PART I:
MDMA Analogues as Lead Compounds for Burkitt’s Lymphoma Drug Discovery

PART II:
Hit-to-Lead Optimisation of a Novel Class of Trypanosomacidal Agents

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B Sc. (Honours)

This thesis is presented for the degree of Doctor of Philosophy of The University of Western Australia
School of Chemistry and Biochemistry
Chemistry
2016
THESIS DECLARATION

I, Stephanie Russell, certify that:

This thesis has been substantially accomplished during enrolment in the degree.

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Technical assistance was kindly provided by Dr Lindsay Byrne for NMR Spectroscopy, Dr Tony Reeder for Mass Spectroscopy, Oscar Del Borrello for Infrared Spectroscopy and Professor Brian Skelton for X-ray crystallography. Associate Professor Dani Ulgiati and Rhonda Mason performed the biological assays described in Chapter 1. Dr Amy Jones (Griffith) carried out the T. brucei growth inhibitions assays, under the supervision of Professor Vicky Avery. Marcel Kaiser (Swiss Tropical Institute) testing some of the compounds described in this thesis against other pathogens, and Kevin Read and Manu De Rycker (Dundee) conducted the mode of action and rate of kill assays, described in Chapter 2.
This thesis contains published work and/or work prepared for publication, some of which has been co-authored.

The work described in Chapter 2 of this thesis contributes to the patent:


A paper that includes some of the work from Chapter 2 has been published:


Student Signature:       Date: October 28th, 2016

Coordinating Supervisor Signature:      Date: October 28th, 2016
This Thesis is submitted to The University of Western Australia for the degree of Doctor of Philosophy.

The work described in this thesis was carried out by the author during the period, March 2010 to May 2014 in the Department of Chemistry at The University of Western Australia, under the supervision of Associate Professor Matthew J. Piggott, except for the period of February 2013–August 2013 which was carried out on an exchange at Dalhousie University in Halifax, Nova Scotia under the supervision of Prof Don Weaver.

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Stephanie Russell

October 2016
Abstract

This thesis describes two unrelated medicinal chemistry projects.

Chapter one details research aimed at drug discovery for Burkitt's lymphoma (BL), an aggressive type of cancer that is best known for its horrific facial tumours.\textsuperscript{1} BL is endemic in equatorial Africa, where it is the most common childhood cancer, affecting as many as 100,000 people each year in that region alone.\textsuperscript{2}

Psychotropic drugs that target the serotonin transporter, specifically methylenedioxymethamphetamine (MDMA, figure A), can induce apoptosis in BL cell lines.\textsuperscript{2} MDMA was therefore chosen as a starting point for BL drug discovery. This project focused on design and synthesis of analogues of MDMA that lack the psychoactivity of MDMA, while improving its selective cytotoxicity.

Two new synthetic routes to the piperonyl ketone precursors required to access the target amines were devised (Scheme A). The first involves a Johnson–Corey–Chaykovsky epoxidation,\textsuperscript{20} followed by regioselective ring-opening/rearrangement\textsuperscript{19} to piperonyl ketone 6. The second used Pd\textsuperscript{29} or Ni-catalysed\textsuperscript{30} addition of arylboronic acids to piperonyl cyanide. Reductive amination\textsuperscript{11} then provided the target amines 7.
Scheme A. Overview of synthetic routes to target MDMA analogues

The activities of 15 target MDMA analogues against two BL cell lines were investigated. Unfortunately, none of these compounds displayed activity worthy of further consideration.

Chapter 2 discusses a hit-to-lead optimisation project for human African trypanosomiasis (HAT), which is a parasitic disease caused by strains of the protozoan *Trypanosoma brucei*. Its impact is predominantly felt in sub-Saharan Africa, where it affects over 500,000 people in 36 countries, and it is one of the major causes of human and livestock mortality in these regions. Very few developments have been made in the way of treatments in the last 30 years, and the present drug regimens are often toxic and ineffective, with developing resistance a real concern.
A recent high-throughput screen of the WEHI (Walter and Eliza Hall Medical Institute) chemical library unearthed several promising hits against the model organism *T. brucei brucei*, with sub-micromolar IC$_{50}$ values and good selectivity$^9$ (Figure B).

![Figure B: Initial lead compounds for the HAT high throughput screen](image)

Synthetic routes were developed that allowed rapid modification of the RHS and LHS (as drawn in this thesis) substituents (R and R', respectively, figure C) in the target compounds. The heterocyclic core and amide linker were also modified.

![Figure C: General structure of amine targets](image)

In total 93 new analogues (62 by the candidate) were synthesized. Clear structure–activity relationships were derived (shown in figure D) and an increase in potency and selectivity of 100 fold was achieved in the most potent compounds (figure E).
Figure D: A summary of the structure–activity relationships discussed in chapter 2.

Figure E: IC\textsubscript{50} values of the two most potent compounds (bottom) compared to the initial lead compound (top).

Activity against related parasitic pathogens, rate-to-kill experiments selectivity (relative to mammalian cell lines) and pharmokinetic properties are also discussed.
Acknowledgments

First and foremost I'd like to thank my supervisor A/Prof. Matthew Piggott. Matt has been extremely supportive and encouraging since day one. The amount I've grown both academically and personally since starting my PhD has been incredible and your patience and support both within my research, and in my personal life will never be forgotten. Thanks for the numerous early morning Skype calls and doing anything in your power to help me succeed.

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## Abbreviations

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<td>2-dimensional</td>
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<td>A°</td>
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<td>acetyl</td>
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<td>ATR</td>
<td>attenuated total reflection</td>
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<td>BL</td>
<td>Burkitt's lymphoma</td>
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<td>Boc</td>
<td>tert-butoxycarbonyl</td>
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<td>bpy</td>
<td>2,2'-bipyridine</td>
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<td>br</td>
<td>broad</td>
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<tr>
<td>Bu</td>
<td>butyl</td>
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<td>CDCO</td>
<td>Centre for Drug Candidate Optimisation</td>
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<td>calculated human plasma protein binding</td>
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<td>DCU</td>
<td>dicyclohexylurea</td>
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<td>(diacetoxyiodo)benzene</td>
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<td>(N,N)-diisopropylethylamine</td>
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<td>DMF</td>
<td>(N,N)-dimethylformamide</td>
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<td>Abbreviation</td>
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<td>dimethyl sulfide</td>
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<td>DNDi</td>
<td>Drugs for Neglected Diseases initiative</td>
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<td>dppe</td>
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<td>EBV</td>
<td>Ebstein–Barr virus</td>
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<tr>
<td>E&lt;sub&gt;H&lt;/sub&gt;</td>
<td>predicted hepatic extraction ratio</td>
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<td>electron withdrawing group</td>
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<tr>
<td>FT</td>
<td>Fourier transform</td>
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<td>g</td>
<td>gram</td>
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<td>hour(s)</td>
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<td>heteronuclear single-quantum correlation spectroscopy</td>
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<td>HTS</td>
<td>high throughput screen</td>
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<tr>
<td>i-</td>
<td>iso</td>
</tr>
<tr>
<td>IC_{50}</td>
<td>half maximal inhibitory concentration</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
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<tr>
<td>JCC</td>
<td>Johnson–Corey–Chaykovsky reaction</td>
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<td>LLE</td>
<td>ligand-lipophilicity efficiency</td>
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<tr>
<td>m</td>
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<td>m</td>
<td>multiplet</td>
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<td>m.p.</td>
<td>melting point</td>
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<td>m/z</td>
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<td>MDMA</td>
<td>3,4-methylenedioxyamphetamine</td>
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<tr>
<td>Me</td>
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<td>MoA</td>
<td>mode of action</td>
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<tr>
<td>nM</td>
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<td>overnight</td>
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<tr>
<td>PMS</td>
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<td>ppm</td>
<td>parts per million</td>
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<tr>
<td>PSA</td>
<td>polar surface area</td>
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<tr>
<td>q</td>
<td>quartet</td>
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<tr>
<td>quant</td>
<td>quantitative</td>
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R\textsubscript{f} retention factor
SAR structure–activity relationship(s)
SEM standard error of the mean
SI selectivity index
S\textsubscript{N}Ar nucleophilic aromatic substitution
solv solvent
t triplet
t-Bu \textit{tert}-butyl
T. b. \textit{Trypanosoma brucei}
T\textsubscript{3}P Propylphosphonic anhydride solution
TBAHS tetrabutylammonium hydrogen sulfate
TBAI tetrabutylammonium iodide
Tf triflyl, trifluoromethanesulfonyl
THF tetrahydrofuran
TLC thin layer chromatography
Uv ultraviolet
v. very
WEHI Walter and Eliza Hall
wt weight
XTT \(5, 5'-(5\text{-phenylcarbonyl})-2\text{H}\text{-tetrazole-3-ium-2,3-diyl})\)
\text{bis}(4\text{-methoxy-2-nitrobenzenesulfonate})
\(\alpha\) alpha
\(\beta\) beta
\(\delta\) delta
\(\mu\) micro
M molar
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Chapter 1:

MDMA Analogues as Lead Compounds for Burkitt’s Lymphoma Drug Discovery
1.1 Introduction

Burkitt’s Lymphoma

Burkitt’s Lymphoma (BL) is an extremely aggressive type of cancer that is best known for its horrific facial tumours. These are the fastest growing tumours known, and can double in size within 24 hours. BL is endemic in equatorial Africa where it is the most common childhood cancer, affecting as many as 100,000 people each year in that region alone. It also occurs elsewhere throughout the world, although much less common, with 200–300 cases diagnosed in the USA annually, for example. The location of the tumours varies in different regions, commonly occurring in the jaws, kidneys and ovaries of African victims, and mostly in the lymph nodes of sufferers from developed nations.

BL is closely associated with the Epstein-Barr virus, which is detected in over 90% of patients infected with the endemic form, 20% of sporadic BL and 40% of HIV associated BL. There is a higher incidence in individuals who have been infected with HIV or malaria, and the Epstein-Barr virus is found in the lymphoma cells of the majority of these patients. Although it is unknown exactly how these infections contribute to the development of BL, it is likely related to chronic suppression of the immune system.

Current therapies for BL are far from ideal, requiring frequent hospital stays and aggressive combination chemotherapies over a six-month period. With treatment, there is a three-year relapse-free survival rate of 80%, but for patients infected with HIV or suffering from other immunodeficiency diseases, the average survival time is only six months. Current chemotherapy is also associated with significant toxicity and is not readily available to most African children, who cannot afford such treatments. It is clear that there is a need for a cheaper, more readily available and less toxic treatment.
for this disease, but with a poor market, BL research is a low priority to pharmaceutical companies.

1.1.2 MDMA

It has been shown that different psychotropic drugs that target the serotonin transporter induce apoptosis in BL cell lines. One example is MDMA (3,4-methylenedioxymethamphetamine), the compound most commonly associated with the illicit drug “ecstasy” (1, Figure 1).

![Figure 1. Structure of MDMA. The drug is commonly sold as the hydrochloride.](image)

MDMA is one of the most common recreational drugs, with up to two million tablets being consumed each year in Britain alone. It is known for its mood enhancing properties, such as increased energy and a state of euphoria, and is often consumed during all night parties to increase alertness. Numerous studies have been undertaken on the pharmacological effects of MDMA and it has been shown that it causes the release of the neurotransmitters serotonin, dopamine and norepinephrine in the central nervous system. The increase extracellular concentration of serotonin, and possibly dopamine, in synapses is achieved, at least in part, by blocking neurotransmitter re-uptake into axon terminals.

There are many side-effects associated with MDMA, ranging from minor complications such as loss of appetite, nausea, muscle aches, insomnia, fatigue, sweating, trismus (inability to open and close jaw), tachycardia, bruxism (the grinding of teeth) and a rapid heart rate, to more serious complications such as rhabdomyolysis
(rapid breakdown of skeletal muscle), and multi-organ failure, leading, in a small number of cases, to sudden death.⁶⁻⁷,⁹ One of the most common serious side-effects of MDMA is hyperthermia, in which an extreme fever of greater than 41.5 °C occurs,⁶⁻⁷ another being hyponatremia, which refers to very low levels of sodium in the serum.⁷ The probability of these conditions occurring is largely dependent on the context in which the drug is consumed.⁶,¹⁰ It has been shown in lab tests involving mice that elevated temperatures and aggregation vastly increase both the behavioural and toxic effects of MDMA.⁹ Also, knowing that elevated temperatures are a side effect of MDMA ingestion, many people consume far too many soft drinks and water causing hyponatremia.¹⁰

It has been found in rats that large doses of MDMA acutely alters dopamine release as well as dopamine metabolites, which results in damage to both the serotonin and dopamine neurones in the brain.¹⁰ Also, in squirrel monkeys, a dose of 5 mg/kg was enough to cause long term damage to the serotonergic neurons.¹⁰ Interestingly, MDMA directly injected into the brain is not neurotoxic, which implies that the peripheral metabolism of this compound is likely responsible for its toxicity.¹⁰

So while the finding of the toxicity of MDMA to BL cell lines is exciting and promising, there are obvious reasons why it cannot be used therapeutically. The psychoactivity and neurological toxicity of this drug are two major obstacles that must be overcome in an acceptable alternative. An acceptable drug candidate would also need to be a substantially more potent; the IC₅₀ of MDMA towards the L3055 BL cell line is only 507 µM.⁵
Analogues of MDMA – an approach to the discovery of new drugs for BL

It has been shown by the late Alexander Shulgin and co-experimenters that the extension of the α or N-substituent of MDMA to anything larger than an ethyl group abolishes psychoactivity, but not necessarily other central activity. Using this information, analogues of MDMA have been designed and synthesized in the Piggott group to examine how the size and electronic properties of the α-substituent affect the toxicity towards a BL cell line. The α-phenyl amine 2 (Figure 2) stood out from the first series of analogues, being almost seven times more potent than MDMA against the BL cell line. Compound 2 was also shown to lack psychoactivity in a rat model. The IC₅₀ values shown below indicate the concentration at which there was a 50% reduction in cell viability.

![Chemical Structures](image)

**Figure 2:** Structures and corresponding IC₅₀ values for MDMA hydrochloride and analogue 2 against the BL cell line L3055.

Based on the activity of 2, a second series of aromatic analogues was synthesized, which further explored stereoelectronic modifications to the α-substituent. The compounds were also tested against a catecholaminergic cell line, SH-SY5Y, which is used as a model of dopaminergic and adrenergic neurons, and has been used to model MDMA-induced neurotoxicity. Two compounds from the second series (3 and 4, Figure 3), were found to be non-toxic to this neuroblastoma cell line, but significantly
more toxic to the BL cells. This suggested that the incorporation of large aromatic α-substituents enhanced toxicity to the BL cell line and also eliminated neurotoxicity. More recent, unpublished work indicates that large N-substituents also improve the BL cell line cytotoxicity.\textsuperscript{13}

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {3};
\node (b) at (2,0) {4};
\draw (a) -- (b);
\end{tikzpicture}
\end{center}

\texttt{IC}_{50}^{}: 12.6 \pm 0.5 \, \mu M \\
\texttt{IC}_{50}^{}: 6.6 \pm 0.4 \, \mu M

\textbf{Figure 3:} Structures and \texttt{IC}_{50}^{} values for MDMA analogues 3 and 4 against the BL cell line L3055.

The mode of action of these compounds is unknown, but has been shown to be independent of the serotonin transporter.\textsuperscript{12} Indeed, analysis of structure-activity relationships reveals a strong correlation between lipophilicity and potency.\textsuperscript{12-13} This is not unexpected based on thermodynamic considerations, but chasing potency gains by further increasing lipophilicity is unlikely to be a successful strategy for BL drug discovery.\textsuperscript{14} Lipophilic compounds tend to be much less target specific and can lead to unwanted, toxic side effects as well as poor water solubility. By ‘tricking’ compounds into the body, the liver is forced to find more extreme ways to deal with them, which can often lead to more toxic and reactive metabolites. Drugs that are excessively hydrophobic are often absorbed into fatty tissues and removed from the blood supply leading to very poor circulation of the compound as well as off target effects (toxicity). Chasing potency by increasing lipophilicity generally just delays the inevitable failure
of the drug candidate leading to a much larger waste of time and resources, which could have been avoided by more circumspect selections earlier on in the process.\textsuperscript{14} In addition, in the case in point, compounds 3 and 4 are poorly water-soluble (even as the hydrochlorides) making biological assays difficult.

1.1.3 Previous syntheses of MDMA analogues in the Piggott Group

Through past research in the Piggott group many different MDMA analogues have been synthesized.\textsuperscript{5} The key step of these syntheses is the preparation of the piperonyl ketones 6 (Scheme 1). To date, most piperonyl ketones have been made by the reaction of an organocuprate, derived from Grignard reagent 5, with a variety of acid chlorides. Reductive amination then yields the desired amines 7 (MDMA analogues). Although the reductive amination is facile, the existing synthesis of the ketones is technically demanding, tedious and not as reliable as desired.

![Scheme 1: Previous synthetic route to target amines](image-url)
1.2 AIMS:

Given the background information above, the aims at the outset of this project were:

1. To design a series of analogues of compounds 2–4 incorporating more polar α-substituents, and/or primary amino groups.
2. To devise an improved synthesis of the key piperonyl ketones.
3. To synthesise the targets designed in aim 1.
4. To evaluate these compounds for activity against a Burkitt’s lymphoma cell line.

1.3 Target Design

The initial aim of this project was to target compounds with a similar shape to 2–4, but with reduced lipophilicity and improved water solubility. This was to be achieved by introducing more polar α-substituents. A logP value is usually calculated (or experimentally determined) to assess the lipophilicity of a compound. The higher the clogP value, the more hydrophobic a compound, and the lower/more negative the value, the more hydrophilic. As a rule of thumb, most orally available drugs have logP values between 0 and 5.14 Figure 4 shows the initially proposed compounds incorporating pyridyl groups. Should these analogues retain or improve on the activity of the parent compound 2, various (iso)quinolines could be targeted to better mimic 3 and 4. In addition, the 4-pyridylphenyl analogues 14–16 would also be explored. It was also desired to determine the necessity of the methylenedioxy group so 17 was also targeted. The clogP values of the current ‘lead compounds’, and the proposed analogues are shown for comparison.
**Figure 4:** Current ‘lead compounds’ and proposed pyridyl analogues with the corresponding clogP values for the neutral (black) and protonated (blue) forms, calculated using Molinspiration.\textsuperscript{15} Since the amines are primarily protonated at physiological pH, cLogD values are closer to the clogP of the protonated form.
1.4 Results and Discussion

The first experimental objective of this project was to devise a new synthetic route to the key piperonyl ketones. Although synthesizing benzyl (and related) ketones via ring opening of epoxides is a well known method, difficulties are often encountered in the form of unwanted side reactions, as well as lack of regioselectivity (Scheme 2).\(^{16,17}\)

\[
\text{O} \quad \text{R} \quad \rightarrow \quad \text{O} \quad \text{R} + \text{O} \quad \text{R} + \text{OH}
\]

\[
\text{Required}
\]

**Scheme 2**: General reaction for the formation of a ketone from its corresponding styrene epoxide and common byproducts.\(^{16,17}\)

Kulawiec and co-workers reported a rearrangement of aryl alkyl epoxides catalysed by Pd(OAc)$_2$ in the presence of a phosphine, which under mild conditions, proceeds through exclusive benzylic C–O cleavage, providing benzyl ketones in good yields.\(^{18}\) The products favoured are those arising from intermediates that can best stabilize the build-up of positive charge as the C–O bond cleaves. For example ketone 19 was produced exclusively and in high yield when epoxide 18 was subjected to these conditions (Scheme 3).\(^{18}\)
Scheme 3: Example of a very efficient and regioselective palladium-catalyzed ring-opening/rearrangement of epoxides under mild conditions.\(^{18}\)

The initial ketone targets in the proposed work were piperonyl pyridyl ketones 21, which could, in principle, be derived from the corresponding epoxides 20 (Scheme 4). Although these targets contained two benzylic carbons, opposed to the single one in the literature example, it was proposed that cleavage of the C–O bond adjacent to the more electron-rich benzodioxole ring system would occur preferentially to the that next to the electron deficient, pyridyl substituent.\(^{18}\)

Scheme 4: Generic synthesis of desired pyridyl ketones 21 from the corresponding epoxides 20.\(^{18}\)

In order to synthesize these ketones the epoxide precursor would first need to be derived. The Johnson–Corey–Chaykovsky reaction seemed a promising method, which could provide rapid access to the desired epoxides, from a single sulfonium salt and a range of cheap, commercially available aldehydes. A very relevant precedent, in which the benzy sulfonyl sulfonium salt 22 reacts with nicotinaldehyde (23) is shown in Scheme 5.\(^{19}\)
Scheme 5: Literature example of a Johnson–Corey–Chaykovsky reaction to give pyridyl epoxide 24 from a sulfonium salt (22) and corresponding aldehyde (23).\textsuperscript{19}

The synthesis of the pyridyl epoxides is shown in Scheme 6. Piperonal (28) was reduced to piperonyl alcohol (29),\textsuperscript{20} using sodium borohydride, then converted to the bromide 30.\textsuperscript{21} A nucleophilic substitution reaction with dimethyl sulfide\textsuperscript{22} then yielded the novel sulfonium bromide 31. The Johnson–Corey–Chaykowsk reaction\textsuperscript{19} of 31 with the three isomeric pyridinecarboxyaldehydes, as well as 2-naphthaldehyde was then undertaken. Pleasingly, these gave each of the required epoxides 24, 25 and 26 as mixtures of stereoisomers (Table 1). In the case of the 2-pyridyl epoxide 26 the isomers were separable by column chromatography, with the cis isomer identified as the one with the larger coupling constant between the two epoxide protons.\textsuperscript{23, 24, 25} The other ratios were determined by analysis of the $^1$H NMR spectra of the mixtures, (Table 1). Although this complicated the NMR spectra, both isomers yielded a single product in the subsequent step so diastereoselectivity was not an issue. The 2-naphthyl epoxide 27 was synthesized, but subsequent attempts were not consistent, and separation from the starting aldehyde was very difficult due to similar mobility Rf's.
Scheme 6: Synthesis of desired epoxides 22 using the Johnson–Corey–
Chaykowski reaction.
Table 1: Synthesis of epoxides by Johnson–Corey–Chaykowski reactions

<table>
<thead>
<tr>
<th>Epoxide</th>
<th>cis</th>
<th>trans</th>
<th>% Yield*</th>
</tr>
</thead>
<tbody>
<tr>
<td>26a</td>
<td>1</td>
<td>-</td>
<td>74</td>
</tr>
<tr>
<td>26b</td>
<td>-</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>25</td>
<td>6</td>
<td>11</td>
<td>84*</td>
</tr>
<tr>
<td>24</td>
<td>2</td>
<td>9</td>
<td>58*</td>
</tr>
<tr>
<td>27</td>
<td>8</td>
<td>2</td>
<td>80</td>
</tr>
</tbody>
</table>

* Yield of mixture of isomers, “isolated” by column chromatography

Despite the JCC reaction worked well for the pyridylaldehydes (58–85 %), it failed in any attempts to form epoxides 34 and 35 (Scheme 7). Although $^1$H NMR spectroscopy indicated that, in some cases, it was possible that the desired product had been formed, the chromatographic mobility of the epoxide was too close to allow proper separation, and the reactions could never be pushed to completion. If future work is to be done with such analogues, alternative methods must be pursued.
Scheme 7: Unsuccessful attempt to prepare epoxides containing an alkene side chain via the Johnson–Corey–Chaykowski reaction.

With the pyridylepoxides in hand, attention turned to the rearrangement to piperonyl ketones. Initially, reactions following the described procedure\textsuperscript{18} led to incomplete conversion, causing yields to be poor, and isolation of the product to be very difficult due to the very similar chromatographic mobility of the starting material and product. Optimisation attempts were made on a known epoxide 36 (synthesized via reaction conditions outlined in Scheme 6) as shown in Table 2.
Table 2: Optimisation of the Pd–catalysed rearrangement of 36.

<table>
<thead>
<tr>
<th>Expt</th>
<th>Solvent</th>
<th>Ligand</th>
<th>Temperature (°C)</th>
<th>Time</th>
<th>Conversion (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>t-BuOH</td>
<td>PPh&lt;sub&gt;3&lt;/sub&gt;</td>
<td>60</td>
<td>18 h</td>
<td>0%</td>
</tr>
<tr>
<td>2</td>
<td>t-BuOH</td>
<td>PPh&lt;sub&gt;3&lt;/sub&gt;</td>
<td>80</td>
<td>48 h</td>
<td>3%</td>
</tr>
<tr>
<td>3</td>
<td>t-BuOH</td>
<td>PPh&lt;sub&gt;3&lt;/sub&gt;</td>
<td>40→reflux</td>
<td>18 h</td>
<td>0%</td>
</tr>
<tr>
<td>4</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;CN</td>
<td>PPh&lt;sub&gt;3&lt;/sub&gt;</td>
<td>40→reflux</td>
<td>18 h</td>
<td>0%</td>
</tr>
<tr>
<td>5</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;CN</td>
<td>PPh&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Reflux</td>
<td>18 h</td>
<td>0%</td>
</tr>
<tr>
<td>6</td>
<td>DMF</td>
<td>PPh&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Reflux</td>
<td>ON</td>
<td>0%</td>
</tr>
<tr>
<td>7</td>
<td>t-BuOH</td>
<td>PBu&lt;sub&gt;3&lt;/sub&gt;</td>
<td>40→60</td>
<td>24 h</td>
<td>0%</td>
</tr>
<tr>
<td>8</td>
<td>t-BuOH</td>
<td>Pd(PPh&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;4&lt;/sub&gt; (0.5 %)</td>
<td>100</td>
<td>48 h</td>
<td>50%</td>
</tr>
<tr>
<td>9</td>
<td>t-BuOH</td>
<td>PBu&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Reflux</td>
<td>18 h</td>
<td>50%</td>
</tr>
<tr>
<td>10</td>
<td>t-BuOH</td>
<td>PPh&lt;sub&gt;3&lt;/sub&gt;*</td>
<td>Reflux</td>
<td>18 h</td>
<td>0%</td>
</tr>
<tr>
<td>11</td>
<td>t-BuOH</td>
<td>PPh&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Reflux</td>
<td>18 h</td>
<td>100%</td>
</tr>
</tbody>
</table>

Catalyst 5% Ligand 5%

<sup>a</sup>PdCl<sub>2</sub> used as catalyst instead of Pd(OAc)<sub>2</sub>

<sup>a</sup>Conversion of starting epoxide to ketone determined by <sup>1</sup>H NMR spectroscopy: ratio of the ketone CH<sub>2</sub> peak integral in comparison to the epoxide CH peak integral of the crude product.

Initially Pd(OAc)<sub>2</sub> (5 mol %) and PPh<sub>3</sub> (15 mol %) were added to a solution of 36 dissolved in t-BuOH and allowed to react at 60 °C overnight. With no products being formed, the same conditions were attempted but at 80 °C and then at 40 °C and slowly increased to reflux overnight, with still none of the desired product produced. With the rationalization that higher boiling solvent may push this reaction to
completion, reactions with DMF were attempted, again to no avail. Different catalysts 
were explored; there was no reaction observed using PdCl₂, but a 50 % conversion to 
products was seen with Pd(PPh₃)₄. Although this was encouraging, the reaction rate 
was also extremely slow. Utilizing the Pd(OAc)₂ but a more electron rich ligand (PBu₃) 
also gave a 50 % conversion to products. Going back to the original conditions but 
beginning the reaction at reflux, instead of ramping up the temperature, complete 
conversion of reactants to products was observed.

As predicted, the ring-opening favoured the desired piperonyl ketone, but not 
completely regioselectively. Both ketone isomers 37a and 37b were formed (3:1 ratio 
respectively), but were able to be separated and isolated via column chromatography, in 
a combined 65% yield. The optimised conditions were applied to the pyridyl epoxides 
24, 25 and 26, and 2-naphthyl epoxide 27 (Table 1). Despite the optimisation efforts on 
the stilbene epoxide 36, this method was not completely regioselective for the desired 
pyridyl ketones (Table 3). In fact, 27 gave only the undesired ketone isomer. This 
decrease in selectivity was perhaps not unexpected given the fact that the desired 
analogues possessed two benzylic carbons, opposed to the one benzylic carbon in the 
precedent. The reaction was also limited in its application. Additional reactions were 
attempted with a 4-bromophenyl substituent with no product being isolated, as well as a 
2-naphthyl substituent. In the latter case, the crude product was messy and the desired 
product was difficult to isolate. This method was not further pursued due to the 
discovery of an improved procedure (see below).
Table 3: Yields and isomeric ratios of ketones from palladium-catalysed ring-opening/rearrangement of benzodioxolyl pyridyl epoxides (20) and 2-naphthyl epoxide (27).

<table>
<thead>
<tr>
<th>Epoxide</th>
<th>Ratio of isomeric products*</th>
<th>Benzodioxolyl ketone</th>
<th>Pyridyl ketone</th>
<th>Isolated Yield (%) of pyridyl ketone</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-pyridyl 26</td>
<td></td>
<td>- (38a)</td>
<td>&gt; 95 % (38b)</td>
<td>67</td>
</tr>
<tr>
<td>3-pyridyl 25</td>
<td></td>
<td>1 (39a)</td>
<td>9 (39b)</td>
<td>54</td>
</tr>
<tr>
<td>4-pyridyl 24</td>
<td></td>
<td>1 (40a)</td>
<td>9 (40b)</td>
<td>61</td>
</tr>
<tr>
<td>2-naphthyl 27</td>
<td></td>
<td>&gt;95% (41a)</td>
<td>- (41b)</td>
<td>47</td>
</tr>
</tbody>
</table>

* Determined by crude $^1$H NMR ratios

In summary, the synthesis of piperonyl ketones described in this section was limited by the failure of the JCC reaction with aliphatic aldehydes and incompatibility of the palladium catalysed ring-opening/rearrangement with a 4-bromophenyl epoxide. It was therefore necessary to find a more versatile method.

1.4.2 Attempted access to piperonyl ketones via Claisen condensation)

A possible route to piperonyl ketones involving a key Claisen condensation is exemplified in Scheme 8. Esterification of piperonylacetic acid$^{26}$ with $t$-butanol gave 43 in 60% yield. The intention was that Claisen condensation of 43 with various esters$^{27}$
would yield the \( \beta \)-ketoesters 45, and protonolysis would lead to decarboxylation,\(^{27}\) providing the desired ketones 6. However, this was not the case and even after multiple attempts (Table 4), only a very complex mixture of products along with possible starting materials was formed, with none of the desired \( \beta \)-ketoesters isolated, thus this route was abandoned.

**Scheme 8**: An attempted approach to piperonyl ketones involving a key Claisen condensation.
**Table 4**: Different esters and conditions attempted for the Claisen condensation of \(t\)-butyl piperonylacetate (43).

<table>
<thead>
<tr>
<th>Ester</th>
<th>Solvent</th>
<th>Temp (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="43" alt="Ester" /></td>
<td>THF</td>
<td>RT</td>
</tr>
<tr>
<td><img src="44" alt="Ester" /></td>
<td>THF</td>
<td>60</td>
</tr>
<tr>
<td><img src="45" alt="Ester" /></td>
<td>DMF</td>
<td>60</td>
</tr>
<tr>
<td><img src="46" alt="Ester" /></td>
<td>THF</td>
<td>Reflux</td>
</tr>
<tr>
<td><img src="47" alt="Ester" /></td>
<td>THF</td>
<td>60</td>
</tr>
<tr>
<td><img src="48" alt="Ester" /></td>
<td>Toluene</td>
<td>100 → reflux</td>
</tr>
</tbody>
</table>

*Drop of 18-crown ether added*
1.4.3 Palladium-catalysed addition of boronic acids to nitriles

Fortunately, a recently described palladium-catalysed addition of boronic acids to nitriles\textsuperscript{28} proved to be applicable to the synthesis of various piperonyl ketones (Scheme 9).

![Scheme 9: Literature coupling reaction of similar compounds using a [(bpy)Pd+(µ-OH)]\textsubscript{2}.(-OTf)\textsubscript{2} catalyst\textsuperscript{28}](image)

The proposed mechanism is shown in Scheme 10.\textsuperscript{28} Initially the dimeric catalyst [(bpy)Pd+(µ-OH)]\textsubscript{2}.(-OTf)\textsubscript{2} dissociates into its monomeric form in the presence of solvent to give species a and begin the catalytic cycle. Upon the introduction of a boronic acid, a temporary intermediate is formed (b) in which the aryl group coordinates to the palladium center, and the transmetallation occurs readily due to boron's affinity for oxygen, to yield c. Coordination of the Lewis acidic palladium to the nitrile facilitates intramolecular nucleophilic addition of the aryl group to sp-hybridised carbon to give intermediate e. A simple protonolysis of e in the presence of solvent, regenerates the catalyst, and the imine f, which upon hydrolysis gives the desired ketones.
Scheme 10. Proposed mechanism for the palladium-catalysed addition of arylboronic acids to nitriles. Taken from Zhao and Lu. 28

Applying this reaction to the known nitrile 28 46 and various commercial boronic acids gave ketones 48–56 in moderate to good yields (Table 5). Initial problems in getting the reaction to go to completion under the reported conditions 28 were overcome by allowing the reaction to proceed open to air, (as a precaution, reactions were originally carried out under argon), as well as omitting the co-solvent CH₃NO₂, and using water as the sole solvent.
Table 5: Synthesis of 6 via palladium-catalyzed addition of boronic acids to nitrile 46.

<table>
<thead>
<tr>
<th>#</th>
<th>Piperonyl ketone</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>48</td>
<td><img src="image1" alt="Image" /></td>
<td>72%</td>
</tr>
<tr>
<td>49</td>
<td><img src="image2" alt="Image" /></td>
<td>80%</td>
</tr>
<tr>
<td>50</td>
<td><img src="image3" alt="Image" /></td>
<td>58%</td>
</tr>
<tr>
<td>51</td>
<td><img src="image4" alt="Image" /></td>
<td>40%</td>
</tr>
<tr>
<td>52</td>
<td><img src="image5" alt="Image" /></td>
<td>56%</td>
</tr>
<tr>
<td>53</td>
<td><img src="image6" alt="Image" /></td>
<td>32%</td>
</tr>
<tr>
<td>54</td>
<td><img src="image7" alt="Image" /></td>
<td>58%</td>
</tr>
<tr>
<td>56</td>
<td><img src="image8" alt="Image" /></td>
<td>72%</td>
</tr>
</tbody>
</table>

* Phenylacetonitrile 46a was used.
The nitrile addition did have some limitations, however. Reaction with 4-bromo- and 4-iodophenylboronic acids was attempted (to give ketones 50 and 51 respectively), which would have provided an opportunity to couple in additional heteroaromatic rings via Suzuki coupling. Unsurprisingly, homocoupling of the boronic acid with itself and the initial product 50 gave side products that complicated isolation. Although a moderate yield was obtained in a few experiments, further attempts were not reliable or consistent, often times with no isolation of pure product. The reaction also failed with the boronic acids shown in Figure 5.

![Figure 5: Boronic acids that were not compatible with the Pd-catalysed addition to piperonyl nitrile 46.](image)

During the course of this work a much cheaper nickel catalyst, Ni(dppe)Cl₂, was reported to effect the same type of reaction. Initial attempts with this catalyst provided issues with conversion of the starting material to product as well as yields.
Optimisation of the conditions using p-bromophenyl boronic acid (Scheme 11) is shown in Table 6.

![Chemical structure](image)

**Table 6: Various reaction conditions used in the optimization of Scheme 11**

<table>
<thead>
<tr>
<th>ZnCl$_2$ (mol %)</th>
<th>Catalyst</th>
<th>Temperature</th>
<th>Time</th>
<th>Conversion*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.25</td>
<td>10%</td>
<td>80</td>
<td>12 h</td>
<td>0%</td>
</tr>
<tr>
<td>1.5</td>
<td>10%</td>
<td>80</td>
<td>12 h</td>
<td>0%</td>
</tr>
<tr>
<td>1.5</td>
<td>100%</td>
<td>80</td>
<td>12 h</td>
<td>80%</td>
</tr>
<tr>
<td>2.5</td>
<td>100%</td>
<td>80</td>
<td>12 h</td>
<td>85%</td>
</tr>
<tr>
<td>5</td>
<td>10%</td>
<td>reflux</td>
<td>18 h</td>
<td>67%</td>
</tr>
<tr>
<td>5</td>
<td>10%</td>
<td>80</td>
<td>48 h</td>
<td>77%</td>
</tr>
<tr>
<td>6</td>
<td>10%</td>
<td>50</td>
<td>12 h</td>
<td>0%</td>
</tr>
</tbody>
</table>

*Based on integrals of ketone CH$_2$ signals in the $^1$H NMR spectrum of the crude product.
Initial experiments began with the conditions reported, but with 1.25 equivalents of ZnCl₂, and 10 % catalyst, none of the desired product was observed. By using a stoichiometric amount of Ni catalyst, the conversion was increased; however, using this is far from ideal. Fortunately, increasing the ratio of Lewis acid ZnCl₂, allowed the reaction to proceed while maintaining the 10 % catalyst loading. After optimisation of the system, it was found that by incorporating a 5:1 ratio of ZnCl₂ to starting material, with 10 mol % Ni catalyst, at 80 °C, the corresponding ketone could be synthesized in high yields. This methodology provides a cheaper, more efficient route to the target compounds and will be used in future research.

1.4.4 Reductive aminations

Once the ketones were in hand, the desired MDMA analogues were synthesized in one step with a reductive amination using sodium cyanoborohydride and methylamine (Scheme 12). Although not an initially planned target, with the isolation of byproduct ketone 55 in hand, the synthesis was carried through to yield 67, which would allow exploration into how changing the amine position would affect potency. Yields varied significantly based on difficulties encountered in purification. The results are shown in Figure 6.

Scheme 12: Reductive amination of ketones 6 to the desired target amines 7.
Figure 6: Target MDMA analogues synthesized via reductive amination and their corresponding yields.

It was of interest to examine primary amines due to their increased polarity, relative to the secondary amines in Figure 6. The syntheses of a limited number of primary amines were achieved using a reductive amination of the ketones 74 using sodium cyanoborohydride, ammonium acetate, and ammonium hydroxide, as shown in Scheme 13. The resulting target primary amines and yields and shown in Figure 7.
A large excess of ammonia was used in hopes of avoiding additional reactions of the primary amine to give the secondary amine. Although some yields are quite poor, no secondary amine was isolated.

Scheme 13: Synthesis of primary amine targets.

Figure 7: Primary amines synthesized and their corresponding yields.
1.5 Biological testing

All target compounds were tested in their hydrochloride form against Raji and Ramos cell lines with the help of Rhonda Mason and A/Prof. Daniela Ulgiati in the School of Chemistry and Biochemistry, UWA. Raji cells are a lymphoblast-like cell line, derived from an 11 year old, male, Burkitt's lymphoma patient from Nigeria in 1963. They contain the Epstein-Barr virus genome. Ramos cells, on the other hand, do not contain the Epstein-Barr virus genome. They are also derived from lymphoblasts and have B-lymphocyte characteristics. They were acquired from a three year old Caucasian male afflicted with sporadic Burkitt's lymphoma. These cell lines were chosen based on precedent and similar testing that has been done.

Cell viability was assessed by XTT/PMS assay\textsuperscript{32}, which is based on the ability of viable cells to metabolise the tetrazolium salt XTT (\textit{82}) to produce an orange formazan dye \textit{83} (Scheme \textit{14}). 5-Methyl-5,10-dihydrophenazine methyl sulfate (PMS, \textit{80}) facilitates this reaction by acting as an electron acceptor, which forms a reactive intermediate that can help reduce XTT to the coloured formazan product.\textsuperscript{33} 4-Hydroxyanisole (\textit{81}, Figure \textit{8}), which is known to be toxic to Burkitt’s lymphoma cell lines,\textsuperscript{33} was used as a standard (positive control) for comparison.

![Structure and systematic names of PMS and 4-hydroxyanisole](image)

\textbf{Figure \textit{8}:} Structure and systematic names of PMS and 4-hydroxyanisole
Scheme 14: XTT is metabolised by viable cells to give an orange formazan dye 83

Cells, together with the MDMA analogues (1 mM or 100 µM final concentrations) were incubated for 72 hours, then treated with XTT/PMS and incubated for a further 6 hours. Viability was determined through comparison of the absorbance at 485 nm relative to a negative control (i.e., treated with 0.065% or 0.0065% DMSO/distilled water). All experiments were conducted in triplicate. An average of the three absorbance values was calculated for each compound. Then each of these averaged values was divided by the absorbance of the control and converted to a percentage to give the percentage viability. (Figures 9–12).

Initial results looked promising, with the majority of compounds at a 1 mM concentration causing a similar percentage of cell death to the standard cytotoxin, 4-hydroxynisole (HA). However, unfortunately the analogues with more polar α-substituents, which were our primary target compounds, were virtually inactive, even at this high concentration. In particular, the α-pyridyl analogues 8–10 had no or very weak activity, which did not correlate well with the aims of this project.
Figure 9: Cell viability results in order of decreasing clogP (salt) for the Raji cell line at a 1 mM test compound concentration. See page 28 (Figure 6) and page 29 (Figure 7) for structures. Results shown are mean +/- SD. Error bars are ± standard deviation.

Figure 10: Cell viability results in order of decreasing clogP (salt) for the Ramos cell line at a 1 mM test compound concentration. See page 28 (Figure 6) and page 29 (Figure 7) for structures. Error bars are ± standard deviation.

Somewhat surprisingly at the lower concentration of 100 µM, very few of the analogues exhibited significant cytotoxicity (Figures 11–12). Instead, many of the compounds seemed to increase the formation of dye, suggesting an increased cell viability (proliferation) or increased metabolic rate. These results are supported by
other concentration-response assays studies within the group in which, as the concentration of MDMA analogue was raised, an apparent increase in cell viability preceded a rapid decrease in viability in the IC$_{50}$ value.$^{13}$ This could be due to a phenomenon called hormesis, in which low doses of a "toxin" have been found to actually be beneficial and increase viability.$^{34}$

**Figure 11**: Cell viability results in order of decreasing clogP (salt) for the Raji cell line at a 100 µM test compound concentration. See page 28 (Figure 6) and page 29 (Figure 7) for structures. Error bars are ± standard deviation.
Taking into consideration the clogP values of the ammonium ions (the predomiant protonation state at the assays pH), which decrease from left to right in Figures 9–12, may help explain some of the initial results. As a general trend, at higher concentrations, it is shown that the more lipophilic the compound (higher clogP), the lower the cell viability. Almost all of the highly lipophilic compounds reduced cell viability at 1 mM in both the Raji and Ramos cell lines, while the polar compounds were inactive or less potent (Figures 9 and 10). In addition, no clear structure activity relationships emerged. These observations suggest that the cytotoxicity of the compounds described in this chapter towards BL cell lines may be due to non-specific activity linked closely with lipophilicity, rather than activity against a specific biological target.

Since the compounds described in this chapter are lipophilic cations, it is possible that their cytotoxicity towards BL cell lines is mediated through cell membrane disruption.
(detergent action). Lipophilic cations are also known to accumulate in certain organelles, such as mitochondria, and mediate their toxicity in this way.\textsuperscript{35}

At the lower concentration of 100 µM, most compounds did not affect cell viability. However, three compounds that stood out were 69, 77 and 79 (Figure 13). Although 69 is very lipophilic, it was interesting to note that the secondary amine was so much more potent than the corresponding primary amine (compound 76, Figure 13). This is in stark contrast, to compounds 77 and 79, whose primary amines were more active than the analogous secondary amines, 73 and 72, respectively (Figure 13). The activity for 73 also implies that the methylenedioxy moiety present in MDMA and all of the other analogues made in this project may not be essential for activity.
Based on these results, nine point IC$_{50}$ curves were determined for the three most potent compounds and are shown in Figures 14–16. Due to the increase in cell viability just before the point of inflection, we were unable to fit the data to provide accurate IC$_{50}$ values. However, by estimation, the IC$_{50}$ values are approximately in the range of 20–40 μM, which were comparable to our standard, hydroxyanisole. As we were looking for compounds with sub-micromolar potency, these results were not encouraging.

Due to this and the success of the project described in Chapter 2, this line of research was not pursued any further.
Figure 14: Concentration vs Cell Viability curve for compound 69.

Figure 15: Concentration vs Cell Viability for compound 77.
1.6 Conclusion

Previous research in the Piggott group has shown that compounds that are structurally similar to MDMA, but are unlikely to be psychoactive, are selectively cytotoxic to Burkitt's lymphoma cell lines. The aim of this project was to improve the synthesis of the key intermediate piperonyl ketones 6 and use this methodology to synthesize and evaluate MDMA analogues with α-substituents of a similar size to those in the most potent compounds identified previously, but with increased polarity.

Two new methods were developed to synthesise the ketone precursors to target MDMA analogues. A Johnson–Corey–Chaykovsky reaction\(^\text{19}\) of aryl aldehydes, followed by palladium-catalyzed ring opening\(^\text{18}\) of the resultant epoxides gave access to some piperonyl ketones. The Johnson–Corey–Chaykovsky reaction was not applicable to aliphatic aldehydes and the ring-opening suffered from regiochemical ambiguity when more electron-rich substituents were present. However, this method did provide target piperonyl pyridyl ketones. Palladium\(^\text{28}\) or nickel-catalyzed\(^\text{29}\) addition of various...
boronic acids to piperonyl nitrile provided an alternative route to key aryl ketone precursors. This method had the advantage of regiochemical certainty, but was not applicable to heterocyclic boronic acids.

Reductive amination\textsuperscript{5, 31} provided 15 target MDMA analogues in total: 11 secondary amines and four primary amines. These were tested for cytotoxicity against both Raji and Ramos cell lines. With the exception of compound 79, only the more lipophilic compounds were found to be cytotoxic, and the potency of 79 was nowhere near the desired range. Continuously adding mass to lead compounds, rather than reassessing the faults and continuing with a new model, can result in costly failures in the drug discovery arena.\textsuperscript{14} There is still potential that potency boosts could be obtained in MDMA analogues without increasing lipophilicity, but it now seems clear that modification of the $\alpha$-substituent is not the way to achieve this. Elucidation of the mode of action of this class of compounds could aid future drug discovery efforts. For these reasons, as well as the success of the candidate’s second project, it was decided to drop the Burkitt’s lymphoma drug discovery project.
1.7 Experimental

General

Unless stated otherwise, all reactions were performed under an atmosphere of argon, at room temperature. Temperatures reported (other than those at reflux) refer to the temperature of the oil bath. Reaction progress was monitored by analytical thin layer chromatography (TLC) using MERCK aluminium-backed TLC plates, manufactured with F254 indicator, and compounds were visualised with a UV lamp (254 nm). All organic extracts were washed with NaCl (saturated aq.), then dried with anhydrous MgSO₄, and solvents were evaporated under reduced pressure at approximately 50 °C. Flash chromatography was performed with either E. Merck or Silicycle silica gel (average particle size: 40–63 µm; average pore size: 60 Å). All solvents were distilled prior to use. Anhydrous DMF was obtained by drying over activated molecular sieves (3A) for 24 h, followed by distillation under reduced pressure onto activated sieves (3A). THF was obtained anhydrous from a Pure Solv 5-Mid Solvent Purification System (Innovative Technology Inc.). Hexanes refers to the hydrocarbon fraction distilling from 64–67 °C. “Ether” refers to diethyl ether. NEt₃ and pyridine were stored over KOH prior to use. All other reagents and materials were purchased from commercial suppliers and used as received.

¹H and ¹³C NMR spectra were obtained using a Varian 400 MHz or Bruker 500 MHz spectrometer (as indicated). Unless stated otherwise, deuterochloroform (CDCl₃) was used as the solvent, with CHCl₃ (¹H, δ = 7.26 ppm) or CDCl₃ (¹³C, δ = 77.16 ppm) being used for calibration. Where D₆-DMSO or D₄-MeOH were used as solvents, CD₃SOCD₂H (¹H, δ = 2.50 ppm) and SO(CD₃)₂ (¹³C, δ = 39.52 ppm), or CD₂OD (¹H, δ = 3.31 ppm) and CD₃OD (¹³C, δ = 49.00 ppm), respectively, were used as the internal standards. Where necessary, ¹H and ¹³C assignments were made using a range of 2D
NMR experiments, namely, COSY, HSQC, and HMBC, acquired with a Bruker AV (600 MHz) spectrometer. Infrared (IR) spectra were acquired with a Perkin–Elmer SpectrumOne FTIR spectrometer on thin films using NaCl plates, or neat using an ATR attachment (as indicated). Mass spectra were recorded with a Waters Autospec instrument using electron impact (EI), electrospray (ESI). Melting points were determined on a Reichert hot stage melting point apparatus.

**Cell culture**

The cell lines Raji (CCL-86™) and Ramos (CRL-8286™) (ATCC, Manassas, Virginia, USA) were cultured in RPMI 1640 medium supplemented with 2 mM glutamine (Invitrogen, Australia), 100 µg/mL penicillin, 100 µg/mL streptomycin (Invitrogen, Australia) and 10% v/v heat-inactivated FBS (Serana, Australia), at 37 °C under 5% CO₂.

**Cytotoxicity Assay**

Cells were cultured to exponential phase and harvested by centrifugation for 5 min at 1000 rpm (200g) The cells were re-suspended and seeded at a final concentration of 2 x 10⁵ cells/mL in culture medium in 96 well, flat-bottomed microplates (Greiner) containing varying concentrations of the putative inhibitors up to a maximum of 0.65% DMSO/water (10 µL). The plates were incubated for 96 h at 37 °C under 5% CO₂.

The XTT labelling mixture was prepared by combining a filter-sterilised (0.2 µm) solution of XTT (1 mg/mL) (Sigma-Aldrich) in RPMI 1640 with a solution of phenazinemethosulfate (0.38 mg/mL, Sigma) in phosphate-buffered saline (0.1 mL).
Freshly prepared XTT labelling mixture (50 µL) was added to the relevant wells and the plates were incubated for 6 h at 37 °C under 5% CO₂. The absorbance was determined using a Fluostar Optima spectrophotometer using a 485 nm excitation filter.

* This solution was formed by mixing XTT solid with RPMI 1640 and warming in a recirculating water bath at 37 °C for up to 10 min. Once all/nearly all of the XTT is dissolved, any remaining solid was removed by syringe filter.

### Assay controls/conditions

An initial screen was done against all compounds using concentrations of 1 mM and 100 µM. A negative control of DMSO/water (0.065% for 1 mM and 0.0065% for 100 µM), and a positive control of 4-hydroxyanisole (at the same concentration as the test compound) was used. All experiments were conducted in triplicate. Compounds that caused <50% cell viability at 100 µM were tested using a nine-point assay to generate an IC₅₀ curve.
Synthesis

Sodium borohydride (1.60 g, 0.044 mol) was added to a stirred solution of 28 (15.0 g, 0.100 mol) in ethanol (20 mL) at 0 °C. After 2 h, or when TLC showed the disappearance of starting material, the solvent was evaporated and 1 M HCl (250 mL) was added to the residue. The solution was extracted with EtOAc (3 × 100 mL) and the extract was washed with water (2 × 100 mL), dried and evaporated. Hexanes (25 mL) was added causing 29 to precipitate as fluffy, white crystals (11.0 g, 75%), m.p.: 48–52 °C [lit. 50–52 °C]. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.76–6.88 (m, 3H, H4'/H6'/H7'), 5.94 (s, 2H, H2'), 4.56 (s, 2H, H1). $^{13}$C NMR (400 MHz, CDCl$_3$) $\delta$ 147.9 (ArO), 147.2 (ArO), 135.0 (C5'), 120.6 (C6'), 108.3 (C4' or C7'), 108.6 (C4' or C7'), 101.1 (C2'), 65.4 (C1). The NMR spectra matched the reported data.$^{20}$

5-(Bromomethyl)benzo[d][1,3]dioxole (piperonyl bromide) (30)$^{21}$

PBr$_3$ (3.0 mL, 0.0319 mol) was carefully added to a stirred solution of 29 (2.00 g, 0.0131 mol) in THF (30 mL) at 0 °C for 30 min, or until TLC showed the disappearance of starting material. The solution was diluted with DCM (100 mL) and washed with
sodium bicarbonate (3 × 20 mL [CAUTION: foaming]), water (3 × 20 mL), dried and evaporated to yield 30 as a light yellow oil (1.30 g, 47%). $^1$H NMR (400 MHz, CDCl₃) δ 6.78–6.81 (m, 3H, 3 × ArH), 5.95 (s, 2H, H2), 4.45 (s, 2H, H1'). The $^1$H NMR spectrum was similar to the reported data.²¹

(Benzo[d][1,3)dioxol-5-ylmethyl)dimethylsulphonium bromide (31)

Dimethyl sulfdide (4.0 mL, 76.1 mmol) was added to a stirred solution of 30 (1.30 g, 6.05 mmol) in DCM (5 mL) and MeOH (3 mL). After 1 h the solvent was evaporated under a stream of nitrogen. The solid residue was triturated with ether (2 × 50 mL) to yield 31 as a white solid (0.703 g, 80%), m.p.: decomposed at 200 °C. $^1$H NMR (400 MHz, DMSO) δ 7.01 (m, 3H, H4'/H6'/H7'), 6.07 (s, 2H, H2'), 4.62 (s, 2H, H1), 2.79 (s, 6H, CH₃ × 2). $^{13}$C NMR (400 MHz, DMSO) δ 148.8 (ArO), 148.3 (ArO), 125.3 (C5'), 121.8 (C6'), 111.0 (C4' or C7'), 109.3 (C4' or C7'), 102.0 (C2'), 46.2 (C1), 23.9 (CH₃ × 2). HRMS (ESI): Observed: 197.0632, C₁₀H₁₃O₂S⁺ requires 197.0636.

**General procedure for the synthesis of epoxides from 31 and aldehydes.** A 50% sodium hydroxide solution (4 mL/mmol aldehyde) was added to a stirred solution/suspension of aldehyde (1 mmol equiv), tetrabutylammonium, hydrogen sulfate (20 mmol equiv) and 31 (1.1 mmol equiv) in DCM (25 mL/mmol aldehyde) and heated at reflux overnight. The organic layer was collected and the aqueous phase was extracted with DCM (3 × 25 mL). The combined organic phase was dried and evaporated and the residue was purified by column chromatography as described below.
(±) trans-2-(3-(Beno[d][1, 3]dioxol-5-yl)(oxiran-2-yl)pyridine (26)

The general procedure was followed with 31 (1.50 g, 5.42 mmol) and 2-pyridinecarboxaldehyde (0.46 mL, 4.92 mmol). Elution with 15:85:1 EtOAc/hexanes and NEt₃ and then 20:80:1 EtOAc/hexanes and NEt₃ gave trans 26a as a light brown oil, (0.939 g, 74%) R<sub>f</sub>: 0.35 (EtOAc/hexanes + NEt₃ (20:80:1). <sup>1</sup>H NMR (400 MHz, CDCl₃) δ trans-diastereomer: 8.58–8.59 (m, 1H, H₆), 7.70 (ddd (app td), J<sub>1</sub> = J<sub>2</sub> = 7.6 Hz, J<sub>3</sub> = 1.6 Hz, 1H, H₄), 7.31 (ddd (app dt), J<sub>1</sub> = 8.0 Hz, J<sub>2</sub> = J<sub>3</sub> = 1.2 Hz, 1H, H₃), 7.24 (ddd J<sub>1</sub> = 7.6 Hz, J<sub>2</sub> = 4.8 Hz, J<sub>3</sub> = 1.2 Hz, 1H, H₅), 6.86 (dd, J<sub>1</sub> = 8.0 Hz, J<sub>2</sub> = 2.0 Hz, 1H, H₄″), 6.78–6.80 (m, 2H, 2 × ArH), 5.96 (s, 2H, H₂″), 4.00 (d, J<sub>1</sub> = 1.6 Hz, 1H, H₂' or H₃″), 3.97 (d, J<sub>1</sub> = 1.6 Hz, 1H, H₂' or H₃″). <sup>13</sup>C NMR (400 MHz, CDCl₃) δ 156.5 (C₂), 149.7 (ArO), 148.2 (ArO), 148.0 (C₆), 137.0 (C₄), 130.7 (C₅″), 123.3 (C₃ or C₅), 120.2 (C₃ or C₅), 120.1 (C₆″), 108.4 (C₄″ or C₇″), 105.8 (C₄″ or C₇″), 101.3 (C₂″), 62.8 (C₂′ or C₃′), 62.0 (C₂′ or C₃′). HRMS (El<sup>+</sup>): Observed: 241.0737, C₁₄H₁₁NO₃ requires 241.0739.

Further elution with 20:80:1 EtOAc/hexanes and NEt₃ gave cis-26b as a light brown oil, (0.134 g, 11%). R<sub>f</sub>: 0.30 (EtOAc/hexanes + NEt₃ (20:80:1). <sup>1</sup>H NMR (400 MHz, CDCl₃) δ 8.45–8.47 (m, 1H, H₆), 7.47–7.52 (m, 1H, H₅), 7.07–7.11 (m, 2H, H₃/H₄), 6.68–6.72 (m, 2H, H₄″ and H₆″ or H₇″), 6.62 (d, J<sub>1</sub> = 8.0 Hz, 1H, H₆″ or H₇″), 5.85–5.86 (m, 2H, H₂″), 4.41 (d, J<sub>1</sub> = 4.4 Hz, 1H, H₂′ or H₃″), 4.37 (d, J<sub>1</sub> = 4.4 Hz, 1H,
H2′ or H3′). 13C NMR (400 MHz, CDCl3) δ: 154.8 (C2), 149.1 (C3a′ or C7a′), 147.4 (C3a′ or C7a′), 147.2 (C6), 136.0 (C4), 127.9 (C5′), 122.7 (C3 or C5), 121.4 (C3 or C5), 120.6 (C6′), 108.0 (C4′ or C7′), 107.5 (C4′ or C7′), 101.1 (C2′), 60.3 (C2′ or C3′), 59.7 (C2′ or C3′). HRMS (EI?): Observed: 241.0749, C14H11NO3 requires 241.0739.

The general procedure was followed with 31 (0.910 g, 3.29 mmol) and 3-pyridinecarboxaldehyde (0.28 mL, 2.94 mmol). Elution with EtOAc/hexanes and triethylamine (20:80:1) gave 25 as an orange oil, (0.604 g, 84%). The diastereomers were unable to be separated. Rf: 0.30 (EtOAc/hexanes + NEt3 20:80:1). Trans-diastereomer: NMR 1H (400 MHz, CDCl3) δ 8.62 (s, 1H, H2), 8.59 (ddd (app dt), J1 = 4.8 Hz, J2 = J3 = 1.6 Hz, 1H, H6), 7.59–7.62 (m, 1H, H4), 7.29–7.32 (m, 1H, H5), 6.79–6.87 (m, 3H, H4′/H6′/H7′), 5.97 (s, 2H, H2′), 3.86 (s, 1H, H2′ or H3′), 3.82 (s, 1H, H2′ or H3′). 13C NMR (400 MHz, CDCl3) δ 149.6 (C2), 148.1 (ArO), 148.0 (ArO), 147.7 (C6), 132.6 (C1), 132.6 (C4), 130.3 (C5′), 123.4 (C5), 119.7 (C6′), 108.3 (C4′ or C7′), 105.4 (C4′ or C7′), 101.2 (C2′), 62.7 (C2′ or C3′), 60.4 (C2′ or C3′). Cis-diastereomer: NMR 1H (400 MHz, CDCl3) δ 8.47 (s, 1H, H2), 8.43 (ddd (app dt), J1 =
4.8 Hz, $J_2 = J_3 = 1.6$ Hz, 1H, H6), 7.43–7.46 (m, 1H, H4), 7.11–7.14 (m, 1H, H5), 6.63–6.66 (m, 3H, H4"/H6"/H7"), 5.85–5.86 (m, 2H, H2"), 4.35 (d, $J_1 = 4.2$ Hz, 1H, H2' or H3'), 4.30 (d, $J_1 = 4.2$ Hz, 1H, H2' or H3'). $^{13}$C NMR (400 MHz, CDCl3) δ 148.9 (C2), 148.5 (C6), 147.4 (ArO), 147.2 (ArO), 134.4 (C4), 130.2 (C1), 127.4 (C5"), 122.7 (C5), 120.3 (C6"), 108.0 (C4" or C7"), 107.0 (C4" or C7"), 101.0 (C2"), 59.4 (C2' or C3'), 57.5 (C2' or C3'). HRMS (EI): Observed: 241.0751, C14H11NO3 requires 241.0739.

(±) 4-((2R,3R)-3-(benzo[d][1,3]dioxol-5-yl)oxiran-2-yl)pyridine (24)

The general procedure was followed with 31 (1.23 g, 4.44 mmol) and 4-pyridinecarboxaldehyde (0.38 mL, 3.99 mmol). Elution with EtOAc/hexanes and triethylamine (30:70:1) gave 24 as a black oil, (0.604 g, 61%). Rf: 0.40 (EtOAc/hexanes + NEt3 70:30:1). Trans-diastereomer: $^1$H NMR (400 MHz, CDCl3) δ 8.41–8.43 (m, 2H, H2/H6), 7.06–7.07 (m, 2H, H3/H5), 6.61–6.69 (m, 3H, H4"/H6"/H7"), 5.78 (s, 2H, H2"), 3.65 (s, 1H, H2' or H3'), 3.61 (s, 1H, H2' or H3'). $^{13}$C NMR (400 MHz, CDCl3) δ 149.6 (C2/C6), 147.8 (C4), 147.7 (ArO), 145.7 (ArO), 129.8 (C5"), 120.0 (C3/C5), 119.5 (C6"), 108.0 (C4" or C7"), 105.1 (C4" or C7"), 101.0 (C2"), 62.6 (C2' or C3' 60.5 (C2' or C3'). Cis-diastereomer: $^1$H NMR (400 MHz, CDCl3) δ 8.25–8.27 (m, 2H, H2/H6), 6.94–6.96 (m, 2H, H3/H5), 6.45–6.60 (m, 3H, H4"/H6"/H7"), 5.65–5.66 (s, 2H, H2"), 4.17 (d, $J_1 = 4.2$ Hz, Hz, 1H, H2' or H3'), 4.08 (d, $J_1 = 4.2$ Hz, Hz, 1H, H2' or H3'). $^{13}$C NMR (400 MHz, CDCl3) δ 148.7 (C2/C6), 147.7 (C4), 146.9 (ArO), 143.2 (ArO), 126.8 (C5"), 119.9 (C3/C5), 119.5 (C6"), 107.6
(C4" or C7"), 106.6 (C4" or C7"), 100.7 (C2"), 62.6 (C2' or C3'), 60.5 (C2' or C3').


The general procedure was followed with 31 (1.25 g, 4.47 mmol) and 2-naphthaldehyde (0.672, 4.28 mmol). Elution with Toluene/hexane and NEt₃ (7.5:92.5:1) gave 27 as a yellow solid, (1.00 g, 80%). Trans-diastereomer: ¹H NMR (400 MHz, CDCl₃) δ 7.75–7.83 (m, 4H, 4 × ArH), 7.41–7.44 (m, 2H, 2 × ArH), 6.33–6.35 (m, 1H, ArH), 6.75–6.85 (m, 3H, H4''/H6''/H7''), 5.89 (s, 2H, H2''), 3.92 (d, J₁ = 1.9 Hz, 1H, H2' or H3'), 3.84 (d, J₁ = 1.9 Hz, 1H, H2' or H3').

Cis-diastereomer: ¹H NMR (400 MHz, CDCl₃) δ 7.87–7.90 (m, 4H, 4 × ArH), 7.65–7.70 (m, 2H, 2 × ArH), 7.50–7.55 (m, 1H, ArH), 6.64–6.72 (m, 3H, H4''/H6''/H7''), 5.67 (s, 2H, H2''), 4.39 (d, J₁ = 4.2 Hz, 1H, H2' or H3'), 4.28 (d, J₁ = 4.2 Hz, 1H, H2' or H3').

**General procedure for the synthesis of ketones from epoxides 24–27 and palladium acetate.** Palladium acetate (~5 mol %) and triphenylphosphine (~15 mol%) were added to a stirred solution of the epoxide (1 equiv.) in tert-butanol (~5 mL per mmol of epoxide) and stirred at reflux overnight. The volatiles were evaporated and the residue was purified by column chromatography as described below.
2-(Benzo[d][1,3]dioxol-5-yl)-1-(pyridin-2-yl)ethanone (38)

The general procedure was followed with 26 (0.320 g, 1.33 mmol). Elution with EtOAc/hexanes (1:10) gave 38 as a yellow solid. (0.107 g, 67%). m.p: 57–61°C. Rf: 0.35 (EtOAc/hexanes 1:10). IR (thin film) cm\(^{-1}\): 1696 cm\(^{-1}\) (C=O). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.69–8.72 (m, 1H, H6'), 8.04 (ddd (app dt), \(J_1= 10.4\) Hz, \(J_2= 3.0\) Hz, \(J_3= 1.4\) Hz, 1H, H3'), 7.81 (t, \(J_1= J_2= 10.0\) Hz, \(J_3= 1.6\) Hz, 1H, H5'), 7.46 (m, \(J_1= J_2= 10.0\) Hz, \(J_3= 1.6\) Hz, 1H, H4'), 6.72–6.83 (m, 3H, H4''/H6''/H7''), 5.91 (s, 2H, H2'), 4.45 (s, 2H, H2). \(^13\)C (400 MHz, CDCl\(_3\)) \(\delta\) 199.3 (C1), 153.2 (C2'), 149.0 (C6'), 147.7 (ArO), 146.5 (ArO), 137.1 (ArH), 128.4 (C5''), 127.3 (ArH), 123.1 (ArH), 122.5 (C6''), 110.5 (C4'' or C7''), 108.4 (C4'' or C7''), 101.0 (C2''), 43.7 (C2). HRMS (EI\(^+\)): Observed: 241.0750, C\(_{14}\)H\(_{11}\)NO\(_3\) requires 241.0739.

2-(Benzo[d][1,3]dioxol-5-yl)-1-(pyridin-3-yl)ethanone (39)

The representative procedure was followed with 25 (0.446 g, 1.85 mmol). Elution using EtOAc/Hexanes (1:4) as eluent, 39 was isolated as a brown solid, (0.243 g, 54%). m.p. 45–47°C. Rf: 0.20 (EtOAc/hexanes 1:5). IR (thin film) cm\(^{-1}\): 1637 (C=O). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 9.16 (d, \(J_1= 10.0\) Hz, 1H, H2'), 8.71 (dd, \(J_1= 4.8\) Hz, \(J_2= 1.6\) Hz, 1H, H6'), 8.20 (ddd (app dt), \(J_1= 8.0\) Hz, \(J_2= J_3= 1.6\) Hz, 1H, H4'), 7.35 (dd, \(J_1=...
8.0 Hz, $J_2 = 5.0$ Hz, 1H, H5'), 6.64–6.72 (m, 3H, H4'/H6''/H7''), 5.87 (s, 2H, H2''), 4.15, (s, 2H, H2). $^{13}$C (400 MHz, CDCl₃) δ 196.5 (C1), 153.5 (C2'), 150.0 (C6'), 148.0 (ArO), 146.8 (ArO), 135.8 (C4'), 131.7 (C3'), 127.0 (C5''), 123.7 (C5'), 122.6 (C6''), 109.8 (C4' or C7''), 108.5 (C4' or C7''), 101.1 (C2''), 45.4 (C2). HRMS (EI⁺): Observed: 241.0750, C₁₄H₁₁NO₃ requires 241.0739.

![Chemical structure](image)

2-(Benzo[d][1,3]dioxol-5-yl)-1-(pyridin-4-yl)ethanone (40)

The representative procedure was followed with 24 (0.503 g, 2.09 mmol). Elution using EtOAc/hexanes (1:1) gave 40 as a light yellow powder, (0.307 g, 61%). m.p: 110–115°C. Rf: 0.25 (EtOAc/hexanes 1:1). IR (thin film) cm⁻¹: 1669 (C=O). $^1$H NMR (400 MHz, CDCl₃) δ 8.76 (s, 2H, H2'/H6'), 7.72 (d, $J_1 = 4.4$ Hz, 2H, H2, H6'), 7.43 (dd, $J_1 = 7.6$ Hz, $J_2 = 1.6$ Hz, 1H, H6''), 6.69 (s, 1H, H4''), 6.65 (d, $J_1 = 8.0$ Hz, 1H, H7''), 5.90 (s, 2H, H2''), 4.15 (s, 2H, H2). HRMS (EI⁺): Observed: 241.0745, C₁₄H₁₁NO₃ requires 241.0739.
1-(Benzo[d][1,3]dioxol-5-yl)-2-(naphthalen-2-yl)ethanone (41)

The representative procedure was followed with 27 (0.898 g, 3.10 mmol). Elution with EtOAc/Hexanes (1:10) and then recrystallization with hexanes gave 41 as a white solid (with none of the desired ketone), (0.418 g, 47%). m.p.: 112–116°C. IR (thin film) cm⁻¹: 1676 cm (C=O). \(^1\)H NMR (400 MHz, CDCl₃) δ 7.76–7.81 (m, 3H, 3 × ArH), 7.70 (br s, 1H, H2'), 7.67 (dd, J₁ = 8.2 Hz, J₂ = 1.8 Hz, 1H, ArH), 7.50 (d, J₁ = 1.8 Hz, 1H, ArH), 7.43–7.46 (m, 2H, 2 × ArH), 7.39 (dd, J₁ = 8.4 Hz, J₂ = 1.8 Hz, 1H, ArH) 6.84 (d, J₁= 8.2 Hz, 1H, ArH), 6.02 (s, 2H, H2''), 4.36 (s, 2H, H1). \(^{13}\)C NMR (400 MHz, CDCl₃) δ 195.9 (C=O), 152.0 (ArO), 148.4 (ArO), 133.7 (ArC), 132.5 (ArC), 131.6 (ArC), 128.5 (ArH), 128.1 (ArH), 127.8 (ArH), 127.8 (ArH), 127.6 (ArH), 126.3 (ArH), 125.9 (ArH), 125.3 (ArH), 108.6 (ArH), 108.1 (ArH), 102.0 (C2''), 45.7 (C1). HRMS (EI⁺): Observed: 290.0956, C₁₉H₁₄O₃ requires 290.0943.

General procedure for the synthesis of ketones from 46 and boronic acids.

[(bpy)Pd(μ-OH)]₂(Otf)₂ (~ 3 mol%) was added to a stirred solution of 46 (1 equiv.) and boronic acid (~1.5 mol equiv) in water (~5 mL for mol equiv.). After stirring at reflux for 48 hours, the aqueous phase was extracted with EtOAc (2 × 50 mL), dried and the volatiles were evaporated. The residue was purified by column chromatography as described below.
2-(Benzo[d][1,3]dioxol-5-yl)-1-(naphthalen-2-yl)ethanone (48)*

The general procedure was followed with 46 (0.125 g, 0.78 mmol) and naphthalene-2-boronic acid (0.200 g, 1.16 mmol). Elution with EtOAc/hexanes (1:20) gave 48 as a white solid, (0.241 g, 72%) m.p: 113−115°C. Rf: 0.30 (5% EtOAc/hexanes). IR (thin film) cm⁻¹: 1682 (C=O). ¹H NMR (400 MHz, CDCl₃) δ 8.54 (s, 1H, H2'), 8.05 (dd, J₁ = 8.4 Hz, J₂ = 2.0 Hz, 1H, ArH), 7.97 (d, J₁ = 7.6 Hz 1H, ArH), 7.88 (dd (app t), J₁ = J₂ = 6.6 Hz, 2H, 2 × ArH), 7.53−7.62 (m, 2H, 2 × ArH), 6.77−6.82 (m, 3H, H4''/H6''/H7''), 5.93 (s, 2H, H2'), 4.33 (s, 2H, H2). HRMS (ESI): Observed: 291.1028, C₁₉H₁₅O₃⁺ requires 291.1021. The NMR data matched those reported.⁵

2-(Benzo[d][1,3]dioxol-5-yl)-1-(4-tert-butylphenyl)ethanone (49)

The general procedure was followed with 46 (0.302 g, 1.87 mmol) and 4-tert-butylphenyl-boronic acid (0.500 g, 2.81 mmol). Elution with EtOAc/hexanes (1:20) gave 49 as an orange solid. (0.443 g, 80%). m.p: 61−66°C. Rf: 0.35 (5% EtOAc/hexanes). IR (thin film) cm⁻¹: 1605 cm⁻¹ (C=O). ¹H NMR (400 MHz, CDCl₃) δ 7.94−7.97 (m, 2H, H2'/H6''), 7.46−7.49 (m, 2H, H3'/H5''), 6.71−6.77 (m, 3H,

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⁵ This compound has been synthesized previously by an alternative route.
H4''/H6''/H7''), 5.92 (s, 2H, H2'), 4.17 (s, 2H, H2), 1.34 (s, 9H, CH3). 13C NMR (400 MHz, CDCl3) δ 191.8 (C=O), 156.9 (C4'), 147.8 (ArO), 146.5 (ArO), 133.9 (C1'), 128.6 (C2'/C6'), 128.3 (C5''), 125.6 (C3'/C5'), 122.5 (C6''), 109.9 (C4'' or C7''), 108.4 (C4'' or C7''), 101.0 (C2''), 45.0 (C2), 35.1 (t-butyl), 31.0 (CH3 × 3). HRMS (EI+): Observed: 296.1412, C19H20O3 requires 296.1412.

![Chemical structure](image)

2-(Benzo[d][1,3]dioxol-5-yl)-1-(4-bromophenyl)ethanone (50)

The general procedure was followed with 46 (0.107 g, 0.664 mmol) and 4-bromophenyl-boronic acid (0.200 g, 0.996 mmol). Elution with EtOAc/hexanes (1:10) gave 50 as a white solid. (0.123 g, 58%). m.p: 68–72°C. Rf: 0.30 (10% EtOAc/hexanes). IR: (thin film) cm⁻¹: 1693 (C=O). 1H NMR (400 MHz, CDCl3) δ 7.83–7.86 (m, 2H, H3'/H5'), 7.58–7.60 (m, 2H, H2'/H6'), 6.75 (d, J1 = 8.0 Hz, 1H, H6'' or H7''), 6.72 (s, 1H, H4''), 6.68 (dd, J1 = 8.0 Hz, J2 = 1.2 Hz, 1H, H6'' or H7''), 5.92 (s, 2H, H2''), 4.14 (s, 2H, H2). 13C NMR (400 MHz, CDCl3) δ 196.7 (C=O), 148.1 (ArO), 146.8 (ArO), 135.3 (C1'), 132.1 (C3'/C5'), 130.2 (C2'/C6'), 128.5 (C4' or C5''), 127.7 (C4' or C5''), 122.6 (C6''), 109.9 (C4'' or C7''), 108.6 (C4'' or C7''), 101.2 (C2''), 45.2 (C2). HRMS (ESI): Observed: 317.9893, C15H11O3Br requires 317.9892.
2-(Benzo[d][1,3]dioxol-5-yl)-1-(4-iodophenyl)ethanone (51)

The general procedure was followed with 46 (0.173 g, 1.06 mmol) and 4-iodophenylboronic acid (0.400 g, 1.61 mmol). Elution with EtOAc/hexanes (1:10) gave 51 as a white solid (0.156 g, 40%). m.p: 98–100°C. R_f: 0.35 (10% EtOAc/hexanes). IR (thin film) cm⁻¹: 1683 (C=O). ¹H NMR (400 MHz, CDCl₃) δ 7.95–7.97 (m, 2H, H₃'/H₅'), 7.45–7.47 (m, 2H, H₂'/H₆'), 6.72–6.78 (m, 3H, H₄''/H₆''/H₇''), 5.86 (s, 2H, C₂''), 4.16 (s, 2H, C₂). ¹³C NMR (400 MHz, CDCl₃) δ 197.1 (C=O), 148.1 (ArO), 146.8 (ArO), 138.1 (C₃'/C₅'), 135.8 (C₁'), 130.1 (C₂'/C₆'), 127.7 (C₅''), 122.6 (ArH), 109.9 (ArH), 108.7 (ArH), 101.3 (C₄'), 101.2 (C₂''), 45.2 (C₂). HRMS (ESI): Observed: 365.9742, C₁₅H₁₁O₃I requires 365.9753.

1,2-Bis(benzo[d][1,3]dioxol-5-yl)ethanone (52)*

The general procedure was followed with 46 (0.239 g, 1.49 mmol) and benzo[d][1,3]dioxol-5-ylboronic acid (0.400 g, 2.41 mmol). Elution with EtOAc/hexanes (1:10) gave 52 as a light yellow solid (0.243 g, 56%). m.p: 100–104°C. R_f: 0.40 (10% EtOAc/hexanes). IR (thin film) cm⁻¹: 1672 (C=O). ¹H NMR (400 MHz,

* This compound has been synthesized previously by an alternative route.
CDCl$_3$ $\delta$ 7.59 (dd, $J_1= 8.0$ Hz, $J_2= 1.6$ Hz, 1H, ArH), 7.44 (d, $J_1 = 1.6$ Hz, 1H, H4' or H4''), 6.82 (d, $J_1 = 8.0$ Hz, 1H, ArH), 6.60–6.75 (m, $J_1$= 8.0 Hz, 3H, 3 × ArH), 6.01 (s, 2H, H2' or H2''), 5.91 (s, 2H, H2' or H2''), 4.09 (s, 2H, H2). $^{13}$C NMR (400 MHz, CDCl$_3$) $\delta$ 195.9 (C=O), 151.9 (ArO), 148.3 (ArO), 147.9 (ArO), 146.6 (ArO), 131.4 (C5' or C5''), 128.4 (C5' or C5''), 125.0 (ArH), 122.5 (ArH), 109.9 (ArH), 108.5 (ArH), 108.4 (ArH), 108.0 (ArH), 102.0 (C2' or C2''), 101.1 (C2' or C2''), 45.0 (C2). HRMS (ESI): Observed: 285.0753, C$_{16}$H$_{13}$O$_5^+$ requires 285.0763. The NMR data matched those reported.$^{36}$

2-(Benzo[d][1,3]dioxol-5-yl)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)ethanone (53)

The general procedure was followed with 46 (0.215 g, 1.33 mmol) and 1, 4-Benzodioxane-6-boronic acid (0.400 g, 2.23 mmol). Elution with EtOAc/Hexanes (1:4) gave 53 as a white solid, (0.127 g, 32%). m.p: 160–165°C. $R_f$: 0.35 (25% EtOAc/hexanes). IR (thin film) cm$^{-1}$: 1607 (C=O). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.52–7.55 (m, 2H, 2 × ArH), 6.90 (d, $J_1= 9.2$ Hz, 1H, ArH), 6.68–6.76 (m, 3H, H4''/H6''/H7''), 5.92 (s, 2H, H2''), 4.25–4.32 (m, $J_1= 7.2$ Hz, $J_2 = 2.0$ Hz, 4H, H2'/H3'), 4.10 (s, 2H, H2). $^{13}$C NMR (400 MHz, CDCl$_3$) $\delta$ 196.3 (C=O), 148.2 (ArO), 148.0 (ArO), 146.6 (ArO), 143.5 (ArO), 130.5 (C6'), 128.5 (ArH), 122.9 (ArH), 122.6 (ArH), 118.3 (ArH), 117.4 (ArH), 109.8 (ArH), 108.6 (ArH), 101.1 (C2''), 64.8 (C2' or C3''), 64.2 (C2' or C3'), 45.0 (C2). HRMS (ESI): Observed: 299.0905, C$_{17}$H$_{15}$O$_5^+$ requires 299.0915.
1-(Naphthalen-2-yl)-2-phenylethanone (54)

The general procedure was followed with 46 (0.182 g, 1.56 mmol) and naphthalene-2-boronic acid (0.400 g, 2.33 mmol). Elution with EtOAc/hexanes (1:20) gave 54 as a white solid, (0.218 g, 58%). m.p: 92–96°C. Rf: 0.40 (5% EtOAc/hexanes). IR (thin film) cm⁻¹: 1682 (C=O). ¹H NMR (400 MHz, CDCl₃) δ 8.47 (s, 1H, H2''), 8.06 (dd, J₁= 8.5 Hz, J₂= 1.8 Hz, 1H, ArH), 7.95 (d, J₁= 8.2 Hz, 1H, ArH), 7.78–7.82 (m, 2H, 2 × ArH), 7.45–7.54 (m, 2H, 2 × ArH), 7.17–7.29 (m, 5H, 5 × ArH), 4.45 (s, 2H, H2). ¹³C NMR (400 MHz, CDCl₃) δ 197.7 (C=O), 135.7 (ArC), 134.8 (ArC), 134.1 (ArC), 132.6 (ArC), 130.5 (ArH), 129.7 (ArH), 129.6 (2 × ArH), 128.8 (2 × ArH), 128.7 (ArH), 128.6 (ArH), 127.9 (ArH), 127.0 (ArH), 126.9 (ArH), 124.4 (ArH), 45.7 (C2). HRMS (EI⁺): Observed: 246.08, C₁₈H₄O requires 246.10. The NMR data matched those reported.²⁸

2-(Benzod][1,3]dioxol-5-yl)-1-(naphthalen-1-yl)ethanone (56)*

The general procedure was followed with 46 (0.125 g, 0.778 mmol) and naphthalene-1-boronic acid (0.200 g, 1.16 mmol). Elution with EtOAc/hexanes (1:20) gave 56 as a

* This compound has been synthesized previously by an alternative route.
light yellow solid, (0.162 g, 72%). m.p: 113–115°C. Rf: 0.30 (5% EtOAc/hexanes). IR (thin film) cm\(^{-1}\): 1682 (C=O). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.53 (d, \(J_1 = 1.2\) Hz, 1H, ArH), 8.05 (dd, \(J_1 = 11.6\) Hz, \(J_2 = 2.4\) Hz, 1H, ArH), 7.96 (d, \(J_1 = 10.4\) Hz, 1H, ArH), 7.85–7.90 (m, 2H, 2 × ArH), 7.53–7.63 (m, 2H, 2 × ArH), 6.81 (s, 1H, H4\("\)), 6.77–6.88 (m (app s), 2H, H6\("\)/H7\("\)), 5.92 (s, 2H, H2\("\)), 4.32 (s, 2H, H2). \(^{13}\)C NMR (400 MHz, CDCl\(_3\)) \(\delta\) 201.6 (C=O), 147.9 (ArO), 146.6 (ArO), 135.5 (C1'), 134.0 (C1a' or C5a'), 132.8 (ArH), 130.5 (C1a' or C5a') 128.4 (ArH), 128.1 (C5\("\)), 127.9 (ArH), 127.8 (ArH), 126.5 (ArH), 125.8 (ArH), 124.3 (ArH), 122.6 (C6\("\)), 109.9 (C4\("\) or C7\("\)), 108.4 (C4\("\) or C7\("\)), 101.0 (C2\("\)), 48.5 (C2). HRMS (ESI): Observed: 291.1028, C\(_{19}\)H\(_{15}\)O\(_3\)\(^+\) requires 291.1021. The NMR data matched those reported.\(^5\)

**General procedure for the synthesis of amines from ketones and sodium cyanoborohydride.** Glacial acetic acid (10 mmol %) was added to a stirred solution of ketone (1 mmol), 33% ethanolic methylamine (30 mmol %), and powdered 3A molecular sieves (10 wt %) in dry THF (5 mL per mmol) at 0°C. After stirring for 10 min, sodium cyanoborohydride (1 mmol %) was added and the solution was stirred at 50 °C for 24 hours. It was then quenched with 1M HCl and vacuum filtered through celite. A NaOH solution (40 mL) was added and the solution was extracted with EtOAc (3 × 50 mL), washed with water (2 × 50 mL), dried, evaporated to give a residue, which was purified by flash chromatography as described below. The free bases were converted to the hydrochloric salts using a hydrochloric acid/MeOH mixture.
2-(Benzo[d][1,3]dioxol-5-yl)-N-methyl-1-(naphthalene-2-yl)ethanamine (4)*

The general procedure was followed with 48 (0.10 g, 0.344 mmol). Elution with EtOAc/hexanes (3:17) gave 4 as a brown oil, (0.0536 g, 51%). Rf: 0.30 (20% EtOAc/hexanes). 1H NMR (400 MHz, CDCl3) δ 7.77–7.87 (m, 3H, 3 × ArH), 7.60 (s, 1H, H2'), 7.45–7.55 (m, 3H, 3 × ArH), 6.70–6.74 (m, 3H, 3 × ArH), 5.91 (s, 2H, H2''), 3.79 (dd, J1 = 8.4 Hz, J2 = 5.6 Hz, 1H, H1), 2.98–3.11 (m, 2H, H2), 2.25 (s, 3H, CH3).

The NMR data matched those reported.5

1-(Benzo[d][1,3]dioxol-5-yl)-N-methyl-2-(naphthalen-2-yl)ethanamine (67)

The general procedure was followed with 55 (0.104 g, 0.358 mmol). Elution with EtOAc/hexanes and AcOH (20:80:1), then 20% EtOAc/hexanes (1:5) and finally 20% EtOAc/hexanes and triethylamine (20:80:1) gave 67 as a white solid, (0.0700 g, 64%). m.p. (salt): 158–160°C. IR (thin film) cm⁻¹: 3336 (NH). 1H NMR (400 MHz, CDCl3) δ 7.76–7.78 (m, 3H, ArH), 7.63 (s, 1H, H2'), 7.42–7.49 (m, 2H, ArH), 7.30 (dd, J1 = 8.4 Hz, J2 = 1.6 Hz, 1H, ArH), 6.95 (s, 1H, H4''), 6.74–6.78 (m, 2H, 2 × ArH), 5.96 (m, 2H, 2 × ArH), 3.66 (s, 3H, CH3).

* This compound has been synthesized previously by an alternative route.
H2")

Salt: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 10.31 (br s, 2H, NH), 7.72–7.79 (m, 2H, 2 × ArH), 7.59 (s, 1H, ArH), 7.40–7.45 (m, 2H, 2 × ArH), 7.22 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.0$ Hz, 1H, ArH), 6.96 (d, $J_1 = 2.0$ Hz), 6.77–6.83 (m, 2H, 2 × ArH), 5.97 (dd, $J_1 = 7.8$ Hz, $J_2 = 1.0$ Hz, ArH), 4.59 (br s, 2H, NH), 4.76 (d, $J_1 = 10.2$ Hz, 1H, H1a), 3.36 (dd, $J_1 = 13.4$ Hz, $J_2 = 10.0$ Hz, 1H, H1b), 2.57 (s, 3H, CH$_3$).

$^{13}$C NMR (400 MHz, CDCl$_3$) $\delta$ 148.0 (ArO), 146.7 (ArO), 137.6 (C1' or C5''), 136.5 (C2α' or C6α''), 133.6 (C2α' or C6α'), 132.4 (C1' or C5''), 128.2 (ArH), 127.9 (ArH), 127.7 (ArH), 127.6 (ArH), 126.1 (ArH), 125.6 (ArH), 120.8 (ArH), 108.1 (ArH), 107.4 (ArH), 101.0 (C2''), 66.6 (C2), 45.6 (C1), 34.7 (CH$_3$).

HRMS (El$^+$): Observed: 306.1501, C$_{20}$H$_{20}$NO$_2$ requires 306.1494.

2-(Benzo[d][1,3]dioxol-5-yl)-N-methyl-1-(pyridin-2-yl)ethanamine (8)

The general procedure was followed with 39 (1.19 g, 4.56 mmol). Elution with EtOAc/hexanes and AcOH (20:80:1), then EtOAc/hexanes (1:5) to removal any residual acetic acid, and finally with EtOAc/hexanes and NEt$_3$ (50:50:1) gave 8 as a brown solid, (0.731 g, 62%). m.p (salt): 115–122°C. R$_f$: 0.40 (80% EtOAc/hexanes + NEt$_3$). IR (thin film) cm$^{-1}$: 3341 (NH). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.67 (d, $J_1 = 4.8$, 1H, H6'), 7.68 (dd (app t), $J_1 = 7.6$, 1H, H4'), 7.22–7.25 (m, 2H, H3'/H5'), 6.76 (d, $J_1 = 8.0$, 1H, H6''), 6.68 (s, 1H, H4''), 6.61 (d, $J_1 = 8.0$ Hz, 1H, H7''), 5.97 (s, 2H, H2'), 3.90 (dd (app t), $J_1 = 6.8$, 1H, H1), 3.06 (dd, $J_1 = 13.2$ Hz, $J_2 = 6.6$ Hz, 2H, H2a), 2.96 (dd, $J_1 = 13.2$ Hz, $J_2 = 8.0$ Hz, 1H, H2b), 2.22 (s, 3H, CH$_3$). Salt: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.79
(br s, 1H, NH), 9.27 (br s, 1H, NH), 8.71 (br d, \( J_1 = 4.8 \) Hz, 1H, H6'), 7.78 (ddd (app td), \( J_1 = 7.4 \) Hz, \( J_2 = 1.8 \) Hz, 1H, H4'), 7.42 (ddd, \( J_1 = 9.0 \) Hz, \( J_2 = 3.7 \) Hz, \( J_3 = 1.2 \) Hz, 1H, H5'), 7.12 (d, \( J_1 = 7.8 \) Hz, 1H, H3'), 6.70 (d, \( J_1 = 8.0 \), H6'' or H7''), 6.59 (d, \( J_1 = 1.6 \) Hz, 1H, H4''), 6.38 (dd, \( J_1 = 8.0 \) Hz, \( J_2 = 1.6 \) Hz, 1H, H6'' or H7''), 5.93 (dd, \( J_1 = 9.0 \) Hz, \( J_2 = 3.7 \) Hz, \( J_3 = 1.2 \) Hz, 1H, H5''), 7.42 (ddd, \( J_1 = 9.0 \) Hz, \( J_2 = 3.7 \) Hz, \( J_3 = 1.2 \) Hz, 1H, H2''), 4.56 (dd, \( J_1 = 10.2 \) Hz, \( J_2 = 4.6 \) Hz, 1H, H1), 3.30−3.41 (m, 1H, H2a), 3.09 (dd, \( J_1 = 13.2 \) Hz, \( J_2 = 9.6 \) Hz, 1H, H2b), 2.61 (s, 3H, CH3). 13C NMR (400 MHz, CDCl3) \( \delta \): 162.4 (C2'), 149.4 (C6'), 147.7 (ArO), 146.0 (ArO), 136.2 (C4'), 132.3 (C5''), 122.4 (C3'), 122.2 (C5' or C6''), 122.1 (C5' or C6''), 109.4 (C4' or C7''), 108.1 (C4' or C7''), 100.7 (C2''), 67.7 (C1), 43.0 (C2), 34.5 (CH3).


2-(Benzo[d][1,3]dioxol-5-yl)-N-methyl-1-(pyridine-3-yl)ethanamine (9)

The general procedure was followed with 40 (0.735 g, 3.05 mmol). Elution with EtOAc/hexanes and AcOH (50:50:1), then EtOAc/hexanes (1:1) to removal any residual acetic acid, and finally with EtOAc and NEt3 (100:1) gave 9 as a brown solid, (0.481 g, 62%). m.p (salt): 237−240°C. Rf: 0.20 (EtOAc). IR (thin film) cm⁻¹: 3307 (NH). 1H NMR (400 MHz, CDCl3) \( \delta \): 8.41−8.43 (m, 2H, H2'/H6'), 7.57 (ddd (app dt), \( J_1 = 6.5 \) Hz, \( J_2 = 3.2 \) Hz, \( J_3 = 1.6 \) Hz, 1H, H4'), 7.18 (m, \( J_1 = 6.4 \) Hz, \( J_2 = 4.0 \) Hz, 1H, H5'), 6.63 (d, \( J_1 = 6.5 \) Hz 1H, H7''), 6.55 (d, \( J_1 = 1.4 \) Hz, 1H, H4''), 6.48 (d, \( J_1 = 6.5 \) Hz, \( J_2 = 1.4 \) Hz, 1H, H6''), 5.87 (s, 2H, H2'), 3.64 (dd, \( J_1 = 11.0 \) Hz, \( J_2 = 5.8 \) Hz, 1H, H1), 2.75 (d, \( J_1 = 6.0 \) Hz, 2H, H2), 2.17 (s, 3H, CH3). 13C NMR (400 MHz, CDCl3) \( \delta \): 149.4 (C2' or C6'), 148.7 (C2' or C6'), 147.78 (ArO), 146.32 (ArO), 138.60 (C3'), 134.80 (C4'), 131.66
(C5"), 123.53 (C5"), 122.3 (C6"), 109.4 (C4" or C7"), 108.3 (C4" or C7"), 100.9 (C2"), 64.6 (C1), 44.6 (C2), 34.6 (Methyl). HRMS (ESI): Observed: 257.1295, C_{15}H_{17}N_{2}O_{2}^+ requires 257.1290.

\[ \text{HRMS (ESI): Observed: 257.1295, } \]
\[ C_{15}H_{17}N_{2}O_{2}^+ \text{ requires 257.1290.} \]

2-(Benzo[d][1,3]dioxol-5-yl)-N-methyl-1-(pyridin-4-yl)ethanamine (10)

The general procedure was followed with 41 (0.565 g, 2.34 mmol). Elution with EtOAc/hexanes and AcOH (25:75:1), then EtOAc/hexanes (1:4) to removal any residual acetic acid, and finally with EtOAc/hexanes and NEt$_3$ (50:50:1) gave 10 as a yellow solid, (0.106 g, 25%). m.p (salt): 257–261°C. R$_f$: 0.25 (50% EtOAc/hexanes + NEt$_3$). IR (thin film) cm$^{-1}$: 3308 (NH). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.49 (d, J = 1.6 Hz, 2H, H2'/H6'), 7.18 (d, J = 1.6 Hz, 2H, H3'/H5'), 6.67 (dd, $J_1 = 8.0$ Hz, J = 2.8 Hz, 1H, H6" or H7''), 6.58 (s, 1H, H4''), 6.51 (d, $J_1 = 8.0$ Hz, 1H, H6" or H7''), 5.88 (s, 2H, H2''), 3.60–3.65 (m, 1H, H1), 2.72–2.77 (m, 2H, H2), 2.18 (s, 3H, CH$_3$). $^{13}$C NMR (400 MHz, CDCl$_3$) $\delta$ 152.6 (C4'), 149.9 (C2'/C6'), 147.8 (ArO), 146.4 (ArO), 131.5 (C5''), 122.6 (C3'/C5'), 122.3 (C6''), 109.4 (C4" or C7''), 108.3 (C4" or C7''), 101.0 (C2"), 66.2 (C1), 44.3 (C2), 34.7 (CH$_3$). HRMS (ESI): Observed: 257.1272, C$_{15}$H$_{17}$N$_2$O$_2$$^+$ requires 257.1290.

\[ \text{2-(Benzo[d][1,3]dioxol-5-yl)-N-methyl-1-(pyridin-4-yl)ethanamine (10)} \]
2-(Benzo[d][1,3]dioxol-5-yl)-1-(4-iodophenyl)-N-methylethanamine (68)

The general procedure was followed with 51 (0.156 g, 0.426 mmol). Elution with EtOAc/hexanes and AcOH (40:60:1), then EtOAc/hexanes (2:3) to removal any residual acetic acid, and finally with EtOAc/hexanes and NEt$_3$ (70:30:1) gave 68 as a clear oil/white solid (salt), (0.0403 g, 26%). m.p (salt): 200–204°C. R$_f$: 0.10 (70% EtOAc/hexanes). IR (thin film) cm$^{-1}$: 3231 (NH). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.62–7.65 (m, 2H, H3'/H5'), 7.03–7.06 (m, 2H, H2'/H6'), 6.71 (d, $J_1$= 8.0 Hz, 1H, ArH), 6.62 (d, $J_1$ = 1.6 Hz, 1H, H4''), 6.56 (dd, $J_1$= 8.0 Hz, $J_2$= 1.6 Hz, 1H, ArH), 5.92 (s, 2H, H2''), 3.61 (dd, $J_1$= 8.4 Hz, $J_2$ = 5.6 Hz, 1H, H1), 2.78 (m, $J_1$= 13.6, $J_2$ = 6.0 Hz, 2H, H2), 2.18 (s, 3H, CH$_3$). Salt: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 10.18 (br s, 2h, NH), 7.70 (d, $J_1$ = 8.4 Hz, 2H, H3'/H5'), 7.19 (d, $J_1$ = 8.8 Hz, 2H, H2'/H6'), 6.59 (d, $J_1$ = 8.0 Hz, 1H, H6'' or H7''), 6.45 (d, $J_1$ = 1.6 Hz, 1H, H4''), 6.38 (dd, $J_1$ = 8.0 Hz, $J_2$ = 1.6 Hz, 1H, H6'' or H7''), 5.88 (s, 2H, H2''), 4.03 (dd, $J_1$ = 10.6 Hz, $J_2$ = 4.2 Hz, 1H, H1), 3.74 (dd, $J_1$ = 13.0 Hz, $J_2$ = 4.2 Hz, 1H, H2a), 3.26 (dd, $J_1$ = $J_2$ = 13.2 Hz, 1H, H2a), 2.48 (s, 3H, CH$_3$). $^{13}$C NMR (400 MHz, CDCl$_3$) $\delta$ 147.8 (ArO), 146.3 (ArO), 143.2 (C1'), 137.6 (C3'/C5'), 132.2 (C5''), 129.5 (C2'/C6'), 122.4 (ArH), 109.5 (ArH), 108.4 (ArH), 101.0 (C2''), 92.4 (C4'), 66.6 (C1), 44.8 (C2), 34.8 (CH$_3$). HRMS (ESI): Observed: 382.0294, C$_{16}$H$_{17}$NO$_2$I$^+$ requires 382.0304.
2-(Benzo[d][1,3]dioxol-5-yl)-1-(4-tert-butylphenyl)-N-methylethanamine (69)

The general procedure was followed with 49 (0.349 g, 1.18 mmol). Elution with EtOAc/hexanes and AcOH (20:80:1), then EtOAc/hexanes (1:5) to removal any residual acetic acid, and finally with EtOAc/hexanes and NEt₃ (50:50:1) gave 69 as a brown solid, (0.222 g, 60%). m.p (salt): 258–261°C. IR (thin film) cm⁻¹: 3337 (NH). ¹H NMR (400 MHz, CDCl₃) δ 7.34 (d, J₁ = 7.2 Hz, 2H, H₃'/H₅'), 7.25 (d, J₁ = 7.2, 2H, H₂'/H₆'), 6.72 (d, J₁ = 7.6, 1H, H₆" or H₇"), 6.67 (s, 1H, H₄"), 6.62 (d, J₁ = 8.0, 1H, H₆" or H₇"), 5.92 (s, 2H, H₂"), 3.65 (dd, J₁ = 8.6 Hz, J₂ = 4.8 Hz, 1H, H₁), 2.86 (dd, J₁ = 13.6 Hz, J₂ = 5.0 Hz, 2H, H₂a), 2.77 (dd, J₁ = 13.6 Hz, J₂ = 8.8 Hz, 2.20 (s, 3H, CH₃), 1.30 (s, 9H, t-butyl). Salt: ¹H NMR (400 MHz, CDCl₃) δ 10.05 (br s, 2H, NH), 7.36 (s, 4H, H₂'/H₃'/H₅'/H₆''), 6.56 (d, J₁ = 8.0 Hz, 1H, H₆" or H₇"), 6.41–6.45 (m, 2H, H₄" and H₆" or H₇"), 5.83 (s, 2H, H₂"), 4.06 (dd, J₁ = 10.8, J₂ = 4.0 Hz, 1H, H₁), 3.75 (dd, J₁ = 13.2 Hz, J₂ = 4.2 Hz, 1H, H₂a), 3.31 (dd, J₁ = 13.1 Hz, J₂ = 10.9 Hz, 1H, H₂b), 2.46 (s, 3H, CH₃), 1.27 (s, 9H, t-butyl). ¹³C NMR (400 MHz, CDCl₃) δ 150.0 (C₄'), 147.8 (ArO), 146.2 (ArO), 140.4 (C₁'), 133.0 (C₅''), 127.0 (2 × ArH), 125.4 (2 × ArH), 122.4 (C₆''), 109.6 (C₄" or C₇''), 108.3 (C₄" or C₇''), 101.0 (C₂"), 66.3 (C₁), 44.9 (C₂), 34.8 (CH₃), 34.6 (t-butyl C), 31.5 (t-butyl). HRMS (ESI): Observed: 312.1961, C₂₀H₂₆NO₄⁺ requires 312.1964.
2-(Benzo[d][1,3]dioxol-5-yl)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-N-methylethanamine (70)

The general procedure was followed with 53 (0.0548 g, 0.187 mmol). Elution with EtOAc/hexanes and AcOH (20:80:1), then EtOAc/hexanes (1:5) to removal any residual acetic acid, and finally with EtOAc/hexanes and NEt₃ (50:50:1) gave 70 as a yellow solid, (0.0414 g, 72%). m.p (salt): 252–254°C. IR (thin film) cm⁻¹: 3339 (NH). ¹H NMR (400 MHz, CDCl₃) δ 6.79–6.82 (m, 2 × ArH), 6.80 (s, 1H, H4'' or H5'), 6.75 (dd, J₁= 8.4 Hz, J₂ = 1.2 Hz, 1H, ArH), 6.70 (d, J₁ = 7.6 Hz, 1H, ArH), 6.64 (s, 1H, H4'' or H5'), 6.59 (d, J₁ = 8.0 Hz, 1H, ArH), 5.92 (s, 2H, H2'''), 4.25 (s, 4H, H2'/H3'), 3.55 (dd, J₁ = 8.2 Hz, J₂ = 5.8 Hz, 1H, H1), 2.82 (dd, J₁ = 13.6 Hz, J₂ = 5.6 Hz, 1H, H2a), 2.73 (dd, J₁ = 13.6 Hz, J₂ = 8.4 Hz, 2.20 (s, 3H, CH₃). Salt: ¹H NMR (400 MHz, CDCl₃) δ 10.02 (br s, 2H, NH), 6.98 (dd, J₁ = 8.4 Hz, J₂ = 2.2 Hz, 1H, H6'' or H7''), 6.90 (d, J₁ = 2.0 Hz, 1H, H4''), 6.86 (d, J₁ = 8.4 Hz, 1H, H6'' or H7''), 6.60 (d, J₁ = 8.4 Hz, 1H, H7' or H8'), 6.45–6.47 (m, 2H, H5' and H7' or H8'), 5.86 (s, 2H, H2'''), 4.17–4.25 (m, 4H, H2'/H3''), 3.92 (dd, J₁ = 10.0 Hz, J₂ = 3.8 Hz, 1H, H1), 3.67 (d, J₁ = 13.4 Hz, J₂ = 3.6 Hz, 1H, H2a), 3.28 ( unresolved dd, 1H, H2b), 2.45 (s, 3H, CH₃). ¹³C NMR (400 MHz, CDCl₃) δ 147.6 (ArO), 146.2 (ArO), 143.6 (ArO), 142.7 (ArO), 136.7 (C6' or C5''), 132.4 (ArH), 122.4 (ArH), 120.4 (ArH), 117.2 (ArH), 116.1 (ArH), 109.6 (ArH), 108.3 (ArH), 101.0 (C2'''), 66.5 (C1), 64.5 (C2' or C3'), 64.5 (C2' or C3'), 44.8 (C2), 34.6 (CH₃). HRMS (ESI): Observed: 314.1389, C₁₈H₂₀NO₄⁺ requires 314.1392.
The general procedure was followed with 52 (0.508 g, 1.79 mmol). Elution with EtOAc/hexanes and AcOH (40:60:1), then EtOAc/hexanes (2:3) to removal any residual acetic acid, and finally with EtOAc/hexanes and NEt₃ (70:30:1) gave 71 as a white solid, (0.188 g, 35%). m.p (salt): 190–195°C. IR (thin film) cm⁻¹: 3338 (NH). ¹H NMR (400 MHz, CDCl₃) δ 6.84 (s, 1H, H₄' or H₄''), 6.69–6.74 (m, 3H, 3 × ArH), 6.63 (s, 1H, H₄' or H₄''), 6.57 (d, 1H, J₁= 8.0 Hz, ArH), 5.92 (d, J₁ = 1.2 Hz, 2H, H₂' or H₂''), 5.90 (d, J₁ = 1.2 Hz, 2H, H₂' or H₂''), 3.57 (dd, J₁ = 6.0 Hz, 1H, H₁), 2.70–2.83 (m, 2H, H₂), 2.19 (s, 3H, CH₃). Salt: ¹H NMR (400 MHz, CDCl₃) δ 7.03 (s, 1H, H₄' or H₄''), 6.82 (d, J₁ = 7.8 Hz, 1H, ArH), 6.75 (d, J₁ = 8.0 Hz, 1H, ArH), 6.61 (d, J₁ = 8.0 Hz, 1H, ArH), 6.45–6.47 (m, H₄' or H₄'' and ArH), 5.60 (dd, J₁ = 13.2 Hz, J₂ = 1.2 Hz, 2H, H₂' or H₂''), 5.87 (s, 2H, H₂' or H₂''), 3.95 (dd, J₁ = 11.0 Hz, J₂ = 4.4 Hz, 1H, H₁), 3.67 (unresolved dd, 1H, H₂a), 3.26 (dd (app t), J₁ = J₂ = 12.0 Hz, 1H, H₂b), 2.47 (s, 3H, CH₃), 1.21 (br s, 2H, NH). ¹³C NMR (400 MHz, CDCl₃) δ 147.9 (ArO), 147.7 (ArO), 146.6 (ArO), 146.1 (ArO), 137.6 (C₅' or C₅''), 132.7 (C₅' or C₅''), 122.3 (ArH), 120.7 (ArH), 109.5 (ArH), 108.2 (ArH), 108.0 (ArH), 107.3 (ArH), 100.9 (C₂' or C₂''), 100.9 (C₂' or C₂''), 66.8 (C₁), 45.0 (C₂), 34.6 (Methyl). HRMS (ESI): Observed: 300.1233, C₁₇H₁₈NO₄⁺ requires 300.1236. The NMR data matched those reported.³⁷

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* This compound has been synthesized previously by an alternative route.
2-(Benza[d][1,3]dioxol-5-yl)-1-(4-bromophenyl)-N-methylethanamine (72)

The general procedure was followed with 50 (0.164 g, 0.511 mmol). Elution with EtOAc/hexanes and AcOH (40:60:1), then EtOAc/hexanes (2:3) to removal any residual acetic acid, and finally with EtOAc/hexanes and NEt₃ (70:30:1) gave 72 as a yellow solid, (0.128 g, 75%). m.p (salt): 210−213°C. Rᵢ: 0.10 (70% EtOAc/hexanes + NEt₃).

IR (thin film) cm⁻¹: 3338 (NH).

¹H NMR (400 MHz, CDCl₃) δ 7.41−7.44 (m, 2H, H₃'/H₅'), 7.15−7.17 (m, 2H, H₂'/H₆'), 6.69 (d, J₁= 8.0 Hz, 1H, H₆''), 6.61 (d, J₁ = 1.6 Hz, 1H, H₄''), 6.54 (dd, J₁= 7.6 Hz, J₂ = 2.0 Hz, 1H, H₇''), 5.91 (s, 2H, H₂''), 3.62 (dd, J₁ = 8.2 Hz, J₂ = 5.8 Hz, 1H, H₁), 2.78 (dd, J₁= 13.6 Hz, J₂ = 5.6 Hz, 1H, H₂a), 2.74 (dd, J₁ = 13.6 Hz, J₂ = 8.4 Hz, 1H, H₂b), 2.18 (s, 3H, CH₃).

Salt: ¹H NMR (400 MHz, CDCl₃) δ 10.21 (br s, 2H, NH), 7.50 (d, J₁ = 8.4 Hz, 2H, H₃'/H₅'), 7.33 (d, J₁ = 8.4 Hz, 2H, H₂'/H₆'), 6.58 (d, J₁ = 8.0 Hz, 1H, H₆'' or H₇''), 6.44 (d, J₁ = 1.6 Hz, 1H, H₄''), 6.38 (dd, J₁ = 8.0 Hz, J₂ = 1.6 Hz, 1H, H₆'' or H₇''), 5.87 (s, 2H, H₂''), 4.06 (dd, J₁ = 11.2 Hz, J₂ = 4.0 Hz, 1H, H₁), 3.76 (dd, J₁ = 13.0 Hz, J₂ = 3.8 Hz, 1H, H₂a), 3.27 (t, J₁ = 12.0 Hz, 1H, H₂b), 2.49 (s, 3H, CH₃).

¹³C NMR (400 MHz, CDCl₃) δ 147.8 (ArO), 146.3 (ArO), 142.5 (C₁'), 132.2 (C₅''), 131.5 (C₃'/C₅'), 129.1 (C₂'/C₆'), 122.4 (C₆''), 109.5 (C₄'' or C₇''), 120.8 (C₄'), 108.3 (C₄'' or C₇''), 101.0 (C₂''), 66.5 (C₁), 44.8 (C₂), 34.7 (CH₃).

\[N\text{-Methyl-1-(naphthalen-2-yl)-2-phenylethanamin (73)}\]

The general procedure was followed with 54 (0.210 g, 0.854 mmol). Elution with EtOAc/hexanes and AcOH (30:70:1), then EtOAc/hexanes (3:7) to removal any residual acetic acid, and finally with EtOAc/hexanes and NEt\(_3\) (70:30:1) gave 73 as a white solid, (0.101 g, 45%). m.p. (salt): 200–206°C. R.f.: 0.25 (50% EtOAc/Hexanes + NEt\(_3\)). IR (thin film) cm\(^{-1}\): 3337 (NH). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.63–7.67 (m, 3H, ArH), 7.62 (s, 1H, H\(_1\)'), 7.32 (dd, \(J_1 = 8.4\) Hz, \(J_2 = 2.0\) Hz, 1H, ArH), 7.25–7.31 (m, 2H, ArH), 7.08–7.12 (m, 2H, 2 \(\times\) ArH), 7.00–7.12 (m, 2H, 2 \(\times\) ArH), 7.00–7.06 (m, 3H, 3 \(\times\) ArH), 3.74 (dd, \(J_1 = 8.4\) Hz, \(J_2 = 5.6\) Hz, 1H, H\(_1\)'), 2.87 (dd, \(J_1 = 13.6\) \(J_2 = 5.6\) Hz, Hz, 1H, H2a), 2.81 (dd, \(J_1 = 13.2\) Hz, \(J_2 = 8.4\) Hz, 1H, H2b), 2.13 (s, 3H, CH\(_3\)). Salt: \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 10.42 (br s, 2H, NH), 7.90 (d, \(J_1 = 8.4\) Hz, 1H, ArH), 7.77–7.83 (m, 2H, 2 \(\times\) ArH), 7.71–7.74 (m, 2H, H1' and ArH), 7.46–7.53 (m, 2H, 2 \(\times\) ArH), 7.07–7.09 (m, 3H, 3 \(\times\) ArH), 6.94–6.96 (m, 2H, 2 \(\times\) ArH), 4.31 (dd, \(J_1 = 11.2\) Hz, \(J_2 = 4.0\) Hz, 1H, H1), 3.96 (dd, \(J_1 = 13.2\) Hz, \(J_2 = 4.0\) Hz, 1H, H2a), 3.56 (dd, \(J_1 = 12.8\) \(J_2 = 11.2\) Hz, 1H, H2b), 2.52 (s, 3H, CH\(_3\)). \(^{13}\)C NMR (400 MHz, CDCl\(_3\)) \(\delta\) 140.9 (C3 or C2'), 138.9 (C3 or C2'), 133.5 (C4a' or C8a'), 133.0 (C4a' or C8a'), 129.4 (ArH \(\times\) 2), 128.6 (ArH \(\times\) 2), 128.2 (ArH), 127.8 (ArH), 127.7 (ArH), 126.5 (ArH), 126.3 (ArH), 126.0 (ArH), 125.6 (ArH), 125.4 (ArH), 67.0 (C1), 45.1 (C2), 34.8 (CH\(_3\)). HRMS (ESI): Observed: 262.1590, C\(_{19}\)H\(_{20}\)N\(^+\) requires 262.1596.
General procedure for the synthesis of primary amines from ketones and sodium cyanoborohydride. Sodium cyanoborohydride (3 mmol %) and 28% aqueous ammonia (15 mL per mmol) were added to a stirred solution of ketone (1 mmol) in a saturated solution of ammonium acetate in ethanol (35 mL per mmol). After stirring for 24 h at reflux, the solution was quenched with 1M HCl and filtered through celite with ether, MeOH and water, evaporated and extracted with dichloromethane (3 × 50 mL). It was washed with 1M NaOH (3 × 50 mL), then dried, filtered and evaporated to give a residue, which was purified by flash chromatography as described below. The free bases were converted to the hydrochloric salts using a hydrochloric acid/MeOH mixture.

2-(Benzo[d][1,3]dioxol-5-yl)-1-(4-(tert-butyl)phenyl)ethanamine (76)

The general procedure was followed with 49 (0.538 g, 1.81 mmol). Elution with EtOAc/hexanes + NEt₃ (30:70:1) and then EtOAc/hexanes and NEt₃ (50:50:1) gave 76 as light yellow crystals, (0.373 g, 68 %). m. p.: 261–263°C. Rf: 0.10 (50% EtOAc/hexanes + NEt₃). IR (thin film) cm⁻¹: 3375 (NH), 3362 (NH). ¹H NMR (400 MHz, CDCl₃) δ 7.36–7.40 (m, 2H, H₃'/H₅'), 7.30–7.34 (m, 2H, H₂'/H₆'), 6.75 (d, J₁= 8.0 Hz, 1H, ArH), 6.72 (d, J₁ = 1.6 Hz, 1H, H₄''), 6.67 (dd, J₁= 8.0 Hz, J₂ = 1.6 Hz, 1H, H₆''), 5.92 (t, J₁ = 1.6 Hz, 2H, H₂''), 4.12 (dd, J₁= 9.2 Hz, J₂= 4.4 Hz, 1H, H₁), 2.95 (dd, J₁= 13.6 Hz, J₂= 4.4 Hz, 1H, H₂a), 2.72 (dd, J₁= 13.4 Hz, J₂= 9.4 Hz, 1H, H₂b), 1.32 (t, tert-butyl). Salt: ¹H NMR (400 MHz, DMSO) δ 8.26 (br s, 3H, NH), 7.35–7.42 (m, 4H, 4 × ArH), 6.76–6.78 (m, 2H, 2 × ArH), 6.61 (dd, J₁ = 7.8 Hz, J₂ = 1.8 Hz, 1H, ArH), 5.95
(s, 2H, H2"), 4.45 (dd, J1 = 8.4 Hz, J2 = 6.8 Hz, 1H, H1), 3.14 (dd, J1 = 13.8 Hz, J2 = 6.4 Hz, 1H, H2), 3.02 (dd, J1 = 13.6 Hz, J2 = 8.6 Hz, 1H, H2), 1.26 (s, 9H, t-buty1). 13C NMR (400 MHz, CDCl3) δ 150.0 (ArO), 147.7 (ArO), 146.1 (C1’ or C4’), 142.7 (C1’ or C4’), 133.2 (C5”), 126.1 (C3’/C5’), 125.4 (C2’/C6’), 122.3 (ArH), 109.6 (ArH), 108.2 (ArH), 100.9 (ArH), 57.3 (C1), 46.2 (C2), 34.5 (t-buty1, C), 31.5 (t-buty1).


1-(Naphthalen-2-yl)-2-phenylethamine (77)*

The general procedure was followed with 54 (0.457 g, 1.86 mmol). Elution with EOAC/hexanes + NEt3 (50:50:1) gave 77 as a yellow solid, (0.250 g, 55%). m.p.: 241–243°C Rf: 0.35 (50% EOAC/hexanes + NEt3). IR (thin film) cm⁻¹: 3056 (NH), 3025 (NH). 1H NMR (400 MHz, CDCl3) δ 7.80–7.84 (m, 4H, 4 × ArH), 7.52 (dd, J1 = 8.4 Hz, J2 = 2.0 Hz, 1H, ArH), 7.45–7.48 (m, 2H, ArH), 7.21–7.32 (m, 5H, 5 × ArH), 4.37 (dd, J1= 8.8 Hz, J2 = 5.2 Hz, 1H, H1), 3.13 (dd, J1 = 13.2 Hz, J2 = 4.8 Hz, 1H, H2a), 2.94 (dd, J1= 13.2 Hz, J2= 8.8 Hz, 1H, H2b). Salt: 1H NMR (400 MHz, DMSO) δ 8.52 (br s, 3H, NH), 7.82–7.94 (m, 4H, ArH), 7.61 (dd, J1 = 8.8 Hz, J2 = 1.6 Hz, 1H, ArH), 7.51–7.53 (m, 2H, ArH), 7.09–7.20 (m, 5H, ArH), 4.69 (dd, J1 = 9.8 Hz, J2 = 5.6 Hz, 1H, H1), 3.39 (dd, J1 = 13.8 Hz, J2 = 5.4 Hz, 1H, H2a), 3.20–3.26 (m, 1H, H2b). 13C NMR (400 MHz, CDCl3) δ 143.1 (C1’ or C3), 139.1 (C1’ or C3), 133.5 (C2a’ or C6a’), 132.9 (C2a’ or C6a’), 129.5 (ArC × 2), 128.6 (ArC × 2), 128.2 (ArC), 127.9

* This compound has been synthesized previously by an alternative route.
(ArC), 127.7 (ArC), 126.5 (ArC), 126.1 (ArC), 125.6 (ArC), 125.1 (ArC), 124.9 (ArC),
57.7 (C1), 46.4 (C2). HRMS (ESI): Observed: 248.1442, C_{18}H_{18}N^+ requires 248.1439.
The NMR data matched those reported.  

2-(Benzo[d][1,3]dioxol-5-yl)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)ethanamine
(78)

The general procedure was followed with 53 (0.170 g, 0.507 mmol). Elution with
EOAC/hexanes + NEt₃ (50:50:1) gave 78 as a light brown solid, (0.0460 g, 24%). m.p.:  
238–240°C  R_f: 0.30 (50% EtOAc/hexanes + NEt₃). IR (thin film) cm⁻¹: 3370 (NH),  
3345 (NH). ¹H NMR (400 MHz, CDCl₃) δ 6.87 (d, J₁ = 1.6 Hz, 1H, H₅'), 6.79–6.82  
(m, 2H, 2 × ArH), 6.72 (d, J₁= 8.0 Hz, 1H, ArH), 6.66 (d, J₁ = 1.6 Hz 1H, ArH), 6.62  
(dd, J₁= 8.0 Hz, J₂ = 1.6 Hz, 1H, ArH), 5.91 (d, J₁ = 1.2 Hz, 2H, H₂'), 4.23–4.25 (m,  
4H, H₂'/H₃'), 4.02 (dd, J₁ = 9.0 Hz, J₂ = 5.0 Hz, 1H, H₁), 2.87 (dd, J₁= 13.6 Hz, J₂= 4.8  
Hz 1H, H₂a), 2.68 (dd, J₁= 13.6 Hz, J₂= 8.8 Hz, 1H, H₂). Salt: ¹H (400 MHz, DMSO)  
δ 8.09 (br s, 3H, NH), 6.98 (br s, 1H, ArH), 6.85 (s, 2H, ArH), 6.78 (d, J₁= 7.9 Hz, 1H,  
ArH), 6.75 (d, J₁ = 1.6 Hz, 2H, 2 × ArH), 6.58 (dd, J₁ = 7.9 Hz, J₂ = 1.6 Hz, 1H, ArH),  
5.96 (t, J₁ = 1.0 Hz, 2H, H₂''), 4.37 (dd, J₁ = 8.4 Hz, J₂ = 6.2 Hz, 1H, H₁), 4.22 (app s,  
4H, H₂'/H₃''), 3.08 (dd, J₁ = 13.8 Hz, J₂ = 6.4 Hz, 1H, H₂a), 2.96 (dd, J₁= 13.8 Hz, J₂=  
9.0 Hz, 1H, H₂b). ¹³C NMR (400 MHz, CDCl₃) δ 147.7 (ArO), 146.2 (ArO), 143.5  
(ArO), 142.6 (ArO), 139.2 (C₆' or C₅''), 133.0 (C₅'' or C₆'), 122.4 (ArH), 119.4 (ArH),  
117.2 (ArH), 115.2 (ArH), 109.6 (ArH), 108.3 (ArH), 100.9 (C₂''), 64.5 (C₂' or C₃'),

|
64.4 (C2' or C3'), 57.1 (C1), 46.2 (C2). HRMS (ESI): Observed: 300.1243, \( \text{C}_{17}\text{H}_{18}\text{NO}_4^+ \)
requires 300.1236.

\[
\begin{align*}
\text{NH}_2 \\
\text{Br}
\end{align*}
\]

2-(Benzo[d][1,3]dioxol-5-yl)-1-(4-bromophenyl)ethanamine (79)

The general procedure was followed with 50 (0.126 g, 0.398 mmol). Elution with EtOAc/hexanes + NEt\(_3\) (50:50:1) gave 79 as a yellow solid, (0.0548 g, 43%). m.p.: 77−80°C. \( R_f \): 0.10 (50% EtOAc/hexanes + NEt\(_3\)). IR (thin film) cm\(^{-1}\): 3384 (NH), 3367 (NH). 1H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.42−7.45 (m, 2H, H3'/H5'), 7.19−7.22 (m, 2H, H2'/H6'), 6.72 (d, \( J = 8.0 \) Hz, 1H, H6'' or H7''), 6.64 (d, \( J = 2.0 \) Hz, 1H, H4''), 6.58 (dd, \( J_1= 8.0 \) Hz, \( J_2 = 1.6 \) Hz, 1H, H6'' or H7''), 5.91 (s, 2H, H2''), 4.10 (dd, \( J_1= 8.4 \) Hz, \( J_2 = 5.6 \) Hz, 1H, H1), 2.86 (dd, \( J_1= 13.6 \) Hz, \( J_2 = 5.2 \) Hz, 1H, H2a), 2.70 (dd, \( J_1= 13.8 \) Hz, \( J_2 = 8.6 \) Hz, 1H, H2b). Salt: 1H (400 MHz, DMSO) \( \delta \) 8.08 (br s, 3H, NH), 7.59 (d, \( J_1 = 8.4 \) Hz, 2H, H3'/H5''), 7.36 (d, \( J_1 = 8.4 \) Hz, 2H, H2'/H6''), 6.77 (d, \( J_1 = 8.0 \) Hz, 1H, H6'' or H7''), 6.73 (d, \( J_1 = 1.2 \) Hz, 1H, H4''), 6.54 (d, \( J_1 = 8.0 \) Hz, \( J_2 = 1.6 \) Hz, 1H, H6'' or H7''), 5.95 (s, 2H, H2''), 4.48 (dd, \( J_1 = 8.8 \) Hz, \( J_2 = 6.4 \) Hz, 1H, H1), 3.11 (dd, \( J_1 = 13.6 \) Hz, \( J_2 = 6.4 \) Hz, 1H, H2a), 2.96 (dd, \( J_1 = 13.8 \) Hz, \( J_2 = 6.2 \) Hz, 1H, H2b). 13C NMR (400 MHz, CDCl\(_3\)) \( \delta \) 147.8 (ArO), 146.3 (ArO), 144.6 (C1'), 132.4 (C5''), 131.6 (C3'/C5'), 128.3 (C2'/C6'), 122.4 (ArH), 120.8 (C4'), 109.6 (ArH), 108.3 (ArH), 101.0 (C2''), 57.2 (C1), 46.2 (C2). HRMS (ES\(^+\)): Observed: 320.0286, \( \text{C}_{15}\text{H}_{15}\text{NO}_2\text{Br}^+ \)
requires 320.0286.
Appendix 1: Selected Spectra
1.9 References


13. Michael Gandy, P. s., thesis work, UWA.


[https://www.atcc.org/~/media/56374CEEC36C47159D2040410828B969.ashx](https://www.atcc.org/~/media/56374CEEC36C47159D2040410828B969.ashx).


Part II: Hit to Lead

Optimisation of Novel Trypanosomacidal Agents
2.1 Introduction

Human African Trypanosomiasis

Human African Trypanosomiasis (HAT) is a potentially fatal parasitic disease, which is caused by strains of the protozoan *Trypanosoma brucei*. *Trypanosoma brucei gambiense* causes chronic human infection in Western and Central Africa, while *Trypanosoma brucei rhodesiense* affects animals and causes acute illness in Eastern and Southern Africa.\(^1\) *T. b. rhodesiense* infection has a rapid onset leading to death within six months, while *T. b. gambiense*, which accounts for 95% of chronic HAT, and has long symptom-free periods that can last several years.\(^2\) The impact of HAT is predominantly felt in sub-Saharan Africa, where over 500,000 people in 36 countries are at risk. It is one of the major causes of human mortality in these regions.\(^3\) Livestock are also susceptible, adding to the burden of the disease.\(^4\)

HAT is transmitted through the bite of a Tsetse fly that has become infected from another mammal. The parasite reproduces in the blood stream and then crosses the blood brain barrier, invading the central nervous system.\(^2\) The early symptoms of infection include fever, itchiness, joint pain and headache, and often go undiagnosed until the parasite has already entered the brain, where it causes dramatic mood swings, poor coordination, soft tissue swelling, confusion, convulsions and a changed sleep pattern in which sufferers sleep all day, giving the disease its common name.\(^2^3\) When left untreated this disease leads to comas and death.\(^3\)

Current drugs for the treatment of HAT (Figure 17) are far from ideal. Most were introduced over 60 years ago and little advancement has been made since\(^4\). Due to their polarity, suramin and pentamidine must be injected, and are unable to cross the blood
brain barrier. They are, therefore, only effective against the first stage of the disease. At this point many sufferers don't even realize that they've been infected.

Figure 17: Current drugs that are used to treat Human African Trypanosomiasis, shown in their predominant protonation states at physiological pH.

Melarsoprol (86) is one of the most commonly used drugs for HAT; it is far from ideal. While effective in many cases, this arsenical is very toxic and causes fatal
reactive encephalopathy in 3–10% of patients. It also needs to be taken intravenously for 14 days, which is certainly not appropriate for poor African conditions.

Eflornithine (85) is much less toxic but must still be administered intravenously, four times a day, for 14 days. Newest to the market is nifurtimox (84), which is orally available, but is not potent enough on its own and needs to be combined with either melarsoprol (86) or eflornithine (85) to be effective.

The present treatments for HAT are often expensive, not easily administered, and some are ineffective once the disease has crossed the blood brain barrier. It is estimated that less than 20% of HAT sufferers have access to treatment, and it is considered one of the most neglected life-threatening diseases. The lack of alternative drugs and absence of a vaccine has made drug resistance a serious threat. Although the correlation has not been confirmed, resistance to melarsoprol was first noticed in the 1970's, and has increased ever since.

Thus, there is an obvious and urgent need for alternative, safer and orally-available treatments for HAT. However, due to the poor market, there is little incentive for pharmaceutical companies to invest in the development of drugs for this disease.

The Drugs for Neglected Diseases initiative (DNDi) is a non-profit organization that provides funding for the development of treatments for neglected diseases, and one of their main focuses is African trypanosomiasis. The organization strives to bridge the gap between the research community and pharmaceutical companies to find treatments for such diseases in underdeveloped countries.
2.1.1 Previous research

In 2010, the DNDi approached Professor Vicky Avery (Eskitis Institute, Griffith University) to screen the 87,926-member Walter and Eliza Hall (WEHI) compound library for compounds active against *T. brucei brucei*.

This livestock-infective strain of trypanosome is easier to work with than the human pathogenic strains, but serves as a good model for them. Professor Jonathan Baell, who was at WEHI at the time, oversaw the hit selection.

Several promising hits were unearthed, including the thiazole WEHI-1203394 (89), and triazole WEHI-1203794 (90). These compounds consist of a fluorophenyl-substituted thiazole or triazole heterocyclic core, a flexible side chain, and an amide substituent. These hits seemed promising due to their potency, good selectivity indices, and simple structures. In particular, facile and divergent modification of the acyl substituent should allow rapid optimisation of this portion of the structure.
Figure 18: Initial triazole and thiazole hit compounds from a high-throughput screen (HTS) of the WEHI compound library. IC$_{50}$ is the concentration of drug causing a 50% reduction in *Trypanosoma brucei brucei* growth. The selectivity index (SI) is the ratio of the IC$_{50}$ against HEK (human embryonic kidney) cells to the IC$_{50}$ of the compounds tested. Thus, drugs that are more selectively toxic to the parasite have high SI values.

2.1.2 Previous work in the Piggott group

Based on the HTS hits 89–90 (Figure 18), PhD exchange student, Marzie Rahmani Khajouei, synthesized a small series of analogues shown in Table 8.
Table 8: IC$_{50}$ and selectivity index results for the first series of analogues, synthesized by Marzie Rahmani Khajouei. For definitions of IC$_{50}$ and SI, see Figure 18, pg 113.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Compound #</th>
<th>R</th>
<th>IC$_{50}$ (µM)</th>
<th>SI</th>
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<tr>
<td>91</td>
<td>H</td>
<td>Inactive</td>
<td>–</td>
</tr>
<tr>
<td>92</td>
<td>Me</td>
<td>Inactive</td>
<td>–</td>
</tr>
<tr>
<td>93</td>
<td>Et</td>
<td>Inactive</td>
<td>–</td>
</tr>
<tr>
<td>94</td>
<td>$\tau$-Pr</td>
<td>5.2</td>
<td>16</td>
</tr>
<tr>
<td>95</td>
<td>$\tau$-Bu</td>
<td>1.7</td>
<td>50</td>
</tr>
<tr>
<td>89</td>
<td>WEHI-1203394</td>
<td>0.80</td>
<td>95</td>
</tr>
<tr>
<td>96</td>
<td>Ph</td>
<td>0.25</td>
<td>336</td>
</tr>
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</table>

Compounds with small acyl substituents, ethyl or smaller (91–93), were inactive (i.e., less than 50% parasite growth inhibition at 10 µM). As the substituents increased in size, so did the potency. The result for the pivalamide (95) was interesting as the only difference between this compound and the initial HTS hit (90) is the presence of a fluoro substituent in the phenyl group. Although the potency dropped a little, there wasn't a dramatic decrease, indicating that the fluorine was not essential for activity. The benzamide (96) (Figure 19) was more potent than the HTS hit, and retained selective toxicity. This result was very important, as the ready availability of a wide range of substituted benzoic acids (or benzoyl chlorides) meant that stereoelectronic modifications of the phenyl group could be thoroughly probed.
Figure 19: New lead benzamide prepared by Marzie Rahmani Khajouei. The SI is shown in brackets.

The route used to synthesize the analogues depicted in Table 8, took advantage of an existing preparation of the key primary amine 102 (Scheme 18). A conjugate addition of sodium phthalimide (97) to methyl vinyl ketone (98) gave 99a. Regioselective bromination gave the α-bromoketone 100a, which was condensed with thiobenzamide to give the thiazole 101b. Hydrazine hydrate cleaved the phthalimide group to give the free amine 102a, which was reacted with various acyl chloride in the presence of a base10 to give the target amides 103.
Although this method worked, it involved quite a few steps and the yields were mediocre. In particular, the phthalimide cleavage was inconsistent, giving poor and variable yields. The primary amine product, which was unusually polar, was difficult to isolate by liquid-liquid extraction from aqueous workups, and streaked badly (with considerable losses) during chromatography, despite the addition of triethylamine to the eluent.
2.2 Aims

Given the background above, the initial aims of this project were as follows:

1) Devise a new, improved synthesis of the key primary amine precursor 102.
2) Design and synthesise a series of substituted benzamides 104 (Figure 20), which explore how stereoelectronic and polarity modifications affect potency.
3) Have these compounds tested for potency against T. brucei brucei, and selectivity by comparison with cytotoxicity to HEK cells.
4) Use the results to determine structure–activity relationships, and inform the design of the next series of analogues.

![Figure 20: Generic structure representing the initial benzamide targets.](image)
2.3 Results and discussion

2.3.1 Synthesis

In order to continue to explore modifications to the acyl substituent, first a new synthesis of the key amine precursor 102 was required. Scheme 19 shows the initially investigated route.

Condensation of dichloroacetone (105) and thiobenzamide (106), as reported, gave the desired chloromethylthiazole 107\(^1\) in excellent yield. Nucleophilic substitution with potassium cyanide\(^2\) afforded the novel nitrile 108. Unfortunately, all attempts to reduce the nitrile 108\(^3\) to the primary amine 102 gave poor yields. Both LiAlH\(_4\)\(^4\) and BH\(_3\)\(^5\) were able to reduce the nitrile to the amine, but this was never isolated in more than a 20% yield, with the bulk of the mass lost. Despite varying reaction times, solvent and temperatures, this yield could not be improved.

**Scheme 19**: Initial route to primary amine 102.
An alternative reduction was attempted using CoCl$_2$ and NaBH$_4$, which generates CoH$_2$ \textit{in situ}\textsuperscript{15} (Scheme 20). Although on a small scale this reaction seemed somewhat promising, after it was scaled up, a yield of only 5% was achieved. The reaction formed a viscous, purple liquid that was insoluble in both aqueous and organic solvents. It is possible that the amine product forms a complex such as 109 with the cobalt, and this complex has poor solubility. Thus, this reaction was abandoned. In retrospect, it is possible that a competing, water-solubilizing and chelating ligand, such as EDTA, might have facilitated workup and improved the recovery of the primary amine.

Scheme 20: Attempted cobalt hydride-mediated reduction of nitrile 108.

One of the consistent issues with this nitrile reduction was the purification and isolation of the primary amine product. As mentioned previously, the free amine 102 is unusually polar, difficult to extract into organic solvents after aqueous workups and streaks badly during column chromatography, even in the presence of triethylamine, and this may explain some of the poor yields. It was proposed that if this polarity issue could be overcome, the reactions might become more facile. The revised synthesis is shown in Scheme 21.
It was rationalized that if the free amine was able to be protected \textit{in situ}, and thus made less polar, the complications in purification could be avoided, and the yield improved. In addition, by protecting and "trapping" the amine \textit{in situ}, side reactions such as dimerizations (reductive amination) can be avoided, allowing the desired product to be synthesized in high yields.\textsuperscript{16} This approach has been used in the nickel boride reduction of nitriles in the presence of Boc-anhydride, which provides the \textit{t}-butyl carbamates in good yield.\textsuperscript{17}

In the current work, the \textit{in situ} protection method worked well, and the carbamate 110 was easily isolated and purified, allowing a substantial improvement in yield (Scheme 21). From here the protecting group was removed with a simple protonolysis\textsuperscript{18}, to give

\textbf{Scheme 21}: New route to 111 \textit{via} a Boc-protected amine.
the dihydrochloride of the primary amine, the point of diversification for the target analogue synthesis. Amidation with various acyl chlorides\textsuperscript{10}, or a carboxylic acid\textsuperscript{19} and a coupling agent was now undertaken.

Acyl chlorides generally gave the cleanest, and highest yielding reactions. However, due to the stability and availability of a wider range of substrates, most reactions were attempted using carboxylic acids and a coupling agent. Initially \textit{N,N'-dicyclohexylcarbodiimide} (DCC, \textsuperscript{112}) in the presence of 1-hydroxybenztriazole (HOBT, \textsuperscript{114})\textsuperscript{20} was used for the amide couplings (Figure 21). Although the reaction worked well, purification was an issue. The by-product, dicyclohexylurea (DCU, \textsuperscript{113}) was very hard to separate from the target amides and required multiple recrystallizations. This led to impure products. By using \textit{N,N,N',N'-tetramethyl-O-(1H-benzotriazol-1-yl)uronium hexafluorophosphate} (HBTU, \textsuperscript{115})\textsuperscript{19} or,1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU, \textsuperscript{116})\textsuperscript{21} along with Hünig's base, these yields were increased and purification was simpler. Using these methods, 28 new amide analogues were synthesized, in yields ranging from 32–90%, as detailed in Table 9 (page 117).
Figure 21: Structures of various coupling agents used, and the by-product DCU (113).

See text for definition of abbreviations.
2.3.2 Biological testing

All target compounds made in this project were subjected to primary screening by our collaborators, Dr Amy Jones and Professor Vicky Avery, at the Eskitis Institute, Griffith University. As with the HTS described briefly in the introduction (pg 113), compounds were tested against *Trypanosoma brucei brucei*, a strain of trypanosome that infects livestock and that is easier, and safer, to work with than the human-infective strains. Concurrently, the compounds were tested against human embryonic kidney (HEK) cells to give an idea of their selectivity. The IC\textsubscript{50} values and selectivity indexes, (in brackets) are shown in Table 9. Each IC\textsubscript{50} was determined in duplicate (at least) and the standard error of mean (SEM) was calculated. SEMs were generally quite small in comparison to the IC\textsubscript{50} values, and have been omitted in Table 9 for clarity. The SEM values are listed in appendix I.

2.3.3 Structure Activity Relationships

Initially a series of monosubstituted benzamides was investigated to explore the effects of stereoelectronic modifications on potency (Table 9). Included in this Table, and shown in blue, are the partial structures and results for compounds that were synthesized by Raphael Rahmani, a postdoctoral collaborator in the group of Professor Jonathan Baell, at the Monash Institute of Pharmaceutical Sciences.
Table 9: Structures, IC₅₀ values (µM), selectivity indexes (SI) and synthetic yields and conditions used for the first series of substituted benzamides. Structures shown in blue represent those compounds synthesized by Raphael Rahmani of Monash University and that in pink by Marzie Rahmani Khajouei, a visiting PhD student in the Piggott lab.

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<td></td>
<td>R</td>
<td>(SI)</td>
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For definitions of IC₅₀ and SI, refer to Figure 18 (pg 113).
The first obvious trend apparent is that any substituent larger than a fluorine atom in the \textit{para} position (130–134), leads to a complete loss of activity. In the \textit{ortho} position, although tolerated, anything larger than a fluoro substituent (118–122) decreases the potency. In this case the drop in potency could be simply due to unfavourable steric interactions with the binding pocket. Alternatively, the \textit{ortho}-substituent may induce unfavourable conformations through steric interactions with the amide functional group.

The most interesting trends relate to the \textit{meta} position. It was found that having an electron-withdrawing group (EWG) at this position was favourable (123, 124, 128), while an electron-donating group was much less preferred (125, 127). For example, chloro and methyl substituents are isosteric but the more electron-deficient chloride 124 was almost ten-fold more potent than the toluamide 125. Even more electron-withdrawing groups such as cyano (128) or a fluoro (123), led to more significant increases in potency. Thus, it appears that, to a certain extent, the electron-withdrawing power of the \textit{meta}-substituent dictates the potency more so than the size of the substituent. It was also noted that the presence of a hydroxyl substituent in the \textit{meta} position (126) rendered the compound inactive, while the OMe group (127), which is bigger, and just as good an electron-donating group, was tolerated. This suggests that it is the polarity of the OH group that results in the loss of activity.

Little is known about the biological target (and mode of action) of this series of compounds, but we assume that it is a protein. With this caveat in mind, the SAR above led to a few general conclusions about the nature of the biological target’s binding pocket. The fact that any \textit{para} substituent besides F is not tolerated, and that a \textit{meta} OH group also produces an inactive compound, leads us to believe that there is likely a tight, hydrophobic pocket that engages with the benzamide phenyl group. Although the
ortho phenol 120 showed some activity, it is possible that an internal H-bond with the amide carbonyl group masks the polarity of this substituent. Preference for an EWG at the meta position, seemingly independent of H-bond acceptor ability (CN is a much better H-bond acceptor than F), suggests that the benzamide might be interacting with an electron-rich binding pocket (e.g. \( \pi \)-interactions with a tyrosine residue).

Having explored the benzamides quite thoroughly, attention turned to a series of analogues in which the phenyl group has been extended, fused with an additional ring, or replaced with a saturated ring (Table 10). Perhaps not unsurprisingly, based on the results for the para-substituted benzamides discussed above, any ring-systems larger than benzene were inactive. However, saturated rings of similar size to a phenyl group were equipotent with the benzamide, leading to the conclusion that size of the acyl substituent is more important than its ability to engage in \( \pi \)-interactions.
Table 10: Structures, IC\textsubscript{50} values, selectivity indexes and conditions used for a series of extended and fused aromatic, and alicyclic amides.

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<th>Yield</th>
<th>Conditions</th>
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</tbody>
</table>

* Structures in blue represent compounds synthesized by Raphael Rahmani of Monash University.

While some of the benzamides were quite potent, the lipophilicity of these compounds was a concern (see Chapter 1, pg 10) (Figure 4). The logP values, which indicate the overall lipophilicity of the molecule Lipophillic Ligand Efficiency, and the values (LLE), which take into account potency as well as lipophilicity, are shown in Table 11. A high LLE value of >6 is desirable (this equates to an IC\textsubscript{50} value of 10 nM and a logP of 2).\textsuperscript{23} The low LLE values of the benzamides inspired the design and synthesis of a
series of six-membered heterocyclic amides to determine if potency could be maintained in more polar analogues (Table 12).
Table 11: IC$_{50}$ values along with (calculated) cLogP and LLE values for the more potent analogues.

<table>
<thead>
<tr>
<th>Compound$^*$</th>
<th>Compound #</th>
<th>IC$_{50}$ (µM)</th>
<th>cLogP*</th>
<th>LLE**</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="structure" /></td>
<td>96</td>
<td>0.25</td>
<td>4.0</td>
<td>2.6</td>
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<tr>
<td><img src="image" alt="structure" /></td>
<td>117</td>
<td>0.47</td>
<td>4.1</td>
<td>2.2</td>
</tr>
<tr>
<td><img src="image" alt="structure" /></td>
<td>123</td>
<td>0.19</td>
<td>4.2</td>
<td>2.6</td>
</tr>
<tr>
<td><img src="image" alt="structure" /></td>
<td>129</td>
<td>0.77</td>
<td>4.2</td>
<td>1.9</td>
</tr>
<tr>
<td><img src="image" alt="structure" /></td>
<td>128</td>
<td>0.13</td>
<td>3.8</td>
<td>3.1</td>
</tr>
<tr>
<td><img src="image" alt="structure" /></td>
<td>140</td>
<td>0.25</td>
<td>4.1</td>
<td>2.5</td>
</tr>
<tr>
<td><img src="image" alt="structure" /></td>
<td>139</td>
<td>0.31</td>
<td>4.6</td>
<td>2.0</td>
</tr>
<tr>
<td><img src="image" alt="structure" /></td>
<td>142</td>
<td>0.30</td>
<td>2.8</td>
<td>3.7</td>
</tr>
<tr>
<td><img src="image" alt="structure" /></td>
<td>143</td>
<td>0.76</td>
<td>2.8</td>
<td>3.3</td>
</tr>
</tbody>
</table>

* cLogP values were calculated using molinspiration$^{24}$

** LLE = -log (IC$_{50}$) - cLogP

# The structures in pink and blue represent compounds synthesized by Marzie Rahmani Khajouei, a visiting PhD student in the Piggott lab, and Raphael Rahmani of Monash University, respectively.
The incorporation of N or O into the 4-position of these analogues considerably decreased the potency, suggesting that the corresponding region of the putative protein-binding pocket is not only shallow, but also hydrophobic. However, the 2 and 3-pyridyl analogues retained potency relative to the benzamide. Although the potency isn't exceptional, and still needs improvement, Table 11 shows an increase in LLE from 2.6 for the benzamide 96, to 3.7 for the 2-pyridyl analogue 142, and this ignores any additional increase in water partitioning due to protonation of the weakly basic pyridine N (i.e., clogD values were not used). This is a significant increase and these results indicated that we were able to increase the polarity of the analogues without significantly diminishing the potency.

The incorporation of two heteroatoms, at least in the pyrazine 145, led to a large drop in potency (Table 12). This suggests that the acyl binding pocket of the target protein can tolerate polarity in one region, but that the diametrically opposed surface is hydrophobic.
Table 12: Structures, IC$_{50}$ values, yields and conditions used for the six-membered heterocyclic amides.

Next a series of five-membered heterocyclic amides was synthesized and evaluated (Table 13). Overall most were moderately active. Perhaps unsurprisingly, the thienylamides had very similar IC$_{50}$ values to the benzamide, thiophene being an
isostere of benzene. The furans 151, 152 and 156 were also quite potent. While a methyl
group improved potency when incorporate adjacent to the amide carbonyl, substituents
at the other positions [i.e. bromo- and methyl furans 158 and 157, respectively], were
much less active, likely due to the steric constraints that were seen is past series. The
drop in potency of the pyrrole 153 relative to the 2-pyridyl analogue 142 suggests that a
hydrogen-bond acceptor is tolerated at the 2-position, but not a hydrogen bond donor.
Once again, polarity on one side of the ring was tolerated, but not on both sides of the
ring (oxazole 154). The result for the thiazole 155 is somewhat puzzling. It might be
expected that 155 would have similar potency to the 2-pyridyl analogue 142, but the
thiazole is four times less potent.
Table 13: Structures, IC<sub>50</sub> values, selectivity indices, yields (final coupling step) and conditions used for the five-membered heteroaromatic amides.

<table>
<thead>
<tr>
<th>#</th>
<th>R&lt;sup&gt;*&lt;/sup&gt;</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt; (µM)</th>
<th>(SI)</th>
<th>Yield</th>
<th>Conditions</th>
</tr>
</thead>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>149</td>
<td>S</td>
<td>0.35</td>
<td>(241)</td>
<td>41%</td>
<td>RCOCl</td>
</tr>
<tr>
<td>150</td>
<td>S</td>
<td>0.23</td>
<td>(179)</td>
<td>83%</td>
<td>HBTU</td>
</tr>
<tr>
<td>151</td>
<td>O</td>
<td>0.80</td>
<td>(77)</td>
<td>78%</td>
<td>HBTU</td>
</tr>
<tr>
<td>152</td>
<td>O</td>
<td>0.35</td>
<td>(240)</td>
<td>27%</td>
<td>HBTU</td>
</tr>
<tr>
<td>153</td>
<td>H</td>
<td>1.6</td>
<td>(13)</td>
<td>27%</td>
<td>HBTU</td>
</tr>
</tbody>
</table>

* Structures in blue represent those compounds synthesized by Dr Raphael Rahmani of Monash University.
A summary of the results and structure–activity relationships thus far is shown in Figure 22. In the benzamides, $p$-substitutions were extremely unfavourable, resulting in inactive compounds, except for the very small fluoro substituent. Similarly, fused or extended ring systems seem to be too large for the target binding site. Ortho-substitution was somewhat tolerated, and cyclopentyl and cyclohexyl rings, as well as 5-membered aromatic heterocycles were quite favourable in this position. These results indicated that the size of the substituent is more important than the aromaticity. Perhaps most interestingly, it was found that substitution in the meta position with an electron withdrawing group was the most favourable and was able to increase the potency and selectivity of the benzamide analogues. It was also noted that selectivity seemed to linearly increase with potency, indicating a parasite-selective mode-of-action (MoA), although what that MoA is has not been determined.

**Figure 22:** A summary of the structure-activity relationships developed in exploring the amide acyl substituent.
2.3.4 Amide Isosteres/bioisosteres

At this point amides had been explored pretty thoroughly, with only modest potency gains. Therefore, it was decided to move on to something a bit different. The amide linkage, being susceptible to hydrolysis, is also potentially a point of metabolic weakness. Thus, analogous functional groups that may be more resistant to hydrolysis were investigated. Shown in Figure 23 are the original targets, two amide isosteres: ureas and carbamates. In addition, a sulfonamide, which although not an isostere, as it is tetrahedral rather than the trigonal planar amide, but which is in some compound classes a bioisostere of amides,25 was also targeted.

![Figure 23: Original amide "isostere" targets](image)

Beginning from the common primary amine dihydrochloride precursor 111, all three classes of analogues were readily available. The reaction with benzenesulfonyl chloride in the presence of Hüning’s base26 yielded the desired sulfonamide 161 (Scheme 22). Although the yield was poor, it provided more than enough material for the initial biological testing. Similarly, reacting 111 with carbamoyl chlorides, in the presence of
triethylamine,\textsuperscript{10} gave access to ureas (171, 172 and 174) in moderate yields, with few impurities.

\begin{center}
\includegraphics[width=\textwidth]{scheme22.png}
\end{center}

\textbf{Scheme 22:} Synthesis of sulfonamide 161 and ureas 162.

In considering how to access a wider range of ureas and carbamates more efficiently and more cheaply, we were inspired by the work of Duspara \textit{et al.}\textsuperscript{27}, who showed that imidazolylureas, which are stable and can be purified by column chromatography and stockpiled, but also readily undergo facile reactions with various amines or alcohols, in the presence of an appropriate base, yield the corresponding ureas and carbamates, respectively (Scheme 23).\textsuperscript{27}
In the current work, shown in Scheme 24 the key imidazolylurea 167 was synthesised by simply reacting the primary amine dihydrochloride 111 with carbonyldiimidazole (163), and was then able to be purified by column chromatography. The reactions of 167 with a variety of primary and secondary amines, in the presence of NEt₃, gave the target ureas 169, 170, and 173 in reasonable yields (Table 14). The yield of the carbamate 168 from the reaction of 167 with sodium isopropoxide was lower, but still acceptable (Table 14).
Scheme 24: Synthetic routes to carbamates and ureas via imidazole 167. See Table 14 for individual reaction yields.

2.3.5 Structure-Activity Relationships

The results of the testing of the urea, carbamate and sulfonamide analogues in the primary assay (growth inhibition of T. b. brucei) are shown in Table 14. While the pivalamide 95 (discussed in section 2.1.2) had modest activity, extension of the bulky group by insertion of an oxygen atom in the t-butyl carbamate 110 led to a complete loss of activity. This raised a question: was it due to the increase in size, or the presence of the carbamate versus the amide? To answer this question, the isopropyl carbamate 168 was synthesized. This was shown to be one of the most active compounds discovered to date, indicating that the t-butyl carbamate was, indeed, simply too large for the acyl binding pocket.

The sulfonamide 161 was completely inactive. This could also be because the elongation of the molecule, by incorporation of the larger S atom, makes the
benzenesulfonamide too large for the target-binding site. Alternatively, the tetrahedral geometry about the sulfur atom (as opposed to trigonal planar geometry of the corresponding amides) may not be tolerated. The synthesis of sulfonamides with smaller (than Ph) substituents were recently tested by other PhD students in the Piggott lab and also found to be inactive, confirming this hypothesis.

The isopropyl urea 169 was significantly less potent than the corresponding carbamate 168. However, in the $N,N'$-diethyl urea 170 the potency was largely recovered. This suggests that the hydrogen bond donor in 169 is unfavourable; presumably strong hydrogen bonds with water in the solvated molecule are not present in the ligand-receptor complex.

Exocyclic ureas were also explored, as these are the closest analogues of the most potent amides. Excitingly, a dramatic increase in potency was seen in these compounds. The pyrrolidine 171 and piperidine 172 derivatives, in particular, are almost 100 times more potent that the original HTS hit! The improved potency of these exocyclic ureas compared to the $N,N'$-diethyl analogue is probably due to entropic factors. There is much more conformational freedom in the diethyl analogue, leading to a large loss of entropy upon binding to the target, whereas the exocyclic ureas are already conformationally restricted, and the loss of entropy on binding would be much less.

The azepane-derived urea 173 was slightly less potent than the smaller-ring compounds, perhaps due to some steric crowding. The morpholinyl urea 174 was much less potent; again confirming that introduction of polarity into the 4-position is unfavourable.
At this point it was decided that the right-hand portion of the series (as drawn in this thesis), had been sufficiently optimized with the piperidinyl urea (as in 172), and the focus turned to modifications of other parts of the molecule.
Table 14: Yields (final step), potency (growth inhibition of *T. b. brucei*) and selectivity indexes (relative to HEK cells) of urea, carbamate, and sulfonamide analogues.

The compound in pink was synthesized by Mahzie Rahmani Khajouei.

![Structure of the compound synthesized by Marzie Rahmani Khajouei](image)

<table>
<thead>
<tr>
<th>R*</th>
<th>IC₅₀ (µM) (SI)</th>
<th>Method*</th>
<th>R</th>
<th>IC₅₀/ Yield</th>
<th>Method*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Yield)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O</td>
<td>1.68 (50)</td>
<td>–</td>
<td>O</td>
<td>0.26 (320)</td>
<td>D</td>
</tr>
<tr>
<td>NH</td>
<td></td>
<td></td>
<td>NH</td>
<td>66%</td>
<td></td>
</tr>
<tr>
<td>95</td>
<td></td>
<td></td>
<td>170</td>
<td></td>
<td></td>
</tr>
<tr>
<td>O</td>
<td>Inactive 55%</td>
<td>–</td>
<td>O</td>
<td>0.05 (1735)</td>
<td>B</td>
</tr>
<tr>
<td>NH</td>
<td></td>
<td></td>
<td>NH</td>
<td>92%</td>
<td></td>
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<tr>
<td>110</td>
<td></td>
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<td>171</td>
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<td></td>
</tr>
<tr>
<td>O</td>
<td>0.22 (385)</td>
<td>C</td>
<td>O</td>
<td>0.028 (2966)</td>
<td>B</td>
</tr>
<tr>
<td>NH</td>
<td>32%</td>
<td></td>
<td>NH</td>
<td>71%</td>
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<td>168</td>
<td></td>
<td></td>
<td>172</td>
<td></td>
<td></td>
</tr>
<tr>
<td>O</td>
<td>0.90 µM (93)</td>
<td>D</td>
<td>O</td>
<td>0.09 (943)</td>
<td>D</td>
</tr>
<tr>
<td>NH</td>
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<td>NH</td>
<td>68%</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>O</td>
<td>Inactive 32%</td>
<td>A</td>
<td>O</td>
<td>0.69 (127)</td>
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<td>NH</td>
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<td></td>
<td>NH</td>
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<td>161</td>
<td></td>
<td></td>
<td>174</td>
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</tbody>
</table>

*The structure in pink represents the compound synthesized by Marzie Rahmani Khajouei, a visiting PhD student in the Piggott lab.

*Methods used to synthesize each analogue are shown in schemes 22 and 24.
2.4 Pyrazoles

2.4.1 Previous work on alternative heterocyclic cores

Previous research by Arthur Toynton, an exchange Honours student in the Piggott group, involved a series of analogues with the thiazole core replaced by a different heterocycle (Figure 24). The tetrazole and triazole analogues all proved to be inactive, which was somewhat surprising given the activity of HTS hit 90. However, when the heterocyclic core was changed to a pyrazole, activity was retained and indeed the benzamide 178 was only slightly less potent than the corresponding thiazole 96. Interestingly, the t-butyl carbamate 179 was active in the pyrazole series, whereas the corresponding thiazole 110 was inactive. This was attributed to the smaller size of the pyrazole; a small contraction of the heterocyclic core now allowed the t-butyl carbamate to fit within the acyl-binding pocket, although probably with some conformational crowding, given the fairly low potency.
Figure 24: Original lead compounds determined by the HTS screen and a summary of results from the triazole, tetrazole and pyrazole series, synthesized by Arthur Toynton, as well as the corresponding analogues in the thiazole series.
Pyrazoles are "privileged" in medicinal chemistry due to their excellent pharmacokinetic properties, including solubility and metabolic stability.\textsuperscript{28} Most importantly, they are common motif in successful drugs on the market (Figure 25).\textsuperscript{29} Given the success of the ureas and carbamates in the thiazole series, it was decided to synthesize a similar series of pyrazoles.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{pyrazole_drugs.pdf}
\caption{Examples of pyrazole drugs}
\end{figure}
2.4.2 Synthesis

The initial synthesis of the key primary amine dihydrochloride 185 is shown in Scheme 25. The synthesis of the Boc-protected aminoethylpyrazole 179 by regioselective N-alkylation\(^{30}\) of 3-phenylpyrazole (183) was problematic. Trace water in the DMF was found to cause consumption of the bromide 184. Even with carefully dried DMF and \(\text{K}_2\text{CO}_3\), and excess bromide, the alkylation could not be pushed to completion. Crushed 3A molecular sieves were also added in an additional attempt, giving a mixture of starting material, impurities and possible product. This made purification very difficult, as the 3-phenylpyrazole 183 and product 179 have very similar chromatographic mobilities. Deprotection with 4 M HCl at room temperature\(^{18}\) was facile giving the dihydrochloride 185 of sufficient purity for subsequent steps; however, given the difficulties with this route, a new synthesis of the primary amine 185 was investigated.

\[\text{Ph-NH} \quad \text{Br-CONH} \quad \text{K}_2\text{CO}_3 \quad \text{DMF} \quad 30-55\% \quad \text{Ph-NH} \quad \text{CONH} \quad \text{HCl/H}_2\text{O} \quad \text{Quantitative} \quad \text{Ph-NH} \quad \text{CONH} \quad \text{Cl}^- \quad \text{Cl}^- \]

Scheme 25: Initial synthesis of amine dihydrochloride 185.

Scheme 26 shows an improved route to 185 involving a key Hofmann rearrangement.\(^{31}\) A base-catalysed conjugate addition\(^{32}\) of phenylpyrazole 183 to methyl acrylate 186
gave 187. Upon refluxing this ester with aqueous ammonia,\textsuperscript{33} the desired primary amide 188 was obtained, but the major product was the carboxylate resulting from hydrolysis. An attempt to overcome this side-reaction by using methanolic ammonia\textsuperscript{34} was not successful – after 24 h at reflux only reactants were present. Allowing the reaction to proceed at room temperature, for 48 h, using ammonium hydroxide, only yielded 30\% of the desired product, with the remaining quantity being starting material. A compromise between acceptable reaction rate and competing hydrolysis was found at 60 °C, providing an acceptable yield (60\%) of the desired amide 188, with the rest of the starting material being converted to the carboxylate. Although the yield is moderate, the separation of the primary amide from the carboxylate by-product was facile and a simple organic extraction was all that was required for purification. However, it is likely that optimising temperature or using non-aqueous ammonia, perhaps under pressure, can improve the yield of this step. Subjecting 188 to a (diacetoxyiodo)benzene-mediated Hofmann rearrangement in methanol\textsuperscript{31} (Scheme 26), gave the methyl carbamate 189 in acceptable yield. The mechanism of the Hofmann rearrangement is outlined in Scheme 27. The carbamate 189 was then hydrolysed with 4 M HCl\textsuperscript{35} to yield the key primary amine dihydrochloride 185.

\textbf{Scheme 26: Improved synthesis of 185 using a Hofmann rearrangement.}
The mechanism of this transformation has not been published, but by analogy with the accepted mechanism for the Br$_2$/NaOH-mediates Hofmann rearrangement$^{36}$, a possible mechanism is outlined in Scheme 27. Since no strong base is used with DIB, it seems likely that general acid-catlaysed amide-enol formation proceeds nucleophilic displacement of acetate from DIB (with the acid generated by methanolyis of DIB). Presumably the NH proton is now very acidic and deprotonation/elimination gives a temporal nitrene, which rearranges to give the isocyanate. Addition of methanol to this isocyanate then gives the methyl carbamate.

\[
\begin{align*}
\text{Scheme 27: Proposed mechanism for the (diaxtoxyiodo)benzene mediated Hofmann rearrangement}^{36}
\end{align*}
\]

Similarly to the thiazole series, the starting pyrazolylethylamine dihydrochloride 185 was reacted with benzenesulfonyl chloride in the presence of Hünig’s base$^{26}$ to give the corresponding sulfonamide 190, and with morpholine-N-carbonyl chloride$^{10}$ to give the corresponding urea 191 (Scheme 28). At the time the poor activity of the
morpholine 174 in the urea series was not known, otherwise this analogue would likely have been omitted. A reaction with carbonyldiimidazole\textsuperscript{27} 163 gave the imidazolyl urea 192, which was then reacted with various amines or alcohols, in the presence of an appropriate base\textsuperscript{27}, to give the desired urea 194 or carbamate 193 targets, respectively.

**Scheme 28:** Synthetic route to sulfonamide 190, ureas 191 and 194 and carbamate 193 via key dihydrochloride 185.

Table 15 shows the results from the biological testing of these compounds. A similar trend in trypanosomacidal activity is seen to that in the thiazole series, although the smaller size of the pyrazole ring, compared to thiazole, seems to have an impact. In this series the \textit{t}-butyl carbamate 179 is active, and not much less so than the isopropyl carbamate 196. This is attributed to the smaller size of the pyrazole ring, compared to the thiazole, which would allow larger terminal substituents to be tolerated. This again contributes to the hypothesis of a tight receptor pocket with little room for larger
substituents. As in the thiazole series, the isopropyl urea 197 is substantially less potent than the corresponding carbamate 196, and potency is again restored in the $N,N$-diethylurea 198, although there is a much more drastic change in potency between the two analogues than in the thiazole series.

Again, not surprisingly, no activity was observed with the sulfonamide 190 and the morpholinylurea 191 has very little activity. With the other exocyclic ureas, we see the same general trend observed in the thiazole series, with the piperidine being the most active, but the pyrazoles are more sensitive to small changes, with a much larger potency drop when the pyrrolidine or azepane substituents were introduced. The differences in the two series are likely due to subtle geometric changes brought about by the different sizes of the heterocyclic cores.
Table 15: Potencies and selectivity indexes for the ureas, carbamates, and sulfonamide in the pyrazole series. The structures highlighted in pink and blue represent compounds synthesized by Arthur Toynton and Raphael Rahmani, respectively.

![Chemical structures](image)

<table>
<thead>
<tr>
<th>#</th>
<th>R</th>
<th>IC_{50} (µM)</th>
<th>(SI)</th>
<th>Yield</th>
<th>#</th>
<th>R</th>
<th>IC_{50} (µM)</th>
<th>(SI)</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>178</td>
<td><img src="image" alt="Structure 1" /></td>
<td>0.33</td>
<td>(125)</td>
<td>198</td>
<td><img src="image" alt="Structure 2" /></td>
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<td>(42)</td>
<td>87%</td>
<td></td>
</tr>
<tr>
<td>195</td>
<td><img src="image" alt="Structure 3" /></td>
<td>0.55</td>
<td>(41)</td>
<td>199</td>
<td><img src="image" alt="Structure 4" /></td>
<td>0.65</td>
<td>(128)</td>
<td>98%</td>
<td></td>
</tr>
<tr>
<td>179</td>
<td><img src="image" alt="Structure 5" /></td>
<td>1.6</td>
<td>(13)</td>
<td>200</td>
<td><img src="image" alt="Structure 6" /></td>
<td>0.12</td>
<td>(680)</td>
<td>94%</td>
<td></td>
</tr>
<tr>
<td>196</td>
<td><img src="image" alt="Structure 7" /></td>
<td>1.0</td>
<td>(82)</td>
<td>201</td>
<td><img src="image" alt="Structure 8" /></td>
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<td>(215)</td>
<td>75%</td>
<td></td>
</tr>
<tr>
<td>197</td>
<td><img src="image" alt="Structure 9" /></td>
<td>7.28</td>
<td>(11)</td>
<td>191</td>
<td><img src="image" alt="Structure 10" /></td>
<td>6.56</td>
<td>(13)</td>
<td>75%</td>
<td></td>
</tr>
<tr>
<td>190</td>
<td><img src="image" alt="Structure 11" /></td>
<td>Inactive/ 34%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The structures in pink and blue represent compounds synthesized by Marzie Rahmani Khajouei, a visiting PhD student in the Piggott lab, and Raphael Rahmani of Monash University, respectively.*
Linker Modifications

The flexible linker between the heterocyclic core and acyl substituent is another obvious point for modification and some attention was devoted to exploring structure activity relationships about this tether. In particular, the importance of the amide/urea/carbamate NH was probed. This work was done prior to the discovery of the urea analogues, and thus focuses on analogues of the benzamide 178.

Synthesis

The ester analogue of benzamide 178 was synthesized by alkylation\textsuperscript{30} of 3-phenyl-1H-pyrazole (183) with commercially available 2-bromoethyl benzoate (202) (Scheme 29). Similarly, alkylation\textsuperscript{30} of 183 with 2-chloro-N-phenylacetamide (204) gave the truncated acetanilide analogue 205, which retains the NH in the same position as the benzamide, but has the carbonyl group on the other side. In both cases, the regioisomeric pyrazoles were formed as minor components, but a simple recrystallization from dichloromethane and hexanes yielded the desired isomers in moderate yield. The identity of the isomers was determined by HMBC NMR spectroscopy, with the definitive correlation indicated in Scheme 29) [H1$\leftrightarrow$C5' (205) and H2$'\leftrightarrow$C5'' (203)]. None of the minor isomer was able to be isolated for testing in either case.
The secondary amine analogue 206 of benzamide 178 was synthesised by a reduction of 178 with borane\textsuperscript{14} (Scheme 30). Although the yield was poor and could likely be improved with experimentation, this reaction gave plenty of material for an initial investigation of activity.

Scheme 30: Synthesis of the secondary amine analogue of benzamide 178.

The "switched" amide analogue of benzamide 178 was synthesised by saponification of the ester 187 (see Scheme 31) with lithium hydroxide\textsuperscript{37} to give the corresponding carboxylic acid 207 (Scheme 31). A simple coupling reaction with aniline using HBTU and DIPEA\textsuperscript{19} gave the desired anilide 208 in moderate yield.
2.4.3 Biological testing

It was found that any alterations to the amide functional group rendered the analogues inactive against *T. b. brucei*. Thus, while it is clear that modifications on the right-hand side (as drawn in this thesis) of the carbonyl group are tolerated, even potency boosting, the precise positioning of the hydrogen bond-donating NH is critical for activity. The lack of activity in the *N*-methyl analogue 209 (Figure 26), synthesized by Raphael Rahmani, could be due to the larger steric bulk of the methyl group, but this explanation is not valid for the ester 203. The hydrogen bond-accepting carbonyl oxygen also seems to be critical for activity in this class of compounds, although a repulsive interaction with the positive charge on the protonated secondary amine 206 may also contribute to its lack of activity.
Figure 26: Inactive analogues of benzamide 178. The structure in blue represents the compound synthesized by Dr Raphael Rahmani of Monash University.

2.5 Metabolic testing

Throughout the drug design, discovery and development process there are certain criteria that are constantly under consideration. Although potency and selectivity are both very important features, there are many other properties of a drug that are crucial before it can make it to market.
The DNDi (see section 2.1, pg 111 for information on the DNDi) provides funding for animal testing; however, certain criteria must be achieved to ensure that the drugs under investigation can actually reach their biological targets \textit{in vivo}, in sufficient and sustained concentration (Table 16).

**Table 16**: DNDi selection criteria for eligibility for \textit{in vivo} testing

<table>
<thead>
<tr>
<th>Potency</th>
<th>MW</th>
<th>PSA$^a$</th>
<th>logD$^b$</th>
<th>Solubility (µM)$^c$</th>
<th>cPPB$^d$</th>
<th>E$_H$ $^e$</th>
</tr>
</thead>
<tbody>
<tr>
<td>(nM)</td>
<td>(g.mol$^{-1}$)</td>
<td>(Å$^2$)</td>
<td>pH 7.4</td>
<td>pH 2</td>
<td>pH 6.5</td>
<td>(%)</td>
</tr>
<tr>
<td><strong>Target</strong></td>
<td>&lt;100</td>
<td>&lt;500</td>
<td>&lt;85</td>
<td>≤5</td>
<td>≥20</td>
<td>≥20</td>
</tr>
</tbody>
</table>

$^a$ Polar surface area, a predictor of passive diffusion through cell membranes, including the blood brain barrier.

$^b$ D = distribution coefficient, a measure of solubility/lipophilicity, also used to predict membrane permeability.

$^c$ Drugs with insufficient water solubility cannot be developed.

$^d$ Human plasma protein binding estimated using a chromatographic method. Drugs that bind too strongly to plasma proteins are not useful.

$^e$ Predicted hepatic extraction ratio calculated from \textit{in vitro} data using human liver microsomes. An E$_H$ of 1 = complete metabolism by the liver at the rate the drug is presented to it by the blood (\textit{i.e.}, complete first-pass metabolism); an E$_H$ of 0 = no metabolism.

The properties in the Table predict the drug-likeness in a candidate compound. A potency of less than 100 nM is desirable to minimise the dose required. Greater potency usually correlates with greater selectivity, although not always.$^{38}$ Following Lipinski's rule of five, a molecular weight less than 500 is desirable, since most orally available drugs fit this criterion.$^{38}$ Compounds should have a polar surface area of < 85 Å$^2$ and a distribution coefficient of ≤ 5, both of which predict the ability of the drug to permeate cell membranes and, in particular, the blood-brain barrier, a requirement for new HAT
treatments. The compound also needs to have sufficient water solubility at various pH values to allow it to be administered orally, and a human plasma protein binding of <99.5%. If it is bound too strongly to the proteins within the blood plasma it will not be available to travel through the cell membranes and diffuse to the desired target site.\(^{39}\) Lastly, for selection for \textit{in vivo} studies, compounds need to have a predicted hepatic extraction ratio of < 0.6 (see Table 16 footnote for definition). A higher rate of metabolism would necessitate high and/or frequent dosing, which is not compatible with treatment of a third-world disease.

As a general rule, all of these criteria must be met before DND\textit{i} will consider animal testing. A few of the more potent compounds (Figure 27) were tested for these key features at the Centre for Drug Optimization (CDCO) at Monash University.\(^{22}\) For clarity, all tests that "passed" are shown in blue, and all tests that "failed" are highlighted in red. Encouragingly, in the two most potent compounds, most of the DND\textit{i} criteria have been met.

Also required by the DND\textit{i} is that the drugs are trypanosomacidal and not just trypanosomastatic. The former is generally preferred in drug discovery because they actually kill the parasite, rather than just inhibit its proliferation.\(^{40}\) This encourages an actual cure for the disease, where as drugs that simply inhibit the growth often lead to disease reoccurrence, as well as an increased risk of drug resistance.\(^{40}\)

Since the initial assays only test for IC\textsubscript{50} values, and can't differentiate how the drugs actually "kill" the parasite, it was necessary to have "Time to Kill" assays in \textit{T. Cruzi} carried out by the Drug Discovery Unit at the University of Dundee.\(^{22}\) The results
showed that the compounds were indeed trypanosomacidal, and although some toxicity was shown, the great degree of selectivity was reassuring that this shouldn't be an issue.

The primary obstacle still left to overcome is the metabolic stability. Despite variations to the structure, the metabolic stability was unsatisfactory in all four compounds tested, although 200 is frustratingly close. Although this was disappointing, it did give some insight into where the possible sites of metabolism are. Initially it was assumed that the thiazole core was a primary site of metabolism; however, in 178, with a pyrazole core, the metabolic stability was still poor. This led us to believe the metabolic lability was due, at least in part, to the phenyl substituent common in all four analogues tested, or at least posed the possibility of multiple sites of metabolism. Modifications to this site form the basis of the following section.

Table 17: Results of the DNDi criteria testing by CDCO.

<table>
<thead>
<tr>
<th>Potency (nM)</th>
<th>Selectivity Index</th>
<th>MW (g.mol⁻¹)</th>
<th>PSA (Å²)</th>
<th>Solubility pH 2 (µM)</th>
<th>Solubility pH 6.5 (µM)</th>
<th>logD</th>
<th>%E₉⁰</th>
<th>cPPB</th>
</tr>
</thead>
<tbody>
<tr>
<td>#</td>
<td>&lt;100</td>
<td>&lt;500</td>
<td>&lt;85</td>
<td>≥20</td>
<td>≥20</td>
<td>≤5</td>
<td>&lt;0.6</td>
<td>&lt;99.5</td>
</tr>
<tr>
<td>123</td>
<td>190</td>
<td>444</td>
<td>326</td>
<td>42</td>
<td>6–12</td>
<td>ND</td>
<td>3.6</td>
<td>0.95</td>
</tr>
<tr>
<td>172</td>
<td>28</td>
<td>2966</td>
<td>315</td>
<td>45</td>
<td>50–100</td>
<td>25–50</td>
<td>3.2</td>
<td>0.91</td>
</tr>
<tr>
<td>178</td>
<td>330</td>
<td>125</td>
<td>291</td>
<td>47</td>
<td>&gt;100</td>
<td>&gt;100</td>
<td>3.2</td>
<td>0.88</td>
</tr>
<tr>
<td>200</td>
<td>60</td>
<td>1735</td>
<td>298</td>
<td>50</td>
<td>&gt;100</td>
<td>&gt;100</td>
<td>2.8</td>
<td>0.69</td>
</tr>
</tbody>
</table>

Metabolic testing was performed at the Centre for Drug Candidate Optimisation at Monash University.
2.5.2 Testing against other pathogens

Although all primary screening in this project was done against *Trypanosoma brucei brucei*, there is interest in testing against HAT pathogenic strains, as well as other protozoan parasites. In particular, compounds that are effective against Chagas disease, which has many similarities to HAT, are highly desirable.

Chagas disease is caused by another species of trypanosome, *Trypanosoma cruzi*, which is transmitted through the bite of "kissing bugs" or through water contaminated with infected faeces.\(^4\) It is endemic in parts of Latin America with over 10 million people affected, and 15,000 deaths each year.\(^4\) The acute symptoms of Chagas disease include skin lesions, swelling of the lymph nodes and tissues, and chronic infections that can lead to heart failure and death.\(^4\) Similar to African Sleeping Sickness, the main drugs used to treat this disease, benznidazole and nifurtimox (Figure 28), can have severe side effects\(^4\) and drug resistance has been observed\(^4\). New treatment options are desperately needed.\(^4\)
A selection of some of the more potent compounds was assessed for activity against the HAT pathogenic strain *T. brucei rhodesiense*, *T. cruzi*, *Plasmodium falciparum*, the causative agent of malaria, and *Leishmania donovani*, which is responsible for leishmaniasis. In addition, cytotoxicity to L6 cells (rat skeletal muscle cells) was assessed. The compounds had only low micromolar activity (i.e., IC\textsubscript{50} values) against *P. falciparum* and *L. donovani*. The results against the trypanosomes (Table 18) were quite promising, with most of the compounds being equipotent, or in some cases more potent, compared to *T. brucei brucei*. This is encouraging and certainly makes this class of compounds more appealing from a drug development perspective – because they may be useful for the treatment of Chagas and HAT.

![Figure 28: Structures of the primary drugs currently used to treat Chagas disease.](image-url)
Table 18: Potency of analogues against other trypanosome pathogens. Compounds were tested at the Swiss Tropical Institute.\textsuperscript{22}

<table>
<thead>
<tr>
<th>#</th>
<th>IC\textsubscript{50} (µM)</th>
<th>T. b. brucei</th>
<th>T. b. rhod.</th>
<th>T. cruzi</th>
<th>Cytotox. L6</th>
</tr>
</thead>
<tbody>
<tr>
<td>96</td>
<td>0.55</td>
<td>0.08</td>
<td>0.55</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>89</td>
<td>0.79</td>
<td>1.5</td>
<td>2.3</td>
<td>62</td>
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</tr>
<tr>
<td>123</td>
<td>0.19</td>
<td>0.21</td>
<td>0.20</td>
<td>50</td>
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<tr>
<td>156</td>
<td>0.13</td>
<td>0.12</td>
<td>0.22</td>
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<td>0.87</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>152</td>
<td>0.35</td>
<td>0.47</td>
<td>2.54</td>
<td>128</td>
<td></td>
</tr>
<tr>
<td>172</td>
<td>0.028</td>
<td>0.014</td>
<td>0.029</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>178</td>
<td>0.33</td>
<td>0.51</td>
<td>0.83</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>200</td>
<td>0.12</td>
<td>0.025</td>
<td>0.17</td>
<td>54</td>
<td></td>
</tr>
</tbody>
</table>
2.6 Conclusion and Future Directions

A total of 81 new analogues (50 by the candidate) of a HTS hit with potent activity against *T. b. brucei* were synthesized during the course of this project. Of these, 19 are more potent than the original HTS hit. Clear structure activity–relationships have been elucidated, as summarized in Figure 29.

![Structure-Activity Relationship Diagram](image)

**Figure 29:** A summary of the structure–activity relationships discussed in this chapter.

Thiazole and pyrazole cores are well tolerated, but the triazole and tetrazoles investigated were not, despite the fact that one of the original HTS hits is a 1,2,4-triazole (albeit, not very potent). Any modifications to the carbamoyl (–NHC=O) moiety lead to complete loss of activity, and it is essential the "components" stay in the original position; that is, truncation of the molecule or juxtaposition of the key hydrogen-bond accepting and donating groups destroys activity.
The most detailed structure–activity relationships were gained through modification of the right hand side of the molecule (as drawn in this thesis), where the maximum size of the substituent was mapped out. An electron–withdrawing group in the meta position was found to be quite favourable in the series of benzamides. Overall, ureas and carbamates were generally more potent than the corresponding amides. Exocyclic ureas, particularly the one derived from piperidine, appear to be optimal. This is encouraging given that piperidines are considered privileged structures in medicinal chemistry\textsuperscript{42} (Figure 30). In this compound a 100-fold increase in potency over that of the original HTS hit was achieved.

![Chemical structures](image)

**Figure 30**: A few examples of piperidine-containing drugs

A selection of compounds from this class was shown to rapidly kill the parasite, rather than inhibit its growth. In addition, these compounds are also potently toxic to other, human pathogenic, trypanosomes. In summary, in the best compounds, all of the criteria set by the DNDi for selection of compounds for in vivo testing have been achieved, with the exception of metabolic stability. Our attempts to overcome the metabolic instability of this class of compounds is detailed in the following section.

Within the Piggott group, attempts to further optimise the right-hand portion of this class of compounds continue. Investigations include the incorporation of substituted and bicyclic exocyclic ureas, and urea non-classical isosteres such as heterocycles. In
addition, the nature of the receptor-binding pocket that accommodates the electron-withdrawing \textit{meta} substituent in the benzamide series is being more conclusively probed, through a series of subtle modifications. For example the 3-fluoro substituted piperidine 214 (Figure 31). It will be interesting to see whether the ability of the fluorine to boost potency in the benzamide series extends to the piperidines.

It would also be extremely interesting to be able to introduce a radioactive tracer into one of our compounds (perhaps with $^{18}$F) to try to determine the mechanism by which they kill the trypanosomes. Being able to follow the radioactive decay of the molecule could provide insight into its metabolism and chemical interactions$^{43}$ (Figure 31). Access to this information may allow a more rational and informed series of analogues to be designed, and would confirm our SAR and what parts of the molecule could, and should, be manipulated.

\[ \text{Figure 31: Suggested analogues for future work} \]
Chapter 2.7- Modifications to the 2-thiazole substituent

2.7.1 Aims

The last major area of potential modification for the thiazole analogues, was the substituent at the 2-position, on the left hand side of the target structures in this thesis. In particular, it was of interest to determine how an increase in polarity, relative to the phenyl group, would affect the potency and selectivity of analogues. Specifically, the three 2-(pyridyl)thiazole analogues 215–217 were targeted (Figure 32).

Figure 32: Generic 2-(pyridyl)thiazole target analogues

2.8 Synthesis

As outlined in Scheme 32, the synthesis of the pyrid-2-yl analogues 222–223 followed that of the phenyl-substituted series (see pg 118). Condensation of commercial pyridine-2-carbothioamide 218 with dichloroacetone 105 formed the desired chloromethylthiazole 219. There was some concern that this compound would be unstable (prone to polymerization), due to the presence of both electrophilic and nucleophilic groups. Thus, it was taken on immediately to the next step. Nucleophilic substitution with potassium cyanide gave the corresponding nitrile 220. As seen previously, attempts to reduce this nitrile to the primary amine 221 were troublesome; this work was done prior to the improvements using the in situ Boc-protection discussed
in section 2.3.1 (pg 120). Reduction with borane–THF complex\textsuperscript{14} did, however, provide 221 in low yields. This amine was then reacted with benzoyl chloride and cyclopentanecarbonyl chloride in the presence of a base\textsuperscript{10} to yield the desired amides 222–223. These chlorides were chosen because at the time the corresponding phenyl analogues were some of the most potent.

Scheme 32: Synthetic route to 2-(pyrid-2-yl)thiazole analogues

Scheme 33: Attempted condensation reaction between pyridine-3-carbothioamide with dichloroacetone
When this method was extended to the 3- and 4-pyridyl substituents, complications were encountered. The initial reaction\textsuperscript{11} between 225 and 105 (Scheme 33) produced a black viscous mixture (likely the polymerized product), which was very hard to extract. Little if any of the chloride 226 was isolated, and this combined with the low yielding reduction step [protection of 220 with a \textit{boc} group\textsuperscript{17} produced no reduction product in these reactions (224, Scheme 32) (see section 2.3.1, pg 120)]. These difficulties led to the development of a new synthesis that is more compatible with the pyridyl compounds (Scheme 34).

\textbf{Scheme 34: Improved synthesis of 2-substitued thiazoles.}

Regioselective bromination of levulinic acid (227) in MeOH, accompanied by Fischer esterification,\textsuperscript{45} gave the \( \alpha \)-bromoketone 228, which was subjected to condensation with various thioamides (229)\textsuperscript{46} to give thiazoles 230–232 (Table 19). These esters
(230–232) were converted to the primary amides 233–235 by treatment with ammonium hydroxide. A (diacetoxyiodo)benzene-mediated Hofmann rearrangement with capture of the intermediate isocyanates by the solvent, MeOH, then gave the methyl carbamates 236–238. The protecting group was removed by refluxing with 4 M hydrochloric acid overnight to yield the desired amines as their di- (239) and tri-hydrochlorides (240–241) after evaporation of the volatiles. These were coupled with benzoyl chloride or cyclopentanecarbonyl chloride to give the desired target compounds.

\[
\text{Table 19: Yields (\%) and compound numbers (\textbf{bold}) for the reactions shown in Scheme 34}
\]

<table>
<thead>
<tr>
<th>R</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>R = Ph</th>
<th>R = cyclopentyl</th>
</tr>
</thead>
<tbody>
<tr>
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<td>43</td>
<td>36</td>
<td>85</td>
<td>41</td>
<td>242</td>
<td>245</td>
</tr>
<tr>
<td><img src="image2" alt="R" /></td>
<td>230</td>
<td>233</td>
<td>236</td>
<td>242</td>
<td></td>
<td></td>
</tr>
<tr>
<td><img src="image3" alt="R" /></td>
<td>231</td>
<td>234</td>
<td>237</td>
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<td></td>
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<tr>
<td><img src="image4" alt="R" /></td>
<td>232</td>
<td>235</td>
<td>238</td>
<td>244</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Although this synthesis was successful, it required quite a few steps and the divergent step occurs quite early on, requiring many parallel steps to get to each target compound. In addition, the bromide 228 was hard to isolate and the condensation step was very messy, especially with the 3-pyridyl substituent 231.
It was around this time that the potency boosting urea moiety was discovered (see section 2.3.5, pg 141), and we decided that it might be desirable to develop a more efficient method would allow a late divergent step (Scheme 35). The known 2-amino-4-chloromethylthiazole hydrochloride (249) was prepared by condensation of thiourea (248) with dichloroacetone (105). The intention was to convert the amine 249 to the corresponding bromide 250, which would allow subsequent Suzuki coupling (etc.) to incorporate the thiazole-2-substituent. This was attempted with a diazotization reaction in the presence of aqueous hydrobromic acid to give 250. This reaction worked in moderate yield, although there was also some substitution of the chloride to give the dibromide 250y. However, both halides led to the same product in the next step, so the mixture was carried through. A simple substitution of the halide using potassium cyanide12 gave nitrile 251 in moderate yield. Unfortunately, applying the reduction/in situ Boc-protection protocol that worked well with the 2-phenylthiazoles (see section, pg 120)17 was unsuccessful. Although the structure of the major product was not confirmed, the appearance of a new singlet in the crude 1H NMR spectrum (presumably the signal for the thiazole-2-proton) suggested that the bromide had been reduced. Attempted reductions with borane produced a crude product that contained no aromatic protons by 1H NMR spectroscopy, indicating that the thiazole had been completely reduced.
Scheme 35: Attempts at a more efficient synthesis of a precursor to various 2-substituted thiazoles.

At this point it was apparent that incorporating a bromide substituent prior to the nitrile reduction was going to pose a problem. By alternating the order of steps and converting 249 to the corresponding nitrile and then reducing it to the Boc-protected amine before the diazotization step, these unwanted reactions may be avoided. The chloride 249 was converted to the corresponding nitrile in moderate yield. Reduction to introduced new issues. Despite many optimization attempts, and addition of extra quantities of catalyst, the reaction would never proceed to completion, which led to purification issues. Very little desired product was isolated, and that which was contained impurities. It is possible that the 2-aminothiazole group coordinates to the nickel thereby shutting down catalysis. It was decided at this point to explore a different synthetic route.
The phthalimide-protected α-bromoketone (100) described previously (See section 2.1.2, pg 116) was condensed with thiourea to give the 2-aminothiazole 256 in excellent yield (Scheme 36). The bromo-deamination step to 257 proved less facile than expected. Attempts were made using NaNO₂ and HBr, and NaNO₂, HCl and NaBr. All were unsuccessful, with none of the desired product being isolated. The disappearance of the singlet due to the thiazole H5 in the ¹H NMR spectra of the crude products of these reactions indicated that the thiazole ring was undergoing electrophilic aromatic substitution under the reaction conditions, although the exact products were never identified. Again, after multiple attempts, this route was abandoned.

Scheme 36: Attempted synthesis of a phthalimide protected 2-bromothiazole.

Other methods (besides diazonium chemistry) were investigated for the synthesis of 2-halothiazoles. Starting from the bromide 100, a substitution reaction with potassium
thiocyanate\textsuperscript{50} gave 257 in good yield (Scheme 37). Cyclisation of this compound with HBr in acetic acid\textsuperscript{50} gave the 2-bromothiazole 255 in good yield. The proposed mechanism for this reaction is shown in Scheme 38. Although deprotection was attempted at this stage, with hydrazine hydrate\textsuperscript{51} or refluxing in hydrochloric acid,\textsuperscript{52} none of the desired primary amine 250 was isolated. The deprotection with hydrazine is likely complicated by an S\textsubscript{N}Ar reaction of hydrazine with the bromothiazole at elevated temperatures. Subsequent work by Raphael Rahmani in the Baell group has shown that under certain conditions, the phthalimide protecting group can be removed with hydrazine hydrate, providing the target bromide 250 in modest yield.

Scheme 37: Successful method for synthesis of variously 2-substituted thiazoles using Suzuki couplings.
During the present work, the tricky deprotection in the presence of the electrophilic bromothiazole group was avoided by carrying out the Suzuki reaction earlier. Although not ideal with respect to economy of steps, this did ultimately provide a pragmatic solution to the problems noted above. Initially poor yields for the Suzuki reaction of the 2-fluorophenyl and 3-fluorophenylboronic acids (263 and 264, respectively) were improved by using two equivalents of the boronic acid, a temperature of 90 °C (as opposed to refluxing), and adding the catalyst in three increments, spread over 24 hours, rather than all at once. These partially optimized conditions provide the coupled products 263–266 in acceptable yields (Table 20). Deprotection at this point with hydrazine hydrate was facile. The volatiles were simply evaporated and the crude mixture was carried on to the next step. Reaction with carbonyldiimidazole as described in section 2.3.4 (pg 137) gave access to the activated ureas 271–274, which were then reacted with piperidine to yield the target compounds 275–278 in moderate yields.
Scheme 38: Proposed mechanism for the formation of the bromothiazole 257.
Table 20: Yields (%) and compound numbers (bold) for coupling reactions shown in Scheme 37.

<table>
<thead>
<tr>
<th>R</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Compound 1]</td>
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<td>39</td>
<td>41</td>
</tr>
<tr>
<td>![Compound 2]</td>
<td>263</td>
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<td>275</td>
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<td>![Compound 3]</td>
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<td>57</td>
<td>71</td>
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<td>272</td>
<td>276</td>
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<td>50</td>
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<td>63</td>
</tr>
<tr>
<td>![Compound 6]</td>
<td>265</td>
<td>273</td>
<td>277</td>
</tr>
<tr>
<td>![Compound 7]</td>
<td>70</td>
<td>70</td>
<td>64</td>
</tr>
<tr>
<td>![Compound 8]</td>
<td>266</td>
<td>274</td>
<td>278</td>
</tr>
</tbody>
</table>
2.9 Biological results and discussion

The IC\textsubscript{50} values and selectivity indexes (in brackets) from the biological testing are shown in Table 21 below.

Surprisingly the thienyl analogues are much less active than the phenyl despite being isosteres. Although none of the analogues had notable potency, it was encouraging that the activity was at least retained. These results indicate that while the IC\textsubscript{50} is not as potent as with phenyl, it is possible to increase the polarity of the molecule without completely diminishing the activity. This could be helpful in future, if solubility issues arise.
Table 21: IC\textsubscript{50} and selectivity values for the first set of left hand side derivative analogues

<table>
<thead>
<tr>
<th>R</th>
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<th>IC\textsubscript{50}</th>
<th>R</th>
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<th>IC\textsubscript{50}</th>
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<td></td>
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<td>140</td>
<td>0.25 \textmu{}M (151)</td>
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<tr>
<td></td>
<td>222</td>
<td>1.1 \textmu{}M (74)</td>
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<td>223</td>
<td>4.0 \textmu{}M (21)</td>
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<td></td>
<td>243</td>
<td>2.7 \textmu{}M (31)</td>
<td></td>
<td>246</td>
<td>6.6 \textmu{}M (13)</td>
</tr>
<tr>
<td></td>
<td>244</td>
<td>3.1 \textmu{}M (27)</td>
<td></td>
<td>247</td>
<td>9.1 \textmu{}M (9)</td>
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<td></td>
<td>245</td>
<td>2.4 \textmu{}M (35)</td>
</tr>
</tbody>
</table>

2.9.1 Metabolic Stability

In the last chapter, the potency had been improved by 100 fold over the HTS hit by the incorporation of a piperidine-urea as in 172 (Figure 33). The only obstacle preventing progression to evaluation of compounds in animal models was the poor metabolic stability of 172 and similar compounds. It was thought that the metabolic liability might be due to phenyl substituent. The incorporation of fluoro substituents is a common ploy to prevent or mitigate oxidative metabolism of aromatic rings, as the
electronegative fluorine removes electron density from the ring, making it harder to oxidize.\textsuperscript{54} The analogues shown in Figure 33 were designed based on this principle. Although F is isosteric with H, it might have been expected that a slight increase in lipophilicity imparted by the halogens would lead to greater potency of antitrypanosomal action. Although this was not realized, potency was at least retained. However, the selectivity, although still good, diminished significantly compared to the lead compound 172, and this may be due to off-target effects associated with increased lipophilicity.

![Chemical structures](image)

**Figure 33**: IC\textsubscript{50} values for growth inhibition of *T. b. brucei*, along with selectivity indexes relative to HEK cells.
The results for the metabolic stability results are shown in Table 22. Unfortunately none of the analogues had improved stability relative to the lead compound 172; if anything they were metabolised more rapidly. Again, this may be associated with increase in lipophilicity imparted by the fluoro substituents, as cytochorome P_{450} enzymes have hydrophobic active sites. On the basis of these results, it seems likely phenyl substituent in 172 is not the primary site of metabolism as was earlier hypothesised.
Table 22: Metabolic stability results for the fluorophenyl analogue series

<table>
<thead>
<tr>
<th>Target</th>
<th>Metabolic Stability %E&lt;sub&gt;H&lt;/sub&gt; (&lt;0.60)</th>
</tr>
</thead>
</table>
| ![Molecule 275](image1.png) | 0.95<sup>a</sup>  
Rapid Degragation<sup>b</sup> |
| ![Molecule 276](image2.png) | 0.95<sup>a</sup>  
Rapid Degragation<sup>b</sup> |
| ![Molecule 277](image3.png) | 0.86<sup>a</sup>  
0.97<sup>b</sup> |
| ![Molecule 278](image4.png) | 0.90<sup>a</sup>  
0.98<sup>b</sup> |

<sup>a</sup>Human  
<sup>b</sup>Mouse
2.10 Conclusions

This chapter detailed the investigation of various synthetic methods that allowed changes to the thiazole-2-substituent. The most successful route gives access to a wide range of analogues via Suzuki couplings. More work is needed to make the synthesis more efficient by postponing the divergent step.

In total 12 novel analogues were synthesized, which explored structure activity relationships of the thiazole-2-subsituent. Although none were significantly more potent than the current lead, they did provide insight on the ability to incorporate heteroatoms, thus increasing the polarity, while retaining activity.

Since rapid metabolism was preventing progression to in vivo studies, metabolism blockers – fluoro substituents – were incorporated into the 2-phenyl substituent. Unfortunately, this led to no improvement in metabolic stability, suggesting that, either metabolism switches to another part of the molecule, or the phenyl group is not an important site of metabolism in the 2-phenylthiazole series.

During the writing of this thesis, work on alternative thiazole-2-subsituents has continued in the Baell research group. Common substituents and many permutations of substitution pattern have been investigated, but all have led to decreases in potency, and no improvements in metabolic stability have been observed.
2.11 Experimental

**4-(Chloromethyl)-2-phenylthiazole (107).** Thio benzamide (13.4 g, 0.0977 mol) was added to a stirred solution of 1,3-dichloroacetone (16.6 g, 0.131 mol) in acetone (250 mL), and the suspension was heated under reflux overnight. The reaction mixture was allowed to cool to room temperature then vacuum-filtered, and the white solid was washed with acetone (3 × 100 mL), then air-dried. The solid was dissolved in conc. sulfuric acid (80 mL) and the solution was stirred for 30 min, then poured onto ice and cold water was added until no more solid precipitated. The precipitate was collected by vacuum filtration, washed with water (3 × 100 mL) and air-dried to yield 107 as a white solid (17.4 g, 85%), m.p.: 43–45 °C [lit. 1153–55 °C]. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.94–7.96 (m, 2H, H$_2$/H$_6'$), 7.43–7.45 (m, 3H, H$_3$/H$_4$/H$_5'$), 7.30 (t, J = 0.8 Hz, 1H, H$_5$), 4.75 (s, 2H, CH$_2$). The $^1$H NMR data matched those reported. 11

**2-(2-Phenylthiazol-4-yl)acetonitrile (108)12**

A mixture of KCN (5.05 g, 0.0775 mol), 107 (14.8 g, 0.0706 mol) and dry DMF (80 ml) under argon at 70°C was stirred for 18 h. The mixture was allowed to cool, was poured onto water (600 ml) and extracted with EtOAc (3 × 30 ml). The extract was
washed with water (3 × 100 ml), brine (3 × 100 ml), dried, and evaporated to yield 108 as a yellow solid (11.3 g, 80%) of sufficient purity for the next step. m.p.: 34-38 °C. IR (ATR) cm⁻¹: 2253 (CN). ¹H NMR (400 MHz): 7.91–7.94 (m, 2H, H₂'/H₆'), 7.44–7.46 (m, 3H, H₃'/H₄'/H₅'), 7.29 (t, J = 1.0 Hz, 1H, H₅), 3.95 (s, 2H, CH₂). This compound was first reported before the advent of spectroscopic characterisation.⁵⁶

\[
\text{\textbf{tert-Butyl (2-(2-phenylthiazol-4-yl)ethyl)carbamate (110)}}
\]

NaBH₄ (3.57 g, 94.4 mmol) was added slowly, over 30 min, to a solution of di-tert-butyl dicarbonate (5.88 g, 26.9 mmol), NiCl₂ (0.320 g, 1.35 mmol) and nitrile 108 (2.62 g, 13.1 mmol) in dry methanol (100 mL) at 0 °C under argon. The reaction mixture was allowed to warm to room temperature and stirring was continued for 90 min. NEt₃ (1.89 mL) was added and the solution was stirred for 30 min before the volatiles were evaporated. The residue was extracted with EtOAc (3 × 300 mL), and the extract was washed with water (3 × 300 mL) and saturated NH₄Cl (3 × 300 mL), dried, filtered and evaporated to yield 110 as an orange oil (3.27 g, 82%). Rf 0.5 (2:3 EtOAc/hexanes + NEt₃). IR (ATR) cm⁻¹: 3337 (NH), 1693 (C=O). ¹H NMR (400 MHz, CDCl₃) δ 7.91–7.94 (m, 2H, H₂''/H₆''), 7.39–7.46 (m, 3H, H₃''/H₄''/H₅''), 6.96 (s, 1H, H₅''), 5.09 (br s, 1H, NH), 3.54 (dt [app.q], J₁= J₂ = 6.4 Hz, 2H, H1), 2.99 (t, J₁ = 6.4 Hz, 2H, H2), 1.44 (s, 9H, CH₃). ¹³C NMR (101 MHz, CDCl₃) δ 168.2 (C₂'), 156.1 (C₄' or C=O), 155.6 (C₄' or C=O), 133.8 (C₁''), 130.1 (C₄''), 129.0 (2 × ArH), 126.6 (2 × ArH), 114.4 (C₅'), 79.3 (O–C), 40.1 (C1), 31.9 (C2), 28.4 (CH₃). HRMS (ESI) m/z observed: 305.1305, C₁₆H₂₁N₂O₂S⁺ [M+H]⁺ requires 305.1318.
4-(2-Ammonioethyl)-2-phenylthiazol-3-ium chloride (111)

Ice-cold conc. HCl (3.0 mL) was slowly added to a solution of 110 (0.569 g, 1.87 mmol) in 1,4-dioxane (5 mL). After 2 h the volatiles were evaporated under a stream of argon to yield 111 as a yellow solid (0.518 g, mmol, quant.), mp = 140–142 °C. IR (ATR) cm⁻¹: 2443–3986 (NH). ¹H NMR (400 MHz, MeOD) δ 8.00–8.03 (m, 2H, H2″/H6″), 7.60 (s, 1H, H5′), 7.54–7.58 (m, 3H, H3″/H4″/H5″), 3.26 (t, J₁ = 7.2 Hz, 2H, H2), 3.16 (t, J₁ = 7.2 Hz, 2H, H1). ¹H NMR (DMSO, 500 MHz): δ 8.53 (br s, ¹H, NH), 8.26 (br. s, 3H, NH₃), 7.90–7.97 (m, 2H, H2″/H6″), 7.54 (s, 1H, H5′), 7.47–7.53 (m, 3H, H3″/H4″/H5″), 3.14–3.22 (m, 2H, H1), 3.08–3.13 (m, 2H, H2). ¹³C NMR (101 MHz, DMSO) δ 167.1 (C2′), 153.0 (C4′), 132.9 (C1′), 130.3 (C4″), 129.2 (2 × ArH), 126.1 (2 × ArH), 116.3 (C5′), 38.1 (C1), 28.8 (C2). HRMS (ESI) m/z observed: 205.0802, C₁₁H₁₃N₂S⁺ [free base + H]⁺ requires 205.0794. Titration with NaOH/phenolphthalein showed the salt to be the dihydrochloride.

**General procedure (A) for the synthesis of amides from 11 and acid chlorides.** Acid chloride (1.5–2 equiv.) was added dropwise to a stirred mixture of triethylamine (2.5 equiv.) and 111 (1 equiv.) in DCM (10 mL per mmol of 111) at 0 °C under argon. The reaction mixture was allowed to warm to room temp and stirring was continued overnight. The volatiles were evaporated and the residue was purified by flash chromatography as described below.
General procedure (B) for the synthesis of amides from 111, carboxylic acids and DCC. 1-Hydroxybenzotriazole hydrate (HOBT) (1.15 equiv.) and 1,3-dicyclohexylcarbodiimide (DCC) (0.191 g, 0.924 mmol) were added to a solution of the carboxylic acid (1.05 equiv.) in DCM (~10 mL per mmol of 111) at 0 °C under argon. After 1 h, 111 (1 equiv) was added and stirring was continued for 24 h or until TLC showed the reaction to be complete. The reaction mixture was diluted with EtOAc (150 mL), then washed with brine (3 × 100 mL), dried and evaporated to give a residue, which was purified by flash chromatography as described below.

General procedure (C) for the synthesis of amides from 111, carboxylic acids and HBTU. A mixture of carboxylic acid (~1.2 equiv.), HBTU (~1.2 equiv.), Hünig’s base (~3.5 equiv.) and primary amine dihydrochloride 111 (1 equiv.) in 1:1 DMF/DCM or MeCN (~10 mL per mmol of 111), under argon, was stirred for 24 h or until the TLC showed the reaction to be complete. [Workup based on 1 mmol of 111] The solvent was evaporated and the residue was partitioned between DCM (~50 mL) and 10% citric acid (~100 mL) and the aqueous phase was extracted with DCM (2 × 50 mL). The combined organic phase was washed with water (50 mL) and brine (50 mL), dried and evaporated to give a residue, which was purified by flash chromatography as described below.
2-Fluoro-N-(2-(2-phenylthiazol-4-yl)ethyl)benzamide (117)

General procedure (C) was followed with 111 (0.138 g, 0.499 mmol) and 2-fluorobenzoic acid (0.100 g, 0.714 mmol). Elution with 1:4 EtOAc/hexanes gave 117 as a yellow solid (0.111 g, 68%), mp = 80–82 °C. IR (ATR) cm⁻¹: 3317 (NH), 1644 (C=O). ¹H NMR (400 MHz, CDCl₃) δ 8.08 (dd [app. dt], J₁ = 8.0 Hz, J₂ = 2.0 Hz, 1H, H4), 7.93–7.97 (m, 2H, H2''/H6''), 7.57 (br. s, 1H, NH), 7.40–7.47 (m, 4H, Ar), 7.24 (ddd [app. dt], J₁ = 7.8 Hz, J₂ = 1.0 Hz, 1H, H5), 7.09 (ddd, J = 12.0, 8.4, 1.2 Hz, 1H, H3), 7.02 (t, J = 0.8 Hz, 1H, H5''), 3.91 (pseudo q., 2H, H1'), 3.12 (t, J = 6.4 Hz, 2H, H2'). ¹³C NMR (101 MHz, CDCl₃) δ 168.5 (C2''), 163.4 (d, J = 3 Hz, C=O), 160.7 (d, J = 249 Hz, C2F), 155.5 (C4''), 133.7 (C1'''), 133.2 (d, J = 9 Hz, C6), 132.1 (d, J = 3 Hz, C4), 130.1 (C4''''), 129.0 (2 × ArH), 126.6 (2 × ArH), 124.8 (d, J = 3 Hz, C5), 121.5 (d, J = 11 Hz, C1), 116.1 (d, J = 25 Hz, C3), 114.5 (C5'''), 39.7 (C1'), 31.1 (C2'). HRMS (ESI) m/z observed: 327.0982, C₁₈H₁₆FN₂O₂S⁻ [M+H]⁺ requires: 327.0967.

2-Methyl-N-(2-(2-phenylthiazol-4-yl)ethyl)benzamide (119)

General procedure (C) was followed with 111 (0.327 g, 1.18 mmol) and o-toluic acid (0.164 g, 1.20 mmol). Elution with 2:3 EtOAc/hexanes gave 119 as a pale-yellow solid
(0.282 g, 74%), mp = 104–105 °C. Rf 0.5 (2:3 EtOAc/hexanes). IR (ATR) cm⁻¹: 3289 (NH), 1621 (C=O). ¹H NMR (400 MHz, CDCl₃) δ 7.86–7.87 (m, 2H, H²''/H⁶''), 7.39–7.41 (m, 4H, H³''/H⁴''/H⁵''/H⁶), 7.25 (ddd [app. dt], J₁ = J₂ = 7.6 Hz, J₃ = 1.6 Hz, 1H, H₄ or H₅), 7.15–7.21 (m, 2H, 2 × ArH), 6.92 (br. s, 1H, NH), 6.90 (s, 1H, C⁵''), 3.85 (dt [app. q], J₁ = J₂ = 6.0 Hz, 2H, C¹'), 3.12 (t, J₁ = 6.4 Hz, 2H, C²'), 2.45 (s, 3H, CH₃). ¹³C NMR (101 MHz, CDCl₃) δ 170.1 (C=O or C²''), 168.3 (C=O or C²''), 155.5 (C⁴''), 136.6 (C¹''), 136.2 (C₁ or C₂), 133.5 (C₁ or C₂), 131.0 (ArH), 130.1 (ArH), 129.8 (ArH), 129.0 (2 × ArH), 126.9 (ArH), 126.4 (2 × ArH), 125.7 (ArH), 114.5 (C⁵''), 39.3 (C¹'), 30.9 (C²'), 19.9 (CH₃). HRMS (ESI) m/z observed: 323.1211, C₁₉H₁₅N₂OS⁺ [M+H]⁺ requires 323.1218.

2-Hydroxy-N-(2-(2-phenylthiazol-4-yl)ethyl)benzamide (120)

General procedure (C) was followed with 111 (0.167 g, 0.602 mmol) and salicylic acid (0.108 g, 0.782 mmol). Elution with 1:4 EtOAc/hexanes gave 120 as a white solid (0.131 g, 67%), mp = 96–98 °C. Rf 0.35 (1.4 EtOAc/hexanes). IR (ATR) cm⁻¹: 3359 (NH), 2583–3099 (OH), 1605 (C=O). ¹H NMR (500 MHz, CDCl₃) δ 12.48 (br. s, 1H, OH), 8.25 (br. s, 1H, NH), 7.94–7.96 (m, 2H, H²''/H⁶''), 7.53 (d, J = 7.2 Hz, 1H, H⁶), 7.45–7.48 (m, 3H, H³''/H⁴''/H⁵''), 7.37 (dd [app. t], J₁ = J₂ = 8.0 Hz, 1H, H⁴), 7.05 (s, 1H, H⁵''), 6.97 (d, J = 8.0 Hz, 1H, H₃), 6.79 (dd [app. t], J₁ = J₂ = 7.2 Hz, 1H, H⁴), 3.81 (dt [app. q], J₁ = J₂ = 5.9 Hz, 2H, H²'), 3.11 (t, J = 6.4 Hz, 2H, H¹'). ¹³C NMR (126 MHz, CDCl₃) δ 170.0 (C=O or C²''), 168.9 (C=O or C²''), 161.7 (C₂), 155.4 (C⁴''), 134.1 (C₃), 133.4 (C¹''), 130.5 (ArH), 129.2 (2 × ArH), 126.6 (2 × ArH), 125.9 (ArH),
118.61 (C3 or C5), 118.58 (C3 or C5), 115.0 (C5''), 114.8 (C1), 39.3 (C1'), 30.2 (C2').

HRMS (ESI) m/z observed: 325.1024, C_{18}H_{17}N_{2}O_{2}S^{+} [M+H]^+ requires 325.1011.

2-Methoxy-N-(2-(2-phenylthiazol-4-yl)ethyl)benzamide (121)

General procedure (B) was followed with 111 (0.200 g, 0.721 mmol) and o-anisic acid (0.115 g, 0.754 mmol). Elution with 1:9 then 2:3 EtOAc/hexanes gave 121 as an orange oil (0.164 g, 74%). Rf 0.3 (3:7 EtOAc/Hexanes). IR (ATR) cm\(^{-1}\): 3341 (NH), 1638 (C=O). \(^1\)H NMR (400 MHz, CDCl\(_3\) \(\delta\) 8.20–8.23 (m, 1H, H6), 8.17 (br s, 1H, NH), 7.94–7.97 (m, 2H, H2''/H6''), 7.40–7.46 (m, 4H, ArH), 7.07 (pseudo t, 1H, H4 or H5), 7.01 (s, 1H, H5''), 6.91 (d, J = 8.4 Hz, 1H, H3), 3.92 (dt [app. q], J\(_1\) = J\(_2\) = 6.4 Hz, 2H, H1'), 3.76 (s, 1H, OMe), 3.14 (t, J\(_1\) = 6.4 Hz, 2H, H2'). \(^{13}\)C NMR (101 MHz, CDCl\(_3\) \(\delta\) 168.1 (C2''), 165.4 (C=O), 157.6 (C2), 155.9 (C4''), 133.9 (C1'''), 132.7 (ArH), 132.3 (ArH), 130.1 (ArH), 129.1 (2 \(\times\) ArH), 126.6 (2 \(\times\) ArH), 121.9 (C1), 121.4 (ArH), 114.6 (C5''), 111.4 (C3), 55.9 (OMe), 39.2 (C1'), 31.6 (C2'). HRMS (ESI) m/z observed: 339.1165, C_{19}H_{18}N_{2}O_{2}S^{+} [M+H]^+ requires 339.1162.
2-Cyano-N-(2-(2-phenylthiazol-4-yl)ethyl)benzamide (122)

General procedure (C) was followed with 111 (0.350 g, 1.26 mmol) and 2-cyanobenzoic acid (0.235 g, 1.59 mmol). Elution with 2:3 EtOAc/hexanes gave 122 as a light yellow oil (0.168 g, 40%). R_f 0.4 (2:3 EtOAc/hexanes). IR (ATR) cm⁻¹: 3276 (NH), 2227 (CN), 1650 (C=O). ¹H NMR (500 MHz, CDCl₃) δ 8.00 (v. br. s, NH), 7.81–7.85 (m, 3H, H₃/H₂''/H₆'''), 7.75 (br. d, J₁ = 8.0 Hz, H₆), 7.59–7.67 (m, 2H, H₄/H₅), 7.35–7.38 (m, 3H, H₃''/H₄''/H₅''), 6.98 (s, 1H, H₅''), 4.23 (t, J₁ = 7.2 Hz, 2H, H₁'), 3.24 (t, J₁ = 7.2 Hz, 2H, H₂'). ¹³C NMR (126 MHz, CDCl₃) δ 168.2 (C₂'' or C=O), 168.0 (C₂'' or C=O), 154.5 (C₄''), 133.7, 133.0 (ArH), 132.3 (ArH), 131.2, 130.0 (ArH), 129.0 (2 × ArH), 126.6 (2 × ArH), 126.5 (ArH), 123.3 (ArH), 121.2 (br. CN), 114.8 (C₅''), 37.8 (C₁'), 30.1 (C₂'). Two pairs of signals are isochronous or too broad to be observed. HRMS (ESI) m/z observed: 334.1028, C₁₉H₁₆N₃O₅⁺ [M+H]^⁺ requires 334.1014.

3-Fluoro-N-(2-(2-phenylthiazol-4-yl)ethyl)benzamide (123)

General procedure (C) was followed with 111 (0.225 g, 0.812 mmol) and 3-fluorobenzoic acid (0.144 g, 1.03 mmol). Elution with 3:10 EtOAc/hexanes gave 123 as a pale-yellow oil (0.109 g, 41%). R_f 0.5 (3:10 EtOAc/hexanes). IR (ATR) cm⁻¹: 3332 (NH), 1644 (C=O). ¹H NMR (500 MHz, CDCl₃) δ 7.94–7.96 (m, 2H, H₂''/H₆''), 7.89–7.92 (m, 3H, H₃/H₂''/H₆''), 7.84 (d, J₁ = 8.0 Hz, H₆), 7.59–7.67 (m, 2H, H₄/H₅), 7.35–7.37 (m, 3H, H₃''/H₄''/H₅''), 6.98 (s, 1H, H₅''), 4.23 (t, J₁ = 7.2 Hz, 2H, H₁'), 3.24 (t, J₁ = 7.2 Hz, 2H, H₂').
(br. s, 1H, NH), 7.57–7.63 (m, 2H, H2/H6), 7.44–7.47 (m, 3H, H3''/H4''/H5''), 7.35–7.40 (m, 1H, H4 or H5), 7.19 (dddd [app. ddt], J1 = J2 = 8.4, J3 = 2.6, J4 = 1.0 Hz, 1H, H4), 7.03 (t, J = 0.8 Hz, 1H, H5''), 3.82 (pseudo q., 2H, H1'), 3.10 (dt, J = 6.0, 0.8 Hz, 2H, H2'). 13C NMR (126 MHz, CDCl3) δ 168.8 (C2''), 166.1 (d, J = 2 Hz, C=O), 162.9 (d, J = 249 Hz, C3F), 155.8 (C4''), 137.3 (d, J = 7 Hz, C3), 133.5 (C1'''), 130.4 (C4''), 130.3 (d, J = 8 Hz, C5), 129.2 (2 × ArH), 126.6 (2 × ArH), 122.7 (d, J = 3 Hz, C6), 118.4 (d, J = 22 Hz, C2 or C4), 114.8 (C5''), 114.4 (J = 23 Hz, C2 or C4), 114.3 (C2), 40.0 (C1'), 30.5 (C2'). HRMS (ESI) m/z observed: 327.0982, C18H16FN2OS+ [M+H]+
requires 327.0967.

3-Methyl-N-(2-(2-phenylthiazol-4-yl)ethyl)benzamide (125)

General procedure (A) was followed with 111 (0.144 g, 0.519 mmol) and m-toluoyl chloride (0.132 ml, 1.00 mmol). Elution with 1:3 EtOAc/hexanes gave 125 as a light brown solid (0.151 g, 90%), mp = 67–70 °C. Rf 0.25 (1:3 EtOAc/hexanes). IR (ATR) cm⁻¹: 3329 (NH), 1640 (C=O). 1H NMR (400 MHz, CDCl3) δ 7.92–7.96 (m, 2H, H2/H6 or H2''/H6''), 7.64 (br s, 1H, NH), 7.62–7.65 (m, 2H, H2/H6 or H2''/H6''), 7.41–7.45 (m, 3H, H3''/H4''/H5'''), 7.28–7.29 (m, 2H, H4/H5), 7.01 (s, 1H, H5''), 3.81–3.85 (pseudo q, 2H, H1'), 3.09 (t, J = 6.0 Hz, 2H, H2'), 2.36 (s, 3H, CH3). 13C NMR (101 MHz, CDCl3) δ 168.5 (C2'' or C=O), 167.6 (C2'' or C=O), 155.9 (C4''), 138.4 (C1'' or C1 or C3), 134.9 (C1'' or C1 or C3), 133.6 (C1'' or C1 or C3), 132.1 (ArH), 130.2 (ArH), 129.1 (2 × ArH), 128.4 (ArH), 127.7 (ArH), 126.5 (2 × ArH),

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124.2 (ArH), 114.6 (C5''), 39.7 (C1'), 30.7 (C2'), 21.5 (CH). HRMS (EI) m/z observed: 322.1144, C_{19}H_{18}N_{2}O_{2}S [M•+] requires 322.1140.

3-Methoxy-N-(2-(2-phenylthiazol-4-yl)ethyl)benzamide (127)

General procedure (A) was followed with 111 (0.311 g, 1.12 mmol) and m-anisoyl chloride (0.29 mL, 2.0 mmol). Elution with 2:3 EtOAc/hexanes gave 127 as a yellow solid (0.266 g 70%), mp = 70–72 °C. Rf 0.5 (1:1 EtOAc/hexanes). IR (ATR) cm⁻¹: 3332 (NH), 1644 (C=O). ¹H NMR (400 MHz, CDCl₃) δ 7.92–7.95 (m, 2H, H₂''''/H₆'''''), 7.69 (br. s, 1H, NH), 7.41–7.45 (m, 4H, H₃'''''/H₄'''''/H₅'''''/H₂), 7.36 (ddd [app. dt], J₁ = 7.6, J₂ = J₃ = 1.4 Hz, 1H, H₆), 7.28 (dd [app. t], J₁ = J₂ = 8.0 Hz, 1H, H₅), 7.01 (s, 1H, H₅''), 7.02 (ddd, J = 8.2, 2.6, 1.0 Hz, 1H, H₄), 3.81 (s, 3H, CH₃), 3.83 (pseudo q. 2H, H₁'), 3.09 (t, J₁ = 6.0 Hz, 2H, H₂'). ¹³C NMR (101 MHz, CDCl₃) δ 167.3 (C2''), 159.9 (C₃ or C=O), 155.8 (C₃ or C=O), 136.5 (C4'''), 133.5 (C1''''), 130.2 (ArH), 129.5 (ArH), 129.1 (2 × ArH), 126.6 (2 × ArH), 118.9 (ArH), 117.6 (ArH), 114.6 (C5''), 112.4 (ArH), 55.5 (CH₃), 39.7 (C1'), 30.7 (C2'). HRMS (EI) m/z observed: 338.1077, C_{19}H_{18}N_{2}O_{2}S [M•+] requires 338.1089.
3-Cyano-N-(2-(2-phenylthiazol-4-yl)ethyl)benzamide (128)

General procedure (C) was followed with 111 (0.309 g, 1.11 mmol) and 3-cyanobenzoic acid (0.207 g, 1.41 mmol). Elution with 2:3 EtOAc/hexanes gave 128 as a yellow oil (0.234 g, 63%). \( R_f \) 0.3 (2:3 EtOAc/hexanes). IR (ATR) cm\(^{-1}\): 3322 (NH), 2231 (CN), 1644 (C=O). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 8.13 (m, 1H, H2), 8.09 (br. s, 1H, NH), 8.08 (ddd, \( J = 8.0 \) Hz, 1.5, 1.0 Hz, 1H, H4 or H6), 7.88–7.90 (m, 2H, H2''/H6''), 7.74 (ddd, \( J = 7.5, 1.5, 1.0 \) Hz, 1H, H4 or H6), 7.50 (ddd [app. dt], \( J_1 = J_2 = 7.5, J_3 = 0.5 \) Hz, 1H, H5), 7.47 (m, 3H, H3'''/H4'''/H5'''), 7.03 (s, 1H, H5''), 3.82 (pseudo q, 2H, H1'). \(^13\)C NMR (126 MHz, CDCl\(_3\)): \( \delta \) 168.9 (C2''), 165.1 (C=O), 155.4 (C4''), 136.1 (C1''''), 134.6 (ArH), 133.1, 131.6 (ArH), 130.7 (ArH), 130.6 (ArH), 129.6 (ArH), 129.3 (2 × ArH), 126.4 (2 × ArH), 118.9 (CN), 115.0 (C5''), 112.9 (C3), 40.0 (C1'), 30.3 (C2'). HRMS (ESI) \( m/z \) observed: 334.1006, \( [M+H]^+ \) requires 334.1014.

4-Fluoro-N-(2-(2-phenylthiazol-4-yl)ethyl)benzamide (129)

General procedure (A) was followed with 111 (0.249 g, 0.898 mmol) and 4-fluorobenzoyl chloride (0.177 mL, 1.50 mmol). Elution with 1:3 EtOAc/hexanes gave 129 as a white solid (0.224 g, 76%), mp = 123–124 °C. \( R_f \) 0.20 (1:3 EtOAc/hexanes). IR (ATR) cm\(^{-1}\): 3333 (NH) 1651 (C=O). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.92–7.95 (m,
2H, H2/H6 or H2''/H6''), 7.83–7.87 (m, 2H, H2/H6 or H2''/H6'''), 7.72 (br s, 1H, NH), 7.45–7.47 (m, 3H, H3''/H4''/H5''), 7.03 (dd [app. t], \(J_{ortho} = J_{H-H} = 8.6\) Hz, 2H, H3/H5), 7.03 (s, 1H, H5''), 3.78 (dt [app. q], \(J_1 = 5.6\) Hz, 2H, H1'), 3.08 (t, \(J = 5.6\) Hz, 2H, H2').

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 168.5 (C2'' of C=O), 166.4 (C2'' of C=O), 164.6 (d, \(J = 250\) Hz, C4), 155.6 (C4''), 133.5 (C1'''), 131.0 (d, \(J = 10\) Hz, C1), 130.3 (C4'''), 129.4 (d, \(J = 10\) Hz, C2/C6), 129.0 (2 × ArH), 126.4 (2 × ArH), 115.4 (d, \(J = 22\) Hz, C3/C5), 114.7 (C5''), 39.8 (C1'), 30.5 (C2'). HRMS (EI) \(m/z\) observed: 326.0880, C\(_{18}\)H\(_{15}\)FN\(_2\)OS \([\text{M}^+\] requires 326.0889.

4-Methyl-N-(2-(2-phenylthiazol-4-yl)ethyl)benzamide (131)

General procedure (C) was followed with 111 (0.200 g, 0.721 mmol) and p-toluic acid (0.091 g, 0.754 mmol). Elution with 2:3 EtOAc/hexanes gave 131 as a yellow solid (0.102 g, 48%), mp = 104–105 °C. \(R_f\) 0.5 (2:3 EtOAc/hexanes). IR (ATR) cm\(^{-1}\): 3268 (NH), 1626 (C=O). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.94–7.97 (m, 2H, H2''/H6'''), 7.72 (d, \(J = 8.4\) Hz, 2H, H2/H6), 7.59 (br. s, 1H, NH), 7.44–7.47 (m, 3H, H3''/H4''/H5'''), 7.20 (d, \(J = 8.4\) Hz, 2H, H3/H5), 7.03 (s, 1H, H5''), 3.83 (dt [app. q], \(J_1 = J_2 = 6.8\) Hz, 2H, H1'), 3.12 (t, \(J = 6.4\) Hz, 2H, H2'), 2.36 (s, 3H, CH\(_3\)). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 168.3 (C=O or C2''), 167.4 (C=O or C2''), 155.7 (C4''), 141.7 (C4), 133.5 (C1'''), 132.0 (C1), 130.2 (ArH), 129.1 (2 × ArH), 129.0 (2 × ArH), 127.0 (2 × ArH), 126.5 (2 × ArH), 114.6 (C5''), 39.6 (C1'), 30.7 (C2'), 21.5 (CH\(_3\)). HRMS (ESI) \(m/z\) observed: 323.1209, C\(_{19}\)H\(_{19}\)N\(_2\)OS\(^+\) \([\text{M+H}]^+\) requires 323.1218.
4-Methoxy-N-(2-(2-phenylthiazol-4-yl)ethyl)benzamide (133)

General procedure (B) was followed with 111 (0.200 g, 0.721 mmol) and p-anisic acid (0.103 g, 0.754 mmol). Elution with 1:9 then 2:3 EtOAc/hexanes gave 133 as a white solid (0.0756 g, 31%), mp = 94–98 °C. R_f 0.35 (2:3 EtOAc/hexanes). IR (ATR) cm⁻¹: 3384 (NH), 1650 (C=O). ¹H NMR (400 MHz, CDCl₃) δ 7.93–7.97 (m, 2H, H₂''/H₆''), 7.78–7.81 (m [AB], 2H, H₂/H₆), 7.75 (br. s, 1H, NH), 7.43–7.47 (m, 3H, H₃''/H₄''/H₅''), 7.02 (s, 1H, H₅''), 6.87–6.91 (m [AB], 2H, H₃/H₅), 3.83 (s, 3H OMe), 3.80–3.84 (m, 2H, H₁'), 3.10 (t, J₁ = 5.6 Hz, 2H, H₂'). ¹³C NMR (101 MHz, CDCl₃) δ 168.0 (C₂''), 165.4 (C=O), 157.6 (C₄), 155.8 (C₄''), 133.8 (C₁'''), 132.7 (ArH), 132.3 (ArH), 130.1 (ArH), 129.0 (2 × ArH), 126.6 (2 × ArH), 121.8 (C₁), 121.3 (ArH), 114.5 (C₅''), 111.4 (C₃/C₅), 55.9 (OMe), 39.2 (C₁'), 31.6 (C₂'). HRMS (ESI) m/z observed: 339.1167, C₁₉H₁₉N₂O₂S⁺ [M+H]⁺ requires 339.1162.

4-Cyano-N-(2-(2-phenylthiazol-4-yl)ethyl)benzamide (134)

General procedure (C) was followed with 111 (0.253 g, 0.913 mmol) and 4-cyanobenzoic acid (0.170 g, 1.16 mmol). Elution with 3:10 EtOAc/hexanes gave 134 as a pale-green solid (0.265 g, 87%), mp = 148–150 °C. R_f 0.3 (3:10 EtOAc/hexanes). IR
(ATR) cm$^{-1}$: 3309 (NH) 2227 (CN), 1631 (C=O). $^1$H NMR (500 MHz, CDCl$_3$) δ 8.06 (br. unresolved t, 1H NH), 7.87–7.93 (m, 4H, 4 × ArH), 7.64–7.67 (m, 2 × ArH), 7.39–7.47 (m, 3H, H3''′/H4''′/H5''′), 7.02 (s, 1H, H5''), 3.80 (pseudo q, 2H, H1'), 3.08 (t, $J = 6.0$ Hz, 2H, H2'). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 168.6 (C2'' or C=O), 165.4 (C2'' or C=O), 155.4 (C4'''), 138.8 (C1'''), 133.4 (C4), 132.4 (2 × ArH), 130.5 (C4''), 129.1 (2 × ArH), 127.8 (2 × ArH), 126.4 (2 × ArH), 118.2 (CN), 114.88 (C5'''), 114.88 (C1), 39.9 (C1'), 30.3 (C2'). HRMS (ESI) m/z observed: 334.1018, C$_{19}$H$_{16}$N$_3$O$_5$ $^+$ [M+H]$^+$ requires 334.1014.

2-Phenyl-N-(2-(2-phenylthiazol-4-yl)ethyl)acetamide (135)

General procedure (A) was followed with 111 (0.210 g, 0.758 mmol) and phenylacetyl chloride (0.172 ml, 1.30 mmol). Elution with 1:3 EtOAc/hexanes gave 135 as a white solid (0.0782 g, 32%), mp = 113–118 °C. R$_f$ 0.25 (1:3 EtOAc/hexanes). IR (ATR) cm$^{-1}$: 3290 (NH), 1657 (C=O). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.81–7.84 (m, 2H, H2''′/H6''′), 7.41–7.43 (m, 3H, H3''′/H4''′/H5''′), 7.19–7.21 (m, 5H, benzyl Ar), 6.79 (s, 1H, H5''), 6.13 (br s, 1H, NH), 3.61 (dt [app. q], $J_1 = J_2 = 6.4$ Hz, 2H, H1'), 3.53 (s, 2H, H2), 2.92 (t, $J = 6.4$ Hz, 2H, H2'). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 171.1 (C=O), 168.2 (C2''), 155.3 (C4''), 135.0 (C1''' or C1'''''), 133.6 (C1'''' or C1''''''), 130.1 (ArH), 129.4 (2 × ArH), 129.0 (2 × ArH), 127.3 (ArH), 126.5 (2 × ArH), 114.5 (C5''), 44.1 (C2), 39.0 (C1'), 31.0 (C2'). HRMS (EI) m/z observed: 322.1147, C$_{19}$H$_{18}$N$_2$OS $^+$ [M$^+$] requires 322.1140.
**N-(2-(2-Phenylthiazol-4-yl)ethyl)-1-naphthamide (136)**

General procedure (B) was followed with 111 (0.218 g, 0.786 mmol) and 1-naphthoic acid (0.138 g, 0.802 mmol). Elution with 1:1 EtOAc/hexanes gave 136 as an orange solid (0.214 g, 75%), mp = 104–106 °C. Rₐ 0.2 (1:1 EtOAc/hexanes). IR (ATR) cm⁻¹: 3288 (NH), 1644 (C=O). ¹H NMR (400 MHz, CDCl₃) δ 8.35–8.37 (m, 1H, H₂), 7.91 (d, 1H, J = 8.4 Hz, H₄), 7.85–7.89 (m, 1H, naphthyl), 7.78–7.81 (m, 2H, H₂''/H₆''), 7.66 (dd, J₁ = 7.0 Hz, J₂ = 1.0 Hz, 1H, H₅ or H₈), 7.48–7.52 (m, 2H, 2 × Ar), 7.33–7.45 (m, 4H, 4 × Ar), 7.24 (br. s, 1H, NH), 7.02 (s, 1H, H₅''), 3.96 (dt [app. q], J₁ = J₂ = 6.2 Hz, 2H, H₁''), 3.18 (t, J = 6.4 Hz, 2H, H₂'). ¹³C NMR (101 MHz, CDCl₃) δ 169.5 (C₂'' or C=O), 168.4 (C₂'' or C=O), 155.5 (C₄''), 134.8 (Ar), 133.8 (Ar), 133.4 (Ar), 130.6 (ArH), 130.3 (Ar), 130.1 (ArH), 129.0 (2 × ArH), 128.3 (ArH), 127.1 (ArH), 126.43 (ArH), 126.39 (2 × ArH), 125.6 (ArH), 125.2 (ArH), 124.8 (ArH), 114.6 (C₅''), 39.6 (C₁'), 30.9 (C₂'). HRMS (ESI) m/z observed: 359.1204, C₂₂H₁₉N₂OS⁺ [M+H]⁺ requires 359.1218.
**N-(2-(2-Phenylthiazol-4-yl)ethyl)-2-naphthamide (137)**

General procedure (B) was followed with 111 (0.218 g, 0.786 mmol) and 2-naphthoic acid (0.138 g, 0.802 mmol). Elution with 1:4 EtOAc/hexanes gave 137 as an orange solid (0.217 g, 77%), mp = 124–125 °C. Rf: 0.3 (1:4 EtOAc/hexanes). IR (ATR) cm⁻¹: 3301 (NH), 1644 (C=O). ¹H NMR (400 MHz, CDCl₃) δ 8.35 (s, 1H, H1), 7.92–7.99 (m, 4H, Ar), 7.84–7.92 (m, 3H, NH + 2 × Ar), 7.51–7.58 (m, 2H, 2 × Ar), 7.41–7.50 (m, 3H, H3"/H4"/H5"), 7.06 (s, 1H, H5"), 3.90 (dt [app. q], J₁ = J₂ = 6.0 Hz, 2H, H1'), 3.16 (t, J₁ = 6.0 Hz, 2H, H2'). ¹³C NMR (101 MHz, CDCl₃) δ 168.7 (C=O or C2''), 167.5 (C=O or C2''), 156.0 (C4''), 134.9 (Ar), 133.6 (Ar), 132.8 (Ar), 132.3 (Ar), 130.4 (ArH), 129.2 (2 × ArH), 129.1 (ArH), 128.5 (ArH), 127.9 (ArH), 127.6 (ArH), 127.4 (ArH), 126.7 (ArH), 126.6 (2 × ArH), 124.0 (ArH), 114.8 (C5"), 39.9 (C1'), 30.7 (C2').

HRMS (ESI) m/z observed: 359.1226, C₂₂H₁₉N₂OŚ⁺ [M+H]⁺ requires 359.1218.

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**2-(Benzceptors|1,3|dioxol-5-yl)-N-(2-(2-phenylthiazol-4-yl)ethyl)acetamide (138)**

General procedure (A) was followed with 111 (0.213 g, 0.768 mmol) and benzo[1,3]dioxol-5-yl-acetyl chloride (0.400 mL, ~2 mmol). Elution with 1:3
EtOAc/hexanes gave 138 as a pale-orange solid (0.182 g, 65%), mp = 113–118 °C. Rf 0.15 (1:1 EtOAc/hexanes). IR (ATR) cm⁻¹: 3295 (NH), 1647 (C=O). ¹H NMR (400 MHz, CDCl₃) δ 7.81–7.85 (m, 2H, H₂''/H₆''), 7.41–7.45 (m, 3H, H₃'''/H₄'''/H₅''''), 6.85 (s, 1H, H₅''), 6.62–6.67 (m, 2H, H₄'''/H₇''''), 6.6 (dd, J = 8.2, 1.4 Hz, 1H, H₆''''), 6.19 (br. s, 1H, NH), 5.81 (s, 2H, H₂''''''), 3.63 (dt [app. q], J₁ = J₂ = 6.2 Hz, 2H, H₁'), 2.94 (t, J = 6.0 Hz, 2H, H₂'). ¹³C NMR (101 MHz, CDCl₃) δ 171.2 (C=O), 168.2 (C₂''), 155.3 (C₄''), 148.0 (ArO), 146.8 (ArO), 133.6 (C₁'''), 130.1 (C₄''''), 129.0 (2 × ArH), 128.6 (C₅''''), 126.4 (2 × ArH), 122.6 (ArH), 114.5 (C₅'''), 109.7 (ArH), 108.6 (ArH), 101.1 (CH₂O₂), 43.6 (C₂), 38.9 (C₁'), 31.0 (C₂'). HRMS (EI) m/z observed: 366.1042, C₂₀H₁₈N₂O₃S [M⁺] requires 366.1038.

**N-(2-(2-Phenylthiazol-4-yl)ethyl)cyclohexanecarboxamide (139)**

General procedure (C) was followed with 111 (0.253 g, 0.913 mmol) and cyclohexanecarboxylic acid (0.511 g, 1.18 mmol). Elution with 1:4 EtOAc/hexanes then 2:3 EtOAc/hexanes gave 139 as a white solid (0.232 g, 80%), mp = 128–130 °C. Rf 0.3 (1:4 EtOAc/hexanes). IR (ATR) cm⁻¹: 3293 (NH), 1637 (C=O). ¹H NMR (400 MHz, CDCl₃) δ 7.93 (m, 2H, H₂''/H₆''), 7.43 (m, 3H, H₃'''/H₄'''/H₅''''), 6.95 (s, 1H, H₅''), 6.55 (br. s, 1H, NH), 3.62 (dt [app. q], J₁ = J₂ = 6.2 Hz, 2H, H₁'), 2.99 (t, J₁ = J₂ = 6.0 Hz, 2H, H₂'), 2.08 (m, 1H, H1), 1.87 (m, 2H, H₂a/H₆a), 1.75 (m, 2H, H₂b/H₆b), 1.64 (m, 1H, H₄a), 1.39 (m, 2H, H₃a/H₅a), 1.22 (m, 3H, H₃b/H₄b/H₅b). ¹³C NMR (101 MHz, CDCl₃) δ 176.2 (C=O), 168.3, (C₂''), 155.8 (C₄''), 133.7 (C₁'''), 130.2 (C₄''''), 129.1 (2 × ArH), 126.5 (2 × ArH), 114.5 (C₅'''), 45.6 (C₁'), 38.9 (C₁), 30.9 (C₂'), 29.8 (C₂/C₆),
25.90 (C4), 25.87 (C3/C5). HRMS (CI) m/z observed: 315.1533, C_{18}H_{23}N_{2}O_{5}^{+} [M+H]^{+} requires 315.1531.

\[ \text{N-}(2-(2-\text{Phenylthiazol}-4-\text{yl})\text{ethyl})\text{picolinamide (142)} \]

General procedure (C) was followed with 111 (0.097 g, 0.35 mmol) and picolinic acid (0.062 g, 0.50 mmol). Elution with 1:1 EtOAc/hexanes gave 142 as a yellow oil (0.078 g, 72%). R_f 0.5 (1:1 EtOAc/hexanes). IR (ATR) cm\(^{-1}\): 3367 (NH), 1663 (C=O). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 9.01 (br. s, 1H, NH), 8.58–8.60 (m, 1H, H6), 8.21–8.23 (m, 1H, H3), 8.06–8.09 (m, 2H, H2''/H6''), 7.41–7.48 (m, 4H, H4 or H5), 7.00 (s, 1H, H5''), 6.88 (dt [app. q], \(J_1 = J_2 = 6.4\) Hz, 2H, H1'), 3.13 (t, \(J_1 = 6.4\) Hz, 2H, H2'). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 168.3 (C2''), 164.5 (C=O), 155.6 (C4''), 150.3 (C2), 148.2 (C6), 137.6 (ArH), 133.8 (C1''), 130.1 (ArH), 129.0 (2 \times ArH), 126.7 (2 \times ArH), 126.1 (ArH), 122.3 (ArH), 114.4 (C5''), 39.1 (C1'), 31.2 (C2'). HRMS (EI) m/z observed: 309.0942, C_{17}H_{13}N_{3}O_{5} [M]^{+} requires 309.0936.

\[ \text{N-}(2-(2-\text{Phenylthiazol}-4-\text{yl})\text{ethyl})\text{nicotinamide (143)} \]

General procedure (B) was followed with 111 (0.200 g, 0.721 mmol) and nicotinic acid (0.093 g, 0.755 mmol). Elution with EtOAc gave 143 as an orange solid (0.109 g, 49%),
mp = 86–88 °C. Rf 0.15 (EtOAc). IR (ATR) cm⁻¹: 3331 (NH), 1607 (C=O). ¹H NMR (400 MHz, CDCl₃) δ 9.03 (s, 1H, H2), 8.69 (br. s, 1H, H6), 8.12 (d, J = 6.4 Hz, 1H, H4), 7.90–7.92 (m, 2H, H2"/H6"), 7.82 (br. s, 1H, NH), 7.43–7.46 (m, 3H, H3"/H4"/H5"), 7.33 (dd [app. t.], J₁ = J₂ = 6.0 Hz, 1H, H5), 7.01 (s, 1H, H5"), 3.85 (dt [app. q], J₁ = J₂ = 5.4 Hz, 2H, H1"), 3.10 (t, J = 5.4 Hz, 2H, H2"). ¹³C NMR (101 MHz, CDCl₃) δ 168.9 (C2"), 165.5 (C=O), 155.6 (C4"), 152.3 (C2), 148.2 (C6), 135.1 (ArH), 133.5, 130.6, 130.5 (ArH), 129.3 (2 × ArH), 126.5 (2 × ArH), 123.5 (ArH), 114.8 (C5"), 39.8 (C1"), 30.6 (C2"). HRMS (ESI) m/z observed: 310.1002, C₁₇H₁₅N₃OS⁺ [M+H]⁺ requires 310.1014.

N-(2-(2-Phenylthiazol-4-yl)ethyl)isonicotinamide (144)

General procedure (B) was followed with 111 (0.200 g, 0.721 mmol) and isonicotinic acid (0.093 g, 0.755 mmol). Elution with 1:1 EtOAc/hexanes gave 144 as a yellow solid (0.116 g, 52%), mp = 108–110 °C. Rf 0.3 (1:1 EtOAc/hexanes). IR (ATR) cm⁻¹: 3323 (NH), 1607 (C=O). ¹H NMR (400 MHz, CDCl₃) δ 8.71 (d, J = 4.4 Hz, 2H, H2/H6), 8.17 (br. s, 1H, NH), 7.90–7.92 (m, 2H, H2"/H6"), 7.74 (d, J = 5.6 Hz, 2H, H3/H5), 7.44–7.48 (m, 3H, H3"/H4"/H5"), 7.05 (s, 1H, H5"), 3.83 (dt [app. q], J₁ = J₂ = 6.4 Hz, 2H, H1"), 3.11 (t, J₁ = 6.4 Hz, 2H, H2"). ¹³C NMR (101 MHz, CDCl₃) δ 168.7 (C2"), 165.3 (C=O), 155.5 (C4"), 150.5 (C2/C6), 142.1 (C4), 133.4 (C1"), 130.4 (C4"), 129.1 (2 × ArH), 126.5 (2 × ArH), 121.1 (C3/C5), 114.8 (C5"), 39.8 (C1"), 30.3 (C2"). HRMS (EI) m/z observed: 309.0931, C₁₇H₁₅N₃OS⁻ [M⁻]⁻ requires: 309.0936.
N-(2-(2-Phenythiazol-4-yl)ethyl)pyrazine-2-carboxamide (145)

General procedure (C) was followed with 111 (0.179 g, 0.646 mmol) and pyrazinecarboxylic acid (0.137 g, 1.10 mmol). Elution with 2:3 EtOAc/hexanes gave 145 as a brown solid (0.160 g, 80%), mp = 81–83 °C. Rf 0.19 (2:3 EtOAc/hexanes). IR (ATR) cm⁻¹: 3327 (NH), 1655 (C=O). ¹H NMR (400 MHz, CDCl₃) δ 9.41 (d, J = 1.6 Hz, 1H, H₃), 8.92 (br. s, 1H, NH), 8.73 (d, J = 2.4 Hz, 1H, H₆), 8.54 (dd [app. t], J₁ = J₂ = 2.6 Hz, 1H, H₅), 8.10–8.20 (m, 2H, H₂''/H₆''), 7.40–7.50 (m, 3H, H₃''/H₄''/H₅''), 7.04 (s, 1H, H₅''), 3.89 (dt [app. q], J₁ = J₂ = 6.3 Hz, 2H, H₁'), 3.15 (t, J = 6.0 Hz, 2H, H₂'). ¹³C NMR (101 MHz, CDCl₃) δ 168.7 (C₂''), 163.2 (C=O), 155.0 (C₄''), 147.2 (pyrazine CH), 144.9 (C₂), 144.5 (pyrazine CH), 142.7 (pyrazine CH), 133.1 (C₁'''), 130.5 (C₄'''), 129.1 (2 × ArH), 126.8 (2 × ArH), 114.6 (C₅''), 39.1 (C₁'), 30.7 (C₂'). HRMS (ESI) m/z observed: 311.1003, C₁₆H₁₅N₄OS⁺ [M+H]⁺ requires 311.0961.

2-Chloro-N-(2-(2-phenylthiazol-4-yl)ethyl)isonicotinamide (146)

General procedure (C) was followed with 111 (0.563 g, 2.03 mmol) and 2-chloroisonicotinic acid (0.259 g, 1.64 mmol). Elution with 1:4 EtOAc/hexanes + NEt₃ then 1:2 EtOAc/hexanes + NEt₃ gave 146 as a yellow solid (0.168 g, 24%). m.p.: 78-81°C. Rf: 0.27 (50% EtOAc/Hexanes + NEt₃). IR (thin film) cm⁻¹: 1610 (C=O), 3313
\( \text{NH} \). \(^1\text{H} \) NMR (500 MHz, CDCl\(_3\)) \( \delta \) 8.64 (s, 1H, H3), 8.47 (d, \( J_1 = 4.8 \) Hz, 1H, H6), 7.81 (m, 2H, H2''/H6''), 7.46 (d, \( J_1 = 4.8 \) Hz, 1H, H5), 7.38 (m, 3H, H3'''/H4'''/H5'''), 7.03 (s, 1H, H5''), 3.86 (dt (app q), \( J_1 = 6.1 \) Hz, \( J_2 = 5.8 \) Hz, 2H, H1''), 3.10 (t, \( J_1 = 6.2 \) Hz, 2H, H2''). \(^{13}\text{C} \) NMR (500 MHz, CDCl\(_3\)) \( \delta \) 168.4 (C2''), 164.2 (C=O), 155.0 (C4''), 150.0 (C6), 148.2 (C3), 142.0 (C2), 133.4 (C4'''), 130.2 (C4', 129.0 (C2''/C6''), 128.0 (C1'''), 126.4 (C3''/C5'''), 123.4 (C5), 114.8 (C5''), 39.7 (C1'), 30.6 (C2'). HRMS (ESI): Observed: 366.0426, C\(_{17}\)H\(_{14}\)ClN\(_3\)NaOS requires 366.0438.

\[ \text{N-(2-(2-Phenylthiazol-4-yl)ethyl)thiophene-2-carboxamide (149)} \]

General procedure (A) was followed with 111 (0.216 g, 0.779 mmol) and 2-thiophenecarbonyl chloride (0.14 mL, 1.3 mmol). Elution with 1:4 EtOAc/hexanes gave 149 as a white solid (0.100 g, 41%), mp = 116–119 °C. \( R_f \) 0.5 (1:4 EtOAc/hexanes). IR (ATR) cm\(^{-1}\): 3319 (NH), 1625 (C=O). \(^1\text{H} \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.96–7.98 (m, 2H, H2''/H6''), 7.52 (dd, \( J = 4.0 \), 1.2 Hz, 1H, C3 or C5), 7.43–7.47 (m, 4H, H3'''/H4'''/H5'''+H3 or H5), 7.35 (br. s, 1H, NH), 7.05 (dd, \( J_1 = 5.0 \), \( J_2 = 4.0 \) Hz, 1H, H4), 7.05 (t, \( J = 0.8 \) Hz, 1H, H5''), 3.83 (dt [app. q], \( J_1 = J_2 = 5.4 \) Hz, 2H, H1''), 3.10 (t, \( J_1 = 5.4 \) Hz, 2H, H2'). \(^{13}\text{C} \) NMR (101 MHz, CDCl\(_3\)) \( \delta \) 168.5 (C2''), 162.0 (C=O), 155.6 (C4''), 139.4 (C1'''), 133.5 (C2'), 130.2 (C4'''), 129.7 (ArH), 129.1 (2 × ArH), 128.1 (ArH), 127.6 (ArH), 126.6 (2 × ArH), 114.7 (C5''), 39.6 (C1'), 30.8 (C2'). HRMS (ESI) \( m/z \) observed: 315.0616, C\(_{16}\)H\(_{15}\)N\(_2\)O\(_2\)S\(_2\)\([\text{M+H}]^+\) requires 315.0626.
**N-(2-(2-Phenylthiazol-4-yl)ethyl)thiophene-3-carboxamide (150)**

General procedure (C) was followed with 111 (0.178 g, 0.642 mmol) and 3-thiophenecarboxylic acid (0.104 g, 0.818 mmol). Elution with 1:4 EtOAc/hexanes gave 150 as a yellow oil (0.168 g, 83%). Rf 0.2 (1:4 EtOAc/hexanes). IR (ATR) cm⁻¹: 3321 (NH), 1633 (C=O). ¹H NMR (500 MHz, CDCl₃) δ 7.93–7.96 (m, 2H, H₂''/H₆''), 7.89 (dd, J = 2.8, 1.2 Hz, 1H, H₂), 7.44–7.46 (m, 4H, NH/H₃'''/H₄'''/H₅'''), 7.42 (dd, J = 5.0, 2.8 Hz, 1H, H₄ or H₅), 7.30 (dd, J = 5.2, 2.8 Hz, 1H, H₄ or H₅), 7.03 (s, 1H, H₅''), 3.80 (dt [app. q], J₁ = J₂ = 5.8 Hz, 2H, H₁'), 3.11 (t, J = 6.0 Hz, 2H, H₂'). ¹³C NMR (126 MHz, CDCl₃) δ 168.7 (C₂''), 163.2 (C=O), 155.4 (C₄''), 138.0 (C₁''''), 133.2 (C₃), 130.5 (C₄'''), 129.2 (2 × ArH), 128.2 (ArH), 126.6 (2 × ArH), 126.4 (ArH), 126.2 (ArH), 114.8 (C₅''), 39.4 (C₁'), 30.6 (C₂'). HRMS (ESI) m/z observed: 315.0626, C₁₆H₁₅N₂O₄S₂⁺ [M+H]⁺ requires 315.0626.

**N-(2-(2-Phenylthiazol-4-yl)ethyl)furan-2-carboxamide (151)**

General procedure (C) was followed with 111 (0.255 g, 0.920 mmol) and 2-furoic acid (0.229 g, 0.826 mmol). Elution with 2:3 EtOAc/hexanes gave 151 as a pale-yellow oil (0.192 g, 78%). Rf 0.45 (2:3 EtOAc/hexanes). IR (ATR) cm⁻¹: 3316 (NH), 1651 (C=O). ¹H NMR (400 MHz, CDCl₃) δ 7.97–8.01 (m, 2H, H₂''/H₆''), 7.69 (br. s, 1H, NH), 7.39–7.45 (m, 4H, H₅/H₃''/H₄''/H₅'''), 7.10 (dd, J = 3.6, 1.0 Hz, 1H, H₃), 6.97 (s, 1H,
H5"

H5"), 6.46 (dd [app. t], J1 = J2 = 3.6 Hz, 1H, H4), 3.79 (dt [app. q], J1 = J2 = 6.4 Hz, 2H, H1'), 3.07 (t, J = 6.4 Hz, 2H, H2'). 13C NMR (101 MHz, CDCl3) δ 168.3 (C2'"), 158.4 (C=O), 155.4 (C4'"), 148.4 (C2), 143.7 (C5), 133.6 (C1''''), 130.1 (C4'''), 128.9 (2 × ArH), 126.5 (2 × ArH), 114.5 (C5'"), 113.8 (C3 or C4), 112.1 (C3 or C4), 36.6 (C1'), 30.8 (C2'). HRMS (ESI) m/z observed: 299.0850, C16H15N2O2S+ [M+H]⁺ requires 299.0854.

N-(2-(2-Phenylthiazol-4-yl)ethyl)-1H-pyrrole-2-carboxamide (153)

General procedure (C) was followed with 111 (0.255 g, 0.920 mmol) and 1H-pyrrole-2-carboxylic acid (0.131 g, 1.18 mmol). Elution with 3:7 EtOAc/hexanes gave 153 as a pale-yellow solid (0.074 g, 27%), mp = 119–121 °C. Rf 0.45 (3:7 EtOAc/hexanes). IR (ATR) cm⁻¹: 3312 (NH), 1620 (C=O). 1H NMR (500 MHz, CDCl3) δ 9.56 (br. s, 1H, NH), 7.95–7.98 (m, 2H, H2''/H6'''), 7.42–7.49 (m, 3H, H3'''/H4'''/H5''''), 7.07 (br. s, 1H, NH), 7.00 (t, J = 0.8 Hz, 1H, H5"), 6.90–6.92 (m, 1H, pyrazole H), 6.56–6.58 (m, 1H, pyrazole H), 6.20–6.23 (m, 1H, pyrazole H), 3.82 (dt [app.q], J1 = J2 = 6.2 Hz, 2H, H1'), 3.08 (t, J1= 6.0 Hz, 2H, H2'). 13C NMR (126 MHz, CDCl3) δ 168.5 (C2'"), 161.4 (C=O), 155.7 (C4'"), 133.7 (C1''''), 130.2 (C4''''), 129.1 (2 × ArH), 126.6 (2 × ArH), 126.4 (C2), 121.5 (C5), 114.6 (C5'"), 109.7 (C3 or C4), 108.9 (C3 or C4), 39.0 (C1'), 31.2 (C2'). HRMS (ESI) m/z observed: 298.1024, C16H16N3OS+ [M+H]⁺ requires 298.1014.
N-(2-(2-Phenylthiazol-4-yl)ethyl)oxazole-5-carboxamide (154)

General procedure (C) was followed with 111 (0.225 g, 0.812 mmol) and oxazole-5-carboxylic acid (0.119 g, 1.07 mmol). Elution with 1:1 EtOAc/hexanes gave 154 as a white solid (0.097 g, 40%) mp = 110–111 °C. Rf 0.15 (1:1 EtOAc/Hexanes). IR (ATR) cm⁻¹: 3360 (NH), 1629 (C=O). ¹H NMR (500 MHz, CDCl₃) δ 7.97–7.99 (m, 2H, H₂''/H₆''), 7.88 (s, 1H, H2), 7.81 (br. s, 1H, NH), 7.72 (s, 1H, H4), 7.46 (m, 3H, H₃''/H₄''/H₅''), 7.02 (t, J = 0.6 Hz, 1H, H5''), 3.82 (pseudo q, 2H, H1'), 3.09 (dt, J = 5.2, 0.6 Hz, 2H, H2'). ¹³C NMR (126 MHz, CDCl₃) δ 168.7 (C2''), 156.9 (C=O or C4''), 155.1 (C=O or C4''), 151.4 (C2), 146.1 (C4), 133.3 (C1''), 130.5 (C4''), 130.1 (C5), 129.1 (2 × ArH), 126.6 (2 × ArH), 114.8 (C5''), 38.9 (C1'), 30.5 (C2'). HRMS (ESI) m/z observed: 300.0816, C₁₅H₁₄N₃O₂S⁺ [M+H]⁺ requires 300.0807.

N-(2-(2-Phenylthiazol-4-yl)ethyl)benzenesulfonamide (161)

Benzenesulfonyl chloride (0.15 mL, 1.2 mmol) was added dropwise to a stirred solution of Hünig's base (0.50 mL, 2.87 mmol) and 111 (0.095 g, 0.35 mmol) in DCM (15 mL) at 0 °C. The solution was allowed to warm to room temperature and stirring was continued overnight. The volatiles were evaporated and the residue was subjected to flash chromatography. Elution with 1:4 EtOAc/hexanes and then 2:3 EtOAc/hexanes gave 161 as a yellow oil (0.039 g, 33%). IR (ATR) cm⁻¹: 3277 (NH), 1158 (S=O). ¹H
NMR (500 MHz, CDCl₃) δ 7.83–7.89 (m, J = 7.5 Hz, H₂/H₆/H₂''/H₆''), 7.42–7.53 (m, 6H, H₃/H₄/H₅/H₃''/H₄''/H₅''), 6.87 (s, 1H, H₅''), 5.75 (br. t, J = 5.5 Hz, 2H, H₂'). ¹³C NMR (126 MHz, CDCl₃) δ 168.7 (C₂''), 154.5 (C₄''), 140.1 (C₁), 133.34 (C₁'''), 132.6 (ArH), 130.36 (ArH), 129.15 (2 × ArH), 129.15 (2 × ArH), 127.1 (2 × ArH), 126.5 (2 × ArH), 114.9 (C₅''), 42.8 (C¹'), 30.7 (C²'). HRMS (ESI) m/z observed: 345.0731, C₁₇H₁₇N₂O₂S₂⁺ [M+H]⁺ requires 345.0731.

N-(2-(2-Phenylthiazol-4-yl)ethyl)-1H-imidazole-1-carboxamide (167)

1,1'-carbonyldiimidazole (0.396 g, 2.44 mmol) was added to a solution of 111 (0.515 g, 1.86 mmol) in DMF (3 mL) and MeCN (9 mL). The solution was allowed to stir for 24 h, then the MeCN was evaporated and the residue was diluted with EtOAc (150 mL) and washed with brine (3 × 50 mL), dried and evaporated. The residue was subjected to flash chromatography. Elution with 1:1 EtOAc/hexanes and then 7:3 EtOAc/hexanes gave 167 as an orange oil (0.438 g, 79%). Rᶠ 0.15 (1:1 EtOAc/hexanes). IR (ATR) cm⁻¹: 3219 (NH), 1712 (C=O). ¹H NMR (500 MHz, CDCl₃) δ 8.29 (br. t, J = 5.0 Hz, 1H, NH), 8.14 (dd [app. t], J₁ = J₂ = 1.2 Hz, 1H, H₂), 7.79–7.83 (m, 2H, H₂''/H₆''), 7.40 (dd [app. t], J₁ = J₂ = 1.4 Hz 1H, H₅), 7.35–7.38 (m, 3H, H₃''/H₄''/H₅''), 6.95 (s, 1H, H₅''), 6.94 (dd, J = 1.6, 0.9 Hz, 1H, H₄), 3.71 (dt [app. q], J₁ = J₂ = 6.0 Hz, 2H, H₁'), 3.04 (t, J = 6.5 Hz, 2H, H₂'). ¹³C NMR (126 MHz, CDCl₃) δ 168.6 (C₂''), 154.8 (C=O), 149.0 (C₄''), 135.9 (C₂), 133.2 (C₁'''), 130.2 (C₄''), 129.7 (C₄), 129.0 (2 ×
ArH), 126.3 (2 × ArH), 116.2 (C5), 114.5 (C5”), 40.5 (C1’), 30.5 (C2’). HRMS (ESI) m/z observed: 299.0971, C_{15}H_{18}N_{4}O_{5}^{+} [M+H]^+ requires 299.0967.

2-Hydroxy-N-(2-(2-phenylthiazol-4-yl)ethyl)benzamide (171)

A solution of 1-pyrrolidinecarbonyl chloride (0.10 mL, 0.70 mmol) in dry DCM (5 mL) was added drop wise to a solution of 111 (0.201 g, 0.725 mmol) and NEt₃ (1.50 mL, 10.8 mmol) in dry DCM (20 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirring was continued overnight. The reaction mixture was diluted with EtOAc (150 mL) and washed with water (3 × 50 mL), dried and evaporated. The residue was subjected to flash chromatography. Elution with 3:7 EtOAc/hexanes gave 171 as a yellow solid (0.201 g, 92%), mp = 101–103 °C. R_f 0.25 (3:7 EtOAc/hexanes). IR (ATR) cm⁻¹: 3355 (NH), 1629 (C=O). ¹H NMR (500 MHz, CDCl₃) δ 7.89–7.91 (m, 2H, H₂'''/H₆'''), 7.39–7.42 (m, 3H, H₃'''/H₄'''/H₅'''), 6.97 (s, 1H, H₅''), 5.24 (br. s, 1H, NH), 3.64 (dt [app. q], J₁ = J₂ = 6.1 Hz, 2H, H₁’), 3.32–3.35 (m, 4H, H₂/H₅), 3.03 (t, J = 6.1 Hz, 2H, H₂’), 1.88 (m, 4H, H₃/H₄). ¹³C NMR (126 MHz, CDCl₃) δ 168.0 (C₂’’), 157.0 (C=O or C₄”), 156.3 (C=O or C₄”), 133.7 (C₁”’), 130.0 (C₄”’), 129.0 (2 × ArH), 126.4 (2 × ArH), 114.3 (C₅”’), 45.5 (C₂/C₅), 40.2 (C₁’), 31.8 (C₂’), 25.6 (C₃/C₄). HRMS (ESI) m/z observed: 324.1132, C_{16}H_{19}N_{3}NaOS^{+} [M+H]^+ requires 324.1141.
N-(2-(2-Phenylthiazol-4-yl)ethyl)piperidine-1-carboxamide (172)

Prepared as described for 171 with 111 (0.472 g, 1.70 mmol) 1-piperidinecarbonyl chloride (0.15 mL, 1.1 mmol) to give 172 as a yellow solid (0.381 g, 71%), mp = 80–81 °C. R_t 0.2 (3:7 EtOAc/hexanes). IR (ATR) cm\(^{-1}\): 3335 (NH), 1613 (C=O). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.86–7.89 (m, 2H, H2'''/H6'''), 7.37–7.41 (m, 3H, H3''/H4''/H5'''), 6.94 (s, 1H, H5''), 5.80 (br. s, 1H, NH), 3.56 (dt [app. q], \(J_1 = J_2 = 5.9\) Hz, 2H, H1'), 3.29–3.34 (m, 4H, H2/H6), 2.97 (t, \(J_1 = 6.2\) Hz, 2H, H2'), 1.49–1.52 (m, 6H, H3/H4/H5). \(^13\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 168.1 (C2''), 157.9 (C=O or C4''), 133.7 (C1''''), 130.1 (C4''''), 129.0 (2 \(\times\) ArH), 126.4 (2 \(\times\) ArH), 114.4 (C=O or C4''), 133.7 (C1''''), 130.1 (C4''''), 129.0 (2 \(\times\) ArH), 126.4 (2 \(\times\) ArH), 114.4 (C5'''), 44.9 (C2/C6), 40.7 (C1'), 31.4 (C2'), 25.7 (C3/C5), 24.6 (C4). HRMS (ESI) m/z observed: 338.1295, C\(_{17}\)H\(_{21}\)N\(_3\)NaOS\(^+\) [M+H\(^+\)] requires 338.1298.

N-(2-(2-Phenylthiazol-4-yl)ethyl)morpholine-4-carboxamide (174)

Prepared as described for 171 with 111 (0.219 g, 0.790 mmol) 4-morpholinecarbonyl chloride (0.100 ml, 0.860 mmol) to give 174 as a white solid (0.120 g, 48%), mp = 98–100 °C. R_t = 0.3 (EtOAc). IR (ATR) cm\(^{-1}\): 3313 (NH), 1610 (C=O). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.86–7.90 (m, 2H, H2''''/H6'''''), 7.41–7.43 (m, 3H, H3''''/H4''''/H5'''''), 6.97 (t, \(J = 0.8\) Hz, 1H, H5'''), 5.94 (br. unresolved t, 1H, NH), 3.62–3.65 (m, 4H, H2/H6), 2.97 (t, \(J = 6.2\) Hz, 2H, H2'), 1.49–1.52 (m, 6H, H3/H4/H5).
3.57–3.60 (m, 2H, H1'), 3.34–3.36 (m, 4H, H3/H5), 2.99 (dt, J = 6.0, 0.8 Hz, 2H, H1').

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 168.2 (C2''), 158.0 (C=O or C4''), 156.2 (C=O or C4''), 133.6 (C1''''), 130.2 (C4''''), 129.1 (2 × ArH), 126.4 (2 × ArH), 114.5 (C5'''), 66.6 (C2/C6), 44.0 (C3/C5), 40.6 (C2''), 31.1 (C1'). HRMS (ESI) m/z observed: 318.1279, C$_{16}$H$_{20}$N$_3$O$_2$S$^+$ [M+H]$^+$ requires 318.1276.

**General procedure for the synthesis of ureas from 167.** Triethylamine (1.1 equiv) and amine (1.0 equiv) were added to a stirred solution of 167 (1.0 equiv) in DCM (~5 mL/mmol of 167) under argon. When TLC indicated the reaction to be complete (generally after overnight), the solvent was evaporated under N$_2$ and the residue was purified by flash chromatography.

**Isopropyl (2-(2-phenylthiazol-4-yl)ethyl)carbamate (168)**

NaH (60% dispersion in mineral oil, 0.028 g, 1.18 mmol) was added to a stirred solution of isopropanol (0.082 ml, 1.07 mmol) and 167 (0.320 g, 1.07 mmol) in dry DMF (10.0 ml) under argon. When TLC indicated the reaction to be complete (generally after overnight), the solution was quenched with water. The reaction mixture was diluted with water and extracted with EtOAc (3 × 50 ml) and the extract was dried and evaporated. The residue was purified by flash chromatography and elution with 1:4 EtOAc/hexanes gave 168 as a white solid (0.099 g, 32%), mp = 55–57 °C. R$_f$ 0.3 (1:4 EtOAc/hexanes). IR (ATR) cm$^{-1}$: 3330 (NH), 1690 (C=O). $^1$H NMR (500 MHz,
CDCl$_3$ $\delta$ 7.91–7.93 (m, 2H, H2''/H6''), 7.39–7.44 (m, 3H, H3''/H4''/H5''), 6.94 (s, 1H, H5'), 5.20 (br. s, 1H, NH), 4.90 (sept, $J$ = 6.0 Hz, 1H, HC–O), 3.58 (dt [app. q], $J_1$ = $J_2$ = 6.5 Hz, 2H, H1), 2.99 (t, $J$ = 6.5 Hz, 2H, H2), 1.21 (d, $J$ = 6.0 Hz, 6H, CH$_3$). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 168.2 (C2'), 156.4 (C=O or C4'), 155.4 (C=O or C4'), 133.7 (C1''), 130.0 (C4''), 126.5 (2 × ArH), 126.5 (2 × ArH), 114.4 (C5'), 68.0 (HC–O), 40.3 (C1), 31.8 (C2), 22.2 (CH$_3$). HRMS (ESI) $m/z$ observed: 291.1168, C$_{15}$H$_{19}$N$_2$O$_2$S$^+$ [M+H]$^+$ requires 291.1167.

![Structure](image)

1-Isopropyl-3-(2-(2-phenylthiazol-4-yl)ethyl)urea (169)

The general procedure was followed with 167 (0.120 g, 0.402 mmol) and isopropylamine (0.03 mL, 0.40 mmol). Elution with 1:4 EtOAc/hexanes gave 169 as a white solid, (0.064 g, 55%), mp = 139–140 °C. $R_f$ 0.2 (1:1 EtOAc/hexanes). IR (ATR) cm$^{-1}$: 3313 (NH), 2966 (NH), 1622 (C=O). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.92–7.94 (m, 2H, H2''/H6''), 7.43–7.45 (m, 3H, H3''/H4''/H5''), 6.99 (s, 1H, H5'), 5.02 (br. s, 1H, NH), 4.18 (br. s, 1H, NH), 3.79 (sept, $J$ = 6.5 Hz, 1H, HC–N), 3.60 (t, $J$ = 6.0 Hz, 2H, H1), 3.01 (t, $J$ = 6.0 Hz, 2H, H2), 1.10 (d, $J$ = 6.5 Hz, 6H, CH$_3$). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 168.4 (C2'), 157.7 (C=O or C4'), 155.7 (C=O or C4'), 133.6 (C1''), 130.3 (C4''), 129.1 (2 × ArH), 126.6 (2 × ArH), 114.7 (C5'), 42.5 (HC–N), 40.1 (C1), 31.9 (C2), 23.6 (CH$_3$). HRMS (ESI) $m/z$ observed: 290.1318, C$_{15}$H$_{20}$N$_2$O$_2$S$^+$ [M+H]$^+$ requires: 290.1327.
1,1-Diethyl-3-(2-(2-phenylthiazol-4-yl)ethyl)urea (170)

The general procedure was followed with 167 (0.120 g, 0.402 mmol) and diethylamine (0.04 mL, 0.40 mmol). Elution with 1:1 EtOAc/hexanes gave 170 as a yellow oil (0.081 g, 66%). Rf 0.35 (1:1 EtOAc/hexanes). IR (ATR) cm$^{-1}$: 3354 (NH), 1622 (C=O). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.89–7.91 (m, 2H, H$_2'''$/H$_6'''$), 7.39–7.43 (m, 3H, H$_3''$/H$_4''$/H$_5'''$), 6.96 (s, 1H, H$_5''$), 5.46 (br. unresolved t, 1H, NH), 3.60 (dt [app. q], $J_1 = J_2 = 6.8$ Hz, 2H, H1), 3.23 (q, $J = 7.0$ Hz, 4H, 2 × CH$_2$), 3.00 (t, $J = 6.2$ Hz, 2H, H2), 1.08 (t, $J = 7.0$ Hz, 6H, CH$_3$). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 168.2 (C$_2'$), 157.5 (C=O or C$_4'$), 156.5 (C=O or C4'), 133.7 (C$_1''$), 130.1 (C$_4''$), 129.0 (2 × ArH), 126.5 (2 × ArH), 114.4 (C$_5'$), 41.2 (HC=), 40.6 (C1), 31.6 (C2), 13.9 (CH$_3$). HRMS (ESI) m/z observed: 304.1494, C$_{16}$H$_{22}$N$_3$OS$^+$ [M+H]$^+$ requires 304.1484.

$N$-(2-(2-Phenylthiazol-4-yl)ethyl)azepane-1-carboxamide (173)

The general procedure was followed with 167 (0.160 g, 0.536 mmol) and azepane (0.060 mL, 0.54 mmol). Elution with 1:1 EtOAc/hexanes then 7:3 EtOAc/hexanes gave 173 as a yellow oil (0.120 g, 68%). Rf 0.35 (1:1 EtOAc/hexanes). IR (ATR) cm$^{-1}$: 2931 (NH), 1627 (C=O). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.88–7.91 (m, 2H, H$_2'''$/H$_6'''$), 7.33–
7.41 (m, 3H, H3''/H4''/H5''), 6.95 (s, 1H, H5''), 5.50 (br. unresolved t, 1H, NH), 3.61 (dt [app. q], \(J_1 = J_2 = 6.4\) Hz, 2H, H1'), 3.37 (t, \(J = 6.0\) Hz, 4H, H2/H7), 2.99 (t, \(J = 6.4\) Hz, 2H, H2'), 1.64 (m, 4H, H4/H5), 1.50 (m, 4H, H3/H6).

\(\text{\textsuperscript{13}}C\) NMR (126 MHz, CDCl\textsubscript{3}) \(\delta\) 168.2 (C2''), 158.0 (C=O or C4''), 156.4 (C=O or C4''), 133.7 (C1'''), 130.1 (C4'''), 129.0 (2 × ArH), 126.4 (2 × ArH), 114.4 (C5''), 46.4 (C2/C7), 40.6 (C1'), 31.6 (C2'), 28.6 (C4/C5), 27.3 (C3/C6). HRMS (ESI) \(m/z\) observed: 330.1635, \(C_{18}H_{24}N_{3}O_{3}\) requires: 330.1640.

**tert-Butyl (2-(3-phenyl-1H-pyrazol-1-yl)ethyl)carbamate (179)**

Potassium carbonate (4.56 g, 33.0 mmol) was added to a stirred solution of 3-phenyl-1H-pyrazole (1.58 g, 11.0 mmol) in DMF (20.0 ml). After 30 minutes \(N\)-(2-bromoethyl)-\(O\)-(\(t\)ert-butyl)hydroxylamine (3.00 g, 13.4 mmol) was added and the solution was stirred for 18 hours at 70 °C. The solution was then extracted with EtOAc (3 × 100 ml), washed with ammonium chloride (3 × 100 ml) and the extract was dried, filtered and the solvent was evaporated. The residue was subjected to flash chromatography and elution with 1:5 EtOAc/Hexanes gave 179 as a yellow oil. (1.74 g, 55%). \(R_f:\) 0.22 (20% EtOAc/Hexanes). IR (ATR) cm\(^{-1}\): 1686 (C=O), 3330 (NH). \(\text{\textsuperscript{1}}H\) NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 7.77–7.81 (m, 2H, H2''/H6''), 7.35–7.41 (m, 3H, H5'/H3''/H5''), 7.33 (tt, \(J_1 = 7.4\) Hz, \(J_2 = 1.2\) Hz, 1H, H4''), 6.57 (d, \(J_1 = 2.3\) Hz, 1H, H4'), 5.05 (br s, 1H, NH), 4.28 (t, \(J_1 = 5.1\) Hz, 2H, H1), 3.63 (t, \(J_1 = 5.3\) Hz, 2H, H2), 1.47 (s, 9H, Methyl). \(\text{\textsuperscript{13}}C\) NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 156.0 (C=O), 152.1 (C3'), 133.5 (C1''), 131.4 (C5'), 128.7 (C3''/C5''), 127.7 (C4''), 125.6 (C2''/C6''), 102.8 (C4'), 79.7 (\(t\)-Butyl), 79.7 (\(t\)-Butyl), 64.4 (t-Butyl), 46.4 (t-Butyl), 31.6 (t-Butyl), 28.6 (t-Butyl).
51.7 (C2), 40.9 (C1), 28.4 (Methyl). HRMS (ESI): Observed: 310.1516, C_{16}H_{21}N_{3}NaO_{2} requires 310.1526.

1-(2-Ammonioethyl)-3-phenyl-1H-pyrazol-2-ium chloride (185)

Conc. HCl (5.00 ml) was added to a stirred solution of 179 (1.28 g, 4.45 mmol) in dry 1,4-dioxane (20.0 ml). The solution was stirred overnight and then the solvent was evaporated to yield 185 as a yellow solid. (1.03 g, 89%). m.p.: 127-130 °C. IR (ATR) cm\(^{-1}\): 2481-3116 (NH). \(^1\)H NMR (500 MHz, MeOD) \(\delta\) 7.98 (d, \(J_1=\) 2.5 Hz, 1H, H5'), 7.86 (d, \(J_1=\) 7.0 Hz, 2H, H2''/H6''), 7.35–7.45 (m, 2H, H3''/H5''), 7.39 (t, \(J_1=\) 7.5 Hz, 1H, H4''), 6.86 (d, \(J_1=\) 2.5 Hz, 1H, H4'), 4.65 (t, \(J_1=\) 6.0 Hz, 2H, H2), 3.55 (t, \(J_1=\) 6.0 Hz, 2H, H1). \(^{13}\)C NMR (500 MHz, MeOD) \(\delta\) 153.3 (C3'), 135.4 (C5'), 132.9 (C1''), 130.1 (2 × ArH), 130.0 (C4''), 127.2 (2 × ArH), 105.1 (C4'), 49.6 (C2), 40.6 (C1). HRMS (ESI): Observed: 188.1184, C_{11}H_{14}N_{3} requires 188.1188.

\(N\)-(2-(3-Phenyl-1H-pyrazol-1-yl)ethyl)cyclopentanecarboxamide (195)

Cyclopentanecarbonyl chloride (0.10 ml, 0.823 mmol), dissolved in dichloromethane (10.0 ml) was added to a stirred solution of 185 (0.150 g, 0.577 mmol) and triethylamine (3.0 ml, 21.5 mmol) in dichloromethane (10.0 ml) At 0 °C. The solution was stirred for 24 hours, then washed with water (3 × 50 ml), extracted with EtOAc (3 × 50 ml), dried, filtered and the solvent was evaporated. The residue was subjected to
flash chromatography and elution with 1:5 EtOAc/Hexanes and then 1:1 EtOAc/Hexanes gave 195 as clear crystals. (0.160 g, 98%). m.p.: 88-90 °C. R.f.: 0.32 (50% EtOAc/Hexanes). IR (ATR) cm⁻¹: 1622 (C=O), 3276 (NH). ¹H NMR (400 MHz, CDCl₃) δ 7.78–7.81 (m, 2H, H2''/H6''), 7.38–7.43 (m, 3H, J₁ = 2.4 Hz, H5''/H3''/H5''), 7.30 (t of t, J₁ = 7.2 Hz, J₂ = 2.0 Hz, 1H, H4''), 6.55 (d, J₁ = 2.4 Hz, 1H, H4''), 6.15 (br s, 1H, NH), 4.27 (t, J₁ = 5.4 Hz, H2'), 3.74 (dt (app q), J₁ = 5.6 Hz, 2H, H1'), 2.46–2.54 (m, 1H, H1), 1.80–1.87 (m, 2H, 2 × cyclopentyl), 1.70–1.80 (m, 4H, 4 × cyclopentyl), 1.50–1.69 (m, 2H, 2 × cyclopentyl). ¹³C NMR (400 MHz, CDCl₃) δ 176.7 (C=O), 152.3 (C3''), 133.5 (C1''), 131.6 (C5'' or C4''), 128.8 (2 × ArH), 127.9 (C5'' or C4''), 125.6 (2 × ArH), 102.9 (C4''), 41.3 (C2'), 46.0 (C1), 40.0 (C1'), 30.5 (C2/C5), 26.0 (C3/C4). HRMS (ESI): Observed: 306.1570, C₁₇H₂₁N₃NaO requires 306.1577.

2-(3-Phenyl-1H-pyrazol-1-yl)ethyl benzoate (203)

In a flame dried flask, potassium carbonate (1.45 g, 10.5 mmol) was added to a stirred solution of 3-phenyl-1H-pyrazole (0.500 g, 3.47 mmol) in anhydrous DMF (5.0 ml). After half an hour, 2-bromoethyl benzoate (1.09 ml, 6.85 mmol) was added and the solution was stirred for 18 hours 70°C. It was then extracted with EtOAc (3 × 20 ml), washed with a saturated ammonium chloride solution (3 × 50 ml), dried, filtered and the solvent was evaporated. The residue was subjected to flash chromatography and elution 20:80:1 EtOAc/Hexanes + NEt₃ gave a white solid. ¹H NMR showed that both isomers present. The desired isomer was isolated by recrystallization with DCM/hexanes to
yield 203 as clear prisms. (0.446 g, 44%). m.p.: 90-92°C. R_f: 0.23 (10% EtOAc/Hexanes). IR (ATR) cm\(^{-1}\): 1705 (C=O). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.99–8.02 (m, 2H, 2 × ArH), 7.78–8.02 (d, \(J_1 = 7.1\) Hz, 2H, 2 × ArH), 7.54–7.59 (m, 1H, H4), 7.48 (d, \(J_1 = 2.3\) Hz, 1H, H5"), 7.37–7.46 (m, 4H, H3"/H5"/H3/H5), 7.28 (t, \(J_1 = 7.4\) Hz, 1H, H4"), 6.56 (d, \(J_1 = 2.4\) Hz, 1H, H4"), 4.74 (t, \(J_1 = 5.5\) Hz, 2H, H1'), 4.55 (t, \(J_1 = 5.5\) Hz, 2H, H2'). \(^13\)C NMR (500 MHz, CDCl\(_3\)) \(\delta\) 166.3 (C=O), 152.3 (C3"), 133.6 (C1"'), 133.4 (C5"), 131.4 (ArC), 129.86 (C1), 129.82 (2 × ArC), 128.7 (2 × ArC), 128.6 (2 × ArC), 127.8 (ArC), 125.8 (2 × ArC), 103.3 (C4"), 63.6 (C1'), 51.3 (C2'). HRMS (ESI): Observed: 315.1110, C\(_{18}\)H\(_{16}\)N\(_2\)NaO\(_2\).

\(\text{N-Phenyl-2-(3-phenyl-1H-pyrazol-1-yl)acetamide (205)}\)

In a flame dried flask, potassium carbonate (1.45 g, 10.5 mmol) was added to a stirred solution of 3-phenyl-1H-pyrazole (0.500 g, 3.47 mmol) in anhydrous DMF (5.00 ml). After 30 minutes, 2-chloroacetanilide (1.00 g, 5.90 mmol) was added and the solution was stirred for 18 hours at 70°C. It was then extracted with EtOAc (3 × 20 ml), washed with a saturated ammonium chloride solution (3 × 50 ml), dried, filtered and the solvent was evaporated. The residue was subjected to flash chromatography and elution with 20:80:1 EtOAc/Hexanes + NEt\(_3\) gave 205 as a white, fluffy solid. \(^1\)H NMR showed only the desired isomer. (0.558 g, 58%). m.p.: 153-154°C. R_f: 0.55 (30% EtOAc/Hexanes). IR (ATR) cm\(^{-1}\): 1677 (C=O), 3459 (NH). \(^1\)H NMR (500 MHZ, CDCl\(_3\)) \(\delta\) 8.68 (br s, 1H, NH), 7.86–7.87 (m, 2H, H2"/H6''), 7.56 (d, \(J_1 = 2.4\) Hz, 1H,
H5'), 7.44–7.47 (m, 4H, H3''/H5''/H2''/H6''), 7.37 (tt, J1 = 7.4 Hz, J2 = 1.1 Hz, 1H, H4''), 7.29 (t, J1 = 8.0 Hz, 2H, H3'/H5'), 7.10 (t, J1 = 7.4 Hz, H, H4''), 6.68 (d, J1 = 2.4 Hz, 1H, H4'), 4.95 (s, 2H, H2).

13C NMR (500 MHz, CDCl3) δ 165.0 (C=O), 154.0 (C3''), 137.2 (C1'''), 133.1 (C5'), 132.7 (C1''), 129.2 (2 × ArC), 129.0 (2 × ArC), 128.5 (ArC), 125.8 (2 × ArC), 124.9 (ArC), 120.1 (2 × ArC), 104.2 (C4'), 55.9 (C2). HRMS (ESI): Observed: 300.1105, C17H15N3NaO requires 300.1107.

N-Benzyl-2-(3-phenyl-1H-pyrazol-1-yl)ethanamine (206)

1 M borane-THF complex (20.0 mL) was added dropwise to a stirred solution of N-(2-(3-phenyl-1H-pyrazol-1-yl)ethyl)benzamide (0.329 g, 1.13 mmol) in THF (5.0 ml) at 0°C. The solution was stirred for 2 hours at reflux, at which point it was cooled in an ice bath where methanol (4 ml), and conc. HCl were slowly added until the solution was acidic. The resulting solution was heated for 30 minutes at reflux, cooled, and the solvent was evaporated. The crude material was washed with 10% NaOH solution (3 × 50 mL), extracted with EtOAc (3 × 30 ml) and washed with water and brine (3 × 30 ml) and the residue was subjected to flash chromatography and elution with EtOAc gave 206 as clear crystals, (0.100 g, 32%). m.p.: 56-57°C. Rf: 0.23 (EtOAc). IR (ATR) cm⁻¹: 3312 (NH). 1H NMR (500 MHz, CDCl3) δ 7.84–7.86 (m, 2H, H2''/H6''), 7.48 (d, J1 = 2.3 Hz, 1H, H5'), 7.42–7.45 (m, 2H, H3''/H5''), 7.27–7.37 (m, J1 = 7.3 Hz, 6H, H3'', H4'', H5'', H6'' H7'', H4''), 6.59 (d, J1 = 2.3 Hz, 1H, H4'), 4.32 (t, J1 = 5.8 Hz, 2H, H2), 3.85 (s, 2H, H1''), 3.16 (t, J1 = 5.8 Hz, 2H, H1), 1.80 (1H, br s, NH). 13C NMR (500 MHz, CDCl3) δ 151.9 (C3'), 140.1 (C2''), 133.7 (C1''), 131.2 (C5'), 128.7 (2 ×
ArC), 128.5 (2 × ArC), 128.2 (2 × ArC), 127.1 (C4" or C5"), 127.1 (C4" or C5"), 125.7 (2 × ArC), 102.8 (C4'), 53.6 (CH2), 52.4 (CH2), 49.0 (CH2). HRMS (ESI): Observed: 278.1663, C18H20N3+ requires 278.1652.

Methyl 3-(3-phenyl-1H-pyrazol-1-yl)propanoate (187)

In a flame dried flask potassium carbonate (7.22 g, 52.2 mmol) was added to a stirred solution of 3-phenyl-1H-pyrazole (2.50 g, 17.3 mmol) in anhydrous DMF (40.0 ml). After stirring for 30 minutes, methyl acrylate (1.60 ml, 17.8 mmol) was added. The solution was allowed to stir for 48 hours. It was then extracted with EtOAc (3 × 100 ml), washed with ammonium chloride and water (3 × 100 ml), dried, filtered and the solvent was evaporated. The residue was subjected to flash chromatography and elution with 1:5 EtOAc/Hexanes to yield 187 as a yellow oil. (2.91 g, 73%). R.f.: 0.27 (10% EtOAc/hexanes). IR (ATR) cm⁻¹: 1732 (C=O). ¹H NMR (500 MHz, CDCl3) δ 7.79–7.81 (m, 2H, H2"/H6"), 7.48 (d, J1 = 2.3 Hz, 1H, H5"), 7.42 (t, J1 = 7.5 Hz, 2H, H3"/H5"), 7.29 (tt, J1 = 7.4 Hz, J2 = 1.4 Hz, 1H, H4"), 6.54 (d, J1 = 2.4 Hz, 1H, H4'), 4.47 (t, J1 = 6.6 Hz, 2H, H2), 3.70 (s, 3H, Methyl), 2.98 (t, J1 = 6.6 Hz, 2H, H1). ¹³C NMR (500 MHz, CDCl3) δ 171.5 (C=O), 151.8 (C3'), 133.6 (C1''), 131.2 (C5'), 128.6 (2 × ArH), 127.6 (C4"), 125.6 (2 × ArH), 102.6 (C4'), 51.8 (Methyl), 47.5 (C2), 34.8 (C1).

3-(3-Phenyl-1H-pyrazol-1-yl)propanoic acid (207)

LiOH (0.0270 g, 1.16 mmol) was added to a stirred solution of 187 (0.240 g, 1.04 mmol) in water (15 ml) and THF (10 mL). The solution was stirred for 90 minutes. The solvent was then evaporated, acidified with 1M HCl and extracted with EtOAc (3 × 50 ml) to give 207 as an orange oil. (0.193 g, 86%). Rf: 0.33 (EtOAc + 1% MeOH). IR (ATR) cm⁻¹: 1703 (C=O), 2518-3142 (OH). ¹H NMR (500 MHz, CDCl₃) δ 8.41 (OH), 7.76–7.78 (m, 2H, H2''/H6''), 7.48 (d, J₁ = 2.3 Hz, 1H, H5'), 7.38–7.41 (m, 2H, H3''/H5''), 7.32 (t, J₁ = 7.4 Hz, 1H, H4''), 6.53 (d, J₁ = 2.3, 1H, H4'), 4.48 (t, J₁ = 6.5 Hz, 2H, H2), 3.00 (t, J₁ = 6.5 Hz, 2H, H1). ¹³C NMR (500 MHz, CDCl₃) δ 175.4 (C=O), 152.1 (C3'), 133.0 (C1''), 131.7 (C5'), 128.7 (2 × ArH), 128.0 (C4''), 125.8 (2 × ArH), 103.1 (C4'), 47.2 (C2), 35.0 (C1). HRMS (ESI): Observed: 239.0798, C₁₂H₁₂N₂NaO₂.

N-Phenyl-3-(3-phenyl-1H-pyrazol-1-yl)propanamide (208)

Propylphosphoric anhydride solution (50%) (0.650 ml, 1.09 mmol) was added dropwise to a stirred solution of 207 (0.197 g, 0.911 mmol), triethylamine (0.320 ml, 2.27 mmol), and aniline (0.083 ml, 0.911 mmol) in anhydrous THF (10.0 ml) at 0°C. The solution was warmed up to room temperature and stirred overnight. It was then quenched with distilled water (20.0 ml) and the solvent was evaporated. The crude product was
extracted with EtOAc (3 × 50.0 ml), and washed with water and 1M HCl (3 × 50.0 ml). The residue was subjected to flash chromatography and elution with 1:5 EtOAc/Hexanes and then 1:1 EtOAc/hexanes to give 208 as a clear oil. (0.162 g, 61%).

R. f.: 0.17 (50% EtOAc/Hexanes). IR (ATR) cm⁻¹: 1629 (C=O), 3353 (NH). ¹H NMR (500 MHz, CDCl₃) δ 8.39 (br s, 1H, NH), 7.81–7.83 (m, 2H, H2''/H6''), 7.41–7.47 (m, 5H, H5', 4 × ArH), 7.33–7.36 (m, 1H, H4''), 7.28–7.31 (m, 2H, H3''/H5''), 7.11 (t, J₁ = 7.4 Hz, 1H, H4''), 6.54 (d, J₁ = 2.3 Hz, 1H, H4'), 4.53 (t, J₁ = 6.2 Hz, 2H, H2), 2.98 (t, J₁ = 6.2 Hz 2H, H1). ¹³C NMR (500 MHz, CDCl₃) δ 168.9 (C=O), 152.2 (C3'), 137.9 (C1''), 133.4 (C1''), 131.9 (C5'), 129.0 (2 × ArC), 128.8 (2 × ArC ), 127.9 (ArC), 125.7 (2 × ArC ), 124.5 (ArC), 120.1 (2 × ArC ), 103.1 (C4'), 48.2 (C2), 38.3 (C1). HRMS (ESI): Observed: 314.1268, C₁₈H₁₇N₃NaO requires 314.1264.

3-(3-Phenyl-1H-pyrazol-1-yl)propanamide (188)

Ammonium hydroxide (30.0 ml) was added to a solution of 187 (0.580 g, 2.51 mmol) in THF (10.0 ml) and was heated at 60 °C for 48 hours. The solvent was evaporated and the crude product was extracted with EtOAc (3 × 50 ml), washed with water and brine (3 × 50 ml), dried, and the solvent was re-evaporated to yield 188 as a brown solid. (0.324 g, 60%). m.p.: 101-103°C. R. f: 0.29 (EtOAc). IR (ATR) cm⁻¹: 1665 (C=O), 3152 (NH), 3336 (NH). ¹H NMR (500 MHz, CDCl₃) δ 7.74–7.76 (m, H2''/H6''), 7.43 (d, J₁ = 2.0 Hz, 1H, H5'), 7.36–7.39 (m, 2H, H3''/H5''), 7.29 (tt, J₁ = 7.4 Hz, J₂ = 1.3 Hz, 1H, H4''), 6.49 (d, J₁ = 2.5 Hz, 1H, H4'), 6.12 (br s, 1H, NH), 5.83 (br s, 1H, NH), 4.43 (t, J₁ = 6.0 Hz, 2H, H2), 2.80 (t, J₁ = 6.0 Hz, 2H, H1). ¹³C NMR (500 MHz, CDCl₃) δ 172.9 (C=O), 152.0 (C3'), 133.4 (C1''), 131.7 (C5'), 128.7 (2 × ArH), 127.8 (C4''), 125.6
(2 × ArH), 102.8 (C4'), 48.0 (C2), 36.5 (C1). HRMS (ESI): Observed: 216.1133, C_{12}H_{14}N_{3}O^+ requires 216.1137.

Methyl (2-(3-phenyl-1H-pyrazol-1-yl)ethyl)carbamate (189)

(Diacetoxyiodo)benzene (1.84 g, 5.55 mmol) was added to a stirred solution of 188 (1.00 g, 4.64 mmol) in methanol (20.0 ml). The solution was stirred at room temperature overnight. The solvent was then evaporated; the crude product was extracted with EtOAc (3 × 50 ml), washed with water and brine (3 × 50 ml), and evaporated off solvent to yield 189 as a yellow oil. (0.581 g, 51%). R.f.: 0.39 (40% EtOAc/ Hexanes). IR (ATR) cm⁻¹: 1696 (C=O), 3334 (NH). ¹H NMR (500 MHz, CDCl₃) δ 7.77–7.79 (m, 2H, H2''/H6''), 7.38–7.41 (m, 3H, H5'/H3''/H5''), 7.30 (tt, J₁ = 7.5 Hz, J₂ = 1.4 Hz, 1H, H4''), 6.54 (d, J₁ = 2.5 Hz, 1H, H4'), 5.26 (br s, 1H, NH), 4.26 (t, J₁ = 5.5 Hz, 2H, H2), 3.66 (m, 5H, H1, Methyl). ¹³C NMR (500 MHz, CDCl₃) δ 157.2 (C=O), 152.3 (C3'), 133.4 (C1''), 131.5 (C5'), 128.8 (C2''/C6''), 127.8 (C4''), 125.7 (C3''/C5''), 102.9 (C4'), 52.3 (C2 or Methyl), 51.7 (C2 or Methyl), 41.4 (C1). HRMS (ESI): Observed: 246.1247, C_{13}H_{16}N_{3}O_{2}^+ requires 246.1243.
1-(2-Ammonioethyl)-3-phenyl-1H-pyrazol-2-ium chloride (185)

4M Hydrochloric acid (10.0 ml) was added to 189 (0.580 g, 2.36 mmol) and the solution was heated at reflux for 4 hours. The solvent was evaporated to yield 185 as a light brown solid. (0.614 g, 100%). m.p.: 129-131 °C. IR (ATR) cm⁻¹: 2481-3116 (NH). ¹H NMR (500 MHz, MeOD) δ 7.98 (d, J₁ = 2.5 Hz, 1H, H₅'), 7.86–7.88 (d, 2H, H₂"/H₆"), 7.44–7.47 (m, 2H, H₃'/H₅''), 7.37 (tt J₁ = 7.5 Hz, J₂ = 1.3 Hz, 1H, H₄''), 6.86 (d, J₁ = 2.5 Hz, 1H, H₄'), 4.65 (t, J₁ = 6.0 Hz, 2H, H₂), 3.55 (t, J₁ = 6.0 Hz, 2H, H₁). ¹³C NMR (500 MHz, MeOD) δ 153.0 (C₃'), 135.4 (C₅'), 132.1 (C₁''), 130.1 (C₄''), 130.0 (C₂'/C₆''), 127.2 (C₃'/C₅''), 105.1 (C₄'), 49.6 (C₂), 40.6 (C₁). HRMS (ESI): Observed: 188.1184, C₁₁H₁₄N₃ requires 188.1188.

N-(2-(3-Phenyl-1H-pyrazol-1-yl)ethyl)benzenesulfonamide (190)

Benzenesulfonyl chloride (0.150 ml, 1.17 mmol) was added dropwise to a stirred solution of Hünig's base (0.50 mL, 2.87 mmol) and 185 (0.090 g, 0.346 mmol) in DCM (15 mL) at 0 °C. The solution was allowed to warm to room temperature and stirring was continued overnight. The solution was diluted with EtOAc (150 mL) and washed with brine (3 × 50 mL), dried and evaporated. The volatiles were evaporated and the residue was subjected to flash chromatography. Elution with 2:3 EtOAc/hexanes gave 190 as a white solid. (0.0385 g, 34%). m.p.: 80-82 °C. IR (ATR) cm⁻¹: 1156 (S=O),
$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.81–7.83 (m, 2H, 2 × ArH), 7.73–7.75 (m, 2H, 2 × ArH), 7.52–7.56 (tt, $J_1$= 7.5 Hz, $J_2$= 1.0 Hz, 1H, ArH), 7.44–7.47 (dd (app t), $J_1$= 7.5 Hz, 2H, 2 × ArH), 7.30–7.33 (m, 2H, H5'', ArH), 6.50 (d, $J_1$= 2.0 Hz, 1H, ArH), 5.60 (br t, $J_1$ = 5.5 Hz, 1H, NH), 4.20 (t, $J_1$= 5.5 Hz, 2H, H2'), 3.45 (dt (app q), $J_1$= 5.5 Hz, 2H, H1').

$^{13}$C NMR (500 MHz, CDCl$_3$) $\delta$ 152.5 (C3''), 139.9 (C1), 133.2 (C1'''), 132.7 (ArH or C5''), 131.7 (ArH or C5''), 129.2 (2 × ArH), 128.7 (2 × ArH), 127.9 (ArH), 127.0 (2 × ArH), 125.6 (2 × ArH), 103.0 (C4''), 51.2 (C2'), 43.3 (C1').

HRMS (ESI): Observed: 328.1125, C$_{17}$H$_{18}$N$_3$O$_2$S$^+$ requires 328.1120.

$N$-(2-(3-Phenyl-1H-pyrazol-1-yl)ethyl)morpholine-4-carboxamide (191)

4-morpholinecarbonyl chloride (0.050 ml, 0.463 mmol) dissolved in dichloromethane (1.0 ml) was added dropwise to a stirred solution of triethylamine (1.50 ml) and 185 (0.0945 g, 0.363 mmol) in dichloromethane (5.0 ml) at 0 °C. The solution was allowed to warm to room temperature and stirring was continued overnight. It was diluted with EtOAc (150 mL) and washed with brine (3 × 50 mL), dried and evaporated. The volatiles were evaporated and the residue was subjected to flash chromatography. Elution with 1:1 EtOAc/hexanes gave 191 as a clear oil. (0.0818 g, 75%). R$_e$: 0.21 (EtOAc). IR (ATR) cm$^{-1}$: 1630 (C=O), 3352 (NH). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.75–7.78 (m, 2H, H2''/H6''), 7.38–7.42 (m, 3H, H5''/H3''/H5''), 7.31 (tt, $J_1$ = 7.5 Hz, $J_2$ = 1.4 Hz, 1H, H4''), 6.54 (d, $J_1$ = 2.5 Hz, 1H, H4''), 5.65 (br s, 1H, NH), 4.28–4.30
(m, 2H, H2'), 3.69–3.72 (m, 2H, H1'), 3.62 (t, J1 = 5.0 Hz, 4H, H3/H5), 3.31 (t, J1 = 5.0 Hz, 4H, H2/H6). 13C NMR (500 MHz, CDCl3) δ 157.8 (C=O), 152.1 (C3''), 133.3 (C1''''), 131.7 (C5''), 128.8 (2 × ArH), 127.9 (C4'''), 125.4 (2 × ArH), 102.8 (C4'''), 66.5 (C3/C5), 51.6 (C2'), 44.0 (C2/C6), 41.4 (C1'). HRMS (ESI): Observed: 301.1653, C16H21N4O2+ requires 301.1665.

N-(2-(3-Phenyl-1H-pyrazol-1-yl)ethyl)-1H-imidazole-1-carboxamide (192)

1,1-carbonyldiimidazole (0.217 g, 1.33 mmol) was added to a solution of 185 (0.230 g, 0.884 mmol) in DMF (2 mL) and MeCN (2 mL). The solution was allowed to stir for 2 h, then the MeCN was evaporated and the residue was diluted with EtOAc (150 mL) and washed with brine (3 × 50 mL), dried and evaporated. The residue was subjected to flash chromatography. Elution with 7:3 EtOAc/hexanes and then EtOAc gave 192 as a yellow oil. (0.114 g, 46%). Rf.: 0.15 (EtOAc). IR (ATR) cm⁻¹: 1624 (C=O), 3320 (NH). 1H NMR (500 MHz, CDCl3) δ 8.10 (s, 1H, H2), 7.77 (br s, 1H, NH), 7.74–7.75 (m, 1H, H2'' or H6''), 7.73–7.74 (m, 1H, H2''' or H6'''), 7.42 (d, J1 = 2.5 Hz, 1H, H5'), 7.38–7.41 (m, 2H, H3'''/H5'''), 7.35 (dd [app br t], J1 = J2 = 1.2 Hz, H5), 7.32 (tt, J1 = 7.5 Hz, J2 = 1.4 Hz, 1H, H4'''), 7.02 (s, 1H, H4), 6.55 (d, J1 = 2.5, 1H, H4'''), 4.35–4.37 (m, 2H, H2''), 3.83–3.86 (m, 2H, H1'). 13C NMR (500 MHz, CDCl3) δ 152.7 (C=O or C3''), 149.1 (C=O or C3'''), 136.0 (C2), 133.0 (C1''''), 131.9 (C5'''), 130.5 (C4), 128.9 (2 × ArH), 128.2 (C4'''), 125.6 (2 × ArH), 116.0 (C5), 103.2 (C4''), 50.7 (C2'), 41.5 (C1'). HRMS (ESI): Observed: 282.1367, C15H16N5O+ requires: 282.1355.
General procedure for the synthesis of ureas from 192. Triethylamine (1.1 equiv) and amine (1.0 equiv) were added to a stirred solution of 192 (1.0 equiv) in DCM (~5 mL/mmole of 192) under argon. When TLC indicated the reaction to be complete (generally after overnight), the solvent was evaporated under argon and the residue was purified by flash chromatography.

Isopropyl (2-(3-phenyl-1H-pyrazol-1-yl)ethyl)carbamate (196)
NaH (60% dispersion in mineral oil, 0.050 g, 2.08 mmol) was added to a stirred solution of isopropanol (0.020 ml, 0.261 mmol) and 192 (0.0700 g, 0.248 mmol) in dry DMF (10.0 ml) under argon. When TLC indicated the reaction to be complete (generally after overnight), the solution was quenched with water. The reaction mixture was diluted with water and extracted with EtOAc (3 × 50 ml) and the extract was dried and evaporated. The residue was purified by flash chromatography and elution with 1:5 EtOAc/hexanes and then 1:1 EtOAc/hexanes gave 196 as a yellow oil (0.0400 g, 59%).

IR (ATR) cm⁻¹: 1696 (C=O), 3335 (NH). ¹H NMR (500 MHz, CDCl₃) δ 7.78–7.80 (m, H₂''/H₆''), 7.38–7.41 (m, 3H, H₅'/H₃''/H₅''), 7.30 (tt, J₁ = 7.5 Hz, J₂ = 1.4 Hz, 1H, H₄''), 6.54 (d, J₁ = 2.5 Hz, 1H, H₄'), 5.03 (br s, 1H, NH), 4.91 (sept, 1H, H₁'''), 4.27 (t, J₁ = 5.4 Hz, 2H, H2), 3.65 (dt (app q), J₁ = J₂ = 5.6 Hz, 2H, H1), 1.22 (d, J₁ = 6.0 Hz, 6H, H₂''). ¹³C NMR (500 MHz, CDCl₃) δ 156.5 (C=O), 152.3 (C3'), 133.5 (C1''), 131.5 (C4'), 128.8 (2 × ArH), 127.8 (C4''), 125.7 (2 × ArH), 103.0 (C5'), 68.5 (C1''), 51.8
(C1), 41.2 (C1), 22.2 (C2''). HRMS (ESI): Observed: 274.1551, C_{13}H_{20}N_{3}O_{2}^{+} requires 274.1556.

\[
\begin{align*}
\text{O} & \quad \text{H} \\
\text{N} & \quad \text{2''} \\
\text{H} & \quad \text{2''} \\
\text{H} & \quad \text{2'} \quad \text{1''} \\
\text{H} & \quad \text{2'} \quad \text{1''} \\
\text{H} & \quad \text{2''} \\
\text{H} & \quad \text{1''} \\
\text{H} & \quad \text{2''} \\
\text{H} & \quad \text{1''} \\
\text{H} & \quad \text{2''} \\
\text{H} & \quad \text{1''} \\
\text{H} & \quad \text{2''} \\
\text{H} & \quad \text{1''} \\
\text{H} & \quad \text{2''} \\
\text{H} & \quad \text{1''} \\
\text{H} & \quad \text{2''} \\
\end{align*}
\]

1-Isopropyl-3-(2-(3-phenyl-1H-pyrazol-1-yl)ethyl)urea (197)

The general procedure was followed with 192 (0.110 g, 0.391 mmol) and isopropylamine (0.030 ml, 0.402 mmol). Elution with EtOAc gave 197 as a white solid (0.0799 g, 75%). m.p.: 160-161 °C. R_{f}: 0.41 (EtOAc). IR (ATR) cm^{−1}: 1632 (C=O), 3334 (NH). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.77–7.79 (m, 2H, H2''/H6''), 7.37–7.41 (m, 3H, H5/H3''/H5''), 7.30 (tt, \(J_1 = 7.4\) Hz, \(J_2 = 1.4\) Hz, 1H, H4''), 6.54 (d, \(J_1 = 2.5\) Hz, 1H, H4'), 4.77 (br s, 1H, NH), 4.22–4.25 (m, 3H, H2, NH), 3.78 (m, \(J_1 = 6.5\) Hz, 1H, H1'''), 3.68 (dt (app q), \(J_1 = 6.0\) Hz, 2H, H1'), 1.09 (d, \(J_1 = 6.5\) Hz, 6H, H2'''). \(^{13}\)C NMR (500 MHz, CDCl\(_3\)) \(\delta\) 157.5 (C=O), 152.3 (C3'), 133.5 (C1''), 131.8 (C5'), 128.8 (2 × ArH), 127.9 (C4''), 125.7 (2 × ArH), 102.9 (C4'), 52.3 (C2), 42.5 (C1'''), 40.8 (C1), 23.5 (C2 ''). HRMS (ESI): Observed: 273.1720, C_{13}H_{21}N_{4}O^{+} requires 273.1715.

\[
\begin{align*}
\text{O} & \quad \text{H} \\
\text{N} & \quad \text{2''} \\
\text{H} & \quad \text{2''} \\
\text{H} & \quad \text{2'} \quad \text{1''} \\
\text{H} & \quad \text{2'} \quad \text{1''} \\
\text{H} & \quad \text{2''} \\
\text{H} & \quad \text{1''} \\
\text{H} & \quad \text{2''} \\
\text{H} & \quad \text{1''} \\
\text{H} & \quad \text{2''} \\
\text{H} & \quad \text{1''} \\
\text{H} & \quad \text{2''} \\
\text{H} & \quad \text{1''} \\
\text{H} & \quad \text{2''} \\
\end{align*}
\]

1,1-Diethyl-3-(2-(3-phenyl-1H-pyrazol-1-yl)ethyl)urea (198)

The general procedure was followed with 192 (0.110 g, 0.391 mmol) and diethylamine (0.050 ml, 0.483 mmol). Elution with 1:1 EtOAc/hexanes gave 198 as a yellow oil (0.0974 g, 87%). R_{f}: 0.15 (50% EtOAc/Hexanes). IR (ATR) cm^{−1}: 1623 (C=O), 3349
(NH). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.77–7.79 (m, 2H, H2''/H6''), 7.37–7.40 (m, 3H, H5'/H3''/H5''), 7.30 (tt, $J_1 = 7.3$ Hz, $J_2 = 1.5$ Hz, 1H, H4''), 6.54 (d, $J_1 = 2.5$ Hz, 1H, H4''), 4.28–4.30 (m, 2H, H2), 3.67–3.70 (m, 1H, H1), 3.22 (q, $J_1 = 7.0$ Hz, 4H, H1'''), 1.08 (t, $J_1 = 7.0$ Hz, 6H, H2''').

$^{13}$C NMR (500 MHz, CDCl$_3$) $\delta$ 157.3 (C=O), 152.2 (C3'), 133.5 (C1''), 131.7 (C5'), 128.7 (2 × ArH), 127.8 (C4''), 125.6 (2 × ArH), 102.7 (C4'), 51.9 (C2), 41.4 (C1), 41.3 (C1'''), 13.9 (C2'''). HRMS (ESI): Observed: 287.1863, C$_{16}$H$_{23}$N$_4$O$^+$ requires 287.1872.

$N$-($2$-($3$-Phenyl-$1$H-pyrazol-$1$-yl)ethyl)piperidine-$1$-carboxamide (200)

The general procedure was followed with 192 (0.100 g, 0.355 mmol) and piperidine (0.030 ml, 0.355 mmol). Elution with 3:2 EtOAc/hexanes gave 200 as a yellow solid (0.0996 g, 94%). m.p: 97–99 °C. R$_s$: 0.29 (EtOAc). IR (ATR) cm$^{-1}$: 1604 (C=O), 3295 (NH). $^1$H NMR (500 MHZ, CDCl$_3$) $\delta$ 7.76–7.78 (m, 2H, H2''/H6''), 7.36–7.39 (m, 3H, H5''/H3''/H5''), 7.29 (tt, $J_1 = 7.4$ Hz, $J_2 = 1.4$ Hz, 1H, H4''), 6.54 (d, $J_1 = 2.3$ Hz, 1H, H4''), 5.47 (br t, $J_1 = 4.8$ Hz, 1H, NH), 4.26–4.28 (m, 2H, H2'), 3.64–3.67 (m, 2H, H1'), 3.28–3.31 (m, 4H, H2/H6), 1.54–1.57 (m, 2H, H4), 1.47–1.51 (m, 4H, H3/H5). $^{13}$C NMR (500 MHz, CDCl$_3$) $\delta$ 157.6 (C=O), 152.0 (C3''), 133.4 (C1''), 131.7 (C5''), 128.7 (2 × ArH), 127.8 (C4''), 125.5 (2 × ArH), 102.6 (C4''), 51.7 (C2''), 44.8 (C2/C6), 41.4 (C1''), 25.6 (C3/C5), 24.4 (C4). HRMS (ESI): Observed: 299.1876, C$_{17}$H$_{23}$N$_4$O$^+$ requires 299.1872.
N-(2-(3-Phenyl-1H-pyrazol-1-yl)ethyl)azepane-1-carboxamide (201)

The general procedure was followed with 192 (0.120 g, 0.427 mmol) and azepane (0.050 ml, 0.448 mmol). Elution with 1:1 EtOAc/hexanes 201 as a yellow oil. (0.0999 g, 75%). Rf: 0.13 (50% EtOAc/Hexanes). IR (ATR) cm⁻¹: 1624 (C=O), 3359 (NH).

¹H NMR (500 MHz, CDCl₃) δ 7.76–7.78 (m, 2H, H₂''/H₆''), 7.36–7.40 (m, 3H, H₅''/H₃''/H₅''), 7.29 (tt, 1H, H₄''), 6.53 (d, J₁ = 2.0 Hz, 1H, H₅'), 5.26 (br s, 1H, NH), 4.27–4.30 (m, 2H, H₂'), 3.67–3.70 (m, 2H, H₁'), 3.33–3.36 (m, 4H, H₂/H₇), 1.63–1.65 (m, 4H, H₄/H₅), 1.50–1.52 (m, 4H, H₃/H₆). ¹³C NMR (500 MHz, CDCl₃) δ 157.8 (C=O), 152.1 (C₃''), 133.5 (C₁'''), 131.7 (C₅''), 128.7 (2 × ArH), 127.8 (C₄'''), 125.6 (2 × ArH), 102.7 (C₄''), 51.9 (C₂'), 46.4 (C₂/C₇), 41.4 (C₁'), 28.6 (2 × Aliph), 27.3 (2 × Aliph). HRMS (ESI): Observed: 313.2038, C₁₈H₂₅N₄O⁺ requires 313.2028.

4-(Chloromethyl)-2-(pyridin-2-yl)thiazole (219)

Pyridinethioamide (5.00 g, 36.2 mmol) was added to a stirred solution of 1,3-dichloroacetone (6.15 g, 48.0 mmol) in acetone (100 mL) under N₂. The reaction mixture was heated under reflux overnight, then allowed to cool. The resulting yellow precipitate was collected by vacuum filtration and washed with acetone. The filtrate was dissolved in sulfuric acid (30 mL) and stirred for 30 min, then poured onto ice. The
aqueous phase was extracted with EtOAc (3 × 250 mL), dried and evaporated to give 219 as orange crystals (2.51 g, 33%), mp = 90–92 °C, pure enough for the following step. Rf 0.25 (1:4 EtOAc/hexanes). 1H NMR (500 MHz, CDCl3): δ 8.61 (d, J = 4.0 Hz, 1H, H6'), 8.20 (d, J = 7.6 Hz, 1H, H3'), 7.79 (dd, J = 6.8 Hz, 7.6 Hz, 1H, H4'), 7.33 (dd, J = 5.2, 6.4 Hz, 1H, H5'), 7.25 (s, 1H, H5), 4.59 (s, 2H, CH2); 13C NMR (126 MHz, CDCl3): δ 169.5 (C2), 153.2 (C2' or C4), 150.6 (C2' or C4), 149.3 (C6'), 136.9 (CH), 124.6 (CH), 119.8 (CH), 119.6 (CH), 40.9 (CH2). HRMS (ESI) m/z observed: 211.0106, C9H8ClN2S + [free base + H]+ requires 211.0092.

2-(2-(Pyridin-2-yl)thiazol-4-yl)acetonitrile (220)

A solution of KCN (0.839 g, 12.9 mmol) and 219 (2.51 g, 11.9 mmol) in dry DMF (30 mL) was stirred at 70 °C overnight, then allowed to cool, diluted with water (200 mL) and extracted with EtOAc (3 × 200 mL). The extract was washed with brine (3 × 200 mL), dried and evaporated to yield 220 as a green oil (1.77 g, 74%), mp = 66–68 °C. Rf 0.3 (1:20:80 NEt3/etOAc/hexanes). IR (thin film) cm⁻¹: 2244 (C≡N). 1H NMR (500 MHz, CDCl3): δ 8.61 (d, J = 4.8 Hz, 1H, H6''), 8.17 (d, J = 8.0 Hz, 1H, H2''), 7.84 (d, J = 8.0 Hz, 1H, H2'), 7.38 (s, 1H, H5'), 7.32–7.41 (m, 1H, H5''), 3.96 (s, 2H, CH2). 13C NMR (126 MHz, CDCl3): 170.4 (C2''), 150.8 (C2'' or C4''), 149.7 (C6''), 146.1 (C2'' or C4''), 137.3 (CH), 125.1 (CH), 119.9 (CH), 118.8 (CH), 116.9 (CN), 21.2 (CH2). HRMS (ESI) m/z observed: 202.0431, C10H8N3S+ [M+H]+ requires 202.0439.
2-(2-(Pyridin-2-yl)thiazol-4-yl)ethanamine (221)

A 1 M BH₃−THF solution (40 mL, 40 mmol) was slowly added to a stirred solution of 220 (1.50 g, 7.45 mmol) in anhydrous THF (10 mL) at 0 °C, under N₂. The solution was allowed to warm to room temperature and then heated under reflux for 2 h. The resulting black solution was cooled, quenched with MeOH (2 mL) then acidified with conc. HCl. The stirred reaction mixture was heated under reflux for 45 min. The THF was evaporated and the residual aqueous phase was basified with K₂CO₃ and extracted with EtOAc (3 × 50 mL). The extract was dried and evaporated to give 221 as a brown oil, (0.382 g, 25%), which was used without further purification or characterization in the next steps.

Methyl 3-(2-(pyridin-3-yl)thiazol-4-yl)propanoate (231)

A stirred solution of methyl 5-bromo-4-oxopentanoate (3.00 g 14.4 mmol) and 3-pyridinethioamide (2.00 g, 14.5 mmol) in MeOH (50 mL) was heated under reflux overnight. The solvent was evaporated and the residue was subjected to flash chromatography. Elution with 1:4 EtOAc/hexanes then 1:1 EtOAc/hexanes gave 231 as a colourless oil (0.787 g, 22%). Rₜ 0.6 (1:50:50 NEt₃/EtOAc/hexanes). IR (thin film) cm⁻¹: 1727 (C=O). ¹H NMR (500 MHz, CDCl₃): δ 9.10 (s, 1H, H₂''), 8.60 (d, J₁ = 4.3 Hz, 1H, H₆''), 8.17 (dt, J₁ = 8.0, 1.6 Hz, 1H, H₄''), 7.33 (dd, J₁ = 8.0, J₂ = 4.9 Hz, 1H, H₅''), 7.00 (s, 1H, H₅''), 3.66 (s, 3H, CH₃), 3.13 (t, J₁ = 7.5 Hz, 2H, H₃), 2.79 (t, J₁ = 7.5
Hz, 2H, H2). 13C NMR (126 MHz, CDCl3): δ 173.3 (C=O), 164.2 (C2'), 157.0 (C4'), 150.6 (C2" or C6"), 147.6 (C2" or C6"), 133.6 (ArH), 129.8 (ArH), 123.8 (ArH), 114.6 (C5'), 51.8 (CH3), 33.4 (C3), 26.8 (C2). HRMS (ESI) m/z observed: 249.0685, C12H13N2O2S+ [M+H]+ requires 249.0692.

Methyl 3-(2-(pyridin-4-yl)thiazol-4-yl)propanoate (232)

A stirred solution of methyl-5-bromo-4-oxopentanoate (1.43 g 6.84 mmol) and 4-pyridinethioamide (0.856 g, 6.19 mmol) in MeOH (40 mL) was heated under reflux overnight. The solvent was evaporated and the residue was subjected to flash chromatography. Elution with 1:4 EtOAc/hexanes then 1:1 EtOAc/hexanes gave 232 as an orange solid (0.907 g, 59%), mp = 55–57 °C. Rf 0.4 (1:1 EtOAc/hexanes). IR (thin film) cm⁻¹: 1599 (C=O). 1H NMR (500 MHz, CDCl3): δ 8.68 (d, J1 = 6.0 Hz, 2H, H2"/H6"), 7.78 (d, J1 = 6.0 Hz, 2H, H3"/H5"), 7.09 (s, 1H, H5'), 3.69 (s, 3H, CH3), 3.16 (t, J1 = 7.4 Hz, 2H, H3), 2.82 (t, J1 = 7.4 Hz, 2H, H2). 13C NMR (126 MHz, CDCl3): δ 173.3 (C=O), 164.9 (C2'), 157.5 (C4'), 150.8 (C2"/C6"), 140.5 (C4"), 120.4 (C3"/C5"), 115.8 (C5'), 51.9 (CH3), 33.5 (C3), 26.8 (C2). HRMS (ESI) m/z observed: 249.0691, C12H13N2O2S+ [M+H]+ requires 249.0692.
Methyl 3-(2-(thiophen-2-yl)thiazol-4-yl)propanoate (230)

A stirred solution of methyl-5-bromo-4-oxopentanoate (1.88 g, 8.99 mmol) and thiophene-2-carbothioamide (1.17 g, 8.20 mmol) in MeOH (40 mL) was heated under reflux overnight. The solvent was evaporated and the residue was subjected to flash chromatography. Elution with 1:9 EtOAc/hexanes then 1:1 EtOAc/hexanes gave 230 as a pale-pink solid (0.997 g, 48%), mp = 55−57 °C. Rf 0.5 (1:4 EtOAc/Hexanes). IR (thin film) cm⁻¹: 1726 (C=O). ¹H NMR (500 MHz, CDCl₃): δ 7.47 (d, J₁ = 3.6 Hz, 1H, H₃''), 7.36 (d, J₁ = 5.0 Hz, 1H, H₅''), 7.06 (pseudo t, 1H, H₄''), 6.86 (s, 1H, H₅'), 3.69 (s, 3H, CH₃), 3.10 (t, J₁ = 7.5 Hz, 2H, H₃), 2.78 (t, J₁ = 7.5 Hz, 2H, H₂). ¹³C NMR (126 MHz, CDCl₃): δ 173.4 (C=O), 161.6 (C2'), 156.1 (C4'), 137.6 (C2''), 127.9 (CH), 127.6 (CH), 126.5 (CH), 113.0 (C5'), 51.8 (CH₃), 33.6 (C3), 26.8 (C2). HRMS (ESI) m/z observed: 276.0128, C₁₁H₁₁NNaO₂S₂⁺ [M+Na]⁺ requires 276.0123.

3-(2-(Pyridin-3-yl)thiazol-4-yl)propanamide (234)

A solution of 231 (0.800 g, 3.22 mmol) in THF (5 mL) and conc. ammonium hydroxide (10 mL) was stirred for 48 h. The volatiles were evaporated and the residue was triturated with EtOAc to yield 234 as a yellow/brown solid (0.300 g, 40%), mp = 147−149 °C. Rf 0.2 (EtOAc). IR (thin film) cm⁻¹: 3375 (NH), 3113 (NH), 1663 (C=O). ¹H NMR (500 MHz, MeOD): δ 9.90 (d, J₁ = 1.8 Hz, 1H, H₂''), 9.45 (dd, J₁ = 4.8, J₂ =
1.4 Hz, 1H, H6''), 9.07 (ddd [app. dt], \(J_1 = 8.0\) Hz, \(J_2 = J_3 = 1.8\) Hz, 1H, H4''), 8.33 (dd, \(J_1 = 7.8, 4.8\) Hz, 1H, H5''), 8.23 (s, 1H, H5'), 8.17 (br s, 1H, NH), 7.62 (br s, 1H, NH), 3.79 (t, \(J_1 = 7.9\) Hz, 2H, H3), 3.32 (t, 2H, H2). HRMS (ESI) \(m/z\) observed: 256.0509, \(C_{11}H_{11}N_{3}NaOS^+ [M+Na]^+\) requires 256.0515.

3-(2-(Pyridin-4-yl)thiazol-4-yl)propanamide (235)

A solution of 232 (0.300 g, 1.21 mmol) in THF (6 mL) and conc. ammonium hydroxide (10 mL) was stirred for 48 h. The volatiles were evaporated and the residue was washed with DCM (3 × 20 mL) to yield 235 as a pale-yellow solid (0.202 g, 72%), \(mp = 161–163^\circ\)C. \(R_f\) 0.7 (1:1:98 NEt$_3$/MeOH/EtOAc). IR (thin film) \(cm^{-1}\): 3244 (NH), 3109 (NH), 1682 (C=O). \(^1\)H NMR (500 MHz, DMSO): \(\delta 8.69\) (d, \(J_1 = 6.0\) Hz, 2H, H2''/H6''), 7.86 (d, \(J_2 = 6.0\) Hz, 2H, H3''/H5''), 7.52 (s, 1H, H5'), 7.37 (br s, 1H, NH), 6.82 (br s, 1H, NH), 3.00 (t, \(J_1 = 7.6\) Hz, 2H, H3), (H2 largely obscured by d$_6$-DMSO peak). \(^13\)C NMR (126 MHz, DMSO): 173.2 (C=O), 163.7 (C2'), 158.0 (C4'), 150.8 (C2''/C6''), 139.6 (C4''), 119.9 (C3''/C5''), 116.8 (C5'), 34.3 (C3), 26.8 (C2). HRMS (ESI) \(m/z\) observed: 256.0513, \(C_{11}H_{11}N_{3}NaOS^+ [M+Na]^+\) requires 256.0515.
3-(2-(Thiophen-2-yl)thiazol-4-yl)propanamide (233)

A solution of **230** (1.00 g, 3.94 mmol) in THF (6 mL) and conc. ammonium hydroxide (15 mL) was stirred for 48 h. The volatiles were evaporated and the solid residue was washed with DCM (3 × 50 mL), then subjected flash chromatography. Elution with 1:240:60 NEt$_3$/EtOAc/hexanes, then 1:1:98 NEt$_3$/MeOH/EtOAc gave **233** as a white solid (0.338 g, 36%), mp = 103–105 °C. R$_f$ 0.3 (1:99 MeOH/EtOAc). IR (thin film) cm$^{-1}$: 3374 (NH), 3171 (NH), 1664 (C=O). $^1$H NMR (500 MHz, DMSO): $\delta$ 7.68 (d, $J_1 = 5.1$ Hz, 1H, H5''), 7.61 (d, $J_1 = 3.0$ Hz, 1H, H3''), 7.38 (br. s, 1H, NH), 7.24 (s, H5'), 7.15 (dd, $J = 4.9$, 3.9 Hz, 1H, H4''), 6.82 (br s, 1H, NH), 2.91 (t, $J = 7.7$ Hz, 2H, H3), 2.46 (t, $J = 7.7$ Hz, 2H, H2). $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 176.9 (C=O), 162.1 (C2'), 155.5 (C4'), 137.0 (C2''), 128.1 (CH), 128.0 (CH), 126.9 (CH'), 113.2 (C5'), 33.8 (C3), 26.2 (C2). HRMS (ESI) m/z observed: 261.0133, C$_{10}$H$_{10}$N$_2$NaOS$_2$ $^+$ [M+Na]$^+$ requires 261.0127.

Methyl (2-(2-(pyridin-3-yl)thiazol-4-yl)ethyl)carbamate (237)

A solution of diacetoxyiodobenzene (0.537 g, 1.62 mmol) and **234** (0.300 g, 1.29 mmol) in dry MeOH (15 mL) was stirred overnight. The solvent was evaporated and the residue was subjected to flash chromatography. Elution with 1:50:50
NEt₃/EtOAc/hexanes gave 237 as a clear oil (0.200 g, 59%). Rᵣ: 0.2 (1:99 NEt₃/EtOAc).

IR (thin film) cm⁻¹: 3205 (NH), 1702 (C=O). ¹H NMR (500 MHz, CDCl₃): δ 9.07 (d, J₁ = 1.7 Hz, 1H, H2''), 8.58 (dd, J₁ = 4.8, 1.3 Hz, 1H, H6''), 8.14 (d, J₁ = 7.9 Hz, 1H H4''), 7.32 (dd, J₁ = 7.9, 4.9, Hz, 1H, H5''), 7.01 (s, 1H, H5''), 5.49 (br. s, 1H, NH), 3.62 (s, 3H, CH₃), 3.57 (dt [app. q], J₁ = J₂ = 6.2 Hz, 2H, H3), 2.98 (t, J₁ = 6.3 Hz, 2H, H2).

¹³C NMR (126 MHz, CDCl₃): δ 164.6 (C3''), 157.2 (C=O or C4''), 155.9 (C=O or C4''), 150.7 (C2'' or C6''), 147.6 (C2'' or C6''), 133.6 (C4''), 129.6 (C3''), 123.8 (C5''), 115.3 (C5'), 52.1 (CH₃), 40.4 (C1), 31.6 (C2). HRMS (ESI) m/z observed: 286.0634, C₁₂H₁₃N₃NaO₂S⁺ [M+Na]⁺ requires 286.0621.

3-(4-(2-Ammonioethyl)thiazol-2-yl)pyridin-1-ium chloride (240)

A stirred solution of 237 (0.200 g, 0.751 mmol) in 4 M HCl (10 mL) was heated under reflux overnight. The solvent was evaporated to yield 240 as a colourless oil (0.209 g, quant.). IR (thin film) cm⁻¹: 3366 (NH), 3030 (NH). ¹H NMR (500 MHz, MeOD): δ 9.52 (s, 1H, H2''), 9.16 (d, J₁ = 7.8 Hz, 1H, H6''), 8.99 (d, J₁ = 5.0 Hz, 1H, H4''), 8.28 (dd [app. t], J₁ = J₂ = 6.4 Hz, 1H, H5''), 7.33 (s, 1H, H5''), 3.39 (t, J₁ = 6.2 Hz, 2H, H1), 3.24 (t, J₁ = 6.4 Hz, 2H, H2). ¹³C NMR (126 MHz, MeOD): δ 162.0 (C2''), 155.7 (C4''), 144.7 (C2'' or C6''), 142.9 (C2'' or C6''), 140.5 (C4''), 134.5 (C3''), 129.3 (C5''), 121.2 (C5''), 40.1 (C1), 29.6 (C2). HRMS (ESI) m/z observed: 206.0745, C₁₀H₁₂N₃S⁺ [free base + H]⁺ requires 206.0746.
Methyl (2-(2-(pyridin-4-yl)thiazol-4-yl)ethyl)carbamate (238)

A mixture of diacetoxyiodobenzene (0.343 g, 1.03 mmol) and 235 (0.200 g, 0.860 mmol) in dry MeOH (8 mL) was stirred overnight. The solvent was evaporated and the residue was subjected to flash chromatography. Elution with 1:20:80 NEt3/EtOAc/hexanes then 1:50:50 NEt3/EtOAc/hexanes gave 238 as a white solid (0.159 g, 70%), mp 91–93 °C. Rf 0.6 (1:50:50 NEt3/EtOAc/hexanes). IR (thin film) cm⁻¹: 3205 (NH), 1701 (C=O). ¹H NMR (500 MHz, CDCl₃): δ 8.65 (d, J₁ = 6.0 Hz, 2H, H₂''/H₆''), 7.74 (d, J₁ = 5.9 Hz, 2H, H₃''/H₅''), 7.09 (s, 1H, H₅''), 5.39 (br. s, 1H, NH), 3.64 (s, 3H, CH₃), 3.58 (dt [app. q], J₁ = J₂ = 6.0 Hz, 2H, H₁), 3.01 (t, J₁ = 6.3 Hz, 2H, H₂). ¹³C NMR (126 MHz, CDCl₃): δ 165.1 (C₂'), 157.5 (C=O or C₄'), 156.4 (C=O or C₄'), 150.7 (C₂''/C₆''), 140.2 (C₄''), 120.3 (C₃''/C₅''), 116.5 (C₅''), 52.1 (CH₃), 40.4 (C₁), 31.7 (C₂). HRMS (ESI) m/z observed: 286.0621, C₁₂H₁₃N₃NaO₂S⁺ [M+Na]⁺ requires 286.0621

4-(4-(2-Ammonioethyl)thiazol-2-yl)pyridin-1-ium chloride (241)

A stirred solution of 238 (0.220 g, 0.759 mmol) in 4 M HCl (15 mL) was heated under reflux overnight. The solvent was evaporated to yield 241 as yellow crystals (0.170 g, quant.), mp = 147–150 °C. Rf 0.4 (1:99 MeOH/EtOAc). IR (thin film) cm⁻¹: 3390 (NH).
1\(^1\)H NMR (500 MHz, DMSO): \(\delta\) 8.88 (s, 2H, H2''/H6''), 8.22 (s, 2H, H3''/H5''), 8.06 (br. s, 3H, NH₃), 7.88 (s, 1H, H5'), 3.22 (pseudo q, 2H, H1), 3.15 (t, 2H, \(J = 7.0\) Hz, H2).

1\(^3\)C NMR (126 MHz, MeOD): \(\delta\) 162.8 (C2'), 157.2 (C4'), 150.2 (C4''), 143.9 (C2''/C6''), 124.8 (C3''/C5''), 124.4 (C5'), 40.3 (C1), 29.9 (C2). HRMS (ESI) \(m/z\) observed: 206.0745, C\textsubscript{10}H\textsubscript{12}N\textsubscript{3}S\textsuperscript{+} [free base + H\textsuperscript{+}] requires 206.0746.

2-(2-(Thiophen-2-yl)thiazol-4-yl)ethanamine (239)

Diacetoxyiodobenzene (0.664 g, 2.00 mmol) was added to a solution of 233 (0.330 g, 1.38 mmol) in distilled water (5 mL) and dioxane (5 mL) and the suspension was stirred for 48 h. The solvent was evaporated to yield 239 as a brown oil of sufficient purity for the following step (0.247 g, 85%). \(R_f\) 0.35 (1:99 MeOH/EtOAc). IR (thin film) cm\(^{-1}\): 3374 (NH), 3171 (NH), 1663 (C=O). \(^1\)H NMR (500 MHz, MeOD): \(\delta\) 7.57 (d, \(J = 3.6\) Hz, 1H, H3'' or H5''), 7.55 (d, \(J = 5.0\) Hz, 1H, H3'' or H5''), 7.29 (s, 1H, H5'), 7.12 (dd, \(J_1 = 4.8, J_2 = 4.0\) Hz, H4''), 5.15 (br. s, 2H, NH), 3.36 (t, \(J = 5.8\) Hz, 2H, H1), 3.16 (t, \(J_1 = 5.8\) Hz, 2H, H2). \(^1\)C NMR (126 MHz, MeOD): \(\delta\) 163.7 (C2'), 153.7 (C4'), 137.3 (C2''), 127.9 (C5''), 127.8 (C4'' or C3''), 126.8 (C4'' or C3''), 115.0 (C5'), 40.1 (C1), 29.8 (C2). HRMS (ESI) \(m/z\) observed: 211.0349, C\textsubscript{9}H\textsubscript{11}N\textsubscript{2}S\textsuperscript{2+} [M+H\textsuperscript{+}] requires 211.0358.

\[N-(2-(2-(Pyridin-2-yl)thiazol-4-yl)ethyl)cyclohexa-2,4-dienecarboxamide (222)\]

Benzoyl chloride (0.063 mL, 0.567 mmol) was added dropwise to a stirred solution of triethylamine (2.0 mL) and 221 (0.169 g, 0.821 mmol) in DCM (20.0 mL) at 0 °C under
The ice-bath was removed and stirring was continued for 90 min. The reaction mixture was diluted with DCM (10 mL) and washed with H₂O (10 mL) and brine (10 mL), dried (MgSO₄) and evaporated to give a brown oil, which was subjected to flash chromatography. Elution with 1:20:80 NEt₃/EtOAc/hexanes gave benzamide 222 as a yellow solid (0.148 g, 84%), mp = 103–105 °C. Rₖ 0.4 (1:50:50 NEt₃/EtOAc/Hexanes). IR (thin film) cm⁻¹: 3300 (NH), 1634 (C=O).¹H NMR (500 MHz, CDCl₃): δ 8.63 (d, J = 4.6 Hz, 1H, H6‴), 8.14 (d, J₁ = 8.0 Hz, 1H, H3‴), 7.80 (d, J₁ = 7.2 Hz, 2H, H2/H6), 7.78 (dd, J₁ = 7.6, 1.6 Hz, 1H, H4‴), 7.50 (t, J₁ = 7.4 Hz, 1H, H4), 7.42 (dd [app. t], J₁ = J₂ = 7.4 Hz, 2H, H3/H5), 7.35 (br. s, 1H, NH), 7.34 (dd, J = 7.4, 7.0 Hz, 1H, H5‴), 7.12 (s, 1H, H5″), 3.86 (dt [app. q], J₁ = J₂ = 6.1 Hz, 2H, H1′), 3.14 (t, J₁ = 6.2 Hz, 2H, H2′).

¹³C NMR (126 MHz, CDCl₃): δ 169.3 (C2″ or C=O), 167.5 (C2’ or C=O), 156.1 (C2‴ or C4″), 151.3 (C2″ or C4″), 149.7 (C6″), 137.1 (CH), 135.0 (C1), 131.4 (CH), 128.6 (2 × ArH), 127.0 (2 × ArH), 124.9 (CH), 119.5 (CH), 117.4 (CH), 39.6 (C1′), 30.9 (C2′).

HRMS (ESI) m/z observed: 332.0813, C₁₇H₁₅N₃NaOS⁺ [M+Na]⁺ requires 332.0828.

**N-(2-(2-(Pyridin-2-yl)thiazol-4-yl)ethyl)cyclopentanecarboxamide (223)**

Cyclopentanecarbonyl chloride (0.061 mL, 0.504 mmol) was added dropwise to a solution of triethylamine (2.0 mL) and 221 (0.156 g, 0.758 mmol) in DCM (20.0 mL) at 0 °C under argon. The ice-bath was removed and stirring was continued for 90 min. The reaction mixture was diluted with DCM (10 mL) and washed with H₂O (10 mL) and brine (10 mL), dried (MgSO₄), evaporated and subjected to flash chromatography. Elution with 1:20:80 NEt₃/EtOAc/hexanes then 1:50:50 NEt₃/EtOAc/hexanes gave 223 as a white solid (0.091 g, 59%), mp = 133–135 °C. Rₖ 0.35 (1:50:50
N-(2-(2-(Pyridin-3-yl)thiazol-4-yl)ethyl)benzamide (243)

A solution of benzoyl chloride (0.10 mL, 0.86 mmol) in DCM (10 mL) was added to a stirred solution of 240 (0.240, 0.863 mmol) and NEt₃ (3.0 mL) in DCM (10 mL) at 0 °C. After stirring overnight the volatiles were evaporated and the residue was subjected to flash chromatography. Elution with 1:60:40 NEt₃/EtOAc/hexanes then 1:99 NEt₃/EtOAc yielded 243 as a yellow oil (0.237 g, 89%). Rf 0.5 (1:50:50 NEt₃/EtOAc/hexanes). IR (thin film) cm⁻¹: 3237 (NH), 1645 (C=O). ¹H NMR (500 MHz, CDCl₃): δ 9.17 (d, J₁ = 2.0 Hz, 1H, H2''), 8.60 (dd, J₁ = 4.8, J₂ = 1.4 Hz, 1H, H6''), 8.15 (ddd [app. dt], J₁ = J₂ = 8.0 Hz, J₃ = 2.0 Hz, 1H, H4''), 7.80 (d, J₁ = 7.0 Hz, 2H, H2/H6), 7.48 (dd [app. t], J₁ = J₂ = 7.4 Hz, 1H, H5''), 7.37–7.44 (m, 3H, H3/H4/H5), 7.31 (br. s, 1H, NH), 7.11 (s, 1H, H5''), 3.86 (dt [app. q], J₁ = J₂ = 6.2 Hz, 2H, H1'), 3.14 (t, J₁ = 6.2 Hz, 2H, H2'). ¹³C NMR (126 MHz, CDCl₃): δ 167.6 (C2'' or C4'').
C=O), 164.7 (C2" or C=O), 156.2 (C4"), 150.7 (C2" or C6"), 147.4 (C2" or C6"), 134.7 (C1), 133.7 (CH), 131.5 (CH), 129.6 (C3"), 128.6 (2 × ArH), 127.0 (2 × ArH), 123.9 (CH), 115.6 (C5"), 39.6 (C1'), 30.8 (C2'). HRMS (ESI) m/z observed: 332.0833, C_{17}H_{15}N_{3}NaOS^{-} [free base + Na]^{+} requires 332.0828.

**N-(2-(2-(Pyridin-3-yl)thiazol-4-yl)ethyl)cyclopentanecarboxamide (246)**

A solution of cyclopentanecarbonyl chloride (0.036 mL, 0.300 mmol) in DCM (5 mL) was added to a stirred solution of 240 (0.090 g, 0.324 mmol) and NEt$_3$ (3.0 mL) in DCM (10 mL) at 0 °C. After stirring overnight the volatiles were evaporated and the residue was subjected to flash chromatography. Elution with 1:20:80 NEt$_3$/EtOAc/hexanes then 1:50:50 NEt$_3$/EtOAc/hexanes yielded 246 as white crystals (0.050 g, 57%), mp = 109–111 °C. $R_f$ 0.25 (1:99 NEt$_3$/EtOAc). IR (thin film) cm$^{-1}$: 3244 (NH), 1637 (C=O). $^1$H NMR (500 MHz, CDCl$_3$): δ 9.16 (d, $J_1 = 1.8$ Hz, 1H, H2''), 8.66 (dd, $J_1 = 4.8$, $J_2 = 1.4$ Hz, 1H, H6''), 8.20 (ddd [app. dt], $J_1 = 8.0$, $J_2 = J_3 = 1.8$ Hz, 1H, H4''), 7.39 (dd [app. t], $J_1 = J_2 = 8.0$ Hz, 1H, H5''), 7.05 (s, 1H, H5''), 3.66 (dt [app.q], $J_1 = J_2 = 6.4$ Hz, 2H, H1'), 3.03 (t, $J_1 = 6.4$ Hz, 2H, H2'), 2.50–2.53 (m, 1H, H1), 1.82–1.86 (m, 6H), 1.70–1.78 (m, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$): δ 176.4 (C=O), 164.8 (C2''), 156.4 (C4''), 150.9 (C2" or C6"'), 147.7 (C2" or C6"'), 133.6 (CH), 129.7 (CH), 123.9 (CH), 115.4 (C5"), 46.1 (C1), 39.0 (C1'), 31.2 (C2'), 30.5 (C2/C5), 26.0 (C3/C4). HRMS (ESI) m/z observed: 324.1138, C$_{16}$H$_{19}$N$_3$NaOS$^{-}$ [M+Na$^+$] requires 324.1141.
**N-(2-(2-(Pyridin-4-yl)thiazol-4-yl)ethyl)benzamide (244)**

A solution of benzoyl chloride (0.060 mL, 0.52 mmol) in DCM (5 mL) was added to a stirred solution of 241 (0.170 g, 0.611 mmol) and NEt₃ (2.0 mL) in DCM (20 mL) at 0 °C. After stirring overnight the volatiles were evaporated and the residue was subjected to flash chromatography. Elution with 1:50:50 NEt₃/EtOAc/hexanes then 1:99 NEt₃/EtOAc yielded 244 as white crystals (0.122 g, 66%), m.p.: 67−70 °C. IR (thin film) cm⁻¹: 3438 (NH), 1634 (C=O). ¹H NMR (500 MHz, CDCl₃): δ 8.69 (d, J₁ = 4.8 Hz, 2H, H₂''/H₆''), 7.78−7.81 (m, 4H, H₂/H₆/H₃''/H₅''), 7.50 (t, J₁ = 7.4 Hz, 1H, H₄), 7.41(dd [app. t], J₁ = J₂ = 7.4 Hz, 2H, H₃/H₅), 7.34 (br s, 1H, NH), 7.17 (s, 1H, H₅''), 3.85 (dt [app. q], J₁ = J₂ = 6.4 Hz, 2H, H₁'), 3.15 (t, J₁ = 6.0 Hz, 2H, H₂'). ¹³C NMR (126 MHz, CDCl₃): δ 167.5 (C₂'' or C=O), 165.4 (C₂'' or C=O), 156.7 (C₄''), 150.8 (C₂''/C₆''), 140.2 (C₄''), 134.8 (C₁), 131.6 (C₄), 128.6 (2 × ArH), 127.0 (2 × ArH), 120.3 (2 × ArH), 116.7 (C₅''), 39.5 (C₁'), 30.8 (C₂'). HRMS (ESI) m/z observed: 332.0815, C₁₇H₁₃N₃NaOS⁺ [M+Na]⁺ requires 332.0828.

**N-(2-(2-(Pyridin-4-yl)thiazol-4-yl)ethyl)cyclopentanecarboxamide (247)**

A solution of cyclopentanecarbonyl chloride (0.121 mL, 1.00 mmol) in DCM (5 mL) was added to a stirred solution of 241 (0.250 g, 0.899 mmol) and NEt₃ (2.0 mL) in DCM (20 mL) at 0 °C. After stirring overnight the volatiles were evaporated and the residue was subjected to flash chromatography. Elution with 1:99 NEt₃/EtOAc yielded
as a white solid (0.136 g, 50%), mp = 110–112 °C. Rf 0.3 (1:50:50 NEt₃/EtOAc/hexanes). IR (thin film) cm⁻¹: 3241 (NH), 1600 (C=O). ¹H NMR (500 MHz, CDCl₃): δ 8.71 (d, J₁ = 5.6 Hz, 2H, H2''/H6''), 7.79 (d, J₁ = 5.6 Hz, 2H, H3''/H5''), 7.12 (s, 1H, H5''), 6.12 (br. s, 1H, NH), 3.68 (dt [app. q], J₁ = J₂ = 6.1 Hz, 2H, H1'), 3.05 (t, J₁ = 6.4 Hz, 2H, H2'), 2.48–2.52 (tt [app. pent.], J₁ = J₂ = 7.8 Hz, 1H, H1), 1.82–1.85 (m, 2H), 1.70–1.79 (m, 4H). ¹³C NMR (126 MHz, CDCl₃): δ 176.4 (C=O), 165.2 (C2''), 156.8 (C4''), 150.7 (C2''/C6''), 140.4 (C4''), 120.4 (C3''/C5''), 116.6 (C5''), 46.1 (C1), 38.9 (C1'), 31.3 (C2''), 30.5 (C2/C5), 26.0 (C3/C4). HRMS (ESI) m/z observed: 302.1309, C₁₆H₂₀N₃O₅⁺ [M+H]⁺ requires 302.1322.

N-(2-(2-(Thiopen-2-yl)thiazol-4-yl)ethyl)benzamide (242)

A solution of benzoyl chloride (0.040 mL, 0.64 mmol) in DCM (2 mL) was added to a stirred solution of 239 (0.110 g, 0.523 mmol) and NEt₃ (2.0 mL) in DCM (10 mL) at 0 °C. After stirring overnight the volatiles were evaporated and the residue was subjected to flash chromatography. Elution with 1:20:80 NEt₃/EtOAc/hexanes then 1:50:50 NEt₃/EtOAc/hexanes yielded 242 as a brown oil (0.067 g, 41%). Rf 0.3 (1:30:70 NEt₃/EtOAc/hexanes). IR (thin film) cm⁻¹: 3337 (NH), 1640 (C=O). ¹H NMR (500 MHz, CDCl₃): δ 7.89 (d, J₁ = 7.4 Hz, 2H, H2/H6), 7.69 (br s, 1H, NH), 7.50 (d, J₁ = 3.2 Hz, 1H, H3''), 7.48 (d, J₁ = 7.2 Hz, 1H, H5''), 7.40–7.46 (m, 3H, H3/H4/H5), 7.09 (dd [app. t], J₁ = J₂ = 4.4 Hz, 1H, H4''), 6.94 (s, 1H, H5''), 3.81 (dt [app. q], J₁ = J₂ = 5.9 Hz, 2H, H1'), 3.06 (t, J₁ = 6.0 Hz, 2H, H2'). ¹³C NMR (126 MHz, CDCl₃): δ 167.3 (C2'' or C=O), 162.2 (C2'' or C=O), 155.5 (C4''), 137.3 (C1 or C2''), 134.8 (C1 or C2''), 131.4
N-(2-(2-(Thiophen-2-yl)thiazol-4-yl)ethyl)cyclopentanecarboxamide (245)

A solution of cyclopentanecarbonyl chloride (0.110 mL, 0.900 mmol) in DCM (5 mL) was added to a stirred solution of 239 (0.240 g, 1.14 mmol) and NEt₃ (4.0 mL) in DCM (10 mL) at 0 °C. After stirring overnight the volatiles were evaporated and the residue was subjected to flash chromatography. Elution with 1:4 EtOAc/hexanes then 1:1 EtOAc/hexanes yielded 245 as colourless prisms (0.095 g, 34%), mp = 105–107 °C. Rᵣ 0.3 (1:20:80 NEt₃/EtOAc/hexanes). IR (thin film) cm⁻¹: 3294 (NH), 1638 (C=O).

¹H NMR (500 MHz, CDCl₃): δ 7.49 (dd, J₁ = 3.8, 1.0 Hz, 1H, H₃''), 7.40 (dd, J₁ = 5.0, 1.0 Hz, 1H, H₅''), 7.09 (dd, J₁ = J₂ = 5.0 Hz, 1H, H₄''), 6.88 (s, 1H, H₅''), 6.46 (br. s, 1H, NH), 3.63 (dt [app. q], J₁ = 6.0 Hz, 2H, H₁'), 2.96 (t, J₁ = 6.2 Hz, 2H, H₂'), 2.51–2.56 (m, 1H, H₁), 1.85–1.89 (m, 2H), 1.71–1.80 (m, 4H), 1.55–1.59 (m, 2H). ¹³C NMR (126 MHz, CDCl₃): δ 176.3 (C=O), 161.9 (C₂''), 155.5 (C₄''), 137.5 (C₂''), 128.0 (CH), 127.7 (CH), 126.6 (CH), 113.7 (C₅''), 46.2 (C₁), 39.0 (C₁'), 30.9 (C₂'), 30.5 (C₂/C₅), 26.0 (C₃/C₄). HRMS (ESI) m/z observed: 329.0740, C₁₅H₁₈N₂NaOS⁺ [M+Na]⁺ requires 329.0753.
2-Amino-4-(chloromethyl)thiazol-3-ium chloride (249). A solution of thiourea (6.49 g, 90.9 mmol) in MeOH (50 mL) was added dropwise over 1 h to a stirred solution of 1,3-dichloroacetone (12.8 g, 100.0 mmol) in acetone (100 mL). After stirring overnight, the solvent was evaporated and the residue was washed with acetone to give 249 as a white solid (13.6 g, 81%). $^1$H NMR (500 MHz, DMSO) δ 9.13 (v. br. s, 2H, NH$_2$), 6.96 (s, 1H, H5'), 4.66 (d, $J = 0.5$ Hz, 2H, H2), (thiazole NH not observed/obscured by/exchanging with H$_2$O). The $^1$H NMR data match those published (although the wrong isomer is reported in that paper).

2-(2-Bromothiazol-4-yl)acetonitrile (251). NaNO$_2$ (0.250 g, 3.67 mmol) was added to a solution of 249 (0.500 g, 3.16 mmol) and conc. H$_2$SO$_4$ (0.68 mL) in water (15 mL) at 0 °C, whereupon an orange foam evolved. The solution was allowed to stir at for 20 min, then 48% aqueous HBr (6.25 mL, 115 mmol) was slowly added. The solution was allowed to stir at room temperature for 1 h, then poured onto ice and extracted with EtOAc (3 × 100 mL). The extract was dried evaporated to give a red/brown oil (300 mg). $^1$H NMR analysis of the crude product showed it to be a mixture of 2-chloro-4-(chloromethyl)thiazole and 2-bromo-4-(chloromethyl)thiazole (250). A portion of this mixture (180 mg) was dissolved in DMF (10 mL) and treated with KCN (0.060 g, 0.929...
mmol). The reaction mixture was stirred overnight, then diluted with water (100 mL) and extracted with EtOAc (3 × 20 mL). The extract was dried and evaporated to yield 251 (0.08 g, 31%). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.28 (t, $J = 1.2$ Hz, H5'), 3.87 (d, $J = 1.2$ Hz, H2). The $^1$H NMR data are similar to those reported.$^{58}$

![Chemical structure of 254](image)

2-(2-Aminothiazol-4-yl)acetonitrile (254). KCN (7.56 g, 116 mmol) was added to a stirred solution of 249 (9.1 g, 49 mmol) in DMF (50 mL). After 48 h the reaction was incomplete, so additional KCN (3.2 g, 49 mmol) was added and stirring as continued overnight. The reaction mixture was diluted with water (200 mL), then extracted with EtOAc (3 × 50 mL). The extract was washed with water (2 × 50 mL) and brine (50 mL), dried and evaporated to give 254 as a brown/red oil (3.0 g, 44%). $^1$H NMR (500 MHz, CDCl$_3$) δ 6.43 (s, 1H, H5'), 5.40 (br s, 2H, NH$_2$), 3.62 (d, $J = 1.2$ Hz, 2H, H2).

![Chemical structure of 262](image)

2-(3-Oxo-4-thiocyanatobutyl)isoindoline-1,3-dione (262)

A solution of KSCN (0.970 g, 9.98 mmol) was added to a stirred solution of 100 (2.58 g, 8.71 mmol) in dry ethanol (50 mL) under Argon. The solution was allowed to stir for 8 h at 80 °C, and the solvent was evaporated. The resulting yellow solid was partitioned between H$_2$O and EtOAc and the organic layer was dried (MgSO$_4$) and evaporated to
yield 262 as a brown solid. (2.00 g, 84%). m.p. 119–121 °C. IR (ATR) cm⁻¹: 2151 (SCN), 1712 (C=O), 1773 (C=O). ¹H NMR (CDCl₃, 400 MHz): δ 7.85–7.87 (m, 2H, Ar), 7.73–7.75 (m, 2H, Ar), 4.09 (s, 2H, CH₂S), 4.04 (t, J = 6.8 Hz, 2H, CH₂N), 3.04 (t, J = 7.1 Hz, 2 H, CH₂CO). ¹³C NMR spectrum (CDCl₃, 101 MHz): δ 198.5 (CO), 168.0 (2 × CO), 134.2 (2 × ArH), 131.8 (2 × Ar), 123.5 (2 × ArH), 111.0 (CN), 43.5 (CH₂S), 39.6 (CH₂N), 32.7 (CH₂). LCMS (ESI) m/z: 275 [M+H]⁺

![Chemical structure](image)

2-(2-(2-Bromothiazol-4-yl)ethyl)isoindoline-1,3-dione (257)

A mixture of 33% HBr in acetic acid (5 mL), 262 (0.700 g, 2.55 mmol) and acetic acid (5 mL) was stirred for 1.5 h at 130 °C, or until TLC showed the disappearance of starting material. Water (100 mL) was added and the mixture was extracted with EtOAc (3 × 100 mL). The extract was washed with water (2 × 100 mL) and brine (2 × 100 mL), dried (MgSO₄) and evaporated to afford 257 as a brown crystalline solid. (0.602 g, 70%). m.p. 106–108 °C. IR (ATR) cm⁻¹: 1702 (C=O), 1773 (C=O). ¹H NMR (CDCl₃, 500 MHz): 7.82–7.84 (m Hz, 2H, 2 × ArH), 7.70–7.72 (m, 2H, 2 × ArH), 6.96 (s, 1H, H5”), 4.03 (t, J₁= 7.0 Hz 2H, H1”), 3.15 (t, J₁= 7.0 Hz, 2H, H2”); ¹³C NMR (CDCl₃): 168.3 (C1/C3), 154.0 (C4”), 153.7 (C2”), 134.1 (2 × ArH), 132.4 (C3a/C7a), 123.4 (2 × ArH), 118.6 (C5”), 37.4 (C1’), 30.4 (C2’). HRMS (ESI): Observed: 336.9658, C₁₃H₁₀N₂O₂SBr requires 336.9646.
2-(2-(2-Fluorophenyl)thiazol-4-yl)ethyl)isoindoline-1,3-dione (263)

N₂ was bubbled through a stirred mixture of 257 (0.620 g, 1.84 mmol) and 2-fluorophenylboronic acid (0.300 g, 2.14 mmol), toluene (20 mL) and 2 M Na₂CO₃ (20 mL) for 20 min. The reaction mixture was heated to 80 °C under N₂ and Pd(PPh₃)₄ (0.070 g, 3 mol%) was added. After 6 h TLC showed the reaction to be incomplete, so additional Pd(PPh₃)₄ (0.100 g, 5 mol%) was added and the reaction mixture was stirred overnight at 80 °C. After cooling the reaction mixture was extracted with EtOAc (3 × 50 mL). The extract was washed with water (3 × 50 mL), dried and evaporated, and the residue was subjected to flash chromatography. Elution with 1:9 EtOAc/hexanes and then 1:4 EtOAc/hexanes gave 263 as a yellow crystalline solid (0.200 g, 31%), mp = 149–151 °C. IR (ATR) cm⁻¹: 1771 (C=O), 1706 (C=O). ¹H NMR (500 MHz, CDCl₃): δ 8.04 (ddd [app. dt], J₁ = J₂ = 7.8 Hz, J₃ = 1.8 Hz, 1H, H₆'''), 7.79–7.82 (m, 2H, H₃/H₆), 7.66–7.69 (m, 2H, H₄/H₅), 7.29–7.33 (m, 1H, H₄'''), 7.08–7.14 (m, 3H, H₅''/H₃''/H₅'''), 4.12 (t, J₁ = 7.0 Hz, 2H, H₁'), 3.25 (dt, J₁ = 7.0, 0.8 Hz, 2H, H₂'). ¹³C NMR (126 MHz, CDCl₃): δ 168.4 (C=O), 160.3 (d, J₁ = 4 Hz, C2''), 160.0 (d, J₁ = 202 Hz, CF), 153.2 (C4''), 134.0 (C4/C7), 132.4, (C3a/C7a), 130.9 (d, J₁ = 7 Hz, ArH), 128.8 (d, J₁ = 2 Hz, ArH), 124.5 (d, J₁ = 3 Hz, ArH), 123.4 (C5/C6), 121.5 (d, J₁ = 9 Hz, C1''), 116.3 (d, J₁ = 7 Hz, C5''), 116.1 (d, J₁ = 17 Hz, C3'''), 37.8 (C1'), 30.0 (C2').

HRMS (ESI) m/z observed: 353.0757, C₁₉H₁₄N₂O₂FS⁺ [M+H]⁺ requires 353.0755.
2-(2-(2-(3-Fluorophenyl)thiazol-4-yl)ethyl)isoindolene-1,3-dione (264)

Prepared as described for 263 with 257 (0.213 g, 0.631 mmol) and 3-fluorophenylboronic acid (0.106 g, 0.758 mmol). Elution with 1:9 EtOAc/hexanes and then 1:4 EtOAc/hexanes gave 264 as an orange solid (0.040 g, 18%), mp = 101–102 °C. IR (ATR) cm⁻¹: 1770 (C=O), 1708 (C=O). ¹H NMR (500 MHz, CDCl₃): δ 7.80–7.84 (m, 2H, H₄/H₇), 7.68–7.72 (m, 2H, H₅/H₆), 7.54 (ddd, J₁ = 7.8, J₂ = 1.6, J₃ = 1.0 Hz, 1H, H₆''), 7.42 (ddd, J₁ = 9.8 Hz, J₂ = 2.6 Hz, J₃ = 1.6 Hz, 1H, H₂''), 7.30 (ddd (app.dt), J₁ = J₂ = 8.0 Hz, J₃ = 5.8 Hz, 1H, H₅''), 7.04 (ddddd [app. ddt], J₁ = J₂ = 8.4 Hz, J₃ = 2.6 Hz, J₄ = 0.9 Hz, 1H, H₄''), 7.02 (s, 1H, H₅''), 4.10 (t, J₁ = 7.0 Hz, 2H, H₁'), 3.21 (t, J₁ = 7.0 Hz, H₂'); ¹³C NMR (101 MHz, CDCl₃): δ 168.4 (C=O), 166.5 (d, J₁ = 2 Hz, C₂''), 163.1 (d, J₁ = 198 Hz, CF), 154.7 (C₄''), 135.7 (d, J₁ = 7 Hz, C₁'''), 134.0 (C₅/C₆), 132.3 (C₃a/C₇a), 130.5 (d, J₁ = 7 Hz, C₅''''), 123.4 (C₄/C₇), 122.3 (d, J₁ = 2 Hz, C₆'''), 116.7 (d, J₁ = 17 Hz, C₂'' or C₄'''), 115.3 (C₅''), 113.3 (d, J₁ = 19 Hz, C₂'' or C₄'''), 37.7 (C₁'), 30.0 (C₂'). HRMS (ESI) m/z observed: 353.0743, C₁₉H₁₄N₂O₂SF⁺ [M+H]⁺ requires 353.0760.
**2-(2-(2-(4-Fluorophenyl)thiazol-4-yl)ethyl)isoindoline-1,3-dione (265)**

Prepared as described for 263 with 257 (0.500 g, 1.48 mmol) and 4-fluorophenylboronic acid (0.300 g, 2.14 mmol) Elution with 1:9 EtOAc/hexanes gave 265 as a yellow solid (0.260 g, 50%), m.p.: 120–122 °C. IR (ATR) cm⁻¹: 1772 (C=O), 1704 (C=O). ¹H NMR (500 MHz, CDCl₃): δ 7.67–7.79 (m, 6H, H₄/H₇/H₅/H₆/H₂‴/H₆‴), 7.00 (dd [app. t], 2H, J₁ = J₂ = 8.0 Hz, H₃‴/H₅‴), 6.96 (s, 1H, H₅″), 4.08 (t, 2H, J₁ = 6.4 Hz, H₁′), 3.20 (t, 2H, J₁ = 6.4 Hz, 2H, H₂″); ¹³C NMR (101 MHz, CDCl₃): δ 168.2 (C=O), 166.6 (C₂″), 163.7 (d, J₁ = 201 Hz, C₄‴), 154.3 (C₄″), 133.9 (C₅/C₆), 132.2 (C₃a/C₇a), 130.0 (d, J₁ = 3 Hz, C₁‴), 128.3 (d, J₁ = 7 Hz, C₂‴/C₆‴), 123.2 (C₄/C₇), 115.8 (d, J₁ = 18 Hz, C₃‴/C₅‴), 114.6 (C₅″), 37.6 (C₁′), 29.9 (C₂″). HRMS (ESI) m/z observed: 353.0716, C₁₉H₁₄N₂O₂FS+ [M+H]+ requires 353.0760.

**2-(2-(2-(2,4-Difluorophenyl)thiazol-4-yl)ethyl)isoindoline-1,3-dione (266)**

Prepared as described for 263 with 257 (0.220 g, 0.650 mmol) and 2,4-difluorophenylboronic acid (0.200 g, 1.23 mmol). Elution with 1:9 EtOAc/hexanes gave 266 as a white, crystalline solid (0.168 g, 70%), m.p.: 168–170 °C. IR (ATR) cm⁻¹: 1769 (C=O), 1704 (C=O). ¹H NMR (500 MHz, CDCl₃): δ 8.01 (m [pseudo q], 1H,
N-(2-(2-(2-Fluorophenyl)thiazol-4-yl)ethyl)-1H-imidazole-1-carboxamide (271)

A stirred solution of hydrazine hydrate (2.5 mL) and 263 (0.200 g, 0.568 mmol) in MeOH (20 mL) under argon was heated under reflux overnight. The volatiles were evaporated and the residue was dissolved in 1:1 MeCN/DMF (20 mL) and treated with 1,1-carbonyldiimidazole (CDI) (0.300 g, 1.85 mmol). After stirring overnight the solvent was evaporated and the residue was diluted with EtOAc (150 mL) and washed with water (3 × 50 mL). The organic phase was dried and evaporated and the residue was subjected to flash chromatography. Elution with 1:1 EtOAc/hexanes and then EtOAc have 271 as a yellow oil, (0.700 g, 39%). IR (ATR) cm⁻¹: 3222 (NH), 1712 (C=O). ¹H NMR (500 MHz, CDCl₃): δ 8.14–8.16 (m, 1H, H2), 8.10 (ddd [app. dt], J₁ = J₂ = 7.6 Hz, J₃ = 1.6 Hz, 1H, H6''), 7.72 (br s, 1H, NH), 7.41–7.45 (m, 1H, H4''), 7.38 (dd [app. t], J₁ = J₂ = 1.5 Hz, H5) 7.27 (ddd [app. dt], J₁ = J₂ = 7.8, J₃ = 1.2 Hz, 1H, H5''), 7.22 (ddd, J₁ = 11.7, J₂ = 8.3, J₃ = 1.0, 1H, H3''), 7.16 (s, 1H, H5''), 7.06 (dd, J₁ =
1.5 Hz, \( J_2 = 1.0 \) Hz, 1H, H4), 3.80 (m [pseudo q], H1'), 3.13 (t, \( J_1 = 6.0 \) Hz, 2H, H2');

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \( \delta 161.7 \) (d, \( J_1 = 4 \) Hz, C2''), 160.0 (d, \( J_1 = 204 \) Hz, CF), 154.3 (C4''), 149.0 (C=O), 136.0 (C2), 131.7 (d, \( J_1 = 7 \) Hz, C6'''), 130.5 (C4), 128.6 (d, \( J_1 = 2 \) Hz, ArH), 124.9 (d, \( J_1 = 2 \) Hz, ArH), 121.2 (d, \( J_1 = 9 \) Hz, C1'''), 116.7 (d, \( J_1 = 17 \) Hz, C3'''), 116.5 (d, \( J_1 = 6 \) Hz, C5''), 116.0 (C5), 40.6 (C1'), 30.1 (C2').

HRMS (ESI) \( m/\z \) observed: 317.0867, C\(_{15}\)H\(_{14}\)N\(_4\)OFS\(^+\) [M+H\(^+\)] requires 317.0872.

\[ \text{N-(2-(2-(3-Fluorophenyl)thiazol-4-yl)ethyl)-1H-imidazole-1-carboxamide (272)} \]

Prepared from 264 (0.038 g, 0.171 mmol) as described for 271. Elution with 3:2 EtOAc/hexanes gave 272 as a brown oil (0.021 g, 57%). IR (ATR) cm\(^{-1}\): 3115 (NH), 1710 (C=O). \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta 8.15 \) (s, 1H, H2), 7.67 (br. s, 1H, NH), 7.64–6.67 (m, 1H, H6'''), 7.60 (ddd [app. dt], \( J_1 = 9.4 \) Hz, \( J_2 = J_3 = 2.0 \) Hz, H2'''), 7.42 (ddd [app. dt], \( J_1 = J_2 = 8.0 \) Hz, \( J_3 = 5.7 \) Hz, 1H, H5'''), 7.37 (s, 1H, H5), 7.13 (ddd [app. dt], \( J_1 = J_2 = 8.2 \) Hz, \( J_3 = 2.8 \) Hz, H4'''), 7.05–7.08 (m, 2H, H4/H5''), 3.79 (dt [app. q], \( J_1 = J_2 = 5.6 \) Hz, 2H, H1'), 3.10 (t, \( J_1 = 6.0 \) Hz, 2H, H2'); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \( \delta 167.4 \) (d, \( J_1 = 3 \) Hz, C2''), 163.2 (d, \( J_1 = 199 \) Hz, CF), 155.3 (C4''), 149.0 (C=O), 136.1 (C2), 135.3 (d, \( J_1 = 6 \) Hz, C1'''), 130.9 (d, \( J_1 = 7 \) Hz, C5'''), 130.6 (C4), 122.2 (d, \( J_1 = 2 \) Hz, C6'''), 117.4 (d, \( J_1 = 17 \) Hz, C2'' or C4'''), 115.8 (C5' or C5), 115.7 (C5' or C5), 113.4 (d, \( J_1 = 19 \) Hz, C2'' or C4'''), 40.5 (C1'), 30.4 (C2'). HRMS (ESI) \( m/\z \) observed: 317.0863, C\(_{15}\)H\(_{14}\)N\(_4\)OFS\(^+\) [M+H\(^+\)] requires 317.0872.
N-(2-(2-(4-Fluorophenyl)thiazol-4-yl)ethyl)-1H-imidazole-1-carboxamide (273)

Prepared from 265 (0.260 g, 0.738 mmol) as described for 271. Elution with 1:1 EtOAc/hexanes and then EtOAc gave 273 as a pale-orange solid (0.070 g, 30%), m.p.: 35–37 °C. IR (ATR) cm$^{-1}$: 3218 (NH), 1703 (C=O). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.13 (dd, $J_1 = 1.2$, $J_2 = 1.1$ Hz, 1H, H2), 7.85–7.88 (m, 2H, H2'''/H6'''), 7.70 (br. unresolved t, 1H, NH), 7.36 (dd [app. t], $J_1 = J_2 = 1.4$ Hz, 1H, H5), 7.13–7.16 (m, 2H, H3'''/H5'''), 7.06 (dd, $J_1 = 1.6$ Hz, $J_2 = 0.8$ Hz, 1H, H4), 7.03 (t, $J_1 = 0.8$ Hz, 1H, H5''), 3.77–3.80 (m [pseudo q], Hz, 2H, H1'), 3.09 (dt, $J_1 = 6.0$, $J_2 = 0.5$ Hz, 2H, H2'); $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 167.9 (C2''), 164.2 (d, $J_1 = 202$ Hz, C4''), 155.1 (C4''), 149.0 (C=O), 136.0 (C2), 130.5 (C4), 129.7 (d, $J_1 = 3$ Hz, C1''), 128.4 (d, $J_1 = 7$ Hz, C2'''/C6'''), 116.4 (d, $J_1 = 18$ Hz, C3'''/C5'''), 115.9 (C5 or C5''), 115.1 (C5 or C5''), 40.6 (C1'), 30.3 (C2'). HRMS (ESI) m/z observed: 317.0877, C$_{15}$H$_{14}$N$_4$OFS$^+$ [M+H]$^+$ requires: 317.0872.

N-(2-(2-(2,4-Difluorophenyl)thiazol-4-yl)ethyl)-1H-imidazole-1-carboxamide (274)

Prepared from 266 (0.100 g, 0.270 mmol) as described for 271. Elution with 3:2 EtOAc/hexanes and then EtOAc gave 274 as a yellow oil (0.0600 g, 70%). IR (ATR) cm$^{-1}$: 3351 (NH), 1616 (C=O). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.14 (br. s, 1H, H2), 8.08 (ddd [app. dt], $J_1 = J_2 = 8.6$ Hz, $J_3 = 6.4$ Hz, 1H, H6''), 7.98 (br. t, $J_1 = 4.6$ Hz, 1H,
NH), 7.39 (br. s, H5), 7.11 (s, 1H, H5''), 6.99 (br. s, 1H, H4), 6.90–6.97 (m, 2H, H3''/H5''), 3.76 (dt [app. q], J1 = J2 = 6.2 Hz, 2H, H1'), 3.10 (t, J1 = 6.4 Hz, 2H, H2').

13C NMR (101 MHz, CDCl3): δ 163.6 (dd, J1 = 204, 10 Hz, CF), 160.3 (d, J1 = 5 Hz, C2''), 160.1 (dd, J1 = 205, 10 Hz, CF), 154.0 (C4''), 149.0 (C=O), 136.0 (C2), 130.1 (C5), 129.8 (dd, J1 = 8, 3 Hz, C6'''), 117.8 (dd, J1 = 9, 3 Hz, C1'''), 116.11 (d, J1 = 6 Hz, C5''), 116.10 (C5), 112.3 (dd, J1 = 17, 3 Hz, C5'''), 104.8 (dd, app. t) J1 = J2 = 21 Hz, C3'''), 40.5 (C1'), 30.4 (C2'). HRMS (ESI) m/z observed: 335.0766, C15H13N4OF2S+[M+H]+ requires 335.0778.

**N-(2-(2-(2-Fluorophenyl)thiazol-4-yl)ethyl)piperidine-1-carboxamide (275)**

Piperidine (0.10 mL, 0.978 mmol) was added to a stirred solution of NEt3 (0.10 mL) and 271 (0.070 g, 0.221 mmol) in DCM (5 mL) at 0 °C. The solution was allowed to warm to room temperature and stirring was continued overnight. The solvent was evaporated and the residue was subjected to flash chromatography. Elution with 3:2 EtOAc/Hexanes then EtOAc gave 275 as a yellow oil (0.030 g, 41%). IR (ATR) cm⁻¹: 3351 (NH), 1616 (C=O). 1H NMR (500 MHz, CDCl3): δ 8.19 (ddd [app. dt], 1H, J1 = J2 = 7.6, J3 = 1.8 Hz, H6''), 7.36–7.40 (m, 1H, H4''), 7.16–7.24 (m, 2H, H3''/H5'''), 7.10 (s, 1H, H5''), 5.65 (br. s, 1H, NH), 3.60 (dt [app. q], J1 = J2 = 6.0 Hz, 2H, H1'), 3.32 (m [pseudo t], 4H, H2/H6), 3.02 (t, J1 = 6.2 Hz, 2H, H2'), 1.48–1.57 (m, 6H, H3/H4/H5); 13C NMR (101 MHz, CDCl3): δ 160.5 (d, J1 = 4 Hz, C2''), 160.0 (d, J1 = 203 Hz, CF), 157.9 (C=O), 155.3 (C4''), 131.1 (d, J1 = 7 Hz, C6''), 128.5 (d, J1 = 2 Hz,
C4'' or C5''), 124.6 (d, $J_1 = 3$ Hz, C4'' or C5''), 121.5 (d, $J_1 = 9$ Hz, C1''), 116.4 (d, $J_1 = 17$ Hz, C3''), 116.0 (d, $J_1 = 7$ Hz, C5''), 44.9, (C2/C6), 40.7 (C1'), 31.3 (C2'), 25.7 (C3/C5), 24.6 (C4). HRMS (ESI) m/z observed: 334.1388, C_{17}H_{21}N_{3}OFS$^+$ [M+H]$^+$ requires 334.1389.

\[\text{N-(2-\text{(2-(3-Fluorophenyl)thiazol-4-yl)ethyl)piperidine-1-carboxamide (276)}}\]

Prepared from 272 (0.0200 g, 0.0632 mmol) as described for 275. Elution with 1:1 EtOAc/Hexanes then EtOAc gave 276 as a yellow oil (0.015 g, 71%). IR (ATR) cm$^{-1}$: 3350 (NH), 1614 (C=O). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.63–7.67 (m, 2H, H2''/H6''), 7.38 (ddd [app. dt], $J_1 = J_2 = 8.1$ Hz, $J_3 = 6.2$ Hz, 1H, H5''), 7.09–7.13 (m, 1H, H4''), 7.01 (s, 1H, H5''), 5.67 (br. s, 1H, NH), 3.59 (dt [app. q], $J_1 = 5.9$ Hz, 2H, H1'), 3.33 (m (pseudo t), 4H, H2/H6), 3.00 (t, $J_1 = 6.2$ Hz, 2H, H2'), 1.49–1.58 (m, 6H, H3/H4/H5).

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 166.6 (d, $J = 3$ Hz, C2''), 163.2 (d, $J = 198$ Hz, CF), 157.9 (C=O or C4''), 156.7 (C=O or C4''), 135.7 (d, $J = 7$ Hz, C1''), 130.7 (d, $J = 7$ Hz, C5''), 122.2 (d, $J = C6''$), 117.0 (d, $J = 17$ Hz, C2'' or C4''), 115.0 (C5''), 113.2 (d, $J = 19$ Hz, C2'' or C4''), 45.0 (C2/C6), 40.7 (C1'), 31.4 (C2'), 25.7 (C3/C5), 24.6 (C4).

HRMS (ESI) m/z observed: 334.1388, C_{17}H_{21}N_{3}OFS$^+$ [M+H]$^+$ requires 334.1389.
**N-(2-(2-(4-Fluorophenyl)thiazol-4-yl)ethyl)piperidine-1-carboxamide (277)**

Prepared from 273 (0.060 g, 0.190 mmol) as described for 275. Elution with 3:2 EtOAc/hexanes and then EtOAc gave 277 as a yellow oil (0.040 g, 63%). IR (ATR) cm⁻¹: 3360 (NH), 1623 (C=O). ¹H NMR (500 MHz, CDCl₃): δ 7.87–7.90 (m, 2H, H₂''/H₆''), 7.09–7.12 (m, 2H, H₃'''/H₅'''), 6.95 (s, 1H, H₅'''), 5.64 (br. s, 1H, NH), 3.57 (dt [app. q], J₁ = 6.0 Hz, 2H, H₁'), 3.31 (m [pseudo t], 4H, H₂/H₆), 2.98 (t, J₁ = 6.2 Hz, 2H, H₂'), 1.47–1.57 (m, 6H, H₃/H₄/H₅). ¹³C NMR (101 MHz, CDCl₃): δ 166.9 (C₂''), 163.9 (d, J₁ = 201 Hz, CF), 157.9 (C=O or C₄''), 156.4 (C=O or C₄''), 130.1 (d, J₁ = 3 Hz, C₁''), 128.3 (d, J₁ = 7 Hz, C₂''/C₆''), 116.1 (d, J₁ = 18 Hz, C₃''/C₅''), 114.4 (C₅''), 44.9 (C₂/C₆), 40.6 (C₁'), 31.4 (C₂'), 25.7 (C₃/C₅), 24.6 (C₄). HRMS (ESI) m/z observed: 334.1382, C₁₇H₂₁N₃OFS⁺ [M+H]⁺ requires 334.1389.

**N-(2-(2-(2,4-Difluorophenyl)thiazol-4-yl)ethyl)piperidine-1-carboxamide (278)**

Prepared from 274 (0.060 g, 0.179 mmol) as described for 275. Elution with 3:2 EtOAc/hexanes then EtOAc gave 278 as a pale-amber solid (0.040 g, 64%), m.p.: 68–70 °C. IR (ATR) cm⁻¹: 3341 (NH), 1614 (C=O). ¹H NMR (500 MHz, CDCl₃): δ 8.19 (ddd [app. dt], J₁ = J₂ = 8.5 Hz, J₃ = 6.4 Hz, 1H, H₆'''), 7.08 (s, 1H, H₅'''), 6.91–6.99 (m, 2H, H₃''/H₅'''), 5.50 (br. s, 1H, NH), 3.58 (dt [app. q], J₁ = 6.0 Hz, 2H, H₁'),
3.32 (m [pseudo t], 4H, H2/H6), 2.99 (t, \(J_1 = 6.2\) Hz, 2H, H2'), 1.47–1.59 (m, 6H, H3/H4/H5). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \(\delta\) 163.6 (dd, \(J_1 = 203\), 10 Hz, CF), 160.2 (dd, \(J_1 = 205\), 10 Hz, CF), 159.8 (d, \(J_1 = 5\) Hz, C2''), 157.9 (C=O or C4''), 155.2 (C=O or C4''), 129.9 (dd, \(J_1 = 8\), \(J_2 = 3\) Hz, C6'''), 118.2 (d, \(J_1 = 9\) Hz, C1'''), 115.8 (d, \(J_1 = 6\) Hz, C5''), 112.2 (dd, \(J_1 = 17\), 3 Hz, C5''''), 104.7 (dd [app. t], \(J_1 = J_2 = 21\) Hz, C3''''), 45.0 (C2/C6), 40.7 (C1'), 31.4 (C2'), 25.7 (C3/C5), 24.6 (C4). HRMS (ESI) \(m/z\) observed: 352.1309, \(C_{17}H_{20}N_{3}OF_{2}S^+\) [M+H]^+ requires 352.1295.
### Appendix 1: Standard Deviations of Active compounds

<table>
<thead>
<tr>
<th>#</th>
<th>SMILES</th>
<th>IC$_{50}$ ($\mu$M)</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>117</td>
<td>FC1=CC=CC=C1C(O)NCC1=CSC(=N1)C1=CC=CC=C1</td>
<td>0.47</td>
<td>0.6</td>
</tr>
<tr>
<td>123</td>
<td>FC1=CC=C1C(O)NCC1=CSC(=N1)C1=CC=CC=C1</td>
<td>0.19</td>
<td>0.01</td>
</tr>
<tr>
<td>129</td>
<td>FC1=CC=C1C(O)NCC1=CSC(=N1)C1=CC=CC=C1</td>
<td>0.77</td>
<td>0.19</td>
</tr>
<tr>
<td>119</td>
<td>CC1=CC=CC=1C(O)NCC1=CSC(=N1)C1=CC=CC=C1</td>
<td>3.3</td>
<td>0.8</td>
</tr>
<tr>
<td>125</td>
<td>CC1=CC=CC(C=O)NCC1=CSC(=N1)C1=CC=CC=C1</td>
<td>3.9</td>
<td>0.8</td>
</tr>
<tr>
<td>120</td>
<td>OC1=C(C=CC=C1)C(O)NCC1=CSC(=N1)C1=CC=CC=C1</td>
<td>2.3</td>
<td>0.1</td>
</tr>
<tr>
<td>121</td>
<td>COC1=CC=C1C(O)NCC1=CSC(=N1)C1=CC=CC=C1</td>
<td>10.6</td>
<td>3.6</td>
</tr>
<tr>
<td>127</td>
<td>COC1=CC=C1C(O)NCC1=CSC(=N1)C1=CC=CC=C1</td>
<td>1.9</td>
<td>0.3</td>
</tr>
<tr>
<td>128</td>
<td>O=C(NCC1=CSC(=N1)C1=CC=CC=C1)N1CC1=C=CC=CC=C1</td>
<td>0.13</td>
<td>0.01</td>
</tr>
<tr>
<td>142</td>
<td>O=C(NCC1=CSC(=N1)C1=CC=CC=C1)N1CC1=C=CC=CC=C1</td>
<td>0.3</td>
<td>0.01</td>
</tr>
<tr>
<td>143</td>
<td>O=C(NCC1=CSC(=N1)C1=CC=CC=C1)N1CC1=C=CC=CC=C1</td>
<td>0.76</td>
<td>0.28</td>
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<tr>
<td>144</td>
<td>O=C(NCC1=CSC(=N1)C1=CC=CC=C1)N1CC1=C=CC=CC=C1</td>
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<tr>
<td>145</td>
<td>O=C(NCC1=CSC(=N1)C1=CC=CC=C1)N1CC1=C=CC=CC=C1</td>
<td>4.1</td>
<td>0.1</td>
</tr>
<tr>
<td>149</td>
<td>O=C(NCC1=CSC(=N1)C1=CC=CC=C1)N1CC1=C=CC=CC=C1</td>
<td>0.35</td>
<td>0.16</td>
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<tr>
<td>150</td>
<td>O=C(NCC1=CSC(=N1)C1=CC=CC=C1)N1CC1=C=CC=CC=C1</td>
<td>0.23</td>
<td>0.03</td>
</tr>
<tr>
<td>153</td>
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<td>1.6</td>
<td>0.4</td>
</tr>
<tr>
<td>151</td>
<td>O=C(NCC1=CSC(=N1)C1=CC=CC=C1)N1CC1=C=CC=CC=C1</td>
<td>0.80</td>
<td>0.11</td>
</tr>
<tr>
<td>171</td>
<td>O=C(NCC1=CSC(=N1)C1=CC=CC=C1)N1CC1=C=CC=CC=C1</td>
<td>0.050</td>
<td>0.04</td>
</tr>
<tr>
<td>172</td>
<td>O=C(NCC1=CSC(=N1)C1=CC=CC=C1)N1CC1=C=CC=CC=C1</td>
<td>0.028</td>
<td>0.001</td>
</tr>
<tr>
<td>174</td>
<td>O=C(NCC1=CSC(=N1)C1=CC=CC=C1)N1CC1=C=CC=CC=C1</td>
<td>0.69</td>
<td>0.22</td>
</tr>
<tr>
<td>168</td>
<td>CC(C)OC(=O)NCC1=CSC(=N1)C1=CC=CC=C1</td>
<td>0.22</td>
<td>0.02</td>
</tr>
<tr>
<td>169</td>
<td>CC(C)NC(=O)NCC1=CSC(=N1)C1=CC=CC=C1</td>
<td>0.90</td>
<td>0.03</td>
</tr>
<tr>
<td>170</td>
<td>CCN(CC)C(=O)NCC1=CSC(=N1)C1=CC=CC=C1</td>
<td>0.26</td>
<td>0.03</td>
</tr>
<tr>
<td>173</td>
<td>O=C(NCC1=CSC(=N1)C1=CC=CC=C1)N1CC1=C=CC=CC=C1</td>
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<td>0.02</td>
</tr>
<tr>
<td>222</td>
<td>O=C(NCC1=CSC(=N1)C1=CC=CC=C1)N1CC1=C=CC=CC=C1</td>
<td>1.1</td>
<td>0.3</td>
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<tr>
<td>223</td>
<td>O=C(NCC1=CSC(=N1)C1=CC=CC=C1)N1CC1=C=CC=CC=C1</td>
<td>4.0</td>
<td>1.5</td>
</tr>
<tr>
<td>243</td>
<td>O=C(NCC1=CSC(=N1)C1=CC=CC=C1)N1CC1=C=CC=CC=C1</td>
<td>2.7</td>
<td>0.3</td>
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<td>246</td>
<td>O=C(NCC1=CSC(=N1)C1=CC=CC=C1)N1CC1=C=CC=CC=C1</td>
<td>6.6</td>
<td>0.3</td>
</tr>
<tr>
<td>244</td>
<td>O=C(NCC1=CSC(=N1)C1=CC=CC=C1)N1CC1=C=CC=CC=C1</td>
<td>3.1</td>
<td>0.9</td>
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<tr>
<td>247</td>
<td>O=C(NCC1=CSC(=N1)C1=CC=CC=C1)N1CC1=C=CC=CC=C1</td>
<td>9.1</td>
<td>1.7</td>
</tr>
<tr>
<td>242</td>
<td>O=C(NCC1=CSC(=N1)C1=CC=CC=C1)N1CC1=C=CC=CC=C1</td>
<td>1.5</td>
<td>0.2</td>
</tr>
<tr>
<td>245</td>
<td>O=C(NCC1=CSC(=N1)C1=CC=CC=C1)N1CC1=C=CC=CC=C1</td>
<td>2.4</td>
<td>0.3</td>
</tr>
<tr>
<td>275</td>
<td>O=C(N1CCCCC1)NCC2=CSC(=C(F)=C(CC=C3)=N2</td>
<td>0.016</td>
<td>0.005</td>
</tr>
<tr>
<td>276</td>
<td>O=C(N1CCCCC1)NCC2=CSC(=C(F)=C(CC=C3)=N2</td>
<td>0.026</td>
<td>0.00002</td>
</tr>
<tr>
<td>277</td>
<td>O=C(N1CCCCC1)NCC2=CSC(=C(F)=C(CC=C3)=N2</td>
<td>0.024</td>
<td>0.0009</td>
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<tr>
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<td>O=C(N1CCCCC1)NCC2=CSC(=C(F)=C(CC=C3)=N2</td>
<td>0.024</td>
<td>0.003</td>
</tr>
<tr>
<td>195</td>
<td>O=C(NCC1=C=CC(=N1)C1=CC=CC=C1)N1CC1=C=CC=CC=C1</td>
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<td>0.03</td>
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<td>CC(C)OC(=O)NCC1=C=CC(=N1)C1=CC=CC=C1</td>
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<td>1.46</td>
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<td>CCN(CC)C(=O)NCC1=C=CC(=N1)C1=CC=CC=C1</td>
<td>1.97</td>
<td>0.29</td>
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<td>0.12</td>
<td>0.006</td>
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<tr>
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<td>0.39</td>
<td>0.035</td>
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<td>6.56</td>
<td>0.66</td>
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223
2.13 References


