1 **Structure–Activity Relationship Studies of Tolfenpyrad Reveal**
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ABSTRACT: Recently, we have discovered that the registered pesticide, tolfenpyrad, unexpectedly and potently inhibits the development of L4 larval stages of the parasitic nematode *Haemonchus contortus* with an IC_{50} value of 0.03 μ M while displaying good selectivity, with an IC_{50} of 37.9 μ M 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, right-hand side, 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) stages of *H. contortus*. Selected compounds from the series also showed promising activity against a panel of other different parasitic nematodes, such as hookworms and whipworms.

34 **INTRODUCTION**

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

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

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Tolfenpyrad (TFP)IC₅₀ xL3: 2.9 μMIC₅₀ L4: 0.03 μM

MCF10A cytotoxicity: 37.9 μM

clogP: 4.6

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

58 insecticidal, fungicidal, or miticidal activities have been
59 observed for this chemical.^{12–15} Furthermore, nothing is
60 known about its SAR against parasitic nematodes. Herein, by
61 utilizing a well-established but proprietary and sophisticated
62 phenotypic drug-screening platform for *H. contortus*,^{16,17} we
63 report, for the first time, comprehensive SAR of TFP for
64 inhibition of L3 motility and L4 development of *H. contortus*
65 larvae and reveal novel modifications that reach subnanomolar
66 levels of L4 larval development inhibition.

67 It can be seen that TFP harbors a large, hydrophobic,
68 electron-rich *p*-methylphenoxybenzyloxy group. From a
69 medicinal chemistry perspective, this chemical property of
70 TFP would be considered suboptimal for a drug candidate that
71 is proposed to be administered, for example, orally to a
72 vertebrate animal affected by worms, as opposed to the
73 application (as pesticide) to the surface of arthropod-affected
74 plants. Therefore, the predominant focus of this study was to
75 explore TFP SAR with a view to maintaining or even
76 increasing potency of TFP, while moving the scaffold into a
77 more druglike physicochemical “space” that might impart
78 improved solubility and metabolic stability properties.

RESULTS AND DISCUSSION

80 The structure of the TFP scaffold can usefully be considered as
81 divided into two main components, namely, the pyrazole-5-
82 carboxamide and the *p*-methylphenoxybenzyloxy parts. For
83 late-stage derivatization of the RHS pyrazole, the *p*-
84 methylphenoxybenzyloxy group was obtained via a nucleo-
85 philic aromatic substitution reaction of *p*-cresol and 4-
86 fluorobenzonitrile, followed by a reduction of the nitrile
87 group, to yield the benzylamine, which was then reacted with
88 the pyrazole-5-carboxylic acid via an amide coupling reaction
89 (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 exsheathed L3 (xL3) stage, using
monepantel and moxidectin as positive control anthelmintics.
Only compounds that resulted in ≥70% motility inhibition of
xL3 larvae at a concentration of 100 μM were subjected to
subsequent dose–response evaluation, to establish IC₅₀ 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 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 (IC₅₀ 0.057 μM). Hence, comparing 3 with 4
suggests some hydrophobicity on the 3-position, which 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 IC₅₀ 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

Scheme 1. Synthetic Pathway of the Tolfenpyrad Scaffold^a ^a(a) K₂CO₃, DMF; (b) LiAlH₄, THF; and (c) HOAt, EDCI-HCl, ACN, or HATU, DIPEA, DMF, or T3P, DIPEA, THF.

Scheme 2. Synthetic Pathway Used for LHS Derivatization^b

11-12 (Table 2)

^b(a) HOAt, EDCI·HCl, ACN, or HATU, DIPEA, DMF, or T3P, DIPEA, THF; (b) CuI, Cs₂CO₃, *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

^ac Log P: 9: 3.9; 10: 3.7.

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

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 IC₅₀ value of 0.08 μM. Compound 22

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			

was synthesized as part of the SAR assessment and also for its potential to serve as a probe for target identification due to the azide-functional group. Click chemistry in activity-based protein profiling for target identification has been extensively reported in the literature.^{26–28} Although the azide-tagged analogue **22** resulted in a dramatic motility reduction in xL3, it still displayed a binding affinity to inhibit L4 development,

which suggests that azide-tagged TFP might find utility for future target identification studies.

From the SAR investigation on the RHS of TFP, we identified that the RHS of compounds **9** and **10** and the LHS of **12** and **23** were optimal for the compounds tested. Having successfully identified these groups, the focus then was on incorporating them to develop a new set of analogues to probe the next generation of SAR, whose results are summarized in

Table 5. SAR on the Middle Region of TFP

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

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-diF	>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

Table 3. For LHS with the pyridinyl moiety, compound 24, with the 4-chloropyrazole RHS, displayed similar activity in 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

improvement in activity, reducing the IC₅₀ 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.

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	

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.

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 IC₅₀ 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 compounds **38** produced a complete loss of activity, whereas the fluoro substituent in **39** maintained the level of potency observed for TFP against both xL3 motility and L4 development. Similar results were observed for the 3-position (**40** and **41**).

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 in the original activity against both xL3 and L4 when the same LHS groups were experimented upon with fluorine substitution at the 3-position of the middle ring, as seen for **44** and **45**. Interestingly, a complete loss of activity against *H. contortus* was observed for compound **46** when an additional fluorine was implemented at the 5-position of the middle ring. These findings indicated a very tight SAR for this region.

Alterations to the ether bridge and the benzylic carbon of TFP were also assessed. Different functional groups were used to replace the oxygen from the ether bridge, such as a methylene group (compound **47**), a carbonyl group (**48**), a sulfur (**49**), or a methylated amine (**50**) (Table 7). However, none of these replacement groups yielded active compounds. A similar result was achieved when the benzylic carbon was methylated to produce **51**. Interestingly, when incorporating the methylene prototype into one of the four most active RHS pyrazoles to produce **52–55** (Table 8), activity was regained, but with no significant improvement with respect to TFP. From these results, the same RHS pyrazoles and the methylene bridge were then experimented upon with the active pyridinyl LHS, with the hope of achieving some improvement in activity. However, the original potency could not be maintained (**56–59**, Table 8).

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 IC₅₀ value of 8.02 μ M for one of our most potent compounds **25**, it was still a great level of selectivity compared to the activity for L4 development 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.

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), *Heligiosomoides polygyrus* (rodent nematode), and *T. muris* (whipworm). It can be seen that all seven compounds displayed 100% inhibition and >70% inhibition of L3 of *A. ceylanicum* at 100 and 10 μ M, respectively. Similar results were seen for adult *H. polygyrus*, where all compounds, except **33**, showed complete inhibition at 100 μ M and >70% inhibition at only 1 μ M. All compounds exhibited >90% inhibition of first larval (L1) stage of *T. muris* at 100 μ M. 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-likeness 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

Table 9. Cytotoxicity Data for Selected Active Compounds on the MCF10A Cell Line

entry	IC ₅₀ (μ M) $\pm$ SD in xL3 motility assay	IC ₅₀ (μ M) $\pm$ SD in L4 development assay	MCF10A cytotoxicity IC ₅₀ (μ M) $\pm$ SEM
TFP	2.57 $\pm$ 0.58	0.025 $\pm$ 0.005	37.90 $\pm$ 3.11
10	4.37 $\pm$ 2.55	0.01 $\pm$ 0.007	13.13 $\pm$ 0.38
23	2.43 $\pm$ 1.42	0.08 $\pm$ 0.006	8.8 $\pm$ 0.34
25	0.38 $\pm$ 0.10	0.0007 $\pm$ 0	8.02 $\pm$ 0.48
27	2.80 $\pm$ 2.26	0.02 $\pm$ 0.01	>50
28	14.47 $\pm$ 7.45	0.19 $\pm$ 0.15	>50
29	0.70 $\pm$ 0.24	0.0008 $\pm$ 0.0001	>50
31	14.8 $\pm$ 9.6	0.17 $\pm$ 0.09	>50
32	3.33 $\pm$ 1.89	0.01 $\pm$ 0.01	>50
33	2.03 $\pm$ 1.82	0.0008 $\pm$ 0.0001	>50
34	1.8 $\pm$ 0.49	0.008 $\pm$ 0.009	>50

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

entry	<i>H. polygyrus</i> adult (% inhibition)		<i>H. polygyrus</i> L3 (% inhibition)	<i>A. ceylanicum</i> L3 (% inhibition)		<i>T. muris</i> L1 (% inhibition)
	10 μ M	1 μ M		100 μ M	10 μ M	
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

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

ID	$c \text{ Log } P^a$		sol^b ($\mu\text{g/mL}$)		$T_{1/2}$ (min)	$\text{CL}_{\text{int, in vitro}}^c$ ($\mu\text{L/min/mg protein}$)	microsome-predicted E_H^d
	pH 2.0	pH 6.5	pH 2.0	pH 6.5			
TFP	4.6	3.1–6.3	<1.6		14	121	N/A
10	3.3	25–50	6.3–2.5		20	87	0.65
23	4.1	1.6–3.1	1.6–3.1		36	48	0.51
27	2.8	6.3–12.5	6.3–12.5		84	21	0.31
28	1.7	>100	25–50		25	69	0.60
29	3.4	3.1–6.3	1.6–3.1		57	30	0.39
31	2.4	9–18	9–18		80	22	0.32
32	2.3	>100	12.5–25		31	55	0.54
33	4.0	1.6–3.1	3.1–6.3		80	22	0.32
34	3.0	4.9–9.8	2.4–4.9		55	31	0.40

^aCalculated using ChemAxon JChem software. ^bKinetic solubility determined by nephelometry (Sol_{pH}). ^cIn vitro intrinsic clearance determined in mouse liver microsomes. ^dPredicted hepatic extraction ratio calculated from in vitro data.

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 larvae of the ovine parasitic nematode, *H. contortus*. Herein, we report a systematic SAR interrogation that has led to the identification of novel modifications that not only improve 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, 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-likeness 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: $c \text{ Log } P$: 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).

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, ^1H 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 benzene) 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 benzene) 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 $\times$ 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 $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ (0.2 equiv) were dissolved in anhydrous MeOH in an oven-dried flask under N_2 . The mixture was cooled to 0 °C before NaBH_4 (7.0 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 $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ (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 benzene) 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 benzene) 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 benzene). 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 benzene) 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. $\text{LiOH} \cdot \text{H}_2\text{O}$ (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 were 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 benzene) 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 benzene) to yield the desired product.

General Procedure F: Primary Amine Synthesis from Aldehyde. Substituted benzaldehyde (1.0 equiv) was dissolved in EtOH (10 mL), $\text{NH}_2\text{OH} \cdot \text{HCl}$ (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. Et₃N (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 O₂ balloon for 18 h. Upon completion, the reaction mixture was filtered and residue was diluted with DCM. Organic layer was washed with cold water and brine, dried over anhydrous Na₂SO₄, 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 Et₃N (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 O₂ for 16 h. Upon completion, the reaction mixture was filtered through a pad of celite and the filtrate was washed with 10% aqueous NaHSO₄ solution and 1 N NaOH solution. The organic layer was extracted and dried over anhydrous Na₂SO₄ and then concentrated in vacuo to give crude product, which was purified by column chromatography (5–20% EtOAc/petroleum benzene) 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 N₂. 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 NH₄Cl 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 (MgSO₄), and concentrated in vacuo to give crude product, which was purified by column chromatography (5–20% EtOAc/petroleum benzene) 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 N₂. 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 (MgSO₄), and concentrated in vacuo to give crude product, which was purified by column chromatography (5–20% EtOAc/petroleum benzene) 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%). ¹H NMR (400 MHz, CDCl₃): 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%). ¹H NMR (400 MHz, CDCl₃): 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*-tolylloxy)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%). ¹H NMR (400 MHz, CDCl₃): 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; ¹³C NMR (101 MHz, CDCl₃): 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*-tolylloxy)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%). ¹H NMR

(400 MHz, CDCl₃): 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; ¹³C NMR (101 MHz, CDCl₃): 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*-tolylloxy)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%). ¹H 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*-tolylloxy)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%). ¹H 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*-tolylloxy)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 NH₄Cl, water, and brine; dried over anhydrous Na₂SO₄; and concentrated in vacuo. Crude product was purified by column chromatography (30% EtOAc in hexane) to afford methyl-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%). ¹H 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*-tolylloxy)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%). ¹H NMR (400 MHz, CDCl₃): 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*-tolylloxy)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%). ¹H NMR (400 MHz, CDCl₃): 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; ¹³C NMR (101 MHz, CDCl₃): 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*-tolylloxy)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). ¹H NMR (400 MHz, CDCl₃): 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). ^1H NMR (400 MHz, CDCl_3) δ = 7.46 (d, J = 8.2 Hz, 2H), 7.36 (d, J = 8.3 Hz, 2H), 7.27 (dd, J = 9.4, 2.4 Hz, 1H), 7.22 (s, br, 1H), 7.10 (s, 1H), 6.60 (d, J = 9.3 Hz, 1H), 4.67 (d, J = 5.8 Hz, 2H), 4.13 (s, 3H), 2.64 (q, J = 7.6 Hz, 2H), 2.10 (s, 3H), 1.24 (t, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (101 MHz, CDCl_3) δ = 161.8, 158.7, 149.6, 142.8, 140.4, 138.0, 135.2, 131.0, 128.5, 127.0, 121.4, 115.2, 107.8, 42.9, 40.6, 19.2, 17.0, 12.8 ppm; LC-MS m/z = 384.8 $[\text{M} + \text{H}]^+$.

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). ^1H 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 $[\text{M} + \text{H}]^+$.

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). ^1H 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 $[\text{M} + \text{H}]^+$.

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%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) 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 $[\text{M} + \text{H}]^+$.

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%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) 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 $[\text{M} + \text{H}]^+$.

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%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) 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 $[\text{M} + \text{H}]^+$.

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%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) 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 $[\text{M} + \text{H}]^+$.

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%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) 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 $[\text{M} + \text{H}]^+$.

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%). ^1H 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 $[\text{M} + \text{H}]^+$.

***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%). ^1H 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 $[\text{M} + \text{H}]^+$.

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%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) 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 $[\text{M} + \text{H}]^+$.

***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-1*H*-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 benzene) to give the title compound as a colorless oil (24%). ^1H NMR (401 MHz, CDCl_3) δ = 7.33 (d, J = 8.6 Hz, 2H), 7.28 (d, J = 8.6 Hz, 2H), 7.01 (d, J = 8.0 Hz, 5H), 4.62 (d, J = 5.8 Hz, 2H), 4.31 (s, 2H), 4.15 (s, 3H), 2.63 (q, J = 7.6 Hz, 2H), 1.24 (t, J = 7.6 Hz, 3H) ppm; ^{13}C NMR (101 MHz, CDCl_3) δ = 183.3, 158.6, 156.5, 149.7, 132.8, 131.0, 130.4, 130.0, 129.3, 119.5, 119.1, 107.0, 54.4, 43.0, 40.8, 19.3, 12.9 ppm; LC-MS: m/z = 424.8 $[\text{M} + \text{H}]^+$.

***N*-(4-(4-Chlorophenoxy)benzyl)-3-ethyl-1-methyl-1H-pyrazole-5-carboxamide (23).** Title compound was prepared according to General procedure C1, starting from (4-(4-chlorophenoxy)phenyl)methanamine HCl and 3-ethyl-1-methyl-1H-pyrazole-5-carboxylic acid to give a yellow oil (58%). ^1H 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 $[\text{M} + \text{H}]^+$.

4-Chloro-1-methyl-*N*-(4-((6-methylpyridin-3-yl)oxy)benzyl)-1H-pyrazole-5-carboxamide (24). General procedure A1 was followed, starting from 6-methylpyridin-3-ol and 4-fluorobenzaldehyde to give 4-((6-methylpyridin-3-yl)oxy)benzaldehyde, which was converted to the corresponding benzylamine according to General procedure F, and then subsequently coupled to 4-chloro-1-methyl-1H-pyrazole-5-carboxylic acid according to General procedure C1 to give the title compound as a yellow oil (35%). ^1H 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 $[\text{M} + \text{H}]^+$.

4-Chloro-*N*-(4-(4-chlorophenoxy)benzyl)-1-methyl-1H-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-1H-pyrazole-5-carboxylic acid to give a white solid (36%). ^1H 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 $[\text{M} + \text{H}]^+$.

4-Chloro-1-methyl-*N*-(4-((2-methylpyrimidin-5-yl)oxy)benzyl)-1H-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-1H-pyrazole-5-carboxylic acid according to General procedure C1 to give the title compound as a yellow oil (16%). ^1H 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 $[\text{M} + \text{H}]^+$.

4-Chloro-*N*-(4-((6-chloropyridin-3-yl)oxy)benzyl)-1-methyl-1H-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-1H-pyrazole-5-carboxylic acid according to General procedure C1 to give the title compound as a yellow oil (23%). ^1H 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 $[\text{M} + \text{H}]^+$.

4-Fluoro-1-methyl-*N*-(4-((6-methylpyridin-3-yl)oxy)benzyl)-1H-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-1H-pyrazole-5-carboxylic acid according to General procedure C1 to give the title compound as a yellow oil (48%). ^1H 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 $[\text{M} + \text{H}]^+$.

***N*-(4-(4-Chlorophenoxy)benzyl)-4-fluoro-1-methyl-1H-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-1H-pyrazole-5-carboxylic acid to give a white solid (17%). ^1H 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 $[\text{M} - \text{H}]^-$.

4-Fluoro-1-methyl-*N*-(4-((2-methylpyrimidin-5-yl)oxy)benzyl)-1H-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-1H-pyrazole-5-carboxylic acid according to General procedure C1 to give the title compound as a yellow oil (18%). ^1H 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 $[\text{M} + \text{H}]^+$.

***N*-(4-((6-Chloropyridin-3-yl)oxy)benzyl)-4-fluoro-1-methyl-1H-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-1H-pyrazole-5-carboxylic acid according to General procedure C1 to give the title compound as a yellow oil (7%). ^1H 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 $[\text{M} + \text{H}]^+$.

4-Chloro-1,3-dimethyl-*N*-(4-((6-methylpyridin-3-yl)oxy)benzyl)-1H-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-1H-pyrazole-5-carboxylic acid according to General procedure C1 to give the title compound as a yellow oil (40%). ^1H 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 $[\text{M} + \text{H}]^+$.

4-Chloro-*N*-(4-(4-chlorophenoxy)benzyl)-1,3-dimethyl-1H-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-1H-pyrazole-5-carboxylic acid to give a yellow solid (37%). ¹H NMR (400 MHz, CDCl₃) 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; ¹³C NMR (101 MHz, CDCl₃) δ = 158.5, 156.6, 155.8, 144.6, 132.8, 131.0, 129.8, 129.3, 128.5, 120.2, 119.2, 108.4, 42.9, 40.7, 11.1 ppm; LC-MS: m/z = 389.8 [M + H]⁺.

4-Chloro-N-(4-((6-chloropyridin-3-yl)oxy)benzyl)-1,3-dimethyl-1H-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-1H-pyrazole-5-carboxylic acid according to General procedure C1 to give the title compound as a yellow oil (10%). ¹H 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)-1H-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-1H-pyrazole-5-carboxylic acid according to General procedure C1 to give the title compound as a yellow oil (12%). ¹H NMR (400 MHz, CDCl₃) 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; ¹³C NMR (101 MHz, CDCl₃) δ = 158.0, 156.8, 153.5, 151.3, 148.1, 145.6, 141.0, 133.0, 132.8 (d, J = 9.2 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-1H-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-1H-pyrazole-5-carboxylic acid to give a colorless oil (30%). ¹H NMR (400 MHz, CDCl₃) 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; ¹³C NMR (101 MHz, CDCl₃) 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-1H-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-1H-pyrazole-5-carboxylic acid according to General procedure C1 to give the title compound as a colorless oil (38%). ¹H NMR (400 MHz, CDCl₃) 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; ¹³C NMR (101 MHz, CDCl₃) δ = 158.0, 157.9, 155.5, 153.1, 148.0, 145.5, 144.9, 140.5, 134.1, 132.6 (d, J = 11.7 Hz), 129.5, 128.57, 124.8, 119.2, 42.4, 40.1, 9.5 (d, J = 3.1 Hz) ppm; LC-MS: m/z = 374.8 [M + H]⁺.

4-Chloro-3-ethyl-1-methyl-N-((5-(p-tolyloxy)pyridin-2-yl)methyl)-1H-pyrazole-5-carboxamide (38). Title compound was prepared according to General procedure C5, starting from 78 and 4-chloro-3-ethyl-1-methyl-1H-pyrazole-5-carboxylic acid to give a white solid (19%). ¹H NMR (400 MHz, DMSO d₆) 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-1H-pyrazole-5-carboxamide (39). Title compound was prepared

according to General procedure C2, starting from 80 and 4-chloro-3-ethyl-1-methyl-1H-pyrazole-5-carboxylic acid to give a colorless gum (62%). ¹H NMR (400 MHz, DMSO-d₆): 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)-1H-pyrazole-5-carboxamide (40). Title compound was prepared according to General procedure C2, starting from 82 and 4-chloro-3-ethyl-1-methyl-1H-pyrazole-5-carboxylic acid to give an off-white solid (23%). ¹H NMR (400 MHz, DMSO-d₆): 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-1H-pyrazole-5-carboxamide (41). Title compound was prepared according to General procedure C2, starting from 84 and 4-chloro-3-ethyl-1-methyl-1H-pyrazole-5-carboxylic acid to give an off-white solid (44%). ¹H NMR (400 MHz, DMSO-d₆): 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-1H-pyrazole-5-carboxamide (42). General procedure C1 was followed, starting from (4-bromo-2-fluorophenyl)methanamine and 4-chloro-3-ethyl-1-methyl-1H-pyrazole-5-carboxylic acid to give N-(4-bromo-2-fluorobenzyl)-4-chloro-3-ethyl-1-methyl-1H-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%). ¹H NMR (400 MHz, CDCl₃) 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; ¹³C NMR (101 MHz, CDCl₃) 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-1H-pyrazole-5-carboxamide (43). Title compound was prepared according to General procedure C2, starting from 86 and 4-chloro-3-ethyl-1-methyl-1H-pyrazole-5-carboxylic acid to give an off-white solid (24%). ¹H NMR (400 MHz, DMSO-d₆): δ 8.90 (s, br, 1H), 7.47–7.41 (m, 3H), 7.08 (d, J = 8.7 Hz, 2H), 6.95 (d, J = 11.3 Hz, 1H), 6.86 (d, J = 7.4 Hz, 1H), 4.48 (d, J = 5.1 Hz, 2H), 3.83 (s, 3H), 2.55–2.50 (m, 2H), 1.16 (t, J = 7.4 Hz, 3H) ppm; LC-MS: m/z = 422.0 [M + H]⁺.

4-Chloro-3-ethyl-N-(3-fluoro-4-((6-methylpyridin-3-yl)oxy)benzyl)-1-methyl-1H-pyrazole-5-carboxamide (44). General procedure A1 was followed, starting from 6-methylpyridin-3-ol and 3,4-difluorobenzaldehyde to give 3-fluoro-4-((6-methylpyridin-3-yl)oxy)benzaldehyde, which was converted to the corresponding benzylamine according to General procedure F, and then subsequently coupled to 4-chloro-3-ethyl-1-methyl-1H-pyrazole-5-carboxylic acid according to General procedure C1 to give the title compound as a yellow oil (28%). ¹H 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; ¹³C 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-1H-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-1H-

pyrazole-5-carboxylic acid according to General procedure C2 to afford the title compound as an off-white solid (28%). ^1H NMR (400 MHz, DMSO- d_6): δ 8.97 (s, br, 1H), 7.43–7.35 (m, 3H), 7.22 (s, br, 2H), 6.98 (d, J = 8.5 Hz, 2H), 4.49 (d, J = 5.3 Hz, 2H), 3.85 (s, 3H), 2.56–2.50 (m, 2H), 1.17 (t, J = 7.4 Hz, 3H) ppm; LC-MS: m/z = 422.1 $[\text{M} + \text{H}]^+$.

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%). ^1H 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 $[\text{M} + \text{H}]^+$.

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%). ^1H 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, 3H) 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 $[\text{M} + \text{H}]^+$.

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%). ^1H 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 $[\text{M} + \text{H}]^+$.

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%). ^1H 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 $[\text{M} + \text{H}]^+$.

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 $\text{Pd}(\text{OAc})_2$ (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 benzene) 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%). ^1H 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 $[\text{M} + \text{H}]^+$.

4-Chloro-3-ethyl-1-methyl-*N*-(1-(4-(*p*-tolyl)oxy)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%). ^1H 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 $[\text{M} + \text{H}]^+$.

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%). ^1H 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 $[\text{M} + \text{H}]^+$.

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%). ^1H 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 $[\text{M} + \text{H}]^+$.

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%). ^1H 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 $[\text{M} + \text{H}]^+$.

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-carbox-

1241 ylic acid according to General procedure C1 to give the title
1242 compound as a white solid (61%). ¹H NMR (400 MHz, CDCl₃) δ =
1243 7.19–7.15 (m, 2H), 7.09 (d, *J* = 8.2 Hz, 2H), 7.03–6.96 (m, 4H),
1244 6.91 (s, br, 1H), 4.50 (d, *J* = 5.7 Hz, 2H), 4.04 (s, 3H), 3.84 (s, 2H),
1245 2.22 (s, 3H), 2.14 (s, 3H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ =
1246 158.5, 144.5, 141.1, 137.9, 135.7, 135.1, 131.1, 129.39, 129.2, 128.8,
1247 127.8, 108.4, 43.3, 41.2, 40.6, 21.0, 11.1 ppm; LC-MS: *m/z* = 367.8
1248 [M + H]⁺.

1249 **4-Fluoro-1-methyl-N-(4-((6-methylpyridin-3-yl)methyl)-**
1250 **benzyl)-1H-pyrazole-5-carboxamide (56).** Title compound was
1251 prepared according to General procedure C1, starting from **94** and 4-
1252 fluoro-1-methyl-1H-pyrazole-5-carboxylic acid to give a colorless oil
1253 (47%). ¹H NMR (400 MHz, CDCl₃) δ = 8.44 (d, *J* = 1.8 Hz, 1H),
1254 7.48 (dd, *J* = 8.0, 2.2 Hz, 1H), 7.30–7.21 (m, 3H), 7.13 (dd, *J* = 14.5,
1255 8.1 Hz, 3H), 6.54 (d, *J* = 5.3 Hz, 1H), 4.55 (d, *J* = 5.8 Hz, 2H), 4.11
1256 (d, *J* = 0.9 Hz, 3H), 3.93 (s, 2H), 2.57 (s, 3H) ppm; ¹³C NMR (101
1257 MHz, CDCl₃) δ = 157.8, 155.0, 146.7, 139.1, 138.9, 136.1, 134.7,
1258 129.3, 128.2, 124.5, 120.9, 120.7, 42.9, 40.7 (d, *J* = 22.0 Hz), 38.2,
1259 22.2 ppm; LC-MS: *m/z* = 338.9 [M + H]⁺.

1260 **4-Fluoro-1,3-dimethyl-N-(4-((6-methylpyridin-3-yl)methyl)-**
1261 **benzyl)-1H-pyrazole-5-carboxamide (57).** Title compound was
1262 prepared according to General procedure C1, starting from **94** and 4-
1263 fluoro-1,3-dimethyl-1H-pyrazole-5-carboxylic acid to give a colorless
1264 oil (32%). ¹H NMR (401 MHz, CDCl₃) δ = 8.61 (s, 1H), 8.01 (d, *J* =
1265 7.1 Hz, 1H), 7.54 (t, *J* = 8.8 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.16
1266 (d, *J* = 8.0 Hz, 2H), 6.60 (d, *J* = 5.7 Hz, 1H), 4.59 (d, *J* = 5.8 Hz, 2H),
1267 4.12–4.06 (m, 5H), 2.80 (s, 3H), 2.22 (s, 3H) ppm; ¹³C NMR (101
1268 MHz, CDCl₃) δ = 158.0, 152.1, 145.4, 141.1, 138.7, 137.2, 136.4,
1269 132.9 (d, *J* = 12.1 Hz), 129.5, 128.6, 127.2, 121.1, 120.8, 42.8, 40.1,
1270 37.9, 19.3, 9.5 (d, *J* = 3.0 Hz) ppm; LC-MS: *m/z* = 352.9 [M + H]⁺.

1271 **4-Chloro-1-methyl-N-(4-((6-methylpyridin-3-yl)methyl)-**
1272 **benzyl)-1H-pyrazole-5-carboxamide (58).** Title compound was
1273 prepared according to General procedure C1, starting from **94** and 4-
1274 chloro-1-methyl-1H-pyrazole-5-carboxylic acid to give a white solid
1275 (35%). ¹H NMR (400 MHz, CDCl₃) δ = 8.28 (d, *J* = 14.6 Hz, 1H),
1276 7.36–7.33 (m, 1H), 7.31–7.26 (m, 1H), 7.20 (d, *J* = 7.8 Hz, 2H),
1277 7.09 (d, *J* = 8.2 Hz, 2H), 6.98 (t, *J* = 7.6 Hz, 1H), 6.93 (s, br, 1H),
1278 4.53 (d, *J* = 5.7 Hz, 2H), 4.10 (s, 3H), 3.85 (s, 2H), 2.44 (s, 3H)
1279 ppm; ¹³C NMR (101 MHz, CDCl₃) δ = 158.3, 156.3, 149.2, 139.8,
1280 136.9, 136.7, 135.6, 133.2, 130.9, 129.3, 128.0, 123.2, 109.6, 43.3,
1281 41.2, 38.3, 23.9 ppm; LC-MS: *m/z* = 354.8 [M + H]⁺.

1282 **4-Chloro-1,3-dimethyl-N-(4-((6-methylpyridin-3-yl)methyl)-**
1283 **benzyl)-1H-pyrazole-5-carboxamide (59).** Title compound was
1284 prepared according to General procedure C1, starting from **94** and 4-
1285 chloro-1,3-dimethyl-1H-pyrazole-5-carboxylic acid to give a white
1286 solid (29%). ¹H NMR (400 MHz, CDCl₃) δ = 8.35 (d, *J* = 1.6 Hz,
1287 1H), 7.35 (dd, *J* = 7.9, 2.3 Hz, 1H), 7.29–7.23 (m, 2H), 7.14 (d, *J* =
1288 8.2 Hz, 2H), 7.06 (d, *J* = 8.0 Hz, 1H), 7.02 (s, br, 1H), 4.58 (d, *J* = 5.7
1289 Hz, 2H), 4.11 (s, 3H), 3.91 (s, 2H), 2.51 (s, 3H), 2.21 (s, 3H) ppm;
1290 ¹³C NMR (101 MHz, CDCl₃) δ = 158.5, 156.2, 149.1, 144.5, 139.7,
1291 137.0, 135.7, 133.3, 131.0, 129.3, 128.0, 123.2, 108.4, 43.2, 40.6, 38.3,
1292 23.9, 11.1 ppm; LC-MS: *m/z* = 368.9 [M + H]⁺.

1293 **3,5-Dimethyl-1H-pyrazole-3,5-dicarboxylate (60).** To a
1294 stirred solution of 1H-pyrazole-3,5-dicarboxylic acid (3.5 g, 22.43
1295 mmol) in EtOH (84 mL) was added SOCl₂ (14 mL) at 0 °C. The
1296 reaction mixture was stirred at room temperature for 18 h. Upon
1297 completion, the reaction was concentrated in vacuo to afford the title
1298 compound (3.5 g, 85%) as an off-white solid. ¹H NMR (400 MHz,
1299 CDCl₃) δ = 7.34 (s, 1H), 3.95 (s, 6H) ppm; LCMS *m/z* = 185.0 [M
1300 + H]⁺.

1301 **3,5-Dimethyl-1-methyl-1H-pyrazole-3,5-dicarboxylate (61).**
1302 To a stirred solution of **60** (3.5 g, 19.02 mmol) and K₂CO₃ (3.94 g,
1303 28.53 mmol) in acetone (100 mL) at room temperature, dimethyl
1304 sulfate (2 mL, 20.92 mmol) was added. The reaction mixture was
1305 stirred at 40 °C for 3 h. After completion, the reaction mixture was
1306 filtered and the filtrate was concentrated in vacuo to afford the title
1307 compound (3.5 g, 93%) as a white solid. ¹H NMR (400 MHz,
1308 CDCl₃) δ = 7.34 (s, 1H), 4.24 (s, 3H), 3.92 (s, 3H), 3.89 (s, 3H)
1309 ppm; LCMS *m/z* = 199 [M + H]⁺.

5-(Methoxycarbonyl)-1-methyl-1H-pyrazole-3-carboxylic 1310
acid (62). To a stirred solution of **61** (4 g, 20.20 mmol) in 1,4- 1311
dioxane (16 mL) and water (40 mL), concentrated H₂SO₄ (0.43 mL, 1312
8.081 mmol) was added dropwise. The reaction mixture was refluxed 1313
for 24 h. Upon completion, the reaction mixture was concentrated in 1314
vacuo to afford a gummy liquid, which was dissolved in CHCl₃ and 1315
filtered. Filtrate was concentrated to afford the title compound (1.2 g, 1316
32%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ = 7.40 (s, 1H), 1317
4.27 (s, 3H), 3.91 (s, 3H) ppm; LCMS *m/z* = 185.0 [M + H]⁺. 1318

Methyl-3-carbamoyl-1-methyl-1H-pyrazole-5-carboxylate 1319
(63). A mixture of **62** (1.2 g, 4.22 mmol) and SOCl₂ (10 mL) was 1320
stirred at 80 °C for 2 h. The reaction mixture was concentrated, 1321
diluted with toluene (10 mL), and ammonia gas was passed into the 1322
reaction mixture at 0 °C for 2 h. After completion, the reaction 1323
mixture was quenched by the addition of cold water and extracted 1324
with 10% MeOH in DCM, dried over anhydrous Na₂SO₄, and 1325
concentrated to give the title compound (0.92 g, 77%) as an off-white 1326
solid, which was used in the next step without purification. ¹H NMR 1327
(400 MHz, DMSO-*d*₆) δ = 7.68 (s, 1H), 7.38 (s, 1H), 7.18 (s, 1H), 1328
4.12 (s, 3H), 3.85 (s, 3H) ppm; LC-MS: *m/z* = 184 [M + H]⁺. 1329

Methyl-3-cyano-1-methyl-1H-pyrazole-5-carboxylate (64). 1330
To a stirred solution of **63** (0.90 g, 4.89 mmol) in DCM (15 mL) 1331
was added DIPEA (2.3 mL, 13.21 mmol) at 0 °C. A solution of 1332
trifluoroacetic anhydride (0.78 mL, 5.63 mmol) in DCM (5 mL) was 1333
then added at 0 °C. The reaction mixture was stirred at 0 °C for 2 h 1334
and then diluted with DCM. The organic layer was washed with 1335
saturated sodium bicarbonate solution, 5% citric acid solution, and 1336
brine; dried over Na₂SO₄; and concentrated in vacuo to afford a 1337
gummy liquid, which was purified by column chromatography (10% 1338
EtOAc in hexane) to afford the title compound (0.80 g, 99%) as off- 1339
white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 7.61 (s, 1H), 4.17 1340
(s, 3H), 3.87 (s, 3H) ppm; LC-MS: *m/z* = 166 [M + H]⁺. 1341

3-Cyano-1-methyl-1H-pyrazole-5-carboxylic acid (65). Title 1342
compound was prepared according to General procedure D1, starting 1343
from **64** to give an off-white solid (37%). ¹H NMR (400 MHz, 1344
DMSO-*d*₆) δ = 14.02 (s, br, 1H), 7.52 (s, 1H), 4.16 (s, 3H) ppm; 1345
LC-MS: *m/z* = 149.9 [M – H]⁺. 1346

Methyl 4-Fluoro-1-methyl-1H-pyrazole-5-carboxylate (66). 1347
To a solution of methyl 1-methyl-1H-pyrazole-5-carboxylate (0.5 g) 1348
in ACN (7 mL) and acetic acid (1.0 mL) was added Selectfluor (1.37 1349
g). The mixture was heated at 100 °C under microwave irradiation for 1350
120 min. Selectfluor (1.37 g) was added to the mixture and heated at 1351
100 °C under microwave irradiation for 60 min. The solvent was 1352
removed in vacuo (water bath was kept at room temperature to avoid 1353
loss of product under vacuum as the product is very volatile), and the 1354
residue was partitioned between DCM (15 mL) and water (25 mL). 1355
The aqueous layer was further extracted with DCM (2 × 10 mL), and 1356
the combined organic layers were concentrated in vacuo (water bath 1357
was kept at room temperature to avoid loss of product under vacuum 1358
as the product is very volatile). The crude product was purified by a 1359
flash chromatography column on silica gel, eluting with a gradient of 1360
0–15% EtOAc/petroleum benzene to give the title compound as a 1361
white solid (0.17 g, 31%). ¹H NMR (400 MHz, CDCl₃) δ = 7.36 (d, *J* 1362
= 4.4 Hz, 1H), 4.13 (d, *J* = 1.0 Hz, 3H), 3.95 (s, 3H). ¹⁹F NMR (376 1363
MHz, CDCl₃) δ = –161.32 (s) ppm; LC-MS: Rt 2.89 min, does not 1364
ionize. 1365

1-Methyl-4-fluoro-1H-pyrazole-5-carboxylic acid (67). Title 1366
compound was prepared according to General procedure D2, starting 1367
from **66** to give a white solid (95% yield). ¹H NMR (400 MHz, 1368
DMSO) δ = 7.60 (d, *J* = 4.3 Hz, 2H), 4.00 (d, *J* = 1.0 Hz, 7H). ¹⁹F 1369
NMR (376 MHz, DMSO) δ = –162.96 (s) ppm, LC-MS Rt 1.17 min, 1370
does not ionize. 1371

(4-(3-Fluoro-4-methylphenoxy)phenyl)methanamine (68). 1372
General procedure A2 was followed, starting from 3-fluoro-4- 1373
methylphenol and 4-fluorobenzonitrile to give 4-(3-fluoro-4- 1374
methylphenoxy)benzonitrile, which was reduced according to General 1375
procedure B2 to give the title compound as a gummy liquid (80%). 1376
¹H NMR (400 MHz, CDCl₃) δ = 7.28–7.25 (m, 2H), 7.11–7.07 (m, 1377
1H), 6.97 (d, *J* = 8.0 Hz, 2H), 6.69–6.64 (m, 2H), 3.85 (s, 2H), 2.22 1378
(s, 3H) ppm; LC-MS: *m/z* = 232 [M + H]⁺. 1379

(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%). ¹H NMR (400 MHz, CDCl₃): 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%). ¹H NMR (400 MHz, CDCl₃): δ 7.59 (d, *J* = 8.7 Hz, 2H), 7.12–7.07 (m, 1H), 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 H₂ 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. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.43 (s, 1H), 6.50 (d, *J* = 8.4 Hz, 1H), 6.20 (d, *J* = 2.7 Hz, 1H), 5.94 (dd, *J* = 8.3, 2.9 Hz, 1H), 4.52 (s, 2H), 3.57 (s, 3H) ppm; LC-MS: *m/z* = 140.0 [M + H]⁺.

5-Methoxybenzo[d]oxazole (72). A stirred solution of **71** (4.5 g, 32.40 mmol) in triethyl orthoformate (50 mL) was refluxed for 16 h. Upon completion, the reaction mixture was cooled to room temperature and concentrated in vacuo. Residue was diluted with EtOAc, and the organic layer was washed with water and brine, dried over anhydrous Na₂SO₄, 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%). ¹H NMR (400 MHz, CDCl₃): 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. BBr₃ (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 Na₂SO₄, 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%). ¹H 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%). ¹H NMR (400 MHz, CDCl₃): 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%). ¹H 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-Chloro-3-ethyl-1-methyl-1H-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-1H-pyrazole-5-carboxylic acid according to General procedure C3 to afford the title compound as a brown solid (39%). ¹H 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%). ¹H 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%). ¹H 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*-tolylloxy)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%). ¹H 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*-tolylloxy)phenyl)methanamine HCl (80). Title compound was prepared according to General procedure B5, starting from **79** to give a pale yellow solid (73%). ¹H 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%). ¹H NMR (400 MHz, CDCl₃): 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%). ¹H 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*-tolylloxy)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%). ¹H NMR (400 MHz, CDCl₃): 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*-tolylloxy)phenyl)methanamine (84). Title compound was prepared according to General procedure B2, starting from **83** to give a gummy liquid (92%). ¹H NMR (400 MHz, CDCl₃): 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%). ¹H NMR (400 MHz, CDCl₃): 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%). ¹H NMR (400 MHz, CDCl₃): 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%). ¹H NMR (400 MHz, CDCl₃): 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 N₂ for 5 min. K₂CO₃ (1.82 g, 13.2 mmol) and PdCl₂ (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 layer was washed with water and brine, dried over anhydrous Na₂SO₄, 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%). ¹H NMR (400 MHz, CDCl₃): 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%). ¹H NMR (400 MHz, CDCl₃) δ = 7.38–7.30 (m, 4H), 7.18–7.13 (m, 2H), 7.04–7.00 (m, 2H), 2.31 (s, 3H) ppm; ¹³C NMR (101 MHz, CDCl₃) 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%). ¹H NMR (400 MHz, CDCl₃) 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; ¹³C NMR (101 MHz, CDCl₃) 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%). ¹H NMR (400 MHz, CDCl₃) 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; ¹³C NMR (101 MHz, CDCl₃) 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 H₂O. The mixture was extracted with EtOAc (3 × 20 mL), and combined organic layers were washed with brine, dried (MgSO₄), and concentrated in vacuo to give crude product, which was purified by column chromatography (5–30% EtOAc/petroleum benzene) to afford the title compound as a yellow oil (55%). ¹H NMR (400 MHz, CDCl₃) 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; ¹³C NMR (101 MHz, CDCl₃) 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), K₄Fe(CN)₆·3H₂O (1.14 mmol), XPhos (0.23 mmol), and KOAc (0.30 mmol) were dissolved in a 1:4 mixture of H₂O/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, NaHCO₃, and brine. The organic layer was dried (MgSO₄), and the solvent was removed in vacuo to afford crude product, which was purified by column chromatography (5–20% EtOAc/petroleum benzene) to yield the title compound as a yellow solid (84%). ¹H NMR (400 MHz, CDCl₃) 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; ¹³C NMR (101 MHz, CDCl₃) 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%). ¹H 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); ¹³C 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

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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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