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Structure−Activity Relationship Studies of Tolfenpyrad Reveal Subnanomolar Inhibitors of *Haemonchus contortus* Development

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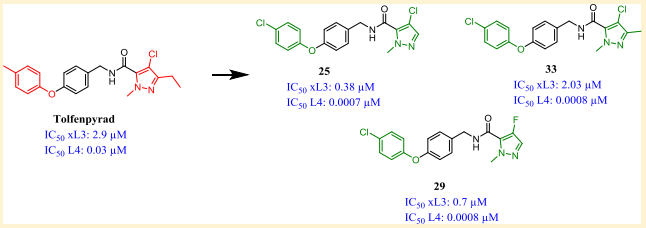
Supporting Information

ABSTRACT: Recently, we have discovered that the registered pesticide, tolfenpyrad, unexpectedly and potently inhibits the development of the L4 larval stage 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 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 subnanomolar level of potency against the chemotherapeutically relevant fourth larval (L4) stage 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 decreased significantly 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 a potent inhibitor of the motility and development of parasitic larvae of *Haemonchus contortus* (*H. 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 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 utilizing a well-

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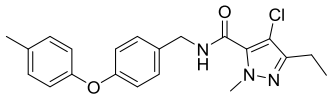


Tolfenpyrad (TFP)
IC_{50} xL3: 2.9 μM
IC_{50} L4: 0.03 μM
MCF10A cytotoxicity: 37.9 μM
clogP: 4.6

Figure 1. Structure, activity, and *c* Log *P* of the tolfenpyrad hit.

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 exsheathed L3 (xL3) motility and L4 development of *H. contortus* larvae and reveal novel modifications that reach subnanomolar levels of L4 larval development inhibition.

It can be seen that TFP harbors a large, hydrophobic, electron-rich *p*-methylphenoxybenzyloxy group. From a medicinal chemistry perspective, this chemical property of TFP would be considered suboptimal 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 druglike physicochemical "space" that might impart improved solubility and metabolic stability properties.

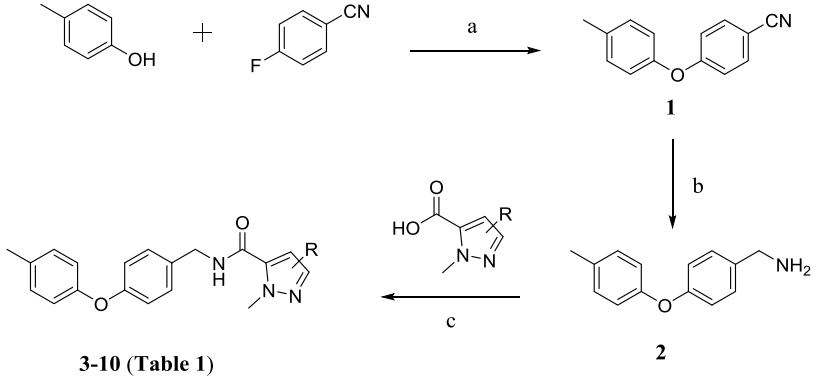
RESULTS AND DISCUSSION

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 benzylamine, which was then reacted with the pyrazole-5-carboxylic acid via an amide coupling reaction (Scheme 1). Likewise, in some cases, the LHS derivatization 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]

To examine SAR, compounds were first subjected to a primary screen, to assess their ability to inhibit the motility of *H. contortus* at the 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 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 inhibition compared to TFP. A similar but diminished loss of activity was observed when the 3-Et group was maintained but the 4-Cl group 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 to 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 five- or six-membered rings, such as furan, thiophene, substituted phenyl ring, or pyridinyl moiety, were all disfavored on the RHS of the scaffold, and therefore, were not explored in this study.[19]

The next aim was to explore SAR on the LHS of TFP, again with a focus on not only improving potency but also enhancing

Scheme 1. Synthetic Pathway of the Tolfenpyrad Scaffold[a]



[a](a) K_2CO_3, DMF; (b) $LiAlH_4$, THF; and (c) HOAt, EDCI·HCl, ACN, or HATU, DIPEA, DMF, or T3P, DIPEA, THF.

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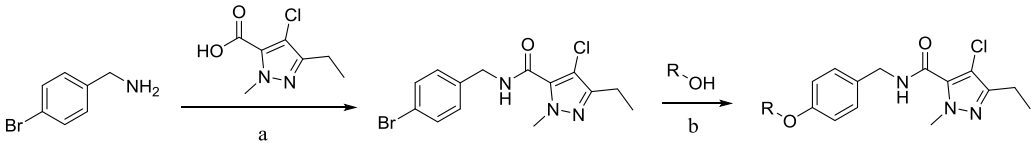
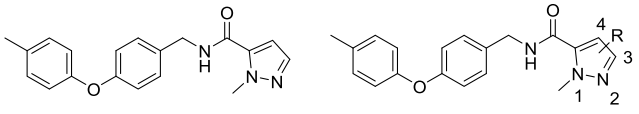
Scheme 2. Synthetic Pathway Used for LHS Derivatization[b]



[b](a) HOAt, EDCI·HCl, ACN, or HATU, DIPEA, DMF, or T3P, DIPEA, THF; (b) CuI, Cs_2CO_3, *N*,*N*-dimethylglycine, 1,4-dioxane.

Table 1. SAR of the RHS Pyrazole[a]



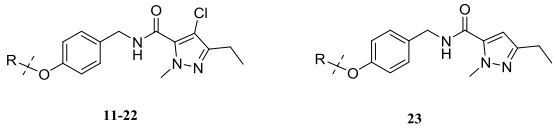
Entry	R	IC_{50} (μM) ± SD in xL3 motility assay	IC_{50} (μM) ± SD in L4 development assay
3		16.3 ± 6.66	0.13 ± 0.10
4	3-Et	10.53 ± 3.44	0.057 ± 0.002
5	3-CN	>100	
6	3-CF_3	>100	
7	4-CN	50 ± 0.001	1.69 ± 0.67
8	4-CF_3	>100	
9[a]	4-Cl	2.97 ± 2.56	0.003 ± 0.004
10[a]	4-F	4.37 ± 2.55	0.01 ± 0.007
TFP		2.9 ± 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]*c* Log *P*: **9**: 3.9; **10**: 3.7.

its physicochemical properties (Table 2). To increase hydrophilicity within the LHS region of TFP, the phenyl ring was replaced by a 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.

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 that the L3 activity was slightly weaker compared to 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 harbors 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

Table 2. SAR of the LHS Region



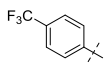
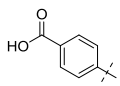
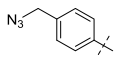
Entry	R	IC_{50} (μM) ± SD in xL3 motility assay	IC_{50} (μM) ± SD in L4 development assay
11		>100	
12		4.0 ± 1.84	0.03 ± 0.01
13		8.67 ± 4.55	0.019 ± 0.011
14		5.2 ± 3.02	0.14 ± 0.05
15		13.33 ± 12.0	0.04 ± 0.005
16		8.43 ± 7.53	0.04 ± 0.01
17		>100	
18		>100	
19		35.07 ± 17.19	0.45 ± 0.04
20		5.30 ± 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

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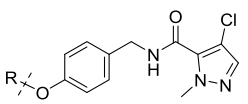
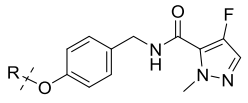
Table 3. Next-Generation SAR on the LHS and RHS Regions of TFP



24-27



28-31

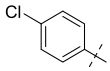
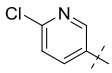
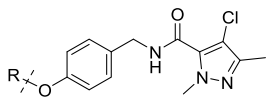
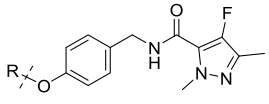
R	Entry	IC_{50} (μM) ± SD in xL3 motility assay	IC_{50} (μM) ± SD in L4 development assay	Entry	IC_{50} (μM) ± SD in xL3 motility assay	IC_{50} (μM) ± SD in L4 development assay
	**24**	3.70 ± 1.84	0.04 ± 0.03	**28**	14.47 ± 7.45	0.19 ± 0.15
	**25**	0.38 ± 0.10	0.0007 ± 0.0001	**29**	0.70 ± 0.24	0.0008 ± 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			

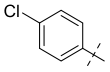
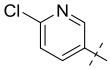
Table 4. Next-Generation SAR with 3-Methyl-4-chloropyrazole and 3-Methyl-4-fluoropyrazole RHS



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			

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-chloropyrazole RHS, displayed similar activity on both xL3 and L4 compared to **12**, whereas **28**, with the 4-fluoropyrazole RHS, caused a moderate loss in activity. Excitingly, compounds **25** and **29** showed a substantial

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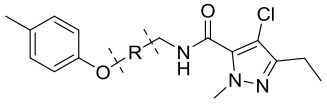
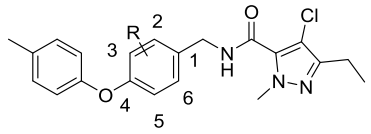
Table 5. SAR on the Middle Region of TFP



38, 40



39, 41

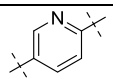
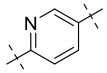
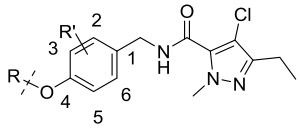
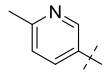
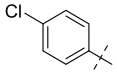
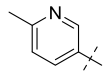
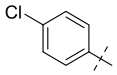
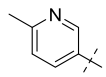
Entry	R	IC_{50} (μM) ± SD in xL3 motility assay	IC_{50} (μM) ± SD in L4 development assay
38		>100	
39	2-F	1.87 ± 1.27	0.08 ± 0.03
40		>100	
41	3-F	2.73 ± 1.59	0.06 ± 0.03
TFP		2.9 ± 0.58	0.03 ± 0.005
Monepantel		0.16 ± 0.008	0.075 ± 0.04
Moxidectin		0.08 ± 0.04	3.45 ± 0.75

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

improvement in activity, reducing the IC_{50} value for xL3 motility and L4 development inhibition to submicromolar and subnanomolar 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.

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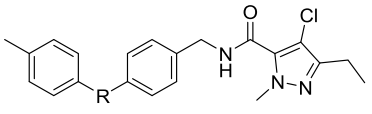
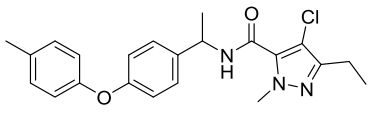
Table 7. SAR on Various Linking Regions of the TFP Scaffold



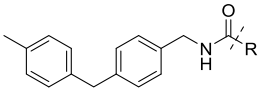
47-50



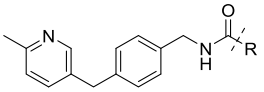
51

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 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	R
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	

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-fluoropyrazole RHS, as a complement to the 4-chloro and 4-fluoropyrazole RHS set (results summarized in Table 4). We included a 3-methyl group based on evidence already discussed for Table 1, which suggested that some hydrophobicity at this position might be favorable. 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 subnanomolar range for L4 development inhibition.

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 compound **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**).

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 were maintained for both **42** and **43**. There was no significant improvement on the original activity against both xL3 and L4 when the same LHS groups were explored with fluorine substitution at the 3-position of the middle ring, as seen for **44** and **45**. Interestingly, a complete

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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.

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 explored 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).

Having successfully identified compounds with significant improvement in activity compared to **TFP**, we selected nine 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 nine 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 compared to the activity for L4 development inhibition of 0.7 nM. It was also encouraging to see that 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 seven 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), *Heligmosomoides polygyrus* (rodent nematode), and *Trichuris muris* (whipworm). It can be seen that all seven compounds displayed 100% inhibition and >70% inhibition of L3 of *A. ceylanicum* at 100 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 six newly developed compounds compared to TFP.

In relation 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 nonparallel SAR, in terms of inhibitory activity observed for *H. contortus* in this study and the arthropod species studied by Okada et al.[14,29]

To assess the drug-likeliness of the TFP scaffold, we subjected TFP and nine 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 to TFP, including key high potency compounds, such as **34**, which with a *c* Log *P* of 3.0 was 40 times less lipophilic than TFP (*c* Log *P* 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 min for **10** to 84 min for **27**.

CONCLUSIONS

We have discovered that TFP potently inhibits the development of L4 stage larva of the ovine parasitic nematode, *H. contortus*. Herein, we report a systematic SAR interrogation

Table 10. Biological Activity Profile of Selected Compounds against a Panel of Parasitic Nematodes

	H. polygyrus adult (% inhibition)		*H. polygyrus* L3 (% inhibition)	*A. ceylanicum* L3 (% inhibition)		*T. muris* L1 (% inhibition)
Entry	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

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Table 11. Key Physicochemical Parameters and in Vitro Metabolic Stability of Selected Compounds

Entry	c Log P[a]	sol[b] (μg/mL) pH 2.0	sol[b] (μg/mL) pH 6.5	$T_{1/2}$ (min)	$CL_{int,\ in\ vitro}$[c] (μL/min/mg protein)	microsome-predicted E_H[d]
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.

that has led to the identification of novel modifications that not only improve druglike physicochemical properties, such as lipophilicity, aqueous solubility, and microsomal degradation half-life, but are also 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 submicromolar or subnanomolar ranges, and at the same time, maintaining selectivity toward 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 are 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: *c* Log *P*: 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 0.01 M HCl (approximately pH 2.0) with the final DMSO concentration being 1%. After 30 min had elapsed, the samples were then analyzed via nephelometry to determine a solubility range (see Bevan et al.[31]).[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 methods. 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 equiv) and nucleophile (1.1 equiv) in DMF (20 mL) was added Cs_2CO_3 (2.0 equiv), and the mixture was stirred at 100 °C for 2 h. Upon completion, the reaction mixture was diluted with EtOAc (50 mL) and organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. Crude product was purified by column chromatography (5−20% EtOAc/petroleum benzine) to yield the desired product.

General Procedure A2: Nucleophilic Aromatic Substitution Reactions. To a stirred solution of arylfluoride (1.0 equiv) and nucleophile (1.0 equiv) in DMF (20 mL), K_2CO_3 (2.0 equiv) was added. The reaction mixture was then stirred at 100 °C overnight. Upon completion, the reaction mixture was extracted with EtOAc, washed with water and 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 the desired product.

General Procedure B1: Nitrile Reduction. $LiAlH_4$ (3.0 equiv) was slowly added to a solution of substituted benzonitrile (1.0 equiv) in anhydrous THF (10 mL). The reaction was stirred at room temperature for 2 h and then cooled on ice before a solution of 1 M NaOH was added. The slurry mixture was then filtered through a pad of celite and filtrate was extracted with EtOAc (3 × 30 mL). Combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. HCl (4 M) in 1,4-dioxane (15 mL) was added to the residue, and then the reaction mixture was 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 the 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, 2 M in THF) was added dropwise under N_2. The 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 and 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, 7.0 M 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 the 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 equiv), di-*tert*-butyl dicarbonate (1.5 equiv), and $NiCl_2{\cdot}6H_2O$ (0.2 equiv) were dissolved in anhydrous MeOH in an

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oven-dried flask under N_2. The mixture was cooled to 0 °C before $NaBH_4$ (7.0 equiv) was added in small portions over 20 min. The reaction mixture was stirred at room temperature for 2 h. Diethylenetriamine (1.0 equiv) was then added, and the reaction mixture was 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 × 20 mL). Combined organic layers were washed with water and brine, dried ($MgSO_4$), and solvent was removed in vacuo to afford the desired Boc-protected benzylamine, which was then stirred in 4 M 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 equiv) and $NiCl_2{\cdot}6H_2O$ (0.2 equiv) were added to a stirred solution of substituted benzonitrile (1.0 equiv) in MeOH (7 mL) at 0 °C. $NaBH_4$ (7.0 equiv) was then added to the reaction mixture in small portions over 30 min. 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 a saturated $NaHCO_3$ solution and 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 equiv), HOAt (2.0 equiv), Et_3N (2.0 equiv), EDCI·HCl (2.0 equiv), and carboxylic acid (2.0 equiv) were dissolved in 3 mL of DMF. The 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 the desired product.

General Procedure C2: Amide Coupling. T_3P (2.0 equiv, 50% in EtOAc) and DIPEA (3.0 equiv) were added to a stirred solution of carboxylic acid (1.0 equiv) and amine (1.0 equiv) 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 and brine, dried over Na_2SO_4, and concentrated in vacuo to give crude product, which was purified by prep-HPLC to afford the 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 further at room temperature for 16 h. Upon completion, the reaction was diluted with EtOAc, washed with water and brine, and 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 the desired product.

General Procedure C4: Amide Coupling. EDCI·HCl (1.2 equiv) and HOAt (1.2 equiv) were added to a solution of carboxylic acid (1 equiv) in ACN (0.8 M) at room temperature. The reaction mixture was heated to 50 °C before amine (1.2 equiv) was added after 10 min. 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 × 10 mL) and washed with water. Combined organic layers were dried over $MgSO_4$ and 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 equiv) in pyridine (5 mL), T_3P (50% in EtOAc, 7.0 equiv) was added and the reaction mixture was stirred for 5 min before amine (free base or HCl salt, 1.0 equiv) was added. The reaction mixture was stirred at room temperature for 16 h. Upon completion, the reaction mixture was diluted with EtOAc. The organic layer was washed with saturated $NaHCO_3$ solution and 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 the 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 dichloromethane (DCM). The reaction mixture was stirred at room temperature overnight. Upon completion, DCM was removed in vacuo and the residue was extracted with EtOAc, washed with water and 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. $LiOH{\cdot}H_2O$ (2.0 equiv) was added to a stirred solution of ester (1.0 equiv) 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 1 N 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 × 10 mL). The aqueous layer was acidified with 1 M HCl to pH ∼ 3 and extracted with EtOAc (3 × 10 mL). Combined organic layers were 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 equiv) was added to a solution of ester (1.0 equiv) 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 1 M HCl to pH ∼ 1. The aqueous was extracted with EtOAc (2 × 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 equiv), substituted phenol (1.5 equiv), CuI (0.1 equiv), Cs_2CO_3 (2.0 equiv), and *N*,*N*-dimethylglycine (0.4 equiv) 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 and 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 × 20 mL), and the combined organic layers were washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. Crude product was purified by column chromatography (5−20% EtOAc/petroleum benzine) to yield the desired product.

General Procedure F: Primary Amine Synthesis from Aldehyde. Substituted benzaldehyde (1.0 equiv) was dissolved in EtOH (10 mL), $NH_2OH{\cdot}HCl$ (1.2 equiv) was then added, and the 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 equiv). The reaction was stirred for another 15 min before basified with excess amount of aqueous NH_3 and 6 M 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

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cold water and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give the desired product, which was used in the next step without any purification.

General Procedure G2: Chan−Lam Coupling. To a stirred solution of substituted phenol (1.0 equiv), aryl boronic acid (2.0 equiv), and Et_3N (5.0 equiv) in DCM (30 mL) was added $Cu(OAc)_2$ (1.0 equiv), 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 1 N NaOH solution. The organic layer was extracted and dried over anhydrous Na_2SO_4 and then 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 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 stirred at room temperature for 1 h. Upon completion, THF was removed in vacuo and saturated NH_4Cl solution was added to the residue, which was then extracted with EtOAc (3 × 10 mL). Combined organic layers were washed with water and 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. Arylhalide (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 stirred at −78 °C for 45 min. Upon completion, water was added to quench the reaction, followed by extraction with EtOAc (3 × 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 added. The reaction was stirred at 140 °C for 3 h. Upon completion of the reaction, the reaction mixture was cooled to room temperature and extracted with EtOAc; washed with saturated NH_4Cl, water, and brine; dried over anhydrous Na_2SO_4; and concentrated in vacuo. Crude product was purified by column chrom atography (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 the 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)-1*H*-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,

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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, and 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 colorless 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, and *m*-CPBA was then added. The reaction mixture was stirred at room temperature for 2 h. DCM was then removed in vacuo and EtOAc was added to the residue. The organic layer was washed with saturated $NaHCO_3$ and 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 equiv) was reacted with triphenylphosphine (1.1 equiv) and CBr_4 (1.1 equiv) 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 equiv). The reaction mixture was stirred at room temperature for 2 h. Upon completion, the reaction was diluted with EtOAc, washed with water and 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),

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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-1_H_-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)-1_H_-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, and 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, and 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 give 4-((6-chloropyridin-3-yl)oxy)benzonitrile, which was converted to the corresponding benzylamine according to General procedure B4, and 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, and 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, and 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 give 4-((6-chloropyridin-3-yl)oxy)benzonitrile, which was converted to the corresponding benzylamine according to General procedure B4, and 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, and 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,

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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 give 4-((6-chloropyridin-3-yl)oxy)benzonitrile, which was converted to the corresponding benzylamine according to General procedure B4, and 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, and 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 give 4-((6-chloropyridin-3-yl)oxy)benzonitrile, which was converted to the corresponding benzylamine according to General procedure B4, and 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)-1*H*-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 colorless 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-1*H*-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, and 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),

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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, and 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-1*H*-pyrazole-5-carboxamido)methyl)-benzoate, which was hydrolyzed according to General procedure D3 to give the corresponding carboxylic acid that 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 $NaHCO_3$ and 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 4 M 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),

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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)-1*H*-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 °C. The reaction mixture was stirred at room temperature for 18 h. Upon completion, the reaction was concentrated in vacuo to afford the title compound (3.5 g, 85%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (s, 1H), 3.95 (s, 6H) ppm; LCMS m/z = 185.0 $[M + H]^+$.

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 sulfate (2 mL, 20.92 mmol) was added. The reaction mixture was stirred at 40 °C for 3 h. After completion, the reaction mixture was filtered and the filtrate was concentrated in vacuo to afford the title compound (3.5 g, 93%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (s, 1H), 4.24 (s, 3H), 3.92 (s, 3H), 3.89 (s, 3H) ppm; LCMS m/z = 199 $[M + H]^+$.

5-(Methoxycarbonyl)-1-methyl-1*H*-pyrazole-3-carboxylic acid (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 the 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 °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, and concentrated to give the title compound (0.92 g, 77%) as an off-white solid, which was used in the 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 and then diluted with DCM. The 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 the 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, DMSO-d_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 the 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 × 10 mL), and the combined organic layers were concentrated in vacuo (water bath was kept at room temperature to avoid loss of product under vacuum as the product is very volatile). The crude product was purified by a 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%).

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^{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, the 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. ^{1}H 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 the organic layer was washed with water and 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 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, 1 M in DCM) was then added dropwise 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. The organic layer was washed with water and 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 colorless 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. The organic

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layer was washed with water and 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 × 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), $K_4Fe(CN)_6{\cdot}3H_2O$ (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 sealed 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 and then extracted with EtOAc and washed with water, $NaHCO_3$, and brine. The 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 at DOI: 10.1021/acs.jmedchem.8b01789.

SMILES molecular formula strings (CSV)

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

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

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