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Article

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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.[1, 2] _ENREF_1 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 *Trypanosoma brucei gambiense* and *T. b. rhodesiense*, transmitted by the bite of infected tsetse flies. *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.[3] *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.[4] Indeed, both forms of the disease are usually fatal if left untreated.[4, 5]

In 2013 HAT was estimated to be responsible for approximately 6,900 deaths[6] _ENREF_6 and 390,000 disability-adjusted life years (DALYs).[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.[1] However, over 60 million people are thought to be at risk of infection,[1] and it is worth noting that historical epidemics have arisen from a base of low prevalence.[1] _ENREF_1Livestock are also susceptible to trypanosomiasis, adding to the burden of the disease, and acting as a parasite reservoir.[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.[3, 8] 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.[3, 9] The more recently approved drug eflornithine, and NECT, are only active against *T. b. gambiense*. Pafuramidine (Figure 1) _ENREF_11was recently taken to clinical trial,[10, 11] but development was abandoned due to renal toxicity.[11] Oxaborole (SCYX-7158) is scheduled to enter clinical trials in 2016,[12-14] and a phase II/III clinical trial on fexinidazole in underway.[15, 16] However, some cross resistance is expected for fexinidazole since its mode of action is similar to that of nifurtimox.[17]

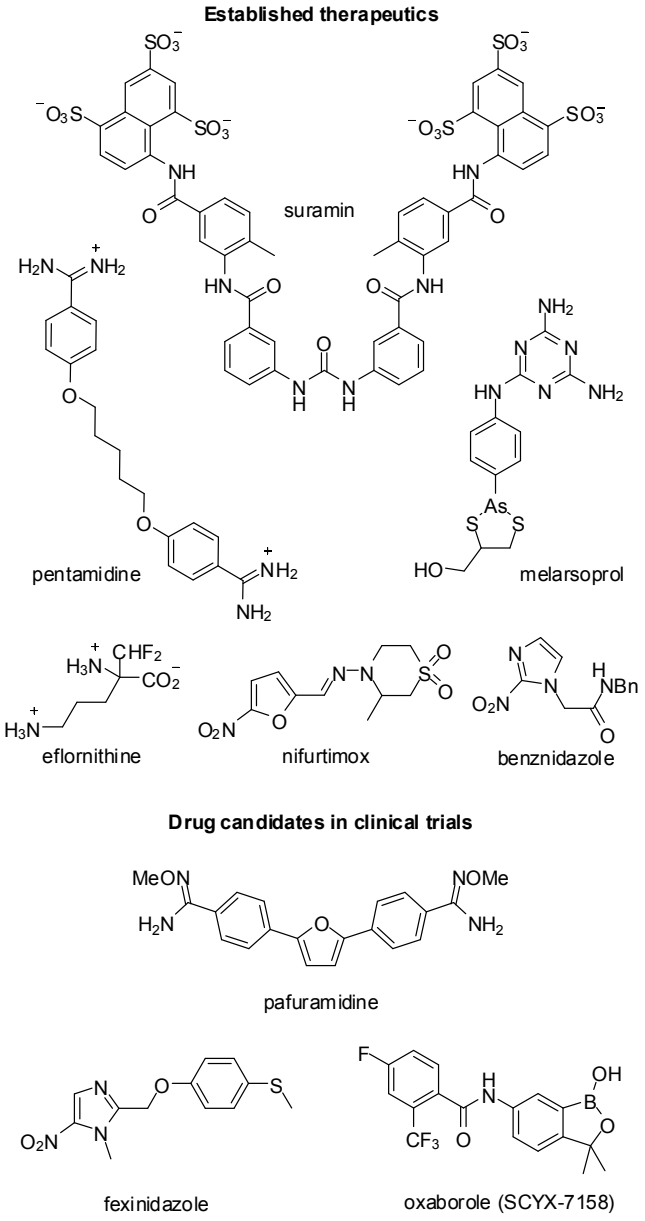


Figure 1. Structures of drugs investigated or currently used for the treatment of HAT and/or Chagas disease.

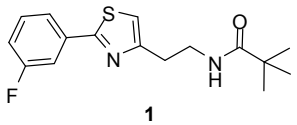
T. cruzi, spread by infected triatomine ('kissing') bugs, is the causative agent of Chagas disease, and is endemic in 21 countries in Latin America, affecting as many as 6–7 million people.[2] The 2013 Global Burden of Disease Study, estimated that Chagas disease was responsible for 10,600

deaths[6] and 339,000 DALYs.[7] 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;[18] indeed it is predicted that as many as 200,000 people will die from Chagasic cardiomyopathy over the next five years.[19] 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.[19, 20] _ENREF_20 [21] Cure is possible during the early acute phase,[22] and indeterminate phase[23] (chronic infection without signs of cardiac disease), but disease diagnosis at these stages is rare.[19]

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 *T. brucei* and *T. cruzi*.[24] Philanthropic organizations such as the Drugs for Neglected Diseases *initiative* (DND*i*) 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.[25]

The efforts of organizations like the DND*i* 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 DND*i*-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*.



1

	IC_{50} (μM)	SI	
T. b. brucei	0.80	>96	(vs HEK)
T. b. rhodesiense	1.5	42	(vs L6)
T. cruzi	2.3	27	(vs L6)

Figure 2. The hit from a HTS of the WEHI compound library against *T. b. brucei*[60] providing the inspiration for this study. SI = selectivity index = IC_{50} mammalian cell line/IC_{50} trypanosome; HEK = human embryonic kidney cells, L6 is a rat skeletal muscle cell line.

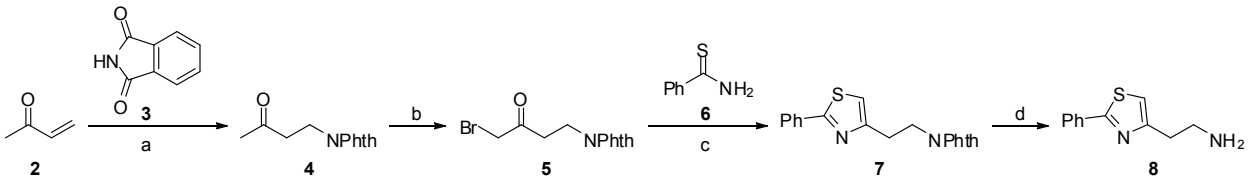
RESULTS AND DISCUSSION

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**[62] 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.

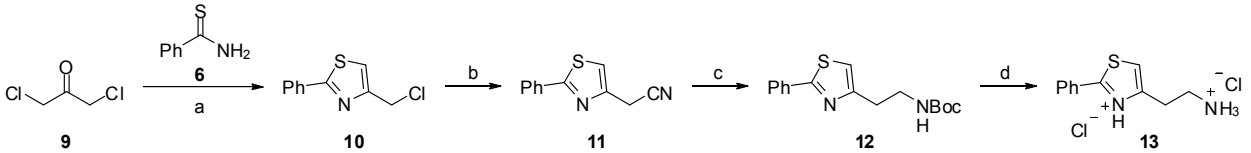
Scheme 1. Initial literature synthesis[62] of key primary amine 8



Reagents, conditions and yields: a) NaOH, EtOAc, 50%; b) Br_2, MeOH 48%; c) *i*-PrOH, HCl, 75%; d) $H_2NNH_2.H_2O$, 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,[63] gave the chloromethylthiazole **10**, which was converted to the corresponding nitrile **11**.[64] Attempts to reduce the nitrile with $LiAlH_4$, BH_3 or cobalt(II) chloride/sodium borohydride[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 *in situ* protection of the primary amine obtained by nickel boride reduction[66] of nitrile **11**, provided the *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.

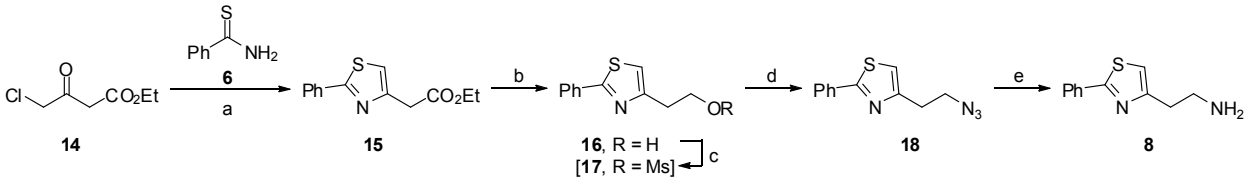
Scheme 2. Improved synthesis of primary amine hydrochloride 13



Reagents, conditions and yields: a) 1. acetone, 2. H_2SO_4, 85%; b) KCN, DMF, 90%; c) 1. $NaBH_4$, $NiCl_2.H_2O$, Boc_2O, MeOH, 2. NEt_3, 82%; d) HCl/H_2O, 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.[67] Again, this synthesis starts with a cyclocondensation of thiobenzamide (**6**), in this case with ethyl chloroacetoacetonate (**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.

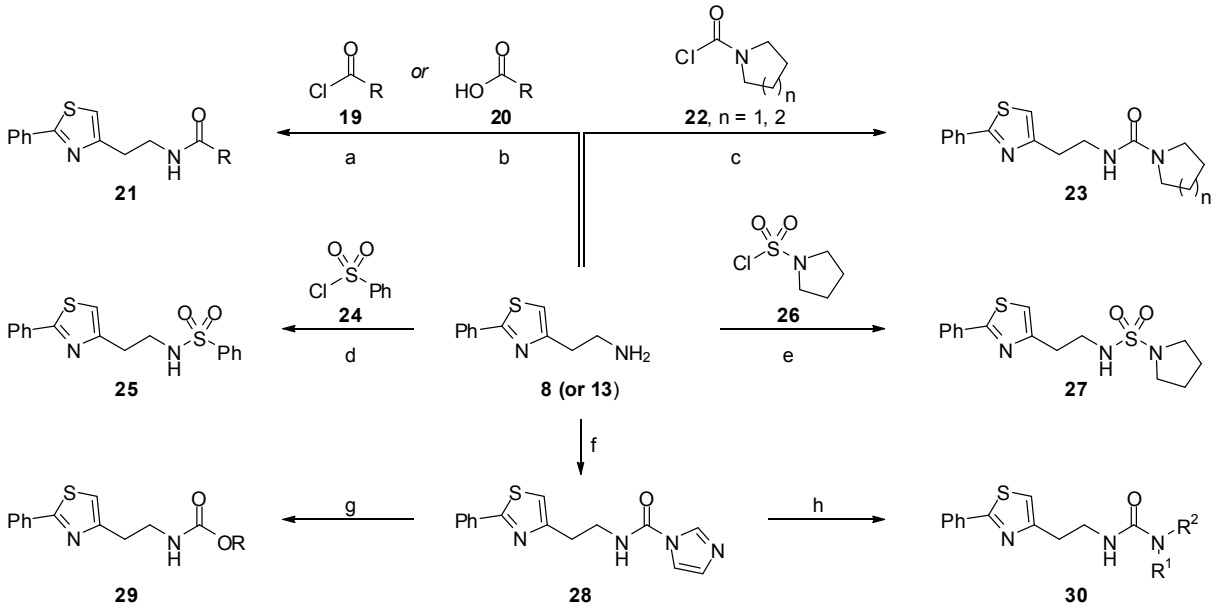


Reagents, conditions and yields: a) $NaHCO_3$, EtOH, reflux, 76%; b) $LiAlH_4$, THF, –78°C, 71%; c) MsCl, NEt_3, THF, 96% (crude); d) NaN_3, THF, reflux, 86%; e) Pd/C, H_2, MeOH, 99%.

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 *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.

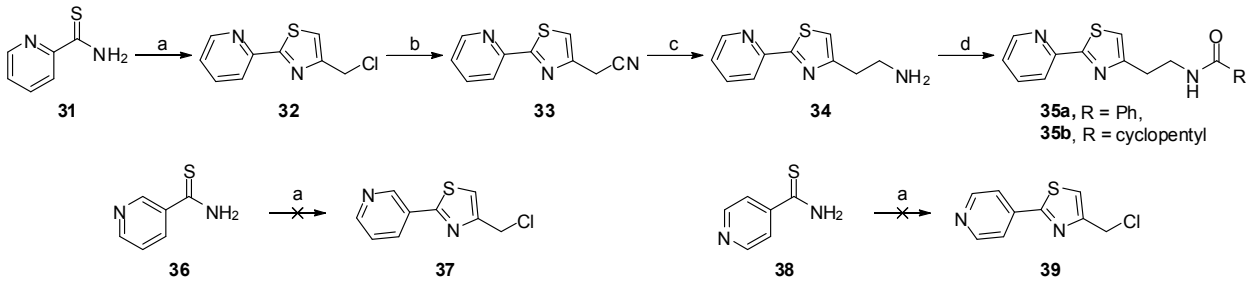


Reagents, conditions and yields: a) **19**, NEt_3, DCM, 57–85%*; b) **20**, DCC, HOBt; or **20**, HBTU, 24–87%*; d) $PhSO_2Cl$, NEt_3, DCM, 40%; c) **22**, n = 1, NEt_3, DCM, 92%; **22**, n = 2, NEt_3, DCM, 71%; d) DIPEA, DCM, 32%; e) **26**, NEt_3, DCM, 41%; f) CDI, MeCN, DMF, 69%; g) ROH, NaH, DMF, 32–55%*; h) HNR^1R^2, NEt_3, 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 outline 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

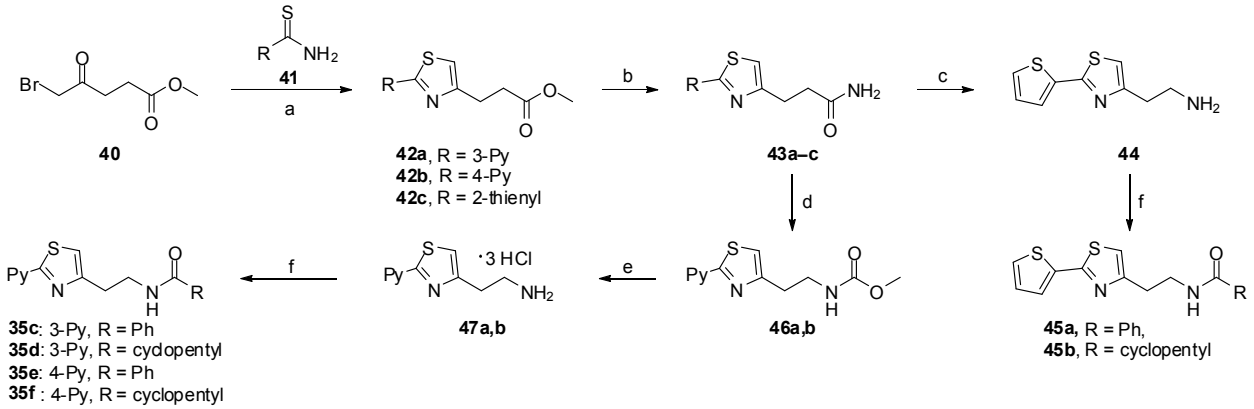


Reagents, conditions and yields: a) 1. acetone, 1,3-dichloroacetone (**9**); 2. H_2SO_4, 33%; b) KCN, DMF, 70°C, 74%; c) BH_3-THF, MeOH, 25%; NEt_3, PhCOCl, 84% *or* cyclopentanecarbonyl chloride, 59%.

To access the other pyridylthiazoles, an alternative route was devised (Scheme 6). The α-bromoketone **40**,[70] 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[71] with capture of the intermediate isocyanates by the solvent to give the methyl carbamates **46**. Hydrolysis yielded the desired amines as their trihydrochlorides **47**, which were acylated to give the target amides **35**. In the case of the 2-(2-thienyl)thiazole **43c**, Hofmann rearrangement[71] in water gave the primary amine **44** directly, and acylation once again provided the target amides **45**.

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

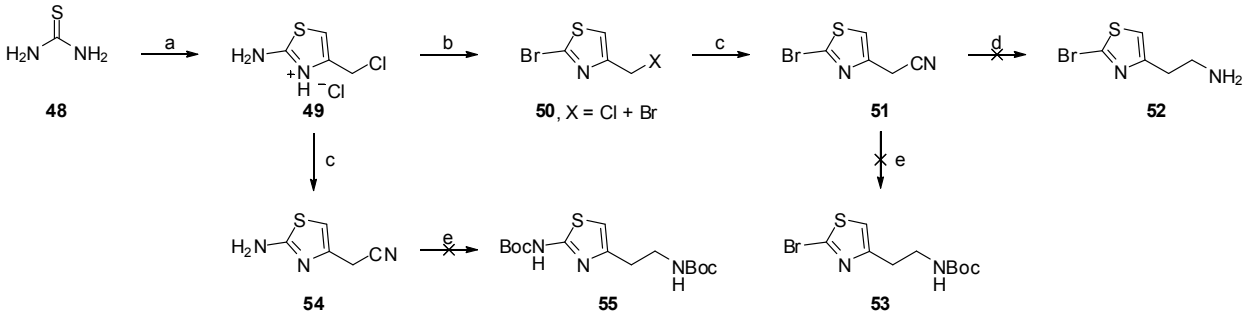


Reagents, conditions and yields: a) MeOH, reflux, 22–60%*; b) conc. NH_3, THF, 45–75%*; c) $PhI(OAc)_2$, H_2O/dioxane, 85%; d) $PhI(OAc)_2$, MeOH, **46a** 59%, **46b** 70%; e) 4 M HCl, reflux, quant.; f) NEt_3, PhCOCl (41–89%) *or* cyclopentanecarbonyl chloride (31–54%)*. Py = pyridyl. *See experimental 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 **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 (**49**), readily prepared from thiourea (**48**) and 1,3-dichloroacetone (**9**).[72] A Sandmeyer reaction[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 ^{1}H 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 ^{1}H NMR spectroscopy, it was not able to be purified.

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

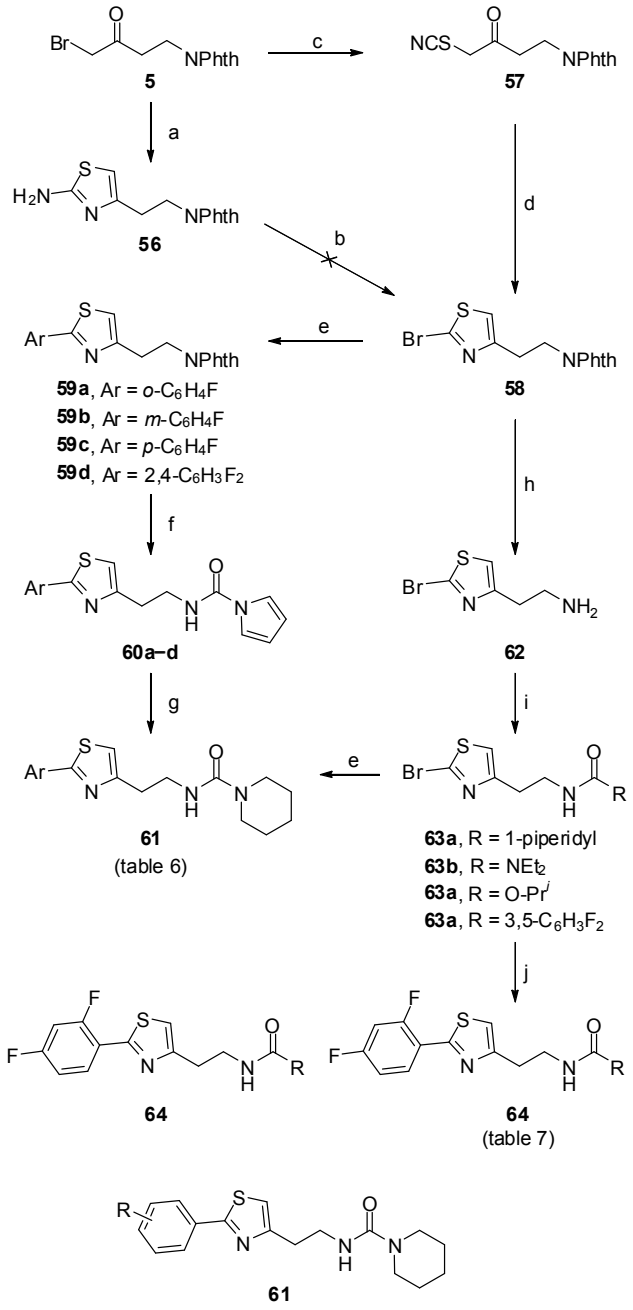


Reagents, conditions and yields: a) acetone, reflux, 82%; b) 1. H_2SO_4, $NaNO_2$, 2. HBr; c). KCN, DMF, 31% (two steps); d) 1. BH_3–THF, MeOH, 2. HCl, 0%; e) 1. $NaBH_4$, $NiCl_2.H_2O$, Boc_2O, MeOH, 2. NEt_3; 0%.

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 ^{1}H 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[75] via the thiocyanate **57**. Initial attempts to remove the phthalimide protecting group were unsuccessful, presumably due to competing S_NAr 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) $NaNO_2$, HBr *or* $NaNO_2$, HCl, NaBr, 0%; c) KSCN, EtOH, 78%; d) HBr, AcOH, reflux, 86%; e) $ArB(OH)_2$, $Pd(PPh_3)_4$, $NaHCO_3$, PhMe, H_2O, 80°C, 40–62%, *or* $ArB(OH)_2$, $PdCl_2dppf$, TBAB, K_2CO_3, dioxane/H_2O 4:1, μw*, 49–73%; f) 1. $H_2NNH_2.H_2O$, MeOH, reflux; 2. CDI, MeCN/DMF, 30–

70% (two steps); g) piperidine, NEt_3, 55–70%; h) $H_2NNH_2.H_2O$, EtOH, 69% ; i) 1. *p*-nitrophenyl chloroformate, NEt_3, DCM, 2. piperidine, 84% (**63a**); j) 1. $H_2NNH_2.H_2O$, EtOH, reflux; 2. ClCOR, NEt_3, 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 IC_{50} values. In parallel, IC_{50} 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]

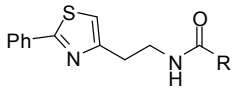


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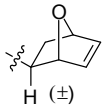
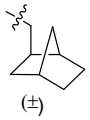
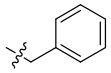
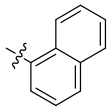
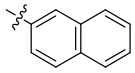
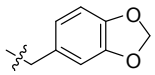
Table 1. Initial SAR around the acyl substituent

#21	R	IC_{50} µM[a] (SI[b]) *T. b. brucei*[d]	IC_{50} µM (SI[c]) *T. cruzi*[e]	#21	R	IC_{50} µM (SI) *T. b. brucei*	IC_{50} µM (SI) *T. cruzi*
a	H	n.i.	n.i.	**i**		5.0 ± 0.2 (17)	–
b	Me	n.i.	n.i.	**j**		5.5 ± 0.1 (15)	–
c	Et	n.i.	n.i.	**k**		n.i.	–
d		5.3 ± 0.3 (16)	40 ± 10.1 (>1.2)	**l**		n.i.	–
e		1.7 ± 0.1 (50)	6.3 ± 0.1 (>7.9)	**m**		n.i.	–
f		0.25 ± 0.01 (334)	0.40 ± 0.04 (>125)	**n**		n.i.	16 ± 8 (>3.1)
g		0.31 ± 0.1 (281)	0.32 ± 0.05 (>158)	**o**		n.i.	40 ± 0 (>1.2)
h		0.25 ± 0.02 (329)	–				

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

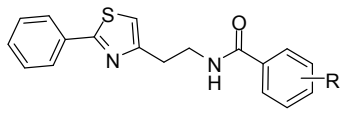
Alicyclic amides were also investigated with both the cyclopentyl- **21h** and cyclohexylcarboxamides **21g** being approximately equipotent with the benzamide **21f**. However, the introduction of an electronegative heteroatom at the 4-position in the tetrahydropyranyl

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 sterics (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 **21Bk**, fitting with the hypothesis discussed earlier, that the target biomolecule contains a hydrophobic acyl-binding pocket.



21B

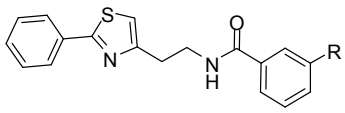
Table 2. Substituted Benzamides 21Ba–21Bq

		ortho-			*meta-*			*para-*	
R	**#21B**	**IC_{50} µM (SI)** ***T. b. brucei***	**IC_{50} µM (SI)** ***T. cruzi***	**#21B**	**IC_{50} µM (SI)** ***T. b. brucei***	**IC_{50} µM (SI)** ***T. cruzi***	**#21B**	**IC_{50} µM (SI)** ***T. b. brucei***	**IC_{50} µM (SI)** ***T. cruzi***
F	**a**	0.47 ± 0.6 (44)	–	**b**	0.19 ± 0.01 (444)	0.50 ± 0.32 (>100)	**c**	0.77 ± 0.19 (54)	–
Cl	**d**	1.5 ± 0.3 (29)	–	**e**	0.42 ± 0.04 (200)	–	**f**	n.i.	–
Me	**g**	3.3 ± 0.8 (2.5)	3.2 ± 0.5 (>15)	**h**	3.9 ± 0.8 (21)	6.3 ± 0.4 (>7.9)	**i**	n.i.	40 ± 12 (1.2)
OH	**j**	2.3 ± 0.1 (18)	7.9 ± 0.7 (>3)	**k**	n.i.	–	–	–	–
OMe	**l**	10.6 ± 3.6 (2.0)	10 ± 0.7 (>5)	**m**	1.9 ± 0.3 (26)	3.2 ± 0.4 (>15)	**n**	n.i.	–
CN	**o**	n.i.	–	**p**	0.13 ± 0.01 (387)	0.79 ± 0.09 (>63)	**q**	n.i.	0.40 ± 0.01 (>126)

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 **21Bo**, bearing the most restrictive cyano group. Interestingly, the salicylamide **21Bj** 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-subsituted 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)[77] 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.



21B

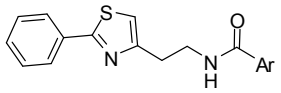
Table 3. Additional 3-substituted benzamides

#21B	R	IC_{50} µM (SI) *T. b. brucei*	IC_{50} µM (SI) *T. cruzi*
r	CF_3	11.6 ± 2.1 (1.8)	n.i.
s	SF_5	n.i.	n.i.
t	SO_2Me	8.5 ± 1.8 (4.9)	40 ± 0.9 (>1.2)
u	C≡CTMS	3.6 ± 0.9 (2.9)	2.0 ± 0.3 (>12)
v	C≡CH	0.76 ± 0.14 (27)	–

See table 1 footnotes for definitions.

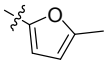
The benzamides exhibited similar SAR against *T. cruzi*, although *meta*-substitution was slightly less well tolerated than in *T. b. brucei*. The biggest difference between the two species is in the activity of the *para*-substituted benzamides: the toluamide **21Bi** was very modestly active, but the 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.



21H

Table 4. Heteroaromatic amides 21Ha–21Ho

#21H	Ar	IC_{50} µM (SI) *T. b. brucei*	IC_{50} µM (SI[a]) *T. cruzi*	#21H	Ar	IC_{50} µM (SI) *T. b. brucei*	IC_{50} µM (SI) *T. cruzi*
a		0.3 ± 0.01 (139)	–	**i**		0.35 ± 0.05 (240)	–
b		0.76 ± 0.28 (110)	2.5 ± 0.05 (>19)	**j**		0.13 ± 0.0006 (666)	–
c		14 ± 1 (3)	40 ± 4 (>1.2)	**k**		2.5 ± 0.1 (12)	5.0 ± 0.4 (>10)
d		4.1 ± 0.1 (20)	32 ± 7 (>1.5)	**l**		1.9 ± 0.3 (22)	–
e		0.35 ± 0.16 (241)	0.40 ± 0.1 (>126)	**m**		0.74 ± 0.2 (113)	2.5 ± 0.3 (>19)
f		0.23 ± 0.03 (179)	–	**n**		n.i.	n.i.
g		1.6 ± 0.4 (13)	6.3 ± 0.1 (>7.9)	**o**		1.2 ± 0.0 (68)	–
h		0.80 ± 0.11 (77)	2.0 ± 0.1 (>25)				

See table 1 footnotes for definitions.

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 electronegative/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

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.

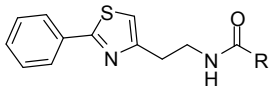
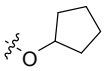
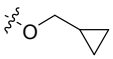
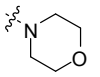


Table 5. Carbamates and ureas

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

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* (IC_{50} = 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* (IC_{50} = 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.*

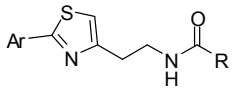
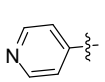
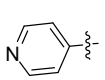


Table 6. Benzamides and cyclopentanecarboxamides bearing heterocycles at the thiazole 2-position. (The corresponding 2-phenylthiazoles are included for comparison)

#	Ar	R	IC_{50} µM (SI) *T. b. brucei*	IC_{50} µM (SI) *T. cruzi*
21f	Ph	Ph	0.25 ± 0.01 (334)	0.40 ± 0.04 (>125)
21h	Ph		0.25 ± 0.02 (329)	–
45a		Ph	1.5 ± 0.2 (40)	–
45b			2.4 ± 0.3 (35)	10 ± 1.4 (>5)
35a		Ph	1.1 ± 0.3 (74)	6.3 ± 0.7 (>7.9)
35b			4.0 ± 1.5 (21)	–
35c		Ph	2.7 ± 0.3 (31)	40 ± 3.7 (>1.2)
35d			6.6 ± 0.3 (13)	20 ± 0.9 (>2.5)
35e		Ph	3.1 ± 0.9 (27)	32 ± 2 (>1.5)
35f			9.1 ± 1.7 (9)	32 ± 13 (>1.5)

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** (IC_{50} *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 IC_{50} 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.

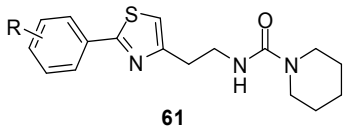


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Table 7. Variation of the thiazole-2-subsituent in piperidine-derived ureas

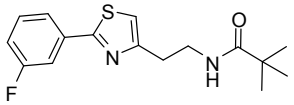
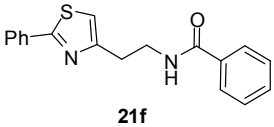
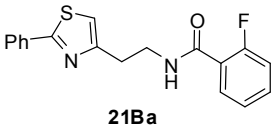
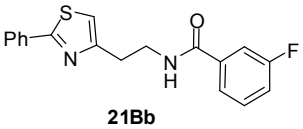
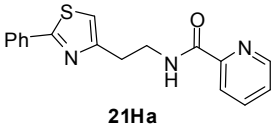
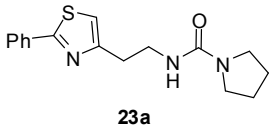
		ortho-			*meta-*			*para-*	
R	**#61**	**IC_{50} µM (SI)** ***T. b. brucei***	**IC_{50} µM (SI)** ***T. cruzi***	**#61**	**IC_{50} µM (SI)** ***T. b. brucei***	**IC_{50} µM (SI)** ***T. cruzi***	**#61**	**IC_{50} µM (SI)** ***T. b. brucei***	**IC_{50} µM (SI)** ***T. cruzi***
F	**a**	0.016 ± 0.005 (650)	0.01 ± 0 (>3981)	**b**	0.026 ± 0.00002 (398)	–	**c**	0.024 ± 0.0009 (431)	0.030 ± 0.01 (>1584)
Cl		–	–	**d**	0.16 ± 0.04 (511)	–	**e**	1.5 ± 0.2 (55)	–
Me	**f**	0.19 ± 0.07 (439)	–		–	–	**g**	3.7 ± 0.5 (22)	–
OMe	**h**	0.50 ± 0.07 (168)	–	**i**	0.67 ± 0.06 (62)	–	**j**	n.i.*	n.i.
CN	**k**	0.56 ± 0.11 (148)	0.79 ± 0.20 (>63)	**l**	0.28 ± 0.01 (149)	–	**m**	0.33 ± 0.06 (125)	–

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

Compound	IC_{50} µM[a]				
	T. b. rhodesiense[b]	*T. cruzi*[c]	*P. falciparum*[d]	*L. donovani*[e]	*L6*[f]
 **1**	1.5 ± 0.4	2.3 ± 0.06	35 ± 3	46 ± 22	62 ± 4
 **21f**	0.078 ± 0.04	0.55 ± 0.18	32 ± 6	25 ± 4	68 ± 8
 **21Ba**	0.42 ± 0.1	1.1 ± 0.3	–	11 ± 6	79 ± 36
 **21Bb**	0.21 ± 0.1	0.20 ± 0.004	41 ± 8	10 ± 2	51 ± 8
 **21Ha**	0.22 ± 0.05	0.9 ± 0.05	65 ± 11	12 ± 2	66 ± 15
 **23a**	0.046 ± 0.014	0.096 ± 0.005	–	17 ± 4	144 ± 7

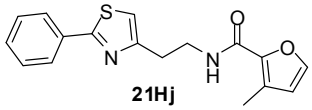
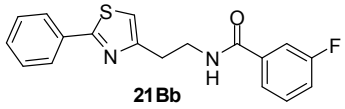
[a]Values are means of two independent experiments ± standard deviation. All assays have been described previously.[78] [b]*T. b. rhodesiense* strain STIB 900, bloodstream form (trypomastigotes). [c]*T. cruzi* Tulahaen C4 strain, amastigote stage. [d]*P. falciparum* K1 strain, erythrocytic stage. [e]*L. donovani* MHOM-ET-67/L82 strain, amastigote stage. [f]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 DND*i* Target Product Profile for HAT.[79] 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).[80] 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 IC_{50} 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

ID	Minimum trypanosomacidal concentration (μM)	Toxic concentration (μM)[a]	IC_{50} (μM)	Max. % inh.
 **21Hj**	0.6	50	0.6	104
 **21Bb**	0.6	17	0.4	106

[a]Concentration at which toxicity to the host (Vero) cells was seen. [b]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.[81] However, the drugability of CYP51 inhibitors has recently been questioned.[82] They act by preventing the biosynthesis of the essential trypanosome membrane lipid ergosterol and,

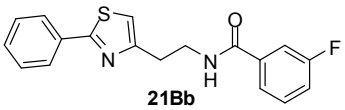
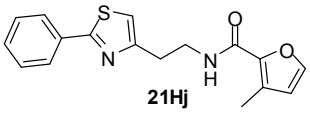
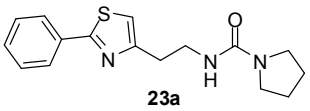
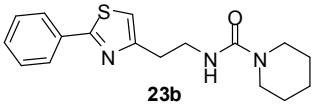
although trypanosomacidal, are slow-acting. CYP51 inhibitors also show variable *T. cruzi* strain-specific activity and, in one study, were unable to clear intracellular infections after seven days of treatment._ENREF_34[82] We were therefore pleased to find that **21Hj** and **21Bb** did not show any CYP51 inhibition using a recently published fluorescence assay.[83] 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.[61]

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%[84] for all compounds.

Table 10. Key physicochemical parameters and predicted protein binding.

	Mw	PSA[a] (Å^2)	logD[b] pH 7.4	Solubility[c] (µg/mL) pH 2	Solubility[c] (µg/mL) pH 6.5	cPPB[d] (%)	CNS MPO[e]
TARGET	< 500	< 85	≤ 5	≥ 20	≥ 20	< 99.5	–
 **21Bb**	326	42	3.6	6–12	ND*	96	4.6
 **21Hj**	312	55	3.5	6–12	6–12	95	4.9
 **23a**	301	45	2.8	>100	50–100	86	5.4
 **23b**	315	45	3.2	50–100	25–50	90	5.2

[a]Calculated using ACD/Laboratories software, version 9. [b]Measured chromatographically.[85] [c]Kinetic solubility determined by nephelometry. [d]Human plasma protein binding estimated using a chromatographic method.[85] [e]pKa and LogP for the CNS MPO calculation[61] were predicted using ACD/Laboratories software, version 9. *Could not be determined.

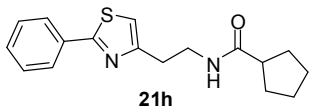
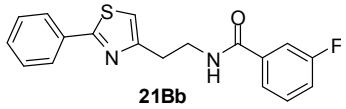
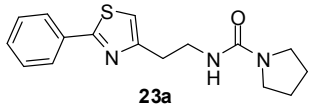
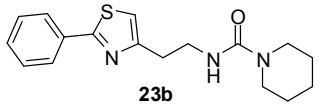
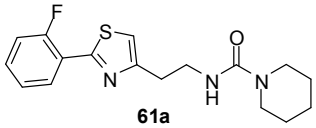
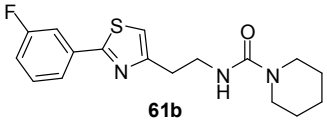
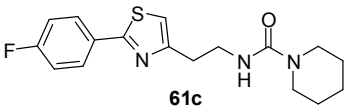
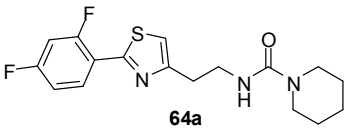
A consistent deficiency of this class of compounds is a lack of metabolic stability, as assessed *in vitro*, using mouse and human liver microsomes (**Table 11**). The first results obtained for **21Bb**, **23a** and **23b**, indicated rapid metabolism by human liver microsomes.

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).

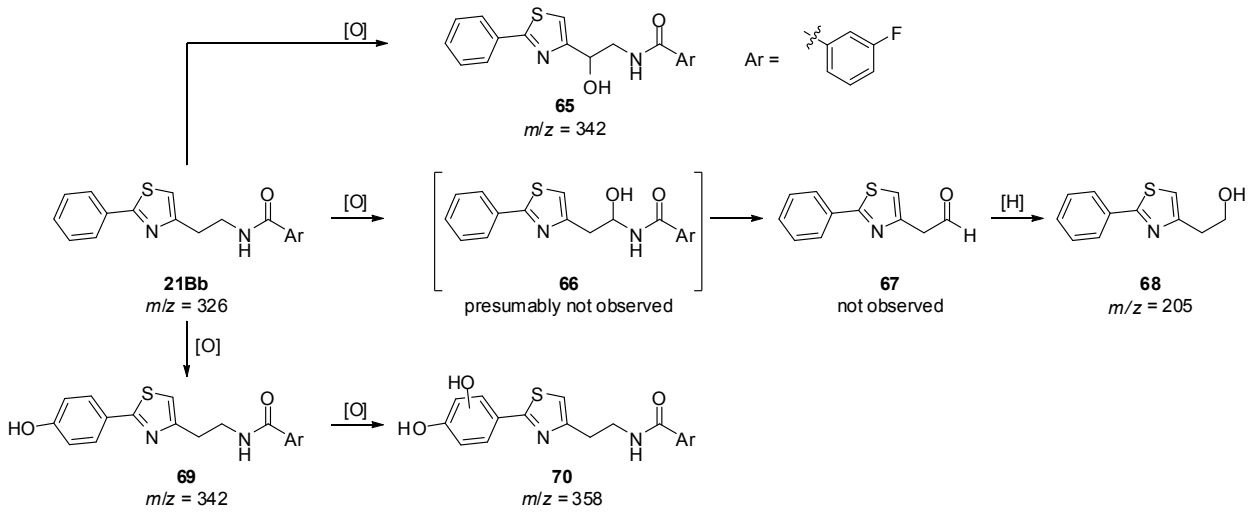
To assess the potential for phase II glucuronidation, **21Bb** was incubated with microsomes in the presence of NADPH and UDPGA (uridine 5'-diphosphoglucuronic acid). Degradation followed by LCMS showed there was no difference in the rate/extent of parent loss compared to that with NADPH alone. However, 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.

	Degradation half-life (min)		*in vitro* CL_{int}[a] (µL/min/mg protein)		Microsome-predicted E_H[b] target = < 0.6	
	Mouse	**Human**	**Mouse**	**Human**	**Mouse**	**Human**
 **21h**	–	**6**	–	296	–	0.92
 **21Bb**	–	4	–	484	–	0.95
 **23a**	–	10	–	177	–	0.88
 **23b**	–	7	–	244	–	0.91
 **61a**	<2	4	>1600	439	>0.97	0.95
 **61b**	<2	4	>1600	445	>0.97	0.95
 **61c**	<2	11	>1600	160	>0.97	0.86
 **64a**	<2	8	>1600	225	>0.97	0.90

[a] In vitro intrinsic clearance determined in human and mouse liver microsomes and [b] 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 sp^3-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.

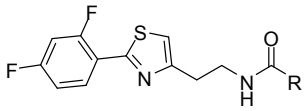
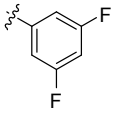


Table 12. 2-(2,4-Diphenylthiazoles): antitrypanosomal activity and in vitro metabolism in human liver microsomes.

#	R	IC_{50} µM (SI) *T. b. brucei*	IC_{50} µM (SI) *T. cruzi*	Half-life (min)	*in vitro* CL_{int} (uL/min/mg protein)	Microsome-predicted E_H DND*i* target = < 0.6
64a		0.024 ± 0.003 (433)	0.020 ± 0.01 (>3162)	5	267	0.93
64b		–	0.25 ± 0.05 (>199)	8	177	0.90
64c		–	0.13 ± 0.005 (>398)	10	135	0.87
64d		–	0.13 ± 0.007 (>398)	6	231	0.92

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),[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.[a]

Treatment[a]	T_{max} (h)	C_{max} (ng/mL)	AUC_{last} (0-t) (h*ng/mL)	C_{max}_D (kg*ng/mL/mg)	[a]$DNAUC_{last}$ (h*ng/mL/mg/kg)[b]
64a	0.25 ± 0.00	212 ± 77	127 ± 31	4.3 ± 1.5	2.54
ABT then **64a**	0.50 ± 0.25	7090 ± 1300	14792 ± 3988	142 ± 26	295

[a] Balb/c mice used, n = 3 ± SD; [b] Blood analysed following oral galvage administration of **64a** (50 mg/kg) in 2% methylcellulose + 0.5% Tween 80; [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**).

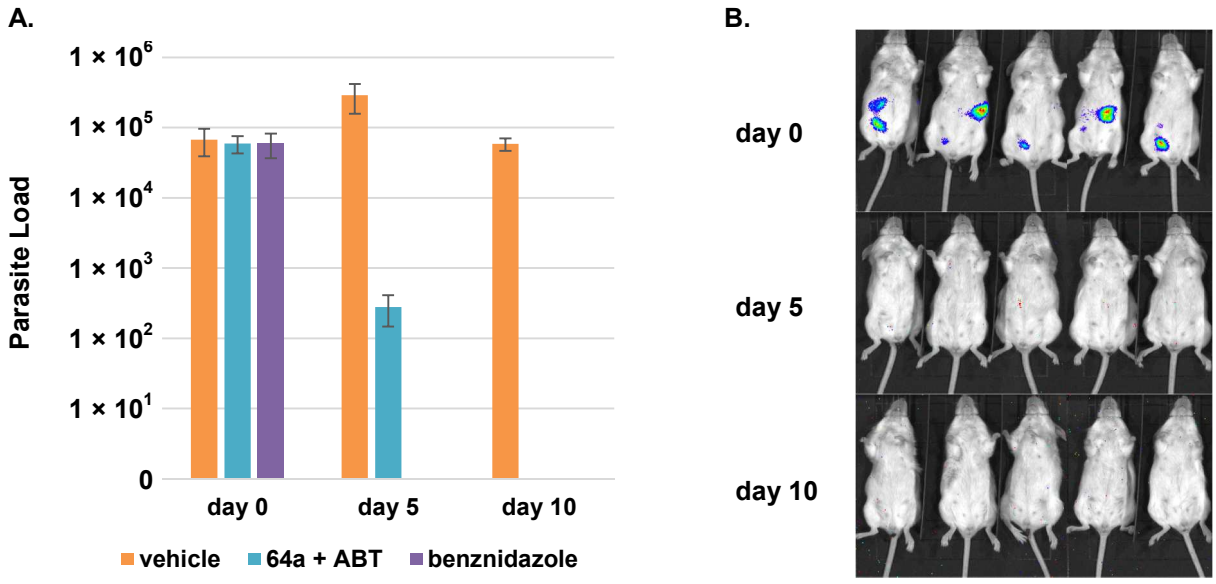


Figure 3. In vivo efficacy study. Balb/c mice infected with the trypomastigote form of transgenic *T. cruzi* Brazil strain expressing firefly luciferase,[40] were treated by oral gavage with vehicle (PBS with 2% methylcellulose and 0.5% Tween 80, once daily); or twice daily **64a** (50 mg/kg, preceded 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,[88] an essential pre-requisite for developing anti-chagasic drugs.

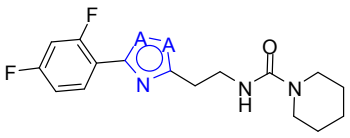
There were physical signs that **64a** is toxic to mice (hunched, ruffled fur, low resistance to handling, etc.). On suspension of treatment, the mice did appear to recover, however. Both the apparent toxicity and parasite rebound can possibly be addressed by improving metabolic stability – allowing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

Compound novelty and related work

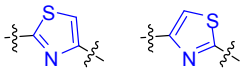
Although a few of the amides described herein are commercially available, and are members of large compound collections, to the best of our knowledge no other significant biological activity has been described for this class of compounds. We were the first group to report this class of anti-trypanosomal compounds.[60] 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.[89]

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.



IC_{50} (nM)



	64a	**70**
T. b. brucei	24	–
T. b. rhodesiense	–	9.9
T. cruzi	20	–

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_{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 *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 ≥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 descibed previously in 60% yield.[62] ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.81−7.85 (m, 2H, 2 × Ar), 7.76−7.80 (m, 2H, 2 × Ar), 7.67–7.72 (m, 2H, 2 × Ar), 7.32–7.38 (3H, m, 3 × 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'). ^{13}C NMR (126 MHz, $CDCl_3$) δ 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 ^{1}H NMR data are similar to those reported at 60 MHz.

2-(2-Phenylthiazol-4-yl)ethanamine (8).[62] Prepared as descibed previously in 50% yield. IR (cm^{-1}): 3368 (NH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 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_2 + H_2O). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.0 (C2'), 156.3 (C4'), 133.8 (C1"), 130.0 (C4"), 129.0 (2 × ArH), 126.6 (2 × ArH), 114.1 (C5'), 41.8 (C1), 35.7 (C2).

4-Chloromethyl-2-phenylthiazole (10).[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 × 100 mL, then air-dried. The solid was dissolved in conc. sulfuric acid (80 mL) and the solution was stirred for 30 min, then poured onto ice and cold water was added until no more solid precipitated. The precipitate was collected by vacuum filtration, washed with water (3 × 100 mL) and air-dried to yield **10** as a white solid (17.4 g, 85%), mp = 43–45 °C [lit.[63] 53–55 °C]. ^{1}H NMR (400 MHz,

$CDCl_3$) δ 7.94−7.96 (m, 2H, H2'/H6'), 7.43−7.45 (m, 3H, H3'/H4'/H5'), 7.30 (t, J_1 = 0.8 Hz, 1H, H5), 4.75 (s, 2H, CH_2). The ^{1}H 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 N_2 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 (Na_2SO_4) and evaporated to give the nitrile **11** as a brown solid (3.75 g, 94%) of sufficient purity for the next step. ^{1}H 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, CH_2). This compound was first reported before the advent of spectroscopic characterisation.[64]

***tert*-Butyl (2-(2-phenylthiazol-4-yl)ethyl)carbamate (12)**. $NaBH_4$ (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), $NiCl_2$ (0.320 g, 1.35 mmol) and nitrile **11** (2.62 g, 13.1 mmol) in dry methanol (100 mL) at 0 °C under N_2. The reaction mixture was allowed to warm to room temperature and stirring was continued for 90 min NEt_3 (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 NH_4Cl (3 × 300 mL), dried, filtered and evaporated to yield **12** as an orange oil (3.27 g, 82%). R_f 0.5 (2:3 EtOAc/hexanes + NEt_3). IR (cm^{-1}): 3337 (NH), 1693 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$) 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], J_1= J_2 = 6.4 Hz, 2H, H1), 2.99 (t, J_1 = 6.4 Hz, 2H, H2), 1.44 (s, 9H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$)

δ 168.2 (C2'), 156.1 (C4' or C=O), 155.6 (C4' or C=O), 133.8 (C1''), 130.1 (C4''), 129.0 (2 × ArH), 126.6 (2 × ArH), 114.4 (C5'), 79.3 (O–C), 40.1 (C1), 31.9 (C2), 28.4 (CH_3). HRMS (ESI) *m/z* observed: 305.1305, $C_{16}H_{21}N_2O_2S^+$ $[M+H]^+$ requires 305.1318.

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 N_2 to yield **13** as a yellow solid (0.518 g, mmol, quant.), mp = 140–142 °C. IR (cm^{-1}): 2443–3986 (NH). ^{1}H 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, J_1 = 7.2 Hz, 2H, H2), 3.16 (t, J_1 = 7.2 Hz, 2H, H1). ^{1}H NMR (DMSO, 500 MHz): δ 8.53 (br s, ^{1}H, NH), 8.26 (br. s, 3H, NH_3), 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). ^{13}C 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, $C_{11}H_{13}N_2S^+$ [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 $NaHCO_3$ (75 mL) and brine (50 mL). The organic layer was dried over $MgSO_4$, 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%). ^{1}H NMR (400 MHz, $CDCl_3$) 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 $LiAlH_4$ (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 Na_2SO_4 and concentrated under vacuum. The resulting material was purified by column chromatography on silica to afford **16** (759 mg, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) 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 NEt_3 (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 Na_2SO_4, 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 NaN_3 (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 Na_2SO_4 and concentrated in vacuum. The crude material was purified by column chromatography on silica to afford **18** (71 mg, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) 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 NEt_3 (0.2 mL) and **8** (0.21 g, 1.0 mmol) in DCM (2 mL) at 0 °C under N_2. The ice-bath was removed and stirring was continued for 90 min The reaction mixture was diluted with DCM (10 mL) and washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$) 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 NEt_3 (2.5 equiv) and **13** (1 equiv) in

DCM (10 mL per mmol of **13**) at 0 °C under N_2. 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 N_2. 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 N_2, 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)ethyl)formamide (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) δ 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) δ 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 (CI) *m/z* observed: 233.0744, $C_{12}H_{13}N_2OS^+$ $[M+H]^+$ requires 233.0743.

***N*-(2-(2-Phenylthiazol-4-yl)ethyl)acetamide (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, $CDCl_3$) δ, 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, $CDCl_3$) δ 170.2

(CO), 168.4 (C2''), 155.6 (C4''), 133.7 (C1''), 130.3 (C4'''), 129.2 (2 × ArH), 126.5 (2 × ArH), 114.6 (C5''), 39.2 (C1'), 31.1 (C2'), 23.6 (CH_3). HRMS (CI) *m/z* observed: 247.0899, $C_{13}H_{15}N_2OS^+$ $[M+H]^+$ requires 247.0900.

***N*-(2-(2-Phenylthiazol-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, $CDCl_3$) δ, 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, 3H, CH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ 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 (CH_3). HRMS (CI) *m/z* observed: 261.1064, $C_{13}H_{15}N_2OS^+$ $[M+H]^+$ requires 261.1056.

***N*-(2-(2-Phenylthiazol-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, $CDCl_3$) δ, 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, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 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 × CH_3). HRMS (CI) *m/z* observed: 275.1211, $C_{15}H_{19}N_2OS^+$ $[M+H]^+$ 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). ^{1}H NMR (400 MHz, $CDCl_3$) 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] J_1 = J_2 = 6.2 Hz, 2H, H1'), 2.99 (t, J = 6.0 Hz, 2H, H2'), 1.19 (s, 9H, CH_3). ^{13}C NMR (126 MHz, $CDCl_3$) 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 × CH_3). HRMS (CI) *m/z* observed: 289.1369, $C_{15}H_{19}N_2OS^+$ $[M+H]^+$ 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). ^{1}H NMR (400 MHz, $CDCl_3$) 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] J_1 = J_2 = 6.8 Hz, 2H, H1'), 3.11 (t, J = 6.4 Hz, 2H, H2'). ^{13}C NMR (101 MHz, $CDCl_3$) 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, $C_{15}H_{19}N_2OS^+$ $[M+H]^+$ 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. R_f 0.3 (1:4 EtOAc/hexanes). IR (cm^{-1}): 3293 (NH), 1637 (C=O). ^{1}H

NMR (400 MHz, $CDCl_3$) δ 7.93 (m, 2H, H2'''/H6'''), 7.43 (m, 3H, H3'''/H4'''/H5'''), 6.95 (s, 1H, H5''), 6.55 (br. s, 1H, NH), 3.62 (dt [app. q], $J_1 = J_2 = 6.2$ Hz, 2H, H1'), 2.99 (t, $J_1 = 6.0$ 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). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.2 (C=O), 168.3, (C2''), 155.8 (C4''), 133.7 (C1'''), 130.2 (C4'''), 129.1 (2 × ArH), 126.5 (2 × ArH), 114.5 (C5''), 45.6 (C1'), 38.9 (C1), 30.9 (C2'), 29.8 (C2/C6), 25.90 (C4), 25.87 (C3/C5). HRMS (CI) *m/z* observed: 315.1533, $C_{18}H_{23}N_2OS^+$ $[M+H]^+$ requires 315.1531.

***N*-(2-(2-Phenylthiazol-4-yl)ethyl)cyclopentanecarboxamide (21h)**. Prepared according to general procedure E with cyclopentanecarboxylic acid. ^{1}H NMR (400 MHz, $CDCl_3$) 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.] $J_1 = J_2 = 6.5$ 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-2*H*-pyran-4-carboxamide (21i)**. Prepared according to general procedure E with tetrahydro-2*H*-pyran-4-carboxylic acid. ^{1}H NMR (400 MHz, $CDCl_3$) 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 $[M + H]^+$.

(±)-(1*R,2*S**,4*R**)-*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. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.91–7.98 (m, 2H), 7.43–7.59

(m, 3H), 6.98 (s, 1H), 5.81 (dd, J = 10.9, 5.8 Hz, 1H), 5.76 (dd, J = 10.4, 6.1 Hz, 1H), 4.81 (dd, J = 6.9, 6.2 Hz, 1H), 4.35–4.41 (m, 1H), 3.59–3.72 (m, 6H), 3.12 (t, J = 6.6 Hz, 2H), 2.26–2.32 (m, 1H), 1.99–2.05 (m, 1H). LRMS (ESI+) *m/z*: 326 $[M + H]^+$.

(±)-2-((1*R,2*S**,4*S**)-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, $CDCl_3$) δ 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, $CDCl_3$) δ 7.81−7.84 (m, 2H, H2'''/H6'''), 7.41−7.43 (m, 3H, H3'''/H4'''/H5'''), 7.19−7.21 (m, 5H, benzyl Ar), 6.79 (s, 1H, H5''), 6.13 (br s, 1H, NH), 3.61 (dt [app. q], $J_1 = J_2$ = 6.4 Hz, 2H, H1'), 3.53 (s, 2H, H2), 2.92 (t, J = 6.4 Hz, 2H, H2'). ^{13}C NMR (101) MHz, $CDCl_3$) δ 171.1 (C=O), 168.2 (C2''), 155.3 (C4''), 135.0 (C1''' or C1''''), 133.6 (C1''' or C1''''), 130.1 (ArH), 129.4 (2 × ArH), 129.0 (2 × ArH), 129.0 (2 × ArH), 127.3 (ArH), 126.5 (2 × ArH), 114.5 (C5''), 44.1 (C2), 39.0 (C1'), 31.0 (C2'). HRMS (EI) *m/z* observed: 322.1147, $C_{19}H_{18}N_2OS$ $[M^{\bullet+}]$ 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-naphthoic 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. R_f 0.2 (1:1 EtOAc/hexanes). IR (cm^{-1}): 3288 (NH), 1644 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$) 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, J_1 = 7.0 Hz, J_2 = 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], $J_1 = J_2$ = 6.2 Hz, 2H, H1'), 3.18 (t, J = 6.4 Hz, 2H, H2'). ^{13}C NMR (101 MHz, $CDCl_3$) 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, $C_{22}H_{19}N_2OS^+$ $[M+H]^+$ 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. R_f 0.3 (1:4 EtOAc/hexanes). IR (cm^{-1}): 3301 (NH), 1644 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$) 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], $J_1 = J_2$ = 6.0 Hz, 2H, H1'), 3.16 (t, J_1 = 6.0 Hz, 2H, H2'). ^{13}C NMR (101 MHz, $CDCl_3$) 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, $C_{22}H_{19}N_2OS^+$ $[M+H]^+$ 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. R_f 0.15 (1:1 EtOAc/hexanes). IR (cm^{-1}): 3295 (NH), 1647 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81−7.85 (m, 2H, H2'''/H6'''), 7.41−7.45 (m, 3H, H3'''/H4'''/H5'''), 6.85 (s, 1H, H5''), 6.62−6.67 (m, 2H, H4''''/H7''''), 6.6 (dd, *J* = 8.2, 1.4 Hz, 1H, H6''''), 6.19 (br. s,1H, NH), 5.81 (s, 2H, H2''''), 3.63 (dt [app. q], *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, $CDCl_3$) δ 171.2 (C=O), 168.2 (C2''), 155.3 (C4''), 148.0 (ArO), 146.8 (ArO), 133.6 (C1'''), 130.1 (C4'''), 129.0 (2 × ArH), 128.6 (C5''''), 126.4 (2 × ArH), 122.6 (ArH), 114.5 (C5''), 109.7 (ArH), 108.6 (ArH), 101.1 (CH_2O_2), 43.6 (C2), 38.9 (C1'), 31.0 (C2'). HRMS (EI) *m/z* observed: 366.1042, $C_{20}H_{18}N_2O_3S$ [$M^{\bullet+}$] 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, $CDCl_3$) δ 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, $CDCl_3$) δ 168.5 (C2''), 163.4 (d, *J* = 3 Hz, C=O), 160.7 (d, *J* = 249 Hz, C2F), 155.5 (C4''), 133.7 (C1'''), 133.2 (d, *J* = 9 Hz, C6), 132.1 (d, *J* = 3 Hz, C4), 130.1 (C4'''), 129.0 (2 × ArH), 126.6 (2 × ArH), 124.8 (d, *J* = 3 Hz, C5), 121.5 (d, *J* = 11 Hz, C1), 116.1 (d, *J* = 25 Hz,

C3), 114.5 (C5''), 39.7 (C1'), 31.1 (C2'). HRMS (ESI) *m/z* observed: 327.0982, $C_{18}H_{16}FN_2OS^+$ $[M+H]^+$ 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%). R_f 0.5 (3:10 EtOAc/hexanes). IR (cm^{-1}): 3332 (NH), 1644 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94–7.96 (m, 2H, H2'''/H6'''), 7.88 (br. s, 1H, NH), 7.57–7.63 (m, 2H, H2/H6), 7.44–7.47 (m, 3H, H3'''/H4'''/H5'''), 7.35–7.40 (m, 1H, H4 or H5), 7.19 (dddd [app. ddt], $J_1 = J_2 = 8.4$, $J_3 = 2.6$, $J_4 =$ 1.0 Hz, 1H, H4), 7.03 (t, $J = 0.8$ Hz, 1H, H5''), 3.82 (pseudo q., 2H, H1'), 3.10 (dt, $J = 6.0$, 0.8 Hz, 2H, H2'). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.8 (C2''), 166.1 (d, $J = 2$ Hz, C=O), 162.9 (d, J = 249 Hz, C3F), 155.8 (C4''), 137.3 (d, $J = 7$ Hz, C3), 133.5 (C1'''), 130.4 (C4'''), 130.3 (d, $J = 8$ Hz, C5), 129.2 (2 × ArH), 126.6 (2 × ArH), 122.7 (d, J = 3 Hz, C6), 118.4 (d, $J = 22$ Hz, C2 or C4), 114.8 (C5''), 114.4 ($J = 23$ Hz, C2 or C4), 114.3 (C2), 40.0 (C1'), 30.5 (C2'). HRMS (ESI) *m/z* observed: 327.0982, $C_{18}H_{16}FN_2OS^+$ $[M+H]^+$ 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. R_f 0.20 (1:3 EtOAc/hexanes). IR (cm^{-1}): 3333 (NH) 1651 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92−7.95 (m, 2H, H2/H6 or H2'''/H6'''), 7.83−7.87 (m, 2H, H2/H6 or H2'''/H6'''), 7.72 (br s, 1H, NH), 7.45−7.47 (m, 3H, H3'''/H4'''/H5'''), 7.03 (dd [app.t], $J_{ortho} = J_{H–F} = 8.6$ Hz, 2H, H3/H5), 7.03 (s, 1H, H5''), 3.78 (dt [app. q], $J = 5.6$ Hz, 2H, H1'), 3.08 (t, $J = 5.6$ Hz, 2H, H2'). ^{13}C NMR

(101 MHz, $CDCl_3$) 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, $C_{18}H_{15}FN_2OS$ [$M^{\bullet+}$] requires 326.0889.

2-Chloro-*N*-(2-(2-phenylthiazol-4-yl)ethyl)benzamide (21Bd). Prepared according to general procedure E with 2-chlorobenzoic acid. ^{1}H NMR (400 MHz, $CDCl_3$) 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. ^{1}H NMR (400 MHz, $CDCl_3$) 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], $J_1 = J_2$ = 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. ^{1}H NMR (400 MHz, $CDCl_3$) 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], $J_1 = J_2$ = 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. R_f 0.5 (2:3 EtOAc/hexanes). IR (cm^{-1}): 3289 (NH), 1621 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86–7.87 (m, 2H, H2'''/H6'''), 7.39–7.41 (m, 4H, H3'''/H4'''/H5'''/H6), 7.25 (ddd [app. dt], $J_1 = J_2 = 7.6$ Hz, $J_3 = 1.6$ 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], $J_1 = J_2 = 6.0$ Hz, 2H, C1'), 3.12 (t, $J_1 = 6.4$ Hz, 2H, C2'), 2.45 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) 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 (CH_3). HRMS (ESI) *m/z* observed: 323.1211, $C_{19}H_{19}N_2OS^+$ $[M+H]^+$ 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. R_f 0.25 (1:3 EtOAc/hexanes). IR (cm^{-1}): 3329 (NH), 1640 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$) 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, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) 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 (CH_3). HRMS (EI) *m/z* observed: 322.1144, $C_{19}H_{18}N_2OS$ $[M^{\bullet+}]$ 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. R_f 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, H2'''/H6'''), 7.73 (d, J = 8.4 Hz, 2H, H2/H6), 7.59 (br. s, 1H, NH), 7.44–7.47 (m, 3H, H3'''/H4'''/H5'''), 7.20 (d, J = 8.4 Hz, 2H, H3/H5), 7.03 (s, 1H, H5''), 3.83 (dt [app. q], $J_1 = J_2$ = 6.8 Hz, 2H, H1'), 3.12 (t, J = 6.4 Hz, 2H, H2'), 2.36 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3 (C=O or C2''), 167.4 (C=O or C2''), 155.7 (C4''), 141.7 (C4), 133.5 (C1'''), 132.0 (C1), 130.2 (ArH), 129.1 (2 × ArH), 129.0 (2 × ArH), 127.0 (2 × ArH), 126.5 (2 × ArH), 114.6 (C5''), 39.6 (C1'), 30.7 (C2'), 21.5 (CH_3). HRMS (ESI) *m/z* observed: 323.1209, $C_{19}H_{19}N_2OS^+$ $[M+H]^+$ 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. R_f 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, H2'''/H6'''), 7.53 (d, J = 7.2 Hz, 1H, H6), 7.47 (m, 3H, H3'''/H4'''/H5'''), 7.37 (dd [app. t], $J_1 = J_2$ = 8.0 Hz, 1H, H4), 7.05 (s, 1H, H5''), 6.97 (d, J = 8.0 Hz, 1H, H3), 6.79 (dd [app. t], $J_1 = J_2$ = 7.2 Hz, 1H, H4), 3.81 (dt [app. q], $J_1 = J_2$ = 5.9 Hz, 2H, H2'), 3.11 (t, J = 6.4 Hz, 2H, H1'). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.0 (C=O or C2''), 168.9 (C=O or C2''), 161.7 (C2), 155.4 (C4''), 134.1 (C3), 133.4 (C1'''), 130.5 (ArH), 129.2 (2 × ArH), 126.6 (2 × ArH), 125.9 (ArH), 118.61 (C3 or C5), 118.58 (C3 or C5),

115.0 (C5''), 114.8 (C1), 39.3 (C1'), 30.2 (C2'). HRMS (ESI) *m/z* observed: 325.1024, $C_{18}H_{17}N_2O_2S^+$ $[M+H]^+$ 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, $CDCl_3$) δ 8.11 (s, ^{1}H), 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, 0.0.754 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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, $C_{19}H_{19}N_2O_2S^+$ $[M+H]^+$ 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. R_f 0.5 (1:1 EtOAc/hexanes). IR (cm^{-1}): 3332 (NH), 1644 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92–7.95 (m, 2H, H2'''/H6'''), 7.69 (br. s, 1H, NH), 7.41–7.45 (m, 4H, H3'''/H4'''/H5'''/H2), 7.36 (ddd [app. dt], 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 = 8.2, 2.6, 1.0 Hz, 1H, H4), 3.81 (s, 3H, CH_3), 3.83 (pseudo q. 2H, H1'), 3.09 (t, J_1 = 6.0 Hz, 2H, H2'). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.3 (C2''), 159.9 (C3 or C=O), 155.8 (C3 or C=O), 136.5 (C4''), 133.5 (C1'''), 130.2 (ArH), 129.5 (ArH), 129.1 (2 × ArH), 126.6 (2 × ArH), 118.9 (ArH), 117.6 (ArH), 114.6 (C5''), 112.4 (ArH), 55.5 (CH_3), 39.7 (C1'), 30.7 (C2'). HRMS (EI) *m/z* observed: 338.1077, $C_{19}H_{18}N_2O_2S$ [$M^{\bullet+}$] 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. R_f 0.35 (2:3 EtOAc/hexanes). IR (cm^{-1}): 3384 (NH), 1650 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93−7.97 (m, 2H, H2'''/H6'''), 7.78−7.81 (m [AB], 2H, H2/H6), 7.75 (br. s, 1H, NH), 7.43−7.47 (m, 3H, H3'''/H4'''/H5'''), 7.02 (s, 1H, H5''), 6.87−6.91 (m [AB], 2H, H3/H5), 3.83 (s, 3H OMe), 3.80−3.84 (m, 2H, H1'), 3.10 (t, J_1 = 5.6 Hz, 2H, H2'). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0 (C2''), 165.4 (C=O), 157.6 (C4), 155.8 (C4''), 133.8 (C1'''), 132.7 (ArH), 132.3 (ArH), 130.1 (ArH), 129.0 (2 × ArH), 126.6 (2 × ArH), 121.8 (C1), 121.3 (ArH), 114.5 (C5''), 111.4 (C3/C5), 55.9 (OMe), 39.2 (C1'), 31.6 (C2'). HRMS (ESI) *m/z* observed: 339.1167, $C_{19}H_{19}N_2O_2S^+$ $[M+H]^+$ 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_f 0.4 (2:3 EtOAc/hexanes). IR (cm^{-1}): 3276 (NH), 2227 (CN), 1650 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (v. br. s, NH), 7.81–7.85 (m, 3H, H3/H2'''/H6'''), 7.75 (br. d, J_1 = 8.0 Hz, H6), 7.59–7.67 (m, 2H, H4/H5), 7.35–7.38 (m, 3H, H3'''/H4'''/H5'''), 6.98 (s, 1H, H5''), 4.23 (t, J_1 = 7.2 Hz, 2H, H1'), 3.24 (t, J_1 = 7.2 Hz, 2H, H2'). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.2 (C2'' or C=O), 168.0 (C2'' or C=O), 154.5 (C4''), 133.7, 133.0 (ArH), 132.3 (ArH), 131.2, 130.0 (ArH), 129.0 (2 × ArH), 126.6 (2 × ArH), 126.5 (ArH), 123.3 (ArH), 121.2 (br. CN), 114.8 (C5''), 37.8 (C1'), 30.1 (C2'). Two pairs of signals are isochronous or too broad to be observed. HRMS (ESI) *m/z* observed: 334.1028, $C_{19}H_{16}N_3OS^+$ $[M+H]^+$ 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_f 0.3 (2:3 EtOAc/hexanes). IR (cm^{-1}): 3322 (NH), 2231 (CN), 1644 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (m, 1H, H2), 8.09 (br. s, 1H, NH), 8.08 (ddd, J = 8.0 Hz, 1.5, 1.0 Hz, 1H, H4 or H6), 7.88–7.90 (m, 2H, H2'''/H6'''), 7.74 (ddd, J = 7.5, 1.5, 1.0 Hz, 1H, H4 or H6), 7.50 (ddd [app. dt], $J_1 = J_2$ = 7.5, J_3 = 0.5 Hz, 1H, H5), 7.47 (m, 3H, H3'''/H4'''/H5'''), 7.03 (s, 1H, H5''), 3.82 (pseudo q, 2H, H1'), 3.11 (t, J = 6.0 Hz, 2H, H2'). ^{13}C NMR (126 MHz, $CDCl_3$): δ 168.9 (C2''), 165.1 (C=O), 155.4 (C4''), 136.1 (C1'''), 134.6 (ArH), 133.1, 131.6 (ArH), 130.7 (ArH), 130.6 (ArH), 129.6 (ArH), 129.3 (2 × ArH), 126.4 (2 × ArH), 118.9 (CN), 115.0 (C5''), 112.9 (C3), 40.0 (C1'), 30.3 (C2'). HRMS (ESI) *m/z* observed: 334.1006, $C_{19}H_{16}N_3O^+$ $[M+H]^+$ 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. R_f 0.3 (3:10 EtOAc/hexanes). IR (cm^{-1}): 3309 (NH) 2227 (CN), 1631 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (br. unresolved t, 1H NH), 7.87–7.93 (m, 4H, 4 × ArH), 7.64–7.67 (m, 2 × ArH), 7.39–7.47 (m, 3H, H3'"/H4'"/H5'"), 7.02 (s, 1H, H5"), 3.80 (pseudo q, 2H, H1'), 3.08 (t, *J* = 6.0 Hz, 2H, H2'). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.6 (C2" or C=O), 165.4 (C2" or C=O), 155.4 (C4"), 138.8 (C1'"), 133.4 (C4), 132.4 (2 × ArH), 130.5 (C4'"), 129.1 (2 × ArH), 127.8 (2 × ArH), 126.4 (2 × ArH), 118.2 (CN), 114.88 (C5"), 114.88 (C1), 39.9 (C1'), 30.3 (C2'). HRMS (ESI) *m/z* observed: 334.1018, $C_{19}H_{16}N_3OS^+$ $[M+H]^+$ 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. R_f = 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: δ 8.36 (s, 1H, H2)^, 8.27 (d, *J* = 8.0 Hz, ^{1}H, H6) 8.11 (s, 1H, H2)*, 8.04 (dd, *J* = 7.8, 0.4 Hz 1H, H6)* 7.88 (br. s, ^{1}H, 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 = J_3 = 0.8 Hz, H4)*, 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, ^{1}H, H5")*^, 3.83–3.88 (m [pseudo q]), 2H, H1'), 3.10–3.14 (m [pseudo t], 2H, H2'). ^{13}C NMR ($CDCl_3$, 101 MHz): δ (major rotamer only) 169.0 (C=O), 166.1 (C2"), 155.7 (C4"), 135.7 (C1'" 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, CF_3), 114.8 (C5"), 40.0 (C1′), 30.5 (C2′). HRMS (ESI) *m/z* observed: 377.0934, $C_{19}H_{16}F_3N_2O_2S^+$ $[M+H]^+$ 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%). R_f = 0.35 (1:1 EtOAc/hexanes). IR (cm^{-1}): 3311 (NH), 1641 (CO). ^{1}H NMR ($CDCl_3$, 500 MHz): Two rotamers, 21:4, * = major, ^ = minor: δ 8.48 (dd [app. t], J_1 = J_2 = 1.8 Hz, 1H, H2)^, 8.26 (dd [app. t], J_1 = J_2 = 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], J_1 = J_2 = 8.0 Hz, ^{1}H, H5)^, 7.50 (dd [app. t], J_1 = J_2 = 8.0 Hz, ^{1}H, H5)*, 7.40–7.47 (m, 3H, H3'"/H4'"/H5'")*^, 7.04 (s, 1H, H5")*^, 3.85 (dt [app. q], J_1 = J_2 = 5.5 Hz, 2H, H1')*^, 3.12 (t, J = 5.5 Hz, 2H, H2'). ^{13}C NMR ($CDCl_3$, 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, CSF_5) 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, $C_{18}H_{16}F_5N_2OS_2^+$ $[M+H]^+$ 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%). R_f = 0.05 (1:1 EtOAc/hexanes). IR (cm^{-1}): 3320 (NH), 1644 (CO). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.40 (dd [app.t.], $J_1 = J_2$ = 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], $J_1 = J_2$ = 6.0 Hz, 2H, H1'), 3.12 (t, J = 6.0 Hz, 2H, H2'), 3.04 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 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 (CH_3), 40.0 (C1'), 30.5 (C2'). HRMS (ESI) *m/z* observed: 387.0848, $C_{18}H_{19}N_2O_3S_2^+$ $[M+H]^+$ 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%). R_f = 0.55 (1:1 EtOAc/hexanes). IR (cm^{-1}): 3276 (NH), 1626 (C=O). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.19 (dd [app. t], $J_1 = J_2$ = 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], $J_1 = J_2$ = 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, H2'''/H6'''/H2), 7.79 (ddd, J = 7.8, 1.8, 1.2 Hz, 1H, H4 or H6), 7.75 (br. s, 1H, NH), 7.58 (ddd, [app. dt] J_1 = 7.8, $J_2 = J_3$ = 1.2 Hz, 1H, H4 or H6), 7.40–7.48 (m, 3H, H3'''/H4'''/H5'''), 7.35 (ddd [app. dt], $J_1 = J_2$ = 7.2, J_3 = 0.6 Hz, 1H, H5), 7.01 (t, J = 0.6 Hz, 1H, H5''), 3.83 (pseudo q, 2H, H1'), 3.10 (dt, J = 6.2, 0.6 Hz, 2H, H2'), 0.23 (s, 9H, CH_3). ^{13}C NMR ($CDCl_3$, 126 MHz): δ 168.7 (C2''), 166.7 (C=O), 155.8 (C4''), 135.3 (C1''' or C1), 134.7 (ArH), 133.5 (C1''' or C1), 130.4 (ArH), 130.3 (ArH), 129.2 (2 × ArH), 128.6 (ArH), 127.3 (ArH), 126.5 (2 × ArH), 123.8 (C3), 114.6 (C5''), 104.3 (≡C), 95.4 (≡C), 39.8 (C1'), 30.7 (C2'), 0.02 (CH_3).

3-Ethynyl-*N*-(2-(2-phenylthiazol-4-yl)ethyl)benzamide (**21Bv**). A saturated solution/suspension of K_2CO_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], $J_1 = J_2 = 1.5$ Hz, 1H, H2) 7.92–7.95 (m, 2H, H2'''/H6'''), 7.85 (br. s, 1H, NH), 7.84 (ddd [app. t], $J_1 = 7.8$, $J_2 = J_3 = 1.5$ Hz, 1H, H4 or H6), 7.59 (ddd, [app. dt] $J_1 = 7.8$, $J_2 = J_3 = 1.2$ Hz, 1H, H4 or H6), 7.40–7.47 (m, 3H, H3'''/H4'''/H5'''), 7.37 (ddd [app. dt], $J_1 = J_2 = 7.8$, $J_3 = 0.6$ 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'). ^{13}C NMR ($CDCl_3$, 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, $C_{20}H_{17}N_2OS^+$ $[M+H]^+$ 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%). R_f 0.5 (1:1 EtOAc/hexanes). IR (cm^{-1}): 3367 (NH), 1663 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$) 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], $J_1 = J_2 = 7.8$ Hz, $J_3 = 1.8$ 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], $J_1 = J_2 = 6.4$ Hz, 2H, H1'), 3.13 (t, $J_1 = 6.4$ Hz, 2H, H2'). ^{13}C NMR (126 MHz, $CDCl_3$) 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, $C_{17}H_{15}N_3OS$ $[M]^{\bullet+}$ 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. R_f 0.15 (EtOAc). IR (cm^{-1}): 3331 (NH), 1607 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (s, 1H, H2), 8.69 (br. s, 1H, H6), 8.12 (d, J = 6.4 Hz, 1H, H4), 7.90–7.92 (m, 2H, H2'''/H6'''), 7.82 (br. s, 1H, NH), 7.43–7.46 (m, 3H, H3'''/H4'''/H5'''), 7.33 (dd [app. t.], $J_1 = J_2$ = 6.0 Hz, 1H, H5), 7.01 (s, 1H, H5''), 3.85 (dt [app. q], $J_1 = J_2$ = 5.4 Hz, 2H, H1'), 3.10 (t, J = 5.4 Hz, 2H, H2'). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.9 (C2''), 165.5 (C=O), 155.6 (C4''), 152.3 (C2), 148.2 (C6), 135.1 (ArH), 133.5, 130.6, 130.5 (ArH), 129.3 (2 × ArH), 126.5 (2 × ArH), 123.5 (ArH), 114.8 (C5''), 39.8 (C1'), 30.6 (C2'). HRMS (ESI) *m/z* observed: 310.1002, $C_{17}H_{16}N_3OS^+$ $[M+H]^+$ requires 310.1014.

***N*-(2-(2-Phenylthiazol-4-yl)ethyl)isonicotinamide (21Hc)**. 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. R_f 0.3 (1:1 EtOAc/hexanes). IR (cm^{-1}): 3323 (NH), 1607 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, J = 4.4 Hz, 2H, H2/H6), 8.17 (br. s, 1H, NH), 7.90–7.92 (m, 2H, H2'''/H6'''), 7.74 (d, J = 5.6 Hz, 2H, H3/H5), 7.44–7.48 (m, 3H, H3'''/H4'''/H5'''), 7.05 (s, 1H, H5''), 3.83 (dt [app. q], $J_1 = J_2$ = 6.4 Hz, 2H, H1'), 3.11 (t, J_1 = 6.4 Hz, 2H, H2'). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.7 (C2''), 165.3 (C=O), 155.5 (C4''), 150.5 (C2/C6), 142.1 (C4), 133.4 (C1'''), 130.4 (C4'''), 129.1 (2 × ArH), 126.5 (2 × ArH), 121.1 (C3/C5), 114.8 (C5''), 39.8 (C1'), 30.3 (C2'). HRMS (EI) *m/z* observed: 309.0931, $C_{17}H_{15}N_3OS$ $[M]^{\bullet+}$ 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. R_f 0.19 (2:3 EtOAc/hexanes). IR (cm^{-1}): 3327 (NH), 1655 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.41 (d, J = 1.6 Hz, 1H, H3), 8.92 (br. s, 1H, NH), 8.73 (d, J = 2.4 Hz, 1H, H6), 8.54 (dd [app. t], $J_1 = J_2$ = 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, $CDCl_3$) δ 168.7 (C2''), 163.2 (C=O), 155.0 (C4''), 147.2 (pyrazine CH), 144.9 (C2), 144.5 (pyrazine CH), 142.7 (pyrazine CH), 133.1 (C1'''), 130.5 (C4'''), 129.1 (2 × ArH), 126.8 (2 × ArH), 114.6 (C5''), 39.1 (C1'), 30.7 (C2'). HRMS (ESI) *m/z* observed: 311.1003, $C_{16}H_{15}N_4OS^+$ $[M+H]^+$ 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. R_f 0.5 (1:4 EtOAc/hexanes). IR (cm^{-1}): 3319 (NH), 1625 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 168.5 (C2''), 162.0 (C=O), 155.6 (C4''), 139.4 (C1'''), 133.5 (C2), 130.2 (C4'''), 129.7 (ArH), 129.1 (2 × ArH), 128.1 (ArH), 127.6 (ArH), 126.6 (2 × ArH), 114.7 (C5''), 39.6 (C1'), 30.8 (C2'). HRMS (ESI) *m/z* observed: 315.0616, $C_{16}H_{15}N_2OS_2^+$ $[M+H]^+$ 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 mmol). Elution with 1:4 EtOAc/hexanes gave **21Hf** as a yellow oil (0.168 g, 83%). R_f 0.2 (1:4 EtOAc/hexanes). IR (cm^{-1}): 3321 (NH), 1633 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93–7.96 (m, 2H, H2'''/H6'''), 7.89 (dd, *J* = 2.8, 1.2 Hz, 1H, H2), 7.44–7.46 (m, 4H, NH/H3'''/H4'''/H5'''), 7.42 (dd, *J* = 5.0, 2.8 Hz, 1H, H4 or H5), 7.30 (dd, *J* = 5.2, 2.8 Hz, 1H, H4 or H5), 7.03 (s, 1H, H5''), 3.80 (dt [app. q], $J_1 = J_2$ = 5.8 Hz, 2H, H1'), 3.11 (t, *J* = 6.0 Hz, 2H, H2'). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.7 (C2''), 163.2 (C=O), 155.4 (C4''), 138.0 (C1'''), 133.2 (C3), 130.5 (C4'''), 129.2 (2 × ArH), 128.2 (ArH), 126.6 (2 × ArH), 126.4 (ArH), 126.2 (ArH), 114.8 (C5''), 39.4 (C1'), 30.6 (C2'). HRMS (ESI) *m/z* observed: 315.0626, $C_{16}H_{15}N_2OS_2^+$ $[M+H]^+$ 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. R_f 0.45 (3:7 EtOAc/hexanes). IR (cm^1): 3312 (NH), 1620 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.56 (br. s, 1H, NH), 7.95–7.98 (m, 2H, H2'''/H6'''), 7.42–7.49 (m, 3H, H3'''/H4'''/H5'''), 7.07 (br. s, 1H, NH), 7.00 (t, *J* = 0.8 Hz, 1H, H5''), 6.90–6.92 (m, 1H, pyrazole H), 6.56–6.58 (m, 1H, pyrazole H), 6.20–6.23 (m, 1H, pyrazole H), 3.82 (dt [app.q], $J_1 = J_2$ = 6.2 Hz, 2H, H1'), 3.08 (t, J_1= 6.0 Hz, 2H, H2'). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.5 (C2''), 161.4 (C=O), 155.7 (C4''), 133.7 (C1'''), 130.2 (C4'''), 129.1 (2 × ArH), 126.6 (2 × ArH), 126.4

(C2), 121.5 (C5), 114.6 (C5''), 109.7 (C3 or C4), 108.9 (C3 or C4), 39.0 (C1'), 31.2 (C2'). HRMS (ESI) *m/z* observed: 298.1024, $C_{16}H_{16}N_3OS^+$ $[M+H]^+$ 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%). R_f 0.45 (2:3 EtOAC/hexanes). IR ($cm^{-1)}$: 3316 (NH), 1651 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$) 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], $J_1 = J_2$ = 3.6 Hz, 1H, H4), 3.79 (dt [app. q], $J_1 = J_2$ = 6.4 Hz, 2H, H1'), 3.07 (t, *J* = 6.4 Hz, 2H, H2'). ^{13}C NMR (101 MHz, $CDCl_3$) 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, $C_{16}H_{15}N_2O_2S^+$ $[M+H]^+$ requires 299.0854.

***N*-(2-(2-Phenylthiazol-4-yl)ethyl)furan-3-carboxamide (21Hi)**. Prepared according to general procedure E with 3-thiophenecarboxylic acid. ^{1}H 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], $J_1 = J_2$ = 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. ^{1}H 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], $J_1 = J_2 = 6.5$ 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) δ 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, $C_{16}H_{14}Br^{79}N_2O_2S^+$ $[M+H]^+$ 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) δ 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) δ 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, $C_{15}H_{14}N_3O_2S^+$ $[M+H]^+$ 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). ^1H NMR (500 MHz, $CDCl_3$) δ 7.97–7.99 (m, 2H, H2'''/H6'''), 7.88 (s, 1H, H2), 7.81 (br. s, 1H, NH), 7.72 (s, 1H, H4), 7.46 (m, 3H, H3'''/H4'''/H5'''), 7.02 (t, J = 0.6 Hz, 1H, H5''), 3.82 (pseudo q, 2H, H1'), 3.09 (dt, J = 5.2, 0.6 Hz, 2H, H2'). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.7 (C2''), 156.9 (C=O or C4''), 155.1 (C=O or C4''), 151.4 (C2), 146.1 (C4), 133.3 (C1'''), 130.5 (C4'''), 130.1 (C5), 129.1 (2 × ArH), 126.6 (2 × ArH), 114.8 (C5''), 38.9 (C1'), 30.5 (C2'). HRMS (ESI) *m/z* observed: 300.0816, $C_{15}H_{14}N_3O_2S^+$ $[M+H]^+$ 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. ^1H NMR (400 MHz, DMSO) δ 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 NEt_3 (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. R_f 0.25 (3:7 EtOAc/hexanes). IR (cm^{-1}): 3355 (NH), 1629 (C=O). ^1H NMR (500 MHz, $CDCl_3$) δ 7.89–7.91 (m, 2H, H2'''/H6'''), 7.39–7.42 (m, 3H, H3'''/H4'''/H5'''), 6.97 (s, 1H, H5''), 5.24 (br. s, 1H, NH), 3.64 (dt [app. q], $J_1 = J_2$ = 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, $CDCl_3$) δ 168.0 (C2"), 157.0 (C=O or C4"), 156.3 (C=O or C4"), 133.7 (C1'"), 130.0 (C4'"), 129.0 (2 × ArH), 126.4 (2 × ArH), 114.3 (C5"), 45.5 (C2/C5), 40.2 (C1'), 31.8 (C2'), 25.6 (C3/C4). HRMS (ESI) *m/z* observed: 324.1132, $C_{16}H_{19}N_3NaOS^+$ $[M+H]^+$ requires 324.1141.

***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, $CDCl_3$) δ 7.88 (m, 2H, H2'"/H6'"), 7.39 (m, 3H, H3"/H4"/H5"), 6.94 (s, 1H, H5"), 5.80 (br. s, 1H, NH), 3.56 (dt [app. q], $J_1 = J_2 = 5.9$ Hz, 2H, H1'), 3.31 (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, $CDCl_3$) δ 168.1 (C2"), 157.9 (C=O or C4"), 156.44 (C=O or C4"), 133.7 (C1'"), 130.1 (C4'"), 129.0 (2 × ArH), 126.4 (2 × 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, $C_{17}H_{21}N_3NaOS^+$ $[M+H]^+$ requires 338.1298.

***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, $CDCl_3$) δ 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, $CDCl_3$) δ 168.2 (C2"), 158.0 (C=O or C4"), 156.2 (C=O or C4"),

133.6 (C1'''), 130.2 (C4'''), 129.1 (2 × ArH), 126.4 (2 × ArH), 114.5 (C5''), 66.6 (C2/C6), 44.0 (C3/C5), 40.6 (C2'), 31.1 (C1'). HRMS (ESI) *m/z* observed: 318.1279, $C_{16}H_{20}N_3O_2S^+$ $[M+H]^+$ 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 Hünig'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). ^{1}H NMR (500 MHz, $CDCl_3$) 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, J_1 = 5.5 Hz, 1H, NH), 3.35 (dt [app.q], $J_1 = J_2$ = 6.5 Hz, 2H, H1'), 2.91 (t, J = 6.5 Hz, 2H, H2'). ^{13}C NMR (126 MHz, $CDCl_3$) 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, $C_{17}H_{17}N_2O_2S_2^+$ $[M+H]^+$ requires 345.0731.

Pyrrolidine-1-sulfonyl chloride (26). A solution of dry pyrrolidine (1.64 mL, 20.0 mmol) in dry Et_2O was added dropwise to a stirred solution of sulfuryl chloride (0.81 mL, 10 mmol) and NEt_3 (2.50 mL, 20 mmol) in ether (10 mL) at –10 °C under N_2. After 2 h the reaction mixture was diluted with dry Et_2O (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. ^{1}H NMR ($CDCl_3$,

400 MHz): δ 3.27 (m, 4H, H2/5), 1.92 (m, 4H, H3/4). ^{13}C NMR ($CDCl_3$, 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,): δ 7.80–7.90 (m, 2H, H2'''/H6'''), 7.40–7.46 (m, 3H, H3'''/H4'''/H5'''), 7.00 (s,1H, H5''), 5.30 (t, *J* = 5.6 Hz, 1H, NH), 3.49 (dt [app. t], $J_1 = J_2$ = 6.1 Hz, 2H, H1'), 3.20–3.30 (m, 4H, H2/5), 3.01–3.10 (t, *J* = 6.2 Hz, 2H, H2'), 1.80–1.90 (m, 4H, H3/4). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 168.6 (C2''), 154.9 (C4''), 133.5 (C1'''), 130.3 (C4'''), 129.1 (2 × ArH), 126.5 (2 × ArH), 114.9 (C5''), 48.1 (C2/5), 43.0 (C1'), 31.2 (C2'), 25.7 (C3/4).

***N*-(2-(2-Phenylthiazol-4-yl)ethyl)-1*H*-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 × 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_f 0.15 (1:1 EtOAc/hexanes). IR (cm^{-1}): 3219 (NH), 1712 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 168.6 (C2''), 154.8 (C=O), 149.0 (C4''), 135.9 (C2), 133.2 (C1'''), 130.2 (C4'''), 129.7 (C4), 129.0 (2 × ArH), 126.3 (2 × ArH), 116.2 (C5), 114.5 (C5''), 40.5 (C1'), 30.5 (C2'). HRMS (ESI) *m/z* observed: 299.0971, $C_{15}H_{15}N_4OS^+$ $[M+H]^+$ 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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, $C_{15}H_{19}N_2O_2S^+$ $[M+H]^+$ 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. R_f = 0.55 (1:1 EtOAc/hexanes). IR (cm^{-1}): 3350 (NH), 1689 (C=O). ^1H NMR ($CDCl_3$, 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, CH_2), 1.56 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 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 × CH_2), 31.8 (C2), 23.8 (2 × CH_2). 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 ºC as a yellow solid (0.105 g, 73%), mp = 40–44 ºC. R_f = 0.55 (50% EtOAc/hexanes). IR (cm^{-1}): 3325 (NH), 1673 (C=O). ^1H NMR ($CDCl_3$, 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, CH_2O), 3.61 (dt [app. q] $J_1 = J_2$ = 6.5 Hz, 2H, H2), 3.01 (t, *J* = 6.5 Hz, 2H, OCH_2), 1.10 (br. s, 1H, cPr CH), 0.50–0.55 (m, 2H), 0.22–0.28

(m, 2H). ^{13}C NMR ($CDCl_3$, 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 (CH_2O), 40.5 (C1), 31.8 (C2), 10.3 (cPr CH), 3.3 (2 × cPr CH_2). LRMS (ESI+) *m/z*: 303 $[M + H]^+$.

General procedure for the synthesis of ureas from 28.[68] NEt_3 (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 N_2. When TLC indicated the reaction to be complete (generally after overnight), the solvent was evaporated under N_2 and the residue was purified by flash chromatography.

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. R_f 0.2 (1:1 EtOAc/hexanes). IR (cm^{-1}): 3313 (NH), 2966 (NH), 1622 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$) 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, CH_3). ^{13}C NMR (126 MHz, $CDCl_3$) 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 (CH_3). HRMS (ESI) *m/z* observed: 290.1318, $C_{15}H_{20}N_3OS^+$ $[M+H]^+$ 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 N_2. 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): δ 9.3 (s, $^+NH_2$ + OH), 3.15–3.23 (m, ^{1}H, CH), 2.54 (s, 3H, NMe), 1.92 (s, Ac), 1.33 (d, J = 6.5 Hz, 6H, 2 × 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): δ 7.90–7.94 (m, 2H, H2"/H6"), 7.40–7.45 (m, 3H, H3"/H4"/H4"), 6.97 (s, 1H, H5'), 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 × CH_3). ^{13}C NMR ($CDCl_3$, 126 MHz): δ 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, $C_{16}H_{21}KN_3OS^+$ $[M+K]^+$ 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%). R_f 0.35 (1:1 EtOAc/hexanes). IR (cm^{-1}): 3354 (NH), 1622 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$) 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], $J_1 = J_2 = 6.8$ Hz, 2H, H1), 3.23 (q, $J = 7.0$ Hz, 4H, 2 × CH_2), 3.00 (t, $J = 6.2$ Hz, 2H, H2), 1.08 (t, $J = 7.0$ Hz, 6H, CH_3). ^{13}C NMR (126 MHz, $CDCl_3$) 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 (CH_3). HRMS (ESI) *m/z* observed: 304.1494, $C_{16}H_{22}N_3OS^+$ $[M+H]^+$ 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. R_f = 0.3 (1:1 EtOAc/hexanes). IR cm^{-1}: 3391 (NH), 1630 (CO).^{1}H NMR ($CDCl_3$, 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], $J_1 = J_2 = 6.0$ Hz, 2H, H1), 3.03 (dt, $J = 6.3$, 0.7 Hz, 2H, H2), 1.20 (d, $J = 7.0$ Hz, 12H, CH_3). ^{13}C NMR ($CDCl_3$, 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 (CH_3). HRMS (ESI) *m/z* observed: 332.1771, $C_{18}H_{26}N_3OS^+$ $[M+H]^+$ 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%). R_f 0.35 (1:1 EtOAc/hexanes). IR (cm^{-1}): 2931 (NH), 1627 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 168.2 (C2''), 158.0 (C=O or C4''), 156.4 (C=O or C4''), 133.7 (C1'''), 130.1 (C4'''), 129.0 (2 × ArH), 126.4 (2 × ArH), 114.4 (C5''), 46.4 (C2/C7), 40.6 (C1'), 31.6 (C2'), 28.6 (C4/C5), 27.3 (C3/C6). HRMS (ESI) *m/z* observed: 330.1635, $C_{18}H_{24}N_3OS^+$ $[M+H]^+$ 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%). R_f = 0.5 (1:1 EtOAc/hexanes). IR (cm^{-1}): 3335 (NH), 1670 (C=O). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 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): δ 168.8 (C2''), 155.4 (C=O or C4''), 151.0 (C=O or C4''), 133.3 (C1'''), 130.3 (C4'''), 129.1 (2 × ArH), 126.5 (2 × ArH), 118.4 (C2/C5), 114.8 (C5''), 111.6 (C3/C4), 40.4 (C1'), 30.4 (C2'). HRMS (ESI) *m/z* observed: 298.1000, $C_{16}H_{16}N_3OS^+$ $[M+H]^+$ requires: 298.1009.

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 N_2. 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. R_f 0.25 (1:4 EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.61 (d, J = 4.0 Hz, 1H, H6'), 8.20 (d, J = 7.6 Hz, 1H, H3'), 7.79 (dd, J = 6.8 Hz, 7.6 Hz, 1H, H4'), 7.33 (dd, J = 5.2, 6.4 Hz, 1H, H5'), 7.25 (s, 1H, H5), 4.59 (s, 2H, CH_2); ^{13}C NMR (126 MHz, $CDCl_3$): 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 (CH_2). HRMS (ESI) *m/z* observed: 211.0106, $C_9H_8ClN_2S^+$ [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. R_f 0.3 (1:20:80 NEt_3/EtOAc/hexanes). IR (cm^{-1}): 2244 (C≡N). ^{1}H NMR (500 MHz,

$CDCl_3$): δ 8.61 (d, J = 4.8 Hz, 1H, H6''), 8.17 (d, J = 8.0 Hz, 1H, H2''), 7.84 (ddd [app. dt], J_1 = J_2 = 8.0 Hz, J_3 = 1.6 Hz, 1H, H4''), 7.38 (s, 1H, H5'), 7.32−7.41 (m, 1H, H5''), 3.96 (s, 2H, CH_2). ^{13}C NMR (126 MHz, $CDCl_3$): 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 (CH_2). HRMS (ESI) *m/z* observed: 202.0431, $C_{10}H_8N_3S^+$ $[M+H]^+$ requires 202.0439.

2-(2-(Pyridin-2-yl)thiazol-4-yl)ethanamine (34). A 1 M BH_3−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 N_2. The solution was allowed to warm o 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 K_2CO_3 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 NEt_3/EtOAc/hexanes gave benzamide **35a** as a yellow solid (0.148 g, 84%), mp = 103−105 °C. R_f 0.4 (1:50:50 NEt_3/EtOAc/Hexanes). IR (cm^{-1}): 3300 (NH), 1634 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$): 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], J_1 = J_2 = 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], J_1 = J_2 = 6.1 Hz, 2H, H1'), 3.14 (t, J = 6.2 Hz, 2H,

H2'). ^{13}C NMR (126 MHz, $CDCl_3$): 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, $C_{17}H_{15}N_3NaOS^+$ $[M+Na]^+$ requires 332.0828.

***N*-(2-(2-(Pyridin-2-yl)thiazol-4-yl)ethyl)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. R_f 0.35 (1:50:50 NEt_3/EtOAc/hexanes). IR (cm^{-1}): 3294 (NH), 1639 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$): δ 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, H5"), 6.27 (br. 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). ^{13}C NMR (126 MHz, $CDCl_3$): δ 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, $C_{16}H_{19}N_3NaOS$ requires 324.1141.

***N*-(2-(2-(Pyridin-3-yl)thiazol-4-yl)ethyl)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%). R_f 0.5

(1:50:50 NEt_3/EtOAc/hexanes). IR (cm^{-1}): 3237 (NH), 1645 (C=O). ^1H NMR (500 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ 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, $C_{17}H_{15}N_3NaOS^+$ [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 NEt_3 (3.0 mL) in DCM (10 mL) at 0 °C. After stirring overnight the volatiles were evaporated and the residue was subjected to flash chromatography. Elution with 1:20:80 NEt_3/EtOAc/hexanes then 1:50:50 NEt_3/EtOAc/hexanes yielded **35d** as white crystals (0.050 g, 51%), mp = 109−111 °C. R_f 0.25 (1:99 NEt_3/EtOAc). IR (cm^{-1}): 3244 (NH), 1637 (C=O). ^1H NMR (500 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ 176.4 (C=O), 164.8 (C2''), 156.4 (C4''), 150.9 (C2''' or C6'''), 147.7 (C2''' or C6'''), 133.6 (CH), 129.7 (CH), 123.9 (CH), 115.4 (C5''), 46.1

(C1), 39.0 (C1'), 31.2 (C2'), 30.5 (C2/C5), 26.0 (C3/C4). HRMS (ESI) *m/z* observed: 324.1138, $C_{16}H_{19}N_3NaOS^+$ $[M+Na]^+$ 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 NEt_3 (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 NEt_3/EtOAc/hexanes then 1:99 NEt_3/EtOAc yielded **35e** as white crystals (0.122 g, 66%), mp = 67−70 °C. IR (cm^{-1}): 3438 (NH), 1634 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$): 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], $J_1 = J_2$ = 7.4 Hz, 2H, H3/H5), 7.34 (br s, 1H, NH), 7.17 (s, 1H, H5''), 3.85 (dt [app. q], $J_1 = J_2$ = 6.4 Hz, 2H, H1'), 3.15 (t, J_1 = 6.0 Hz, 2H, H2'). ^{13}C NMR (126 MHz, $CDCl_3$): 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, $C_{17}H_{15}N_3NaOS^+$ $[M+Na]^+$ 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 NEt_3 (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 NEt_3/EtOAc yielded **35f** as a white solid (0.136 g, 50%), mp = 110−112 °C. R_f 0.3 (1:50:50 NEt_3/EtOAc/hexanes). IR (cm^{-1}): 3241 (NH), 1600 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$): 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], $J_1 = J_2 = 6.1$ Hz, 2H, H1'), 3.05 (t, $J_1 = 6.4$ Hz, 2H, H2'), 2.48−2.52 (tt [app. pent.], $J_1 = J_2 = 7.8$ Hz, 1H, H1), 1.82−1.85 (m, 2H), 1.70−1.79 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 176.4 (C=O), 165.2 (C2''), 156.8 (C4''), 150.7 (C2'''/C6'''), 140.4 (C4'''), 120.4 (C3'''/C5'''), 116.6 (C5''), 46.1 (C1), 38.9 (C1'), 31.3 (C2'), 30.5 (C2/C5), 26.0 (C3/C4). HRMS (ESI) *m/z* observed: 302.1309, $C_{16}H_{20}N_3OS^+$ $[M+H]^+$ requires 302.1322.

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 NEt_3/EtOAc/hexanes). IR (cm^{-1}): 1727 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$): 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, CH_3), 3.13 (t, $J = 7.5$ Hz, 2H, H3), 2.79 (t, $J = 7.5$ Hz, 2H, H2). ^{13}C NMR (126 MHz, $CDCl_3$): 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 (CH_3), 33.4 (C3), 26.8 (C2). HRMS (ESI) *m/z* observed: 249.0685, $C_{12}H_{13}N_2O_2S^+$ $[M+H]^+$ 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. R_f 0.4 (1:1

EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): 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, CH_3), 3.16 (t, *J* = 7.4 Hz, 2H, H3), 2.82 (t, *J* = 7.4 Hz, 2H, H2). ^{13}C NMR (126 MHz, $CDCl_3$): 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 (CH_3), 33.5 (C3), 26.8 (C2). HRMS (ESI) *m/z* observed: 249.0691, $C_{12}H_{13}N_2O_2S^+$ $[M+H]^+$ 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. R_f 0.5 (1:4 EtOAc/Hexanes). IR (cm^{-1}): 1726 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$): 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, CH_3), 3.10 (t, *J* = 7.5 Hz, 2H, H3), 2.78 (t, *J* = 7.5 Hz, 2H, H2). ^{13}C NMR (126 MHz, $CDCl_3$): 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 (CH_3), 33.6 (C3), 26.8 (C2). HRMS (ESI) *m/z* observed: 276.0128, $C_{11}H_{11}NNaO_2S_2^+$ $[M+Na]^+$ 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. R_f 0.2 (EtOAc). IR (cm^{-1}): 3375 (NH), 3113 (NH), 1663 (C=O). ^{1}H 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], J_1 = 8.0 Hz, J_2 = J_3 = 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), 3.79 (t, J = 7.9 Hz, 2H, H3), 3.32 (t, 2H, H2). HRMS (ESI) *m/z* observed: 256.0509, $C_{11}H_{11}N_3NaOS^+$ $[M+Na]^+$ 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. R_f 0.7 (1:1:98 NEt_3/MeOH/EtOAc). IR (cm^{-1}): 3244 (NH), 3109 (NH), 1682 (C=O). ^{1}H 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 d_6-DMSO peak). ^{13}C NMR (126 MHz, DMSO): 173.2 (C=O), 163.7 (C2'), 158.0 (C4'), 150.8 (C2''/C6''), 139.6 (C4''), 119.9 (C3''/C5''), 116.8 (C5'), 34.3 (C3), 26.8 (C2). HRMS (ESI) *m/z* observed: 256.0513, $C_{11}H_{11}N_3NaOS^+$ $[M+Na]^+$ 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 NEt_3/EtOAc/hexanes, then 1:1:98 NEt_3/MeOH/EtOAc gave **43c** as a white solid (0.338 g, 36%), mp = 103−105 °C. R_f 0.3 (1:99 MeOH/EtOAc). IR (cm^{-1}): 3374 (NH), 3171 (NH), 1664 (C=O). ^{1}H 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, H5'), 7.15 (dd, J = 4.9, 3.9

Hz, 1H, H4''), 6.82 (br s, 1H, NH), 2.91 (t, *J* = 7.7 Hz, 2H, H3), 2.46 (t, *J* = 7.7 Hz, 2H, H2. ^{13}C NMR (126 MHz, $CDCl_3$): 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, $C_{10}H_{10}N_2NaOS_2^+$ $[M+Na]^+$ 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%). R_f 0.35 (1:99 MeOH/EtOAc). IR (cm^{-1}): 3374 (NH), 3171 (NH), 1663 (C=O). ^{1}H 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). ^{13}C 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, $C_9H_{11}N_2S_2^+$ $[M+H]^+$ 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 NEt_3 (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 NEt_3/EtOAc/hexanes then 1:50:50 NEt_3/EtOAc/hexanes yielded **45a** as a brown oil (0.067 g, 41%). R_f 0.3 (1:30:70 NEt_3/EtOAc/hexanes). IR (cm^1): 3337 (NH), 1640 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$): 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], $J_1 = J_2$ = 4.4 Hz, 1H, H4'''), 6.94 (s, 1H, H5''), 3.81 (dt [app. q], $J_1 = J_2$ = 5.9 Hz, 2H, H1'), 3.06 (t, J_1 = 6.0 Hz, 2H, H2'). ^{13}C NMR (126 MHz, $CDCl_3$): 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, $C_{16}H_{14}N_2NaOS^+$ $[M+Na]^+$ 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 NEt_3 (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. R_f 0.3 (1:20:80 NEt_3/EtOAc/hexanes). IR (cm^{-1}): 3294 (NH), 1638 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$): 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, $J_1 = J_2$ = 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). ^{13}C NMR (126 MHz, $CDCl_3$): 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, $C_{15}H_{18}N_2NaOS^+$ $[M+Na]^+$ 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 NEt_3/EtOAc/hexanes gave **46a** as a clear oil (0.200 g, 59%). Rf 0.2 (1:99 NEt_3/EtOAc). IR (cm^{-1}): 3205 (NH), 1702 (C=O). ^1H NMR (500 MHz, $CDCl_3$): 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, CH_3), 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, $CDCl_3$): 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 (CH_3), 40.4 (C1), 31.6 (C2). HRMS (ESI) *m/z* observed: 286.0634, $C_{12}H_{13}N_3NaO_2S^+$ $[M+Na]^+$ 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 NEt_3/EtOAc/hexanes then 1:50:50 NEt_3/EtOAc/hexanes gave **46b** as a white solid (0.159 g, 70%), mp 91−93 °C. Rf 0.6 (1:50:50 NEt_3/EtOAc/hexanes). IR (cm^{-1}): 3205 (NH), 1701 (C=O). ^1H NMR (500 MHz, $CDCl_3$): 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, CH_3), 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, $CDCl_3$): 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 (CH_3), 40.4 (C1), 31.7 (C2). HRMS (ESI) *m/z* observed: 286.0621, $C_{12}H_{13}N_3NaO_2S^+$ $[M+Na]^+$ 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_1 = 6.4 Hz, 2H, H2). ^{13}C NMR (126 MHz, MeOD): δ 162.0 (C2'), 155.7 (C4'), 144.7 (C2'' or C6''), 142.9 (C2'' or C6''), 140.5 (C4''), 134.5 (C3''), 129.3 (C5''), 121.2 (C5'), 40.1 (C1), 29.6 (C2). HRMS (ESI) *m/z* observed: 206.0745, $C_{10}H_{12}N_3S^+$ [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. R_f 0.4 (1:99 MeOH/EtOAc). IR (cm^{-1}): 3390 (NH). ^{1}H NMR (500 MHz, DMSO): δ 8.88 (s, 2H, H2''/H6''), 8.22 (s, 2H, H3''/H5''), 8.06 (br. s, 3H, NH_3), 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): δ 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, $C_{10}H_{12}N_3S^+$ [free base + H]$^+$ requires 206.0746.

2-Amino-4-(chloromethyl)thiazol-3-ium chloride (49).[92] 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) δ 9.13 (v. br. s, 2H, NH_2), 6.96 (s, 1H, H5'), 4.66 (d, J = 0.5 Hz, 2H, H2), (thiazole NH not observed/obscured by/exchanging with H_2O). 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_2SO_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.[93] 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.[94]

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, 2H, 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) δ 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_2O and EtOAc and the organic layer was dried (Na_2SO_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): δ 7.85–7.87 (m, 2H, Ar), 7.73–7.75 (m, 2H, Ar), 4.09 (s, 2H, CH_2S), 4.04 (t, J = 6.8 Hz, 2H, CH_2N), 3.04 (t, J = 7.1 Hz, 2 H, CH_2CO). ^{13}C NMR spectrum ($CDCl_3$, 101 MHz): δ 198.5 (CO), 168.0 (2 × CO), 134.2 (2 × ArH), 131.8 (2 × Ar), 123.5 (2 × ArH), 111.0 (CN), 43.5 (CH_2S), 39.6 (CH_2N), 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_2SO_4) and evaporated to afford **58** as yellow solid (3.6 g, 86%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 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, 2 H, CH_2N), 3.16 (t, J = 7.1 Hz, 2 H, 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). N_2 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 Na_2CO_3 (20 mL) for 20 min The reaction mixture was heated to 80 °C under N_2 and $Pd(PPh_3)_4$ (0.070 g, 3 mol%) was added. After 6 h TLC showed the reaction to be incomplete, so additional $Pd(PPh_3)_4$ (0.100 g, 5 mol%) was added and the reaction mixture was stirred overnight at 80 °C. After cooling the reaction miture 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). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04 (ddd [app. dt], J_1 = J_2 = 7.8 Hz, J_3 = 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'). ^{13}C NMR (126 MHz, $CDCl_3$): 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, $C_{19}H_{14}N_2O_2FS^+$ $[M+H]^+$ 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). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.80−7.84 (m, 2H, H4/H7), 7.68−7.72 (m, 2H, H5/H6), 7.54 (ddd, J_1 = 7.8, 1.6, 1.0 Hz, 1H, H6'''), 7.42 (ddd, J_1 = 9.8 Hz, J_2 = 2.6 Hz, J_3 = 1.6 Hz, 1H, H2'''), 7.30 (ddd (app.dt), J_1 = J_2 = 8.0 Hz, J_3 = 5.8 Hz, 1H, H5'''), 7.04 (dddd [app. ddt], J_1 = J_2 = 8.4 Hz, J_3 = 2.6 Hz, J_4 = 0.9 Hz, 1H, H4'''), 7.02 (s, 1H, H5''), 4.10 (t, J_1 = 7.0 Hz, 2H, H1'), 3.21 (t, J_1 = 7.0 Hz, H2'); ^{13}C NMR (101 MHz, $CDCl_3$): 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, $C_{19}H_{14}N_2O_2SF^+$ $[M+H]^+$ 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). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67–7.79 (m, 6H, H4/H7/H5/H6/H2'''/H6'''), 7.00 (dd [app. t], 2H, J_1 = J_2 = 8.0 Hz, H3'''/H5'''), 6.96 (s, 1H, H5''),

4.08 (t, 2H, J_1 = 6.4 Hz, H1'), 3.20 (t, 2H, J_1 = 6.4 Hz, 2H, H2'); ^{13}C NMR (101 MHz, $CDCl_3$): 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, $C_{19}H_{14}N_2O_2FS+$ $[M+H]^+$ 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, $CDCl_3$): δ 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, $CDCl_3$): δ 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, $C_{19}H_{13}N_2O_2F_2S^+$ $[M+H]^+$ requires 371.0666.

***N*-(2-(2-(2-Fluorophenyl)thiazol-4-yl)ethyl)-1*H*-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, $CDCl_3$): δ 8.14–8.16 (m, 1H, H2), 8.10 (ddd [app. dt], $J_1 = J_2$ = 7.6 Hz, J_3 = 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, J_1 = 1.5 Hz, J_2 = 1.0 Hz, 1H, H4), 3.80 (m [pseudo q], H1'), 3.13 (t, J_1 = 6.0 Hz, 2H, H2'); ^{13}C NMR (101 MHz, $CDCl_3$): 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), 121.2 (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, $C_{15}H_{14}N_4OFS^+$ $[M+H]^+$ requires 317.0872.

***N*-(2-(2-(3-Fluorophenyl)thiazol-4-yl)ethyl)-1*H*-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). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.15 (s, 1H, H2), 7.67 (br. s, 1H, NH), 7.64–6.67 (m, 1H, H6'''), 7.60 (ddd [app. dt], J_1 = 9.4 Hz, $J_2 = J_3$ = 2.0 Hz, H2'''), 7.42 (ddd [app. dt], $J_1 = J_2$ = 8.0 Hz, J_3 = 5.7 Hz, 1H, H5'''), 7.37 (s, 1H, H5), 7.13 (ddd [app. dt], $J_1 = J_2$ = 8.2 Hz, J_3 = 2.8 Hz, H4'''), 7.05−7.08 (m, 2H, H4/H5''), 3.79 (dt [app. q], $J_1 = J_2$ = 5.6 Hz, 2H, H1'), 3.10 (t, J_1 = 6.0 Hz, 2H, H2'); ^{13}C NMR (101 MHz, $CDCl_3$): 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, $C_{15}H_{14}N_4OFS^+$ $[M+H]^+$ requires 317.0872.

***N*-(2-(2-(4-Fluorophenyl)thiazol-4-yl)ethyl)-1*H*-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), 1703 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$): 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], $J_1 = J_2$ = 1.4 Hz, 1H, H5), 7.13−7.16 (m, 2H, H3'''/H5'''), 7.06 (dd, J_1 = 1.6 Hz, 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'); ^{13}C NMR (101 MHz, $CDCl_3$): 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, $C_{15}H_{14}N_4OFS^+$ $[M+H]^+$ requires: 317.0872.

***N*-(2-(2-(2,4-Difluorophenyl)thiazol-4-yl)ethyl)-1*H*-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). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14 (br. s, 1H, H2), 8.08 (ddd [app. dt], $J_1 = J_2$ = 8.6 Hz, J_3 = 6.4 Hz, 1H, H6'''), 7.98 (br. t, J_1 = 4.6 Hz, 1H, NH), 7.39 (br. s, H5), 7.11 (s, 1H, H5''), 6.99 (br. s, 1H, H4), 6.90–6.97 (m, 2H, H3'''/H5'''), 3.76 (dt [app. q], $J_1 = J_2$ = 6.2 Hz, 2H, H1'), 3.10 (t, J_1 = 6.4 Hz, 2H, H2'). ^{13}C NMR (101 MHz, $CDCl_3$): 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] $J_1 = J_2$ = 21 Hz, C3'''), 40.5 (C1'), 30.4 (C2'). HRMS (ESI) *m/z* observed: 335.0766, $C_{15}H_{13}N_4OF_2S^+$ $[M+H]^+$ 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 NEt_3 (0.10 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, $CDCl_3$): δ 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, $CDCl_3$): δ 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 = 7 Hz, C6'''), 128.5 (d, J = 2 Hz, C4''' or C5'''), 124.6 (d, J = 3 Hz, C4''' or C5'''), 121.5 (d, J = 9 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, $C_{17}H_{21}N_3OFS^+$ $[M+H]^+$ 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, $CDCl_3$): δ 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, $CDCl_3$): δ 166.6 (d, J = 3 Hz, C2''), 163.2 (d, J = 198 Hz, CF), 157.9 (C=O or C4''), 156.7 (C=O or C4''), 135.7 (d, J = 7 Hz, C1'''), 130.7 (d, J = 7 Hz, C5'''), 122.2 (d, J = C6'''), 117.0 (d, J = 17 Hz, C2''' or C4'''), 115.0 (C5''), 113.2 (d, J = 19 Hz, C2''' or C4'''), 45.0 (C2/C6), 40.7 (C1'), 31.4 (C2'), 25.7 (C3/C5), 24.6 (C4). HRMS (ESI) *m/z* observed: 334.1388, $C_{17}H_{21}N_3OFS^+$ $[M+H]^+$ 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). ^{1}H NMR (500 MHz, $CDCl_3$): 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], J_1 = 6.0 Hz, 2H, H1'), 3.31 (m [pseudo t], 4H, H2/H6), 2.98 (t, J_1 = 6.2 Hz, 2H, H2'), 1.47–1.57 (m, 6H, H3/H4/H5). ^{13}C NMR (101 MHz, $CDCl_3$): 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, $C_{17}H_{21}N_3OFS^+$ $[M+H]^+$ requires 334.1389.

General procedure (F) for the synthesis of phenylthiazoles by Suzuki coupling with 63a. 2-Bromothiazole **63a** (1.0 equiv), potassium carbonate (4.0 equiv), arylboronic acid (1.2 equiv), tetrabutylammonium bromide (0.1 equiv.), $PdCl_2$ (0.05 equiv) and dppf (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) δ 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) δ 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) δ 7.85 (d, J = 9.0 z, 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) δ 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-Methoxyphenyl)thiazol-4-yl)ethyl)piperidine-1-carboxamide (61h).** Prepared according to general procedure F with 2-methoxyphenylboronic acid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (dd, J = 8.2, 1.6 Hz, 1H), 7.42 (ddd [app. dt], $J_1 = J_2$ = 8.1 Hz, J_3 = 1.7 Hz, 1H), 7.04–7.10 (m, 3H), 5.87 (br s, 1H), 4.05 (s, 3H), 3.62 (dt [app. q], $J_1 = J_2$ = 5.2 Hz, 2H), 3.29–3.44 (m, 4H), 3.01–3.06 (m, 2H), 1.48–1.65 (m, 6H). LRMS (ESI+) *m/z* 346 $[M+H]^+$.

***N*-(2-(2-(3-Methoxyphenyl)thiazol-4-yl)ethyl)piperidine-1-carboxamide (61i)**. Prepared according to general procedure F with 3-methoxyphenylboronic acid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (m, 2H), 7.37 (dd [app. t], $J_1 = J_2$ = 7.9 Hz, 1H), 6.97–7.02 (m, 2H), 5.68 (br s, 1H), 3.90 (s, 3H), 3.63 (dt [app. q], $J_1 = J_2$ = 5.6 Hz, 2H), 3.31–3.42 (m, 4H), 3.03 (t, J = 6.1 Hz, 2H), 1.49–1.65 (m, 6H). LRMS (ESI+) *m/z* 346 $[M+H]^+$.

***N*-(2-(2-(4-Methoxyphenyl)thiazol-4-yl)ethyl)piperidine-1-carboxamide (61j).** Prepared according to general procedure F with 4-methoxyphenylboronic acid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85–7.91 (m, 2H), 6.94–6.99 (m, 2H), 6.92 (s, 1H), 5.79 (br s, 1H), 3.89 (s, 3H), 3.62 (dt [app. q], $J_1 = J_2$ = 5.4 Hz, 2H), 3.31–3.43 (m, 4H), 2.92–3.09 (m, 2H), 1.49–1.66 (m, 6H). LRMS (ESI+) *m/z* 346 $[M+H]^+$.

***N*-(2-(2-(2-Cyanophenyl)thiazol-4-yl)ethyl)piperidine-1-carboxamide (61k).** Prepared according to general procedure F with 2-cyanophenylboronic acid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 7.9 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.70 (dd [app. t], $J_1 = J_2$ = 7.2 Hz, 1H), 7.55 (dd [app. t], $J_1 = J_2$ = 7.6 Hz, 1H), 7.16 (s, 1H), 5.53 (br s, 1H), 3.74 (dt [app. q], $J_1 = J_2$ = 5.8 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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_2SO_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): δ 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): δ 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_2SO_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): δ 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): δ 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 NEt_3 (1 mL) and isopropyl chloroformate solution (0.59 mL, 0.59 mmol) were added, and the reaction mixture was stirred at 60 °C for 2h, then cooled in an ice bath and filtered. The filtrate was washed with water (2 × 30 mL), brine (2 × 30 mL), dried (Na_2SO_4) 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%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.94 (s, 1H, H5'), 4.90 (m, 1H, OCH), 3.52 (dt [app. q], $J_1 = J_2 = 5.9$ Hz, 2H, H1), 2.94 (t, $J = 6.5$ Hz, 2H, H2), 1.21 (d, $J = 6.3$ Hz, 6H, CH_3). 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 NEt_3 (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 (Na_2SO_4) 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%). ^{1}H NMR ($CDCl_3$, 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], $J_1 = J_2 = 6.0$ Hz, 2H, C2'); 3.03 (t, $J = 6.2$ Hz, 2H, C1').

^{13}C NMR ($CDCl_3$, 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, $CDCl_3$): δ 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, $CDCl_3$): δ 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, $C_{17}H_{20}N_3OF_2S^+$ $[M+H]^+$ requires 352.1295.

Method B: A mixture of **63a** (600 mg, 1.89 mmol), K_2CO_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_2SO_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_2CO_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_2SO_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, ^{1}H, H6"), 7.09 (s, ^{1}H, H5'), 6.92–7.00 (m, 2H, H3"/5"), 5.22 (br. s, ^{1}H, 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'"), 41.1 (2 × NCH_2), 40.4 (C1), 31.4 (C2), 13.8 (2 × CH_3). LCMS (ESI) $m/z = 340$ $[M+H]^+$.

Isopropyl (2-(2-(2,4-difluorophenyl)thiazol-4-yl)ethyl)carbamate (64c). A mixture of **63c** (25 mg, 0.085 mmol), K_2CO_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_2SO_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 [app. q] $J_1 = J_2$ = 6.0 Hz, 2H, H1), 3.03 (t, J = 6.3 Hz, 2H, H2), 1.23 (d, J = 6.1 Hz, 6H, CH_3). ^{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 × CH_3). LCMS (ESI) *m/z*: 327 $[M+H]^+$.

***N*-(2-(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_2CO_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 %), $PdCl_2$(dppf) (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_2SO_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 ($AA'X_2$, ~*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-*T. cruzi* activity assessment

Trypomastigote forms from transgenic *T. cruzi* Brazil strain expressing firefly luciferase[40] were purified, diluted in PBS and injected ip in Balb/c mice (10^7 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.*, *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; DND*i*, 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; S_NAr, nucleophilic aromatic substitution; *T.*, *Trypanosoma*; T_{max}, time to peak plasma concentration; UDPGA, uridine 5'-diphosphoglucuronic acid; WEHI, Walter and Eliza Hall Institute; quant., quantitative;

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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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