H]$^+$ 222.1713, found 222.1710.

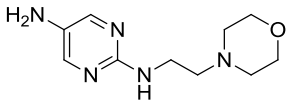
N^2-(2-Morpholinoethyl)pyridine-2,5-diamine, (525)



Compound **525** was synthesised according to general procedure V, using the following reagents: *N*-(2-morpholinoethyl)-5-nitropyridin-2-amine (**514**) (409 mg, 1.62 mmol), 10% Pd/C (40 mg) and MeOH (15 mL). The crude brown red (342 mg, 95%) was used in the next step without further purification; R_f = 0.56 (amine silica, DCM:MeOH, 97:3); λ_{max} (EtOH)/nm 254.6, 339.4; IR (neat) ν_{max}/cm^{-1} 3317, 2958, 2929, 2875, 2797, 1615, 1576, 1498, 1419; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.37 (4H, brs, NC*H*$_2$ $_{morpholine}$), 2.42 (2H, t, *J* = 6.7 Hz, ArNHCH$_2$C*H*$_2$N), 3.21 (2H, td, *J* = 6.7, 5.7 Hz, ArNHC*H*$_2$CH$_2$), 3.57 (4H, t, *J* = 4.6 Hz, OC*H*$_2$ $_{morpholine}$), 4.26 (2H, brs, ArN*H*$_2$), 5.33 (1H, t, *J* = 5.7 Hz, ArN*H*CH$_2$), 6.30 (1H, d, *J* = 8.6 Hz, H-3), 6.81 (1H, dd, *J* = 8.6, 2.8 Hz, H-4), 7.45 (1H, d, *J* = 2.8 Hz, H-5); ^{13}C NMR (126 MHz, DMSO-d_6) δ 38.7 (ArNH*C*H$_2$), 53.4

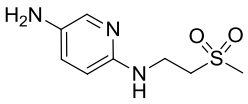
(N*C*H$_{2\ morpholine}$), 57.8 (ArNHCH$_2$*C*H$_2$N), 66.2 (O*C*H$_{2\ morpholine}$), 108.1 (C-3), 125.3 (C-4), 133.2 (C-5), 135.3 (C-6), 151.7 (C-2); LRMS (ES$^+$) *m/z* 207.2 [M+H]$^+$; HRMS (NSI) calcd for $C_{11}H_{19}N_4O$ [M+H]$^+$ 223.1553, found 223.1550.

N^2-(2-Morpholinoethyl)pyrimidine-2,5-diamine, (526)



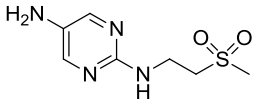
Compound **526** was synthesised according to general procedure D', using the following reagents: *N*-(2-morpholinoethyl)-5-nitropyrimidin-2-amine (**515**) (480 mg, 1.89 mmol), THF (18.9 mL) and methanol (18.9 mL). The pale yellow solid (394 mg, 93%) was used in the next step without further purification; R_f = 0.42 (amine silica, EtOAc, 100%); m.p. 98.5-100.5 °C; λ_{max} (EtOH)/nm 249.8; IR (neat) ν_{max}/cm^{-1} 3404, 3276, 2963, 2932, 2918, 2818, 1613, 1574, 1527, 1454, 1424; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.34 – 2.39 (4H, m, NC*H*$_{2\ morpholine}$), 2.41 (2H, t, *J* = 6.8 Hz, NHCH$_2$C*H*$_2$N), 3.27 (2H, td, *J* = 6.8, 5.8 Hz, NHC*H*$_2$CH$_2$N), 3.55 (4H, t, *J* = 4.7 Hz, OC*H*$_{2\ morpholine}$), 4.39 (2H, brs, ArN*H*$_2$), 5.93 (1H, t, *J* = 5.8 Hz, ArN*H*CH$_2$), 7.79 (2H, s, H-4, 6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 38.3 (ArNH*C*H$_2$), 53.4 (N*C*H$_{2\ morpholine}$), 57.6 (CH$_2$*C*H$_2$N), 66.2 (O*C*H$_{2\ morpholine}$), 133.6 (C-5), 144.6 (C-4, 6), 156.4 (C-2); LRMS (ES$^+$) *m/z* 224.4 [M+H]$^+$; HRMS (NSI) calcd for $C_{10}H_{18}N_5O$ [M+H]$^+$ 224.1506, found 224.1504.

N^2-(2-(Methylsulfonyl)ethyl)pyridine-2,5-diamine, (527)



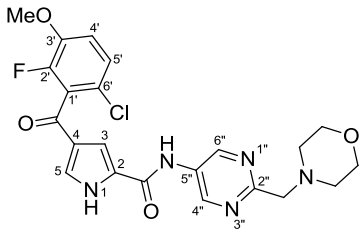
Compound **527** was synthesised according to general procedure V, using the following reagents: *N*-(2-(methylsulfonyl)ethyl)-5-nitropyridin-2-amine (**516**) (350 mg, 1.43 mmol) and MeOH (30 mL). The crude red oil (293 mg, 95%) was used in the next step without further purification; R_f = 0.63 (amine silica, DCM:MeOH, 97:3); λ_{max} (EtOH)/nm 251.4, 333.2; IR (neat) ν_{max}/cm^{-1} 3341, 3017, 2923, 2096, 1994, 1615, 1578, 1498, 1405; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.98 (3H, s, SO$_2$C*H*$_3$), 3.29 (2H, t, *J* = 6.8 Hz, C*H*$_2$SO$_2$CH$_3$), 3.55 (2H, dt, *J* = 6.8, 6.0 Hz, ArNHC*H*$_2$), 4.36 (2H, brs, ArN*H*$_2$), 5.84 (1H, t, *J* = 6.0 Hz, ArN*H*CH$_2$), 6.33 (1H, d, *J* = 8.6 Hz, H-3), 6.84 (1H, dd, *J* = 8.6, 2.8 Hz, H-4), 7.49 (1H, d, *J* = 2.8 Hz, H-6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 35.6 (ArNH*C*H$_2$), 41.2 (SO$_2$*C*H$_3$), 53.5 (*C*H$_2$SO$_2$CH$_3$), 109.0 (C-3), 125.5 (C-4), 132.9 (C-6), 136.0 (C-5), 150.7 (C-2); LRMS (ES$^+$) *m/z* 216.4 [M+H]$^+$; HRMS (NSI) calcd for $C_8H_{14}N_3O_2S$ [M+H]$^+$ 216.0801, found 216.0798.

N^2-(2-(Methylsulfonyl)ethyl)pyrimidine-2,5-diamine, (528)



Compound **528** was synthesised according to general procedure D', using the following reagents: *N*-(2-(methylsulfonyl)ethyl)-5-nitropyrimidin-2-amine (**517**) (200 mg, 0.81 mmol), THF (8.1 mL) and methanol (8.1 mL). The crude product was purified by column chromatography (amine silica gel, DCM:MeOH, 1:0 → 98:2) to yield the *title compound* as a pale yellow solid (97 mg, 55%); R_f = 0.28 (amine silica, DCM:MeOH, 98:2); m.p. 128.5-130.5 °C; λ_{max} (EtOH)/nm 248.6; IR (neat) ν_{max}/cm^{-1} 3377, 3260, 2997, 2981, 1617, 1581, 1539, 1463, 1445, 1434, 1278, 1129, 1115; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.99 (s, 3H, $CH_2SO_2CH_3$), 3.30 (t, *J* = 6.9 Hz, 2H, $CH_2SO_2CH_3$), 3.58 (td, *J* = 6.9, 6.0 Hz, 2H, $ArNHCH_2CH_2$), 4.50 (brs, 2H, $ArNH_2$), 6.37 (t, *J* = 6.0 Hz, 1H, $ArNHCH_2$), 7.83 (s, 2H, H-4, 6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 35.4 ($ArNHCH_2$), 41.0 (SO_2CH_3), 53.3 (CH_2SO_2), 134.4 (C-5), 144.5 (C-4, 6), 155.6 (C-2); LRMS (ES$^+$) *m/z* 217.2 [M+H]$^+$; HRMS (NSI) calcd for $C_7H_{13}N_4O_2S$ [M+H]$^+$ 217.0754, found 217.0751.

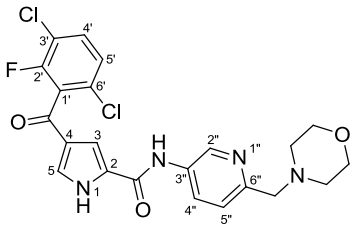
4-(6-Chloro-2-fluoro-3-methoxybenzoyl)-*N*-(2-(morpholinomethyl)pyrimidin-5-yl)-1*H*-pyrrole-2-carboxamide, (529)



Compound **529** was synthesised according to general procedure Y, using the following reagents: 4-(6-chloro-2-fluoro-3-methoxybenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**) (80 mg, 0.27 mmol), triethylamine (94 µL, 68 mg, 0.67 mmol), 2-chloro-1-methylpyridinium iodide (76 mg, 0.30 mmol), 2-(morpholinomethyl)pyrimidin-5-amine (**442**) (65 mg, 0.34 mmol) and DCM (2.7 mL). The crude yellow solid was purified by column chromatography (silica gel, DCM:MeOH, 1:0 → 94:6) to yield the *title compound* as a white solid (21 mg, 17%); R_f = 0.29 (DCM:MeOH, 94:6); m.p. 140.5-142.5 °C; λ_{max} (EtOH)/nm 292.6; IR (neat) ν_{max}/cm^{-1} 3125, 2933, 2855, 1641, 1578, 1555, 1519, 1473, 1438, 1272; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.47 (4H, t, *J* = 4.7 Hz, NCH_2 $_{morpholine}$), 3.56 (4H, t, *J* = 4.7 Hz, CH_2O $_{morpholine}$), 3.66 (2H, s, $ArCH_2N$), 3.90 (3H, s, $ArOCH_3$), 7.33 (1H, dd, *J* = 9.0, 9.0 Hz, H-4'), 7.39 (1H, dd, *J* = 9.0, 1.4 Hz, H-5'), 7.46 (1H, s, H-3), 7.55 (1H, s, H-5), 9.08 (2H, s, H-4", 6"), 10.42 (1H, s, CONHAr), 12.81 (1H,

s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 53.2 (N*C*H$_{2\ morpholine}$), 56.5 (ArO*C*H$_3$), 64.2 (Ar*C*H$_2$N), 66.2 (*C*H$_2$O $_{morpholine}$), 112.1 (C-3), 115.2 (C-4'), 120.2 (d, *J* = 4.8 Hz, C-6'), 125.3 (C-2 or C-4), 125.6 (d, *J* = 3.7 Hz, C-5'), 127.7 (C-2 or C-4), 128.4 (d, *J* = 19.9 Hz, C-1'), 129.7 (C-5), 132.5 (C-5"), 146.5 (d, *J* = 10.6 Hz, C-3'), 147.9 (C-4", 6"), 147.9 (d, *J* = 247.2 Hz, C-2'), 158.8 (*C*ONHAr), 161.1 (C-2"), 183.7 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -136.2 (ArF); LRMS (ES$^+$) *m/z* 474.4 [M(^{35}Cl)+H]$^+$, 476.4 [M(^{37}Cl)+H]$^+$; HRMS (NSI) calcd for $C_{22}H_{22}ClFN_5O_4$ [M(^{35}Cl)+H]$^+$ 474.1339, found 474.1331.

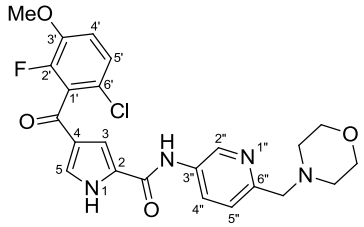
4-(3,6-Dichloro-2-fluorobenzoyl)-*N*-(6-(morpholinomethyl)pyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (530)



Compound **530** was synthesised according to general procedure Y, using the following reagents: 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**) (100 mg, 0.33 mmol), triethylamine (115 µL, 84 mg, 0.83 mmol), 2-chloro-1-methylpyridinium iodide (93 mg, 0.36 mmol), 6-(morpholinomethyl)pyridin-3-amine (**543**) (80 mg, 0.41 mmol) and DCM (3.3 mL). The crude yellow solid was purified by column chromatography (amine silica gel, DCM:MeOH, 1:0 → 97:3) to yield the *title compound* as a white solid (70 mg, 44%); R_f = 0.34 (amine silica, DCM:MeOH, 97:3); m.p. 245.0-247.0 °C; λ_{max} (EtOH)/nm 295.6; IR (neat) ν_{max}/cm^{-1} 3243, 3119, 2956, 2917, 2854, 2814, 1639, 1590, 1526, 1492, 1446; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.40 (4H, t, *J* = 4.7 Hz, NC*H*$_{2\ morpholine}$), 3.55 (2H, s, ArC*H*$_2$N), 3.58 (4H, t, *J* = 4.7 Hz, C*H*$_2$O $_{morpholine}$), 7.42 (1H, d, *J* = 8.5 Hz, H-5"), 7.49 – 7.54 (2H, m, H-3 and H-5'), 7.62 (1H, s, H-5), 7.78 (1H, dd, *J* = 8.7, 8.4 Hz, H-4'), 8.11 (1H, dd, *J* = 8.5, 2.4 Hz, H-4"), 8.80 (1H, d, *J* = 2.4 Hz, H-2"), 10.22 (1H, s, CON*H*Ar), 12.75 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 53.3 (N*C*H$_{2\ morpholine}$), 63.7 (Ar*C*H$_2$N), 66.2 (*C*H$_2$O $_{morpholine}$), 111.4 (C-3), 119.4 (d, *J* = 18.2 Hz, C-3'), 122.7 (C-5"), 124.8 (C-2 or C-4), 126.9 (d, *J* = 3.7 Hz, C-5'), 127.6 (C-4"), 128.5 (C-2 or C-4), 129.1 (d, *J* = 23.1 Hz, C-1'), 129.2 (d, *J* = 5.0 Hz, C-6'), 130.2 (C-5), 131.9 (C-4'), 134.1 (C-3"), 140.7 (C-2"), 152.8 (C-6"), 153.9 (d, *J* = 248.6 Hz, C-2'), 158.6 (*C*ONHAr), 182.6 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.6 (ArF); LRMS (ES$^+$) *m/z* 477.4 [M(^{35}Cl^{35}Cl)+H]$^+$, 479.4

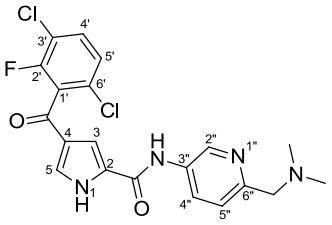
[M(^{35}Cl^{37}Cl)+H]$^+$; HRMS (NSI) calcd for $C_{22}H_{20}Cl_2FN_4O_3$ [M(^{35}Cl^{35}Cl)+H]$^+$ 477.0891, found 477.0880.

4-(6-Chloro-2-fluoro-3-methoxybenzoyl)-*N*-(6-(morpholinomethyl)pyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (531)



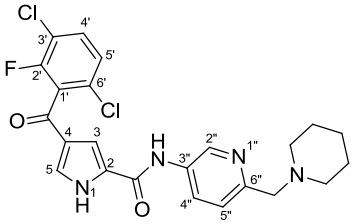
Compound **531** was synthesised according to general procedure Y, using the following reagents: 4-(6-chloro-2-fluoro-3-methoxybenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**) (100 mg, 0.34 mmol), triethylamine (117 µL, 85 mg, 0.84 mmol), 2-chloro-1-methylpyridinium iodide (94 mg, 0.37 mmol), 6-(morpholinomethyl)pyridin-3-amine (**543**) (81 mg, 0.42 mmol) and DCM (3.4 mL). The crude yellow solid was purified by column chromatography (amine silica gel, DCM:MeOH, 1:0 → 97:3) to yield the *title compound* as a white solid (45 mg, 28%); R_f = 0.32 (amine silica, DCM:MeOH, 97:3); m.p. 219.0-221.0 °C; λ_{max} (EtOH)/nm 295.8; IR (neat) ν_{max}/cm^{-1} 3228, 2931, 2854, 2799, 1655, 1639, 1554, 1534, 1473, 1437, 1400; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.40 (4H, t, *J* = 4.5 Hz, NC*H*$_{2\ morpholine}$), 3.54 (2H, s, ArC*H*$_2$N), 3.58 (4H, t, *J* = 4.5 Hz, C*H*$_2$O $_{morpholine}$), 3.90 (3H, s, ArOC*H*$_3$), 7.33 (1H, dd, *J* = 9.0, 8.9 Hz, H-4'), 7.39 (1H, dd, *J* = 9.0, 0.9 Hz, H-5'), 7.42 (1H, d, *J* = 8.5 Hz, H-5"), 7.47 (1H, s, H-3 or H-5), 7.48 (1H, s, H-3 or H-5), 8.10 (1H, dd, *J* = 8.5, 2.5 Hz, H-4"), 8.80 (1H, d, *J* = 2.5 Hz, H-2"), 10.22 (1H, s, CON*H*Ar), 12.68 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 53.3 (N*C*H$_{2\ morpholine}$), 56.5 (ArO*C*H$_3$), 63.7 (Ar*C*H$_2$N), 66.2 (*C*H$_2$O $_{morpholine}$), 111.5 (C-3), 115.2 (C-4'), 120.2 (d, *J* = 4.9 Hz, C-6'), 122.7 (C-5"), 125.2 (C-2 or C-4), 125.6 (d, *J* = 3.5 Hz, C-5'), 127.6 (C-4"), 128.2 (C-2 or C-4), 128.4 (d, *J* = 20.0 Hz, C-1'), 129.4 (C-5), 134.1 (C-3"), 140.7 (C-2"), 146.4 (d, *J* = 10.5 Hz, C-3'), 148.0 (d, *J* = 247.2 Hz, C-2'), 152.7 (C-6"), 158.6 (*C*ONHAr), 183.7 (Ar*C*O); ^{19}F NMR (471 MHz, DMSO-d_6) δ -136.1 (ArF); LRMS (ES$^+$) *m/z* 473.5 [M(^{35}Cl)+H]$^+$, 475.4 [M(^{37}Cl)+H]$^+$; HRMS (NSI) calcd for $C_{23}H_{23}ClFN_4O_4$ [M(^{35}Cl)+H]$^+$ 473.1386, found 473.1377.

4-(3,6-Dichloro-2-fluorobenzoyl)-*N*-(6-((dimethylamino)methyl)pyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (532)



Compound **532** was synthesised according to general procedure Y, using the following reagents: 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**) (150 mg, 0.50 mmol), triethylamine (173 µL, 126 mg, 1.24 mmol), 2-chloro-1-methylpyridinium iodide (140 mg, 0.55 mmol), 6-((dimethylamino)methyl)pyridin-3-amine (**544**) (94 mg, 0.62 mmol) and DCM (5 mL). The crude yellow solid was purified by column chromatography (amine silica gel, DCM:MeOH, 1:0 → 97:3) to yield the *title compound* as a white solid (17 mg, 8%); R_f = 0.28 (amine silica, DCM:MeOH, 97:3); m.p. 136.5-138.5 °C; λ_{max} (EtOH)/nm 294.6; IR (neat) ν_{max}/cm^{-1} 3179, 3118, 2924, 2855, 2776, 1637, 1590, 1555, 1526, 1491, 1446, 1391; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.18 (6H, s, $CH_2N(CH_3)_2$), 3.49 (2H, s, $ArCH_2N$), 7.40 (1H, d, *J* = 8.5 Hz, H-5”), 7.48 – 7.54 (2H, m, H-3 and H-5’), 7.62 (1H, s, H-5), 7.78 (1H, dd, *J* = 8.4, 8.4 Hz, H-4’), 8.11 (1H, dd, *J* = 8.5, 2.5 Hz, H-4”), 8.79 (1H, d, *J* = 2.5 Hz, H-2”), 10.22 (1H, s, CONHAr), 12.76 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 45.1 ($CH_2N(CH_3)_2$), 64.6 ($ArCH_2N$), 111.4 (C-3), 119.3 (d, *J* = 18.1 Hz, C-1’), 122.5 (C-5”), 124.7 (C-2 or C-4), 126.9 (d, *J* = 3.8 Hz, C-5’), 127.6 (C-4”), 128.5 (C-2 or C-4), 129.1 (d, *J* = 22.3 Hz, C-3’), 129.2 (d, *J* = 5.6 Hz, C-6’), 130.1 (C-5), 131.8 (C-4’), 134.0 (C-3”), 140.6 (C-2”), 153.6 (C-6”), 153.8 (d, *J* = 248.7 Hz, C-2’), 158.6 (CONHAr), 182.6 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.7 (ArF); LRMS (ES$^+$) *m/z* 435.3 [M(^{35}Cl^{35}Cl)+H]$^+$, 437.3 [M(^{35}Cl^{37}Cl)+H]$^+$; HRMS (NSI) calcd for $C_{20}H_{18}Cl_2FN_4O_2$ [M(^{35}Cl^{35}Cl)+H]$^+$ 435.0785, found 435.0785.

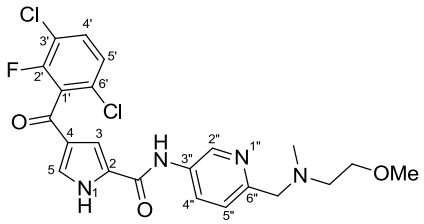
4-(3,6-Dichloro-2-fluorobenzoyl)-*N*-(6-(piperidin-1-ylmethyl)pyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (533)



Compound **533** was synthesised according to general procedure Y, using the following reagents: 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**) (150 mg,

0.50 mmol), triethylamine (173 µL, 126 mg, 1.24 mmol), 2-chloro-1-methylpyridinium iodide (140 mg, 0.55 mmol), 6-(piperidin-1-ylmethyl)pyridin-3-amine (**545**) (119 mg, 0.62 mmol) and DCM (5 mL). The crude yellow solid was purified by column chromatography (amine silica gel, DCM:MeOH, 1:0 → 97:3) to yield the *title compound* as a white solid (64 mg, 27%); R_f = 0.29 (amine silica, DCM:MeOH, 97:3); m.p. 242.5-244.5 °C; λ_{max} (EtOH)/nm 295.4; IR (neat) ν_{max}/cm^{-1} 3278, 3116, 2934, 2852, 2803, 1663, 1640, 1545, 1529, 1446, 1299; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.33 – 1.44 (2H, m, NCH$_2$CH$_2$C*H*$_2$), 1.44 – 1.58 (4H, m, NCH$_2$C*H*$_2$CH$_2$), 2.37 (4H, brs, NC*H*$_2$CH$_2$CH$_2$), 3.51 (2H, s, ArC*H*$_2$N), 7.40 (1H, d, *J* = 8.5 Hz, H-5”), 7.48 – 7.55 (2H, m, H-3 and H-5’), 7.62 (1H, s, H-5), 7.78 (1H, dd, *J* = 8.4, 8.4 Hz, H-4’), 8.09 (1H, dd, *J* = 8.5, 2.5 Hz, H-4”), 8.79 (1H, d, *J* = 2.5 Hz, H-2”), 10.22 (1H, s, CON*H*Ar), 12.76 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 23.8 (NCH$_2$CH$_2$*C*H$_2$), 25.5 (NCH$_2$*C*H$_2$CH$_2$), 54.0 (N*C*H$_2$CH$_2$CH$_2$), 64.0 (Ar*C*H$_2$N), 111.3 (C-3), 119.3 (d, *J* = 18.3 Hz, C-1’), 122.4 (C-5”), 124.7 (C-2 or C-4), 126.9 (d, *J* = 3.6 Hz, C-5’), 127.6 (C-4”), 128.4 (C-2 or C-4), 129.1 (d, *J* = 22.7 Hz, C-3’), 129.2 (d, *J* = 5.2 Hz, C-6’), 130.1 (C-5), 131.8 (C-4’), 133.9 (C-3”), 140.6 (C-2”), 153.5 (C-6”), 153.8 (d, *J* = 248.6 Hz, C-2’), 158.5 (*C*ONHAr), 182.6 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.6 (ArF); LRMS (ES$^+$) *m/z* 475.3 [M(^{35}Cl^{35}Cl)+H]$^+$, 477.3 [M(^{35}Cl^{37}Cl)+H]$^+$; HRMS (NSI) calcd for $C_{23}H_{22}Cl_2FN_4O_2$ [M(^{35}Cl^{35}Cl)+H]$^+$ 475.1098, found 475.1085.

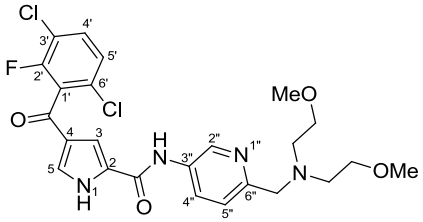
4-(3,6-Dichloro-2-fluorobenzoyl)-*N*-(6-(((2-methoxyethyl)(methyl)amino)methyl) pyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (534)



Compound **534** was synthesised according to general procedure Y, using the following reagents: 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**) (150 mg, 0.50 mmol), triethylamine (173 µL, 126 mg, 1.24 mmol), 2-chloro-1-methylpyridinium iodide (140 mg, 0.55 mmol), 6-(((2-methoxyethyl)(methyl)amino)methyl)pyridin-3-amine (**534**) (121 mg, 0.62 mmol) and DCM (5 mL). The crude yellow solid was purified by column chromatography (amine silica gel, DCM:MeOH, 1:0 → 97:3) to yield the *title compound* as a white solid (42 mg, 18%); R_f = 0.30 (amine silica, DCM:MeOH, 97:3); m.p. 188.5-190.5 °C; λ_{max} (EtOH)/nm 295.0; IR (neat) ν_{max}/cm^{-1} 3283, 3113, 2924, 1638, 1590, 1526, 1491, 1446, 1392, 1286; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.20 (3H, s,

NC*H*$_3$), 2.56 (2H, t, *J* = 5.9 Hz, NC*H*$_2$CH$_2$OMe), 3.23 (3H, s, CH$_2$OC*H*$_3$), 3.45 (2H, t, *J* = 5.9 Hz, NCH$_2$C*H*$_2$OMe), 3.59 (2H, s, ArC*H*$_2$N), 7.41 (1H, d, *J* = 8.5 Hz, H-5"), 7.48 - 7.54 (2H, m, H-3 and H-5'), 7.62 (1H, s, H-5), 7.78 (1H, dd, *J* = 8.4, 8.4 Hz, H-4'), 8.10 (1H, dd, *J* = 8.5, 2.6 Hz, H-4"), 8.79 (1H, d, *J* = 2.6 Hz, H-2"), 10.21 (1H, s, CON*H*Ar), 12.76 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 42.6 (N*C*H$_3$), 56.0 (N*C*H$_2$CH$_2$OMe), 58.0 (CH$_2$O*C*H$_3$), 63.0 (Ar*C*H$_2$N), 70.3 (NCH$_2$*C*H$_2$OMe), 111.4 (C-3), 119.3 (d, *J* = 18.2 Hz, C-1'), 122.5 (C-5"), 124.8 (C-2 or C-4), 126.9 (d, *J* = 3.8 Hz, C-5'), 127.6 (C-4"), 128.5 (C-2 or C-4), 129.2 (d, *J* = 22.7 Hz, C-3'), 129.2 (d, *J* = 5.2 Hz, C-6'), 130.1 (C-5), 131.8 (C-4'), 133.9 (C-3"), 140.6 (C-2"), 153.8 (d, *J* = 248.6 Hz, C-2'), 154.0 (C-6"), 158.6 (*C*ONHAr), 182.6 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.6 (ArF); LRMS (ES$^+$) *m/z* 479.3 [M(^{35}Cl^{35}Cl)+H]$^+$, 481.3 [M(^{35}Cl^{37}Cl)+H]$^+$; HRMS (NSI) calcd for $C_{22}H_{22}Cl_2FN_4O_3$ [M(^{35}Cl^{35}Cl)+H]$^+$ 479.0148, found 479.0135.

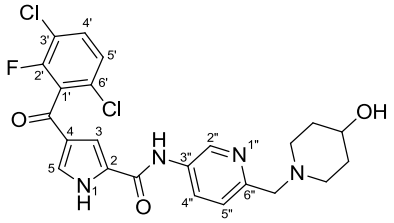
N-(6-((bis(2-methoxyethyl)amino)methyl)pyridin-3-yl)-4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxamide, (535)



Compound **535** was synthesised according to general procedure Y, using the following reagents: 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**) (150 mg, 0.50 mmol), triethylamine (173 µL, 126 mg, 1.24 mmol), 2-chloro-1-methylpyridinium iodide (140 mg, 0.55 mmol), 6-((bis(2-methoxyethyl)amino)methyl)pyridin-3-amine (**247**) (149 mg, 0.62 mmol) and DCM (5 mL). The crude yellow solid was purified by column chromatography (amine silica gel, DCM:MeOH, 1:0 → 97:3) to yield the *title compound* as a white solid (53 mg, 20%); R_f = 0.34 (amine silica, DCM:MeOH, 97:3); m.p. 165.0-167.0 °C; λ_{max} (EtOH)/nm 295.4; IR (neat) ν_{max}/cm^{-1} 3178, 3114, 2924, 2873, 2818, 1636, 1589, 1554, 1525, 1490, 1445, 1391; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.68 (4H, t, *J* = 6.0 Hz, N(C*H*$_2$CH$_2$OMe)$_2$), 3.21 (6H, s, N(CH$_2$CH$_2$OC*H*$_3$)$_2$), 3.40 (4H, t, *J* = 6.0 Hz, N(CH$_2$C*H*$_2$OMe)$_2$), 3.73 (2H, s, ArC*H*$_2$N), 7.44 (1H, d, *J* = 8.5 Hz, H-5"), 7.48 – 7.56 (2H, m, H-3 and H-5'), 7.62 (1H, s, H-5), 7.78 (1H, dd, *J* = 8.4, 8.4 Hz, H-4'), 8.08 (1H, dd, *J* = 8.5, 2.6 Hz, H-4"), 8.78 (1H, d, *J* = 2.6 Hz, H-2"), 10.20 (1H, s, CON*H*Ar), 12.75 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 53.4 (N(*C*H$_2$CH$_2$OMe)$_2$), 58.0 (N(CH$_2$CH$_2$O*C*H$_3$)$_2$), 60.2 (Ar*C*H$_2$N), 70.6 (N(CH$_2$*C*H$_2$OMe)$_2$), 111.3 (C-3), 119.3 (d, *J* = 18.0 Hz, C-1'), 122.3 (C-5"), 124.7 (C-2 or C-4), 126.9 (d, *J* = 3.8 Hz, C-5'), 127.6

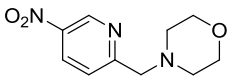
(C-4”), 128.5 (C-2 or C-4), 129.1 (d, *J* = 22.9 Hz, C-3’), 129.2 (d, *J* = 5.2 Hz, C-6’), 130.1 (C-5), 131.8 (C-4’), 133.8 (C-3”), 140.5 (C-2”), 153.8 (d, *J* = 248.5 Hz, C-2’), 154.7 (C-6”), 158.5 (*C*ONHAr), 182.6 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.6 (ArF); LRMS (ES$^+$) *m/z* 523.3 [M(^{35}Cl^{35}Cl)+H]$^+$, 525.4 [M(^{35}Cl^{37}Cl)+H]$^+$; HRMS (NSI) calcd for $C_{24}H_{26}Cl_2FN_4O_4$ [M(^{35}Cl^{35}Cl)+H]$^+$ 523.1310, found 523.1294.

4-(3,6-Dichloro-2-fluorobenzoyl)-*N*-(6-((4-hydroxypiperidin-1-yl)methyl)pyridin-3-yl)-1*H*-pyrrole-2-carboxamide, (536)



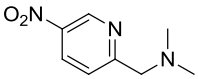
Compound **536** was synthesised according to general procedure Y, using the following reagents: 4-(3,6-dichloro-2-fluorobenzoyl)-1*H*-pyrrole-2-carboxylic acid (**250**) (150 mg, 0.50 mmol), triethylamine (173 µL, 126 mg, 1.24 mmol), 2-chloro-1-methylpyridinium iodide (140 mg, 0.55 mmol), 1-((5-aminopyridin-2-yl)methyl)piperidin-4-ol (**548**) (129 mg, 0.62 mmol) and DCM (5 mL). The crude yellow solid was purified by column chromatography (amine silica gel, DCM:MeOH, 1:0 → 97:3) to yield the *title compound* as a white solid (57 mg, 23%); R_f = 0.28 (amine silica, DCM:MeOH, 97:3); m.p. 148.5-150.5 °C; λ_{max} (EtOH)/nm 295.4; IR (neat) ν_{max}/cm^{-1} 3219, 2925, 2853, 1637, 1591, 1555, 1527, 1492, 1446; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.40 (2H, dddd, *J* = 13.1, 9.7, 9.7 and 3.7 Hz, C*H*$_2$CHOH), 1.71 (2H, ddd, *J* = 13.1, 3.6 and 3.6 Hz, C*H*$_2$CHOH), 2.02 - 2.17 (2H, m, NC*H*$_2$CH$_2$), 2.69 (2H, dd, *J* = 13.1, 5.6 Hz, NC*H*$_2$CH$_2$), 3.40 – 3.49 (1H, m, CH$_2$C*H*OH), 3.53 (2H, s, ArC*H*$_2$N), 4.47 – 4.62 (1H, m, CH$_2$CHO*H*), 7.40 (1H, d, *J* = 8.5 Hz, H-5”), 7.47 – 7.56 (2H, m, H-3 and H-5’), 7.62 (1H, s, H-5), 7.78 (1H, dd, *J* = 8.4, 8.4 Hz, H-4’), 8.10 (1H, dd, *J* = 8.5, 2.5 Hz, H-4”), 8.79 (1H, d, *J* = 2.5 Hz, H-2”), 10.22 (1H, s, CON*H*Ar), 12.76 (1H, s, NH-pyrrole); ^{13}C NMR (126 MHz, DMSO-d_6) δ 34.4 (*C*H$_2$CHOH), 51.0 (NCH$_2$CH$_2$), 63.3 (Ar*C*H$_2$N), 66.1 (CH$_2$*C*HOH), 111.3 (C-3), 119.3 (d, *J* = 18.1 Hz, C-1’), 122.5 (C-5”), 124.7 (C-2 or C-4), 126.9 (d, *J* = 3.7 Hz, C-5’), 127.6 (C-4”), 128.4 (C-2 or C-4), 129.0 (d, *J* = 22.8 Hz, C-3’), 129.2 (d, *J* = 5.5 Hz, C-6’), 130.1 (C-5), 131.8 (C-4’), 133.9 (C-6”), 140.6 (C-2”), 153.6 (C-6”), 153.8 (d, *J* = 248.7 Hz, C-2’), 158.5 (*C*ONHAr), 182.6 (ArCO); ^{19}F NMR (471 MHz, DMSO-d_6) δ -116.6 (ArF); LRMS (ES$^+$) *m/z* 491.3 [M(^{35}Cl^{35}Cl)+H]$^+$, 493.3 [M(^{35}Cl^{37}Cl)+H]$^+$; HRMS (NSI) calcd for $C_{23}H_{22}Cl_2FN_4O_3$ [M(^{35}Cl^{35}Cl)+H]$^+$ 491.1048, found 491.1038.

4-((5-Nitropyridin-2-yl)methyl)morpholine, (537)



To 5-nitropicolinaldehyde (**473**) (300 mg, 1.97 mmol) in 2,2,2-trifluoroethanol (10 mL) was added morpholine (173 µL, 172 mg, 1.97 mmol). The resulting solution was stirred at 38 °C for 1 h. Once cooled at 0 °C, sodium borohydride was carefully added. The resulting mixture was allowed to warm to RT and then stirred for 30 min. Upon completion, the solvent was removed *in vacuo*. The crude residue was dissolved in EtOAc (30 mL), neutralised by washing with saturated aq. NH_4Cl (20 mL), washed with water and brine (20 mL, respectively), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel, petrol:EtOAc, 1:0 → 1:1) to yield the *title compound* as a pale yellow solid (301 mg, 68%); R_f = 0.22 (petrol:EtOAc, 1:1); m.p. 73.5-75.5 °C; λ_{max} (EtOH)/nm 249.8, 274.0; IR (neat) ν_{max}/cm^{-1} 3043, 2980, 2862, 2851, 2810, 1598, 1577, 1516, 1355, 1342, 1333; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.40 - 2.47 (4H, m, NC$H_{2\ morpholine}$), 3.60 (4H, t, *J* = 4.7 Hz, OC$H_{2\ morpholine}$), 3.74 (2H, s, ArCH_2N), 7.76 (1H, d, *J* = 8.6 Hz, H-3), 8.57 (1H, dd, *J* = 8.6, 2.7 Hz, H-4), 9.29 (1H, d, *J* = 2.7 Hz, H-6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 53.2 (N$CH_{2\ morpholine}$), 63.4 (ArCH_2N), 66.2 (O$CH_{2\ morpholine}$), 123.1 (C-3), 131.9 (C-4), 143.2 (C-5), 144.1 (C-6), 165.1 (C-2); LRMS (ES^+) *m/z* 224.3 $[M+H]^+$; HRMS (NSI) calcd for $C_{10}H_{14}N_3O_3$ $[M+H]^+$ 224.1030, found 224.1025.

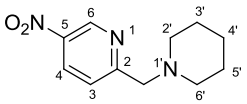
***N*,*N*-Dimethyl-1-(5-nitropyridin-2-yl)methanamine, (538)**



To 5-nitropicolinaldehyde (**473**) (200 mg, 1.31 mmol) in 1,2-dichloroethane (4 mL) was added dimethylamine (2.0 M solution in THF, 723 µL, 1.46 mmol). The resulting solution was stirred at RT for 5 min before sodium triacetoxyborohydride (418 mg, 1.97 mmol) was added in several portions. The resulting reaction mixture was stirred at RT for 16 h. Upon completion, the reaction was diluted with DCM (10 mL), quenched by addition of saturated aq. $NaHCO_3$ (10 mL) and stirred for 1 h. The layers were separated and the aqueous phase extracted with DCM (3 × 20 mL). The combined organic extracts were washed with water and brine (40 mL, respectively), dried over $MgSO_4$ and concentrated *in vacuo*. The crude yellow oil was purified by column chromatography (amine silica gel, petrol:EtOAc, 1:0 → 9:1) to yield the *title compound* as a yellow liquid (150 mg, 63%); R_f = 0.30 (amine silica, petrol:EtOAc, 9:1); λ_{max} (EtOH)/nm 248.0, 277.0; IR (neat)

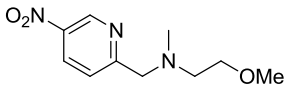
ν_{max}/cm^{-1} 3054, 3027, 2972, 2944, 2859, 2821, 2775, 1639, 1597, 1576, 1519, 1469, 1345; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.22 (6H, s, $CH_2N(CH_3)_2$), 3.66 (2H, s, $ArCH_2N$), 7.72 (1H, d, *J* = 8.6 Hz, H-3), 8.57 (1H, dd, *J* = 8.6, 2.7 Hz, H-4), 9.28 (1H, d, *J* = 2.7 Hz, H-6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 45.2 ($CH_2N(CH_3)_2$), 64.5 ($ArCH_2N$), 123.0 (C-3), 131.9 (C-4), 143.1 (C-5), 144.0 (C-6), 165.9 (C-2); LRMS (ES$^+$) *m/z* 182.2 [M+H]$^+$; HRMS (NSI) calcd for $C_8H_{12}N_3O_2$ [M+H]$^+$ 182.0924, found 182.0922.

5-Nitro-2-(piperidin-1-ylmethyl)pyridine, (539)



To 5-nitropicolinaldehyde (**473**) (300 mg, 1.97 mmol) in 1,2-dichloroethane (6 mL) was added piperidine (214 μL, 185 mg, 2.17 mmol). The resulting solution was stirred at RT for 5 min before sodium triacetoxyborohydride (627 mg, 2.96 mmol) was added portionwise. The resulting reaction mixture was stirred at RT for 16 h. Upon completion, the reaction was diluted with DCM (10 mL), quenched by addition of saturated aq. $NaHCO_3$ (10 mL) and stirred for 1 h. The layers were separated and the aqueous phase extracted with DCM (3 × 20 mL). The combined organic extracts were washed with water and brine (40 mL, respectively), dried over $MgSO_4$ and concentrated *in vacuo*. The crude yellow oil was purified by column chromatography (amine silica gel, petrol:EtOAc, 1:0 → 95:5) to yield the *title compound* as a yellow solid (258 mg, 59%); R_f = 0.28 (amine silica, petrol:EtOAc, 95:5); m.p. 50.0-52.0 °C; λ_{max} (EtOH)/nm 250.6, 274.4; IR (neat) ν_{max}/cm^{-1} 2930, 2848, 2791, 2751, 1596, 1576, 1515, 1465, 1352, 1338; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.39 - 1.43 (2H, m, H-4'), 1.51 – 1.55 (4H, m, H-3', 5'), 2.33 - 2.44 (4H, m, H-2', 6'), 3.69 (2H, brs, $ArCH_2N$), 7.73 (1H, d, *J* = 8.6 Hz, H-3), 8.56 (1H, dd, *J* = 8.6, 2.7 Hz, H-4), 9.28 (1H, d, *J* = 2.7 Hz, H-6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 23.7 (C-4'), 25.6 (C-3', 5'), 54.1 (C-2', 6'), 64.0 ($ArCH_2N$), 122.8 (C-3), 131.8 (C-4), 143.1 (C-5), 144.0 (C-6), 166.0 (C-2); LRMS (ES$^+$) *m/z* 222.2 [M+H]$^+$; HRMS (NSI) calcd for $C_{11}H_{16}N_3O_2$ [M+H]$^+$ 222.1237, found 222.1235.

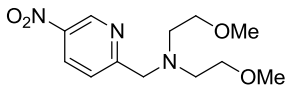
2-Methoxy-*N*-methyl-*N*-((5-nitropyridin-2-yl)methyl)ethanamine, (540)



To 5-nitropicolinaldehyde (**473**) (300 mg, 1.97 mmol) in 1,2-dichloroethane (6 mL) was added (2-methoxyethyl)methylamine (236 μL, 193 mg, 2.17 mmol). The resulting solution was stirred at RT for 5 min before sodium triacetoxyborohydride (627 mg, 2.96 mmol) was

added portionwise. The resulting reaction mixture was stirred at RT for 16 h. Upon completion, the reaction was diluted with DCM (10 mL), quenched by addition of saturated aq. $NaHCO_3$ (10 mL) and stirred for 1 h. The layers were separated and the aqueous phase extracted with DCM (3 × 20 mL). The combined organic extracts were washed with water and brine (40 mL, respectively), dried over $MgSO_4$ and concentrated *in vacuo*. The crude yellow oil was purified by column chromatography (amine silica gel, petrol:EtOAc, 1:0 → 9:1) to yield the *title compound* as a yellow liquid (308 mg, 69%); R_f = 0.29 (amine silica, petrol:EtOAc, 9:1); λ_{max} (EtOH)/nm 249.0, 277.2; IR (neat) ν_{max}/cm^{-1} 3071, 2930, 2816, 1638, 1596, 1576, 1520, 1449, 1345; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.24 (3H, s, NCH_3), 2.61 (2H, t, J = 5.8 Hz, NCH_2CH$_2$OMe), 3.23 (3H, s, CH$_2$OCH_3), 3.47 (2H, t, J = 5.8 Hz, NCH$_2$CH_2OMe), 3.79 (2H, s, ArCH_2N), 7.75 (1H, d, J = 8.6 Hz, H-3), 8.57 (1H, dd, J = 8.6, 2.7 Hz, H-4), 9.28 (1H, d, J = 2.7 Hz, H-6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 42.7 (N*C*H$_3$), 56.2 (N*C*H$_2$CH$_2$OMe), 58.0 (CH$_2$O*C*H$_3$), 63.0 (Ar*C*H$_2$N), 70.2 (NCH$_2$*C*H$_2$OMe), 122.9 (C-3), 131.8 (C-4), 143.1 (C-5), 143.9 (C-6), 166.5 (C-2); LRMS (ES$^+$) *m/z* 226.2 [M+H]$^+$; HRMS (NSI) calcd for $C_{10}H_{16}N_3O_3$ [M+H]$^+$ 226.1186, found 226.1187.

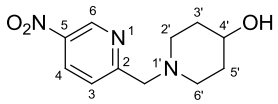
2-Methoxy-*N*-(2-methoxyethyl)-*N*-((5-nitropyridin-2-yl)methyl)ethanamine, (541)



To 5-nitropicolinaldehyde (**473**) (300 mg, 1.97 mmol) in 1,2-dichloroethane (6 mL) was added bis(2-methoxyethyl) amine (320 μL, 289 mg, 2.17 mmol). The resulting solution was stirred at RT for 5 min before sodium triacetoxyborohydride (627 mg, 2.96 mmol) was added in several portions. The resulting reaction mixture was stirred at RT for 16 h. Upon completion, the reaction was diluted with DCM (10 mL), quenched by addition of saturated aq. $NaHCO_3$ (10 mL) and stirred for 1 h. The layers were separated and the aqueous phase extracted with DCM (3 × 20 mL). The combined organic extracts were washed with water and brine (40 mL, respectively), dried over $MgSO_4$ and concentrated *in vacuo*. The crude yellow oil was purified by column chromatography (amine silica gel, petrol:EtOAc, 1:0 → 9:1) to yield the *title compound* as a yellow liquid (419 mg, 79%); R_f = 0.36 (amine silica, petrol:EtOAc, 9:1); λ_{max} (EtOH)/nm 294.6; IR (neat) ν_{max}/cm^{-1} 2979, 2925, 2875, 2817, 1595, 1577, 1519, 1457, 1345; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.72 (4H, t, J = 5.8 Hz, N(CH_2CH$_2$OMe)$_2$), 3.19 (6H, s, N(CH$_2$CH$_2$OCH_3)$_2$), 3.41 (4H, t, J = 5.8 Hz, N(CH$_2$CH_2OMe)$_2$), 3.94 (2H, s, ArCH_2N), 7.81 (1H, d, J = 8.7 Hz, H-3), 8.57 (1H, dd, J = 8.7, 2.6 Hz, H-4), 9.27 (1H, d, J = 2.6 Hz, H-6); ^{13}C NMR (126 MHz,

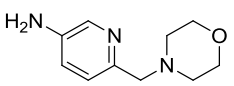
DMSO-d_6) δ 53.8 (N(*C*H_2CH$_2$OMe)$_2$), 58.0 (N(CH$_2$CH$_2$O*C*H$_3$)$_2$), 60.5 (Ar*C*H$_2$N), 70.6 (N(CH$_2$*C*H$_2$OMe)$_2$), 122.7 (C-3), 131.7 (C-4), 143.0 (C-5), 143.9 (C-6), 167.6 (C-2); LRMS (ES$^+$) *m/z* 270.5 [M+H]$^+$; HRMS (NSI) calcd for $C_{12}H_{20}N_3O_4$ [M+H]$^+$ 238.1186, found 238.1187.

1-((5-Nitropyridin-2-yl)methyl)piperidin-4-ol, (542)



To 5-nitropicolinaldehyde (**473**) (300 mg, 1.97 mmol) in 1,2-dichloroethane (6 mL) was added 4-hydroxypiperidine (219 mg, 2.17 mmol). The resulting solution was stirred at RT for 5 min before sodium triacetoxyborohydride (627 mg, 2.96 mmol) was added portionwise. The resulting reaction mixture was stirred at RT for 16 h. Upon completion, the reaction was diluted with DCM (10 mL), quenched by addition of saturated aq. $NaHCO_3$ (10 mL) and stirred for 1 h. The layers were separated and the aqueous phase extracted with DCM (3 × 20 mL). The combined organic extracts were washed with water and brine (40 mL, respectively), dried over $MgSO_4$ and concentrated *in vacuo*. The crude yellow oil was purified by column chromatography (amine silica gel, petrol:EtOAc, 1:0 → 3:7) to yield the *title compound* as a yellow solid (351 mg, 75%); R_f = 0.34 (amine silica, petrol:EtOAc, 7:3); m.p. 92.5-94.5 °C; λ_{max} (EtOH)/nm 250.8, 274.6; IR (neat) ν_{max}/cm^{-1} 3242, 3042, 2954, 2921, 2852, 1595, 1572, 1515, 1466, 1352, 1320; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.37 – 1.48 (2H, m, H-3', 5'$_{axial}$), 1.72 (2H, dddd, *J* = 12.3, 4.9, 2.6 and 2.6 Hz, H-3', 5'$_{equ}$), 2.15 (2H, ddd, *J* = 12.3, 10.5 and 2.6 Hz, H-2', 6'$_{axial}$), 2.69 (2H, ddd, *J* = 10.5, 4.3 and 4.3 Hz, H-2', 6'$_{equ}$), 3.47 (1H, ddd, *J* = 8.6, 4.3 and 4.2 Hz, H-4'), 3.70 (2H, s, ArC*H*$_2$N), 4.57 (1H, d, *J* = 4.2 Hz, CHO*H*), 7.73 (1H, d, *J* = 8.6 Hz, H-3), 8.56 (1H, dd, *J* = 8.6, 2.7 Hz, H-4), 9.27 (1H, d, *J* = 2.7 Hz, H-6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 34.4 (C-3', 5'), 51.1 (C-2', 6'), 63.2 (Ar*C*H$_2$N), 65.9 (C-4'), 122.8 (C-3), 131.9 (C-4), 143.1 (C-5), 144.0 (C-6), 166.0 (C-2); LRMS (ES$^+$) *m/z* 238.2 [M+H]$^+$; HRMS (NSI) calcd for $C_{11}H_{16}N_3O_3$ [M+H]$^+$ 238.1186, found 238.1187.

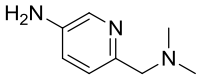
6-(Morpholinomethyl)pyridin-3-amine, (543)



Compound **543** was synthesised according to general procedure D', using the following reagents: 4-((5-nitropyridin-2-yl)methyl)morpholine (**537**) (300 mg, 1.34 mmol), THF (13.4 mL) and methanol (13.4 mL). The crude off-white solid (234 mg, 90%) was used in

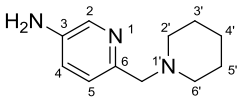
the next step without further purification; R_f = 0.20 (amine silica, DCM:MeOH, 98:2); m.p. 86.5-88.5 °C; λ_{max} (EtOH)/nm 246.4, 305.0; IR (neat) ν_{max}/cm^{-1} 3411, 3316, 3175, 2959, 2918, 2878, 2857, 2806, 2761, 1646, 1599, 1568, 1495; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.30 – 2.37 (4H, m, NC$H_{2\ morpholine}$), 3.37 (2H, s, ArCH_2N), 3.51 – 3.58 (4H, m, OC$H_{2\ morpholine}$), 5.16 (2H, brs, ArNH_2), 6.88 (1H, dd, *J* = 8.3, 2.8 Hz, H-4), 7.03 (1H, d, *J* = 8.3 Hz, H-3), 7.84 (1H, d, *J* = 2.8 Hz, H-6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 53.2 (N$CH_{2\ morpholine}$), 63.8 (ArCH_2N), 66.2 (O$CH_{2\ morpholine}$), 120.4 (C-4), 123.1 (C-3), 135.2 (C-6), 143.4 (C-2 or C-5), 144.6 (C-2 or C-5); LRMS (ES$^+$) *m/z* 194.2 [M+H]$^+$; HRMS (NSI) calcd for $C_{10}H_{16}N_3O$ [M+H]$^+$ 194.1288, found 194.1284.

6-((Dimethylamino)methyl)pyridin-3-amine, (544)



Compound **544** was synthesised according to general procedure D', using the following reagents: *N*,*N*-dimethyl-1-(5-nitropyridin-2-yl)methanamine (**538**) (200 mg, 1.10 mmol), THF (11 mL) and methanol (11 mL). The crude yellow oil (155 mg, 93%) was used in the next step without further purification; R_f = 0.24 (amine silica, EtOAc, 100%); λ_{max} (EtOH)/nm 247.2, 306.2; IR (neat) ν_{max}/cm^{-1} 3321, 3190, 2972, 2939, 2858, 2817, 2773, 1630, 1597, 1572, 1491, 1454; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.11 (6H, s, CH_2N(CH_3)$_2$), 3.30 (2H, s, ArCH_2N), 5.15 (2H, brs, ArNH_2), 6.88 (1H, dd, *J* = 8.3, 2.7 Hz, H-4), 7.01 (1H, d, *J* = 8.3 Hz, H-5), 7.82 (1H, d, *J* = 2.7 Hz, H-2); ^{13}C NMR (126 MHz, DMSO-d_6) δ 45.0 (CH_2N(CH_3)$_2$), 64.7 (ArCH_2N), 120.5 (C-4), 122.9 (C-5), 135.0 (C-2), 143.3 (C-3 or C-6), 145.7 (C-3 or C-6); LRMS (ES$^+$) *m/z* 152.2 [M+H]$^+$; HRMS (NSI) calcd for $C_8H_{14}N_3$ [M+H]$^+$ 152.1179, found 152.1182.

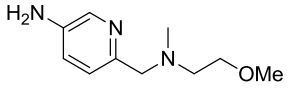
6-(Piperidin-1-ylmethyl)pyridin-3-amine, (545)



Compound **545** was synthesised according to general procedure D', using the following reagents: 5-nitro-2-(piperidin-1-ylmethyl)pyridine (**539**) (230 mg, 1.04 mmol), THF (10.4 mL) and methanol (10.4 mL). The yellow oil (190 mg, 95%) was used in the next step without further purification; R_f = 0.33 (amine silica, EtOAc, 100%); λ_{max} (EtOH)/nm 247.2, 305.8; IR (neat) ν_{max}/cm^{-1} 3317, 3190, 2927, 2852, 2787, 2750, 1626, 1591, 1571, 1490; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.31 – 1.41 (2H, m, H-4'), 1.41 – 1.50 (4H, m, H-3', 5'), 2.29 (4H, brs, H-2', 6'), 3.33 (2H, s, ArCH_2N), 5.13 (2H, brs, ArNH_2), 6.88 (1H,

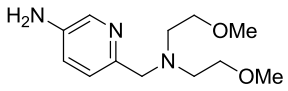
dd, *J* = 8.3, 2.7 Hz, H-4), 7.01 (1H, d, *J* = 8.3 Hz, H-5), 7.83 (1H, d, *J* = 2.7 Hz, H-2); ^{13}C NMR (126 MHz, DMSO-d_6) δ 24.0 (C-4'), 25.6 (C-3', 5'), 53.9 (C-2', 6'), 64.2 (Ar*C*H$_2$N), 120.4 (C-4), 122.8 (C-5), 135.1 (C-2), 143.2 (C-3 or C-6), 145.5 (C-3 or C-6); LRMS (ES$^+$) *m/z* 192.3 [M+H]$^+$; HRMS (NSI) calcd for $C_{11}H_{18}N_3$ [M+H]$^+$ 192.1495, found 192.1493.

6-(((2-Methoxyethyl)(methyl)amino)methyl)pyridin-3-amine, (546)



Compound **546** was synthesised according to general procedure D', using the following reagents: 2-methoxy-*N*-methyl-*N*-((5-nitropyridin-2-yl)methyl)ethanamine (**540**) (280 mg, 1.24 mmol), THF (12.4 mL) and methanol (12.4 mL). The crude orange oil (231 mg, 95%) was used in the next step without further purification; R_f = 0.42 (amine silica, EtOAc, 100%); λ_{max} (EtOH)/nm 246.6, 306.0; IR (neat) ν_{max}/cm^{-1} 3328, 3200, 2930, 2876, 2838, 2810, 1629, 1596, 1572, 1491; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.18 (3H, s, NC*H*$_3$), 2.55 (2H, t, *J* = 5.9 Hz, NC*H*$_2$CH$_2$OMe), 3.22 (3H, s, CH$_2$OC*H*$_3$), 3.43 (2H, t, *J* = 5.9 Hz, NCH$_2$C*H*$_2$OMe), 3.48 (2H, s, ArC*H*$_2$N), 5.19 (2H, brs, ArN*H*$_2$), 6.89 (1H, dd, *J* = 8.3, 2.7 Hz, H-4), 7.04 (1H, d, *J* = 8.3 Hz, H-5), 7.84 (1H, d, *J* = 2.7 Hz, H-2); ^{13}C NMR (126 MHz, DMSO-d_6) δ 42.2 (N*C*H$_3$), 55.6 (N*C*H$_2$CH$_2$OMe), 57.9 (CH$_2$O*C*H$_3$), 62.7 (Ar*C*H$_2$N), 70.0 (NCH$_2$*C*H$_2$OMe), 120.4 (C-4), 123.2 (C-5), 135.1 (C-2), 143.5 (C-3 or C-6), 144.9 (C-3 or C-6); LRMS (ES$^+$) *m/z* 196.3 [M+H]$^+$; HRMS (NSI) calcd for $C_{10}H_{18}N_3O$ [M+H]$^+$ 196.1444, found 196.1444.

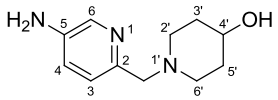
6-((bis(2-Methoxyethyl)amino)methyl)pyridin-3-amine, (547)



Compound **547** was synthesised according to general procedure D', using the following reagents: 2-methoxy-*N*-(2-methoxyethyl)-*N*-((5-nitropyridin-2-yl)methyl)ethanamine (**547**) (390 mg, 1.45 mmol), THF (14.5 mL) and methanol (14.5 mL). The yellow oil (330 mg, 95%) was used in the next step without further purification; R_f = 0.30 (amine silica, petrol:EtOAc, 3:7); λ_{max} (EtOH)/nm 245.0, 305.0; IR (neat) ν_{max}/cm^{-1} 3339, 3205, 2978, 2924, 2876, 2816, 1630, 1597, 1572, 1491; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.61 (4H, t, *J* = 6.2 Hz, N(C*H*$_2$CH$_2$OMe)$_2$), 3.19 (6H, s, N(CH$_2$CH$_2$OC*H*$_3$)$_2$), 3.36 (4H, t, *J* = 6.2 Hz, N(CH$_2$C*H*$_2$OMe)$_2$), 3.55 (2H, brs, ArC*H*$_2$N), 5.13 (2H, brs, ArN*H*$_2$), 6.89 (1H, dd, *J* = 8.3, 2.7 Hz, H-4), 7.05 (1H, d, *J* = 8.3 Hz, H-5), 7.82 (1H, d, *J* = 2.7 Hz, H-2); ^{13}C NMR

(126 MHz, DMSO-d_6) δ 53.2 (N($CH_2CH_2OMe)_2$), 58.0 (N($CH_2CH_2OCH_3)_2$), 60.1 (ArCH_2N), 70.6 (N($CH_2CH_2OMe)_2$), 120.5 (C-4), 122.9 (C-5), 135.0 (C-2), 143.2 (C-3 or C-6), 146.3 (C-3 or C-6); LRMS (ES^+) *m/z* 240.3 $[M+H]^+$; HRMS (NSI) calcd for $C_{12}H_{22}N_3O_2$ $[M+H]^+$ 240.1707, found 240.1706.

1-((5-Aminopyridin-2-yl)methyl)piperidin-4-ol, (548)



Compound **548** was synthesised according to general procedure D', using the following reagents: 1-((5-nitropyridin-2-yl)methyl)piperidin-4-ol (**542**) (340 mg, 1.43 mmol), THF (14.3 mL) and methanol (14.3 mL). The white solid (285 mg, 96%) was used in the next step without further purification; R_f = 0.28 (amine silica, EtOAc, 100%); m.p. 206.5-208.5 °C; λ_{max} (EtOH)/nm 246.2, 304.4; IR (neat) ν_{max}/cm^{-1} 3383, 3312, 3192, 3101, 2951, 2937, 2884, 2827, 1637, 1597, 1573, 1500; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.29 - 1.40 (2H, m, H-3', 5'), 1.62 – 1.72 (2H, m, H-3', 5'), 1.99 (2H, t, *J* = 10.1 Hz, H-2', 6'), 2.57 – 2.70 (2H, m, H-2', 6'), 3.34 (2H, s, ArCH_2N), 3.42 (1H, brs, H-4'), 4.53 (1H, s, CHO*H*), 5.14 (2H, brs, ArNH_2), 6.88 (1H, dd, *J* = 8.3, 2.7 Hz, H-4), 7.01 (1H, d, *J* = 8.3 Hz, H-3), 7.82 (1H, d, *J* = 2.7 Hz, H-6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 34.5 (C-3', 5'), 51.0 (C-2', 6'), 63.5 (ArCH_2N), 66.5 (C-4'), 120.5 (C-4), 122.9 (C-3), 135.1 (C-6), 143.3 (C-2 or C-5), 145.6 (C-2 or C-5); LRMS (ES^+) *m/z* 208.3 $[M+H]^+$; HRMS (NSI) calcd for $C_{11}H_{18}N_3O$ $[M+H]^+$ 208.1444, found 208.1444.

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