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Utilization of an active site mutant receptor for the identification of potent and selective atypical 5-HT_{2C} receptor agonists

Joseph Carpenter[a], Ying Wang [a*], Gang Wu[a], Jianxin Feng[a], Xiang-Yang Ye, Christian L. Morales[a], Matthias Broekema[a], Karen A. Rossi[a], Keith, J. Miller, Brian J. Murphy[a], Ginger Wu, Sarah E. Malmstrom, Anthony V. Azzara[a], Philip M. Sher, John M. Fevig, Andrew Alt, Robert L. Bertekap Jr. [a], Mary Jane Cullen, Timothy M. Harper, Kimberly Foster[a], Emily Luk[a], Qian Xiang[a], Mary F. Grubb[a], Jeffrey A. Robl, and Dean A. Wacker[a*]*

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KEYWORDS: Obesity, serotonin, 5-HT_{2C}, 5-HT_{2B}, 5-HT_{2A}, agonist, heterocycle, weight loss, safety, mutant receptor, allosteric

ABSTRACT: Agonism of the 5-HT_{2C} receptor represents one of the most well-studied and clinically-proven mechanisms for pharmacological weight reduction. Selectivity over the closely related 5-HT_{2A} and 5-HT_{2B} receptors is critical as their activation has been shown to lead to undesirable side-effects and major safety concerns. In this communication, we report the development of a new screening paradigm which utilizes an active site mutant D134A (D3.32) 5-HT_{2C} receptor to identify atypical agonist structures. We additionally report the discovery and optimization of a novel class of non-basic heterocyclic amide agonists of 5-HT_{2C}. SAR investigations around the screening hits provided a diverse set of potent agonists at 5-HT_{2C} with

high selectivity over the related 5-HT_{2A} and 5-HT_{2B} receptor subtypes. Further optimization through replacement of the amide with a variety of 5- and 6-membered heterocycles led to the identification of 6-(1-ethyl-3-(quinolin-8-yl)-1H-pyrazol-5-yl)pyridazin-3-amine (**69**). Oral administration of **69** to rats reduced food intake in an ad libitum feeding model, which could be completely reversed by a selective 5-HT_{2C} antagonist.

Introduction. The ever-increasing prevalence of obesity represents a great burden on global human health. As a major risk factor for type II diabetes, coronary heart disease, heart failure and stroke, obesity and its co-morbidities account for a growing number of worldwide deaths each year.[1-3] In 2014, it was estimated that 13% of the world's adult population were considered obese and 42 million children under the age of 5 were obese in 2013.[4] Conceptually, the prevention and treatment of obesity can be accomplished through diet and exercise, but unfortunately, many people are unable to attain significant and lasting reductions in body weight through these methods alone. Drug-based therapy may provide an opportunity for these patients to achieve clinically beneficial weight loss and concomitant reductions in incidence of associated co-morbidities.[5]

The neurotransmitter serotonin (5-hydroxytryptamine or 5-HT, Figure 1) is known to play a critical role in the regulation of numerous neurological functions including mood, sexual desire and function, appetite, sleep, memory, learning, and temperature regulation.[6, 7] There are 14 serotonin receptor subtypes, all of which are G protein-coupled receptors (GPCR) with the exception of the ligand-gated ion channel 5-HT_3. Serotonin's effects on appetite and feeding have been shown to be largely controlled through the expression and activation of the 5-HT_{2C} receptor. [8] Lorcaserin (Figure 1) elicits its response through activation of the 5-HT_{2C} receptor, which remains among the most well-studied and proven mechanisms for pharmacological weight

reductions.[9, 10] The 2012 FDA approval of lorcaserin was an important milestone for the treatment of obesity, as it represents the first regulatory approval of a weight loss drug in over a decade.

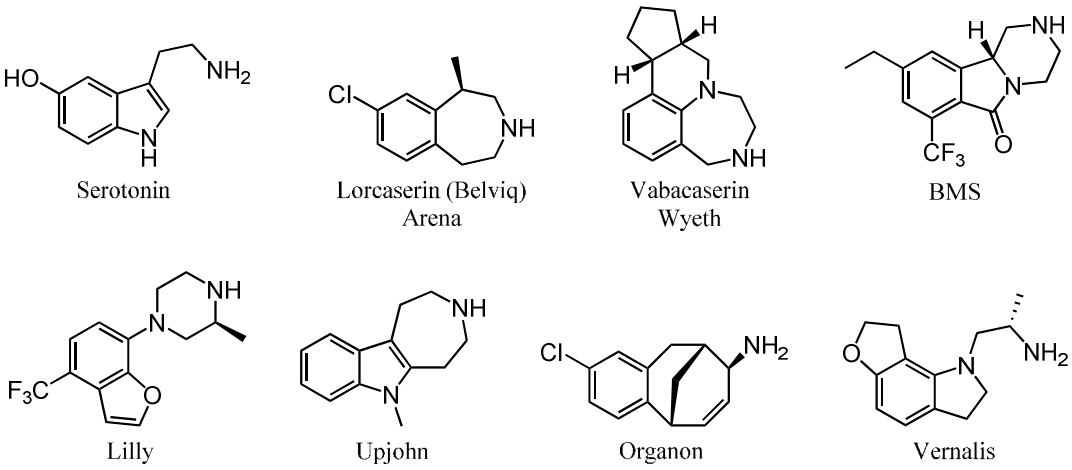


Figure 1. 5-HT_{2C} agonist structures.

Despite lorcaserin's approval, the search for highly selective 5-HT_{2C} agonists remains an attractive area of research, as agonism of the closely related 5-HT_{2A} and 5-HT_{2B} receptors can lead to hallucinations and potentially fatal fibrotic cardiac valvulopathy, respectively.[11-16] The discovery and development of novel agonist structures may enable greater efficacy with a differentiated safety and tolerability profile through better selectivity versus the 2A and 2B receptor subtypes. A major hindrance to developing selective agonists is the highly-conserved nature of the serotonin binding site across all receptor subtypes. Aromatic amino acids (Phe, Tyr, Trp) form what has been coined the aromatic box, which interact with the indole portion of serotonin while a conserved Asp residue serves to anchor the agonist through formation of a tight salt-bridge with serotonin's basic nitrogen.[17] It should not be surprising then, that typical 5-HT_{2C} agonists (Figure 1) consist of a hydrophobic aryl or heteroaryl ring system tethered to a basic nitrogen that is capable of mimicking the interactions observed with serotonin.[18-24] These

common structural features are typically considered indispensable for active site binding and receptor activation, and likely contribute to poor receptor subtype selectivity. In addition to the adverse events such as valvular hypertrophy and CNS-based events mentioned previously, the amphiphilic nature of these common structures has also been implicated in various off-target toxicities such as ion channel inhibition and phospholipidosis.[25-28]

Allosteric modulation of GPCR's is emerging as a promising new strategy for the identification of novel chemical entities for the treatment of a variety of central nervous system disorders.[29] In 2003, Dinh and coworkers reported on the discovery of a positive allosteric modulator (PAM) of 5-HT_{2C} which enhanced both the binding and functional potency of serotonin in several mammalian cell lines with no analogous effect on the related 2A and 2B receptors.[30] In principle, a positive allosteric modulator of 5-HT_{2C} could act to enhance the in vivo activity of endogenous serotonin which is known to be elevated in the fed state, and could lead to enhanced satiety, an overall reduction of food intake and concomitant weight reduction. Moreover, because allosteric compounds would not bind to the serotonin site, they would likely have a structure quite divergent from that of classical 5-HT_{2C} agonists. In turn, we reasoned that these atypical structures could provide an opportunity to not only obtain high selectivity over closely related serotonin subtypes, but also avoid common aforementioned toxicities associated with the typical 5-HT_{2C} pharmacophore.

Lead Identification. Given the possibilities presented by an allosteric modulator, we embarked on a journey to identify novel positive allosteric modulators of 5-HT_{2C}. In order to realize this outcome, we screened the BMS compound library in PAM mode using serotonin as the agonist. Unfortunately, no positive allosteric modulators were found, but we did identify nearly 50,000 compounds that exhibited 5-HT_{2C} agonism. Although our original goal of identifying a positive

allosteric modulator was not achieved, we were intrigued by the number of atypical structures that did not conform to the classic 5-HT_{2C} agonist pharmacophore. From this set of screening hits, we considered the possibility of identifying a completely unique series of compounds that could allow for a deviation from the known selectivity and toxicity concerns that plague the field. After eliminating all of the known 5-HT_{2C} agonists and any additional compounds with high structural similarity to known 5-HT_{2C} agonists (i.e., compounds that contained an aromatic ring with a 2-3 atom tether to a basic amine moiety), we were left with approximately 18,000 compounds that did not fit the typical basic amine containing pharmacophore. From this set, 68 unique high-potency compounds with differentiated chemical structures were chosen for purification and retesting. To our disappointment, none of the compounds retained any 5-HT_{2C} potency following purification, which was likely attributed to removal of contaminants in the deck sample. Four representative examples of screening hits are given in Figure 2. As indicated in red, these compounds possess embedded substructures that are well-known 5-HT_{2C} agonists that could be remnants of synthetic impurities or liberated during deterioration of the parent molecule upon long-term storage in DMSO. Although these results were discouraging, we still wondered if within the remaining screening hits there were compounds where the 5-HT_{2C} potency was attributed to the parent molecule and not a possible impurity or degradant.

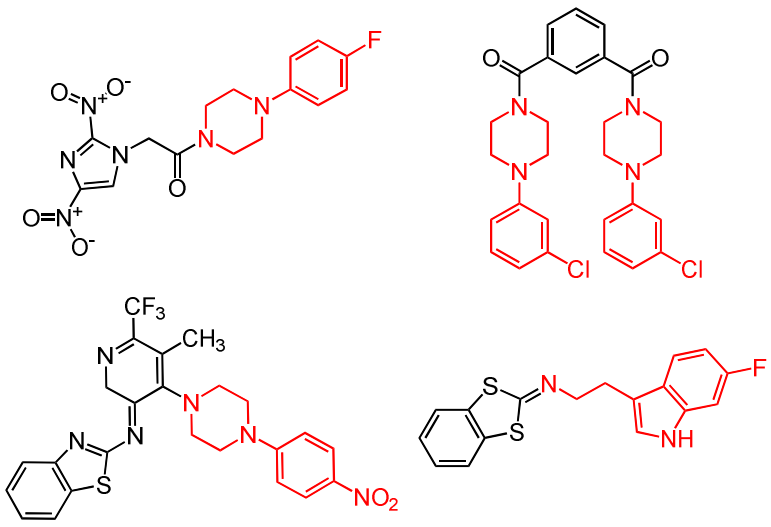
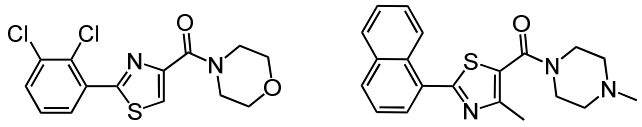


Figure 2. Screening hits with embedded 5-HT_{2C} agonist sub-structures indicated in red.

Purification and retesting of 18,000 compounds was not feasible, so an alternative approach to evaluating these hits was needed. We reasoned that this selection process could be accomplished by site-selective mutagenesis of the 5-HT_{2C} receptor active site. Our hypothesis was that while the residues that form the aromatic box are necessary for the receptor's agonist activity, the active site aspartic acid (Asp 134, D3.32) was only important for amine binding and could be mutated without impacting receptor function. This mutant receptor should not respond to compounds whose activity was driven by amine binding eliminating any samples contaminated with classical 5-HT_{2C} agonist impurities. This approach was not without significant risk as mutation of Asp 134 could lead to a misfolded protein, or a functionally inactive receptor, even if the protein was able to adopt the proper tertiary structure. The desired D134A mutant was prepared and found to have no functional activity in the presence of serotonin or several additional known 5-HT_{2C} agonists. However, upon screening against our compound library several hits were obtained which were agonists at both the wild-type and mutant receptor, but they were not active in a parental cell line that lacks the 5-HT_{2C} receptor. The screening hits were

also tested for PAM activity in the presence of serotonin and were found to have no impact on serotonin's binding or functional response.

Among the high throughput screening hits identified, two thiazole-based leads **1** and **2** were found to give promising 5-HT_{2C} agonism in both the wild-type and D134A mutant receptors, while being completely devoid of functional activity at the 5-HT_{2A} and 5-HT_{2B} receptors (Figure 3). Furthermore, these leads could be divided into three simple fragments (aryl ring, heterocyclic core, and carboxamide) that should allow for rapid SAR evaluation of each segment. These features, together with their low molecular weight and polar surface area represented an attractive starting point for the optimization of a novel chemical series for brain-penetrant 5-HT_{2C} agonists.



1

5-HT_{2C} EC_{50} (IA) = 120 nM (0.8)
D134A 5-HT_{2C} EC_{50} = 2 nM
5-HT_{2A} EC_{50} = >10000 nM
5-HT_{2B} EC_{50} = >10000 nM
PSA = 41

2

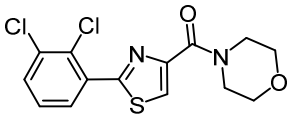
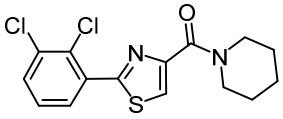
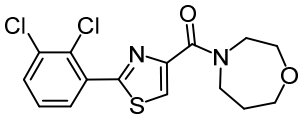
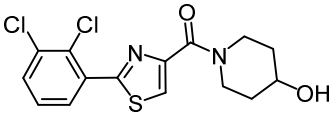
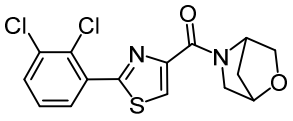
5-HT_{2C} EC_{50} (IA) = 83 nM (0.8)
D134A 5-HT_{2C} EC_{50} = 130 nM
5-HT_{2A} EC_{50} = >10000 nM
5-HT_{2B} EC_{50} = >10000 nM
PSA = 36

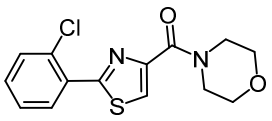
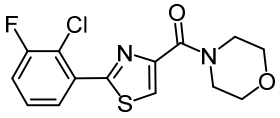
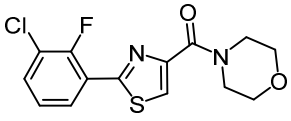
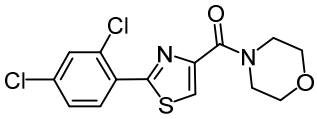
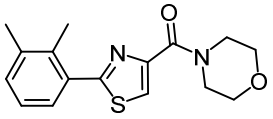
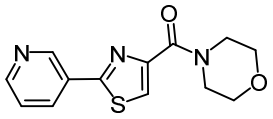
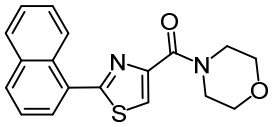
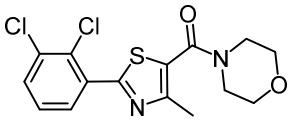
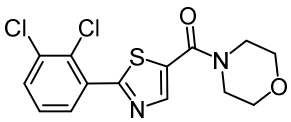
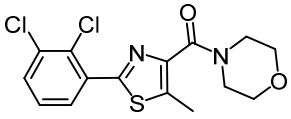
Figure 3. Novel thiazole-based leads from HTS.

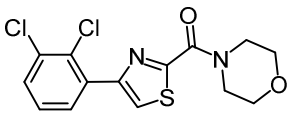
Initial investigations focused on amide SAR of **1**, as we were wary of the hydrophobic aryl ring system coupled with a basic amine functionality present in **2** which was reminiscent of the traditional 5-HT_{2C} agonist pharmacophore we hoped to avoid due to potential off-target toxicity. For thiazole compound **1**, over 100 amide variations were prepared (alkyl, heteroalkyl, aryl, heteroaryl) resulting in mostly inactive compounds with only a few close analogs showing similar levels of potency or receptor activation (Table 1, **3**-**6**). Similarly, attempts to modify the dichlorophenyl moiety with differentially substituted mono- and bicyclic aryl and heteroaryls led

to compounds with diminished 5-HT_{2C} potency (**7**-**13**). We next turned our efforts to the evaluation of the thiazole core (**14**-**17**). Morpholine amides of several isomeric and methyl substituted thiazoles were prepared and although most of the core replacements resulted in significant reductions in potency, this exercise led to identification of compound **17** with promising 5-HT_{2C} potency of 28 nM and full intrinsic activity. Unfortunately, as we had seen with modifications to **1**, we were again met with disappointment as the improved 5-HT_{2C} potency of **17** did not translate broadly to more potent derivatives upon further modification (data not shown). Variation of the amide revealed narrow SAR, and given an in vitro human half-life of less than two minutes, this thiazole isomer series was not progressed.

Table 1. Modifications of lead thiazole **1**.

Compound	Structure	5-HT_{2C}	
		EC_{50}[a] (nM)	IA[b]
1		119/128	0.8
3		3100/3700	0.3
4		320/733	0.5
5		679/840	0.7
6		129/315	0.8

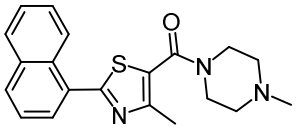
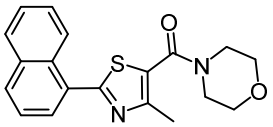
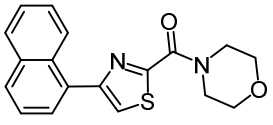
7		4600 ± 1300	0.1
8		>10000	--
9		1272/2402	0.3
10		>10000	--
11		501/705	0.7
12		>10000	--
13		766/1168	0.6
14		>10000	--
15		>10000	--
16		1520 ± 634	0.6

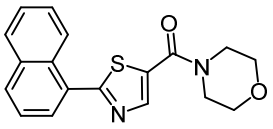
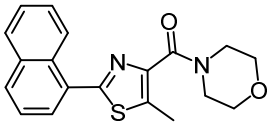
17		18/38	0.8

[a] EC_{50} values were calculated from dose-response curves. Functional screenings were carried out in HEK293E cells expressing the human 5-HT_{2C} receptor. EC_{50} determination experiments were performed at least in triplicate and the values are presented as Mean ± SD unless indicated otherwise or by inclusion of two values. Positive control was mCPP which gave 5-HT_{2C}, EC_{50} = 15 ± 4 nM. All compounds were functionally inactive (EC_{50} > 10 μM) at 5-HT_{2A} and 5-HT_{2B}. [b] Intrinsic activity (IA) for all compounds as compared to serotonin at 3 μM (defined as IA = 1).

After our unsuccessful attempt to identify a tractable lead from **1** we shifted our efforts to modification of screening hit **2** (Table 2). We were pleased to find that the morpholine amide analog **18** retained the 5-HT_{2C} potency of **2** without the basic amine functionality we had hoped to avoid. In an attempt to gain potency, we inserted the thiazole core from **17** to give **19**, but despite the apparent similarities of leads **1** and **2**, the SAR was found to diverge and this substitution resulted in a loss of potency. This variance was also exemplified by **13** (Table 1), as incorporation of the 1-naphthyl core from screening hit **2** into **1** resulted in a nearly 8-fold loss of potency. Removal of the 4-methyl substituent (**20**, Table 2), or swapping the location of nitrogen and sulfur (**21**) were also detrimental to 5-HT_{2C} potency, and thus **18** was chosen for further optimization.

Table 2. Modification of thiazole lead **2**.

Compound	Structure	5-HT_{2C}	
		EC_{50}[a] (nM)	IA[b]
2		43/123	0.8
18		95/115	0.8
19		729/1623	0.6

20		1522/2271	0.6
21		2780 ± 788	0.3

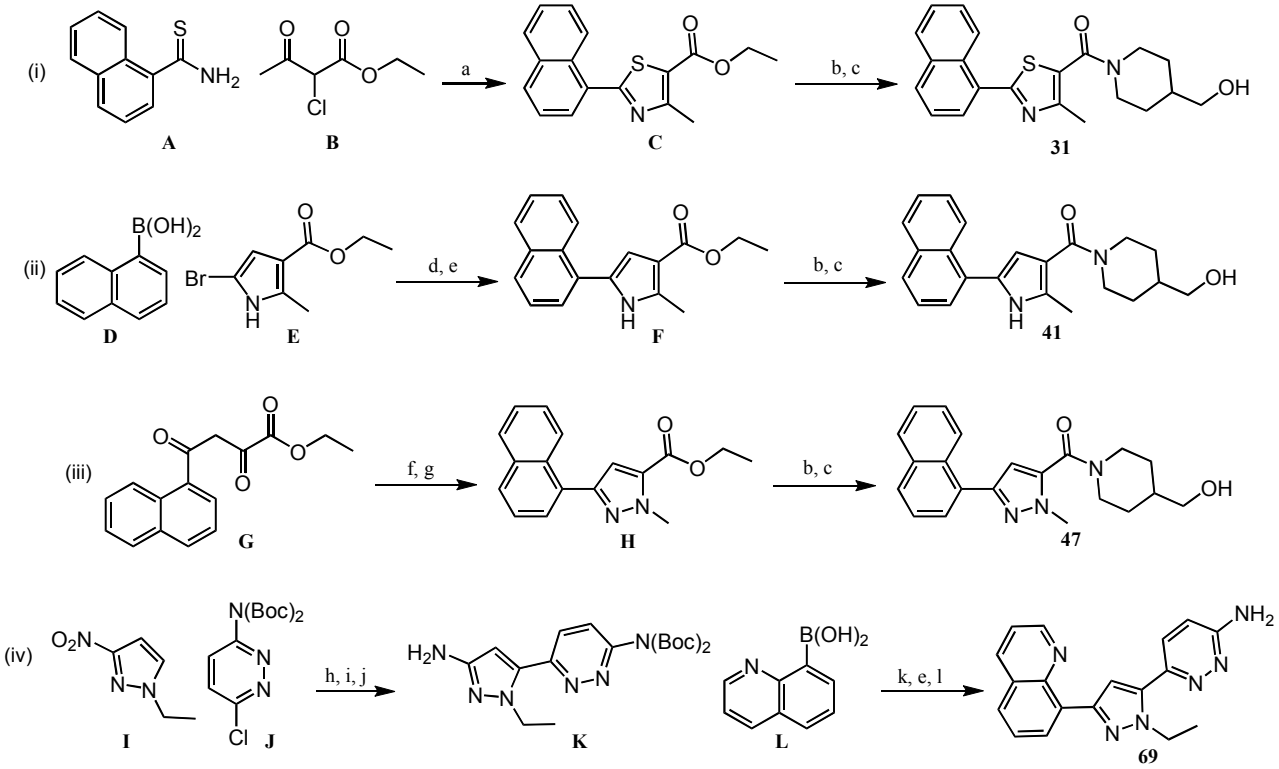
[a] EC_{50} values were calculated from dose-response curves. Functional screenings were carried out in HEK293E cells expressing the human 5-HT_{2A}, 5-HT_{2B}, or 5-HT_{2C} receptor. EC_{50} determination experiments were performed at least in triplicate and the values are presented as Mean ± SD unless indicated otherwise or by inclusion of two values. Positive control was mCPP which gave 5-HT_{2C}, EC_{50} = 15 ± 4 nM. All compounds were functionally inactive (EC_{50} > 10 μM) at 5-HT_{2A} and 5-HT_{2B}. [b] Intrinsic activity (IA) for all compounds as compared to serotonin at 3 μM (defined as IA = 1).

Chemistry. A general synthetic approach to analogs of thiazole lead **2** is outlined in Scheme 1 as exemplified by three key compounds **31**, **41**, and **47**. For thiazole **31**, synthesis commenced with condensation of naphthylene-1-thiocarboxamide (**A**) with ethyl 2-chloro-3-oxobutanoate (**B**) to give the thiazole ester intermediate **C**. The carboxylic acid, obtained via saponification, underwent facile amide coupling with piperidin-4-ylmethanol to give thiazole amide **31** in the three-step process depicted in Scheme 1 line (i). Pyrrole **41** (line ii) was prepared through an initial Suzuki coupling between naphthalene-1-boronic acid (**D**) and commercially available or readily synthesized ethyl 5-bromo-2-methyl-1H-pyrrole-3-carboxylate (**E**), followed by saponification of **F** and amide coupling to yield the final product. For the synthesis of pyrazole **47** (line iii) we employed a condensation of ethyl 4-(naphthalen-1-yl)-2,4-dioxobutanoate (**G**) with hydrazine and subsequent alkylation with iodomethane to give the N-methyl pyrazole ester intermediate (**H**). As with previous examples, final compound **47** was readily obtained by hydrolysis and amide coupling.

As described in line (iv) commercially available 1-ethyl-3-nitro-1H-pyrazole (**I**) was converted to the corresponding pinacol boronic ester prior to Suzuki coupling with bis-Boc protected 6-chloropyridazin-3-amine (**J**). During optimization of this coupling, we found that the more

reactive 1,1'-bis(di-*tert*-butylphosphino)ferrocene (dtbpf) ligand was vastly superior to the more commonly used 1,1'-bis(diphenylphosphino)ferrocene (dppf) ligand at forging the biaryl union. Reduction of the nitro group and conversion of the resultant amino pyrazole (**K**) to the corresponding bromo pyrazole under Sandmeyer conditions set up a penultimate Suzuki coupling with quinoline-8-boronic acid (**L**). Deprotection of the Boc protecting groups was facilitated with TFA to give compound **69**.

Scheme 1. Synthesis of key compounds **31**, **41**, **47**, and **69**.

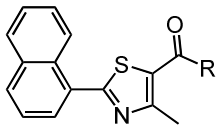


Reagents: (a) EtOH, 80 °C, sealed tube. (b) LiOH, THF/H_2O/MeOH, rt. (c) Piperidin-4-ylmethanol, T_3P, CH_2Cl_2, Et_3N, rt. (d) NBS, DMF, rt. (e) $PdCl_2(dppf)_2$, Cs_2CO_3, dioxane, 90-100 °C, sealed tube. (f) Hydrazine, AcOH, 90 °C. (g) CH_3I, Cs_2CO_3, MeCN, rt. (h) LDA, isopropyl pinacol borate, −78 °C to rt, THF. (i) $PdCl_2(dtbpf)_2$, Cs_2CO_3, dioxane, 80 °C, sealed tube. (j) H_2, Pd/C, MeOH, rt. (k) *t*BuONO, Cu(I)Br, LiBr, acetonitrile, 50 °C. (l) TFA, rt.

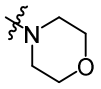
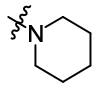
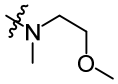
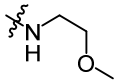
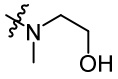
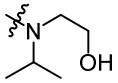
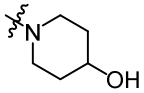
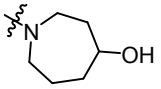
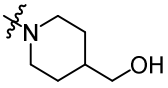
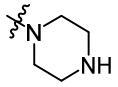
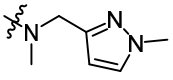
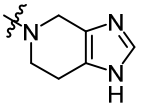
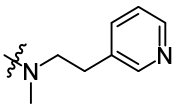
Lead Optimization. To our satisfaction, we discovered that further SAR investigation of **18** gave rise to a diverse set of compounds that exhibited appreciable 5-HT_{2C} potency while being completely devoid of functional activity at 5-HT_{2A} and 5-HT_{2B} (Table 3). Although the primary

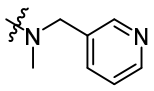
carboxamide **22** was inactive, we found that with the appropriate amide substitution we were able to retain and even improve the full-agonist activity and potency of **18**. For example, simple acyclic and cyclic aliphatic amides **23**-**24** were functionally active with an EC_{50} as low as 24 nM in the case of piperidine amide **24**. Further amide SAR revealed that tertiary and cyclic amides were preferred, as secondary amides typically lacked potency or gave only partial 5-HT_{2C} agonism (**25** vs. **26**). Results were also sensitive to steric bulk as exemplified by the complete loss of potency for **28** vs. **27**. Although we were pleased with the potency attainable in this series, most compounds tested suffered from poor metabolic stability when incubated with human and rat liver microsomes. In an effort to improve metabolic stability, heteroatoms were introduced into the amide chain with mixed results (**25**-**32**). Hydroxylation of the amide side chains (**27**, **29**-**31**) not only improved microsomal stability, but also retained or increased 5-HT_{2C} potency, with the hydroxymethyl piperidine amide **31** being optimal. We were somewhat surprised to find the decrease in potency for piperizine amide **32** given the presence of a basic secondary amine and structural similarity to traditional 5-HT_{2C} agonists. Importantly, this may suggest that **32** acts through an alternative mode of binding and receptor activation than that of serotonin. Nitrogen-containing heterocycles **33**-**36** were synthesized with the intent of further improving microsomal stability, and although several were well-tolerated, they did not improve stability or provide a clear advantage relative to the non-heterocycles in terms of potency.

Table 3. Amide SAR: 5-HT_{2C} EC_{50}, and microsomal stability.



Compound	R	5-HT_{2C}		Metstab: Human/Rat
		EC_{50}[a] (nM)	IA[b]	% Remaining[c]

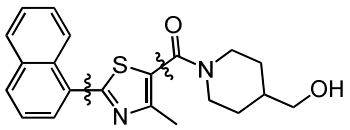
18		95/115	0.8	50/6
22		>10000	--	ND
23		59/72	1.0	ND
24		24 ± 6	1.0	24/1
25		14 ± 1	0.9	28/7
26		>10000	--	ND
27		30/50	0.9	67/22
28		>10000	--	28/7
29		47 ± 18	0.9	84/34
30		17/25	0.9	50/8
31		6 ± 3	1.1	80/24
32		1040 ± 1320	0.4	ND
33		13/19	1.0	ND
34		68 ± 38	1.0	70/15
35		38/39	0.7	<1/1

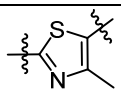
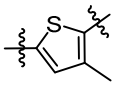
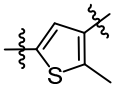
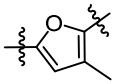
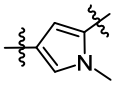
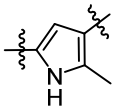
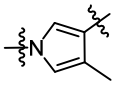
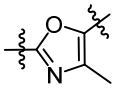
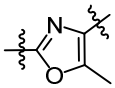
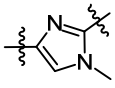
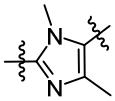
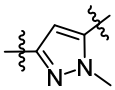
36		12/15	0.8	5/4

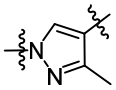
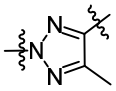
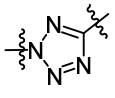
[a] EC_{50} values were calculated from dose-response curves. Functional screenings were carried out in HEK293E cells expressing the human 5-HT_{2A}, 5-HT_{2B}, or 5-HT_{2C} receptor. EC_{50} determination experiments were performed at least in triplicate and the values are presented as Mean ± SD unless indicated otherwise or by inclusion of two values. Positive control was mCPP which gave 5-HT_{2C}, EC_{50} = 15 ± 4 nM. All compounds were functionally inactive (EC_{50} > 10 μM) at 5-HT_{2A} and 5-HT_{2B}. [b] Intrinsic activity (IA) for all compounds as compared to serotonin at 3 μM (defined as IA = 1). [c] Compounds were incubated with human or rat liver microsomes at 5 mM. Values represent % parent remaining after 10 minutes. ND = not determined.

At this juncture, we chose to evaluate 5-membered heterocyclic replacements for the thiazole core with the hope of identifying a molecule that would retain 5-HT_{2C} potency and selectivity while further improving metabolic stability. Holding the naphthyl ring system and hydroxymethyl piperidine amide of **31** constant, we systematically modified the core heterocycle structure (Table 4). Our anticipation, based on previous observations with different thiazole isomers, was that changing the effective ring size and geometry by moving or replacing the sulfur atom would be detrimental to 5-HT_{2C} activity, but again the SAR was mostly unpredictable. Cores containing one heteroatom were generally tolerated, but as observed with thiazoles, the potency could vary dramatically between isomeric structures. Both thiophene isomers **37** and **38** retained 5-HT_{2C} potency (20 nM, 83 nM, respectively), but gave no improvement in terms of microsomal stability. However, furan **39** was >250 fold less potent than isomer **31**. Pyrrole **41** (12 nM) was the most potent single nitrogen-containing heterocycle with isomers **40** and **42** losing 3-30 fold potency at 5-HT_{2C}. Of the cores containing multiple heteroatoms, oxazoles, imidazoles, triazoles and tetrazoles (**43-46**, **49-50**) were not ideal giving ~16-700 fold loss in potency relative to thiazole **31**. Pyrazoles **47** and **48** on the other hand were potent (6, 16 nM), and as a result of this exercise we had several potent, selective 5-HT_{2C} agonists within this series that we chose to advance for further in vitro and in vivo profiling.

Table 4. Core replacement of thiazole **31**.



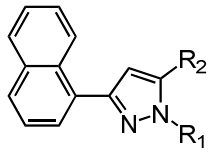
Compound	Core	5-HT$_{2C}$		5-HT$_{2B}$		5-HT$_{2A}$		Metstab Human/Rat % Remaining[c]
		EC$_{50}$[a] (nM)	IA[b]	EC$_{50}$[a] (nM)	IA[b]	EC$_{50}$[a] (nM)	IA[b]	
31		6.0 ± 3	1.0	>10000	--	>10000	--	80/24
37		20 ± 14	1.0	>10000	--	>5000	--	87/20
38		47/119	0.8	>10000	--	>10000	--	66/23
39		1032/2000	0.7	>10000	--	>10000	--	--
40		41/45	1.0	>10000	--	>10000	--	76/57
41		12 ± 7	0.9	>10000	--	>10000	--	76/44
42		369/433	0.7	>10000	--	>10000	--	67/18
43		63/140	0.9	>10000	--	>10000	--	33/24
44		381/575	1.0	>10000	--	>10000	--	62/16
45		1804/3525	0.7	>10000	--	>10000	--	--
46		1870 ± 422	0.4	>10000	--	>10000	--	--
47		6 ± 4	1.0	>10000	--	75 ± 62[d]	0.1	92/37

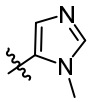
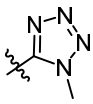
48		16 ± 9	1.0	>10000	--	>10000	--	88/51
49		334/385	1.0	>10000	--	>10000	--	58/24
50		4100/>10000	0.3	>10000	--	>10000	--	--

[a] EC_{50} values were calculated from dose-response curves. Functional screenings were carried out in HEK293E cells expressing the human 5-HT_{2A}, 5-HT_{2B}, or 5-HT_{2C} receptor. EC_{50} determination experiments were performed at least in triplicate and the values are presented as Mean ± SD unless indicated otherwise or by inclusion of two values. Positive control was mCPP which gave 5-HT_{2C}, EC_{50} = 15 ± 4 nM; 5-HT_{2B}, EC_{50} = 287 ± 94 nM; 5-HT_{2A}, EC_{50} = 290 ± 110 nM. [b] Intrinsic activity for all compounds as compared to serotonin at 3 μM (defined as 1). [c] Compounds were incubated with human or rat liver microsomes at 5mM. Values represent % parent remaining after 10 minutes. [d] EC_{50} values represent the average of multiple test occasions, several of which indicated no functional 5-HT_{2A} activity. ND = not determined.

Given the promising metabolic stability in human liver microsomes and the higher overall plasma and brain exposures observed for compound **47** (Table 7), the pyrazole core represented an attractive lead for additional SAR investigations. With the intent of further increasing lipophilicity via changes to the polar amide moiety, we prepared a set of heterocyclic amide isosteres. Various 5- or 6-membered heteroaryl amide replacements were investigated (Table 5). N-methyl imidazole **51** (73 nM) was a promising initial result, and we found that by changing the core pyrazole alkyl substituent to ethyl to give **52**, we gained approximately two-fold potency at 5-HT_{2C} (32 nM). Unfortunately these compounds suffered from poor microsomal metabolic stability. Introduction of the isomeric imidazole **53** or pyrazole **54** resulted in a substantial loss of functional activity and potency (4120 nM, 3500 nM respectively), which was only partially restored in the case of triazole **55** or tetrazole **56** (400 nM, 450 nM respectively). With respect to six-membered heterocyclic amide replacements, pyridine **57** and pyrimidine **58** lacked sufficient 5-HT_{2C} potency for advancement, whereas pyridazines **59** and **60** exhibited good potency, intrinsic activity and selectivity for 5-HT_{2C}.

Table 5. Amide Isostere SAR: 5-HT_{2C} EC_{50}, and microsomal stability.



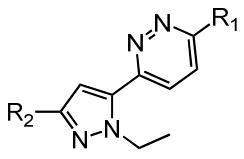
Compound	R_1	R_2	5-HT_{2C}		5-HT_{2B}		5-HT_{2A}		Metstab: Human % Remaining[c]
			EC_{50}[a] (nM)	IA[b]	EC_{50}[a] (nM)	IA[b]	EC_{50}[a] (nM)	IA[b]	
51	Me		88/58	0.9	>10000	--	93, 126	0.2	15
52	Et		37/27	0.8	>10000	--	>10000	--	5
53	Et		3850/4391	0.2	>10000	--	>10000	--	ND
54	Et		3460/>5000	0.3	>10000	--	>10000	--	ND
55	Et		190/616	0.7	>10000	--	>10000	--	4
56	Et		450 ± 357	0.6	>5000	--	1800, >2500	0.2	4
57	Et		576/613	0.8	>5000	--	>5000	--	ND
58	Et		1697/1903	0.4	>5000	--	>5000	--	ND
59	Me		40/25	1.2	>10000	--	>5000	--	12
60	Et		15 ± 7	1.2	>10000	--	884 ± 820[d]	0.2	17

[a] EC_{50} values were calculated from dose-response curves. Functional screenings were carried out in HEK293E cells expressing the human 5-HT_{2A}, 5-HT_{2B}, or 5-HT_{2C} receptor. EC_{50} determination experiments were performed at

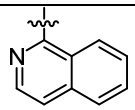
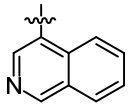
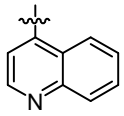
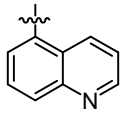
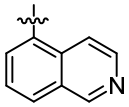
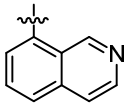
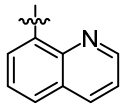
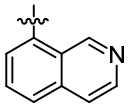
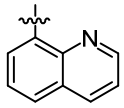
least in triplicate and the values are presented as Mean ± SD unless indicated otherwise or by inclusion of two values. Positive control was mCPP which gave 5-HT_{2C}, EC_{50} = 15 ± 4 nM; 5-HT_{2B}, EC_{50} = 287 ± 94 nM; 5-HT_{2A}, EC_{50} = 290 ± 110 nM. [b] Intrinsic activity for all compounds as compared to serotonin at 3 μM (defined as 1). [c] Compounds were incubated with human or rat liver microsomes at 5mM. Values represent % parent remaining after 10 minutes. [d] EC_{50} values represent the average of multiple test occasions, several of which indicated no functional 5-HT_{2A} activity. ND = not determined.

Having established that the pyridazine ring was optimal for 5-HT_{2C} potency and activity, detailed metabolite profiling of **60** revealed the naphthalene ring to be particularly susceptible to oxidative metabolism, and thus further SAR exploration focused on its stabilization via incorporation of a nitrogen atom into the ring system (Table 6). To this end, we prepared a series of compounds with a single nitrogen atom in each position around the naphthalene ring with the intent of blocking the major site of oxidative degradation. While analogs **61**-**63** exhibited ~20-30 fold diminished 5-HT_{2C} potency, and analogs **64**-**65** were >100 fold less potent, we were pleased to find that isoquinoline **66** at 28 nM was comparable to **60**. Moreover, quinoline **67** gave a marked improvement in 5-HT_{2C} potency (2 nM) but remained highly prone to oxidative metabolism. We again turned to metabolite identification to determine what region of **67** was subject to oxidative degradation and found that the liability had now shifted to the pyridazine. Introduction of an amino substituent at the 3-position on the pyridazine was found to partially mitigate its metabolism and retain or even improve 5-HT_{2C} potency for compounds **68** and **69** relative to the unsubstituted analogs (7 nM, 79% remaining, 5 nM, 61% remaining respectively).[31]

Table 6. Amide Isostere SAR: 5-HT_{2C}, 5-HT_{2B}, 5-HT_{2A} EC_{50}, and microsomal stability.



Compound	R_1	R_2	5-HT_{2C}	5-HT_{2B}	5-HT_{2A}	Metstab:

			EC_{50}[a] (nM)	IA[b]	EC_{50}[a] (nM)	IA[b]	EC_{50}[a] (nM)	IA[b]	Human % Remaining[c]
61	H		291/518	0.8	>10000	--	>10000	--	ND
62	H		530 ± 144	0.7	>10000	--	>10000	--	ND
63	H		315/396	0.6	>10000	--	>10000	--	ND
64	H		4528/4731	0.3	>10000	--	>10000	--	ND
65	H		1600 ± 804	0.7	>5000	--	>5000	--	ND
66	H		13/43	0.7	>10000	--	>10000	--	16
67	H		2 ± 0	1.0	6 ± 3[d]	0.2	151 ± 58[d]	0.2	8
68	NH_2		7[e]	1.1	>5000	--	>10000	--	79
69	NH_2		5 ± 3	0.8	48 ± 41[d]	0.4	635 ± 862[d]	0.2	61

[a] EC_{50} values were calculated from dose-response curves. Functional screenings were carried out in HEK293E cells expressing the human 5-HT_{2A}, 5-HT_{2B}, or 5-HT_{2C} receptor. EC_{50} determination experiments were performed at least in triplicate and the values are presented as Mean ± SD unless indicated otherwise or by inclusion of two values. Positive control was mCPP which gave 5-HT_{2C}, EC_{50} = 15 ± 4 nM; 5-HT_{2B}, EC_{50} = 287 ± 94 nM; 5-HT_{2A}, EC_{50} = 290 ± 110 nM. [b] Intrinsic activity for all compounds as compared to serotonin at 3 μM (defined as 1). [c] Compounds were incubated with human or rat liver microsomes at 5mM. Values represent % parent remaining after 10 minutes. [d] EC_{50} values represent the average of multiple test occasions, several of which indicated no functional 5-HT_{2A} activity. [e] EC_{50} value represents results from a single experiment. ND = not determined.

Pharmacokinetics. Compounds **31, 41**, **47** and **69** were selected for further in vitro profiling and rat pharmacokinetic studies, the data for which is given in Table 7. These studies were designed

to assess the permeability of each compound along with relative exposure of the compounds in the brain versus the plasma. In general, the compounds had excellent pH independent permeability as measured by a parallel artificial membrane permeability assay (PAMPA), in addition to Caco-2 ratios that suggested good permeability with a low probability of transporter mediated efflux. In a preliminary experiment, compound **31** was administered orally (P.O.) to rats at a dose of 30 mg/kg and the brain and plasma concentrations were determined 7 hours post administration. Given the low in vitro rat microsomal stability of **31** ($T_{½}$ = 6 min), we were not surprised to observe low exposures (736 nM plasma, 35 nM brain, b/p = 0.05) with a short half-life. In an attempt to circumvent degradation of the compound through oxidative first-pass metabolism, compound **31** was subsequently administered intravenously (I.V.) at 1 mg/kg and its brain and plasma concentrations were determined at 1 hour post dose. Despite the modified dosing protocol, low plasma and brain concentrations were again observed for **31** (569 nM, 76 nM respectively, b/p = 0.15). Taken together, the low brain to plasma concentrations were surprising considering the high PAMPA permeability and lack of Caco-2 efflux. In an attempt to understand possible reasons for low brain exposure, several follow up studies were conducted utilizing P-glycoprotein and breast cancer resistance protein (Pgp, BCRP) transporter knockout mice and specially engineered cellular systems that overexpress these membrane transporters. These experiments ultimately revealed that compound **31** was a substrate of rodent Pgp and BCRP transporters, but exhibited no significant in vitro affinity for human Pgp or BCRP transporters.

Given to our lack of high throughput rodent Pgp and BCRP assays, and with no clear advantage to I.V. administration, we chose to move forward with oral administration of the remaining compounds as the means to determine if high rodent brain exposure would be feasible

within our current series of heterocyclic 5-HT_{2C} agonists. Compounds **41** and **47** were subsequently administered to rats according to the original oral dosing regimen (30 mg/kg P.O.) and, as with compound **31**, we observed reasonable plasma concentrations for compounds **41** and **47**, but relative brain penetration was again low (b/p = 0.3, 0.2 respectively). On the other hand, when compound **69** was administered orally at 30 mg/kg, it exhibited higher plasma and brain exposures (7.5 μM, 3.9 μM respectively) with an increased brain to plasma ratio (0.9) relative to compounds **31**, **41**, and **47**.

Table 7. In vitro and in vivo profiling of selected 5-HT_{2C} agonists.

Compound	PAMPA (nm/s) pH 5.5/7.4	Caco-2 (nm/s) Efflux ratio (BA/AB)	Protein binding (% bound) human/rat	Microsomal T ½ (min) human/rat	Exposure (nM)[a, b]		B/P ratio[a]
					Plasma	Brain	
31	607/739	0.5 (175/329)	99.5/99.6	21/6	736[c]	35[c]	0.05
41	624/492	1.3 (219/172)	98.3/92.5	41/11	1137[d]	202[d]	0.2
47	588/613	0.5 (168/323)	97.7/92.4	36/8	2476[e]	721[e]	0.3
69	727/889	0.7 (528/777)	93.8/92.1	16/25	7543[f]	3920[f]	0.9

[a] The value represents the average of three male animals. Plasma and brain concentrations were determined after the indicated time. The brain sample were diluted (1:2(vol: weight)) with water before homogenization. The dilution factor is 3. [b] The compound was dosed orally at 30 mg/kg. Dosing vehicle: 0.15% docusate sodium; 2% polyvinyl pyrrolidinone - K; 97.85% water. [c] Plasma and brain concentration were determined at 7 h. [d] Plasma and brain concentration were determined at 1 h [e] Plasma and brain concentration were determined at 2 h. [f] Plasma and brain concentration were determined at 3 h.

Based on its potency, and overall pharmacokinetic properties, compound **69** was chosen for evaluation in a rodent efficacy model (Figure 4). In an acute feeding model, ~225 gram male Sprague–Dawley rats were orally administered **69** one hour prior to free access to food and water.[32] In this study, **69** showed a dose-dependent reduction in food pellet consumption. Specifically, the 3 and 10 mg/kg dose groups exhibited reduced food intake for the first 4 hours and the 30 mg/kg group showed reduced food intake over the entire sampling period. The effect observed at the 30 mg/kg dose was equivalent to the cannabinoid type-1 (CB1) receptor blocker, rimonabant, which was used as a positive control. Moreover, there was no effect on locomotor

activity as assessed by light beam breaks, and no reduction in water intake. In order to determine if the observed food intake reduction was driven by 5-HT_{2C} agonism, a subsequent study was conducted with **69** either alone or in combination with **70** (SB-243213, Figure 5), a selective 5-HT_{2C} antagonist.[33] Indeed the feeding effects of **69** were completely reversed by co-administration of **70** suggesting a 5-HT_{2C} mechanism-based reduction in food intake (Figure 5). The modest reduction of feeding observed at late time points with the **70** alone and **70** + **69** may be due to the anxiolytic properties of **70**.[33]

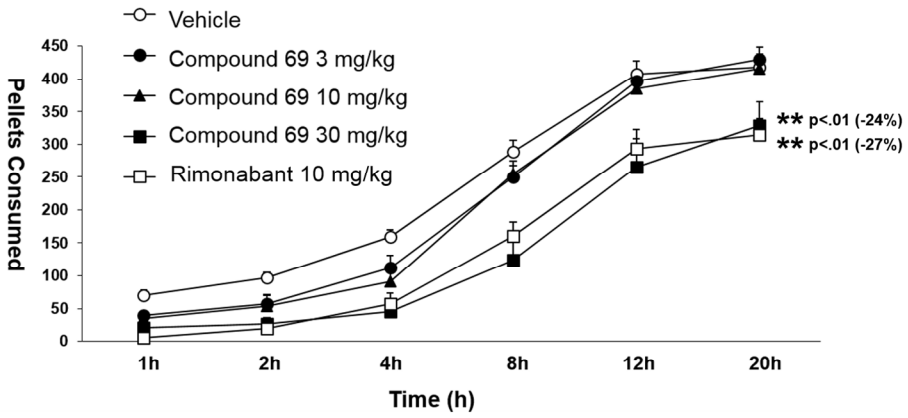


Figure 4. Rat ad-libitum feeding model with 5-HT_{2C} agonist **69**.[a]

[a] The values represent the average of six male animals. Cumulative food intake was analyzed via repeated-measure between-group analysis of variance using StatView software (Scientific Computing, Cary, North Carolina). Time points with overall significance were further analyzed with Bonferroni post-hoc tests to determine between-group significance.

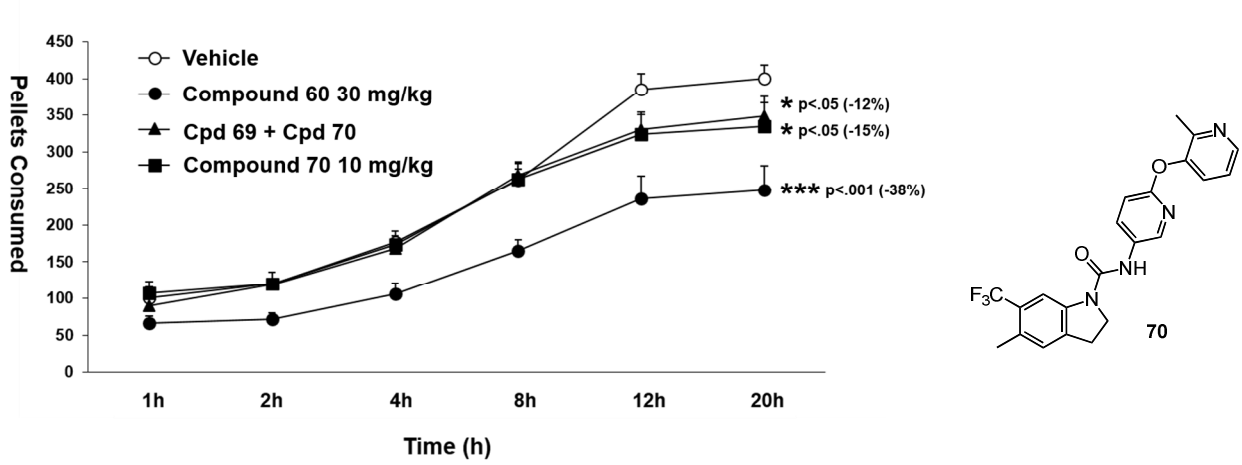


Figure 5. Reversal in the rat ad-libitum feeding model with 5-HT_{2C} antagonist **70**.[a]

[a] The values represent the average of six male animals. Cumulative food intake was analyzed via repeated-measure between-group analysis of variance using StatView software (Scientific Computing, Cary, North Carolina). Time points with overall significance were further analyzed with Bonferroni post-hoc tests to determine between-group significance.

Conclusion. A new screening protocol utilizing an active site mutant receptor was developed for the identification of novel 5-HT_{2C} receptor agonists. This protocol successfully enabled the discovery of a series of heterocycles which exhibited good potency at 5-HT_{2C}. Further, with few exceptions, these compounds were found to have excellent subtype functional selectivity against the closely related 5-HT_{2B} and 5-HT_{2A} receptors. These results, combined with promising in vitro and in vivo profiles, make the compounds described attractive candidates for further investigation. Moreover, these compounds represent a significant structural divergence from what has typically been considered a requisite for agonism of the 5-HT_{2C} receptor, namely exclusion of the basic amine that is proposed to interact with the active site Asp134 residue. This unique structural series may additionally lead to clinical candidates with improved efficacy, tolerability and toxicity profiles compared to presently known 5-HT_{2C} agonists.

Experimental Section.

Chemistry. All non-aqueous reactions were carried out under an argon or nitrogen atmosphere at room temperature, unless otherwise noted. All reagents and solvents were purchased from commercial sources and were used without further purification or distillation, unless otherwise stated. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator using a water bath. Chromatographic purification of products was accomplished using Teledyne Isco ICN 60 32-64 mesh SiO_2 pre-packed columns. Thin-layer chromatography (TLC) was performed on Silicycle 0.25 mm SiO_2 F-254 plates. Visualization of the developed chromatogram was performed by fluorescence quenching or by anisaldehyde, ceric ammonium molybdate, or potassium permanganate stain. ^1H and ^{13}C NMR spectra were recorded on a Bruker 500 (500 MHz and 125 MHz) unless otherwise noted. Chemical shifts (δ) are reported from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 7.26, C_6D_6: δ 7.15, CD_3OD: δ 4.78, 3.31: DMSO-d_6: δ 2.50 CD_3CN: δ 1.94). Data are reported as follows: chemical shift (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, h = heptet, br = broad, m = multiplet), integration, coupling constants (Hz), and assignment. Unless noted otherwise, the reported ^1H NMR signals were assigned using standard NMR techniques or by a direct comparison to the ^1H NMR spectra of corresponding starting materials. Analytical high-pressure liquid chromatography (HPLC) and LCMS analyses were conducted using Shimadzu LC-10AS pumps and a SPD-10AV UV-vis detector set at 220 nm with the MS detection performed with a Micromass Platform LC spectrometer. All compounds were found to be ≥95% pure by HPLC analysis unless otherwise noted.

General procedure for amide coupling: General method A.

Triethylamine (3 equiv.) and 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide (T3P) (2 equiv.) were added to a stirring suspension of the appropriate carboxylic acid (1

equiv.) in an appropriate solvent (0.1M) at room temperature. After 5 minutes, the desired amine (1.5 equiv.) was added and the mixture was stirred at room temperature until LCMS analysis indicated completion. The crude reaction mixture was then loaded directly onto an Isco SiO_2 cartridge for purification. Alternatively, the products could be purified via preparative HPLC. The desired fractions were combined and concentrated to give the designated amide products.

General procedure for Suzuki coupling: General method B.

A degassed mixture of the appropriate heteroaryl halides (2 equiv.), 1-ethyl-3-(naphthalen-1-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1 equiv.), tetrakis(triphenylphosphine)palladium(0) (0.15 equiv.), and K_3PO_4 (3 equiv.) in N-methyl-2-pyrrolidinone (0.3M) was heated to 95-100 °C until LCMS analysis indicated completion. The reaction mixture was cooled to room temperature and then purified by preparative HPLC (Phenomenex Luna 21.2 × 100 mm column; mobile phase A = 10:90 methanol: water with 0.1% trifluoroacetic acid; mobile phase B = 90:10 methanol: water with 0.1% trifluoroacetic acid or Waters XBridge C18, 19 × 100 mm column; mobile phase A = 5:95 acetonitrile: water with 10-mM ammonium acetate; mobile phase B = 95:5 acetonitrile: water with 10-mM ammonium acetate). Alternatively, the crude reaction mixtures could be purified by Isco SiO_2 flash chromatography. The desired fractions were combined and concentrated to give the designated products.

(2-(2,3-Dichlorophenyl)thiazol-4-yl)(morpholino)methanone (1). Step 1. Lithium hydroxide monohydrate (0.5 g, 12 mmol) was added to a stirring solution of ethyl 2-bromothiazole-4-carboxylate (0.6 g, 2.4 mmol) in tetrahydrofuran (23 mL), water (4.6 mL) and methanol (2.3 mL). After 1.5 hours the reaction mixture was diluted with ethyl acetate and acidified to ~pH 2 with 1.0 N HCl. The organic layer was washed with brine, dried over Na_2SO_4,

filtered and the solvent removed in vacuo to give 2-bromothiazole-4-carboxylic acid (0.5 g, 2.4 mmol, 100% yield) as a pale-yellow solid. The product was used without further purification. MS (ESI) *m/z:* 207.7 $[M+H]^+$; ^1H NMR (400MHz, DMSO-d_6) δ 13.29 (br. s., 1H), 8.45 (s, 1H).

Step 2. To a solution of 2-bromothiazole-4-carboxylic acid (330 mg, 1.6 mmol) and morpholine (140 mg, 1.6 mmol) in dichloromethane (6 mL) was added Hunig's Base (0.8 mL, 4.8 mmol) followed by 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide (T3P), 50% solution in ethyl acetate (1.5 mL, 2.9 mmol). The resulting solution was stirred under argon at room temperature for 2 hours until complete by HPLC analysis. The reaction was loaded onto a SiO_2 flash column via a solid cartridge was purified by Isco flash chromatography (0-75% ethyl acetate/hexanes) to afford (2-bromothiazol-4-yl)(morpholino)methanone (380 mg, 1.4 mmol, 87% yield) as an off-white solid. MS (ESI) *m/z:* 279.0 $[M+H]^+$; ^1H NMR (400MHz, $CDCl_3$) δ 7.87 (s, 1H), 3.85 (br. s., 2H), 3.67 (br. s., 6H).

Step 3. To a solution of (2-bromothiazol-4-yl)(morpholino)methanone (50 mg, 0.18 mmol) and (2,3-dichlorophenyl)boronic acid (41 mg, 0.22 mmol) in tetrahydrofuran (4 mL) and water (1 mL) was added K_2CO_3 (62 mg, 0.45 mmol). The mixture was degassed with a stream of argon for several minutes. $Pd(dppf)Cl_2$ (7.4 mg, 9.0 μmol) was then added and the reaction mixture was heated with stirring to 80 °C in a sealed vial. After 2 hours, the reaction vessel was removed from heat and stirred overnight. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous $NaHCO_3$, washed with brine, dried over Na_2SO_4 and concentrated in vacuo to afford an oil. The material was taken up in minimal dichloromethane and purified on SiO_2 via Isco flash chromatography (0-100% ethyl acetate/hexanes, 15 min linear gradient, Isco 12 g column). The desired fractions were combined and concentrated to give **1** (25 mg, 0.07 mmol, 38% yield) as a pale-yellow solid. MS (ESI) mass calculated for $[M+H]^+$

($C_{14}H_{13}Cl_2N_2O_2S$) requires *m/z* 343.0, found *m/z* 343.1; ^{1}H NMR (500MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.94 (dd, *J*=8.0, 1.7 Hz, 1H), 7.51 (dd, *J*=8.0, 1.4 Hz, 1H), 7.26 (t, *J*=7.8 Hz, 1H), 3.98 (br. s., 2H), 3.81-3.64 (m, 6H).

(4-Methyl-2-(naphthalen-1-yl)thiazol-5-yl)(4-methylpiperazin-1-yl)methanone, TFA (2). Step 1. Ethyl 2-chloro-3-oxobutanoate (2.7 mL, 19 mmol) was added to a solution of naphthalene-1-carbothioamide (3.5 g, 19 mmol) in ethanol (19 mL). The reaction vessel was sealed and heated to 80 °C for 19 hours and then cooled to room temperature. The excess solvent was removed in vacuo and the residue was purified on SiO_2 via Isco flash chromatography (0-20% ethyl acetate/hex, Isco 120 g column) to give ethyl 4-methyl-2-(naphthalen-1-yl)thiazole-5-carboxylate (4.6 g, 15 mmol, 82% yield) as a waxy white solid. MS (ESI) *m/z*: 298.1 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (d, *J*=8.53 Hz, 1H), 7.98 (d, *J*=8.28 Hz, 1H), 7.89-7.95 (m, 1H), 7.85 (dd, *J*=1.13, 7.15 Hz, 1H), 7.49-7.66 (m, 3H), 4.40 (q, *J*=7.19 Hz, 2H), 2.89 (s, 3H), 1.42 (t, *J*=7.15 Hz, 3H).

Step 2. Lithium hydroxide monohydrate (1.3 g, 31 mmol) was added to a rapidly stirring suspension of ethyl 4-methyl-2-(naphthalen-1-yl)thiazole-5-carboxylate (4.6 g, 16 mmol) in tetrahydrofuran (118 mL), water (24 mL) and methanol (12 mL). The reaction mixture was stirred at room temperature for 14 hours and was then diluted with ethyl acetate and acidified to pH 3 with 10% aqueous citric acid. The organic phase was washed with brine and the combined aqueous layers were further extracted with ethyl acetate (2x100 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated in vacuo to give 4-methyl-2-(naphthalen-1-yl)thiazole-5-carboxylic acid. The product was used subsequently without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.43 (br. s., 1H), 8.81 (d, *J*=8.28 Hz, 1H), 8.14 (d, *J*=8.28 Hz, 1H), 8.02-8.08 (m, 1H), 7.96 (dd, *J*=1.25, 7.28 Hz, 1H), 7.58-7.73 (m, 3H), 2.78

(s, 3H).

Step 3. Prepared according to general method A with 4-methyl-2-(naphthalen-1-yl)thiazole-5-carboxylic acid and 1-methylpiperazine to give **2**; MS (ESI) mass calculated for $[M+H]^+$ ($C_{20}H_{22}N_3OS$) requires *m/z* 352.1, found *m/z* 352.1; ^{1}H NMR (400MHz, DMSO-d_6) δ 8.91 - 8.81 (m, *J*=7.8, 1.3 Hz, 1H), 8.14 (d, *J*=8.3 Hz, 1H), 8.10 - 8.04 (m, 1H), 7.93 (dd, *J*=7.3, 1.0 Hz, 1H), 7.72 - 7.60 (m, 3H), 4.30 (br. s., 2H), 3.18 (br. s., 2H), 2.85 (br. s., 2H), 2.55 (s, 3H), 1.53 - 1.41 (m, 2H), 1.00 - 0.92 (m, 2H) spectrum is partially obscured by DMSO and H_2O peaks.

(2-(2,3-Dichlorophenyl)thiazol-4-yl)(piperidin-1-yl)methanone (3). Step 1. 2,3-Dichlorobenzothioamide (5.0 g, 24 mmol) and 3-bromo-2-oxopropanoic acid (4.2 g, 26 mmol) were dissolved in acetonitrile (120 mL) and heated to 80 °C for 1 hour. After being cooled to room temperature the excess solvent was removed in vacuo and the solid was triturated with diethyl ether until the washings were colorless. The resultant solid was dried in vacuo to give 2-(2,3-dichlorophenyl)thiazole-4-carboxylic acid (6.2 g, 23 mmol, 94% yield) as a tan solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.68 (s, 1H), 8.11 (dd, *J*=7.9, 1.6 Hz, 1H), 7.83 (dd, *J*=8.0, 1.5 Hz, 1H), 7.55 (t, *J*=7.9 Hz, 1H).

Step 2. Prepared according to general method A with 2-(2,3-dichlorophenyl)thiazole-4-carboxylic acid and piperidine to give **3**. MS (ESI) mass calculated for $[M+H]^+$ ($C_{15}H_{15}Cl_2N_2OS$) requires *m/z* 341.0, found *m/z* 341.4; ^{1}H NMR (500 MHz, methanol-d_4) δ 8.07 (dd, *J*=7.9, 1.5 Hz, 1H), 8.05 (s, 1H), 7.65 - 7.62 (m, 1H), 7.42 - 7.37 (m, 1H), 3.83 - 3.68 (m, 4H), 1.84 - 1.60 (m, 6H).

(2-(2,3-Dichlorophenyl)thiazol-4-yl)(1,4-oxazepan-4-yl)methanone (4). Prepared according to general method A with 2-(2,3-dichlorophenyl)thiazole-4-carboxylic acid and 1,4-

oxazepane to give **4**. MS (ESI) mass calculated for $[M+H]^+$ ($C_{15}H_{15}C_{l2}N_2O_2S$) requires *m/z* 357.0, found *m/z* 357.4; ^{1}H NMR (500 MHz, CD_3OD) δ 8.17 (d, *J*=7.9 Hz, 1H), 8.02 (ddd, *J*=18.8, 7.9, 1.5 Hz, 1H), 7.63 (dd, *J*=8.2, 1.7 Hz, 1H), 7.40 (t, *J*=7.9 Hz, 1H), 4.08 - 3.98 (m, 2H), 3.96 - 3.82 (m, 6H), 2.14 - 2.00 (m, 2H).

(2-(2,3-Dichlorophenyl)thiazol-4-yl)(4-hydroxypiperidin-1-yl)methanone (5). Prepared according to general method A with 2-(2,3-dichlorophenyl)thiazole-4-carboxylic acid and piperidin-4-ol to give **5**. MS (ESI) mass calculated for $[M+H]^+$ ($C_{15}H_{15}C_{l2}N_2O_2S$) requires *m/z* 357.0, found *m/z* 357.1; ^{1}H NMR (500MHz, $CDCl_3$) δ 8.00 (d, *J*=1.7 Hz, 1H), 7.98 (s, 1H), 7.50 (dd, *J*=8.0, 1.7 Hz, 1H), 7.26 (t, *J*=8.0 Hz, 1H), 4.24 - 4.15 (m, 2H), 3.99 - 3.92 (m, 1H), 3.53 - 3.43 (m, 1H), 3.39 - 3.32 (m, 1H), 2.00 - 1.87 (m, 2H), 1.64 - 1.56 (m, 2H) OH proton is not observed.

2-Oxa-5-azabicyclo[2.2.1]heptan-5-yl(2-(2,3-dichlorophenyl)thiazol-4-yl)methanone (6). Prepared according to general method A with 2-(2,3-dichlorophenyl)thiazole-4-carboxylic acid and 2-oxa-5-azabicyclo[2.2.1]heptane, HCl to give **6**. MS (ESI) mass calculated for $[M+H]^+$ ($C_{15}H_{13}Cl_2N_2O_2S$) requires *m/z* 355.0, found *m/z* 355.0; ^{1}H NMR (400MHz, $CDCl_3$) δ 8.34 (d, *J*=8.5 Hz, 1H), 8.09 - 7.95 (m, 1H), 7.60 (ddd, *J*=8.0, 6.3, 1.5 Hz, 1H), 7.36 (td, *J*=7.9, 5.3 Hz, 3H), 4.73 (d, *J*=5.3 Hz, 1H), 4.11 (br. s., 2H), 4.07 (d, *J*=7.0 Hz, 1H), 4.00 - 3.89 (m, 1H), 3.71 (d, *J*=2.5 Hz, 1H).

(2-(2-Chlorophenyl)thiazol-4-yl)(morpholino)methanone (7). Step 1. 2-chlorobenzothioamide (1.5 g, 8.7 mmol) and 3-bromo-2-oxopropanoic acid (1.5 g, 8.7 mmol) were dissolved in dioxane (29 mL) and heated with stirring to 90 °C for 2 hours in a sealed reaction vial. The reaction mixture was transferred to a round bottom flask and concentrated in vacuo. The resultant solid was triturated with diethyl ether until the washings were colorless. The

remaining solid was dried in vacuo to give 2-(2-chlorophenyl)thiazole-4-carboxylic acid as a tan solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 13.15 (br. s., 1H), 8.64 (s, 1H), 8.24 - 8.14 (m, 1H), 7.72 - 7.63 (m, 1H), 7.59 - 7.47 (m, 2H).

Step 2. Prepared according to general method A with 2-(2-chlorophenyl)thiazole-4-carboxylic acid and morpholine to give **7**. MS (ESI) mass calculated for $[M+H]^+$ ($C_{14}H_{14}ClN_2O_2S$) requires *m/z* 309.0, found *m/z* 309.1; ^{1}H NMR (500MHz, $CDCl_3$) δ 8.08 - 8.04 (m, 1H), 8.04 (s, 1H), 7.48 - 7.43 (m, 1H), 7.34 - 7.29 (m, 2H), 4.01 (br. s., 2H), 3.81 - 3.66 (m, 6H).

(2-(2-Chloro-3-fluorophenyl)thiazol-4-yl)(morpholino)methanone (8). Step 1. A mixture of (2-chloro-3-fluorophenyl)boronic acid (86 mg, 0.50 mmol), methyl 2-bromothiazole-4-carboxylate (100 mg, 0.45 mmol), and K_2CO_3 (75 mg, 0.54 mmol) in toluene (3.4 mL) and methanol (1.1 mL) was degassed under argon for 20 minutes and then $PdCl_2$(dppf) (20 mg, 0.03 mmol) was added and the reaction flask was sealed and heated with stirring to 100 °C. After 5 hours the crude reaction mixture was loaded onto an Isco SiO_2 cartridge for purification by Isco flash chromatography (0-100% ethyl acetate/hexanes, Isco 4 g column) to give methyl 2-(2-chloro-3-fluorophenyl)thiazole-4-carboxylate (70 mg, 0.26 mmol, 57% yield) as a white solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.15 (dd, J=8.0, 1.3 Hz, 1H), 7.44 - 7.35 (m, 2H), 3.97 (s, 3H).

Step 2. Lithium hydroxide monohydrate (54.1 mg, 1.3 mmol) was added to a rapidly stirring solution of methyl 2-(2-chloro-3-fluorophenyl)thiazole-4-carboxylate (70 mg, 0.26 mmol) in tetrahydrofuran (2.5 mL), water (0.4 mL) and methanol (0.2 mL). After stirring at room temperature for 1 hour the reaction mixture was diluted with ethyl acetate/water and acidified to pH 2 with 1N aqueous HCl. The organic layer was separated, washed with brine and

the combined aqueous layers were further extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo to give 2-(2-chloro-3-fluorophenyl)thiazole-4-carboxylic acid (67 mg, 0.26 mmol, 100% yield). ^{1}H NMR (400MHz, DMSO-d_6) δ 13.76 (br. s., 1H), 8.54 (s, 1H), 8.11 (d, J=7.5 Hz, 1H), 7.69 - 7.55 (m, 2H).

Step 3. Prepared according to general method A with 2-(2-chloro-3-fluorophenyl)thiazole-4-carboxylic acid and morpholine to give **8**. MS (ESI) mass calculated for $[M+H]^+$ ($C_{14}H_{13}ClFN_2O_2S$) requires *m/z* 327.0, found *m/z* 327.0; ^{1}H NMR (400MHz, $CDCl_3$) δ 8.12 - 8.03 (m, 2H), 7.38 (td, *J*=8.0, 5.3 Hz, 1H), 7.33 - 7.28 (m, 1H), 3.80 (d, *J*=4.5 Hz, 8H).

(2-(3-Chloro-2-fluorophenyl)thiazol-4-yl)(morpholino)methanone (9). Step 1. 3-chloro-2-fluorobenzamide (0.2 g, 1.2 mmol) and phosphorus (V) sulfide (0.10 g, 0.23 mmol) were dissolved in dioxane and heated with stirring to 90 °C for 2 hours. At this point, complete conversion to the thioamide was determined by LCMS. 3-bromo-2-oxopropanoic acid (0.20 g, 1.2 mmol) was then added and the reaction mixture was heated with stirring to 90 °C for an additional 2 hours. After being cooled to room temperature, the excess solvent was removed and the residue was purified on SiO_2 via Isco flash chromatography (0-100% ethyl acetate/hexanes, Isco 12 g column) to give 2-(3-chloro-2-fluorophenyl)thiazole-4-carboxylic acid as a light-pink solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.68 (s, 1H), 8.25 - 8.14 (m, 1H), 7.83 - 7.73 (m, 1H), 7.44 (t, *J*=8.0 Hz, 1H).

Step 2. Prepared according to general method A with 2-(3-chloro-2-fluorophenyl)thiazole-4-carboxylic acid and morpholine to give **9**. MS (ESI) mass calculated for $[M+H]^+$ ($C_{14}H_{13}ClFN_2O_2S$) requires *m/z* 327.0, found *m/z* 327.1; ^{1}H NMR (400MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.58 - 7.47 (m, 1H), 7.24 (m, 2H), 4.08 (br. s., 2H), 3.83 (br. s., 6H).

(2-(2,4-Dichlorophenyl)thiazol-4-yl)(morpholino)methanone (10). Step 1. Lithium

hydroxide monohydrate (0.50 g, 12 mmol) was added to a stirring solution of ethyl 2-bromothiazole-4-carboxylate (0.56 g, 2.4 mmol) in tetrahydrofuran (23 mL), water (4.6 mL) and methanol (2.3 mL). After 1.5 hours the reaction mixture was diluted with ethyl acetate and acidified to pH 2 with 1.0 N aqueous HCl. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo to give 2-bromothiazole-4-carboxylic acid (0.50 g, 2.4 mmol, 100% yield) as a pale-yellow solid. The product was used without further purification. MS (ESI) *m/z:* 207.7 $[M+H]^+$; ^{1}H NMR (400MHz, DMSO-d_6) δ 13.29 (br. s., 1H), 8.45 (s, 1H).

Step 2. To a solution of 2-bromothiazole-4-carboxylic acid (330 mg, 1.6 mmol) and morpholine (140 mg, 1.6 mmol) in dichloromethane (6 mL) was added Hunig's Base (0.83 mL, 4.8 mmol) followed by 1-propanephosphonic acid cyclic anhydride (T3P), 50% solution in ethyl acetate (1.5 mL, 2.9 mmol). The resulting solution was stirred under argon at room temperature for 2 hours until complete conversion was determined by LCMS analysis. The crude reaction mixture was loaded onto a SiO_2 flash column via a solid cartridge purified on SiO_2 via Isco flash chromatography (0-75% ethyl acetate/hexanes) to afford (2-bromothiazol-4-yl)(morpholino)methanone (380 mg, 1.4 mmol, 87% yield) as an off-white solid. MS (ESI) *m/z:* 279.0 $[M+H]^+$; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.87 (s, 1H), 3.85 (br. s., 2H), 3.67 (br. s., 6H).

Step 3. A mixture of (2-bromothiazol-4-yl)(morpholino)methanone (40 mg, 0.14 mmol), (2,4-dichlorophenyl)boronic acid (33 mg, 0.17 mmol), Pd(dppf)Cl_2 (5.9 mg, 7.2 μmol) and K_2CO_3 (50 mg, 0.36 mmol) in tetrahydrofuran (1.0 mL) and water (1.0 mL) was degassed by bubbling argon through the mixture, and then the reaction vessel was sealed and heated with stirring at 80 °C overnight. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified on SiO_2 via Isco flash chromatography (0-50% ethyl acetate/hexanes). The

product was further purified by preparatory-HPLC (Shimadzu VP-ODS 20 × 50 mm; 30-100% solvent B in solvent A over 5 min; A = 10:90 methanol: water with 0.1% trifluoroacetic acid, B = 90:10 methanol: water with 0.1% trifluoroacetic acid, 20 mL/min). The product containing fraction was extracted with ethyl acetate, washed with water and brine, dried over $MgSO_4$, filtered and concentrated in vacuo to afford **10** (15 mg, 0.04 mmol, 30% yield) as a white solid. MS (ESI) mass calculated for $[M+H]^+$ ($C_{14}H_{13}Cl_2N_2O_2S$) requires *m/z* 343.0, found *m/z* 343.1; ^{1}H NMR (400MHz, $CDCl_3$) δ 8.13 (s, 1H), 8.11 (s, 1H), 7.55 (d, *J*=2.2 Hz, 1H), 7.38 (dd, *J*=8.5, 1.9 Hz, 1H), 4.05 (br. s., 2H), 3.90 - 3.71 (m, 6H).

(2-(2,3-Dimethylphenyl)thiazol-4-yl)(morpholino)methanone (11). A mixture of (2-bromothiazol-4-yl)(morpholino)methanone (40 mg, 0.14 mmol), (2,3-dimethylphenyl)boronic acid (26 mg, 0.17 mmol), Pd(dppf)Cl_2 (5.9 mg, 7.2 μmol) and K_2CO_3 (50 mg, 0.36 mmol) in tetrahydrofuran (1.0 mL) and water (1.0 mL) was degassed by bubbling argon through the mixture, and then the reaction vessel was sealed and heated with stirring at 80 °C overnight. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic was dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified on SiO_2 via Isco flash chromatography (0-50% ethyl acetate/hexanes) to afford **11** (31 mg, 0.10 mmol, 70% yield) as a colorless film. MS (ESI) mass calculated for $[M+H]^+$ ($C_{16}H_{19}N_2O_2S$) requires *m/z* 303.1, found *m/z* 303.1; ^{1}H NMR (500MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.42 (d, *J*=7.7 Hz, 1H), 7.30 - 7.26 (m, 1H), 7.22 - 7.16 (m, 1H), 4.09 (br. s., 2H), 3.82 (br. s., 4H), 3.74 (br. s., 2H), 2.42 (s, 3H), 2.38 (s, 3H).

Morpholino(2-(pyridin-3-yl)thiazol-4-yl)methanone (12). Prepared according to general method A with 2-(pyridin-3-yl)thiazole-4-carboxylic acid and morpholine to give **12**. MS (ESI) mass calculated for $[M+H]^+$ ($C_{13}H_{14}N_3O_2S$) requires *m/z* 276.1, found *m/z* 276.0; ^{1}H NMR

(400MHz, $CDCl_3$) δ 9.22 - 9.16 (m, 1H), 8.71 (dd, *J*=4.8, 1.5 Hz, 1H), 8.22 (dt, *J*=8.0, 2.0 Hz, 1H), 8.05 (s, 1H), 7.43 (ddd, *J*=8.0, 4.8, 0.8 Hz, 1H), 4.08 (br. s., 2H), 3.83 (br. s., 6H).

Morpholino(2-(naphthalen-1-yl)thiazol-4-yl)methanone (13). Step 1. Naphthalene-1-carbothioamide (0.25 g, 1.3 mmol) and 3-bromo-2-oxopropanoic acid (0.22 g, 1.3 mmol) were dissolved in dioxane (6.7 mL). The reaction mixture was then heated with stirring in a sealed vial at 100 °C for 20 hours. The solvent was then removed in vacuo and the residue was triturated with diethyl ether until the washings were clear. The resultant solid was dried in vacuo to give 2-(naphthalen-1-yl)thiazole-4-carboxylic acid (0.25 g, 0.98 mmol, 73% yield) as a white solid. MS (ESI) *m/z*: 256.0 $[M+H]^+$; ^{1}H NMR (400MHz, DMSO-d_6) δ 13.18 (br. s., 1H), 8.84 (d, *J*=8.3 Hz, 1H), 8.64 (s, 1H), 8.13 (d, *J*=8.3 Hz, 1H), 8.06 (d, *J*=7.5 Hz, 1H), 7.96 (d, *J*=7.0 Hz, 1H), 7.73 - 7.59 (m, 3H).

Step 2. Prepared according to general method A with 2-(naphthalen-1-yl)thiazole-4-carboxylic acid and morpholine to give **13** as a gum. MS (ESI) mass calculated for $[M+H]^+$ ($C_{18}H_{17}N_2O_2S$) requires *m/z* 325.1, found *m/z* 325.1; ^{1}H NMR (400MHz, $CDCl_3$) δ 8.80 - 8.73 (m, 1H), 8.13 (s, 1H), 7.99 (d, *J*=8.3 Hz, 1H), 7.96 - 7.91 (m, 1H), 7.85 (dd, *J*=7.3, 1.3 Hz, 1H), 7.64 - 7.51 (m, 3H), 4.14 (br. s., 2H), 3.91 - 3.73 (m, 6H).

(2-(2,3-Dichlorophenyl)-4-methylthiazol-5-yl)(morpholino)methanone (14). Step 1. A solution of 2,3-dichlorobenzothioamide (0.1 g, 0.48 mmol) and methyl 2-chloro-3-oxobutanoate (0.06 mL, 0.48 mmol) in dioxane (2.4 mL) was heated with stirring at 100 °C in a sealed vial. After 36 hours the reaction mixture was cooled to room temperature and the solvent was removed in vacuo giving methyl 2-(2,3-dichlorophenyl)-4-methylthiazole-5-carboxylate (0.14 g, 0.46 mmol, 95% yield) as a yellow solid that was used subsequently without further purification.

MS (ESI) *m/z*: 301.9 $[M+H]^+$; ^1H NMR (400MHz, $CDCl_3$) δ 8.23 (dd, *J*=8.0, 1.5 Hz, 1H), 7.59 (dd, *J*=8.0, 1.5 Hz, 1H), 7.34 (t, *J*=8.0 Hz, 1H), 3.93 (s, 3H), 2.82 (s, 3H).

Step 2. Lithium hydroxide monohydrate (39 mg, 0.93 mmol) was added to a rapidly stirring solution of methyl 2-(2,3-dichlorophenyl)-4-methylthiazole-5-carboxylate (140 mg, 0.46 mmol) in tetrahydrofuran (4.4 mL), water (0.89 mL) and methanol (0.44 mL). After stirring at room temperature for 2 hours the reaction mixture was diluted with ethyl acetate and water and then acidified to ~ pH 1 with 1N aqueous HCl. The organic layer was washed with brine, dried over Na_2SO_4, filtered and the solvent was removed in vacuo to give 2-(2,3-dichlorophenyl)-4-methylthiazole-5-carboxylic acid (13 mg, 0.46 mmol, 99% yield) as a white solid. MS (ESI) *m/z*: 288.0 $[M+H]^+$; 1H NMR (400MHz, DMSO-d_6) δ 13.52 (br. s., 1H), 8.20 (dd, *J*=8.0, 1.5 Hz, 1H), 7.84 (dd, *J*=8.0, 1.5 Hz, 1H), 7.54 (t, *J*=7.9 Hz, 1H), 2.71 (s, 3H).

Step 3. Prepared according to general method A with 2-(2,3-dichlorophenyl)-4-methylthiazole-5-carboxylic acid (26 mg, 0.09 mmol) and morpholine (8.6 µl, 0.10 mmol) to give **14** (27 mg, 0.07 mmol, 81% yield) as a white solid. MS (ESI) mass calculated for $[M+H]^+$ ($C_{15}H_{15}Cl_2N_2O_2S$) requires *m/z* 357.0, found *m/z* 357.0; ^1H NMR (400MHz, $CDCl_3$) δ 8.14 (dd, *J*=8.0, 1.5 Hz, 1H), 7.57 (dd, *J*=7.9, 1.6 Hz, 1H), 7.38 - 7.29 (m, 1H), 3.85 - 3.56 (m, 8H), 2.54 (s, 3H).

(2-(2,3-Dichlorophenyl)thiazol-5-yl)(morpholino)methanone (15). Step 1. To a rapidly stirring solution of ethyl 2-(2,3-dichlorophenyl)thiazole-5-carboxylate (48 mg, 0.16 mmol) in tetrahydrofuran (2 mL) methanol (1 mL) and water (1 mL) was added lithium hydroxide monohydrate (5.7 mg, 0.24 mmol). The reaction mixture was stirred room temperature until complete conversion was determined by LCMS analysis. The reaction mixture was then diluted with ethyl acetate and washed successively with 0.1M HCl, water, brine, dried over $MgSO_4$,

filtered and concentrated in vacuo to afford 2-(2,3-dichlorophenyl)thiazole-5-carboxylic acid (41 mg, 0.15 mmol, 94% yield) as an off-white solid. The product was used without further purification. MS (ESI) *m/z:* 276.0 $[M+H]^+$.

Step 2. Prepared according to general method A with 2-(2,3-dichlorophenyl)thiazole-5-carboxylic acid (41 mg, 0.15 mmol) and morpholine (13 mg, 0.15 mmol) to afford **15** (36 mg, 0.10 mmol, 69% yield) as an off-white solid. MS (ESI) mass calculated for $[M+H]^+$ ($C_{14}H_{13}Cl_2N_2O_2S$) requires *m/z* 343.0, found *m/z* 343.1; ^{1}H NMR (500MHz, $CDCl_3$) δ 8.16 (dd, *J*=8.0, 1.7 Hz, 1H), 8.07 (s, 1H), 7.59 (dd, *J*=7.8, 1.5 Hz, 1H), 7.35 (t, *J*=8.0 Hz, 1H), 3.84 - 3.74 (m, 8H).

(2-(2,3-Dichlorophenyl)-5-methylthiazol-4-yl)(morpholino)methanone (16). Step 1. 2,3-dichlorobenzothioamide (0.1 g, 0.48 mmol) was added to a solution of methyl 3-bromo-2-oxobutanoate (0.10 g, 0.53 mmol) in ethanol (1.0 mL). The reaction vessel was sealed and heated with stirring at 80 °C for 18 hours. The excess solvent was removed in vacuo and the residue was purified on SiO_2 via Isco flash chromatography (0-40% ethyl acetate/hex, Isco 24 g column) to give a mixture of methyl 2-(2,3-dichlorophenyl)-5-methylthiazole-4-carboxylate and ethyl 2-(2,3-dichlorophenyl)-5-methylthiazole-4-carboxylate. The mixture was carried on to the next step.

Step 2. Lithium hydroxide monohydrate (16 mg, 0.39 mmol) was added to a rapidly stirring solution of the mixture from step 1 (120 mg, 0.39 mmol) in tetrahydrofuran (3.8 mL), water (0.87 mL) and methanol (0.38 mL). After stirring at room temperature for 12 hours the solvent was removed in vacuo and the solid was dried in vacuo to give 2-(2,3-dichlorophenyl)-5-methylthiazole-4-carboxylic acid, lithium salt (120 mg, 0.40 mmol, 100% yield) as a white solid. The product was used in the next step without purification. ^{1}H NMR (400MHz, DMSO-d_6)

δ 8.05 (dd, *J*=7.9, 1.6 Hz, 1H), 7.69 (dd, *J*=8.0, 1.5 Hz, 1H), 7.51 - 7.41 (m, 1H), 2.74 (s, 3H).

Step 3. Prepared according to general method A with 2-(2,3-dichlorophenyl)-5-methylthiazole-4-carboxylic acid, lithium salt (20 mg, 0.07 mmol) and morpholine (7.0 µl, 0.08 mmol) to give **16** (20 mg, 0.06 mmol, 81% yield) as a white solid. MS (ESI) mass calculated for $[M+H]^+$ ($C_{15}H_{15}Cl_2N_2O_2S$) requires *m/z* 357.0, found *m/z* 357.0; ^{1}H NMR (400MHz, $CDCl_3$) δ 8.00 (dd, *J*=7.9, 1.6 Hz, 1H), 7.55 (dd, *J*=8.0, 1.5 Hz, 1H), 7.31 (t, *J*=7.9 Hz, 1H), 3.83 (br. s., 4H), 3.75 - 3.68 (m, 4H), 2.68 (s, 3H).

(4-(2,3-Dichlorophenyl)thiazol-2-yl)(morpholino)methanone (17). Step 1. Lithium hydroxide monohydrate (9.0 µl, 0.33 mmol) was added to a rapidly stirring solution of ethyl 4-(2,3-dichlorophenyl)thiazole-2-carboxylate (82 mg, 0.27 mmol) in tetrahydrofuran (2.6 mL), water (0.5 mL) and methanol (0.3 mL). After stirring at room temperature for 2 hours the reaction mixture was diluted with ethyl acetate and water and then acidified to pH 1 with 1N aqueous HCl. The organic layer was washed with brine, dried over Na_2SO_4, filtered and the solvent was removed in vacuo to give 4-(2,3-dichlorophenyl)thiazole-2-carboxylic acid (75 mg, 0.27 mmol, 100% yield) as a white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.42 (s, 1H), 7.75 (ddd, *J*=13.4, 8.0, 1.5 Hz, 2H), 7.49 (t, *J*=7.9 Hz, 1H).

Step 2. Prepared according to general method A with 4-(2,3-dichlorophenyl)thiazole-2-carboxylic acid (20 mg, 0.07 mmol) and morpholine (6.7 mg, 0.08 mmol) to give **17** (22 mg, 0.06 mmol, 89% yield) as a gum. MS (ESI) mass calculated for $[M+H]^+$ ($C_{14}H_{13}Cl_2N_2O_2S$) requires *m/z* 343.0, found *m/z* 343.0; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.66 (dd, *J*=7.8, 1.8 Hz, 1H), 7.52 (dd, *J*=8.0, 1.8 Hz, 1H), 7.30 (t, *J*=7.9 Hz, 1H), 4.57 - 4.49 (m, *J*=3.8 Hz, 2H), 3.89 - 3.76 (m, 6H).

4-((4-Methyl-2-(1-naphthyl)-1,3-thiazol-5-yl)carbonyl)morpholine (18). Step 1. Ethyl

2-chloro-3-oxobutanoate (2.7 mL, 19 mmol) was added to a solution of naphthalene-1-carbothioamide (3.5 g, 19 mmol) in ethanol (19 mL). The reaction vessel was sealed and heated with stirring at 80 °C for 19 hours and then cooled to room temperature. The excess solvent was removed in vacuo. The residue was purified on SiO_2 via Isco flash chromatography (0-20% ethyl acetate/hex, Isco 120 g column) to give ethyl 4-methyl-2-(naphthalen-1-yl)thiazole-5-carboxylate (4.6 g, 15 mmol, 82% yield) as a waxy white solid. MS (ESI) *m/z*: 298.1 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.77 (d, *J*=8.53 Hz, 1H), 7.98 (d, *J*=8.28 Hz, 1H), 7.89-7.95 (m, 1H), 7.85 (dd, *J*=1.13, 7.15 Hz, 1H), 7.49-7.66 (m, 3H), 4.40 (q, *J*=7.19 Hz, 2H), 2.89 (s, 3H), 1.42 (t, *J*=7.15 Hz, 3H).

Lithium hydroxide monohydrate (1.3 g, 31 mmol) was added to a rapidly stirring suspension of ethyl 4-methyl-2-(naphthalen-1-yl)thiazole-5-carboxylate (4.6 g, 15 mmol) in tetrahydrofuran (120 mL), water (24 mL) and methanol (12 mL). The reaction mixture was stirred at room temperature for 14 hours and was then diluted with ethyl acetate and acidified to pH 3 with 10% aqueous citric acid. The organic phase was washed with brine and the combined aqueous layers were further extracted with ethyl acetate (2 × 100 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated in vacuo. The product was used in subsequent steps without further purification. ^1H NMR (400 MHz, DMSO-d_6) δ 13.43 (br. s., 1H), 8.81 (d, *J*=8.28 Hz, 1H), 8.14 (d, *J*=8.28 Hz, 1H), 8.02-8.08 (m, 1H), 7.96 (dd, *J*=1.25, 7.28 Hz, 1H), 7.58-7.73 (m, 3H), 2.78 (s, 3H).

Step 3. Prepared according to general method A with 4-methyl-2-(naphthalen-1-yl)thiazole-5-carboxylic acid and morpholine to give **18**. MS (ESI) mass calculated for $[M+H]^+$ ($C_{19}H_{19}N_2O_2S$) requires *m/z* 339.1, found *m/z* 339.1; ^1H NMR (400MHz, $CDCl_3$) δ 8.76 (dd,

J=8.4, 0.9 Hz, 1H), 7.97 (d, J=8.3 Hz, 1H), 7.95 - 7.89 (m, 1H), 7.81 (dd, J=7.3, 1.3 Hz, 1H), 7.66 - 7.49 (m, 3H), 3.83 - 3.69 (m, 8H), 2.62 (s, 3H).

Morpholino(4-(naphthalen-1-yl)thiazol-2-yl)methanone (19). Step 1. Bromine (0.07 mL, 1.3 mmol) was added to a solution of 1-(naphthalen-1-yl)ethanone (0.22 g, 1.3 mmol) in acetic acid (6.6 mL). The reaction mixture was stirred at room temperature for 24 hours and was then concentrated in vacuo. The residue was loaded directly onto an Isco SiO_2 cartridge for purification via Isco flash chromatography (0-20% ethyl acetate/hexanes, 15 min linear gradient, Isco 24 g column). The desired fractions were combined and concentrated to give 2-bromo-1-(naphthalen-1-yl)ethanone (0.29 g, 1.2 mmol, 88% yield) as a colorless oil.

Step 2. Ethyl 2-amino-2-thioxoacetate (0.19 g, 1.4 mmol) was added to a solution of 2-bromo-1-(naphthalen-1-yl)ethanone (0.29 g, 1.2 mmol) in ethanol (5.8 mL). The reaction mixture was heated with stirring at 80 °C in a sealed vial for 16 hours and then the solvent was removed in vacuo. The residue was then loaded directly onto an Isco SiO_2 cartridge for purification via Isco flash chromatography (0-20% ethyl acetate/hexanes, 15 min linear gradient, Isco 4 g column). The desired fractions were combined and concentrated to give ethyl 4-(naphthalen-1-yl)thiazole-2-carboxylate (0.26 g, 0.94 mmol, 80% yield) as a waxy white solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 8.19 - 8.12 (m, 1H), 7.95 - 7.89 (m, 2H), 7.74 (s, 1H), 7.71 (dd, *J*=7.2, 1.1 Hz, 1H), 7.57 - 7.49 (m, 3H), 4.54 (q, *J*=7.0 Hz, 2H), 1.48 (t, *J*=7.2 Hz, 3H).

Step 3. Lithium hydroxide monohydrate (0.20 g, 4.7 mmol) was added to a rapidly stirring solution of ethyl 4-(naphthalen-1-yl)thiazole-2-carboxylate (0.26 g, 0.94 mmol) in tetrahydrofuran (9.0 mL), water (1.8 mL) and methanol (0. 9 mL). After stirring at room temperature for 1.5 hours the reaction mixture was diluted with ethyl acetate and water and then acidified to pH 1 with 1.0 N aqueous HCl. The organic layer was washed with brine, dried over

Na_2SO_4, filtered and the solvent was removed in vacuo to give a brown oil. The residue was purified on SiO_2 via Isco flash chromatography (0-40% ethyl acetate/hexanes, Isco 40 g column) to give only the decarboxylated product 4-(naphthalen-1-yl)thiazole after concentration. There were additional fractions that contained the correct product by LCMS, but they also gave the decarboxylated product upon concentration. Because of this decomposition pathway, crude Isco fractions of 4-(naphthalen-1-yl)thiazole-2-carboxylic acid in ethyl acetate/hexanes were taken as a solution into the next step and thus no further characterization was possible.

Step 4. Triethylamine (33 µl, 0.24 mmol) and 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide (T3P) (120 µl, 0.20 mmol) were added to the Isco fractions from step 3 containing 4-(naphthalen-1-yl)thiazole-2-carboxylic acid and morpholine (8.2 µl, 0.09 mmol) in dichloromethane (1.1 mL). The reaction mixture was stirred at room temperature for 3 hours and was then loaded directly onto a SiO_2 cartridge for purification via Isco flash chromatography (0-100% ethyl acetate/hexanes, 15 min linear gradient, Isco 4 g column). The product was further purified by preparativeHPLC (Sunfire 5µ C18 30 × 100 mm column, 15 minute gradient from 10 to 100% B in A, A = 10:90 methanol: water with 0.1% trifluoroacetic acid, B = 90:10 methanol: water with 0.1% trifluoroacetic acid). The desired fraction was concentrated to give **19** (15 mg, 0.04 mmol, 56% yield) as a sticky solid. MS (ESI) mass calculated for $[M+H]^+$ ($C_{18}H_{17}N_2O_2S$) requires *m/z* 325.1, found *m/z* 325.2; ^{1}H NMR (400MHz, $CDCl_3$) δ 8.21 - 8.15 (m, 1H), 7.97 - 7.91 (m, 2H), 7.71 - 7.65 (m, 2H), 7.59 - 7.48 (m, 3H), 4.58 (br. s., 2H), 3.86 (d, *J*=6.3 Hz, 4H), 3.76 (br. s., 2H).

Morpholino(2-(naphthalen-1-yl)thiazol-5-yl)methanone (Compound 20). Step 1. A solution of naphthalene-1-carbothioamide (0.1 g, 0.53 mmol) and ethyl 2-chloro-3-oxopropanoate (1.8 mL, 0.53 mmol) in dioxane (2.7 mL) was heated with stirring at 100 °C in a

sealed vial. After 36 hours the reaction mixture was cooled to room temperature and the solvent was removed in vacuo. Ethyl 2-(naphthalen-1-yl)thiazole-5-carboxylate (0.15 g, 0.53 mmol, 99% yield) was obtained as a yellow solid and was used without purification.

Step 2. Lithium hydroxide monohydrate (0.12 g, 2.8 mmol) was added to a stirring solution of ethyl 2-(naphthalen-1-yl)thiazole-5-carboxylate (0.15 g, 0.53 mmol) in tetrahydrofuran (5.4 mL), water (1.1 mL) and methanol (0.54 mL). After stirring at room temperature for 3 hours the reaction mixture was diluted with ethyl acetate and water and acidified to pH 1 with 1N aqueous HCl. The organic layer was washed with brine and the combined aqueous layers were further extracted with ethyl acetate. The organic extracts were dried over Na_2SO_4, filtered and the solvent was removed in vacuo to give a red solid that was carried directly to the next step.

Step 3. Triethylamine (33 µl, 0.24 mmol) and 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide (T3P) (120 µl, 0.20 mmol) were added to a solution of the solid from step 2 containing 2-(naphthalen-1-yl)thiazole-5-carboxylic acid (20 mg, 0.08 mmol) and morpholine (8.5 mg, 0.10 mmol) in dichloromethane (1.1 mL) at room temperature. The reaction mixture was stirred for 4 hours and was then loaded directly onto an Isco SiO_2 cartridge for purification via Isco flash chromatography (0-100% ethyl acetate/hexanes, 15 min linear gradient, Isco 4 g column). The residue required further purification by preparatory HPLC (Sunfire 5µ C18 30x100 mm column, 15 minute gradient from 10 to 100% B in A, A = 10:90 methanol: water with 0.1% trifluoroacetic acid, B = 90:10 methanol: water with 0.1% trifluoroacetic acid). The product containing fractions were combined and concentrated to give **20** (12 mg, 0.04 mmol, 46% yield) as a gum. MS (ESI) mass calculated for $[M+H]^+$ ($C_{18}H_{17}N_2O_2S$) requires *m/z* 325.1, found *m/z* 325.1; ^{1}H NMR (400MHz, $CDCl_3$) δ 8.73 (dd,

J=8.3, 1.0 Hz, 1H), 8.17 (s, 1H), 8.01 (d, *J*=8.3 Hz, 1H), 7.96 - 7.92 (m, 1H), 7.85 (dd, *J*=7.2, 1.1 Hz, 1H), 7.66 - 7.51 (m, 3H), 3.90 - 3.78 (m, 8H).

(5-Methyl-2-(naphthalen-1-yl)thiazol-4-yl)(morpholino)methanone (21). Step 1. Naphthalene-1-carbothioamide (0.1 g, 0.53 mmol) was added to a solution of methyl 3-bromo-2-oxobutanoate (0.12 g, 0.59 mmol) in ethanol (1.1 mL). The reaction vessel was sealed and heated with stirring at 80 °C for 18 hours. The solvents were removed in vacuo and the residue was purified on SiO_2 via Isco flash chromatography (0-40% ethyl acetate/hexanes, Isco 24 g column) to give a mixture of methyl 5-methyl-2-(naphthalen-1-yl)thiazole-4-carboxylate and ethyl 5-methyl-2-(naphthalen-1-yl)thiazole-4-carboxylate as a yellow oil.

Step 2. Lithium hydroxide monohydrate (17 mg, 0.41 mmol) was added to a rapidly stirring solution of the mixture from step 1 (120 mg, 0.41 mmol) in tetrahydrofuran (4.0 mL), water (0.8 mL) and methanol (0.4 mL). After stirring at room temperature for 12 hours the solvent was removed in vacuo and the solid was dried to give 5-methyl-2-(naphthalen-1-yl)thiazole-4-carboxylic acid, lithium salt (114 mg, 0.41 mmol, 100% yield) as a white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.76 - 8.67 (m, 1H), 8.07 - 7.99 (m, 2H), 7.81 (dd, *J*=7.3, 1.0 Hz, 1H), 7.65 - 7.56 (m, 3H), 2.75 (s, 3H).

Step 3. Prepared according to general method A with 5-methyl-2-(naphthalen-1-yl)thiazole-4-carboxylic acid, lithium salt and morpholine to give **21** as a white solid. MS (ESI) mass calculated for $[M+H]^+$ ($C_{19}H_{19}N_2O_2S$) requires *m/z* 339.1, found *m/z* 339.1; ^{1}H NMR (400MHz, $CDCl_3$) δ 8.84 - 8.76 (m, 1H), 7.99 - 7.88 (m, 2H), 7.79 (dd, *J*=7.3, 1.3 Hz, 1H), 7.63 - 7.48 (m, 3H), 3.94 - 3.67 (m, 8H), 2.71 (s, 3H).

4-Methyl-2-(naphthalen-1-yl)thiazole-5-carboxamide (22). Prepared according to general method A with 4-methyl-2-(naphthalen-1-yl)thiazole-5-carboxylic acid and ammonium

chloride to give **22**. MS (ESI) mass calculated for $[M+H]^+$ ($C_{15}H_{13}N_2OS$) requires *m/z* 269.1, found *m/z* 269.0; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (d, *J*=8.53 Hz, 1H), 7.99 (d, *J*=8.28 Hz, 1H), 7.93 (d, *J*=7.28 Hz, 1H), 7.84 (dd, *J*=1.13, 7.15 Hz, 1H), 7.48-7.67 (m, 3H), 5.69 (br. s., 2H), 2.88 (s, 3H).

N,N,4-Trimethyl-2-(naphthalen-1-yl)thiazole-5-carboxamide (**23**). Prepared according to general method A with 4-methyl-2-(naphthalen-1-yl)thiazole-5-carboxylic acid and dimethylamine to give **23**. MS (ESI) mass calculated for $[M+H]^+$ ($C_{17}H_{17}N_2OS$) requires *m/z* 297.1, found *m/z* 297.0; ^{1}H NMR (500MHz, CD_3OD) δ 7.20 (d, *J*=7.9 Hz, 1H), 6.63 (d, *J*=7.9 Hz, 1H), 6.59 - 6.54 (m, 1H), 6.42 (d, *J*=6.4 Hz, 1H), 6.22 (s, 2H), 6.24 - 6.15 (m, 2H), 1.81 (s, 6H), 1.19 (s, 3H).

1-((4-Methyl-2-(1-naphthyl)-1,3-thiazol-5-yl)carbonyl)piperidine (24). Prepared according to general method A with 4-methyl-2-(naphthalen-1-yl)thiazole-5-carboxylic acid and piperidine to give **24**. MS (ESI) mass calculated for $[M+H]^+$ ($C_{20}H_{21}N_2OS$) requires *m/z* 337.1, found 337.0; ^{1}H NMR (500 MHz, CD_3OD) δ 8.57 (d, *J*=7.93 Hz, 1H), 7.99 (d, *J*=8.42 Hz, 1H), 7.89-7.94 (m, 1H), 7.75-7.80 (m, 1H), 7.50-7.58 (m, 3H), 3.51-3.81 (m, 4H), 2.54 (s, 3H), 1.74 (d, *J*=4.46 Hz, 2H), 1.67 (br. s., 4H).

N-(2-Methoxyethyl)-N,4-dimethyl-2-(naphthalen-1-yl)thiazole-5-carboxamide (**25**). Prepared according to general method A with 4-methyl-2-(naphthalen-1-yl)thiazole-5-carboxylic acid and 2-methoxy-N-methylethanamine to give **25**. MS (ESI) mass calculated for $[M+H]^+$ ($C_{19}H_{21}N_2O_2S$) requires *m/z* 341.1, found 341.0; 1H NMR (500MHz, DMSO-d_6) δ 8.85 (d, *J*=8.4 Hz, 1H), 8.11 (d, *J*=8.4 Hz, 1H), 8.05 (d, *J*=7.4 Hz, 1H), 7.91 (d, *J*=7.4 Hz, 1H), 7.71 - 7.59 (m, 3H), 3.73 - 3.46 (m, 4H), 3.05 (br. s., 3H), 2.47 (s, 4H) additional peaks lost under H_2O peak.

N-(2-Methoxyethyl)-4-methyl-2-(naphthalen-1-yl)thiazole-5-carboxamide (26). Prepared according to general method A with 4-methyl-2-(naphthalen-1-yl)thiazole-5-carboxylic acid and 2-methoxyethanamine to give **26**. MS (ESI) mass calculated for $[M+H]^+$ ($C_{18}H_{19}N_2O_2S$) requires *m/z* 327.1, found 327.0; ^{1}H NMR (500MHz, CD_3OD) δ 7.16 (d, *J*=7.4 Hz, 1H), 6.61 (d, *J*=7.9 Hz, 1H), 6.57 - 6.52 (m, 1H), 6.40 (d, *J*=6.4 Hz, 1H), 6.20 - 6.13 (m, 1H), 2.94 (s, 2H), 2.20 (s, 4H), 2.02 (s, 3H), 1.38 (s, 3H).

N-(2-Hydroxyethyl)-N,4-dimethyl-2-(naphthalen-1-yl)thiazole-5-carboxamide (27). Prepared according to general method A with 4-methyl-2-(naphthalen-1-yl)thiazole-5-carboxylic acid and 2-(methylamino)ethanol to give **27**. MS (ESI) mass calculated for $[M+H]^+$ ($C_{18}H_{19}N_2O_2S$) requires *m/z* 327.1, found 327.0; ^{1}H NMR (500MHz, DMSO-d_6) δ 8.85 (d, *J*=7.9 Hz, 1H), 8.11 (d, *J*=7.9 Hz, 1H), 8.07 - 8.01 (m, 1H), 7.91 (d, *J*=6.9 Hz, 1H), 7.74 - 7.54 (m, 3H), 4.86 (t, *J*=5.2 Hz, 1H), 3.70 - 3.50 (m, 3H), 3.05 (br. s., 3H), 2.47 (s, 3H).

N-(2-Hydroxyethyl)-N-isopropyl-4-methyl-2-(naphthalen-1-yl)thiazole-5-carboxamide (28). Prepared according to general method A with 4-methyl-2-(naphthalen-1-yl)thiazole-5-carboxylic acid and 2-(isopropylamino)ethanol to give **28**. MS (ESI) mass calculated for $[M+H]^+$ ($C_{20}H_{23}N_2O_2S$) requires *m/z* 355.1, found 355.1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (br. s., 1H), 8.73 (d, *J*=8.53 Hz, 1H), 7.88-8.06 (m, 2H), 7.79-7.87 (m, 1H), 7.44-7.68 (m, 3H), 4.93 (t, *J*=5.40 Hz, 1H), 4.75 (t, *J*=5.40 Hz, 1H), 4.07 (br. s., 1H), 3.41 (br. s., 2H), 2.90 (s, 1H), 2.87 (s, 2H), 1.47 (d, *J*=6.53 Hz, 6H).

(4-Hydroxypiperidin-1-yl)(4-methyl-2-(naphthalen-1-yl)thiazol-5-yl)methanone (29). Prepared according to general method A with 4-methyl-2-(naphthalen-1-yl)thiazole-5-carboxylic acid and piperidin-4-ol to give **29**. MS (ESI) mass calculated for $[M+H]^+$ ($C_{20}H_{21}N_2O_2S$) requires *m/z* 353.1, found 353.2; ^{1}H NMR (400MHz, $CDCl_3$) δ 8.77 (d, *J*=8.5 Hz, 1H), 7.97 (d, *J*=8.3 Hz,

1H), 7.94 - 7.88 (m, 1H), 7.82 (dd, *J*=7.3, 1.3 Hz, 1H), 7.65 - 7.49 (m, 3H), 4.06 (tt, *J*=7.8, 3.7 Hz, 2H), 3.46 (t, *J*=9.3 Hz, 2H), 2.61 (s, 3H), 2.04 - 1.93 (m, 2H), 1.72 - 1.59 (m, 4H).

(4-Hydroxyazepan-1-yl)(4-methyl-2-(naphthalen-1-yl)thiazol-5-yl)methanone (30). Prepared according to general method A with 4-methyl-2-(naphthalen-1-yl)thiazole-5-carboxylic acid and azepan-4-ol to give **30**. MS (ESI) mass calculated for $[M+H]^+$ ($C_{21}H_{23}N_2O_2S$) requires *m/z* 367.1, found 367.1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (d, *J*=8.53 Hz, 1H), 7.96 (d, *J*=8.28 Hz, 1H), 7.92 (dd, *J*=1.00, 8.28 Hz, 1H), 7.81 (dd, *J*=1.13, 7.15 Hz, 1H), 7.50-7.64 (m, 3H), 4.03 (br. s., 1H), 3.52-3.87 (m, 4H), 2.60 (s, 3H), 1.96-2.21 (m, 2H), 1.72-1.99 (m, 4H), 1.45 (br. s., 1H).

(4-(Hydroxymethyl)piperidin-1-yl)(4-methyl-2-(naphthalen-1-yl)thiazol-5-yl)methanone (31). Prepared according to general method A with 4-methyl-2-(naphthalen-1-yl)thiazole-5-carboxylic acid and piperidin-4-ylmethanol to give **31**. MS (ESI) mass calculated for $[M+H]^+$ ($C_{21}H_{23}N_2O_2S$) requires *m/z* 367.1, found 367.1; ^{1}H NMR (400MHz, $CDCl_3$) δ 8.77 (d, *J*=8.5 Hz, 1H), 7.96 (d, *J*=8.3 Hz, 1H), 7.94 - 7.87 (m, 1H), 7.81 (dd, *J*=7.2, 1.1 Hz, 1H), 7.65 - 7.48 (m, 4H), 3.58 (t, *J*=5.6 Hz, 2H), 3.02 (br. s., 2H), 2.59 (s, 3H), 1.95 - 1.75 (m, 4H), 1.38 - 1.22 (m, 3H).

(4-Methyl-2-(naphthalen-1-yl)thiazol-5-yl)(piperazin-1-yl)methanone, HCl (32). Prepared according to general method A with 4-methyl-2-(naphthalen-1-yl)thiazole-5-carboxylic acid and *tert*-butyl piperazine-1-carboxylate to give **32** after HCl mediated deprotection. MS (ESI) mass calculated for $[M+H]^+$ ($C_{19}H_{20}N_3OS$) requires *m/z* 338.1, found 338.1; ^{1}H NMR (400MHz, $CDCl_3$) δ 9.11 (br. s., 1H), 8.48 (d, *J*=8.5 Hz, 1H), 8.05 (d, *J*=8.3 Hz, 1H), 7.99 - 7.92 (m, 1H), 7.80 (d, *J*=7.0 Hz, 1H), 7.69 - 7.50 (m, 3H), 4.09 (br. s., 4H), 3.42 (br. s., 4H), 2.66 (s, 3H).

N,4-Dimethyl-N-((1-methyl-1H-pyrazol-4-yl)methyl)-2-(1-naphthyl)-1,3-thiazole-5-carboxamide (**33**). Prepared according to general method A with 4-methyl-2-(naphthalen-1-yl)thiazole-5-carboxylic acid and N-methyl-1-(1-methyl-1H-pyrazol-3-yl)methanamine to give **33**. MS (ESI) mass calculated for $[M+H]^+$ ($C_{21}H_{21}N_4OS$) requires *m/z* 377.1, found 377.1; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.84 (d, *J*=8.42 Hz, 1H), 8.11 (d, *J*=8.42 Hz, 1H), 8.05 (d, *J*=7.43 Hz, 1H), 7.92 (d, *J*=6.94 Hz, 1H), 7.70 (br. s., 1H), 7.59-7.68 (m, 3H), 7.40 (br. s., 1H), 4.48 (s, 2H), 3.82 (s, 3H), 2.97 (s, 3H), 2.46 (s, 3H).

(6,7-Dihydro-1H-imidazo[4,5-c]pyridin-5(4H)-yl)(4-methyl-2-(naphthalen-1-yl)thiazol-5-yl)methanone (34). Prepared according to general method A with 4-methyl-2-(naphthalen-1-yl)thiazole-5-carboxylic acid and 4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine to give **34**. MS (ESI) mass calculated for $[M+H]^+$ ($C_{21}H_{19}N_4OS$) requires *m/z* 375.1, found 375.1; ^{1}H NMR (400MHz, $CDCl_3$) δ 8.72 (d, *J*=8.3 Hz, 1H), 8.51 (s, 1H), 7.97 (d, *J*=8.3 Hz, 1H), 7.93 - 7.87 (m, 1H), 7.80 (dd, *J*=7.2, 1.1 Hz, 1H), 7.66 - 7.47 (m, 3H), 4.83 (br. s., 2H), 3.96 (t, *J*=4.6 Hz, 2H), 2.90 (br. s., 2H), 2.60 (s, 3H).

N,4-Dimethyl-2-(1-naphthyl)-N-(2-(3-pyridinyl)ethyl)-1,3-thiazole-5-carboxamide (35). Prepared according to general method A with 4-methyl-2-(naphthalen-1-yl)thiazole-5-carboxylic acid and N-methyl-2-(pyridin-3-yl)ethan-1-amine to give **35**. MS (ESI) mass calculated for $[M+H]^+$ ($C_{23}H_{22}N_3OS$) requires *m/z* 388.1, found 388.1; ^{1}H NMR (500 MHz, CD_3OD) δ 8.53 (d, *J*=8.42 Hz, 1H), 8.41 (d, *J*=3.47 Hz, 1H), 7.98 (d, *J*=8.42 Hz, 1H), 7.90-7.94 (m, 1H), 7.74 (d, *J*=6.44 Hz, 1H), 7.51-7.57 (m, 3H), 7.36 (br. s., 1H), 4.28 (s, 1H), 3.83 (br. s., 2H), 3.14 (br. s., 3H), 3.04 (br. s., 2H), 2.43 (s, 3H).

N,4-Dimethyl-2-(1-naphthyl)-N-(3-pyridinylmethyl)-1,3-thiazole-5-carboxamide (36). Prepared according to general method A with 4-methyl-2-(naphthalen-1-yl)thiazole-5-

carboxylic acid and N-methyl-1-(pyridin-3-yl)methanamine to give **36**. MS (ESI) mass calculated for $[M+H]^+$ ($C_{22}H_{20}N_3OS$) requires *m/z* 374.1, found 374.1; ^{1}H NMR (500 MHz, CD_3OD) δ 8.57 (d, *J*=8.42 Hz, 2H), 8.51 (dd, *J*=1.49, 4.95 Hz, 1H), 7.99 (d, *J*=8.42 Hz, 1H), 7.90-7.94 (m, 1H), 7.82 (br. s., 1H), 7.77 (d, *J*=6.94 Hz, 1H), 7.50-7.57 (m, 3H), 7.44 (dd, *J*=4.95, 7.43 Hz, 1H), 4.80 (s, 2H), 3.12 (s, 3H), 2.56 (s, 3H).

(4-(Hydroxymethyl)piperidin-1-yl)(3-methyl-5-(naphthalen-1-yl)thiophen-2-yl)methanone (37). Step 1. A mixture of 1-bromonaphthalene (180 mg, 0.86 mmol), (5-formyl-4-methylthiophen-2-yl)boronic acid (140 mg, 0.82 mmol), $PdCl_2$(dppf)-CH_2Cl_2 adduct (20 mg, 0.02 mmol) and K_2CO_3 (280 mg, 2.06 mmol) in tetrahydrofuran (3 mL) and water (1.5 mL) was degassed by bubbling argon through the mixture. The reaction flask was sealed and then heated with stirring at 75 °C overnight. The reaction mixture was diluted with ethyl acetate, washed with water and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified on SiO_2 via Isco flash chromatography (0-10% ethyl acetate/hexanes) to afford 3-methyl-5-(naphthalen-1-yl)thiophene-2-carbaldehyde (40 mg, 0.16 mmol, 19% yield). ^{1}H NMR (500MHz, $CDCl_3$) δ 10.11 (s, 1H), 8.23 - 8.16 (m, 1H), 7.96 - 7.89 (m, 2H), 7.61 - 7.48 (m, 4H), 7.14 (s, 1H), 2.67 (s, 3H).

Step 2. A solution of sodium chlorite (32 mg, 0.28 mmol) in water (0.3 mL) was added dropwise to a solution of 3-methyl-5-(naphthalen-1-yl)thiophene-2-carbaldehyde (40 mg, 0.16 mmol) and sodium dihydrogen phosphate (28 mg, 0.24 mmol) in DMSO (1 mL), the resulting suspension was allowed to stir under argon at room temperature overnight. The reaction mixture was diluted with water, acidified to pH 3 with 1N aqueous HCl, extracted twice with ethyl acetate and concentrated to an oil which became a light yellow solid upon standing. The solid was then triturated with hexane to afford 3-methyl-5-(naphthalen-1-yl)thiophene-2-carboxylic

acid (46 mg, 0.15 mmol, 94% yield) after drying in vacou. The product was used in subsequent steps without further purification.

Step 3. Prepared according to general method A with 3-methyl-5-(naphthalen-1-yl)thiophene-2-carboxylic acid and piperidin-4-ylmethanol to give **37**. MS (ESI) mass calculated for $[M+H]^+$ ($C_{22}H_{24}NO_2S$) requires *m/z* 366.1, found 366.1; ^{1}H NMR (500MHz, $CDCl_3$) δ 8.29 - 8.23 (m, 1H), 7.93 - 7.85 (m, 2H), 7.59 - 7.46 (m, 4H), 7.00 (s, 1H), 4.42 (br. s., 2H), 3.57 (d, *J*=5.8 Hz, 2H), 3.06 - 2.94 (m, 2H), 2.35 (s, 3H), 1.90 - 1.83 (m, 2H), 1.43 (dt, *J*=14.2, 7.2 Hz, 1H), 1.36 - 1.29 (m, 2H).

(4-(Hydroxymethyl)piperidin-1-yl)(2-methyl-5-(naphthalen-1-yl)thiophen-3-yl)methanone (38). Step 1. To a solution of 5-bromo-2-methylthiophene-3-carboxylic acid (100 mg, 0.45 mmol) and piperidin-4-ylmethanol (55 mg, 0.48 mmol) in dichloromethane (2.0 mL) was added Hunig's base (0.24 mL, 1.4 mmol) followed by 1-propanephosphonic acid cyclic anhydride (T3P), 50% solution in ethyl acetate (0.42 mL, 0.81 mmol). The resulting solution was stirred under argon at room temperature for 30 minutes. The reaction mixture was loaded onto an Isco SiO_2 column for purification via Isco flash chromatography (0-40% ethyl acetate/hexanes) to afford (5-bromo-2-methylthiophen-3-yl)(4-(hydroxymethyl)piperidin-1-yl)methanone (110 mg, 0.35 mmol, 76% yield). MS (ESI) *m/z*: 320.0 $[M+H]^+$; ^{1}H NMR (500MHz, $CDCl_3$) δ 6.80 (s, 1H), 4.64 (d, *J*=11.3 Hz, 1H), 3.68 (d, *J*=6.6 Hz, 1H), 3.48 - 3.37 (m, 2H), 2.98 (d, *J*=11.3 Hz, 1H), 2.77 - 2.60 (m, 2H), 2.35 (s, 3H), 1.80 (d, *J*=10.7 Hz, 1H), 1.39 - 1.30 (m, 1H), 1.25 - 1.13 (m, 1H), 1.07 (d, *J*=9.4 Hz, 1H).

Step 2. A mixture of naphthalen-1-ylboronic acid (25.0 mg, 0.14 mmol), (5-bromo-2-methylthiophen-3-yl)(4-(hydroxymethyl)piperidin-1-yl)methanone (44 mg, 0.14 mmol), $PdCl_2$(dppf)-CH_2Cl_2 adduct (3.4 mg, 4.2 μmol) and K_2CO_3 (49 mg, 0.35 mmol) in

tetrahydrofuran (1 mL) and water (0.5 mL) was degassed by bubbling argon through the mixture for several minutes. The reaction flask was sealed and then heated with stirring at 80 °C for 2 hours until LCMS analysis indicated complete conversion. The reaction mixture was diluted with 0.1 M aqueous HCl and extracted twice with ethyl acetate. The organic layers were dried over $MgSO_4$, filtered and concentrated to dryness in vacuo. The residue was purified on SiO_2 via Isco flash chromatography (0-100% ethyl acetate/hexanes) to afford **38** (35 mg, 0.09 mmol, 66% yield); MS (ESI) mass calculated for $[M+H]^+$ ($C_{22}H_{24}NO_2S$) requires *m/z* 366.1, found 366.2; ^{1}H NMR (500MHz, $CDCl_3$) δ 8.28 - 8.22 (m, 1H), 7.92 - 7.87 (m, 1H), 7.85 (d, *J*=8.3 Hz, 1H), 7.56 - 7.43 (m, 4H), 7.02 (s, 1H), 4.77 (br. s., 1H), 3.92 (br. s., 1H), 3.52 (br. s., 2H), 3.07 (br. s., 1H), 2.78 (br. s., 1H), 2.54 (s, 3H), 1.93 - 1.72 (m, 4H), 1.34 - 1.30 (m, 1H).

(4-(Hydroxymethyl)piperidin-1-yl)(3-methyl-5-(naphthalen-1-yl)furan-2-yl)methanone (39). Step 1. To a degassed solution of methyl 5-bromo-3-methylfuran-2-carboxylate (230 mg, 1.0 mmol), naphthalen-1-ylboronic acid (270 mg, 1.6 mmol) and K_2CO_3 (440 mg, 3.2 mmol) in dioxane (9 mL) and water (3 mL) was added $Pd(Ph_3P)_4$ (73 mg, 0.06 mmol). The reaction mixture was stirred at 100 °C overnight. The reaction mixture was then cooled to room temperature, diluted with water and extracted 3 times with dichloromethane. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified on SiO_2 via Isco flash chromatography (0-35% ethyl acetate/hexanes) to give methyl 3-methyl-5-(naphthalen-1-yl)furan-2-carboxylate (190 mg, 0.72 mmol, 69% yield). ^{1}H NMR (500MHz, $CDCl_3$) δ 8.44 - 8.38 (m, 1H), 7.94 - 7.87 (m, 2H), 7.82 (dd, *J*=7.2, 1.1 Hz, 1H), 7.61 - 7.50 (m, 3H), 6.71 (s, 1H), 3.95 (s, 3H), 2.49 (s, 3H).

Step 2. To a solution of methyl 3-methyl-5-(naphthalen-1-yl)furan-2-carboxylate (190 mg, 0.71 mmol) in tetrahydrofuran (5 mL) was added a 1M aqueous solution of lithium

hydroxide (2.1 mL, 2.1 mmol).The reaction mixture was stirred at room temperature until LCMS analysis indicated complete conversion. The reaction mixture was then washed with 1N aqueous HCl and extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain 3-methyl-5-(naphthalen-1-yl)furan-2-carboxylic acid (170 mg, 0.67 mmol, 94% yield) ^{1}H NMR (500MHz, $CDCl_3$) δ 8.47 - 8.41 (m, 1H), 7.92 (d, *J*=8.3 Hz, 2H), 7.85 (dd, *J*=7.2, 1.1 Hz, 1H), 7.63 - 7.58 (m, 1H), 7.57 - 7.52 (m, 2H), 6.76 (s, 1H), 2.53 (s, 3H).

Step 3. Prepared according to general method A with 3-methyl-5-(naphthalen-1-yl)furan-2-carboxylic acid and piperidin-4-ylmethanol to give **39**. MS (ESI) mass calculated for $[M+H]^+$ ($C_{22}H_{24}NO_3$) requires *m/z* 350.2, found 350.0; ^{1}H NMR (500MHz, $CDCl_3$) δ 8.43 - 8.36 (m, 1H), 7.94 - 7.85 (m, 2H), 7.73 (dd, *J*=7.3, 1.2 Hz, 1H), 7.60 - 7.49 (m, 3H), 6.68 (s, 1H), 4.58 (br. s., 2H), 3.55 (d, *J*=5.8 Hz, 2H), 2.39 (s, 3H), 1.91 - 1.78 (m, 3H), 1.52 (br. s., 3H), 1.42 - 1.28 (m, 2H).

(4-(Hydroxymethyl)piperidin-1-yl)(1-methyl-4-(naphthalen-1-yl)-1H-pyrrol-2-yl)methanone (40). Step 1. To a degassed solution of methyl 4-bromo-1-methyl-1H-pyrrole-2-carboxylate (0.62 g, 2.8 mmol), naphthalen-1-ylboronic acid (0.61 g, 3.5 mmol) and K_2CO_3 (0.98 g, 7.1 mmol) in dioxane (11 mL) and water (3.5 mL) was added $Pd(Ph_3P)_4$ (0.16 g, 0.14 mmol). The reaction mixture was heated with stirring at 100 °C. After 18 hours, LCMS analysis indicated complete conversion and the reaction mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified on SiO_2 via Isco flash chromatography (0-100% ethyl acetate/hexanes) to give methyl 1-methyl-4-(naphthalen-1-yl)-1H-pyrrole-2-carboxylate. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 - 8.20 (m, 1H), 7.96 - 7.87 (m, 1H), 7.85 - 7.77 (dt, *J* = 8.0, 1.1 Hz, 1H), 7.57 -

7.41 (m, 4H), 7.26 - 7.20 (d, *J* = 2.0 Hz, 1H), 7.10 - 7.01 (d, *J* = 2.2 Hz, 1H), 4.13 - 4.03 (s, 3H), 3.99 - 3.83 (s, 3H).

Step 2. To a suspension of methyl 1-methyl-4-(naphthalen-1-yl)-1H-pyrrole-2-carboxylate (0.62 g, 2.3 mmol) in methanol (23 mL) was added 1N aqueous lithium hydroxide (7.7 mL, 7.7 mmol). The mixture was heated with stirring at 50 °C while the reaction progress was monitored periodically by LCMS. Once complete, the reaction mixture was cooled to room temperature, diluted with water (20 mL) and acidified with 1N aqueous HCl giving a white precipitate. The solid was collected via suction filtration and dried to afford 1-methyl-4-(naphthalen-1-yl)-1H-pyrrole-2-carboxylic acid. ^{1}H NMR (500MHz, $CDCl_3$) δ 8.25 (d, *J*=5.8 Hz, 1H), 7.90 (d, *J*=5.2 Hz, 1H), 7.81 (d, *J*=7.4 Hz, 1H), 7.58 - 7.43 (m, 4H), 7.38 (br. s., 1H), 7.10 (br. s., 1H), 4.07 (br. s., 3H).

Step 3. To a suspension of 1-methyl-4-(naphthalen-1-yl)-1H-pyrrole-2-carboxylic acid (13 mg, 0.05 mmol), piperidin-4-ylmethanol (8.8 mg, 0.08 mmol), HOBT (12.0 mg, 0.08 mmol), and EDC (20 mg, 0.10 mmol) in DMF (510 µl) was added Hunig's base (36 µl, 0.20 mmol) slowly. The resulting mixture was stirred at room temperature overnight giving complete conversion based on HPLC analysis. The excess solvent was removed in vacuo and the residue was purified via preparativeHPLC (Sunfire 5µ C18 30 × 100 mm column, 10 minute gradient from 10 to 100% B in A, A = 10:90 methanol: water with 0.1% trifluoroacetic acid, B = 90:10 methanol: water with 0.1% trifluoroacetic acid). The fractions containing desired product were passed through a $NaHCO_3$-polymer supported cartridge to remove TFA. The solvents were then removed in vacuo to give **40**. MS (ESI) mass calculated for $[M+H]^+$ ($C_{22}H_{25}N_2O_2$) requires *m/z* 349.2, found 348.9; ^{1}H NMR (500MHz, $CDCl_3$) δ 8.28 (dd, *J*=8.3, 1.4 Hz, 1H), 7.91 - 7.85 (m, 1H), 7.78 (d, *J*=7.7 Hz, 1H), 7.53 - 7.40 (m, 4H), 6.94 (d, *J*=1.9 Hz, 1H), 6.59 (d, *J*=1.9 Hz, 1H),

4.64 (d, *J*=12.7 Hz, 2H), 3.89 (s, 3H), 3.56 (d, *J*=5.8 Hz, 2H), 2.98 (br. s., 2H), 1.90 - 1.77 (m, 3H), 1.37 - 1.22 (m, 2H).

(4-(Hydroxymethyl)piperidin-1-yl)(2-methyl-5-(naphthalen-1-yl)-1H-pyrrol-3-yl)methanone (41). Step 1. To a round bottom flask containing ethyl 2-methyl-1H-pyrrole-3-carboxylate (0.5 g, 3.3 mmol) in DMF (13 mL) was added N-bromosuccinimide (0.61 g, 3.4 mmol). The reaction mixture was stirred at room temperature for 40 minutes. Water (40 mL) was added resulting in precipitate formation. The solid was isolated by suction filtration to give ethyl 5-bromo-2-methyl-1H-pyrrole-3-carboxylate. ^{1}H NMR (400MHz, DMSO-d_6) δ 11.88 (br. s., 1H), 6.31 (s, 1H), 4.14 (q, *J*=7.1 Hz, 2H), 2.37 (s, 3H), 1.23 (t, *J*=7.1 Hz, 3H).

Step 2. To a degassed solution of ethyl 5-bromo-2-methyl-1H-pyrrole-3-carboxylate (0.75 g, 3.2 mmol), naphthalen-1-ylboronic acid (0.70 g, 4.0 mmol) and K_2CO_3 (1.1 g, 8.1 mmol) in dioxane (34 mL) and water (11 mL) was added $Pd(Ph_3P)_4$ (0.19 g, 0.16 mmol). The reaction mixture was heated with stirring at 100 °C until LCMS analysis indicated complete conversion. Most of the solvent was removed and the residue was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified on SiO_2 via Isco flash chromatography (0-60% ethyl acetate/hexanes). The product containing fractions were combined and concentrated to afford ethyl 2-methyl-5-(naphthalen-1-yl)-1H-pyrrole-3-carboxylate. ^{1}H NMR (400MHz, $CDCl_3$) δ 8.32 (br. s., 1H), 8.29 - 8.23 (m, 1H), 7.94 - 7.87 (m, 1H), 7.86 - 7.78 (m, 1H), 7.56 - 7.51 (m, 2H), 7.51 - 7.47 (m, 2H), 6.84 (d, *J*=2.9 Hz, 1H), 4.34 (q, *J*=7.0 Hz, 2H), 2.66 (s, 3H), 1.39 (t, *J*=7.2 Hz, 3H).

Step 3. To a suspension of ethyl 2-methyl-5-(naphthalen-1-yl)-1H-pyrrole-3-carboxylate (0.66 g, 2.4 mmol) in methanol (24 mL) was added 1N aqueous lithium hydroxide (7.8 mL, 7.8

mmol). The mixture was heated to 50 °C while the reaction was monitored periodically by LCMS. After 17 hours there was remaining starting material so additional methanol (10 mL) and 1N aqueous lithium hydroxide (5 mL) were added and heating was increased to 70 °C. After 48 hours LCMS indicated complete consumption of starting material and formation of desired product. The reaction mixture was cooled to room temperature and extracted with ethyl acetate (3 × 10 mL). The organic layers were discarded and the aqueous layer was acidified with 1N aqueous HCl giving precipitate formation. The suspension was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated and then lyophilized to afford 2-methyl-5-(naphthalen-1-yl)-1H-pyrrole-3-carboxylic acid which was used without further purification.

Step 4. To a solution of 2-methyl-5-(naphthalen-1-yl)-1H-pyrrole-3-carboxylic acid (100 mg, 0.40 mmol), piperidin-4-ylmethanol (92 mg, 0.80 mmol), HOBT (91 mg, 0.60 mmol) and EDC (150 mg, 0.80 mmol) in dichloromethane (4 mL) was added Hunig's base (0.28 mL, 1.6 mmol). The reaction mixture was stirred at room temperature overnight. The reaction mixture was washed with sat $NaHCO_3$ and extracted with dichloromethane. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was dissolved in acetonitrile, filtered and purified by preparative HPLC (Sunfire 5μ C18 30 × 100 mm column, 10 minute gradient from 10 to 100% B in A, A = 10:90 methanol: water with 0.1% trifluoroacetic acid, B = 90:10 methanol: water with 0.1% trifluoroacetic acid) to give **41** (97 mg, 0.26 mmol, 66% yield). MS (ESI) mass calculated for $[M+H]^+$ ($C_{22}H_{25}N_2O_2$) requires *m/z* 349.2, found 349.0; ^{1}H NMR (500MHz, $CDCl_3$) δ 8.33 (br. s., 1H), 8.30 - 8.25 (m, 1H), 7.93 - 7.85 (m, 1H), 7.84 - 7.78 (m, 1H), 7.55 - 7.49 (m, 2H), 7.49 -

7.45 (m, 2H), 6.42 (d, *J*=2.8 Hz, 1H), 4.54 (br. s., 2H), 3.54 (d, *J*=5.8 Hz, 2H), 2.92 (br. s., 2H), 2.47 (s, 3H), 1.85 - 1.74 (m, 3H), 1.36 - 1.17 (m, 2H).

(4-(Hydroxymethyl)piperidin-1-yl)(4-methyl-1-(naphthalen-1-yl)-1H-pyrrol-3-yl)methanone (42). Step 1. To ethyl 4-methyl-1H-pyrrole-3-carboxylate (0.5 g, 3.3 mmol), naphthalen-1-ylboronic acid (0.59 g, 3.4 mmol), and pyridine (0.53 mL, 6.5 mmol) in DMF (16 mL) was added copper (II) acetate (0.60 g, 3.3 mmol) and 1 gram of crushed 4 Å molecular sieves. The resulting deep blue mixture was stirred at 70 °C in a sealed vial overnight. At this point, additional boronic acid (0.5 g) was added and heating was continued for an additional 18 hours giving partial conversion to desired product. The dark-blue reaction mixture was diluted with ethyl acetate and filtered through a pad of Celite. The filtrate was washed with a 1:1 mixture of saturated aqueous NH_4Cl-$NaHCO_3$ and brine. The combined organics were dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified on SiO_2 via Isco flash chromatography (0-100% ethyl acetate/hexanes) to afford ethyl 4-methyl-1-(naphthalen-1-yl)-1H-pyrrole-3-carboxylate as a yellow oil.

Step 2. To a solution of ethyl 4-methyl-1-(naphthalen-1-yl)-1H-pyrrole-3-carboxylate (44 mg, 0.16 mmol) in tetrahydrofuran (1.6 mL) was added 1N aqueous lithium hydroxide (470 µl, 0.47 mmol).The reaction mixture was stirred at room temperature overnight giving no conversion to desired product. The reaction mixture was then heated to 50 °C and monitored by LCMS, but little conversion was observed. Additional 1N aqueous lithium hydroxide (470 µL) and methanol (1.5 mL) were added and heating was increased to 60 °C overnight giving complete conversion. The reaction mixture was washed with 1N aqueous HCl and extracted with ethyl acetate. The combined organics were dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain 4-methyl-1-(naphthalen-1-yl)-1H-pyrrole-3-carboxylic acid (36 mg,

0.14 mmol, 90% yield). The product was used subsequently without further purification or characterization.

Step 3. To a suspension of 4-methyl-1-(naphthalen-1-yl)-1H-pyrrole-3-carboxylic acid (12 mg, 0.05 mmol), piperidin-4-ylmethanol (8.0 mg, 0.07 mmol), HOBT (11 mg, 0.07 mmol), and EDC (18 mg, 0.09 mmol) in DMF (540 µl) was added Hunig's base (32 µl, 0.19 mmol) slowly. The resulting mixture was stirred at room temperature overnight. The reaction mixture was quenched with saturated aqueous NH_4Cl (4 mL) and extracted with ethyl acetate (3 × 4 mL). The combined organic layers were washed with H_2O, brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by reverse phase HPLC (Sunfire 5µ C18 30 × 100 mm column, 10 minute gradient from 10 to 100% B in A, A = 10:90 acetonitrile: water with 0.1% trifluoroacetic acid, B = 90:10 acetonitrile: water with 0.1% trifluoroacetic acid) to give **42**. MS (ESI) mass calculated for $[M+H]^+$ ($C_{22}H_{25}N_2O_2$) requires *m/z* 349.2, found 349.2; ^{1}H NMR (500MHz, $CDCl_3$) δ 7.95 - 7.91 (m, 1H), 7.88 (d, *J*=8.0 Hz, 1H), 7.81 (dd, *J*=8.3, 0.8 Hz, 1H), 7.58 - 7.53 (m, 1H), 7.53 - 7.49 (m, 2H), 7.46 - 7.41 (m, 1H), 7.03 (d, *J*=2.2 Hz, 1H), 6.76 (dd, *J*=2.2, 1.1 Hz, 1H), 4.53 (br. s., 2H), 3.55 (t, *J*=5.5 Hz, 2H), 2.95 (br. s., 2H), 2.25 (d, *J*=0.8 Hz, 3H), 1.88 - 1.74 (m, 3H), 1.35 (t, *J*=5.4 Hz, 1H), 1.32 - 1.19 (m, 2H).

(4-(Hydroxymethyl)piperidin-1-yl)(4-methyl-2-(naphthalen-1-yl)oxazol-5-yl)methanone (43). Step 1. Ethyl 2-chloro-3-oxobutanoate (0.53 mL, 3.6 mmol) was added to a solution of 1-naphthamide (0.25 g, 1.5 mmol) in ethanol (1.5 mL). The reaction vessel was sealed and heated to 110 °C for 24 hours. Additional ethyl 2-chloro-3-oxobutanoate (0.53 mL, 3.6 mmol) was added but it was found to only increase the number of impurities being formed so the reaction was cooled to room temperature and the excess solvent was removed in vacuo. The residue was purified on SiO_2 via Isco flash chromatography (0-30% ethyl acetate/hexanes, Isco

40 g column) to give ethyl 4-methyl-2-(naphthalen-1-yl)oxazole-5-carboxylate (0.15 g, 0.53 mmol, 36% yield) as a waxy white solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 9.28 (d, *J*=8.5 Hz, 1H), 8.35 (d, *J*=7.3 Hz, 1H), 8.02 (d, *J*=8.3 Hz, 1H), 7.93 (d, *J*=7.8 Hz, 1H), 7.68 (t, *J*=7.7 Hz, 1H), 7.62 - 7.54 (m, 2H), 4.46 (q, *J*=7.3 Hz, 2H), 2.64 (s, 3H), 1.45 (t, *J*=7.2 Hz, 3H).

Step 2. Lithium hydroxide monohydrate (0.11 g, 2.7 mmol) was added to a solution of ethyl 4-methyl-2-(naphthalen-1-yl)oxazole-5-carboxylate (0.15 g, 0.53 mmol) in tetrahydrofuran (4.1 mL), water (0.82 mL) and methanol (0.41 mL). After 16 hours the reaction was diluted with water and ethyl acetate and acidified to pH 1 with 1.0N HCl. The organic layer was washed with brine and the combined aqueous layers were further extracted with ethyl acetate. The combined organics were dried over Na_2SO_4, filtered and the solvent removed in vacuo giving 4-methyl-2-(naphthalen-1-yl)oxazole-5-carboxylic acid (0.13 g, 0.50 mmol, 95% yield) as a white solid. The product was used in the next step without further purification. ^{1}H NMR (400MHz, DMSO-d_6) δ 13.56 (br. s., 1H), 9.21 (d, *J*=8.5 Hz, 1H), 8.27 (dd, *J*=7.3, 1.3 Hz, 1H), 8.19 (d, *J*=8.3 Hz, 1H), 8.07 (d, *J*=8.0 Hz, 1H), 7.77 - 7.61 (m, 3H), 2.54 (s, 3H).

Step 3. Prepared according to general method A with 4-methyl-2-(naphthalen-1-yl)oxazole-5-carboxylic acid and piperidin-4-ylmethanol to give **43**. MS (ESI) mass calculated for $[M+H]^+$ ($C_{21}H_{23}N_2O_3$) requires *m/z* 351.2, found 351.2; ^{1}H NMR (400MHz, $CDCl_3$) δ 9.25 (d, *J*=8.8 Hz, 1H), 8.19 (dd, *J*=7.4, 1.1 Hz, 1H), 8.00 (d, *J*=8.3 Hz, 1H), 7.93 (d, *J*=8.3 Hz, 1H), 7.67 (ddd, *J*=8.5, 7.0, 1.5 Hz, 1H), 7.61 - 7.53 (m, 2H), 4.54 (br. s., 2H), 3.59 (t, *J*=5.5 Hz, 2H), 3.05 (br. s., 2H), 2.56 (s, 3H), 1.97 - 1.81 (m, 3H), 1.47 - 1.31 (m, 3H).

(4-(Hydroxymethyl)piperidin-1-yl)(5-methyl-2-(naphthalen-1-yl)oxazol-4-yl)methanone (44). Step 1. 1-naphthamide (0.2 g, 1.2 mmol) was added to a solution of methyl 3-bromo-2-oxobutanoate (0.30 g, 1.4 mmol) in dioxane (5.8 mL). The reaction vial was sealed

and slowly heated to 90 °C. After 1 hour, LCMS analysis indicated formation of the desired product. The reaction was cooled to room temperature and the solvent was removed in vacuo. The residue was purified on SiO_2 via Isco flash chromatography (0-40% ethyl acetate/hexanes, Isco 24 g column) to give methyl 5-methyl-2-(naphthalen-1-yl)oxazole-4-carboxylate (0.08 g, 0.3 mmol, 24% yield) as a thick oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.19 (d, *J*=7.78 Hz, 1H), 8.21 (dd, *J*=1.26, 7.28 Hz, 1H), 7.99 (d, *J*=8.03 Hz, 1H), 7.91 (d, *J*=8.03 Hz, 1H), 7.67 (ddd, *J*=1.51, 6.96, 8.60 Hz, 1H), 7.51-7.60 (m, 2H), 3.99 (s, 3H), 2.79 (s, 3H).

Step 2. Lithium hydroxide monohydrate (59 mg, 1.4 mmol) was added to a rapidly stirring mixture of methyl 5-methyl-2-(naphthalen-1-yl)oxazole-4-carboxylate (75 mg, 0.28 mmol) in tetrahydrofuran (2.2 mL), methanol (0.22 mL) and water (0.43 mL). After 3 hours LCMS analysis indicated the reaction had reached completion. The reaction mixture was diluted with ethyl acetate and acidified to pH 1 with 1 N HCl. The organic layer was washed with brine and the aqueous layers were extracted further with ethyl acetate. The combined organics were dried over Na_2SO_4, filtered and the solvent was removed in vacuo to give 5-methyl-2-(naphthalen-1-yl)oxazole-4-carboxylic acid (58 mg, 0.23 mmol, 81% yield) as a light brown solid. The product was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.06 (s, 1H), 9.26 (d, *J*=8.53 Hz, 1H), 8.20 (d, *J*=7.28 Hz, 1H), 8.14 (d, *J*=8.03 Hz, 1H), 8.06 (d, *J*=7.78 Hz, 1H), 7.61-7.77 (m, 3H), 2.72 (s, 3H).

Step 3. Prepared according to general method A with 5-methyl-2-(naphthalen-1-yl)oxazole-4-carboxylic acid and piperidin-4-ylmethanol to give **44**. MS (ESI) mass calculated for $[M+H]^+$ ($C_{21}H_{23}N_2O_3$) requires *m/z* 351.2, found 351.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.28 (d, *J*=9.03 Hz, 1H), 8.20 (dd, *J*=1.25, 7.53 Hz, 1H), 7.97 (d, *J*=8.28 Hz, 1H), 7.92 (d, *J*=8.78 Hz,

1H), 7.61-7.69 (m, 1H), 7.50-7.60 (m, 2H), 4.63-5.09 (m, 2H), 3.59 (d, *J*=6.02 Hz, 2H), 3.21 (br. s., 1H), 2.83 (d, *J*=16.56 Hz, 1H), 2.69 (s, 3H), 1.80-1.99 (m, 3H), 1.30-1.43 (m, 2H).

(4-(Hydroxymethyl)piperidin-1-yl)(1-methyl-4-(naphthalen-1-yl)-1H-imidazol-2-yl)methanone (45). Step 1. N-Bromosuccinimide (1.4 g, 7.8 mmol) was added to a stirring solution of ethyl 1-methyl-1H-imidazole-2-carboxylate (1.0 g, 6.5 mmol) in anhydrous tetrahydrofuran (17 mL) at approximately –5 °C (ice-salt bath). The reaction mixture was kept at that temperature for 2 hours and then allowed to achieve room temperature for 16 hours. The solvent was evaporated in vacuo to afford an oil/solid mixture. LCMS analysis indicated a mixture of desired product with some isomeric bromination product and bis-brominated product. The crude reaction mixture was purified on SiO_2 via Isco flash chromatography (10-40% ethyl acetate/hexanes) to afford ethyl 4-bromo-1-methyl-1H-imidazole-2-carboxylate (400 mg, 1.7 mmol, 26% yield). ^{1}H NMR (500MHz, $CDCl_3$) δ 6.99 (s, 1H), 4.38 (q, *J*=7.2 Hz, 2H), 3.97 (s, 3H), 1.38 (t, *J*=7.2 Hz, 3H).

Step 2. To a degassed solution of ethyl 4-bromo-1-methyl-1H-imidazole-2-carboxylate (0.40 g, 1.7 mmol), naphthalen-1-ylboronic acid (0.36 g, 2.1 mmol) and K_2CO_3 (0.59 g, 4.2 mmol) in dioxane (18 mL) and water (5.9 mL) was added $Pd(Ph_3P)_4$ (0.10 g, 0.09 mmol). The reaction mixture was stirred at 90 °C while being monitored by LCMS. Once the reaction was complete, lithiium hydroxide monohydrate (3.5 eq. 14 mg) was added and the reaction mixture was heated in a 50 °C oil bath for 5 hours until LCMS indicated complete hydrolysis. The reaction mixture was cooled to room temperature, acidified with 1 N aqueous HCl and extracted with ethyl acetate (3 × 5 mL). The organic layers were found by LCMS to contain mostly impurities and only a trace amount of desired product. The aqueous layer was found to contain the desired product and was concentrated in vacuo. The residue was purified by HPLC (Sunfire

5μ C18 30 × 100 mm column, 10 minute gradient from 10 to 100% B in A, A = 10:90 acetonitrile: water with 0.1% trifluoroacetic acid, B = 90:10 acetonitrile: water with 0.1% trifluoroacetic acid) to give 1-methyl-4-(naphthalen-1-yl)-1H-imidazole-2-carboxylic acid (125 mg, 0.50 mmol, 29% yield) as a light yellow solid. ^{1}H NMR (500MHz, $CDCl_3$) δ 8.00 - 7.94 (m, 1H), 7.94 - 7.88 (m, 2H), 7.60 (d, *J*=6.9 Hz, 2H), 7.56 - 7.46 (m, 4H), 7.26 (s, 1H), 4.16 (s, 3H).

Step 3. Prepared according to general method A with 1-methyl-4-(naphthalen-1-yl)-1H-imidazole-2-carboxylic acid and piperidin-4-ylmethanol to give **45**. MS (ESI) mass calculated for $[M+H]^+$ ($C_{21}H_{24}N_3O_2$) requires *m/z* 350.2, found 350.0; ^{1}H NMR (500MHz, $CDCl_3$) δ 8.52 (dd, *J*=6.2, 3.4 Hz, 1H), 7.92 - 7.86 (m, 1H), 7.84 (d, *J*=8.0 Hz, 1H), 7.72 (d, *J*=7.2 Hz, 1H), 7.54 - 7.46 (m, 3H), 7.25 (s, 1H), 4.96 (d, *J*=11.3 Hz, 1H), 4.77 (d, *J*=13.2 Hz, 1H), 3.99 (s, 3H), 3.56 (d, *J*=5.8 Hz, 2H), 3.28 (t, *J*=12.8 Hz, 1H), 2.86 (td, *J*=12.9, 2.3 Hz, 1H), 1.96 - 1.80 (m, 3H), 1.52 - 1.41 (m, 2H), 1.41 - 1.30 (m, 1H).

(1,4-Dimethyl-2-(naphthalen-1-yl)-1H-imidazol-5-yl)(4-(hydroxymethyl)piperidin-1-yl)methanone (46). Step 1. Rigorously degassed dioxane (3.0 mL) was added to a vial containing $PdCl_2$(dppf) (110 mg, 0.15 mmol), Cs_2CO_3 (0.65 g, 2.0 mmol), ethyl 2-bromo-4-methyl-1H-imidazole-5-carboxylate (230 mg, 1.0 mmol) and naphthalen-1-ylboronic acid (210 mg, 1.2 mmol). The reaction vial was sealed and heated to 90 °C overnight. The reaction mixture was cooled to room temperature and passed through a 0.45 μm nylon filter. The excess solvents were removed in vacuo and the residue was purified on SiO_2 via Isco flash chromatography (0-30% ethyl acetate/hexanes, Isco 40 g column) to give ethyl 4-methyl-2-(naphthalen-1-yl)-1H-imidazole-5-carboxylate (190 mg, 0.67 mmol, 67% yield) as a gum. ^{1}H NMR (400MHz, $CDCl_3$) δ 8.61 (d, *J*=8.1 Hz, 1H), 8.06 - 7.84 (m, 2H), 7.75 (dd, *J*=7.0, 0.9 Hz, 1H), 7.65 - 7.41 (m, 4H), 4.38 (q, *J*=7.1 Hz, 2H), 2.65 (s, 3H), 1.42 (t, *J*=7.0 Hz, 3H).

Step 2. Ethyl 2-(3,4-dihydroquinoxalin-1(2H)-yl)-4-methylthiazole-5-carboxylate (28 mg, 0.1 mmol) and K_2CO_3 (28 mg, 0.20 mmol) were added to a stirring solution of iodomethane (28 mg, 0.20 mmol) in acetone (5 mL) at room temperature under argon. The reaction mixture was stirred at room temperature overnight. The desired product was evident by LCMS analysis, but there was a major side product with *m/z* of the desired product + 14. The excess solvent was removed and the crude product was used directly in the next step.

Step 3. To a solution of ethyl 1,4-dimethyl-2-(naphthalen-1-yl)-1H-imidazole-5-carboxylate (29 mg, 0.10 mmol) in 2 mL tetrahydrofuran /methanol (1:1) was added aqueous 5 N NaOH (0.06 mL, 0.30 mmol). The reaction mixture was heated with stirring at 50 °C overnight giving complete conversion by LCMS analysis. To the reaction mixture was then added 2.0 mL of 0.1N aqueous HCl resulting in precipitate formation. The solid was collected by suction filtration, washed with water and dried in vacuo to yield 1,4-dimethyl-2-(naphthalen-1-yl)-1H-imidazole-5-carboxylic acid as a tan solid. The crude product was used directly in the next step without further purification.

Step 4. Prepared according to general method A with 1,4-dimethyl-2-(naphthalen-1-yl)-1H-imidazole-5-carboxylic acid and piperidin-4-ylmethanol to give **46**. MS (ESI) mass calculated for $[M+H]^+$ ($C_{22}H_{26}N_3O_2$) requires *m/z* 364.2, found 364.2; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.98-9.12 (m, 1H), 8.93 (d, *J*=7.43 Hz, 1H), 8.24 (d, *J*=8.25 Hz, 1H), 7.89 (d, *J*=7.98 Hz, 1H), 7.67 (t, *J*=7.29 Hz, 1H), 7.50 (dd, *J*=3.99, 7.01 Hz, 1H), 3.56 (br. s., 2H), 2.87 (d, *J*=7.43 Hz, 5H), 1.82 (br. s., 3H), 1.40 (t, *J*=7.57 Hz, 4H), 1.29 (d, *J*=10.45 Hz, 2H).

(4-(Hydroxymethyl)piperidin-1-yl)(1-methyl-3-(naphthalen-1-yl)-1H-pyrazol-5-yl)methanone (47). Step 1. A mixture of ethyl 4-(naphthalen-1-yl)-2,4-dioxobutanoate (7.0 g, 26 mmol) and hydrazine (0.85 mL, 27 mmol) in acetic acid (65 mL) was heated at 90 °C for 4

hours. The reaction mixture was then cooled to room temperature and concentrated under reduced pressure to remove excess acetic acid. The residue was purified on SiO_2 via Isco flash chromatography (0-50% ethyl acetate/hexanes, Isco 120 g column) to give ethyl 3-(naphthalen-1-yl)-1H-pyrazole-5-carboxylate (6.0 g, 22 mmol, 86% yield) as a pale-yellow solid. ^{1}H NMR (500MHz, $CDCl_3$) δ 8.22 (d, *J*=4.7 Hz, 1H), 7.95 - 7.89 (m, 2H), 7.62 (dd, *J*=7.0, 1.0 Hz, 1H), 7.57 - 7.49 (m, 3H), 7.14 (s, 1H), 4.45 (q, *J*=7.2 Hz, 2H), 1.44 (t, *J*=7.2 Hz, 3H), 1.02 (d, *J*=6.6 Hz, 1H).

Step2. To a stirred suspension of ethyl 3-(naphthalen-1-yl)-1H-pyrazole-5-carboxylate (5.9 g, 22 mmol) and Cs_2CO_3 (9.4 g, 29 mmol) in acetonitrile (170 mL) was slowly added iodomethane (1.5 mL, 24 mmol). The reaction mixture was stirred at room temperature for 2 hours. LCMS of the reaction mixture indicated the formation of two regio-isomers of methylated products. The solvent was evaporated to dryness and the residue was suspended in ethyl acetate, and washed with water, brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified on SiO_2 via Isco flash chromatography (0-30% ethyl acetate/hexanes, Isco 220 g column). Fractions of the first eluting, less polar, peak were collected and concentrated under reduced pressure to give the desired isomer ethyl 1-methyl-3-(naphthalen-1-yl)-1H-pyrazole-5-carboxylate (3.1 g, 11 mmol, 49% yield) as a colorless oil. ^{1}H NMR (500MHz, $CDCl_3$) δ 8.47 - 8.42 (m, 1H), 7.92 - 7.89 (m, 1H), 7.88 (d, *J*=8.3 Hz, 1H), 7.68 (dd, *J*=7.0, 1.2 Hz, 1H), 7.57 - 7.48 (m, 3H), 7.16 (s, 1H), 4.42 (q, *J*=7.2 Hz, 2H), 4.33 (s, 3H), 1.43 (t, *J*=7.2 Hz, 3H). Fractions of the second eluting, more polar, peak were collected and concentrated under reduced pressure to give ethyl 1-methyl-5-(naphthalen-1-yl)-1H-pyrazole-3-carboxylate (2.6 g, 9.2 mmol, 41% yield) as a light-yellow oil. ^{1}H NMR (500MHz, $CDCl_3$) δ 7.99 (d, *J*=8.3 Hz, 1H), 7.96 - 7.92 (m,

1H), 7.59 - 7.48 (m, 4H), 7.46 (dd, *J*=7.0, 1.2 Hz, 1H), 6.95 (s, 1H), 4.47 (q, *J*=7.2 Hz, 2H), 3.72 (s, 3H), 1.45 (t, *J*=7.2 Hz, 3H).

Step 3. To a solution of ethyl 1-methyl-3-(naphthalen-1-yl)-1H-pyrazole-5-carboxylate (0.24 g, 0.87 mmol) in tetrahydrofuran (1.1 mL) and water (1.1 mL) was added lithium hydroxide monohydrate (0.07 g, 2.9 mmol). The reaction mixture was stirred at room temperature while being monitored by LCMS. After 2 days the reaction mixture was cooled to 0 °C and neutralized with 1N aqueous HCl. The mixture was extracted with ethyl acetate (2 × 2 mL), and then the combined organic layers were washed with H_2O (2 × 5 mL), brine (5 mL), dried over Na_2SO_4, filtered and concentrated to dryness. The solid was dried in vacuo and the crude product was used in next reaction without further purification.

Step 4. Prepared according to general method A with 1-methyl-3-(naphthalen-1-yl)-1H-pyrazole-5-carboxylic acid and piperidin-4-ylmethanol to give **47**. MS (ESI) mass calculated for $[M+H]^+$ ($C_{21}H_{24}N_3O_2$) requires *m/z* 350.2, found 350.0; ^{1}H NMR (500MHz, $CDCl_3$) δ 8.50 - 8.43 (m, 1H), 7.91 - 7.88 (m, 1H), 7.87 (d, *J*=8.3 Hz, 1H), 7.67 (dd, *J*=7.0, 1.2 Hz, 1H), 7.55 - 7.48 (m, 3H), 6.60 (s, 1H), 4.78 (br. s., 1H), 4.09 (s, 3H), 3.56 (d, *J*=3.6 Hz, 2H), 3.15 (br. s., 1H), 2.84 (br. s., 1H), 1.97 - 1.75 (m, 3H), 1.61 (br. s., 2H), 1.41 - 1.18 (m, 2H).

(4-(Hydroxymethyl)piperidin-1-yl)(3-methyl-1-(naphthalen-1-yl)-1H-pyrazol-4-yl)methanone (48). Step 1. To a solution of ethyl 3-methyl-1H-pyrazole-4-carboxylate (1.6 g, 10 mmol) and naphthalen-1-ylboronic acid (1.8 g, 11 mmol) in DMF (30 mL) was added copper (II) acetate (1.8 g, 10 mmol), pyridine (1.6 mL, 20 mmol) and 2.5 grams of crushed 4Å molecular sieves. The resulting deep blue mixture was stirred in a loosely capped flask under air at room temperature until LCMS analysis indicated complete conversion (approximately 2 days). The dark blue reaction mixture was diluted with ethyl acetate and saturated aqueous NH_4Cl, and then

stirred vigorously in a round bottom flask. The layers were then separated and the organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered through a pad of SiO_2 and concentrated in vacuo to afford a purple oil. The residue was purified on SiO_2 via Isco flash chromatography (0-60% ethyl acetate/hexanes, Isco 80 g column). Product containing fractions were combined and concentrated to afford ethyl 3-methyl-1-(naphthalen-1-yl)-1H-pyrazole-4-carboxylate (1.7 g, 6.1 mmol, 61% yield) as a yellow solid. ^{1}H NMR (500MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.99 - 7.91 (m, 2H), 7.86 - 7.77 (m, 1H), 7.61 - 7.50 (m, 4H), 4.36 (q, *J*=7.2 Hz, 2H), 2.63 (s, 3H), 1.39 (t, *J*=7.2 Hz, 3H).

Step 2. To a solution of ethyl 3-methyl-1-(naphthalen-1-yl)-1H-pyrazole-4-carboxylate (1.4 g, 5.1 mmol) in methanol (25 mL) was added 1 N aqueous NaOH (20 mL, 20 mmol). The reaction mixture was stirred at 55 °C while being monitored by LCMS. The reaction was complete within 3 hours. The heat was turned off and stirring was continued at room temperature overnight. The reaction mixture was acidified with 12 N HCl and extracted with ethyl acetate. The organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo to afford 3-methyl-1-(naphthalen-1-yl)-1H-pyrazole-4-carboxylic acid (1.3 g, 4.9 mmol, 95% yield) as a tan solid. The product was used without further purification.

Step 3. Prepared according to general method A with 3-methyl-1-(naphthalen-1-yl)-1H-pyrazole-4-carboxylic acid and piperidin-4-ylmethanol to give **48**. MS (ESI) mass calculated for $[M+H]^+$ ($C_{21}H_{24}N_3O_2$) requires *m/z* 350.2, found 350.2; ^{1}H NMR (500MHz, $CDCl_3$) δ 7.97 - 7.91 (m, 2H), 7.89 - 7.84 (m, 1H), 7.83 (s, 1H), 7.59 - 7.51 (m, 4H), 3.55 (br. s., 2H), 2.98 (br. s., 2H), 2.49 (s, 3H), 1.90 - 1.77 (m, 3H), 1.49 (br. s., 1H), 1.36 - 1.22 (m, 2H).

(4-(Hydroxymethyl)piperidin-1-yl)(5-methyl-2-(naphthalen-1-yl)-2H-1,2,3-triazol-4-yl)methanone (49). Step 1. To a 0 °C solution of naphthalen-1-amine (1.4 g, 10 mmol) in

ethanol (4 mL) and water (4 mL) was added concentrated HCl (2.2 mL, 74 mmol) followed by sodium nitrite (0.69 g, 10 mmol) dissolved in water (1.5 mL). The reaction mixture was stirred at −5 °C for 10 minutes. This mixture was then slowly added to a mixture of ethyl 3-oxobutanoate (1.3 g, 10 mmol), sodium acetate (4.1 g, 50 mmol), 1M aqueous sodium carbonate (10 mL, 10 mmol), and ethanol (20 mL) at 0 °C. The resulting mixture was stirred for 2 hours, and then diluted with water and extracted with ethyl acetate (2 × 100 mL). The combined organic extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated in vacuo to give the crude product, which was used in the next step without purification.

Step 2. To the crude (E)-ethyl 2-(2-(naphthalen-1-yl)hydrazono)-3-oxobutanoate (2.8 g, 10 mmol) from the previous step in ethanol (40 mL) was added copper (II) chloride (3.0 g, 22 mmol) and ammonium acetate (7.7 g, 100 mmol). The reaction mixture was heated to reflux for 4 hours and then cooled to room temperature and poured into a mixture of ice and concentrated HCl. Some solid was observed, which was collected by filtration. The filtrate was extracted with ethyl acetate and the collected organic layer was dried over Na_2SO_4, filtered and concentrated to dryness. The residue was combined with the solids collected via filtration and further purified on SiO_2 via Isco flash chromatography (0-100% ethyl acetate/hexanes, 80 g column) to yield ethyl 5-methyl-2-(naphthalen-1-yl)-2H-1,2,3-triazole-4-carboxylate (2.3 g, 8.2 mmol, 82% yield) as tan solid.

Step 3. To a solution of ethyl 5-methyl-2-(naphthalen-1-yl)-2H-1,2,3-triazole-4-carboxylate (2.0g, 7.1 mmol) in tetrahydrofuran (40 mL) was added 2M NaOH (11 mL, 21 mmol. The reaction mixture was stirred at room temperature overnight under argon to give complete conversion. 2 N HCl was added until pH 4. The solid product that had formed was

collected by suction filtration and further washed with water (3 × 2 mL). The product was dried overnight and used directly in the next step.

Step 4. Prepared according to general method A with 5-methyl-2-(naphthalen-1-yl)-2H-1,2,3-triazole-4-carboxylic acid and piperidin-4-ylmethanol to give **49**. MS (ESI) mass calculated for $[M+H]^+$ ($C_{20}H_{23}N_4O_2$) requires *m/z* 351.2, found 351.1; ^{1}H NMR (400MHz, $CDCl_3$) δ 8.24 - 8.15 (m, 1H), 8.01 - 7.89 (m, 2H), 7.77 (dd, *J*=7.5, 1.1 Hz, 1H), 7.61 - 7.50 (m, 3H), 4.81 (d, *J*=13.1 Hz, 1H), 4.54 (d, *J*=13.4 Hz, 1H), 3.52 (dd, *J*=5.8, 4.3 Hz, 2H), 3.23 - 3.11 (m, 1H), 2.82 (td, *J*=12.8, 2.4 Hz, 1H), 2.61 (s, 3H), 1.96 - 1.75 (m, 3H), 1.66 (br. s., 1H), 1.33 (d, *J*=12.1 Hz, 2H).

(4-(Hydroxymethyl)piperidin-1-yl)(2-(naphthalen-1-yl)-2H-tetrazol-5-yl)methanone (50). Step 1. To a −5 °C solution of naphthalen-1-amine (1.8 g, 12 mmol) in ethanol (8 mL) and water (8 mL) was added concentrated HCl (4.5 mL, 150 mmol) followed by sodium nitrite (0.86 g, 12 mmol) dissolved in 1.5 mL water. The reaction mixture was stirred at −5 °C for 10 minutes. This solution was used in step 2.

Step 2. Ethyl 2-oxoacetate (3.5 g, 17 mmol) and benzenesulfonohydrazide (2.0 g, 12 mmol) in a 100 mL round bottom flask was added ethanol (30 mL) at room temperature. After 1 hour, the ethanol was evaporated and the residue was taken up in Pyridine (20 mL) and cooled to −5 °C. To this mixture was then added the cooled solution from step 1 and the reaction mixture was allowed to achieve room temperature. After stirring at room temperature overnight LCMS analysis indicated formation of desired product. Volatile solvents were removed in vacuo and the residue was partitioned between ethyl acetate (25 mL) and brine (25 mL). The organic layer was collected, dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was used directly in the next step.

Step 3. The crude product from step 2 was taken up in 2 N NaOH (0.5 mL, 1.0 mmol) and stirred at 50 °C overnight giving complete hydrolysis based on LCMS analysis. The reaction mixture was diluted with 5 mL of 1 N NaOH and extracted with ethyl acetate (5 mL). To the aqueous layer was added 6 mL of 1 N HCl giving precipitate formation. The solid was collected by suction filtration, washed with water (2 × 2 mL) and dried overnight to give 2-(naphthalen-1-yl)-2H-tetrazole-5-carboxylic acid (0.2 g, 0.9 mmol, 46% yield) as a dark solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J*=8.36 Hz, 1H), 7.96-8.05 (m, 2H), 7.92 (d, *J*=6.82 Hz, 1H), 7.53-7.74 (m, 3H).

Step 4. Prepared according to general method A with 2-(naphthalen-1-yl)-2H-tetrazole-5-carboxylic acid and piperidin-4-ylmethanol to give **50**. MS (ESI) mass calculated for $[M+H]^+$ ($C_{18}H_{20}N_5O_2$) requires *m/z* 338.2, found 338.1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J*=8.14 Hz, 1H), 8.02-8.07 (m, 1H), 8.00 (dd, *J*=3.63, 5.83 Hz, 1H), 7.90 (dd, J=1.10, 7.48 Hz, 1H), 7.54-7.73 (m, 2H), 4.89 (tdd, J=2.34, 4.40, 13.15 Hz, 1H), 4.38 (td, J=2.01, 13.59 Hz, 1H), 3.58 (dd, J=3.96, 5.94 Hz, 2H), 3.20-3.34 (m, 1H), 2.92 (dt, J=2.97, 12.93 Hz, 1H), 2.08 (s, 3H), 1.82-1.99 (m, 3H).

1-Methyl-5-(1-methyl-1H-imidazol-2-yl)-3-(naphthalen-1-yl)-1H-pyrazole Formic Acid Salt (51). Step 1. A mixture of naphthalen-1-ylboronic acid (1.7 g, 9.6 mmol), 3-bromo-1-methyl-1H-pyrazole (1.0 g, 6.0 mmol), tetrakis(triphenylphosphine)palladium(0) (0.49 g, 0.42 mmol), and K_3PO_4 (3.8 g, 18 mmol) in N-methyl-2-pyrrolidinone (10 mL) was heated with stirring at 90 °C under an argon atmosphere for 4 days. The reaction mixture was cooled to room temperature, diluted with water and then extracted with diethyl ether (3 × 50 mL). The combined extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified on SiO_2 via Isco flash chromatography (0-50% ethyl acetate/hexanes) to give 1-methyl-3-(naphthalen-1-yl)-

1H-pyrazole (1.023 g, 78 % yield) as a pale yellow oil. MS (ESI) *m/z*: 209.1 $[M+H]^+$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (ddt, *J* = 1.2, 3.4, 6.4 Hz, 1H), 7.96-7.82 (m, 2H), 7.70 (dd, *J* = 1.3, 7.1 Hz, 1H), 7.58-7.47 (m, 4H), 6.58 (d, *J* = 2.2 Hz, 1H), 4.06 (s, 3H).

Step 2. To a solution of 1-methyl-3-(naphthalen-1-yl)-1H-pyrazole (280 mg, 1.3 mmol) in tetrahydrofuran (4.3 mL) at −78 °C was added n-butyllithium (2.0 M solution in pentane, 0.84 mL, 1.7 mmol) dropwise. The mixture was stirred at −78 °C for 2 hours and at −40 °C for 1 hour. The reaction mixture was re-cooled to −78 °C followed by addition of 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.32 mL, 1.5 mmol) dropwise. After stirring at −78 °C for 20 minutes, the reaction mixture was warmed to room temperature and stirred for 45 minutes. The mixture was then cooled to 0 °C and quenched with water. Acetic acid was then added dropwise to the cold mixture until the pH of the aqueous layer was ~ 6-7. The resulting mixture was extracted three times with ethyl acetate. The combined organic extracts were washed with brine: water (1:1), dried over Na_2SO_4, filtered and concentrated in vacuo to give 1-methyl-3-(naphthalen-1-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (490 mg with 75% purity, 86% yield) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58-8.48 (m, 1H), 7.96-7.82 (m, 2H), 7.74-7.66 (m, 1H), 7.58-7.45 (m, 3H), 7.06 (s, 1H), 4.24 (s, 3H), 1.41 (s, 12H).

Step 3. A mixture of 2-iodo-1-methyl-1H-imidazole (32 mg, 0.16 mmol), 1-methyl-3-(naphthalen-1-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (23 mg, 0.05 mmol), tetrakis(triphenylphosphine)palladium(0) (8.5 mg, 7.4 μmol), and K_3PO_4 (31 mg, 0.15 mmol) in N-methyl-2-pyrrolidinone (160 μL) was purged with argon and then heated with stirring at 100 °C for 21 hours. The reaction mixture was cooled to room temperature and then purified by preparative HPLC. (Waters XBridge C18, 19 × 200 mm column; mobile phase A =

5:95 acetonitrile: water with 0.1% formic acid; mobile phase B = 95:5 acetonitrile: water with 0.1% formic acid). Fractions containing the desired product were combined and dried via centrifugal evaporation to give **51** (5.7 mg, 32% yield). MS (ESI) mass calculated for $[M+H]^+$ ($C_{18}H_{17}N_4$) requires *m/z* 289.1, found 289.2; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.82-8.65 (m, 1H), 8.05-7.92 (m, 2H), 7.80 (d, *J* = 7.0 Hz, 1H), 7.65-7.53 (m, 3H), 7.41 (s, 1H), 7.15 (s, 1H), 7.10 (s, 1H), 4.14 (s, 3H), 3.83 (s, 3H).

1-Ethyl-5-(1-methyl-1H-imidazol-2-yl)-3-(naphthalen-1-yl)-1H-pyrazole TFA Salt (52). Step 1. To a solution of N,N-dimethyl-1H-pyrazole-1-sulfonamide (8.3 g, 48 mmol) in tetrahydrofuran (110 mL) at −78 °C was added n-butyllithium (2.0 M in pentane, 28 mL, 57 mmol) dropwise. The resulting mixture was stirred at −78 °C for 15 minutes followed by dropwise addition of 1,2-dibromotetrachloroethane (17 g, 52 mmol) in tetrahydrofuran (25 mL). After stirring at −78 °C for 15 minutes, the mixture was allowed to warm to room temperature and stirred for 1.5 hours. The mixture was then quenched with water and extracted three times with ethyl acetate. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by Isco flash column chromatography on SiO_2 (0-25% ethyl acetate/hexanes) to give 5-bromo-N,N-dimethyl-1H-pyrazole-1-sulfonamide (6.9 g, 57%) as a light yellow oil. MS (ESI) *m/z*: 255.8 $(M+2+H)^+$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, *J* = 1.7 Hz, 1H), 6.43 (d, *J* = 1.7 Hz, 1H), 3.07 (s, 6H).

Step 2. To a degassed mixture of naphthalen-1-ylboronic acid (7.0 g, 41 mmol), 5-bromo-N,N-dimethyl-1H-pyrazole-1-sulfonamide (6.9 g, 27 mmol), and K_2CO_3 (12 g, 90 mmol) in dioxane (100 mL) and water (34 mL) was added tetrakis(triphenylphosphine)palladium(0) (0.94 g, 0.82 mmol). The reaction mixture was heated with stirring at 100 °C for 3 hours, cooled to room temperature and then partitioned between water and ethyl acetate. The organic layer was

separated, and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified on SiO_2 via Isco flash column chromatography (0-50% ethyl acetate/hexanes) to give N,N-dimethyl-5-(naphthalen-1-yl)-1H-pyrazole-1-sulfonamide (7.8 g, 96%) as a light yellow solid. MS (ESI) *m/z*: 302.0 $[M+H]^+$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (t, *J* = 4.7 Hz, 1H), 7.90 (dd, *J* = 1.5, 7.8 Hz, 1H), 7.82 (d, *J* = 1.6 Hz, 1H), 7.61 (dd, *J* = 1.2, 8.4 Hz, 1H), 7.56-7.43 (m, 4H), 6.46 (d, *J* = 1.6 Hz, 1H), 2.92 (s, 6H).

Step 3. A mixture of N,N-dimethyl-5-(naphthalen-1-yl)-1H-pyrazole-1-sulfonamide (6.3 g, 21 mmol) and TFA (8.0 mL, 100 mmol) was stirred at room temperature for 4 hours and then concentrated in vacuo. The residue was taken up in ethyl acetate and washed with aqueous 1.5 M K_2HPO_4 solution. The aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with brine-water (2:1), dried over Na_2SO_4, filtered and concentrated in vacuo to give 5-(naphthalen-1-yl)-1H-pyrazole (4.4 g, quantitative yield) as a yellow solid. MS (ESI) *m/z*: 195.0 $[M+H]^+$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32-8.25 (m, 1H), 7.93-7.86 (m, 2H), 7.67 (d, *J* = 2.1 Hz, 1H), 7.61 (dd, *J* = 1.2, 7.1 Hz, 1H), 7.54-7.48 (m, 3H), 6.61 (d, *J* = 2.2 Hz, 1H).

Step 4. To a stirring mixture of 5-(naphthalen-1-yl)-1H-pyrazole (3.0 g, 15 mmol) and Cs_2CO_3 (7.0 g, 22 mmol) in acetonitrile (100 mL) was slowly added iodoethane (1.4 mL, 17 mmol). The reaction mixture was stirred at room temperature overnight, heated to 65 °C for 3.5 hours and then cooled to room temperature. The reaction mixture was then concentrated in vacuo and the residue was partitioned between ethyl acetate and water. The organic layer was separated, and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The

residue was purified on SiO_2 via Isco flash column chromatography (eluting with 100% hexanes, 100% CH_2Cl_2 and then 0-5% ethyl acetate/hexanes) to give the desired isomer of 1-ethyl-3-(naphthalen-1-yl)-1H-pyrazole (1.9 g, 55% yield) as a light yellow solid. MS (ESI) *m/z*: 222.9 $[M+H]^+$; ^1H NMR (500 MHz, $CDCl_3$) δ 8.59-8.45 (m, 1H), 7.95-7.80 (m, 2H), 7.69 (dd, *J* = 1.3, 7.0 Hz, 1H), 7.57-7.43 (m, 4H), 6.55 (d, *J* = 2.2 Hz, 1H), 4.31 (q, *J* = 7.3 Hz, 2H), 1.59 (t, *J* = 7.3 Hz, 3H).

Step 5. To a solution of 1-ethyl-3-(naphthalen-1-yl)-1H-pyrazole (1.0 g, 4.5 mmol) in tetrahydrofuran (15 mL) at −78 °C was added n-butyllithium (2.0 M solution in pentane, 2.9 mL, 5.8 mmol) dropwise. The mixture was stirred at −78 °C for 1.5 hours and at −40 °C for 1 hour. The reaction mixture was re-cooled to −78 °C followed by slow addition of 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.1 mL, 5.4 mmol). After stirring at −78 °C for 30 minutes, the mixture was warmed to room temperature and stirred for 90 minutes. The mixture was then cooled to 0 °C and quenched with water. Acetic acid was then added dropwise to the cold mixture until the pH of the aqueous layer was ~ 6-7. The mixture was extracted three times with ethyl acetate. The combined extracts were washed with brine: water (1:1), dried over Na_2SO_4, filtered and concentrated in vacuo to give 1-ethyl-3-(naphthalen-1-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.6 g, quantitative yield) as an oil, which became a grey solid upon standing. ^1H NMR (500 MHz, $CDCl_3$) δ 8.59-8.37 (m, 1H), 7.88-7.84 (m, 1H), 7.82 (dt, *J* = 1.0, 8.3 Hz, 1H), 7.68 (dd, *J* = 1.3, 7.1 Hz, 1H), 7.51-7.45 (m, 3H), 7.02 (s, 1H), 4.57 (q, *J* = 7.2 Hz, 2H), 1.53 (t, *J* = 7.2 Hz, 3H), 1.39 (s, 12H).

Step 6. Prepared according to general method B with 2-iodo-1-methyl-1H-imidazole to give **52** (12 mg, 58% yield) as a colorless gum. MS (ESI) mass calculated for $[M+H]^+$

($C_{19}H_{19}N_4$) requires *m/z* 303.2, found 303.1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50-8.39 (m, 1H), 7.96-7.86 (m, 2H), 7.74-7.63 (m, 2H), 7.59-7.46 (m, 3H), 7.29 (br s, 1H), 6.88 (s, 1H), 4.31 (q, *J* = 7.2 Hz, 2H), 3.85 (s, 3H), 1.51 (t, *J* = 7.2 Hz, 3H).

1-Ethyl-5-(1-methyl-1H-imidazol-5-yl)-3-(naphthalen-1-yl)-1H-pyrazole, TFA (53). Prepared according to general method B with 5-iodo-1-methyl-1H-imidazole to give **53**. MS (ESI) mass calculated for $[M+H]^+$ ($C_{19}H_{19}N_4$) requires *m/z* 303.2, found 303.1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.06 (br s, 1H), 8.52-8.44 (m, 1H), 7.96-7.86 (m, 2H), 7.71 (dd, *J* = 1.3, 7.0 Hz, 1H), 7.62-7.49 (m, 4H), 6.78 (s, 1H), 4.22 (q, *J* = 7.2 Hz, 2H), 3.85 (s, 3H), 1.54 (t, *J* = 7.2 Hz, 3H).

2-Ethyl-2'-methyl-5-(naphthalen-1-yl)-2H,2'H-3,3'-bipyrazole (54). Prepared according to general method B with 5-bromo-1-methyl-1H-pyrazole to give **54**. MS (ESI) mass calculated for $[M+H]^+$ ($C_{19}H_{19}N_4$) requires *m/z* 303.2, found 303.1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60-8.53 (m, 1H), 7.94-7.85 (m, 2H), 7.74 (dd, *J* = 1.2, 7.1 Hz, 1H), 7.64 (d, *J* = 2.0 Hz, 1H), 7.57-7.48 (m, 3H), 6.67 (s, 1H), 6.48 (d, *J* = 2.0 Hz, 1H), 4.22 (q, *J* = 7.2 Hz, 2H), 3.91 (s, 3H), 1.50 (t, *J* = 7.2 Hz, 3H).

5-(1-Ethyl-3-(naphthalen-1-yl)-1H-pyrazol-5-yl)-1-methyl-1H-1,2,4-triazole (55). Prepared according to general method B with 5-bromo-1-methyl-1H-1,2,4-triazole to give **55**. MS (ESI) mass calculated for $[M+H]^+$ ($C_{18}H_{18}N_5$) requires *m/z* 304.2, found 304.2; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.78-8.64 (m, 1H), 8.19 (s, 1H), 8.09-7.90 (m, 2H), 7.81 (d, *J* = 7.1 Hz, 1H), 7.66-7.51 (m, 3H), 7.29 (s, 1H), 4.54 (q, *J* = 7.2 Hz, 2H), 4.06 (s, 3H), 1.46 (t, *J* = 7.1 Hz, 3H).

5-(1-Ethyl-3-(naphthalen-1-yl)-1H-pyrazol-5-yl)-1-methyl-1H-tetrazole (56). Step 1. To a solution of n-butyllithium (2.0 M solution in pentane, 3.6 mL, 7.3 mmol) in tetrahydrofuran (5.0 mL) at −78 °C was added dropwise, 1-methyl-1H-tetrazole (0.5 g, 6.1 mmol) in tetrahydrofuran (2.0 mL). The mixture was stirred at −78 °C for 10 minutes followed by the addition of a solution of iodine (1.8 g, 7.3 mmol) in tetrahydrofuran (2.0 mL). The reaction mixture was warmed to room temperature, stirred for 1 hour, and then concentrated in vacuo. The residue was partitioned between water (30 mL) and diethyl ether (30 mL). The organic layer was separated and the aqueous layer was further extracted with diethyl ether (3 × 30 mL). The combined organic layers were washed with water, brine, dried over Na_2SO_4, filtered and concentrated in vacuo to give 5-iodo-1-methyl-1H-tetrazole (0.48 g, 36% yield) as a yellow solid. MS (ESI) *m/z*: 210.9 $[M+H]^+$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.11 (s, 1H).

Step 2. Prepared according to general method B with 5-iodo-1-methyl-1H-tetrazole to give **56** (6.6 mg, 48% yield). MS (ESI) mass calculated for $[M+H]^+$ ($C_{17}H_{17}N_6$) requires *m/z* 305.1, found 305.2; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.72-8.64 (m, 1H), 8.04-7.97 (m, 2H), 7.83 (dd, *J* = 1.2, 7.1 Hz, 1H), 7.64-7.55 (m, 3H), 7.45 (s, 1H), 4.57 (q, *J* = 7.2 Hz, 2H), 4.27 (s, 3H), 1.51 (t, *J* = 7.2 Hz, 3H).

2-(1-Ethyl-3-(naphthalen-1-yl)-1H-pyrazol-5-yl)pyridine (57). Prepared according to general method B with 2-bromopyridine to give **57**. MS (ESI) mass calculated for $[M+H]^+$ ($C_{20}H_{18}N_3$) requires *m/z* 300.1, found 300.1; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.81-8.65 (m, 2H), 8.09-7.87 (m, 4H), 7.78 (dd, *J* = 1.2, 7.1 Hz, 1H), 7.63-7.51 (m, 3H), 7.43 (ddd, *J* = 2.2, 4.8, 6.7 Hz, 1H), 7.22 (s, 1H), 4.75 (q, *J* = 7.1 Hz, 2H), 1.44 (t, *J* = 7.1 Hz, 3H).

2-(1-Ethyl-3-(naphthalen-1-yl)-1H-pyrazol-5-yl)pyrimidine (58). Prepared according to general method B with 2-bromopyrimidine to give **58**. MS (ESI) mass calculated for $[M+H]^+$ ($C_{19}H_{17}N_4$) requires *m/z* 301.1, found 301.2; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.98 (d, *J* = 4.9 Hz, 2H), 8.68 (dd, *J* = 1.7, 7.9 Hz, 2H), 8.03-7.98 (m, 1H), 7.96 (d, *J* = 8.1 Hz, 1H), 7.79 (dd, *J* = 1.2, 7.2 Hz, 1H), 7.58 (dddd, *J* = 2.6, 6.0, 8.3, 12.4 Hz, 2H), 7.51 (t, *J* = 4.9 Hz, 1H), 7.37 (s, 1H), 4.89 (q, *J* = 7.1 Hz, 2H), 1.48 (t, *J* = 7.1 Hz, 3H).

3-(1-Methyl-3-(naphthalen-1-yl)-1H-pyrazol-5-yl)pyridazine (59). Prepared according to the procedures described for compound **51** with substitution of 3-bromopyridazine for 2-iodo-1-methyl-1H-imidazole at Step 3. MS (ESI) mass calculated for $[M+H]^+$ ($C_{18}H_{15}N_4$) requires *m/z* 287.1, found 287.2; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.30 (d, *J* = 4.3 Hz, 1H), 8.79-8.65 (m, 1H), 8.32-8.20 (m, 1H), 8.00 (dd, *J* = 7.4, 16.0 Hz, 2H), 7.89 (dt, *J* = 3.9, 8.9 Hz, 1H), 7.83-7.77 (m, 1H), 7.60 (td, *J* = 3.6, 6.5, 7.1 Hz, 3H), 7.42 (t, *J* = 2.6 Hz, 1H), 4.35 (t, *J* = 2.4 Hz, 3H).

3-(1-Ethyl-3-(naphthalen-1-yl)-1H-pyrazol-5-yl)pyridazine (60). Prepared according to general method B with 3-bromopyridazine to give **60**. MS (ESI) mass calculated for $[M+H]^+$ ($C_{19}H_{17}N_4$) requires *m/z* 301.1, found 301.2; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.28 (d, *J* = 4.9 Hz, 1H), 8.72 (d, *J* = 7.9 Hz, 1H), 8.26-8.21 (m, 1H), 8.02-7.99 (m, 1H), 7.97 (d, *J* = 8.3 Hz, 1H), 7.90-7.85 (m, 1H), 7.79 (d, *J* = 7.0 Hz, 1H), 7.62-7.55 (m, 3H), 7.39 (d, *J* = 1.2 Hz, 1H), 4.78 (q, *J* = 7.1 Hz, 2H), 1.49 (t, *J* = 7.1 Hz, 3H).

1-(1-Ethyl-5-(pyridazin-3-yl)-1H-pyrazol-3-yl)isoquinoline, TFA (61). Step 1. To a degassed mixture of (1H-pyrazol-5-yl)boronic acid (0.54 g, 4.8 mmol), 1-bromoisoquinoline (0.50 g, 2.4 mmol) and K_2CO_3 (1.0 g, 7.2 mmol) in dioxane (18 mL) and water (6.0 mL) was added tetrakis(triphenylphosphine)palladium(0) (0.17 g, 0.14 mmol). The reaction mixture was

heated with stirring to 90 °C. After heating at 90 °C for 12 hours, the reaction mixture was cooled to room temperature and additional (1H-pyrazol-5-yl)boronic acid (0.54 g, 4.8 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.17 g, 0.14 mmol) were added and the mixture was further degassed. The reaction was then heated at 90 °C for an additional 10 hours, cooled to room temperature, and partitioned between water and ethyl acetate. The organic layer was separated, and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified on SiO_2 via Isco flash column chromatography (0-100% ethyl acetate/ hexanes) to give 1-(1H-pyrazol-5-yl)isoquinoline (0.37 g, 79% yield) as an orange oil. MS (ESI) *m/z*: 196.0 $[M+H]^+$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.78 (d, *J* = 8.6 Hz, 1H), 8.58 (d, *J* = 5.7 Hz, 1H), 7.91-7.84 (m, 1H), 7.78-7.69 (m, 2H), 7.67-7.59 (m, 3H), 7.01 (d, *J* = 2.2 Hz, 1H), 3.49 (s, 1H).

Step 2. To a stirring mixture of 1-(1H-pyrazol-5-yl)isoquinoline (0.36 g, 1.9 mmol) and Cs_2CO_3 (0.85 g, 2.6 mmol) in acetonitrile (18 mL) was slowly added iodoethane (0.17 mL, 2.1 mmol). The reaction mixture was heated to 60 °C for 8 hours, concentrated to dryness, and the residue was partitioned between ethyl acetate and water. The organic layer was separated, and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified on SiO_2 via Isco flash column chromatography (0-50% ethyl acetate/hexanes) to give the desired isomer 1-(1-ethyl-1H-pyrazol-3-yl)isoquinoline (0.22 g, 54% yield) as an off-white solid. MS (ESI) *m/z*: 224.0 $[M+H]^+$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.12 (dt, *J* = 1.1, 8.5 Hz, 1H), 8.58 (d, *J* = 5.6 Hz, 1H), 7.82 (dt, *J* = 1.0, 8.2 Hz, 1H), 7.66 (ddd, *J* = 1.3, 6.8, 8.2 Hz, 1H),

7.63-7.57 (m, 2H), 7.52 (d, J = 2.4 Hz, 1H), 6.94 (d, J = 2.2 Hz, 1H), 4.32 (q, J = 7.4 Hz, 2H), 1.59 (t, J = 7.3 Hz, 3H).

Step 3. To a solution of 1-(1-ethyl-1H-pyrazol-3-yl)isoquinoline (0.14 g, 0.62 mmol) in tetrahydrofuran (2.0 mL) at −78 °C was added LDA (0.37 mL, 0.74 mmol) dropwise. The mixture was stirred at −78 °C for 5 minutes followed by addition of 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.15 mL, 0.74 mmol). After stirring at −78 °C for 30 minutes, the reaction was quenched with water and then warmed to 0 °C (ice bath). Acetic acid was then added dropwise to the cold mixture until the pH of the aqueous layer was ~ 6-7. The mixture was extracted three times with ethyl acetate. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo to give 1-(1-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-3-yl)isoquinoline (0.23 g, quantitative yield) as an orange oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.03-8.94 (m, 1H), 8.58 (d, J = 5.6 Hz, 1H), 7.83 (dt, J = 0.9, 8.1 Hz, 1H), 7.67 (ddd, J = 1.3, 6.8, 8.2 Hz, 1H), 7.62-7.58 (m, 2H), 7.37 (s, 1H), 4.59 (q, J = 7.2 Hz, 2H), 1.54 (t, J = 7.2 Hz, 3H), 1.37 (s, 12H).

Step 4. To a degassed mixture of 1-(1-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-3-yl)isoquinoline (31 mg, 0.09 mmol), 3-bromopyridazine (21 mg, 0.13 mmol), and K_3PO_4 (56 mg, 0.26 mmol) in dioxane (0.73 mL) and water (0.15 mL) was added tetrakis(triphenylphosphine)palladium(0) (15 mg, 0.01 mmol). The reaction mixture was heated with stirring at 90 °C for 12 hours, cooled to room temperature, and then purified by preparative HPLC (XBridge C18, 19 × 200 mm column; mobile phase A = 5:95 acetonitrile: water with 0.1% trifluoroacetic acid; mobile phase B = 95:5 acetonitrile: water with 0.1% trifluoroacetic acid). Fractions containing the desired product were combined and dried via centrifugal evaporation to give **61** (14 mg, 37% yield). MS (ESI) mass calculated for $[M+H]^+$ ($C_{18}H_{16}N_5$)

requires *m/z* 302.1, found 302.2; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.36 (d, *J* = 8.8 Hz, 1H), 9.29 (d, *J* = 4.3 Hz, 1H), 8.60 (d, *J* = 4.7 Hz, 1H), 8.28 (d, *J* = 8.6 Hz, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 7.94 (t, *J* = 4.4 Hz, 1H), 7.88 (p, *J* = 4.0, 4.6 Hz, 2H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.69 (d, *J* = 3.3 Hz, 1H), 4.83 (p, *J* = 6.3, 7.0 Hz, 2H), 1.52 (q, *J* = 6.3 Hz, 3H).

4-(1-Ethyl-5-(pyridazin-3-yl)-1H-pyrazol-3-yl)isoquinoline, Formic Acid Salt (62). Prepared according to the procedures described for compound **61** with 4-bromoisoquinoline at Step 1. Final purification was accomplished by preparative HPLC (XBridge C18, 19 × 200 mm column; mobile phase A = 5:95 acetonitrile: water with 0.1% formic acid; mobile phase B = 95:5 acetonitrile: water with 0.1% formic acid) to give **62**. MS (ESI) mass calculated for $[M+H]^+$ ($C_{18}H_{16}N_5$) requires *m/z* 302.1, found 302.2; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.39 (s, 1H), 9.29 (d, *J* = 4.8 Hz, 1H), 8.87 (d, *J* = 8.7 Hz, 1H), 8.84 (s, 1H), 8.25 (t, *J* = 8.2 Hz, 2H), 7.98-7.87 (m, 2H), 7.80 (t, *J* = 7.7 Hz, 1H), 7.56 (s, 1H), 4.80 (q, *J* = 7.2 Hz, 2H), 1.50 (t, *J* = 7.1 Hz, 3H).

4-(1-Ethyl-5-(pyridazin-3-yl)-1H-pyrazol-3-yl)quinoline (63). Prepared according to the procedures described for compound **61** with 4-bromoquinoline at Step 1. Final purification was accomplished by preparative HPLC (XBridge C18, 19 × 200 mm column; mobile phase A = 5:95 acetonitrile: water with 10-mM ammonium acetate; mobile phase B = 95:5 acetonitrile: water with 10-mM ammonium acetate) to give **63**. MS (ESI) mass calculated for $[M+H]^+$ ($C_{18}H_{16}N_5$) requires *m/z* 302.1, found 302.2; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.29 (d, *J* = 4.7 Hz, 1H), 9.10 – 8.88 (m, 2H), 8.25 (d, *J* = 8.7 Hz, 1H), 8.11 (d, *J* = 8.5 Hz, 1H), 7.90 (dt, *J* = 4.5, 9.3 Hz, 1H), 7.84 (q, *J* = 6.3, 7.8 Hz, 2H), 7.72 (d, *J* = 8.9 Hz, 1H), 7.63 (t, *J* = 2.5 Hz, 1H), 4.81 (p, *J* = 6.5 Hz, 2H), 1.51 (dt, *J* = 5.5, 8.5 Hz, 3H).

5-(1-Ethyl-5-(pyridazin-3-yl)-1H-pyrazol-3-yl)quinoline (64). Prepared according to the procedures described for compound **61** with 5-bromoquinoline at Step 1. Final purification was accomplished by preparative HPLC (XBridge C18, 19 × 200 mm column; mobile phase A = 5:95 acetonitrile: water with 10-mM ammonium acetate; mobile phase B = 95:5 acetonitrile: water with 10-mM ammonium acetate) to give **64**. MS (ESI) mass calculated for $[M+H]^+$ ($C_{18}H_{16}N_5$) requires *m/z* 302.1, found 302.2; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.29 (d, *J* = 6.2 Hz, 2H), 8.99 (d, *J* = 3.9 Hz, 1H), 8.24 (d, *J* = 8.5 Hz, 1H), 8.08 (d, *J* = 8.2 Hz, 1H), 7.95 (d, *J* = 7.3 Hz, 1H), 7.89 (q, *J* = 7.7, 8.4 Hz, 2H), 7.66 (dd, *J* = 4.0, 9.1 Hz, 1H), 7.48 (s, 1H), 4.78 (q, *J* = 7.4 Hz, 2H), 1.50 (t, *J* = 7.3 Hz, 3H).

5-(1-Ethyl-5-(pyridazin-3-yl)-1H-pyrazol-3-yl)isoquinoline, TFA (65). Step 1. 5-(1-Ethyl-1H-pyrazol-3-yl)isoquinoline was prepared according to procedures described for compound **52** (Steps 2 to 4) with isoquinolin-5-ylboronic acid at Step 2. Final purification was accomplished by preparative HPLC (Phenomenex Luna Axia C18 30 × 100 mm column; mobile phase A = 10:90 methanol: water with 0.1% trifluoroacetic acid; mobile phase B = 90:10 methanol: water with 0.1% trifluoroacetic acid) to give 5-(1-ethyl-1H-pyrazol-3-yl)isoquinoline. MS (ESI) *m/z*: 224.1 $[M+H]^+$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.27 (app brs, 1H), 8.55 (app brs, 1H), 8.46 (d, *J* = 5.7 Hz, 1H), 7.96-7.88 (m, 2H), 7.62 (dd, *J* = 6.5, 8.9 Hz, 1H), 7.52 (d, *J* = 2.4 Hz, 1H), 6.56 (d, *J* = 2.2 Hz, 1H), 4.29 (q, *J* = 7.3 Hz, 2H), 1.58 (td, *J* = 2.4, 7.3 Hz, 3H).

Step 2. To a solution of 5-(1-ethyl-1H-pyrazol-3-yl)isoquinoline (0.12 g, 0.56 mmol) in tetrahydrofuran (1.8 mL) at −78 °C was added LDA (0.39 mL, 0.78 mmol) dropwise. The mixture was stirred at −78 °C for 15 minutes followed by addition of 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.15 mL, 0.72 mmol). The reaction was then gradually warm to room temperature. After stirring at room temperature for 1 hour, the mixture was cooled to 0 °C

(ice bath) and quenched with water. Acetic acid was then added dropwise to the cold mixture until the pH of the aqueous layer was ~ 6-7. The mixture was extracted three times with ethyl acetate. The combined extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo to give 5-(1-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-3-yl)isoquinoline (0.23 g, quantitative yield) as an orange oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.27 (d, *J* = 1.0 Hz, 1H), 8.54 (d, *J* = 6.0 Hz, 1H), 8.44 (dt, *J* = 0.9, 6.0 Hz, 1H), 7.93 (td, *J* = 1.1, 7.4 Hz, 2H), 7.63 (dd, *J* = 7.2, 8.2 Hz, 1H), 7.04 (s, 1H), 4.57 (q, *J* = 7.2 Hz, 2H), 1.54 (t, *J* = 7.2 Hz, 3H), 1.39 (s, 12H).

Step 3. To a degassed mixture of 5-(1-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-3-yl)isoquinoline (32 mg, 0.09 mmol), 3-bromopyridazine (22 mg, 0.14 mmol), and K_3PO_4 (58.6 mg, 0.28 mmol) in dioxane (0.77 mL) and water (0.15 mL) was added tetrakis(triphenylphosphine)palladium(0) (16 mg, 0.01 mmol). The resulting mixture was heated at 90 °C for 12 hours, cooled to room temperature and then purified by preparative HPLC (XBridge C18, 19 × 200 mm column; mobile phase A = 5:95 acetonitrile: water with 0.1% trifluoroacetic acid; mobile phase B = 95:5 acetonitrile: water with 0.1% trifluoroacetic acid). Fractions containing the desired product were combined and dried via centrifugal evaporation to give **65** (21 mg, 54% yield). MS (ESI) mass calculated for $[M+H]^+$ ($C_{18}H_{16}N_5$) requires *m/z* 302.1, found 302.2; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.70 (s, 1H), 9.30 (d, *J* = 4.9 Hz, 1H), 9.06 (d, *J* = 6.4 Hz, 1H), 8.68 (d, *J* = 6.5 Hz, 1H), 8.38 (d, *J* = 8.2 Hz, 1H), 8.34 (d, *J* = 7.3 Hz, 1H), 8.23 (d, *J* = 8.6 Hz, 1H), 7.97 (t, *J* = 7.7 Hz, 1H), 7.94-7.88 (m, 1H), 7.57 (s, 1H), 4.79 (q, *J* = 7.2 Hz, 2H), 1.51 (t, *J* = 7.1 Hz, 3H).

8-(1-Ethyl-5-(pyridazin-3-yl)-1H-pyrazol-3-yl)isoquinoline, TFA (66). Prepared according to the procedures described for compound **61** with 8-bromoisoquinoline at Step 1.

Final purification was accomplished by preparative HPLC (XBridge Shield RP18, 19 × 250 mm column; mobile phase A = 5:95 acetonitrile: water with 0.1% trifluoroacetic acid; mobile phase B = 95:5 acetonitrile: water with 0.1% trifluoroacetic acid) to give **66**. MS (ESI) mass calculated for $[M+H]^+$ ($C_{18}H_{16}N_5$) requires *m/z* 302.1, found 302.2; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.40 (s, 1H), 9.33 (d, *J* = 4.9 Hz, 1H), 8.68 (d, *J* = 6.0 Hz, 1H), 8.26 (t, *J* = 7.4 Hz, 2H), 8.18 (t, *J* = 7.5 Hz, 2H), 8.09 (t, *J* = 7.7 Hz, 1H), 7.94 (dd, *J* = 4.9, 8.6 Hz, 1H), 7.65 (s, 1H), 4.82 (q, *J* = 7.1 Hz, 2H), 1.54 (t, *J* = 7.1 Hz, 3H).

8-(1-Ethyl-5-(pyridazin-3-yl)-1H-pyrazol-3-yl)quinoline, TFA (67). Step 1. 8-(1-Ethyl-1H-pyrazol-3-yl)quinoline was prepared according to the procedures described for compound **52** (Steps 2 to 4) with quinolin-8-ylboronic acid at Step 2 to give the desired intermediate. MS (ESI) *m/z*: 224.0 $[M+H]^+$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.99 (dd, *J* = 1.8, 4.1 Hz, 1H), 8.27 (dd, *J* = 1.5, 7.3 Hz, 1H), 8.17 (dd, *J* = 1.9, 8.2 Hz, 1H), 7.78 (dd, *J* = 1.5, 8.1 Hz, 1H), 7.59 (dd, *J* = 7.2, 8.2 Hz, 1H), 7.53 (d, *J* = 2.2 Hz, 1H), 7.40 (dd, *J* = 4.1, 8.3 Hz, 1H), 7.22 (d, *J* = 2.2 Hz, 1H), 4.29 (q, *J* = 7.3 Hz, 2H), 1.56 (t, *J* = 7.4 Hz, 3H).

Step 2**.** To a solution of 8-(1-ethyl-1H-pyrazol-3-yl)quinoline (1.8 g, 8.3 mmol) in tetrahydrofuran (28 mL) at −78 °C was added LDA (5.8 mL, 12 mmol) dropwise. The reaction mixture was stirred at −78 °C for 45 min followed by addition of 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.0 mL, 9.9 mmol). The mixture was gradually warm to room temperature. After stirring at room temperature for 1 hour, the mixture was cooled to 0 °C (ice bath) and then quenched with water. Acetic acid was then added dropwise to the cold mixture until the pH of the aqueous layer was ~ 6-7. The mixture was extracted three times with ethyl acetate. The combined extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The resultant orange oil was then co-evaporated with CH_2Cl_2 to yield 8-

(1-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-3-yl)quinoline (3.1 g, quantitative yield) as a sticky orange solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.98 (dd, *J* = 1.9, 4.1 Hz, 1H), 8.26 (dd, *J* = 1.6, 7.2 Hz, 1H), 8.16 (dd, *J* = 1.9, 8.2 Hz, 1H), 7.77 (dd, *J* = 1.5, 8.1 Hz, 1H), 7.67 (s, 1H), 7.58 (dd, *J* = 7.2, 8.1 Hz, 1H), 7.40 (dd, *J* = 4.1, 8.2 Hz, 1H), 4.56 (q, *J* = 7.2 Hz, 2H), 1.50 (t, *J* = 7.2 Hz, 3H), 1.37 (s, 12H).

Step 3. To a degassed mixture of 8-(1-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-3-yl)quinoline (0.04 g, 0.10 mmol), 3-bromopyridazine (0.02 g, 0.15 mmol), and K_3PO_4 (0.06 g, 0.30 mmol) in dioxane (0.83 mL) and water (0.17 mL) was added tetrakis(triphenylphosphine)palladium(0) (0.02 g, 0.02 mmol). The resulting mixture was heated at 90 °C for 10 hours, cooled to room temperature and then purified by preparative HPLC (Phenex Luna AXIA C18 30 × 100 mm column; mobile phase A = 10:90 acetonitrile: water with 0.1% trifluoroacetic acid; mobile phase B = 90:10 acetonitrile: water with 0.1% trifluoroacetic acid). Fractions containing the desired product were combined and dried via centrifugal evaporation to give **67** (10 mg, 24% yield) as a light brown solid. MS (ESI) mass calculated for $[M+H]^+$ ($C_{18}H_{16}N_5$) requires *m/z* 302.1, found 302.1; ^{1}H NMR (500 MHz, CD_3OD) δ 9.45 (dq, *J* = 1.8, 5.5 Hz, 1H), 9.30-9.24 (m, 2H), 8.69 (dd, *J* = 1.3, 7.4 Hz, 1H), 8.36 (dd, *J* = 1.2, 8.2 Hz, 1H), 8.24 (dd, *J* = 1.6, 8.6 Hz, 1H), 8.18 (ddd, *J* = 1.6, 5.3, 7.0 Hz, 1H), 8.08 (t, *J* = 7.8 Hz, 1H), 7.92 (dd, *J* = 5.0, 8.6 Hz, 1H), 7.77 (s, 1H), 4.99 (q, *J* = 7.2 Hz, 2H), 1.62 (t, *J* = 7.2 Hz, 3H).

6-(1-Ethyl-3-(isoquinolin-8-yl)-1H-pyrazol-5-yl)pyridazin-3-amine (68). Prepared according to procedures described for compound **61** with 8-bromoisoquinoline at Step 1 and 6-chloropyridazin-3-amine at Step 3. Final purification was accomplished by Isco flash chromatography on SiO_2 (0-10% MeOH/CH_2Cl_2) to give **68**. MS (ESI) mass calculated for $[M+H]^+$ ($C_{18}H_{17}N_6$) requires *m/z* 317.1, found 317.1; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.17 (d,

J = 1.1 Hz, 1H), 8.56 (d, *J* = 5.6 Hz, 1H), 8.07-7.81 (m, 4H), 7.77 (d, *J* = 9.2 Hz, 1H), 7.20 (s, 1H), 6.92 (d, *J* = 9.2 Hz, 1H), 6.67 (s, 2H), 4.69 (q, *J* = 7.1 Hz, 2H), 1.46 (t, *J* = 7.1 Hz, 3H).

6-(1-ethyl-3-(quinolin-8-yl)-1H-pyrazol-5-yl)pyridazin-3-amine (69). Step 1. LDA (8.8 mL, 18 mmol) was added to a −78 °C solution of 1-ethyl-3-nitro-1H-pyrazole (1.9 g, 14 mmol) in tetrahydrofuran (41 mL). After 40 minutes, 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.8 mL, 19 mmol) was added and the reaction was stirred at −78 °C for 1 hour. There was still starting material remaining so an additional 1 mL of LDA was added. After 1 hour all of the starting material was consumed. The reaction mixture was gradually warmed to 0 °C before being quenched with water and AcOH (3.1 mL, 54 mmol). The mixture was then extracted with ethyl acetate (2 × 75 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo to give 1-ethyl-3-nitro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole as a brown oil. By ^{1}H NMR the isolated product is the pinacol ester but hydrolyzes to the boronic acid on LCMS. The product was used without further purification in the next step. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (s, 1H), 4.51 (q, *J*=7.19 Hz, 2H), 1.49 (t, *J*=7.26 Hz, 3H), 1.37 (s, 11H).

Step 2. Cesium carbonate (9.0 g, 27.5 mmol), (6-chloro-pyridazin-3-yl)-dicarbamic acid *tert*-butyl ester (3.6 g, 11 mmol) and 1-ethyl-3-nitro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (3.5 g, 13 mmol) were suspended in dioxane (55 mL) and the mixture was deoxygenated by bubbling argon through the suspension for 15 minutes. After degassing was complete, 1,1'-bis(di-*tert*-butylphosphino)ferrocene palladium dichloride (0.36 g, 0.55 mmol) and 1,1'-bis(di-*tert*-butylphosphino)ferrocene (0.37 g, 0.77 mmol) were added and the reaction vessel was sealed and heated to 80 °C for 2.5 hours. At this time, LCMS analysis indicated predominantly the desired product with a small amount of unreacted chloropyridazine. The

reaction mixture was diluted with ethyl acetate, filtered through Celite and concentrated in vacuo. The residue was purified on SiO_2 via Isco flash chromatography (0-50% ethyl acetate/hexanes, Isco 80 g column) to give the desired nitropyrazole (2.7 g, 6.2 mmol, 56% yield) as a tan amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77-7.82 (m, 1H), 7.71-7.76 (m, 1H), 7.26 (s, 1H), 4.85 (q, *J*=7.12 Hz, 2H), 1.54-1.56 (m, 5H), 1.53 (s, 17H).

Step 3. Palladium on carbon (10% Degussa type) (0.66 g, 0.62 mmol) was added to a flask containing a solution of the nitropyrazole product from step 2 (2.7 g, 6.2 mmol) in methanol (89 mL) that had been degassed and back-filled with argon. A hydrogen filled balloon was affixed to the flask and the system was purged with hydrogen for 5 minutes. The reaction mixture was stirred under hydrogen balloon atmosphere for 3 hours, purged with nitrogen and filtered through Celite. The filtrate was concentrated in vacuo to give the amino pyrazole (2.2 g, 5.3 mmol, 86% yield) as an off-white solid. The product was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J*=9.02 Hz, 1H), 7.52 (d, *J*=9.02 Hz, 1H), 6.00 (s, 1H), 4.56 (q, *J*=7.19 Hz, 2H), 3.69 (s, 2H), 1.49 (s, 18H), 1.43 (t, *J*=7.15 Hz, 3H).

Step 4. *tert*-Butyl nitrite (0.49 mL, 3.7 mmol) was added to a mixture of copper(I) bromide (0.53 g, 3.7 mmol) and lithium bromide (0.27 g, 3.1 mmol) in acetonitrile (18.5 mL). After 10 minutes this mixture was added to a flask containing a suspension of the aminopyrazole from step 3 (1.0 g, 2.5 mmol) in acetonitrile (6.2 mL). The reaction mixture was stirred at room temperature and after 1 hour and then heated with stirring at 50 °C for 2 hours until the desired product predominated by LCMS analysis. The reaction mixture was diluted with ethyl acetate and then washed with saturated aqueous $NaHCO_3$ and then brine. The collected organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified on SiO_2 via Isco flash chromatography (0-50% ethyl acetate/heptane, Isco 40g gold column) to give the

bromopyrazole (0.67 g, 1.4 mmol, 58% yield) as a white solid. ^{1}H NMR (500MHz, $CDCl_3$) δ 7.70 (d, *J*=8.8 Hz, 1H), 7.61 (d, *J*=9.1 Hz, 1H), 6.65 (s, 1H), 4.72 (q, *J*=7.2 Hz, 2H), 1.50 (s, 18H), 1.50 - 1.45 (m, 4H).

Step 5. The bromopyrazole product from step 4 (0.25 g, 0.53 mmol), quinolin-8-ylboronic acid (0.10 g, 0.59 mmol), and cesium carbonate (0.44 g, 1.3 mmol) were suspended in dioxane (5.3 mL) and the mixture was degassed by bubbling argon through the suspension for 5 minutes. 1,1'-bis(diphenylphosphino)ferrocene palladium dichloride (0.04 g, 0.05 mmol) was added and the reaction vessel was sealed and heated to 100 °C for 2 hours. The reaction mixture was cooled to room temperature, transferred to a round bottom flask and concentrated onto SiO_2 (sufficient quantity to give a free-flowing solid). This solid was purified on SiO_2 via Isco flash chromatography (0-100% ethyl acetate/hexanes, Isco 24 g column) to give the desired product (0.24 g, 0.46 mmol, 87% yield) as a white solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 9.02 (dd, *J*=4.1, 1.9 Hz, 1H), 8.42 (dd, *J*=7.3, 1.3 Hz, 1H), 8.23 (dd, *J*=8.3, 1.9 Hz, 1H), 7.99 (d, *J*=8.8 Hz, 1H), 7.85 (dd, *J*=8.1, 1.3 Hz, 1H), 7.80 (s, 1H), 7.70 - 7.62 (m, 1H), 7.55 (d, *J*=9.0 Hz, 1H), 7.46 (dd, *J*=8.1, 4.2 Hz, 1H), 4.94 (q, *J*=7.0 Hz, 2H), 1.61 - 1.56 (m, 3H), 1.49 (s, 18H).

Step 6. The product from step 5 (0.24 g, 0.46 mmol) was taken up in TFA (2.0 mL). After 2 hours the excess TFA was removed in vacuo. The resulting solid was lyophilized from water to give the TFA salt of **69** (0.2 g, 0.46 mmol, 99% yield) as a pale-yellow solid. A portion of the product was further purified by preparative HPLC (Phenomenex Luna Axia 5μ C18 30 × 100mm column; mobile phase A = 10:90 methanol: water with 0.1% trifluoroacetic acid; mobile phase B = 90:10 methanol: water with 0.1% trifluoroacetic acid over 10 min). The desired fractions were partitioned between ethyl acetate and 1M aqueous K_2HPO_4. The aqueous layer was further extracted with two small portions of ethyl acetate and the combined organic extracts were

washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo to give a pale yellow solid. The solid was lyophilized from water to give **69**. MS (ESI) mass calculated for $[M+H]^+$ ($C_{18}H_{17}N_6$) requires *m/z* 317.1, found 317.1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.00 (dd, *J* = 1.9, 4.2 Hz, 1H), 8.38 (dd, *J* = 1.6, 7.3 Hz, 1H), 8.21 (dd, *J* = 1.9, 8.3 Hz, 1H), 7.81 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.70 (d, *J* = 9.2 Hz, 1H), 7.66 – 7.61 (m, 1H), 7.57 (s, 1H), 7.43 (dd, *J* = 4.1, 8.3 Hz, 1H), 6.85 (d, *J* = 9.1 Hz, 1H), 4.89 – 4.78 (m, 4H), 1.55 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125MHz, $CDCl_3$) δ 157.95, 149.80, 148.13, 146.21, 145.89, 138,64, 136.52, 131.96, 128.99, 128.70, 128.21, 127.74, 126.62, 120.83, 114.62, 109.02, 47.18, 16.90.

Functional Assays for the 5-HT$_{2A}$, 5-HT$_{2B}$ and 5-HT$_{2C}$ Receptors. HEK293E cells stably expressing the human 5-HT$_{2A}$, 5-HT$_{2B}$, or 5-HT$_{2C}$ receptors were maintained Dulbecco's modified Eagle's media with high glucose (DMEM; Gibco BRL) containing 10% dialyzed fetal bovine serum (FBS) and 500μg/mL G418 (Gibco BRL). The recombinant expression system expressed moderate levels of 5-HT$_{2A}$, 5-HT$_{2B,}$ or 5-HT$_{2C}$ receptors (~400-795 fmol/mg of protein). The VNV isoform of 5HT$_{2C}$ was used for pharmacological studies.[34] The cells were lifted with 2 mL Cellstripper (Mediatech/Cellgro) and plated at a density of 20,000 cells/25 μL/well onto poly-D-lysine-coated 384-well plates (Biocoat; Becton Dickinson, Bedford, MA) in phenol red free Dulbecco's modified Eagle's media (DMEM; Gibco BRL) containing a high concentration of glucose without FBS. Following an overnight (~15-18 hours) incubation at 37 °C, the cell plates were removed from the incubator and dye loading buffer (25 μl of 1x Hanks BSS without calcium and magnesium with 25 mM HEPES) containing 5 μM of the calcium dye reagent Fluo-4 was added to each well. Following the dye loading of the cells for 1 hour at room temperature, the cell plates were transferred to the FLIPR^{384} (Molecular Devices, Sunnyvale, CA). Eleven concentrations of test compounds in 25 μL loading buffer were added to the cell

plate on the FLIPR^{384} to determine a concentration-response curve and the changes in fluorescence units due to the elevation of intracellular calcium was monitored for a period of ninety seconds. The raw data from time sequence recording was normalized to the percentage response obtained from the positive control (Serotonin 3 μM) on the same plate and analyzed to fit the four-parameter logistic equation in order to assess compound's potency (EC_{50}) and efficacy (Intrinsic Activity) from the 384-FLIPR agonist assay.

Rat Pharmacokinetic Study. All animal protocols were approved by the Bristol- Myers Squibb Co. Animal Care and Use Committee. Male Sprague Dawley rats obtained from Charles River Laboratories, weighing between 200 - 250g were used. Animals were allowed free access to a standard laboratory chow and water. They were housed in a constant temperature-humidity environment. Three rats were used in each of the intravenous (I.V.) and oral (P.O.) arms of the studies. The vehicle consisted of polyethylene glycol 400:Tween 80:water (15:1:84, v/v). Blood was sampled from the jugular vein at 0.25, 0.5, 1, 2, 4, 6, 8, 10 and 24 h post dose. Plasma was obtained after centrifugation of the blood samples. Following protein precipitation using acetonitrile and subsequent centrifugation, samples were analyzed using LC/MS-MS.

Rat 20 h Ad Libitum Feeding Assay. All animal protocols were approved by the Bristol- Myers Squibb Co. Animal Care and Use Committee. Compounds were assessed for their ability to reduce food consumption during a 20 hour period, which began at the onset of the dark cycle. Male Sprague Dawley rats, obtained from Charles River Laboratories, were trained in operant chambers (Coulbourn Instruments, Allentown, PA) equipped with a lever, a food hopper, a water bottle with photocells, and an infrared activity monitor. Rats were trained on a fixed ratio three (FR3) response paradigm which required three consecutive bar presses in order to obtain a food pellet (Research Diets custom 45mg pellets (21.3% Protein; 3.8% Fat, 54% Carbohydrate).

The number of bar presses and pellets consumed serve as the measure of food intake by the animal. Rats (n = 6) were administered (PO) test compound or vehicle (14% PPG, 1% Tween, 85% water, v/v) 60 minutes prior to the onset of the dark cycle. Treated animals were then placed in individual operant boxes for a 20 hour period (12 h of dark cycle and the first 8 h of the light cycle). Percent reduction in food intake was calculated as the ratio of total food intake of drug-treated animals divided to the total food intake of vehicle-treated counterparts. Simultaneous measurements of water intake and locomotor activity are also measured during the period to evaluate potential adverse effects. Cumulative food intake was analyzed via repeated-measure between-group analysis of variance using StatView software (Scientific Computing, Cary, North Carolina). Time points with overall significance were further analyzed with Bonferroni post-hoc tests to determine between-group significance.

ASSOCIATED CONTENT

Supporting Information:

The Supporting Information is available free of charge on the ACS Publications website at

DOI:

Additional data for compound **69** (PDF)

Compound molecular formula strings (CSV)

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Notes

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ABBREVIATIONS USED

5-HT, 5-hydroxytryptamine, serotonin; D, aspartic acid; A, alanine; SAR, structure activity relationship; GPCR, G-protein coupled receptor; FDA, U.S. Food and Drug Administration; Phe, phenylalanine; Tyr, tyrosine; Trp, tryptophan; Asp, aspartic acid; CNS, central nervous system; PAM, positive allosteric modulator; BMS, Bristol-Myers Squibb; DMSO, dimethyl sulfoxide; TFA, trifluoroacetic acid; HEK 293E, human embryonic kidney-293E cell; mCPP, *meta*-chlorophenylpiperazine; PAMPA, parallel artificial membrane permeability assay; Caco-2, human epithelial colorectal adenocarcinoma cells; Pgp, P-glycoprotein; BCRP, breast cancer resistance protein; Metstab, metabolic stability; b/p, brain to plasma ratio; H/R, human/rat.

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