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Identification of 5-substituted 2-acylaminothiazoles that activate Tat mediated transcription in HIV-1 latency models

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KEYWORDS

HIV-1, AIDS, latency, thiazole.

ABSTRACT

The persistent reservoir of cells latently infected with Human Immunodeficiency Virus (HIV) integrated proviral DNA necessitates lifelong suppressive antiretroviral therapy (ART). Epigenetic targeted compounds have shown promise as potential latency reversing agents, however these drugs have undesirable toxicity and lack specificity for HIV. We utilised a novel HEK293 derived FlpIn dual-reporter cell line, that quantifies specific HIV provirus reactivation (LTR promoter) relative to non-specific host cell gene expression (CMV promoter), to identify the 5-substituted-2-acylaminothiazole hit class. Here, we describe the optimization of the hit class, defining the functionality necessary for HIV gene activation and for improving *in vitro* metabolism and solubility. The optimized compounds displayed enhanced HIV gene expression in HEK293 and Jurkat 10.6 latency cellular models and increase unspliced HIV RNA in resting CD4+ T cells isolated from HIV-infected individuals on ART, demonstrating the potential of the 2-acylaminothiazole class as latency reversing agents.

INTRODUCTION

Antiretroviral therapies (ART) for HIV-infected individuals has transformed HIV-1 infection from a fatal illness into a chronic manageable disease.[1] ART dramatically improves health, returns life expectancy to normal and significantly reduces the risk of HIV transmission. However, although ART suppresses HIV to undetectable levels, discontinuation results in the rapid rebound of the virus to pre-treatment levels.[2]

HIV persists in individuals on suppressive ART in resting CD4+ T cells that contain an intact, replication-competent integrated latent HIV provirus which is unaffected by ART.[3, 4] One strategy being developed to eliminate latently infected cells is referred to as the "shock and kill" approach. This approach aims to activate proviral DNA templated RNA transcription and in subsequent steps mRNA processing, protein translation and virion production so the infected cells are identified and then destroyed by either by immune-mediated processes and/or viral cytopathic effects.[5, 6] The shock and kill approach used in conjunction with ART could potentially deplete replication competent virus from an infected individual.

Many existing epigenetic modulators have been investigated as strategies to activate HIV transcription and several have advanced to clinical trials yielding varied results. In clinical trials, Vorinostat (Figure 1), a histone deacetylase (HDAC) inhibitor, showed enhanced levels of HIV RNA expression in CD4+ T cells in blood from HIV-infected individuals on ART.[7, 8] However, there were no statistically significant changes in plasma HIV RNA, concentration of HIV DNA, integrated DNA and inducible virus in CD4+ T-cells. In addition, significant

changes in host gene expression were also observed highlighting safety concerns with its long-term use. Similar findings have been described with other HDAC inhibitors, including Panobinostat[9, 10] and Romidepsin[11, 12] (Figure 1). JQ1 (Figure 1), a bromodomain and extra-terminal motif (BET) protein inhibitor, can also reactivate HIV by enhancing transcription processivity in both Jurkat latency (J.Lat) clones and primary CD4+ T-cell models.[13, 14] JQ1 also possesses a short half-life in humans[15] and moreover is associated with mild cytotoxicity[16] making it an unsuitable clinical candidate for chronic regimens. Finally, these epigenetic modulators lack specificity for HIV-1 transcriptional activation and are of modest potency with respect to virus activation. Therefore, there is an unmet need to identify new latency reversing agents (LRAs) with a novel mechanism of action.

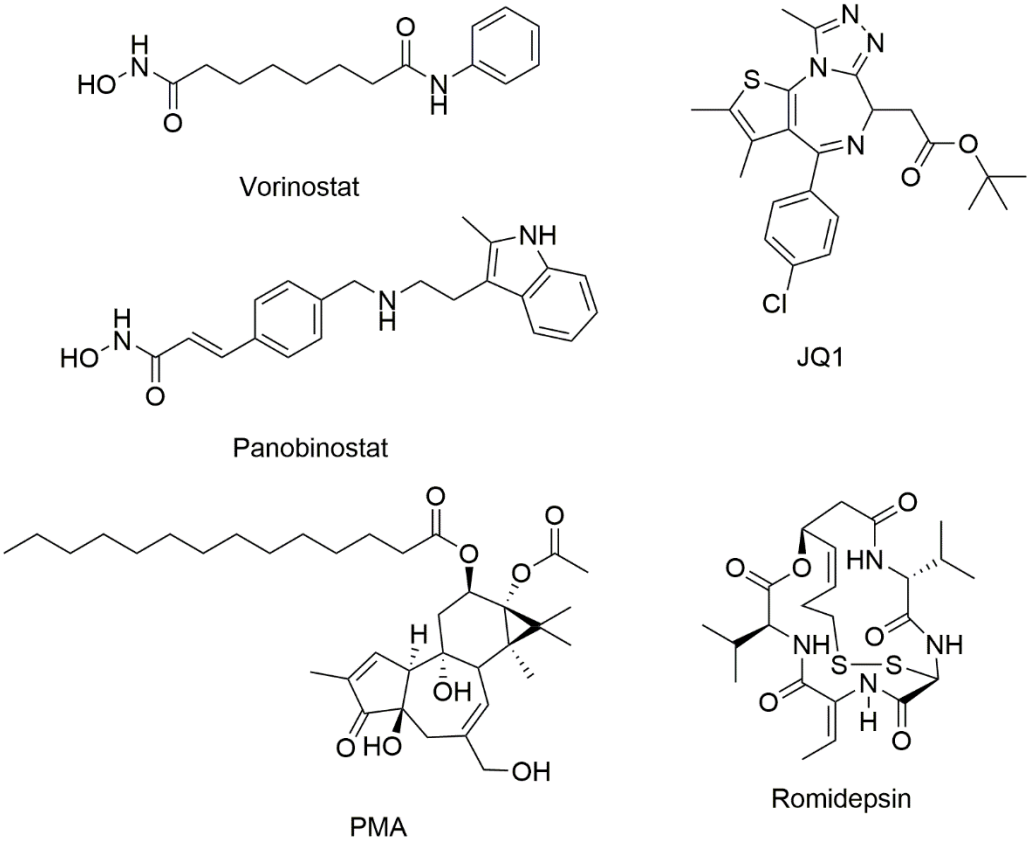

Figure 1. Structures of small molecules commonly used as latency reversing agents in the "shock and kill" strategy.

In latently infected cells, HIV-1 is predominantly integrated into the non-coding introns of transcriptionally active host genes.[17] Transcription of pre-mRNA from the strong upstream cellular promoter reads through the HIV provirus within these introns.[13, 18] Alternative RNA splicing can lead to the formation of chimeric cellular Tat (trans-activator of transcription) mRNAs[19-21] that translate basal levels of Tat protein using internal ribosome entry site (IRES)-mediated translation.[22] HIV transcription is then stimulated by Tat binding to the trans-activation response element and recruits the positive transcription elongation factor-b (pTEFb) enhancing Long Terminal Repeat (LTR) driven HIV transcription. Tat is the master regulator for HIV gene expression and is key in promoting productive viral infection.[23, 24] Therefore, identifying novel small molecules that complement low level Tat expression is potentially a viable strategy to increase HIV transcription in latently infected cells.

We recently developed a dual luciferase reporter cellular assay to identify small molecules capable of activating HIV-1 gene expression (Figure S1).[25, 26] The HEK293 derived reporter cell line, named FlpIn.FM, mimics HIV-1 post integration latency and read-through transcription by translating a low level of HIV-1 Tat – human growth hormone chimeric protein using a IRES mechanism. The cell line expresses a HIV-1 Nef – click beetle red (CBR) fusion protein driven by Tat from the long terminal repeat (LTR) HIV promoter, allowing for detection of viral gene expression. The cell line also contains a click beetle green (CBG) luciferase reporter driven from a cytomegalovirus (CMV) promoter allowing the detection of non-specific host cell protein expression. The dual reporter FlpIn.FM cell line was characterized for its high responsiveness to Tat and shown to be applicable for detecting latency

reversing agents. In this study, Vorinostat and JQ1 (Figure 1) were shown to enhance the LTR CBR response, but also increased CMV or host cell reporter to similar levels,[25, 26] consistent with literature.[27] This study established the FlpIn.FM HEK293 cell line as an effective tool for identifying novel latency reversing agents that act via a Tat-dependent mechanism.

We utilised the FlpIn.FM HEK293 cellular assay to screen a chemically diverse library of 114,000 small molecules[28, 29] to primarily identify compounds capable of enhancing HIV LTR (CBR) activity. The CMV (CBG) reporter was used to monitor Tat non-dependent or non-specific host cell gene expression. The high throughput screen identified the 2-acylaminothiazole **1** (Figure 2) as a hit compound and possessed an EC_{50} of 24 μM for the HIV LTR reporter, while displaying no detectable activity for the CMV reporter at the highest concentration tested (40 μM) (Table 1).

To demonstrate the hit compound **1** was genuinely activating gene expression and not an assay artefact, two counterscreen approaches were implemented. The first counterscreen utilized the FlpIn.RV HEK293 cell line in which the luciferase reporters were reversed in comparison to the FlpIn.FM cell line (Figure S1). Using the FlpIn.RV cell line, the hit compound **1** was shown to possess an EC_{50} of 29 μM against the LTR (CBG) reporter while the EC_{50} for the CMV (CBR) reporter was >40 μM (Figure S2), consistent with the activity of compound **1** using the FlpIn.FM cell line. The second counter screen assay involved the addition of compound **1** to the FlpIn.FM cell line followed immediately by the addition of and incubation with luciferase reagents (time point 0 hours in Figure S3A). Under these conditions no bioluminescence signal was measured compared to incubation with the compound for 48 hours (Figure S3B). Collectively the counterscreen

data demonstrated hit compound **1** was not an assay interference artefact and was genuinely activating LTR gene expression.

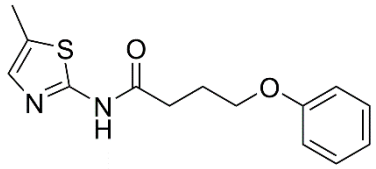

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Figure 2. Hit compound **1** identified from a high throughput screen of a diverse chemical library of 114,000 compounds using FlpIn.FM dual reporter HEK293 cellular assay.

Herein, we describe the optimization and the characterization of the structure activity relationship (SAR) of the 5-substituted 2-acylaminothiazole scaffold to generate a series of compounds with enhanced HIV LTR activity in the FlpIn.FM cell line. Physicochemical parameters were also assessed in parallel and assisted in the design and selection of analogues for further evaluation in HIV-1 cellular models. Compounds with suitable properties and activity in the FlpIn.FM HEK293 cellular assay were then evaluated in the Jurkat latently infected cell line and subsequently in CD4+ T cells from HIV-infected individuals on suppressive ART.

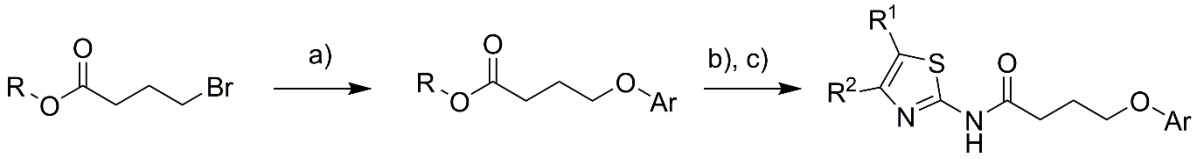
RESULTS AND DISCUSSION

The initial focus of optimising the 2-acylaminothiazole class was to establish the SAR, providing a foundation to improve LTR reporter activity using the FlpIn.FM HEK293 cell line. The hit 2-acylaminothiazole compound **1**, possessed limited aqueous solubility (<1 μM

at pH 6.5) and was rapidly degraded by both human and mouse liver microsomes (CL_{int} 175 and 815 μL/min/mg protein, respectively) (Table 10). The thiazole moiety potentially possesses intrinsic *in vivo* toxicity, because of cytochrome P450-mediated oxidative conversion of the 4,5-unsaturated bond to an epoxide acting as a trap for nucleophiles.[30] The physicochemical properties, *in vitro* metabolism and the thiazole toxicophore are factors taken into consideration during the optimization of the 2-acylaminothiazole series.

Chemistry

The general synthetic route (Scheme 1) undertaken to generate the 5-substituted 2-acylaminothiazole analogues involved alkylation of a substituted phenol with a protected halogenated butanoate. Subsequent deprotection of the ester and then an amide coupling to a substituted 2-aminothiazole gave the 2-acylaminothiazole product.



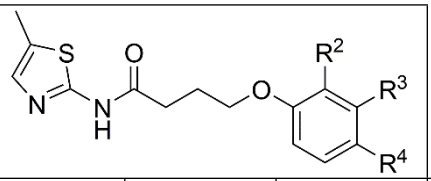
Scheme 1. General pathway to synthesize 2-acylaminothiazole analogues. *Reagents and conditions:* (a) substituted phenol, K_2CO_3 or NaH, MeCN or DMF; (b) For R = Et: LiOH, MeOH, H_2O, 50°C; For R = *t*Bu: HCl, dioxane, 20°C; (c) substituted 2-acylaminothiazole, EDC.HCl, DMAP, DCM.

Structure and activity relationship

To establish the SAR, we systematically investigated moieties on the 2-acylamino scaffold independently and the effect on LTR reporter activity in the FlpIn.FM HEK293 cell line. We first investigated substitution on the phenoxy ring with different functionality to determine whether the steric and electronic nature of groups would affect LTR activity (Table 1). It was shown that substitution of the 2- and 4- positions on the phenoxy ring were generally not tolerated, except for the 2-methoxy substitution (**12**), that possessed enhanced LTR activity (EC_{50} 1.2 μM), and the 2-methyl substitution (**2**) that was equally as active (EC_{50} 19 μM) compared to **1**. The 2-methoxy substitution **12** also gave an increase in CMV reporter activity (EC_{50} 6.2 μM) and therefore further iterations to the 2-position of the phenoxy ring were not further pursued. In contrast, 3-methyl (**3**), 3-chloro (**6**), 3-trifluoromethyl (**8**) and 3-nitrile (**10**) substituents enhanced activity, all possessing LTR EC_{50} values of approximately 1 to 2 μM. The 3-chloro and 3-trifluoromethyl analogues (**6** and **8**) did not display CMV reporter activity at the highest concentration tested (EC_{50} >40 μM), but the 3-methyl and 3-nitrile analogues (**3** and **10**) exhibited CMV reporter activity (EC_{50} of 2.1 and 9.9 μM respectively). Electron donating substituents, such as hydroxyl (**15**), amino (**17**) and aminoacyl (**19**) were not tolerated in the 3-position (LTR EC_{50}s all >40 μM). A methyl carboxylate group in the 3-position (**23**) was also detrimental to activity (LTR EC_{50}s all >40 μM) suggesting larger polar substituents were not tolerated. The 3-methylene hydroxy group (**21**) was accepted (LTR EC_{50} 6.4 μM), but also exhibited the CMV reporter activity (EC_{50} 7.1 μM). Thus, the activity data on the phenoxy ring substitution indicated 3-chloro and 3-trifluormethyl possessed the largest improvement in LTR activity while not

affecting the CMV reporter (EC_{50} values >40 μM), but the 3-methyl and 3-methylene hydroxy substitution conveyed equipotent LTR and CMV activity. This selectivity data suggested that electron withdrawing groups in the 3-position were the most effective at enhancing LTR activity while only minimally effecting the CMV reporter. The 3-chloro and 3-trifluormethyl modifications (**6** and **8**) slightly increased in cLogP, translating into a minor increase in LipE (2.1 and 1.5) while the nitrile analogue (**10**) exhibited a 2-fold improvement in LipE (2.7) compared to the hit compound **1** (LipE 1.4). Metabolically the 3-trifluoromethyl substitution (**8**) prevents O-dealkylation of the phenoxy group, while the 3-chloro (**6**) and 3-nitrile (**10**) substitution did not block O-dealkylation (Table S2).

Table 1. The activity of aryl substitution in the FlpIn.FM dual reporter cell assay.

Cmpd								
	R^2	**R^3**	**R^4**	**LTR EC_{50}**	**CMV EC_{50}**	**cLog P** [b]	**PSA (Å²)** [b]	**LipE** [c]

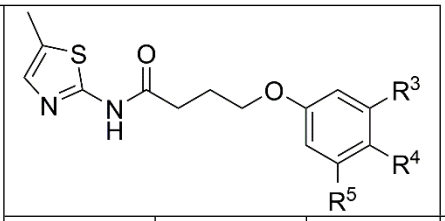
				(SD) μM [a]	(SD) μM [a]			
1	H	H	H	24 (3.6)	>40	3.2	51	1.4
2	CH_3	H	H	19 (1.6)	>40	3.8	51	0.9
3	H	CH_3	H	1.7 (0.2)	2.1 (0.7)	3.8	51	2.0
4	H	H	CH_3	>40	>40	3.8	51	-
5	Cl	H	H	>40	>40	3.8	51	-
6	H	Cl	H	1.3 (0.2)	>40	3.8	51	2.1
7	H	H	Cl	>40	>40	3.8	51	-
8	H	CF_3	H	2.6 (0.7)	>40	4.1	51	1.5
9	H	H	CF_3	>40	>40	4.1	51	-
10	H	CN	H	1.5 (0.3)	9.9 (4.4)	3.1	75	2.7
11	H	H	CN	>40	>40	3.1	75	-
12	OCH_3	H	H	1.2 (0.3)	6.2 (1.1)	3.1	60	2.8
13	H	OCH_3	H	>40	>40	3.1	60	-
14	H	H	OCH_3	>40	>40	3.1	60	-
15	H	OH	H	>40	>40	2.9	71	-
16	H	H	OH	>40	>40	2.9	71	-
17	H	NH_2	H	>40	>40	2.4	77	-
18	H	H	NH_2	>40	>40	2.4	77	-
19	H	NHAc	H	>40	>40	2.5	80	-
20	H	H	NHAc	>40	>40	2.5	80	-
21	H	CH_2OH	H	6.4 (1.4)	7.1 (2.4)	2.5	71	2.7
22	H	H	CH_2OH	>40	>40	2.5	71	-
23	H	CO_2CH_3	H	>40	>40	3.2	78	-
24	H	H	CO_2CH_3	>40	>40	3.2	78	-

[a] EC_{50} data represents means and SDs for three or more independent experiments measuring bioluminescence of in the HEK293 FlpIn.FM dual reporter cell line following exposure to compounds in a 10-point dilution series for 48 h. [b] Calculated using ChemAxon software.[23] [c] Calculated using the LTR EC_{50} value.

We then explored the effect of disubstitution of the phenoxy ring on LTR activity, primarily concentrating on maintaining one of the electron withdrawing substituents in the 3-position while altering the functionality at either the 4- or 5-position (Table 2). Analogues that possessed either a 3-chloro or 3-trifluoromethyl group with a 4-chloro substituent (**26** and **27**) displayed slightly decreased LTR activity (EC_{50} 9.2 and 3.6 μM) compared to their 3-monosubstituted parent compounds **6** and **8** (EC_{50} 1.3 and 2.6 μM). The

3-chloro-4-methyl substituted analogue (**25**) displayed an EC_{50} of 4.7 μM indicating the installation of a 4-methyl group was not beneficial to activity. Consistent with activity values for monosubstituted analogues, addition of 4-chloro and 4-nitrile substituents on 3-methyl phenoxy ring, the 3-methyl-4-chloro or 3-methyl-4-nitrile analogues (**28** and **29**) were detrimental to LTR activity (EC_{50} 13 and >40 μM). 3,5-Disubstitution was also detrimental to the LTR activity of analogues **30-31** and **33** (EC_{50} >10 μM) compared to 3-mono substituted compounds (EC_{50}s <3 μM). Overall 3,4-distubsutituon was tolerated but did not enhance LTR activity and the addition of extra hydrophobic functionality in the 4-position also decreased LipE values. Therefore, this suggested mono-substitution with electron withdrawing groups in the 3-position of the phenoxy ring were the most effective at increasing LTR activity while not increasing the CMV reporter activity.

Table 2. Activity of analogues with aryl disubstitution on Flp.FM dual reporter cell activity.

Cmpd								
	R³	**R⁴**	**R⁵**	**LTR EC_{50}** (SD) μM [a]	**CMV EC_{50}** (SD) μM [a]	**cLogP** [b]	**PSA** (Å²) [b]	**LipE** [c]
1	H	H	H	24 (3.6)	>40	3.2	51	1.4
25	Cl	CH_3	H	4.7 (1.0)	>40	4.4	51	0.9
26	Cl	Cl	H	9.2 (1.5)	>40	4.5	51	0.5
27	Cl	CF_3	H	3.6 (0.8)	>40	4.7	51	0.7
28	CH_3	Cl	H	13 (2.9)	38	4.4	51	0.5
29	CH_3	CN	H	>40	>40	3.7	75	-
30	F	H	F	40 (2.8)	>40	3.5	51	0.9
31	Cl	H	Cl	>40	>40	4.5	51	-
32	Cl	H	CH_3	3.3 (1.1)	>40	4.4	51	1.1
33	CN	H	CN	11 (3.0)	>40	3.0	99	2.0
34	CH_3	H	CH_3	2.3 (0.3)	>40	4.3	51	1.3

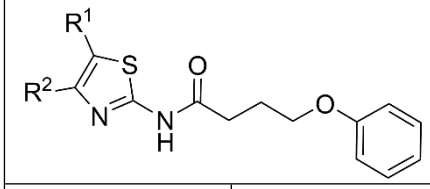
[a] EC_{50} data represents means and SDs for three or more independent experiments measuring bioluminescence of in the HEK293 FlpIn.FM dual reporter cell line following exposure to compounds in a 10-point dilution series for 48 h. [b] Calculated using ChemAxon software.[23] [c] Calculated using the LTR EC_{50} value.

Thiazoles are known toxicophores and are susceptible to cytochrome P450 mediated oxidative metabolism of the 4,5-double bond to produce an epoxide.[31] The epoxide formed can either act as a trap for nucleophiles or can be further oxidized to form reactive di-carbonyl and thioamide metabolites.[32] Meloxicam, a marketed nonsteroidal anti-inflammatory analgesic, possesses a 5-methyl 2-aminothiazole. Metabolism studies show that a 5-methyl substitution present on the thiazole in Meloxicam can delay or circumvent

this oxidative pathway.[33] However, the metabolic outcome cannot always be predicted with new chemical entities. Compound **1** is rapidly degraded in the presence of human and mouse liver microsomes (Table 10). Identification of metabolite masses in this study revealed several points of metabolism on the 2-acylaminothiazole scaffold (Table S2). Two +16 mass metabolites were identification that were predicted to correspond to either the oxidation of the 5-methyl substituent, oxidation of the phenol ring or epoxidation of the thiazole ring. To de-risk the potential inherent metabolic and toxicophoric liability of the thiazole we investigated two strategies. Firstly, determine functional group tolerance in the 4- and 5-position on the thiazole ring that may inadvertently mitigate oxidative metabolism of the 4,5-unsaturated bond. The second approach was to replace the thiazole with suitable isosteric 5- and 6-membered heterocyclic systems.

We first examined the effects of substitution in the 4- and 5-position of the thiazole ring on LTR activity while keeping the scaffold of compound **1** constant (Table 3). In this set of analogues, it was shown deleting the 5-methyl substituent (**35**) resulted in a loss of LTR activity. 4-Methyl and 4,5-dimethyl substitution of the thiazole (**47** and **50**) also resulted in loss activity, indicating the 4- and 5- positions of the thiazole system were sensitive to change and the 5-substitution was critical for activity. Analogues with 4-trifluromethyl and 4-nitrile substitution (**48** and **49**) were also generated and demonstrated functionality other than a methyl group in the 5-position of the thiazole was not accepted.

Table 3. The activity of 4- and 5-thiazole substitution in the Flp.FM dual reporter cell assay.

Cmpd							
	R^1	**R^2**	**LTR EC_{50}** (SD) μM [a]	**CMV EC_{50}** (SD) μM [a]	**cLog P** [b]	**PSA** (Å²) [b]	**LipE** [c]
1	CH_3	H	24 (3.6)	>40	3.2	51	1.4
35	H	H	>40	>40	2.6	51	-
36	Cl	H	5.0 (1.0)	>40	3.4	51	1.9
37	Br	H	3.7 (0.8)	>40	3.5	51	1.9
38	CF_3	H	2.9 (0.9)	8.4 (3.8)	3.6	51	1.9
39	CH_2CH_3	H	4.7 (1.2)	7.2 (2.0)	3.7	51	1.6
40	*i*Pr	H	6.4 (1.2)	32 (15)	4.0	51	1.2
41	*i*Bu	H	>40	>40	4.3	51	-
42	Ph	H	>40	>40	4.2	51	-
43	CN	H	11 (0.9)	>40	2.6	75	2.4
44	COOH	H	>40	>40	2.4	89	-
45	$CONH_2$	H	>40	>40	1.6	94	-
46	$CONMe_2$	H	>40	>40	2.0	72	-
47	H	CH_3	>40	>40	2.7	51	-
48	H	CF_3	>40	>40	3.9	51	-
49	H	CN	>40	>40	2.8	75	-
50	CH_3	CH_3	>40	>40	3.4	51	-

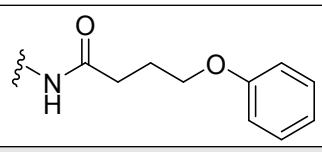
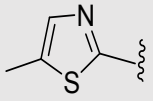
[a] EC_{50} data represents means and SDs for three or more independent experiments measuring bioluminescence of in the HEK293 FlpIn.FM dual reporter cell line following exposure to compounds in a 10-point dilution series for 48 h. [b] Calculated using ChemAxon software.[23] [c] Calculated using the LTR EC_{50} value. **1** is included for comparison.

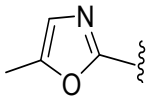
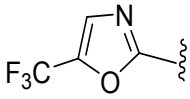
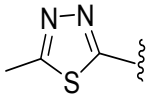
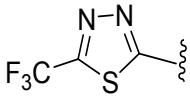
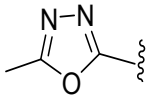
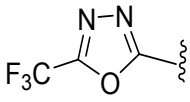
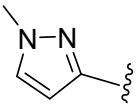
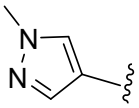
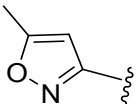
Tolerance of functionality and steric volume in the 5-position of the thiazole were then explored (Table 3). Replacing the 5-methyl group (**1**) with electron withdrawing chloro or bromo halogens (**36** and **37**) gave a 5-fold enhancement in LTR activity (EC_{50} 5.0 and 3.7 μM) without effecting the CMV reporter (EC_{50} >40 μM). 5-Trifluoromethyl substitution of the thiazole (**38**) improved LTR activity 8-fold (EC_{50} 2.9 μM) but introduced CMV reporter activity (EC_{50} 8.4 μM). Replacing the 5-methyl group (**1**) with larger substitution such as ethyl and isopropyl groups (**39** and **40**) improved LTR activity (EC_{50} 4.7 and 6.4 μM), but also increased CMV reporter activity (EC_{50} 7.2 and 32 μM). Analogues with substituents larger than an isopropyl such as a 5-isobutyl and 5-phenyl substituents (**41** and **42**) were inactive. A 5-nitrile substituent (**43**) was tolerated (11 μM), but larger polar groups such as a carboxylic acid, carboxamide and dimethyl carboxamide at the 5-position (**44**, **45** and **46**) were detrimental to LTR activity (EC_{50}s >40 μM). The SAR of the 5-position of the thiazole suggested hydrophobic and nitrile substituents with smaller steric size than an isopropyl group were ideally occupying a pocket of the cellular target responsible for LTR activity, however compounds that possess a 5-substitutent larger steric volume than a methyl or bromo, were also potentially occupying a pocket of the cellular target conferring CMV reporter activity. Compared to analogues substituted with hydrophobic functionality, analogue **43** with a nitrile group in the 5-position possessed lower cLogP (2.6) and enhanced LipE (2.4) and therefore was the most effective according to these parameters.

In vitro metabolism studies were undertaken with analogue **43** in the presence of human and mouse liver microsomes to determine if the 5-nitrile thiazole substitution circumvents metabolic epoxidation of the thiazole ring. The metabolism results show there was no difference in the human intrinsic clearance with **43** compared to the 5-methyl ortholog (**1**), but there was an improvement in mouse intrinsic clearance (Table 10). Mass spectrometry analysis of the metabolites in the liver microsome study showed there was a reduction in the number of oxidative metabolism events with **43** compared to the 5-methyl ortholog (**1**) (Table S2). It was proposed this difference was due to hydroxylation of the 5-methyl group of **1** and therefore epoxidation of the 4,5-thiazole double bond was not observed under the in vitro liver microsome conditions. It was concluded, inclusion of the 5-nitrile substituent blocked 5-methyl hydroxylation and amide bond hydrolysis was responsible for the improvement in mouse intrinsic clearance of analogue **43** compared to the 5-methyl ortholog **1**.

Another approach to avoid thiazole related metabolism and improve physicochemical properties was to explore suitable isosteric replacements of the thiazole with either 5-methyl or 5-trifluoromethyl substitution (Table 4). 5-Membered heterocycles including oxazoles (**51** and **52**), 1,3,4-thiadiazoles (**53**, **54**) and 1,3,4-oxadiazoles (**55**, **56**) were examined, but none of these analogues displayed LTR reporter activity (Table 4). N-Methylated pyrazoles (**57** and **58**) and 5-methyl isooxazole (**59**) were also inactive (Table 4), highlighting the addition of an extra hetero nitrogen in the 4-postion and the exchange of the thiazole sulfur for an oxygen or carbon atom in 5-membered heterocyclic systems were not tolerated.

Table 4. Activity of 5-membered thiazole isosteres in the FlpIn.FM dual reporter cell assay.

Cmpd		LTR EC_{50} (SD) μM [a]	CMV EC_{50} (SD) μM [a]	cLogP [b]	PSA (Å^2) [b]	LipE [c]
1		24 (3.6)	>40	3.2	51	1.4

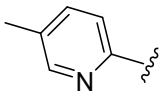
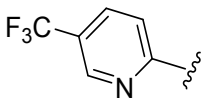
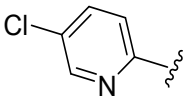
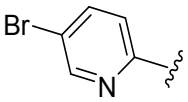
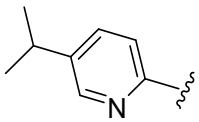
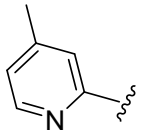
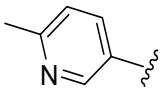
51		>40	>40	2.1	64	-
52		>40	>40	2.7	64	-
53		>40	>40	1.8	64	-
54		>40	>40	3.0	64	-
55		>40	>40	1.0	77	-
56		>40	>40	2.2	77	-
57		>40	>40	2.3	56	-
58		>40	>40	1.7	56	-
59		>40	>40	2.4	64	-

[a] EC_{50} data represents means and SDs for three or more independent experiments measuring bioluminescence of in the HEK293 FlpIn.FM dual reporter cell line following exposure to compounds in a 10-point dilution series for 48 h. [b] Calculated using ChemAxon software.[23] [c] Calculated using the LTR EC_{50} value. **1** is included for comparison.

5-Methyl pyridine was also attempted as a suitable 6-membered heterocyclic isostere of the 5-methyl thiazole system (Table 5). The 5-methyl pyridine analogue (**60**) exhibited comparable LTR reporter activity (EC_{50} 20 μM) and CMV reporter activity (EC_{50} 39 μM) to the thiazole ortholog **1**. This data demonstrated the pyridyl system was a potential

replacement for the thiazole, and therefore several 5-subtituted pyridyl analogues were generated and their LTR and CMV activities (Table 5) compared to the activity of the 5-substituted thiazole orthologs (Table 3). The chloro and bromo substitution in the 5-position of the pyridine (**62** and **63**) resulted in a 3-fold improvement in LTR activity (EC_{50} of 6.7 and 8.0 μM) compared to the 5-methyl pyridine analogue **60** (EC_{50} 20 μM). The 3-fold shift in LTR activity was slightly less than the 5-fold shift between the halogenated thiazole analogues **36** and **37**, and the 5-methyl thiazole analogue **1**. The 5-trifluoromethyl pyridine analogue **61** displayed equipotent LTR and CMV activity (EC_{50} 14 and 32 μM, respectively) compared to the methyl pyridine analogue **60** (EC_{50} 20 and 39 μM respectively), but decreased LTR and CMV activity when compared to the 5-trifluoromethyl thiazole ortholog **38** (EC_{50} 2.9 and 8.4 μM). The 5-isopropyl pyridine analogue (**64**) exhibited no LTR activity (EC_{50} >40 μM), in contrast to the LTR activity (EC_{50} 6.4 μM) exhibited by the 5-isopropyl thiazole ortholog **40**. Moving the pyridinyl endocyclic nitrogen to the 2-position (**66**) or the methyl substitution to the 4-position (**65**) also eliminated LTR activity. Collectively, this activity data demonstrated that although the 5-substituted pyridyl system was a suitable isostere for the 5-functionalized thiazole, the pyridyl system generally displayed decreased LTR reporter activity and a smaller selectivity window over the CMV reporter compared to the thiazole analogues. Furthermore, the pyridyl system did not enhance physicochemical properties or LipE and therefore was not further pursued.

Table 5. Activity of 6-membered thiazole isosteres in the FlpIn.FM dual reporter cell assay.

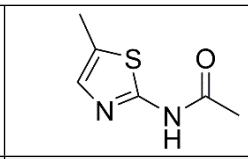
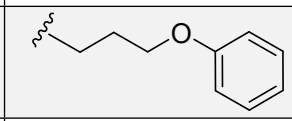
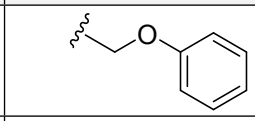
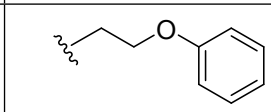
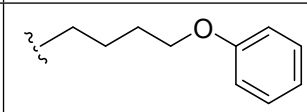
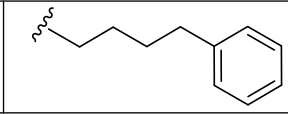
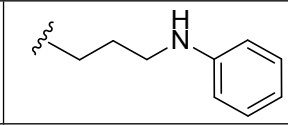
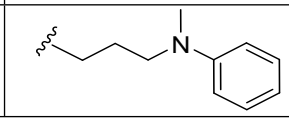
Cmpd		LTR EC_{50} (SD) μM [a]	CMV EC_{50} (SD) μM [a]	cLog P [b]	PSA (Å^2) [b]	LipE [c]
60		20 (0.6)	39 (0.5)	3.1	51	1.6
61		13 (1.0)	32 (5.7)	3.5	51	1.4
62		6.7 (1.4)	>40	3.2	51	2.0
63		8.0 (1.7)	>40	3.4	51	1.7
64		>40	>40	3.9	51	-
65		>40	>40	3.1	51	-
66		>40	>40	2.2	51	-

[a] EC_{50} data represents means and SDs for three or more independent experiments measuring bioluminescence of in the HEK293 FlpIn.FM dual reporter cell line following exposure to compounds in a 10-point dilution series for 48 h. [b] Calculated using ChemAxon software.[23] [c] Calculated using the LTR EC_{50} value.

We next determined whether the length of the three-carbon chain, between the phenoxy and the carboxamide, was optimum for LTR activity (Table 6). Shortening the chain to one- or two-carbons (**67** and **68**) or extending the chain to four-carbons (**69**)

eliminated LTR activity, suggesting the three-carbon chain between the phenoxy and the carboxamide is necessary for LTR activity. We then investigated the importance of the oxygen atom on the phenoxy group by replacing it with carbon and nitrogen atoms. It was shown that exchange of the phenoxy oxygen with a carbon atom (**70**) resulted in a 2-fold improvement in LTR activity (EC_{50} 13 μM) compared to its phenoxy counterpart **1** (EC_{50} 24 μM), but also introduced CMV reporter activity (EC_{50} 34 μM) (Table 6). Replacing the phenoxy group with aniline (**71**) preserved the LTR activity (EC_{50} 22 μM) but also increased the CMV reporter activity (EC_{50} 27 μM). Substituting the oxygen of the phenoxy group with a N-methyl group (**72**) increased both the LTR and CMV reporter activity (EC_{50} 6.3 and 14 μM respectively) compared to the phenoxy comparator compound **1**. This data highlighted that a carbon atom was a suitable replacement for the oxygen, and although not tested, **70** would be metabolically devoid of the O-dealkylation observed with the phenoxy analogue **1** in the presence of liver microsomes (Table S2). However, compound **70** possesses significantly higher cLogP and decreased LipE compared to the complementary phenoxy analogue **1**, and therefore incorporation of the carbon-linked phenyl would only be considered in future work if metabolic O-dealkylation was not overcome.

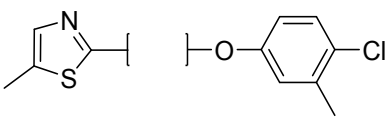
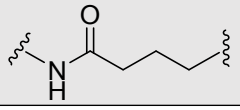
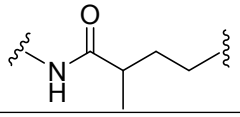
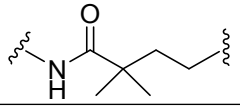
Table 6. The activity of acyl carbon chain in the Flp.FM dual reporter cell assay.

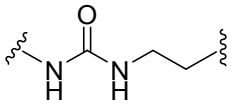
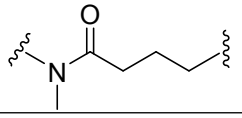
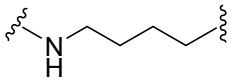
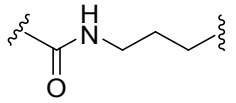
Cmpd		LTR EC_{50} (SD) μM [a]	CMV EC_{50} (SD) μM [a]	cLogP [b]	PSA (Å^2) [b]	LipE [c]
1		24 (3.6)	>40	3.2	51	1.4
67[d]		>40	>40	3.8	51	-
68		>40	>40	3.0	51	-
69[d]		>40	>40	4.8	51	-
70		13 (0.8)	34 (1.0)	4.4	41	0.5
71		22 (5.1)	27 (9.5)	2.9	54	1.8
72		6.3 (0.6)	14 (4.0)	3.5	45	1.7

[a] EC_{50} data represents means and SDs for three or more independent experiments measuring bioluminescence of in the HEK293 FlpIn.FM dual reporter cell line following exposure to compounds in a 10-point dilution series for 48 h. [b] Calculated using ChemAxon software.[23] [c] Calculated using the LTR EC_{50} value. [d] Analogues both have 4-chloro-3-methyl substitution on the phenoxy ring. **1** is included for comparison.

We further explored the three-carbon chain, between the phenoxy and the carboxamide, concentrating on modification of the carbonyl alpha-carbon (Table 7). The addition of a methyl substitution (**73**) displayed a 2-fold loss in LTR reporter potency (EC_{50} 23 μM) and maintained CMV selectivity (EC_{50} >40 μM), compared to the comparator **28** (EC_{50} 38 μM). Gem dimethyl substitution of the carbonyl alpha-carbon (**74**) resulted in a complete loss of LTR activity. Replacing the carbonyl alpha-carbon with a nitrogen atom to form a urea in (**75**) improved LTR activity 8-fold (EC_{50} 2.8 μM) but resulted in an increase in CMV reporter activity (EC_{50} 5.0 μM). Noting the effect of the urea moiety on LTR activity, we next explored the configuration of the amide (Table 7). Methylation of the amide NH (**76**) and removal of the amide carbonyl (**77**) resulted in loss of LTR reporter activity. In addition, reversing the configuration of the amide bond (**78**) also eliminated LTR activity, highlighting the importance of both the presence and configuration of the amide moiety.

Table 7. The activity of acyl variations in the FlpIn.FM dual reporter cell assay.

Cmpd		**LTR EC_{50}** (SD) μM [a]	**CMV EC_{50}** (SD) μM [a]	**cLogP** [b]	**PSA** (Å^2) [b]	**LipE** [c]
28		13 (2.9)	38	4.4	51	0.5
73		23 (8.0)	>40	4.9	51	-0.3
74		>40	>40	5.5	51	-

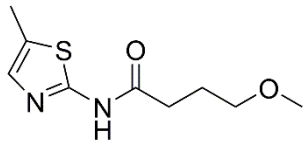
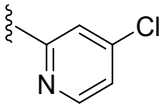
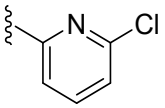
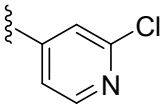
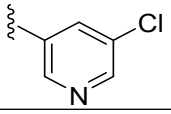
75		2.8 (1.1)	5.0 (1.4)	3.9	63	1.7
76		> 40	> 40	4.2	42	-
77		> 40	> 40	4.8	34	-
78		> 40	> 40	3.6	51	-

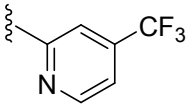
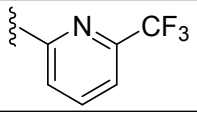
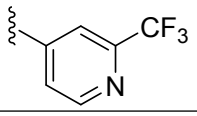
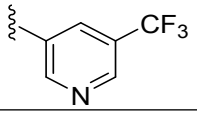
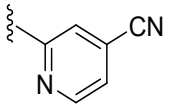
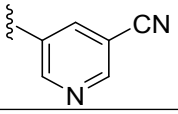
[a] EC_{50} data represents means and SDs for three or more independent experiments measuring bioluminescence of in the HEK293 FlpIn.FM dual reporter cell line following exposure to compounds in a 10-point dilution series for 48 h. [b] Calculated using ChemAxon software.[23] [c] Calculated using the LTR EC_{50} value. **28** is included for comparison.

To improve the aqueous solubility and reduce overall cLogP of the 2-acylaminothiazole series we next replaced the hydrophobic phenoxy aryl ring with differentially substituted pyridines, concentrating on substitution in the meta position (Table 8) to mimic 3-chloro, 3-trifluoromethyl or 3-nitrile phenoxy systems (**6**, **8**, **10**) that conferred to greatest LTR activity (Table 1). Analogues **79-88** were generated with the endocyclic nitrogen in 2-, 4-, 5- and 6- positions with either chloro, trifluoromethyl or nitrile in the 3-position. The 3-chloro substituted analogues with the heterocyclic nitrogen in the 6-, 2- and 5- positions (**79**, **80** and **82** respectively) displayed comparable LTR activity (EC_{50} 2.7, 4.7 and 2.9 μM) to the non-endocyclic nitrogen ortholog **6** (EC_{50} 1.3 μM) while maintaining 10-fold greater activity window over the CMV reporter (EC_{50} 34, 39 and >40 μM). The 3-chloro substituted 4-endocyclic nitrogen derivative **81** exhibited no LTR reporter activity. The 3-trifluoromethyl and 3-nitrile pyridinyl analogues (**83-85** and **87-88**) all displayed no LTR activity, except for the 3-trifluoromethyl 5-endocyclic nitrogen derivative (**86**, LTR EC_{50}

11 μM) with no observable CMV activity (EC_{50} >40 μM). This data demonstrated the SAR between the 3-substituted phenoxy and the pyridinyl analogues was not entirely conserved. Although cLogP of the pyridinyl analogue (**79**, **80** and **82**) was improved compared to phenoxy compound **6**, the LipE was only notably enhanced in the case of **82**. Furthermore, aqueous solubility of the pyridinyl analogues **80** and **82** at both pH 2 and 6.5 was not significantly improved compared to the phenoxy comparator **6** (<1 μM) (Table 10). Metabolism was also not improved with **80**, but an improvement in intrinsic clearance was observed with the pyridinyl analogue **82** (CL_{int} human 86; mouse 340 μL/min/mg protein) compared to **6** (CL_{int} human 340; mouse >866 μL/min/mg protein) (Table 10). Overall, incorporating a heterocyclic nitrogen in the phenoxy ring was not beneficial for LTR activity and did not dramatically improve physicochemical properties, and therefore integration of other pyridinyl or heterocyclic systems were not further considered.

Table 8. Activity of heterocyclic aryl analogues in the Flp.FM dual reporter cell assay.

Cmpd		**LTR EC_{50}** (SD) μM [a]	**CMV EC_{50}** (SD) μM [a]	**cLog P** [b]	**PSA** (Å^2) [b]	**LipE** [c]
79		2.7 (0.9)	34 (6.8)	3.2	64	2.4
80		4.7 (0.3)	39 (2.0)	3.4	64	1.9
81		>40	>40	2.8	64	-
82		2.9 (0.6)	>40	2.6	64	2.9

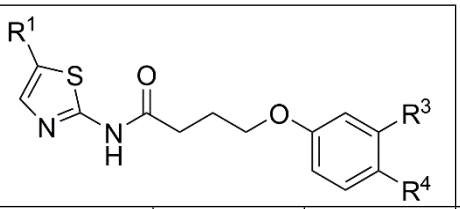
83		>40	>40	3.5	64	-
84		>40	>40	3.9	64	-
85		>40	>40	3.3	64	-
86		11 (2.4)	>40	2.9	64	2.1
87		>40	>40	2.5	88	-
88		>40	>40	1.9	88	-

[a] EC_{50} data represents means and SDs for three or more independent experiments measuring bioluminescence of in the HEK293 FlpIn.FM dual reporter cell line following exposure to compounds in a 10-point dilution series for 48 h. [b] Calculated using ChemAxon software.[23] [c] Calculated using the LTR EC_{50} value.

Earlier SAR established 3-chloro, 3-nitrile or 3-trifluoromethyl substitution on the phenoxy aryl group was important for enhancing LTR activity (Tables 1 and 2). In addition, chloro, nitrile or trifluoromethyl substitutions on the 5-position of the aminothiazole ring also increased LTR activity (Table 3). To improve LTR activity we next examined combining substituents that conferred the greatest LTR activity in the 5-position of the thiazole and the 3-position of the phenoxy group (Table 9). The analogues generated (**89-97**) all possessed EC_{50} values between approximately 1 and 4 μM for the LTR reporter except for **92** and **95** which exhibited 30 and 10-fold selectivity over the CMV reporter. This data indicates there were no significant improvements in LTR activity from combining the substituents from the 3-phenoxy or the 5-thiazole positions compared to orthologs in Table 1 and 3. The majority of analogues (**89-97**) displayed CMV reporter activity comparable to

the LTR reporter. To improve LTR activity and selectivity, 3,4-disubstitution on the phenoxy aryl group (from Table 2) was combined with both the 5-chloro and the 5-trifluromethyl thiazole to give analogues **98-102** (Table 9). These analogues also displayed EC_{50} values between approximately 1 and 4 μM for the LTR reporter. Analogues **98** and **101** displayed comparable LTR activity to the CMV reporter, but analogues **99**, **100** and **102** exhibited a 20- to 10-fold increase in LTR activity compared to the CMV reporter. Overall, the combination of substitution on the 5-position of the thiazole and the 3-substituted phenoxy aryl moiety was not beneficial for LTR activity nor LTR selectivity compared to analogues incorporating substitution only on the 3-position of the phenoxy group, such as **6** or **8** (Table 1) or analogues incorporating substitution on the 5-position of the thiazole, such as **36** and **37** (Table 3). Furthermore, the physicochemical properties (cLogP, PSA), LipE and aqueous solubility of the analogues with a combination of substituents were not improved compared to their comparators (Table 10). However, metabolic stability in the presence of human and mouse liver microsomes was significantly improved with the analogues **96** (CL_{int} human 22; mouse 56 μL/min/mg protein) and **97** (CL_{int} human 30; mouse 78 μL/min/mg protein) compared to the hit compound **1** and the other analogues in Table 10.

Table 9. Activity of combinations of substitution in the Flp.FM dual reporter cell assay.

Cmpd								
	R^1	**R^3**	**R^4**	**LTR EC_{50}** (SD) μM [a]	**CMV EC_{50}** (SD) μM [a]	**cLogP** [b]	**PSA** (Å^2) [b]	**LipE** [c]

1	CH_3	H	H	24 (3.6)	>40	3.2	51	1.4
89	Cl	Cl	H	1.3 (0.1)	2.9 (0.1)	4.0	51	1.9
90	CN	Cl	H	0.9 (0.3)	2.0 (1.0)	3.2	75	2.8
91	CF_3	Cl	H	3.0 (1.1)	3.9 (2.1)	4.2	51	1.3
92	Cl	CN	H	1.4 (0.03)	>40	3.2	75	2.7
93	CN	CN	H	3.7 (1.3)	4.0 (2.8)	2.4	99	3.0
94	CF_3	CN	H	0.8 (0.2)	2.7 (0.8)	3.5	75	2.6
95	Cl	CF_3	H	4.7 (0.3)	>40	4.2	51	1.0
96	CN	CF_3	H	3.1 (0.6)	5.7 (3.2)	3.5	75	2.0
97	CF_3	CF_3	H	2.2 (0.6)	15 (6.0)	4.5	51	1.2
98	Cl	Cl	Cl	2.6 (0.5)	4.1 (0.6)	4.6	51	1.0
99	Cl	CH_3	Cl	1.9 (0.3)	>40	4.5	51	1.2
100	Cl	Cl	CH_3	2.7 (0.8)	31.0 (6.6)	4.5	51	1.1
101	CF_3	CH_3	Cl	4.3 (0.7)	11.1 (4.9)	4.7	51	0.7
102	Br	CH_3	Cl	3.6 (0.9)	26 (3.5)	4.7	51	0.8

[a] EC_{50} data represents means and SDs for three or more independent experiments measuring bioluminescence of in the HEK293 FlpIn.FM dual reporter cell line following exposure to compounds in a 10-point dilution series for 72 h. [b] Calculated using ChemAxon software.[23] [c] Calculated using the LTR EC_{50} value. **1** is included for comparison.

Table 10. Physicochemical and metabolism properties of selected compounds.

	Solubility [a]		**Human liver microsomes**			**Mouse liver microsomes**				
Cmpd	**pH 6.5** (μM)	**pH 2.0** (μM)	**Half-life** (min)	**in vitro CL_{int}** (μL/min/mg protein)	**Predicted E_H** [b]	**Half-life** (min)	**in vitro CL_{int}** (μL/min/mg protein)	**Predicted E_H** [b]	**PSA** ($Å^2$) [c]	**cLogP** [c]

1	< 1.1	1.1 - 2.3	10	175	0.87	2	815	n.d.	51	3.2
6	< 1.1	< 1.1	5	340	0.93	< 2	> 866	n.d.	51	3.9
8	< 1.1	< 1.1	9	186	0.88	< 2	> 866	n.d.	51	4.1
10	< 1.1	< 1.1	10	172	0.87	4	460	0.91	75	3.1
36	< 1.2	< 1.2	19	90	0.78	2	814	n.d.	51	3.4
40	< 1.2	< 1.2	7	232	n.d.	2	740	n.d.	51	4.0
43	1.1 - 2.2	1.1 - 2.2	9	198	0.89	15	114	n.d.	75	2.6
75	< 1.6	1.6 - 3.1	16	105	0.81	< 2	> 866	> 0.94	63	3.9
80	< 1.2	< 1.2	7	250	0.91	< 2	> 866	n.d.	64	2.7
82	3.1 - 6.3	1.6 - 3.1	20	86	0.77	6	308	0.87	64	2.6
90	< 1.6	< 1.6	15	115	0.82	8	224	n.d.	75	3.2
96	< 1.6	< 1.6	80	22	0.46	31	56	n.d.	75	3.5
97	< 1.6	< 1.6	58	30	0.54	22	78	0.63	51	4.5

[a] Estimated by nephelometry. [b] Predicted hepatic extraction (E_H) ratio based on in vitro intrinsic clearance (CL_{int}). [c] Calculated using ChemAxon software.[23] n.d. – not determined.

In summary of the structure activity relationship, we established the LTR reporter activity in the HEK293 derived FlpIn.FM reporter cell line is sensitive to the size and polarity of substituents on the thiazole and the phenoxy ring of the 2-acylaminothiazole scaffold (Figure 3). On the thiazole moiety, substitution of the 4-position was not tolerated, while alkyl groups such as Me, Et and *i*Pr were accepted on the 5-position, but not *i*Bu or a phenyl group. Electron withdrawing functionality such as a chloro, nitrile or trifluoromethyl in the 5-position of the thiazole were optimal for LTR reporter activity and likely mitigated the oxidative metabolism of the 4,5-thiazole bond. The thiazole moiety could not be replaced with a variety of 5-membered heterocycles, but a 5-substituted pyridine group was shown to be a suitable isostere. The 2-acylamino moiety and the 3-carbon alkyl chain were also shown to be important for maintain LTR activity. Substitution such as a methyl, chloro, nitrile or trifluoromethyl group in the 3-position of phenoxy aryl

ring were optimal for enhancing LTR reporter activity. Oxidative metabolism of the phenoxy group was reduced with the 3-trifluoromethyl group present (**96** and **97**).

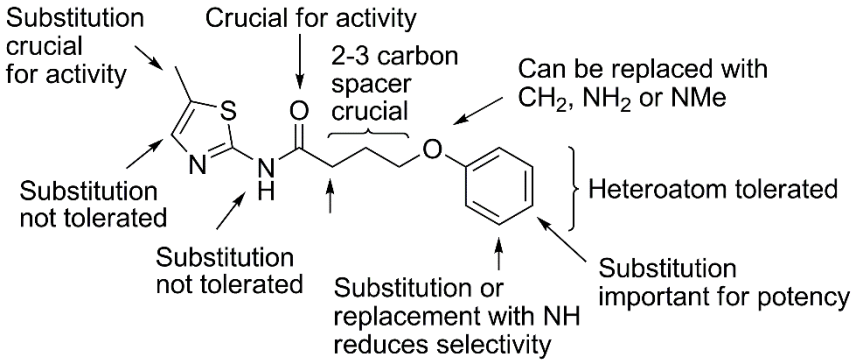


Figure 3. Summary of the structure activity relationship.

The CMV reporter was also sensitive to the size and polarity of substituents on the thiazole and the phenoxy ring of the 2-acylaminothiazole scaffold. In most instances, modifications that enhanced LTR activity also increased CMV activity. Several analogues, such as **6**, **8**, **25**, **27**, **36**, **37, 82**, **92**, **95** and **99** displayed selectivity for the LTR reporter, while not affecting the CMV reporter, but overall the structure activity relationship in relation to selectivity between the LTR and CMV reporter was not clear. It is not known whether the 2-acylaminothiazole series targets multiple cellular targets that are responsible for the perplexing LTR and CMV activity observed. Identifying the mechanism by which the 2-aminaocylthiazole series enhances gene expression may help decipher the LTR and CMV reporter activity.

Evaluation of cellular cytotoxicity

The FlpIn.FM CMV reporter was designed to detect increases that might occur in expression levels of off-target host cell proteins. To determine whether increased CMV reporter activity is related to host cell cytotoxicity, we evaluated a selection of compounds in a Cell Titre Glo growth inhibition assay using HepG2 cells (Table 11 and Table S1). It was shown all the selected analogues and known LRAs inhibited HepG2 cell growth to varying degrees of potency in this assay. However, there was no correlation between HepG2 cell growth inhibition and CMV reporter activity. For example, **1**, **37** **43**, **82**, **95** and **99** did not exhibit CMV reporter activity at the highest concentration tested (40 μM) but did display cell growth inhibition (CC_{50}s of 9.0, 1.6, 4.0, 1.7, 2.5 and 4.4 μM respectively). However, there was a correlation between cell growth inhibition, as measured by Cell Titre Glo, and LTR reporter activity. A possible explanation for this correlation, was that the LTR reporter activity was reaching a maximum at which cellular homeostasis is disturbed causing cell growth arrest.

Table 11. Evaluation of selected compounds and literature LRAs in cellular assays.

	HepG2[a] (Cell Titre Glo)	**HEK293**[b] (MTS)	**FlpIn.FM** [c]			**J.Lat10.6FM** [d]		
Cmpd	**CC_{50}** (SD) µM	**CC_{50}** (SD) µM	**LTR EC_{50}** (SD) µM	**CMV EC_{50}** (SD) µM	**Max LTR activity%** [at cmpd conc in µM]	**LTR EC_{50}** (SD) µM	**CMV EC_{50}** (SD) µM	**Max LTR activity%** [at cmpd conc in µM]
1	9.0 (2.2)	>20	24 (3.6)	>40	48 [20]	>40	>40	4.9 [20]
37	1.6	>20	3.7 (0.8)	>40	58 [5]	>40	>40	12 [20]
43	4.0 (0.3)	>20	11 (0.9)	>40	59 [20]	>40	28 (12)	21 [20]
82	1.7 (0.2)	>20	2.9 (0.6)	>40	24 [1.3]	25 (6.1)	18 (3.6)	19 [10]
90	0.42 (0.04)	>20	0.9 (0.3)	2.0 (1.0)	24 [0.31]	3.1 (0.8)	2.0 (0.5)	18 [2.5]
95	2.5 (0.2)	>20	4.7 (0.3)	>40	29 [2.5]	>40	19 (1.3)	21 [20]
96	1.5 (0.2)	>20	3.1 (0.6)	5.7 (3.2)	26 [1.3]	11 (4.5)	6.3 (1.5)	20 [5]
97	2.7 (0.4)	20 (0.5)	2.2 (0.6)	15 (6.0)	21 [2.5]	10 (2.0)	13 (1.7)	18 [5]
99	4.4 (0.5)	>20	1.9 (0.3)	>40	39 [1.3]	>40	29 (3.9)	15 [20]
102	4.0 (0.3)	>20	3.6 (0.9)	26 (3.5)	26 [0.63]	>40	>40	19 [20]

Romidepsin	0.01 (<0.01)	0.004 (0.4)	0.001 (<0.01)	0.02 (<0.01)	19 [0.005]	0.22 (0.73)	0.52 (0.12)	61 [0.01]
Vorinostat	12 (0.6)	2.3 (0.2)	4.6 (1.2)	>40	22 [2.5]	2.3 (0.2)	1.9 (0.6)	60 [5]
Panobinostat	<0.078	0.028 (0.2)	1.8 (0.7)	0.06 (0.03)	31 [0.2]	0.13 (0.03)	0.04 (0.01)	59 [0.1]
JQ1 (+)	9.2 (3.7)	>20	14 (0.7)	>40	33 [5]	8.1 (2.0)	>40	34 [2.5]

[a] CC_{50} data represents means and SDs for three HepG2 growth inhibition experiments in a 10-point dilution series over 48 h. Cell Titre-Glo was used to quantify cell growth inhibition. [b] CC_{50} data represents means and SDs for three MTS assay experiments in a 10-point dilution series over 48 h. [c] HEK293 FlpIn.FM values taken from other tables for comparison. [c] EC_{50} data represents means and SDs for three independent experiments measuring bioluminescence of in the J.Lat10.6FM dual reporter line following exposure to compounds in a 10-point dilution series for 48 h. PMA - phorbol 12-myristate 13-acetate.

An MTS cytotoxicity assay using HEK293 cells was also performed on the same selection of compounds (Table 11, Figure S5, Table S1) to examine whether there was a difference in sensitivity between Cell Titre Glo and MTS assay formats. In the MTS assay, **97** was the only compound that exhibited cell cytotoxicity (CC_{50} of 20 μM). Notably, the HEK293 cell line was less sensitive to treatment with a selection of compounds compared to the HepG2 cell line using Cell Titre Glo (Table S1). However, the MTS activity of known LRAs, Vorinostat and Romidepsin, were consistent with Cell Titre Glo activity in HepG2 cells (Table 11). The cell growth inhibition observed with the clinically used LRAs is known to be directly related to their mechanism of action. Future efforts will be directed at determining the cause of the cell growth inhibition of the 2-acylaminothiazole series and whether it is related to the mechanism of action or activation of the LTR reporter. Ultimately, it is not expected that cell growth inhibition observed with the 2-

acylaminothiazole series can be mitigated while maintaining LTR reporter activity and further raises concerns whether LRAs can be developed without undesirable cell toxicity.

Evaluation of analogues in the Jurkat Latency 10.6 clone, J.Lat10.6FM

The standard J.Lat 10.6 clone is a latently infected T-cell line commonly employed to evaluate the activity of LRAs to activate the HIV LTR.[34] This J.Lat clone contains a full-length integrated HIV-1 genome with green fluorescent protein (GFP) in place of the Nef gene, and a frameshift in Env producing non-functional Env protein that makes any progeny virion non-infectious. We engineered the standard J.Lat 10.6 cell line into a duel reporter cell line by transducing a cell population with a CMV-*DS.Red*^{EXP} lentivirus that leads to the stable integration of a *DS.Red* gene that expresses the red fluorescent protein (RFP) reporter driven from a CMV immediate early promoter. Thus, in the resulting J.Lat10.6FM cells, GFP expression measures activation of latent HIV and RFP expression models non-specific host gene expression.[25, 35] Treatment of J.Lat10.6FM with TNF-α or compound activates viral gene expression which is measured by the expression of GFP and quantified by fluorescence activated flow cytometry analysis.

We evaluated a selection of 2-acylaminothiazole compounds using the dual reporter J.Lat10.6FM cell line and benchmarked them against several known LRAs (Table 11 and Figure S6). Compounds **1**, **37**, **43**, **95**, **99** and **102** variably enhanced the LTR GFP reporter to a low level but an EC_{50} could not be determined at the highest concentration tested (40 μM). Compounds **82**, **90**, **96** and **97** enhanced the activity of the LTR GFP reporter in the

J.Lat10.6FM cell line to significant levels (EC_{50} values of 25, 3.1, 11 and 10 μM respectively), but also raised CMV RFP reporter activity to a comparable level (EC_{50} = 18, 2.0, 6.3 and 13 μM respectively). In general, there was a robust correlation between the HEK293 FlpIn.FM LTR activity and the J.Lat10.6FM LTR activity, for example the compounds **82**, **90**, **96** and **97** that most potently enhance FlpIn.FM LTR activity also significantly increase the J.Lat10.6FM LTR reporter activity. Compounds **90**, **96** and **97** also increased the J.Lat10.6FM LTR reporter activity comparable to levels observed with other known LRAs, Vorinostat and JQ1 (EC_{50} 2.3 and 8.1 μM), but Romidepsin and Panobinostat were significantly more potent (EC_{50} 0.22 and 0.13 μM). Aside from JQ1, the known LRAs also increased CMV CBR reporter activity at a similar potency in the J.Lat10.6FM 10.6 cell line. In summary, compounds from the 2-acylaminothiazole series were approximately 5-fold less active in the J.Lat10.6FM cell line compared to the activity observed in the surrogate FlpIn.FM HEK293 cell line. In addition, the 2-acylaminothiazole series enhanced HIV-1 gene transcription to the levels of activity comparable to the known LRAs, JQ1 and Vorinostat.

Evaluation of 2-acylaminothiazoles against targets known to be associated with HIV latency

To determine a possible mechanism by which 2-acylaminothiazole analogues enhance HIV-1 gene transcription in the cellular models, a representative compound was profiled against a panel of epigenetic enzymes known to be associated with HIV transcription and

a kinase panel (Tables S3-S7). The bromodomain protein, Brd4, is known to inhibit Tat-transactivation and is a major barrier to latency reactivation and the BET bromodomain inhibitor, JQ1 (Figure 1), is a known LRA and has been shown to dissociate Brd4 from the HIV promoter to allow Tat driven HIV transcription.[36] A representative 2-acylaminothiazole compound was evaluated against domain 1 and domain 2 of Brd4, but did not did not show activity at the highest concentration tested. (IC_{50} >100 μM) (Table S3). When profiled against all histone deacetylase (HDAC) isoforms and SIRT1 (Table S4), **102** displayed no inhibitory activity. **102** was also tested against nine methyltransferases and four acetyltransferases[37] previously linked to HIV-1 transcriptional modulation in patients with chronic HIV-1 infection and latency (Table S5 and S6). The only target from this panel with detectable inhibitory activity was SET1b complex (IC_{50} of 14 μM), however this was not considered pharmacologically relevant due to the modest activity (EC_{50} of 3.6 μM) observed for **102** in the HEK293 FlpIn.FM cell line.

The 2-acylaminothiazole possess a kinase hinge binding motif and its structure is closely related to other cyclin dependant kinase inhibitors such as PHA690509 [38] and inhibitors described by Peterson et al.[39] **102** was screened against 369 kinases at a concentration of 5 μM (Table S7). In this panel, **102** did not inhibit any kinase to an appreciable level (>40% inhibition). The highest inhibition noted was for GSK3a (31%), IRAK3 (37%) and LIMK1 (33%). Therefore, it is unlikely this kinase activity is responsible for the LTR and CMV activity observed of the 2-acylaminothiazole class in the HIV latency cell models. Collectively, screening the 2-acylaminothiazole compound against kinases and epigenetic

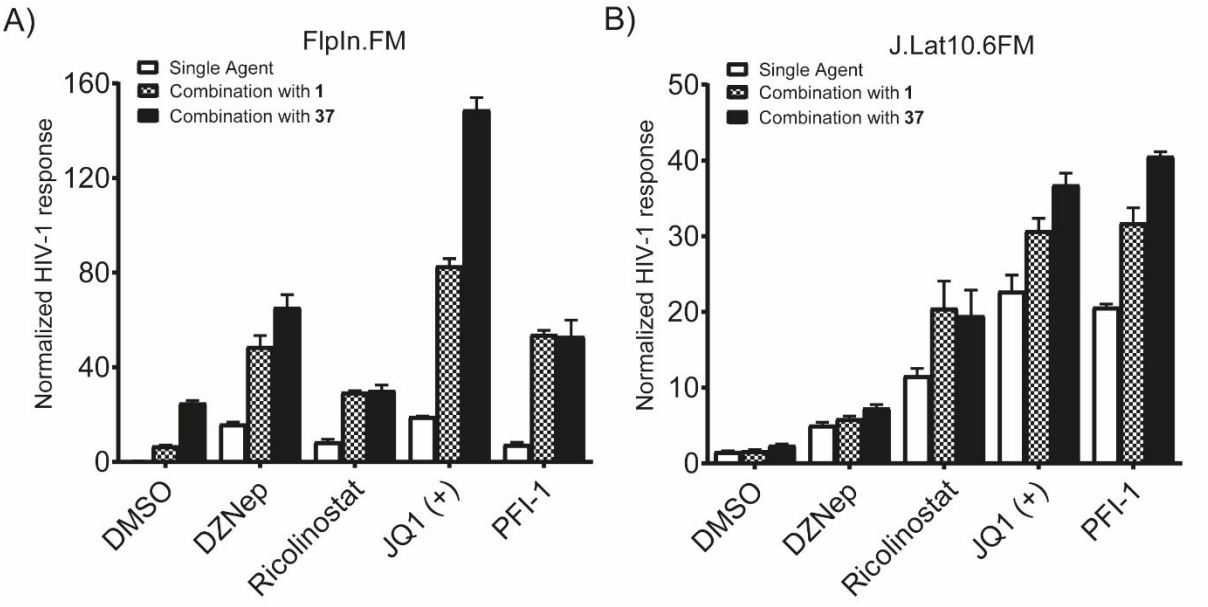
targets, suggests this scaffold may target a protein not previously associated with HIV transcription or latency.

Evaluation of 2-aminoacylthaizoles in combination with known LRAs using the HEK293 FlpIn.FM and J.Lat10.6FM cellular models

Historically, known LRAs have shown limited capacity to enhance HIV transcripts in CD4+ T-cells from infected individuals *ex vivo* when used as a single agent.[13] Work from other groups have shown combinations of two or more LRAs significantly increase HIV transcripts when compared with a single agent.[40] To determine if the HIV latency activity of the 2-aminoacylthaizole class could be synergistically enhanced, we evaluated representative 2-aminoacylthaizole compounds, **1** and **37**, in combination with a selection of literature LRAs. In this study, **1** and **37** were trialled in combination with the histone methyltransferase inhibitor, DZNep,[41] the HDAC inhibitor, Ricolinostat,[42] and the BET bromodomain inhibitors, JQ1 and PFI-1,[43] in both the HEK293 FlpIn.FM and J.Lat10.6FM cell lines at a concentration of 10 μM (Figure 4A and B). The Bliss Independence model was used to quantitate drug synergy (Figure 4C). Drug combinations which possess a Bliss Independence score (BIs) greater than zero are considered as synergistic.[44]

The results of the combination study show **1** or **37** combined with DZNep according to the BIs acted in synergy in the FlpIn.FM line, resulting in a greater than 2-fold improvement compared to **1** and **37** as single agents. However, in the J.Lat10.6FM line, **1** or **37** combined with DZNep exhibited an additive effect. Ricolinostat in combination with

1 or **37** did not show experimentally significant synergy in either the J.Lat10.6FM or the FlpIn.FM line and therefore the enhanced HIV response was considered additive. **1** or **37** in combination with either bromodomain inhibitors JQ1 or PFI-1 demonstrated a strong synergistic response in the FlpIn.FM cell line compared to the single agent activity. The synergy of **1** in combination with JQ1 in the J.Lat10.6FM line was not statistically significant, however, **37** demonstrated modest synergy (BIs of 0.12) with JQ1 in the J.Lat10.6FM cellular model, while PFI-1 displayed modest synergy with both **1** and **37** in the J.Lat10.6FM cellular line. Collectively, the synergy data suggests a Brd inhibitor is the most promising partner agent for use in combination with the 2-aminoacylthaizole class.



C)

Drug in combination with compound	FlpIn.FM		J.Lat10.6FM	
	Bliss independence scores for compound (SD)		Bliss independence scores for compound (SD)	
	1	37	1	37
DZNep	0.27 (0.08)	0.23 (0.08)	-0.01 (0.02)	0.00 (0.01)
Ricolinostat	0.15 (0.11)	-0.07 (0.03)	0.07 (0.08)	0.06 (0.08)
JQ1	0.68 (0.38)	1.00 (0.12)	0.07 (0.07)	0.12 (0.08)
PFI-1	0.40 (0.14)	0.16 (0.09)	0.10 (0.04)	0.18 (0.01)

Figure 4. Effect of **1** and **37** in combination with known LRAs on HIV-1 LTR expression in **A.** FlpIn.FM and **B.** JLat10.6FM cell lines. The cell lines were treated with **1** or **37** as single agents (10 μM) or in combination with either DZNep, Ricolinostat, JQ1 or PFI-1 (10 μM) for 48 h. The results are presented as percent activation relative to PMA control. Mean and SD are determined from three independent experiments. **C.** Bliss independence scores for **1** and **37** in combination with known LRAs.

Evaluation of analogues in CD4+ T-cells from HIV infected individuals on ART

HIV-1 infected patient derived CD4+ T lymphocytes are universally used to evaluate LRAs with promising activity in the immortalized lymphocytes, such as the J.Lat 10.6 cellular

model. Here, CD4+ T cells were isolated from HIV-infected individuals on suppressive ART using leukapheresis, and the CD4+ T cells were then treated with compounds for 72 h at a concentration that did not have dose limiting toxicity. Intracellular HIV RNA transcripts were then isolated and quantified by RT-qPCR.

Treatment of the donor isolated HIV-1 infected CD4+ T cells with 2.5 μM of the 2-acylaminothiazoles, **37** or **96**, resulted in an approximate 2-fold increase in unspliced HIV RNA compared to the vehicle control (Figure 5). The activity observed with **37** or **96** was comparable to the level of activation observed with the known LRA, JQ1 (Figure 5). This data is consistent with JQ1 displaying similar potency to **96** in the J.Lat10.6FM 10.6 cell line (Table 11). Significant variation in activity between donor samples for treatment of **37**, **96** and JQ1 was observed in this study. Natural variations between patient genotypes commonly results in significant differences to LRA response in patient CD4+ T-cell samples.[40] The apparent increase in response variability between **37** and **96** compared to JQ1 is not statistically significant, but may suggest **37** and **96** act via a mechanism which is more susceptible genetic diversity compared to the cellular target of JQ1, Brd4. In summary, this proof-of-principle study demonstrates the 2-acylaminothiazoles, **37** and **96**, increase unspliced HIV-1 RNA transcripts in primary infected from HIV-infected individuals on ART.

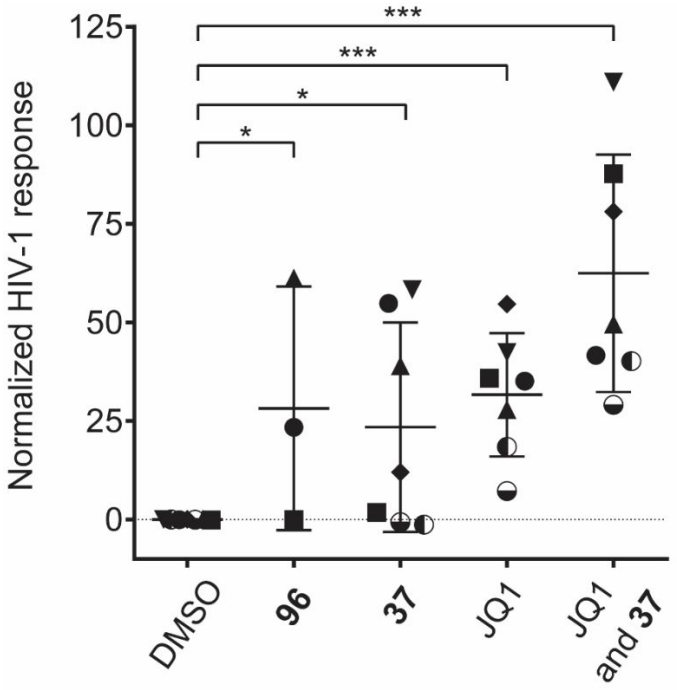


Figure 5. Latency reversing activity of compounds using total CD4+ T-cells isolated from HIV-infected individuals on suppressive ART. Unspliced HIV transcripts were quantified using RT-qPCR upon exposure to DMSO vehicle, compound **37** (2.5 μM), **96** (2.5 μM), JQ1 (1 μM) and a combination of **37** (2.5 μM) and JQ1 (1 μM) for 72 h. HIV transcripts were normalized using the positive control (PMA) and negative control (DMSO). Each data point is an individual participant sample indicated by the shape. The black lines represent median and SD. Statistical analysis - unpaired t-test. Bliss independence scores for **37** and JQ1 in combination is 0.17 (SD 0.09).

Combination of the 2-acylaminothiazole class with bromodomain inhibitor was shown to be synergistic in both FlpIn.FM and JLat10.6FM cell lines (Figure 4). To determine if 2-acylaminothiazole class with bromodomain inhibitor would have the same synergistic effect in primary cells, we evaluated **37** in combination with JQ1 in the patient derived HIV-1 infected CD4+ T cell samples. **37** and JQ1 were used at concentrations of 2.5 μM and

1 μM respectively because combined at this concentration they did not possess dose limiting toxicity. The results shown in Figure 5 show a significant enhancement in HIV RNA transcripts when treated with a combination of **37** and JQ1 compared to the effect of the single agents alone. The calculated BIs of the **37** and JQ1 combination study was 0.17 indicating a modest synergistic effect. As the bromodomains of Brd4 are inhibitory to the action of tat in HIV-1, it is logical that combining a BET bromodomain inhibitor (JQ1) with a tat dependant LRA, such as a 2-acylaminothiazole compound, has a synergistic effect on HIV-1 expression. This result also complements our findings that the 2-acylaminothiazole class does not target Brd4. Collectively, the data suggests 2-acylaminothiazole class possess synergistic activation of HIV RNA transcripts when used in combination with BET inhibitor, JQ1, however, because of the statistical significance of the data presented and genetic variabilities between donor HIV infected CD4+ T-cells, we cannot confidently conclude the results are synergistic. Nevertheless, the overall outcome recapitulates the synergy results witnessed by other groups using LRAs which possess differing mechanisms of action.[45, 46]

CONCLUSIONS

In summary of the work presented here, we utilised FlpIn.FM HEK293 cellular assay to screen a library of diverse compounds and identified the 2-acylaminothiazole hit **1**, with modest LTR reporter activity (EC_{50} 23 μM) and no CMV reporter activity (EC_{50} >40 μM), as a starting point to develop a novel HIV latency reversing agent. In the first phase of

optimization, we explored and established the SAR of the 2-acylaminothiazole scaffold (Figure 3). The SAR study revealed the 5-substituted 2-acylaminothiazole, an unsubstituted 3-carbon chain and a meta-substituted phenoxy aryl group were all required for FlpIn.FM LTR reporter activity. Nitrile, chloro or trifluoromethyl substitution in the 5-position of thiazole and a methyl, nitrile, chloro or trifluoromethyl substitution in the 3-position of the phenoxy aryl group imparted the greatest FlpIn.FM LTR reporter activity. The optimization of 2-acylaminothiazole series produced compounds with 20-fold greater LTR reporter activity than the screening hit **1**.

The SAR in relation to the FlpIn.FM CMV reporter activity was not well-defined and only a small cohort of the most potent LTR active compounds (**6**, **8**, **25**, **27**, **37**, **80**, **82**, **92**, **95**, **99** and **100**) with LTR reporter EC_{50} <5 μM, displayed 5-fold or greater selectivity between the LTR and the CMV reporter activity. Nevertheless, this selectivity profile was comparable to known LRAs, such as Romidepsin and Panobinostat (Table 11). The increase in LTR activity known LRAs and the 2-acylaminothiazole class strongly correlated with HepG2 cell growth inhibition using Cell Titre Glo. It is unknown whether the cell growth inhibition is related to mechanism conferring increased LTR activity or the 2-acylaminothiazole class targets an unrelated mechanism. The reduction and ideally elimination of the cell growth inhibition and CMV reporter activity will be a focus of future optimization. Identification of the cellular target(s) responsible for the LTR and CMV activity of the 2-acylaminothiazole class may enable a structure guided approach to understand and dissect the reporter selectivity and potentially address cellular toxicity. To address this, we screened the a 2-acylaminothiazole analogue against a panel epigenetic

targets related to HIV latency and kinases (Tables S3-7), however, no pharmacologically relevant inhibition of these targets was observed, suggesting the 2-acylaminothiazole class likely acts by targeting a protein not commonly associated with HIV transcription. Currently, the mechanism of action of the 2-acylaminothiazole series remains unknown.

The physicochemical properties of the 2-acylaminothaizole series were monitored while establishing the SAR. The hit compound **1** possessed low aqueous solubility and was rapidly degraded in the presence of both human and mouse liver microsomes. To address the aqueous solubility, polar substituents, such as nitrile functionality, were introduced to the 5-position of the thiazole and 3-position of the phenoxy aryl ring, and a heteroatom was introduced into aryl ring of the phenoxy group. However, these iterations did not significantly improve aqueous solubility (Table 11). In vitro metabolism studies of the 2-acylaminothaizole series identified several metabolites predicted to originate from oxidative metabolism of the 3,4-bond of the thiazole, hydrolysis of the carboxamide, dealkylation of the phenoxy group and oxidation of phenoxy aryl ring. Installing a chloro or a nitrile in the 5-position of thiazole and a trifluoromethyl functionality in the 3-position of the phenoxy ring (analogues **96** and **97**) (Table 11) limited the number of metabolism events and significantly improved intrinsic clearance compared to the hit compound **1**. Improving the LTR activity and selectivity will be the primary focus of future optimization, but improving physicochemical properties, such as aqueous solubility and *in vitro* metabolism, will also be key to further development and in vivo pharmacokinetics of the 2-acylaminothaizole class.

A selection of 2-acylaminothiazole compounds were evaluated in a J.Lat T-cell line engineered with a dual reporter system (J.Lat10.6FM). Several compounds (**82**, **96** and **97**) displayed modest LTR-GFP reporter activity (EC_{50} 10 – 25 μM) and **90** comparable activity (EC_{50} 3.1 μM) to Vorinostat and JQ1 (EC_{50} 2.3 and 8.1 μM). Compounds **37** and **96** also increased unspliced HIV RNA in latent viral resting CD4+ T cells isolated from patients on ART. **37** also acted in synergy with BET Brd inhibitor, JQ1, in the HIV HEK293 and J.Lat cellular models and HIV infected patient derived CD4+ T-cell lines. The activity observed with the 2-acylaminothaizole series in the universally employed HIV cellular models provides evidence of the potential of the compound series as a LRA and may provide a component of a curative therapy for the HIV positive individuals on lifelong suppressive ART.

EXPERIMENTAL SECTION

Biology Experimental

HEK293 FlpIn.FM dual reporter cellular assay. FlpIn.FM HEK293 cells were maintained in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% FCS. Assay plates (Corning clear bottom tissue culture treated 384-well plates) were created by transferring 50 nL of a 10 point 1 in 2 serial dilution of compounds (DMSO solubilized) into columns 1-22 using an Echo 550 Acoustic dispenser (LabCyte Inc.). 50 nL of 5 μM PMA was transferred to column 23 as a positive control (final assay concentration of 10 nM) and 50

nL of DMSO vehicle was transferred to column 24 (negative control). 1500 cells in 25 μL of DME media with 5% FCS is transferred to each well of the assay plate using a Multidrop reagent dispenser. Plates are left at room temperature in a single layer for one hour to allow adhesion to commence and are then incubated at 37°C and 5% CO_2 for a 48 h. ChromaGlo substrate solution is prepared according to the manufacturer's instructions. Assay plates are cooled to 20°C prior to addition of 10 μL of ChromaGlo reagent to each assay plate well. The plates are incubated at 20°C for 2 min and plates read on a plate reader (Em 613 nm and 537 nm). Percent activity of each compound is calculated for the ClickBeetle Red (CBR) luminescence and ClickBeetle Green luminescence (CBG) according to the following equation, % activity = 100 – (100*(luminescence$_{compound}$ – mean luminescence$_{negative\ control}$ / mean luminescence$_{positive\ control}$ – mean luminescence$_{negative\ control}$)). For calculating the EC_{50} values of LTR and CMV-driven gene expression, the raw data was first normalized between the DMSO treated negative control (set to 0%) and the PMA treated positive control (set to 100%). The data was plotted and EC_{50} values calculated using: XY analysis, Nonlinear regression (curve fit), [Agonist] vs. normalized response – Variable slope analysis on GraphPad Prism V7.0.

Jurkat Latency 10.6 clone (J.Lat10.6FM) dual reporter cellular assay. The dual reporter J.Lat10.6FM dual reporter cell line was generated using previously described protocols.[35] The evaluation of compounds in the dual reporter J.Lat10.6FM dual reporter cell line was adapted from a previously described method.[35] Briefly, cells are maintained in RPMI 1640, 90%; FBS, 10%; supplemented with penicillin G (100 U/mL), streptomycin (100 μg/mL), L-

glutamine (2 mM, 0.3 mg/mL) media. $4x10^4$ J.Lat cells were seeded into a 96 well format in 50 μL of complete RPMI (supplemented with 10% FCS and 1% Pen/Strep). Compounds were then added in 50 μL of complete RPMI, and cells assessed for fluorescent activity 48 h later, using a FACSCalibur. Using GraphPad Prism, percentage positive populations were normalized using the positive control (TNFα) and negative control (DMSO). The EC_{50} was calculated in the same manner as for the HEK293 FlpIn.FM dual reporter cellular assay.

CD4+ T-cells from HIV-infected individuals on ART. Leukocytes were collected from participants using leukapheresis at the Alfred hospital Melbourne, Australia with full informed consent. Peripheral blood mononuclear cells (PBMCs) were then isolated and frozen at -80°C. Frozen vials were then thawed and total CD4+ T cells ($CD8^-/CD14^-/CD15^-/CD16^-/CD19^-/CD36^-/CD56^-/CD123^-/GlyA^-/TCR\gamma\delta^-$) isolated using CD4+ T cell isolation kits (Miltenyi Biotec). $5x10^6$ CD4+ T cells were seeded in 24 well plates in 1 mL complete RF10. Compounds were then added in 1 mL of complete RF10 and cells harvested using TRIzol reagent 72 h later. Whole cell RNA was isolated by phenol chloroform precipitation, DNAse treated and cDNA synthesized using SuperScript III reverse transcriptase (Invitrogen). HIV-1 RNA was then detected using qPCR. Absolute RNA was back calculated using standard curves of known quantity, and the data normalized using the positive control (PMA/PHA) and negative control (DMSO) using GraphPad Prism software.

HepG2 cell growth inhibition assay. HepG2 cells were cultured in Dulbeccos modified eagles medium (DMEM) supplemented with 10% fetal calf serum (FCS), in a humidified incubator at 37˚C and 5% CO_2. Assay plates were created by seeding 1000 cells in 50 μl DMEM with 10% FCS into each well of 384 well tissue culture treated plates (Greiner). 10-point dilution

series of compounds were prepared in DMSO; a volume of 100 nL was transferred using a pin tool into the assay plates containing cells. Positive (DMSO only) and negative (10 μM Bortezomib) growth controls were included on the same plates. Plates are left at room temperature in a single layer for one hour to allow adhesion to commence and are then incubated at 37°C and 5% CO_2 for a 48 h. Cytotoxicity was determined using Cell Titer Glo (Promega) and calculated as a percentage using DMSO as the positive growth control and 10 μM Bortezomib as a negative growth control. EC_{50} values were calculated using a 4-parameter log dose, non-linear regression analysis, with sigmoidal dose response (variable slope) curve fit using Graph Pad Prism (ver 6.05). 0 and 100% constraint parameters were used for curve fitting.[47]

MTS cell viability/proliferation assay. MTS reagent is a tetrazolium salt used to determine the relative viability of a sample by measuring bulk metabolism. Viable cells metabolize the MTS tetrazolium molecule to its formazan product, which is readily detectible by colorimetric analysis. $2.5x10^4$ FlpIn.FM cells were seeded in 50 μL complete media and incubated for 24 h. Then 50 μL of each compound in a dilution series, DMSO vehicle control and sodium arsenite [200 μM] control, prepared in OPTI-MEM was added and incubated for 48 h. 20 μL MTS reagent (Cell Titre 96® Aqueous One Solution Cell Proliferation Assay (Promega, WI, USA) was added to cells in 100 μL of growth media and incubated for 2 h. Bulk cell metabolism (a surrogate for viability and cell activation) was measured as per the manufacturer's instructions with a Thermo Multiskan Ascent plate reader (Thermo Fischer) at 492 nm. For analyzing data, the average value of the no cells wells was subtracted from all the raw data. Each sample was then normalized to the signal from sodium arsenite wells (negative control at 0%) and vehicle control wells (positive control at 100%). The data was plotted and EC_{50} values calculated

using: XY analysis, Nonlinear regression (curve fit), [Agonist] vs. normalized response – Variable slope analysis on GraphPad Prism V7.0.

Solubility determination using nephelometry. Compound in DMSO was spiked into either pH 6.5 phosphate buffer or 0.01 M HCl (pH 2.0) with the final DMSO concentration being 1%. Samples were then analyzed via nephelometry to determine a solubility range.[48]

In vitro metabolism using mouse and human liver microsomes. Metabolic stability was assessed by incubating test compounds individually (1 μM) at 37°C with either mouse or human liver microsomes. The metabolic reaction was initiated by the addition of an NADPH regenerating system and quenched at various time points over the incubation period by the addition of acetonitrile. The relative loss of parent compound and formation of metabolic products was monitored by LC-MS. Test compound concentration versus time data was fitted to an exponential decay function to determine the first-order rate constant for substrate depletion. In cases where clear deviation from first-order kinetics was evident, only the initial linear portion of the profile was utilized to determine the degradation rate constant (k). Each substrate depletion rate constant was then used to calculate an in vitro intrinsic clearance value (CL_{int}, *in vitro*) according to the equation, CL_{int}, *in vitro* = k/microsomal protein content (0.4 mg protein/mL); $t_{1/2} = \ln(2)/k$; $E_H = CL_{int}/Q + CL_{int}$.[49] The scaling parameters determined in literature[50] were used in the aforementioned calculations. For metabolite identification compounds were incubated under the same conditions. Following protein precipitation with acetonitrile, samples were centrifuged for 4 min at 4,500 rpm. The supernatant was removed and analyzed by LC/MS. in silico predication for potential structure-based metabolic transformations was conducted for compounds and compared to those detected under ESI

positive ionization mode in the presence of NADPH-supplemented mouse liver microsomes for 60 min.

Chemistry Experimental

General chemistry procedures. Solvents were obtained commercially and used without further purification. Analytical thin-layer chromatography was performed on Merck silica gel $60F_{254}$ aluminium-backed plates and were visualized by fluorescence quenching under UV light or by $KMnO_4$ staining. Chromatography was performed with silica gel 60 (particle size 0.040-0.063 μm) using an automated purification system. NMR spectra were recorded on a Bruker Avance DRX 300. Chemical shifts are reported in ppm on the δ scale and referenced to the appropriate solvent peak. MeOD and $CDCl_3$ contain H_2O.

LCMS were recorded on either a Waters LCMS system composed of a Waters 3100 Mass Detector, Waters 2996 Diode Array Detector, Waters 2545 Binary Pump, Waters SFO System Fluidics Organizer and a Waters 2767 Sample Manager (Method A), or an Agilent LCMS system composed of an Agilent G6120B Mass Detector, 1260 Infinity G1312B Binary pump, 1260 Infinity G1367E HiPALS autosampler and 1260 Infinity G4212B Diode Array Detector (Method B). Conditions for LCMS Method A were as follows, column: Kinetex TM XB-C18 5μm 4.6 x 50mm, injection volume 10 μL, 5-100% B over 3 min (solvent A: water 0.1% formic acid; solvent B: AcCN 0.1% formic acid), flow rate: 1.5 mL/min, detection: 100-600 nm, acquisition time: 6 min. Conditions for LCMS Method B were as follows, column: Poroshell 120 EC-C18, 2.1 x 50mm 2.7 Micron at 20 ºC, injection volume 2 μL, gradient: 5-100% B over 3 min (solvent A: water 0.1% formic acid; solvent B: AcCN

0.1% formic acid), flow rate: 0.8 mL/min, detection: 254 nm, acquisition time: 5 min. LCMS conditions used to assess purity of final compounds were as follows, column: Phenomenex Gemini C18, 2.0 x 50 mm; injection volume 20 μL; gradient: 0-100% Buffer B over 6 min (buffer A: 0.1% formic acid in autoclaved MilliQ water; buffer B: 0.1% formic acid in 100% acetonitrile), flow rate: 1.0 mL/min, detection: 214 or 224 nm. Unless otherwise noted, all compounds were found to be >95% pure by this method.

HRMS were acquired by Jason Dang at the Monash Institute of Pharmaceutical Sciences Spectrometry Facility using an Agilent 1290 infinity 6224 TOF HPLC. Column used was RRHT 2.1 x 50 mm 1.8 μm C18. Gradient was applied over the 5 min with the flow rate of 0.5 mL/min. For MS: Gas temperature was 325ºC; drying gas 11 L/min; nebulizer 45 psig and the fragmentor 125V.

Compounds **1**, **3**, **4**, **7, 14**, **28**, **47**, **50, 60, 62** were purchased from commercial vendors and used without further purification.

General Procedure A. N-(5-Methylthiazol-2-yl)-4-(o-tolyloxy)butanamide (**2**). **104** (31 mg, 0.16 mmol), 5-methyl-2-aminothiazole (21 mg, 0.16 mmol), EDCI (31 mg, 0.16 mmol), and DMAP (1.9 mg, 0.016 mmol) in DCE (5 mL) were stirred at 45ºC for 16 h. To the reaction was added 10% citric acid solution (10 mL) and the mixture extracted with DCM (2 x 10 mL). The organic layer was then washed with 10% $NaHCO_3$ solution (1 x 15 mL), dried with $MgSO_4$ and concentrated *in vacuo*. The crude residue was then purified by column chromatography gradient eluting with 100% CyHex to 50% EtOAc/CyHex to obtain **2** as a white solid (22 mg, 47%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22 - 7.11 (m, 2H), 7.08 (d, *J* 1.3

Hz, 1H), 6.91 - 6.79 (m, 2H), 4.10 (t, *J* 5.8 Hz, 2H), 2.80 (t, *J* 7.4 Hz, 2H), 2.38 (d, *J* 1.3 Hz, 3H), 2.36 - 2.25 (m, 2H), 2.21 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4, 158.6, 156.8, 132.9, 130.6, 127.2, 126.8, 126.6, 120.4, 110.9, 66.7, 32.5, 24.6, 16.1, 11.5. MS, m/z = 291 (100) $[M+H]^+$. HRMS found: (M + H) 291.1165; $C_{15}H_{18}N_2O_3S$ requires (M +H), 291.1162.

4-(2-Chlorophenoxy)-N-(5-methylthiazol-2-yl)butanamide (**5**). General Procedure A was followed using **106** (31 mg, 0.14 mmol) and 5-methyl-2-aminothiazole (16 mg, 0.14 mmol) to obtain **5** as a white solid (17 mg, 38%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37 (dd, *J* 7.70, 1.5 Hz, 1H), 7.25 - 7.16 (m, 2H), 6.96 - 6.88 (m, 2H), 4.16 (t, *J* 5.7 Hz, 2H), 2.85 (t, *J* 7.3 Hz, 2H), 2.40 (d, *J* 1.3 Hz, 3H), 2.38 - 2.27 (m, 2H). MS, m/z = 311 (100) $[M+H]^+$, 313 (30). HRMS found: (M + H) 311.0622; $C_{14}H_{15}ClN_2O_3S$ requires (M +H), 311.0616.

4-(3-Chlorophenoxy)-N-(5-methylthiazol-2-yl)butanamide (**6**). General Procedure A was followed using **108** (30 mg, 0.14 mmol) and 5-methyl-2-aminothiazole (16 mg, 0.14 mmol) to obtain **6** as a white solid (10 mg, 23%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24 - 7.14 (m, 1H), 7.14 – 7.09 (m, 1H), 6.94 (ddd, *J* 8.0, 1.8, 1.0 Hz, 1H), 6.89 (t, *J* 2.2 Hz, 1H), 6.77 (ddd, *J* 8.4, 2.4, 0.9 Hz, 1H), 4.08 (t, *J* 5.8 Hz, 2H), 2.75 (t, *J* 7.3 Hz, 2H), 2.42 (d, *J* 1.1 Hz, 3H), 2.34 - 2.22 (m, 2H). MS, m/z = 311 (100) $[M+H]^+$, 313 (30). ^{13}C NMR (75 MHz, d_6-DMSO): δ 170.4, 159.4, 156.2, 134.6, 133.7, 130.8, 125.9, 120.4, 114.5, 113.5, 67.2, 31.4, 24.1, 11.1. HRMS found: (M + H) 311.0620; $C_{14}H_{15}ClN_2O_3S$ requires (M +H), 311.0616.

N-(5-Methylthiazol-2-yl)-4-(3-(trifluoromethyl)phenoxy)butanamide (**8**). General Procedure A was followed using **110** (30 mg, 0.12 mmol) and 5-methyl-2-aminothiazole (14 mg, 0.12 mmol) to obtain **8** as a white solid (25 mg, 68%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44 - 7.34 (m, 1H), 7.25 - 7.17 (m, 1H), 7.16 - 7.09 (m, 2H), 7.05 (dd, *J* 8.1, 2.4 Hz, 1H),

4.14 (t, *J* 5.7 Hz, 2H), 2.79 (t, *J* 7.3 Hz, 2H), 2.41 (d, *J* 1.3 Hz, 3H), 2.38 - 2.21 (m, 2H). MS, m/z = 345 (100) $[M+H]^+$. HRMS found: (M + H) 345.0887; $C_{15}H_{15}F_3N_2O_2S$ requires (M +H), 345.0879.

N-(5-Methylthiazol-2-yl)-4-(4-(trifluoromethyl)phenoxy)butanamide (**9**). General Procedure A was followed using **112** (50 mg, 2.01 mmol) and 5-methyl-2-aminothiazole (23 mg, 2.01 mmol) to obtain **9** as a white solid (40 mg, 58%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 (d, *J* 8.9 Hz, 2H), 7.11 (s, 1H), 6.95 (d, *J* 8.6 Hz, 2H), 4.14 (t, *J* 5.9 Hz, 2H), 2.77 (t, *J* 7.2 Hz, 2H), 2.41 (s, 3H), 2.34-2.27 (m, 2H). MS, m/z = 345 $[M + H]^+$. HRMS found: (M + H) 345.0886; $C_{15}H_{15}F_3N_2O_2S$ requires (M +H), 345.0879.

4-(3-Cyanophenoxy)-N-(5-methylthiazol-2-yl)butanamide (**10**). General Procedure A was followed using **114** (30 mg, 0.15 mmol) and 5-methyl-2-aminothiazole (17 mg, 0.15 mmol) to obtain **10** as a white solid (12 mg, 27%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37 (td, *J* 7.76, 0.99 Hz, 1H), 7.25 (dt, *J* 7.7, 1.2 Hz, 1H), 7.16 - 7.07 (m, 3H), 4.12 (t, *J* 5.9 Hz, 2H), 2.75 (t, *J* 7.0 Hz, 2H), 2.43 (d, *J* 1.3 Hz, 3H), 2.36 - 2.24 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.0, 158.7, 158.1, 132.8, 130.4, 127.5, 124.6, 119.5, 118.6, 117.5, 113.3, 77.4, 77.2, 76.6, 67.1, 32.3, 24.4, 11.6. MS, m/z = 302 (100) $[M+H]^+$. HRMS found: (M + H) 302.0960; $C_{15}H_{15}N_3O_2S$ requires (M +H), 302.0958.

4-(4-Cyanophenoxy)-N-(5-methylthiazol-2-yl)butanamide (**11**). General Procedure A was followed using **116** (50 mg, 2.40 mmol) and 5-methyl-2-aminothiazole (27 mg, 2.40 mmol) to obtain **11** as a white solid (40 mg, 56%).^{1}H NMR (300 MHz, $CDCl_3$): 7.58 (d, *J* 9.3 Hz, 2H), 7.09 (s, 1H), 6.93 (d, *J* 9.3 Hz, 2H), 4.15 (t, *J* 5.7 Hz, 2H), 2.79-2.74 (m, 2H), 2.42 (s,

3H), 2.32-2.25 m, 2H). MS, m/z = 302 $[M + H]^+$. HRMS found: (M + H) 302.0961; $C_{15}H_{15}N_3O_2S$ requires (M +H), 302.0958.

4-(2-Methoxyphenoxy)-N-(5-methylthiazol-2-yl)butanamide (**12**). General Procedure A was followed using **118** (30 mg, 0.14 mmol) and 5-methyl-2-aminothiazole (16 mg, 0.14 mmol) to obtain **12** as a white solid (26 mg, 59%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.16 (q, *J* 1.3 Hz, 1H), 7.02 – 6.80 (m, 4H), 4.14 (t, *J* 5.9 Hz, 2H), 3.84 (s, 3H), 2.80 (t, *J* 7.2 Hz, 2H), 2.4 (d, *J* 1.3 Hz, 3H), 2.35 - 2.25 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.5, 158.3, 149.6, 148.2, 133.3, 126.9, 121.4, 120.9, 113.8, 111.9, 68.0, 55.7, 32.5, 24.6, 11.5. MS, m/z = 307 (100) $[M+H]^+$. HRMS found: (M + H) 307.1116; $C_{15}H_{18}N_2O_3S$ requires (M +H), 307.1111.

4-(3-Methoxyphenoxy)-N-(5-methylthiazol-2-yl)butanamide (**13**). General Procedure A was followed using **121** (32 mg, 0.15 mmol) and 5-methyl-2-aminothiazole (17 mg, 0.15 mmol) to obtain **13** as a white solid (40 mg, 86%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21 - 7.12 (m, 2H), 6.55 - 6.41 (m, 3H), 4.08 (t, *J* 5.8 Hz, 2H), 3.78 (s, 3H), 2.78 (t, *J* 7.3 Hz, 2H), 2.40 (d, *J* 1.1 Hz, 3H), 2.33 - 2.19 (m, 2H). MS, m/z = 307 (100) $[M+H]^+$ HRMS found: (M + H) 307.1112; $C_{15}H_{18}N_2O_3S$ requires (M +H), 307.1111.

4-(3-Hydroxyphenoxy)-N-(5-methylthiazol-2-yl)butanamide (**15**). General Procedure C was followed using **122** (40 mg, 0.20 mmol) and 5-methyl-2-aminothiazole (23 mg, 0.20 mmol). Residue was then purified by reverse phase preparatory HPLC using a gradient of 95% water/ACN to 100% ACN to obtain **15** as a white solid (2.5 mg, 4%). ^{1}H NMR (300 MHz, d_6-Acetone): δ 7.11 - 7.02 (m, 2H), 6.46 - 6.38 (m, 3H), 4.04 (t, *J* 6.2 Hz, 2H), 2.74 (t,

J 7.4 Hz, 2H), 2.37 (d, *J* 1.1 Hz, 3H), 2.23 - 2.11 (m, 2H). MS, m/z = 293 (100) $[M+H]^+$. HRMS found: (M + H) 293.0954; $C_{14}H_{16}N_2O_3S$ requires (M +H), 293.0954.

4-(4-Hydroxyphenoxy)-N-(5-methylthiazol-2-yl)butanamide (**16**). General Procedure A was followed using **124** (30 mg, 0.15 mmol) and 5-methyl-2-aminothiazole (17 mg, 0.15 mmol). The crude residue was then purified by reverse phase preparatory HPLC using a gradient of 95% water/ACN to 100% ACN to obtain **16** as a white solid (2.8 mg, 8%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.11 (s, 1H), 6.77 (ad, *J* 1.1 Hz, 4H), 4.02 (t, *J* 5.8 Hz, 2H), 2.72 (t, *J* 7.3 Hz, 2H), 2.41 (d, *J* 1.3 Hz, 3H), 2.23 (t, *J* 6.5 Hz, 2H). MS, m/z = 293 (100) $[M+H]^+$. HRMS found: (M + H) 293.0959; $C_{14}H_{16}N_2O_3S$ requires (M +H), 293.0954.

4-(3-Aminophenoxy)-N-(5-methylthiazol-2-yl)butanamide (**17**). **127** (250 mg, 0.780 mmol) was suspended in 32% HCl (0.39 mL, 3.89 mmol) and MeOH (5 mL) in a sealed tube. Iron dust (217 mg, 3.89 mmol) was then added and the reaction stirred at reflux for 4 h. The reaction was then cooled to 20°C and filtered through Celite and washed with MeOH (30 mL). The solvent was then evaporated *in vacuo* and residue dissolved in EtOAc (50 mL). 2M NaOH (50 mL) was added and the biphasic layer was then separated. The EtOAc layer was then washed with water (30 mL), brine (30 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was then purified by reverse phase preparatory HPLC using a gradient of 95% water/ACN to 100% ACN to obtain **17** as a white solid (1.3 mg, 5%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.13 (d, *J* 1.3 Hz, 1H), 7.06 (t, *J* 8.1 Hz, 1H), 6.27 - 6.37 (m, 2H), 6.19 - 6.27 (m, 1H), 4.04 (t, *J* 5.8 Hz, 2H), 2.73 (t, *J* 7.3 Hz, 2H), 2.42 (d, *J* 1.1 Hz, 3H), 2.17 - 2.32 (m, 2H). MS, m/z = 292 (100) $[M+H]^+$. HRMS found: (M + H) 292.1117; $C_{14}H_{17}N_3O_2S$ requires (M +H), 292.1114.

4-(4-Aminophenoxy)-N-(5-methylthiazol-2-yl)butanamide (**18**). The procedure used for **17** was followed using **130** (200 mg, 0.62 mmol) to obtain **18** as a white solid (105 mg, 57%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.15 (d, *J* 1.3 Hz, 1H), 6.78 - 6.69 (m, 2H), 6.68 - 6.58 (m, 2H), 4.01 (t, *J* 5.7 Hz, 2H), 2.75 (t, *J* 7.3 Hz, 2H), 2.41 (d, *J* 1.1 Hz, 3H), 2.31 - 2.15 (m, 2H). MS, m/z = 292 (100) $[M+H]^+$. HRMS found: (M + H) 292.1113; $C_{14}H_{17}N_3O_2S$ requires (M +H), 292.1114.

4-(3-Acetamidophenoxy)-N-(5-methylthiazol-2-yl)butanamide (**19**). **17** (12 mg, 0.040 mmol) and K_2CO_3 (34 mg, 0.25 mmol) were dissolved in acetone (2 mL) and cooled to 0°C. Acetyl chloride (0.02 mL, 0.25 mmol) was then added dropwise and reaction stirred for 20 h at 20°C. The reaction mixture was then filtered and concentrated *in vacuo*. The crude residue was then purified by column chromatography gradient eluting with 100% CyHex to 100% EtOAc to obtain **19** as a white solid (1.6 mg, 12%). ^{1}H NMR (300 MHz, MeOD): δ 7.26 (t, *J* 2.2 Hz, 1H), 7.22 - 7.13 (m, 1H), 7.10 – 6.99 (m, 2H), 6.65 (dd, *J* 8.1, 2.4 Hz, 1H), 4.05 (t, *J* 6.1 Hz, 2H), 2.67 (t, *J* 7.3 Hz, 2H), 2.40 (d, *J* 1.3 Hz, 3H), 2.19 (q, *J* 6.5 Hz, 2H), 2.12 (s, 3H). MS, m/z = 334 (100) $[M+H]^+$. HRMS found: (M + H) 334.1225; $C_{16}H_{19}N_3O_3S$ requires (M +H), 334.1220.

4-(4-Acetamidophenoxy)-N-(5-methylthiazol-2-yl)butanamide (**20**). The procedure used for **19** was followed using **18** (15 mg, 0.050 mmol) to obtain **20** as a white solid (5.4 mg, 31%). ^{1}H NMR (300 MHz, MeOD): δ 7.41 (d, *J* 8.8 Hz, 2H), 7.08 (s, 1H), 6.86 (d, *J* 9.2 Hz, 2H), 4.05 (t, *J* 5.8 Hz, 2H), 2.67 (t, *J* 7.4 Hz, 2H), 2.40 (s, 4H), 2.17 -2.10 (m, 5H). MS, m/z = 334 (100) $[M+H]^+$. HRMS found: (M + H) 334.1226; $C_{16}H_{19}N_3O_3S$ requires (M +H), 334.1220.

4-(3-(Hydroxymethyl)phenoxy)-N-(5-methylthiazol-2-yl)butanamide (**21**). General Procedure A was followed using **133** (32 mg, 0.15 mmol) and 5-methyl-2-aminothiazole (17 mg, 0.15 mmol) to obtain **21** as a white solid (12 mg, 68%) in 60% purity. The crude residue was then purified by reverse phase preparatory HPLC using a gradient of 95% water/ACN to 100% ACN to obtain **21** (1.2 mg, 2.6%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25 (d, *J* 7.92 Hz, 2H), 7.14 - 7.08 (m, 1H), 6.98 - 6.89 (m, 2H), 6.87 - 6.76 (m, 1H), 4.67 (s, 2H), 4.09 (t, *J* 5.8 Hz, 2H), 2.71 (t, *J* 7.2 Hz, 2H), 2.42 (d, *J* 1.3 Hz, 3H), 2.35 - 2.12 (m, 2H). MS, m/z = 307 (100) $[M+H]^+$. HRMS found: (M + H) 307.1115; $C_{15}H_{18}N_2O_3S$ requires (M +H), 307.1111.

4-(4-(Hydroxymethyl)phenoxy)-N-(5-methylthiazol-2-yl)butanamide (**22**). General Procedure A was followed using **135** (58 mg, 0.28 mmol) and 5-methyl-2-aminothiazole (32 mg, 0.28 mmol). The crude product was then purified by reverse phase preparatory HPLC using a gradient of 95% water/ACN to 100% ACN to obtain **22** as a white solid (1.2 mg, 1%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31 (s, 2H), 7.11 (d, *J* 1.3 Hz, 1H), 6.89 (d, *J* 8.8 Hz, 2H), 4.63 (s, 2H), 4.09 (t, *J* 5.8 Hz, 2H), 2.72 (t, *J* 7.3 Hz, 2H), 2.42 (d, *J* 1.1 Hz, 3H), 2.33 - 2.17 (m, 2H). MS, m/z = 307 (100) $[M+H]^+$. HRMS found: (M + H) 307.1113; $C_{15}H_{18}N_2O_3S$ requires (M +H), 307.1111.

Methyl 3-[4-[(5-methylthiazol-2-yl)amino]-4-oxo-butoxy]benzoate (**23**). General Procedure A was followed using **137** (25 mg, 0.10 mmol) and 5-methyl-2-aminothiazole (14 mg, 0.13 mmol) to obtain **23** as a white solid (12 mg, 34%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66 - 7.60 (m, 1H), 7.54 (dd, *J* 1.5, 2.4 Hz, 1H), 7.33 (t, *J* 7.9 Hz, 1H), 7.14 - 7.04 (m, 2H), 4.13 (t, *J* 5.8 Hz, 2H), 3.91 (s, 3H), 2.77 (t, *J* 7.4 Hz, 2H), 2.40 (d, *J* 1.3 Hz, 3H), 2.38 - 2.17

(m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3, 166.8, 158.7, 158.4, 133.0, 131.5, 129.4, 127.3, 122.1, 119.6, 114.7, 67.0, 52.1, 32.5, 24.7, 11.5. MS, m/z = 335 (100) $[M+H]^+$. HRMS found: (M + H) 335.1066; $C_{16}H_{18}N_2O_4S$ requires (M +H), 335.1060.

Methyl 4-[4-[(5-methylthiazol-2-yl)amino]-4-oxo-butoxy]benzoate (**24**). General Procedure A was followed using **139** (25 mg, 0.10 mmol) and 5-methyl-2-aminothiazole (14 mg, 0.13 mmol) to obtain **24** as a white solid (31 mg, 88%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.04 – 7.89 (m, 2H), 7.11 (d, *J* 1.32 Hz, 1H), 6.95 - 6.81 (m, 2H), 4.24 - 4.06 (m, 2H), 3.89 (s, 3H), 2.76 (t, *J* 7.2 Hz, 2H), 2.40 (d, *J* 1.3 Hz, 3H), 2.36 - 2.18 (m, 2H). MS, m/z = 335 (100) $[M+H]^+$. HRMS found: (M + H) 335.1068; $C_{16}H_{18}N_2O_4S$ requires (M +H), 335.1060.

4-(4-Chloro-3-methylphenoxy)-N-(5-methylthiazol-2-yl)butanamide (**25**). General Procedure A was followed using **141** (50 mg, 0.24 mmol) and 5-methyl-2-aminothiazole (28 mg, 0.24 mmol) to obtain **25** as a white solid (55 mg, 75%). ^{1}H NMR (300 MHz, d_6-DMSO): δ 7.11 (d, *J* 8.4 Hz, 1H), 6.88 (d, *J* 2.4 Hz, 1H), 6.71 (dd, *J* 8.37 and 2.5 Hz), 4.00 (t, *J* 6.0 Hz, 2H), 2.59 (t, J 7.3 Hz, 2H), 2.31 (s, 3H), 2.17-2.06 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 170.4, 157.4, 156.2, 134.6, 133.5, 131.6, 127.0, 125.8, 114.8, 113.6, 67.1, 31.4, 24.1, 18.5, 11.0. MS, m/z = 325 $[M + H]^+$. HRMS found: (M + H) 325.0778; $C_{15}H_{17}ClN_2O_2S$ requires (M +H), 325.0772.

4-(3,4-Dichlorophenoxy)-N-(5-methylthiazol-2-yl)butanamide (**26**). General Procedure A was followed using **143** (50 mg, 0.20 mmol) and 5-methyl-2-aminothiazole (23 mg, 0.20 mmol) to obtain **26** as a white solid (35 mg, 51%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31 (d, *J* 9.0 Hz, 1H), 7.10 (s, 1H), 7.00 (d, *J* 2.7 Hz, 1H), 6.73 (dd, *J* 8.7 and 2.7 Hz, 1H), 4.06 (t, *J* 6.0

Hz, 2H), 2.75 (t, *J* 7.2 Hz, 2H), 2.43 (s, 3H), 2.29-2.24 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 170.3, 157.9, 156.1, 134.6, 131.5, 130.9, 125.8, 122.3, 116.4, 115.4, 67.6, 31.3, 24.0, 11.0. MS, m/z = 345 $[M+H]^+$, 347. HRMS found: (M + H) 345.0231; $C_{14}H_{14}Cl2N_2O_2S$ requires (M +H), 345.0226.

4-(4-Chloro-3-(trifluoromethyl)phenoxy)-N-(5-methylthiazol-2-yl)butanamide (**27**). General Procedure A was followed using **145** (50 mg, 0.18 mmol) and 5-methyl-2-aminothiazole (20 mg, 0.18 mmol) to obtain **27** as a white solid (60 mg, 90%). ^{1}H NMR (300 MHz, d_6-DMSO): δ 7.61 (d, *J* 8.3 Hz, 1H), 7.27-7.22 (m, 3H), 7.10 (s, 1H), 4.10 (t, *J* 6.15 Hz, 2H), 2.57 (t, *J* 7.3 Hz, 2H), 2.33 (s, 3H), 2.09-2.00 (m, 2H). MS, m/z = 379 $[M + H]^+$. HRMS found: (M + H) 378.0418; $C_{15}H_{14}ClF_3N_2O_2S$ requires (M +H), 378.0411.

4-(3-Chloro-4-cyanophenoxy)-N-(5-methylthiazol-2-yl)butanamide (**29**). General Procedure A was followed using **147** (50 mg, 0.21 mmol) and 5-methyl-2-aminothiazole (24 mg, 0.21 mmol) to obtain **29** as a white solid (65 mg, 93%). ^{1}H NMR (300 MHz, d_6-DMSO): δ 7.85 (d, *J* 8.8 Hz, 1H), 7.28 (d, *J* 2.4 Hz, 1H), 7.08-7.03 (m, 2H), 4.13 (t, *J* 6.2 Hz, 2H), 2.55 (t, *J* 7.4 Hz, 2H), 2.31 (s, 3H), 2.07-1.98 (m, 2H). MS, m/z = 336 $[M + H]^+$. HRMS found: (M + H) 336.0579; $C_{15}H_{14}ClN_3O_2S$ requires (M +H), 336.0568.

4-(3,5-Difluorophenoxy)-N-(5-methylthiazol-2-yl)butanamide (**30**). General Procedure A was followed using **149** (16 mg, 0.074 mmol) and 5-methyl-2-aminothiazole (8.5 mg, 0.074 mmol) to obtain **30** as a white solid (13 mg, 55%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.09 (d, *J* 1.1 Hz, 1H), 6.47 - 6.32 (m, 3H), 4.05 (t, *J* = 5.8 Hz, 2H), 2.71 (t, *J* = 7.2 Hz, 2H), 2.41 (d, *J* =

1.32 Hz, 3H), 2.19 - 2.31 (m, 2H). MS, m/z = 313 (100) $[M+H]^+$. HRMS found: (M + H) 313.0821; $C_{14}H_{14}F_2N_2O_2S$ requires (M +H), 313.0817.

4-(3,5-Dichlorophenoxy)-N-(5-methylthiazol-2-yl)butanamide (**31**). General Procedure A was followed using **151** (20 mg, 0.080 mmol) and 5-methyl-2-aminothiazole (9.2 mg, 0.080 mmol) to obtain **31** as a white solid (8 mg, 27%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.08 (s, 1H), 6.95 (s, 1H), 6.77 (s, 2H), 4.06 (t, *J*= 5.83 Hz, 2H), 2.70 (t, *J*= 6.82 Hz, 2H), 2.42 (s, 3H), 2.15 - 2.32 (m, 2H). MS, m/z = 345(100) $[M+H]^+$, 347 (60). HRMS found: (M + H) 345.0231; $C_{14}H_{14}Cl_2N_2O_2S$ requires (M +H), 345.0226.

4-(3-Chloro-5-methyl-phenoxy)-N-(5-methylthiazol-2-yl)butanamide (**32**). General Procedure A was followed using **153** (16 mg, 0.070 mmol) and 5-methyl-2-aminothiazole (8.0 mg, 0.070 mmol) to obtain **32** as a white solid (4 mg, 19%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.12 (q, *J* 1.3 Hz, 1H), 6.76 (dt, *J* 0.7, 1.5 Hz, 1H), 6.69 (t, *J* 1.9 Hz, 1H), 6.57 (dt, *J* 0.7, 1.5 Hz, 1H), 4.05 (t, *J* 5.8 Hz, 2H), 2.74 (t, *J* 7.3 Hz, 2H), 2.41 (d, *J* 1.1 Hz, 3H), 2.35 - 2.18 (m, 5H). MS, m/z = 325 (100) $[M+H]^+$, 327 (30). HRMS found: (M + H) 325.0776; $C_{15}H_{17}ClN_2O_2S$ requires (M +H), 325.0772.

4-(3,5-Dicyanophenoxy)-N-(5-methylthiazol-2-yl)butanamide (**33**). General Procedure A was followed using **155** (15 mg, 0.065 mmol) and 5-methyl-2-aminothiazole (7.4 mg, 0.065 mmol) to obtain **33** as a white solid (4 mg, 19%). ^{1}H NMR (300 MHz, d_6-Acetone): δ 7.80 (t, *J* 1.3 Hz, 1H), 7.67 (d, *J*= 1.3 Hz, 2H), 7.06 - 7.00 (m, 1H), 4.31 (t, *J* 6.3 Hz, 2H), 2.75 (t, *J* 7.0 Hz, 2H), 2.37 (d, *J* 1.3 Hz, 3H), 2.28 - 2.17 (m, 2H). ^{13}C NMR (75 MHz, d_6-DMSO): δ

170.2, 158.8, 156.1, 134.6, 127.8, 125.9, 123.0, 117.0, 113.7, 68.2, 31.2, 23.8, 11.0. MS, m/z = 327 (100). HRMS found: (M) 326.0834; $C_{16}H_{14}N_4O_2S$ requires (M +H), 326.0832.

4-(3,5-Dimethylphenoxy)-N-(5-methylthiazol-2-yl)butanamide (**34**). General Procedure A was followed using **157** (15 mg, 0.072 mmol) and 5-methyl-2-aminothiazole (8.2 mg, 0.072 mmol) to obtain **34** as a white solid (13 mg, 57%). %). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.17 (d, *J* 1.1 Hz, 1H), 6.62 - 6.59 (m, 1H), 6.52 (s, 2H), 4.05 (t, *J* 5.7 Hz, 2H), 2.76 (t, *J* 7.4 Hz, 2H), 2.41 (d, *J* 1.3 Hz, 3H), 2.32 - 2.10 (m, 8H). MS, m/z = 305 (100) $[M+H]^+$. HRMS found: (M + H) 305.1326; $C_{16}H_{20}N_2O_2S$ requires (M +H), 305.1318.

4-Phenoxy-N-(thiazol-2-yl)butanamide (**35**). Procedure A was followed using 4-phenoxybutyric acid (50 mg, 0.28 mmol) and 2-aminothiazole (28 mg, 0.28 mmol) to obtain **35** as a white solid (30 mg, 41%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50 (s, 1H), 7.29-7.23 (m, 2H), 6.98-6.85 (4H, m), 4.09 (t, J 5.9 Hz, 2H), 2.82-2.77 (m, 2H), 2.31-2.25 (m, 2H). MS, m/z = 263 $[M + H]^+$. HRMS found: (M + H) 263.0850; $C_{13}H_{14}N_2O_2S$ requires (M +H), 263.0849.

N-(5-Chlorothiazol-2-yl)-4-phenoxybutanamide (**36**). General Procedure A was followed using 4-phenoxybutyric acid (50 mg, 0.28 mmol) and 5-chloro-2-aminothiazole hydrochloride (48 mg, 0.28 mmol) to obtain **36** as a white solid (52 mg, 63%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35-7.27 (3H, m), 6.99-6.89 (3H, m), 4.09 (t, *J* 5.7 Hz, 2H), 2.77 (t, *J* 7.2 Hz, 2.32-2.23 (m, 2H). MS, m/z = 297 $[M + H]^+$, 299. HRMS found: (M + H) 297.0460; $C_{13}H_{13}ClN_2O_2S$ requires (M +H), 297.0459.

N-(5-Bromothiazol-2-yl)-4-phenoxybutanamide (**37**). General Procedure A was followed using 4-phenoxybutyric acid (50 mg, 0.28 mmol) and 5-bromo-2-aminothiazole

hydrobromide (48 mg, 0.28 mmol) to obtain **37** as a white solid (40 mg, 42%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42 (s, 1H), 7.42-7.27 (m, 2H), 6.99-6.90 (m, 3H), 4.09 (t, *J* 5.6 Hz, 2H), 2.77 (t, *J* 7.1 Hz, 2H), 2.32-2.23 (m, 2H). ^{13}C NMR (75 MHz, d_6-DMSO): δ 171.4, 158.4, 158.4, 138.6, 129.4, 120.5, 114.4, 101.3, 66.5, 31.4, 24.1. MS, m/z = 341 $[M + H]^+$, 343. HRMS found: (M + H) 340.9947; $C_{13}H_{13}BrN_2O_2S$ requires (M +H), 340.9954.

4-Phenoxy-N-(5-(trifluoromethyl)thiazol-2-yl)butanamide (**38**). General Procedure A was followed using 4-phenoxybutyric acid (26 mg, 0.14 mmol) and 5-(trifluoromethyl)thiazol-2-amine (20 mg, 0.12 mmol) to obtain **38** as a white solid (12 mg, 31%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.83 (s, 1H), 7.33 - 7.24 (m, 2H), 7.02 – 6.93 (m, 1H), 6.92 – 6.85 (m, 2H), 4.11 (t, *J*5.6 Hz, 2H), 2.81 (t, *J*7.0 Hz, 2H), 2.37 - 2.24 (m, 2H). MS, m/z = 331 (100) $[M+H]^+$. HRMS found: (M + H) 331.0725; $C_{14}H_{13}F_3N_2O_2S$ requires (M +H), 331.0723.

N-(5-Ethylthiazol-2-yl)-4-phenoxybutanamide (**39**). General Procedure A was followed using 4-phenoxybutyric acid (50 mg, 0.28 mmol) and 5-ethylthiazol-2-amine (36 mg, 0.28 mmol) to obtain **39** as a white solid (54 mg, 67%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31-7.25 (m, 2H), 7.15 (s, 1H), 6.98-6.88 (3H, m), 4.09 (t, *J*5.8 Hz, 2H), 2.84-2.76 (m, 4H), 2.31-2.23 (m, 2H), 1.32 (t, *J*7.5 Hz, 3H). MS, m/z = 291 $[M + H]^+$. HRMS found: (M + H) 291.1161; $C_{15}H_{18}N_2O_2S$ requires (M +H), 291.1162.

N-(5-Isopropylthiazol-2-yl)-4-phenoxybutanamide (**40**). General Procedure A was followed using 4-phenoxybutyric acid (40 mg, 0.22 mmol) and **158** (38 mg, 0.27 mmol) to obtain **40** as a white solid (43 mg, 64%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 - 7.28 (m, 1H), 7.26 - 7.24 (m, 1H), 7.14 (d, *J*0.9 Hz, 1H), 7.01 – 6.85 (m, 3H), 4.13 – 4.06 (m, 2H), 3.15 (td,

J 6.8, 0.9 Hz, 1H), 2.81 (t, *J* 7.3 Hz, 2H), 2.34 - 2.22 (m, 3H), 1.35 (d, *J* 7.0 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6, 158.7, 158.2, 140.6, 130.0, 129.4, 120.8, 114.4, 66.6, 32.6, 27.5, 24.7, 24.5. MS, m/z = 305 (100) $[M+H]^+$. HRMS found: (M + H) 305.1321; $C_{16}H_{20}N_2O_2S$ requires (M +H), 305.1318.

N-(5-(tert-Butyl)thiazol-2-yl)-4-phenoxybutanamide (**41**). General Procedure A was followed using 4-phenoxybutyric acid (23 mg, 0.13 mmol) and **159** (24 mg, 0.15 mmol) to obtain **41** as a white solid (15 mg, 37%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 – 7.23 (m, 2H), 7.11 (s, 1H), 6.99 - 6.84 (m, 3H), 4.10 (t, *J* 5.8 Hz, 2H), 2.78 (t, *J* 7.2 Hz, 2H), 2.34 - 2.19 (m, 2H), 1.38 (s, 9H). MS, m/z = 319 (100) $[M+H]^+$. HRMS found: (M + H) 319.1479; $C_{17}H_{22}N_2O_2S$ requires (M +H), 319.1475.

4-Phenoxy-N-(5-phenylthiazol-2-yl)butanamide (**42**). General Procedure A was followed using 4-phenoxybutyric acid (23 mg, 0.13 mmol) and **160** (27 mg, 0.15 mmol) to obtain **42** as a white solid (22 mg, 51%). ^{1}H NMR (300 MHz, d_6-DMSO): δ 7.67 - 7.53 (m, 2H), 7.47 - 7.36 (m, 2H), 7.36 - 7.21 (m, 2H), 6.99 - 6.85 (m, 2H), 4.02 (t, *J* 6.2 Hz, 2H), 2.64 (t, *J* 7.4 Hz, 2H), 2.16 – 1.99 (m, 2H). MS, m/z = 339 (100) $[M+H]^+$. HRMS found: (M + H) 339.1165; $C_{19}H_{18}N_2O_2S$ requires (M +H), 339.1162.

N-(5-Cyanothiazol-2-yl)-4-phenoxybutanamide (**43**). General Procedure A was followed using 4-phenoxybutyric acid (50 mg, 0.28 mmol) and 2-aminothiazole-5-carbonitrile (35 mg, 0.28 mmol) to obtain **43** as a white solid (52 mg, 65%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.01 (s, 1H), 7.34-7.28 (m, 2H), 7.01-6.90 (m, 3H), 4.12 (t, *J* 5.5 Hz, 2H), 2.81 (t, *J* 7.1 Hz, 2H), 2.34-2.25 (m, 2H). ^{13}C NMR (75 MHz, d_6-DMSO): δ 172.3, 162.1, 158.4, 150.0, 129.4,

120.5, 114.4, 114.3, 114.3, 113.4, 97.2, 66.4, 31.6, 24.0. MS, m/z = 288 $[M+H]^+$. HRMS found: (M + H) 288.0794; $C_{14}H_{13}N_3O_2S$ requires (M +H), 288.0801.

2-(4-Phenoxybutanamido)thiazole-5-carboxylic acid (**44**). General Procedure C was followed using **161** (135 mg, 0.40 mmol) to obtain **44** as a white solid (92 mg, 74%). ^1H NMR (300 MHz, $CDCl_3$): δ 7.38 - 7.22 (m, 2H), 7.01 – 6.84 (m, 3H), 4.04 (t, *J* 6.1 Hz, 2H), 2.61 (t, *J* 7.4Hz, 2H), 2.22 - 2.22 (m, 2H). MS, m/z = 307 (100) $[M+H]^+$. HRMS found: (M + H) 307.0751; $C_{14}H_{14}N_2O_4S$ requires (M +H), 307.0747.

2-(4-Phenoxybutanamido)thiazole-5-carboxamide (**45**). General Procedure A was followed using 4-phenoxybutyric acid (13 mg, 0.072 mmol) and **162** (10 mg, 0.072 mmol) to obtain **45** (2.4 mg, 11%) as a white solid. ^1H NMR (300 MHz, $CDCl_3$): δ 7.19 - 7.34 (m, 3H), 6.84 - 6.98 (m, 3H), 4.00 (t, *J* = 6.05 Hz, 2H), 2.58 (t, *J* = 7.37 Hz, 2H), 1.98 - 2.19 (m, 2H). MS, m/z = 306 (100) $[M+H]^+$. HRMS found: (M + H) 304.0758; $C_{14}H_{15}N_3O_3S$ requires (M +H), 304.0761.

N,N-Dimethyl-2-(4-phenoxybutanamido)thiazole-5-carboxamide (**46**). General Procedure A was followed using **44** (6.5 mg, 0.021 mmol) and dimethylamine hydrochloride (2.6 mg, 0.032 mmol) to obtain **46** (1.1 mg, 15%) as a white solid. ^1H NMR (300 MHz, $CDCl_3$): δ 11.00 (s, 1H), 7.79 (s, 1H), 7.33 - 7.21 (m, 2H), 7.00 – 6.84 (m, 3H), 4.08 (t, *J* 5.6 Hz, 2H), 3.16 (s, 6H), 2.78 (t, *J* 7.2 Hz, 2H), 2.36 – 2.19 (m, 2H). MS, m/z = 334 (100) $[M+H]^+$. HRMS found: (M + H) 334.1224; $C_{16}H_{19}N_3O_3S$ requires (M +H), 334.1220.

4-Phenoxy-N-(4-(trifluoromethyl)thiazol-2-yl)butanamide (**48**). General Procedure A was followed using 4-phenoxybutyric acid (25 mg, 0.14 mmol) and 4-trifluoromethyl-thiazole-

2-yl amine (23 mg, 0.14 mmol). The crude product was then purified by reverse phase preparatory HPLC using a gradient of 95% water/ACN to 100% ACN to obtain **48** as a white solid (1.5 mg, 3%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41 (s, 1H), 7.32 (d, *J* 8.8 Hz, 2H), 7.03 – 6.90 (m, 3H), 4.11 (t, *J* 5.7 Hz, 2H), 2.75 (t, *J* 7.0 Hz, 2H), 2.27 (dt, *J* 12.6, 6.4 Hz, 2H). MS, m/z = 331 (100) $[M+H]^+$. HRMS found: (M + H) 331.0727; $C_{14}H_{13}F_3N_2O_2S$ requires (M +H), 331.0723.

N-(4-Cyanothiazol-2-yl)-4-phenoxybutanamide (**49**). General Procedure A was followed using 4-phenoxybutyric acid (25 mg, 0.14 mmol) and 2-aminothiazole-4-carbonitrile (17 mg, 0.14 mmol) to obtain **49** as a white solid (2.4 mg, 6%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (d, *J* 0.9 Hz, 1H), 7.35 -7.27 (m, 2H), 7.01 – 6.80 (m, 3H), 4.09 (t, *J* 5.7 Hz, 2H), 2.77 (t, *J* 6.9 Hz, 2H), 2.31 – 2.18 (m, 2H). MS, m/z = 288 (100) $[M+H]^+$. HRMS found: (M + H) 288.0798; $C_{14}H_{13}N_3O_2S$ requires (M +H), 288.0801.

N-(5-Methyloxazol-2-yl)-4-phenoxybutanamide (**51**). General Procedure A was followed using 4-phenoxybutyric acid (15 mg, 0.084 mmol) and 2-amino-5-methyloxazole (8.2 mg, 0.084 mmol) to obtain **51** (4.3 mg, 20%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 – 7.22 (m, 2H), 6.98 – 6.84 (m, 3H), 6.57 (d, *J* = 1.3 Hz, 1H), 4.10 - 4.04 (m, 2H), 2.80 - 2.65 (m, 2H), 2.31 (d, *J* = 1.1 Hz, 3H), 2.26 - 2.16 (m, 2H). MS, m/z = 261 (100) $[M+H]^+$. HRMS found: (M + H) 261.1236; $C_{14}H_{16}N_2O_3$ requires (M +H), 261.1234.

4-Phenoxy-N-(5-(trifluoromethyl)oxazol-2-yl)butanamide (**52**). General Procedure A was followed using 4-phenoxybutyric acid (50 mg, 0.28 mmol) and 5-(trifluoromethyl)oxazol-2-amine (42 mg, 0.28 mmol) to obtain **52** (35 mg, 40%) as a white solid. ^{1}H NMR (300 MHz,

$CDCl_3$): δ 7.48 (s, 1H), 7.33-7.26 (m, 2H), 6.99-6.89 (m, 3H), 4.10-4.02 (m, 2H), 2.74-2.68 (m, 2H), 2.27-2.12 (m, 2H). MS, m/z = 315 $[M+H]^+$. HRMS found: (M + H) 315.0948; $C_{14}H_{13}F_3N_2O_3$ requires (M + H), 315.0951.

N-(5-Methyl-1,3,4-thiadiazol-2-yl)-4-phenoxybutanamide (**53**). General Procedure A was followed using 4-phenoxybutyric acid (50 mg, 0.28 mmol) and 5-methyl-1,3,4-thiadiazol-2-amine (32 mg, 0.28 mmol) to obtain **53** (50 mg, 65%). ^{1}H NMR (300 MHz, d_6-DMSO): δ 7.30-7.24 (m, 1H), 6.94-6.88 (m, 1H), 4.00 (t, *J* 6.3 Hz, 2H), 2.66-2.60 (m, 5H), 2.09-2.00 (m, 2H). ^{13}C NMR (75 MHz, d_6-DMSO): δ 170.9, 159.0, 158.4, 129.4, 129.4, 129.4, 120.5, 114.4, 66.5, 31.5, 24.1, 14.7. MS, m/z = 278 $[M + H]^+$. HRMS found: (M + H) 278.0959; $C_{13}H_{15}N_3O_2S$ requires (M + H), 278.0958.

4-Phenoxy-N-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)butanamide (**54**). General Procedure A was followed using 4-phenoxybutyric acid (50 mg, 0.28 mmol) and 5-(trifluoromethyl)-1,3,4-thiadiazol-2-amine (47 mg, 0.28 mmol) to obtain **54** (70 mg, 76%). ^{1}H NMR (300 MHz, d_6-DMSO): δ 7.30-7.24 (m, 2H), 6.94-6.87 (m, 3H), 4.04 (t, *J* 6.3 Hz, 2H), 2.74 (t, *J* 7.3 Hz, 2H), 2.13-2.04 (m, 2H). MS, m/z = 332 $[M + H]^+$. HRMS found: (M + H) 332.0678; $C_{13}H_{12}F_3N_3O_2S$ requires (M + H), 332.0675.

N-(5-Methyl-1,3,4-oxadiazol-2-yl)-4-phenoxybutanamide (**55**). General Procedure A was followed using 4-phenoxybutyric acid (50 mg, 0.28 mmol) and 5-methyl-1,3,4-oxadiazol-2-amine (28 mg, 0.28 mmol) to obtain **55** (55 mg, 76%). ^{1}H NMR (300 MHz, d_6-DMSO): δ 7.62 (s, 1H), 7.29-7.22 (m, 2H), 6.93-6.87 (m, 3H), 4.04-3.95 (m, 2H), 2.85 (t, *J* 7.3 Hz, 2H),

2.21 (s, 3H), 2.07-1.98 (m, 2H). MS, m/z = 262 $[M + H]^+$. HRMS found: (M + H) 262.1171; $C_{13}H_{15}N_3O_3$ requires (M + H), 262.1186.

4-Phenoxy-N-(5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl)butanamide (**56**). General Procedure A was followed using 4-phenoxybutyric acid (50 mg, 0.28 mmol) and 5-(trifluoromethyl)-1,3,4-oxadiazol-2-amine (43 mg, 0.28 mmol) to obtain **56** (50 mg, 57%). ^1H NMR (300 MHz, d_6-DMSO): δ 7.28-7.23 (m, 2H), 6.92-6.88 (m, 3H), 3.99 (t, *J* 6.3 Hz, 2H), 2.63 (t, J 7.1 Hz, 2H), 2.06-1.96 (m, 2H). MS, m/z = 316 $[M + H]^+$. HRMS found: (M + H) 316.0917; $C_{13}H_{12}F_3N_3O_3$ requires (M + H), 316.0904.

N-(1-Methyl-1H-pyrazol-3-yl)-4-phenoxybutanamide (**57**). General Procedure A was followed using 4-phenoxybutyric acid (50 mg, 0.28 mmol) and 1-methyl-1H-pyrazol-3-amine (27 mg, 0.28 mmol) to obtain **57** (40 mg, 53%). ^1H NMR (300 MHz, d_6-DMSO): δ 10.35 (s, 1H), 7.51 (d, *J* 2.2 Hz, 1H), 7.30-7.24 (m, 2H), 6.93-6.89 (m, 3H), 6.43 (s, 1H), 3.97 (t, *J* 6.4 Hz, 2H), 3.72 (s, 3H), 2.45 (t, *J* 7.4 Hz, 2H), 2.03-1.94 (m, 2H). MS, m/z = 260 $[M + H]^+$. HRMS found: (M + H) 260.1395; $C_{14}H_{17}N_3O_2$ requires (M + H), 260.1394.

N-(1-Methyl-1H-pyrazol-4-yl)-4-phenoxybutanamide (**58**). General Procedure A was followed using 4-phenoxybutyric acid (50 mg, 0.28 mmol) and 1-methyl-1H-pyrazol-4-amine (27 mg, 0.28 mmol) to obtain **58** (65 mg, 90%). ^1H NMR (300 MHz, d_6-DMSO): δ 9.90 (s, 1H), 7.82 (s, 1H), 7.34 (s, 1H), 7.28-7.23 (m, 2H), 6.92-6.87 (m, 2H), 3.96 (t, *J* 6.4 Hz, 2H), 3.75 (s, 3H), 2.39 (t, *J* 7.26 Hz, 2H), 2.02-1.93 (m, 2H). HRMS found: (M + H) 260.1394; $C_{14}H_{17}N_3O_2$ requires (M + H), 260.1394.

N-(5-Methylisoxazol-3-yl)-4-phenoxybutanamide (**59**). General Procedure A was followed using 4-phenoxybutyric acid (50 mg, 0.28 mmol) and 5-methylisoxazol-3-amine (27 mg, 0.28 mmol) to obtain **59** (30 mg, 42%). ^{1}H NMR (300 MHz, d_6-DMSO): δ 10.86 (s, 1H), 7.28-7.22 (m, 2H), 6.92-6.87 (m, 3H), 6.61 (s, 1H), 3.96 (t, *J* 6.4 Hz, 2H), 2.52-2.48 (m, 2H), 2.34 (s, 3H), 2.02-1.93 (m, 2H). MS, m/z = 261 $[M + H]^+$. HRMS found: (M + H) 261.1230; $C_{14}H_{16}N_2O_3$ requires (M + H), 261.1234.

4-Phenoxy-N-(5-(trifluoromethyl)pyridin-2-yl)butanamide (**61**). General Procedure A was followed using 4-phenoxybutyric acid (50 mg, 0.28 mmol) and 2-amino-5-(trifluoromethyl)pyridine (45 mg, 0.28 mmol) to obtain **61** (15 mg, 17%). ^{1}H NMR (300 MHz, d_6-DMSO): δ 8.69 (s, 1H), 8.30 (d, *J* 8.9 Hz, 1H), 8.16 (dd, *J* 8.9 and 2.7 Hz), 7.29-7.24 (m, 2H), 6.94-6.89 (m, 3H), 4.01 (t, *J* 6.33 Hz, 2H), 2.63 (t, *J* 7.3 Hz, 2H), 2.07-2.00 (m, 2H). MS, m/z = 325 $[M + H]^+$. HRMS found: (M + H) 325.1153; $C_{16}H_{15}F_3N_2O_2$ requires (M + H), 325.1158.

N-(5-Bromopyridin-2-yl)-4-phenoxybutanamide (**63**). General Procedure A was followed using 4-phenoxybutyric acid (50 mg, 0.28 mmol) and 2-amino-5-bromopyridine (48 mg, 0.28 mmol) to obtain **63** (20 mg, 22%). ^{1}H NMR (300 MHz, d_6-DMSO): δ 10.65 (s, 1H), 8.39 (d, J 2.5 Hz, 1H), 8.07 (d, J 8.9 Hz, 1H), 7.97 (dd, *J* 8.9 and 2.6 Hz, 1H), 7.28-7.22 (m, 2H), 6.91-6.87 (m, 3H), 3.97 (t, *J* 6.4 Hz, 2H), 2.56 (t, *J* 7.4 Hz, 2H), 2.04-1.95 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.8, 158.5, 151.0, 148.4, 140.5, 129.4, 120.4, 115.0, 114.4, 113.1, 66.6, 32.6, 24.3. MS, m/z = 335 $[M + H]^+$, 337. HRMS found: (M + H) 335.0391; $C_{15}H_{15}BrN_2O_2$ requires (M + H), 335.0390.

N-(5-Isopropylpyridin-2-yl)-4-phenoxybutanamide (**64**). General Procedure A was followed using 4-phenoxybutyric acid (25 mg, 0.14 mmol) and 2-amino-5-isopropylpyridine (19 mg, 0.14 mmol) to obtain **64** as a white solid (9.1 mg, 22%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.17 (br s, 1H), 8.15 - 8.08 (m, 2H), 7.60 - 7.32 (m, 1H), 7.31 - 7.22 (m, 3H), 6.98 - 6.86 (m, 3H), 4.06 (t, *J* 5.9 Hz, 2H), 2.90 (quin, *J* 6.9 Hz, 1H), 2.61 (t, *J* 7.3 Hz, 2H), 2.32 - 2.13 (m, 2H), 1.25 (d, *J* 6.8 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.9, 158.7, 149.4, 145.7, 139.9, 136.4, 129.4, 120.8, 114.5, 113.8, 66.6, 34.0, 31.2, 24.9, 23.7. MS, m/z = 299 (100) $[M+H]^+$. HRMS found: (M + H) 299.1755; $C_{18}H_{22}N_2O_2$ requires (M +H), 299.1754.

N-(4-Methylpyridin-2-yl)-4-phenoxybutanamide (**65**). General Procedure A was followed using 4-phenoxybutyric acid (50 mg, 0.28 mmol) and 2-amino-4-methylpyridine (30 mg, 0.28 mmol) to obtain **65** as a white solid (45 mg, 60%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.38 (br s, 1H), 8.16-8.08 (m, 2H), 7.56 (dd, *J* 8.0 and 1.8 Hz, 1H), 7.31-7.25 (m, 2H), 6.99-6.89 (m, 3H), 4.08 (t, *J* 6.0 Hz, 2H), 2.65 (t, *J* 7.2 Hz, 2H), 2.31 (s, 3H), 2.28-2.19 (m, 2H). MS, m/z = 271 $[M + H]^+$. HRMS found: (M + H) 271.1443; $C_{16}H_{18}N_2O_2$ requires (M +H), 271.1441.

N-(6-Methylpyridin-2-yl)-4-phenoxybutanamide (**66**). General Procedure A was followed using 4-phenoxybutyric acid (50 mg, 0.28 mmol) and 2-amino-5-methylpyridine (30 mg, 0.28 mmol) to obtain **66** as a white solid (45 mg, 60%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.52 (br s, 1H), 8.13-8.10 (m, 2H), 7.32-7.26 (m, 2H), 6.99-6.89 (m, 4H), 4.06 (t, *J* 6.0 Hz, 2H), 2.65 (t, *J* 7.5 Hz, 2H), 2.39 (s, 3H), 2.27-2.20 (m, 2H). MS, m/z = 271 $[M + H]^+$. HRMS found: (M + H) 271.1444; $C_{16}H_{18}N_2O_2$ requires (M +H), 271.1444.

2-(4-Chloro-3-methylphenoxy)-N-(5-methylthiazol-2-yl)acetamide (**67**). General Procedure A was followed using **164** (30 mg, 0.15 mmol) and 5-methyl-2-aminothiazole (17 mg, 0.15 mmol) to obtain **67** as a white solid (31 mg, 70%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31 - 7.22 (m, 1H), 6.78 (d, *J* 3.1 Hz, 1H), 6.69 (dd, *J* 8.8, 3.1 Hz, 1H), 4.69 (s, 2H), 2.42 (d, *J* 1.3 Hz, 3H), 2.35 (s, 3H). MS, m/z = 297 (100) $[M+H]^+$, 299 (30). HRMS found: (M + H) 297.0464; $C_{13}H_{13}ClN_2O_2S$ requires (M +H), 297.0459.

2-(4-Chloro-3-methylphenoxy)-N-(5-methylthiazol-2-yl)acetamide (**68**). General Procedure A was followed using 3-phenoxypropanoic acid (15 mg, 0.090 mmol) and 5-methyl-2-aminothiazole (10 mg, 0.090 mmol) to obtain **68** as a white solid (15 mg, 64%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.22 (br. s., 1H), 7.33 - 7.27 (m, 2H), 7.09 (d, *J* 1.3 Hz, 1H), 7.02 – 6.90 (m, 3H), 4.39 (t, *J* 6.1 Hz, 2H), 2.97 (t, *J* 6.1 Hz, 2H), 2.40 (d, *J* = 1.1 Hz, 3H). MS, m/z = 263 (100) $[M+H]^+$. HRMS found: (M + H) 263.0851; $C_{13}H_{14}N_2O_2S$ requires (M +H), 263.0849.

5-(4-Chloro-3-methyl-phenoxy)-N-(5-methylthiazol-2-yl)pentanamide (**69**). General Procedure A was followed using **166** (25 mg, 0.10 mmol) and 5-methyl-2-aminothiazole (14 mg, 0.14 mmol) to obtain **69** as a white solid (15 mg, 43%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.19 (d, *J* 8.8 Hz, 1H), 7.03 (d, *J* 1.3 Hz, 1H), 6.77 - 6.71 (m, 1H), 6.69 - 6.56 (m, 1H), 3.97 (t, *J* 5.8 Hz, 2H), 2.69 - 2.57 (m, 2H), 2.38 (d, *J* 1.1 Hz, 3H), 2.32 (s, 3H), 2.05 – 1.82 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.7, 158.5, 157.4, 137.0, 132.8, 129.6, 127.4, 125.8, 117.0, 113.0, 67.6, 35.6, 28.6, 21.8, 20.3, 11.5. MS, m/z = 339 (100) $[M+H]^+$. HRMS found: (M + H) 339.0936; $C_{16}H_{19}ClN_2O_2S$ requires (M +H), 339.0929.

N-(5-Methylthiazol-2-yl)-5-phenylpentanamide (**70**). General Procedure A was followed using 5-phenylpentanoic acid (50 mg, 0.28 mmol) and 5-methyl-2-aminothiazole (32 mg, 0.28 mmol) to obtain **70** as a white solid (52 mg, 68%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32-7.17 (m, 5H), 7.03 (s, 1H), 2.68 (t, *J* 7.4 Hz, 2H), 2.54 (t, *J* 6.9 Hz, 2H), 2.42 (s, 3H), 1.85-1.70 (m, 4H). MS, m/z = 275 $[M + H]^+$.

N-(5-Methylthiazol-2-yl)-4-(phenylamino)butanamide (**71**). **170** (5.5 mg, 0.16 mmol) was dissolved in a 1:3 mixture of TFA/DCM (4 mL) and stirred at 20°C for 30 min. The solvent was then evaporated *in vacuo* and the crude residue dissolved in EtOAc (10 mL) which was then successively washed with a 10% solution of $NaHCO_3$ (10 mL), water (10 mL) and brine (10 mL). The organic layer was then dried with Na_2SO_4 and concentrated *in vacuo* to obtain **71** as a white solid (3.3 mg, 83%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22 - 7.12 (m, 2H), 7.04 (d, *J* 1.1 Hz, 1H), 6.71 (tt, *J* 7.3, 1.1 Hz, 1H), 6.65 - 6.57 (m, 2H), 3.27 (t, *J* 6.6 Hz, 2H), 2.66 (t, *J* 7.2 Hz, 2H), 2.40 (d, *J* 1.1 Hz, 3H), 2.11 (quin, *J* 6.9 Hz, 2H). MS, m/z = 276 (100) $[M+H]^+$. HRMS found: (M + H) 276.1167; $C_{14}H_{17}N_3OS$ requires (M +H), 276.1165.

4-(Methyl(phenyl)amino)-N-(5-methylthiazol-2-yl)butanamide (**72**). General Procedure A was followed using **172** (36 mg, 0.19 mmol) and 5-methyl-2-aminothiazole (21 mg, 0.19 mmol) to obtain **72** as a white solid (36 mg, 67%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30 - 7.15 (m, 2H), 6.96 (d, *J* 1.3 Hz, 1H), 6.79 - 6.65 (m, 3H), 3.45 (t, *J* 6.9 Hz, 2H), 2.94 (s, 3H), 2.59 (t, *J* 7.3 Hz, 2H), 2.38 (d, *J* 1.1 Hz, 3H), 2.09 (quin, *J* 7.1 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.5, 158.5, 149.4, 132.9, 129.2, 129.1, 127.2, 116.5, 112.4, 51.9, 38.2, 33.1, 22.5, 11.5. MS, m/z = 290 (100) $[M+H]^+$. HRMS found: (M + H) 290.1324; $C_{15}H_{19}N_3OS$ requires (M +H), 290.1322.

4-(4-Chloro-3-methylphenoxy)-2-methyl-N-(5-methylthiazol-2-yl)butanamide (**73**). General Procedure A was followed using **175** (18 mg, 74 μmol) and 5-methyl-2-aminothiazole (8.5 mg, 0.074 mmol) to obtain **73** as a clear oil (23 mg, 92%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21 - 7.10 (m, 2H), 6.71 - 6.61 (m, 1H), 6.61 - 6.49 (m, 1H), 4.10 – 3.86 (m, 2H), 3.10 – 2.89 (m, 1H), 2.42 (d, *J* 1.32 Hz, 3H), 2.39 – 2.24 (m, 4H), 2.07 – 1.87 (m, 1H), 1.35 (d, *J* 7.04 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.1, 158.5, 157.2, 157.1, 157.1, 136.9, 133.1, 129.5, 129.5, 127.2, 125.9, 116.9, 112.9, 112.9, 65.4, 37.4, 33.0, 20.2, 17.7, 11.5. MS, m/z = 339 (100) $[M+H]^+$, 341(30). HRMS found: (M + H) 339.0932; $C_{16}H_{19}ClN_2O_2S$ requires (M +H), 339.0929.

4-(4-Chloro-3-methylphenoxy)-2,2-dimethyl-N-(5-methylthiazol-2-yl)butanamide (**74**). General Procedure A was followed using **178** (19 mg, 0.070 mmol) and 5-methyl-2-aminothiazole (8.5 mg, 0.074 mmol) to obtain **74** as a clear oil (8.9 mg, 34%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.17 (d, *J* 8.6 Hz, 1H), 7.12 - 7.08 (m, 1H), 6.66 (d, *J* 3.3 Hz, 1H), 6.63 - 6.52 (m, 1H), 4.02 (t, *J* 6.3 Hz, 2H), 2.42 (d, *J* 1.3 Hz, 3H), 2.29 (s, 3H), 2.15 (t, *J* 6.3 Hz, 2H), 1.39 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.9, 156.9, 156.9, 136.9, 134.1, 129.5, 127.6, 126.0, 117.0, 112.9, 64.6, 41.3, 39.4, 25.6, 20.2, 11.5. MS, m/z = 353 (100) $[M+H]^+$, 355 (30). HRMS found: (M + H) 353.1092; $C_{17}H_{21}ClN_2O_2S$ requires (M +H), 353.1085.

1-(2-(4-Chloro-3-methylphenoxy)ethyl)-3-(5-methylthiazol-2-yl)urea (**75**). **179** (23 mg, 0.098 mmol), **180** (22 mg, 0.12 mmol) and triethylamine (41 μL, 0.29 mmol) was dissolved in dioxane (1 mL) and stirred at 70°C for 20 h The solvent was then evaporated *in vacuo* and the crude residue dissolved in EtOAc (20 mL) which was successively washed with water (15 mL) and brine (15 mL). The organic layer was dried with Na_2SO_4 and

concentrated *in vacuo*. The crude product was then purified by reverse phase preparatory HPLC using a gradient of 95% water/ACN to 100% ACN to obtain **75** as a white solid (3.1 mg, 9%). ^{1}H NMR (300 MHz, d_6-Acetone): δ 7.27 (d, *J* 8.8 Hz, 1H), 6.99 - 6.87 (m, 2H), 6.83 (dd, *J* 8.7, 3.0 Hz, 1H), 4.12 (t, *J* 5.5 Hz, 2H), 3.70 - 3.59 (m, 2H), 2.40 - 2.27 (m, 6H). MS, m/z = 326 (100) $[M+H]^+$, 328 (30). HRMS found: (M + H) 326.0729; $C_{14}H_{16}ClN_3O_2S$ requires (M +H), 326.0725.

4-(4-Chloro-3-methylphenoxy)-N-methyl-N-(5-methylthiazol-2-yl)butanamide (**76**). **28** (29 mg, 0.089 mmol) was dissolved in THF (3 mL) and cooled to 0°C under a N_2 atmosphere. Sodium hydride (60% in mineral oil) (7.8 mg, 0.18 mmol) was then added portion wise and reaction stirred at this temperature for 30 min. Iodomethane was then added and the reaction which was then allowed to warm to 20°C and then stirred at reflux for 16 h. The reaction mixture was then quenched with a saturated solution of NH_4Cl (15 mL) and then diluted with EtOAc (15 mL). The organic layer was isolated and then washed successively with water (15 mL) and brine (15 mL). The organic layer was dried with Na_2SO_4 and concentrated *in vacuo*. The crude precipitate was then purified by column chromatography gradient eluting with 100% CyHex to 20% EtOAc/CyHex to obtain **76** as a yellow oil (6.3 mg, 21%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.23 (d, *J* 8.8 Hz, 1H), 7.16 (d, *J* 1.1 Hz, 1H), 6.78 (d, *J* 3.1 Hz, 1H), 6.68 (dd, *J* 8.58, 3.1 Hz, 1H), 4.07 (t, *J* 5.7 Hz, 2H), 3.69 (s, 3H), 2.84 (t, *J* 6.9 Hz, 2H), 2.41 (d, *J* 1.1 Hz, 3H), 2.35 (s, 3H). MS, m/z = 339 (100) $[M+H]^+$, 341 (30). HRMS found: (M + H) 339.0932; $C_{16}H_{19}ClN_2O_2S$ requires (M +H), 339.0929.

N-(4-(4-Chloro-3-methylphenoxy)butyl)-5-methylthiazol-2-amine (**77**). **183** (12 mg, 0.030 mmol) was dissolved in a 1:3 mixture of TFA/DCM (4 mL) and stirred at 20°C for 2 h. The

reaction mixture was then concentrated *in vacuo* and the crude residue dissolved in EtOAc (10 mL). The organic layer was then washed successively with a saturated solution of $NaHCO_3$ (10 mL), water (10 mL) and brine (10 mL). The organic layer dried with Na_2SO_4 and concentrated *in vacuo* to obtain **77** as a yellow oil (6.6 mg, 70%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.09 (d, *J* 8.6 Hz, 1H), 6.86 (d, *J* 2.6 Hz, 1H), 6.76 - 6.62 (m, 2H), 4.01 – 3.90 (m, 2H), 3.39 – 3.26 (m, 2H), 2.36 - 2.24 (m, 6H), 2.00 - 1.81 (m, 4H), MS, m/z = 311(100) $[M+H]^+$, 313(30). HRMS found: (M + H) 311.0982; $C_{15}H_{19}ClN_2OS$ requires (M +H), 311.0979.

5-Methyl-N-(3-phenoxypropyl)thiazole-2-carboxamide (**78**). General Procedure A was followed using **185** (15 mg, 0.10 mmol) and 5-methylthiazole-2-carboxylic acid (17 mg, 0.12 mmol) to obtain **78** as a clear oil (22 mg, 80%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 (br s, 1H), 7.52 (q, *J* 1.1 Hz, 1H), 7.34 – 7.26 (m, 2H), 7.00 – 6.89 (m, 3H), 4.11 (t, *J* 5.9 Hz, 2H), 3.67 (q, *J* 6.5 Hz, 2H), 2.58 – 2.48 (m, 3H), 2.13 (quin, *J* 6.3 Hz, 2H). MS, m/z = 277 (100) $[M+H]^+$. HRMS found: (M + H) 277.1008; $C_{14}H_{16}N_2O_2S$ requires (M +H), 277.1005.

4-((4-Chloropyridin-2-yl)oxy)-N-(5-methylthiazol-2-yl)butanamide (**79**). General Procedure A was followed using **187** (12 mg, 0.048 mmol) and 5-methyl-2-aminothiazole (5.4 mg, 0.048 mmol) to obtain **79** as a white solid (12 mg, 81%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07 (dd, *J* 5.7, 0.4 Hz, 1H), 7.08 (d, *J* 1.3 Hz, 1H), 6.88 (dd, *J* 5.7, 1.76 Hz, 1H), 6.71 (dd, *J* 1.8, 0.7 Hz, 1H), 4.43 (t, *J* 6.1 Hz, 2H), 2.69 (t, *J* 7.3 Hz, 2H), 2.41 (d, *J* 1.3 Hz, 3H), 2.31 - 2.17 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ170.3, 164.5, 158.3, 147.6, 145.5, 133.0, 127.3, 117.7, 111.1, 65.3, 32.7, 24.6, 11.6. MS, m/z = 312 (100) $[M+H]^+$, 314 (30). HRMS found: (M + H) 312.0571; $C_{13}H_{14}ClN_3O_2S$ requires (M +H), 312.0568.

4-((6-Chloropyridin-2-yl)oxy)-N-(5-methylthiazol-2-yl)butanamide (**80**). General Procedure C was followed using **189** (34 mg, 0.13 mmol) and 5-methyl-2-aminothiazole (15 mg, 0.13 mmol) to obtain **80** as a white solid (34 mg, 81%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 - 7.43 (m, 1H), 7.07 (d, *J* 1.3 Hz, 1H), 6.93 - 6.84 (m, 1H), 6.62 - 6.53 (m, 1H), 4.42 (t, *J* 6.1 Hz, 2H), 2.70 (t, *J* 7.4 Hz, 2H), 2.40 (d, *J* 0.9 Hz, 3H), 2.26 (quin, *J* 6.7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3, 163.3, 158.4, 148.4, 140.6, 132.9, 127.2, 116.4, 108.9, 65.5, 32.7, 24.5, 11.6. MS, m/z = 312 (100) $[M+H]^+$, 314 (30). HRMS found: (M + H) 312.0575; $C_{13}H_{14}ClN_3O_2S$ requires (M +H), 312.0568.

4-((2-Chloropyridin-4-yl)oxy)-N-(5-methylthiazol-2-yl)butanamide (**81**). General Procedure A was followed using **191** (34 mg, 0.13 mmol) and 5-methyl-2-aminothiazole (15 mg, 0.13 mmol). The crude residue was then purified by reverse phase preparatory HPLC using a gradient of 95% water/ACN to 100% ACN to obtain **81** as a white solid (5.1 mg, 12%). ^{1}H NMR (300 MHz, d_6-Acetone): δ10.75 (s, 1H), 8.16 - 8.11 (m, 1H), 7.00 (q, *J* 1.3 Hz, 1H), 6.97 - 6.93 (m, 1H), 6.93 - 6.85 (m, 1H), 4.21 (t, *J* 6.3 Hz, 2H), 2.71 (t, *J* 7.3 Hz, 2H), 2.33 (d, *J* 1.3 Hz, 3H), 2.26 - 2.08 (m, 2H). MS, m/z = 312 (100) $[M+H]^+$, 314 (30). HRMS found: (M + H) 312.0573; $C_{13}H_{14}ClN_3O_2S$ requires (M +H), 312.0568.

4-((5-Chloropyridin-3-yl)oxy)-N-(5-methylthiazol-2-yl)butanamide (**82**). General Procedure A was followed using **193** (40 mg, 0.16 mmol) and 5-methyl-2-aminothiazole (18 mg, 0.16 mmol to obtain **82** as a white solid (41 mg, 83%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.19 (dd, *J* 4.4, 2.2 Hz, 2H), 7.19 (t, *J* 2.2 Hz, 1H), 7.09 (d, *J* 1.3 Hz, 1H), 4.14 (t, *J* 5.8 Hz, 2H), 2.74 (t, *J* 7.2 Hz, 2H), 2.42 (d, *J* 1.3 Hz, 3H), 2.36 - 2.22 (m, 2H). ^{13}C NMR (75 MHz, d_6-DMSO): δ 170.3, 156.1, 155.2, 139.9, 136.7, 134.6, 131.1, 125.9, 120.9, 67.8, 31.3, 24.0,

21.9, 11.0. MS, m/z = 312 (100) $[M+H]^+$, 314 (30) $[M+H]^+$. HRMS found: (M + H) 312.0572; $C_{13}H_{14}ClN_3O_2S$ requires (M +H), 312.0568.

N-(5-Methylthiazol-2-yl)-4-((4-(trifluoromethyl)pyridin-2-yl)oxy)butanamide (**83**). General Procedure A was followed using **195** (20 mg, 0.070 mmol) and 5-methyl-2-aminothiazole (8 mg, 0.070 mmol). The crude residue was then purified by reverse phase preparatory HPLC using a gradient of 95% Water/ACN to 100% ACN to obtain **83** as a white solid (2.5 mg, 10%). ^{1}H NMR (300 MHz, MeOD): δ 8.34 (d, *J* 5.5 Hz, 1H), 7.45 - 7.12 (m, 1H), 7.07 (q, *J* 1.2 Hz, 1H), 6.94 (dt, *J* 1.5, 0.8 Hz, 1H), 4.47 (t, *J* 6.1 Hz, 2H), 2.65 (t, *J* 7.3 Hz, 2H), 2.39 (d, *J* 1.1 Hz, 3H), 2.30 - 2.14 (m, 2H). MS, m/z = 346 (100) $[M+H]^+$. HRMS found: (M + H) 346.0836; $C_{14}H_{14}F_3N_3O_2S$ requires (M +H), 346.0832.

N-(5-Methylthiazol-2-yl)-4-((6-(trifluoromethyl)pyridin-2-yl)oxy)butanamide (**84**). General Procedure A was followed using **197** (40 mg, 0.14 mmol) and 5-methyl-2-aminothiazole (16 mg, 0.14 mmol) to obtain **84** as a white solid (34 mg, 71%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 (ddd, *J* 8.3, 7.5, 0.7 Hz, 1H), 7.24 (d, *J* 7.3 Hz, 1H), 7.06 (q, *J* 1.1 Hz, 1H), 6.87 - 6.81 (m, 1H), 4.48 (t, *J* 6.1 Hz, 2H), 2.72 (t, *J* 7.4 Hz, 2H), 2.40 (d, *J* 1.3 Hz, 3H), 2.33 - 2.22 (m, 2H). MS, m/z = 346 (100) $[M+H]^+$. HRMS found: (M + H) 346.0836; $C_{14}H_{14}F_3N_3O_2S$ requires (M +H), 346.0832.

N-(5-Methylthiazol-2-yl)-4-((2-(trifluoromethyl)pyridin-4-yl)oxy)butanamide (**85**). General Procedure A was followed using **199** (40 mg, 0.14 mmol) and 5-methyl-2-aminothiazole (16 mg, 0.14 mmol) to obtain **85** as a white solid (5.7 mg, 24%). ^{1}H NMR (300 MHz, MeOD): δ 8.48 (d, *J* 5.7 Hz, 1H), 7.28 (d, *J* 2.4 Hz, 1H), 7.17 (dd, *J* 5.8, 2.5 Hz,

1H), 7.06 (q, *J* 1.3 Hz, 1H), 4.26 (t, *J* 6.1 Hz, 2H), 2.66 (t, *J* 7.2 Hz, 2H), 2.38 (d, *J* 1.1 Hz, 3H), 2.29 - 2.16 (m, 2H). MS, m/z = 346 (100) $[M+H]^+$. HRMS found: (M + H) 346.0835; $C_{14}H_{14}F_3N_3O_2S$ requires (M +H), 346.0832.

N-(5-Methylthiazol-2-yl)-4-((5-(trifluoromethyl)pyridin-3-yl)oxy)butanamide (**86**). General Procedure A was followed using **201** (33 mg, 0.12 mmol) and 5-methyl-2-aminothiazole (13 mg, 0.12 mmol). The crude residue was then purified by reverse phase preparatory HPLC using a gradient of 95% Water/ACN to 100% ACN to obtain **86** as a white solid (2.8 mg, 7%). ^{1}H NMR (300 MHz, d_6-Acetone): δ 8.56 - 8.44 (m, 2H), 7.64 (t, *J* 2.1 Hz, 1H), 7.04 (q, *J* 1.2 Hz, 1H), 4.31 (t, *J* 6.3 Hz, 2H), 2.77 (t, *J* 7.2 Hz, 2H), 2.36 (d, *J* 1.3 Hz, 3H), 2.32 - 2.17 (m, 2H). MS, m/z = 346 (100) $[M+H]^+$. HRMS found: (M + H) 346.0836; $C_{14}H_{14}F_3N_3O_2S$ requires (M +H), 346.0832.

4-((4-Cyanopyridin-2-yl)oxy)-N-(5-methylthiazol-2-yl)butanamide (**87**). General Procedure A was followed using **203** (19 mg, 0.078 mmol) and 5-methyl-2-aminothiazole (13 mg, 0.12 mmol). The crude residue was then purified by reverse phase preparatory HPLC using a gradient of 95% water/ACN to 100% ACN to obtain **87** as a white solid (3.2 mg, 14%). ^{1}H NMR (300 MHz, d_6-Acetone): δ 10.80 (br. s., 1H), 8.38 (dd, *J* 5.3, 0.9 Hz, 1H), 7.28 (dd, *J* 5.3, 1.3 Hz, 1H), 7.12 (t, *J* 1.1 Hz, 1H), 7.05 (d, *J* 1.3 Hz, 1H), 4.46 (t, *J* 6.4 Hz, 2H), 2.72 (t, *J* 7.3 Hz, 2H), 2.37 (d, *J* 1.1 Hz, 2H), 2.27 - 2.13 (m, 2H). MS, m/z = 303 (100) $[M+H]^+$. HRMS found: (M + H) 303.0912; $C_{14}H_{14}N_4O_2S$ requires (M +H), 303.0910.

4-((5-Cyanopyridin-3-yl)oxy)-N-(5-methylthiazol-2-yl)butanamide (**88**). General Procedure A was followed using **205** (20 mg, 0.082 mmol) and 5-methyl-2-aminothiazole

(9.4 mg, 0.82 mmol). The crude residue was then purified by reverse phase preparatory HPLC using a gradient of 95% water/ACN to 100% ACN to obtain **88** as a white solid (18 mg, 70%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.48 (t, *J* 2.3 Hz, 2H), 7.38 (dd, *J* 2.9, 1.8 Hz, 1H), 7.08 (s, 1H), 4.18 (t, *J* 5.9 Hz, 2H), 2.75 (t, *J* 6.9 Hz, 2H), 2.43 (d, *J* 1.1 Hz, 3H), 2.32 (quin, *J* 6.4 Hz, 2H). MS, m/z = 303 (100) $[M+H]^+$. HRMS found: (M + H) 303.0914; $C_{14}H_{14}N_4O_2S$ requires (M +H), 303.0910.

4-(3-Chlorophenoxy)-N-(5-chlorothiazol-2-yl)butanamide (**89**). General Procedure A was followed using **108** (9.0 mg, 0.042 mmol) and 5-chlorothiazol-2-amine hydrochloride (8.6 mg, 0.050 mmol) to obtain **89** as a white solid (4.2 mg, 30%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 (s, 1H), 7.22 - 7.14 (m, 1H), 6.97 - 6.91 (m, 1H), 6.89 (t, *J* 2.2 Hz, 1H), 6.77 (ddd, *J* 8.4, 2.4, 0.9 Hz, 1H), 4.07 (t, *J* 5.6 Hz, 2H), 2.74 (t, *J* 7.3 Hz, 2H), 2.36 - 2.18 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4, 159.2, 157.2, 135.0, 133.6, 130.3, 121.2, 114.8, 112.8, 66.8, 32.6, 24.5. MS, m/z = 331 (100) $[M]^+$, 333 (70). HRMS found: (M + H) 331.0069; $C_{13}H_{12}Cl_2N_2O_2S$ requires (M +H), 331.0069.

4-(3-Chlorophenoxy)-N-(5-cyanothiazol-2-yl)butanamide (**90**). General Procedure C was followed using **108** (12 mg, 0.056 mmol) and 2-aminothiazole-5-carbonitrile (8.4 mg, 0.067 mmol). The crude residue was then purified by reverse phase preparatory HPLC using a gradient of 95% water/ACN to 100% ACN to obtain **90** as a white solid (6.4 mg, 36%). ^{1}H NMR (300 MHz, d_6-Acetone): δ 8.16 (s, 1H), 7.32 - 7.21 (m, 1H), 6.98 - 6.91 (m, 2H), 6.91 - 6.83 (m, 1H), 4.15 (t, *J* 6.2 Hz, 2H), 2.87 (t, *J* 7.2 Hz, 2H), 2.30 - 2.17 (m, 2H). MS, m/z = 331 (100) $[M+H]^+$, 333 (70). HRMS found: (M + H) 322.0412; $C_{14}H_{12}ClN_3O_2S$ requires (M +H), 322.0412.

4-(3-Chlorophenoxy)-N-(5-(trifluoromethyl)thiazol-2-yl)butanamide (**91**). General Procedure A was followed using **108** (9.0 mg, 0.042 mmol) and 5-(trifluoromethyl)thiazol-2-amine (8.5 mg, 0.050 mmol) to obtain **91** as a white solid (12 mg, 79%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80 (q, *J* 1.3 Hz, 1H), 7.22 - 7.12 (m, 1H), 6.93 (ddd, *J* 7.9, 2.0, 0.9 Hz, 1H), 6.85 (t, *J* 2.2 Hz, 1H), 6.74 (ddd, *J* 8.4, 2.6, 0.9 Hz, 1H), 4.08 (t, *J* 5.7 Hz, 2H), 2.79 (t, *J* 7.2 Hz, 2H), 2.38 - 2.17 (m, 2H). MS, m/z = 365 (100) $[M+H]^+$, 367 (30). HRMS found: (M + H) 365.0332; $C_{14}H_{12}ClF_3N_2O_2S$ requires (M +H), 365.0333.

N-(5-Chlorothiazol-2-yl)-4-(3-cyanophenoxy)butanamide (**92**). General Procedure A was followed using **114** (12 mg, 0.059 mmol) and 5-chlorothiazol-2-amine hydrochloride (12 mg, 0.070 mmol) to obtain **92** as a white solid (3.8 mg, 20%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41 - 7.34 (m, 1H), 7.28 (s, 1H), 7.25 - 7.23 (m, 1H), 7.17 - 7.07 (m, 2H), 4.10 (t, *J* 5.8 Hz, 2H), 2.72 (t, *J* 7.2 Hz, 2H), 2.36 - 2.18 (m, 2H). MS, m/z = 322 (100) $[M+H]^+$, 324 (30). HRMS found: (M + H) 322.0412; $C_{14}H_{12}ClN_3O_2S$ requires (M +H), 322.0412.

4-(3-Cyanophenoxy)-N-(5-cyanothiazol-2-yl)butanamide (**93**). General Procedure A was followed using **114** (12 mg, 0.059 mmol) and 2-aminothiazole-5-carbonitrile (8.8 mg, 0.070 mmol). The crude residue was then purified by reverse phase preparatory HPLC using a gradient of 95% water/ACN to 100% ACN to obtain **93** as a white solid (1.0 mg, 5.5%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.98 (s, 1 H), 7.43 -7.38 (m, 2 H), 7.18 - 7.14 (m, 2 H), 4.13 (t, *J* 5.7 Hz, 3H), 2.84 - 2.72 (m, 4 H), 2.39 - 2.23 (m, 5 H). MS, m/z = 313 (100) $[M+H]^+$. HRMS found: (M - H) 311.0617; $C_{15}H_{12}N_4O_2S$ requires (M +H), 311.0608.

4-(3-Cyanophenoxy)-N-(5-(trifluoromethyl)thiazol-2-yl)butanamide (**94**). General Procedure A was followed using **114** (12 mg, 0.059 mmol) and 5-(trifluoromethyl)thiazol-2-amine (12 mg, 0.070 mmol) to obtain **94** as a white solid (2.8 mg, 21%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.71 (br s, 1H), 7.78 (q, *J* 1.4 Hz, 1H), 7.44 - 7.31 (m, 1H), 7.28 - 7.27 (m, 1H), 7.18 - 7.06 (m, 2H), 4.12 (t, *J* 5.7 Hz, 2H), 2.79 (t, *J* 7.0 Hz, 2H), 2.43 - 2.18 (m, 2H). MS, m/z = 356 (100) $[M+H]^+$. HRMS found: (M + H) 356.0675; $C_{15}H_{12}F_3N_3O_2S$ requires (M +H), 356.0675.

N-(5-Chlorothiazol-2-yl)-4-(3-(trifluoromethyl)phenoxy)butanamide (**95**). General Procedure A was followed using **110** (15 mg, 0.060 mmol) and 5-chlorothiazol-2-amine hydrochloride (12 mg, 0.073 mmol) to obtain **95** as a white solid (8.5 mg, 39%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.88 (s, 1H), 7.43 - 7.35 (m, 1H), 7.31 (d, *J* 0.4 Hz, 1H), 7.22 (d, *J* 7.9 Hz, 1H), 7.14 - 7.03 (m, 2H), 4.12 (t, *J* 5.7 Hz, 2H), 2.74 (t, *J* 7.2 Hz, 2H), 2.36 – 2.18 (m, 2H). MS, m/z = 365 (100) $[M+H]^+$, 367 (30). HRMS found: (M + H) 365.0335; $C_{14}H_{12}ClF_3N_2O_2S$ requires (M +H), 365.0333.

N-(5-Cyanothiazol-2-yl)-4-(3-(trifluoromethyl)phenoxy)butanamide (**96**). General Procedure A was followed using **110** (15 mg, 0.060 mmol) and 2-aminothiazole-5-carbonitrile (9.1 mg, 0.073 mmol) to obtain **96** as a white solid (7.6 mg, 35%). ^{1}H NMR (300 MHz, d_6-acetone): δ ppm 8.15 (s, 1H), 7.54 - 7.47 (m, 1H), 7.29 - 7.13 (m, 3H), 4.22 (t, *J* 6.2 Hz, 2H), 2.92 - 2.85 (m, 2H) 2.34 - 2.18 (m, 2H). MS, m/z = 356 (100) $[M+H]^+$. HRMS found: (M + H) 356.0674; $C_{15}H_{12}F_3N_3O_2S$ requires (M +H), 356.0675.

4-(3-(Trifluoromethyl)phenoxy)-N-(5-(trifluoromethyl)thiazol-2-yl)butanamide (**97**). General Procedure A was followed using **110** (15 mg, 0.060 mmol) and 5-(trifluoromethyl)thiazol-2-amine (12 mg, 0.073 mmol) to obtain **97** as a white solid (5.4 mg, 22%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.11 (br. s., 1H), 7.79 (q, *J* 1.17 Hz, 1H), 7.43 - 7.33 (m, 1H), 7.27 - 7.18 (m, 1H), 7.13 - 6.99 (m, 2H), 4.13 (t, *J* 5.7 Hz, 2H), 2.80 (t, *J* 7.0 Hz, 2H), 2.38 - 2.25 (m, 2H). MS, m/z = 399 (100) $[M+H]^+$. HRMS found: (M + H) 399.0597; $C_{15}H_{12}F_6N_2O_2S$ requires (M +H), 399.0596.

N-(5-Chlorothiazol-2-yl)-4-(3,4-dichlorophenoxy)butanamide (**98**) General Procedure A was followed using **143** (50 mg, 0.20 mmol) and 5-chlorothiazol-2-amine hydrochloride (34 mg, 0.20 mmol) to obtain **98** as a white solid (30 mg, 43%). ^{1}H NMR (300 MHz, d_6-DMSO): δ 7.50-7.47 (m, 2H), 7.16 (d, J 2.9 Hz, 1H), 6.90 (dd, J 8.9 and 2.9 Hz, 1H), 4.01 (t, J 6.2 Hz, 2H), 2.58 (t, J 7.2 Hz, 2H), 2.03-1.98 (m, 2H). MS, m/z = 365 [M + H]+, 367. HRMS found: (M + H) 364.9683; $C_{13}H_{12}Cl_3N_2O_2S$ requires (M +H), 364.9680.

4-(4-Chloro-3-methylphenoxy)-N-(5-chlorothiazol-2-yl)butanamide (**99**). General Procedure A was followed using **206** (50 mg, 0.22 mmol) and 5-chlorothiazol-2-amine hydrochloride (38 mg, 0.22 mmol) to obtain **99** as a white solid (30 mg, 42%). ^{1}H NMR (300 MHz, d_6-DMSO): δ 7.47 (s, 1H), 7.25 (d, *J* 8.8 Hz, 1H), 6.87 (d, *J* 2.9 Hz, 1H), 7.73 (dd, *J* 8.9 and 3.1 Hz), 3.96 (t, *J* 6.2 Hz, 2H), 2.58 (t, J 7.3 Hz, 2H), 2.24 (3H, s), 2.05-1.96 (2H, m). ^{13}C NMR (75 MHz, d_6-DMSO): δ 171.8, 157.7, 156.4, 136.9, 136.0, 129.9, 125.0, 118.2, 117.6, 114.1, 67.4, 31.8, 24.5, 20.2. MS, m/z = 345 $[M + H]^+$, 347. HRMS found: (M + H) 345.0226; $C_{14}H_{14}Cl_2N_2O_2S$ requires (M +H), 345.0226.

4-(3-Chloro-4-methylphenoxy)-N-(5-methylthiazol-2-yl)butanamide (**100**). General Procedure A was followed using **141** (50 mg, 0.22 mmol) and 5-chlorothiazol-2-amine hydrochloride (45 mg, 0.26 mmol) to obtain **100** as a white solid (14 mg, 19%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 (s, 1H), 7.16 - 7.01 (m, 1H), 6.91 (d, *J* 2.6 Hz, 1H), 6.71 (dd, *J* 8.3, 2.5 Hz, 1H), 4.05 (t, *J* 5.7 Hz, 2H), 2.73 (t, *J* 7.3 Hz, 2H), 2.32 - 2.21 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.5, 157.2, 157.2, 134.7, 133.6, 131.3, 128.3, 115.0, 113.0, 66.8, 32.7, 24.6, 19.0. MS, m/z = 345 (100) [M], 347 (70). HRMS found: (M + H) 345.0230; $C_{14}H_{14}Cl_2N_2O_2S$ requires (M +H), 345.0226.

4-(4-Chloro-3-methylphenoxy)-N-(5-(trifluoromethyl)thiazol-2-yl)butanamide (**101**). General Procedure A was followed using **206** (33 mg, 0.14 mmol) and 5-(trifluoromethyl)thiazol-2-amine (20 mg, 0.12 mmol) to obtain **101** as a white solid (16 mg, 36%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82 (s, 1H), 7.22 (d, *J* 8.8 Hz, 1H), 6.75 (d, *J* 3.1 Hz, 1H), 6.65 (dd, *J* 8.8, 3.1 Hz, 1H), 4.06 (t, *J* 5.7 Hz, 2H), 2.79 (t, *J* 7.0 Hz, 2H), 2.37 - 2.23 (m, 5H). MS, m/z = 379 (100) $[M+H]^+$, 381 (30). HRMS found: (M + H) 379.0491; $C_{15}H_{14}ClF_3N_2O_2S$ requires (M +H), 379.0489.

5-Bromo-N-(3-(4-chloro-3-methylphenoxy)propyl)thiazole-2-carboxamide (**102**). General Procedure A was followed using **206** (50 mg, 0.21 mmol) and 5-bromo-2-aminothiazole hydrobromide (74 mg, 0.28 mmol) to obtain **102** as a white solid (40 mg, 47%). ^{1}H NMR (300 MHz, d_6-DMSO): δ 7.53 (s, 1H), 7.27 (d, *J* 8.7 Hz, 1H), 6.89 (d, *J* 3.0 Hz), 6.76 (dd, *J* 8.5 and 2.8 Hz, 1H), 3.98 (t, *J* 6.2 Hz, 2H), 2.59 (t, *J* 7.2 Hz, 2H), 2.07-1.98 (m, 2H). MS, m/z = 391 $[M + H]^+$, 389.

General Procedure B. Ethyl 4-(o-tolyloxy)butanoate (**103**). *o*-Cresol (79 μL, 0.77 mmol), ethyl bromobutyrate (111 μL, 0.77 mmol) and K_2CO_3 (322 mg, 2.3 mmol) were dissolved in DMF (4 mL) and stirred for 16 h at 90°C. The solvent was then evaporated, and the crude residue dissolved in EtOAc (15 mL) which was then washed with water (10 mL), brine (10 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was then purified by column chromatography gradient eluting with 100% CyHex to 15% EtOAc/CyHex to obtain **103** as a clear oil (150 mg, 88%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22 - 7.13 (m, 2H), 6.94 - 6.79 (m, 2H), 4.19 (q, *J* 7.3 Hz, 2H), 4.04 (t, *J* 5.9 Hz, 2H), 2.63 - 2.54 (m, 2H), 2.27 (s, 3H), 2.24 - 2.11 (m, 2H), 1.30 (t, *J* 7.2 Hz, 3H). MS, m/z = 223 (100) $[M+H]^+$.

General Procedure C. 103 (150 mg, 0.67 mmol) and LiOH (38 mg, 1.6 mmol) in a solution of THF (2 mL) and water (2 mL) was stirred for 4 h at 20°C. The solution was then acidified with 1N HCl and extracted with Et_2O (2 x 10 mL). The organic layers were combined and washed with brine (20 mL), dried with Na_2SO_4, and concentrated *in vacuo* to obtain **104** as a white solid (126 mg, 96%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.23 - 7.12 (m, 2H), 6.94 - 6.80 (m, 2H), 4.06 (t, *J* 6.1 Hz, 2H), 2.66 (t, *J* 7.3 Hz, 2H), 2.26 (s, 3H), 2.24 - 2.12 (m, 2H)· MS, m/z = 193 (100) $[M-H]^-$.

Ethyl 4-(2-chlorophenoxy)butanoate (**105**). General Procedure B was followed using 2-chlorophenol (79 μL, 0.77 mmol) and ethyl bromobutyrate (111 μL, 0.77 mmol) to obtain **105** as a clear oil (130 mg, 70%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24- 7.10 (m, 2H), 6.95 -

6.76 (m, 2H), 4.19 (q, *J* 7.3 Hz, 2H), 4.04 (t, *J* 5.9 Hz, 2H), 2.63 - 2.52 (m, 2H), 2.27 (s, 3H), 2.24 - 2.10 (m, 2H), 1.30 (t, *J* 7.2 Hz, 3H). MS, m/z = 243 (100) $[M+H]^+$.

4-(2-Chlorophenoxy)butanoic acid (**106**). General Procedure C was followed using **105** (130 mg, 0.54 mmol) to obtain **106** as a white solid (126 mg, 96%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.23 - 7.12 (m, 2H), 6.94 - 6.80 (m, 2H), 4.06 (t, *J* 6.1 Hz, 2H), 2.66 (t, *J* 7.3 Hz, 2H), 2.26 (s, 3H), 2.24 - 2.12 (m, 2H). MS, m/z = 213 (100) $[M-H]^-$, 215 (30).

Ethyl 4-(3-chlorophenoxy)butanoate (**107**). General Procedure B was followed using 3-chlorophenol (87 mg, 0.68 mmol) and ethyl bromobutyrate (89 μL, 0.62 mmol) to obtain **107** as a clear oil (129 mg, 87%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25 - 7.15 (m, 1H), 6.98 - 6.87 (m, 2H), 6.79 (ddd, *J* 8.4, 2.4, 0.9 Hz, 1H), 4.17 (q, *J* 7.0 Hz, 2H), 4.01 (t, *J* 6.16 Hz, 2H), 2.52 (t, *J* 7.3 Hz, 2H), 2.19 – 2.05 (m, 2H), 1.28 (t, *J* 7.2 Hz, 3H). MS, m/z = 243 (100) $[M+H]^+$, 245 (30).

4-(3-Chlorophenoxy)butanoic acid (**108**). General Procedure C was followed using **106** (129 mg, 0.53 mmol) to obtain **108** as a clear solid (105 mg, 92%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26 - 7.16 (m, 1H), 7.01 – 6.87 (m, 2H), 6.79 (ddd, *J* 8.4, 2.4, 0.9 Hz, 1H), 4.03 (t, *J* 6.1 Hz, 2H), 2.61 (t, *J* 7.2 Hz, 2H), 2.20 – 2.07 (m, 2H). MS, m/z = 213 (100) $[M-H]^-$.

Ethyl 4-(3-(trifluoromethyl)phenoxy)butanoate (**109**). General Procedure B was followed using 3-trifluoromethylphenol (93 μL, 0.77 mmol) and ethyl bromobutyrate (111 μL, 0.77 mmol) to obtain **109** as a clear oil (187 mg, 88%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39 (t, *J* 7.9 Hz, 1H), 7.21 (d, *J* 7.7 Hz, 1H), 7.13 (s, 1H), 7.07 (dd, *J* 8.4, 2.2 Hz, 1H), 4.17 (q, *J* 7.0 Hz,

2H), 4.06 (t, *J* 6.1 Hz, 2H), 2.48 - 2.60 (m, 2H), 2.21 - 2.08 (m, 2H), 1.28 (t, *J* 7.2 Hz, 3H). MS, m/z = 277 (100) $[M+H]^+$.

4-(3-(Trifluoromethyl)phenoxy)butanoic acid (**110**). General Procedure C was followed using **109** (185 mg, 0.67 mmol) to obtain **110** as a clear solid (159 mg, 96%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40 (t, *J* 8.0 Hz, 1H), 7.23 (d, *J* 7.9 Hz, 1H), 7.14 (s, 1H), 7.11 - 7.04 (m, 1H), 4.09 (t, *J* 6.1 Hz, 2H), 2.63 (t, *J* 7.2 Hz, 2H), 2.18 (dt, *J* 13.3, 6.7 Hz, 2H). MS, m/z = 247 (100) $[M-H]^-$.

Ethyl 4-(4-(trifluoromethyl)phenoxy)butanoate (**111**). Sodium hydride (60% in mineral oil) (113 mg, 2.84 mmol) was added to stirred solution of 4-(trifluoromethyl)phenol (416 mg, 2.56 mmol) in DMF (3 mL) at 0°C. After 15 min of stirring, a solution of ethyl bromobutyrate (500 mg, 2.56 mmol) in DMF (1 mL) was added dropwise over 1 min at 0°C. The solution was then stirred for 16 h at 20°C. 2N HCl was added and the solution extracted with Et_2O (2 x 15 mL). The organic layer was washed with brine (20 mL), dried with $MgSO_4$ and concentrated *in vacuo*. The crude residue was then purified by column chromatography gradient eluting with 100% CyHex to 35% EtOAc to obtain **111** as an oil (700 mg, 98%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54 (d, *J* 9.0 Hz, 2H), 6.96 (d, *J* 9.0 Hz, 2H), 4.17 (q, *J* 7.3 Hz, 2H), 4.07 (t, *J* 6.1 Hz, 2H), 2.54 (t, *J* 7.2 Hz, 2H), 2.20-2.11 (2H, m), 1.29 (t, *J* 7.2 Hz, 3H).

4-(4-(Trifluoromethyl)phenoxy)butanoic acid (**112**). General Procedure C was followed using **111** (590 mg, 2.14 mmol) to obtain **112** as a solid (520 mg, 98%). ^{1}H NMR (300 MHz,

$CDCl_3$): δ 7.56 (d, *J* 9.0 Hz, 2H), 6.97 (d, *J* 9.0 Hz, 2H), 4.09 (t, *J* 5.7 Hz, 2H), 2.62 (t, *J* 7.2 Hz, 2H), 2.21-2.12 (2H, m).

Ethyl 4-(3-cyanophenoxy)butanoate (**113**). General Procedure A was followed using 3-hydroxybenzonitrile (92 μL, 0.77 mmol) and ethyl bromobutyrate (111 μL, 0.77 mmol) to obtain **113** as a clear oil (140 mg, 78%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42 - 7.32 (m, 1H), 7.29 - 7.21 (m, 1H), 7.18 - 7.08 (m, 2H), 4.17 (q, *J* 7.3 Hz, 2H), 4.04 (t, *J* 6.05 Hz, 2H), 2.57 - 2.46 (m, 2H), 2.24 - 2.04 (m, 2H), 1.27 (t, *J* 7.2 Hz, 3H). MS, m/z = 234 (100) $[M+H]^+$.

4-(3-Cyanophenoxy)butanoic acid (**114**). General Procedure B was followed using **113** (63 mg, 0.60 mmol). The crude residue was then purified by column chromatography gradient eluting with 100% CyHex to 100% EtOAc obtain **114** as a white solid (63 mg, 51%). 1H NMR (300 MHz, $CDCl_3$): δ 7.42 - 7.33 (m, 1H), 7.29 - 7.20 (m, 1H), 7.17 - 7.09 (m, 2H), 4.06 (t, *J* 6.1 Hz, 2H), 2.61 (t, *J* 7.2 Hz, 2H), 2.21 - 2.09 (m, 2H). MS, m/z = 204 (100) $[M-H]^-$.

Ethyl 4-(4-cyanophenoxy)butanoate (**115**). General Procedure D was followed using 4-hydroxybenzonitrile (500 mg, 4.20 mmol) and ethyl bromobutyrate (819 mg, 4.20 mmol) to obtain **115** as an oil (600 mg, 61%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 (d, *J* 9.1 Hz, 2H), 6.95 (d, *J* 10.6 Hz, 2H), 4.09 (t, *J* 6.0 Hz, 2H), 2.64-2.59 (m, 2H), 2.21-2.13 (m, 2H).

4-(4-Cyanophenoxy)butanoic acid (**116**). General Procedure C was followed using **115** (500 mg, 2.14 mmol) to obtain **116** as a solid (430 mg, 98%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 (d, *J* 9.0 Hz, 2H), 6.95 (d, *J* 9.0 Hz, 2H), 4.16 (q, *J* 7.1 Hz, 2H), 4.08 (t, *J* 6.2 Hz, 2H), 2.53 (t, *J* 7.2 Hz, 2H), 2.21-2.13 (m, 2H) 1.28 (t, J 7.1 Hz, 3H).

Ethyl 4-(2-Methoxyphenoxy)butanoate (**117**). General Procedure B was followed using 2-methoxyphenol (84 mg, 0.68 mmol) and ethyl bromobutyrate (89 μL, 0.62 mmol) to obtain **117** as a clear oil (118 mg, 80%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.99 - 6.85 (m, 4H), 4.16 (q, *J* 7.0 Hz, 2H), 4.09 (t, *J* 6.4 Hz, 2H), 3.88 (s, 3H), 2.60 - 2.51 (t, *J* 7.5 Hz, 2H), 2.23 - 2.11 (m, 2H), 1.32 - 1.23 (t, *J* 6.4 Hz, 3H). MS, m/z = 239 (100) $[M+H]^+$.

4-(2-Methoxyphenoxy)butanoic acid (**118**). General Procedure C was followed using **117** (118 mg, 0.50 mmol) to obtain **118** as a clear solid (80 mg, 77%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.99 - 6.79 (m, 4H), 4.07 (t, *J* 6.2 Hz, 2H), 3.85 (s, 3H), 2.62 (t, *J* 7.3 Hz, 2H), 2.23 - 2.08 (m, 2H). MS, m/z = 209 (100) $[M-H]^-$.

Ethyl 4-(3-hydroxyphenoxy)butanoate (**119**). General Procedure B was followed using resorcinol (1.4 g, 12 mmol) and ethyl bromobutyrate (889 μL, 6.2 mmol) to obtain **119** as a clear oil (720 mg, 52%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.12 (t, *J* 8.0 Hz, 1H), 6.51 - 6.38 (m, 3H), 4.18 (q, *J* 7.3 Hz, 2H), 3.97 (t, *J* 6.1 Hz, 2H), 2.53 (t, *J* 7.4 Hz, 2H), 2.17 - 2.02 (m, 2H), 1.28 (t, *J* 7.2 Hz, 3H). MS, m/z = 225 (100) $[M+H]^+$.

Ethyl 4-(3-methoxyphenoxy)butanoate (**120**). General Procedure B was followed using **119** (100 mg, 0.45 mmol) and iodomethane (56 μL, 0.89 mmol) to give **120** as a clear oil (91 mg, 86%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.19 (t, *J* 8.0 Hz, 1H), 6.57 - 6.45 (m, 3H), 4.17 (q, *J* 7.1 Hz, 2H), 4.01 (t, *J* 6.1 Hz, 2H), 2.53 (t, *J* 7.3 Hz, 2H), 2.20 - 2.04 (m, 2H), 1.28 (t, *J* 7.2 Hz, 3H). MS, m/z = 239 (100) $[M+H]^+$.

4-(3-Methoxyphenoxy)butanoic acid (**121**). General Procedure C was followed using **120** (91 mg, 0.38 mmol) to obtain **121** as a white solid (67 mg, 83%). ^{1}H NMR (300 MHz, $CDCl_3$):

δ 7.20 (t, *J* 8.1 Hz, 1H), 6.58 - 6.42 (m, 3H), 4.03 (t, *J* 6.1 Hz, 2H), 3.81 (s, 3H), 2.61 (t, *J* 7.3 Hz, 2H), 2.20 - 2.08 (m, 2H). MS, m/z = 209 (100) $[M-H]^-$.

4-(3-Hydroxyphenoxy)butanoic acid (**122**). General Procedure C was followed using **119** (60 mg, 0.27 mmol) to obtain **122** as a white solid (44 mg, 84%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20 - 7.08 (m, 1H), 6.54 - 6.38 (m, 3H), 4.02 (t, *J* 6.1 Hz, 2H), 2.60 (t, *J* 7.3 Hz, 2H), 2.22 - 2.05 (m, 2H). MS, m/z = 195 (100) $[M-H]^-$.

Ethyl 4-(4-hydroxyphenoxy)butanoate (**123**). General Procedure B was followed using hydroquinone (1.4 g, 12 mmol) and ethyl bromobutyrate (889 μL, 6.2 mmol) to obtain **123** as an orange solid (670 mg, 49%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.84 - 6.71 (m, 4H), 4.17 (q, *J* 7.2 Hz, 2H), 3.96 (t, *J* 6.1 Hz, 2H), 2.59 - 2.43 (m, 2H), 2.16 - 2.00 (m, 2H), 1.28 (t, *J* 7.2 Hz, 3H). MS, m/z = 225 (100) $[M+H]^+$.

4-(4-Hydroxyphenoxy)butanoic acid (**124**). General Procedure B was followed using **123** (66 mg, 0.29 mmol) to obtain **124** as a white solid (56 mg, 98%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.85 - 6.72 (m, 4H), 3.98 (t, *J* 6.1 Hz, 2H), 2.60 (t, *J* 7.3 Hz, 2H), 2.19 - 2.08 (m, 2H). MS, m/z = 195 (100) $[M-H]^-$.

Ethyl 4-(3-nitrophenoxy)butanoate (**125**). General Procedure B was followed using 3-nitrophenol (350 mg, 2.52 mmol) and ethyl bromobutyrate (364 μL, 2.42 mmol) to give **125** as a clear oil (553 mg, 87%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88 - 7.79 (m, 1H), 7.74 (t, *J* 2.2 Hz, 1H), 7.51 - 7.51 (m, 1H), 7.19 - 7.26 (m, 1H), 4.16 - 4.25 (m, 2H), 4.06 - 4.16 (m, 2H), 2.55 (t, *J* 7.3 Hz, 2H), 2.18 (quin, *J* 6.7 Hz, 2H), 1.22 - 1.36 (m, 3H). MS, m/z = 254 (100) $[M+H]^+$.

4-(3-Nitrophenoxy)butanoic acid (**126**). General Procedure C was followed using **125** (553 mg, 2.18 mmol) to obtain **126** as a white solid (459 mg, 93%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85 (ddd, *J* 8.1, 2.2, 0.9 Hz, 1H), 7.74 (t, *J* 2.3 Hz, 1H), 7.45 (t, *J* 8.1 Hz, 1H), 7.23 (ddd, *J* 8.3, 2.6, 1.0 Hz, 1H), 4.14 (t, *J* 6.1 Hz, 2H), 2.64 (t, *J* 7.2 Hz, 2H), 2.28 - 2.12 (m, 2H). MS, m/z = 224 (100) $[M-H]^-$.

N-(5-Methylthiazol-2-yl)-4-(3-nitrophenoxy)butanamide (**127**). General Procedure A was followed using **126** (459 mg, 2.04 mmol) and 5-methyl-2-aminothiazole (232 mg, 2.04 mmol) to obtain **127** as a white solid (429 mg, 65%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87 - 7.81 (m, 1H), 7.73 (t, *J* 2.2 Hz, 1H), 7.49 - 7.37 (m, 1H), 7.25 - 7.17 (m, 1H), 7.10 (d, *J* 1.1 Hz, 1H), 4.18 (t, *J* 5.8 Hz, 2H), 2.74 (t, *J* 7.2 Hz, 2H), 2.43 (d, *J* 1.3 Hz, 3H), 2.40 - 2.24 (m, 2H). MS, m/z = 322 (100) $[M+H]^+$.

Ethyl 4-(4-nitrophenoxy)butanoate (**128**). General Procedure B was followed using 4-nitrophenol (400 mg, 2.88 mmol) and ethyl bromobutyrate (415 μL, 2.88 mmol) to give **128** as yellow crystals (648 mg, 89%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.25 – 8.15 (m, 2H), 7.01 – 6.90 (m, 2H), 4.23 – 4.07 (m, 4H), 2.61 – 2.48 (m, 2H), 2.25 – 2.08 (m, 2H), 1.35 1.21 (m, 3H). MS, m/z = 254 (100) $[M+H]^+$.

4-(4-Nitrophenoxy)butanoic acid (**129**). General Procedure B was followed using **128** (500 mg, 1.97 mmol) to obtain **129** as a white solid (459 mg, 93%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.28- 8.16 (m, 2H), 7.03 – 6.92 (m, 2H), 4.16 (t, *J* 6.1 Hz, 2H), 2.64 (t, *J* 7.2 Hz, 2H), 2.27 – 2.10 (m, 2H). MS, m/z = 224 (100) $[M-H]^-$.

N-(5-Methylthiazol-2-yl)-4-(4-nitrophenoxy)butanamide (**130**). General Procedure A was followed using **129** (440 mg, 1.95 mmol) and 5-methyl-2-aminothiazole (223 mg, 1.95 mmol) to obtain **130** as a white solid (431 mg, 68%). ^{1}H NMR (300 MHz, d_6-Acetone): δ 8.23 (d, *J* 9.2 Hz, 2H), 7.15 (d, *J* 9.2 Hz, 2H), 7.06 (s, 1H), 4.29 (t, *J* 6.4 Hz, 2H), 2.74 - 2.72 (m, 2H), 2.38 (d, *J* 1.1 Hz, 3H), 2.33 - 2.17 (m, 2H). MS, m/z = 322 (100) $[M+H]^+$.

3-(Hydroxymethyl)phenol (**131**). Sodium borohydride (62 mg, 1.64 mmol) was slowly added to a stirred solution of 3-hydroxybenzaldehyde (200 mg, 1.64 mmol) in EtOH (20 mL). Ammonium carbonate (157 mg, 1.64 mmol) was then added and reaction stirred for a further 10 min. The reaction mixture was then filtered through Celite. The filtrate was then evaporated *in vacuo* to give **131** as a clear oil (200 mg, 98%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28 - 7.21 (m, 1H), 6.96 - 6.88 (m, 2H), 6.81 - 6.76 (m, 1H), 5.12 (s, 1H), 4.68 (d, *J* 5.1 Hz, 2H).

Ethyl 4-(3-(hydroxymethyl)phenoxy)butanoate (**132**). General Procedure B was followed **131** (203 mg, 1.64 mmol) and ethyl bromobutyrate (148 μL, 1.03 mmol) to obtain **132** as a clear oil (169 mg, 69%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 - 7.22 (m, 1H), 6.98 - 6.91 (m, 2H), 6.88 - 6.79 (m, 1H), 4.68 (d, *J* 5.9 Hz, 2H), 4.16 (q, *J* 7.0 Hz, 2H), 4.03 (t, *J* 6.1 Hz, 2H), 2.57 - 2.49 (m, 2H), 2.18 - 2.07 (m, 2H), 1.28 (t, *J* 7.2 Hz, 3H). MS, m/z = 261 (100) [M+Na].

4-(3-(Hydroxymethyl)phenoxy)butanoic acid (**133**). General Procedure C was followed using **132** (169 mg, 0.71 mmol) to obtain **133** as a white solid (129 mg, 87%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31 - 7.21 (m, 1H), 6.97 - 6.87 (m, 2H), 6.87 - 6.78 (m, 1H), 4.66 (s, 2H), 4.03 (t, *J* 6.1 Hz, 2H), 2.63 - 2.52 (m, 2H), 2.19 - 2.06 (m, 2H). MS, m/z = 209 (100) $[M-H]^-$.

Ethyl 4-(4-(hydroxymethyl)phenoxy)butanoate (**134**). General Procedure B was followed using 4-(hydroxymethyl)phenol (68 mg, 0.62 mmol) and ethyl bromobutyrate (89 µL, 0.62 mmol) to obtain **134** as a clear oil (74 mg, 50%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 - 7.24 (m, 2H), 6.92 - 6.84 (m, 2H), 4.60 (br s, 2H), 4.15 (q, *J* 7.3 Hz, 2H), 4.01 (t, *J* 6.2 Hz, 2H), 2.52 (t, *J* 7.3 Hz, 2H), 2.18 - 2.05 (m, 2H), 1.27 (t, *J* 7.2 Hz, 3H). MS, m/z = 261 (100) [M+Na].

4-(4-(Hydroxymethyl)phenoxy)butanoic acid (**135**). General Procedure C was followed using **134** (70 mg, 0.29 mmol) to obtain **135** as a white solid (58 mg, 94%). ^{1}H NMR (300 MHz, MeOD): δ 7.31 - 7.20 (m, 2H), 6.96 - 6.86 (m, 2H), 4.53 (s, 1.5H), 4.45 (s, 0.5H), 4.06 – 3.96 (m, 2H), 2.50 (t, *J* 7.4 Hz, 2H), 2.14 – 1.98 (m, 2H). MS, m/z = 209 (100) $[M-H]^-$.

Methyl 3-(4-tert-butoxy-4-oxo-butoxy)benzoate (**136**). General Procedure B was followed using methyl 3-hydroxybenzoate (82 mg, 0.54 mmol) and *tert*-butyl 4-bromobutyrate (0.080 mL, 0.45 mmol) to obtain **136** as a clear oil (88 mg, 66%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (td, J = 1.2, 7.7 Hz, 1H), 7.55 (dd, *J* = 1.5, 2.4 Hz, 1H), 7.33 (t, *J* = 8.0 Hz, 1H), 7.09 (ddd, *J* = 1.0, 2.6, 8.3 Hz, 1H), 4.04 (t, *J* = 6.2 Hz, 2H), 3.91 (s, 3H), 2.44 (t, *J* = 7.37 Hz, 2H), 2.08 (quin, *J* = 6.71 Hz, 2H), 1.46 (s, 9H). MS, m/z = 239 (100) [M-*t*Bu].

4-(3-Methoxycarbonylphenoxy)butanoic acid (**137**). **136** (88 mg, 0.30 mmol) was dissolved in 4M HCl in dioxane (5 mL) and stirred at 40°C for 4 h. The reaction mixture was then concentrated *in vacuo* to obtain **137** as a white solid (71 mg, 100%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.6 (td, *J* 1.2, 7.8 Hz, 1H), 7.55 (dd, *J* 1.5, 2.4 Hz, 1H), 7.34 (t, *J* 7.9 Hz, 1H), 7.09 (ddd, *J* 0.9, 2.7, 8.3 Hz, 1H), 4.08 (t, *J* 6.1 Hz, 2H), 3.92 (s, 3H), 2.61 (t, *J* 7.3 Hz, 2H), 2.15 (quin, *J* 6.6 Hz, 2H). MS, m/z = 237 (100) $[M-H]^-$.

Methyl 4-(4-tert-butoxy-4-oxo-butoxy)benzoate (**138**). General Procedure B was followed using methyl 4-hydroxybenzoate (82 mg, 0.54 mmol) and *tert*-butyl 4-bromobutyrate (0.080 mL, 0.45 mmol) to obtain **138** as a clear oil (96 mg, 73%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05 – 7.88 (m, 2H), 6.97 - 6.86 (m, 2H), 4.06 (t, *J* 6.3 Hz, 2H), 3.89 (s, 3H), 2.44 (t, *J* 7.4 Hz, 2H), 2.09 (quin, *J* 6.7 Hz, 2H), 1.45 (s, 9H). MS, m/z = 239 (100) [M-*t*Bu].

4-(4-Methoxycarbonylphenoxy)butanoic acid (**139**). The procedure used for **137** was followed using **138** (96 mg, 0.33 mmol) to obtain **139** as a white solid (78 mg, 100%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.04 – 7.90 (m, 2H), 6.97 - 6.85 (m, 2H), 4.01 - 4.13 (m, 2H), 3.89 (s, 3H), 2.61 (t, *J* 7.2 Hz, 2H), 2.15 (quin, *J* 6.6 Hz, 2H). MS, m/z = 237 (100) $[M-H]^-$.

Ethyl 4-(3-chloro-4-methylphenoxy)butanoate (**140**). General Procedure B was followed using 3-chloro-4-methylphenol (1.0 g, 7.01 mmol) and ethyl bromobutyrate (1.21 mL, 8.42 mmol) to obtain **140** as a clear oil (1.7 g, 96%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.16 - 7.07 (m, 1H), 6.91 (d, *J* 2.4 Hz, 1H), 6.72 (dd, *J* 8.5, 2.5 Hz, 1H), 4.17 (q, *J* 7.3 Hz, 2H), 3.99 (t, J 7.3 Hz, 2H), 2.50 (m, 2H), 2.31 (s, 3H), 2.19 – 2.03 (m, 2H), 1.28 (t, J 7.2 Hz ,3H). MS, m/z = 257 (100) $[M+H]^+$, 259 (30).

4-(3-Chloro-4-methylphenoxy)butanoic acid (**141**). General Procedure C was followed using **140** (1.70 g, 6.62 mmol) to obtain **141** as a white solid (1.42 g, 94%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.12 (dd, *J* 8.4, 0.44 Hz, 1H), 6.92 (d, *J* 2.6 Hz, 1H), 6.72 (dd, *J* 8.5, 2.75 Hz, 1H), 4.00 (t, *J* 6.1 Hz, 2H), 2.60 (t, *J* 7.3 Hz, 2H), 2.31 (s, 3H), 2.20 - 2.06 (m, 2H). MS, m/z = 226 (100) $[M-H]^-$.

Ethyl 4-(3,4-dichlorophenoxy)butanoate (**142**). General Procedure D was followed using 3,4-dichlorophenol (500 mg, 3.07 mmol) and ethyl bromobutyrate (598 mg, 3.07 mmol) to obtain **142** as a clear oil (645 mg, 76%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (d, *J* 8.9 Hz, 1H), 7.00 (d, *J* 2.9 Hz, 1H), 6.75 (dd, *J* 8.9 and 2.9 Hz, 1H), 4.16 (q, *J* 7.2 Hz, 2H), 3.99 (t, *J* 6.3 Hz, 2H), 2.51 (t, *J* 7.5 Hz, 2H), 2.16-2.07 (m, 2H), 1.27 (t, *J* 7.1 Hz, 3H).

4-(3,4-Dichlorophenoxy)butanoic acid (**143**). General Procedure C was followed using **142** (570 mg, 2.06 mmol) to obtain **143** as a solid (490 mg, 96%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 (d, *J* 9.0 Hz, 1H), 7.00 (d, *J* 2.7 Hz, 1H), 6.75 (dd, *J* 8.7 and 2.8 Hz, 1H), 4.01 (t, *J* 6.3 Hz, 2H), 2.60 (t, *J* 7.2 Hz, 2H), 2.17-2.10 (m, 2H).

Ethyl 4-(3-chloro-4-(trifluoromethyl)phenoxy)butanoate (**144**). General Procedure D was followed using 3-chloro-4-(trifluoromethyl)phenol (500 mg, 2.54 mmol) and ethyl bromobutyrate (329 μL, 2.54 mmol) to obtain **144** as a clear oil (470 mg, 60%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39 (d, *J* 8.7 Hz, 1H), 7.20 (d, *J* 3.0 Hz, 1H), 6.99 (dd, *J* 8.8 and 3.0 Hz, 1H), 4.17 (q, *J* 7.1 Hz, 2H), 4.04 (t, *J* 6.1 Hz, 2H), 2.53 (t, *J* 7.2 Hz, 2H), 2.19-2.11 (m, 2H), 1.28 (t, *J* 7.1 Hz, 3H).

4-(3-Chloro-4-(trifluoromethyl)phenoxy)butanoic acid (**145**). General Procedure C was followed using **144** (420 mg, 1.35 mmol) to obtain **145** as a solid (360 mg, 94%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39 (d, *J* 8.8 Hz, 1H), 7.21 (d, *J* 3.0 Hz, 1H), 6.98 (dd, *J* 9.0 and 3.0 Hz, 1H), 4.06 (t, *J* 6.3 Hz, 2H), 2.53 (t, *J* 7.2 Hz, 2H), 2.20-2.11 (m, 2H).

Ethyl 4-(3-chloro-4-cyanophenoxy)butanoate (**146**). General Procedure D was followed using 2-chloro-4-hydroxybenzonitrile (500 mg, 3.26 mmol) and ethyl bromobutyrate (420

μL, 3.26 mmol) to obtain **146** as a white solid (400 mg, 46%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58 (d, *J* 8.7 Hz, 1H), 7.02 (d, *J* 2.4 Hz, 1H), 6.87 (dd, *J* 8.8 and 2.4 Hz, 1H), 4.17 (q, *J* 7.1 Hz, 2H), 4.09 (t, *J* 6.2 Hz, 2H), 2.52 (t, *J* 7.3 Hz, 2H), 2.19-2.11 (m, 2H), 1.28 (t, *J* 7.1 Hz, 3H).

4-(3-Chloro-4-cyanophenoxy)butanoic acid (**147**). General Procedure C was followed using **146** (330 mg, 1.46 mmol) to obtain **147** as a solid (330 mg, 95%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58 (d, *J* 8.7 Hz, 1H), 7.02 (d, *J* 2.4 Hz, 1H), 6.86 (dd, *J* 8.7 and 2.4 Hz, 1H), 4.10 (t, *J* 6.1 Hz, 2H), 2.60 (t, *J* 7.2 Hz, 2H), 2.21-2.12 (m, 2H).

Ethyl 4-(3,5-difluorophenoxy)butanoate (**148**). General Procedure B was followed using 3,5-difluorophenol (100 mg, 0.77 mmol) and ethyl bromobutyrate (111 μL, 0.77 mmol) to obtain **148** as a white solid (148 mg, 79%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.50 - 6.29 (m, 3H), 4.16 (q, *J* 7.1 Hz, 2H), 3.98 (t, *J* 6.2 Hz, 2H), 2.57 - 2.43 (m, 2H), 2.18 - 2.03 (m, 2H), 1.32 - 1.18 (m, 3H). MS, m/z = 245 (100) $[M+H]^+$.

4-(3,5-Difluorophenoxy)butanoic acid (**149**). General Procedure C was followed using **148** (125 mg, 0.52 mmol) to obtain **149** as a white solid (110 mg, 99%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.52 - 6.30 (m, 3H), 4.00 (t, *J* 6.1 Hz, 2H), 2.59 (t, *J* 7.2 Hz, 2H), 2.21 - 2.07 (m, 2H). MS, m/z = 215 (100) $[M-H]^-$.

Ethyl 4-(3,5-dichlorophenoxy)butanoate (**150**). General Procedure B was followed using 3,5-dichlorophenol (125 mg, 0.77 mmol) and ethyl bromobutyrate (111 μL, 0.77 mmol) to obtain **150** as a white solid (165 mg, 77%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.97 - 6.90 (m,

1H), 6.79 (d, *J* 1.8 Hz, 2H), 4.16 (q, *J* 7.3 Hz, 2H), 3.99 (t, *J* 6.2 Hz, 2H), 2.55 - 2.41 (m, 2H), 2.16 - 2.03 (m, 2H), 1.27 (t, *J* 7.2 Hz, 3H). MS, m/z = 277 (100) $[M+H]^+$, 279 (60).

4-(3,5-Dichlorophenoxy)butanoic acid (**151**). General Procedure C was followed using **150** (165 mg, 0.60 mmol) to obtain **151** as a white solid (145 mg, 98%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.96 (q, *J* 2.2 Hz, 1H), 6.85 - 6.72 (m, 2H), 4.01 (t, *J* 5.9 Hz, 2H), 2.59 (t, *J* 7.0 Hz, 2H), 2.13 (quin, *J* 6.6 Hz, 2H). MS, m/z = 247 (100) $[M-H]^-$, 249 (60).

Ethyl 4-(3-chloro-5-methyl-phenoxy)butanoate (**152**). General Procedure B was followed using 3-chloro-5-methyl-phenol (110 mg, 0.77 mmol) and ethyl bromobutyrate (111 µL, 0.77 mmol) to obtain **152** as a white solid (142 mg, 72%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.76 (s, 1H), 6.70 (t, *J* 2.1 Hz, 1H), 6.64 - 6.55 (m, 1H), 4.16 (q, *J* 7.2 Hz, 2H), 3.98 (t, *J* 6.2 Hz, 2H), 2.50 (t, *J* 7.3 Hz, 2H), 2.16 - 2.02 (m, 2H), 1.27 (t, *J* 7.2 Hz, 3H). MS, m/z = 257 (100) $[M+H]^+$, 259 (30).

4-(3-Chloro-5-methylphenoxy)butanoic acid (**153**). General Procedure C was followed using **152** (142 mg, 0.55 mmol) to obtain **153** as a white solid (125 mg, 98%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.80 - 6.75 (m, 1H), 6.75 - 6.68 (m, 1H), 6.63 - 6.57 (m, 1H), 3.99 (t, *J* 6.1 Hz, 2H), 2.59 (t, *J* 7.3 Hz, 2H), 2.30 (d, *J* 0.4 Hz, 3H), 2.20 – 1.97 (m, 2H). MS, m/z = 227 (100) $[M-H]^-$.

tert-Butyl 4-(3,5-dicyanophenoxy)butanoate (**154**). General Procedure B was followed using 5-hydroxybenzene-1,3-dicarbonitrile (111 mg, 0.77 mmol) and *tert*-butyl 4-bromobutanoate (172 µL, 0.77 mmol) to obtain **154** as a white solid (92 mg, 42%). ^{1}H NMR

(300 MHz, $CDCl_3$): δ 7.51 (t, *J* 1.4 Hz, 1H), 7.37 (d, *J* 1.3 Hz, 2H), 4.07 (t, *J* 6.3 Hz, 2H), 2.43 (t, *J* 7.2 Hz, 2H), 2.10 (quin, *J* 6.7 Hz, 2H), 1.50 - 1.41 (m, 9H). MS, m/z = 287 (100) $[M+H]^+$.

4-(3,5-Dicyanophenoxy)butanoic acid (**155**). **154** was dissolved in 4N HCl in dioxane (5 mL) and stirred for 3 h at 20°C. The reaction mixture was then concentrated *in vacuo* to obtain **155** as a white solid (74 mg, 100%). ^1H NMR (300 MHz, $CDCl_3$): δ 7.52 (s, 1H), 7.37 (d, *J* 1.1 Hz, 2H), 4.17 - 4.04 (m, 2H), 2.67 - 2.52 (m, 2H), 2.24 - 2.03 (m, 2H). MS, m/z = 231 (100)

Ethyl 4-(3,5-dimethylphenoxy)butanoate (**156**). General Procedure B was followed using 3,5-dimethylphenol (94 mg, 0.77 mmol) and ethyl bromobutyrate (111 μL, 0.77 mmol) to obtain **156** as a white solid (121 mg, 67%). ^1H NMR (300 MHz, $CDCl_3$): δ 6.65 – 6.60 (m, 1H), 6.54 (s, 2H), 4.16 (q, *J* 7.2 Hz, 2H), 3.99 (t, *J* 6.2Hz, 2H), 2.52 (t, *J* 7.4 Hz, 2H), 2.30 (s, 6H), 2.17 - 2.03 (m, 2H), 1.28 (t, *J* 7.2 Hz, 3H). MS, m/z = 237 (100) $[M+H]^+$.

4-(3,5-Dimethylphenoxy)butanoic acid (**157**). General Procedure C was followed using **156** (121 mg, 0.51 mmol) to obtain **157** as a white solid (87 mg, 82%). ^1H NMR (300 MHz, $CDCl_3$): δ 6.64 - 6.59 (m, 1H), 6.57 - 6.51 (m, 2H), 4.01 (t, *J* 6.1 Hz, 2H), 2.60 (t, *J* 7.4 Hz, 2H), 2.30 (d, *J* 0.4 Hz, 6H), 2.21 - 2.03 (m, 2H). MS, m/z = 207 (100) $[M-H]^-$.

5-Isopropylthiazol-2-amine (**158**). To a stirred mixture of 3-methylbutanal (2.5 g, 29 mmol) in Et_2O/dioxane (25 mL, 0.10 mL) at -5°C was added bromine (1.64 mL, 32 mmol) over 2 h. After sustaining the bromine color (1 h), it was neutralised with a saturated aqueous solution of $NaHCO_3$ (15 mL). The organic layer was then separated and successively washed with water (2 x 20 mL), brine (2 x 20 mL), dried with Na_2SO_4 and concentrated *in vacuo* to

obtain a crude residue. The crude material was then added directly to a stirred solution of thiourea (2.21 g, 29 mmol) in THF (30 mL) and heated at reflux for 16 h. The reaction was then cooled to 20°C and quenched with saturated aqueous solution of $NaHCO_3$ (15 mL). The THF was evaporated *in vacuo* and then the residue was dissolved in EtOAc (35 mL). The organic layer was successively washed with water (2 x 20 mL), brine (2 x 20 mL), dried with Na_2SO_4 and concentrated *in vacuo* to obtain a crude residue. The crude residue was then purified by column chromatography gradient eluting with 100% CyHex to 60% EtOAc to obtain **158** as an oil (1.47 g, 36%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.73 (d, *J* 1.1 Hz, 1H), 3.00 (td, *J* 6.8, 1.10 Hz, 1H), 1.27 (d, *J* 6.8 Hz, 6H). MS, m/z = 143 (100) $[M+H]^+$.

5-(*tert*-Butyl)thiazol-2-amine (**159**). Pyrrolidine (360 µL, 4.39 mmol) and *p*-toluenesulfonic acid monohydrate (760 mg, 3.99 mmol) were added to a stirred solution of 3,3-dimethylbutanal (0.50 mL, 4.0 mmol) and 4 Å sieves in cyclohexane (7 mL). The reaction was then heated at reflux for 4 h. The reaction was then filtered, and cyclohexane removed *in vacuo*. The crude residue was then dissolved in MeOH (4 mL) and cooled to -5°C. Sulfur (128 mg, 4.0 mmol) and a solution of cyanamide (1.7 mg, 4.0 mmol) in MeOH (1 mL) was then added and the reaction was allowed to stir at 20°C for 12 h. After concentration *in vacuo* the crude residue was then purified by column chromatography gradient eluting with 100% CyHex to 60% EtOAc to obtain **159** as a solid (124 mg, 20%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.73 (s, 1H), 1.33 (s, 9H). MS, m/z = 157 (100) $[M+H]^+$.

5-Phenylthiazol-2-amine (**160**). The procedure used for **158** was followed using 2-phenylacetaldehyde (2.5 g, 21 mmol) to obtain **160** as a brown solid (734 mg, 20%). ^{1}H

NMR (300 MHz, $CDCl_3$): δ 7.45 - 7.42 (m, 2H), 7.39 -7.36 (m, 2H), 7.31 (s, 1H), 7.28 - 7.27 (m, 1H). MS, m/z = 177 (100) $[M+H]^+$.

Ethyl 2-(4-phenoxybutanoylamino)thiazole-5-carboxylate (**161**). General Procedure A was followed using 4-phenoxybutyric acid (390 mg, 2.16 mmol) and ethyl 2-aminothiazole-5-carboxylate (447 mg, 2.60 mmol) to obtain **161** (138 mg, 19%) as a white solid. ^1H NMR (300 MHz, $CDCl_3$): δ 8.16 (s, 1H), 7.31 – 7.21 (m, 2H), 6.98 - 6.84 (m, 3H), 4.36 (q, *J* = 7.0 Hz, 2H), 4.09 (t, *J* 5.7 Hz, 2H), 2.80 (t, *J* 7.0 Hz, 2H), 2.36 - 2.20 (m, 2H), 1.37 (t, *J* 7.2 Hz, 3H). MS, m/z = 335 (100) $[M+H]^+$.

2-Aminothiazole-5-carboxamide (**162**). 2-Aminothiazole-5-carbonitrile (50 mg, 0.40 mmol) was stirred in sulfuric acid (0.85 mL, 16 mmol) at 20°C for 1 h. The reaction mixture was then basified to pH 8 with saturated $NaHCO_3$ solution and extracted with EtOAc (30 mL). The organic layer was then successively washed with water (20 mL), brine (20 mL), dried with Na_2SO_4 and concentrated *in vacuo* to obtain **162** (29 mg, 51%) as a white solid. ^1H NMR (300 MHz, $CDCl_3$): δ 7.63 (s, 1H), 7.36 (s, 1H), 5.51 (br s, 2H). MS, m/z = 144 (100) $[M+H]^+$.

***tert*-Butyl 2-(4-chloro-3-methylphenoxy)acetate** (**163**). General Procedure B was followed using 4-chloro-3-methylphenol (146 μL, 1.03 mmol) and *tert*-butyl bromoacetate (152 μL, 1.03 mmol) to obtain **163** as a clear oil (223 mg, 85%). ^1H NMR (300 MHz, $CDCl_3$): δ 7.24 (d, *J* 8.8 Hz, 1H), 6.80 (d, *J* 2.9 Hz, 1H), 6.68 (dd, *J* 8.7, 3.0 Hz, 1H), 4.49 (s, 2H), 2.35 (s, 3H), 1.50 (s, 9H). MS, m/z = 279 (100) [M+Na].

2-(4-Chloro-3-methylphenoxy)acetic acid (**164**). **163** (223 mg, 0.87 mmol) was dissolved in 4N HCl in dioxane (5 mL) and stirred for 5 h at 20°C. The reaction mixture was then concentrated *in vacuo* to obtain **164** as a white solid (174 mg, 100%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25 (s, 1H), 6.84 (d, *J* 2.6 Hz, 1H), 6.72 (d, *J* 8.4 Hz, 1H), 4.67 (s, 2H), 2.37 (s, 3H). MS, m/z = 199 (100) $[M-H]^-$, 201 (30).

***tert*-Butyl 5-(4-chloro-3-methyl-phenoxy)pentanoate** (**165**). General Procedure B was followed using 4-chloro-3-methyl-phenol (72 mg, 0.51 mmol) and *tert*-butyl 5-bromopentanoate (120 mg, 0.51 mmol) to obtain **165** as a clear oil (115 mg, 76%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25 - 7.17 (m, 1H), 6.77 (d, *J* 2.9 Hz, 1H), 6.66 (dd, *J* = 3.0, 8.7 Hz, 1H), 3.96 - 3.90 (m, 2H), 2.40 - 2.24 (m, 5H), 1.88 - 1.67 (m, 4H), 1.46 (s, 9H). MS, m/z = (100) 243 [M-*t*Bu].

5-(4-Chloro-3-methyl-phenoxy)pentanoic acid (**166**). The procedure used for **137** was followed using **165** (115 mg, 0.38 mmol) to obtain **166** as a white solid (93 mg, 100%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21 (d, *J* 8.6 Hz, 1H), 6.77 (d, *J* 2.4 Hz, 1H), 6.71 - 6.62 (m, 1H), 4.03 – 3.88 (m, 2H), 2.52 – 2.41 (m, 2H), 2.34 (s, 3H), 1.96 – 1.76 (m, 4H). MS, m/z = 241 (100) $[M-H]^-$.

***tert*-Butyl phenylcarbamate** (**167**). Aniline (290 μL, 3.20 mmol) and Boc anhydride (703 mg, 3.20 mmol) were dissolved in DCM (10 mL) and stirred at 20°C for 5 d. The organic layer was then washed successively with 1M HCl (10 mL), a saturated solution of $NaHCO_3$ (10 mL), water (10 mL) and brine (10 mL). The organic layer was dried with Na_2SO_4 and concentrated *in vacuo* to obtain **167** as an off white solid (597 mg, 96%). ^{1}H NMR (300

MHz, $CDCl_3$): δ 7.43 - 7.29 (m, 4H), 7.09 - 7.02 (m, 1H), 6.47 (br s, 1H), 1.54 (s, 9H). MS, m/z = 290 (100) [M-*t*Bu].

Ethyl 4-((*tert*-butoxycarbonyl)(phenyl)amino)butanoate (**168**). General Procedure D was followed using **167** (140 mg, 0.72 mmol) and ethyl bromobutyrate (136 μL, 0.94 mmol) to obtain **168** as a white solid (11 mg, 5%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39 - 7.29 (m, 2H), 7.25 - 7.15 (m, 3H), 4.12 (q, *J* 7.0 Hz, 2H), 3.74 - 3.65 (m, 2H), 2.34 (t, *J* 7.5 Hz, 2H), 1.89 (quin, *J* 7.4 Hz, 2H), 1.44 (s, 9H), 1.28 - 1.21 (m, 3H). MS, m/z = 330 (100) [M+Na].

4-((*tert*-Butoxycarbonyl)(phenyl)amino)butanoic acid (**169**). General Procedure C was followed using **168** (11 mg, 0.036 mmol) to obtain **169** as a clear oil (8.0 mg, 80%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41 - 7.31 (m, 2H), 7.25 - 7.15 (m, 3H), 3.77 - 3.66 (m, 2H), 2.41 (t, *J* 7.4 Hz, 2H), 1.88 (quin, *J* 7.3 Hz, 2H), 1.44 (s, 9H). MS, m/z = 278 (100) $[M-H]^-$.

***tert*-Butyl (4-((5-methylthiazol-2-yl)amino)-4-oxobutyl)(phenyl)carbamate** (**170**). General Procedure A was followed using **169** (6.0 mg, 0.022 mmol) and 5-methyl-2-aminothiazole (2.5 mg, 0.022 mmol) to obtain **170** as a white solid (5.5 mg, 59%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39 - 7.31 (m, 2H), 7.26 - 7.13 (m, 3H), 7.09 (d, *J* 1.1 Hz, 1H), 3.78 (t, *J* 6.8 Hz, 2H), 2.56 (t, *J* 7.3 Hz, 2H), 2.42 (d, *J* 1.1 Hz, 3H), 2.00 (quin, *J* 7.0 Hz, 2H). MS, m/z = 376 (100) $[M+H]^+$.

Ethyl 4-(methyl(phenyl)amino)butanoate (**171**). General Procedure B was followed using *N*-methylaniline (166 μL, 1.54 mmol) and ethyl bromobutyrate (148 μL, 1.00 mmol) to obtain **171** as a clear oil (169 mg, 75%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 - 7.19 (m, 2H),

6.83 - 6.68 (m, 3H), 4.18 (q, *J* 7.1 Hz, 2H), 3.46 - 3.34 (m, 2H), 2.97 (s, 3H), 2.47 - 2.32 (m, 2H), 2.04 – 1.87 (m, 2H), 1.30 (t, *J* 7.0 Hz, 3H). MS, m/z = 225 (100) $[M+H]^+$.

4-(Methyl(phenyl)amino)butanoic acid (**172**). General Procedure C was followed using **171** (169 mg, 0.76 mmol) to obtain **172** as a clear oil (144 mg, 98%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 – 7.27 (m, 2H), 6.82 - 6.70 (m, 3H), 3.48 - 3.33 (m, 2H), 2.96 (s, 3H), 2.45 (t, *J* 7.2 Hz, 2H), 1.96 (quin, *J* 7.3 Hz, 2H). MS, m/z = 194 (100) $[M+H]^+$.

Ethyl 4-(4-chloro-3-methylphenoxy)butanoate (**173**). General Procedure D was followed using 4-chloro-3-methylphenol (2.5 g, 17.4 mmol) and ethyl bromobutyrate (3.75 g, 19.4 mmol) to obtain **173** as an oil (2.9 g, 65%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22 (d, *J* 8.7 Hz, 1H), 6.79-6.77 (m, 1H), 6.69-6.65 (m, 1H), 4.23-4.12 (m, 2H), 4.04-3.96 (m, 2H), 2.57 (m, 2H), 2.35 (s, 3H), 2.16-2.09 (m, 2H), 1.33-1.25 (m, 3H).

N-(5-Isopropylpyridin-2-yl)-4-phenoxybutanamide (**174**). To a solution of *N*,*N*-diisopropylamine (487 μL, 3.5 mmol) in anhydrous THF (6 mL) at -78°C was added 1.4 M BuLi in hexanes (2.2 mL, 3.1 mmol) dropwise under N_2 atmosphere. The reaction was then warmed to 0°C, stirred for 30 min and then cooled to -78°C again. **173** (638 mg, 2.49 mmol) in THF (6 mL) was then added dropwise and the reaction stirred at this temperature for 45 min. Iodomethane (464 μL, 7.46 mmol) was then added in one portion and the solution warmed to 20°C and stirred for 16 h. The solution was then quenched with a saturated NH_4Cl aqueous solution (10 mL), diluted with water (30 mL) and extracted with Et_2O (3 × 25 mL). The organic extracts were combined and washed with brine (20 mL), dried with Na_2SO_4 and evaporated *in vacuo*. The crude residue was then purified by column

chromatography gradient eluting with 100% CyHex to 5% EtOAc/CyHex to obtain **174** as a clear oil (45 mg, 7%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22 (d, *J* 8.6 Hz, 1H), 6.77 (d, *J* 3.1 Hz, 1H), 6.67 (dd, *J* 8.5, 3.2 Hz, 1H), 4.22 - 4.09 (m, 2H), 4.04 – 3.90 (m, 2H), 2.79 - 2.63 (m, 1H), 2.35 (s, 3H), 2.19 (ddt, *J* 14.2, 8.0, 6.2, 6.2 Hz, 1H), 1.88 (dq, *J* 14.0, 6.2 Hz, 1H), 1.33 – 1.19 (m, 6H). MS, m/z = 271 (100) $[M+H]^+$.

4-(4-Chloro-3-methylphenoxy)-2-methylbutanoic acid (**175**). General Procedure C was followed using **174** (45 mg, 0.67 mmol) to obtain **175** as a clear oil (36 mg, 89%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22 (d, *J* 8.8 Hz, 1H), 6.81 - 6.75 (m, 1H), 6.71 - 6.64 (m, 1H), 4.01 (t, *J* 6.2 Hz, 2H), 2.86 - 2.73 (m, 1H), 2.35 (s, 3H), 2.22 (ddt, *J* 14.2, 8.0, 6.1, 6.1 Hz, 1H), 1.92 (dq, *J* 14.2, 6.1 Hz, 1H), 1.30 (d, *J* 7.0 Hz, 3H). MS, m/z = 241 (100) $[M-H]^-$.

4-(2-Bromoethoxy)-1-chloro-2-methylbenzene (**176**). 1,2-Dibromoethane (3.6 mL, 42 mmol), K_2CO_3 (1.5 g, 11 mmol), and 4-chloro-3-methyl-phenol (600 mg, 4.2 mmol) were dissolved in DMF (8 mL) and heated at 100°C for 8 d under a N_2 atmosphere. The reaction was then filtered through Celite and the filtrate concentrated *in vacuo*. The crude residue was then purified by column chromatography gradient eluting with 100% CyHex to 5% EtOAc/CyHex to obtain **176** as a clear oil (200 mg, 19%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25 (d, *J* 8.80 Hz, 1H), 6.85 - 6.78 (m, 1H), 6.76 - 6.65 (m, 1H), 4.27 (t, *J* 6.2 Hz, 2H), 3.64 (t, *J* 6.2 Hz, 2H), 2.37 (s, 3H).

Ethyl 4-(4-chloro-3-methylphenoxy)-2,2-dimethylbutanoate (**177**). LiHMDS (1.7 mL, 1.70 mmol) was added to a solution of dry THF (3 mL) and cooled to -78°C under a N_2 atmosphere. To this stirred solution was added DMPU (373 μL, 3.10 mmol) followed by

ethyl isobutyrate (104 μL, 0.77 mmol). The solution was warmed to -5°C and stirred at this temperature for 2 h. **176** (200 mg, 0.80 mmol) was then added and reaction stirred at 0°C for 4 h. The reaction mixture was then diluted with EtOAc (35 mL) and successively washed with 1M HCl (20 mL) and brine (20 mL). The organic layer was dried with Na_2SO_4 and evaporated *in vacuo*. The crude residue was then purified by column chromatography gradient eluting with 100% CyHex to 7% EtOAc/CyHex to obtain **177** as a clear oil (24 mg, 11%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22 (d, *J* 8.8 Hz, 1H), 6.75 (d, *J* 2.6 Hz, 1H), 6.68 - 6.62 (m, 1H), 4.15 (q, *J* 7.2 Hz, 2H), 3.98 (t, *J* 6.9 Hz, 2H), 2.35 (s, 3H), 2.06 (t, *J* 6.8 Hz, 2H), 1.30 - 1.23 (m, 9H). MS, m/z = 285 (100) $[M+H]^+$, 287 (30).

4-(4-Chloro-3-methylphenoxy)-2,2-dimethylbutanoic acid (**178**). General Procedure C was followed using **177** (24 mg, 0.080 mmol) to obtain **178** as a clear oil (19 mg, 89%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25 - 7.16 (m, 1H), 6.75 (d, *J* 2.9 Hz, 1H), 6.64 (dd, *J* 8.7, 2.8 Hz, 1H), 4.01 (q, *J* 6.9 Hz, 2H), 2.33 (s, 3H), 2.16 - 2.05 (m, 2H), 1.35 - 1.27 (m, 6H). MS, m/z = 255 (100) $[M-H]^-$, 257 (30).

Phenyl (5-methylthiazol-2-yl)carbamate (**179**). 5-Methyl-2-aminothiazole (1.5 g, 13 mmol) was dissolved in pyridine (8 mL) and cooled to 0°C under a N_2 atmosphere. Phenyl chloroformate (3.6 mL, 29 mmol) was then added dropwise and reaction stirred for 5 h at this temperature. The reaction was then quenched with water (10 mL) and the resulting precipitate filtered off. The crude solid was then purified by column chromatography gradient eluting with 100% DCM to obtain **179** as a white solid (590 mg, 19%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48 - 7.36 (m, 2H), 7.31 - 7.26 (m, 2H), 7.24 - 7.22 (m, 1H), 7.10 (d, *J* 1.3 Hz, 1H), 2.37 (d, *J* 1.1 Hz, 3H). MS, m/z = 235 $[M+H]^+$.

2-(4-Chloro-3-methylphenoxy)ethanamine (**180**). 4-Chloro-3-methylphenol (100 mg, 0.45 mmol) and K_2CO_3 (185 mg, 1.34 mmol) were dissolved in DMF (3 mL) and stirred for 10 min. *tert*-Butyl (2-bromoethyl)carbamate (64 mg, 0.45 mmol) was then added and reaction stirred at 100°C for 16 h. The solvent was then evaporated *in vacuo* and the crude residue dissolved in EtOAc (20 mL) which was successively washed with water (15 mL) and brine (15 mL). The organic layer was dried with Na_2SO_4 and concentrated *in vacuo*. The crude precipitate was then purified by column chromatography gradient eluting with 100% CyHex to 10% EtOAc/CyHex to obtain the Boc protected intermediate as a clear oil (109 mg, 86%). MS, m/z = 229 (100) [M-*t*Bu], 231 (30). The intermediate was then dissolved in a 1:3 mixture of TFA/DCM (4 mL) and stirred at 20°C for 1 h. The solvent was then evaporated *in vacuo* and the crude residue dissolved in EtOAc (10 mL) which was then successively washed with a 10% solution of $NaHCO_3$ (10 mL), water (10 mL) and brine (10 mL). The organic layer dried with Na_2SO_4 and concentrated *in vacuo* to obtain **180** as a clear oil (78 mg, 96%). MS, m/z = 186 (100) $[M+H]^+$, 188 (30). ^1H NMR (300 MHz, d_6-Acetone): δ 7.28 - 7.23 (m, 1H), 6.93 (d, *J* 2.64 Hz, 1H), 6.80 (dd, *J* 8.69, 2.97 Hz, 1H), 4.18 (t, *J* 6.05 Hz, 1H), 3.59 - 3.52 (m, 2H), 2.34 - 2.31 (m, 3H). MS, m/z = 186 (100) $[M+H]^+$, 188 (30).

***tert*-Butyl (5-methylthiazol-2-yl)carbamate** (**181**). 5-Methyl-2-aminothiazole (500 mg, 0.18 mmol) was dissolved in DCM (20 mL) and cooled to 0°C under a N_2 atmosphere. Boc anhydride (1.70 g, 7.77 mmol) was then added portion wise to the reaction which was warmed to 20°C and stirred for 16 h. The organic layer was then washed successively with water (20 mL) and brine (20 mL). The organic layer was then dried with Na_2SO_4 and

concentrated *in vacuo*. The crude material was then purified by column chromatography gradient eluting with 100% CyHex to 10% EtOAc/CyHex to obtain **181** as a white powder (363 mg, 39%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.11 (d, *J* 1.5 Hz, 1H), 2.46 (d, *J* 1.3 Hz, 3H), 1.57 (s, 9H).

***tert*-Butyl (4-bromobutyl)(5-methylthiazol-2-yl)carbamate** (**182**). General Procedure D was followed using **181** (360 mg, 1.68 mmol) and 1,4-dibromobutane (401 μL, 3.36 mmol) to obtain **182** as a clear oil (49 mg, 8%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.98 - 7.12 (m, 1H), 4.10 (t, *J* 6.9 Hz, 2H), 3.39 - 3.51 (m, 2H), 2.37 (d, *J* 1.3 Hz, 3H), 1.78 - 2.02 (m, 4H), 1.60 (s, 9H). MS, m/z = 294 (100) [M-*t*Bu].

***tert*-Butyl (4-(4-chloro-3-methylphenoxy)butyl)(5-methylthiazol-2-yl)carbamate** (**183**). General procedure D was followed using **182** (22 mg, 0.063 mmol) and 4-chloro-3-methylphenol (12 mg, 0.082 mmol) to give **183** as a clear oil (12 mg, 48%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21 (d, *J* 8.8 Hz, 1H), 6.77 (d, *J* 2.6 Hz, 1H), 6.70 (dd, *J* 8.7, 3.0 Hz, 1H), 4.15 (t, *J* 6.8 Hz, 2H), 3.99 - 3.92 (m, 2H), 2.40 - 2.30 (m, 6H), 1.95 - 1.75 (m, 4H), 1.58 (s, 9H). MS, m/z = 355 (100) [M-*t*Bu], 357 (30).

***tert*-Butyl N-(3-phenoxypropyl)carbamate** (**184**). General procedure B was followed using *tert*-butyl N-(3-bromopropyl)carbamate (110 mg, 0.46 mmol) and phenol (65 mg, 0.69 mmol) to give **184** as a clear oil (63 mg, 35%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 - 7.25 (m, 2H), 6.99 - 6.88 (m, 3H), 4.79 (br s, 1H), 3.34 (q, *J* = 6.4 Hz, 2H), 1.99 (quin, *J* = 6.3 Hz, 2H), 1.45 (s, 9H). MS, m/z = 152 (100) $[M\text{-}99]^+$.

3-Phenoxypropan-1-amine (**185**). The procedure used for **78** was followed using **184** (63 mg, 0.25 mmol) to obtain **185** as a white solid (33 mg, 87%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31 - 7.23 (m, 2H), 7.00 – 6.92 (m, 1H), 6.91 – 6.83 (m, 2H), 4.05 (t, *J* 5.8 Hz, 2H), 3.15 (t, *J* 6.9 Hz, 2H), 2.25 – 1.90 (m, 2H). MS, m/z = 152 (100) $[M+H]^+$.

***tert*-Butyl 4-((4-chloropyridin-2-yl)oxy)butanoate** (**186**). General Procedure B was followed using 4-chloro-2-hydroxypyridine (87 mg, 0.67 mmol) and *tert*-butyl 4-bromobutyrate (119 μL, 0.67 mmol) to obtain **186** as a clear oil (44 mg, 24%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.03 (dd, *J* 5.5, 0.4 Hz, 1H), 6.86 (dd, *J* 5.5, 1.76 Hz, 1H), 6.7 (dd, *J* 1.76, 0.4 Hz, 1H), 4.32 (t, *J* 6.4 Hz, 2H), 2.44 - 2.31 (m, 2H), 2.12 – 1.96 (m, 2H), 1.44 (m, 9H). MS, m/z = 272 (100) $[M+H]^+$, 274 (30).

4-((4-Chloropyridin-2-yl)oxy)butanoic acid hydrochloride (**187**). The procedure used for **186** was followed using **186** (44 mg, 0.16 mmol) to obtain **187** as a white solid (40 mg, 98%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.09 – 8.03 (m, 1H), 6.95 – 6.89 (m, 1H), 6.80 (d, *J* 5.9 Hz, 1H), 4.47 - 4.33 (m, 2H), 2.65 - 2.47 (m, 2H), 2.21 - 2.07 (m, 2H). MS, m/z = 216 (100) $[M+H]^+$, 218 (30).

***tert*-Butyl 4-((6-chloropyridin-2-yl)oxy)butanoate** (**188**). General Procedure B was followed using 2-chloro-6-hydroxypyridine (87 mg, 0.67 mmol) and *tert*-butyl 4-bromobutyrate (119 μL, 0.67 mmol) to obtain **188** as a clear oil (112 mg, 61%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50 (dd, *J* 8.1, 7.5 Hz, 1H), 6.88 (dd, *J* 7.5, 0.7 Hz, 1H), 6.63 (dd, *J* 8.1, 0.7 Hz, 1H), 4.32 (t, *J* 6.4 Hz, 2H), 2.44 - 2.33 (m, 2H), 2.12 – 1.99 (m, 2H), 1.45 (s, 9H). MS, m/z = 272 (100) $[M+H]^+$, 274 (30).

4-((6-Chloropyridin-2-yl)oxy)butanoic acid hydrochloride (**189**). The procedure used for **164** was followed using **188** (112 mg, 0.41 mmol) to obtain **189** as a white solid (99 mg, 95%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56 - 7.45 (m, 1H), 6.93 - 6.84 (m, 1H), 6.66 - 6.59 (m, 1H), 4.39 - 4.29 (m, 2H), 2.61 - 2.48 (m, 2H), 2.19 - 2.02 (m, 2H). MS, m/z = 216 (100) $[M+H]^+$, 218 (30).

***tert*-Butyl 4-((2-chloropyridin-4-yl)oxy)butanoate** (**190**). General Procedure B was followed using 2-chloro-4-hydroxypyridine (87 mg, 0.67 mmol) and *tert*-butyl 4-bromobutyrate (119 μL, 0.67 mmol) to obtain **190** as a clear oil (121 mg, 66%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.19 (d, *J* 5.7 Hz, 1H), 6.83 (d, *J* 2.2 Hz, 1H), 6.75 (dd, *J* 5.9, 2.20 Hz, 1H), 4.06 (t, *J* 6.3 Hz, 2H), 2.42 (t, *J* 7.3 Hz, 2H), 2.09 (quin, *J* 6.7 Hz, 2H), 1.46 (s, 9H). MS, m/z = 272 (100) $[M+H]^+$, 274 (30).

4-((2-Chloropyridin-4-yl)oxy)butanoic acid hydrochloride (**191**). The procedure used for **164** was followed using **190** (121 mg, 0.44 mmol) to obtain **191** as a white solid (110 mg, 98%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.27- 8.20 (m, 1H), 6.89 – 6.85 (s, 1H), 6.82 – 6.76 (m, 1H), 4.12 (q, *J* 6.0 Hz, 2H), 2.64 - 2.51 (m, 2H), 2.19 - 2.09 (m, 2H). MS, m/z = 216 (100) $[M+H]^+$, 218 (30).

***tert*-Butyl 4-((5-chloropyridin-3-yl)oxy)butanoate** (**192**). General Procedure B was followed using 5-chloropyridin-3-ol (87 mg, 0.67 mmol) and *tert*-butyl 4-bromobutyrate (119 μL, 0.67 mmol) to obtain **192** as a clear oil (119 mg, 65%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.19 (t, *J* 2.3 Hz, 2H), 7.21 (t, *J* 2.3 Hz, 1H), 4.05 (t, *J* 6.2 Hz, 2H), 2.48 - 2.39 (m, 2H), 2.15 - 2.04 (m, 2H), 1.46 (m, 9H). MS, m/z = 272 (100) $[M+H]^+$, 274 (30).

4-((5-Chloropyridin-3-yl)oxy)butanoic acid hydrochloride (**193**). The procedure used for **164** was followed using **192** (119 mg, 0.44 mmol) to obtain **193** as a white solid (110 mg, 100%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.33 – 8.21 (m, 2H), 7.49 (s, 1H), 4.19 - 4.09 (m, 2H), 2.59 (t, *J* 6.9 Hz, 2H), 2.25 – 2.13 (m, 2H). MS, m/z = 216 (100) $[M+H]^+$, 218 (30).

***tert*-Butyl 4-((4-(trifluoromethyl)pyridin-2-yl)oxy)butanoate** (**194**). General Procedure B was followed using 2-hydroxy-4-(trifluoromethyl)pyridine (110 mg, 0.67 mmol) and *tert*-butyl 4-bromobutyrate (119 μL, 0.67 mmol) to obtain **194** as a clear oil (41 mg, 20%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.36 - 8.24 (m, 1H), 7.10 - 7.02 (m, 1H), 7.01 - 6.94 (m, 1H), 4.39 (t, *J* 6.4 Hz, 2H), 2.46 – 2.36 (m, 2H), 2.17 – 2.02 (m, 2H), 1.46 (m, 9H). MS, m/z = 306 (100) $[M+H]^+$.

4-((4-(Trifluoromethyl)pyridin-2-yl)oxy)butanoic acid hydrochloride (**195**). The procedure used for **164** was followed using **194** (41 mg, 0.13 mmol) to obtain **195** as a white solid (38 mg, 100%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.56 (d, *J* 5.7 Hz, 1H), 7.20 (d, *J* 2.2 Hz, 1H), 7.00 – 6.95 (m, 1H), 4.17 (t, *J* 6.2 Hz, 2H), 2.62 (t, *J* 7.0 Hz, 2H), 2.27 - 2.12 (m, 2H). MS, m/z = 250 (100) $[M+H]^+$.

***tert*-Butyl 4-((6-(trifluoromethyl)pyridin-2-yl)oxy)butanoate** (**196**). General Procedure B was followed using 6-(trifluoromethyl)pyridin-2-ol (110 mg, 0.67 mmol) and *tert*-butyl 4-bromobutyrate (119 μL, 0.67 mmol) to obtain **196** as a clear oil (139 mg, 67%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.19 (d, *J* 5.7 Hz, 1H), 6.83 (d, *J* 2.2 Hz, 1H), 6.75 (dd, *J* 5.9, 2.2 Hz, 1H), 4.06 (t, *J* 6.3 Hz, 2H), 2.42 (t, *J* 7.3 Hz, 2H), 2.09 (quin, *J* 6.7 Hz, 2H), 1.46 (s, 9H). MS, m/z = 306 (100) $[M+H]^+$.

4-((6-(Trifluoromethyl)pyridin-2-yl)oxy)butanoic acid hydrochloride (**197**). The procedure used for **164** was followed using **196** (139 mg, 0.46 mmol) to obtain **197** as a white solid (129 mg, 99%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75 - 7.64 (m, 1H), 7.25 (d, *J* 7.3 Hz, 1H), 6.90 (d, *J* 8.6 Hz, 1H), 4.43 (t, *J* 6.2 Hz, 2H), 2.62 - 2.53 (m, 2H), 2.21 - 2.08 (m, 2H). MS, m/z = 250 (100) $[M+H]^+$.

***tert*-Butyl 4-((2-(trifluoromethyl)pyridin-4-yl)oxy)butanoate** (**198**). General Procedure B was followed using 2-(trifluoromethyl)pyridin-4-ol (110 mg, 0.67 mmol) and *tert*-butyl 4-bromobutyrate (119 μL, 0.67 mmol) to obtain **198** as a clear oil (135 mg, 66%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.52 (dd, *J* 5.7, 0.7 Hz, 1H), 7.18 (d, *J* 2.4 Hz, 1H), 6.95 (dd, *J* 5.7, 2.4 Hz, 1H), 4.11 (t, *J* 6.3 Hz, 2H), 2.43 (t, *J* 7.2 Hz, 2H), 2.10 (quin, *J* 6.7 Hz, 2H), 1.45 (s, 9H). MS, m/z = 306 (100) $[M+H]^+$.

4-((2-(Trifluoromethyl)pyridin-4-yl)oxy)butanoic acid hydrochloride (**199**). The procedure used for **164** was followed using **198** (135 mg, 0.44 mmol) to obtain **199** as a white solid (126 mg, 100%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.56 (d, *J* 5.7 Hz, 1H), 7.20 (d, *J* 2.2 Hz, 1H), 6.99 – 6.95 (m, 1H), 4.17 (t, *J* 6.2 Hz, 2H), 2.62 (t, *J* 7.0 Hz, 2H), 2.15 - 2.25 (m, 2H). MS, m/z = 250 (100) $[M+H]^+$.

***tert*-Butyl 4-((5-(trifluoromethyl)pyridin-3-yl)oxy)butanoate** (**200**). General Procedure B was followed using 5-(trifluoromethyl)pyridin-3-ol (73 mg, 0.45 mmol) and *tert*-butyl 4-bromobutyrate (80 μL, 0.45 mmol) to obtain **200** as a clear oil (60 mg, 44%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.51 - 8.44 (m, 2H), 7.40 - 7.34 (m, 1H), 4.11 (t, *J* 6.2 Hz, 2H), 2.45 (t, *J* 7.0 Hz, 2H), 2.21 - 2.02 (m, 2H), 1.46 (s, 9H). MS, m/z = 306 (100) $[M+H]^+$.

4-((5-(Trifluoromethyl)pyridin-3-yl)oxy)butanoic acid hydrochloride (**201**). The procedure used for **164** was followed using **200** (60 mg, 0.20 mmol) to obtain **201** as a white solid (63 mg, 100%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.69 – 8.44 (m, 2H), 7.60 - 7.46 (m, 1H), 4.33 - 4.10 (m, 3H), 2.61 (t, *J* 6.2 Hz, 2H), 2.27 - 2.11 (m, 2H). MS, m/z = 250 (100) $[M+H]^+$.

***tert*-Butyl 4-((4-cyanopyridin-2-yl)oxy)butanoate** (**202**). General Procedure B was followed using 2-hydroxyisonicotinonitrile (81 mg, 0.67 mmol) and *tert*-butyl 4-bromobutyrate (119 μL, 0.67 mmol) to obtain **202** as a clear oil (41 mg, 23%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.28 (dd, *J* 5.3, 0.9 Hz, 1H), 7.06 (dd, *J* 5.3, 1.3 Hz, 1H), 6.97 (t, *J* 1.1 Hz, 1H), 4.37 (t, *J* 6.4 Hz, 2H), 2.45 - 2.36 (m, 2H), 2.14 – 1.99 (m, 2H), 1.45 (s, 9H). MS, m/z = 263 (100) $[M+H]^+$.

4-((4-Cyanopyridin-2-yl)oxy)butanoic acid hydrochloride (**203**). The procedure used for **164** was followed using **202** (41 mg, 0.16 mmol) to obtain **203** as a clear oil (38 mg, 100%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.37 – 8.19 (m, 2H), 7.49 (s, 1H), 4.22 - 4.12 (m, 2H), 2.59 (t, *J* 6.9 Hz, 2H), 2.24 – 2.15 (m, 2H).

***tert*-Butyl 4-((5-cyanopyridin-3-yl)oxy)butanoate** (**204**). General Procedure B was followed using 5-hydroxypyridine-3-carbonitrile (65 mg, 0.54 mmol) and *tert*-butyl 4-bromobutyrate (95 μL, 0.54 mmol) to obtain **204** as a clear oil (100 mg, 71%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.50 - 8.37 (m, 2H), 7.39 (dd, *J* 2.9, 1.5 Hz, 1H), 4.07 (t, *J* 6.2 Hz, 2H), 2.41 (t, *J* 7.2 Hz, 2H), 2.15 - 2.01 (m, 2H), 1.43 (s, 9H). MS, m/z = 263 (100) $[M+H]^+$.

4-((5-Cyanopyridin-3-yl)oxy)butanoic acid hydrochloride (**205**). The procedure used for **164** was followed using **204** (100 mg, 0.38 mmol) to obtain **205** as a clear oil (93 mg, 100%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.57 - 8.47 (m, 2H), 7.45 (dd, *J* 2.9, 1.8 Hz, 1H), 4.15 (t, *J* 6.2 Hz, 2H), 2.61 (t, *J* 7.0 Hz, 2H), 2.11 - 2.28 (m, 2H). MS, m/z = 207 (100) $[M+H]^+$.

4-(4-Chloro-3-methylphenoxy)butanoic acid (**206**). General Procedure C was followed using **173** (2.8 g, 10.9 mmol) to obtain **206** as a white solid (2.4 g, 96%). ^{1}H NMR (300 MHz, d_6-DMSO): δ 7.29-7.21 (m, 2H), 6.78 (s, 1H), 6.70-6.65 (m, 1H), 4.02-3.97 (m, 2H), 2.62-2.56 (m, 2H), 2.17-2.08 (m, 2H).

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ABBREVIATIONS

AIDS	acquired immunodeficiency syndrome
BET	bromodomain and extra terminal domain
ART	antiretroviral therapy
CBG	click beetle green

CBR	click beetle red
CD4	cluster of differentiation 4
CL_{int}	intrinsic clearance
CMV	cytomegalovirus
GFP	green fluorescent protein
HDAC	histone deacetylase
HEK293	human embryonic kidney cells 293
HIV	human immunodeficiency virus
IRES	internal ribosome entry site
J.Lat	Jurkat T lymphocyte latency line
KO	knock out
LipE	lipophilic efficiency
LRA	latency reversing agent
LTR	long terminal repeat
Nef	nucleotide exchange factor
PBMC	peripheral blood mononuclear cells
PMA	phorbol 12-myristate 13-acetate
PSA	polar surface area
pTEFb	positive transcription elongation factor-b
Tat	trans-activator of transcription protein

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ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge on the ACS Publications website. Supporting Information pdf contains: Synthetic pathways for specific analogues; Schematic of the FlpIn HEK293 dual reporter cell lines; counterscreen activity data; compound dose response curves; in vitro metabolite data; target panel screening data. Molecular formula strings and biological data (CSV file).

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GRAPHICAL ABSTRACT