Journal of Medicinal Chemistry

Article

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J. Med. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.jmedchem.8b01789 • Publication Date (Web): 20 Dec 2018

ACS Publications

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Structure-activity relationship studies of tolfenpyrad reveal sub-nanomolar inhibitors of *Haemonchus contortus* development

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ABSTRACT

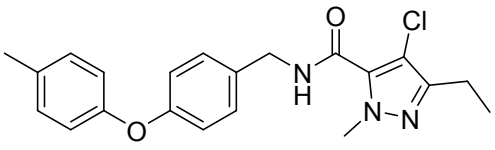
Recently, we discovered that the registered pesticide, tolfenpyrad (TFP), unexpectedly and potently inhibits the development of L4 larval stages of the parasitic nematode *Haemonchus contortus* with an IC_{50} value of 0.03 μM while displaying good selectivity, with an IC_{50} of 37.9 μM for cytotoxicity. As a promising molecular template for medicinal chemistry optimization, we undertook anthelmintic structure-activity relationships (SAR) for this chemical. Modifications of the left hand side (LHS), right hand side (RHS), and middle section of the scaffold were explored to produce a set of 57 analogues. Analogues **25**, **29** and **33** were shown to be the most potent compounds of the series, with IC_{50} values at a sub-nanomolar levels of potency against the chemotherapeutically-relevant fourth larval (L4) stages of *H. contortus*. Selected compounds from the series also showed promising activity against a panel of other different parasitic nematodes such as hookworms and whipworms.

INTRODUCTION

Parasitic worms, particularly gastrointestinal roundworms (nematodes), are major pathogens of livestock animals and cause diseases that, through productivity losses, adversely impact the agricultural, meat and dairy industries.[1,2] The control of these worms relies heavily on the use of anthelmintic chemotherapy. However, the effectiveness of many anthelmintics around the world has significantly decreased due to widespread drug resistance in such worms resulting from the excessive and uncontrolled use of these drugs.[3–6] Therefore, the discovery of new anthelmintics with novel modes of action and that are active against drug-resistant parasites is in high demand.[7]

Recently, we identified tolfenpyrad (TFP, **Figure 1**) to be potently inhibitory of the motility and development of parasitic larvae of *Haemonchus contortus*[8,9], a parasitic nematode of major economic importance in ruminants. TFP is a registered pesticide used in many countries to control arthropod pests on infested crops.[10] Along with the closely related tebufenpyrad, it belongs to the pyrazole-5-carboxamide class of complex I inhibitors, which interrupt electron transport through inhibiting NADH:ubiquinone oxoreductase.[11] Despite being reported in 1996,[12] published SAR interrogation of

tolfenpyrad is relatively limited, even though marked insecticidal, fungicidal or miticidal activities have been observed for this chemical.[12–15] Furthermore, nothing is known about its SAR against parasitic nematodes. Herein, by utilising a well-established but proprietary and sophisticated phenotypic drug screening platform for *H. contortus*,[16,17] we report, for the first time, comprehensive SAR of TFP for inhibition of L3 motility and L4 development of *H. contortus* larvae and reveal novel modifications that reach sub-nM levels of L4 larval development inhibition.



Tolfenpyrad (TFP)
IC_{50} xL3: 2.9 μM
IC_{50} L4: 0.03 μM
MCF10A cytotoxicity: 37.9 μM
clogP: 4.6

Figure 1 Structure, activity and cLogP of the tolfenpyrad hit.

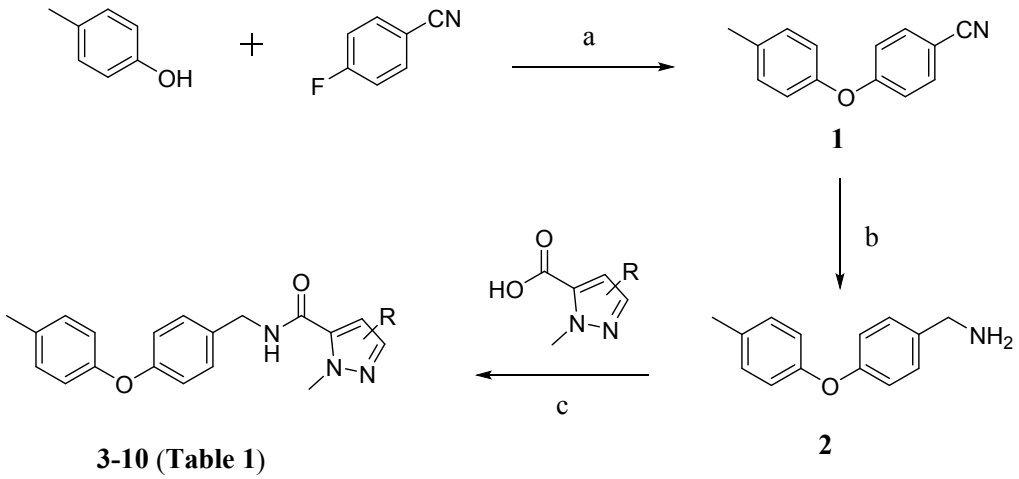
It can be seen that TFP harbours a large, hydrophobic, electron-rich *p*-methylphenoxybenzyloxy group. From a medicinal chemistry perspective, this chemical property of TFP would be considered to be sub-optimal for a drug candidate that is

proposed to be administered, for example, orally to a vertebrate animal affected by worms, as opposed to the application (as pesticide) to the surface of arthropod-affected plants. Therefore, the predominant focus of this study was to explore TFP SAR with a view to maintaining or even increasing potency of TFP, while moving the scaffold into a more drug-like physicochemical 'space' that might impart improved solubility and metabolic stability properties.

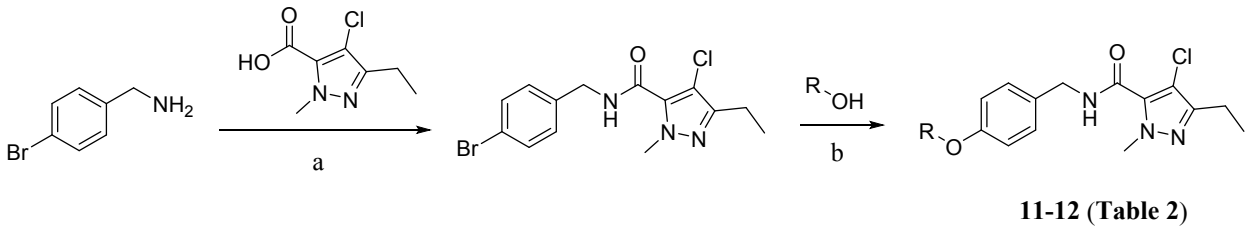
RESULTS AND DISCUSSION

The structure of the TFP scaffold can usefully be considered as divided into two main components, namely the pyrazole-5-carboxamide and the *p*-methylphenoxybenzyloxy parts. For late-stage derivatization of the RHS pyrazole, the *p*-methylphenoxybenzyloxy group was obtained *via* a nucleophilic aromatic substitution reaction of *p*-cresol and 4-fluorobenzonitrile, followed by a reduction of the nitrile group, to yield the benzyl amine, which was then reacted with the pyrazole-5-carboxylic acid *via* an amide coupling reaction (Scheme 1). Likewise, in some cases the LHS derivatisation process could be performed in reverse order, so that the RHS pyrazole was to be installed

first to form a 4-halobenzylamide intermediate, which was then subjected to an Ullmann-type coupling with a phenoxy species (**Scheme 2**). The CuI/*N,N*-dimethylglycine was an efficient catalytic system for the Ullmann-type coupling, as reported by Ma *et al.*[18]



Scheme 1 Synthetic pathway of the tolfenpyrad scaffold, a) K_2CO_3, DMF; b) $LiAlH_4$, THF; c) HOAt, EDCI.HCl, ACN, or HATU, DIPEA, DMF or T3P®, DIPEA, THF.



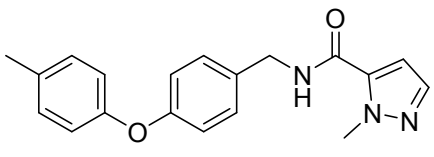
Scheme 2 A synthetic pathway used for LHS derivatisation, a) HOAt, EDCI.HCl, ACN, or HATU, DIPEA, DMF or T3P®, DIPEA, THF, b) CuI, Cs_2CO_3, *N,N*-dimethylglycine, 1,4-dioxane.

To examine SAR, compounds were first subjected to a primary screen to assess their ability to inhibit the motility of *H. contortus* at the exsheathed L3 (xL3) stage, using

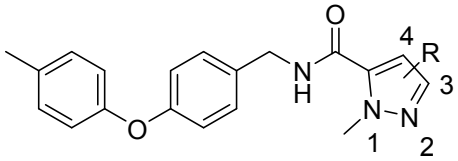
monepantel and moxidectin as positive control anthelmintics. Only compounds that resulted in ≥ 70% motility inhibition of xL3 larvae at a concentration of 100 μM were subjected to subsequent dose-response evaluation, to establish IC_{50} values, and then further assessed in the *H. contortus* L4 development assay. The first aim of the study was to explore the chemical space on the RHS pyrazole of TFP, and simultaneously to reduce the overall hydrophobicity by removing some or all of the substituents on the pyrazole, and to introduce functional groups with differing steric and electronic effects. The results of this exploration are summarized in **Table 1**. Loss of both the 3-Et and 4-Cl on the pyrazole ring (**3**) led to a moderate decrease in inhibitory potency of xL3 motility and a slight reduction in L4 development compared to TFP. A similar but diminished loss of activity was observed when the 3-Et group was maintained but the 4-Cl removed, to give **4**, which still exhibited relatively potent L4 larval development inhibition (IC_{50} 0.057 μM). Hence, comparing **3** with **4** suggests some hydrophobicity on the 3-position is favorable. Implementing nitrile or trifluoromethyl groups at the 3- or 4-position led to either a complete or substantial loss of activity, as seen for compounds **5-8**. Interestingly, by keeping the 4-Cl group in place and removing the ethyl group on the pyrazole to give **9**,

we observed a 10-fold improvement in the inhibition of L4 development compared with TFP, furnishing a single-digit nM IC_{50} value of 3 nM. A 3-fold improvement of potency to inhibit L4 development was also observed in the case of **10** compared to TFP, where the 4-Cl was replaced with 4-F. The results exhibited by **9** and **10** were encouraging, as both the aims of increasing potency and partially reducing hydrophobicity were attained. From our recent SAR study on a broadly related 1-methyl-1*H*-pyrazole-5-carboxamide derived from a different screening campaign against *H. contortus*, we discovered that other 5- or 6-membered rings such as furan, thiophene, substituted phenyl ring or pyridinyl moiety were all disfavored on the RHS of the scaffold and therefore are not explored in this study.[19]

Table 1 SAR of the RHS pyrazole.



3



4-10

Entry	R	IC_{50} (μM) ± SD in xL3 motility assay	IC_{50} (μM) ± SD in L4 development assay
3	-	16.3 ± 6.66	0.13 ± 0.10

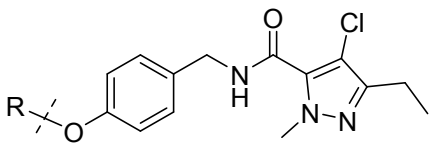
4	3-Et	10.53 ± 3.44	0.057 ± 0.002
5	3-CN	>100	
6	3-CF_3	>100	
7	4-CN	50 ± 0.001	1.69 ± 0.67
8	4-CF_3	>100	
9[a]	4-Cl	2.97 ± 2.56	0.003 ± 0.004
10[a]	4-F	4.37 ± 2.55	0.01 ± 0.007
TFP		2.9 ± 0.58	0.03 ± 0.005
Monepantel		0.16 ± 0.008	0.075 ± 0.04
Moxidectin		0.08 ± 0.04	3.45 ± 0.75

[a]cLogP: **9**: 3.9; **10**: 3.7

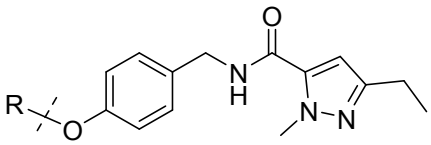
The next aim was to explore SAR on the LHS of TFP, again with a focus on not only improving potency but also enhancing physicochemical properties (**Table 2**). In order to increase hydrophilicity within the LHS region of TFP, the phenyl ring was replaced by the pyridine moiety, as demonstrated by **11**, **12** and **13**. Gratifyingly, of these three pyridinyl compounds, while **11** completely lost activity, **12** and **13** maintained potent

inhibitory activity against L4 development with respective IC_{50} values of 0.03 and 0.019 μM, and a small loss of activity against xL3 motility.

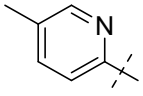
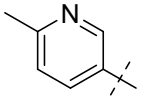
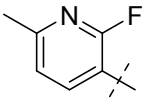
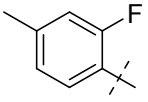
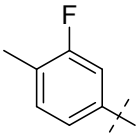
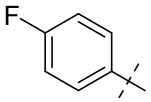
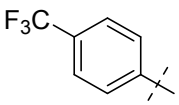
Table 2 SAR of the LHS region.

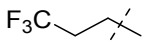
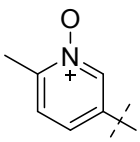
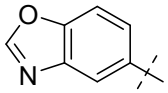
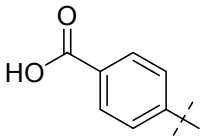
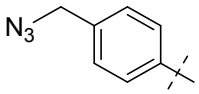
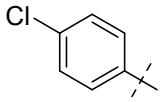


11-22



23

Entry	R	IC_{50} (μM) ± SD in xL3 motility assay	IC_{50} (μM) ± SD in L4 development assay
11		>100	
12		4.0 ± 1.84	0.03 ± 0.01
13		8.67 ± 4.55	0.019 ± 0.011
14		5.2 ± 3.02	0.14 ± 0.05
15		13.33 ± 12.0	0.04 ± 0.005
16		8.43 ± 7.53	0.04 ± 0.01
17		>100	

18		>100	
19		35.07 ± 17.19	0.45 ± 0.04
20		5.30 ± 3.0	0.34 ± 0.32
21		>100	
22		50 ± 0	0.16 ± 0.11
23		2.43 ± 1.42	0.08 ± 0.006
TFP		2.9 ± 0.58	0.03 ± 0.005
Monepantel		0.16 ± 0.008	0.075 ± 0.04
Moxidectin		0.08 ± 0.04	3.45 ± 0.75

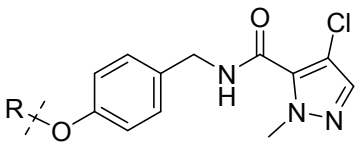
The roles of fluorine in medicinal chemistry are well established, in terms of enhancement of metabolic stability, potency and permeability.[20–22] Therefore, in addition to inclusion of a fluorine substituent in pyridinyl compound **13**, a "fluorine walk" was undertaken for TFP itself, as testified by compounds **14-16**. Here, it can be seen the L3 activity was slightly weaker compared with TFP but potent inhibitory activity on L4

development was maintained, in particular for **15** and **16**, for which the IC_{50} value of both was 0.04 μM. When the trifluoromethyl group was investigated, both the aromatic ring (**17**) and aliphatic chain (**18)** variants caused a complete loss of inhibitory activity. Heterocyclic *N*-oxides have been successfully used as therapeutic agents.[23–25] For this reason, we synthesized and tested analogue **19**, which harbours a pyridine *N*-oxide group. However, a substantial loss of activity against *H. contortus* was observed in relation to both xL3 motility and L4 development. Benzoxazole species, such as **20**, did not improve the original potency for either xL3 motility or L4 development, while carboxylic acid **21**, a reported metabolite of TFP,[10] was not tolerated. Activity was maintained in both xL3 and L4 when the *p*-methyl group was replaced with a *p*-chloro, as seen for **23**, which exhibited a potent L4 development IC_{50} value of 0.08 μM. Compound **22** was synthesized as part of the SAR assessment and also for its potential to serve as a probe for target identification due to the azide-functional group. Click chemistry in activity-based protein profiling for target identification has been extensively reported in the literature.[26–28] Although the azide-tagged analogue **22** resulted in a dramatic motility reduction in xL3, it

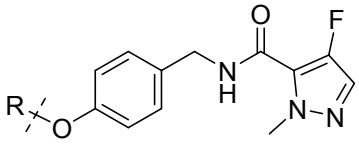
still displayed a binding affinity to inhibit L4 development, which suggests that azide-tagged TFP might find utility for future target identification studies.

From the SAR investigation on the RHS of TFP, we identified that the RHS of compounds **9** and **10**, and the LHS of **12** and **23** were optimal for the compounds tested. Having successfully identified these groups, the focus then was on incorporating them to develop a new set of analogues to probe the next generation of SAR, whose results are summarized in **Table 3**. For LHS with the pyridinyl moiety, compound **24**, with the 4-chloro pyrazole RHS, displayed similar activity in both xL3 and L4 compared to **12**, whereas **28**, with the 4-fluoro pyrazole RHS, caused a moderate loss in activity. Excitingly, compounds **25** and **29** showed a substantial improvement in activity, reducing the IC_{50} value for xL3 motility and L4 development inhibition to sub μM and sub nM ranges, respectively. Furthermore, we also extended the SAR scope for the LHS by testing the pyrimidine (**26** and **30**) and 2-chloro pyridinyl (**27** and **31**) species. However, **26** and **30** caused a complete loss in activity, whereas no significant improvement in activity was observed for **27** and **31**. The loss in activity caused by **26** and **30** suggested a specific binding interaction exerted by the LHS region.

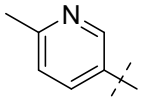
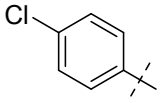
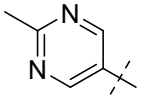
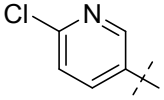
Table 3 Next generation SAR on the LHS and RHS regions of TFP.



24-27



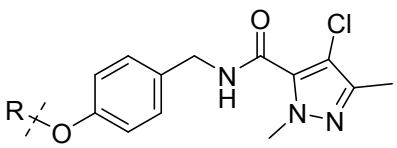
28-31

R	Entry	IC_{50} (μM) ± SD in xL3 motility assay	IC_{50} (μM) ± SD in L4 development assay	Entry	IC_{50} (μM) ± SD in xL3 motility assay	IC_{50} (μM) ± SD in L4 development assay
	**24**	3.70 ± 1.84	0.04 ± 0.03	**28**	14.47 ± 7.45	0.19 ± 0.15
	**25**	0.38 ± 0.10	0.0007 ± 0.0001	**29**	0.70 ± 0.24	0.0008 ± 0.0001
	**26**	>100		**30**	>100	
	**27**	2.80 ± 2.26	0.02 ± 0.01	**31**	14.8 ± 9.6	0.17 ± 0.09
TFP		2.9 ± 0.58	0.03 ± 0.005			
Monepantel		0.16 ± 0.008	0.075 ± 0.04			
Moxidectin		0.08 ± 0.04	3.45 ± 0.75			

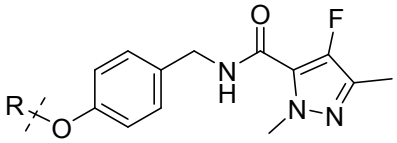
From **Table 3**, the LHS groups that resulted in active compounds were selected for the development of a similar set of analogues, but with the 3-methyl-4-chloro and 3-

methyl-4-fluoro pyrazole RHS, as a complement to the 4-chloro and 4-fluoro pyrazole RHS set (results summarized in **Table 4**). We included a 3-methyl group based on evidence already discussed for **Table 1** that suggested some hydrophobicity at this position might be favourable. Overall, similar activities against *H. contortus* xL3 motility and L4 development were observed within the two sets of analogues. In particular, compounds **32**, **35** and **37** maintained the activity originally observed for TFP. Compounds **33, 34** and **36** achieved an IC_{50} value in the sub-nM range for L4 development inhibition.

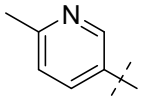
Table 4 Next generation SAR with 3-methyl-4-chloropyrazole and 3-methyl-4-fluoropyrazole RHS.

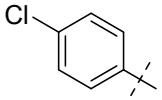
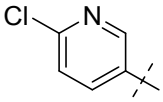


32-34



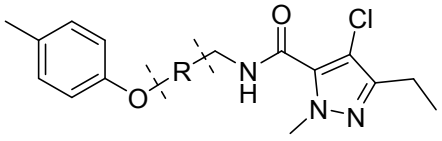
35-37

R	Entry	IC_{50} (μM) ± SD in xL3 motility assay	IC_{50} (μM) ± SD in L4 development assay	Entry	IC_{50} (μM) ± SD in xL3 motility assay	IC_{50} (μM) ± SD in L4 development assay
	**32**	3.33 ± 1.89	0.01 ± 0.01	**35**	7.73 ± 4.41	0.05 ± 0.03

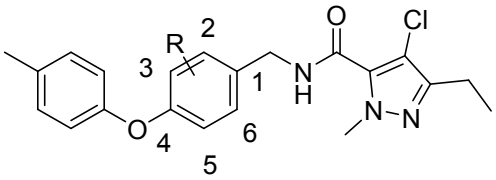
	**33**	2.03 ± 1.82	0.0008 ± 0.0001	**36**	2.63 ± 1.60	0.004 ± 0.004
	**34**	1.8 ± 0.49	0.008 ± 0.009	**37**	2.56 ± 1.74	0.03 ± 0.02
TFP		2.9 ± 0.58	0.03 ± 0.005			
Monepantel		0.16 ± 0.008	0.075 ± 0.04			
Moxidectin		0.08 ± 0.04	3.45 ± 0.75			

These encouraging results for the LHS and RHS of TFP paved the way to explore SAR on the middle ring by testing the fluoro substituent and the pyridinyl moiety. The results are summarized in **Table 5**. At the 2-position, the pyridinyl group in compounds **38** produced a complete loss of activity, whereas the fluoro substituent in **39** maintained the level of potency observed for TFP against both xL3 motility and L4 development. Similar results were observed for the 3-position (**40** and **41**).

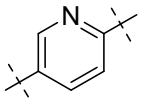
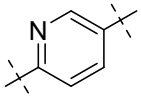
Table 5 SAR on the middle region of TFP.



38, 40



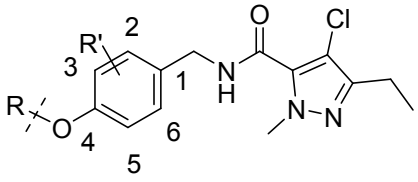
39, 41

Entry	R	IC_{50} (μM) ± SD in xL3 motility assay	IC_{50} (μM) ± SD in L4 development assay
38		>100	
39	2-F	1.87 ± 1.27	0.08 ± 0.03
40		>100	
41	3-F	2.73 ± 1.59	0.06 ± 0.03
TFP		2.9 ± 0.58	0.03 ± 0.005
Monepantel		0.16 ± 0.008	0.075 ± 0.04
Moxidectin		0.08 ± 0.04	3.45 ± 0.75

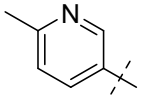
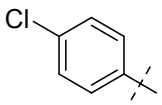
From these results, it was decided to incorporate the fluoro-substituted prototype, with the two previously identified optimal LHS and the original RHS of TFP being kept constant. This evaluation resulted in a set of analogues summarized in **Table 6**. When fluorine substitution was explored at the 2-position, a 10-fold improvement in the inhibition

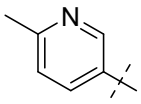
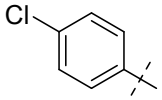
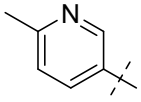
of L4 development was achieved for compound **42** compared to TFP, while **43** displayed the original L4 development activity. The originally observed levels of activity against xL3 by TFP was maintained for both **42** and **43**. There was no significant improvement in the original activity against both xL3 and L4 when the same LHS groups were experimented upon with fluorine substitution at the 3-position of the middle ring, as seen for **44** and **45**. Interestingly, a complete loss of activity against *H. contortus* was observed for compound **46** when an additional fluorine was implemented at the 5-position of the middle ring. These findings indicated a very tight SAR for this region.

Table 6 Next generation SAR on the LHS and middle region of TFP.



42-46

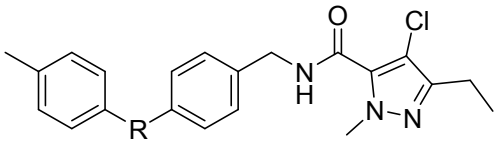
Entry	R	R'	IC_{50} (μM) ± SD in xL3 motility assay	IC_{50} (μM) ± SD in L4 development assay
42		2-F	1.8 ± 1.57	0.003 ± 0.004
43		2-F	2.07 ± 0.40	0.04 ± 0.01

44		3-F	9.47 ± 4.29	0.03 ±0.02
45		3-F	2.67 ± 0.79	0.035 ± 0.005
46		3,5-*di*F	>100	
	TFP		2.9 ± 0.58	0.03 ± 0.005
	Monepantel		0.16 ± 0.008	0.075 ± 0.04
	Moxidectin		0.08 ± 0.04	3.45 ± 0.75

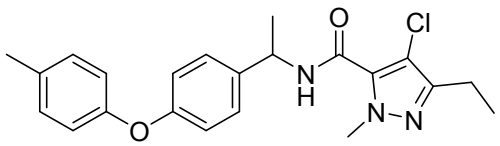
Alterations to the ether bridge and the benzylic carbon of TFP were also assessed. Different functional groups were used to replace the oxygen from the ether bridge, such as a methylene group (compound **47**), a carbonyl group (**48**), a sulfur (**49**) or a methylated amine (**50**) (**Table 7**). However, none of these replacement groups yielded active compounds. A similar result was achieved when the benzylic carbon was methylated to produce **51**. Interestingly, when incorporating the methylene prototype into one of the four most active RHS pyrazoles to produce **52-55** (**Table 8**), activity was regained, but with no significant improvement with respect to TFP. From these results, the same RHS pyrazoles and the methylene bridge were then experimented upon with the active

pyridinyl LHS, with the hope of achieving some improvement in activity. However, the original potency could not be maintained (**56-59**, **Table 8**).

Table 7 SAR on various linking regions of the TFP scaffold.



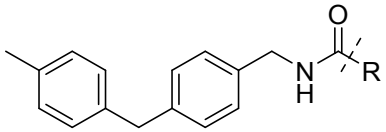
47-50



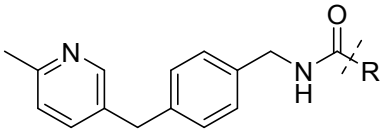
51

Entry	R	IC_{50} (μM) ± SD in xL3 motility assay
47	CH_2	>100
48	CO	>100
49	S	>100
50	N-Me	>100
51	-	>100

Table 8 Next generation SAR when incorporating the methylene bridge into the TFP scaffold.

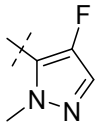
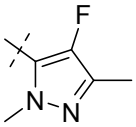
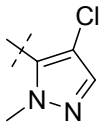
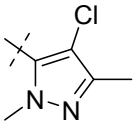


52-55



56-59

Entry	IC_{50} (μM) ± SD in xL3	IC_{50} (μM) ± SD in L4	Entry	IC_{50} (μM) ± SD in xL3	IC_{50} (μM) ± SD in L4	R

	motility assay	development assay		motility assay	development assay	
52	3.5 ± 1.5	0.19 ± 0.15	**56**	>100		
53	3.0 ± 0	0.07 ± 0.06	**57**	49.5 ± 0.5	0.97 ± 0.46	
54	3.15 ± 2.35	0.04 ± 0.01	**58**	5.2 ± 1.2	0.23 ± 0.12	
55	3.07 ± 2.07	0.04 ± 0.02	**59**	7.2 ± 0.2	0.19 ± 0.08	
	TFP			2.9 ± 0.58	0.03 ± 0.005	
	Monepantel			0.16 ± 0.008	0.075 ± 0.04	
	Moxidectin			0.08 ± 0.04	3.45 ± 0.75	

Having successfully identified compounds with significant improvement in activity compared to **TFP**, we selected 9 compounds with high potency in inhibiting L4 development to test for their cytotoxicity on the MCF10A cell line, and the results are summarized in **Table 9**. We were delighted to observe high selectivity for the 9 compounds tested, particularly for compounds **27-29** and **31-34**. Despite the low cytotoxic

IC_{50} value of 8.02 μM for one of our most potent compounds **25**, it was still a great level of selectivity when compared to the activity for L4 development of 0.7 nM. It was also encouraging to see our other most potent compounds **29** and **33** were not cytotoxic. These results reinforced the potential of the TFP scaffold to be a novel scaffold with anthelmintic activity.

Table 9 Cytotoxicity data for selected active compounds on the MCF10A cell line.

Entry	IC_{50} (μM) ± SD in xL3 motility assay	IC_{50} (μM) ± SD in L4 development assay	MCF10A Cytotoxicity IC_{50} (μM) ± SEM
TFP	2.57 ± 0.58	0.025 ± 0.005	37.90 ± 3.11
10	4.37 ± 2.55	0.01 ± 0.007	13.13 ± 0.38
23	2.43 ± 1.42	0.08 ± 0.006	8.8 ± 0.34
25	0.38 ± 0.10	0.0007 ± 0	8.02 ± 0.48
27	2.80 ± 2.26	0.02 ± 0.01	> 50
28	14.47 ± 7.45	0.19 ± 0.15	> 50
29	0.70 ± 0.24	0.0008 ± 0.0001	> 50
31	14.8 ± 9.6	0.17 ± 0.09	> 50
32	3.33 ± 1.89	0.01 ± 0.01	> 50
33	2.03 ± 1.82	0.0008 ± 0.0001	> 50

34	1.8 ± 0.49	0.008 ± 0.009	> 50

To construct a biological activity profile for TFP and its scaffold, we selected 7 compounds, including TFP as a control, to test for activity on three other parasitic nematodes at various concentrations (**Table 10**). The panel included *Ancylostoma ceylanicum* (hookworm), *Heligosomoides polygyrus* (rodent nematode) and *T. muris* (whipworm). It can be seen that all seven compounds displayed 100% inhibition and > 70% inhibition of L3 of *A. ceylanicum* at 100 μM and 10 μM, respectively. Similar results were seen for adult *H. polygyrus*, where all compounds, except **33**, showed complete inhibition at 100 μM and > 70% inhibition at only 1 μM. All compounds exhibited > 90% inhibition of first larval (L1) stage of *T. muris* at 100 μM. There was an obvious improvement in the inhibition of *H. polygyrus* L3 for the 6 newly developed compounds compared with TFP.

Table 10 Biological activity profile of selected compounds against a panel of parasitic nematodes.

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
TFP	100	73.4	32.4	100	94.85	100
10	100	85.9	91.8	100	100	91.97
23	100	100	89.2	100	98.8	100
27	100	100	100	100	73.15	100
29	100	90.6	93.7	100	98.8	93.45
33	96.5	96.9	66.9	100	81.6	100
34	100	100	99.2	100	85.4	100

In relations to the SAR for the previously reported pesticidal activity by Okada *et al.*[12,29], while compounds **17**, **48** and **49** were inactive against *H. contortus* in this study, they displayed high potency against *Nephotettix cincticeps* (for **17**) and both *Myzus persicae* and *Plutella xylostella* (for **48** and **49**). Likewise, compound **4** with moderate activity against *H. contortus* was not potent against *Myzus persicae*.[14,29] These results indicated a non-parallel SAR, in terms of inhibitory activity observed for *H. contortus* in this study and the arthropod species studied by Okada *et al.*[14,29]

In order to assess the drug-likeliness of the TFP scaffold, we subjected TFP and 9 other representative analogues (**Table 11**) to different experiments, which determined key physicochemical and metabolic parameters. The results showed that all of our key

compounds had reduced hydrophobicity compared with TFP, including key high potency compounds such as **34**, which with a cLogP of 3.0 was 40 times less lipophilic than TFP (cLogP 4.6). This change, in turn, led to an improvement in aqueous solubility at pH 6.5 for all compounds, with some, such as **28**, being around 20-fold more soluble. At pH 2.0, solubility was also improved for most compounds, except **23**, **29** and **33**. Concomitant with decreased lipophilicity and improved solubility, all selected compounds displayed a longer microsomal half-life than that observed for TFP, ranging from 20 for **10** to 84 minutes for **27**.

Table 11 Key physicochemical parameters and *in vitro* metabolic stability of selected compounds.

ID	cLogP[a]	Sol[b] (μg/mL)		$T_{1/2}$ (min)	$CL_{int,\ in\ vitro}$[c] (μL/min/mg protein)	microsome-predicted E_H[d]
		pH 2.0	pH 6.5			
TFP	4.6	3.1-6.3	< 1.6	14	121	N/A
10	3.3	25-50	6.3-2.5	20	87	0.65
23	4.1	1.6-3.1	1.6-3.1	36	48	0.51
27	2.8	6.3-12.5	6.3-12.5	84	21	0.31
28	1.7	> 100	25-50	25	69	0.60
29	3.4	3.1-6.3	1.6-3.1	57	30	0.39
31	2.4	9-18	9-18	80	22	0.32

32	2.3	> 100	12.5-25	31	55	0.54
33	4.0	1.6-3.1	3.1-6.3	80	22	0.32
34	3.0	4.9-9.8	2.4-4.9	55	31	0.40

[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

We have discovered that TFP potently inhibits the development of L4 stage larvae of the ovine parasitic nematode, *H. contortus*. Herein, we report a systematic SAR interrogation that has led to the identification of novel modifications that not only improve drug-like physicochemical properties, such as lipophilicity, aqueous solubility and microsomal degradation half-life, but that are exquisitely potent. For example, **25**, **29** and **33** achieved a remarkable improvement in inhibitory activity against both xL3 motility and L4 development, reducing the original and already impressive IC_{50} values of TFP down to the sub-μM or sub-nM ranges, at the same time, maintaining selectivity towards the parasite. TFP, as a pesticide, was reported to be a complex I inhibitor that disrupts the respiratory electron transport chain in mitochondria.[11,30] However, the specific biological

target(s) of this series of compounds in nematodes is/are unknown. With a moderately potent inhibitory affinity observed against L4 development, compound **22** might represent a potential tool for target identification. Having established a comprehensive antiparasitic SAR herein, we are now embarking on pathway identification and further downstream efficacy assessment and hope to report on these efforts in due course.

EXPERIMENTAL SECTION

The nematode assays and cytotoxicity assay is as described by Le *et al.*[19]

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: cLogP: Partition coefficients, reflecting the lipophilic character of the neutral structure.

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 analyzed via Nephelometry to determine a solubility range. See Bevan *et al.*[31]

In vitro Metabolic Stability

The procedure is as described by Le *et al.*[19]

CHEMISTRY EXPERIMENTAL

All solvents and reagents were used directly from commercial suppliers unless otherwise stated. All of the final compounds had purities greater than 95% based on analytical HPLC, ^{1}H NMR and LC-MS. General chemistry experimental conditions were as reported by Le *et al.*[19]

General procedure A1: Nucleophilic aromatic substitution reactions

To a stirred solution of arylfluoride (1.0 eq), and nucleophile (1.1 eq) in DMF (20 mL), was added Cs_2CO_3 (2.0 eq) and the mixture was stirred at 100 °C for 2 h. Upon completion, reaction mixture was diluted with EtOAc (50 mL) and organic layer was

washed with water, brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Crude product was purified by column chromatography (5-20% EtOAc/petroleum benzine) to yield desired product.

General procedure A2: Nucleophilic aromatic substitution reactions

To a stirred solution of arylfluoride (1.0 eq) and nucleophile (1.0 eq) in DMF (20 mL), K_2CO_3 (2.0 eq) was added. The reaction mixture was then stirred at 100 °C overnight. Upon completion, the reaction mixture was extracted with EtOAc, washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Crude product was purified by column chromatography (5-20% EtOAc/petroleum benzine) to yield desired product.

General procedure B1: Nitrile reduction

$LiAlH_4$ (3.0 eq) was slowly added to a solution of substituted benzonitrile (1.0 eq) in anhydrous THF (10 mL). The reaction was left stirred at room temperature for 2 h then cooled on ice before a solution of 1M NaOH was added. The slurry mixture was then filtered through a pad of celite and filtrate was extracted with EtOAc (3 x 30 mL). Combined organic layers was dried ($MgSO_4$) and concentrated *in vacuo*. 4M HCl in 1,4-

dioxane (15 mL) was added to the residue then the reaction mixture was left stirred at room temperature overnight. Precipitate of the resulting HCl salt was then filtered, washed with diethyl ether and dried in a vacuum oven to yield desired product as an HCl salt.

General procedure B2: Nitrile reduction

A stirred solution of substituted benzonitrile (2.39 mmol) in THF (10 mL) was cooled to 0 °C and $LiAlH_4$ solution (2.4 mL, 2M in THF) was added dropwise under N_2. Reaction mixture was stirred at room temperature for 3 h. and then quenched with saturated Na_2SO_4 solution dropwise. The slurry mixture was filtered through a pad of celite and washed thoroughly with EtOAc. The filtrate was washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to yield the desired benzylamine, which was taken to the next step without any purification.

General procedure B3: Nitrile reduction

To a stirred solution of substituted benzonitrile (1.06 mmol) in MeOH (10 mL) was added Raney Ni (1.16 mmol), followed by NH_3 (1 mL, 7.0M in MeOH). The reaction mixture was stirred at room temperature for 3 h. Upon completion, the reaction mixture

was filtered through a pad of celite and filtrate was concentrated *in vacuo* to yield the desired benzylamine, which was taken directly to the next step without further purification.

General procedure B4: Nitrile reduction

Substituted benzonitrile (1.0 eq), di-*tert*-butyl dicarbonate (1.5 eq), and $NiCl_2.6H_2O$ (0.2 eq) were dissolved in anhydrous MeOH in an oven-dried flask under N_2. The mixture was cooled to 0 °C before $NaBH_4$ (7.0 eq) was added in small portions over 20 min. The reaction mixture was left stirred at room temperature for 2 h. Diethylenetriamine (1.0 eq) was then added and the reaction mixture was left stirred for another 15 min before MeOH was removed *in vacuo*. Saturated solution of $NaHCO_3$ was added to the residue and extracted with EtOAc (3 x 20 mL). Combined organic layers were washed with water, brine, dried ($MgSO_4$) and solvent was removed *in vacuo* to afford the desired Boc-protected benzylamine, which was then stirred in 4M solution of HCl in 1,4-dioxane at 60 °C for 2 h to yield the corresponding HCl salt upon filtration of precipitate.

General procedure B5: Nitrile reduction

Di-*tert*-butyl dicarbonate (2.0 eq) and $NiCl_2{\cdot}6H_2O$ (0.2 eq) was added to a stirred solution of substituted benzonitrile (1.0 eq) in MeOH (7 mL) at 0 °C. $NaBH_4$ (7.0 eq) was

then added to the reaction mixture in small portions over 30 minutes. The reaction mixture was stirred at room temperature for 1 h before it was filtered through a pad of celite. The filtrate was diluted with EtOAc, washed with saturated $NaHCO_3$ solution, brine, dried over Na_2SO_4 and concentrated *in vacuo* to yield crude product without further purification.

General procedure C1: 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 before EtOAc was added. The organic layer was washed with water, dried ($MgSO_4$) and solvent was removed *in vacuo* to give crude product, which was purified by column chromatography (5-10% EtOAc/Petroleum benzine) to yield desired product.

General procedure C2: Amide coupling

T_3P® (2.0 eq, 50% in EtOAc) and DIPEA (3.0 eq) were added to a stirred solution of carboxylic acid (1.0 eq) and amine (1.0 eq) in THF (5 mL). The reaction mixture was stirred at room temperature for 6 h before EtOAc was added. The organic layer was

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 C3: Amide coupling

HATU (0.97 mmol) and DIPEA (1.28 mmol) were added to a stirred solution of carboxylic acid (0.54 mmol) in DMF (5.0 mL). The solution was stirred for 5 min before amine (0.71 mmol) was added and the reaction was stirred at room temperature for 16 h. Upon 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 (5-20% EtOAc/petroleum benzine) to yield desired product.

General procedure C4: Amide coupling

EDCI.HCl (1.2 eq.) and HOAt (1.2 eq.) were added to a solution of carboxylic acid (1 eq.) in ACN (0.8 M) at room temperature. The reaction mixture was heated to 50 ^oC before amine (1.2 eq.) was added after 10 minutes. The reaction was stirred at this temperature overnight before it was cooled to room temperature and concentrated *in vacuo*. The residue was extracted with EtOAc (2 x 10 mL), washed with water. 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 C5: Amide coupling

To a stirred solution of carboxylic acid (1.0 eq) in pyridine (5 mL), T_3P® (50% in EtOAc, 7.0 eq) was added and the reaction mixture was stirred for 5 minutes before amine (free base or HCl salt, 1.0 eq) was added. The reaction mixture was stirred at room temperature for 16 h. Upon completion, reaction mixture was diluted with EtOAc. Organic layer was washed with saturated $NaHCO_3$ solution, brine, dried over anhydrous Na_2SO_4 and solvent was concentrated *in vacuo*. Crude product was purified by column chromatography (5-20% EtOAc/petroleum benzine) to yield desired product.

General procedure C6: Amide coupling

Carboxylic acid (14.58 mmol), amine HCl (16.04 mmol), EDCI.HCl (16.04 mmol) and Et_3N (32.08 mmol) were dissolved in DCM. The reaction mixture was left stirred at room temperature overnight. Upon completion, DCM was removed *in vacuo* and the

residue was extracted with EtOAc, washed with water, brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford crude product, which was purified by column chromatography to yield the desired product.

General procedure D1: Ester hydrolysis

$LiOH.H_2O$ (2.0 eq) was added to a stirred solution of ester (1.0 eq) in a 3:1 mixture of THF:H_2O. The reaction mixture was stirred at room temperature for 3 h before THF was removed *in vacuo*. Aqueous layer was then 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 D2: Ester hydrolysis

NaOH (23.75 mmol) was added to a solution of ester (1.04 mmol) in EtOH (10 ml). The mixture was stirred at room temperature overnight before solvent was removed in *vacuo*. The residue 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 D3: Ester hydrolysis

LiOH (5.0 eq) was added to a solution of ester (1.0 eq) in THF (10 mL). The reaction was stirred at room temperature overnight before THF was removed *in vacuo*. Water (20 mL) was then added to the residue, followed by 1M HCl to pH~1. The aqueous was extracted with EtOAc (2 x 10 mL). Combined organic layers was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the desired carboxylic acid without further purification.

General procedure E1: Ullmann-type coupling

In a microwave tube charged with a magnetic stirrer bar, arylhalide (1.0 eq), substituted phenol (1.5 eq), CuI (0.1 eq), Cs_2CO_3 (2.0 eq) and *N,N*-dimethylglycine (0.4 eq) were dissolved in 1,4-dioxane. The tube was sealed with a cap and placed in a microwave reactor heated at 110 °C for 2 h. Upon completion, the reaction mixture was diluted with EtOAc, washed with H_2O, brine, dried ($MgSO_4$) and solvent was removed *in vacuo* to afford crude product. Crude was purified by column chromatography (5-20% EtOAc/petroleum benzine) to yield the desired product.

General procedure E2: Ullmann-type coupling

Substituted thiophenol (4.03 mmol), K_2CO_3 (8.05 mmol) and arylhalide (6.04 mmol) were dissolved in toluene (5 mL) in a sealed tube. The mixture was degassed for 0.5 h before 1,10-phenanthroline (0.4 mmol) and CuI (0.4 mmol) were added. The reaction mixture was stirred at 130 °C for 2 h. Upon completion, the reaction mixture was filtered through a pad of celite. The filtrate was extracted with EtOAc (3 x 20 mL) and combined organic layers was washed with water, brine, dried ($MgSO_4$) and concentrated *in vacuo*. Crude product was purified by column chromatography (5-20% EtOAc/petroleum benzine) to yield desired product.

General procedure F: Primary amine synthesis from aldehyde

Substituted benzaldehyde (1.0 eq) was dissolved in EtOH (10 mL), $NH_2OH.HCl$ (1.2 eq) was then added and reaction mixture was stirred at room temperature for 1 h before 3 mL of concentrated HCl (37%) was added, followed by Zn dust (2.5 eq). The reaction was left stirred for another 15 min before basified with excess amount of aqueous NH_3 and 6M NaOH solution. The resulting slurry mixture was filtered through a pad of celite and diluted with EtOAc. The organic was washed with water, dried ($MgSO_4$) and

concentrated *in vacuo* to afford the desired benzylamine as a free base, which was carried through to the next step without any purification.

General procedure G1: Chan-Lam coupling

To a stirred solution of substituted phenol (3.01 mmol) in DCM (10 mL), aryl boronic acid (9.03 mmol) was added. Et_3N (6.02 mmol) and $Cu(OAc)_2$ (3.01 mmol) were then added and the reaction mixture was degassed for 5 min. The reaction mixture was stirred under O_2 balloon for 18 h. Upon completion, the reaction mixture was filtered and residue was diluted with DCM. Organic layer was washed with cold water, brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give desired product, which was used in the next step without any purificaiton.

General procedure G2: Chan-Lam coupling

To a stirred solution of substituted phenol (1.0 eq), aryl boronic acid (2.0 eq) and Et_3N (5.0 eq) in DCM (30 mL) was added $Cu(OAc)_2$ (1.0 eq), followed by 4 Å molecular sieves (0.5 g). The reaction mixture was then stirred under O_2 for 16 h. Upon completion, the reaction mixture was filtered through a pad of celite and the filtrate was washed with 10% aqueous $NaHSO_4$ solution and 1N NaOH solution. The organic layer was extracted

and dried over anhydrous Na_2SO_4, then concentrated *in vacuo* to give crude product, which was purified by column chromatography (5-20% EtOAc/petroleum benzine) to yield the desired product.

Gerneral procedure H1: Weinreb ketone synthesis

Weinreb amide (0.3 mmol) was dissolved in anhydrous THF (5 mL) in an oven-dried round bottom flask under N_2. The mixture was cooled in an ice bath to 0 °C before Grignard reagent (0.7 mmol) was added. The reaction mixture was left stirred at room temperature for 1h. Upon completion, THF was removed *in vacuo* and saturated NH_4Cl solution was added to the residue, which was then extracted with EtOAc (3 x 10 mL). Combined organic layers were washed with water, brine, dried ($MgSO_4$) and concentrated *in vacuo* to give crude product, which was purified by column chromatography (5-20% EtOAc/petroleum benzine) to yield the desired product.

General procedure H2: Weinreb ketone synthesis

Aryl halide (24.4 mmol) was dissolved in anhydrous THF (15 mL) in an oven-dried round bottom flask under N_2. The mixture was cooled to -78 °C before *n*BuLi (2.5 M in hexane, 24.4 mmol) was added dropwise and the mixture was left stirred for 30 min. A

solution of Weinreb amide (12.2 mmol) in THF (10 mL) was then added. The reaction mixture was left stirred at -78 °C for 45 min. Upon completion, water was added to quench the reaction, followed by extraction with EtOAc (3 x 20 mL). Combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give crude product, which was purified by column chromatography (5-20% EtOAc/petroleum benzine) to yield the desired product.

4-(*p*-Tolyloxy)benzonitrile (1)

Title compound was prepared according to **General Procedure A1**, starting from *p*-cresol and 4-fluorobenzonitrile to give a colorless oil (1.9 g, 37%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56 (d, J = 8.8 Hz, 2H), 7.19 (d, J = 8.3 Hz, 2H), 6.98-6.93 (m, 4H), 2.36 (s, 3H) ppm; LC-MS: m/z = 210.3 $[M + H]^+$.

(4-(*p*-Tolyloxy)phenyl)methanamine (2)

Title compound was prepared according to **General Procedure B2**, starting from **1** to give a colorless oil (78%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23-7.26 (m, 2H), 7.1 (d, J = 8.1 Hz, 2H), 6.94 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 8.3 Hz, 2H), 3.83 (br, 2H), 2.32 (s, 3H) ppm. LC-MS: m/z = 214.3 $[M + H]^+$.

1-Methyl-*N*-(4-(p-tolyloxy)benzyl)-1*H*-pyrazole-5-carboxamide (3)

Title compound was prepared according to **General Procedure C1**, starting from **2** and 1-methyl-1*H*-pyrazole-5-carboxylic acid to give a brown oil (74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.31 (s, *J* = 1.8 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 2H), 7.05 (d, *J* = 8.5 Hz, 2H), 6.88 – 6.77 (m, 4H), 6.54 (s, br, 1H), 6.43 (d, *J* = 2.1 Hz, 1H), 4.43 (d, *J* = 5.7 Hz, 2H), 4.08 (s, 3H), 2.24 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 159.9, 157.6, 154.5, 137.6, 135.1, 133.2, 132.1, 130.3, 129.3, 119.2, 118.5, 106.4, 43.0, 39.3, 20.7 ppm; LC-MS: *m/z* = 321.9 $[M + H]^+$.

3-Ethyl-1-methyl-*N*-(4-(p-tolyloxy)benzyl)-1*H*-pyrazole-5-carboxamide (4)

Title compound was prepared according to **General Procedure C1**, starting from **2** and 3-ethyl-1-methyl-1*H*-pyrazole-5-carboxylic acid to give a colorless oil (21%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.20 – 7.00 (m, 4H), 6.93 – 6.77 (m, 4H), 6.32 (s, br, 1H), 6.21 (d, *J* = 7.0 Hz, 1H), 4.43 (d, *J* = 6.0 Hz, 2H), 4.03 (d, *J* = 7.1 Hz, 4H), 2.54 – 2.48 (m, 2H), 2.24 (d, *J* = 6.8 Hz, 3H), 1.13 (t, *J* = 7.6 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 160.0, 157.5, 154.5, 153.00, 135.6, 133.2, 132.1, 130.4, 129.3, 119.2, 118.6, 104.2, 43.0, 38.9, 21.2, 20.8, 13.9 ppm; LC-MS: *m/z* = 349.9.

3-Cyano-1-methyl-*N*-(4-(*p*-tolyloxy)benzyl)-1*H*-pyrazole-5-carboxamide (5)

Title compound was prepared according to **General Procedure C2**, starting from **2** and **65** to give an off-white solid (26%). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.25 (t, J = 5.8 Hz, 1H), 7.50 (s, 1H), 7.31 (d, J = 8.5 Hz, 2H), 7.18 (d, J = 8.2 Hz, 2H), 6.93 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 4.42 (d, J = 5.8 Hz, 2H), 4.15 (s , 3H), 2.28 (s , 3H) ppm; LC-MS: m/z = 347.1 $[M + H]^+$.

1-Methyl-*N*-(4-(*p*-tolyloxy)benzyl)-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxamide (6)

Title compound was prepared according to **General Procedure C3**, starting from **2** and 1-methyl-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxylic acid to give a yellow solid (60%). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.20 (t, J = 5.6 Hz, 1H), 7.35 (s, 1H), 7.31 (d, J = 8.5 Hz, 2H), 7.19 (d, J = 8.2 Hz, 2H), 6.93 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 8.3 Hz, 2H), 4.42 (d, J = 5.6 Hz, 2H), 4.14 (s, 3H), 2.27 (s, 3H); ppm; LC-MS: m/z = 390.1 $[M + H]^+$.

4-Cyano-1-methyl-*N*-(4-(*p*-tolyloxy)benzyl)-1*H*-pyrazole-5-carboxamide (7)

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 D1** to give the corresponding carboxylic acid that was subsequently coupled to **59** according to **General Procedure C2** to give title compound as an off white solid (68%). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.48 (br, 1H), 8.12 (s, 1H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.19 (d, *J* = 7.9 Hz, 2H), 6.95-6.89 (m, 4H), 4.47 (d, *J* = 5.4 Hz, 2H), 3.95 (s, 3H), 2.29 (s, 3H) ppm; LC-MS: *m/z* = 347.2 $[M + H]^+$.

1-Methyl-*N*-(4-(*p*-tolyloxy)benzyl)-4-(trifluoromethyl)-1*H*-pyrazole-5-carboxamide (8)

Title compound was prepared according to **General Procedure C3**, starting from **2** and 1-methyl-4-(trifluoromethyl)-1*H*-pyrazole-5-carboxylic acid to give a white solid (53%). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* = 7.65 (s, 1H), 7.26 (d, *J* = 8.4 Hz, 2H), 7.13 (d, *J* = 8.3 Hz, 2H), 6.95 (d, *J* = 8.5 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 6.41 (d, *J* = 5.6 Hz, 1H), 4.57 (d, *J* = 5.6 Hz, 2H), 4.09 (s, 3H), 2.32 (s, 3H) ppm; LC-MS: *m/z* = 390.1 $[M + H]^+$.

4-Chloro-1-methyl-*N*-(4-(p-tolyloxy)benzyl)-1*H*-pyrazole-5-carboxamide (9)

Title compound was prepared according to **General Procedure C1**, starting from (4-(4-chlorophenoxy)phenyl)methanamine HCl and 4-chloro-1-methyl-1*H*-pyrazole-5-carboxylic acid to give a white solid (19%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.43 (s, 1H), 7.31 – 7.27 (m, 2H), 7.14 (d, *J* = 8.2 Hz, 2H), 7.01 – 6.88 (m, 5H), 4.60 (d, *J* = 5.7 Hz, 2H), 4.19 (s, 3H), 2.33 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 158.3, 157.6, 154.5, 136.7, 133.3, 131.7, 131.0, 130.4, 129.2, 119.3, 118.6, 109.6, 43.1, 41.2, 20.8 ppm; LC-MS: *m/z* = 355.8 $[M + H]^+$.

4-Fluoro-1-methyl-N-(4-(p-tolyloxy)benzyl)-1H-pyrazole-5-carboxamide (10)

Title compound was prepared according to **General Procedure C4**, starting from **2** and **67** to give a white solid (62% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.36 (d, *J* = 4.5 Hz, 1H), 7.34 – 7.27 (m, 1H), 7.16 (d, *J* = 8.1 Hz, 2H), 7.03 – 6.90 (m, 4H), 6.51 (s, 1H), 4.60 (d, *J* = 5.7 Hz, 2H), 4.19 (d, *J* = 0.9 Hz, 3H), 2.36 (s, 3H) ppm; LC-MS *m/z* = 339.9 $[M + H]^+$.

4-Chloro-3-ethyl-1-methyl-*N*-(4-((5-methylpyridin-2-yl)oxy)benzyl)-1*H*-pyrazole-5-carboxamide (11)

General procedure C1 was followed, starting from 4-chloro-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxylic acid and (4-bromophenyl)methanamine HCl to give *N*-(4-bromobenzyl)-4-chloro-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxamide, which was subsequently coupled to 5-methylpyridin-2-ol according to **General Procedure E1** to give the title compound as a white solid (20% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.46 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 8.3 Hz, 2H), 7.27 (dd, *J* = 9.4, 2.4 Hz, 1H), 7.22 (s, br, 1H), 7.10 (s, 1H), 6.60 (d, *J* = 9.3 Hz, 1H), 4.67 (d, *J* = 5.8 Hz, 2H), 4.13 (s, 3H), 2.64 (q, *J* = 7.6 Hz, 2H), 2.10 (s, 3H), 1.24 (t, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 161.8, 158.7, 149.6, 142.8, 140.4, 138.0, 135.2, 131.0, 128.5, 127.0, 121.4, 115.2, 107.8, 42.9, 40.6, 19.2, 17.0, 12.8 ppm; LC-MS *m/z* = 384.8 $[M + H]^+$.

4-Chloro-3-ethyl-1-methyl-*N*-(4-((6-methylpyridin-3-yl)oxy)benzyl)-1*H*-pyrazole-5-carboxamide (12)

General procedure C1 was followed, starting from 4-chloro-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxylic acid and (4-bromophenyl)methanamine HCl to give *N*-(4-bromobenzyl)-4-chloro-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxamide, which was subsequently coupled to 6-methylpyridin-2-ol according to **General Procedure E1** to give

the title compound as a white solid (12% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.27 (d, *J* = 2.7 Hz, 1H), 7.32 (d, *J* = 8.7 Hz, 2H), 7.22 (dd, *J* = 8.5, 2.8 Hz, 1H), 7.12 (d, *J* = 8.5 Hz, 1H), 7.05 (s, br, 1H), 6.98 – 6.94 (m, 2H), 4.60 (d, *J* = 5.8 Hz, 2H), 4.13 (s, 3H), 2.62 (q, *J* = 7.6 Hz, 2H), 2.53 (s, 3H), 1.22 (t, *J* = 7.6 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 158.6, 156.7, 153.5, 151.4, 149.7, 140.8, 132.9, 131.0, 129.4, 126.9, 123.9, 118.7, 107.7, 42.9, 40.7, 23.6, 19.3, 12.9 ppm; LC-MS *m/z* = 384.8 $[M + H]^+$.

4-Chloro-3-ethyl-*N*-(4-((2-fluoro-6-methylpyridin-3-yl)oxy)benzyl)-1-methyl-1*H*-pyrazole-5-carboxamide (13)

General procedure A1 was followed, starting from 2-fluoro-6-methylpyridin-3-ol and 4-fluorobenzaldehyde to give 4-((2-fluoro-6-methylpyridin-3-yl)oxy)benzaldehyde, which was converted to the corresponding benzylamine according to **General procedure F**, then subsequently coupled to 4-chloro-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxylic acid according to **General procedure C1** to give the title compound as a brown solid (46% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.36 – 7.28 (m, 3H), 7.03 (s, br, 1H), 6.98 (d, *J* = 7.9 Hz, 1H), 6.95 – 6.90 (m, 2H), 4.59 (d, *J* = 5.8 Hz, 2H), 4.11 (s, 3H), 2.60 (q, *J* = 7.6 Hz, 2H), 2.46 (s, 3H), 1.21 (t, *J* = 7.6 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 158.6,

156.4, 155.7, 153.3, 151.6 (d, *J* = 12.5 Hz), 149.6, 136.3 (d, *J* = 26.5 Hz), 132.9, 131.4 (d, *J* = 3.7 Hz), 131.0, 129.3, 121.4 (d, *J* = 4.5 Hz), 117.6, 107.7, 42.9, 40.6, 23.2, 19.3, 12.8 ppm; LC-MS *m/z* = 402.8 $[M + H]^+$.

4-Chloro-3-ethyl-*N*-(4-(3-fluoro-4-methylphenoxy)benzyl)-1-methyl-1*H*-pyrazole-5-carboxamide (14)

Title compound was prepared according to **General Procedure C2**, starting from **68** and 4-chloro-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxylic acid to give an off white solid (25%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.92 (t, *J* = 5.6 Hz, 1H), 7.37 (d, *J* = 8.3 Hz, 2H), 7.27 (t, *J* = 8.5 Hz, 1H), 7.01 (d, *J* = 8.3 Hz, 2H), 6.82 (d, *J* = 10.9 Hz, 1H), 6.73 (d, *J* = 6.3 Hz, 1H), 4.46 (d, *J* = 5.6 Hz, 2H), 3.84 (s, 3H), 2.57-2.53 (m, 2H), 2.19 (s, 3H), 1.16 (t, *J* = 7.4 Hz, 3H) ppm; LC-MS: *m/z* = 402.1 $[M + H]^+$.

4-Chloro-3-ethyl-*N*-(4-(2-fluoro-4-methylphenoxy)benzyl)-1-methyl-1*H*-pyrazole-5-carboxamide (15)

Title compound was prepared according to **General Procedure C2**, starting from **69** and 4-chloro-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxylic acid to give a colourless gum (21%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.90 (t, *J* = 5.8 Hz, 1H), 7.32 (d, *J* = 8.5 Hz, 2H),

7.21 (d, *J* = 11.6 Hz, 1H), 7.09-7.02 (m, 2H), 6.91 (d, *J* = 8.4 Hz, 2H), 4.43 (d, *J* = 5.9 Hz, 2H), 3.83 (s, 3H), 2.57-2.53 (m, 2H), 2.32 (s, 3H), 1.16 (t, *J* = 7.5 Hz, 3H) ppm; LC-MS: *m/z* = 402.1 $[M + H]^+$.

4-Chloro-3-ethyl-*N*-(4-(4-fluorophenoxy)benzyl)-1-methyl-1*H*-pyrazole-5-carboxamide (16)

General procedure B2 was followed, starting from **70**, to give (4-(4-fluorophenoxy)phenyl)methanamine, which was subsequently coupled to 4-chloro-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxylic acid according to **General procedure C2** to give the title compound as a light yellow gum (37%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.91 (s, br,, 1H), 7.35 (d, *J* = 8.3 Hz, 2H), 7.22 (t, *J* = 8.8 Hz, 2H), 7.06-7.03 (m, 2H), 6.97 (d, *J* = 8.3 Hz, 2H), 4.45 (d, *J* = 5.8 Hz, 2H), 3.83 (s, 3H), 2.57-2.53 (m, 2H), 1.16 (t, *J* = 7.4 Hz, 3H) ppm; LC-MS: *m/z* = 388.1 $[M + H]^+$.

4-Chloro-3-ethyl-1-methyl-*N*-(4-(4-(trifluoromethyl)phenoxy)benzyl)-1*H*-pyrazole-5-carboxamide (17)

General procedure A2 was followed, starting from 4-(trifluoromethyl)phenol and 4-fluorobenzonitrile to give 4-(4-(trifluoromethyl)phenoxy)benzonitrile, which was then

reduced according to **General procedure B2** to give the corresponding benzylamine that was subsequently coupled to 4-chloro-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxylic acid according to **General procedure C3** to give the title compound as a white solid (19%). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.95 (t, J = 5.7 Hz, 1H), 7.73 (d, J = 8.5 Hz, 2H), 7.43 (d, J = 8.2 Hz, 2H), 7.12 (m, 4H), 4.49 (d, J = 5.7 Hz, 2H), 3.84, (s, 3H), 2.57-2.50 (m, 2H), 1.16 (t, J = 7.4 Hz, 3H), ppm; LC-MS: m/z = 438.2 $[M + H]^+$.

4-Chloro-3-ethyl-1-methyl-*N*-(4-(3,3,3-trifluoropropoxy)benzyl)-1*H*-pyrazole-5-carboxamide (18)

General procedure A2 was followed, starting from 3,3,3-trifluoropropan-1-ol and 4-fluorobenzonitrile to give 4-(3,3,3-trifluoropropoxy)benzonitrile, which was then reduced according to **General procedure B2** to give the corresponding benzylamine that was subsequently coupled to 4-chloro-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxylic acid according to **General procedure C3** to give the title compound as an off white solid (50 mg, 14%). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.86 (t, J = 5.7 Hz, 1H), 7.27 (d, J = 8.5 Hz, 2H), 6.93 (d, J = 8.6 Hz, 2H), 4.39 (d, J = 6.0 Hz, 2H), 4.18 (t, J = 5.9 Hz, 2H), 3.82

(s, 3H), 2.81-2.72 (m, 2H), 2.50-2.56 (m, 2H), 1.15 (t, *J* = 7.5 Hz, 3H) ppm; LC-MS: *m/z* = 390.1 $[M + H]^+$.

5-(4-((4-Chloro-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxamido)methyl)phenoxy)-2-methylpyridine 1-oxide (19)

Compound **12** (0.3 mmol) was dissolved in DCM, *m*-CPBA was then added. The reaction mixture was left stirred at room temperature for 2 h. DCM was then removed *in vacuo* and EtOAc was added to the residue. The organic was washed with saturated $NaHCO_3$, brine, dried ($MgSO_4$) and concentrated *in vacuo* to give crude product, which was then purified by column chromatography (5% MeOH/DCM) to give the title compound as a yellow oil (13%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.07 (d, *J* = 2.0 Hz, 1H), 7.38 (d, *J* = 8.6 Hz, 2H), 7.18 (d, *J* = 8.7 Hz, 1H), 7.08 (s, br, 1H), 7.05 – 7.02 (m, 2H), 6.91 (d, *J* = 8.7 Hz, 1H), 4.63 (d, *J* = 5.9 Hz, 2H), 4.14 (s, 3H), 2.63 (q, *J* = 7.6 Hz, 2H), 2.49 (s, 3H), 1.23 (t, *J* = 7.5 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 158.7, 154.7, 154.6, 149.7, 144.2, 134.7, 131.2, 130.9, 129.7, 126.1, 120.0, 117.1, 107.8, 42.9, 40.8, 19.3, 17.2, 12.9 ppm; LC-MS: *m/z* = 400.8 $[M + H]^+$.

N-(4-(Benzo[*d*]oxazol-5-yloxy)benzyl)-4-chloro-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxamide (20)

General procedure B3 was followed, starting from **74** to give the desired benzylamine, which was subsequently coupled to 4-chloro-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxylic acid according to **General procedure C3** to afford the title compound as a brown solid (10%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (t, J = 4.8 Hz, 1H), 7.55 (d, J = 8.7 Hz, 1H), 7.40 (s, 1H), 7.32 (d, J = 7.8 Hz, 2H), 7.12-7.10 (m, 1H), 6.99-6.97 (m, 3H), 4.60 (d, J = 4.8 Hz, 2H), 4.13 (s, 3H), 2.63-2.61 (m, 2H), 1.23 (t, J = 7.7 Hz, 3H) ppm; LCMS: m/z = 411.2 $[M + H]^+$.

4-(4-((4-Chloro-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxamido)methyl)phenoxy)benzoic acid (21)

Title compound was prepared according to **General Procedure D1**, starting from **76** to give a white solid (17%). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.8 (s, br,, 1H), 8.95 (t, J = 5.9 Hz, 1H), 7.93 (d, J = 8.6 Hz, 2H), 7.42 (d, J = 8.3 Hz, 2H), 7.10 (d, J = 8.4 Hz, 2H), 7.01 (d, J = 8.6 Hz, 2H), 4.49 (d, J = 5.9 Hz, 2H), 3.84 (s, 3H), 2.57-2.49 (m, 2H), 1.16 (t, J = 7.6 Hz, 3H) ppm; LC-MS: m/z = 414.1 $[M + H]^+$.

***N*-(4-(4-(Azidomethyl)phenoxy)benzyl)-4-chloro-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxamide (22)**

General procedure C1 was followed, starting from 4-hydroxybenzylamine and 4-chloro-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxylic acid to give 4-chloro-3-ethyl-*N*-(4-hydroxybenzyl)-1-methyl-1*H*-pyrazole-5-carboxamide, which was then coupled to (4-iodophenyl)methanol according to **General procedure E1** to give 4-chloro-3-ethyl-N-(4-(4-(hydroxymethyl)phenoxy)benzyl)-1-methyl-1H-pyrazole-5-carboxamide. This resulting product (1.0 eq) was reacted with triphenylphosphine (1.1 eq) and CBr_4 (1.1 eq) in DCM at room temperature for 2 h. DCM was then removed *in vacuo* and DMF was added to the residue, followed by NaN_3 (5.5 eq). The reaction mixture was left stirred at room temperature for 2 h. Upon completion, the reaction was diluted with EtOAc, washed with water, brine and the organic layer was dried over $MgSO_4$. Solvent was removed *in vacuo* to afford crude product, which was purified by column chromatography (5-20% EtOAc/petroleum benzine) to give the title compound as a colorless oil (24%). ^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.33 (d, *J* = 8.6 Hz, 2H), 7.28 (d, *J* = 8.6 Hz, 2H), 7.01 (d, *J* = 8.0 Hz, 5H), 4.62 (d, *J* = 5.8 Hz, 2H), 4.31 (s, 2H), 4.15 (s, 3H), 2.63 (q, *J* = 7.6 Hz, 2H), 1.24

(t, *J* = 7.6 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 183.3, 158.6, 156.5, 149.7, 132.8, 131.0, 130.4, 130.0, 129.3, 119.5, 119.1, 107.0, 54.4, 43.0, 40.8, 19.3, 12.9 ppm; LC-MS: *m/z* = 424.8 $[M + H]^+$.

N-(4-(4-Chlorophenoxy)benzyl)-3-ethyl-1-methyl-1H-pyrazole-5-carboxamide (23)

Title compound was prepared according to **General Procedure C1**, starting from (4-(4-chlorophenoxy)phenyl)methanamine HCl and 3-ethyl-1-methyl-1*H*-pyrazole-5-carboxylic acid to give a yellow oil (58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.32 – 7.25 (m, 4H), 6.99 – 6.90 (m, 4H), 6.39 (s, br, 1H), 6.31 (s, 1H), 4.54 (d, *J* = 5.8 Hz, 2H), 4.12 (s, 3H), 2.61 (q, *J* = 7.6 Hz, 2H), 1.21 (t, *J* = 7.6 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 160.1, 156.6, 155.8, 153.0, 135.5, 133.2, 129.8, 129.5, 128.5, 120.2, 119.2, 104.2, 42.9, 39.0, 21.3, 13.9 ppm; LC-MS: *m/z* = 369.9 $[M + H]^+$.

4-Chloro-1-methyl-N-(4-((6-methylpyridin-3-yl)oxy)benzyl)-1H-pyrazole-5-carboxamide (24)

General procedure A1 was followed, starting from 6-methylpyridin-3-ol and 4-fluorobenzaldehyde to give 4-((6-methylpyridin-3-yl)oxy)benzaldehyde, which was converted to the corresponding benzylamine according to **General procedure F**, then

subsequently coupled to 4-chloro-1-methyl-1*H*-pyrazole-5-carboxylic acid according to **General procedure C1** to give the title compound as a yellow oil (35%).^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.26 (d, *J* = 2.8 Hz, 1H), 7.43 (d, *J* = 4.0 Hz, 1H), 7.37 – 7.32 (m, 3H), 7.20 (d, *J* = 8.5 Hz, 1H), 7.06 – 6.96 (m, 3H), 4.62 (d, *J* = 5.8 Hz, 2H), 4.19 (s, 3H), 2.61 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.6, 158.4, 156.1, 155.7, 136.8, 133.4, 130.9, 129.6, 129.0, 128.2, 124.6, 119.0, 109.7, 43.0, 41.3, 22.9 ppm; LC-MS: *m/z* = 356.8 $[M + H]^+$.

4-Chloro-*N*-(4-(4-chlorophenoxy)benzyl)-1-methyl-1*H*-pyrazole-5-carboxamide (25)

Title compound was prepared according to **General Procedure C1**, starting from (4-(4-chlorophenoxy)phenyl)methanamine HCl and 4-chloro-1-methyl-1*H*-pyrazole-5-carboxylic acid to give a white solid (36%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.44 (d, *J* = 1.3 Hz, 1H), 7.35 – 7.24 (m, 4H), 7.06 – 6.89 (m, 5H), 4.61 (d, *J* = 5.7 Hz, 2H), 4.19 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 158.4, 156.6, 155.8, 136.7, 132.7, 130.9, 129.9, 129.3, 128.5, 120.2, 119.2, 109.6, 43.0, 41.2 ppm; LC-MS: *m/z* = 375.7 $[M + H]^+$.

4-Chloro-1-methyl-*N*-(4-((2-methylpyrimidin-5-yl)oxy)benzyl)-1*H*-pyrazole-5-carboxamide (26)

General procedure A1 was followed, starting from 2-methylpyrimidin-5-ol and 4-fluorobenzonitrile to give 4-((2-methylpyrimidin-5-yl)oxy)benzonitrile, which was converted to the corresponding benzylamine according to **General procedure B4**, then subsequently coupled to 4-chloro-1-methyl-1*H*-pyrazole-5-carboxylic acid according to **General procedure C1** to give the title compound as a yellow oil (16%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.39 (s, 2H), 7.44 (s, 1H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.00 (d, *J* = 8.2 Hz, 3H), 4.63 (d, *J* = 5.8 Hz, 2H), 4.18 (s, 3H), 2.72 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 163.1, 158.4, 155.8, 149.7, 147.9, 136.8, 133.7, 130.8, 129.6, 118.8, 109.7, 42.9, 41.3, 25.2 ppm; LC-MS: *m/z* = 357.8 $[M + H]^+$.

4-Chloro-*N*-(4-((6-chloropyridin-3-yl)oxy)benzyl)-1-methyl-1*H*-pyrazole-5-carboxamide (27)

General procedure A1 was followed, starting from 6-chloropyridin-3-ol and 4-fluorobenzonitrile to give4-((6-chloropyridin-3-yl)oxy)benzonitrile, which was converted to the corresponding benzylamine according to **General procedure B4**, then subsequently coupled to 4-chloro-1-methyl-1*H*-pyrazole-5-carboxylic acid according to **General procedure C1** to give the title compound as a yellow oil (23%). ^{1}H NMR (400 MHz, MeOD)

δ = 8.08 (dd, *J* = 2.5, 1.1 Hz, 1H), 7.50 – 7.38 (m, 6H), 7.09 – 7.03 (m, 2H), 4.58 (s, 2H), 3.99 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 158.4, 155.9, 152.2, 138.3, 136.7, 136.7, 133.5, 130.9, 129.6, 128.4, 124.8, 119.0, 109.6, 42.9, 41.2, 22.6 ppm; LC-MS: *m/z* = 376.8 $[M + H]^+$.

4-Fluoro-1-methyl-*N*-(4-((6-methylpyridin-3-yl)oxy)benzyl)-1*H*-pyrazole-5-carboxamide (28)

General procedure A1 was followed, starting from 6-methylpyridin-3-ol and 4-fluorobenzaldehyde to give 4-((6-methylpyridin-3-yl)oxy)benzaldehyde, which was converted to the corresponding benzylamine according to **General procedure F**, then subsequently coupled to 4-fluoro-1-methyl-1*H*-pyrazole-5-carboxylic acid according to **General procedure C1** to give the title compound as a yellow oil (48%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.27 (d, *J* = 2.6 Hz, 1H), 7.33 – 7.27 (m, 3H), 7.21 (dd, *J* = 8.5, 2.8 Hz, 1H), 7.11 (d, *J* = 8.5 Hz, 1H), 6.97 – 6.93 (m, 2H), 6.56 (s, br, 1H), 4.57 (d, *J* = 5.8 Hz, 2H), 4.14 (d, *J* = 0.9 Hz, 3H), 2.52 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 157.8, 156.7, 153.4, 151.3, 150.0, 147.5, 140.8, 132.9, 129.4, 126.9, 124.39, 123.8, 118.6, 42.6, 40.8, 23.6 ppm; LC-MS: *m/z* = 340.9 $[M + H]^+$.

***N*-(4-(4-Chlorophenoxy)benzyl)-4-fluoro-1-methyl-1*H*-pyrazole-5-carboxamide (29)**

Title compound was prepared according to **General Procedure C1**, starting from (4-(4-chlorophenoxy)phenyl)methanamine HCl and 4-fluoro-1-methyl-1*H*-pyrazole-5-carboxylic acid to give a white solid (17%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.35 – 7.25 (m, 5H), 7.00 – 6.91 (m, 4H), 6.51 (s, br, 1H), 4.59 (d, *J* = 5.8 Hz, 2H), 4.17 (d, *J* = 1.0 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 157.8, 156.6, 155.8, 150.1, 147.6, 132.9, 129.9, 129.4, 128.6, 124.4, 120.2, 119.2, 42.7, 40.9 ppm; LC-MS: *m/z* = 357.9 $[M - H]^-$.

4-Fluoro-1-methyl-*N*-(4-((2-methylpyrimidin-5-yl)oxy)benzyl)-1*H*-pyrazole-5-carboxamide (30)

General procedure A1 was followed, starting from 2-methylpyrimidin-5-ol and 4-fluorobenzonitrile to give 4-((2-methylpyrimidin-5-yl)oxy)benzonitrile, which was converted to the corresponding benzylamine according to **General procedure B4**, then subsequently coupled to 4-fluoro-1-methyl-1*H*-pyrazole-5-carboxylic acid according to **General procedure C1** to give the title compound as a yellow oil (18%). ^{1}H NMR (400 MHz, MeOD) δ = 8.43 (s, 2H), 7.45 – 7.41 (m, 3H), 7.11 – 7.06 (m, 2H), 4.56 (s, 2H), 4.03 (d, *J* = 0.8 Hz, 3H), 2.66 (s, 3H) ppm; ^{13}C NMR (101 MHz, MeOD) δ = 163.3, 156.4, 151.9,

151.1, 148.4, 148.4, 136.6, 130.6, 125.6, 120.10, 120.0, 43.3, 40.3, 24.6 ppm; LC-MS: *m/z* = 341.9 $[M + H]^+$.

_N_-(4-((6-Chloropyridin-3-yl)oxy)benzyl)-4-fluoro-1-methyl-1_H_-pyrazole-5-carboxamide (31)

General procedure A1 was followed, starting from 6-chloropyridin-3-ol and 4-fluorobenzonitrile to give4-((6-chloropyridin-3-yl)oxy)benzonitrile, which was converted to the corresponding benzylamine according to **General procedure B4**, then subsequently coupled to 4-fluoro-1-methyl-1*H*-pyrazole-5-carboxylic acid according to **General procedure C1** to give the title compound as a yellow oil (7%). ^{1}H NMR (400 MHz, MeOD) δ = 8.09 (dd, *J* = 2.4, 1.1 Hz, 1H), 7.46 – 7.39 (m, 5H), 7.09 – 7.04 (m, 2H), 4.56 (d, *J* = 4.2 Hz, 2H), 4.03 (d, *J* = 0.8 Hz, 3H) ppm; ^{13}C NMR (101 MHz, MeOD) δ = 186.5, 185.2, 178.6, 175.6, 173.2, 171.0, 166.4, 160.5, 160.1, 156.3, 155.6, 150.4, 73.3, 70.3 ppm; LC-MS: *m/z* = 360.8 $[M + H]^+$.

4-Chloro-1,3-dimethyl-_N_-(4-((6-methylpyridin-3-yl)oxy)benzyl)-1_H_-pyrazole-5-carboxamide (32)

General procedure A1 was followed, starting from 6-methylpyridin-3-ol and 4-fluorobenzaldehyde to give 4-((6-methylpyridin-3-yl)oxy)benzaldehyde, which was converted to the corresponding benzylamine according to **General procedure F**, then subsequently coupled to 4-chloro-1,3-dimethyl-1*H*-pyrazole-5-carboxylic acid according to **General procedure C1** to give the title compound as a yellow oil (40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.28 (d, *J* = 2.8 Hz, 1H), 7.33 – 7.29 (m, 2H), 7.21 (dd, *J* = 8.4, 2.9 Hz, 1H), 7.11 (d, *J* = 8.5 Hz, 1H), 7.03 (s, br, 1H), 6.98 – 6.93 (m, 2H), 4.59 (d, *J* = 5.8 Hz, 2H), 4.12 (s, 3H), 2.53 (s, 3H), 2.22 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 158.5, 156.8, 153.5, 151.3, 144.6, 141.0, 132.8, 131.0, 129.3, 126.8, 123.8, 118.6, 108.5, 42.9, 40.7, 23.7, 11.1 ppm; LC-MS: *m/z* = 370.8 $[M + H]^+$.

4-Chloro-*N*-(4-(4-chlorophenoxy)benzyl)-1,3-dimethyl-1*H*-pyrazole-5-carboxamide (33)

Title compound was prepared according to **General Procedure C1**, starting from (4-(4-chlorophenoxy)phenyl)methanamine HCl and 4-chloro-1,3-dimethyl-1*H*-pyrazole-5-carboxylic acid to give a yellow solid (37%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.34 – 7.26 (m, 4H), 7.04 (s, br, 1H), 7.00 – 6.90 (m, 4H), 4.61 (d, *J* = 5.8 Hz, 2H), 4.13 (s, 3H), 2.23 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 158.5, 156.6, 155.8, 144.6, 132.8, 131.0,

129.8, 129.3, 128.5, 120.2, 119.2, 108.4, 42.9, 40.7, 11.1 ppm; LC-MS: *m/z* = 389.8 [M + H]$^+$.

4-Chloro-*N*-(4-((6-chloropyridin-3-yl)oxy)benzyl)-1,3-dimethyl-1*H*-pyrazole-5-carboxamide (34)

General procedure A1 was followed, starting from 6-chloropyridin-3-ol and 4-fluorobenzonitrile to give4-((6-chloropyridin-3-yl)oxy)benzonitrile, which was converted to the corresponding benzylamine according to **General procedure B4**, then subsequently coupled to 4-chloro-1,3-dimethyl-1*H*-pyrazole-5-carboxylic acid according to **General procedure C1** to give the title compound as a yellow oil (10%). ^{1}H NMR (400 MHz, MeOD) δ = 8.09 (d, *J* = 1.1 Hz, 1H), 7.48 – 7.41 (m, 4H), 7.07 (dd, *J* = 8.5, 1.7 Hz, 2H), 4.58 (s, 2H), 3.93 (d, *J* = 1.7 Hz, 3H), 2.20 (d, *J* = 1.7 Hz, 3H) ppm; LC-MS: *m/z* = 390.8 [M + H]$^+$.

4-Fluoro-1,3-dimethyl-*N*-(4-((6-methylpyridin-3-yl)oxy)benzyl)-1*H*-pyrazole-5-carboxamide (35)

General procedure A1 was followed, starting from 6-methylpyridin-3-ol and 4-fluorobenzaldehyde to give 4-((6-methylpyridin-3-yl)oxy)benzaldehyde, which was converted to the corresponding benzylamine according to **General procedure F**, then

subsequently coupled to 4-fluoro-1,3-dimethyl-1*H*-pyrazole-5-carboxylic acid according to **General procedure C1** to give the title compound as a yellow oil (12%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.29 (d, *J* = 2.7 Hz, 1H), 7.32 – 7.28 (m, 2H), 7.23 – 7.19 (m, 1H), 7.12 (d, *J* = 8.5 Hz, 1H), 6.99 – 6.94 (m, 2H), 6.52 (s, br, 1H), 4.58 (d, *J* = 5.8 Hz, 2H), 4.10 (d, *J* = 0.8 Hz, 3H), 2.54 (s, 3H), 2.21 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 158.0, 156.8, 153.5, 151.3, 148.1, 145.6, 141.0, 133.0, 132.8 (d, *J* = 11.7 Hz), 129.4, 126.8, 123.8, 118.7, 42.6, 40.2, 23.7, 9.7 (d, *J* = 3.2 Hz) ppm; LC-MS: *m/z* = 354.9 $[M + H]^+$.

***N*-(4-(4-Chlorophenoxy)benzyl)-4-fluoro-1,3-dimethyl-1*H*-pyrazole-5-carboxamide (36)**

Title compound was prepared according to **General Procedure C1**, starting from (4-(4-chlorophenoxy)phenyl)methanamine HCl and 4-fluoro-1,3-dimethyl-1*H*-pyrazole-5-carboxylic acid to give a colorless oil (30%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.34 – 7.25 (m, 4H), 7.01 – 6.90 (m, 4H), 6.52 (s, br, 1H), 4.59 (d, *J* = 5.8 Hz, 2H), 4.10 (d, *J* = 0.8 Hz, 3H), 2.22 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 157.9, 156.4, 155.7, 148.0, 145.5, 132.9, 132.63, 129.7, 129.2, 128.4, 120.1, 119.1, 42.5, 40.1, 9.5 (d, *J* = 3.2 Hz) ppm; LC-MS: *m/z* = 373.8 $[M + H]^+$.

N-(4-((6-Chloropyridin-3-yl)oxy)benzyl)-4-fluoro-1,3-dimethyl-1*H*-pyrazole-5-carboxamide (37)

General procedure A1 was followed, starting from 6-chloropyridin-3-ol and 4-fluorobenzonitrile to give4-((6-chloropyridin-3-yl)oxy)benzonitrile, which was converted to the corresponding benzylamine according to **General procedure B4**, then subsequently coupled to 4-fluoro-1,3-dimethyl-1*H*-pyrazole-5-carboxylic acid according to **General procedure C1** to give the title compound as a colorless oil (38%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.11 – 8.07 (m, 1H), 7.33 – 7.28 (m, 2H), 7.23 (d, *J* = 1.9 Hz, 2H), 6.99 – 6.93 (m, 2H), 6.60 (d, *J* = 6.0 Hz, 1H), 4.56 (d, *J* = 5.9 Hz, 2H), 4.05 (d, *J* = 0.9 Hz, 3H), 2.17 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 158.0, 157.9, 155.5, 153.1, 148.0, 145.5, 144.9, 140.5, 134.1, 132.6 (d, *J* = 11.7 Hz), 129.5, 128.57, 124.8, 119.2, 42.4, 40.1, 9.5 (d, *J* = 3.1 Hz) ppm; LC-MS: *m/z* = 374.8 $[M + H]^+$.

4-Chloro-3-ethyl-1-methyl-N-((5-(p-tolyloxy)pyridin-2-yl)methyl)-1H-pyrazole-5-carboxamide (38)

Title compound was prepared according to **General Procedure C5**, starting from **78** and 4-chloro-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxylic acid to give a white solid

(19%). ^{1}H NMR (400 MHz, DMSO d_6): δ 8.94 (t, *J* = 5.6 Hz, 1H), 8.28 (s, 1H), 7.39 (s, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 6.96 (d, *J* = 8.4 Hz, 2H), 4.56 (d, *J* = 5.6 Hz, 2H), 3.87 (s, 3H), 2.58-2.50 (m, 2H), 2.30 (s, 3H), 1.17 (t, *J* = 7.5 Hz, 3H) ppm; LC-MS: *m/z* = 385.1 $[M + H]^+$.

4-Chloro-3-ethyl-*N*-(2-fluoro-4-(*p*-tolyloxy)benzyl)-1-methyl-1*H*-pyrazole-5-carboxamide (39)

Title compound was prepared according to **General Procedure C2**, starting from **80** and 4-chloro-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxylic acid to give a colourless gum (62%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.88 (t, *J* = 5.6 Hz, 1H), 7.39 (t, *J* = 8.6 Hz, 1H), 7.22 (d, *J* = 8.2 Hz, 2H), 6.96 (d, *J* = 8.4 Hz, 2H), 6.84-6.80 (m, 1H), 6.77 (dd, *J* = 8.4, 2.36 Hz, 1H), 4.46 (d, *J* = 5.7 Hz, 2H), 3.83 (s, 3H), 2.56-2.50 (m, 2H), 2.30 (s, 3H), 1.16 (t, *J* = 7.5 Hz, 3H) ppm; LC-MS: *m/z* = 402.1 $[M + H]^+$.

4-Chloro-3-ethyl-1-methyl-*N*-((6-(*p*-tolyloxy)pyridin-3-yl)methyl)-1*H*-pyrazole-5-carboxamide (40)

Title compound was prepared according to **General Procedure C2**, starting from **82** and 4-chloro-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxylic acid to give an off white solid

(23%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.93 (t, *J* = 5.7 Hz, 1H), 8.10 (s, 1H), 7.80 (d, *J* = 6.4 Hz, 1H), 7.20 (d, *J* = 8.1 Hz, 2H), 6.99-6.96 (m, 3H), 4.43 (d, *J* = 5.7 Hz, 2H), 3.83 (s, 3H), 2.54-2.50 (m, 2H), 2.31 (s, 3H), 1.16 (t, *J* = 7.5 Hz, 3H) ppm; LC-MS: *m/z* = 385.1 $[M + H]^+$.

4-Chloro-3-ethyl-*N*-(3-fluoro-4-(*p*-tolyloxy)benzyl)-1-methyl-1*H*-pyrazole-5-carboxamide (41)

Title compound was prepared according to **General Procedure C2**, starting from **84** and 4-chloro-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxylic acid to give an off white solid (44%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.96 (s, br,, 1H), 7.35-7.32 (m, 1H), 7.18-7.07 (m, 4H), 6.86 (d, *J* = 8.0 Hz, 2H), 4.48 (d, *J* = 5.3 Hz, 2H), 3.84 (s, 3H), 2.56-2.50 (m, 2H), 2.27 (s, 3H), 1.17 (t, *J* = 7.3 Hz, 3H) ppm; LC-MS: *m/z* = 402.2 $[M + H]^+$.

4-Chloro-3-ethyl-*N*-(2-fluoro-4-((6-methylpyridin-3-yl)oxy)benzyl)-1-methyl-1*H*-pyrazole-5-carboxamide (42)

General procedure C1 was followed, starting from (4-bromo-2-fluorophenyl)methanamine and 4-chloro-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxylic acid to give *N*-(4-bromo-2-fluorobenzyl)-4-chloro-3-ethyl-1-methyl-1*H*-pyrazole-5-

carboxamide, which was then coupled to 6-methylpyridin-3-ol according to **General procedure E1** to give the title compound as a colorless oil (37%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.27 (s, 1H), 7.34 (t, *J* = 8.4 Hz, 1H), 7.23 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.13 (s, br, 2H), 6.74 – 6.66 (m, 2H), 4.60 (d, *J* = 5.9 Hz, 2H), 4.09 (s, 3H), 2.59 (q, *J* = 7.6 Hz, 2H), 2.52 (s, 3H), 1.20 (t, *J* = 7.6 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 162.8, 160.3, 158.6, 158.2 (d, *J* = 10.7 Hz), 154.3, 149.6, 141.2, 131.1 (d, *J* = 5.8 Hz), 130.9, 127.4, 119.7 (d, *J* = 15.2 Hz), 113.6 (d, *J* = 3.4 Hz), 107.7, 105.9, 105.69, 40.6, 37.2 (d, *J* = 3.2 Hz), 23.7, 19.2, 12.8 ppm; LC-MS: *m/z* = 402.8 $[M + H]^+$.

4-Chloro-*N*-(4-(4-chlorophenoxy)-2-fluorobenzyl)-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxamide (43)

Title compound was prepared according to **General Procedure C2**, starting from **86** and 4-chloro-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxylic acid to give an off white solid (24%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.90 (s, br, 1H), 7.47-7.41 (m, 3H), 7.08 (d, *J* = 8.7 Hz, 2H), 6.95 (d, *J* = 11.3 Hz, 1H), 6.86 (d, *J* = 7.4 Hz, 1H), 4.48 (d, *J* = 5.1 Hz, 2H), 3.83 (s, 3H), 2.55-2.50 (m, 2H), 1.16 (t, *J* = 7.4 Hz, 3H) ppm; LC-MS: *m/z* = 422.0 $[M + H]^+$.

4-Chloro-3-ethyl-N-(3-fluoro-4-((6-methylpyridin-3-yl)oxy)benzyl)-1-methyl-1H-pyrazole-5-carboxamide (44)

General procedure A1 was followed, starting from 6-methylpyridin-3-ol and 3,4-difluorobenzaldehyde to give 3-fluoro-4-((6-methylpyridin-3-yl)oxy)benzaldehyde, which was converted to the corresponding benzylamine according to **General procedure F**, then subsequently coupled to 4-chloro-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxylic acid according to **General procedure C1** to give the title compound as a yellow oil (28%). ^{1}H NMR (400 MHz, MeOD) δ 8.12 (d, *J* = 2.7 Hz, 1H), 7.34 – 7.21 (m, 4H), 7.14 (t, *J* = 8.3 Hz, 1H), 4.58 (s, 2H), 3.94 (s, 3H), 2.62 (q, *J* = 7.6 Hz, 2H), 2.49 (s, 3H), 1.22 (t, *J* = 7.6 Hz, 3H) ppm; ^{13}C NMR (101 MHz, MeOD) δ = 160.8, 156.6, 154.1, 153.9 (d, *J* = 6.7 Hz), 151.0, 143.1 (d, *J* = 11.8 Hz), 138.8, 138.3 (d, *J* = 6.2 Hz), 134.7, 126.5, 125.6, 125.3 (d, *J* = 3.5 Hz), 123.2 (d, *J* = 0.9 Hz), 117.4 (d, *J* = 19.0 Hz), 108.9, 43.3, 39.4, 22.9, 19.9, 13.2 ppm; LC-MS: *m/z* = 402.8 $[M + H]^{+}$.

4-Chloro-*N*-(4-(4-chlorophenoxy)-3-fluorobenzyl)-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxamide (45)

General procedure B2 was followed, starting from **87** to give the desired benzylamine, which was subsequently coupled to 4-chloro-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxylic acid according to **General procedure C2** to afford the title compound as an off white solid (28%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.97 (s, br,, 1H), 7.43-7.35 (m, 3H), 7.22 (s, br,, 2H), 6.98 (d, *J* = 8.5 Hz, 2H), 4.49 (d, *J* = 5.3 Hz, 2H), 3.85 (s, 3H), 2.56-2.50 (m, 2H), 1.17 (t, *J* = 7.4 Hz, 3H) ppm; LC-MS: *m/z* = 422.1 $[M + H]^+$.

4-Chloro-*N*-(3,5-difluoro-4-((6-methylpyridin-3-yl)oxy)benzyl)-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxamide (46)

General procedure A1 was followed, starting from 6-methylpyridin-3-ol and 3,4,5-trifluorobenzaldehyde to give 3,5-difluoro-4-((6-methylpyridin-3-yl)oxy)benzaldehyde, which was converted to the corresponding benzylamine according to **General procedure F**, then subsequently coupled to 4-chloro-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxylic acid according to **General procedure C1** to give the title compound as a white solid (31%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.25 (d, *J* = 2.8 Hz, 1H), 7.21 – 7.12 (m, 2H), 7.09 (d, *J* = 8.5 Hz, 1H), 7.05 – 6.98 (m, 2H), 4.62 (d, *J* = 6.1 Hz, 2H), 4.14 (s, 3H), 2.64 (q, *J* = 7.6 Hz, 2H), 2.52 (s, 3H), 1.24 (t, *J* = 7.6 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 158.9,

157.30 (d, *J* = 4.7 Hz), 154.7 (d, *J* = 4.9 Hz), 152.9, 152.4, 149.8, 137.2, 136.6, 130.6, 123.6 (d, *J* = 27.7 Hz), 111.7 (d, *J* = 5.6 Hz), 111.5 (d, *J* = 5.6 Hz), 108.0, 42.4, 40.9, 23.4, 19.3, 12.9 ppm; LC-MS: *m/z* = 420.8 $[M + H]^+$.

4-Chloro-3-ethyl-1-methyl-*N*-(4-(4-methylbenzyl)benzyl)-1*H*-pyrazole-5-carboxamide (47)

General procedure B1 was followed, starting from **88**, to give the corresponding benzylamine, which was subsequently coupled to 4-chloro-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxylic acid according to **General procedure C1** to give the title compound as a white solid (45%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.28 – 7.24 (m, 2H), 7.18 (d, *J* = 8.1 Hz, 2H), 7.11 – 7.05 (m, 4H), 6.99 (s, br, 1H), 4.60 (d, *J* = 5.7 Hz, 2H), 4.14 (s, 3H), 3.93 (s, 2H), 2.62 (q, *J* = 7.6 Hz, 2H), 2.31 (s, 3H), 1.23 (t, *J* = 7.6 Hz, 3fH) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 158.6, 149.7, 141.1, 137.9, 135.8, 135.2, 129.4, 129.3, 128.9, 128.3, 127.9, 107.7, 43.3, 41.3, 40.8, 21.1, 19.3, 12.9 ppm; LC-MS: *m/z* = 381.9 $[M + H]^+$.

4-Chloro-3-ethyl-1-methyl-*N*-(4-(4-methylbenzoyl)benzyl)-1*H*-pyrazole-5-carboxamide (48)

General procedure C1 was followed, starting from methyl 4-(aminomethyl)benzoate HCl and 4-chloro-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxylic acid to give methyl 4-((4-chloro-3-ethyl-1-methyl-1H-pyrazole-5-carboxamido)methyl)benzoate, which was hydrolyzed according to **General procedure D3** to give the corresponding carboxylic acid that was subsequently turned into a Weinreb amide according to **General procedure C1**. The resulting Weinreb amide was subjected to **General procedure H1**, reacting with p-tolylmagnesium bromide to give the title compound as a white solid (78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.73 – 7.68 (m, 2H), 7.63 (d, *J* = 8.2 Hz, 2H), 7.38 (d, *J* = 8.2 Hz, 2H), 7.22 – 7.18 (m, 2H), 7.09 (s, br, 1H), 4.65 (d, *J* = 5.9 Hz, 2H), 4.07 (s, 3H), 2.57 (q, *J* = 7.6 Hz, 2H), 2.36 (s, 3H), 1.17 (t, *J* = 7.6 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 196.0, 158.8, 149.7, 143.4, 142.0, 137.4, 134.9, 130.9, 130.6, 130.38, 129.1, 127.3, 107.8, 43.2, 40.8, 21.7, 19.3, 12.9 ppm; LC-MS: *m/z* = 395.9 $[M + H]^+$.

4-Chloro-3-ethyl-1-methyl-*N*-(4-(p-tolylthio)benzyl)-1*H*-pyrazole-5-carboxamide (49)

General procedure B1 was followed, starting from **89** to give the corresponding benzylamine, which was subsequently coupled to 4-chloro-3-ethyl-1-methyl-1*H*-pyrazole-

5-carboxylic acid to give the title compound as a yellow solid (79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.33 – 7.28 (m, 2H), 7.25 (d, *J* = 7.7 Hz, 4H), 7.14 (d, *J* = 7.9 Hz, 2H), 7.01 (s, br, 1H), 4.59 (d, *J* = 5.8 Hz, 2H), 4.14 (s, 3H), 2.63 (q, *J* = 7.6 Hz, 2H), 2.35 (s, 3H), 1.23 (t, *J* = 7.6 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 158.6, 149.7, 138.0, 136.9, 135.8, 132.6, 131.0, 131.0, 130.2, 130.0, 128.4, 107.7, 43.1, 40.8, 21.2, 19.3, 12.9 ppm; LC-MS: *m/z* = 399.8 $[M + H]^+$.

4-Chloro-3-ethyl-1-methyl-*N*-(4-(methyl(p-tolyl)amino)benzyl)-1*H*-pyrazole-5-carboxamide (50)

N,4-dimethylaniline (2.48 mmol) was dissolved in 1,4-dioxane in a microwave tube, followed by boc-protected (4-bromophenyl)methanamine (2.97 mmol), rac-BINAP (0.25 mmol) and Cs_2CO_3 (4.95 mmol). The reaction mixture was degassed for 0.5 h before $Pd(OAc)_2$ (0.12 mmol) was added. The tube was then sealed and placed in a microwave reactor to react at 110 °C for 1 h. Upon completion, the reaction mixture was diluted with EtOAc, washed with $NaHCO_3$, brine, dried over $MgSO_4$ and concentrated *in vacuo* to afford crude product, which was purified by column chromatography (5-20% EtOAc/petroleum benzine) to give *tert*-butyl (4-(methyl(*p*-tolyl)amino)benzyl)carbamate.

This resulting product was then reacted with 4M HCl in 1,4-dioxane at 60 °C for 2 h to give the corresponding benzylamine as a free base, which was subsequently coupled to 4-chloro-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxylic acid according to **General procedure C1** to give the title compound as a yellow oil (19%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.12 (d, *J* = 8.7 Hz, 2H), 7.05 (d, *J* = 8.1 Hz, 2H), 6.96 – 6.91 (m, 2H), 6.86 (s, br, 1H), 6.82 – 6.76 (m, 2H), 4.46 (d, *J* = 5.5 Hz, 2H), 4.06 (s, 3H), 3.20 (s, 3H), 2.59 – 2.51 (m, 2H), 2.24 (s, 3H), 1.15 (t, *J* = 7.6 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 158.5, 149.6, 149.0, 146.4, 132.8, 131.2, 130.1, 128.7, 128.0, 123.3, 117.7, 107.6, 43.2, 40.7, 40.4, 20.8, 19.3, 12.9 ppm; LC-MS: *m/z* = 396.9 $[M + H]^+$.

4-Chloro-3-ethyl-1-methyl-*N*-(1-(4-(p-tolyloxy)phenyl)ethyl)-1*H*-pyrazole-5-carboxamide (51)

General procedure C1 was followed, starting from 1-(4-bromophenyl)ethan-1-amine HCl and 4-chloro-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxylic acid to give *N*-(1-(4-bromophenyl)ethyl)-4-chloro-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxamide, which was then coupled to *p*-cresol according to **General procedure E1** to give the title compound as a yellow oil (12%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.30 (d, *J* = 8.5 Hz, 2H), 7.14 (d, *J*

= 8.2 Hz, 2H), 7.06 (d, *J* = 7.3 Hz, 1H), 6.94 (dd, *J* = 19.5, 8.5 Hz, 4H), 5.28 – 5.19 (m, 1H), 4.13 (s, 3H), 2.67 (q, *J* = 7.6 Hz, 2H), 2.34 (s, 3H), 1.60 (d, *J* = 6.9 Hz, 3H), 1.23 (t, *J* = 7.6 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 157.6, 157.6, 154.4, 150.2, 136.5, 133.3, 131.5, 130.4, 127.5, 119.4, 118.5, 108.3, 49.3, 40.2, 22.3, 20.8, 19.0, 13.0 ppm; LC-MS: *m/z* = 397.9 $[M + H]^+$.

4-Fluoro-1-methyl-*N*-(4-(4-methylbenzyl)benzyl)-1*H*-pyrazole-5-carboxamide (52)

General procedure B2 was followed, starting from **88**, to give the corresponding benzylamine, which was subsequently coupled to 4-fluoro-1-methyl-1*H*-pyrazole-5-carboxylic acid according to **General procedure C1** to give the title compound as a white solid (28%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.33 (d, *J* = 4.5 Hz, 1H), 7.28 – 7.24 (m, 2H), 7.19 (d, *J* = 8.2 Hz, 2H), 7.13 – 7.06 (m, 4H), 6.51 (d, *J* = 4.2 Hz, 1H), 4.59 (d, *J* = 5.7 Hz, 2H), 4.17 (d, *J* = 1.0 Hz, 3H), 3.94 (s, 2H), 2.32 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 157.7 (d, *J* = 4.2 Hz), 150.0, 147.5, 141.2, 137.9, 135.7, 135.3, 129.4, 129.3, 128.8, 127.9, 124.3 (d, *J* = 13.4 Hz), 43.0, 41.2, 40.8, 21.1 ppm; LC-MS: *m/z* = 337.9 $[M + H]^+$.

4-Fluoro-1,3-dimethyl-*N*-(4-(4-methylbenzyl)benzyl)-1*H*-pyrazole-5-carboxamide (53)

General procedure B2 was followed, starting from **88**, to give the corresponding benzylamine, which was subsequently coupled to 4-fluoro-1,3-dimethyl-1*H*-pyrazole-5-carboxylic acid according to **General procedure C1** to give the title compound as a white solid (46%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.25 – 7.21 (m, 2H), 7.16 (d, *J* = 8.2 Hz, 2H), 7.11 – 7.03 (m, 4H), 6.50 (d, *J* = 5.3 Hz, 1H), 4.56 (d, *J* = 5.7 Hz, 2H), 4.08 (d, *J* = 0.8 Hz, 3H), 3.92 (s, 2H), 2.30 (s, 3H), 2.20 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 157.9 (d, *J* = 4.3 Hz), 148.0, 145.5, 141.1, 137.9, 135.7, 135.3, 132.7 (d, *J* = 11.7 Hz), 129.3, 129.2, 128.8, 127.8, 42.9, 41.2, 40.1, 21.0, 9.6 (d, *J* = 3.1 Hz) ppm; LC-MS: *m/z* = 351.9 $[M + H]^+$.

4-Chloro-1-methyl-*N*-(4-(4-methylbenzyl)benzyl)-1*H*-pyrazole-5-carboxamide (54)

General procedure B2 was followed, starting from **88**, to give the corresponding benzylamine, which was subsequently coupled to 4-chloro-1-methyl-1*H*-pyrazole-5-carboxylic acid according to **General procedure C1** to give the title compound as a white solid (57%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.34 (s, 1H), 7.18 (d, *J* = 8.2 Hz, 2H), 7.10 (d, *J* = 8.2 Hz, 2H), 7.03 – 6.96 (m, 4H), 6.88 (s, br, 1H), 4.51 (d, *J* = 5.7 Hz, 2H), 4.10 (s, 3H), 3.85 (s, 2H), 2.23 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 158.3, 141.2, 137.9,

136.7, 135.7, 135.0, 131.0, 129.4, 129.3, 128.8, 127.9, 109.6, 43.4, 41.2, 41.2, 21.1 ppm; LC-MS: *m/z* = 353.9 $[M + H]^+$.

4-Chloro-1,3-dimethyl-*N*-(4-(4-methylbenzyl)benzyl)-1*H*-pyrazole-5-carboxamide (55)

General procedure B2 was followed, starting from **88**, to give the corresponding benzylamine, which was subsequently coupled to 4-chloro-1,3-dimethyl-1*H*-pyrazole-5-carboxylic acid according to **General procedure C1** to give the title compound as a white solid (61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.19 – 7.15 (m, 2H), 7.09 (d, *J* = 8.2 Hz, 2H), 7.03 – 6.96 (m,4H), 6.91 (s, br, 1H), 4.50 (d, *J* = 5.7 Hz, 2H), 4.04 (s, 3H), 3.84 (s, 2H), 2.22 (s, 3H), 2.14 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 158.5, 144.5, 141.1, 137.9, 135.7, 135.1, 131.1, 129.39, 129.2, 128.8, 127.8, 108.4, 43.3, 41.2, 40.6, 21.0, 11.1 ppm; LC-MS: *m/z* = 367.8 $[M + H]^+$.

4-Fluoro-1-methyl-*N*-(4-((6-methylpyridin-3-yl)methyl)benzyl)-1*H*-pyrazole-5-carboxamide (56)

Title compound was prepared according to **General Procedure C1**, starting from **94** and 4-fluoro-1-methyl-1*H*-pyrazole-5-carboxylic acid to give a colorless oil (47%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.44 (d, *J* = 1.8 Hz, 1H), 7.48 (dd, *J* = 8.0, 2.2 Hz, 1H), 7.30

– 7.21 (m, 3H), 7.13 (dd, *J* = 14.5, 8.1 Hz, 3H), 6.54 (d, *J* = 5.3 Hz, 1H), 4.55 (d, *J* = 5.8 Hz, 2H), 4.11 (d, *J* = 0.9 Hz, 3H), 3.93 (s, 2H), 2.57 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 157.8, 155.0, 146.7, 139.1, 138.9, 136.1, 134.7, 129.3, 128.2, 124.5, 120.9, 120.7, 42.9, 40.7 (d, *J* = 22.0 Hz), 38.2, 22.2 ppm; LC-MS: *m/z* = 338.9 $[M + H]^+$.

4-Fluoro-1,3-dimethyl-*N*-(4-((6-methylpyridin-3-yl)methyl)benzyl)-1*H*-pyrazole-5-carboxamide (57)

Title compound was prepared according to **General Procedure C1**, starting from **94** and 4-fluoro-1,3-dimethyl-1*H*-pyrazole-5-carboxylic acid to give a colorless oil (32%). ^{1}H NMR (401 MHz, $CDCl_3$) δ = 8.61 (s, 1H), 8.01 (d, *J* = 7.1 Hz, 1H), 7.54 (t, *J* = 8.8 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 6.60 (d, *J* = 5.7 Hz, 1H), 4.59 (d, *J* = 5.8 Hz, 2H), 4.12 – 4.06 (m, 5H), 2.80 (s, 3H), 2.22 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 158.0, 152.1, 145.4, 141.1, 138.7, 137.2, 136.4, 132.9 (d, *J* = 12.1 Hz), 129.5, 128.6, 127.2, 121.1, 120.8, 42.8, 40.1, 37.9, 19.3, 9.5 (d, *J* = 3.0 Hz) ppm; LC-MS: *m/z* = 352.9 $[M + H]^+$.

4-Chloro-1-methyl-*N*-(4-((6-methylpyridin-3-yl)methyl)benzyl)-1*H*-pyrazole-5-carboxamide (58)

Title compound was prepared according to **General Procedure C1**, starting from **94** and 4-chloro-1-methyl-1*H*-pyrazole-5-carboxylic acid to give a white solid (35%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.28 (d, *J* = 14.6 Hz, 1H), 7.36 – 7.33 (m, 1H), 7.31 – 7.26 (m, 1H), 7.20 (d, *J* = 7.8 Hz, 2H), 7.09 (d, *J* = 8.2 Hz, 2H), 6.98 (t, *J* = 7.6 Hz, 1H), 6.93 (s, br, 1H), 4.53 (d, *J* = 5.7 Hz, 2H), 4.10 (s, 3H), 3.85 (s, 2H), 2.44 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 158.3, 156.3, 149.2, 139.8, 136.9, 136.7, 135.6, 133.2, 130.9, 129.3, 128.0, 123.2, 109.6, 43.3, 41.2, 38.3, 23.9 ppm; LC-MS: *m/z* = 354.8 $[M + H]^+$.

4-Chloro-1,3-dimethyl-N-(4-((6-methylpyridin-3-yl)methyl)benzyl)-1H-pyrazole-5-carboxamide (59)

Title compound was prepared according to **General Procedure C1**, starting from **94** and 4-chloro-1,3-dimethyl-1*H*-pyrazole-5-carboxylic acid to give a white solid (29%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.35 (d, *J* = 1.6 Hz, 1H), 7.35 (dd, *J* = 7.9, 2.3 Hz, 1H), 7.29 – 7.23 (m, 2H), 7.14 (d, *J* = 8.2 Hz, 2H), 7.06 (d, *J* = 8.0 Hz, 1H), 7.02 (s, br, 1H), 4.58 (d, *J* = 5.7 Hz, 2H), 4.11 (s, 3H), 3.91 (s, 2H), 2.51 (s, 3H), 2.21 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 158.5, 156.2, 149.1, 144.5, 139.7, 137.0, 135.7, 133.3, 131.0,

129.3, 128.0, 123.2, 108.4, 43.2, 40.6, 38.3, 23.9, 11.1 ppm; LC-MS: *m/z* = 368.9 [M + H]$^+$.

3,5-Dimethyl-1*H*-pyrazole-3,5-dicarboxylate (60)

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 ^oC. 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. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.34 (s, 1H), 3.95 (s, 6H) ppm; LCMS *m/z* = 185.0 [M + H] $^+$.

3,5-Dimethyl-1-methyl-1*H*-pyrazole-3,5-dicarboxylate (61)

To a stirred solution of **60** (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 ^oC 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. ^1H 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 (62)

To a stirred solution of **61** (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 (63)

A mixture of **62** (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 (64)

To a stirred solution of **63** (0.90 g, 4.89 mmol) in DCM (15 mL) was added DIPEA (2.3 mL, 13.21 mmol) at 0 °C. A solution of trifluroacetic anhydride (0.78 mL, 5.63 mmol) in DCM (5 mL) was then added at 0 °C. The reaction mixture was stirred at 0 °C for 2 h then diluted with DCM. Organic layer was washed with saturated sodium bicarbonate 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 (65)

Title compound was prepared according to **General Procedure D1**, starting from **64** to give an off-white solid (37%). ^{1}H NMR (400 MHz, DMSOd_6): δ = 14.02 (s, br,, 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 (66)

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 = -161.32 (s) ppm; LC-MS: Rt 2.89 min, does not ionize.

1-Methyl-4-fluoro-1*H*-pyrazole-5-carboxylic acid (67)

Title compound was prepared according to **General Procedure D2**, starting from **66** to give a white solid (95% yield). ^{1}H NMR (400 MHz, DMSO) δ = 7.60 (d, *J* = 4.3 Hz, 2H), 4.00 (d, *J* = 1.0 Hz, 7H). ^{19}F NMR (376 MHz, DMSO) δ = -162.96 (s) ppm, LC-MS Rt 1.17 min, does not ionize.

(4-(3-Fluoro-4-methylphenoxy)phenyl)methanamine (68)

General procedure A2 was followed, starting from 3-fluoro-4-methylphenol and 4-fluorobenzonitrile to give 4-(3-fluoro-4-methylphenoxy)benzonitrile, which was reduced according to **General procedure B2** to give the title compound as a gummy liquid (80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28-7.25 (m, 2H), 7.11-7.07 (m, 1H), 6.97 (d, *J* = 8.0 Hz, 2H), 6.69-6.64 (m, 2H), 3.85 (s, 2H), 2.22 (s, 3H) ppm; LC-MS: *m/z* = 232 $[M + H]^+$.

(4-(2-Fluoro-4-methylphenoxy)phenyl)methanamine (69)

General procedure A2 was followed, starting from 2-fluoro-4-methylphenol and 4-fluorobenzonitrile to give 4-(2-fluoro-4-methylphenoxy)benzonitrile, which was reduced according to **General procedure B2** to give the title compound as a gummy liquid (75%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25-7.22 (m, 2H), 6.99-6.90 (m, 5H), 3.82 (s, 2H), 2.23 (s, 3H) ppm; LC-MS: *m/z* = 232 $[M + H]^+$.

4-(4-Fluorophenoxy)benzonitrile (70)

Title compound was prepared according to **General Procedure A2**, starting from 4-fluorophenol and 4-fluorobenzonitrile to give a gummy liquid (50%). ^{1}H NMR (400 MHz,

$CDCl_3$): δ 7.59 (d, *J* = 8.7 Hz, 2H), 7.12-7.07 (m, H), 7.05-7.01 (m, 2H), 6.96 (d, *J* = 8.7 Hz, 2H) ppm; LC-MS: *m/z* = 214 $[M + H]^+$.

2-Amino-4-methoxyphenol (71)

To a stirred solution of 4-methoxy-2-nitrophenol (7 g, 41.38 mmol) in EtOAc (15 mL) and MeOH (30 mL), Pd/C (10%, 1 g) was added. The reaction mixture was stirred under H_2 for 16 h. Upon completion, reaction mixture was filtered through a pad of celite and washed with EtOAc. The Filtrate was concentrated *in vacuo* to afford the title compound (4.5 g, 78%) as a white solid. ^1H NMR (400 MHz, DMSO-d_6): *δ* = 8.43 (s, 1H), 6.50 (d, *J* = 8.4 Hz, 1H), 6.20 (d, *J* = 2.7 Hz, 1H), 5.94 (dd, *J* = 8.3, 2.9 Hz, 1H), 4.52 (s, 2H), 3.57 (s, 3H) ppm; LC-MS: *m/z* = 140.0 $[M + H]^+$.

5-Methoxybenzo[*d*]oxazole (72)

A stirred solution of **71** (4.5 g, 32.40 mmol) in triethyl orthoformate (50 mL) was refluxed for 16 h. Upon completion, the reaction mixture was cooled to room temperature and concentrated *in vacuo*. Residue was diluted with EtOAc and organic layer was washed with water, brine, then 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 as a yellow solid (3.6 g, 75%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (s, 1H), 7.44 (d, J = 8.9 Hz, 1H), 7.24 (d, J = 2.4 Hz, 1H), 6.97 (dd, J = 8.9, 2.5 Hz, 1H), 3.83 (d, J = 6.6 Hz, 3H) ppm; LCMS: m/z = 149.9 $[M + H]^+$.

Benzo[*d*]oxazol-5-ol (73)

A stirred solution of **72** (3 g, 20.13 mmol) in DCM (30 mL) was cooled to -20 °C. BBr_3 (100 mL, 100.70 mmol, 1M in DCM) was then added drop wise to the reaction mixture. The reaction was stirred at room temperature for 16 h. Upon completion, the reaction mixture was quenched with MeOH and extracted with DCM. Organic layer was 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 the title compound as brown solid (0.75 g, 28%). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.49 (s, 1H), 8.59 (s, 1H), 7.53 (d, J = 8.7 Hz, 1H), 7.06 (d, J = 1.6 Hz, 1H), 6.86-6.84 (m, 1H) ppm; LC-MS: m/z = 136.0 $[M + H]^+$.

4-(Benzo[*d*]oxazol-5-yloxy)benzonitrile (74)

Title compound was prepared according to **General Procedure A1**, starting from **73** and 4-fluorobenzonitrile to give a white solid (61%). ^{1}H NMR (400 MHz, $CDCl_3$): δ =

8.15 (s, 1H), 7.62-7.58 (m, 3H), 7.49 (d, *J* = 2.3 Hz, 1H), 7.13 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.00-6.97 (m, 2H) ppm; LCMS: *m/z* = 237.1 $[M + H]^+$.

Ethyl 4-(4-cyanophenoxy)benzoate (75)

Title compound was prepared according to **General Procedure G1**, starting from ethyl 4-hydroxybenzoate and (4-cyanophenyl)boronic acid to give a brown solid (52%). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.0. (d, *J* = 8.6 Hz, 2H), 7.90 (d, *J* = 8.7 Hz, 2H), 7.24 (t, *J* = 8.3 Hz, 4H), 4.31 (q, *J* = 7.1 Hz, 2H), 1.31 (t, *J* = 7.0 Hz, 3H); ppm; LC-MS: *m/z* = 268.3 $[M + H]^+$.

Ethyl 4-(4-((4-chloro-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxamido)methyl)phenoxy)benzoate (76)

General procedure B3 was followed, starting from **75** to give the desired benzylamine, which was subsequently coupled to 4-chloro-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxylic acid according to **General procedure C3** to afford the title compound as a brown solid (39%). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.95 (t, *J* = 6.0 Hz, 1H), 7.95 (d, *J* = 8.7 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 8.4 Hz, 2H), 7.03 (d, *J* = 8.8 Hz, 2H),

4.50 (d, *J* = 6.0 Hz, 2H), 4.29 (q, *J* = 7.0 Hz, 2H), 3.84 (s, 3H), 2.57-2.50 (m, 2H), 1.30 (t, *J* = 7.0 Hz, 3H), 1.16 (t, *J* = 7.6 Hz, 3H) ppm; LC-MS: *m/z* = 442.3 $[M + H]^+$.

5-(*p*-Tolyloxy)picolinonitrile (77)

Title compound was prepared according to **General Procedure A2**, starting from *p*-cresol and 5-fluoropicolinonitrile to give a white solid (52%). ^{1}H NMR (400 MHz, DMSO d_6): δ 8.50 (s, 1H), 8.00 (d, *J* = 8.6 Hz, 1H), 7.44-7.41 (m, 1H) 7.30 (d, *J* = 7.7 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 2.33 (s, 3H) ppm; LC-MS: *m/z* = 210.8 $[M + H]^+$.

(5-(*p*-Tolyloxy)pyridin-2-yl)methanamine HCl (78)

Title compound was prepared according to **General Procedure B5**, starting from **77** to give a white solid (34%). ^{1}H NMR (400 MHz, DMSO d_6): δ 8.38 (s, br,, 3H), 7.50-7.47 (m, 2H), 7.24 (d, *J* = 7.2 Hz, 2H), 6.97 (d, *J* = 7.7 Hz, 2H), 4.15 (d, *J* = 4.2 Hz, 2H), 2.31 (s, 3H) ppm; LC-MS: *m/z* = 215.0 $[M + H]^+$.

2-Fluoro-4-(*p*-tolyloxy)benzonitrile (79)

Title compound was prepared according to **General Procedure G2**, starting from 2-fluoro-4-hydroxybenzonitrile and *p*-tolylboronic acid to give a colourless oil (18%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.50 (t, *J* = 8.0 Hz, 1H), 7.22 (d, *J* = 8.1 Hz, 2H), 6.95 (d, *J*

= 8.2 Hz, 2H), 6.78-6.67 (m, 1H), 6.69 (dd, *J* = 10.6, 2.0 Hz, 1H), 2.37 (s, 3H) ppm; LC-MS: *m/z* = 228.1 $[M + H]^+$.

(2-Fluoro-4-(*p*-tolyloxy)phenyl)methanamine HCl (80)

Title compound was prepared according to **General Procedure B5**, starting from **79** to give a pale yellow solid (73%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.25 (s, br,, 3H), 7.53 (t, *J* = 8.6 Hz, 1H), 7.25 (d, *J* = 8.3 Hz, 2H), 6.97 (d, *J* = 8.4 Hz, 2H), 6.91-6.88 (m, 1H), 6.84 (dd, *J* = 8.5, 2.3 Hz, 1H), 4.01 (s, 2H), 2.31 (s, 3H) ppm; LC-MS: *m/z* = 232.0 $[M + H]^+$.

6-(*p*-Tolyloxy)nicotinonitrile (81)

Title compound was prepared according to **General Procedure A2**, starting from *p*-cresol and 6-chloronicotinonitrile to give a pale yellow solid (92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45 (d, *J* = 1.7 Hz, 1H), 7.89 (dd, *J* = 8.6, 2.08 Hz, 1H), 7.23 (d, *J* = 8.2 Hz, 2H), 7.02-6.94 (m, 3H), 2.37 (s, 3H) ppm; LC-MS: *m/z* = 211 $[M + H]^+$.

(6-(*p*-Tolyloxy)pyridin-3-yl)methanamine HCl (82)

Title compound was prepared according to **General Procedure B5**, starting from **81** to give a white solid (52%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.28 (br, 3H), 8.20 (s,

1H), 7.95 (d, *J* = 9.0 Hz, 1H), 7.22 (d, *J* = 7.9 Hz, 2H), 7.05 (d, *J* = 8.1 Hz, 1H), 6.99 (d, *J* = 7.8 Hz, 2H), 4.05-3.95 (m, 2H), 2.32 (s, 3H) ppm; LC-MS: *m/z* = 215 $[M + H]^+$.

3-Fluoro-4-(*p*-tolyloxy)benzonitrile (83)

Title compound was prepared according to **General Procedure A2**, starting from 3,4-difluorobenzonitrile and *p*-cresol to give a colorless oil (85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, *J* = 10.0 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 7.20 (d, *J* = 8.0 Hz, 2H), 6.96-6.88 (m, 3H), 2.36 (s, 3H) ppm; LC-MS: *m/z* = 228.0 $[M + H]^+$.

(3-Fluoro-4-(*p*-tolyloxy)phenyl)methanamine (84)

Title compound was prepared according to **General Procedure B2**, starting from **83** to give a gummy liquid (92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15-7.09 (m, 3H), 7.02-6.93 (m, 2H), 6.86 (d, *J* = 8.2 Hz, 2H), 3.88 (s, br,, 2H), 2.31 (s, 3H) ppm; LC-MS: *m/z* = 232.1 $[M + H]^+$.

4-(4-Chlorophenoxy)-2-fluorobenzonitrile (85)

Title compound was prepared according to **General Procedure G2**, starting from 2-fluoro-4-hydroxybenzonitrile and (4-chlorophenyl)boronic acid to give a colorless oil (55%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56-7.52 (m, 1H), 7.39 (d, *J* = 8.5 Hz, 2H), 7.02 (d,

J = 8.5 Hz, 2H), 6.79 (d, *J* = 8.5 Hz, 1H), 6.73 (d, *J* = 10.1 Hz, 1H) ppm; LC-MS: *m/z* = 248.1 $[M + H]^+$.

(4-(4-Chlorophenoxy)-2-fluorophenyl)methanamine (86)

Title compound was prepared according to **General Procedure B2**, starting from **85** to give a gummy liquid (92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.23 (m, 3H), 6.97-6.92 (m, 2H), 6.76-6.67 (m, 2H), 3.90 (s, br,, 2H) ppm; LC-MS: *m/z* = 252.1 $[M + H]^+$.

4-(4-Chlorophenoxy)-3-fluorobenzonitrile (87)

Title compound was prepared according to **General Procedure A2**, starting from 3,4-difluorobenzonitrile and 4-chlorophenol to give a colorless oil (75%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, *J* = 8.4 Hz, 1H), 7.40-7.35 (m, 3H), 7.00-6.96 (m, 3H) ppm; LC-MS: *m/z* = 248.0 $[M + H]^+$.

4-(4-Methylbenzyl)benzonitrile (88)

A solution of 4-(chloromethyl)benzonitrile (1 g, 6.60 mmol) and *p*-tolylboronic acid (1.08 g, 7.92 mmol) in DMF (10.0 mL) and water (2.0 mL) was degassed under N_2 for 5 min. K_2CO_3 (1.82 g, 13.2 mmol) and $PdCl_2$ (0.12 g, 0.66 mmol) were then added to the reaction mixture. The reaction mixture was stirred at 90 °C for 3 h. Upon completion, the

reaction mixture was cooled and diluted with EtOAc. Organic layer was washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford crude product, which was purified by column chromatography (5% EtOAc in hexane) to give the title compound as a white solid (88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56-7.54 (m, 3H), 7.26 (d, J = 9.0 Hz, 1H), 7.11 (d, J = 7.7 Hz, 2H), 7.03 (d, J = 7.7 Hz, 2H), 3.98 (s, 2H), 2.32 (s, 3H) ppm; LC-MS: m/z = 208.0 $[M + H]^+$.

4-(p-Tolylthio)benzonitrile (89)

Title compound was prepared according to **General Procedure E2**, starting from 4-methylbenzenethiol and 4-iodobenzonitrile to give a white solid (58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.38 – 7.30 (m, 4H), 7.18 – 7.13 (m, 2H), 7.04 – 7.00 (m, 2H), 2.31 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 146.6, 140.0, 135.0, 132.3, 130.8, 126.9, 126.8, 118.9, 108.4, 21.4 ppm; LC-MS: m/z = 225.9 $[M + H]^+$.

***N*-Methoxy-*N*,6-dimethylnicotinamide (90)**

Title compound was prepared according to **General Procedure C6**, starting from 6-methylnicotinic acid and *N*,*O*-Dimethylhydroxylamine HCl to give a yellow oil (91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.70 (s, 1H), 7.79 (dd, J = 8.1, 2.2 Hz, 1H), 7.07 (d, J = 8.1

Hz, 1H), 3.41 (s, 3H), 3.22 (s, 3H), 2.45 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.3, 160.5, 148.6, 136.4, 126.7, 122.4, 61.0, 33.0, 24.2 ppm; LC-MS: *m/z* = 180.9 $[M + H]^+$.

(4-Bromophenyl)(6-methylpyridin-3-yl)methanone (91)

Title compound was prepared according to **General Procedure H2**, starting from **90** and 1,4-dibromobenzene to give a yellow solid (68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.77 (d, *J* = 1.0 Hz, 1H), 7.92 (dd, *J* = 8.1, 2.2 Hz, 1H), 7.61 – 7.53 (m, 4H), 7.23 (d, *J* = 8.0 Hz, 1H), 2.58 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 193.8, 163.0, 150.6, 137.5, 135.8, 131.9, 131.4, 130.1, 128.2, 123.2, 24.8 ppm; LC-MS: *m/z* = 275.8 $[M + H]^+$, 277.8 $[M + 2]^+$.

5-(4-Bromobenzyl)-2-methylpyridine (92)

Compound **91** (5.79 mmol), hydrazine monohydrate (57.94 mmol) and KOH (23.18 mmol) were dissolved in ethylene glycol (10 mL), followed by stirring at 150 °C for 1 h. Upon completion, the reaction mixture was cooled to room temperature and diluted with H_2O. The mixture was extracted with EtOAc (3 x 20 mL) and combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give crude product,

which was purified by column chromatography (5-30% EtOAc/petroleum benzine) to afford the title compound as a yellow oil (55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.35 (d, *J* = 2.0 Hz, 1H), 7.41 – 7.36 (m, 2H), 7.30 (dd, *J* = 8.0, 2.3 Hz, 1H), 7.06 – 6.98 (m, 3H), 3.86 (s, 2H), 2.50 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.5, 149.2, 139.2, 136.7, 132.7, 131.7, 130.5, 123.2, 120.3, 38.0, 24.0 ppm; LC-MS: *m/z* = 261.8 $[M + H]^+$, 263.8 $[M + 2]^+$.

4-((6-Methylpyridin-3-yl)methyl)benzonitrile (93)

Compound **92** (2.29 mmol), $K_4Fe(CN)_6.3H_2O$ (1.14 mmol), XPhos (0.23 mmol), and KOAc (0.30 mmol) were dissolved in a 1:4 mixture of H_2O:1,4-dioxane in a seal tube charged with a magnetic stirring bar. The mixture was degassed for 0.5 h before $Pd(dba)_3$ was added. The reaction was stirred vigorously (≥ 1000 rpm) at 100 °C for 1 h. Upon completion, the reaction mixture was cooled to room temperature then extracted with EtOAc, washed with water, $NaHCO_3$, brine. Organic layer was dried ($MgSO_4$) and solvent was removed *in vacuo* to afford crude product, which was purified by column chromatography (5-20% EtOAc/petroleum benzine) to yield the title compound as a yellow solid (84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.29 (d, *J* = 1.6 Hz, 1H), 7.53 – 7.46

(m, 2H), 7.26 (dd, *J* = 7.9, 2.3 Hz, 1H), 7.22 – 7.16 (m, 2H), 7.02 (d, *J* = 7.9 Hz, 1H), 3.92 (s, 2H), 2.45 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.9, 149.3, 145.8, 136.8, 132.5, 131.7, 129.6, 123.3, 118.8, 110.5, 38.7, 24.0 ppm; LC-MS: *m/z* = 209.0 $[M + H]^+$.

(4-((6-Methylpyridin-3-yl)methyl)phenyl)methanamine HCl (94)

Title compound was prepared according to **General Procedure B4**, starting from **93** to give a yellow solid (86%). ^{1}H NMR (400 MHz, DMSO) δ = 8.70 (d, *J* = 1.8 Hz, 1H), 8.48 (s, br, 3H), 8.31 (d, *J* = 8.3 Hz, 1H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.2 Hz, 2H), 4.13 (d, *J* = 10.8 Hz, 2H), 3.96 (q, *J* = 5.6 Hz, 2H), 2.70 (s, 3H); ^{13}C NMR (101 MHz, DMSO) δ = 151.6, 145.4, 140.1, 139.4, 137.9, 132.5, 129.4, 128.9, 127.4, 41.7, 36.4, 18.8 ppm; LC-MS: *m/z* = 214.0 $[M + H]^+$.

Interference Compounds. All final compounds have been examined for the presence of substructures classified as Pan Assay Interference Compounds (PAINS) using a KNIME workflow.[32,33]

ASSOCIATED CONTENT

Supporting Information.

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

SMILES molecular formula strings (CSV)

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ACKNOWLEDGEMENTS

Support from the Australian Research Council (ARC), Medicines for Malaria Venture (MMV), and Yourgene Bioscience is gratefully acknowledged. Fellowship

support (J.B.) was from the National Health and Medical Research Council of Australia (NHMRC) (2012-2016 Senior Research Fellowship #1020411, 2017- Principal Research Fellowship #1117602). Also acknowledged is Australian Federal Government Education Investment Fund Super Science Initiative and the Victorian State Government, Victoria Science Agenda Investment Fund for infrastructure support, and the facilities, and the scientific and technical assistance of the Australian Translational Medicinal Chemistry Facility (ATMCF), Monash Institute of Pharmaceutical Sciences (MIPS). ATMCF is supported by Therapeutic Innovation Australia (TIA). TIA is supported by the Australian Government through the National Collaborative Research Infrastructure Strategy (NCRIS) program. The Centre for Drug Candidate Optimisation, Monash Institute of Pharmaceutical Sciences, is acknowledged for their conduct of the ADME screening studies. The Peter McCallum Cancer Centre is acknowledged for their conduct of the cytotoxicity studies.

ABBREVIATIONS USED

ACN, acetonitrile; DCM, dichloromethane; LHS, left hand side; RHS, right hand side; TFP, tolfenpyrad.

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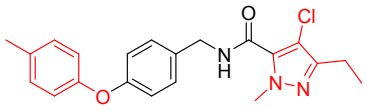
Table of Contents Graphic

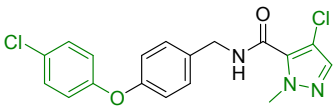
Graphical abstract



Tolfenpyrad

IC_{50} xL3: 2.9 µM

IC_{50} L4: 0.03 µM



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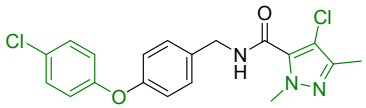

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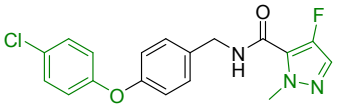

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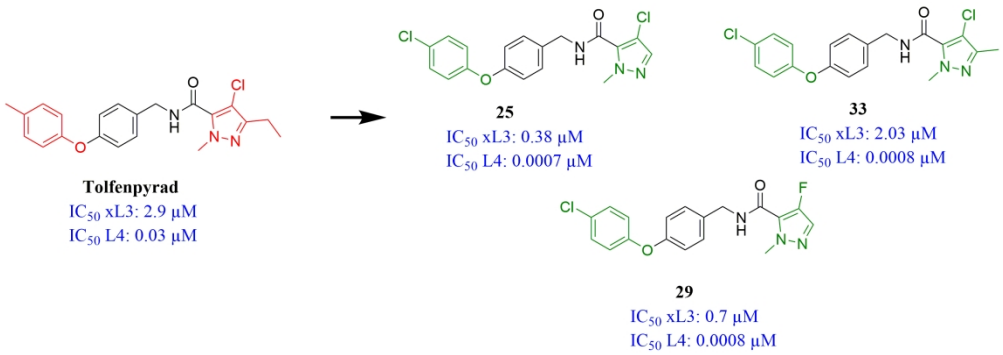

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