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Hit-to-Lead Optimisation of a Novel Class of Potent, Broad-Spectrum Trypanosomacides

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ABSTRACT

The parasitic trypanosomes *Trypanosoma brucei* and *T. cruzi* are responsible for significant human suffering in the form of human African trypanosomiasis (HAT) and Chagas disease. Drugs currently available to treat these neglected diseases leave much to be desired. Herein we report optimisation of a novel class of $N$-(2-(2-phenylthiazol-4-yl)ethyl)amides, carbamates and ureas, which rapidly, selectively, and potently kill both species of trypanosome. The mode of action of these compounds is unknown, but does not involve CYP51 inhibition. They do, however, exhibit clear structure–activity relationships, consistent across both trypanosome species. Favourable physicochemical parameters place the best compounds in CNS drug-like chemical space but, as a class, they exhibit poor metabolic stability. One of the best compounds (64a) cleared all signs of *T. cruzi* infection in mice when CYP metabolism was inhibited, with sterile cure achieved in one mouse. This family of compounds thus shows significant promise for trypanosomiasis drug discovery.
INTRODUCTION

Human African trypanosomiasis (HAT, African sleeping sickness) and Chagas disease (American trypanosomiasis) are related parasitic diseases causing significant morbidity and mortality in sub-Saharan Africa and South America, respectively.\textsuperscript{1, 2} There is a critical need for new treatment options for these diseases, which affect millions of the world’s poorest people.

HAT is caused by the protozoans \textit{Trypanosoma brucei gambiense} and \textit{T. b. rhodesiense}, transmitted by the bite of infected tsetse flies. \textit{T. b. gambiense} is prevalent in Western and Central Africa, accounting for 98\% of reported cases. It causes chronic human infection, and has long symptom-free periods that can last several years.\textsuperscript{3} \textit{T. b. rhodesiense} infection occurs primarily in Eastern and Southern Africa, and results in acute illness, leading to death within months if treatment is not received.\textsuperscript{4} Indeed, both forms of the disease are usually fatal if left untreated.\textsuperscript{4, 5}

In 2013 HAT was estimated to be responsible for approximately 6,900 deaths\textsuperscript{6} and 390,000 disability-adjusted life years (DALYs).\textsuperscript{7} Fortunately, the number of infections has reduced in recent times, with less than 4,000 confirmed new cases in 2014, although the actual number is estimated to be around 20,000.\textsuperscript{1} However, over 60 million people are thought to be at risk of infection,\textsuperscript{1} and it is worth noting that historical epidemics have arisen from a base of low prevalence.\textsuperscript{1} Livestock are also susceptible to trypanosomiasis, adding to the burden of the disease, and acting as a parasite reservoir.\textsuperscript{1}
HAT consists of two stages: the first is characterised by the spread of the parasite in the blood and the lymphatic system; the second stage of the disease occurs when the parasite crosses the blood brain barrier. Early symptoms 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 the changed sleep patterns for which the disease is commonly named. Coma and eventual death ensue.

Treatment of HAT is difficult, especially in the CNS stage. Only a few drugs are available (Figure 1): suramin and pentamidine for the early, peripheral stage of the disease (stage I), and melarsoprol, eflornithine and its combination therapy with nifurtimox (NECT) for stage II. These drugs are difficult to administer, toxic, and expensive. As an example of the issues associated with the current therapies, melarsoprol was introduced for the treatment of HAT in 1949 and is still being used, even though it must be administered intravenously for 10–26 days, has side-effects that often results in patient non-compliance, and causes fatal reactive encephalopathy in 3–10% of patients. The more recently approved drug eflornithine, and NECT, are only active against *T. b. gambiense*. Pafuramidine (Figure 1) was recently taken to clinical trial, but development was abandoned due to renal toxicity. Oxaborole (SCYX-7158) is scheduled to enter clinical trials in 2016, and a phase II/III clinical trial on fexinidazole in underway. However, some cross resistance is expected for fexinidazole since its mode of action is similar to that of nifurtimox.
Figure 1. Structures of drugs investigated or currently used for the treatment of HAT and/or Chagas disease.

*T. cruzi*, spread by infected triatomine (‘kissing’) bugs, is the causative agent of Chagas disease, and is endemic in 21 countries in Latin America, affecting as many as 6–7 million people.\(^2\) The 2013 Global Burden of Disease Study, estimated that Chagas disease was responsible for 10,600
As with HAT, Chagas disease develops in two stages. During the acute phase, the parasite multiplies and spreads in the patient’s blood, without symptoms in most cases. The chronic stage is characterised by cardiac disorders and digestive alterations, due to the accumulation of the parasite in the relevant organs and, if left untreated, can be fatal. It is worth noting that Chagas disease has been reported to be one of the leading worldwide causes of myocarditis; indeed it is predicted that as many as 200,000 people will die from Chagasic cardiomyopathy over the next five years. Only two drugs are currently available to treat Chagas disease: nifurtimox and benznidazole (Figure 1), but these also have adverse side-effects, and neither can treat, chronic Chagas disease. Cure is possible during the early acute phase, and indeterminate phase (chronic infection without signs of cardiac disease), but disease diagnosis at these stages is rare.

Clearly, there is an urgent need for alternative, safer and orally-available treatments for trypanosomiasis. However, due to the poor market, there is little incentive for pharmaceutical companies to invest in the development of drugs for these diseases. Collaborative initiatives between Pharma and academic groups with a focus on neglected third world diseases have emerged and are becoming more common. For example, the Tres Cantos Open Lab Foundation, which is supported by GSK, recently published the results of a high-throughput screen (HTS) against several kinetoplastid parasites, including \textit{T. brucei} and \textit{T. cruzi}. Philanthropic organizations such as the Drugs for Neglected Diseases initiative (DNDi) also play a major role in the discovery and development of new drugs for these diseases, funding projects and making assays more available to the research community.
The efforts of organizations like the DNDi and Tres Cantos Open Lab Foundation have increased awareness about neglected parasitic diseases, and inspired many new trypanosomiasis drug discovery programs. Most campaigns have focused on either *T. brucei*\(^{13,26-36}\) or *T. cruzi*\(^{37-42}\); fewer have involved a concerted effort to discover leads that are effective against both pathogenic species,\(^{43-53}\) despite the economies of broad-spectrum drug development, especially for neglected diseases.

We previously reported the results of a DNDi-sponsored high-throughput screen (HTS) of the \(~80,000\)-strong Walter and Eliza Hall Institute (WEHI) Stage 1 compound library for compounds inhibiting the growth of *T. b. brucei*, a human non-infective species that is commonly used in drug discovery as a surrogate for the human pathogens.\(^{54}\) Eleven hits with novel, drug-like structures and physicochemical properties were identified. We have already published the hit-to-lead optimisation of five of these hits.\(^{55-59}\) Herein we report our work based on hit 1 (Figure 2).\(^{60}\) This compound offers a very attractive starting point for hit-to-lead optimisation since it exhibits good physicochemical properties, including a low molecular weight (306 g.mol\(^{-1}\)), a low polar surface area (41 Å\(^2\)), which is necessary for CNS penetration\(^{61}\) in order to treat the second stage of HAT, and a relatively simple structure amenable to analogue synthesis. Importantly, it is also modestly active against *T. cruzi*. 
RESULTS AND DISCUSSION

Synthesis

Acyl modifications

One of the appealing qualities of HTS hit 1 (Figure 2) is the possibility of rapid access to amide analogues to allow optimisation of the acyl substituent. A Gabriel-like synthesis of the primary amine 8 required for this purpose was used initially (Scheme 1). Thus, conjugate addition of phthalimide (3) to methyl vinyl ketone (2) gave adduct 4. Regioselective bromination followed by condensation with thiobenzamide (6) provided the thiazole 7. Deprotection was inefficient, possibly because of difficulties isolating the primary amine 8, which was unusually polar, difficult to extract from aqueous solutions and chromatograph. For this reason alternative routes to 8 were explored.
Scheme 1. Initial literature synthesis\textsuperscript{62} of key primary amine 8

Reagents, conditions and yields: a) NaOH, EtOAc, 50%; b) Br\textsubscript{2}, MeOH 48%; c) i-PrOH, HCl, 75%; d) H\textsubscript{2}NNH\textsubscript{2}:H\textsubscript{2}O, 48%.

An improved synthesis was devised (Scheme 2), providing 13, the hydrochloride salt of 8, which was considerably more efficiently than the original route. Condensation of thiobenzamide (6) and 1,3-dichloroacetone (9) as reported,\textsuperscript{63} gave the chloromethylthiazole 10, which was converted to the corresponding nitrile 11.\textsuperscript{64} Attempts to reduce the nitrile with LiAlH\textsubscript{4}, BH\textsubscript{3} or cobalt(II) chloride/sodium borohydride\textsuperscript{65} suffered, in some cases, from competing reduction of the thiazole, but more generally from the difficulty in isolating the primary amine 8, as noted earlier. Ultimately, an \textit{in situ} protection of the primary amine obtained by nickel boride reduction\textsuperscript{66} of nitrile 11, provided the \textit{t}-butyl carbamate 12, which was much easier to isolate and purify, in good yield. Protonolysis then provided the dihydrochloride 13, which was used directly in subsequent steps.

Scheme 2. Improved synthesis of primary amine hydrochloride 13

Reagents, conditions and yields: a) 1. acetone, 2. H\textsubscript{2}SO\textsubscript{4}, 85%; b) KCN, DMF, 90%; c) 1. NaBH\textsubscript{4}, NiCl\textsubscript{2}:H\textsubscript{2}O, Boc\textsubscript{2}O, MeOH, 2. NEt\textsubscript{3}, 82%; d) HCl/H\textsubscript{2}O, dioxane, quant.
In parallel, an alternative preparation of 8 that avoids the use of cyanide was investigated, based on a previously described synthesis of a methylthiazole.\textsuperscript{57} Again, this synthesis starts with a cyclocondensation of thiobenzamide (6), in this case with ethyl chloroacetoacetate (14). The resulting ester (15) was reduced to the primary alcohol (16), which was activated by mesylation. Due to its reactivity, the mesylate 17 was not purified or characterised but immediately subjected to nucleophilic substitution to give azide 18, which was reduced to yield the primary amine 8, under conditions that did not require an aqueous workup.

**Scheme 3. Alternative synthesis of primary amine 8.**

\[
\begin{align*}
\text{14} & \xrightarrow{\text{a}} \text{15} & \text{a) NaHCO}_3, \text{EtOH, reflux, 76\%}} &
\text{b) LiAlH}_4, \text{THF, \text{–78\degreeCelsius, 71\%}} &
\text{c) MsCl, NEt}_3, \text{THF, 96\% (crude)}} &
\text{d) NaN}_3, \text{THF, reflux, 86\%} &
\text{e) Pd/C, H}_2, \text{MeOH, 99\%}}
\end{align*}
\]

The primary amine 8, or dihydrochloride 13, was acylated to give a series of amides 21, either by condensation with acid chlorides 19, or carboxylic acids 20 in the presence of a coupling agent (Scheme 4). The yields for the DCC couplings were compromised by difficult separations from the byproduct DCU, hence the move to the ‘friendlier’ coupling agents HBTU or EDCI. The \textit{m}-ethynylbenzamides (see Table 3) were prepared by Sonogashira coupling of the corresponding iodide to give 21Bu, followed by desilylation, affording 21Bv.
The phenylsulfonamide 25, sulfamide 27 and exocyclic ureas 23 were prepared by condensation of 8 or 13 with benzenesulfonyl chloride (24), pyrrolidine-1-sulfonyl chloride (26) or the appropriate carbamoyl chloride 22, respectively. To access a wider range of ureas and carbamates more efficiently, the aminium hydrochloride 13 was converted into the activated imidazole-N-carboxamide 28, which is chromatographically stable and could be stockpiled, but was easily transformed to urea 30 or carbamate 29 targets by reaction with an amine or alkoxide, respectively.68

Scheme 4. Synthesis of target amides, carbamates, ureas, sulfonamide and sulfamide.

Reagents, conditions and yields: a) 19, NEt3, DCM, 57–85%*; b) 20, DCC, HOBT; or 20, HBTU, 24–87%*; d) PhSO2Cl, NEt3, DCM, 40%; c) 22, n = 1, NEt3, DCM, 92%; 22, n = 2, NEt3, DCM, 71%; d) DIPEA, DCM, 32%; e) 26, NEt3, DCM, 41%; f) CDI, MeCN, DMF, 69%; g) ROH, NaH, DMF, 32–55%*; h) HNR1R2, NEt3, DCM, 55–68%*. *See experimental section for individual reaction yields. Isopropylmethylamine was prepared by reductive amination of acetone.69
Variation of the thiazole-2-substituent

Initial efforts in this area (Scheme 5) commenced with similar strategies to those outlined above. Commercial 2-pyridinethioamide (31) condensed with 1,3-dichloroacetone (9) to give the chloromethylthiazole 32 in modest yield. We were concerned about the propensity of this compound to polymerise, and indeed the analogous reactions of 3- (36) and 4-pyridinethioamide (38) produced complex mixtures, which were abandoned. However, it was possible to convert 32 to the corresponding nitrile 33. Borane reduction (the superior reduction/in situ protection described in scheme 2 had not been developed yet), provided the required primary amine 34 in low yield, which was then acylated to give the target amides 35a and b.

Scheme 5. Initial route to 2-(2-pyridyl)thiazole targets

Reagents, conditions and yields: a) 1. acetone, 1,3-dichloroacetone (9); 2. H₂SO₄, 33%; b) KCN, DMF, 70°C, 74%; c) BH₃-THF, MeOH, 25%; NE₃, PhCOCl, 84% or cyclopentanecarbonyl chloride, 59%.

To access the other pyridylthiazoles, an alternative route was devised (Scheme 6). The α-bromoketone 40, available in one step from levulinic acid, was condensed with several thioamides 41 to give the corresponding thiazoles 42, and ammonolysis, provided the primary amides 43. The 2-(pyridyl)thiazoles 43a/b were subjected to a (diacetoxyiodo)benzene-mediated
Hofmann rearrangement\textsuperscript{71} with capture of the intermediate isocyanates by the solvent to give the methyl carbamates \textsuperscript{46}. Hydrolysis yielded the desired amines as their trihydrochlorides \textsuperscript{47}, which were acylated to give the target amides \textsuperscript{35}. In the case of the 2-(2-thienyl)thiazole \textsuperscript{43c}, Hofmann rearrangement\textsuperscript{71} in water gave the primary amine \textsuperscript{44} directly, and acylation once again provided the target amides \textsuperscript{45}.

**Scheme 6. Alternative route to target amides involving a Hofmann rearrangement**

Reagents, conditions and yields: a) MeOH, reflux, 22–60%*; b) conc. NH\textsubscript{3}, THF, 45–75%*; c) PhI(OAc)\textsubscript{2}, H\textsubscript{2}O/dioxane, 85%; d) PhI(OAc)\textsubscript{2}, MeOH, 46\textsubscript{a} 59%, 46\textsubscript{b} 70%; e) 4 M HCl, reflux, quant.; f) NE\textsubscript{3}, PhCOCl (41–89%) or cyclopentanecarbonyl chloride (31–54%)*. Py = pyridyl.

*See experimental for individual reaction yields.

The obvious deficiency of the two routes outlined above is their early divergent steps. We therefore targeted a synthon that could be elaborated later in the synthesis; specifically, we sought a 2-halothiazole such as \textsuperscript{53} (Scheme 7) to take advantage of late-stage transition metal-catalysed coupling to introduce various substituents. Efforts began with 2-amino-4-chloromethylthiazole hydrochloride (\textsuperscript{49}), readily prepared from thiourea (\textsuperscript{48}) and 1,3-dichloroacetone (\textsuperscript{9}).\textsuperscript{72} A Sandmeyer reaction\textsuperscript{73} was accompanied by partial halogen exchange,
giving 50, and chemoselective substitution of this mixture provided the nitrile 51. However, attempted nickel boride reduction/in situ Boc-protection to give 53, was accompanied by dehalogenation, and it appeared (from the lack of aromatic signals in the ¹H NMR spectrum of the crude product) that borane reduced the thiazole moiety with no evidence for the desired primary amine 52. In an attempt to circumvent the incompatibility of the bromothiazole with reductive conditions, the chloride 49 was converted to the corresponding nitrile 54. Unfortunately, the nickel boride reduction/in situ Boc-protection was again largely unsuccessful; although small amounts of the putative dicarbamate 55 were detected by ¹H NMR spectroscopy, it was not able to be purified.

**Scheme 7. First attempted synthesis of a 2-bromothiazole synthon**

Reagents, conditions and yields: a) acetone, reflux, 82%; b) 1. H₂SO₄, NaNO₂, 2. HBr; c). KCN, DMF, 31% (two steps); d) 1. BH₃–THF, MeOH, 2. HCl, 0%; e) 1. NaBH₄, NiCl₂·H₂O, Boc₂O, MeOH, 2. NEt₃; 0%.

Problems with the reduction of the nitrile prompted us to reinvestigate the phthalimide protecting group (Scheme 8). Thus, cyclocondensation of thiourea (48) with the bromoketone 5 gave the 2-aminothiazole hydrobromide 56 in excellent yield.⁷⁴ However, attempted Sandmeyer reactions under various conditions were unsuccessful; in all cases the absence of the expected thiazole
singlet in the 1H NMR spectra of the crude products of these reactions points to electrophilic aromatic substitution at the 3-position, although the nature of the electrophile was not determined. Fortunately the 2-bromothiazole 58 was accessible via the thiocyanate 57. Initial attempts to remove the phthalimide protecting group were unsuccessful, presumably due to competing SNAr reactions of hydrazine at the thiazole 2-position. Thus, 58 was subjected to Suzuki couplings with a range of arylboronic acids, to provide 59a–d. Deprotection, followed immediately by treatment of the primary amine with CDI gave the activated ureas 60 a–d, which were reacted with piperidine (at this point the potency-boost afforded by the exocyclic ureas had been discovered) affording the target compounds 61. Subsequently, conditions to effect the deprotection of 58 were developed, and carbamoylation of the primary amine 62 provided urea 63a, allowing diversification by Suzuki coupling in the final step. In addition, carbamoylation, carboxylation or acylation of crude 62, provided N,N-diethylurea 63b, isopropyl carbamate 63c and 2,5-difluorobenzamide 63d, respectively. Suzuki coupling then gave the 2-(2,4-difluorophenyl)thiazoles 64b–d, which were targeted, primarily, to elucidate metabolism and improve stability (see below).
Scheme 8. Divergent synthesis of variously 2-arylated thiazoles

Reagents, conditions and yields: 

a) thiourea (48), MeOH, reflux, 89%; 
b) NaNO₂, HBr or NaNO₂, HCl, NaBr, 0%; 
c) KSCN, EtOH, 78%; 
d) HBr, AcOH, reflux, 86%; 
e) ArB(OH)₂, Pd(PPh₃)₄, NaHCO₃, PhMe, H₂O, 80°C, 40–62%, or ArB(OH)₂, PdCl₂dpff, TBAB, K₂CO₃, dioxane/H₂O 4:1, µw*, 49–73%; 
f) 1. H₂NNH₂·H₂O, MeOH, reflux; 2. CDI, MeCN/DMF, 30–
70% (two steps); g) piperidine, NEt₃, 55–70%; h) H₂NNH₂·H₂O, EtOH, 69%; i) 1. p-nitrophenyl chloroformate, NEt₃, DCM, 2. piperidine, 84% (63a); j) 1. H₂NNH₂·H₂O, EtOH, reflux; 2. CICOR, NEt₃, EtOAc*; *See experimental section for individual reaction yields.

**Anti-trypanosomal activity**

Target compounds were firstly screened at 10 µM in the Alamar Blue growth inhibition assay against *T. b. brucei* used to identify hit 1.⁵⁴ Compounds causing 50% or greater inhibition at this concentration were then subjected to a concentration-response study, allowing determination of IC₅₀ values. In parallel, IC₅₀ values for cytotoxicity to human embryonic kidney (HEK) cells were measured for active compounds, and a selectivity index (SI) was calculated.

Based on the promising activity of this series against *T. b. brucei*, target compounds were also screened against *T. cruzi* using an intracellular imaging assay with rat cardiomyocyte (H9c2) cells as the host.²⁴, ⁷⁶ Cytotoxicity to the host cells was assessed in parallel.

**Potency optimisation in the acyl substituent**

The first series of compounds investigated (Table 1) explored the size of the acyl substituent (right hand side [RHS] as drawn) and the significance of the fluorine atom in hit 1. The synthetic precursors, phthalimide 7 and primary amine 8 (Scheme 1), were completely inactive against *T. b. brucei*, emphasising the importance of the amide functional group. Small amides (21a–c) displayed little activity, but this improved with the size of the alkyl group, giving an early suggestion that the acyl substituent engages with a hydrophobic pocket in the biomolecular target. Alternatively, or perhaps in addition, a greater rate of enzymatic hydrolysis of the less
sterically hindered amides might be responsible for the lack of activity, although we have no
evidence to support this notion. As expected, the pivalamide 21e, differing from hit 1 only in the
lack of a meta-fluorine atom in the phenyl substituent, retained activity, although there was an
approximate halving of potency. However, the benzamide 21f bettered the potency of hit 1
against T. b. brucei and T. cruzi. Subsequent to the initiation of this project, the Tres Cantos open
Lab Foundation/GSK HTS mentioned in the introduction also identified 21f as being active
against T. brucei and T. cruzi.24
**Table 1. Initial SAR around the acyl substituent**

<table>
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<tr>
<th>#21</th>
<th>R</th>
<th>IC₅₀ µM</th>
<th>IC₅₀ µM</th>
<th>#21</th>
<th>R</th>
<th>IC₅₀ µM</th>
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<td></td>
<td></td>
<td>(SI&lt;sup&gt;a&lt;/sup&gt;)</td>
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<td></td>
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<td>(SI)</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>T. b. brucei</td>
<td>T. cruzi</td>
<td></td>
<td></td>
<td>T. b. brucei</td>
<td>T. cruzi</td>
</tr>
<tr>
<td>a</td>
<td>H</td>
<td>n.i.</td>
<td>n.i.</td>
<td>i</td>
<td>O</td>
<td>5.0 ± 0.2 (17)</td>
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</tr>
<tr>
<td>b</td>
<td>Me</td>
<td>n.i.</td>
<td>n.i.</td>
<td>j</td>
<td>O</td>
<td>5.5 ± 0.1 (15)</td>
<td>–</td>
</tr>
<tr>
<td>c</td>
<td>Et</td>
<td>n.i.</td>
<td>n.i.</td>
<td>k</td>
<td>O</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>d</td>
<td></td>
<td>5.3 ± 0.3 (16)</td>
<td>40 ± 10.1 (&gt;1.2)</td>
<td>l</td>
<td>O</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>e</td>
<td></td>
<td>1.7 ± 0.1 (50)</td>
<td>6.3 ± 0.1 (&gt;7.9)</td>
<td>m</td>
<td>O</td>
<td>16 ± 8 (&gt;3.1)</td>
<td>–</td>
</tr>
<tr>
<td>f</td>
<td></td>
<td>0.25 ± 0.01 (334)</td>
<td>0.40 ± 0.04 (&gt;125)</td>
<td>n</td>
<td>O</td>
<td>n.i.</td>
<td>40 ± 0 (&gt;1.2)</td>
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<tr>
<td>g</td>
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<td>0.31 ± 0.1 (281)</td>
<td>0.32 ± 0.05 (&gt;158)</td>
<td>o</td>
<td>O</td>
<td>n.i.</td>
<td>40 ± 0 (&gt;1.2)</td>
</tr>
<tr>
<td>h</td>
<td></td>
<td>0.25 ± 0.02 (329)</td>
<td>–</td>
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</table>

<sup>a</sup> All IC₅₀ values are the average two independent experiments ± standard deviation.  
<sup>b</sup> SI = Selectivity index relative to HEK293 cells.  
<sup>c</sup> SI = Selectivity index relative to the host H9c2 cells. n.i. = no inhibition = < 50% inhibition at 10 µM. “–” indicates that the compound was not tested.  
<sup>d</sup> Lister 427 bloodstream form.  
<sup>e</sup> Tulahuen strain engineered to express β-galactosidase.<sup>24, 75</sup>

Alicyclic amides were also investigated with both the cyclopentyl- 21h and cyclohexylcarboxamides 21g being approximately equipotent with the benzamide 21f. However, the introduction of an electronegative heteroatom at the 4-position in the tetrahydropyranyl
derivate 21i led to a substantial loss of potency, suggesting a preference for hydrophobic character at this position. The oxabicyclo[2.2.1]heptane 21j has a similar potency to 21i and at this stage we cannot say whether the relatively poor activity is due to steric crowding or the common oxygen atom. However extension (21l), ring-fusion (21m–o) or the incorporation of larger bicyclic acyl substituents (21k) led to substantial drops or a complete loss of activity, presumably because they are too large for the acyl-binding pocket.

The clear SAR in this small series, activity against both trypanosome species, and excellent selectivity index of the more potent analogues, encouraged us to further explore this class of compounds, with an initial focus on stereoelectronic modifications to the RHS phenyl group, through the series of benzamides 21B depicted in Table 2. As in the first series, for simplicity and economy, 2-phenylthiazoles were targeted with the view that the potency boosting meta-fluorine (present in hit 1) could be reinstalled once the acyl substituent had been optimised.

Against T. b. brucei, in all cases para-substitution in the benzamides was deleterious, with activity lost in all but the p-fluoro analogue 21Bc. The halving of potency of this compound relative to the benzamide 21B is most likely due to steric (rather than electronics) as an ortho-fluorine 21Ba had little effect on activity, while the m-fluorobenzamide 21Bb was marginally more potent. Indeed, meta-substitution was generally best tolerated, albeit accompanied by a loss of potency when the substituent is electron-donating (21Bh, 21Bm). The difference in activity of the isosteric m-methyl 21Bh and m-chloro 21Be analogues is telling, and exemplifies a definite preference for electron-withdrawing substituents at the meta-position. Indeed, the nitrile 21Bp is the most active of the substituted benzamides. In contrast to the other results, activity was lost in
the phenol $^{21}B_k$, fitting with the hypothesis discussed earlier, that the target biomolecule contains a hydrophobic acyl-binding pocket.

![Structure of 21B](image)

**Table 2. Substituted Benzamides $^{21}B_a–21B_q$**

<table>
<thead>
<tr>
<th>R</th>
<th>ortho-</th>
<th>meta-</th>
<th>para-</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$^{21}B_a$</td>
<td>$^{21}B_b$</td>
<td>$^{21}B_c$</td>
</tr>
<tr>
<td>$^{21}B$</td>
<td>IC$_{50}$ µM</td>
<td>IC$_{50}$ µM</td>
<td>IC$_{50}$ µM</td>
</tr>
<tr>
<td>F</td>
<td>0.47 ± 0.6</td>
<td>–</td>
<td>0.19 ± 0.01</td>
</tr>
<tr>
<td></td>
<td>(44)</td>
<td>–</td>
<td>(444)</td>
</tr>
<tr>
<td>Cl</td>
<td>1.5 ± 0.3</td>
<td>–</td>
<td>0.42 ± 0.04</td>
</tr>
<tr>
<td></td>
<td>(29)</td>
<td>–</td>
<td>(200)</td>
</tr>
<tr>
<td>Me</td>
<td>3.3 ± 0.8</td>
<td>3.2 ± 0.5</td>
<td>3.9 ± 0.8</td>
</tr>
<tr>
<td></td>
<td>(2.5)</td>
<td>(&gt;15)</td>
<td>(21)</td>
</tr>
<tr>
<td>OH</td>
<td>2.3 ± 0.1</td>
<td>7.9 ± 0.7</td>
<td>3.9 ± 0.1</td>
</tr>
<tr>
<td></td>
<td>(18)</td>
<td>(&gt;3)</td>
<td>(18)</td>
</tr>
<tr>
<td>OMe</td>
<td>10.6 ± 3.6</td>
<td>10 ± 0.7</td>
<td>1.9 ± 0.3</td>
</tr>
<tr>
<td></td>
<td>(2.0)</td>
<td>(&gt;5)</td>
<td>(26)</td>
</tr>
<tr>
<td>CN</td>
<td>n.i.</td>
<td>–</td>
<td>0.13 ± 0.01</td>
</tr>
<tr>
<td></td>
<td>(387)</td>
<td>(&gt;63)</td>
<td>(387)</td>
</tr>
</tbody>
</table>

See table 1 footnotes for definitions.

In most cases ortho-substitution was also tolerated, although associated with drops in potency. This could reflect a reduction in conformational freedom imparted by the ortho-substituent, as supported by the complete loss of activity in the nitrile $^{21}B_0$, bearing the most restrictive cyano group. Interestingly, the salicylamide $^{21}B_j$ retained activity, possibly due to masking of the polarity of the phenolic hydroxyl by an intramolecular hydrogen bond.
Given the apparent preference for an electron-withdrawing substituent at the meta-position, we decided to investigate an expanded series of 3-substituted benzamides (Table 3). Somewhat surprisingly, a trifluoromethyl substituent (21Br) was deleterious to activity, being less potent than the corresponding toluamide 21Bh. This probably reflects the slightly larger size of the trifluoromethyl group (isosteric with an isopropropyl group by some measures) relative to methyl. There was a complete loss of activity with the larger pentafluorosulfanyl substituent (21Bs) and activity was also poor with the more polar methylsulfone 21Bt. The ethynylbenzamide 21Bv was the most potent in this small series, and even the TMS derivative 21Bu retained activity. These results, along with those summarised in table 2, suggest that a combination of steric and electronic factors determine the affinity of meta-substituted benzamides, and hint at a narrow neck in the binding site that can conformably accommodate a chlorine atom, and linear substituents like cyano and ethynyl, but not the slightly bulkier trifluoromethyl group.

![Chemical Structure](image)

Table 3. Additional 3-substituted benzamides

<table>
<thead>
<tr>
<th>#21B</th>
<th>R</th>
<th>IC₅₀ µM (SI)</th>
<th>IC₅₀ µM (SI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>r</td>
<td>CF₃</td>
<td>11.6 ± 2.1 (1.8)</td>
<td>n.i.</td>
</tr>
<tr>
<td>s</td>
<td>SF₃</td>
<td>n.i.</td>
<td>n.i.</td>
</tr>
<tr>
<td>t</td>
<td>SO₂Me</td>
<td>8.5 ± 1.8 (4.9)</td>
<td>40 ± 0.9 (&gt;1.2)</td>
</tr>
<tr>
<td>u</td>
<td>C≡CTMS</td>
<td>3.6 ± 0.9 (2.9)</td>
<td>2.0 ± 0.3 (&gt;12)</td>
</tr>
<tr>
<td>v</td>
<td>C≡CH</td>
<td>0.76 ± 0.14 (27)</td>
<td>–</td>
</tr>
</tbody>
</table>

See table 1 footnotes for definitions.
The benzamides exhibited similar SAR against *T. cruzi*, although *meta*-substitution was slightly less well tolerated than in *T. b. brucei*. The biggest difference between the two species is in the activity of the *para*-substituted benzamides: the toluamide 21Bi was very modestly active, but the nitrile 21Bq was one of the more potent compounds tested. It is possible that the *T. cruzi* target tolerates a broader range of conformations/poses of the bound molecules, allowing the placement of small linear substituents, at both the *meta* and *para*-positions, into the narrow cleft mentioned above.

Heteroaromatic amides 21H were also investigated (Table 4); against *T. b. brucei*, the picolinamide 21Ha was equipotent with the benzamide 21f, and the nicotinamide 21Hb retained significant activity; but the incorporation of an extra, diametrically-opposed nitrogen, in pyrazine 21Hd, led to a significant loss of potency, perhaps suggesting amphiphilic character on opposite sides of the acyl-binding pocket. The greatest drop in potency amongst these 6-membered *N*-heterocyclic amides was observed in the 4-pyridylamide 21Hc, again indicating an aversion to hydrogen-bond acceptors at the 4-position.
5-Membered heteroaromatic amides were then explored (Table 4). Unsurprisingly, the 2- and 3-thiophenecarboxamides (21He and 21Hf, respectively) were approximately equipotent with the isosteric benzamide 21f against *T. b. brucei*. The furans were also active, with the 3-furyl derivative 21Hi being twice as potent as the 2-furyl 21Hh, reinforcing a preference for electronnegative/electron-withdrawing substituents 3-atoms from the amide carbonyl group. The approximate halving in potency of the 2-furyl derivative 21Hh relative to the corresponding thiophene 21He is likely due to inadequate filling of the acyl group binding pocket by the

Table 4. Heteroaromatic amides 21Ha–21Ho

<table>
<thead>
<tr>
<th>#21H</th>
<th>Ar</th>
<th>IC50 µM (SI)</th>
<th>IC50 µM (SI*)</th>
<th>#21H</th>
<th>Ar</th>
<th>IC50 µM (SI)</th>
<th>IC50 µM (SI*)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><em>T. b. brucei</em></td>
<td><em>T. cruzi</em></td>
<td></td>
<td></td>
<td><em>T. b. brucei</em></td>
<td><em>T. cruzi</em></td>
</tr>
<tr>
<td>a</td>
<td></td>
<td>0.3 ± 0.01 (139)</td>
<td>–</td>
<td>i</td>
<td></td>
<td>0.35 ± 0.05 (240)</td>
<td>–</td>
</tr>
<tr>
<td>b</td>
<td></td>
<td>0.76 ± 0.28 (110)</td>
<td>2.5 ± 0.05 (&gt;19)</td>
<td>j</td>
<td></td>
<td>0.13 ± 0.0006 (666)</td>
<td>–</td>
</tr>
<tr>
<td>c</td>
<td></td>
<td>14 ± 1 (3)</td>
<td>40 ± 4 (&gt;1.2)</td>
<td>k</td>
<td></td>
<td>2.5 ± 0.1 (12)</td>
<td>5.0 ± 0.4 (&gt;10)</td>
</tr>
<tr>
<td>d</td>
<td></td>
<td>4.1 ± 0.1 (20)</td>
<td>32 ± 7 (&gt;1.5)</td>
<td>l</td>
<td></td>
<td>1.9 ± 0.3 (22)</td>
<td>–</td>
</tr>
<tr>
<td>e</td>
<td></td>
<td>0.35 ± 0.16 (241)</td>
<td>0.40 ± 0.1 (&gt;126)</td>
<td>m</td>
<td></td>
<td>0.74 ± 0.2 (113)</td>
<td>2.5 ± 0.3 (&gt;19)</td>
</tr>
<tr>
<td>f</td>
<td></td>
<td>0.23 ± 0.03 (179)</td>
<td>–</td>
<td>n</td>
<td></td>
<td>n.i. n.i.</td>
<td>n.i. n.i.</td>
</tr>
<tr>
<td>g</td>
<td></td>
<td>1.6 ± 0.4 (13)</td>
<td>6.3 ± 0.1 (&gt;7.9)</td>
<td>o</td>
<td></td>
<td>1.2 ± 0.0 (68)</td>
<td>–</td>
</tr>
<tr>
<td>h</td>
<td></td>
<td>0.80 ± 0.11 (77)</td>
<td>2.0 ± 0.1 (&gt;25)</td>
<td></td>
<td></td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

See table 1 footnotes for definitions.
smaller furan, as the introduction of a 5-methyl substituent in 21Hj saw a significant enhancement of activity. However, a 3-methyl as in 21Hl, or the larger bromo substituent in 21Hk, were not as well tolerated, suggestive of steric crowding in the region of these substituents, and fitting with a putative hydrophobic pocket of limited depth.

The introduction of additional heteroatoms into the acyl heteroaromatic substituent led to a drop in potency in the thiazole 21Ho and a complete loss of activity in the more polar oxazole 21Hn. In contrast, the 5-isoxazole 21Hm, with electronegative atoms in the 2- and 3-positions relative to the amide, was only slightly less active than the benzamide 21f, once again indicating a tolerance of, or preference for, electronegative atoms at these positions.

With the exception of the thiophenes, most of the polar heteroaromatic amides tested were substantially less potent against T. cruzi, perhaps suggesting less tolerance to polarity in the acyl-binding pocket of the biological target in this species. Alternatively, since in the T. cruzi assay the parasites are within mammalian host cells, the reduced potency of the heteroaromatic amides could be explained by poor uptake through the host cell membrane.

A series of ureas and carbamates has also been investigated (Table 5). The synthetic intermediate – tert-butyl carbamate 12 – showed no activity against T. b. brucei at 10 µM, which was not unexpected given the lack of tolerance for large acyl substituents observed earlier. Indeed, the slightly smaller isopropyl 29a and cyclopentyl carbamates 29b had potencies similar to the most active amides, against both species. In contrast, to the carbamate 29a, the N-isopropylurea 30a was significantly less active, particularly against T. cruzi. We tentatively
attributed this drop in potency to the additional hydrogen bond donor (NH), which presumably is well solvated and possibly not engaged in a target binding interaction. To examine this hypothesis, we tested the \(N,N\)-dialkylureas 30b and c and, indeed, activity was restored close to that of the carbamate 29a in \(T. b. brucei\), but not \(T. cruzi\). The diisopropyl derivative 30d, on the other hand, is clearly too large. Exocyclic ureas proved to be the most potent of all compounds examined in this study, with the piperidine 23b being optimal, amongst the 5- (23a), 6- (23b) and 7-membered (30e) rings, against both species. As before, the introduction of an oxygen at the 4-position in the morpholine-derived urea 23c led to a dramatic loss of activity, especially against \(T. cruzi\), supporting the hypothesis that the acyl-binding pocket in the biological target of this species is particularly hydrophobic. The enhanced potency of the ureas relative to the carbamates and amides could possibly be explained by enhanced hydrogen-bond donating ability of the carbonyl group in the former, although subtle steric/geometric effects due to the increased planarisation of the urea nitrogen cannot be ruled out at this time. The dramatically reduced potency of the pyrrole-derived urea 30f is somewhat surprising, and could reflect a lack of hydrolytic stability under the reaction conditions. Alternatively (or in addition), this urea has comparable potency to the electronically analogous 5-membered heteroaromatic amides; the poor electron-donating ability of the heterocyclic nitrogen may be responsible for the drop in potency of 30f relative to the other ureas.
Table 5. Carbamates and ureas

<table>
<thead>
<tr>
<th>#</th>
<th>R</th>
<th>IC₅₀ µM (SI)</th>
<th>IC₅₀ µM (SI)</th>
<th>#</th>
<th>R</th>
<th>IC₅₀ µM (SI)</th>
<th>IC₅₀ µM (SI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>T. b. brucei</td>
<td>T. cruzi</td>
<td></td>
<td></td>
<td>T. b. brucei</td>
<td>T. cruzi</td>
</tr>
<tr>
<td>12</td>
<td>O</td>
<td>n.i.</td>
<td>–</td>
<td>30d</td>
<td>N</td>
<td>9.6 ± 3.5</td>
<td>32 ± 3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>30d</td>
<td>N</td>
<td>(10)</td>
<td>(&gt;1.5)</td>
</tr>
<tr>
<td>29a</td>
<td>O</td>
<td>0.22 ± 0.02</td>
<td>0.40 ± 0.009</td>
<td>23a</td>
<td>N</td>
<td>0.050 ± 0.040</td>
<td>0.32 ± 0.007</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(385)</td>
<td>(&gt;125)</td>
<td></td>
<td></td>
<td>(1735)</td>
<td>(&gt;158)</td>
</tr>
<tr>
<td>29b</td>
<td>O</td>
<td>0.30 ± 0.004</td>
<td>0.40 ± 0.009</td>
<td>23b</td>
<td>N</td>
<td>0.028 ± 0.001</td>
<td>0.039 ± 0.003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(280)</td>
<td>(&gt;125)</td>
<td></td>
<td></td>
<td>(2966)</td>
<td>(&gt;1258)</td>
</tr>
<tr>
<td>29c</td>
<td>O</td>
<td>0.97 ± 0.05</td>
<td>3.2 ± 0.5</td>
<td>23c</td>
<td>N</td>
<td>0.69 ± 0.22</td>
<td>3.2 ± 0.07</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(86)</td>
<td>(&gt;15)</td>
<td></td>
<td></td>
<td>(127)</td>
<td>(&gt;15)</td>
</tr>
<tr>
<td>30a</td>
<td>N</td>
<td>0.90 ± 0.03</td>
<td>1.6 ± 0</td>
<td>30e</td>
<td>N</td>
<td>0.091 ± 0.021</td>
<td>0.12 ± 0.003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(93)</td>
<td>(&gt;31)</td>
<td></td>
<td></td>
<td>(943)</td>
<td>(&gt;398)</td>
</tr>
<tr>
<td>30b</td>
<td>N</td>
<td>0.39 ± 0.09</td>
<td>1.1 ± 0.3</td>
<td>30e</td>
<td>N</td>
<td>1.1 ± 0.07</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(212)</td>
<td>(&gt;50)</td>
<td></td>
<td></td>
<td>(38)</td>
<td></td>
</tr>
<tr>
<td>30c</td>
<td>N</td>
<td>0.26 ± 0.03</td>
<td>1.0 ± 0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(320)</td>
<td>(&gt;50)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

See table 1 footnotes for definitions.

The benzenesulfonamide analogue 25 (Scheme 4) was also prepared and evaluated, but demonstrated no activity against *T. b. brucei* at 10 µM and only weak activity against *T. cruzi* (IC₅₀ = 20 µM). We hypothesized that this could be due to lengthening the molecule as a result of incorporation of the large sulfur atom. To examine this possibility, and to better mimic the ureas, the slightly smaller sulfamide 27 (Scheme 4) was prepared and tested, but this was also inactive against *T. b. brucei*, and less potent than the sulfonamide against *T. cruzi* (IC₅₀ = 32 µM). These results suggest that it is the tetrahedral geometry of the sulfonamide and sulfamide functional groups that results in loss of activity.
**SAR concerning the thiazole-2-subsituent**

Initial efforts in this area began in parallel with the optimisation of the acyl substituent, hence the first compounds targeted were cyclopentanecarboxamides and benzamides (Table 6). In contrast to the acyl modifications, replacement of the left hand side (LHS) phenyl substituent with 2-thienyl (45a/b) led to a substantial drop in potency. Pyridyl substituents (35a–f) were also deleterious, especially against *T. cruzi.*

![Chemical structure](image)

**Table 6. Benzamides and cyclopentanecarboxamides bearing heterocycles at the thiazole 2-position.** (The corresponding 2-phenylthiazoles are included for comparison)

<table>
<thead>
<tr>
<th>#</th>
<th>Ar</th>
<th>R</th>
<th>IC₅₀ µM (SI) T. b. brucei</th>
<th>IC₅₀ µM (SI) T. cruzi</th>
</tr>
</thead>
<tbody>
<tr>
<td>21f</td>
<td>Ph</td>
<td>Ph</td>
<td>0.25 ± 0.01 (334)</td>
<td>0.40 ± 0.04 (&gt;125)</td>
</tr>
<tr>
<td>21h</td>
<td>Ph</td>
<td></td>
<td>0.25 ± 0.02 (329)</td>
<td>–</td>
</tr>
<tr>
<td>45a</td>
<td>S</td>
<td>Ph</td>
<td>1.5 ± 0.2 (40)</td>
<td>–</td>
</tr>
<tr>
<td>45b</td>
<td>S</td>
<td></td>
<td>2.4 ± 0.3 (35)</td>
<td>10 ± 1.4 (&gt;5)</td>
</tr>
<tr>
<td>35a</td>
<td>N</td>
<td>Ph</td>
<td>1.1 ± 0.3 (74)</td>
<td>6.3 ± 0.7 (&gt;7.9)</td>
</tr>
<tr>
<td>35b</td>
<td>N</td>
<td></td>
<td>4.0 ± 1.5 (21)</td>
<td>–</td>
</tr>
<tr>
<td>35c</td>
<td></td>
<td>Ph</td>
<td>2.7 ± 0.3 (31)</td>
<td>40 ± 3.7 (&gt;1.2)</td>
</tr>
<tr>
<td>35d</td>
<td></td>
<td></td>
<td>6.6 ± 0.3 (13)</td>
<td>20 ± 0.9 (&gt;2.5)</td>
</tr>
<tr>
<td>35e</td>
<td></td>
<td>Ph</td>
<td>3.1 ± 0.9 (27)</td>
<td>32 ± 2 (&gt;1.5)</td>
</tr>
<tr>
<td>35f</td>
<td></td>
<td></td>
<td>9.1 ± 1.7 (9)</td>
<td>32 ± 13 (&gt;1.5)</td>
</tr>
</tbody>
</table>

See table 1 footnotes for definitions.
Subsequently, the potently anti-trypanosomal piperidine-derived urea 23b (Table 5) had been discovered, and the remaining analogues with variation at the thiazole 2-position kept this RHS moiety constant (Table 7). Additionally, target design was influenced by early metabolite identification studies (see below) that indicated the thiazole phenyl substituent was prone to CYP-mediated oxidation. Although a meta-fluoro substituent gave a potency boost in the HTS hit 1 (IC₅₀ T. b. brucei = 0.48 µM vs 1.7 for the des-fluoro analogue 21e [Table 1]), the 2-(fluorophenyl)thiazoles 61a–c and 64a were of similar potency to the 2-phenylthiazole 23b. Other modifications were unfavourable, although ortho and meta-substituted analogues still had sub-micromolar IC₅₀ values. The para-substituted analogues were considerably less potent, with the exception of the nitrile 61m, which is perhaps better tolerated due to its linear geometry.

A diagram summarizing the SAR detailed in this paper is included in the supplementary information.
Table 7. Variation of the thiazole-2-subsituent in piperidine-derived ureas

<table>
<thead>
<tr>
<th></th>
<th>ortho-</th>
<th></th>
<th>meta-</th>
<th></th>
<th>para-</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>IC₅₀ µM (SI)</td>
<td></td>
<td>IC₅₀ µM (SI)</td>
<td></td>
<td>IC₅₀ µM (SI)</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>0.016 ± 0.005 (650)</td>
<td>0.01 ± 0 (&gt;3981)</td>
<td>0.026 ± 0.00002 (398)</td>
<td>–</td>
<td>c</td>
<td>0.024 ± 0.0009 (431)</td>
</tr>
<tr>
<td>Cl</td>
<td>–</td>
<td>–</td>
<td>d</td>
<td>0.16 ± 0.04 (511)</td>
<td>–</td>
<td>e</td>
</tr>
<tr>
<td>Me</td>
<td>0.19 ± 0.07 (439)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>g</td>
<td>3.7 ± 0.5 (22)</td>
</tr>
<tr>
<td>OMe</td>
<td>0.50 ± 0.07 (168)</td>
<td>–</td>
<td>i</td>
<td>0.67 ± 0.06 (62)</td>
<td>–</td>
<td>j</td>
</tr>
<tr>
<td>CN</td>
<td>0.56 ± 0.11 (148)</td>
<td>0.79 ± 0.20 (&gt;63)</td>
<td>l</td>
<td>0.28 ± 0.01 (149)</td>
<td>–</td>
<td>m</td>
</tr>
</tbody>
</table>

See table 1 footnotes for definitions.* >50% activity at 10 µM but did not reach 100% activity at 42 µM

Activity against other parasites

A selection of compounds was assessed for activity against other protozoan parasites (Table 8) – T. b. rhodesiense, Plasmodium falciparum and Leishmania donovani, causative agents of HAT, malaria and leishmaniasis respectively – alongside known antiprotozoal drugs, and toxicity to the rat skeletal muscle cell line, L6. In addition, these compounds were reassessed for activity against T. cruzi, providing independent corroboration of the results presented above. All compounds showed only modest activity against P. falciparum and L. donovani, but it was encouraging to see that activity was maintained against the human pathogenic T. b. rhodesiense. As in the model trypanosome T. b. brucei, the thiazolylurea 23a is particularly potent.
Table 8. Activity of selected compounds against other pathogenic protozoans

<table>
<thead>
<tr>
<th>Compound</th>
<th>T. b. rhodesiense&lt;sup&gt;b&lt;/sup&gt;</th>
<th>T. cruzi&lt;sup&gt;c&lt;/sup&gt;</th>
<th>P. falciparum&lt;sup&gt;d&lt;/sup&gt;</th>
<th>L. donovani&lt;sup&gt;e&lt;/sup&gt;</th>
<th>L6&lt;sup&gt;f&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5 ± 0.4</td>
<td>2.3 ± 0.06</td>
<td>35 ± 3</td>
<td>46 ± 22</td>
<td>62 ± 4</td>
</tr>
<tr>
<td>21f</td>
<td>0.078 ± 0.04</td>
<td>0.55 ± 0.18</td>
<td>32 ± 6</td>
<td>25 ± 4</td>
<td>68 ± 8</td>
</tr>
<tr>
<td>21Ba</td>
<td>0.42 ± 0.1</td>
<td>1.1 ± 0.3</td>
<td>–</td>
<td>11 ± 6</td>
<td>79 ± 36</td>
</tr>
<tr>
<td>21Bb</td>
<td>0.21 ± 0.1</td>
<td>0.20 ± 0.004</td>
<td>41 ± 8</td>
<td>10 ± 2</td>
<td>51 ± 8</td>
</tr>
<tr>
<td>21Ha</td>
<td>0.22 ± 0.05</td>
<td>0.9 ± 0.05</td>
<td>65 ± 11</td>
<td>12 ± 2</td>
<td>66 ± 15</td>
</tr>
<tr>
<td>23a</td>
<td>0.046 ± 0.014</td>
<td>0.096 ± 0.005</td>
<td>–</td>
<td>17 ± 4</td>
<td>144 ± 7</td>
</tr>
</tbody>
</table>

<sup>a</sup>Values are means of two independent experiments ± standard deviation. All assays have been described previously.<sup>78</sup> <sup>b</sup>T. b. rhodesiense strain STIB 900, bloodstream form (tryomastigotes). <sup>c</sup>T. cruzi Tulahaen C4 strain, amastigote stage. <sup>d</sup>P. falciparum K1 strain, erythrocytic stage. <sup>e</sup>L. donovani MHOM-ET-67/L82 strain, amastigote stage. <sup>f</sup>Rat skeletal myoblast L-6 cell line.

**Time to kill**

Fast-acting trypanosomacidal drugs are preferred over trypanosomastatic drugs, as the former class allow for rapid treatment regimes, and reduce the risk of developed resistance, as mentioned in the DNDi Target Product Profile for HAT.<sup>79</sup> As our primary assays do not
discriminate between growth inhibition and parasite death, selected compounds were assessed in a *T. cruzi* rate-of-kill assay (Table 9). The amides 21Hj and 21Bb killed *T. cruzi* intracellular amastigotes rapidly, with rate-of-kill profiles similar to the fast acting drug nifurtimox, and faster than posaconazole (Supplementary figure 3). In addition, the extent of parasite clearance achieved by these amides is similar to nifurtimox. The IC₅₀ values determined in this assay are similar to those in the growth inhibition assays for *T. b. brucei* and *T. cruzi*, and comparable to nifurtimox. These compounds also exhibited some level of toxicity at 50 and 17 µM, respectively. Given the excellent selectivity indices observed earlier (especially in the ureas), we do not see this as problematic, but it should be noted that toxicity of the ureas to Vero cells has not been assessed.

**Table 9. *T. cruzi* time-to-kill assay results**

<table>
<thead>
<tr>
<th>ID</th>
<th>Minimum trypanosomacidal concentration (µM)</th>
<th>Toxic concentration (µM)</th>
<th>IC₅₀ (µM)</th>
<th>Max. % inh.</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="21Hj" /></td>
<td>0.6</td>
<td>50</td>
<td>0.6</td>
<td>104</td>
</tr>
<tr>
<td><img src="image" alt="21Bb" /></td>
<td>0.6</td>
<td>17</td>
<td>0.4</td>
<td>106</td>
</tr>
</tbody>
</table>

*Concentration at which toxicity to the host (Vero) cells was seen. *Percent inhibition of infected cell number at 96 h normalized to DMSO control (0% effect) and nifurtimox (100% effect).

**Mode of Action**

A number of Chagas drug-discovery/development programs have focused on cytochrome P51 inhibitors. However, the drugability of CYP51 inhibitors has recently been questioned. They act by preventing the biosynthesis of the essential trypanosome membrane lipid ergosterol and,
although trypanosomacidal, are slow-acting. CYP51 inhibitors also show variable *T. cruzi* strain-specific activity and, in one study, were unable to clear intracellular infections after seven days of treatment.\(^8^2\) We were therefore pleased to find that 21Hj and 21Bb did not show any CYP51 inhibition using a recently published fluorescence assay.\(^8^3\) The mode of action of this class is not known at this time.

**Physicochemical Parameters and Metabolic Assays**

Key physicochemical and metabolic parameters were determined for the most potently antitrypanosomal benzamide 21Bb and ureas 23a/b. When compared against the criteria set by the DND\(i\) for progression to *in vivo* studies (*Table 10*), the only problem is the solubility of 21Bb at low pH. All of the compounds have a low polar surface area (below 85Å\(^2\)), suggesting they can passively traverse the blood-brain barrier. This property is crucial for the treatment of the second stage of HAT. Indeed all compounds have a CNS multiparameter optimization (MPO) score around 5, placing them in similar chemical space to most marketed CNS drugs.\(^6^1\)

In addition to dramatically boosting potency, the introduction of the urea functional group increases water solubility (compared to the benzamides), which is important for oral availability and the minimisation of off-target effects. Plasma protein binding (cPPB) is well below the usually accepted limit of 99.5%\(^8^4\) for all compounds.
Table 10. Key physicochemical parameters and predicted protein binding.

<table>
<thead>
<tr>
<th>Mw (Å²)</th>
<th>PSA</th>
<th>logD</th>
<th>Solubility (µg/mL)</th>
<th>cPPB (%)</th>
<th>CNS MPO (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TARGET</td>
<td>&lt; 500</td>
<td>&lt; 85</td>
<td>≤ 5</td>
<td>≥ 20</td>
<td>≥ 20</td>
</tr>
<tr>
<td>21Bb</td>
<td>326</td>
<td>42</td>
<td>3.6</td>
<td>6–12</td>
<td>ND*</td>
</tr>
<tr>
<td>21Hj</td>
<td>312</td>
<td>55</td>
<td>3.5</td>
<td>6–12</td>
<td>6–12</td>
</tr>
<tr>
<td>23a</td>
<td>301</td>
<td>45</td>
<td>2.8</td>
<td>&gt;100</td>
<td>50–100</td>
</tr>
<tr>
<td>23b</td>
<td>315</td>
<td>45</td>
<td>3.2</td>
<td>50–100</td>
<td>25–50</td>
</tr>
</tbody>
</table>

aCalculated using ACD/Laboratories software, version 9. bMeasured chromatographically. cKinetic solubility determined by nephelometry. dHuman plasma protein binding estimated using a chromatographic method. epKa and LogP for the CNS MPO calculation were predicted using ACD/Laboratories software, version 9. *Could not be determined.

A consistent deficiency of this class of compounds is a lack of metabolic stability, as assessed in vitro, using mouse and human liver microsomes (Table 11). The first results obtained for 21Bb, 23a and 23b, indicated rapid metabolism by human liver microsomes.

To shed light on the metabolic fate of 21Bb, metabolite identification was undertaken (Scheme 9). When incubated with NADPH-supplemented human liver microsomes, 21Bb was completely consumed over 60 min A metabolite with a mass of 205 Da was detected, consistent with oxidative
dealkylation of the amide to give alcohol 68, presumably via hemiacetal 66 and aldehyde 67. Two mono-oxygenated metabolites with mass [M+16]$^+$ were also detected. MS/MS suggests these are derived by hydroxylation of the ethylene linker and the phenyl group of the phenylthiazole moiety, and thus structures 65 and 69 seem most likely, although the regiochemistry of the phenyl hydroxylation reaction has not been confirmed. A secondary metabolite 70 having a mass of [M+32]$^+$ was also detected, corresponding to a second hydroxylation of the phenyl group of 69 (again, as indicated by MS/MS).

To assess the potential for phase II glucuronidation, 21Bb was incubated with microsomes in the presence of NADPH and UDPGA (uridine 5'-diphosphoglucuronic acid). Degradation followed by LCMS showed there was no difference in the rate/extent of parent loss compared to that with NADPH alone. However, the metabolite profiles differed in that a reduction in the amount of the M+16 and M+32 metabolites was observed, with a corresponding generation of putative secondary glucuronides. In microsomal samples devoid of cofactors, a minor loss (around 14% over 60 minutes) of 21Bb was observed associated with the detection of 65 and 68, indicating a minor contribution of non-NADPH mediated metabolism to the formation of these metabolites.
Table 11. Metabolic stability parameters based on NADPH-dependent degradation profiles in human and mouse liver microsomes.

<table>
<thead>
<tr>
<th>Degradation half-life (min)</th>
<th>in vitro ( \text{CL}_{\text{int}} ) (µL/min/mg protein)</th>
<th>Microsome-predicted ( \text{En}^b ) target = &lt; 0.6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse Human</td>
<td>Mouse</td>
<td>Human</td>
</tr>
<tr>
<td>21h</td>
<td>–</td>
<td>6</td>
</tr>
<tr>
<td>21Bb</td>
<td>–</td>
<td>4</td>
</tr>
<tr>
<td>23a</td>
<td>–</td>
<td>10</td>
</tr>
<tr>
<td>23b</td>
<td>–</td>
<td>7</td>
</tr>
<tr>
<td>61a</td>
<td>&lt;2</td>
<td>4</td>
</tr>
<tr>
<td>61b</td>
<td>&lt;2</td>
<td>4</td>
</tr>
<tr>
<td>61c</td>
<td>&lt;2</td>
<td>11</td>
</tr>
<tr>
<td>64a</td>
<td>&lt;2</td>
<td>8</td>
</tr>
</tbody>
</table>
In vitro intrinsic clearance determined in human and mouse liver microsomes and predicted hepatic extraction ratio calculated from in vitro data as previously described.85

Scheme 9. Putative in vitro metabolism of 21Bb in NADPH-supplemented human and mouse liver microsomes, based on LCMS and MS/MS analysis. (Stereochemistry of the sp3-C hydroxylations is ignored in this scheme).

The apparent hydroxylation of the LHS-phenyl substituent in 21Bb, encouraged us to examine the fluorinated analogues 63a–d of the more potent ureas (Table 11). However, fluorination had no significant impact on metabolic stability. These studies indicated that the major metabolic liability of this class of compounds is the ethyl linker and/or that CYP-mediated hydroxylation switches to the non-fluorinated molecular terminus. To assess the second possibility, and the importance of the piperidine moiety to metabolic stability, several 2,4-difluorophenylthiazoles 64a–d were prepared and assessed (Table 12). At least against T. cruzi, these compounds were significantly more potent than their non-fluorinated congeners. The N,N-diethylurea 64b was marginally more metabolically stable than the piperidine 64a, and the isopropyl carbamate showed further improvement. However, the tetrafluoride 64d has a degradation half-life
comparable with its non-fluorinated counterpart 23b (Table 11). It seems likely that the slight improvements in the metabolic stability of 64b and 64c are a result of increased polarity, and together the results suggest the flexible linker is the metabolic weak point in this class of compounds.

![Chemical structure]

Table 12. 2-(2,4-Diphenylthiazoles): antitrypanosomal activity and in vitro metabolism in human liver microsomes.

<table>
<thead>
<tr>
<th>#</th>
<th>R</th>
<th>IC₅₀ µM (SI) T. b. brucei</th>
<th>IC₅₀ µM (SI) T. cruzi</th>
<th>Half-life (min)</th>
<th>in vitro CL_{int} (uL/min/mg protein)</th>
<th>Microsome-predicted EH DND/i target = &lt; 0.6</th>
</tr>
</thead>
<tbody>
<tr>
<td>64a</td>
<td>N</td>
<td>0.024 ± 0.003 (433)</td>
<td>0.020 ± 0.01 (&gt;3162)</td>
<td>5</td>
<td>267</td>
<td>0.93</td>
</tr>
<tr>
<td>64b</td>
<td>N</td>
<td>–</td>
<td>0.25 ± 0.05 (&gt;199)</td>
<td>8</td>
<td>177</td>
<td>0.90</td>
</tr>
<tr>
<td>64c</td>
<td>O</td>
<td>–</td>
<td>0.13 ± 0.005 (&gt;398)</td>
<td>10</td>
<td>135</td>
<td>0.87</td>
</tr>
<tr>
<td>64d</td>
<td>F</td>
<td>–</td>
<td>0.13 ± 0.007 (&gt;398)</td>
<td>6</td>
<td>231</td>
<td>0.92</td>
</tr>
</tbody>
</table>

See tables 1 and 11 for definitions.

**In vivo studies**

When administered orally to mice 64a was absorbed but, as predicted by the in vitro assays, rapidly metabolised (Table 13). However, when the mice were pretreated with the non-selective
CYP-inhibitor 1-aminobenzotriazole (ABT),\textsuperscript{86,87} exposure of 64a increased by two orders of magnitude (Table 13). Tolerability was also found to be excellent in this study.

**Table 13. In vivo pharmacokinetics of 64a in mice, with and without 1-aminobenzotriazole (ABT) pretreatment.\textsuperscript{a}**

<table>
<thead>
<tr>
<th>Treatment\textsuperscript{a}</th>
<th>(T_{\text{max}}) (h)</th>
<th>(C_{\text{max}}) (ng/mL)</th>
<th>(\text{AUC}_{\text{last}}) (0-t) (h*ng/mL)</th>
<th>(C_{\text{max,D}}) (kg*ng/mL/mg)</th>
<th>(\text{DNAUC}_{\text{last}}) (h*ng/mL/mg/kg)\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>64a</td>
<td>0.25 ± 0.00</td>
<td>212 ± 77</td>
<td>127 ± 31</td>
<td>4.3 ± 1.5</td>
<td>2.54</td>
</tr>
<tr>
<td>ABT then 64a</td>
<td>0.50 ± 0.25</td>
<td>7090 ± 1300</td>
<td>14792 ± 3988</td>
<td>142 ± 26</td>
<td>295</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Balb/c mice used, n = 3 ± SD; \textsuperscript{b} Blood analysed following oral galvage administration of 64a (50 mg/kg) in 2\% methylcellulose + 0.5\% Tween 80; \textsuperscript{c} DNAUC, dose normalized.

On the basis of the in vivo pharmacokinetics, compound 64a was assessed for efficacy in *T. cruzi* infected mice pretreated with ABT, alongside the positive control benznidazole. After five days of twice daily treatment with 64a (50 mg/kg), parasite load was halved, and undetectable after ten days (**Figure 3**).
**Figure 3. In vivo efficacy study.** Balb/c mice infected with the trypomastigote form of transgenic *T. cruzi* Brazil strain expressing firefly luciferase\(^4\) were treated by oral gavage with vehicle (PBS with 2% methylcellulose and 0.5% Tween 80, once daily); or twice daily 64a (50 mg/kg, preceded by ip ABT 50 mg/kg 30 min prior); or benznidazole (100 mg/kg, once daily). Graph A shows parasite load from day 0 of treatment (5 days post infection). On imaging days mice were anesthetized before being injected ip with 150 mg/kg of D-luciferin potassium-salt (Goldbio) dissolved in PBS. Mice were imaged 5 to 10 min after injection of luciferin with an IVIS 100 in vivo imaging system (Panel B).
While the demonstration of efficacy in this vivo proof-of-concept study is very encouraging, it also raised some new challenges, in addition to metabolic lability, that will need to be addressed to progress this class of compounds. Following treatment, and after a recovery period, the mice were immune-suppressed, with mixed results: parasite rebound was observed in three/four mice, while the fourth remained parasite free. These results are promising, considering that, to date, only a few drugs have been able to induce parasitological cure (i.e., sterile clearance) of *T. cruzi* in mice,\(^8^8\) an essential pre-requisite for developing anti-chagasic drugs.

There were physical signs that 64a is toxic to mice (hunched, ruffled fur, low resistance to handling, etc.). On suspension of treatment, the mice did appear to recover, however. Both the apparent toxicity and parasite rebound can possibly be addressed by improving metabolic stability – allowing lower doses that are effective over longer duration.

**Compound novelty and related work**

Although a few of the amides described herein are commercially available, and are members of large compound collections, to the best of our knowledge no other significant biological activity has been described for this class of compounds. We were the first group to report this class of anti-trypanosomal compounds.\(^6^0\) At the time we initiated this project, and prior to publication of our patent, there was no report of a systematic SAR study on this, or a closely related class of compounds, for any biological activity.

During revision of this manuscript, Tidwell and co-workers reported work on the *T. b. rhodesiense* activity of a closely related series of compounds, mainly regioisomeric thiazoles.\(^8^9\)
Interestingly, they also honed in on piperidine-derived ureas (e.g. 70) as the most potent compounds (Figure 4), suggesting a mode of action in common with the series described herein; they also encountered the same problems with metabolic stability. A comparison of the *T. brucei* activity of the isomeric compounds from both groups is included in the supplementary information.

![IC50 (nM)](image)

<table>
<thead>
<tr>
<th>Compound</th>
<th>IC50 (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>64a</td>
<td>24</td>
</tr>
<tr>
<td>70</td>
<td>9.9</td>
</tr>
</tbody>
</table>

**Figure 4.** Comparison of isomeric thiazoles: 64a from the current work and 70 from Tidwell and co-workers.89

**Conclusion**

*Trypanosoma brucei brucei* growth inhibition-guided optimisation of the HTS-hit 1 (Figure 2), has unveiled a novel class of *N*-(2-(2-phenylthiazol-4-yl)ethyl)amides, carbamates and ureas that are also active in vitro against *T. b. rhodesiense*, and *T. cruzi*, causative agents of human African trypanosomiasis (HAT) and Chagas disease, respectively. Structure–activity relationships in the two species of parasite, while subtly different, are suggestive of an orthologous protein target. This target is not the commonly encountered CYP51, but at this time no more can be said about the mode of action of this class of compounds. Selected compounds were shown to be trypanosomacidal, and to kill rapidly, desirable attributes in new drugs for trypanosomiasis.
The best compounds within the series, piperidine-derived ureas, are potent in vitro, with IC\textsubscript{50} values below 20 nM, are well tolerated by several mammalian cell lines (selectivity indexes well above 1000), and have CNS drug-like physicochemical parameters. However, as a class, these compounds are highly susceptible to CYP-mediated metabolism. In an in vivo proof-of-concept experiment, in which CYP metabolism was inhibited by 1-aminobenzotriazole compound, 64a was able to reduce parasite load in \textit{T. cruzi} infected mice to undetectable levels after ten days of twice-daily treatment. One of four mice remained parasite free after immune suppression (i.e. sterile cure). There were some signs that 64a is toxic to mice, although rapid recovery was observed post-treatment.

Preliminary metabolite identification of a selection of compounds within this class indicates that the flexible linker is a point of susceptibility. Attempts to address this problem are ongoing. Nonetheless, the excellent potency, broad spectrum activity and likelihood that these compounds have a novel mode of action make them promising leads for further investigation.

**EXPERIMENTAL**

**General**

All target compounds (i.e. assessed in biological assays) were \( \geq 95\% \) pure by HPLC with 254 nm detection, and sufficiently pure by \(^1\)H NMR spectroscopy. None of the target compounds reported herein have substructures commonly associated with PAINS.\(^{90}\)

All biological assays have been reported previously, as cited in the Results and Discussion.
Synthesis

2-(2-(2-Phenylthiazol-4-yl)ethyl)isoindoline-1,3-dione (7). Prepared as described previously in 60% yield.\textsuperscript{62} \textsuperscript{1}H NMR (600 MHz, CDCl\textsubscript{3}) \(\delta\) 7.81–7.85 (m, 2H, 2 \times Ar), 7.76–7.80 (m, 2H, 2 \times Ar), 7.67–7.72 (m, 2H, 2 \times Ar), 7.32–7.38 (3H, m, 3 \times Ar), 6.99 (s, 1H, H5'), 4.11 (t, \(J_1 = 6.6\) Hz, 2H, H1'), 3.23 (t, \(J_1 = 6.6\) Hz, 2H, H2'). \textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}) \(\delta\) 168.4 (C2'' or CO), 168.1 (C2'' or CO), 154.4 (C4''), 134.0, 133.8, 132.4, 130.0, 128.9, 126.6, 114.7 (C5''), 37.7 (C1'), 30.2 (C2'). The \textsuperscript{1}H NMR data are similar to those reported at 60 MHz.

2-(2-Phenylthiazol-4-yl)ethanamine (8).\textsuperscript{62} Prepared as described previously in 50% yield. IR (cm\textsuperscript{-1}): 3368 (NH). \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 7.90–7.94 (m, 2H, H2''/H6''), 7.36–7.43 (m, 3H, H3''/H4''/H5''), 6.96 (t, \(J = 1.0\) Hz, 1H, H5'), 3.07–3.17 (m, 2H, H2), 2.94 (t, \(J_1 = 6.5\) Hz, 2H, H1), 1.71 (br. s, NH\textsubscript{2} + H2O). \textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}) \(\delta\) 168.0 (C2'), 156.3 (C4'), 133.8 (C1''), 130.0 (C4''), 129.0 (2 \times ArH), 126.6 (2 \times ArH), 114.1 (C5''), 41.8 (C1), 35.7 (C2).

4-Chloromethyl-2-phenylthiazole (10).\textsuperscript{63} Thiobenzamide (6) (13.4 g, 97.7 mmol) was added to a stirred solution of 1,3-dichloroacetone (9) (16.6 g, 131 mmol) 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 \times 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 \times 100 mL) and air-dried to yield 10 as a white solid (17.4 g, 85%), mp = 43–45 °C [lit.\textsuperscript{63} 53–55 °C]. \textsuperscript{1}H NMR (400 MHz,
CDCl₃) δ 7.94–7.96 (m, 2H, H2'/H6'), 7.43–7.45 (m, 3H, H3'/H4'/H5'), 7.30 (t, J₁ = 0.8 Hz, 1H, H5), 4.75 (s, 2H, CH₂). The ¹H NMR data matched those reported.⁶³

2-(2-Phenylthiazol-4-yl)acetonitrile (11). A mixture of KCN (13.2 g, 202 mmol), 9 (4.61 g, 20.0 mmol) and dry DMF (40 mL) under N₂ was stirred at 60 °C for 36 h. The mixture was allowed to cool, diluted with water (300 mL) and extracted with EtOAc (3 × 100 mL). The extract was washed with water (100 mL) and brine (2 × 100 mL), dried (Na₂SO₄) and evaporated to give the nitrile 11 as a brown solid (3.75 g, 94%) of sufficient purity for the next step. 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.⁶⁴

tert-Butyl (2-(2-phenylthiazol-4-yl)ethyl)carbamate (12). 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 11 (2.62 g, 13.1 mmol) in dry methanol (100 mL) at 0 °C under N₂. 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 12 as an orange oil (3.27 g, 82%). Rr 0.5 (2:3 EtOAc/hexanes + NEt₃). IR (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),
2-(2-Phenylthiazol-4-yl)ethanamine dihydrochloride (13). Ice-cold conc. HCl (3.0 mL) was slowly added to a solution of 12 (0.569 g, 1.87 mmol) in 1,4-dioxane (5 mL). After 2 h the volatiles were evaporated under a stream of N₂ to yield 13 as a yellow solid (0.518 g, mmol, quant.), mp = 140–142 °C. IR (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 (126 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.

Ethyl 2-(2-Phenylthiazol-4-yl)acetate (15). To a suspension of thiobenzamide (10 g, 73 mmol) in EtOH (100 mL) was added ethyl chloroacetoacetate (11.5 mL, 80.2 mmol, 1.1 eq), and the reaction mixture was heated to reflux for 8 h. The EtOH was evaporated under vacuum and the residue dissolved in EtOAc (100 mL). The resulting solution was washed with water (60 mL), saturated NaHCO₃ (75 mL) and brine (50 mL). The organic layer was dried over MgSO₄, and concentrated under vacuum. The crude residue was then purified by column chromatography on silica (petroleum spirit / EtOAc gradient) to afford 15 (15.9 g, 88%). ¹H NMR (400 MHz, CDCl₃)
δ 7.90–8.01 (m, 2H), 7.40–7.70 (m, 3H), 7.13 (s, 1H), 3.98 (dt [app. q], $J_1 = J_2 = 6.7$ Hz, 2H), 3.58 (s, 2H), 1.48 (t, $J = 6.7$ Hz, 3H). LRMS (ESI+) m/z: 248 [M + H]^+.

2-(2-Phenylthiazol-4-yl)ethan-1-ol (16). To a solution of 15 (1 g, 4 mmol) in dry THF (15 mL) cooled to −78 °C, was added LiAlH₄ (306 mg, 8.09 mmol). The mixture was stirred at −78 °C for 1 h and then allowed to warm to room temperature. After completion of the reaction was indicated by TLC, 1 M HCl (10 mL) was carefully added to reaction mixture followed by EtOAc (15 mL). The organic layer was collected and the aqueous layer extracted with EtOAc (2 × 15 mL). The combined organic layers were dried over Na₂SO₄ and concentrated under vacuum. The resulting material was purified by column chromatography on silica to afford 16 (759 mg, 91%). ¹H NMR (400 MHz, CDCl₃) δ 7.89–8.05 (m, 2H), 7.50–7.75 (m, 3H), 7.07 (s, 1H), 5.02 (br. s, 1H), 3.58 (t, $J = 6.9$ Hz, 2H), 2.96 (t, $J = 6.9$ Hz, 2H). LRMS (ESI+) m/z: 206 [M + H]^+.

2-(2-Phenylthiazol-4-yl)ethyl methanesulfonate (17). To a solution of 16 (100 mg, 0.49 mmol) and NEt₃ (81 μL, 0.58 mmol) in DCM (1 mL) at 0 °C was added dropwise methanesulfonyl chloride (45 μL, 0.59 mmol). The reaction was stirred at rt until completion was indicated by TLC. The solution was partitioned between DCM (5 mL) and 1 M HCl (5 mL). The organic phase was washed with brine, dried over Na₂SO₄, and concentrated in vacuum. This crude material (112 mg) was used in the next step without further purification or characterisation.

4-(2-Azidoethyl)-2-phenylthiazole (18). To a solution of 16 (100 mg, 0.353 mmol) in dry DMF (1 mL) was added NaN₃ (31 mg, 0.49 mmol). The mixture was heated to 60 °C. After TLC indicated completion of the reaction, the mixture was cooled to room temperature and diluted with
EtOAc (10 mL). The solution was washed with water (3 × 10 mL) and brine (10 mL). The organic layer was dried over Na₂SO₄ and concentrated in vacuum. The crude material was purified by column chromatography on silica to afford 18 (71 mg, 87%). ¹H NMR (400 MHz, CDCl₃) δ 7.89–8.10 (m, 2H), 7.50–7.78 (m, 3H), 6.99 (s, 1H), 2.48 (t, J = 7.0 Hz, 2H), 1.90 (t, J = 7.0 Hz, 2H). LRMS (ESI+) m/z: 231 [M + H]⁺.

4-(2-Aminoethyl)-2-phenylthiazole (19). Method B: To a solution of 16 (100 mg, 0.434 mmol) in MeOH (3 mL) was added 10% Pd/C (46 mg, 10 mol%). The suspension was placed under a hydrogen atmosphere and left stirring for 5 h. The mixture was then filtered and the solvents removed under vacuum. The resulting amine 8 (89 mg, quant.), identical with the material described above, was used in the next step without further purification.

**General procedure (A) for the synthesis of amides from 8 and acid chlorides.** Acid chloride (1.3 mmol) was added dropwise to a stirred solution of NEt₃ (0.2 mL) and 8 (0.21 g, 1.0 mmol) in DCM (2 mL) at 0 °C under N₂. 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. Unless otherwise indicated, the oily residue was dissolved in a minimum of DCM. Precipitation with hexanes gave the products as powders, which were collected and dried.

**General procedure (B) for the synthesis of amides from 13 and acid chlorides.** Acid chloride (1.5–2 equiv) was added dropwise to a stirred mixture of NEt₃ (2.5 equiv) and 13 (1 equiv) in DCM (10 mL per mmol of 13) at 0 °C under N₂. 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 (C) for the synthesis of amides from 13, 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 13) at 0 °C under N₂. After 1 h, 13 (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 (D) for the synthesis of amides from 13, 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 13 (1 equiv) in 1:1 DMF/DCM or MeCN (~10 mL per mmol of 13), under N₂, was stirred for 24 h or until the TLC showed the reaction to be complete. [Workup based on 1 mmol of 13] 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.

**General Procedure (E) for the synthesis of amides from 8, carboxylic acids and EDCI.** To a solution of the amine 8 (0.39 mmol) in DMF (0.5 M final concentration) was added the
carboxylic acid (0.47 mmol), EDCI (0.47 mmol) and DMAP (0.04 mmol). The reaction mixture was stirred at 45 °C for 18 h the diluted with water (2 mL) and extracted with EtOAc (× 3). The extract was dried and evaporated and the residue was purified by column chromatography, eluting with 10% EtOAc/petroleum spirit to obtain the desired product.

*N*-\(2\)-(2-Phenylthiazol-4-yl)ethylformamide (21a). A solution of 8 (0.21 g, 1.0 mmol) in ethyl formate (2 mL) was heated under reflux for 4 h. The excess ethyl formate was evaporated and the residue was dissolved in a minimum of DCM. Precipitation with hexanes gave the formamide 21a as an off-white powder (0.17 g, 71%), mp = 90–92 °C. IR (cm\(^{-1}\)): 3274 (NH), 1651 (C=O). \(^1\)H NMR (500 MHz, DMSO) \(\delta\) 8.08 (br. s, 1H, NH), 8.01 (d, \(J = 1.5\) Hz, 1H, CHO), 7.90–7.95 (m, 2H, H2''/H6'''), 7.46–7.52 (m, 3H, H3''/H4''/H5'''), 7.41 (s, 1H, H5'''), 3.47 (dt [app. q] \(J_1 = J_2 = 7.0\) Hz, 2H, H1''), 2.91 (t, \(J = 7.0\) Hz, 2H, H2''). \(^{13}\)C NMR (126 MHz, DMSO) \(\delta\) 166.5 (C2''), 161.1 (C=O), 155.1 (C4''), 133.2 (C1''''), 130.1 (C4'''), 129.2 (2 × ArH), 126.0 (2 × ArH), 115.3 (C5'''), 36.8 (C1'), 31.1 (C2'). HRMS (Cl) m/z observed: 233.0744, \(\text{C}_{12}\text{H}_{13}\text{N}_{2}\text{OS}^+ [\text{M+H}]^+\) requires 233.0743.

*N*-\(2\)-(2-Phenylthiazol-4-yl)ethylacetamide (21b). Following general procedure (A) with acetyl chloride gave 21b as an off-white powder (0.18 g, 71%), mp = 80–82 °C. IR (cm\(^{-1}\)): 3283 (NH), 1649 (C=O). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\), 7.90–7.96 (m, 2H, H2''/H6'''), 7.40–7.49 (m, 3H, H3''/H4''/H5'''), 6.98 (s, 1H, H5'''), 6.36 (br. s, 1H, NH), 3.65 (dt [app. q] \(J_1 = J_2 = 6.5\) Hz, 2H, H1''), 3.01 (t, \(J = 6.5\) Hz, 2H, H2''), 1.99 (s, 3H, CH\(_3\)). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 170.2 (CO), 168.4 (C2''), 155.6 (C4'''), 133.7 (C1''''), 130.3 (C4'''), 129.2 (2 × ArH), 126.5 (2 × ArH),
N-(2-(2-Phenylothiazol-4-yl)ethyl)propionamide (21c). Following general procedure (A) with propionyl chloride gave 21c as an off-white powder (0.21 g, 78%), mp = 78–80 °C. IR (cm\(^{-1}\)): 3307 (NH), 1639 (C=O). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\), 7.90–7.95 (m, 2H, H2''/H6''), 7.40–7.48 (m, 3H, H3''/H4''/H5''), 6.97 (s, 1H, H5''), 6.40 (br. s, 1H, NH), 3.66 (dt [app. q] \(J_1 = J_2 = 6.5\) Hz, 2H, H1''), 3.00 (t, \(J = 6.5\) Hz, 2H, H2''), 2.22 (q, \(J = 7.5\) Hz, 2H, H2), 1.15 (t, \(J = 7.5\) Hz, 2H, CH3). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 173.9 (CO), 168.4 (C2''), 155.7 (C4''), 133.7 (C1''), 130.2 (C4''), 129.1 (2 × ArH), 126.5 (2 × ArH), 114.5 (C5''), 39.0 (C1''), 31.1 (C2''), 30.0 (C2), 10.0 (CH3). HRMS (CI) \(m/z\) observed: 261.1064, C\(_{13}\)H\(_{15}\)N\(_2\)O\(_{2}\)S\(^+\) [M+H]\(^+\) requires 261.1056.

N-(2-(2-Phenylothiazol-4-yl)ethyl)isobutyramide (21d). Following general procedure (A) with isobutyryl chloride gave 21d as an off-white powder (0.24 g, 85%), mp = 88–90 °C. IR (cm\(^{-1}\)): 3299 (NH), 1639 (C=O). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\), 7.86–7.91 (m, 2H, H2''/H6''), 7.42–7.48 (m, 3H, H3''/H4''/H5''), 6.97 (s, 1H, H5''), 6.41 (br. s, 1H, NH), 3.65 (dt [app. q] \(J_1 = J_2 = 6.0\) Hz, 2H, H1''), 3.01 (t, \(J = 6.0\) Hz, 2H, H2''), 2.35 (sept, \(J = 6.8\) Hz, 1H, H2), 1.15 (d, \(J = 6.8\) Hz, 6H, CH3). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 177.0 (CO), 168.4 (C2''), 155.8 (C4''), 133.6 (C1''), 130.2 (C4''), 129.1 (2 × ArH), 126.5 (2 × ArH), 114.5 (C5''), 38.9 (C1''), 35.9 (C2), 31.1 (C2''), 19.8 (2 × CH3). HRMS (CI) \(m/z\) observed: 275.1211, C\(_{15}\)H\(_{19}\)N\(_2\)O\(_{2}\)S\(^+\) [M+H]\(^+\) requires 275.1213.
**N-(2-(2-Phenylthiazol-4-yl)ethyl)pivalamide (21e).** Following general procedure (A) with pivaloyl chloride gave 21e as an off-white powder (0.17 g, 57%), mp = 62–64 °C. IR (cm⁻¹): 3366 (NH), 1638 (C=O). ¹H NMR (400 MHz, CDCl₃) δ, 7.92–7.96 (m, 2H, H2''/H6''), 7.42–7.46 (m, 3H, H3''/H4''/H5''), 6.96 (s, 1H, H5''), 6.78 (br. s, 1H, NH), 3.62 (dt [app. q] J₁ = J₂ = 6.2 Hz, 2H, H1'), 2.99 (t, J = 6.0 Hz, 2H, H2'), 1.19 (s, 9H, CH₃). ¹³C NMR (126 MHz, CDCl₃) δ 178.6 (CO), 168.5 (C2''), 156.0 (C4''), 133.7 (C1''), 130.2 (C4''), 129.1 (2 × ArH), 126.5 (2 × ArH), 114.5 (C5''), 39.2 (C1''), 38.8 (C2'), 31.0 (C2'), 27.7 (3 × CH₃). HRMS (CI) m/z observed: 289.1369, C₁₅H₁₉N₂O₂S⁺ [M+H]⁺ requires 289.1369.

**N-(2-(2-Phenylthiazol-4-yl)ethyl)benzamide (21f).** Following general procedure (A) with benzoyl chloride gave 21f as an off-white powder (0.19 g, 60%), mp = 90–92 °C. IR (cm⁻¹): 3327 (NH), 1639 (C=O). ¹H NMR (400 MHz, CDCl₃) δ, 7.92–7.98 (m, 2H, H2''/H6''), 7.82–7.86 (m, 2H, H2/6), 7.67 (br. s, 1H, NH), 7.38–7.52 (m, 6H, ArH), 7.03 (s, 1H, H5''), 3.84 (dt [app. q] J₁ = J₂ = 6.8 Hz, 2H, H1'), 3.11 (t, J = 6.4 Hz, 2H, H2'). ¹³C NMR (101 MHz, CDCl₃) δ 168.6 (CO or C2''), 167.4 (CO or C2''), 155.8 (C4''), 135.0 (C1), 133.5 (C1''), 131.4 (C4 or C4''), 130.4 (C4 or C4''), 129.1 (2 × ArH), 128.6 (2 × ArH), 127.1 (2 × ArH), 126.6 (2 × ArH), 114.7 (C5''), 39.7 (C1''), 30.7 (C2''). HRMS (CI) m/z observed: 309.1063, C₁₅H₁₉N₂O₂S⁺ [M+H]⁺ requires 309.1056.

**N-(2-(2-Phenylthiazol-4-yl)ethyl)cyclohexanecarboxamide (21g).** General procedure (D) was followed with 13 (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 21g as a white solid (0.232 g, 80%), mp = 128–130 °C. Rf 0.3 (1:4 EtOAc/hexanes). IR (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), 5.62 (dt [app. q], J₁ = J₂ = 6.2 Hz, 2H, H1″), 2.99 (t, J₁ = 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, 155.8, 133.7, 136.2, 129.1 (2 × ArH), 126.5, 114.5 (C5″), 45.6, 38.9, 30.9 (C2′), 29.8 (C2/C6), 25.90 (C4), 25.87 (C3/C5). HRMS (CI) m/z observed: 315.1533, C₁₈H₂₃N₂O₅S⁺ [M+H]+ requires 315.1531.

N-(2-(2-Phenylthiazol-4-yl)ethyl)cyclopentanecarboxamide (21h). Prepared according to general procedure E with cyclopentanecarboxylic acid. ¹H NMR (400 MHz, CDCl₃) δ 8.09 (br. s, 1H), 7.95–8.05 (m, 2H), 7.40–7.55 (m, 3H), 6.96 (s, 1H), 3.69 (dt [app.q.] J₁ = J₂ = 6.5 Hz, 2H), 3.15 (t, J = 6.5 Hz, 2H), 2.42–2.55 (m, 1H), 1.48–1.80 (m, 8H). LRMS (ESI+) m/z: 301 [M + H]⁺.

N-(2-(2-Phenylthiazol-4-yl)ethyl)tetrahydro-2H-pyran-4-carboxamide (21i). Prepared according to general procedure E with tetrahydro-2H-pyran-4-carboxylic acid. ¹H NMR (400 MHz, CDCl₃) δ 7.92–8.05 (m, 3H), 7.45–7.61 (m, 3H), 6.95 (s, 1H), 3.59–3.72 (m, 6H), 3.03 (t, J = 6.8 Hz, 2H), 2.56 (t, J = 7.2 Hz, 2H), 2.42–2.55 (m, 1H), 1.90–2.05 (m, 2H), 1.75–1.83 (m, 2H). LRMS (ESI+) m/z: 317 [M + H]⁺.

(±)-(1R*,2S*,4R*)-N-(2-(2-Phenylthiazol-4-yl)ethyl)-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxamide (21j). Prepared according to general procedure E with 7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylic acid. ¹H NMR (400 MHz, CDCl₃) δ 8.01 (s, 1H), 7.91–7.98 (m, 2H), 7.43–7.59
(+/-)-2-((1R*,2S*,4S*)-Bicyclo[2.2.1]heptan-2-yl)-N-(2-(2-phenylthiazol-4-yl)ethyl)acetamide (21k). Prepared according to general procedure E with bicyclo[2.2.1]heptan-2-ylacetic acid. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.04 (s, 1H), 7.90–7.95 (m, 2H), 7.48–7.61 (m, 3H), 6.97 (s, 1H), 3.58 (dt [app. q], $J_1 = J_2 = 6.8$ Hz, 2H), 3.04 (t, $J = 6.7$ Hz, 2H), 1.95–2.25 (m, 4H), 1.20–1.70 (m, 11H). LRMS (ESI+) $m/z$: 340 [M + H]$^+$.  

2-Phenyl-N-(2-(2-phenylthiazol-4-yl)ethyl)acetamide (21l). General procedure (B) was followed with 13 (0.210 g, 0.758 mmol) and phenylacetyl chloride (0.172 ml, 1.30 mmol). Elution with 1:3 EtOAc/hexanes gave 21l as a white solid (0.0782 g, 32%), mp = 113–118 °C. R$_f$ 0.25 (1:3 EtOAc/hexanes). IR (cm$^{-1}$): 3290 (NH), 1657 (C=O). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.81–7.84 (m, 2H, H$_2''$/H$_6''$), 7.41–7.43 (m, 3H, H$_3''$/H$_4''$/H$_5''$), 7.19–7.21 (m, 5H, benzyl Ar), 6.79 (s, 1H, H$_5''$), 6.13 (br s, 1H, NH), 3.61 (dt [app. q], $J_1 = J_2 = 6.4$ Hz, 2H, H$_1'$), 3.53 (s, 2H, H$_2$), 2.92 (t, $J = 6.4$ Hz, 2H, H$_2'$). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 171.1 (C=O), 168.2 (C$_2''$), 155.3 (C$_4''$), 135.0 (C$_1''$ or C$_1'''$), 133.6 (C$_1''$ or C$_1'''$), 130.1 (ArH), 129.4 (2 × ArH), 129.0 (2 × ArH), 129.0 (2 × ArH), 127.3 (ArH), 126.5 (2 × ArH), 114.5 (C$_5''$), 44.1 (C$_2$), 39.0 (C$_1'$), 31.0 (C$_2'$). 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 (21m). General procedure (C) was followed with 13 (0.218 g, 0.786 mmol) and 1-naphthalic acid (0.138 g, 0.802 mmol). Elution with 1:1
EtOAc/hexanes gave **21m** as an orange solid (0.214 g, 75%), mp = 104–106 °C. Rf 0.2 (1:1 EtOAc/hexanes). IR (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 (21n).** General procedure (C) was followed with **13** (0.218 g, 0.786 mmol) and 2-naphthoic acid (0.138 g, 0.802 mmol). Elution with 1:4 EtOAc/hexanes gave **21m** as an orange solid (0.217 g, 77%), mp = 124–125 °C. Rf 0.3 (1:4 EtOAc/hexanes). IR (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, C₂₂H₁₉N₂OS⁺ [M+H]⁺ requires 359.1218.
2-(Benzo[d][1,3]dioxol-5-yl)-N-(2-(2-phenylthiazol-4-yl)ethyl)acetamide (21o). General procedure (B) was followed with 13 (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 21l as a pale-orange solid (0.182 g, 65%), mp = 113–118 °C. Rf 0.15 (1:1 EtOAc/hexanes). IR (cm$^{-1}$): 3295 (NH), 1647 (C=O). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 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], $J = 6.0$ Hz, 2H, H1'), 3.44 (s, 2H, H2), 2.94 (t, $J = 6.0$ Hz, 2H, H2'). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 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 (CH$_2$O$_2$), 43.6 (C2), 38.9 (C1'), 31.0 (C2'). HRMS (EI) $m/z$ observed: 366.1042, C$_{20}$H$_{18}$N$_2$O$_3$S [M$^+$] requires 366.1038.

2-Fluoro-N-(2-(2-phenylthiazol-4-yl)ethyl)benzamide (21Ba). General procedure (D) was followed with 13 (0.138 g, 0.499 mmol) and 2-fluorobenzoic acid (0.100 g, 0.714 mmol). Elution with 1:4 EtOAc/hexanes gave 21Ba as a yellow solid (0.111 g, 68%), mp = 80–82 °C. IR (cm$^{-1}$): 3317 (NH), 1644 (C=O). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.08 (ddd [app. dt], $J_1 = 8.0$ Hz, $J_2 = 2.0$ 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], $J_1 = 7.8$ Hz, $J_2 = 1.0$ 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'). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 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, C_{18}H_{16}FN_{2}OS^{+} [M+H]^{+} requires: 327.0967.

3-Fluoro-N-(2-(2-phenylthiazol-4-yl)ethyl)benzamide (21Bb). General procedure (D) was followed with 13 (0.225 g, 0.812 mmol) and 3-fluorobenzoic acid (0.144 g, 1.03 mmol). Elution with 3:10 EtOAc/hexanes gave 21Bb as a pale-yellow oil (0.109 g, 41%). Rf 0.5 (3:10 EtOAc/hexanes). IR (cm$^{-1}$): 3332 (NH), 1644 (C=O). $^{1}$H NMR (500 MHz, CDCl$_{3}$) $\delta$ 7.94–7.96 (m, 2H, H$_2'''$/H$_6'''$), 7.88 (br. s, 1H, NH), 7.57–7.63 (m, 2H, H$_2$/H$_6$), 7.44–7.47 (m, 3H, H$_3''$/H$_4''$/H$_5''$), 7.35–7.40 (m, 1H, H$_4$ or H$_5$), 7.19 (dddd [app. ddt], $J_1 = J_2 = 8.4$, $J_3 = 2.6$, $J_4 = 1.0$ Hz, 1H, H$_4$), 7.03 (t, $J = 0.8$ Hz, 1H, H$_5''$), 3.82 (pseudo q., 2H, H$_1'$), 3.10 (dt, $J = 6.0$, 0.8 Hz, 2H, H$_2'$). $^{13}$C NMR (126 MHz, CDCl$_{3}$) $\delta$ 168.8 (C$_{2''}$), 166.1 (d, $J = 2$ Hz, C=O), 162.9 (d, $J = 249$ Hz, C$_3$F), 155.8 (C$_4''$), 137.3 (d, $J = 7$ Hz, C$_3$), 133.5 (C$_1'''$), 130.4 (C$_4''''$), 130.3 (d, $J = 8$ Hz, C$_5$), 129.2 (2 × ArH), 126.6 (2 × ArH), 122.7 (d, $J = 3$ Hz, C$_6$), 118.4 (d, $J = 22$ Hz, C$_2$ or C$_4$), 114.8 (C$_5''''$), 114.4 (J = 23 Hz, C$_2$ or C$_4$), 114.3 (C$_2$), 40.0 (C$_1''$), 30.5 (C$_2'$). HRMS (ESI) m/z observed: 327.0982, C$_{18}$H$_{16}$FN$_{2}$OS$^{+}$ [M+H]$^{+}$ requires 327.0967.

4-Fluoro-N-(2-(2-phenylthiazol-4-yl)ethyl)benzamide (21Bc). General procedure (B) was followed with 13 (0.249 g, 0.898 mmol) and 4-fluorobenzoyl chloride (0.177 mL, 1.50 mmol). Elution with 1:3 EtOAc/hexanes gave 21Bc as a white solid (0.224 g, 76%), mp = 123–124 °C. Rf 0.20 (1:3 EtOAc/hexanes). IR (cm$^{-1}$): 3333 (NH) 1651 (C=O). $^{1}$H NMR (400 MHz, CDCl$_{3}$) $\delta$ 7.92–7.95 (m, 2H, H$_2$/H$_6$ or H$_2'''$/H$_6'''$), 7.83–7.87 (m, 2H, H$_2$/H$_6$ or H$_2'''$/H$_6'''$), 7.72 (br s, 1H, NH), 7.45–7.47 (m, 3H, H$_3''$/H$_4''$/H$_5''$), 7.03 (dd [app. t], $J_{ortho} = J_{H\cdot F} = 8.6$ Hz, 2H, H$_3$/H$_5$), 7.03 (s, 1H, H$_5''$), 3.78 (dt [app. q], $J = 5.6$ Hz, 2H, H$_1'$), 3.08 (t, $J = 5.6$ Hz, 2H, H$_2'$). $^{13}$C NMR
(101 MHz, CDCl₃) δ 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, C₁₈H₁₅FN₂OS [M⁺] requires 326.0889.

2-Chloro-N-(2-(2-phenylthiazol-4-yl)ethyl)benzamide (21Bd). Prepared according to general procedure E with 2-chlorobenzoic acid. ¹H NMR (400 MHz, CDCl₃) δ 7.85–7.91 (m, 2H), 7.64 (dd, J = 7.6, 1.8 Hz, 1H), 7.28–7.42 (m, 6H), 7.11 (br. s, 1H), 7.03 (s, 1H), 3.90 (dt [app q.], J = 5.8 Hz, 2H), 3.14 (t, J = 6.3 Hz, 2H). LRMS (ESI+) m/z: 343/345 [M+H]+.

3-Chloro-N-(2-(2-phenylthiazol-4-yl)ethyl)benzamide (21Be). Prepared according to general procedure E with 3-chlorobenzoic acid. ¹H NMR (400 MHz, CDCl₃) δ 7.95–8.02 (m, 2H), 7.90–7.95 (m, 2H), 7.65–7.70 (m, 1H), 7.45–7.55 (m, 3H), 7.30–7.35 (m, 1H), 7.05 (s, 1H), 3.86 (dt [app. q.], J₁ = J₂ = 6.6 Hz, 2H), 3.15 (t, J = 6.8 Hz, 2H). LRMS (ESI+) m/z: 343/345 [M + H]+.

4-Chloro-N-(2-(2-phenylthiazol-4-yl)ethyl)benzamide (21Bf). Prepared according to general procedure E with 4-chlorobenzoic acid. ¹H NMR (400 MHz, CDCl₃) δ 7.90–8.00 (m, 2H), 7.75–7.90 (m, 3H), 7.35–7.42 (m, 3H), 7.45–7.55 (m, 3H), 7.38 (d, J = 8.6 Hz, 1H), 7.05 (s, 1H), 3.85 (dt [app q.], J₁ = J₂ = 6.7 Hz, 2H), 3.13 (t, J = 6.7 Hz, 2H). LRMS (ESI+) m/z: 343/345 [M + H]+.

2-Methyl-N-(2-(2-phenylthiazol-4-yl)ethyl)benzamide (21Bg). General procedure (D) was followed with 13 (0.327 g, 1.18 mmol) and o-toluic acid (0.164 g, 1.20 mmol). Elution with 2:3
EtOAc/hexanes gave **21Bg** as a pale-yellow solid (0.282 g, 74%), mp = 104–105 °C. Rf 0.5 (2:3 EtOAc/hexanes). IR (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, C₁₉H₁₉N₂OS⁺ [M+H]+ requires 323.1218.

**3-Methyl-N-(2-(2-phenylthiazol-4-yl)ethyl)benzamide (21Bh).** General procedure (B) was followed with **13** (0.144 g, 0.519 mmol) and m-toluoyl chloride (0.132 ml, 1.00 mmol). Elution with 1:3 EtOAc/hexanes gave **21Bh** as a light brown solid (0.151 g, 90%), mp = 67–70 °C. Rf 0.25 (1:3 EtOAc/hexanes). IR (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), 124.2 (ArH), 114.6 (C5''), 39.7 (C1'), 30.7 (C2'), 21.5 (CH₃). HRMS (EI) m/z observed: 322.1144, C₁₉H₁₈N₂OS [M•+] requires 322.1140.
4-Methyl-N-(2-(2-phenylthiazol-4-yl)ethyl)benzamide (21Bi). General procedure (D) was followed with 13 (0.200 g, 0.721 mmol) and p-toluic acid (0.091 g, 0.754 mmol). Elution with 2:3 EtOAc/hexanes gave 21Bi as a yellow solid (0.112 g, 48%), mp = 104–105 °C. Rf 0.5 (2:3 EtOAc/hexanes). IR (cm$^{-1}$): 3268 (NH), 1626 (C=O). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.94–7.97 (m, 2H, H$_2'''$/H$_6'''$), 7.73 (d, $J = 8.4$ Hz, 2H, H$_2$/H$_6$), 7.59 (br. s, 1H, NH), 7.44–7.47 (m, 3H, H$_3'''$/H$_4'''$/H$_5'''$), 7.20 (d, $J = 8.4$ Hz, 2H, H$_3$/H$_5$), 7.03 (s, 1H, H$_5''$), 3.83 (dt [app. q], $J_1 = J_2 = 6.8$ Hz, 2H, H$_1''$), 3.12 (t, $J = 6.4$ Hz, 2H, H$_2''$), 2.36 (s, 3H, CH$_3$). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 168.3 (C=O or C$_2''$), 167.4 (C=O or C$_2'''$), 155.7 (C$_4'''$), 141.7 (C$_4''$), 133.5 (C$_1'''$), 130.2 (ArH), 129.1 (2 × ArH), 129.0 (2 × ArH), 127.0 (2 × ArH), 126.5 (2 × ArH), 114.6 (C$_5'''$), 39.6 (C$_1'$), 30.7 (C$_2'$), 21.5 (CH$_3'$). HRMS (ESI) m/z observed: 323.1209, C$_{19}$H$_{19}$N$_2$OS$^+$$[M+H]^+$ requires 323.1218.

2-Hydroxy-N-(2-(2-phenylthiazol-4-yl)ethyl)benzamide (21Bj). General procedure (D) was followed with 13 (0.167 g, 0.602 mmol) and salicylic acid (0.108 g, 0.782 mmol). Elution with 1:4 EtOAc/hexanes gave 21Bi as a white solid (0.131 g, 67%), mp = 96–98 °C. Rf 0.35 (1.4 EtOAc/hexanes). IR (cm$^{-1}$): 3359 (NH), 2583–3099 (OH), 1605 (C=O). $^1$H NMR (500 MHz, CDCl$_3$) δ 12.48 (br. s, 1H, OH), 8.25 (br. s, 1H, NH), 7.97 (m, 2H, H$_2'''$/H$_6'''$), 7.53 (d, $J = 7.2$ Hz, 1H, H$_6$), 7.47 (m, 3H, H$_3'''$/H$_4'''$/H$_5'''$), 7.37 (dd [app. t], $J_1 = J_2 = 8.0$ Hz, 1H, H$_4$), 7.05 (s, 1H, H$_5''$), 6.97 (d, $J = 8.0$ Hz, 1H, H$_3$), 6.79 (dd [app. t], $J_1 = J_2 = 7.2$ Hz, 1H, H$_4$), 3.81 (dt [app. q], $J_1 = J_2 = 5.9$ Hz, 2H, H$_2''$), 3.11 (t, $J = 6.4$ Hz, 2H, H$_1''$). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 170.0 (C=O or C$_2''$), 168.9 (C=O or C$_2'''$), 161.7 (C$_2$), 155.4 (C$_4''$), 134.1 (C$_3$), 133.4 (C$_1'''$), 130.5 (ArH), 129.2 (2 × ArH), 126.6 (2 × ArH), 125.9 (ArH), 118.61 (C$_3$ or C$_5$), 118.58 (C$_3$ or C$_5$),...
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.

3-Hydroxy-N-(2-(2-phenylthiazol-4-yl)ethyl)benzamide (21Bk). Prepared according to general procedure E with 3-hydroxybenzoic acid. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.11 (s, 1H), 7.93–8.00 (m, 2H), 7.53–7.59 (m, 5H), 7.29–7.35 (br. s, 1H), 7.20–7.27 (m, 1H), 6.99 (s, 1H), 3.84 (dt [app. q], $J_1 = J_2 = 6.6$ Hz, 2H), 3.15 (t, $J = 6.6$ Hz, 2H). LRMS (ESI+) m/z: 325 [M + H]^+.

2-Methoxy-N-(2-(2-phenylthiazol-4-yl)ethyl)benzamide (21Bl). General procedure (C) was followed with 13 (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 21Bl as an orange oil (0.164 g, 74%). R$_f$ 0.3 (3:7 EtOAc/Hexanes). IR (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 × ArH), 126.6 (2 × 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_{19}N_{2}O_{2}S^{+} [M+H]^+ requires 339.1162.

3-Methoxy-N-(2-(2-phenylthiazol-4-yl)ethyl)benzamide (21Bm). General procedure (B) was followed with 13 (0.311 g, 1.12 mmol) and $m$-anisoyl chloride (0.29 mL, 2.0 mmol). Elution
with 2:3 EtOAc/hexanes gave **21Bm** as a yellow solid (0.266 g 70%), mp = 70–72 °C. Rf 0.5 (1:1 EtOAc/hexanes). IR (cm\(^{-1}\)): 3332 (NH), 1644 (C=O). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 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], \(J_1 = 7.6, J_2 = J_3 = 1.4\) Hz, 1H, H6), 7.28 (dd [app. t], \(J_1 = J_2 = 8.0\) Hz, 1H, H5), 7.01 (s, 1H, H5''), 7.02 (ddd, \(J_1 = 8.2, 2.6, 1.0\) Hz, 1H, H4), 3.81 (s, 3H, CH3), 3.83 (pseudo q. 2H, H1'), 3.09 (t, \(J_1 = 6.0\) Hz, 2H, H2'). \(^13\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 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.

4-Methoxy-N-(2-(2-phenylthiazol-4-yl)ethyl)benzamide (21Bn). General procedure (C) was followed with 13 (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 **21Bn** as a white solid (0.0756 g, 31%), mp = 94–98 °C. Rr 0.35 (2:3 EtOAc/hexanes). IR (cm\(^{-1}\)): 3384 (NH), 1650 (C=O). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 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, \(J_1 = 5.6\) Hz, 2H, H2'). \(^13\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 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, C\(_{19}\)H\(_{19}\)N\(_2\)O\(_2\)S\(^+\) [M+H\(^+\)] requires 339.1162.
2-Cyano-N-(2-(2-phenylthiazol-4-yl)ethyl)benzamide (21Bo). General procedure (D) was followed with 13 (0.350 g, 1.26 mmol) and 2-cyanobenzoic acid (0.235 g, 1.59 mmol). Elution with 2:3 EtOAc/hexanes gave 21Bo as a light yellow oil (0.168 g, 40%). R<sub>f</sub> 0.4 (2:3 EtOAc/hexanes). IR (cm<sup>-1</sup>): 3276 (NH), 2227 (CN), 1650 (C=O). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.00 (v. br. s, NH), 7.81–7.85 (m, 3H, H<sub>3</sub>/H<sub>2'''</sub>/H<sub>6'''</sub>), 7.75 (br. d, <i>J</i> = 8.0 Hz, H<sub>6</sub>), 7.59–7.67 (m, 2H, H<sub>4</sub>/H<sub>5</sub>), 7.35–7.38 (m, 3H, H<sub>3'''</sub>/H<sub>4'''</sub>/H<sub>5'''</sub>), 6.98 (s, 1H, H<sub>5''</sub>), 4.23 (t, <i>J</i> = 7.2 Hz, 2H, H<sub>1'.</sub>), 3.24 (t, <i>J</i> = 7.2 Hz, 2H, H<sub>2'.</sub>). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 168.2 (C<sub>2'''</sub> or C=O), 168.0 (C<sub>2'''</sub> or C=O), 154.5 (C<sub>4''</sub>), 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 (C<sub>5'''</sub>), 37.8 (C<sub>1'''</sub>), 30.1 (C<sub>2'''</sub>). Two pairs of signals are isochronous or too broad to be observed. HRMS (ESI) <i>m/z</i> observed: 334.1028, C<sub>19</sub>H<sub>16</sub>N<sub>3</sub>O<sub>5</sub>S<sup>+</sup> [M+H]<sup>+</sup> requires 334.1014.

3-Cyano-N-(2-(2-phenylthiazol-4-yl)ethyl)benzamide (21Bp). General procedure (D) was followed with 13 (0.309 g, 1.11 mmol) and 3-cyanobenzoic acid (0.207 g, 1.41 mmol). Elution with 2:3 EtOAc/hexanes gave 21Bp as a yellow oil (0.234 g, 63%). R<sub>f</sub> 0.3 (2:3 EtOAc/hexanes). IR (cm<sup>-1</sup>): 3322 (NH), 2231 (CN), 1644 (C=O). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.13 (m, 1H, H<sub>2</sub>), 8.09 (br. s, 1H, NH), 8.08 (ddd, <i>J</i> = 8.0 Hz, 1.5, 1.0 Hz, 1H, H<sub>4</sub> or H<sub>6</sub>), 7.88–7.90 (m, 2H, H<sub>2'''</sub>/H<sub>6'''</sub>), 7.74 (ddd, <i>J</i> = 7.5, 1.5, 1.0 Hz, 1H, H<sub>4</sub> or H<sub>6</sub>), 7.50 (ddd [app. dt], <i>J</i><sub>1</sub> = <i>J</i><sub>2</sub> = 7.5, <i>J</i><sub>3</sub> = 0.5 Hz, 1H, H<sub>5</sub>), 7.47 (m, 3H, H<sub>3'''</sub>/H<sub>4'''</sub>/H<sub>5'''</sub>), 7.03 (s, 1H, H<sub>5''</sub>), 3.82 (pseudo q, 2H, H<sub>1'.</sub>), 3.11 (t, <i>J</i> = 6.0 Hz, 2H, H<sub>2'.</sub>). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): δ 168.9 (C<sub>2''</sub>), 165.1 (C=O), 155.4 (C<sub>4''</sub>), 136.1 (C<sub>1'''</sub>), 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 (C<sub>5'''</sub>), 112.9 (C<sub>3</sub>), 40.0 (C<sub>1'''</sub>), 30.3 (C<sub>2'''</sub>). HRMS (ESI) <i>m/z</i> observed: 334.1006, C<sub>19</sub>H<sub>16</sub>N<sub>3</sub>O<sub>5</sub> [M+H]<sup>+</sup> requires 334.1014.
4-Cyano-N-(2-(2-phenylthiazol-4-yl)ethyl)benzamide (21Bq). General procedure (D) was followed with 13 (0.253 g, 0.913 mmol) and 4-cyanobenzoic acid (0.170 g, 1.16 mmol). Elution with 3:10 EtOAc/hexanes gave 21Bq as a pale-green solid (0.265 g, 87%), mp = 148–150 °C. Rf 0.3 (3:10 EtOAc/hexanes). IR (cm\(^{-1}\)) 3309 (NH), 2227 (CN), 1631 (C=O). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 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'). \(^1\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 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''), 39.9 (C1'), 30.3 (C2'). HRMS (ESI) m/z observed: 334.1018, \(\text{C}_{19}\text{H}_{16}\text{N}_{3}\text{OS}^+ [M+H]^+\) requires 334.1014.

N-(2-(2-Phenylthiazol-4-yl)ethyl)-3-(trifluoromethyl)benzamide (21Br). General procedure (D) was followed with 13 (0.061 g, 0.25 mmol) and 3-trifluoromethylbenzoic acid (0.072 g, 0.38 mmol). Elution with DCM gave 21Br as a yellow gum that solidified at –20 °C as pale brown needles (47 mg, 57%), mp = 88–91 °C. Rf = 0.55 (1:1 EtOAc/hexanes). IR (cm\(^{-1}\)) 3295 (NH), 1637 (CO). \(^1\)H NMR (CDCl\(_3\), 400 MHz): Two rotamers, 10:3, * = major, † = minor: \(\delta\) 8.36 (s, 1H, H2'), 8.27 (d, \(J = 8.0\) Hz, 1H, H6) 8.11 (s, 1H, H2)*, 8.04 (dd, \(J = 7.8, 0.4\) Hz 1H, H6)* 7.88 (br. s, 1H, NH)*, 7.83–7.86 (m, 2H, H2''/H6'')*, 7.82 (d, \(J = 7.6\) Hz, 1H, H4)*, 7.74 (ddd [app. dt], \(J_1 = 7.6, J_2 = 0.8\) Hz, 1H, H5)*, 7.59 (dd [app. t], \(J_1 = J_2 = 8.0\) Hz, 1H, H5)†, 7.59 (ddd, \(J = 8.4, 7.6, 0.4\) Hz, 1H, H5)*, 7.40–7.43 (m, 3H, H3''/H4''/H5''), 7.03 (s, 1H, H5'')*, 3.83–3.88 (m [pseudo q]), 2H, H1'), 3.10–3.14 (m [pseudo t], 2H, H2'). \(^1\)C NMR (CDCl\(_3\), 101 MHz): \(\delta\) (major rotamer only) 169.0 (C=O), 166.1 (C2''), 155.7 (C4''), 135.7 (C3''' or C1), 133.4 (C1'' or C1), 131.2
(q, J = 32 Hz, C3), 130.6 (ArH), 130.4 (ArH), 129.3 (ArH), 129.2 (2 × ArH), 128.1 (q, J = 4 Hz, C2 or C4), 126.5 (2 × ArH), 124.0 (q, J = 4 Hz, C2 or C4), 123.9 (q, J = 273 Hz, CF3), 114.8 (C5"), 40.0 (C1'), 30.5 (C2'). HRMS (ESI) m/z observed: 377.0934, C19H16F3N2O2S+ [M+H]+ requires: 377.0930.

**N-(2-(2-Phenylthiazol-4-yl)ethyl)-3-(pentafluorosulfonyl)benzamide** (21Bs). General procedure (D) was followed with 13 (0.060 g, 0.25 mmol) and 3-(pentafluorosulfanyl)benzoic acid (0.095 g, 0.38 mmol) giving a pale yellow gum (0.129 g), which was vacuum-filtered through a column of silica and eluted with DCM. The filtrate was subjected to flash chromatography. Elution with 1:24 MeOH/DCM gave benzamide 21Bs as a pale yellow gum (0.058 g, 60%). Rf = 0.35 (1:1 EtOAc/hexanes). IR (cm⁻¹): 3311 (NH), 1641 (CO). ¹H NMR (CDCl₃, 500 MHz): Two rotamers, 21:4, * = major, ^ = minor: δ 8.48 (dd [app. t], J₁ = J₂ = 1.8 Hz, 1H, H2)^, 8.26 (dd [app. t], J₁ = J₂ = 1.8 Hz, 1H, H2)*, 8.22 (d, J = 8.0 Hz, 1H, H4 or H6)^, 7.80 (d, J = 7.5 Hz, 1H, H4 or H6), 7.85–7.95 (m, 4H, 3 × ArH + NH)^, 7.57 (dd [app. t], J₁ = J₂ = 8.0 Hz, 1H, H5)^, 7.50 (dd [app. t], J₁ = J₂ = 8.0 Hz, 1H, H5)*, 7.40–7.47 (m, 3H, H3"/H4"/H5")^, 7.04 (s, 1H, H5")*, 3.85 (dt [app. q], J₁ = J₂ = 5.5 Hz, 2H, H1')^, 3.12 (t, J = 5.5 Hz, 2H, H2'). ¹³C NMR (CDCl₃, 126 MHz): major rotamer only δ 168.9 (C=O or C2"), 165.6 (C=O or C2"), 155.6 (C4"), 154.2 (app. t, CSF₅) 136.0 (Ar), 133.4 (Ar), 130.5, (ArH), 130.0 (ArH), 129.2 (2 × ArH), 129.1 (ArH), 128.7 (app. t, C2 or C4', 126.5 (2 × ArH), 125.1 (app. t, C2 or C4), 114.9 (C5"), 40.1 (C1'), 30.4 (C2'). HRMS (ESI) m/z observed: 435.0643, C₁₈H₁₆F₅N₂O₂S₂⁺ [M+H]^+ requires: 435.0619.

**3-(Methylsulfonyl)-N-(2-(2-phenylthiazol-4-yl)ethyl)benzamide** (21Bt). General procedure (D) was followed with 13 (0.060 g, 0.22 mmol) and 3-methylsulfonylbenzoic acid (0.076 g, 0.38
mmol) giving a pale brown gum (0.092 g), which was subjected to flash chromatography. Elution with 1:49 MeOH/DCM gave benzamide 21Bt as a colourless gum (0.058 g, 68%). Rf = 0.05 (1:1 EtOAc/hexanes). IR (cm⁻¹): 3320 (NH), 1644 (CO). ¹H NMR (CDCl₃, 600 MHz): δ 8.40 (dd [app. t.], J₁ = J₂ = 1.8 Hz, 1H, H2), 8.13 (ddd, J = 7.8, 1.8, 1.2 Hz, 1H, H4 or H6), 8.13 (ddd, J = 7.8, 1.5, 1.0 Hz, 1H, H4 or H6), 7.92–7.94 (m, 2H, H2''/H6''), 7.87 (br. unresolved t, 1H, NH), 7.63 (ddd [app. dt], J = 7.8, <0.6 Hz, 1H, H5), 7.42–7.48 (m, 3H, H3''/H4''/H5''), 7.04 (s, 1H, H5''), 3.85 (dt [app. q], J₁ = J₂ = 6.0 Hz, 2H, H1'), 3.12 (t, J = 6.0 Hz, 2H, H2'), 3.04 (s, 3H, CH₃). ¹³C NMR (CDCl₃, 151 MHz): δ 168.8 (C=O or C2''), 165.5 (C=O or C2''), 155.6 (C4''), 141.2 (Ar), 136.5 (Ar), 133.4 (Ar), 132.5 (ArH), 130.4 (2 × ArH), 129.3 (ArH), 126.5 (2 × ArH), 126.0 (ArH), 114.8 (C5''), 44.5 (CH₃), 40.0 (C1'), 30.5 (C2'). HRMS (ESI) m/z observed: 387.0848, C₁₈H₁₉N₂O₃S₂⁺ [M+H]⁺ requires: 387.0832.

3-Iodo-N-(2-(2-phenylthiazol-4-yl)ethyl)benzamide. General procedure (D) was followed with 13 (0.164 g, 0.592 mmol) and 3-iodobenzoic acid (0.197 g, 0.794 mmol) giving a brown oil (0.292 g), which was subjected to flash chromatography. Elution with 1:4 EtOAc/hexanes gave the title benzamide as white solid (0.124 g, 48%). Rf = 0.55 (1:1 EtOAc/hexanes). IR (cm⁻¹): 3276 (NH), 1626 (C=O). ¹H NMR (CDCl₃, 600 MHz): δ 8.19 (dd [app. t], J₁ = J₂ = 1.3 Hz, 1H, H2), 7.92–7.95 (m, 2H, H2''/H6''), 7.82 (ddd, J = 7.8, 1.5, 0.6 Hz, 1H, H4 or H6), 7.80 (ddd, J = 7.8, 1.8, 1.2 Hz, 1H, H4 or H6), 7.77 (br. s, 1H, NH), 7.42–7.50 (m, 3H, H3''/H4''/H5''), 7.15 (dd [app. t], J₁ = J₂ = 7.8 Hz, 1H, H5), 7.03 (t, J = 0.6 Hz, 1H, H5''), 3.82 (pseudo q, 2H, H1'), 3.10 (dt, J = 6.0 Hz, 0.6 Hz, 2H, H2').
**N-(2-(2-Phenylthiazol-4-yl)ethyl)-3-((trimethylsilyl)ethynyl)benzamide (21Bu).** PdCl$_2$(PPh$_3$)$_2$ (5 mg, 3 mol%), copper iodide (2 mg, 5 mol%) and trimethylsilylacetylene (0.07 mL, 0.5 mmol) were added to a stirred, degassed solution of 3-iodo-N-(2-(2-phenylthiazol-4-yl)ethyl)benzamide (0.10 g, 0.23 mmol) in NEt$_3$ (1 mL) and acetonitrile (1 mL) under N$_2$. After 21 h the reaction mixture was diluted with DCM (50 mL) and filtered through a pad of silica to give a brown oil (0.118 g), which was subjected to flash chromatography. Elution with 1:9 EtOAc/hexanes gave benzamide 21Bu as a yellow gum (0.067 g, 74%). R$_f$ = 0.5 (1:1 EtOAc/hexanes). IR (cm$^{-1}$): 3321 (NH), 2160 (C≡C), 1640 (C=O). $^1$H NMR (CDCl$_3$, 600 MHz): δ 7.92–7.95 (m, 3H, H$_2'''$/H$_6'''$/H$_2$), 7.79 (ddd, $J_1$ = 7.8, $J_2$ = 1.2 Hz, 1H, H$_4$ or H$_6$), 7.75 (br. s, 1H, NH), 7.58 (ddd, [app. dt], $J_1$ = 7.8, $J_2$ = 1.2 Hz, 1H, H$_4$ or H$_6$), 7.40–7.48 (m, 3H, H$_3'''$/H$_4'''$/H$_5'''$), 7.01 (t, $J$ = 0.6 Hz, 1H, H$_5''$), 3.83 (pseudo q, 2H, H$_1''$), 3.10 (dt, $J$ = 6.2, 0.6 Hz, 2H, H$_2'''$), 0.23 (s, 9H, CH$_3$). $^{13}$C NMR (CDCl$_3$, 126 MHz): δ 168.7 (C$_2'''$), 166.7 (C=O), 155.8 (C$_4'''$), 135.3 (C$_1'''$ or C$_1$), 134.7 (ArH), 133.5 (C$_1'''$ or C$_1$), 130.4 (ArH), 130.3 (ArH), 129.2 (2 × ArH), 128.6 (ArH), 127.3 (ArH), 126.5 (2 × ArH), 123.8 (C$_3$), 114.6 (C$_5'''$), 104.3 (=C), 95.4 (=C), 39.8 (C$_1'''$), 30.7 (C$_2'''$), 0.02 (CH$_3$).

**3-Ethynyl-N-(2-(2-phenylthiazol-4-yl)ethyl)benzamide (21Bv).** A saturated solution/suspension of K$_2$CO$_3$ in MeOH (0.5 mL) was added to a stirred solution of 21Bu (0.060 g, 0.15 mmol) in CHCl$_3$ (0.5 mL) under N$_2$. After 4 h the reaction mixture was diluted with water (30 mL), and extracted with CHCl$_3$ (3 × 10 mL). The extract was washed with brine (10 mL), dried and evaporated to give the terminal alkyne 21Bv as a colourless gum (0.042 g, 42%). R$_f$ = 0.4 (1:1 EtOAc/hexanes). IR (cm$^{-1}$): 3286 (NH), 1639 (C=O). $^1$H NMR (CDCl$_3$, 600 MHz): δ 7.97 (dd [app. t], $J_1$ = 1.5 Hz, 1H, H$_2$) 7.92–7.95 (m, 2H, H$_2'''$/H$_6'''$), 7.85 (br. s, 1H, NH),
7.84 (ddd [app. t], J₁ = 7.8, J₂ = J₃ = 1.5 Hz, 1H, H4 or H6), 7.59 (ddd, [app. dt] J₁ = 7.8, J₂ = J₃ = 1.2 Hz, 1H, H4 or H6), 7.40–7.47 (m, 3H, H3'''/H4'''/H5'''), 7.37 (ddd [app. dt], J₁ = J₂ = 7.8, J₃ = 0.6 Hz, 1H, H5), 7.01 (s = 0.6 Hz, 1H, H5''), 3.82 (pseudo q, 2H, H1'), 3.10 (s, 1H, ≡CH), 3.09 (t, J = 5.7 Hz, 2H, H2'). ¹³C NMR (CDCl₃, 151 MHz): δ 168.7 (C2''), 166.5 (C=O), 155.8 (C4''), 135.3 (C1'' or C1), 134.8 (ArH), 133.5 (C1'' or C1), 130.6 (ArH), 130.2 (ArH), 129.2 (2 × ArH), 128.7 (ArH), 127.7 (ArH), 126.5 (2 × ArH), 122.7 (C3), 114.7 (C5''), 82.9 (≡C), 78.2 (≡CH), 39.8 (C1'), 30.6 (C2'). HRMS (ESI) m/z observed: 333.1048, C₂₀H₁₇N₂OS⁺ [M+H]⁺ requires: 333.1056.

N-(2-(2-Phenylthiazol-4-yl)ethyl)picolinamide (21Ha). General procedure (D) was followed with 13 (0.097 g, 0.35 mmol) and picolinic acid (0.062 g, 0.50 mmol). Elution with 1:1 EtOAc/hexanes gave 21Ha as a yellow oil (0.078 g, 72%). Rf 0.5 (1:1 EtOAc/hexanes). IR (cm⁻¹): 3367 (NH), 1663 (C=O). ¹H NMR (500 MHz, CDCl₃) δ 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'''), 7.84 (ddd [app. dt], J₁ = J₂ = 7.8 Hz, J₃ = 1.8 Hz, 1H, H4 or H5), 7.41–7.48 (m, 4H, H4 or H5 and H3'''/H4'''/H5'''), 7.00 (s, 1H, H5''), 3.88 (dt [app. q], J₁ = J₂ = 6.4 Hz, 2H, H1'), 3.13 (t, J₁ = 6.4 Hz, 2H, H2'). ¹³C NMR (126 MHz, CDCl₃) δ 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 × ArH), 126.7 (2 × ArH), 126.1 (ArH), 122.3 (ArH), 114.4 (C5''), 39.1 (C1'), 31.2 (C2'). HRMS (EI) m/z observed: 309.0942, C₁₇H₁₅N₃OS [M]⁺ requires 309.0936.

N-(2-(2-Phenylthiazol-4-yl)ethyl)nicotinamide (21Hb). General procedure (C) was followed with 13 (0.200 g, 0.721 mmol) and nicotinic acid (0.093 g, 0.755 mmol). Elution with EtOAc
gave 21Hb as an orange solid (0.109 g, 49%), mp = 86–88 °C. Rf 0.15 (EtOAc). IR (cm$^{-1}$): 3331 (NH), 1607 (C=O). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 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.], $J_1 = J_2 = 6.0$ Hz, 1H, H5), 7.01 (s, 1H, H5''), 3.85 (dt [app. q], $J_1 = J_2 = 5.4$ Hz, 5H, H1''), 3.10 (t, $J = 5.4$ Hz, 2H, H2'). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 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, C$_{17}$H$_{16}$N$_3$OS$^+$ [M+H]$^+$ requires 310.1014.

N-(2-(2-Phenylthiazol-4-yl)ethyl)isonicotinamide (21He). General procedure (C) was followed with 13 (0.200 g, 0.721 mmol) and isonicotinic acid (0.093 g, 0.755 mmol). Elution with 1:1 EtOAc/hexanes gave 21Hc as a yellow solid (0.116 g, 52%), mp = 108–110 °C. Rf 0.3 (1:1 EtOAc/hexanes). IR (cm$^{-1}$): 3323 (NH), 1607 (C=O). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 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], $J_1 = J_2 = 6.4$ Hz, 2H, H1''), 3.11 (t, $J_1 = 6.4$ Hz, 2H, H2'). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 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, C$_{17}$H$_{15}$N$_3$OS [M]$^+$ requires: 309.0936.

N-(2-(2-Phenylthiazol-4-yl)ethyl)pyrazine-2-carboxamide (21Hd). General procedure (D) was followed with 13 (0.179 g, 0.646 mmol) and pyrazinecarboxylic acid (0.137 g, 1.10 mmol). Elution with 2:3 EtOAc/hexanes gave 21Hd as a brown solid (0.160 g, 80%), mp = 81–83 °C. Rf
0.19 (2:3 EtOAc/hexanes). IR (cm$^{-1}$): 3327 (NH), 1655 (C=O). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$
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], $J_1 = J_2 = 2.6$ 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], $J_1 = J_2 = 6.3$ Hz, 2H, H1'), 3.15 (t, $J = 6.0$ Hz, 2H, H2'). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$
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, C$_{16}$H$_{15}$N$_4$O$_2$S$^+$ [M+H]$^+$ requires 311.0961.

$N$-(2-(2-Phenylthiazol-4-yl)ethyl)thiophene-2-carboxamide (21He). General procedure (B) was followed with 13 (0.216 g, 0.779 mmol) and 2-thiophenecarbonyl chloride (0.14 mL, 1.3 mmol). Elution with 1:4 EtOAc/hexanes gave 21He as a white solid (0.100 g, 41%), mp = 116–119 °C. Rf 0.5 (1:4 EtOAc/hexanes). IR (cm$^{-1}$): 3319 (NH), 1625 (C=O). $^1$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'). $^{13}$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), 126.8 (2 × ArH), 114.6 (C5''), 39.1 (C1'), 30.7 (C2'). HRMS (ESI) m/z observed: 315.0616, C$_{16}$H$_{15}$N$_2$OS$_2$$^+$ [M+H]$^+$ requires 315.0626.

$N$-(2-(2-Phenylthiazol-4-yl)ethyl)thiophene-3-carboxamide (21Hf). General procedure (D) was followed with 13 (0.178 g, 0.642 mmol) and 3-thiophenecarboxylic acid (0.104 g, 0.818
Elution with 1:4 EtOAc/hexanes gave 21Hf as a yellow oil (0.168 g, 83%). Rf 0.2 (1:4 EtOAc/hexanes). IR (cm\(^{-1}\)): 3321 (NH), 1633 (C=O). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 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], \(J_1 = J_2 = 5.8\) Hz, 2H, H1'), 3.11 (t, \(J = 6.0\) Hz, 2H, H2'). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 168.7 (C2''), 163.2 (C=O), 155.4 (C4''), 138.0 (C1'''), 133.2 (C3), 130.5 (C4''), 129.2 (2 \(\times\) ArH), 128.2 (ArH), 126.6 (2 \(\times\) ArH), 126.4 (ArH), 126.2 (ArH), 114.8 (C5''), 39.4 (C1'), 30.6 (C2'). HRMS (ESI) \(m/z\) observed: 315.0626, C\(_{16}\)H\(_{15}\)N\(_2\)O\(_2\)S\(^+\) [M+H]\(^+\) requires 315.0626.

\(N\)-(2-(2-Phenylthiazol-4-yl)ethyl)-1\(H\)-pyrrole-2-carboxamide (21Hg). General procedure (D) was followed with 13 (0.255 g, 0.920 mmol) and 1\(H\)-pyrrole-2-carboxylic acid (0.131 g, 1.18 mmol). Elution with 3:7 EtOAc/hexanes gave 21Hg as a pale-yellow solid (0.074 g, 27%), mp = 119–121 °C. Rf 0.45 (3:7 EtOAc/hexanes). IR (cm\(^{-1}\)): 3312 (NH), 1620 (C=O). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 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], \(J_1 = J_2 = 6.2\) Hz, 2H, H1'), 3.08 (t, \(J = 6.0\) Hz, 2H, H2'). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 168.5 (C2''), 161.4 (C=O), 155.7 (C4''), 133.7 (C1'''), 130.2 (C4''), 129.1 (2 \(\times\) ArH), 126.6 (2 \(\times\) 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, C\(_{16}\)H\(_{16}\)N\(_3\)O\(_2\)S\(^+\) [M+H]\(^+\) requires 298.1014.
**N-(2-(2-Phenylthiazol-4-yl)ethyl)furan-2-carboxamide (21Hh).** General procedure (D) was followed with 13 (0.255 g, 0.920 mmol) and 2-furoic acid (0.229 g, 0.826 mmol). Elution with 2:3 EtOAc/hexanes gave 21Hh as a pale-yellow oil (0.192 g, 78%). Rf 0.45 (2:3 EtOAc/hexanes). IR (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''), 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)furan-3-carboxamide (21Hi).** Prepared according to general procedure E with 3-thiophenecarboxylic acid. ¹H NMR (400 MHz, DMSO) δ 8.58 (s, 1H), 8.05 (d, J = 1.0 Hz, 1H), 7.80–7.95 (m, 2H), 7.45–7.59 (m, 3H), 7.25 (d, J = 8.0 Hz, 1H), 7.11 (d, J = 8.1 Hz, 1H), 3.60 (dt [app. q], J₁ = J₂ = 7.2 Hz, 2H), 3.11 (t, J = 7.1 Hz, 2H). LRMS (ESI+) m/z: 299 [M + H]⁺.

**3-Methyl-N-(2-(2-phenylthiazol-4-yl)ethyl)furan-2-carboxamide (21Hj).** Prepared according to general procedure E with 3-methyl-2-furoic acid. ¹H NMR (400 MHz, DMSO) δ 8.12 (br. s, 1H), 7.99–8.09 (m, 2H), 7.80 (d, J = 7.0 Hz, 1H), 7.30–7.42 (m, 4H), 6.92 (s, 1H), 6.60 (d, J = 7.5 Hz, 1H), 3.69 (dt [app. q], J₁ = J₂ = 6.5 Hz, 2H), 3.19 (t, J = 6.5 Hz, 2H), 2.66 (s, 3H). LRMS (ESI+) m/z: 313 [M + H]⁺.
4-Bromo-N-(2-(2-phenylthiazol-4-yl)ethyl)furan-2-carboxamide (21Hk). Prepared according to general procedure E with 4-bromo-2-furoic acid. $^1$H NMR (400 MHz, DMSO) $\delta$ 8.62 (t, $J = 5.7$ Hz, 1H), 8.11 (d, $J = 0.8$ Hz, 1H), 7.81–7.99 (m, 2H), 7.45–7.59 (m, 3H), 7.42 (s, 1H), 7.24 (d, $J = 0.8$ Hz, 1H), 3.58 (dt [app. q] $J_1 = J_2 = 7.1$ Hz, 2H), 3.00 (t, $J = 7.2$ Hz, 2H). HRMS (ESI) $m/z$ observed: 376.9960, C$_{16}$H$_{14}$Br$_7$N$_2$O$_2$S$^+$ [M+H]$^+$ requires: 376.9954.

5-Methyl-N-(2-(2-phenylthiazol-4-yl)ethyl)furan-2-carboxamide 21Hl. Prepared according to general procedure E with 5-methyl-2-furoic acid. $^1$H NMR (400 MHz, DMSO) $\delta$ 8.08 (br. s, 1H), 7.95–8.04 (m, 2H), 7.29–7.39 (m, 4H), 6.51 (d, $J = 8.1$ Hz, 1H), 6.90 (s, 1H), 3.78 (dt [app. q], $J = 7.2$ Hz, 2H), 3.13 (t, $J = 7.2$ Hz, 2H), 2.59 (s, 3H). LRMS (ESI+) $m/z$: 313 [M + H]$^+$.

N-(2-(2-Phenylthiazol-4-yl)ethyl)isoxazole-3-carboxamide (21Hm). Prepared according to general procedure E with 3-isoxazolecarboxylic acid. $^1$H NMR (400 MHz, DMSO) $\delta$ 9.08 (d, $J = 1.7$ Hz, 1H), 8.94 (t, $J = 5.6$ Hz, 1H), 7.81–8.06 (m, 2H), 7.45–7.58 (m, 3H), 7.44 (s, 1H), 6.88 (d, $J = 1.7$ Hz, 1H), 3.63 (dt [app. q], $J_1 = J_2 = 7.2$ Hz, 2H), 3.03 (t, $J = 7.2$ Hz, 2H). HRMS (ESI) $m/z$ observed: 300.0802, C$_{15}$H$_{14}$N$_3$O$_2$S$^+$ [M+H]$^+$ requires: 300.0801.

N-(2-(2-Phenylthiazol-4-yl)ethyl)oxazole-5-carboxamide (21Hn). General procedure (D) was followed with 13 (0.225 g, 0.812 mmol) and oxazole-5-carboxylic acid (0.119 g, 1.07 mmol). Elution with 1:1 EtOAc/hexanes gave 21Hg as a white solid (0.097 g, 40%) mp = 110–111 °C. R$_f$ 0.15 (1:1 EtOAc/Hexanes). IR (cm$^{-1}$): 3360 (NH), 1629 (C=O). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.97–7.99 (m, 2H, H$_2''$/H$_6'''$), 7.88 (s, 1H, H$_2$), 7.81 (br. s, 1H, NH), 7.72 (s, 1H, H$_4$), 7.46 (m, 3H, H$_3''$/H$_4''$/H$_5'''$), 7.02 (t, $J = 0.6$ Hz, 1H, H$_5''$), 3.82 (pseudo q, 2H, H$_1''$), 3.09 (dt, $J = 5.2$, 0.6
Hz, 2H, H2'). $^{13}$C NMR (126 MHz, CDCl₃) $\delta$ 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)thiazole-4-carboxamide (21Ho). Prepared according to general procedure E with thiazole-4-carboxylic acid. $^1$H NMR (400 MHz, DMSO) $\delta$ 9.31 (s, 1H), 8.52 (s, 1H), 8.14 (br. s, 1H), 7.95–8.10 (m, 2H), 7.30–7.42 (m, 4H), 6.94 (s, 1H), 3.81 (dt [app. q], $J_1 = J_2 = 6.2$ Hz, 2H), 3.21 (t, $J = 6.4$ Hz, 2H). LRMS (ESI+) $m/z$: 316 [M + H]⁺.

$N$-(2-(2-Phenylthiazol-4-yl)ethyl)pyrrolidine-1-carboxamide (23a). A solution of 1-pyrrolidinecarbonyl chloride (0.10 mL, 0.70 mmol) in dry DCM (5 mL) was added dropwise to a solution of 13 (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 23a as a yellow solid (0.201 g, 92%), mp = 101–103 °C. Rₚ 0.25 (3:7 EtOAc/hexanes). IR (cm⁻¹): 3355 (NH), 1629 (C=O). $^1$H NMR (500 MHz, CDCl₃) $\delta$ 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], $J_1 = J_2 = 6.1$ 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). $^{13}$C NMR (126 MHz, CDCl₃) $\delta$ 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.

\textit{N-(2-(2-Phenylthiazol-4-yl)ethyl)piperidine-1-carboxamide (23b)}. Prepared as described for 23a with 13 (0.472 g, 1.70 mmol) 1-piperidinecarbonyl chloride (0.15 mL, 1.1 mmol) to give 23b as a yellow solid (0.381 g, 71%), mp = 80–81 °C. R_{f} 0.2 (3:7 EtOAc/hexanes). IR (cm\(^{-1}\)): 1613 (C=O), 3335 (NH). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.88 (m, 2H, H\(_2'''/H6'''\)), 7.39 (m, 3H, H\(_3'''/H4'''/H5'''\)), 6.94 (s, 1H, H5''), 5.80 (br. s, 1H, NH), 3.56 (dt [app. q], \(J_1 = J_2 = 5.9\) Hz, 2H, H\(_1'\)), 3.31 (m, 4H, H2/H6), 2.97 (t, \(J_1 = 6.2\) Hz, 2H, H2'), 1.51 (m, 6H, H3/H4/H5). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 168.1 (C2''), 157.9 (C=O or C4''), 156.44 (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.

\textit{N-(2-(2-Phenylthiazol-4-yl)ethyl)morpholine-4-carboxamide (23c)}. Prepared as described for 23a with 13 (0.219 g, 0.790 mmol) 4-morpholinecarbonyl chloride (0.100 ml, 0.860 mmol) to give 23c as a white solid (0.120 g, 48%), mp = 98–100 °C. R_{f} = 0.3 (EtOAc). IR (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), 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\(_3\)) \(\delta\) 168.2 (C2''), 157.9 (C=O or C4''), 156.0 (C=O or C4''), 133.6 (C1''''), 130.2 (C4''''), 129.1 (2 \(\times\) ArH), 126.4 (2 \(\times\) 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.

**N-(2-(2-Phenylthiazol-4-yl)ethyl)benzenesulfonamide (25).** Benzenesulfonyl chloride (0.15 mL, 1.2 mmol) was added dropwise to a stirred solution of Hüning’s base (0.50 mL, 2.87 mmol) and 13 (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 25 as a yellow oil (0.039 g, 33%). IR (cm⁻¹): 3277 (NH), 1158 (S=O). ¹H NMR (500 MHz, CDCl₃) δ 7.83–7.89 (m, J = 7.5 Hz, 4H, 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, J₁ = 5.5 Hz, 1H, NH), 3.35 (dt [app.q], J₁ = J₂ = 6.5 Hz, 2H, H₁'), 2.91 (t, J = 6.5 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, C_{17}H_{17}N_{2}O_{2}S_{2}\ [M+H]^+ requires 345.0731.

**Pyrrolidine-1-sulfonyl chloride (26).** A solution of dry pyrrolidine (1.64 mL, 20.0 mmol) in dry Et₂O was added dropwise to a stirred solution of sulfuryl chloride (0.81 mL, 10 mmol) and NEt₃ (2.50 mL, 20 mmol) in ether (10 mL) at −10 °C under N₂. After 2 h the reaction mixture was diluted with dry Et₂O (5 mL) and vacuum-filtered through Celite. The filtrate was evaporated to give 26 as a colourless oil (0.186 g, 65%) of sufficient purity for the next step. ¹H NMR (CDCl₃, 400 MHz): δ 3.27 (m, 4H, H₂/5), 1.92 (m, 4H, H₃/4). ¹³C NMR (CDCl₃, 101 MHz): δ 65.5 (C₂/5), 25.1 (C₃/4).
\(N\)-(2-(2-Phenylthiazol-4-yl)ethyl)pyrrolidine-1-sulfonamide (27).\) A solution of 26 (0.186 g, 1.20 mmol), NEt\(_3\) (0.41 mL, 3.0 mmol) and 13 (0.121 g, 0.53 mmol) in DCM (1 mL) was stirred for 18 h. The reaction mixture was diluted with DCM (50 mL) and washed with 1 M HCl (20 mL), water (20 mL) and brine (20 mL), dried (MgSO\(_4\)) and evaporated to give a brown oil (0.22 g), which was subjected to flash chromatography. Elution with 1:19 MeOH/DCM gave the sulfamide 27 as a yellow oil (0.071 g, 41%). IR (cm\(^{-1}\)): 3250 (NH). \(^1\)H NMR (CDCl\(_3\), 400 MHz,): \(\delta\) 7.80–7.90 (m, 2H, H\(_2''''/H_6''''\)), 7.40–7.46 (m, 3H, H\(_3''''/H_4''''/H_5''''\)), 7.00 (s, 1H, H\(_5''\)), 5.30 (t, \(J = 5.6\) Hz, 1H, NH), 3.49 (dt [app. t], \(J_1 = J_2 = 6.1\) Hz, 2H, H\(_1''\)), 3.20–3.30 (m, 4H, H\(_2/5\)), 3.01–3.10 (t, \(J = 6.2\) Hz, 2H, H\(_2''\)), 1.80–1.90 (m, 4H, H\(_3/4\)). \(^{13}\)C NMR (CDCl\(_3\), 101 MHz): \(\delta\) 168.6 (C\(_2''\)), 154.9 (C\(_4''\)), 133.5 (C\(_1''''\)), 130.3 (C\(_4''''\)), 129.1 (2 \(\times\) ArH), 126.5 (2 \(\times\) ArH), 114.9 (C\(_5''\)), 48.1 (C\(_2/5\)), 43.0 (C\(_1''\)), 31.2 (C\(_2''\)), 25.7 (C\(_3/4\)).

\(N\)-(2-(2-Phenylthiazol-4-yl)ethyl)-1H-imidazole-1-carboxamide (28).\) 1,1-carbonyldiimidazole (0.396 g, 2.44 mmol) was added to a solution of 13 (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 \(\times\) 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 28 as an orange oil (0.438 g, 79%). \(R_t\) 0.15 (1:1 EtOAc/hexanes). IR (cm\(^{-1}\)): 3219 (NH), 1712 (C=O). \(^1\)H NMR (500 MHz, CDCl\(_3\)\): \(\delta\) 8.29 (br. t, \(J = 5.0\) Hz, 1H, NH), 8.14 (dd [app. t], \(J_1 = J_2 = 1.2\) Hz, 1H, H2), 7.79–7.83 (m, 2H, H2''''/H6''''), 7.40 (dd [app. t], \(J_1 = J_2 = 1.4\) 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], \(J_1 = J_2 = 6.0\) Hz, 2H, H1''), 3.04 (t, \(J = 6.5\) Hz, 2H,
H2'). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 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$_{15}$N$_4$OS$^+$ [M+H]$^+$ requires 299.0967.

**General procedure for the synthesis of carbamates from 28.**$^{68}$ NaH (60% dispersion in mineral oil, 1.1 equiv) was added to a stirred solution of alcohol (1.0 equiv) and 28 (1.0 equiv) in dry DMF (~5 mL/mmol of 28) under N$_2$. When TLC indicated the reaction to be complete (generally after overnight), the solvent was evaporated under N$_2$. Alternatively, the reaction mixture was diluted with water and extracted with EtOAc and the extract was dried and evaporated. The residue was purified by flash chromatography.

**Isopropyl (2-(2-phenylthiazol-4-yl)ethyl)carbamate (29a).** The general procedure was followed with 28 (0.320 g, 1.07 mmol) and isopropanol (0.08 mL, 1.1 mmol). Elution with 1:4 EtOAc/hexanes gave 29a as a white solid (0.099 g, 32%), mp = 55–57 °C. R$_f$ 0.3 (1:4 EtOAc/hexanes). IR (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''), 129.0 (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.
Cyclopentyl (2-(2-phenylthiazol-4-yl)ethyl)carbamate (29b). Following the general procedure with 28 (0.153 g, 0.513 mmol) and cyclopentanol gave the crude product as a brown oil (0.214 g), which was subjected to flash chromatography. Elution with 2:5 EtOAc/hexanes gave the 29b as a yellow oil, which solidified at –20 °C as a pale yellow solid (0.071 g, 44%), mp = 74–80 °C. Rf = 0.55 (1:1 EtOAc/hexanes). IR (cm⁻¹): 3350 (NH), 1689 (C=O). ¹H NMR (CDCl₃, 500 MHz): δ 7.93 (dd, J = 6.8, 1.3 Hz, 2H, H₂''/H₆''), 7.43 (m, 3H, H₃'''/H₄'''/H₅'''), 6.96 (s, 1H, H₅''), 5.16 (br. s, 1H, NH), 5.09 (br. app. s, OCH), 3.59 (m, 2H, C₁), 3.00 (t, J = 5.0 Hz, 2H, C₂), 1.78–1.88 (m, 2H), 1.68 (app. br. s, 4H, CH₂), 1.56 (m, 2H, CH₂). ¹³C NMR (CDCl₃, 126 MHz): δ 168.3 (C₂'), 156.7 (C=O or C₄'), 155.5 (C=O or C₄'), 133.7 (Ar), 130.1 (Ar), 129.1 (ArH), 126.6 (ArH), 114.5 (C₅'), 77.5 (HC–O), 40.4 (C₁), 32.9 (2 × CH₂), 31.8 (C₂), 23.8 (2 × CH₂). LRMS (ESI+) m/z: 317 [M + H]+.

Cyclopropylmethyl (2-(2-phenylthiazol-4-yl)ethyl)carbamate (29c). Following the general procedure with 28 (0.189 g, 0.634 mmol) and cyclopropanemethanol gave the crude product as a yellow gum (0.291 g), which was subjected to flash chromatography. Elution with 1:5 EtOAc/hexanes gave 29c as a yellow oil, which solidified at –20 °C as a yellow solid (0.105 g, 73%), mp = 40–44 °C. Rf = 0.55 (50% EtOAc/hexanes). IR (cm⁻¹): 3325 (NH), 1673 (C=O). ¹H NMR (CDCl₃, 500 MHz): δ 7.88–7.94 (m, 2H, H₂''/H₆''), 7.37–7.45 (m, 3H, H₃'''/H₄'''/H₅'''), 6.96 (s, 1H, H₅''), 5.24 (s, 1H, NH), 3.89 (d, J = 7.0 Hz, 2H, CH₂O), 3.61 (dt [app. q] J₁ = J₂ = 6.5 Hz, 2H, H₂), 3.01 (t, J = 6.5 Hz, 2H, OCH₂), 1.10 (br. s, 1H, cPr CH), 0.50–0.55 (m, 2H), 0.22–0.28 (m, 2H). ¹³C NMR (CDCl₃, 101 MHz): δ 168.3 (C₂'), 156.9 (C=O or C₄'), 155.5 (C=O or C₄'), 133.8 (Ar, C₁''), 130.2 (Ar, C₄''), 129.1 (ArH), 126.7 (ArH), 114.6 (C₅'), 69.8 (CH₂O), 40.5 (C₁), 31.8 (C₂), 10.3 (cPr CH), 3.3 (2 × cPr CH₂). LRMS (ESI+) m/z: 303 [M + H]+.
**General procedure for the synthesis of ureas from 28.** NEt₃ (1.1 equiv) and amine (1.0 equiv) were added to a stirred solution of 28 (1.0 equiv) in DCM (~5 mL/mmol of 28) under N₂. When TLC indicated the reaction to be complete (generally after overnight), the solvent was evaporated under N₂ and the residue was purified by flash chromatography.

**1-Isopropyl-3-(2-(2-phenylthiazol-4-yl)ethyl)urea (30a).** The general procedure was followed with 28 (0.120 g, 0.402 mmol) and isopropylamine (0.03 mL, 0.40 mmol). Elution with 1:4 EtOAc/hexanes gave 30a as a white solid, (0.064 g, 55%), mp = 139–140 °C. Rₚ 0.2 (1:1 EtOAc/hexanes). IR (cm⁻¹): 3313 (NH), 2966 (NH), 1622 (C=O). ¹H NMR (500 MHz, CDCl₃) δ 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, CH₃). ¹³C NMR (126 MHz, CDCl₃) δ 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 (CH₃). HRMS (ESI) m/z observed: 290.1318, C₁₅H₂₀N₃OS⁺ [M+H]⁺ requires: 290.1327.

**Isopropylmethylamine hydrochloride (N-methylpropan-2-aminium chloride).** Acetic acid (30.0 mL, 525 mmol) was slowly added to a stirred solution of methylamine (33% in ethanol, 20.5 mL, 165 mmol) and acetone (3.75 mL, 51.1 mmol) with powdered 3A sieves (4.74 g) at 0 °C under N₂. The mixture was allowed to warm to room temperature and stirring was continued for 30 min Sodium cyanoborohydride (3.32 g, 52.8 mmol) was added and the suspension was stirred at room temperature overnight. The reaction mixture was poured onto ice-cold 1 M HCl
(250 mL) and concentrated under N$_2$. MeOH was added to the resulting slurry and the suspension was filtered. The filtrate was evaporated to give a white slurry (18.2 g), which was suspended in hot CHCl$_3$, filtered and evaporated to give a brown gel (5.317 g) consisting of a mixture of the containing 55mol% isopropylmethylamine hydrochloride (67% yield) and 45mol% AcOH, which was used without further purification in the next step. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 9.3 (s, $^+\text{NH}_2 + \text{OH}$), 3.15–3.23 (m, $^1\text{H}$, CH), 2.54 (s, 3H, NMe), 1.92 (s, Ac), 1.33 (d, $J = 6.5$ Hz, 6H, $2 \times \text{Me}$) This compound has been described$^{91}$ previously but no NMR data have been reported.

1-Isopropyl-1-methyl-3-(2-(2-phenylthiazol-4-yl)ethyl)urea (30b). Following the general procedure with 28 (0.149 g, 0.499 mmol), methylisopropylamine hydrochloride (0.08 g, 0.5 mmol) and an extra two equivalents of NEt$_3$ to account for the hydrochloride gave the crude product as a brown slurry (0.319 g), which was subjected to flash chromatography. Elution with EtOAc gave 30b as a yellow oil (0.102 g, 67%), which solidified to an off-white solid at –20 °C, mp = 96–102 °C. $R_f$ = 0.15 (1:1 EtOAc/hexanes). IR (cm$^{-1}$): 3325 (NH), 1612 (C=O). $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.90–7.94 (m, 2H, H$_2''$/H$_6''$), 7.40–7.45 (m, 3H, H$_3''$/H$_4''$/H$_4'$), 6.97 (s, 1H, H$_5'$), 5.51 (br. s, 1H, NH), 4.48 (sept., $J = 6.5$ Hz, 1H, CHN), 3.62 (dt [app. q], $J_1 = J_2 = 5.5$ Hz, 2H, H1), 3.01 (t, $J = 6.0$ Hz, 2H, H2), 2.69 (s, 3H, NCH$_3$), 1.07 (d, $J = 7.0$ Hz, 6H, $2 \times \text{CH}_3$).

$^{13}$C NMR (CDCl$_3$, 126 MHz): $\delta$ 168.2 (C2'), 158.1 (C=O or C4'), 156.5 (C=O or C4'), 133.7 (C1''), 130.1 (C4''), 129.0 (2 × ArH), 126.4 (2 × ArH), 114.4 (C5'), 45.2 (NCH), 40.7 (C1), 31.6 (C2), 26.8 (NCH$_3$), 20.1 (2 × CH$_3$). HRMS (ESI) $m/z$ observed: 342.1049, C$_{16}$H$_{21}$KN$_3$OS$^+$ [M+K]$^+$ requires: 342.1037.
1,1-Diethyl-3-(2-(2-phenylthiazol-4-yl)ethyl)urea (30c). The general procedure was followed with 28 (0.120 g, 0.402 mmol) and diethylamine (0.04 mL, 0.40 mmol). Elution with 1:1 EtOAc/hexanes gave 30c as a yellow oil (0.081 g, 66%). Rf 0.35 (1:1 EtOAc/hexanes). IR (cm⁻¹): 3354 (NH), 1622 (C=O). ¹H NMR (500 MHz, CDCl₃) δ 7.89–7.91 (m, 2H, H2"/H6"), 7.39–7.43 (m, 3H, H3"/H4"/H5"), 6.96 (s, 1H, H5'), 5.46 (br. unresolved t, 1H, NH), 3.60 (dt [app. q], J₁ = J₂ = 6.8 Hz, 2H, H1), 3.23 (q, J = 7.0 Hz, 4H, 2 × CH₂), 3.00 (t, J = 6.2 Hz, 2H, H2), 1.08 (t, J = 7.0 Hz, 6H, CH₃). ¹³C NMR (126 MHz, CDCl₃) δ 168.2 (C2'), 157.5 (C=O or C4'), 156.5 (C=O or C4'), 133.7 (C1''), 130.1 (C4''), 129.0 (2 × ArH), 126.5 (2 × ArH), 114.4 (C5'), 41.2 (HC–N), 40.6 (C1), 31.6 (C2), 13.9 (CH₃). HRMS (ESI) m/z observed: 304.1494, C₁₆H₂₂N₃OS⁺ [M+H]⁺ requires 304.1484.

1,1-Diisopropyl-3-(2-(2-phenylthiazol-4-yl)ethyl)urea (30d). Following the general procedure with 28 (0.195g, 0.654) and diisopropylamine gave the crude product as a brown oil (0.242 g), which was subjected to flash chromatography. Elution with 2:5 EtOAc/hexanes gave 30d as off-white rhomboids (0.119 g, 55%), mp = 100–104 °C. Rf = 0.3 (1:1 EtOAc/hexanes). IR cm⁻¹: 3391 (NH), 1630 (CO).¹H NMR (CDCl₃, 500 MHz): δ 7.94–7.92 (m, 2H, H2"/H6"), 7.42 (m, 3H, H3"/H4"/H5"), 6.98 (s, 1H, H5'), 5.21 (s, 1H, NH), 3.88–3.85 (sept., J = 7.0 Hz, 2H, NCH), 3.64 (dt [apparent q], J₁ = J₂ = 6.0 Hz, 2H, H1), 3.03 (dt, J = 6.3, 0.7 Hz, 2H, H2), 1.20 (d, J = 7.0 Hz, 12H, CH₃). ¹³C NMR (CDCl₃, 126 MHz): δ 168.2 (C2'), 157.3 (C=O or C4'), 156.6 (C=O or C4'), 133.7 (C1''), 130.0 (C4''), 128.9 (2 × ArH) 126.5 (2 × ArH), 114.4 (C5'), 45.0 (NCH), 40.3 (C1), 31.5 (C2), 21.3 (CH₃). HRMS (ESI) m/z observed: 332.1771, C₁₈H₂₆N₃OS⁺ [M+H]⁺ requires: 332.1792.
\(N\)-(2-(2-Phenylthiazol-4-yl)ethyl)azepane-1-carboxamide (30e).\) The general procedure was followed with 28 (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 30e as a yellow oil (0.120 g, 68%). Rf 0.35 (1:1 EtOAc/hexanes). IR (cm\(^{-1}\)): 2931 (NH), 1627 (C=O). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.88–7.91 (m, 2H, H2''/H6''), 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). \(^13\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 168.2 (C2''), 158.0 (C=O or C4''), 156.4 (C=O or C4''), 133.7 (C1'''), 130.1 (C4'''), 129.0 (2 \(\times\) ArH), 126.4 (2 \(\times\) 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, \(C_{18}H_{24}N_3OS^+\) [M+H]\(^+\) requires: 330.1640.

\(N\)-(2-(2-Phenylthiazol-4-yl)ethyl)-1\(H\)-pyrrole-1-carboxamide (30f).\) NaH (60% suspension in mineral oil, 0.013 g, 0.28 mmol) was added to a stirred solution of 28 (0.077 g, 0.25 mmol) and pyrrole (distilled immediately before use, 0.02 mL, 0.3 mmol) in dry DMF (2 mL) at room temperature under N\(_2\). The reaction mixture was stirred for 7 d then the solvent removed to give a brown gum (0.095 g), which was subjected to flash chromatography. Elution with 1:4 EtOAc/hexanes gave the urea 30i as an off-white powder (0.033 g, 44%). Rf = 0.5 (1:1 EtOAc/hexanes). IR (cm\(^{-1}\)): 3335 (NH), 1670 (C=O). \(^1\)H NMR (CDCl\(_3\), 600 MHz): \(\delta\) 7.92–7.96 (m, 2H, H2''/H6''), 7.45–7.48 (m, 3H, H3''/H4''/H5''), 7.34 (br. s, 1H, NH), 7.27 (dd [app. t], \(J_1 = J_2 = 1.2\) Hz, 2H, H2/H5), 7.03 (s, 1H, H5''), 6.26 (dd [app. t], \(J_1 = J_2 = 2.0\) Hz, 2H, H3/H4), 3.79 (pseudo q, 2H, H1'), 3.10 (t, \(J = 6.0\) Hz, 2H, H2'). \(^13\)C NMR (CDCl\(_3\), 151 MHz): \(\delta\) 168.8 (C2''), 155.4 (C=O or C4''), 151.0 (C=O or C4''), 133.3 (C1'''), 130.3 (C4''), 129.1 (2 \(\times\) ArH), 126.5 (2 \(\times\) ArH), 124.3 (2 \(\times\) ArH), 113.6 (C3/C6). HRMS (ESI) \(m/z\) observed: 330.1635, \(C_{18}H_{24}N_3OS^+\) [M+H]\(^+\) requires: 330.1640.
4-(Chloromethyl)-2-(pyridin-2-yl)thiazole (32). 2-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 32 as orange crystals (2.51 g, 33%), mp = 90–92 °C, pure enough for the following step. Rr 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, J₁ = 6.8 Hz, 7.6 Hz, 1H, H4'), 7.33 (dd, J₁ = 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 (33). A solution of KCN (0.839 g, 12.9 mmol) and 32 (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 33 as a green oil (1.77 g, 74%), mp = 66–68 °C. Rr 0.3 (1:20:80 NEt₃/EtOAc/hexanes). IR (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 (ddd [app. dt], J₁ = J₂ = 8.0 Hz, J₃ = 1.6 Hz, 1H, H4"), 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 (34). A 1 M BH₃−THF solution (40 mL, 40 mmol) was slowly added to a stirred solution of 33 (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 34 as a brown oil, (0.382 g, 25%), which was used without further purification or characterization in the next steps.

N-(2-(2-(Pyridin-2-yl)thiazol-4-yl)ethyl)benzamide (35a). Following general procedure (A) with benzoyl chloride gave a brown oil, which was subjected to flash chromatography. Elution with 1:20:80 NEt₃/EtOAc/hexanes gave benzamide 35a as a yellow solid (0.148 g, 84%), mp = 103−105 °C. Rₜ 0.4 (1:50:50 NEt₃/EtOAc/Hexanes). IR (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, J = 8.0 Hz, 1H, H₃'''), 7.80 (d, J = 7.2 Hz, 2H, H₂/H₆), 7.78 (dd, J = 7.6, 1.6 Hz, 1H, H₄''), 7.50 (t, J = 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, J = 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, C_{17}H_{15}N_{3}NaOS^+ [M+Na]^+ requires 332.0828.

\( N-(2-(2-(\text{Pyridin-2-yl})\text{thiazol-4-yl})\text{ethyl})\text{cyclopentanecarboxamide (35b)} \). Following general procedure (A) with cyclopentanecarbonyl chloride gave a brown oil, which was subjected to flash chromatography. Elution with 1:20:80 NEt_3/EtOAc/hexanes then 1:50:50 NEt_3/EtOAc/hexanes gave 35b as a white solid (0.091 g, 59%), mp = 133–135 °C. Rf 0.35 (1:50:50 NEt_3/EtOAc/hexanes). IR (cm\(^{-1}\)): 3294 (NH), 1639 (C=O). ¹H NMR (500 MHz, CDCl_3): \( \delta \) 8.60 (d, \( J = 4.6 \) Hz, 1H, H6”), 8.12 (d, \( J = 8.0 \) Hz, 1H, H3”), 7.78 (ddd [app. dt], \( J_1 = J_2 = 7.8 \) Hz, \( J_2 = 1.8 \) Hz, 1H, H4”), 7.31–7.34 (m, 1H, H5”), 7.07 (s, 1H, NH), 3.65 (dt [app. q], \( J_1 = J_2 = 6.2 \) Hz, 2H, H1’), 3.01 (t, \( J = 6.4 \) Hz, 2H, H2’), 2.48–2.54 (m, 1H, H1), 1.69–1.88 (m, 6H), 1.51–1.60 (m, 2H). ¹³C NMR (126 MHz, CDCl_3): \( \delta \) 176.3 (C=O), 169.1 (C2”), 156.1 (C2” or C4”), 151.4 (C2” or C4”), 149.7 (C6”), 137.1 (CH), 124.6 (CH), 119.6 (CH), 117.2 (CH), 46.1 (C1), 39.0 (C1’), 31.3 (C2’), 30.5 (C2/C5), 26.0 (C3/C4). HRMS (ESI) m/z observed: 324.1128, C_{16}H_{19}N_{3}NaOS requires 324.1141.

\( N-(2-(2-(\text{Pyridin-3-yl})\text{thiazol-4-yl})\text{ethyl})\text{benzamide (35c)} \). A solution of benzoyl chloride (0.10 mL, 0.86 mmol) in DCM (10 mL) was added to a stirred solution of 47a (0.240, 0.863 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 1:60:40 NEt_3/EtOAc/hexanes then 1:99 NEt_3/EtOAc yielded 35c as a yellow oil (0.237 g, 89%). Rr 0.5 (1:50:50 NEt_3/EtOAc/hexanes). IR (cm\(^{-1}\)): 3237 (NH), 1645 (C=O). ¹H NMR (500 MHz, CDCl_3): \( \delta \) 9.17 (d, \( J = 2.0 \) Hz, 1H, H2”), 8.60 (dd, \( J = 4.8 \), 1.4 Hz, 1H, H6”), 8.15 (ddd [app. dt], \( J_1 = J_2 = 8.0 \) Hz,
$J_3 = 2.0$ Hz, 1H, H4''), 7.80 (d, $J = 7.0$ Hz, 2H, H2/H6), 7.48 (dd [app. t], $J_1 = J_2 = 7.4$ 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], $J_1 = J_2 = 6.2$ Hz, 2H, H1'), 3.14 (t, $J = 6.2$ Hz, 2H, H2'). $^{13}$C NMR (126 MHz, CDCl3): $\delta$ 167.6 (C2'' or 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, C17H15N3NaOS$^+$ [free base + Na]$^+$ requires 332.0828.

$N$-(2-(2-(Pyridin-3-yl)thiazol-4-yl)ethyl)cyclopentanecarboxamide (35d). A solution of cyclopentanecarbonyl chloride (0.036 mL, 0.300 mmol) in DCM (5 mL) was added to a stirred solution of 47a (0.090 g, 0.324 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 1:20:80 NEt3/EtOAc/hexanes then 1:50:50 NEt3/EtOAc/hexanes yielded 35d as white crystals (0.050 g, 51%), mp = 109–111 °C. Rf 0.25 (1:99 NEt3/EtOAc). IR (cm$^{-1}$): 3244 (NH), 1637 (C=O). $^1$H NMR (500 MHz, CDCl3): $\delta$ 9.16 (d, $J = 1.8$ Hz, 1H, H2''), 8.66 (dd, $J = 4.8$, 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''), 6.18 (br. s, 1H, NH), 3.66 (dt [app.q], $J_1 = J_2 = 6.4$ Hz, 2H, H1'), 3.03 (t, $J = 6.4$ 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, CDCl3): $\delta$ 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, C16H19N3NaOS$^+$ [M+Na]$^+$ requires 324.1141.
**N-(2-(2-(Pyridin-4-yl)thiazol-4-yl)ethyl)benzamide (35e).** A solution of benzoyl chloride (0.060 mL, 0.52 mmol) in DCM (5 mL) was added to a stirred solution of 47b (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 35e as white crystals (0.122 g, 66%), mp = 67–70 °C. IR (cm⁻¹): 3438 (NH), 1634 (C=O). ¹H NMR (500 MHz, CDCl₃): δ 8.69 (d, J = 4.8 Hz, 2H, H₂''/H₆''), 7.78–7.81 (m, 4H, H₂/H₆/H₃''/H₅''), 7.50 (t, J = 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 = J₂ = 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, C₁₇H₁₅N₃NaOS⁺ [M+Na]⁺ requires 332.0828.

**N-(2-(2-(Pyridin-4-yl)thiazol-4-yl)ethyl)cyclopentanecarboxamide (35f).** A solution of cyclopentanecarbonyl chloride (0.121 mL, 1.00 mmol) in DCM (5 mL) was added to a stirred solution of 47b (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 35f as a white solid (0.136 g, 50%), mp = 110–112 °C. Rₚ 0.3 (1:50:50 NEt₃/EtOAc/hexanes). IR (cm⁻¹): 3241 (NH), 1600 (C=O). ¹H NMR (500 MHz, CDCl₃): δ 8.71 (d, J = 5.6 Hz, 2H, H₂''/H₆''), 7.79 (d, J = 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
Methyl 3-(2-(pyridin-3-yl)thiazol-4-yl)propanoate (42a). A stirred solution of methyl 5-bromo-4-oxopentanoate (40) (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 42a as a colourless oil (0.787 g, 22%). Rf 0.6 (1:50:50 NEt3/EtOAc/hexanes). IR (cm⁻¹): 1727 (C=O). ¹H NMR (500 MHz, CDCl₃): δ 9.10 (s, 1H, H₂''), 8.60 (d, J = 4.3 Hz, 1H, H₆''), 8.17 (dt, J = 8.0, 1.6 Hz, 1H, H₄''), 7.33 (dd, J = 8.0, 4.9 Hz, 1H, H₅''), 7.00 (s, 1H, H₅''), 3.66 (s, 3H, CH₃), 3.13 (t, J = 7.5 Hz, 2H, H₃), 2.79 (t, J = 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 (42b). 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 42b as an orange solid (0.907 g, 59%), mp = 55–57 °C. Rf 0.4 (1:1 EtOAc/hexanes). ¹H NMR (500 MHz, CDCl₃): δ 8.68 (d, J = 6.0 Hz, 2H, H₂''/H₆''), 7.78 (d, J = 6.0 Hz, 2H, H₃''/H₅''), 7.09 (s, 1H, H₅''), 3.69 (s, 3H, CH₃), 3.16 (t, J = 7.4 Hz, 2H, H₃), 2.82 (t, J = 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 (42c).** 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 42c as a pale-pink solid (0.997 g, 48%), mp = 55–57 °C. Rf 0.5 (1:4 EtOAc/Hexanes). IR (cm⁻¹): 1726 (C=O). 1H NMR (500 MHz, CDCl3): δ 7.47 (d, J = 3.6 Hz, 1H, H3''), 7.36 (d, J = 5.0 Hz, 1H, H5''), 7.06 (pseudo t, 1H, H4''), 6.86 (s, 1H, H5'), 3.69 (s, 3H, CH3), 3.10 (t, J = 7.5 Hz, 2H, H3), 2.78 (t, J = 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 (43a).** A solution of 42a (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 43a as a yellow/brown solid (0.300 g, 40%), mp = 147–149 °C. Rf 0.2 (EtOAc). IR (cm⁻¹): 3375 (NH), 3113 (NH), 1663 (C=O). 1H NMR (500 MHz, MeOD): δ 9.90 (d, J = 1.8 Hz, 1H, H2''), 9.45 (dd, J = 4.8, 1.4 Hz, 1H, H6''), 9.07 (ddd [app. dt], J₁ = 8.0 Hz, J₂ = J₃ = 1.8 Hz, 1H, H4''), 8.33 (dd, J = 7.8, 4.8 Hz, 1H, H5''), 8.23 (s, 1H, H5'), 8.17 (br s, 1H, NH), 7.62 (br s, 1H, NH), 7.39 (t, J = 7.9 Hz, 2H, H3), 3.32 (t, 2H, H2). HRMS (ESI) m/z observed: 256.0509, C11H11N3NaOS+ [M+Na]+ requires 256.0515.
3-(2-(Pyridin-4-yl)thiazol-4-yl)propanamide (43b). A solution of 42b (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 43b as a pale-yellow solid (0.202 g, 72%), mp = 161-163 °C. Rf 0.7 (1:1:98 NEt₃/MeOH/EtOAc). IR (cm⁻¹): 3244 (NH), 3109 (NH), 1682 (C=O). ¹H NMR (500 MHz, DMSO): δ 8.69 (d, J = 6.0 Hz, 2H, H₂''/H₆''), 7.86 (d, J = 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 = 7.6 Hz, 2H, H₃), (H₂ largely obscured by d₆-DMSO peak). ¹³C 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, C₁₁H₁₁N₃NaOS⁺ [M+Na]⁺ requires 256.0515.

3-(2-(Thiophen-2-yl)thiazol-4-yl)propanamide (43c). A solution of 42c (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 NEt₃/EtOAc/hexanes, then 1:1:98 NEt₃/MeOH/EtOAc gave 43c as a white solid (0.338 g, 36%), mp = 103–105 °C. Rf 0.3 (1:99 MeOH/EtOAc). IR (cm⁻¹): 3374 (NH), 3171 (NH), 1664 (C=O). ¹H NMR (500 MHz, DMSO): δ 7.68 (d, J = 5.1 Hz, 1H, H₅''), 7.61 (d, J = 3.0 Hz, 1H, H₃''), 7.38 (br. s, 1H, NH), 7.24 (s, 1H, NH), 6.82 (br s, 1H, NH), 2.91 (t, J = 7.7 Hz, 2H, H₃), 2.46 (t, J = 7.7 Hz, 2H, H₂. ¹³C NMR (126 MHz, CDCl₃): δ 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, C₁₀H₁₀N₂NaOS₂⁺ [M+Na]⁺ requires 261.0127.
2-(2-(Thiophen-2-yl)thiazol-4-yl)ethanamine (44). Diacetoxyiodobenzene (0.664 g, 2.00 mmol) was added to a solution of 43c (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 44 as a brown oil of sufficient purity for the following step (0.247 g, 85%). Rf 0.35 (1:99 MeOH/EtOAc). IR (cm⁻¹): 3374 (NH), 3171 (NH), 1663 (C=O). ¹H NMR (500 MHz, MeOD): δ 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 = 4.8, 4.0 Hz, H4''), 5.15 (br. s, 2H, NH), 3.36 (t, J = 5.8 Hz, 2H, H1), 3.16 (t, J = 5.8 Hz, 2H, H2). ¹³C NMR (126 MHz, MeOD): δ 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, C₉H₁₁N₂S₂⁺ [M+H]⁺ requires 211.0358.

N-(2-(2-(Thiophen-2-yl)thiazol-4-yl)ethyl)benzamide (45a). A solution of benzoyl chloride (0.040 mL, 0.64 mmol) in DCM (2 mL) was added to a stirred solution of 44 (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 45a as a brown oil (0.067 g, 41%). Rf 0.3 (1:30:70 NEt₃/EtOAc/hexanes). IR (cm⁻¹): 3337 (NH), 1640 (C=O). ¹H NMR (500 MHz, CDCl₃): δ 7.89 (d, J = 7.4 Hz, 2H, H2/H6), 7.69 (br s, 1H, NH), 7.50 (d, J = 3.2 Hz, 1H, H3'''), 7.48 (d, J = 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 (C4), 128.6 (2 × ArH), 128.1 (CH), 127.8 (CH),
127.2 (2 × ArH), 126.9 (CH), 113.9 (C5''), 39.6 (C1'), 30.6 (C2'). HRMS (ESI) m/z observed: 337.0432, C_{16}H_{14}N_{2}NaOS^+ [M+Na]^+ requires 337.0440.

N-(2-(2-(Thiophen-2-yl)thiazol-4-yl)ethyl)cyclopentanecarboxamide (45b). A solution of cyclopentanecarbonyl chloride (0.110 mL, 0.900 mmol) in DCM (5 mL) was added to a stirred solution of 44 (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 45b as colourless prisms (0.095 g, 34%), mp = 105−107 °C. Rf 0.3 (1:20:80 NEt₃/EtOAc/hexanes). IR (cm⁻¹): 3294 (NH), 1638 (C=O). ¹H NMR (500 MHz, CDCl₃): δ 7.49 (dd, J = 3.8, 1.0 Hz, 1H, H3''), 7.40 (dd, J = 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], J = 6.0 Hz, 2H, H1'), 2.96 (t, J = 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, C_{15}H_{18}N_{2}NaOS^+ [M+Na]^+ requires 329.0753.

Methyl (2-(2-(pyridin-3-yl)thiazol-4-yl)ethyl)carbamate (46a). A solution of diacetoxyiodobenzene (0.537 g, 1.62 mmol) and 43a (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 46a as a clear oil (0.200 g, 59%). Rf 0.2 (1:99 NEt₃/EtOAc). IR (cm⁻¹): 3205 (NH), 1702 (C=O). ¹H NMR (500 MHz, CDCl₃): δ 9.07 (d, J = 1.7 Hz, 1H, H2''), 8.58 (dd, J = 4.8, 1.3 Hz, 1H, H6''), 8.14 (d, J = 7.9 Hz, 1H H4''),
7.32 (dd, $J = 7.9, 4.9$ Hz, 1H, H5”), 7.01 (s, 1H, H5”), 5.49 (br. s, 1H, NH), 3.62 (s, 3H, CH3), 3.57 (dt [app. q], $J_1 = J_2 = 6.2$ Hz, 2H, H3), 2.98 (t, $J = 6.3$ Hz, 2H, H2). $^{13}$C 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.

**Methyl (2-(2-(pyridin-4-yl)thiazol-4-yl)ethyl)carbamate (46b).** A mixture of diacetoxyiodobenzene (0.343 g, 1.03 mmol) and 43b (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 46b as a white solid (0.159 g, 70%), mp 91−93 °C. Rf 0.6 (1:50:50 NEt3/EtOAc/hexanes). IR (cm$^{-1}$): 3205 (NH), 1701 (C=O). $^1$H NMR (500 MHz, CDCl3): δ 8.65 (d, $J = 6.0$ Hz, 2H, H2”/H6”), 7.74 (d, $J = 5.9$ 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], $J_1 = J_2 = 6.0$ Hz, 2H, H1), 3.01 (t, $J = 6.3$ Hz, 2H, H2). $^{13}$C 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

**2-(2-(Pyridin-3-yl)thiazol-4-yl)ethanamine dihydrochloride (47a).** A stirred solution of 46a (0.200 g, 0.751 mmol) in 4 M HCl (10 mL) was heated under reflux overnight. The solvent was evaporated to yield 47a as a colourless oil (0.209 g, quant.). IR (cm$^{-1}$): 3366 (NH), 3030 (NH). $^1$H NMR (500 MHz, MeOD): δ 9.52 (s, 1H, H2”), 9.16 (d, $J = 7.8$ Hz, 1H, H6”), 8.99 (d, $J = 5.0$ Hz, 1H, H4”), 8.28 (dd [app. t], $J_1 = J_2 = 6.4$ Hz, 1H, H5”), 7.33 (s, 1H, H5’), 3.39 (t, $J_1 = 6.2$ Hz, 2H,
H1), 3.24 (t, \(J = 6.4\) Hz, 2H, H2). \(^{13}\)C NMR (126 MHz, MeOD): \(\delta \) 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, \(C_{10}H_{12}N_{3}S^{+}\) [free base + H]\(^+\) requires 206.0746.

2-(2-(Pyridin-4-yl)thiazol-4-yl)ethanaminium chloride (47b). A stirred solution of 46b (0.600 g, 2.25 mmol) in 4 M HCl (15 mL) was heated under reflux overnight. The solvent was evaporated to yield 47b as yellow crystals (0.627 g, quant.), mp = 147−150 °C. Rf 0.4 (1:99 MeOH/EtOAc). IR (cm\(^{-1}\)): 3390 (NH). \(^1\)H NMR (500 MHz, DMSO): \(\delta \) 8.88 (s, 2H, H2''/H6''), 8.22 (s, 2H, H3''/H5''), 7.88 (s, 1H, H5'), 3.22 (pseudo q, 2H, H1), 3.15 (t, 2H, \(J = 7.0\) Hz, H2). \(^{13}\)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, \(C_{10}H_{12}N_{3}S^{+}\) [free base + H]\(^+\) requires 206.0746.

2-Amino-4-(chloromethyl)thiazol-3-i um chloride (49). 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 49 as a white solid (13.6 g, 81 %). \(^1\)H NMR (500 MHz, DMSO) \(\delta \) 9.13 (v. br. s, 2H, NH2), 6.96 (s, 1H, H5'), 4.66 (d, \(J = 0.5\) Hz, 2H, H2), (thiazole NH not observed/obscured by/exchanging with H2O). The \(^1\)H NMR data match those published (although the wrong isomer is reported in that paper).\(^{92}\)

2-(2-Bromothiazol-4-yl)acetonitrile (51). NaNO\(_2\) (0.250 g, 3.67 mmol) was added to a solution of 49 (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 (50). 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 51 as a brown oil (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.

2-(2-Aminothiazol-4-yl)acetonitrile (54). KCN (7.56 g, 116 mmol) was added to a stirred solution of 49 (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 54 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, H2).

2-(2-(2-Aminothiazol-4-yl)ethyl)isoindoline-1,3-dione hydrobromide (56). Thiourea (1.2 g, 17 mmol) was added to a stirred solution of 5 (5.50 g, 18.6 mmol) in MeOH (100 mL). The solution was heated under reflux for 7 h, then cooled. The resulting suspension was filtered and the precipitate was washed with EtOAc (3 × 50 mL) to give 56 as a pale-brown solid (4.52 g, 89%).
$^1$H NMR (500 MHz, DMSO) $\delta$ 9.01 (br. s, 2H, NH$_2$), 7.82–7.87 (m, 4H, 4 × ArH), 6.57 (s, 1H, H5'), 3.84 (t, 2H, $J = 6.3$ Hz, H1), 2.83 (t, $J = 6.3$ Hz, 2H, H2). The imidazolium NH was not observed.

2-(3-Oxo-4-thiocyanatobutyl)isoindoline-1,3-dione (57). A solution of KSCN (1.89 g, 19.5 mmol) in dry acetone (20 mL) was added to a stirred solution of 5 (4.8 g, 16 mmol) in dry acetone (100 mL) under N$_2$. The solution was allowed to stir for 2 h, then filtered (to remove precipitated KBr) and the filtrate was evaporated. The resulting yellow solid was partitioned between H$_2$O and EtOAc and the organic layer was dried (Na$_2$SO$_4$) and evaporated. The resulting yellow oil (5.2 g) was purified by flash chromatography. Elution with cyclohexane/EtOAc 8:2 to 6:4) afforded 57 as a yellow solid (3.4 g, 76%). $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.85–7.87 (m, 2H, Ar), 7.73–7.75 (m, 2H, Ar), 4.09 (s, 2H, CH$_2$S), 4.04 (t, $J = 6.8$ Hz, 2H, CH$_2$N), 3.04 (t, $J = 7.1$ Hz, 2H, CH$_2$CO). $^{13}$C NMR spectrum (CDCl$_3$, 101 MHz): $\delta$ 198.5 (CO), 168.0 (2 × CO), 134.2 (2 × ArH), 131.8 (2 × Ar), 123.5 (2 × ArH), 111.0 (CN), 43.5 (CH$_2$S), 39.6 (CH$_2$N), 32.7 (CH$_2$). LCMS (ESI) $m/z$: 275 [M+H]$^+$. 

2-(2-(2-Bromothiazol-4-yl)ethyl)isoindoline-1,3-dione (58). A mixture of 33% HBr in acetic acid (30 mL), 57 (3.4 g, 12 mmol) and DCM (50 mL) was stirred for 24 h. Water (50 mL) was added and the mixture was extracted with EtOAc (3 × 40 mL). The extract was washed with water (2 × 50 mL) and brine (2 × 50 mL), dried (Na$_2$SO$_4$) and evaporated to afford 58 as yellow solid (3.6 g, 86%). $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.83–7.87 (m, 2H, ArH), 7.71–7.73 (m, 2H, ArH), 6.97 (s, 1H, CH) 4.04 (t, $J = 7.1$ Hz, 2H, CH$_2$N), 3.16 (t, $J = 7.1$ Hz, 2H, CH$_2$). $^{13}$C NMR (CDCl$_3$,
101 MHz): δ 168.1 (2 × CO), 153.8 (C4"), 135.5 (C2"), 133.9 (2 × ArH), 132.0 (2 × Ar), 123.3 (2 × ArH), 118.4 (C5"), 37.2 (C1'), 30.2 (C2'). LCMS (ESI) m/z: 337 [M+H]^+.

2-(2-(2-(2-Fluorophenyl)thiazol-4-yl)ethyl)isoindoline-1,3-dione (59a). N₂ was bubbled through a stirred mixture of 58 (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 59a as a yellow crystalline solid (0.200 g, 31%), mp = 149−151 °C. IR (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, J = 7.0 Hz, 2H, H1'), 3.25 (dt, J = 7.0, 0.8 Hz, 2H, H2'). ¹³C NMR (126 MHz, CDCl₃): δ 168.4 (C=O), 160.3 (d, J = 4 Hz, C2'”), 160.0 (d, J = 202 Hz, CF), 153.2 (C4'’), 134.0 (C4/C7), 132.4, (C3a/C7a), 130.9 (d, J = 7 Hz, ArH), 128.8 (d, J = 2 Hz, ArH), 124.5 (d, J = 3 Hz, ArH), 123.4 (C5/C6), 121.5 (d, J = 9 Hz, C1'”), 116.3 (d, J = 7 Hz, C5'”), 116.1 (d, J = 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)isoindoline-1,3-dione (59b). Prepared as described for 59a with 58 (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 59b as an orange solid (0.040 g, 18%), mp = 101–102 °C. IR (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, 1.6, 1.0 Hz, 1H, H₆′′), 7.42 (ddd, J₁ = 9.8 Hz, J₂ = 2.6 Hz, J₅ = 1.6 Hz, 1H, H₂′′′), 7.30 (ddd [app.dt], J₁ = J₂ = 8.0 Hz, J₃ = 5.8 Hz, 1H, H₅′′′), 7.04 (ddd [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, J = 2 Hz, C₂″′), 163.1 (d, J = 198 Hz, CF), 154.7 (C₄″′), 135.7 (d, J = 7 Hz, C₁″′), 134.0 (C₅/C₆), 132.3 (C₃a/C₇a), 130.5 (d, J = 7 Hz, C₅″′), 123.4 (C₄/C₇), 122.3 (d, J = 2 Hz, C₆″′), 116.7 (d, J = 17 Hz, C₂″″ or C₄″″), 115.3 (C₅″″), 113.3 (d, J = 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 (59c). Prepared as described for 59a with 58 (0.500 g, 1.48 mmol) and 4-fluorophenylboronic acid (0.300 g, 2.14 mmol). Elution with 1:9 EtOAc/hexanes gave 59c as a yellow solid (0.260 g, 50%), mp = 120–122 °C. IR (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, J = 201 Hz, C₄″′), 154.3 (C₄″′), 133.9 (C₅/C₆), 132.2 (C₃a/C₇a), 130.0 (d, J = 3 Hz, C₁″′), 128.3 (d, J = 7 Hz, C₂″′/C₆″′), 123.2 (C₄/C₇), 115.8 (d, J = 18 Hz, C₃″″/C₅″″), 114.6 (C₅″″), 37.6 (C₁′), 29.9 (C₂′). HRMS (ESI) m/z observed: 353.0716, C₁₉H₁₄N₂O₂SF⁺ [M+H]⁺ requires 353.0760.
2-(2-(2-(2,4-Difluorophenyl)thiazol-4-yl)ethyl)isoindoline-1,3-dione (59d). Prepared as described for 59a with 58 (0.220 g, 0.650 mmol) and 2,4-difluorophenylboronic acid (0.200 g, 1.23 mmol). Elution with 1:9 EtOAc/hexanes gave 59d as a white, crystalline solid (0.168 g, 70%), mp = 168−170 °C. IR (cm$^{-1}$): 1769 (C=O), 1704 (C=O). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.01 (m [pseudo q], 1H, H6''), 7.80–7.81 (m, 2H, H4/H7), 7.68–7.70 (m, 2H, H5/H6), 7.09 (s, 1H, H5''), 6.82–6.90 (m, 2H, H3'''/H5'''), 4.10 (t, $J_1 = 7.0$ Hz, H1''), 3.23 (t, $J_1 = 7.0$ Hz, 2H, H2'); $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 168.3 (C=O), 163.3 (dd, $J = 203$, 10 Hz, CF), 160.0 (dd, $J = 204$, 10 Hz, CF), 161.0 (d, $J = 10$ Hz, C2''), 159.3 (d, $J = 4$ Hz, C4''), 134.0 (C5/C6), 132.3 (C3a/C7a), 129.9 (dd, $J = 8$, 3 Hz, C6''), 123.3 (C4/C7), 118.0 (dd, $J = 9$, 3 Hz, C1'''), 115.8 (d, $J = 7$ Hz, C5'''), 112.0 (dd, $J = 17$, 3 Hz, C5'''), 104.2 (dd [app. t], $J_1 = J_2 = 21$ Hz, C3'''), 37.6 (C1'), 29.8 (C2'). HRMS (ESI) $m/z$ observed: 371.0648, C$_{19}$H$_{13}$N$_2$O$_2$F$_2$S$^+$ [M+H]$^+$ requires 371.0666.

$N$-(2-(2-(2-Fluorophenyl)thiazol-4-yl)ethyl)-1H-imidazole-1-carboxamide (60a). A stirred solution of hydrazine hydrate (2.5 mL) and 59a (0.200 g, 0.568 mmol) in MeOH (20 mL) under N$_2$ 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 60a as a yellow oil, (0.700 g, 39%). IR (cm$^{-1}$): 3222 (NH), 1712 (C=O). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.14–8.16 (m, 1H, H2), 8.10 (ddd [app. dt], $J_1 = J_2 = 7.6$ Hz, $J_5 = 1.6$ Hz, 1H, H6''), 7.72 (br s, 1H, NH), 7.41–7.45 (m, 1H, H4''), 7.38 (dd [app. t], $J_1 = J_2 = 1.5$ Hz, H5) 7.27 (ddd [app. dt], $J_1 = J_2 = 7.8$, 1.2 Hz, 1H, H5''), 7.22 (ddd, $J = 11.7$, 8.3, 1.0, 1H, H3'''), 7.16 (s, 1H, H5''),
7.06 (dd, J1 = 1.5 Hz, J2 = 1.0 Hz, 1H, H4), 3.80 (m [pseudo q], H1'), 3.13 (t, J1 = 6.0 Hz, 2H, H2'); 13C NMR (101 MHz, CDCl3): δ 161.7 (d, J = 4 Hz, C2''), 160.0 (d, J = 204 Hz, CF), 154.3 (C4''), 149.0 (C=O), 136.0 (C2), 131.7 (d, J = 7 Hz, C6''), 130.5 (C4), 128.6 (d, J = 2 Hz, ArH), 124.9 (d, J = 2 Hz, ArH), 112.1 (d, J = 9 Hz, C1''), 116.7 (d, J = 17 Hz, C3''), 116.5 (d, J = 6 Hz, C5''), 116.0 (C5), 40.6 (C1'), 30.1 (C2'). HRMS (ESI) m/z observed: 317.0867, C15H14N4OFS+ [M+H]+ requires 317.0872.

**N-(2-(2-(3-Fluorophenyl)thiazol-4-yl)ethyl)-1H-imidazole-1-carboxamide (60b).** Prepared from 59b (0.038 g, 0.171 mmol) as described for 60a. Elution with 3:2 EtOAc/hexanes gave 60b as a brown oil (0.021 g, 57%). IR (cm⁻¹): 3115 (NH), 1710 (C=O). 1H NMR (500 MHz, CDCl3): δ 8.15 (s, 1H, H2), 7.67 (br. s, 1H, NH), 7.64–6.67 (m, 1H, H6''), 7.60 (ddd [app. dt], J1 = 9.4 Hz, J2 = J3 = 2.0 Hz, H2''), 7.42 (ddd [app. dt], J1 = J2 = 8.0 Hz, J3 = 5.7 Hz, 1H, H5''), 7.37 (s, 1H, H5), 7.13 (dd [app. dt], J1 = J2 = 5.6 Hz, 2H, H1'), 3.10 (t, J1 = 6.0 Hz, 2H, H2'); 13C NMR (101 MHz, CDCl3): δ 167.4 (d, J = 3 Hz, C2''), 163.2 (d, J = 199 Hz, CF), 155.3 (C4''), 149.0 (C=O), 136.1 (C2), 135.3 (d, J = 6 Hz, C1''), 130.9 (d, J = 7 Hz, C5''), 130.6 (C4), 122.2 (d, J = 2 Hz, C6''), 117.4 (d, J = 17 Hz, C2'' or C4''), 115.8 (C5'' or C5), 115.7 (C5'' or C5), 113.4 (d, J = 19 Hz, C2'' or C4''), 40.5 (C1'), 30.4 (C2'). HRMS (ESI) m/z observed: 317.0863, C15H14N4OFS+ [M+H]+ requires 317.0872.

**N-(2-(2-(4-Fluorophenyl)thiazol-4-yl)ethyl)-1H-imidazole-1-carboxamide (60c).** Prepared from 59b (0.260 g, 0.738 mmol) as described for 60a. Elution with 1:1 EtOAc/hexanes and then EtOAc gave 60c as a pale-orange solid (0.070 g, 30%), mp = 35–37 °C. IR (cm⁻¹): 3218 (NH),
1H NMR (500 MHz, CDCl₃): δ 8.13 (dd, J = 1.2, 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], J₁ = J₂ = 1.4 Hz, 1H, H5), 7.13–7.16 (m, 2H, H3''/H5''), 7.06 (dd, J₁ = 1.6 Hz, 0.8 Hz, 1H, H4), 7.03 (t, J = 0.8 Hz, 1H, H5''), 3.77–3.80 (m [pseudo q], Hz, 2H, H1''), 3.09 (dt, J = 6.0, 0.5 Hz, 2H, H2'').

13C NMR (101 MHz, CDCl₃): δ 167.9 (C2''), 164.2 (d, J = 202 Hz, C4''), 155.1 (C4''), 149.0 (C=O), 136.0 (C2), 130.5 (C4), 129.7 (d, J = 3 Hz, C1''), 128.4 (d, J = 7 Hz, C2''/C6''), 116.4 (d, J = 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, C₁₅H₁₄N₄OF₅S⁺ [M+H]⁺ requires: 317.0872.

N-(2-(2-(2,4-Difluorophenyl)thiazol-4-yl)ethyl)-1H-imidazole-1-carboxamide (60d). Prepared from 59d (0.100 g, 0.270 mmol) as described for 60a. Elution with 3:2 EtOAc/hexanes and then EtOAc gave 60d as a yellow oil (0.060 g, 70%). IR (cm⁻¹): 3351 (NH), 1616 (C=O). 1H NMR (500 MHz, CDCl₃): δ 8.14 (br. s, 1H, H2), 8.08 (ddd [app. dt], J₁ = J₂ = 8.6 Hz, 1H, H6''), 7.98 (br. t, J₁ = 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, J = 204, 10 Hz, CF), 160.3 (d, J = 5 Hz, C2''), 160.1 (dd, J = 205, 10 Hz, CF), 154.0 (C4''), 149.0 (C=O), 136.0 (C2), 130.1 (C5), 129.8 (dd, J = 8, 3 Hz, C6''), 117.8 (dd, J = 9, 3 Hz, C1''), 116.11 (d, J = 6 Hz, C5''), 116.10 (C5), 112.3 (dd, J = 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 (61a). Piperidine (0.10 mL, 0.978 mmol) was added to a stirred solution of NEt₃ (0.1 mL) and 60a (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 61a as a yellow oil (0.030 g, 41%). IR (cm$^{-1}$): 3351 (NH), 1616 (C=O). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.19 (ddd [app. dt], 1H, $J_1 = J_2 = 7.6, J_3 = 1.8$ 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], $J_1 = J_2 = 6.0$ Hz, 2H, H1$'$), 3.32 (m [pseudo t], 4H, H2/H6), 3.02 (t, $J_1 = 6.2$ Hz, 2H, H2$'$), 1.48–1.57 (m, 6H, H3/H4/H5); $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 160.5 (d, $J = 4$ Hz, C2$''$), 160.0 (d, $J = 203$ Hz, CF), 157.9 (C=O), 155.3 (C4$''$), 131.1 (d, $J = 9$ Hz, C6$''$), 128.5 (d, $J = 2$ Hz, C4$'''$ or C5$'''$), 124.6 (d, $J = 3$ Hz, C4$'''$ or C5$'''$), 121.5 (d, $J = 7$ Hz, C1$''$), 116.4 (d, $J = 17$ Hz, C3$'''$), 116.0 (d, $J = 7$ 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.

$N$-(2-(2-(3-Fluorophenyl)thiazol-4-yl)ethyl)piperidine-1-carboxamide (61b). Prepared from 60b (0.0200 g, 0.0632 mmol) as described for 61a. Elution with 1:1 EtOAc/Hexanes then EtOAc gave 61b as a yellow oil (0.015 g, 71%). IR (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, $J = 6$ Hz, C2$'''$/C4$'''$), 117.0 (d, $J = 17$ Hz, C2$'''$/C4$'''$), 115.0 (C5$'''$), 113.2 (d, $J = 19$ Hz, C2$'''$/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, C17H21N3OFS+ [M+H]+ requires 334.1389.

*N-(2-(2-(4-Fluorophenyl)thiazol-4-yl)ethyl)piperidine-1-carboxamide (61c)*. Prepared from 60c (0.060 g, 0.190 mmol) as described for 61a. Elution with 3:2 EtOAc/hexanes and then EtOAc gave 61c as a yellow oil (0.040 g, 63%). IR (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, J = 201 Hz, CF), 157.9 (C=O or C₄''), 156.4 (C=O or C₄''), 130.1 (d, J = 3 Hz, C₁''''), 128.3 (d, J = 7 Hz, C₂''/C₆'''), 116.1 (d, J = 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.

**General procedure (F) for the synthesis of phenylthiazoles by Suzuki coupling with 63a.** 2-Bromo(thiazole) 63a (1.0 equiv), potassium carbonate (4.0 equiv), arylboronic acid (1.2 equiv), tetrabutylammonium bromide (0.1 equiv.), PdCl₂ (0.05 equiv) and dpff (0.055 equiv) were combined in a microwave reactor vessel with 4:1 dioxane and water (0.5 M final concentration). The reaction mixture was irradiated in a CEM microwave at 130 °C for 30 min, then cooled, diluted with EtOAc and filtered through Celite. The filtrate was evaporated and the residue was purified by column chromatography, eluting with EtOAc/hexanes to give the desired product.
**N-(2-(2-(3-Chlorophenyl)thiazol-4-yl)ethyl)piperidine-1-carboxamide (61d).** Prepared according to general procedure F with 3-chlorophenylboronic acid. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.01 (s, 1H), 7.94 (d, $J$ = 8.4 Hz, 1H), 7.35 (d, $J$ = 7.9 Hz, 1H), 7.27 (m, 1H), 6.93 (s, 1H), 5.63 (br. s, 1H), 3.63 (dt [app. q], $J_1$ = $J_2$ = 6.5 Hz, 2H), 3.35–3.42 (m, 4H), 3.09 (t, $J$ = 6.5 Hz, 2H), 1.63–1.50 (m, 6H). LRMS (ESI+) $m/z$ 350, 352 [M+H]$^+$. 

**N-(2-(2-(4-Chlorophenyl)thiazol-4-yl)ethyl)piperidine-1-carboxamide (61e).** Prepared according to general procedure F with 4-chlorophenylboronic acid. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.09 (d, $J$ = 8.7 Hz, 2H), 7.63 (d, $J$ = 8.5 Hz, 2H), 6.97 (s, 1H), 5.59 (br s, 1H), 3.62 (dt [app. q], $J_1$ = $J_2$ = 6.4 Hz, 2H), 3.35–3.42 (m, 4H), 3.10 (t, $J$ = 6.5 Hz, 2H), 1.50–1.63 (m, 6H). LRMS (ESI+) $m/z$ 350, 352 [M+H]$^+$. 

**N-(2-(2-(o-Tolyl)thiazol-4-yl)ethyl)piperidine-1-carboxamide (61f).** Prepared according to general procedure F with 2-tolylboronic acid. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.85 (d, $J$ = 9.0 Hz, 1H), 7.30–7.40 (m, 3H), 6.96 (s, 1H), 5.79 (br s, 1H), 3.63 (dt [app. q], $J_1$ = $J_2$ = 6.5 Hz, 2H), 3.36–3.42 (m, 4H), 3.04 (t, $J$ = 6.7 Hz, 2H), 2.55 (s, 3H), 1.53–1.63 (m, 6H). LRMS (ESI+) $m/z$ 330 [M+H]$^+$. 

**N-(2-(2-(p-Tolyl)thiazol-4-yl)ethyl)piperidine-1-carboxamide (61g).** Prepared according to general procedure F with 4-tolylboronic acid. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.83 (d, $J$ = 9.0 Hz, 2H), 7.24 (d, $J$ = 9.0 Hz, 2H), 6.96 (s, 1H), 5.83 (br s, 1H), 3.62 (dt [app. q], $J_1$ = $J_2$ = 6.5 Hz, 2H), 3.35–3.40 (m, 4H), 3.02 (t, $J$ = 6.6 Hz, 2H), 2.42 (s, 3H), 1.53–1.63 (m, 6H). LRMS (ESI+) $m/z$ 330 [M+H]$^+$. 
\(N-(2-(2-(2\text{-Methoxyphenyl})\text{thiazol-4-yl})\text{ethyl})\text{piperidine-1-carboxamide (61h)}\). Prepared according to general procedure F with 2-methoxyphenylboronic acid. \(1^\text{H} \text{NMR (400 MHz, CDCl}_3\) \(\delta 8.36 \text{ (dd, } J = 8.2, 1.6 \text{ Hz, 1H}), 7.42 \text{ (ddd [app. dt], } J_1 = J_2 = 8.1 \text{ Hz, } J_3 = 1.7 \text{ Hz, 1H}), 7.04–7.10 \text{ (m, 3H), 5.87 \text{ (br s, 1H), 4.05 \text{ (s, 3H), 3.62 \text{ (dt [app. q], } J_1 = J_2 = 5.2 \text{ Hz, 2H), 3.29–3.44 \text{ (m, 4H), 3.01–3.06 \text{ (m, 2H), 1.48–1.65 \text{ (m, 6H). LRMS (ESI+) } m/z 346 \text{ [M+H]{+}}.}

\(N-(2-(2-(3\text{-Methoxyphenyl})\text{thiazol-4-yl})\text{ethyl})\text{piperidine-1-carboxamide (61i)}\). Prepared according to general procedure F with 3-methoxyphenylboronic acid. \(1^\text{H} \text{NMR (400 MHz, CDCl}_3\) \(\delta 7.52 \text{ (m, 2H), 7.37 \text{ (dd [app. t], } J_1 = J_2 = 7.9 \text{ Hz, 1H), 6.97–7.02 \text{ (m, 2H), 5.68 \text{ (br s, 1H), 3.90 \text{ (s, 3H), 3.63 \text{ (dt [app. q], } J_1 = J_2 = 5.6 \text{ Hz, 2H), 3.31–3.42 \text{ (m, 4H), 3.03 \text{ (t, } J = 6.1 \text{ Hz, 2H), 1.49–1.65 \text{ (m, 6H). LRMS (ESI+) } m/z 346 \text{ [M+H]{+}}.}

\(N-(2-(2-(4\text{-Methoxyphenyl})\text{thiazol-4-yl})\text{ethyl})\text{piperidine-1-carboxamide (61j)}\). Prepared according to general procedure F with 4-methoxyphenylboronic acid. \(1^\text{H} \text{NMR (400 MHz, CDCl}_3\) \(\delta 7.85–7.91 \text{ (m, 2H), 6.94–6.99 \text{ (m, 2H), 6.92 \text{ (s, 1H), 5.79 \text{ (br s, 1H), 3.89 \text{ (s, 3H), 3.62 \text{ (dt [app. q], } J_1 = J_2 = 5.4 \text{ Hz, 2H), 3.31–3.43 \text{ (m, 4H), 2.92–3.09 \text{ (m, 2H), 1.49–1.66 \text{ (m, 6H). LRMS (ESI+) } m/z 346 \text{ [M+H]{+}}.}

\(N-(2-(2-(2\text{-Cyanophenyl})\text{thiazol-4-yl})\text{ethyl})\text{piperidine-1-carboxamide (61k)}\). Prepared according to general procedure F with 2-cyanophenylboronic acid. \(1^\text{H} \text{NMR (400 MHz, CDCl}_3\) \(\delta 7.94 \text{ (d, } J = 7.9 \text{ Hz, 1H), 7.84 \text{ (d, } J = 8.0 \text{ Hz, 1H), 7.70 \text{ (dd [app. t], } J_1 = J_2 = 7.2 \text{ Hz, 1H), 7.55 \text{ (dd [app. t], } J_1 = J_2 = 7.6 \text{ Hz, 1H), 7.16 \text{ (s, 1H), 5.53 \text{ (br s, 1H), 3.74 \text{ (dt [app. q], } J_1 = J_2 = 5.8 \text{ Hz, 2H), 3.31–3.43 \text{ (m, 4H), 2.92–3.09 \text{ (m, 2H), 1.49–1.66 \text{ (m, 6H). LRMS (ESI+) } m/z 346 \text{ [M+H]{+}}.}\)
Hz, 2H), 3.27–3.35 (m, 4H), 3.12 (t, \(J = 5.9\) Hz, 2H), 1.39–1.63 (m, 6H). LRMS (ESI+) \(m/z\) 341 [M+H]+.

**N-(2-(2-(3-Cyanophenyl)thiazol-4-yl)ethyl)piperidine-1-carboxamide (61l).** Prepared according to general procedure F with 3-cyanophenylboronic acid. \(^1\)H NMR (400 MHz, CDCl3) \(\delta\) 8.27 (s, 1H), 8.14 (d, \(J = 8.0\) Hz, 1H), 7.72 (d, \(J = 7.7\) Hz, 1H), 7.58 (t, \(J = 7.8\) Hz, 1H), 7.10 (s, 1H), 5.45 (br s, 1H), 3.64 (dt [app. q], \(J_1 = J_2 = 5.9\) Hz, 2H), 3.33–3.45 (m, 4H), 3.06 (t, \(J_1 = 6.2\) Hz, 2H), 1.46–1.78 (m, 6H). LRMS (ESI+) \(m/z\) 341 [M+H]+.

**N-(2-(2-(4-Cyanophenyl)thiazol-4-yl)ethyl)piperidine-1-carboxamide (61m).** Prepared according to general procedure F with 4-cyanophenylboronic acid. \(^1\)H NMR (400 MHz, CDCl3) \(\delta\) 7.93–7.98 (m, 2H), 7.63–7.68 (m, 2H), 7.05 (s, 1H), 5.33 (br s, 1H), 3.55 (t, \(J = 6.0\) Hz, 2H), 3.33–3.20 (m, 4H), 2.97 (t, \(J_1 = 6.2\) Hz, 2H), 1.40–1.58 (m, 6H). LRMS (ESI+) \(m/z\) 341 [M+H]+.

**N-(2-(2-Bromothiazol-4-yl)ethyl)piperidine-1-carboxamide (63a).** A mixture of 58 (1.0 g, 3.0 mmol), EtOH (50 mL) and hydrazine monohydrate (5 mL) was heated under reflux for 1 h, then cooled to 0 °C. The resulting suspension was filtered, and the filtrate was evaporated. The residue (crude amine 62) was dissolved in EtOAc (50 mL) and treated with NEt\(_3\) (3 mL) and piperidine-1-carbonyl chloride (0.56 mL, 4.5 mmol). The reaction mixture was stirred for 12 h at which point TLC showed the reaction to be incomplete. Additional NEt\(_3\) (1 mL) and piperidine-1-carbonyl chloride (0.19 mL, 1.5 mmol) were added and the reaction mixture was stirred at 60 °C for 4 h, then cooled in an ice bath before being filtered. The filtrate was washed with water (2 × 30 mL), brine (2 × 30 mL), dried (Na\(_2\)SO\(_4\)) and evaporated to give a brown solid (1.2 g, which was purified
by flash chromatography. Elution with cyclohexane/EtOAc 1:1 to 3:7) afforded 63a (670 mg, 72%) as a yellow oil. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 6.94 (s, 1H, H5''), 5.30 (br. s, $^1$H, NH), 3.50 (dt [app. q], $J_1 = J_2 = 6.1$ Hz, 2H, H1'), 3.28 (m [app. t], $J' = 5.1$ Hz, 4H, C2/6) 2.92 (t, $J = 6.6$ Hz, 2H, H2'), 1.47–1.58 (m, 6H, H3/4/5). $^{13}$C NMR (CDCl$_3$, 101 MHz): $\delta$ 157.6 (CO or C4''), 155.6 (CO or C4''), 135.3 (C2'') 118.1 (C5'') 44.7 (C2/6) 40.2 (C1') 31.5 (C2') 25.5 (C3/5), 24.3 (C4). LCMS (ESI) m/z: 306 [M+H]$^+$. 

3-(2-(2-Bromothiazol-4-yl)ethyl)-1,1-diethylurea (63b). A stirred solution of crude 62, prepared as described for 63a from 58 (100 mg, 0.297 mmol), in EtOAc (5 mL), was treated with NEt$_3$ (1 mL) and diethylcarbamoyl chloride (0.113 mL, 0.890 mmol) and heated under reflux for 1 h. The reaction mixture was allowed to cool, then diluted with water (30 mL) and extracted with EtOAc (3 × 20 mL). The extract was washed with brine (3 × 30 mL), dried (Na$_2$SO$_4$) and evaporated to give a yellow oil (150 mg), which was purified by flash chromatography. Elution with cyclohexane/EtOAc 1:1 to 3:7) afforded 63b as a colorless oil (50 mg, 55%). $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 6.94 (s, 1H, H5'), 5.19 (br. s, 1H, NH), 3.52 (dt [app. q], $J_1 = J_2 = 5.9$ Hz, 2H, H1), 3.23 (q, $J = 7.1$ Hz, 4H, NCH$_2$), 2.93 (t, $J = 6.2$ Hz, 2H, C2), 1.10 (t, $J = 7.1$ Hz, 6H, CH$_3$. $^{13}$C NMR (CDCl$_3$, 101 MHz): $\delta$ 157.2 (C=O or C4') 155.8 (C=O or C4') 135.3 (C2') 118.1 (C5') 41.1 (2 × NCH$_2$), 40.0 (C1), 31.5 (2), 13.8 (2 × CH$_3$). LCMS (ESI) m/z: 306 [M+H]$^+$. 

Isopropyl [(2-(2-bromothiazol-4-yl)ethyl])carbamate (63c). Crude 62, prepared as described for 63a from 58 (200 mg, 0.593 mmol), was dissolved in EtOAc (50 mL) and treated with NEt$_3$ (2 mL) and a 1 M solution of isopropyl chloroformate in toluene (0.89 mL, 890 mmol). The reaction mixture was stirred for 4 h at 60 °C, at which point TLC showed the reaction to be
incomplete. Additional NEt₃ (1 mL) and isopropyl chloroformate solution (0.59 mL, 0.59 mmol) were added, and the reaction mixture was stirred at 60 °C for 2 h, then cooled in an ice bath and filtered. The filtrate was washed with water (2 × 30 mL), brine (2 × 30 mL), dried (Na₂SO₄) and evaporated to give a yellow oil (100 mg), which was purified by flash chromatography. Elution with cyclohexane/EtOAc 1:0 to 7:3 afforded 63c as a colorless oil (25 mg, 14%). ¹H NMR (CDCl₃, 400 MHz): δ 6.94 (s, 1H, H₅′), 4.90 (m, 1H, OCH), 3.52 (dt [app. q], J₁ = J₂ = 5.9 Hz, 2H, H₁), 2.94 (t, J = 6.5 Hz, 2H, H₂), 1.21 (d, J = 6.3 Hz, 6H, CH₃). LCMS (ESI) m/z = 293 [M+H]⁺.

**N-(2-(2-Bromothiazol-4-yl)ethyl)-3,5-difluorobenzamide (63d).** Crude 62, prepared as described for 63a from 58 (200 mg, 0.593 mmol), was dissolved in EtOAc (5 mL) and treated with NEt₃ (0.5 mL) and 3,5-difluorobenzoyl chloride (314 mg, 1.78 mmol). The reaction mixture was stirred for 12 h then cooled in an ice bath before being filtered. The filtrate was diluted with EtOAc (20 mL) and washed with water (2 × 30 mL) and brine (2 × 30 mL), dried (Na₂SO₄) and evaporated to give a yellow solid (600 mg), which was purified by flash chromatography. Elution with cyclohexane/EtOAc (1:0 to 7:3) afforded 63d as a yellow solid (120 mg, 58%). ¹H NMR (CDCl₃, 400 MHz): δ 7.51 (br. s, 1H, NH), 7.29–7.34 (m, 2H, H₁/₆), 6.99 (s, 1H, H₅″); 6.88–6.93 (m, 1H, H₄), 3.73 (dt [app. q], J₁ = J₂ = 6.0 Hz, 2H, C₂′); 3.03 (t, J = 6.2 Hz, 2H, C₁′). ¹³C NMR (CDCl₃, 101 MHz): δ 164.9 (CO), 162.8 (dd, J = 250, 12 Hz, 2 × CF), 154.7 (C₄″), 137.8 (t, J = 8 Hz, C₁), 135.9 (CBr), 118.5 (C₅″), 110.2 (dd, J = 18, 8 Hz, C₂/₆); 106.6 (t, J = 25 Hz, C₄), 39.4 (C₁′), 30.5 (C₂′). LCMS (ESI) m/z: 347 [M+H]⁺.
**N-(2-(2-(2,4-Difluorophenyl)thiazol-4-yl)ethyl)piperidine-1-carboxamide (64a).** *Method A:* Prepared from **60d** (0.060 g, 0.179 mmol) as described for **61a**. Elution with 3:2 EtOAc/hexanes then EtOAc gave **64a** as a pale-amber solid (0.040 g, 64%), mp = 68–70 °C. IR (cm\(^{-1}\)): 3341 (NH), 1614 (C=O). \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 8.19 (ddd [app. dt], \(J_1 = J_2 = 8.5\) Hz, \(J_3 = 6.4\) 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], \(J = 6.0\) 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, \(J = 203\), 10 Hz, CF), 160.2 (dd, \(J = 205\), 10 Hz, CF), 159.8 (d, \(J = 5\) Hz, C2''), 157.9 (C=O or C4''), 155.2 (C=O or C4''), 129.9 (dd, \(J = 8\), 3 Hz, C6''), 118.2 (d, \(J = 9\) Hz, C1'''), 115.8 (d, \(J = 6\) Hz, C5''), 112.2 (dd, \(J = 17\), 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.

**Method B:** A mixture of **63a** (600 mg, 1.89 mmol), K\(_2\)CO\(_3\) (1.04 g, 7.54 mmol), (2,4-difluorophenyl)boronic acid (417 mg, 2.64 mmol), TBAB (61 mg, 10 mol%), PdCl\(_2\)(dppf) (97 mg, 5 mol %) and 4:1 dioxane/water (20 mL) in a microwave reactor vessel was irradiated in a microwave at 110 °C (3 bars) for 1 h. The reaction mixture was cooled and diluted with EtOAc (30 mL), washed with water (2 × 25 mL) and brine (2 × 25 mL), dried (Na\(_2\)SO\(_4\)) and evaporated to give a brown oil (970 mg), which was purified by flash chromatography. Elution with cyclohexane/EtOAc 8:2 to 6:4 afforded **64a** as a brown solid (480 mg, 72 %), identical with the material described above.

**3-(2-(2-(2,4-Difluorophenyl)thiazol-4-yl)ethyl)-1,1-diethylurea (64b).** A mixture of **63b** (50 mg, 0.16 mmol), K\(_2\)CO\(_3\) (90 mg, 0.65 mmol), (2,4-difluorophenyl)boronic acid (31 mg, 0.20
mmol), TBAB (5 mg, 10 mol %), PdCl\(_2\)(dppf) (6 mg, 5 mol %) and 4:1 dioxane/water (5 mL) in a microwave reactor vessel was irradiated in a microwave at 120 °C (3 bars) for 45 min. The reaction mixture was cooled and diluted with EtOAc (10 mL), washed with water (2 × 15 mL) and brine (2 × 15 mL), dried (Na\(_2\)SO\(_4\)) and evaporated to give a brown oil (55 mg), which was purified by flash chromatography. Elution with cyclohexane/EtOAc (1:1 to 3:7) afforded 64b as yellow oil (27 mg, 49 %). \(^1\)H NMR (CDCl\(_3\), 400 MHz): δ 8.19–8.25 (m, 1H, H6''), 7.09 (s, 1H, H5''), 6.92–7.00 (m, 2H, H3''/5''), 5.22 (br. s, 1H, NH), 3.63 (dt [app. q], J\(_1\) = J\(_2\) = 6.0 Hz, 2H, H1); 3.24 (q, J = 7.1 Hz, 4H, NCH\(_2\)), 3.04 (t, J = 6.1 Hz, 2H, H2), 1.08 (t, J = 7.3 Hz, 6H, CH\(_3\)). \(^{13}\)C NMR (CDCl\(_3\), 101 MHz): δ 163.4 (dd, J = 255, 12 Hz, CF), 160.0 (dd, J = 255, 12 Hz, CF, CF), 159.5 (C2''); 157.2 (C=O or C4'); 155.2 (C=O or C4'); 129.8 (dd, J = 10, 4 Hz, C6''); 118.1 (dd, J = 12, 4 Hz, C1'''); 115.6 (115.8 (d, J = 8 Hz, C5''); 112.0 (dd, J = 22, 4 Hz, C5'') 104.5 (dd [app. t], J\(_1\) = J\(_2\) = 26 Hz, C3''). 13C NMR (CDCl\(_3\), 101 MHz): δ 163.4 (dd, J = 255, 12 Hz, CF), 160.0 (dd, J = 255, 12 Hz, CF, CF), 159.5 (C2''); 157.2 (C=O or C4'); 155.2 (C=O or C4'); 129.8 (dd, J = 10, 4 Hz, C6''); 118.1 (dd, J = 12, 4 Hz, C1'''); 115.6 (115.8 (d, J = 8 Hz, C5''); 112.0 (dd, J = 22, 4 Hz, C5'') 104.5 (dd [app. t], J\(_1\) = J\(_2\) = 26 Hz, C3''). Isopropyl (2-(2-(2,4-difluorophenyl)thiazol-4-yl)ethyl)carbamate (64c). A mixture of 63c (25 mg, 0.085 mmol), K\(_2\)CO\(_3\) (47 mg, 0.34 mmol), (2,4-difluorophenyl)boronic acid (16 mg, 0.10 mmol), TBAB (5 mg, 10 mol %), PdCl\(_2\)(dppf) (6 mg, 5 mol %) and 4:1 dioxane/water (5 mL) in a microwave reactor vessel was irradiated in a microwave at 110 °C (3 bars) for 1 h. The reaction mixture was cooled and diluted with EtOAc (30 mL), washed with water (2 × 25 mL) and brine (2 × 25 mL), dried (Na\(_2\)SO\(_4\)) and evaporated to give a brown oil (70 mg), which was purified by flash chromatography. Elution with cyclohexane/EtOAc 8:2 to 6:4) afforded 64c as white solid (19 mg, 66%). \(^1\)H NMR (CDCl\(_3\), 400 MHz): δ 8.24–8.30 (m, 1H, H6''), 7.09 (s, 1H, H5''), 6.92–7.02 (m, 2H, H3'/H5''), 5.10 (br. s,1H, NH), 4.92 (sept., J = 6.2 Hz, 1H, OCH); 3.58–3.63 (dt
$J_1 = J_2 = 6.0$ Hz, 2H, H1), 3.03 (t, $J = 6.3$ Hz, 2H, H2), 1.23 (d, $J = 6.1$ Hz, 6H, CH3).

$^{13}$C NMR (CDCl$_3$, 101 MHz): 163.4 (dd, $J = 255$, 12 Hz, CF), 160.0 (dd, $J = 255$, 12 Hz, CF), 159.5 (C2'); 156.3 (C=O or C4'); 154.2 (C=O or C4'), 130.0 (dd, $J = 10$, 4 Hz, C6"'), 118.0 (dd, $J = 12$, 4 Hz, C1"), 115.6 (d, $J = 8$ Hz, C5"'), 112.1 (dd, $J = 22$, 4 Hz, C5"'), 104.4 (dd [app. t], $J_1 = J_2 = 26$ Hz, C3"'), 68.0 (OCH), 40.2 (C1), 31.5 (C2), 22.2 (2 × CH3). LCMS (ESI) m/z: 327 [M+H]$^+$.  

$\text{N-(2-((2,4-Difluorophenyl)thiazol-4-yl)ethyl)-3,5-difluorobenzamide (64d).}$ A mixture of 63d (120 mg, 0.346 mmol) (25 mg, 0.085 mmol), K$_2$CO$_3$ (191 mg, 1.38 mmol) (47 mg, 0.34 mmol), (2,4-difluorophenyl)boronic acid (76 mg, 0.484 mmol), TBAB (11 mg, 10 mol %), PdCl$_2$(dpff) (18 mg, 5 mol %) and 4:1 dioxane/water (5 mL) in a microwave reactor vessel was irradiated in a microwave at 110 °C (3 bars) for 1 h. The reaction mixture was cooled and diluted with EtOAc (10 mL), washed with water (2 × 15 mL) and brine (2 × 15 mL), dried (Na$_2$SO$_4$) and evaporated to give a brown oil (140 mg), which was purified by flash chromatography. Elution with cyclohexane then 6:4 cyclohexane/EtOAc afforded 64d as white solid (96 mg, 73%). $^1$H NMR (CDCl$_3$, 400 MHz): δ 8.17–8.23 (m, 1H, H6"'), 7.85 (br. s, 1H, NH), 7.35–7.37 (m, 2H, ArH); 7.14 (s, 1H, H5"'); 6.91–7.01 (m, 3H, ArH), 3.78–3.82 (m, 2H, H1"'), 3.11 (t, $J = 5.8$ Hz, 2H, H2'). $^{13}$C NMR (CDCl$_3$, 101 MHz): δ 164.7 (t, $J = 3$ Hz, C=O), 163.5 (dd, $J = 255$, 12 Hz, C2"F or C4"F), 162.9 (J = 251, 12 Hz, C3F/C5F), 160.2 (dd, $J = 6$, 2 Hz, C2"'), 160.0 (dd, $J = 256$, 12 Hz, C2"F or C4"F), 154.4 (C4"'), 138.2 (t, $J = 8$ Hz, C1), 129.6 (dd, $J = 10$, 4 Hz, C6"') 117.7 (dd, $J = 12$, 3 Hz, C1"'), 115.9 (d, $J = 8$ Hz, C5"'), 112.2 (dd, $J = 22$, 4 Hz, C5"'), 110.3 (AA'X$_2$, $\sim J = 19$, 7 Hz, C2/6), 106.6 (t or dd [app. t], $J = 26$ Hz, C4 or C3"'); 104.6 (t or dd [app. t], $J = 26$ Hz, C4 or C3"'), 39.8 (C1"'), 30.2 (C2'). LCMS (ESI) m/z: 381 [M+H]$^+$.  

In vivo anti-\textit{T. cruzi} activity assessment

Trypomastigote forms from transgenic \textit{T. cruzi} Brazil strain expressing firefly luciferase\textsuperscript{40} were purified, diluted in PBS and injected ip in Balb/c mice (10\textsuperscript{7} trypomastigotes per mouse). Four days after infection the mice were anesthesized by inhalation of isofluorane (controlled flow of 1.5\% isofluorane in air was administered through a nose cone via a gas anesthesia system). Mice were injected intraperitonealy with 150 mg/kg of D-luciferin potassium-salt (Goldbio) dissolved in PBS. Mice were imaged 5 to 10 min after injection of luciferin with an IVIS 100 (Xenogen, Alameda, CA) and the data acquisition and analysis were performed with the software LivingImage (Xenogen). One day later (5 days after infection) treatments started in three groups of mice. Group 1: vehicle alone (PBS with 2\% methylcellulose and 0.5\% Tween 80, administered by oral gavage); group 2: ABT (50 mg/kg 2x daily, administered intraperitonealy) and compound 64a (50 mg/kg 2 × daily 30 min later, administered by oral gavage); group 3: Benznidazole (100 mg/kg once daily administered by oral gavage). Treatments were continued for 10 days. On the days indicated in Figure 3, mice were imaged again after anesthesia and injection of luciferin as described above. Parasite load is expressed as the luciferase signal in arbitrary units. Mean values of all animals in each group ± SD were calculated. Immune-suppression was started 30 days after the last day of treatment. Mice were treated with cyclophosphamide (200 mg/kg once every 2–3 days, five doses total) and imaged 10 days after beginning of cyclophosphamide treatment.
ASSOCIATED CONTENT

Supporting Information. SAR summary diagram, exemplar compound numbering schemes, intracellular *T. cruzi* rate-of-kill profiles, and comparison with related regioisomers. “This material is available free of charge via the Internet at http://pubs.acs.org.”

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Abbreviations used

ABT, 1-aminobenzotriazole; app., apparent (NMR signal multiplicity); AUC, area under the curve; *b.*, *b. brucei*; br, broad (spectral); CDI, carbonyldimidazole; CL_{int}, intrinsic clearance; C_{max}, peak plasma concentration; C_{max,D}, C_{max} divided by dose; DALYs, disability-adjusted life years; DCU, *N*,*N’*-dicyclohexylurea; DIPEA, diisopropylethylamine; DNAUC; oral dose-normalized AUC; DNDi, Drugs for Neglected Diseases initiative; dppf, 1,1’-bis(diphenylphosphino)ferrocene; EDCI, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; E_{H}, hepatic extraction ratio; GSK, GlaxoSmithKline; HAT, Human African trypanosomiasis; HBTU, 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; HOBt, *N*-hydroxybenzotriazole; LHS, left hand side (as drawn); LRMS, low resolution mass spectrum/spectrometry; µw, microwave irradiation; M, molecule (mass spectrometry); MPO, multiparameter optimization (score); NECT, nifurtimox/eflornithine combination therapy; PAINS, pan assay interference compounds; Phth, phthalimidyl; RHS, right hand side (as drawn);
SI, selectivity index; SNAr, nucleophilic aromatic substitution; T., Trypanosoma; T\textsubscript{max}, time to peak plasma concentration; UDPGA, uridine 5'-diphosphoglucuronic acid; WEHI, Walter and Eliza Hall Institute; quant., quantitative;

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**Author Contributions**

*The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.*

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**Notes**

All animal studies were ethically reviewed and carried out in accordance with Animals (Scientific Procedures) Act 1986 and the GSK Policy on the Care, Welfare and Treatment of Animals.
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SI = selectivity index vs HEK293 (T. b. b.) and H9c2 cells (T. c.)
CNS MPO score = 5.2

50 mg/kg, 2 x daily + ABT
day 0
day 10

T. cruzi infected mice