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Article

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Optimization of Novel 1-Methyl-1*H*-Pyrazole-5-carboxamides Leads to High Potency Larval Development Inhibitors of the Barber's Pole Worm

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ABSTRACT

A phenotypic screen of a diverse library of small molecules for inhibition of the development of larvae of the parasitic nematode *Haemonchus contortus* led to the identification of a 1-methyl-1*H*-pyrazole-5-carboxamide derivative with an IC_{50} of 0.29 μM.

Medicinal chemistry optimization targeted modifications on the left-hand side (LHS), middle section and right-hand side (RHS) of the scaffold in order to elucidate the structure-activity relationship (SAR). Strong SAR allowed for the iterative and directed assembly of a focus set of 64 analogues, from which compound **60** was identified as the most potent compound, inhibiting the development of the fourth larval (L4) stage with an IC_{50} of 0.01 μM. In contrast, only 18% inhibition of the mammary epithelial cell line MCF10A viability was observed, even at concentrations as high as 50 μM.

KEYWORDS *Haemonchus*, Nematodes, Anthelmintics, Pyrazole-5-carboxamide.

INTRODUCTION

Parasitic worms (helminths) are major causes of diseases of humans, other animals and plants worldwide.[1] Besides the socioeconomic impact on humans, parasitic helminths of livestock animals cause substantial productivity losses, reaching billions of dollars per annum.[2] For instance, gastrointestinal roundworms (nematodes) are the main cause of reduced weight gain, weight loss, poor meat and milk production and mortality in farm animals. In this context, nematodes of the order Strongylida are of paramount importance as pathogens,[2] and in particular the barber's pole worm *Haemonchus contortus* (*H. contortus*) represents this order and is one of the most pathogenic members, affecting hundreds of millions of small ruminants (including sheep and goats) worldwide.[2,3]

The control of *H. contortus* and other strongylid nematodes has relied heavily on the treatment of ruminants with a small number of anthelmintic drugs. These broad-spectrum anthelmintics work mainly by inhibiting muscle contraction, leading to a paralysis of nematodes or via the disruption of microtubule function.[4] The excessive and

uncontrolled use of these anthelmintics has provoked the development of drug resistant worms.[5,6] The two newer groups of anthelmintics, namely amino-acetonitrile derivatives (e.g. monepantel) and derquantel (**Figure 1**), have been effective at combating multi-resistant nematodes, but emerging resistance is proving problematic.[7–10] Recent reports disclose selenophene and thiophene derivatives, acrylonitrile-based compounds, and 2-phenylimidazo[1,2-b]pyridazine derivatives, each with potent *in vitro* activity against *H. contortus*, but drug development has yet to be undertaken.[11–13] Thus, given the expansion of resistance to existing anthelmintics, the search for new chemical entities with nematocidal or nematostatic activity remains crucial.

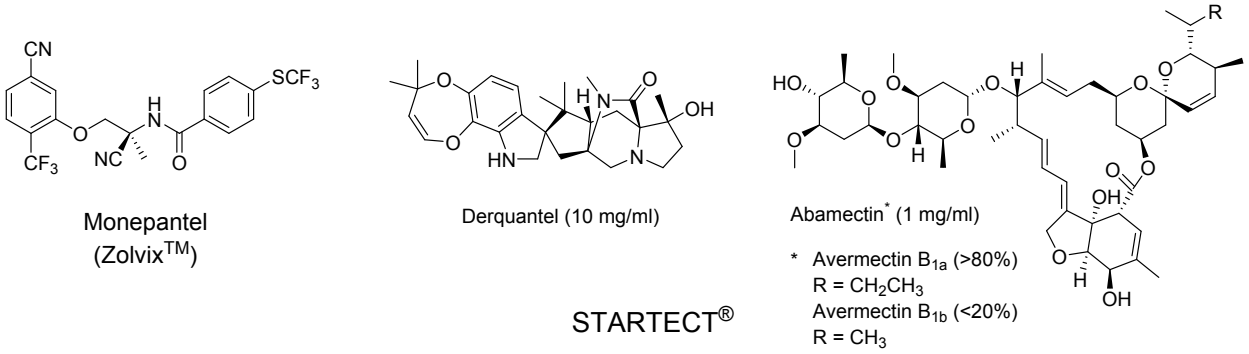
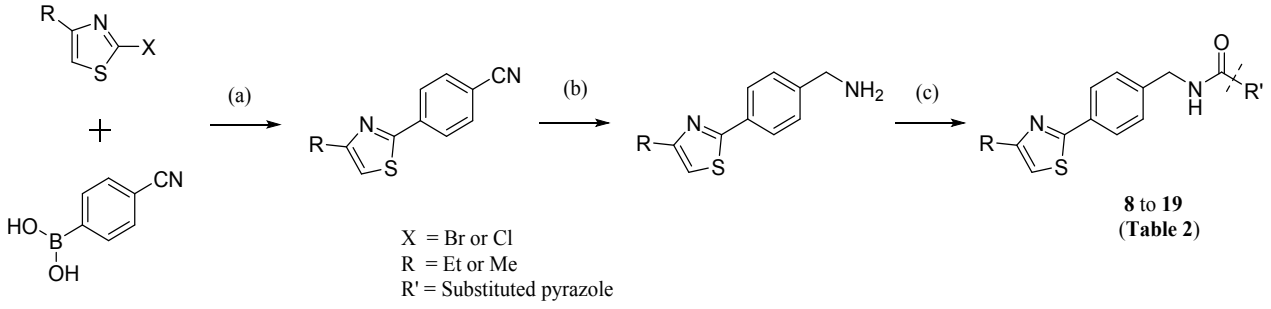


Figure 1. Some current anthelmintic drugs used to treat nematodiases of livestock animals.

Our ultimate goal is to discover an orally administered anthelmintic for livestock. With this focus in mind, our team established a phenotypic screening platform[14] that assesses the motility and development of parasitic larvae of *H. contortus*; the use of this platform has yielded a number of compounds with anthelmintic activity *in vitro*.[13–18] For instance, we have screened the 'Pathogen Box' (www.pathogenbox.org) from the Medicines for Malaria Venture (MMV; www.mmv.org) to discover that the approved pesticide, tolfenpyrad, possesses potent anthelmintic activity against *H. contortus*.[16] We also screened a high quality, diverse library of ~13,500 synthetic small molecules to discover a proline derivative with similarly interesting anthelmintic activity.[18] From the latter screen, we also identified a 1-methyl-1*H*-pyrazole-5-carboxamide hit, designated **SN00799639** (**1**), which we have not yet reported on. Here, were describe medicinal chemistry optimization and elucidation of the structure-activity relationship (SAR) for **1**, iteratively guided by results from our phenotypic assay for *H. contortus*.

RESULTS AND DISCUSSION

The construction of the LHS, middle section, and RHS of the scaffold is depicted in **Scheme 1**. For late-stage RHS derivatisation, from **Scheme 1**, the thiazole halide building block for the LHS was subjected to a Suzuki coupling reaction for a C-C bond formation with the middle ring section harbouring a nitrile group, which was subsequently reduced to give the free amine that served as the precursor for subsequent RHS amide coupling reaction. The same synthetic principle was applied when varying LHS or middle section.



Scheme 1 (a) $Pd(dppf)Cl_2$, K_2CO_3, dioxane/H_2O, 110 °C or $Pd(PPh_3)_4$, toluene, 80 °C; (b) $LiAlH_4$, THF; (c) HOAt, EDCI, ACN, 80 °C or HATU, DIPEA, DMF or T_3P®, DIPEA, THF.

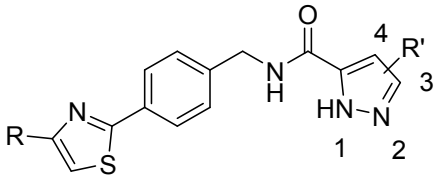
To examine SAR, compounds were first subjected to a primary biological assay that assessed the motility of *H. contortus* at the exsheathed L3 (xL3) stage, using monepantel and moxidectin as positive control anthelmintics. Only compounds that

resulted in ≥ 70% motility inhibition of xL3 larvae at 100 μM concentration were then subjected to subsequent dose-response experiments to obtain IC_{50} values and then further assessed in the L4 development assay.

Prior to the synthesis of carboxamide derivatives, initial mining of the high throughput deck for analogues led to the purchase and screening of broadly related analogues, but none of them was active (see **Supporting Information**). A set of analogues with closely related structures of **1** was also obtained from commercial sources to assess SAR; results are summarized in **Table 1**. This set mainly probed the substitution pattern of the RHS pyrazole and the results clearly indicate the importance of the 1-alkyl group, which was crucial to maintain activity against *H contortus*, as neither the des-alkyl pyrazole nor the 2-alkyl pyrazole were tolerated (**4**-**7**). Replacing the ethyl group on the LHS thiazole with either a methyl (**2**) or *iso*-propyl (**3**) group had minor effects, and resulted in comparable IC_{50} values of 10.7 and 12.0 μM respectively. In relation to the measured cytotoxicity, the methyl substituents on the thiazole ring exerted only 1% inhibition of mammal epithelial cell viability at 50 μM. Therefore, thiazole with the methyl

substituent from **2** was considered as interchangeable with the original thiazole from **1** in this SAR study.

Table 1 SAR of commercially resourced compounds closely related to the initial hit compound **1**



1 to **7**

Entry #	R	R'	IC_{50} (μM) ± SD in xL3 motility assay	IC_{50} (μM) ± SD in L4 development assay	MCF10A Cytotoxicity*
1	Et	1-Me	8.40 ± 1.40	0.29 ± 0.10	24.4%
2	Me	1-Me	10.7 ± 5.43	0.37 ± 0.13	1%
3	*Iso*-prop	1-Me	12.0 ± 3.38	0.33 ± 0.16	44%
4	Et	2-Me	> 100		
5	Et	2-Et	>100		
6	Me	2-Et	>100		
7	Me	1-H	>100		

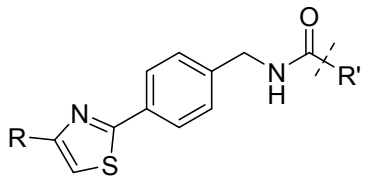
#Compounds purchased from ChemDiv (www.chemdiv.com).

*Inhibition at 50 μM.

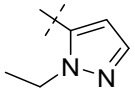
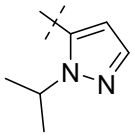
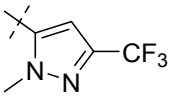
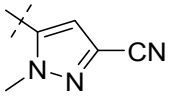
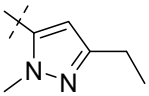
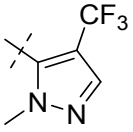
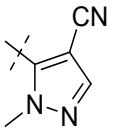
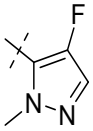
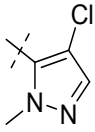
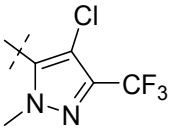
Tight SAR was observed from the diverse modifications on the RHS pyrazole (**Table 2**). In order to first explore the chemical space of the 1-position of the pyrazole, the methyl group was replaced with ethyl and *iso*-propyl to produce analogues **8** and **9**, respectively. However, this replacement led to a complete loss of activity. For the 3-

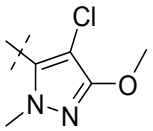
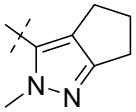
position of the pyrazole, we experimented with electron withdrawing groups, such as CF_3 and CN as seen for analogues **10** and **11**; however, none of these groups was active. In contrast, when adding an ethyl group also at the 3-position to give **12**, activity against both xL3 motility and L4 development was regained. When CF_3 and CN groups were each probed at the 4-position of the pyrazole (compounds **13** and **14**), activity could not be retained. A 4-F substituent gave rise to analogue **15**, exhibited comparable activity to the original hit **1**, in terms of inhibition of both xL3 motility and L4 development. Similar to the observation with **1**, compound **15** had low cytotoxicity (< 25%) against mammal epithelial cell proliferation when tested at a concentration of 50 μM. Interestingly, when Cl in place of F was probed at the same position (**16**), activity against xL3 motility was completely lost. Although having an additional CF_3 group at the 3-postion (**17**) did not retrieve any activity, activity was 'recovered' when the methoxy group was evaluated (**18**). A bulky aliphatic group, such as cyclopentane (**19**), was not tolerated. In summary, among the substituents explored for position 4, a fluoro in the 4-position of the pyrazole group was regarded as the most favored.

Table 2 SAR of the RHS pyrazole.



8 to **19**

Entry	R	R'	IC_{50} (μM) ± SD in xL3 motility assay	IC_{50} (μM) ± SD in L4 development assay	MCF10A Cytotoxicity*
8	Me		>100		
9	Me		>100		
10	Et		>100		
11	Et		>100		
12	Me		27.70 ± 18.75	0.71 ± 0.29	26.9%
13	Et		>100		
14	Et		>100		
15	Me		14.50 ± 1.22	0.53 ± 0.24	21.7%
16	Me		>100		
17	Et		>100		

18	Me		24.7 ± 17.9	0.24 ± 0.12	N/A[#]
19	Me		>100		

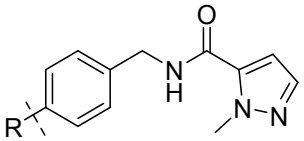
*Inhibition at 50 μM.

[#]Not assessed.

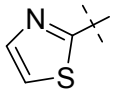
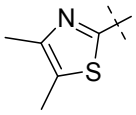
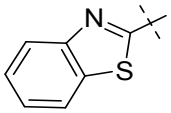
To explore SAR of the LHS of the scaffold (**Table 3**), we first probed different substitutions of the thiazole, such as the des-methyl analogue (**20**), 4,5-dimethyl (**21**), benzothiazole (**22**) or the regioisomer **23**, as well as a methylene insertion between the middle phenyl ring section and the thiazole (compound **24**). However, none of these analogues affected *H. contortus* xL3 motility or L4 development. The incorporation of hydrophobic electron-withdrawing species to the thiazole ring, such as 4-Cl (compound **25**) or fluoroalkyl (**26-28**), resulted in moderate inhibitory activity on L4 development, with IC_{50} values ranging from 0.73 to 3.25 μM. Next, we investigated other 5-membered ring isosteres of the thiazole, such as the substituted imidazole **29**, pyrazoles **30** and **31**, triazoles **32** to **34**, and oxazoles **35** and **36**. Of these compounds, **31** displayed moderate activity, while the rest were completely inactive. In contrast, potent activity was observed with a set of oxadiazoles (**37-39**). For the 1,2,4-oxadiazole **37** an IC_{50} value of 0.18 μM

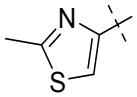
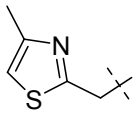
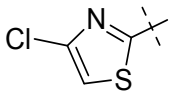
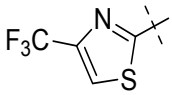
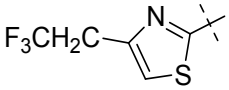
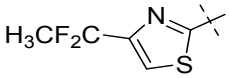
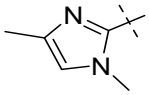
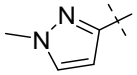
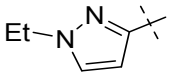
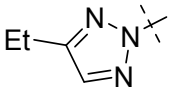
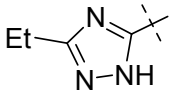
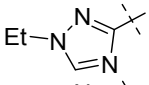
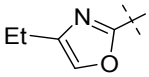
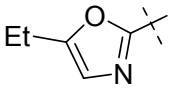
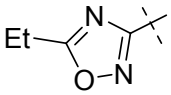
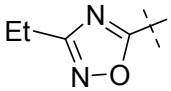
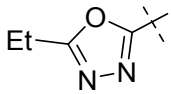
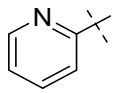
was observed for the inhibition of L4 development, which was a clear improvement from the original hit **1**. The regioisomeric 1,2,4-oxadiazole **38** was also quite potent, with an IC_{50} value of 0.69 μM for inhibition of L4 development. Interestingly, the 1,3,4-oxadiazole **39** was inactive. In addition to 5-membered rings, we also explored 6-membered rings such as pyridine, pyridazine and pyrazine (**40**-**42**), but did not observe any activity with those. Overall, from the investigation of the LHS SAR, and in light of the observed selectivity towards *H. contortus* over mammalian cells, the 1,2,4-oxadiazole moiety was considered the best LHS scaffold.

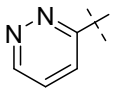
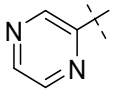
Table 3 SAR of the LHS region



20 to **42**

Entry	R	IC_{50} (μM) ± SD in xL3 motility assay	IC_{50} (μM) ± SD in L4 development assay	MCF10A Cytotoxicity*
20		>100		
21		>100		
22		>100		

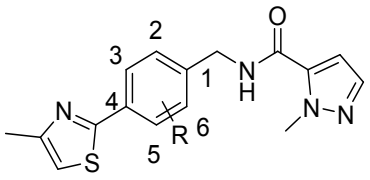
23		>100		
24		>100		
25		65.3 ± 13.2	3.25 ± 1.27	34.8%
26		50 ± 0.00	3.27 ± 2.01	22.5%
27		14.3 ± 5.40	0.73 ± 0.23	29%
28		23.7 ± 1.48	1.50 ± 0.56	31.1%
29		>100		
30		>100		
31		28.5 ± 4.95	4.87 ± 0.51	23.5%
32		>100		
33		>100		
34		>100		
35		>100		
36		>100		
37		5.53 ± 4.10	0.18 ± 0.04	21%
38		16.5 ± 10.64	0.69 ± 0.38	25.5%
39		>100		
40		>100		

41		>100
42		>100

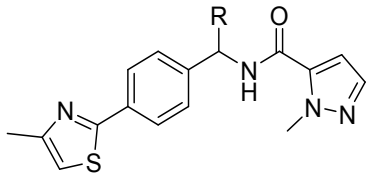
*Inhibition at 50 μM.

The SAR for the middle section of **1** was probed next, and the results are shown in **Table 4**. On the 2-position of the ring, the F substituent (**43**) displayed moderate activity against both xL3 motility and L4 development, while substituents such as the methoxy (**44**), methyl (**45**) or pyridinyl group (**46**) all led to a total loss of activity against xL3 motility. The same set of substituents, when investigated at the 3-position of the ring, produced similar results in terms of activity, such that the 3-F substituent (**47**) maintained the original activity against L4 development, while the analogues **48-50** were inactive. Methylation or cyanation of the benzylic carbon (**51** and **52,** as racemic mixtures) also resulted in inactivity.

Table 4 SAR of the middle section



43 to **50**



51 and **52**

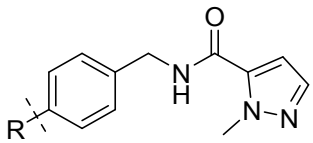
ID	R	IC_{50} (μM) ± SD in xL3 motility assay	IC_{50} (μM) ± SD in L4 development assay	MCF10A Cytotoxicity*
43	2-F	39.5 ± 21.9	1.8 ± 0.001	29.8%
44	2-OCH_3	>100		
45	2-Me	>100		
46	2-Pyridinyl	>100		
47	3-F	22.1 ± 3.05	0.24 ± 0.20	27.5%
48	3-OCH_3	>100		
49	3-Me	>100		
50	3-Pyridinyl	>100		
51	Me	>100		
52	CN	>100		

*Inhibition at 50 μM.

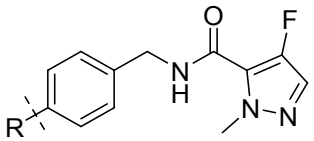
Following our discovery of novel oxadiazoles **37** and **38**, we set out to combine all determined favorable groups of the RHS and middle section, as well as to modify the alkyl substituent of the oxadiazole (**Table 5**). Replacing the ethyl group of the oxadiazole with either methyl, *n*-propyl or fluoroalkyl groups led to a slight loss of xL3 motility and L4 development inhibition compared with the parent oxadiazoles (compounds **53**, **54**, **57**, **58**, and **59**). Substituents such as *iso*-propyl or *cyclo*-propyl (compounds **55** and **56**) modestly improved the activity of the original oxadiazole **37**. By retaining the ethyl group of the oxadiazole and incorporating the favorable 4-fluoropyrazole on the RHS, we observed a 10-fold improvement in L4 development inhibitory activity for **60**, and 2-fold improvement

for **61,** compared with **37** and **38** respectively. Not only was a significant improvement observed, these compounds also displayed a further reduction in cytotoxicity compared with **37** and **38**. When probing the reverse amide **62**, no activity was observed. This result might suggest that a specific orientation of the amide moiety is required for binding to the target. Retaining the 4-fluoropyrazole RHS and replacing the middle phenyl ring with the favored fluoro-substituted ring afforded **63** and **64**. Neither of those compounds showed an activity at the order of that observed for **60**, but rather has activities at the level of the parent oxadiazole **37**.

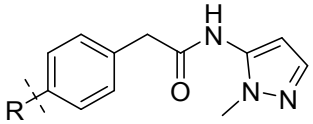
Table 5 Oxadiazole refinement SAR



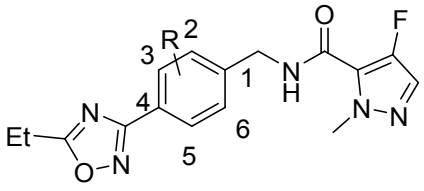
53 to **59**



60 and **61**

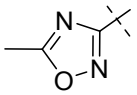
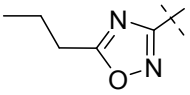
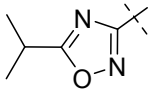
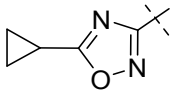
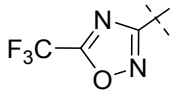
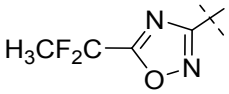
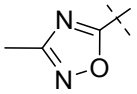
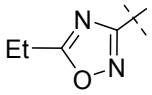
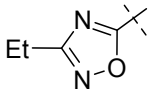
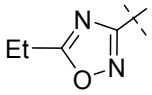


62



63 and **64**

Entry	R	IC_{50} (μM) ± SD in xL3 motility assay	IC_{50} (μM) ± SD in L4 development assay	MCF10A Cytotoxicity*

53		13.9 ± 6.52	0.32 ± 0.04	24%
54		11.3 ± 2.40	0.24 ± 0.05	31%
55		6.80 ± 1.23	0.11 ± 0.02	31.5%
56		5.57 ± 4.12	0.08 ± 0.01	26.4%
57		10.7 ± 7.99	0.2 ± 0.0	28.3%
58		11.1 ± 7.85	0.96 ± 0.03	25%
59		34.5 ± 6.50	0.95 ± 0.85	27%
60		5.67 ± 0.470	0.01 ± 0.01	18%
61		16.5 ± 5.23	0.35 ± 0.04	14%
62		>100		
63	2-F	13.1 ± 8.05	0.1 ± 0.0	N/A[#]
64	3-F	17.4 ± 6.12	0.27 ± 0.11	N/A[#]

*Inhibition at 50 μM.

[#] Not assessed.

Clearly, the potent activity established for the optimized oxadiazole **60** indicates a successful additive SAR which typically suggests specific target engagement. However, we also note that interpretation of SAR in cell-based phenotypic assays may be influenced by factors such as differences in serum protein binding, permeability and/or efflux mechanisms, and therefore cannot be entirely exclude other contributions to the

observed SAR. Despite this, we have observed sharp positive and negative SAR throughout the evaluation of this compound series. These latter observations agree with the notion of specific target engagement. This might be attributable to the nature of the SAR set, which is dominated by heterocyclic interchange rather than gross changes in hydrogen-bond donating properties, lipophilicity and polarity, such that factors outside specific target engagement are relatively similar across the compound series.

As a representative of the newly discovered bioactive 1,2,4-oxadiazole moiety, compound **37** was subjected to testing in motility assays against a panel of different parasitic nematodes at various concentrations (**Table 6**). This panel included *Heligosomoides polygyrus*, a rodent nematode which is related to *H. contortus*;[19] *Ancylostoma ceylanicum*, commonly known as hookworm, also related to *H. contortus*; and *Trichuris muris*, commonly known as whipworm, belonging to the adenophorean nematodes. From the results summarized in **Table 6**, it can be seen that **37** exerted 100% inhibition on *H. polygyrus* adults at the concentration of 10 μM, and both third-stage larvae (L3s) of *A. ceylanicum* and first-stage larvae (L1s) of *T. muris* at 100 μM. When tested at

1 μM on *H. polygyrus* adults, at 100 μM on *H. polygyrus* L3s, and at 10 μM on *A. ceylanicum* L3s, compound **37** displayed >80% inhibition. These promising results suggested that the oxadiazole scaffold could be a medium to broad-spectrum nematocidal or nematostatic scaffold.

Table 6 Biological activity profile of the 1,2,4-oxadiazole **37** against a panel of select parasitic nematodes. Results are given in percent.

Entry	*H. polygyrus* Adult (% inhibition)		*H. polygyrus* L3 (% inhibition)	*A. ceylanicum* L3 (% inhibition)		*T. muris* L1 (% inhibition)
	10 μM	1 μM	100 μM	100 μM	10 μM	100 μM
37	100	87.5	92	100	84.2	100

To assess the drug-likeliness of this 1-methyl-1*H*-pyrazole-5-carboxamide series, we evaluated various physicochemical and metabolic parameters for the original hit **1**, as well as the two oxadiazoles **37** and **38**. The results are summarized in **Table 7** and show that moving from the initial thiazole to oxadiazole did not markedly affect the molecular weight (MW) and cLogD; both values are within Lipinski's rule-of-5[20] for bioavailable compounds. The polar surface area (PSA) increased slightly, but still remains well within limits preferred for optimum cellular permeability and oral bioavailability of drug

candidates.[21] In addition, compound **37** exhibited a 2-fold improved aqueous solubility at pH 2.0 and 4-fold at pH 6.5, while **38** exhibited a 2-fold improvement at pH 6.5. The greatly reduced microsomal degradation, going from the original thiazole to oxadiazole, resulted in longer microsomal half-lifes, ranging from 37 to 73 minutes. All three compounds (**1**, **37** and **38**) displayed an intermediate predicted hepatic clearance.

Table 7 Key physicochemical parameters and in vitro metabolic stability of selected compounds

Entry	MW[a]	PSA[a] (Å^2)	cLogD[a] (pH 7.4)	Sol[b] (µg/mL) pH 2.0	Sol[b] (µg/mL) pH 6.5	$T_{1/2}$ (min)	CL_{int}[c], *in vitro* (µL/min/mg)	Predicted E_H[d]
1	326	59.8	2.6	25-50	12.5-25	22	80	0.63
37	311	85.8	2.0	50-100	50-100	37	47	0.50
38	311	85.8	2.0	25-50	25-50	73	24	0.34

[a]Calculated using ChemAxon JChem software; [b]kinetic solubility determined by nephelometry (Sol_{pH}); [c]*in vitro* intrinsic clearance determined in mouse liver microsomes; [d]predicted hepatic extraction ratio calculated from *in vitro* data.

CONCLUSIONS

In the search for novel anthelmintics, we developed a compound set based on hit compound **1** which was discovered in a high-throughput screening of proline derivatives

using the *H. contortus* motility assay. The novel series of 1-methyl-1*H*-pyrazole-5-carboxamide derivatives reported here resulted from a variety of modifications made to the original screening hit **1** with the goal of improving potency and establishing SAR. Members of this compound series show promise as inhibitors of the development of the parasitic nematode *H. contortus in vitro* and yielded a very tight SAR. The novel 1,2,4-oxadiazole **60** exhibited a remarkable improvement in the inhibition of L4 development, achieving an IC_{50} value of 10 nM. A hallmark of this chemotype is its very low *in vitro* toxicity when tested in a mammalian epithelial cell type. Current efforts are directed toward progressing the best compounds to the next stages of drug discovery.

EXPERIMENTAL SECTION

Nematode assays

H. contortus xL3 motility and L4 development assays

Analogues of **SN00799639** were screened firstly at a concentration of 100 μM against exsheathed third-stage larvae (xL3s) of *H. contortus* in 96-well microculture plates (cat. no. 3635; Corning 3650, Life Sciences, USA) using relevant control compounds (i.e.

moxidectin and monepantel).[15] In brief, compounds were dissolved to a stock concentration of 10 mM in dimethyl sulfoxide (DMSO; cat no. 2225; Ajax Finechem, Australia). Using these stock solutions, compounds were then individually diluted to a final concentration of 100 µM into Luria Bertani medium (LB) supplemented with 100 IU/mL of penicillin, 100 µg/mL of streptomycin and 2.5 µg/mL of amphotericin (LB*). Compounds were dispensed (in triplicate) into wells of a 96-well microculture plate using a multichannel pipette. In addition, the negative controls (LB*, LB* + 0.5% solvent; six wells each), and positive controls (20 µM of monepantel; Zolvix, Novartis Animal Health, Switzerland and 20 µM of moxidectin; Cydectin, Virbac, France; triplicate wells) and xL3s (~300/well) were dispensed into wells of the plate using an automated multichannel pipette (Viaflo Assist/II, Integra Biosciences, Switzerland). After incubation at 38 °C and 10% CO_2 for 72 h, a video recording (5 sec) was taken of each well of the 96-well microculture plate (containing xL3s) using a grayscale camera (Rolera bolt, Q imaging Scientific Coms, Canada) and a motorized X-Y axis stage (BioPoint 2, Ludl Electronics Products, USA). Individual videos were processed to calculate a motility index (MI) using an algorithm described previously.[14] For compounds with anti-xL3 activity, half maximum

inhibitory concentration (IC_{50}) values estimated from 19-point dose-response curves. Compounds were also tested for their ability to affect the development of xL3s to L4s and IC_{50} were determined from a 8-point dose response curve.[14,15] Both assays (xL3 motility and L4 development) were performed at least in duplicates on separate days, three times per assay (three wells for each concentration). Motility index data from each assay were converted to a percentage compared with respect to the negative control (LB* + 0.5% solvent), and IC_{50} values determined using a variable slope four-parameter equation, constraining the top value to 100% and using a least squares (ordinary) fit model (v.6 GraphPad Software).

A. ceylanicum L3 motility assay

A. ceylanicum larvae (L3) were obtained by filtering the faeces from infected hamsters and cultivating the eggs for 9 days in the dark at 24 °C.[22] L3s were washed in penicillin and streptomycin-supplemented tap water and kept under refrigeration until used. For each compound, three worms were placed in each well of a 24-well plate, using 2 wells per compound. Levamisole (50 μM) was used as a positive-control compound.

Worms were incubated at 37 °C and 5% v/v CO_2 for 72 h in the presence of 50 µM of each compound, and culture medium, which was composed of Hanks' Balanced Salt Solution (HBSS) supplemented with 10% fetal calf serum, 25 µg/ml of amphotericin B, 100 U/ml of penicillin and 100 µg/ml of streptomycin.. Thereafter, the condition of the worms was microscopically evaluated.

T. muris L1 motility assay

For *T. muris*, 40 L1s were placed in each well of a 96-well plate and incubated for 24 h at 37 °C and 5% v/v CO_2 in the presence of 100 µl RPMI-1640 medium with amphotericin B (12.5 µg/ml), penicillin (500 U/ml), streptomycin (500 µg/ml) and 100 µM of the compound to be tested. Levamisole (100 µM) was used as a positive-control compound. Each compound was tested in duplicate. At 24 h, the total number of L1s per well was counted. The larvae were then stimulated with 100 µl hot water and motile L1s were counted as described by Keiser *et al.*[22]

H. polygyrus L3 motility assay

To screen against *H. polygyrus* L3s, female NMRI mice were infected with 80 *H. polygyrus* L3 and following infection patency, *H. polygyrus* eggs were obtained from infected feces as described.[22] Collected eggs were placed on agar and incubated for 9 days at 24 °C (in the dark), to allow the L3 to hatch. To test the compounds, 40 L3s were placed in each well of a 96-well plate. Worms were incubated in the presence of 100 µl RPMI 1640 medium, supplemented with 0.63 µg/ml amphotericin B, 500 U/ml penicillin, 500 µg/ml streptomycin, and compound (10 or 100 µM) to be tested. Each compound was tested in duplicate. 1 % DMSO and culture medium and 100 µM levamisole served as a negative and positive controls respectively. Following incubation for 72 h, the total number of L3 larvae per well was counted, the larvae were stimulated with 100 µl hot water (~80 °C), and the moving L3s were counted.

H. polygyrus adult motility assay

To test compounds on *H. polygyrus* adults, female mice were infected as described above and dissected two weeks post-infection to collect adult worms. Three adult worms were placed in each well of a 24-well plate and incubated with culture medium and 50 µM

of the test compound in duplicate. Adult worms incubated with medium only, and 50 μM levamisole and ivermectin served as negative and positive control, respectively. Worms were kept in an incubator at 37 °C and 5 % CO_2 for 72 h and, subsequently, microscopically evaluated using a viability scale from 3 to 0 as described previously.[22]

Cytotoxicity assay

Compounds were tested for cytotoxicity on non-cancerous ('normal') mammary epithelial cell line (MCF10A) as described by Jiao *et al.*[16] In brief, MCF10A cells (~700 cells/well) were plated into 384-well, black walled plates (Corning, New York, USA) using a liquid handling dispenser (BioTek, Vermont, USA). Cells were cultured in DMEM-F12 containing 100 ng/ml cholera toxin (Sigma-Aldrich, St Louis, USA), 20 ng/ml human epidermal growth factor (EGF, Life Technologies, Carsbad, USA), 10 μg/ml insulin (human; Novo Nordisk Pharmaceuticals Pty Ltd., Bagsværd, Denmark), 5% horse serum (Life Technologies, Australia) and 0.5 μg/ml hydrocortisone (Sigma-Aldrich, St Louis, USA). Following a 24 h incubation (37 °C and 5% CO_2), the growth medium was aspirated

and compounds were added starting at 50 μM as well as positive- (monepantel) and negative- (medium ± 0.5% DMSO) controls. Compounds were titrated to generate a 5-point dose-response curve (in quadruplicate) and incubated for a further 48 h. To measure cell proliferation, cells were fixed and stained with 4′,6-diamidino-2-phenylindole (DAPI; 1:1000) and individual wells imaged at 10-times magnification, covering 16 fields (~90% of well) using a high content imager (Cellomics Cell Insight Personal Cell Imager, ThermoFisher Scientific, Bartlesville, USA) at a fixed exposure time of 0.12 s. Viable cells were counted using the Target Activation BioApplication within the Cellomics Scan software and normalized to the cell density in wells without compound. Experiments were repeated twice on two different days.

Physicochemical experimental

Calculated physicochemical parameters using ChemAxon JChem software

A range of physicochemical properties evaluating drug-likeliness and likely oral absorption characteristics were calculated using the ChemAxon chemistry cartridge via

JChem for Excel software (version 16.4.11). A brief description of each parameter is provided below:

MW: Molecular Weight

$PSA_{pH\ 7.4}$: Polar surface area, also inversely correlates with membrane permeability

$cLogD_{pH\ 7.4}$: Distribution coefficient, reflecting the partitioning properties of the ionised molecule at a specific pH.

Kinetic Solubility Estimation using Nephelometry (Sol_{pH})

Compound in DMSO was spiked into either pH 6.5 phosphate buffer or 0.01M HCl (approximately pH 2.0) with the final DMSO concentration being 1%. After 30 minutes had elapsed, samples were then analysed via Nephelometry to determine a solubility range. See Bevan *et al.*[23]

In vitro Metabolic Stability

Incubation:

The metabolic stability assay was performed by incubating each test compound in mouse liver microsomes (XenoTech, lot # 1510256) at 37 °C and a protein concentration of 0.4 mg/mL. The metabolic reaction was initiated by the addition of an NADPH-regenerating system and quenched at various time points over a 60 minute incubation period by the addition of ACN containing diazepam as internal standard. Control samples (containing no NADPH) were included (and quenched at 2, 30 and 60 minutes) to monitor for potential degradation in the absence of cofactor. Microsomal incubations were performed at a substrate concentration of 0.5 μM.

Data analysis:

Species scaling factors from Ring *et al.*[24] were used to convert the *in vitro* CL_{int} (μL/min/mg) to an *in vivo* CL_{int} (mL/min/kg). Hepatic blood clearance and the corresponding hepatic extraction ratio (E_H) were calculated using the well stirred model of hepatic extraction in each species, according to the "*in vitro* $T_{1/2}$" approach described in Obach *et al.*[25] The E_H was then used to classify compounds as low (< 0.3), intermediate (0.3-0.7), high (0.7-0.95) or very high (> 0.95) extraction compounds.

Chemistry experimental

Experimental conditions (Exp1):

All solvents and reagents were used directly from commercial suppliers unless otherwise stated. TLC analyses were performed on pre-coated silica gel aluminium-backed plates (Merck 60 F254) and visualised under UV light (254 nm). Purification by column chromatography was based on the methods described by Still *et al.*[26] using SiliaFlash® P60 silica gel (40-63 μm). All of the final compounds had purities greater than 95% based on analytical HPLC, ^{1}H NMR and LC-MS. Compound purity was analysed on an Agilent 1260 Infinity Analytical HPLC system with the flow rate of 1 mL/min the following technical information: 1260 Degasser, 1260 Bin Pump, 1260 HiP ALS, 1260 TCC, 1260 DAD. Column used: Zorbax Eclipse Plus C18 Rapid Resolution 4.6 x 100mm 3.5-Micron. Solvent A: 99.9% water, 0.1% TFA, solvent B: 99.9% ACN, 0.1% TFA. Compounds were analysed through one of the following methods. Gradient: a gradient of 5-100% solvent B in solvent A over 10 mins; hydrophobic: a gradient of 5-80% solvent B in solvent A over 0.6 min, then 80-100% of solvent B in solvent A over 9.4 mins;

hydrophilic: a gradient of 5-25% of solvent B 8.5 mins, then 25-100% solvent B in solvent A over 1.5 mins. LC/MSD Chemstation Rev.B.04.03 coupled with Masshunter Easy Access Software managed the running and processing of samples. LC-MS $[M+H]^+$ of compounds was analysed on an AGILENT UHPLC/MS 1260/6120 system with the following technical information. Pump: 1260 Infinity G1312B Binary pump; autosampler: 1260 Infinity G1367E 1260 HiP ALS; detector: 1290 Infinity G4212A 1290 DAD. LC conditions: reverse phase HPLC analysis; column: Poroshell 120 EC-C18 3.0 X 50mm 2.7-Micron; column temperature: 35°C; injection Volume: 1 µL; flow rate: 1 mL/min. Solvent A: 99.9% water, 0.1% formic acid, solvent B: 99.9% ACN, 0.1% formic acid, gradient: 5-100% of solvent B in solvent A over 3.8 mins. Gradient takes 4 minutes to get to 100% solvent B in solvent A; maintain for 3 minutes and a further 3 minutes to get back to the original 5% solvent B in solvent A. MS conditions: ion source: Quadrupole, ion mode: API-ES, drying gas temp: 350°C; capillary voltage (V): 3000 (positive); capillary voltage (V): 3000 (negative); scan range: 100-1000; step size: 0.1 s; acquisition time: 5min. LC/MSD Chemstation Rev.B.04.03 coupled with Masshunter Easy Access Software managed the running and processing of samples. All ^{1}H NMR, ^{13}C NMR and ^{19}F

NMR of small molecules were performed on the Avance III Nanobay 400 MHz Bruker spectrometer coupled to the BACS 60 automatic sample changer and spectra were processed in MestReNova[27]. Chemical shifts (δ, ppm) are reported relative to the solvent peak ($CDCl_3$: 7.26 [^1H] or 77.16 [^{13}C]; DMSO-d6: 2.50 [^1H] or 39.52 [^{13}C]). Proton resonances are annotated as: chemical shift (δ) in ppm, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad), coupling constant (*J*, Hz), and number of protons. Microwave reactions were performed on a CEM discovery fitted with an intellivent explorer unit. The temperature range of the unit is -80 °C to 300 °C, a pressure range of 0-27 bar, power range of 0-300 W and no pre-stirring was required.

Experimental conditions (Exp2):

All of the final compounds had purities greater than 95% based on analytical HPLC, ^1H NMR and LC-MS. Compound purity was analysed on an Agilent 1260 Infinity Analytical HPLC system with the flow rate of 1 mL/min the following technical information: 1260 Degasser, 1260 Bin Pump, 1260 HiP ALS, 1260 TCC, 1260 DAD. Column used: Zorbax Eclipse Plus C18 Rapid Resolution 4.6 x 100mm 3.5-Micron. Solvent A: 99.9%

water, 0.1% TFA, solvent B: 99.9% ACN, 0.1% TFA. Compounds were analysed through one of the following methods. Gradient: a gradient of 5-100% solvent B in solvent A over 10 mins; hydrophobic: a gradient of 5-80% solvent B in solvent A over 0.6 min, then 80-100% of solvent B in solvent A over 9.4 mins; hydrophilic: a gradient of 5-25% of solvent B 8.5 mins, then 25-100% solvent B in solvent A over 1.5 mins. LC/MSD Chemstation Rev.B.04.03 coupled with Masshunter Easy Access Software managed the running and processing of samples. ^{1}H spectra were recorded at 400.20&400.10 on a Bruker Avance II &III spectrometer, using solvents from Merck Laboratories. Chemical shifts (δ, ppm) are reported relative to the solvent peak (CDCl3: 7.25 [1H]; DMSO-d6: 2.50 [1H]). Proton resonances are annotated as: chemical shift (δ), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad), coupling constant (J, Hz), and number of protons. LC-MS analysis was carried out using the following method: 5 minutes LC-MS was performed on the columns (i) Zorbax Extend C18; Column length: 50 mm; Internal diameter of column: 4.6 mm; Particle Size: 5 micron (ii) X-bridge C18; Column length: 50 mm; Internal diameter of column: 4.6 mm; Particle Size: 5 micron, Temperature: 25°C. API 2000 Mass Spectrometer from Applied Biosystems Triple quadruple (Q1 scan) mass spectrometer.

Ionisation method: Electrospray. Polarity: positive ions.Capillary (kV) 5.5, DP(V)50.00, Entrance Potential (V)10, Focusing Potential (V) 400, Source Temperature (°C) 200, Ion Source Gas1 (Psi) 40, Ion Source Gas 2 (Psi) 50, Curtain Gas (Psi)40. Mass range: 100 to 800 amu, 4500V(Positive mode) 5500V(Negative mode) UV Wavelength range (nm): 220 to 260. Method Shimadzu Prominence with the following HPLC gradient conditions: Solvent A: 10Mm NH4OAc in Water and Solvent B: Acetonitrile. Flow rate: 1.2 ml/min. Mobile phase: from 90% [10 mM NH4OAc in water] and 10% [CH3CN] to 70% [10 mM NH4OAc in water] and 30% [CH3CN] in 1.5 min, further to 10% [10 mM NH4OAc in water] and 90% [CH3CN] in 3.0 min, held this mobile phase composition up to 4.0 min and finally back to initial condition in 5.0 min.

General procedure A1: Suzuki coupling reactions

To a microwave tube equipped with a magnetic stirring bar, halide (1.0 eq), boronic acid or boronic ester (1.0 eq), and K_2CO_3 (2 eq) were dissolved in a 1:4 mixture of H_2O:1,4-dioxane. The mixture was de-gassed for at least 0.5 h before $Pd(dppf)Cl_2$ (0.05 eq) was added. The reaction tube was sealed with a cap and heated in a microwave

reactor at 110 °C for 2 h. Upon completion (confirmed TLC and/or LC-MS), EtOAc was added to the reaction tube and the mixture was filtered through a pad of celite and washed with excess EtOAc. The filtrate was then washed with water then brine. The organic layer was then dried ($MgSO_4$) and solvent was removed *in vacuo* to afford crude product which was purified by column chromatography to yield desired product.

General procedure A2: Suzuki coupling reactions

A stirred solution of halide (3.12 mmol) and boronic acid (6.24 mmol) in 1,4-dioxane (8 mL) and water (1 mL), was degassed with argon for 5 min. After that Cs_2CO_3 (7.80 mmol) and $Pd(PPh_3)_4$ (0.19 mmol) were added. The reaction mixture was stirred at 100 °C for 16 h. The reaction mixture was cooled and diluted with EtOAc. Combined organic layer was washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated. The crude was purified by column chromatography to yield desired product.

General procedure A3: Suzuki coupling reactions

To a stirred solution of halide (1.0 eq) in ACN (15 mL), was added boronic acid (1.0 eq) followed by aqueous Na_2CO_3 (2.5 eq) solution. The mixture was degassed for 15

min with N_2 and then $Pd(PPh_3)_4$ (0.05 eq) was added. Reaction mixture was heated at 100 °C for 20 h, then cooled to room temperature and aqueous layer was extracted with EtOAc. Combined organic layer was washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated. Crude mass obtained was purified by column chromatography to yield desired product.

General procedure A4: Suzuki coupling reactions

To a mixture of halide (2.29 mmol) and boronic acid (3.43 mmol) in EtOH (1 mL)/ toluene (10 mL)/ H_2O (1 mL) was added Na_2CO_3 (4.57 mmol). Reaction mixture was degassed by sparging with argon 15 min before $Pd(dppf)Cl_2.CH_2Cl_2$ (0.22 mmol) was added. Reaction mixture was heated at 100 °C for 16 h under argon. Reaction mixture was cooled to room temperature and concentrated *in vacuo*. Residue was diluted with water and aqueous layer was extracted with EtOAc. Combined organic layer was washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Crude was purified by column chromatography to yield desired product.

General procedure A5: Suzuki coupling reactions

In a sealed tube, a solution of aryl halide (10.93 mmol) and bis(pinacolato)diboron (12.02 mmol) in DMSO (15 mL), was degassed with argon for 10 min. $Pd(dppf)Cl_2$.DCM (1.09 mmol) and KOAc (37.16 mmol) were then added and again degassed for 10 min. The reaction mixture was stirred at 100 °C for 12 h. Upon completion, the reaction mixture was cooled, then extracted with EtOAc. Combined organic layer was washed with water, brine, dried over Na_2SO_4 and concentrated. Crude product was purified by column chromatography to give the desired boronic ester. The resulting boronic ester (0.62 mmol) and halothiazole (0.56 mmol) in 1,4-dioxane (5 mL) and water (0.5 mL), was degassed with argon for 10 min. KOAc (0.56 mmol) and $PdCl_2$(dppf).DCM (0.057 mmol) were then added to the reaction mixture. The reaction mixture was heated at 100 °C for 16 h, then extracted with EtOAC, washed with water, brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Crude product was purified by column chromatography to yield desired product.

General procedure A6: Suzuki coupling reactions

To a microwave tube equipped with a magnetic stirring bar, halide (1.0 eq), bis(pinacolato)diboron (1.0 eq), and K_2CO_3 (2 eq) were dissolved in a 1:4 mixture of H_2O:1,4-dioxane. The mixture was de-gassed for at least 0.5 h before $Pd(dppf)Cl_2$ (0.05 eq) was added. The reaction tube was sealed with a cap and heated in a microwave reactor at 110 °C for 2 h. Upon completion (confirmed TLC and/or LC-MS), EtOAc was added to the reaction tube and the mixture was filtered through a pad of celite and washed with excess EtOAc. The filtrate was then washed with water then brine. The organic layer was then dried ($MgSO_4$) and solvent was removed *in vacuo* to afford crude product which was put through a silica plug to give the desired boronic ester. The resulting boronic ester was then subjected to a Suzuki coupling reaction according to **General procedure A1** to yield the desired product.

General procedure B1: Nitrile reduction

To a solution of benzonitrile (1.0 eq) in anhydrous THF (10 mL), $LiAlH_4$ (3.0 eq) was slowly added. The reaction was left stirred at room temperature for 2 h. Upon completion (confirmed by TLC and/or LC-MS), reaction mixture was cooled on ice before

a solution of 1M NaOH was added. The slurry mixture was then filtered through a pad of celite. The filtrate was extracted with EtOAc (3 x 30 mL) and combined organic was dried ($MgSO_4$) and concentrated *in vacuo*. To the residue after removal of solvent, 15 mL of 4M HCl in 1,4-dioxane was added. The reaction mixture was left stirred at room temperature overnight. Precipitate of the resulting hydrochloride salt was then filtered, washed with diethyl ether, then dried in a vacuum oven to yield desired product as a hydrochloride salt.

General procedure B2: Nitrile reduction

To a stirred solution of benzonitrile (1.0 eq) in THF (5.0 mL) was added $LiAlH_4$ solution (2M in THF, 2.5 eq) drop wise at 0 °C. The reaction mixture was stirred at room temperature for 3 h. After that the reaction mixture was quenched with saturated Na_2SO_4 solution (2.0 mL) at 0 °C and diluted with EtOAc (20 mL). Reaction mixture was filtered through a celite bed and washed thoroughly with EtOAc. Combined filtrate was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to yield desired product as a free base.

General procedure B3: Nitrile reduction

To a stirred solution of benzonitrile (1.0 eq) in mEtOH (40 mL) at 0 °C, was added boc anhydride (2.0 eq) and $NiCl_2 \cdot 6H_2O$ (0.1 eq). $NaBH_4$ (7.0 eq) was then added in small portions over a period of 30 min at 0 °C. The resulting reaction mixture containing black precipitate was allowed to warm to room temperature and left to stir for 12 h. Reaction mixture was diluted with ice water and aqueous layer was extracted with EtOAc. Combined organic layer was washed with aqueous $NaHCO_3$ solution, water and brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. To the residue after removal of solvent, 5 mL of 4M HCl in 1,4-dioxane was added. The reaction mixture was left stirred at room temperature overnight. Precipitate of the resulting hydrochloride salt was then filtered, washed with diethyl ether, then dried in a vacuum oven to yield desired product as a hydrochloride salt.

General procedure C: Cyanation

A solution of aryl halide (1.0 eq) in DMF (15 mL) was degassed with argon for 10 mimutes. After that $Zn(CN)_2$ (1.5 eq), Xanthphos (0.2 eq) and $Pd_2(dba)_3$ (0.1 eq) were

added. Then the reaction mixture was stirred at 110 °C for 16 h. Reaction mixture was cooled to room temperature and diluted with water. Aqueous layer was extracted with EtOAc. Combined organic layer was washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated. Crude compound was purified by column chromatography to yield desired product.

General procedure D1: Thiazole ring cyclization

To a stirred solution of haloketone (1.0 eq) in EtOH (30 mL), thiourea or thioamide (1.0-1.5 eq) was added. The reaction mixture was stirred at reflux until completion (confirmed by TLC). Upon completion, reaction mixture was cooled to room temperature and diluted with water. Aqueous layer was extracted with EtOAc, washed with water, brine, dried over anhydrousNa_2SO_4 and concentrated to afford desired product which was used in next step without purification.

General procedure D2: Thiazole ring cyclization

A mixture of thiobenzamide (4.63 mmol) and haloketone (4.63 mmol) in EtOH (10 mL) was stirred at 60 °C for 3 h. Reaction mixture was concentrated and the residue

obtained was washed with acetone and n-pentane to afford an orange solid mass which was mixed with p-toluenesulfonic acid (0.46 mmol) in toluene (30 mL) and heated at reflux for 20 h in a Dean-stark apparatus. After removal of the solvent, the residue was diluted with diethyl ether. The resulting solution was washed with water, brine, and dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude was washed with n-pentane to afford desired product.

General procedure D3: Thiazole ring cyclization

A solution of haloketone (2.78 mmol) and thioamide (2.31 mmol) in ACN (7 mL) was heated at 80 °C overnight in a sealed tube. Upon completion, the reaction mixture was concentrated *in vacuo* and filtered through a pad of silica gel to give desired product.

General procedure E1: Sandmeyer reactions

To a stirred solution of amine (7.8 mmol) in ACN (10 mL), was added ^{t}BuONO (7.8 mmol) drop wise at 0 °C. Then the reaction mixture was allowed to warm to room temperature and $CuBr_2$ (7.8 mmol) was added. The reaction mixture was stirred at 100 °C for 4 h. After completion of reaction, reaction mixture was cooled to room temperature

and diluted with water. Aqueous layer was extracted with EtOAc, combined organic layer was washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated. Crude was purified by column chromatography to yield desired product.

General procedure E2: Sandmeyer reactions

A suspension of CuBr (6.75 mmol) in ACN (10 mL), was added ^{t}BuONO (6.75 mmol) at 0 °C. A solution of amine (6.75 mmol) in ACN (10 mL) was added dropwise under N_2 at 0 °C and the resulting mixture was stirred at 50 °C for 30 min. Upon completion, the reaction mixture was cooled to room temperature and diluted with water. Aqueous layer was extracted with EtOH (3 x 30 mL), combined organic layer was washed with saturated NH_4Cl solution, water, brine, then dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give crude product, which was purified by column chromatography to afford desired product.

General procedure F1: Ester hydrolysis

To a stirred solution of ester (1.0 eq) in a 3:1 mixture of THF:H_2O, LiOH.H_2O (2.0 eq) was added. The reaction mixture was stirred at room temperature for 3 h. Upon

completion, THF was removed from reaction mixture. Aqueous layer was neutralized by 1N HCl and extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford the desired carboxylic acid without further purification.

General procedure F2: Ester hydrolysis

To a solution of ester (1.04 mmol) in EtOH (10 ml) was added NaOH (23.75 mmol). The mixture was stirred at room temperature overnight. The solvent was removed in *vacuo* to give a white solid, which was redissolved in water and washed with EtOAc (3 x 10 mL). The aqueous was acidified with 1 M HCl to pH~3 and extracted with EtOAc (3 x 10 mL). Combined organic layers was dried ($MgSO_4$) and solvent was removed in *vacuo* to give the desired carboxylic acid without further purification.

General procedure F3: Ester hydrolysis

To a solution of ester (2.93 mmol) in THF (10 mL) was added LiOH (5.86 mmol). The reaction was left stirred at room temperature overnight. THF was removed *in vacuo* and water (20 mL) was added, followed by 1M HCl to pH~1. The aqueous was extracted

with EtOAc (2 x 10 mL). Combined organic was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the desired carboxylic acid without further purification.

General procedure G1: Amide coupling

Amine (either as free base or HCl salt, 1.0 eq), HOAt (2.0 eq), Et_3N (2.0 eq), EDCI.HCl (2.0 eq) and carboxylic acid (2.0 eq) were dissolved in 3 mL of DMF. Reaction mixture was heated at 80 °C until completion (confirmed by TLC and/or LC-MS). Upon completion, EtOAc was added to the reaction mixture. The organic was washed with water, dried ($MgSO_4$) and solvent was removed *in vacuo* to give the crude product, which was purified by column chromatography to yield desired product.

General procedure G2: Amide coupling

To a stirred solution of carboxylic acid (0.54 mmol) in DMF (5.0 mL) was added HATU (0.97 mmol) and DIPEA (1.28 mmol). The solution was stirred for 5 min before amine (0.71 mmol) was added. The reaction mixture was stirred at room temperature for 16 h. After completion the reaction was diluted with EtOAc, washed with water, brine,

then dried over anhydrous Na_2SO_4. Solvent was then removed *in vacuo* to give crude product, which was purified by column chromatography to yield desired product.

General procedure G3: Amide coupling

To a stirred solution of carboxylic acid (0.99 mmol) in DCM (5 mL) was added Et_3N (2.98 mmol), EDCI.HCl (1.19 mmol) and HOBt (1.19 mmol) at room temperature. After 5 min, amine (1.19 mmol) was then added. The reaction mixture was stirred at room temperature for overnight, then extracted with DCM, washed with saturated $NaHCO_3$ solution, brine, dried over anhydrous Na_2SO_4 and concentrated to afford crude product which was purified by column chromatography to yield desired product.

General procedure G4: Amide coupling

To a stirred solution of carboxylic acid (1.0 eq) and amine (1.0 eq) in THF (5 mL), T_3P® (2.0 eq, 50% in EtOAc) and DIPEA (3.0 eq) were added. The reaction mixture was stirred at room temperature for 6 h. upon completion, the reaction mixture was diluted with EtOAc, washed with saturated $NaHCO_3$ solution, brine, dried over Na_2SO_4 and

concentrated *in vacuo* to give crude product, which was purified by prep-HPLC to afford desired product.

General procedure G5: Amide coupling

To a solution of carboxylic acid (1 eq.) in ACN (0.8 M) was added EDCI.HCl (1.2 eq.) and HOAt (1.2 eq.) at room temperature. The mixture was heated to 50 ^{o}C and after 10 min, amine (1.2 eq.) was added. The mixture was allowed to stir at this temperature overnight. The reaction was then cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between water and EtOAc. The aqueous layer was further washed with EtOAc (2 x 10 mL). Combined organic layers were dried over $MgSO_4$, then loaded directly onto silica. The crude product was purified by silica gel chromatography (Isolera Biotage, 0-50% EtOAc/petroleum benzine). Product-containing fractions were combined and concentrated *in vacuo* to give the desired product.

General procedure H: Amidoxime formation

To a stirred solution of nitrile (1.0 eq) in EtOH (20 mL) were added K_2CO_3 (2.0 eq) and $NH_2OH.HCl$ (1.5 eq). The reaction mixture was stirred at reflux for 16h. Upon

completion, the reaction was diluted with EtOAc and organic layer was washed with water, brine, dried over anhydrous Na_2SO_4 then concentrated *in vacuo* to afford the desired amidoxime.

General procedure I1: Boc protection

Amine (18.54 mmol) was dissolved in a mixture of 10 % aqueous NaOH (25 mL) and EtOH (50 mL). The solution was cooled to 0 °C and boc-anhydride (20.4 mmol) was added slowly. The reaction mixture was stirred at room temperature for 18 h. Upon completion, EtOH was removed *in vacuo* and water was added. The aqueous layer was acidified slowly with a saturated solution of citric acid (20 mL). The precipitate formed was filtered and dried in a vacuum oven to yield desired boc-protected amine.

General procedure I2: Boc protection

To a stirred solution amine (1.0 eq) in DCM (8 mL) was added di-*tert*-butyl-dicarbonate (1.0 eq) slowly, followed by Et_3N (3.0 eq). Reaction mixture was stirred at room temperature for 16 h. Upon completion, reaction mixture was concentrated *in vacuo* and the residue was diluted with saturated aqueous $NaHCO_3$ solution. Aqueous layer was

extracted with DCM (3 x 10 mL). Combined organic layers was washed with water, brine and dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Crude product was purified by column chromatography (20% EtOAc in hexane) to yield desired boc-protected amine.

General procedure J1: 1,2,4-oxadiazole ring cyclization

To a stirred solution of carboxylic acid (1.0 eq) in DMF (8 mL) was added HATU (2.5 eq) and DIPEA (3.0 eq). The reaction mixture was stirred for 5 minutes before amidoxime (1.0 eq) was added. The reaction mixture was stirred at room temperature for 16 h, then refluxed at 110 °C for 16 h. Upon completion, EtOAc was added and organic layer was washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give crude product, which was purified by column chromatography to yield desired product.

General procedure J2: 1,2,4-oxadiazole ring cyclization

Amidoxime (1.0 eq), carboxylic acid (1.0 eq), HOBt (1.2 eq) and EDCI.HCl (1.3 eq) were dissolved in 3 mL of DMF in a microwave tube. The reaction mixture was left stirred at room temperature for 0.5 h, then heated in a microwave reactor at 180 °C for 20 min.

EtOAc was then added and organic layer was washed with water, brine, dried ($MgSO_4$) and concentrated *in vacuo*. Crude product was purified by column chromatography to yield desired product.

General procedure K: Boc deprotection

To a stirred solution of Boc-protected amine (1.65 mmol) in 1,4-dioxane (5 mL), 4M HCl in 1,4-dioxane (5 mL) was added and the reaction mixture was stirred at room temperature for 1 h. Upon completion, the resulting HCl salt precipitate was filtered, washed with diethyl ether, dried in vacuum oven and directly taken for the next step.

General procedure L: Radical reactions

A stirred solution of methylbenzonitrile (1.0 eq) in 1,2-dichloroethane (240 mL) was degassed under N_2 for 20 minutes before NBS (1.0 eq) and AIBN (0.1 eq) were added. The reaction mixture was stirred at 80 °C for 6 h. Upon completion, the reaction mixture was cooled to room temperature and extracted with DCM. Combined organic layers was washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*.

Crude product was purified by column chromatography (5% EtOAc in hexane) to yield desired product.

General procedure M: Amine synthesis from phthalimide precursor

To a stirred solution of alkylhalide (1.0 eq) in DMF (70 mL) were added phthalimide (1.7 eq) and CS_2CO_3 (3.0 eq). Reaction mixture was stirred at room temperature for 4 h. upon completion, the reaction mixture was extracted with EtOAc. Organic layer was washed with water, brine and dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Crude product was purified by column chromatography (30% EtOAc in hexane) to afford desired product, which was then on-reacted with hydrazine hydrate (3.0 eq) in *n*-butanol (20 mL) at 80°C for 1 h. Upon completion, reaction mixture was cooled to room temperature. A voluminous precipitate was formed which was filtered off. The filtrate was concentrated *in vacuo* to give crude product, which was purified by column chromatography (neutral Al_2O_3, 10% MeOH in DCM) to yield desired product.

1-Ethyl-*N*-(4-(4-methylthiazol-2-yl)benzyl)-1*H*-pyrazole-5-carboxamide (8) (Exp1)

Title compound was prepared according to **General Procedure G1**, starting from **66** and 1-ethyl-1H-pyrazole-5-carboxylic acid to give a white solid (30%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.85 (d, *J* = 8.5 Hz, 2H), 7.44 (d, *J* = 2.1 Hz, 1H), 7.35 (d, *J* = 8.5 Hz, 2H), 6.87 (s, br, 1H), 6.51 (d, *J* = 2.1 Hz, 2H), 4.65 – 4.57 (m, 4H), 2.49 (d, *J* = 1.0 Hz, 3H), 1.45 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.1, 159.9, 154.0, 139.6, 137.8, 134.4, 133.4, 128.3, 127.0, 113.7, 106.4, 46.9, 43.3, 17.3, 16.0 ppm; LC-MS: *m/z* = 326.9 $[M + H]^+$.

1-Isopropyl-*N*-(4-(4-methylthiazol-2-yl)benzyl)-1*H*-pyrazole-5-carboxamide (9) (Exp1)

Title compound was prepared according to **General Procedure G1**, starting from **66** and 1-isopropyl-1H-pyrazole-5-carboxylic acid to give a white solid (42%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.84 (d, *J* = 8.3 Hz, 2H), 7.45 (d, *J* = 1.9 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 0.9 Hz, 1H), 6.71 (s, br, 1H), 6.50 (d, *J* = 2.0 Hz, 1H), 5.57 – 5.47 (m, 1H), 4.55 (d, *J* = 5.9 Hz, 2H), 2.46 (d, *J* = 0.9 Hz, 3H), 1.47 (d, *J* = 6.6 Hz, 6H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.5, 160.6, 154.2, 140.0, 138.0, 134.7, 133.4, 128.5, 127.2, 114.0, 106.7, 52.2, 43.5, 23.1, 17.5 ppm; LC-MS: *m/z* = 341.1 $[M + H]^+$.

N-(4-(4-Ethylthiazol-2-yl)benzyl)-1-methyl-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxamide (10) (Exp2)

Title compound was prepared according to **General Procedure G2**, starting from **70** and 1-methyl-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxylic acid to give a white solid (39%). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.29 (br, 1H), 7.89 (d, J = 7.8 Hz, 2H), 7.44 (d, J = 7.6 Hz, 2H), 7.38 (s, 1H), 7.31 (s, 1H), 4.50 (d, J = 5.1 Hz, 2H), 4.15 (s, 3H), 2.80-2.77 (m, 2H), 1.26 (t, J = 7.3 Hz, 3H), ppm; LC-MS: m/z = 395.0 $[M + H]^+$.

3-Cyano-*N*-(4-(4-ethylthiazol-2-yl)benzyl)-1-methyl-1*H*-pyrazole-5-carboxamide (11) (Exp2)

Title compound was prepared according to **General Procedure G3**, starting from **70** and **76** to give an off-white solid (29%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.33 (br s, 1H), 7.89 (d, J = 8.8 Hz, 2H), 7.52 (s, 1H), 7.43 (d, J = 7.9 Hz, 2H), 7.32 (s, 1H), 4.50 (d , J = 5.6 Hz, 2H), 4.16 (s, 3H), 2.77 (q, J = 7.4 Hz, 2H), 1.26 (t, J = 7.4, 3H) ppm; LC-MS: m/z = 352.1$[M + H]^+$.

3-Ethyl-1-methyl-*N*-(4-(4-methylthiazol-2-yl)benzyl)-1*H*-pyrazole-5-carboxamide (12) (Exp1)

Title compound was prepared according to **General Procedure G1**, starting from **66** and 3-ethyl-1-methyl-1*H*-pyrazole-5-carboxylic acid to give a white solid (50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.81 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 8.3 Hz, 2H), 6.87 (s, br, 1H), 6.84 (d, *J* = 0.9 Hz, 1H), 6.35 (s, 1H), 4.51 (d, *J* = 5.9 Hz, 2H), 4.09 (s, 3H), 2.56 (q, *J* = 7.6 Hz, 2H), 2.45 (d, *J* = 0.9 Hz, 3H), 1.16 (t, *J* = 7.6 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.1, 160.1, 153.9, 152.9, 139.7, 135.4, 133.1, 128.2, 126.8, 113.6, 104.4, 43.0, 38.9, 21.2, 17.2, 13.8 ppm; LC-MS: *m/z* = 340.9 $[M + H]^+$.

***N*-(4-(4-Ethylthiazol-2-yl)benzyl)-1-methyl-4-(trifluoromethyl)-1*H*-pyrazole-5-carboxamide (13) (Exp2)**

Title compound was prepared according to **General Procedure G2**, starting from **70** and 1-methyl-4-(trifluoromethyl)-1*H*-pyrazole-5-carboxylic acid to give an off-white solid (30%). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* = 7.93 (d, *J* = 8.1 Hz, 2H), 7.67 (s, 1H), 7.38

(d, *J* = 8.0 Hz, 2H), 6.88 (s, 1H), 6.49 (br s, 1H), 4.65 (d, *J* = 5.5 Hz, 2H), 4.10 (s, 3H), 2.86 (q, *J* = 7.4 Hz, 2H), 1.34 (t, *J* =7.5 Hz, 3H) ppm; LC-MS: *m/z* = 395.2 $[M + H]^+$.

4-Cyano-*N*-(4-(4-ethylthiazol-2-yl)benzyl)-1-methyl-1*H*-pyrazole-5-carboxamide (14) (Exp2)

To a stirred solution of 4-iodo-1-methyl-1*H*-pyrazole-5-carboxylic acid methyl ester (700 mg, 2.63 mmol) in DMF (10 mL), CuCN (472 mg, 5.26 mmol) was then added. The reaction was stirred at 140 °C for 3 h. Upon completion, the reaction mixture was cooled to room temperature and extracted with EtOAc, washed with saturated NH_4Cl, water, brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Crude product was purified by column chromatography (30% EtOAc in hexane) to afford methy-4-cyano-1-methyl-1*H*-pyrazole-5-carboxylate as a white solid, which was directly subjected to **General Procedure F1** to give the corresponding carboxylic acid that was subsequently coupled to **70** according to **General Procedure G4** to give title compound as an off-white solid (56%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.58 (br, 1H), 8.14 (s, 1H), 7.90 (d, *J* = 7.8

Hz, 2H), 7.49 (d, *J* = 7.8 Hz, 2 H), 7.32 (s, 1H), 4.56 (d, *J* = 5.2 Hz, H), 3.96 (s, 3H), 2.79-2.75 (m, 2H), 1.27 (t, *J* = 7.3 Hz, 3H) ppm; LC-MS: *m/z* = 352.2 $[M + H]^+$.

4-Fluoro-1-methyl-*N*-(4-(4-methylthiazol-2-yl)benzyl)-1*H*-pyrazole-5-carboxamide (15) (Exp1)

Title compound was prepared according to **General Procedure G5**, starting from **66** and **78** to give a white solid (50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.95 (d, *J* = 8.3 Hz, 2H), 7.42 (d, *J* = 8.2 Hz, 2H), 7.37 (d, *J* = 4.5 Hz, 1H), 6.90 (d, *J* = 0.8 Hz, 1H), 6.59 (s, 1H), 4.68 (d, *J* = 5.8 Hz, 2H), 4.20 (d, *J* = 0.7 Hz, 3H), 2.53 (d, *J* = 0.8 Hz, 3H) ppm; LC-MS: *m/z* = 330.9 $[M + H]^+$.

4-Chloro-1-methyl-*N*-(4-(4-methylthiazol-2-yl)benzyl)-1*H*-pyrazole-5-carboxamide (16) (Exp1)

Title compound was prepared according to **General Procedure G1**, starting from **66** and 4-chloro-1-methyl-1*H*-pyrazole-5-carboxylic acid to give a white solid (22%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.92 (d, *J* = 8.3 Hz, 2H), 7.45 – 7.38 (m, 3H), 7.04 (s, br, 1H), 6.87 (d, *J* = 0.9 Hz, 1H), 4.67 (d, *J* = 5.8 Hz, 2H), 4.19 (s, 3H), 2.50 (d, *J* = 0.9 Hz, 3H)

ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.1, 158.4, 154.0, 139.2, 136.8, 133.4, 130.9, 128.2, 127.0, 113.7, 109.7, 43.3, 41.32, 17.4 ppm; LC-MS: *m/z* = 346.8 $[M + H]^+$.

4-Chloro-*N*-(4-(4-ethylthiazol-2-yl)benzyl)-1-methyl-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxamide (17) (Exp2)

Title compound was prepared according to **General Procedure G2**, starting from **70** and 4-chloro-1-methyl-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxylic acid to give a white solid (14%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 7.9 Hz, 2H), 6.99 (br, 1H), 6.88 (s, 1H), 4.68 (d, J = 5.4 Hz, 2H), 4.23 (s, 3H), 2.86 (q, J = 7.4 Hz, 2H), 1.34 (t, J =7.4 Hz, 3H) ppm; LC-MS: *m/z* = 429.0 $[M + H]^+$.

4-Chloro-3-methoxy-1-methyl-*N*-(4-(4-methylthiazol-2-yl)benzyl)-1*H*-pyrazole-5-carboxamide (18) (Exp1)

To a solution of methyl 3-methoxy-1-methyl-1*H*-pyrazole-5-carboxylate (0.5 g, 2.94 mmol) in toluene (10 mL) was added SO_2Cl_2 (0.48 mL, 5.88 mmol) dropwise. The mixture was heated at 100 °C for 2 h, then cooled to room temperature. Water (20 mL) was added, and the aqueous layer was extracted with EtOAc (2 x 10 mL). Combined

organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to afford methyl 4-chloro-3-methoxy-1-methyl-1*H*-pyrazole-5-carboxylate, which was directly subjected to **General Procedure F3** to give the corresponding carboxylic acid, which was subsequently coupled to **66** according to **General Procedure G3** to give title compound (20%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.92 (d, *J* = 8.3 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.02 (s, br, 1H), 6.87 (s, 1H), 4.65 (d, *J* = 5.7 Hz, 2H), 4.06 (s, 3H), 3.96 (s, 3H), 2.50 (s, 3H) ppm; LC-MS: *m/z* = 376.8 $[M + H]^+$.

2-Methyl-*N*-(4-(4-methylthiazol-2-yl)benzyl)-2,4,5,6-tetrahydrocyclopenta[c]pyrazole-3-carboxamide (19) (Exp1)

Title compound was prepared according to **General Procedure G1**, starting from **66** and 2-methyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazole-3-carboxylic acid to give a white solid (20%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.92 (d, *J* = 8.2 Hz, 2H), 7.37 (d, *J* = 8.1 Hz, 2H), 6.88 (s, 1H), 6.04 (s, br, 1H), 4.63 (d, *J* = 5.9 Hz, 2H), 4.17 (s, 3H), 2.77 – 2.70 (m, 4H), 2.51 (s, 3H), 2.49 – 2.42 (m, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.1, 160.3,

159.2, 154.0, 139.8, 133.4, 129.2, 128.1, 127.0, 125.4, 113.7, 43.2, 39.8, 30.0, 24.7, 24.6, 17.4 ppm; LC-MS: *m/z* = 352.8 $[M + H]^+$.

1-Methyl-*N*-(4-(thiazol-2-yl)benzyl)-1*H*-pyrazole-5-carboxamide (20) (Exp1)

Title compound was prepared according to **General Procedure A1**, starting from **79** and 2-bromothiazole to give a brown solid (63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.91 (d, *J* = 8.3 Hz, 2H), 7.84 (d, *J* = 3.2 Hz, 1H), 7.42 (d, *J* = 2.0 Hz, 1H), 7.37 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 3.3 Hz, 1H), 6.63 (s, br, 1H), 6.54 (d, *J* = 2.0 Hz, 1H), 4.59 (d, *J* = 5.9 Hz, 2H), 4.19 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.9, 160.0, 143.8, 139.8, 137.7, 135.0, 133.2, 128.4, 127.1, 119.11, 106.4, 43.2, 39.5 ppm; LC-MS: *m/z* = 299.1 $[M + H]^+$.

***N*-(4-(4,5-Dimethylthiazol-2-yl)benzyl)-1-methyl-1*H*-pyrazole-5-carboxamide (21) (Exp1)**

Title compound was prepared according to **General Procedure A1**, starting from **79** and 2-bromo-4,5-dimethylthiazole to give a brown solid (57%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.66 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 2.1 Hz, 1H), 7.17 (d, *J* = 8.3 Hz, 2H), 6.97 (s, br, 1H), 6.51 (d, *J* = 2.1 Hz, 1H), 4.43 (d, *J* = 5.9 Hz, 2H), 4.09 (s, 3H), 2.27 (d, *J*

= 11.6 Hz, 6H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 163.2, 160.3, 149.6, 139.5, 137.9, 135.4, 133.5, 128.4, 127.1, 126.7, 106.9, 43.4, 39.7, 15.1, 11.8 ppm; LC-MS: *m/z* = 326.9 $[M + H]^+$.

N-(4-(Benzo[*d*]thiazol-2-yl)benzyl)-1-methyl-1*H*-pyrazole-5-carboxamide (22) (Exp1)

Title compound was prepared according to **General Procedure A1** starting from **79** and 2-chlorobenzo[*d*]thiazole to give a brown solid (50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.04 (t, *J* = 6.9 Hz, 3H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 1H), 7.46 – 7.34 (m, 4H), 6.61 (s, br, 1H), 6.56 (s, 1H), 4.62 (d, *J* = 5.9 Hz, 2H), 4.21 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.5, 160.1, 154.2, 140.9, 137.7, 135.1, 135.0, 133.2, 128.4, 128.1, 126.5, 125.4, 123.3, 121.7, 106.4, 43.3, 39.5 ppm; LC-MS: *m/z* = 348.9 $[M + H]^+$.

1-Methyl-N-(4-(2-methylthiazol-4-yl)benzyl)-1*H*-pyrazole-5-carboxamide (23) (Exp1)

Title compound was prepared according to **General Procedure A1**, starting from **79** and 4-bromo-2-methylthiazole to give a brown solid (56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.60 (s, 1H), 7.61 (d, *J* = 8.3 Hz, 2H), 7.39 (d, *J* = 2.1 Hz, 1H), 7.36 (d, *J* = 8.3 Hz, 2H), 6.76 (s, br, 1H), 6.53 (d, *J* = 2.1 Hz, 1H), 4.58 (d, *J* = 5.8 Hz, 2H), 4.18 (s, 3H), 2.57

(s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 160.0, 151.3, 149.4, 137.6, 137.2, 135.2, 134.4, 129.0, 128.3, 127.9, 106.5, 43.3, 39.4, 12.6 ppm; LC-MS: *m/z* = 312.9 $[M + H]^+$.

1-Methyl-*N*-(4-((4-methylthiazol-2-yl)methyl)benzyl)-1*H*-pyrazole-5-carboxamide (24) (Exp2)

Intermediate **82** was subjected to **General Procedure B2** to give the corresponding benzylamine, which was subsequently coupled to 1-methyl-1*H*-pyrazole-5-carboxylic acid according to **General procedure G4** to afford title compound as a gummy liquid (31%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42 (d, J = 1.8 Hz, 1H), 7.33-7.28 (m, 4H), 6.73 (s, 1H), 6.46 (d, J = 1.8 Hz, 1H), 6.23 (br s, 1H), 4.56 (d, J = 5.6 Hz, 2H), 4.27 (s, 2H), 4.19 (s, 3H), 2.41 (s, 3H) ppm; LC-MS: *m/z* = 327.1 $[M + H]^+$.

***N*-(4-(4-Chlorothiazol-2-yl)benzyl)-1-methyl-1*H*-pyrazole-5-carboxamide (25) (Exp1)**

Title compound was prepared according to **General Procedure G1**, starting from **79** and 2-bromo-4-chlorothiazole to give a brown solid (43%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.86 (d, J = 8.3 Hz, 2H), 7.41 (d, J = 2.1 Hz, 1H), 7.36 (d, J = 8.3 Hz, 2H), 7.07 (s, 1H), 6.61 (s, br, 1H), 6.54 (d, J = 2.1 Hz, 1H), 4.59 (d, J = 6.0 Hz, 2H), 4.18 (s, 3H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.2, 159.7, 140.3, 139.8, 137.4, 134.6, 131.8, 128.1, 126.4, 112.8, 106.2, 42.8, 39.1 ppm; LC-MS: *m/z* = 332.9 $[M + H]^+$.

1-Methyl-*N*-(4-(4-(trifluoromethyl)thiazol-2-yl)benzyl)-1*H*-pyrazole-5-carboxamide (26) (Exp2)

Intermediate **84** was subjected to **General Procedure B2** to give the corresponding benzylamine, which was subsequently coupled to 1-methyl-1*H*-pyrazole-5-carboxylic acid according to **General procedure G4** to afford title compound as a white solid (28%). ^{1}H NMR (400 MHz, DMSO-d_6): *δ* = 9.10 (br, 1H), 8.54 (s, 1H), 7.97 (d, *J* = 8.1 Hz, 2H), 7.48-7.46 (m, 3H), 6.92 (s, 1H), 4.50 (d, *J* = 5.9 Hz, 2H), 4.06 (s, 3H) ppm; LC-MS: *m/z* = 367.2 $[M + H]^+$.

1-Methyl-*N*-(4-(4-(2,2,2-trifluoroethyl)thiazol-2-yl)benzyl)-1*H*-pyrazole-5-carboxamide (27) (Exp2)

General procedure D3 was followed, starting from 1-bromo-4,4,4-trifluorobutan-2-one and 4-bromo-thiobenzamide to give 2-(4-bromophenyl)-4-(2,2,2-trifluoroethyl)-1,3-thiazole, which was subjected to cyanation, then reduction according to **General**

procedure C and **General procedure B2** respectively to give the corresponding benzylamine, which was subsequently coupled to 1-methyl-1*H*-pyrazole-5-carboxylic acid according to **General procedure G4** to afford title compound as a white solid (22%). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.08 (t, J = 5.3 Hz, 1H), 7.90 (d, J = 8.0 Hz, 2H), 7.70 (s, 1H), 7.47-7.43 (m, 3H), 6.91 (s, 1H), 4.49 (d, J = 5.3 Hz, 2H), 4.06 (s, 3H), 3.90-3.84 (m, 2H) ppm; LC-MS: *m/z* = 381.1 $[M + H]^+$.

***N*-(4-(4-(1,1-Difluoroethyl)thiazol-2-yl)benzyl)-1-methyl-1*H*-pyrazole-5-carboxamide (28) (Exp2)**

Title compound was prepared according to **General Procedure G4**, starting from **90** and 1-methyl-1*H*-pyrazole-5-carboxylic acid to give a white solid (16%). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.20-8.90 (m, 1 H), 8.08 (s, 1H), 7.94 (d, J = 8.1 Hz, 2H), 7.47-7.45 (m, 3H), 6.92 (d, J = 1.7 Hz, 1H), 4.50 (d, J = 5.8 Hz, 2H), 4.06 (s, 3H), 2.06 (t, J = 18.8 Hz, 3H); ppm; LC-MS: *m/z* = 363.2 $[M + H]^+$.

***N*-(4-(1,4-Dimethyl-1*H*-imidazol-2-yl)benzyl)-1-methyl-1*H*-pyrazole-5-carboxamide (29) (Exp1)**

Title compound was prepared according to **General Procedure A1**, starting from **79** and 2-bromo-1,4-dimethyl-1*H*-imidazole to give a brown solid (37%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.49 (s, 1H), 7.40 – 7.30 (m, 3H), 7.18 (d, *J* = 7.9 Hz, 2H), 6.72 (s, br, 1H), 6.65 (s, 1H), 4.47 (d, *J* = 5.4 Hz, 2H), 4.15 (s, 3H), 3.59 (s, 3H), 2.15 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 160.3, 146.8, 139.1, 137.5, 137.0, 135.3, 128.9, 128.7, 127.5, 119.1, 107.1, 42.6, 39.4, 34.2, 13.2 ppm; LC-MS: *m/z* = 310.2 $[M + H]^+$.

1-Methyl-*N*-(4-(1-methyl-1*H*-pyrazol-3-yl)benzyl)-1*H*-pyrazole-5-carboxamide (30) (Exp1)

Title compound was prepared according to **General Procedure A1**, starting from **79** and 3-bromo-1-methyl-1*H*-pyrazole to give a white solid (31%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.73 (d, *J* = 8.2 Hz, 2H), 7.37 (dd, *J* = 14.0, 2.1 Hz, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 6.64 (s, br, 1H), 6.51 (dd, *J* = 3.2, 2.3 Hz, 2H), 4.54 (d, *J* = 5.8 Hz, 2H), 4.17 (s, 3H), 3.91 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 159.9, 151.1, 137.6, 136.9, 135.2, 133.1, 131.5, 128.2, 126.0, 106.4, 103.0, 43.4, 39.4, 39.1 ppm; LC-MS: *m/z* = 296.0 $[M + H]^+$.

_N_-(4-(1-Ethyl-1_H_-pyrazol-3-yl)benzyl)-1-methyl-1_H_-pyrazole-5-carboxamide (31) (Exp2)

Intermediate **94** was subjected to **General Procedure B2** to give the corresponding benzylamine, which was subsequently coupled to 1-methyl-1*H*-pyrazole-5-carboxylic acid according to **General procedure G4** to afford title compound as a brown gummy liquid (23%). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.01 (br, 1H), 7.74-7.73 (m, 3H), 7.46 (s, 1H), 7.31 (d, J = 8.0 Hz, 2H), 6.90 (s, 1H), 6.64 (s, 1H), 4.44, (d, J = 5.9 Hz, 2H), 4.15 (q, J = 7.3 Hz, 2H), 4.06 (s, 3H), 1.39 (t, J = 7.2 Hz, 3H) ppm; LC-MS: m/z = 310.3 $[M+H]^+$.

_N_-(4-(4-Ethyl-2_H_-1,2,3-triazol-2-yl)benzyl)-1-methyl-1_H_-pyrazole-5-carboxamide (32) (Exp2)

Intermediate **95** was subjected to **General Procedure B2** to give the corresponding benzylamine, which was subsequently coupled to 1-methyl-1*H*-pyrazole-5-carboxylic acid according to **General procedure G2** to afford title compound as a white solid (66%). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.07 (t, J = 5.5 Hz, 1H), 7.94-7.91 (m, 3H), 7.47-7.45 (m, 3H), 6.91 (s, 1H), 4.49 (d, J = 5.5 Hz, 2H), 4.07 (s, 3H), 2.75 (q, J = 7.6 Hz, 2H), 1.27 (t, J = 7.4 Hz, 3H) ppm; LC-MS: m/z = 311.2 $[M + H]^+$.

_N_-(4-(3-Ethyl-1_H_-1,2,4-triazol-5-yl)benzyl)-1-methyl-1_H_-pyrazole-5-carboxamide (33) (Exp2)

Title compound was prepared according to **General Procedure G2**, starting from **98** and 1-methyl-1_H_-pyrazole-5-carboxylic acid to give a white solid (40 mg, 33%). ^{1}H NMR (400 MHz, DMSO-d_6, 100 ^{o}C): δ = 13.33 (br s, 1H), 8.71 (t, J = 5.2 Hz, 1H), 7.94 (d, J = 7.0 Hz, 2H), 7.41 (d, J = 8.0 Hz, 3H), 6.86 (s, 1H), 4.49 (d, J =5.2 Hz, 2H), 4.06 (s, 3H), 2.75-2.66 (m, 2H), 1.28 (t, J = 7.1 Hz, 3H) ppm. LC-MS: m/z = 311.2 $[M + H]^+$.

_N_-(4-(1-Ethyl-1_H_-1,2,4-triazol-3-yl)benzyl)-1-methyl-1_H_-pyrazole-5-carboxamide (34) (Exp2)

To a stirred solution of **100** (0.25 g, 0.78 mmol) in pyridine (10.0 mL), ethyl-hydrazine HCl (0.42 g, 4.37 mmol) was added. Reaction mixture was stirred at room temperature for 16 h then concentrated *in vacuo*. Residue was washed with diethyl ether (2 x 10 mL) to afford _N_-(4-((2-ethylhydrazineyl)(imino)methyl)benzyl)-1-methyl-1_H_-pyrazole-5-carboxamide, which was dissolved in formic acid (4.0 mL) and stirred at 80 ^{o}C for 16 h. Reaction mixture was cooled to room temperature and quenched with saturated

$NaHCO_3$ solution. Aqueous layer was extracted with EtOAc (3 x 10 mL). Combined organic layer was washed with water, brine and dried over anhydrous Na_2SO_4 then concentrated *in vacuo*. Crude product was purified by column chromatography (2% MeOH in DCM) to afford title compound (26%) as an off white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.01 (t, J = 5.6 Hz, 1H), 8.51 (s, 1H), 7.92 (d, J = 8.1 Hz, 2H), 7.43 (d, J = 1.6 Hz, 1H), 7.35 (d, J = 8.0 Hz, 2H), 6.89 (d, J = 1.7 Hz, 1H), 4.45 (d, J = 6.0 Hz, 2H), 4.20 (q, J = 7.3 Hz, 2H), 4.03 (s, 3H), 1.40 (t, J = 7.2 Hz, 3H) ppm; LC-MS: *m/z* = 311.2 $[M + H]^+$.

***N*-(4-(4-Ethyloxazol-2-yl)benzyl)-1-methyl-1*H*-pyrazole-5-carboxamide (35) (Exp1)**

Title compound was prepared according to **General Procedure A1**, starting from **79** and 2-bromo-4-ethyloxazole to give a brown solid (55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.00 (d, J = 8.3 Hz, 2H), 7.44 (d, J = 2.1 Hz, 1H), 7.40 (d, J = 8.7 Hz, 3H), 6.52 (d, J = 2.1 Hz, 1H), 6.38 (s, br, 1H), 4.63 (d, J = 5.9 Hz, 2H), 4.21 (s, 3H), 2.62 (q, J = 7.6 Hz, 2H), 1.28 (t, J = 7.5 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 160.9, 159.8, 144.2,

139.7, 137.6, 134.9, 133.5, 128.0, 127.3, 126.7, 106.2, 43.2, 39.3, 19.9, 12.6 ppm; LC-MS: *m/z* = 310.9 $[M + H]^+$.

N-(4-(5-Ethyloxazol-2-yl)benzyl)-1-methyl-1H-pyrazole-5-carboxamide (36) (Exp1)

Title compound was prepared according to **General Procedure A1**, starting from **79** and 2-bromo-5-ethyloxazole to give a brown solid (94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.95 (d, *J* = 7.1 Hz, 2H), 7.42 (s, 1H), 7.37 (d, *J* = 7.2 Hz, 2H), 6.81 (s, 1H), 6.56 (s, br, 1H), 6.54 (s, 1H), 4.60 (d, *J* = 3.9 Hz, 2H), 4.20 (s, 3H), 2.84 – 2.67 (q, *J* = 7.6 Hz, 2H), 1.30 (t, *J* = 7.5 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 160.2, 159.9, 154.5, 139.5, 137.6, 134.9, 128.0, 127.3, 126.4, 122.9, 106.3, 43.2, 39.3, 19.1, 11.8 ppm; LC-MS: *m/z* = 310.9 $[M + H]^+$.

N-(4-(5-Ethyl-1,2,4-oxadiazol-3-yl)benzyl)-1-methyl-1H-pyrazole-5-carboxamide (37) (Exp2)

Title compound was prepared according to **General Procedure J1**, starting from **101** and propionic acid to give a white solid (38%). ^{1}H NMR (400 MHz, DMSO-d_6): *δ* = 9.09 (br, 1H), 7.97 (d, *J* = 7.9 Hz, 2H), 7.48 (d, *J* = 8.0 Hz, 3H), 6.92 (s, 1H), 4.51 (d, *J* =

5.5 Hz, 2H), 4.06 (s, 3H), 3.01 (q, *J* = 7.4 Hz, 2H), 1.33 (t, *J* = 7.5 Hz, 3H); ppm; LC-MS: *m/z* = 312.2 $[M + H]^+$.

N-(4-(3-Ethyl-1,2,4-oxadiazol-5-yl)benzyl)-1-methyl-1*H*-pyrazole-5-carboxamide (38) (Exp2)

General procedure J1 was followed, starting from **102** and **103** to give *tert*-butyl (4-(3-ethyl-1,2,4-oxadiazol-5-yl)benzyl)carbamate, which was then subjected to **General procedure K** to give the corresponding HCl salt, which was subsequently coupled to 1-methyl-1*H*-pyrazole-5-carboxylic acid according to **General procedure G4** to afford the title compound as an off white solid (63%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.13 (t, *J* = 5.7 Hz, 1H), 8.07 (d, *J* = 8.0 Hz, 2H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.48 (s, 1H), 6.93 (s, 1H), 4.54 (d, *J* = 5.8 Hz, 2H), 4.06 (s, 3H), 2.79 (q, *J* = 7.5, 2H), 1.28 (t, *J* = 7.5 Hz, 3H) ppm; LC-MS: *m/z* = 312.2 $[M + H]^+$.

N-(4-(5-Ethyl-1,3,4-oxadiazol-2-yl)benzyl)-1-methyl-1*H*-pyrazole-5-carboxamide (39) (Exp1)

General procedure G1 was followed, starting from methyl 4-(aminomethyl)benzoate HCl and 1-methyl-1*H*-pyrazole-5-carboxylic acid to give methyl 4-((1-methyl-1*H*-pyrazole-5-carboxamido)methyl)benzoate, which was then directly reacted with hydrazide monohydrate (9.15 mmol) in EtOH at room temperature overnight. Upon completion, EtOH was removed *in vacuo* and iced water was added to residue, resulting white precipitate was filtered, dried and re-dissolved in EtOH. Propionaldehyde (0.3 mmol) was then added and the reaction was refluxed for 3 h then cooled to room temperature. EtOH was removed *in vacuo* and the residue was dissolved in minimal amout of DMSO. K_2CO_3 (1.1 mmol) and I_2 (0.4 mmol) was then added and the reaction was stirred at 100 °C for 4 h. Upon completion (monitored by TLC), EtOAc was added to the reaction and organic was washed with $Na_2S_2O_3$, then water, then dried ($MgSO_4$). Solvent was removed *in vacuo* to give crude produce, which was purified by column chromatography in 0-5% MeOH/DCM to give the title compound as a white solid (10%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.93 (d, *J* = 8.4 Hz, 2H), 7.41-7.38 (m,, 3H), 6.91 (s, br, 1H), 6.61 (d, *J* = 2.1 Hz, 1H), 4.62 (d, *J* = 6.0 Hz, 2H), 4.18 (s, 3H), 2.93 (q, *J* = 7.6 Hz, 2H), 1.41 (t, *J* = 7.6 Hz, 3H) ppm; LCMS: *m/z* = 311.9 $[M + H]^+$.

1-Methyl-*N*-(4-(pyridin-2-yl)benzyl)-1*H*-pyrazole-5-carboxamide (40) (Exp1)

Title compound was prepared according to **General Procedure A1**, starting from **79** and 2-bromopyridine to give a pink gummy liquid (10%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.91 (d, *J* = 5.4 Hz, 1H), 8.44 (t, *J* = 7.7 Hz, 1H), 8.07 (d, *J* = 7.7 Hz, 1H), 7.82 (d, *J* = 8.3 Hz, 3H), 7.54 (d, *J* = 8.2 Hz, 2H), 7.49 (d, *J* = 2.1 Hz, 1H), 7.24 (d, *J* = 5.8 Hz, 1H), 6.69 s, br, 1H), 4.64 (d, *J* = 5.9 Hz, 2H), 4.19 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 160.0, 153.6, 145.6, 143.1, 142.7, 137.4, 135.4, 129.9, 129.2, 128.6, 125.4, 124.8, 107.1, 43.1, 39.1 ppm; LCMS: *m/z* = 293.0 $[M + H]^+$.

1-Methyl-*N*-(4-(pyridazin-3-yl)benzyl)-1*H*-pyrazole-5-carboxamide (41) (Exp1)

Title compound was prepared according to **General Procedure A1**, starting from **79** and 3-bromopyridazine to give a brown solid (25%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.09 (dd, *J* = 4.9, 1.5 Hz, 1H), 7.94 (d, *J* = 8.3 Hz, 2H), 7.81 (dd, *J* = 8.6, 1.5 Hz, 1H), 7.51 (dd, *J* = 8.6, 4.9 Hz, 1H), 7.40 (d, *J* = 8.3 Hz, 2H), 7.38 (d, *J* = 2.1 Hz, 1H), 7.29 (s, br, 1H), 6.65 (d, *J* = 2.1 Hz, 1H), 4.60 (d, *J* = 6.0 Hz, 2H), 4.17 (s, 3H) ppm; ^{13}C NMR (101

MHz, $CDCl_3$) δ 160.2, 159.2, 150.0, 140.3, 137.6, 135.5, 135.1, 128.3, 127.5, 127.0, 124.0, 106.7, 43.1, 39.4; LCMS *m/z* = 293.9 $[M + H]^+$.

1-Methyl-*N*-(4-(pyrazin-2-yl)benzyl)-1*H*-pyrazole-5-carboxamide (42) (Exp1)

Title compound was prepared according to **General Procedure A1**, starting from **79** and 2-bromopyrazine to give a white (10%). ^1H NMR (400 MHz, $CDCl_3$) δ = 8.99 (d, *J* = 1.5 Hz, 1H), 8.62 (dd, *J* = 2.5, 1.6 Hz, 1H), 8.50 (d, *J* = 2.5 Hz, 1H), 7.99 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 2.1 Hz, 1H), 6.53 (d, *J* = 2.1 Hz, 2H), 4.65 (d, *J* = 5.9 Hz, 2H), 4.21 (d, *J* = 3.7 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 160.0, 152.4, 144.3, 143.1, 142.2, 139.8, 137.7, 135.9, 135.0, 128.5, 127.5, 106.4, 43.3, 39.5 ppm; LCMS *m/z* = 293.9 $[M + H]^+$.

***N*-(2-Fluoro-4-(4-methylthiazol-2-yl)benzyl)-1-methyl-1*H*-pyrazole-5-carboxamide (43) (Exp2)**

Title compound was prepared according to **General Procedure G4**, starting from **104** and 1-methyl-1*H*-pyrazole-5-carboxylic acid to give a white solid (46%). ^1H NMR (400 MHz, DMSO-d_6): *δ* = 9.05 (t, *J* = 6.0 Hz, 1H), 7.73-7.67 (m, 2H), 7.48-7.47 (m, 2H), 7.37

(s, 1H), 6.93 (d, *J* = 1.9 Hz, 1H), 4.50 (d, *J* = 5.8 Hz, 2H), 4.05 (s, 3H), 2.42 (s, 3H) ppm; LC-MS: *m/z* = 331.2 $[M + H]^+$.

_N_-(2-Methoxy-4-(4-methylthiazol-2-yl)benzyl)-1-methyl-1_H_-pyrazole-5-carboxamide (44) (Exp1)

General procedure G1 was followed, starting from (4-bromo-2-methoxyphenyl)methanamine and 1-methyl-1*H*-pyrazole-5-carboxylic acid to give *N*-(4-bromo-2-methoxybenzyl)-1-methyl-1*H*-pyrazole-5-carboxamide, which was then subjected to **General procedure A6** to afford the title compound as a white solid (42%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.53 (s, 1H), 7.42-7.38 (m, 2H), 7.33 (d, *J* = 7.7 Hz, 1H), 6.87 (s, 1H), 6.63 (s, br, 1H), 6.48 (d, *J* = 1.8 Hz, 1H), 4.58 (d, *J* = 5.9 Hz, 2H), 4.16 (s, 3H), 3.96 (s, 3H), 2.50 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.2, 159.8, 158.0, 153.9, 137.6, 135.4, 134.8, 130.2, 127.6, 119.3, 113.8, 108.2, 106.2, 55.8, 39.4, 39.3, 17.3 ppm; LC-MS: *m/z* = 342.9 $[M + H]^+$.

1-Methyl-_N_-(2-methyl-4-(4-methylthiazol-2-yl)benzyl)-1_H_-pyrazole-5-carboxamide (45) (Exp1)

General procedure G1 was followed, starting from (4-bromo-2-methylphenyl)methanamine HCl and 1-methyl-1*H*-pyrazole-5-carboxylic acid to give *N*-(4-bromo-2-methylbenzyl)-1-methyl-1*H*-pyrazole-5-carboxamide, which was then subjected to **General procedure A6** to afford the title compound as a white solid (39%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.73 (s, 1H), 7.66 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.40 (d, *J* = 2.1 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 1H), 6.86 (d, *J* = 0.9 Hz, 1H), 6.54 (d, *J* = 2.1 Hz, 1H), 6.52 (s, br, 1H), 4.56 (d, *J* = 5.6 Hz, 2H), 4.18 (s, 3H), 2.48 (d, *J* = 0.9 Hz, 3H), 2.36 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.3, 159.8, 153.9, 137.7, 137.2, 137.2, 135.0, 133.3, 128.9, 128.4, 124.4, 113.6, 106.4, 41.4, 39.4, 19.1, 17.3 ppm; LC-MS: *m/z* = 326.9 $[M + H]^+$.

1-Methyl-*N*-((5-(4-methylthiazol-2-yl)pyridin-2-yl)methyl)-1*H*-pyrazole-5-carboxamide (46) (Exp2)

General procedure B3 was followed, starting from **105** to give (5-(4-methylthiazol-2-yl)pyridin-2-yl)methanamine HCl, which was subsequently coupled to 1-methyl-1*H*-pyrazole-5-carboxylic acid according to **General procedure G4** to give the title compound

as an off-white solid (15%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.16 (t, *J* = 5.8 Hz, 1H), 9.03 (s, 1H), 8.26-8.24 (m, 1H), 7.49-7.41 (m, 3H), 6.96 (d, *J* = 1.6 Hz, 1H), 4.58 (d, *J* = 5.8Hz, 2H), 4.06 (s, 3H), 2.44 (s, 3H) ppm; LC-MS: *m/z* = 314.3 $[M + H]^+$.

N-(3-Fluoro-4-(4-methylthiazol-2-yl)benzyl)-1-methyl-1H-pyrazole-5-carboxamide (47) (Exp2)

Title compound was prepared according to **General Procedure G4**, starting from **106** and 1-methyl-1*H*-pyrazole-5-carboxylic acid to give a white solid (15% yields). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.09 (t, *J* = 5.9 Hz, 1H), 8.17 (t, *J* = 7.8 Hz, 1H), 7.46 (d, *J* = 9.8 Hz, 2H), 7.34-7.28 (m, 2H), 6.92 (s, 1H), 4.50 (d, *J* = 5.9 Hz, 2H), 4.06 (s, 3H), 2.45 (s, 3H) ppm; LC-MS: *m/z* = 331.0 $[M + H]^+$.

N-(3-Methoxy-4-(4-methylthiazol-2-yl)benzyl)-1-methyl-1H-pyrazole-5-carboxamide (48) (Exp1)

General procedure G1 was followed, starting from (4-bromo-3-methoxyphenyl)methanamine and 1-methyl-1*H*-pyrazole-5-carboxylic acid to give *N*-(4-bromo-3-methoxybenzyl)-1-methyl-1*H*-pyrazole-5-carboxamide, which was then

subjected to **General procedure A6** to afford the title compound as a brown solid (33% yields). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.28 (d, *J* = 8.0 Hz, 1H), 7.44 (d, *J* = 2.1 Hz, 1H), 6.97 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.95 – 6.93 (m, 2H), 6.56 (s, br, 1H), 6.55 (d, *J* = 2.1 Hz, 1H), 4.58 (d, *J* = 5.9 Hz, 2H), 4.21 (s, 3H), 3.98 (s, 3H), 2.50 (d, *J* = 0.9 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 161.4, 160.0, 156.6, 151.9, 140.3, 137.7, 135.1, 128.8, 122.0, 120.3, 114.9, 110.9, 106.4, 55.7, 43.5, 39.5, 17.3; LC-MS: *m/z* = 342.8 $[M + H]^+$.

1-Methyl-*N*-(3-methyl-4-(4-methylthiazol-2-yl)benzyl)-1*H*-pyrazole-5-carboxamide (49) (Exp1)

General procedure G1 was followed, starting from (4-bromo-3-methylphenyl)methanamine HCl and 1-methyl-1*H*-pyrazole-5-carboxylic acid to give *N*-(4-bromo-3-methylbenzyl)-1-methyl-1*H*-pyrazole-5-carboxamide, which was then subjected to **General procedure A6** to afford the title compound as a brown solid (41% yields). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.64 (d, *J* = 7.9 Hz, 1H), 7.40 (d, *J* = 2.1 Hz, 1H), 7.18 (s, 1H), 7.15 (d, *J* = 7.9 Hz, 1H), 6.93 (d, *J* = 0.9 Hz, 1H), 6.72 (s, br, 1H), 6.53 (d, *J* = 2.1 Hz, 1H), 4.53 (d, *J* = 5.9 Hz, 2H), 4.17 (s, 3H), 2.53 (s, 3H), 2.49 (d, *J* = 0.9 Hz, 3H)

ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.5, 160.0, 153.1, 138.8, 137.6, 137.0, 135.1, 132.7, 130.6, 130.4, 125.3, 114.3, 106.5, 43.1, 39.4, 21.4, 17.3 ppm; LC-MS: *m/z* = 326.9 $[M + H]^+$.

1-Methyl-*N*-((6-(4-methylthiazol-2-yl)pyridin-3-yl)methyl)-1*H*-pyrazole-5-carboxamide (50) (Exp2)

General procedure B3 was followed, starting from **107** to give the corresponding HCl salt, which was subsequently coupled to 1-methyl-1*H*-pyrazole-5-carboxylic acid according to **General procedure G4** to give the title compound as an off-white solid (19%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.10 (t, *J* = 5.8 Hz, 1H), 8.57 (d, *J* = 1.2 Hz, 1H), 8.07 (d, *J* = 8.0 Hz, 1H), 7.85 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.47 (d, *J* = 2.0 Hz, 1H), 7.40 (s, 1H), 6.90 (d, *J* = 2.0 Hz, 1H), 4.51 (d, *J* = 5.9 Hz, 2H), 4.06 (s, 3H), 2.44 (s, 3H) ppm; LC-MS: *m/z* = 314.3 $[M + H]^+$.

1-Methyl-*N*-(1-(4-(4-methylthiazol-2-yl)phenyl)ethyl)-1*H*-pyrazole-5-carboxamide (51) (Exp1)

General procedure G1 was followed, starting from 1-(4-bromophenyl)ethan-1-amine HCl and 1-methyl-1H-pyrazole-5-carboxylic acid to give *N*-(1-(4-bromophenyl)ethyl)-1-methyl-1*H*-pyrazole-5-carboxamide, which was then subjected to **General procedure A6** to afford the title compound as a brown gummy liquid (35% yields). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.91 (d, *J* = 8.2 Hz, 2H), 7.45 – 7.43 (m, 1H), 7.41 (d, *J* = 8.2 Hz, 2H), 6.87 (s, 1H), 6.51 (d, *J* = 1.5 Hz, 1H), 6.23 (s, br, 1H), 5.31 – 5.22 (m, 1H), 4.16 (s, 3H), 2.50 (s, 3H), 1.60 (d, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.1, 159.3, 154.0, 148.5, 144.5, 137.7, 133.3, 127.0, 126.8, 113.6, 106.3, 48.9, 39.4, 21.8, 17.4 ppm; LC-MS: *m/z* = 326.9 $[M + H]^+$.

N-(Cyano(4-(4-methylthiazol-2-yl)phenyl)methyl)-1-methyl-1*H*-pyrazole-5-carboxamide (52) (Exp1)

General procedure G1 was followed, starting from 2-amino-2-(4-bromophenyl)ACN and 1-methyl-1H-pyrazole-5-carboxylic acid to give *N*-((4-bromophenyl)(cyano)methyl)-1-methyl-1*H*-pyrazole-5-carboxamide, which was then subjected to **General procedure A6** to afford the title compound as a yellow solid (43%

yields). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.80 (d, *J* = 8.4 Hz, 2H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.45 (d, *J* = 2.1 Hz, 1H), 7.42 (d, *J* = 8.3 Hz, 2H), 6.95 (d, *J* = 0.8 Hz, 1H), 6.77 (d, *J* = 2.1 Hz, 1H), 6.30 (d, *J* = 8.5 Hz, 1H), 4.23 (s, 3H), 2.50 (d, *J* = 0.6 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.3, 158.9, 154.2, 137.8, 134.6, 134.0, 127.6, 127.1, 116.7, 114.6, 107.5, 43.5, 39.7, 17.0 ppm; LC-MS: *m/z* = 337.9 $[M + H]^+$.

1-Methyl-*N*-(4-(5-methyl-1,2,4-oxadiazol-3-yl)benzyl)-1*H*-pyrazole-5-carboxamide (53) (Exp2)

Title compound was prepared according to **General Procedure J1**, starting from **101** and acetic acid to give a white solid (21%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.09 (t, *J* = 5.8 Hz, 2H), 7.97 (d, *J* = 8.0 Hz, 2H), 7.50-7.48 (m, 2H), 6.92 (d, *J* = 1.6 Hz, 1H), 4.51 (d, *J* = 5.8 Hz, 2H), 4.06 (s, 3H), 2.65 (s, 3H) ppm; LC-MS: *m/z* = 298.3 $[M + H]^+$.

1-Methyl-*N*-(4-(5-propyl-1,2,4-oxadiazol-3-yl)benzyl)-1*H*-pyrazole-5-carboxamide (54) (Exp1)

Title compound was prepared according to **General Procedure J2**, starting from **101** and butyric acid to give a brown solid (34%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.00 (d,

J = 8.4 Hz, 2H), 7.40-7.35 (m, 3H), 6.80 (s, br, 1H), 6.55 (d, *J* = 2.1 Hz, 1H), 4.59 (d, *J* = 6.0 Hz, 2H), 4.15 (s, 3H), 2.89 (t, *J* = 7.5 Hz, 2H), 1.93 – 1.82 (m, 2H), 1.03 (t, *J* = 7.4 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 180.0, 167.9, 160.0, 141.0, 137.6, 135.0, 128.1, 127.8, 126.4, 106.5, 43.2, 39.4, 28.5, 20.2, 13.7 ppm; LC-MS: *m/z* = 325.9 $[M + H]^+$.

N-(4-(5-Isopropyl-1,2,4-oxadiazol-3-yl)benzyl)-1-methyl-1H-pyrazole-5-carboxamide (55) (Exp1)

Title compound was prepared according to **General Procedure J2**, starting from **101** and isobutyric acid to give a brown solid (35%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.02 (d, *J* = 8.4 Hz, 2H), 7.39 (dd, *J* = 6.5, 5.3 Hz, 3H), 6.67 (s, br, 1H), 6.54 (d, *J* = 2.1 Hz, 1H), 4.60 (d, *J* = 6.0 Hz, 2H), 4.17 (s, 3H), 3.32 – 3.21 (m, 1H), 1.44 (d, *J* = 7.0 Hz, 6H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 184.1, 167.9, 160.0, 140.9, 137.7, 135.0, 128.1, 127.9, 126.5, 106.5, 43.2, 39.4, 27.6, 20.2 ppm; LC-MS: *m/z* = 325.9 $[M + H]^+$.

N-(4-(5-Cyclopropyl-1,2,4-oxadiazol-3-yl)benzyl)-1-methyl-1H-pyrazole-5-carboxamide (56) (Exp2)

Title compound was prepared according to **General Procedure J1**, starting from **101** and cyclopropanecarboxylic acid to give a white solid (28%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.09 (t, *J* = 5.9 Hz, 1H), 7.93 (d, *J* = 8.2 Hz, 2H), 7.48-7.46 (m, 3H), 6.92 (d, *J* = 1.9 Hz, 1H), 4.51 (d, *J* = 6.0 Hz, 2H), 4.06 (s, 3H), 2.43-2.36 (m, 1H), 1.30-1.25 (m, 2H), 1.20-1.16 (m, 2H) ppm; LC-MS: *m/z* = 324.3 $[M + H]^+$.

1-Methyl-*N*-(4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzyl)-1*H*-pyrazole-5-carboxamide (57) (Exp2)

Title compound was prepared according to **General Procedure J1**, starting from **101** and TFA to give a brown solid (15%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.12 (t, *J* = 5.8 Hz, 1H), 8.05 (d, *J* = 8.1 Hz, 2H), 7.55 (d, *J* = 8.2 Hz, 2H), 7.48 (d, *J* = 1.9 Hz, 1H), 6.93 (d, *J* = 2.0 Hz, 1H), 4.54 (d, *J* = 6.0 Hz, 2H), 4.06 (s, 3H) ppm; LC-MS: *m/z* = 352.1 $[M + H]^+$.

_N_-(4-(5-(1,1-Difluoroethyl)-1,2,4-oxadiazol-3-yl)benzyl)-1-methyl-1*H*-pyrazole-5-carboxamide (58) (Exp2)

Title compound was prepared according to **General Procedure J1**, starting from **101** and 2,2-difluoropropanoic acid to give a white solid (27%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.12 (t, *J* = 5.9 Hz, 1H), 8.03 (d, *J* = 8.16 Hz, 2H), 7.53 (d, *J* = 8.2 Hz, 2H), 7.48 (d, *J* = 1.9 Hz, 1H), 6.93 (d, *J* = 2.0 Hz, 1H), 4.53 (d, *J* = 6.0 Hz, 2H), 4.06 (s, 3H), 2.24 (t, *J* = 19.6 Hz, 3H) ppm; LC-MS: *m/z* = 348.1 $[M + H]^+$.

Synthesis of 1-methyl-*N*-{[4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl]methyl}-1*H*-pyrazole-5-carboxamide (59) (Exp2)

General procedure J1 was followed, starting from **102** and N-hydroxyacetimidamide to give *tert*-butyl (4-(3-methyl-1,2,4-oxadiazol-5-yl)benzyl)carbamate, which was then subjected to **General procedure K** to give the corresponding HCl salt, which was subsequently coupled to 1-methyl-1*H*-pyrazole-5-carboxylic acid according to **General procedure G4** to afford the title compound as a white solid (22%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.12 (t, *J* = 5.8 Hz, 1H), 8.06 (d, *J* = 8.1 Hz, 2H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.48 (d, *J* = 1.8 Hz, 1H), 6.93 (d, *J* = 1.8 Hz, 1H), 4.54 (d, *J* = 5.8 Hz, 2H), 4.06 (s, 3H), 2.41 (s, 3H) ppm; LC-MS: *m/z* = 298 $[M + H]^+$.

***N*-(4-(5-Ethyl-1,2,4-oxadiazol-3-yl)benzyl)-4-fluoro-1-methyl-1*H*-pyrazole-5-carboxamide (60) (Exp2)**

Title compound was prepared according to **General Procedure J1**, starting from **109** and propionic acid to give a white solid (23%). ^{1}H NMR (400 MHz, DMSO-d_6) (MMV1558288): δ = 8.80 (br, 1H), 7.97 (d, J = 7.80 Hz, 2H), 7.60 (d, J = 3.9Hz, 1H), 7.50 (d, J = 7.7 Hz, 2H), 4.53 (d, J = 5.4 Hz, 2H), 3.95 (s, 3H), 3.01 (q, J = 7.5 Hz, 2H), 1.34 (t, J = 7.3 Hz, 3H) ppm; LC-MS: m/z = 330.1 $[M + H]^+$.

***N*-(4-(3-Ethyl-1,2,4-oxadiazol-5-yl)benzyl)-4-fluoro-1-methyl-1*H*-pyrazole-5-carboxamide (61) (Exp2)**

General procedure J1 was followed, starting from **102** and **103** to give *tert*-butyl (4-(3-ethyl-1,2,4-oxadiazol-5-yl)benzyl)carbamate, which was then subjected to **General procedure K** to give the corresponding HCl salt, which was subsequently coupled to 4-fluoro-1-methyl-1*H*-pyrazole-5-carboxylic acid according to **General procedure G2** to afford the title compound as a white solid (31%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.82

(s, 1H), 8.07 (d, *J* = 8.2 Hz, 2H), 7.57 (dd, *J* = 8.0 Hz, 3H), 4.55 (d, *J* = 5.6 Hz, 2H), 3.95 (s, 3H), 2.78 (q, *J* = 7.4, 2H), 1.28 (t, *J* = 7.4 Hz, 3H), LC-MS: *m/z* = 328 $[M - H]^+$.

2-(4-(5-Ethyl-1,2,4-oxadiazol-3-yl)phenyl)-*N*-(1-methyl-1*H*-pyrazol-5-yl)acetamide (62) (Exp1)

General procedure G1 was followed, starting from 2-(4-cyanophenyl)acetic acid and 1-methyl-1*H*-pyrazol-5-amine to give 2-(4-cyanophenyl)-*N*-(1-methyl-1*H*-pyrazol-5-yl)acetamide, which was subjected to **General procedure H** to form the amidoxime, then **General procedure J2** with propionic acid to give the title compound as a white solid (34%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.11 (d, *J* = 8.1 Hz, 2H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.38 (d, *J* = 1.6 Hz, 1H), 7.14 (s, br, 1H), 6.18 (d, *J* = 1.8 Hz, 1H), 3.82 (s, *J* = 9.9 Hz, 2H), 3.59 (s, 3H), 2.98 (q, *J* = 7.6 Hz, 2H), 1.46 (t, *J* = 7.6 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.8, 167.8, 167.2, 138.4, 137.0, 130.0, 128.4, 126.8, 102.8, 100.5, 43.7, 35.6, 20.4, 10.9 ppm; LC-MS: *m/z* = 311.9 $[M + H]^+$.

***N*-(4-(5-Ethyl-1,2,4-oxadiazol-3-yl)-2-fluorobenzyl)-4-fluoro-1-methyl-1*H*-pyrazole-5-carboxamide (63) (Exp2)**

General procedure K was followed, starting from **111** to give the desired free base, which was subsequently coupled to 4-fluoro-1-methyl-1*H*-pyrazole-5-carboxylic acid according to **General procedure G2** to afford the title compound as an off-white solid (25%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.77 (t, *J* = 5.8 Hz, 1 H), 7.84 (d, *J* = 7.9 Hz, 1 H), 7.73 (d, *J* = 10.7 Hz, 1 H), 7.60 (d, *J* = 4.3 Hz, 1 H), 7.58-7.54 (m, 1 H), 4.57 (d, *J* = 5.8 Hz, 2 H), 3.95 (s, 3 H), 3.02 (q, *J* = 7.4 Hz, 2 H), 1.34 (t, *J* = 7.5 Hz, 3 H) ppm; LC-MS: *m/z* = 348.2 $[M + H]^+$.

_N_-(4-(5-Ethyl-1,2,4-oxadiazol-3-yl)-3-fluorobenzyl)-4-fluoro-1-methyl-1*H*-pyrazole-5-carboxamide (64) (Exp2)

General procedure K was followed, starting from **113** to give the desired free base, which was subsequently coupled to 4-fluoro-1-methyl-1*H*-pyrazole-5-carboxylic acid according to **General procedure G2** to afford the title compound as an off-white solid (40%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.81 (t, *J* = 5.9 Hz, 1 H), 7.98 (t, *J* = 7.6 Hz, 1 H), 7.61 (d, *J* = 4.3 Hz, 1 H), 7.38-7.34 (m, 2 H), 4.55 (d, *J* = 5.9 Hz, 2 H), 3.95 (s, 3 H), 3.02 (q, *J* = 7.6 Hz, 2 H), 1.34 (t, *J* = 7.5 Hz, 3 H) ppm; LC-MS: *m/z* = 348.2 $[M + H]^+$.

4-(4-Methylthiazol-2-yl)benzonitrile (65) (Exp1)

Title compound was prepared according to **General Procedure A1**, starting from 2-bromo-4-methylthiazole and (4-cyanophenyl)boronic acid to give a yellow solid (76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.02 (d, *J* = 8.4 Hz, 2H), 7.69 (d, *J* = 8.4 Hz, 2H), 6.98 (s, 1H), 2.51 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 164.9, 154.8, 137.6, 132.7, 126.8, 118.5, 115.4, 113.0, 17.2 ppm; LC-MS: *m/z* = 201.1 $[M + H]^+$.

(4-(4-Methylthiazol-2-yl)phenyl)methanamine HCl (66) (Exp1)

Title compound was prepared according to **General Procedure B1**, starting from **65** to give a yellow solid (98%). ^{1}H NMR (400 MHz, DMSO) δ = 8.65 (s, br, 3H), 7.95 (d, *J* = 8.3 Hz, 2H), 7.62 (d, *J* = 8.3 Hz, 2H), 7.37 (d, *J* = 0.9 Hz, 1H), 4.05 (q, *J* = 5.6 Hz, 2H), 2.43 (d, *J* = 0.7 Hz, 3H) ppm. ^{13}C NMR (101 MHz, DMSO) δ = 165.7, 153.0, 136.0, 132.8, 129.8, 126.0, 115.1, 66.3, 16.7 ppm; LC-MS: *m/z* = 205.1 $[M + H]^+$.

4-Ethyl-1,3-thiazol-2-amine (67) (Exp2)

Title compound was prepared according to **General Procedure D1**, starting from 1-bromo-2-butanone and thiourea to give a gummy liquid (82%) which was used in next step without purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.06 (s, 1H), 5.10 (br, 2H), 2.55 (q, J = 7.6 Hz, 2H), 1.22 (t, J = 7.4 Hz, 3H) ppm; LC-MS: m/z = 129.0 $[M + H]^+$.

2-Bromo-4-ethyl-1,3-thiazole (68) (Exp2)

Title compound was prepared according to **General Procedure E1**, starting from **67** to give a brown gummy liquid (40%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.82 (s, 1H), 2.77 (q, J = 7.2 Hz, 2H), 1.26 (t, J = 7.4 Hz, 3H) ppm; LC-MS: m/z = 192 $[M]^+$, 194 $[M + 2]^+$.

4-(4-Ethyl-1,3-thiazol-2-yl)benzonitrile (69) (Exp2)

Title compound was prepared according to **General Procedure A2**, starting from **68** and (4-cyanophenyl)boronic acid to give a pale yellow solid (51%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (d, J = 8.4 Hz, 2H), 7.70 (d, J = 8.4 Hz, 2H), 6.99 (s, 1H), 2.90-2.82 (m, 2H), 1.34 (t, J = 7.60 Hz, 3H) ppm; LC-MS: m/z = 215.0 $[M + H]^+$.

(4-(4-Ethylthiazol-2-yl)phenyl)methanamine (70) (Exp2)

Title compound was prepared according to **General Procedure B2**, starting from **69** to give a pale yellow solid (86%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 7.9 Hz, 2H), 6.85 (s, 1H), 3.90 (s, 2H), 2.85 (q, J = 7.4 Hz, 2H), 1.33 (t, J = 7.4 Hz, 3H) ppm; LC-MS: m/z = 219.0 $[M + H]^+$.

Dimethyl 1*H*-pyrazole-3,5-dicarboxylate (71) (Exp2)

To a stirred solution of 1*H*-pyrazole-3,5-dicarboxylic acid (3.5 g, 22.43 mmol) in EtOH (84 mL), was added $SOCl_2$ (14 mL) at 0 ^{o}C. The reaction mixture was stirred at room temperature for 18 h. Upon completion, the reaction was concentrated *in vacuo* to afford title compound (3.5 g, 85%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (s, 1H), 3.95 (s, 6H) ppm; LCMS m/z = 185.0 $[M + H]^+$.

Dimethyl 1-methyl-1*H*-pyrazole-3,5-dicarboxylate (72) (Exp2)

To a stirred solution of **71** (3.5 g, 19.02 mmol) and K_2CO_3 (3.94 g, 28.53 mmol) in acetone (100 mL) at room temperature, dimethyl suphate (2 mL, 20.92 mmol) was added . The reaction mixture was stirred at 40 ^{o}C for 3 h. After completion the reaction mixture was filtered and filtrate was concentrated *in vacuo* to afford title compound (3.5 g, 93%)

as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (s, 1H), 4.24 (s, 3H), 3.92 (s, 3H), 3.89 (s, 3H) ppm; LCMS *m/z* = 199 $[M + H]^+$.

5-(Methoxycarbonyl)-1-methyl-1*H*-pyrazole-3-carboxylic acid (73) (Exp2)

To a stirred solution of **72** (4 g, 20.20 mmol) in 1,4-dioxane (16 mL) and water (40 mL), concentrated H_2SO_4 (0.43 ml, 8.081 mmol) was added dropwise. The reaction mixture was refluxed for 24 h. Upon completion, the reaction mixture was concentrated *in vacuo* to afford a gummy liquid which was dissolved in $CHCl_3$ and filtered. Filtrate was concentrated to afford title compound (1.2 g, 32%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (s, 1H), 4.27 (s, 3H), 3.91 (s, 3H) ppm; LCMS *m/z* = 185.0 $[M + H]^+$.

Methyl-3-carbamoyl-1-methyl-1*H*-pyrazole-5-carboxylate (74) (Exp2)

A mixture of **73** (1.2 g, 4.22 mmol) and $SOCl_2$ (10 mL) was stirred at 80 ^{o}C for 2 h. The reaction mixture was concentrated, diluted with toluene (10 mL) and ammonia gas was passed into the reaction mixture at 0 °C for 2 h. After completion the reaction mixture was quenched by the addition of cold water and extracted with 10% MeOH in DCM, dried over anhydrous Na_2SO_4, concentrated to give title compound (0.92 g, 77%) as an off-

white solid which was used in next step without purification. ^{1}H NMR (400 MHz, DMSO d_6): δ = 7.68 (s, 1H), 7.38 (s, 1H), 7.18 (s, 1H), 4.12 (s, 3H), 3.85 (s, 3H) ppm; LC-MS: *m/z* = 184 $[M + H]^+$

Methyl-3-cyano-1-methyl-1*H*-pyrazole-5-carboxylate (75) (Exp2)

To a stirred solution of **74** (0.90 g, 4.89 mmol) in DCM (15 mL) was added DIPEA (2.3 mL, 13.21 mmol) at 0 ^{o}C. A solution of trifluroacetic anhydride (0.78 mL, 5.63 mmol) in DCM (5 mL) was then added at 0 ^{o}C. The reaction mixture was stirred at 0 ^{o}C for 2 h then diluted with DCM. Organic layer was washed with saturated $NaHCO_3$ solution, 5% citric acid solution and brine, dried over Na_2SO_4 and concentrated *in vacuo* to afford a gummy liquid which was purified by column chromatography (10% EtOAc in hexane) to afford title compound (0.80 g, 99 %) as off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.61 (s, 1H), 4.17 (s, 3H), 3.87 (s, 3H) ppm; LC-MS: *m/z* = 166 $[M + H]^+$.

3-Cyano-1-methyl-1*H*-pyrazole-5-carboxylic acid (76) (Exp2)

Title compound was prepared according to **General Procedure F1**, starting from **75** to give an off-white solid (37%). ^{1}H NMR (400 MHz, DMSOd_6): δ = 14.02 (br s, 1H), 7.52 (s, 1H), 4.16 (s, 3H) ppm; LC-MS: *m/z* = 149.9 [M - H]$^+$.

Methyl 4-fluoro-1-methyl-1*H*-pyrazole-5-carboxylate (77) (Exp1)

To a solution of methyl 1-methyl-1*H*-pyrazole-5-carboxylate (0.5 g) in ACN (7 mL) and acetic acid (1.0 mL) was added Selectfluor (1.37 g). The mixture was heated at 100 °C under microwave irradiation for 120 min. Selectfluor (1.37 g) was added to the mixture and heated at 100 °C under microwave irradiation for 60 min. The solvent was removed in *vacuo* (**water bath was kept at room temperature to avoid loss of product under vacuum as product is very volatile**) and the residue was partitioned between DCM (15 ml) and water (25 ml). The aqueous layer was further extracted with DCM (2 x 10 ml) and the combined organic layers concentrated in *vacuo* (**water bath was kept at room temperature to avoid loss of product under vacuum as product is very volatile**). The crude product was purified by flash chromatography column on silica gel, eluting with a gradient of 0-15% EtOAc/petroleum benzine to give the title compound as a white solid (0.17 g, 31%). ^{1}H

NMR (400 MHz, $CDCl_3$) δ = 7.36 (d, *J* = 4.4 Hz, 1H), 4.13 (d, *J* = 1.0 Hz, 3H), 3.95 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ = -161.3 (s) ppm; LC-MS: Rt 2.89 min, does not ionize.

1-Methyl-4-fluoro-1*H*-pyrazole-5-carboxylic acid (78) (Exp1)

Title compound was prepared according to **General Procedure F2**, starting from **77** to give a white solid (95% yield). ^1H NMR (400 MHz, MeOD) δ 7.40 (d, *J* = 4.2 Hz, 1H), 4.06 (d, *J* = 0.7 Hz, 3H); LC-MS Rt 1.17 min, does not ionize.

1-Methyl-*N*-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-1*H*-pyrazole-5-carboxamide (79) (Exp1)

Title compound was prepared according to **General Procedure G1**, starting from (4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanamine and 1-methyl-1*H*-pyrazole-5-carboxylic acid to give a white solid (74%). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.77 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 2.1 Hz, 1H), 7.29 (t, *J* = 8.1 Hz, 2H), 6.59 (s, br, 1H), 6.50 (d, *J* = 2.1 Hz, 1H), 4.56 (d, *J* = 5.8 Hz, 2H), 4.15 (s, 3H), 1.32 (s, 12H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.2, 159.9, 140.9, 137.6, 135.3, 135.1, 127.1, 106.4, 83.9, 43.6, 39.3, 24.9 ppm; LC-MS: *m/z* = 341.9 $[M + H]^+$.

2-(4-Bromophenyl)ethanethioamide (80) (Exp2)

To a stirred solution of 2-(4-bromophenyl)acetonitrile (0.5 g, 2.55 mmol) in pyridine (7 mL) was added Et_3N (7 mL). Reaction mixture was cooled to 0 °C and H_2S gas was passed through for 10 min. The reaction mixture was stirred at 50 °C for 16 h, then cooled to room temperature and diluted with EtOAc (20 mL). Organic layer was washed with 1N HCl solution, water, brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Crude product was purified by column chromatography (5% EtOAc in hexane) to afford title compound (0.55 g, 94%) as an off white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.50 (br s, 1H), 9.38 (br s, 1H), 7.50 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 8.2 Hz, 2H), 3.78 (s, 2H) ppm; LC-MS: *m/z* = 308 $[M+H]^+$, 310 $[M+H]^+$.

2-(4-Bromobenzyl)-4-methylthiazole (81) (Exp2)

Title compound was prepared according to **General Procedure D1**, starting from **80** and chloroacetone to give a gummy liquid (64%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43 (d, J = 8.1 Hz, 2H), 7.17 (d, J = 8.0 Hz, 2H), 6.73 (s, 1H), 4.22 (s, 2H), 2.41 (s, 3H) ppm; LC-MS: *m/z* = 268 $[M]^+$, 270 $[M + 2]^+$.

4-((4-Methylthiazol-2-yl)methyl)benzonitrile (82) (Exp2)

Title compound was prepared according to **General Procedure C**, starting from **81** to give a yellow solid (92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (d, J = 8.1 Hz, 2H), 7.43 (d, J = 8.0 Hz, 2H), 6.80 (s, 1H), 4.36 (s, 2H), 2.45 (s, 3H) ppm; LC-MS: m/z = 215 $[M + H]^+$.

2-(4-Bromophenyl)-4-(trifluoromethyl)-1,3-thiazole (83) (Exp2)

Title compound was prepared according to **General Procedure D2**, starting from 4-bromo-thiobenzamide and 3-bromo-1,1,1-trifluoro-propan-2-one to give an off-white solid (52 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 (d, J = 8.3 Hz, 2H), 7.74 (s, 1H), 7.59 (d, J = 8.2 Hz, 2H) ppm; LC-MS: m/z = 308 $[M]^+$, 310 $[M+H]^+$.

4-(4-(Trifluoromethyl)thiazol-2-yl)benzonitrile (84) (Exp2)

Title compound was prepared according to **General Procedure C**, starting from **83** to give a yellow solid (0.4 g, 98 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (d, J = 8.3 Hz, 2H), 7.84 (s, 1H), 7.76 (d, J = 8.3 Hz, 2H) ppm; LC-MS: m/z = 255.2 $[M + H]^+$.

2-Bromo-1,3-thiazole-4-carboxylic acid (85) (Exp2)

Title compound was prepared according to **General Procedure F1**, starting from 2-bromo-1,3-thiazole-4-carboxylic acid ethyl ester to give a white solid (91%). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.31 (s, 1H), 8.46 (s, 1H) ppm; LC-MS: *m/z* = 207.9 $[M + H]^+$, 209.9 $[M+ H]^+$.

2-Bromo-*N*-methoxy-*N*-methyl-1,3-thiazole-4-carboxamide (86) (Exp2)

Title compound was prepared according to **General Procedure G2**, starting from **85** and *N,O*-dimethylhydroxylamine HCl to give a brown gum (66%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (s, 1H), 3.77 (s, 3H), 3.40 (s, 3H) ppm; LC-MS: *m/z* = 251.1 $[M + H]^+$, 253.1 $[M + H]^+$.

1-(2-Bromo-1,3-thiazol-4-yl)ethan-1-one (87) (Exp2)

To a stirred solution of **86** (6 g, 23.9 mmol) in THF (25 mL) was added CH_3MgBr (8 mL, 3M in THF) dropwise at 0 °C. Reaction mixture was stirred at 0 °C for 1 h. After completion of reaction, reaction mixture was quenched by the addition of saturated NH_4Cl

solution. Aqueous layer was extracted with EtOAc (3 x 20 mL) and combined organic layer was washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Crude product was purified by column chromatography (5% EtOAc in hexane) to afford title compound (0.6 g, 12%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (s, 1H), 2.64 (s, 3H) ppm; LC-MS: *m/z* = 206.2 $[M + H]^+$, 208.2 $[M + H]^+$.

2-Bromo-4-(1,1-difluoroethyl)-1,3-thiazole (88) (Exp2)

To a solution of **87** (600 mg, 2.91 mmol) in DCE (7 mL) was added DAST (3.8 mL, 29.13 mmol). The mixture was taken in a sealed tube and heated at 80 °C for 48 h. Upon completion, reaction mixture was cooled room temperature and quenched with solid Na_2CO_3, followed by ice water. Aqueous layer was extracted with EtOAc (3 x 10 mL). Combined organic layer was washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Crude product was purified by column chromatography (5% EtOAc in hexane) to afford title compound (350 mg, 53%) as brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (s, 1H), 2.00 (t, *J* = 18.4 Hz, 3H) ppm; LC-MS: *m/z* = 228.2 $[M + H]^+$, 230.1 $[M + H]^+$.

4-(4-(1,1-Difluoroethyl)thiazol-2-yl)benzonitrile (89) (Exp2)

Title compound was prepared according to **General Procedure A3**, starting from **88** and (4-cyanophenyl)boronic acid to give a white solid (57%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (d, J = 8.2 Hz, 2H), 7.74 (d, J = 8.2 Hz, 2H), 7.65 (s, 1H), 2.08 (t, J = 18.4 Hz, 3H) ppm; LC-MS: m/z = 251.3 $[M + H]^+$.

(4-(4-(1,1-Difluoroethyl)thiazol-2-yl)phenyl)methanamine (90) (Exp2)

Title compound was prepared according to **General Procedure B2**, starting from **89** to give a white solid (89%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (d, J = 8.1 Hz, 2H), 7.51 (s, 1H), 7.39 (d, J = 8.0 Hz, 2H), 3.92 (s, 2H), 2.07 (t, J = 18.4 Hz, 3H) ppm; LC-MS: m/z = 255.3 $[M + H]^+$.

1-Ethyl-3-nitro-1*H*-pyrazole (91) (Exp2)

NaH (60% dispersion in mineral oil) (1.3 g, 34.07 mmol) was added portion wise to a solution of 3-nitro-1*H*-pyrazole (3.5 g, 30.97 mmol) in dry DMF (30 mL) under argon. Reaction mixture was stirred for 5 min and then ethyl iodide (2.9 mL, 37.16 mmol) was

added dropwise and stirred to 80 °C for 3 h. Upon completion, reaction mixture was cooled to room temperature and neutralized with saturated $NaHCO_3$ solution. Aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Crude product was purified by column chromatography (30% EtOAc in hexane) to afford title compound (3.25 g, 74%) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (d, J = 2.0 Hz, 1H), 6.88 (d, J = 7.3 Hz, 1H), 4.25 (q, J = 7.3 Hz, 2H), 1.55 (t, J = 7.3 Hz, 3H) ppm; LC-MS: *m/z* = 142.1 $[M + H]^+$.

1-Ethyl-1*H*-pyrazol-3-amine (92) (Exp2)

A stirred solution of **91** (2 g, 14.18 mmol) in MeOH (20 mL) was degassed under N_2 for 5 min. Then Pd/C (10%) (0.15 g) was added portion wise to the reaction mixture and stirred under H_2 balloon for 5 h. Upon completion, reaction mixture was filtered through a pad of celite and washed thoroughly with MeOH. Filtrate was concentrated *in vacuo* to afford title compound (1.4 g, 89%) as brown liquid. ^{1}H NMR (400 MHz, $CDCl_3$):

δ = 7.10 (d, J = 1.2 Hz, 1H), 5.49 (d, J = 1.4 Hz, 1H), 3.94 (q, J = 7.2 Hz, 2H), 3.58 (br, 2 H), 1.39 (t, J = 7.2 Hz, 3H) ppm; LC-MS: m/z = 112 $[M + H]^+$.

3-Bromo-1-ethyl-1*H*-pyrazole (93) (Exp2)

Title compound was prepared according to **General Procedure E2**, starting from **92** to give a brown liquid (25%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (d, J = 1.6 Hz, 1H), 6.23 (d, J = 1.6 Hz, 1H), 4.12 (q, J = 7.3 Hz, 2H), 1.47 (t, J = 7.2 Hz, 3H) ppm; LC-MS: m/z = 175.2 $[M + H]^+$, 177.2 $[M + H]^+$ (1:1 bromo pattern).

4-(1-Ethyl-1*H*-pyrazol-3-yl)benzonitrile (94) (Exp2)

Title compound was prepared according to **General Procedure A4**, starting from **93** and (4-cyanophenyl)boronic acid to give a yellow solid (36%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (d, J = 8.1 Hz, 2H), 7.65 (d, J = 8.1 Hz, 2H), 7.44 (d, J = 1.5 Hz, 1H), 6.58 (d, J = 1.5 Hz, 1H), 4.22 (q, J = 7.2 Hz, 2H), 1.54 (t, J = 7.4 Hz, 3H) ppm; LC-MS: m/z = 198.3 $[M + H]^+$.

4-(4-Ethyl-2*H*-1,2,3-triazol-2-yl)benzonitrile (95) (Exp2)

To a solution of trimethylsilyl azide (2 g, 17.40 mmol) in a 9:1 mixture of DMF:MeOH (20 mL) in a sealed tube was added CuI (0.17 g, 0.87 mmol). Butyne gas was purged through the reaction mixture for 15 min at 0 °C. The reaction mixture was then stirred at 70 °C for 6 h, then cooled to room temperature and diluted with EtOAc, washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford 4-ethyl-1*H*-1,2,3-triazole, which was then reacted with 4-fluorobenzonitrile (0.62 g, 5.15 mmol) in DMF (7 mL) and K_2CO_3 (1.42 g, 10.31 mmol) at 100 °C for 8 h. Upon completion, reaction mixture was diluted with EtOAc, washed with water, brine, dried (Na_2SO_4) and concentrated *in vacuo*. Crude product was purified by column chromatography (20% EtOAc in hexane) to afford title compound (0.6 g, 59%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (dd, J = 7.0, 1.7 Hz, 2H), 7.76-7.73 (m, 2H), 7.64 (s, 1H), 2.79 (q, J = 7.6 Hz, 2H), 1.32 (t, J = 7.6 Hz, 3H) ppm; LC-MS: *m/z* = 199.1 $[M + H]^+$.

5-(4-Bromophenyl)-3-ethyl-1*H*-1,2,4-triazole (96) (Exp2)

To a mixture of 4-bromobenzonitrile (1.1 g, 6.15 mmol) and propionamidine HCl (1.0 g, 9.23 mmol) in DMSO (10 mL) was added Cs_2CO_3 (6 g, 18.50 mmol), followed by CuBr (0.04 g, 0.308 mmol). The reaction mixture was stirred at 120 °C overnight then cooled to room temperature and diluted with EtOAc, washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Crude product was purified by column chromatography (50% EtOAc in hexane) to afford title compound (34%) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, *J* = 7.9 Hz, 2H), 7.56 (d, *J* = 7.1 Hz, 2H), 2.88 (q, *J* = 7.3 Hz, 2H), 1.40 (t, *J* = 7.5 Hz, 3H) ppm; LC-MS: *m/z* = 252.0 $[M + H]^+$, 254.0 $[M + H]^+$ (1:1 bromo pattern).

4-(3-Ethyl-1*H*-1,2,4-triazol-5-yl)benzonitrile (97) (Exp2)

Title compound was prepared according to **General Procedure C**, starting from **96** to give a white solid (76%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.60 (br s, 1H), 8.19 (d, *J* = 7.9 Hz, 2H), 7.71 (d, *J* = 7.8 Hz, 2H), 2.95-2.88 (m, 2H), 1.41 (t, *J* = 7.5 Hz, 3H) ppm; LC-MS: *m/z* = 199.1 $[M+H]^+$.

(4-(3-Ethyl-1*H*-1,2,4-triazol-5-yl)phenyl)methanamine (98) (Exp2)

Title compound was prepared according to **General Procedure B2**, starting from **97** to give a yellow gum (80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, *J* = 7.3 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 3.60 (t, *J* = 6.6 Hz, 2H), 2.87 (q, *J* = 7.6 Hz, 2H), 0.93 (t, *J* = 7.3 Hz, 3H) ppm; LC-MS: *m/z* = 203.1 $[M+H]^+$.

N-(4-Cyanobenzyl)-1-methyl-1H-pyrazole-5-carboxamide (99) (Exp2)

Title compound was prepared according to **General Procedure G2**, starting from 4-aminomethyl-benzonitrile and 1-methyl-1*H*-pyrazole-5-carboxylic acid to give a white solid (55%). ^{1}H NMR (400 MHz, DMSO-d_6): *δ* = 9.10 (t, *J* = 5.8 Hz, 1H), 7.81 (d, *J* = 7.7 Hz, 2H), 7.50-7.47 (m, 3H), 6.91 (s, 1H), 4.51 (d, *J* = 5.8 Hz, 2H), 4.04 (s, 3H). LC-MS: *m/z* = 241.1 $[M + H]^+$.

Ethyl 4-((1-methyl-1H-pyrazole-5-carboxamido)methyl)benzimidate HCl (100) (Exp2)

A stirred solution of **99** (0.35 g, 1.46 mmol) in EtOH (8.0 mL) was cooled to 0 °C and HCl gas was passed through over 45 min. Reaction mixture was stirred at room temperature for 30 min, then concentrated *in vacuo*. Crude product was washed with diethyl ether (2 x 20 mL) to afford title compound (0.22 g, 89%) as an off white solid. ^{1}H

NMR (400 MHz, DMSO-d_6): δ = 11.99 (br s, 1H), 11.4 (br s, 1H), 9.23 (t, J = 5.9 Hz, 1H), 8.07 (d, J = 8.1 Hz, 2H), 7.57 (d, J = 8.1 Hz, 2H), 7.47 (d, J = 1.2 Hz, 1H), 6.96 (d, J = 1.3 Hz, 1H), 4.62 (q, J = 6.9 Hz, 2H), 4.54 (d, J = 5.8 Hz, 2H), 4.04 (s, 3H), 1.47 (t, J = 6.8 Hz, 3H) ppm; LC-MS: *m/z* = 287.2 $[M + H]^+$.

***N*-(4-(*N'*-Hydroxycarbamimidoyl)benzyl)-1-methyl-1*H*-pyrazole-5-carboxamide (101) (Exp2)**

Title compound was prepared according to **General Procedure H**, starting from **99** to give a white solid (47%) which was taken for next step without purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.58 (s, 1H), 9.02 (t, J = 6.0 Hz, 1H), 7.63 (d, J = 8.2 Hz, 2H), 7.46 (d, J = 1.9 Hz, 1H), 7.29 (d, J = 8.2 Hz, 2H), 6.90 (d, J = 1.9 Hz, 1H), 5.78 (s, 2H), 4.44 (d, J = 6.0 Hz, 2H), 4.06 (s, 3H) ppm; LC-MS: *m/z* = 274.1 $[M + H]^+$.

4-(((*tert*-Butoxycarbonyl)amino)methyl)benzoic acid (102) (Exp2)

Title compound was prepared according to **General Procedure I1**, starting from 4-aminomethyl-benzoic acid to give a white solid (1.8 g, 39%). ^{1}H NMR (400 MHz, DMSO-

d_6): δ 12.78 (br s, 1H), 7.89 (d, *J* = 7.8 Hz, 2H), 7.47 (t, *J* = 5.4 Hz, 1H), 7.33 (d, *J* = 7.7 Hz, 2H), 4.18 (d, *J* = 5.4 Hz, 2H), 1.39 (s, 9H) ppm; LC-MS: *m/z* = 252 $[M + H]^+$.

N-Hydroxypropionimidamide (103) (Exp2)

Title compound was prepared according to **General Procedure H**, starting from propionitrile to give a pale yellow liquid (87%). ^{1}H NMR (400 MHz, DMSO-d_6): *δ* = 8.72 (s, 1H), 5.28 (s, 2H), 1.99-1.93 (m, 2H), 1.01 (t, *J* = 7.4 Hz, 3H) ppm; LCMS: *m/z* = 89 $[M + H]^+$.

(2-Fluoro-4-(4-methylthiazol-2-yl)phenyl)methanamine HCl (104) (Exp2)

General procedure A3 was followed, starting from 2-bromo-4-methylthiazole and (4-cyano-3-fluorophenyl)boronic acid to give 2-fluoro-4-(4-methyl-1,3-thiazol-2-yl)benzonitrile**,** which was subjected to **General procedure B3** to give the title compound as white solid (80%)

^{1}H NMR (400 MHz, $CDCl_3$): *δ* = 8.55 (br, 3H), 7.83-7.77 (m, 2H), 7.73-7.69 (m, 1H), 7.43 (s, 1H), 4.11-4.07 (m, 2H), 2.40 (s, 3H) ppm; LCMS *m/z* = 223.1 $[M + H]^+$.

5-(4-Methylthiazol-2-yl)picolinonitrile (105) (Exp2)

Title compound was prepared according to **General Procedure A5**, starting from 5-bromopicolinonitrile to give title compound as a white solid (88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.22 (d, *J* = 1.8 Hz, 1H), 8.35 (dd, *J* = 8.1, 2.0 Hz, 1H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.07 (s, 1H), 2.54 (s, 3H) ppm; LC-MS: *m/z* = 202.3 $[M + H]^+$.

(3-Fluoro-4-(4-methylthiazol-2-yl)phenyl)methanamine (106) (Exp2)

To a stirring solution of 3-fluoro-4-iodo-benzonitrile (2.5 g, 10.12 mmol) in a mixture of THF (20 mL) and diethyl ether (20 mL), iPrMgCl (6 mL, 2M in diethyl ether) was added dropwise at -78 °C under N_2. The mixture was stirred at -78 °C for another 1.5 h before triisopropyl borate (3.74 mL, 16.19 mmol) was added dropwise. The mixture was then stirred at -78 °C for 15 min then allowed to warm to room temperature. After 3 h at room temperature, 2M HCl was added and reaction mixture was stirred at room temperature for 20 min. Reaction mixture was diluted with water, extracted with EtOAc, combined organic layer washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated to afford the 4-(dihydroxyboranyl)-3-fluorobenzonitrile, which was directly subjected to a

Suzuki coupling reaction according to **General procedure A3** to give 3-fluoro-4-(4-methylthiazol-2-yl)benzonitrile, which was then subjected to **General procedure B2** to give the title compound as a colourless oil (32%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.11 (t, *J* = 7.9 Hz, 1H), 7.42 (s, 1H), 7.39-7.36 (m, 1H), 7.29 (d, *J* = 7.9 Hz, 1H), 3.77 (s, 2H), 2.45 (s, 3H) ppm; LC-MS: *m/z* = 223.0 $[M + H]^+$.

6-(4-Methylthiazol-2-yl)nicotinonitrile (107) (Exp2)

A mixture of 5-bromopicolinonitrile (50 mg, 0.27 mmol), $(NH_4)_2S$ (0.02 mL, 0.3 mmol) and Et_3N (0.04 mL, 0.3 mmol) in pyridine (1 mL) was stirred at 50 °C for 4 h. Upon completion, the reaction mixture was cooled and extracted with EtOAc (3 x 10 mL). Combined organic layer was washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give 5-bromopyridine-2-carbothioamide, which was directly subjected to cyclization according to **General procedure D1** to give 2-(5-bromopyridin-2-yl)-4-methylthiazole, which was then subjected to **General procedure C** to give title compound as a brown solid (54%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.83 (s, 1H), 8.27

(d, J = 8.2 Hz, 1H), 8.03 (dd, J = 8.3, 1.7 Hz, 1H), 7.12 (s, 1H), 2.53 (s, 3H) ppm; LC-MS: m/z = 202.2 $[M + H]^+$.

_N_-(4-Cyanobenzyl)-4-fluoro-1-methyl-1_H_-pyrazole-5-carboxamide (108) (Exp2)

Title compound was prepared according to **General Procedure G2**, starting from 4-(aminomethyl)benzonitrile and 4-fluoro-1-methyl-1_H_-pyrazole-5-carboxylic acid to give a colorless liquid (97%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (d, J = 8.2 Hz, 2H), 7.43 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 4.9 Hz, 1H), 4.66 (d, J = 6.0 Hz, 2H), 4.14 (s, 3H) ppm; LC-MS: m/z = 259.2 $[M + H]^+$.

4-Fluoro-_N_-(4-(_N_′-hydroxycarbamimidoyl)benzyl)-1-methyl-1_H_-pyrazole-5-carboxamide (109) (Exp2)

Title compound was prepared according to **General Procedure H**, starting from **108** to give a yellow gum (69%). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.59 (s, 1H), 8.74 (br s, 1H), 7.64-7.58 (m, 3H), 7.30 (d, J = 7.9 Hz, 2H), 5.78 (s, 2H), 4.46 (d, J = 5.7 Hz, 2H), 3.94 (s, 3H) ppm; LC-MS: m/z = 292.2 $[M + H]^+$.

tert-Butyl (4-cyano-2-fluorobenzyl)carbamate (110) (Exp2)

General procedure L was followed, starting from 3-fluoro-4-methylbenzonitrile to afford 4-(bromomethyl)-3-fluorobenzonitrile as a colorless oil, which was then converted to the desired benzylamine according to **General procedure M**. The resulting benzylamine was subsequently protected according to **General procedure I2** to give an off-white solid (45%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50-7.40 (m, 2 H), 7.35-7.30 (m, 1 H), 5.00 (s, 1 H), 4.39 (s, 2 H), 1.45 (s, 9 H) ppm; LCMS: *m/z* = 195.2 $[M-56 + H]^+$.

tert-Butyl (4-(5-ethyl-1,2,4-oxadiazol-3-yl)-2-fluorobenzyl)carbamate (111) (Exp2)

General procedure H was followed, starting from **110** to give the desired amidoxime, which was then subjected to **General procedure J1** with propionic acid to give the title compound as a white solid (53%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, *J* = 7.3 Hz, 1 H), 7.75 (d, *J* = 10.2 Hz, 1 H), 7.44 (br s, 1 H), 4.93 (s, 1 H), 4.40 (s, 2 H), 2.96 (q, *J* = 6.7 Hz, 2 H), 1.46-1.44 (m, 12 H) ppm; LCMS: *m/z* = 322.4 $[M + H]^+$.

tert-Butyl (4-cyano-3-fluorobenzyl)carbamate (112) (Exp2)

Gerneal procedure L was followed, starting from 2-fluoro-4-methylbenzonitrile to afford 4-(bromomethyl)-2-fluorobenzonitrile as a colorless oil, which was then converted to the desired benzylamine according to **General procedure M**. The resulting benzylamine was subsequently protected according to **General procedure I2** to give an off-white solid (68%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (t, *J* = 6.8 Hz, 1 H), 7.17-7.12 (m, 2 H), 4.98 (br s, 1 H), 4.35 (d, *J* = 4.8 Hz, 2 H), 1.45 (s, 9 H) ppm; LCMS: *m/z* = 251.4 $[M + H]^+$.

***tert*-Butyl (4-(5-ethyl-1,2,4-oxadiazol-3-yl)-3-fluorobenzyl)carbamate (113) (Exp2)**

General procedure H was followed, starting from **112** to give the desired amidoxime, which was then subjected to **General procedure J1** with propionic acid to give the title compound as a white solid (21%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (t, *J* = 7.6 Hz, 1 H), 7.18-7.13 (m, 2 H), 4.95 (br, 1 H), 4.36 (d, *J* = 5.3 Hz, 2 H), 2.98 (q, *J* = 7.6 Hz, 2 H), 1.48 (t, *J* = 7.7 Hz, 3 H), 1.38 (s, 9 H) ppm; LCMS: *m/z* = 321.9 $[M + H]^+$.

Interference Compounds. All final compounds have been examined for the presence of substructures classified as Pan Assay Interference Compounds (PAINS) using a KNIME workflow.[28,29]

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website. Initial SAR from mining the HTS deck (PDF). SMILES molecular formula strings (CSV)

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ABBREVIATIONS USED

ACN, acetonitrile; DCM, dichloromethane; HTS, high throughput screen; LHS, left hand side; RHS, right hand side.

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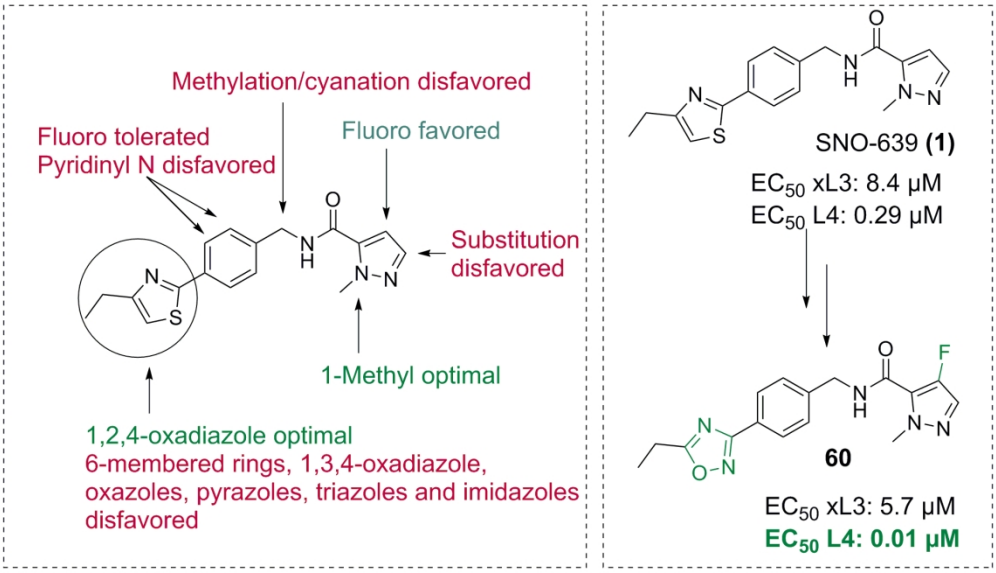

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