Discovery and Optimization of a Novel Carboxamide Scaffold with Selective Antimalarial Activity

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ABSTRACT

Artemisinin combination therapies (ACTs) are critical components of malaria control worldwide. Alarmingly, ACTs have begun to fail, owing to the rise in artemisinin resistance. Thus, there is an urgent need for an expanded set of novel antimalarials to generate new combination therapies. Herein, through a virtual high-throughput screen (vHTS), cheminformatics-driven down-selection, and structure-activity relationship (SAR) studies, we have identified a 1,2,4-triazole-containing carboxamide scaffold; while the most promising triazole displayed 519 nM potency against the asexual blood stages of the parasite, this activity was unable to be surpassed. Scaffold hopping efforts then revealed three alternative cores with up to a 2.5-fold increase in potency from the aforementioned front-runner triazole. The lead compound of this class, a deuterated picolinamide, displays moderate aqueous solubility (13.4 μM) and metabolic stability ($CLint_{app}$ HLM 17.3 μL/min/mg) *in vitro*, as well as moderate oral bioavailability (% F 16.2) in *in vivo* pharmacokinetic studies. Front-runners representing three cores were confirmed potent against a panel of three clinical isolates harboring different resistance profiles, suggesting a novel mechanism of action, and the lead compound displayed a slow-to-moderate rate of killing (average PRR 2.4) in a parasite reduction ratio assay, making the series appealing for further development.

INTRODUCTION

Malaria, caused by protozoan parasites of the genus *Plasmodium*, is the most detrimental parasitic disease impacting humans today. An estimated 263 million infections occurred in 2023 alone, wherein approximately 597,000 cases resulted in fatalities[1]. This is an increase of 11 million cases from 2022[1] and 25 million cases since 2000[2]. While there have been recent developments in antimalarial treatments[3] and a decrease in fatalities in 2023 from years prior[1], there is still much to be done to continue to control and eventually eradicate this disease.

Antimalarial drugs are an essential tool complementing other malaria control approaches, such as vector control and vaccination. One of the first fast-acting antimalarial drugs, chloroquine, was discovered in 1934 as a replacement to quinine. Resistance emerged to this 4-amino-quinoline in the early 1950s, shortly after it was introduced as a treatment option[4]. In attempts to combat resistance, artemisinin combination therapies (ACTs) were then employed. Artemisinin (or one of its derivatives), a very potent and fast-acting component, rapidly clears the majority of parasitemia before it is metabolically degraded. Though artemisinin has a short half-life, a slow-acting component of the ACT reduces the remaining parasite burden. Slow-actors are typically more susceptible to developing resistance, but this threat is lessened by the low parasitemia levels following exposure to artemisinin[5]. Historically these ACTs have been incredibly efficacious at treating malaria and tackling antimalarial resistance. However, partial artemisinin resistance was first detected in 2001 and has been increasing in prevalence in recent years, yielding treatment failure rates of 10% on average and as high as 22.6% in Cambodia (artesunate-amodiaquine ACT)[5]. Alarmingly, artemisinin resistance is established in the Greater Mekong Subregion and has been recently reported in Sub-Saharan Africa, where over 90% of malaria cases occur[6-9]. Thus, it is paramount to identify novel compounds that can be formulated into future combination therapies.

Medicines for Malaria Venture, a nonprofit research institute aimed at bringing new antimalarials to the market, has defined several target candidate profiles (TCPs) for novel compounds[10]. Each TCP is meant to fulfill a need within malaria-endemic regions, such as chemoprotection, chemoprevention, and the single-dose radical cure; TCP-1 focuses on asexual blood-stage killers[10], wherein compounds of this class are expected to have strong potency against the asexual blood stages of the parasite and the ability to clear parasitemia rapidly.

Through a virtual high-throughput screen and cheminformatics-driven down-selection of *in silico* hits, we have identified a distinct antimalarial chemotype. The initial hit, ZINC19910518, displays high nanomolar potency when assessed against the asexual blood stages of a multi-drug-resistant *P. falciparum* isolate (*Pf*ABS, strain W2) with no cytotoxicity against mammalian cells. Through periphery changes and a scaffold hopping study, this molecule led to the identification of several low-nanomolar potent antimalarials. At 30 mg/kg (PO), the lead compound, a deuterated picolinamide, displays moderate oral bioavailability (% F 16.2), a half-life of 1.54 h, and approximately 3 hours of coverage above the EC_{50}. When assessed in a miniaturized PRR format, a slow-to-moderate rate of killing (average PRR 2.4) was noted. Taken together, herein we present a promising new

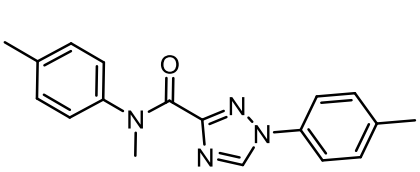
antimalarial scaffold that we aim to develop into a TCP-1 candidate to serve as part of a future combination therapy.

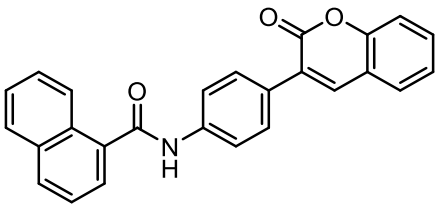
RESULTS AND DISCUSSION

Virtual high-throughput screen, hit identification, and SAR-by-catalog

This work began with a large-scale virtual high-throughput screen against an efflux pump, *Plasmodium falciparum* formate nitrate transporter (*Pf*FNT, PF3D7_0316600, PDB: 6VQR)[11], using Glide programMaestro (Schrödinger, LLC)[12] (**Figure S1**). Ultimately, 39 structurally diverse *in silico* hits were purchased from Specs and tested in a phenotypic whole-cell assay against a multi-drug-resistant line (strain W2) of the asexual blood stages of *Plasmodium falciparum* (*Pf*ABS); 2 active scaffolds were identified (**Table 1**). To further probe these chemotypes, cluster members were purchased to assess for limited structure-activity insights; 16 triazoles and 5 coumarins were purchased for an SAR-by-catalog, wherein 11 triazoles and 2 coumarins displayed potency *in vitro* (EC_{50} <10 μM) (**Table S1**, **Table S2**). The coumarin scaffold was plagued by cytotoxicity (HepG2 CC_{50}) and inconsistent potency among analogs, so additional follow-up on this series was abandoned. Conversely, the triazoles were consistently potent with no adverse cytotoxicity and the scaffold was not disclosed with antimalarial activity, making it a novel antimalarial chemotype. Select screening hits were re-synthesized in-house to validate the scaffold and its activity profile; the observed trends of purchased material were replicated with a slight reduction of potency (**Table S1**). These data warranted a hit optimization of the 1,2,4-triazole carboxamide series.

Table 1: Initial hits from virtual high-throughput screen. EC_{50} and CC_{50} data represents geometric means for at least two independent experiments.



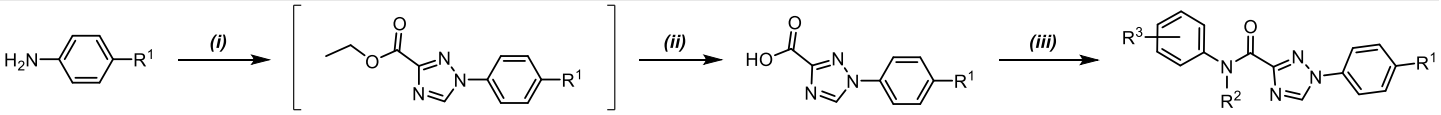


	ZINC19910518	**ZINC2055685**
EC_{50} (W2) (μM)	0.857	>4.05
pEC_{50} (W2)	6.07 ± 0.13	<5.39 ± 0.27
CC_{50} (HepG2) (μM)	>10.0	1.16
pCC_{50} (HepG2)	<5.00	5.94 ± 0.01

Design and synthesis of 1,2,4-triazole carboxamides

The triazole synthesis (**Scheme 1**) began with the *in situ* formation of a diazonium salt, followed by cyclization to form the 1,2,4-triazole core[13]. Hydrolysis with lithium hydroxide monohydrate afforded the carboxylic acid. The subsequent Schotten-Baumann amidation then yielded the final analogs (**3**-**44**).

Scheme 1: Synthesis of Compounds 3-44[a]



1a R^1=Cl
1b R^1=CH_3
1c R^1=CH_2CH_3
1d R^1=$CH(CH_3)_2$
1e R^1=OCH_3

2a R^1=Cl
2b R^1=CH_3
2c R^1=CH_2CH_3
2d R^1=$CH(CH_3)_2$
2e R^1=OCH_3

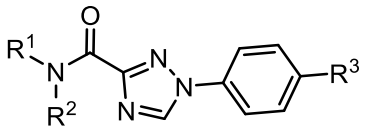
3	R^1=Cl, R^2=H, R^3=4-CH_2CH_3	**10**	R^1=Cl, R^2=CH_3, R^3=4-$COCH_3$	**17**	R^1=CH_3, R^2=H, R^3=4-Cl
4	R^1=CH_3, R^2=CH_3, R^3=4-CH_2CH_3	**11**	R^1=Cl, R^2=H, R^3=3,4-Cl	**18**	R^1=CH_3, R^2=CH_3, R^3=4-Cl
5	R^1=Cl, R^2=H, R^3=3,4-CH_3	**12**	R^1=Cl, R^2=CH_3, R^3=3,4-Cl	**19**	R^1=Cl, R^2=H, R^3=4-Cl
6	R^1=Cl, R^2=CH_3, R^3=3,4-CH_3	**13**	R^1=Cl, R^2=H, R^3=4-F	**20**	R^1=Cl, R^2=CH_3, R^3=4-Cl
7	R^1=Cl, R^2=H, R^3=4-NO_2	**14**	R^1=Cl, R^2=CH_3, R^3=4-F	**21**	R^1=Cl, R^2=CH_3, R^3=H
8	R^1=Cl, R^2=CH_3, R^3=4-NO_2	**15**	R^1=Cl, R^2=H, R^3=4-CF_3	**22**	R^1=Cl, R^2=CH_3, R^3=4-CH_3
9	R^1=Cl, R^2=H, R^3=4-$COCH_3$	**16**	R^1=Cl, R^2=CH_3, R^3=4-CF_3	**23**	R^1=Cl, R^2=CH_3, R^3=4-$C(CH_3)_3$
24	R^1=Cl, R^2=CH_3, R^3=4-OCH_3	**31**	R^1=CH_2CH_3, R^2=CH_3, R^3=4-CH_3	**38**	R^1=$CH(CH_3)_2$, R^2=CH_3, R^3=3-CH_3
25	R^1=Cl, R^2=CH_3, R^3=3-CH_3	**32**	R^1=CH_2CH_3, R^2=CH_3, R^3=4-OCH_3	**39**	R^1=$CH(CH_3)_2$, R^2=CH_3, R^3=3,4-CH_3
26	R^1=CH_3, R^2=CH_3, R^3=4-CH_3	**33**	R^1=CH_2CH_3, R^2=CH_3, R^3=3-CH_3	**40**	R^1=OCH_3, R^2=CH_3, R^3=4-Cl
27	R^1=CH_3, R^2=CH_3, R^3=4-OCH_3	**34**	R^1=CH_2CH_3, R^2=CH_3, R^3=3,4-CH_3	**41**	R^1=OCH_3, R^2=CH_3, R^3=4-CH_3
28	R^1=CH_3, R^2=CH_3, R^3=3-CH_3	**35**	R^1=$CH(CH_3)_2$, R^2=CH_3, R^3=4-Cl	**42**	R^1=OCH_3, R^2=CH_3, R^3=4-OCH_3
29	R^1=CH_3, R^2=CH_3, R^3=3,4-CH_3	**36**	R^1=$CH(CH_3)_2$, R^2=CH_3, R^3=4-CH_3	**43**	R^1=OCH_3, R^2=CH_3, R^3=3-CH_3
30	R^1=CH_2CH_3, R^2=CH_3, R^3=4-Cl	**37**	R^1=$CH(CH_3)_2$, R^2=CH_3, R^3=4-OCH_3	**44**	R^1=OCH_3, R^2=CH_3, R^3=3,4-CH_3

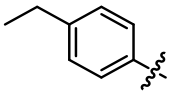
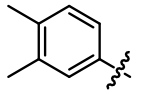
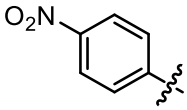
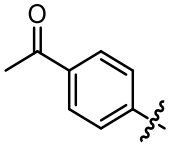
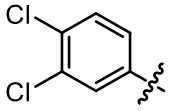
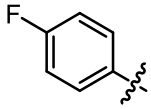
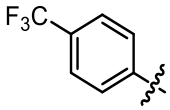
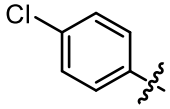
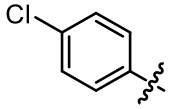
[a]**Reagents and conditions:** ***(i)*** conc. HCl/H_2O, $NaNO_2$ in H_2O, 0 °C *then* NaOAc, ethyl isocyanoacetate, H_2O/MeOH, 0 °C 30 min, then 23 °C, 16 h; ***(ii)*** LiOH•H_2O, THF/H_2O, 23 °C, 16 h; and ***(iii)*** $(COCl)_2$, anhydrous THF/DCM/DMF, 0 °C, then 23 °C 30 min *then* R_3R_2NH, NEt_3, anhydrous THF/DCM, 23 °C, 16 h.

Initial structure-activity relationship studies of triazoles

In the SAR-by-catalog of additional triazole cluster members, two matched pairs displayed an interesting trend: a tertiary, *N*-methyl amide displayed potency, but its secondary, H-substituted amide was inactive (>10.0 μM) (**Table S1**). This prompted further investigation of the amide substitution in the SAR study. Following in-house synthesis of nine matched pairs (**Table 2**), the methyl was found to be critical to activity, wherein the analogous non-methylated molecule was inactive (>10.0 μM) or less active by comparison. Many of the methylated analogs display EC_{50}'s in the 1-3 μM range, despite variations in sterics, electronics, and lipophilicity, suggesting that modifications at R^1 do not have a large bearing on the observed potency. However, a noticeable increase in potency is seen when R^3 is Cl (**19** and **20**) versus CH_3 (**17** and **18**), suggesting that R^3 has a dominant effect on potency.

Table 2: Investigation of the effect of amide substitution (H versus CH_3) and initial probing of phenyl substituents. EC_{50} and CC_{50} data represent geometric means for at least two independent experiments.

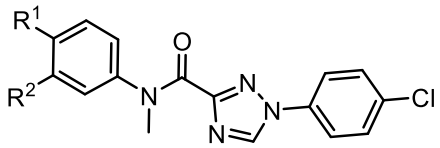


ID	R^1	R^2	R^3	EC_{50} (W2) (μM)	pEC_{50} ± SD (W2)	CC_{50} (HepG2) (μM)	pCC_{50} ± SD (HepG2)
3		H	Cl	>6.93	<5.16 ± 0.28	>10.0	<5.00
4		CH_3		>5.24	<5.28 ± 0.22	>10.0	<5.00
5		H	Cl	>2.89	<5.54 ± 0.47	>10.0	<5.00
6		CH_3		2.36	5.63 ± 0.14	>10.0	<5.00
7		H	Cl	>10.0	<5.00	>10.0	<5.00
8		CH_3		2.28	5.64 ± 0.10	>10.0	<5.00
9		H	Cl	>10.0	<5.00	>10.0	<5.00
10		CH_3		2.42	5.62 ± 0.08	>10.0	<5.00
11		H	Cl	>10.0	<5.00	>10.0	<5.00
12		CH_3		0.927	6.03 ± 0.13	>10.0	<5.00
13		H	Cl	>5.88	<5.23 ± 0.25	>10.0	<5.00
14		CH_3		1.78	5.75 ± 0.19	>10.0	<5.00
15		H	Cl	>6.44	<5.19 ± 0.26	>10.0	<5.00
16		CH_3		3.79	5.42 ± 0.20	>6.93	<5.16 ± 0.28
17		H	CH_3	>10.0	<5.00	>10.0	<5.00
18		CH_3		1.68	5.77 ± 0.16	>10.0	<5.00
19		H	Cl	>6.44	<5.19 ± 0.26	>10.0	<5.00
20		CH_3		0.519	6.28 ± 0.23	>10.0	<5.00

Next, the amide-adjacent ring (**Table 3**, R^1) was probed via Topliss scheme[14] and the Craig plot[15, 16]. It was known from the hit resynthesis (**Table S1**) that 4-chloro (**20**) displayed greater potency than an unsubstituted ring (4-H, **21**), thus leading towards a 3,4-dichloro with a 2-fold decrease in potency (**12**, EC_{50} 0.927 μM), and subsequently trifluoromethyl (**16**) and nitro (**8**). However, both analogs did not yield a potency improvement, displaying EC_{50}'s

of 3.79 and 2.28 μM respectively. Knowing that a 4-methyl (**22**) was also more potent than an unsubstituted ring, the respective follow-up analogs, 3,4-dimethyl (**6**) and *tert*-butyl (**23**), were evaluated but they were also less potent (EC_{50}'s of 2.36 and >8.03 μM respectively). Given the lack of success in applying Topliss scheme at this ring system, we attempted to utilize the Craig plot instead, synthesizing analogs from each quadrant (**Table S3**). However, not only was there a lack of potency improvement, but no trends could be gleaned from these analogs. Through both approaches, few conclusions could be made. Hydrophilic substituents were consistently less active, but weakly lipophilic substituents (e.g., Cl and CH_3) continued to display moderate potencies. As an alternative approach, a sampling of aliphatic and heteroaromatic rings were trialed, but few were active, and none were more potent than **20** (**Table S4**). This supports the finding from **Table 1** that modifications about the amide-adjacent ring have only modest effects on potency.

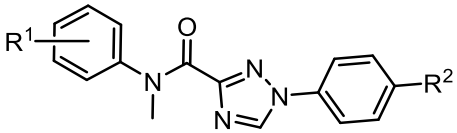
Table 3: Investigation of amide-adjacent ring via the Topliss scheme. EC_{50} and CC_{50} data represent geometric means for at least two independent experiments.



ID	R^1	R^2	EC_{50} (W2) (μM)	pEC_{50} ± SD (W2)	CC_{50} (HepG2) (μM)	pCC_{50} ± SD (HepG2)
21	H	H	>13.84	<4.86 ± 0.15	>10.0	<5.00
20	Cl	H	0.519	6.28 ± 0.23	>10.0	<5.00
12	Cl	Cl	0.927	6.03 ± 0.13	>10.0	<5.00
16	CF_3	H	3.79	5.42 ± 0.20	>6.93	<5.16 ± 0.28
8	NO_2	H	2.28	5.64 ± 0.10	>10.0	<5.00
22	CH_3	H	0.556	6.25 ± 0.26	>10.0	<5.00
6	CH_3	CH_3	2.36	5.63 ± 0.14	>10.0	<5.00
23	$C(CH_3)_3$	H	>8.03	<5.10 ± 0.21	>1.76	<5.75 ± 0.17

To further investigate the finding that changes at the triazole-adjacent ring strongly impact potency (**Table 1**), additional modifications were made here (**Table 4**, R^2). Substituents of increasing lipophilicities and one hydrophilic substituent (OCH_3) were included; as expected, a methoxy at R^2 resulted in a global loss of potency (**41**-**44**). When R^1 is 4-chloro, an ethyl (**30**, EC_{50} 0.574 μM) or isopropyl (**35**, EC_{50} 0.847 μM) at R^2 delivered comparable potencies to **20**. When R^1 is modified to alternative substituents (e.g., 4-CH_3, 4-OCH_3, 3-CH_3, 3,4-CH_3), an R^2 of ethyl or isopropyl continued to mimic the trends of a chloro substituent (**Table 4**). However, though ethyl- and isopropyl-bearing compounds display tolerable potencies, their lipophilic ligand efficiencies (LLEs) worsen as a result of increased lipophilicity (**Table 4**, LogP, **30**-**39**).

Table 4: Investigation of *para*- substitutions at the triazole-adjacent ring. EC_{50} and CC_{50} data represent geometric means for at least two independent experiments. LLE = lipophilic ligand efficiency; LLE = pEC_{50}-LogP (calculated via StarDrop, version 7.4.0.35635).



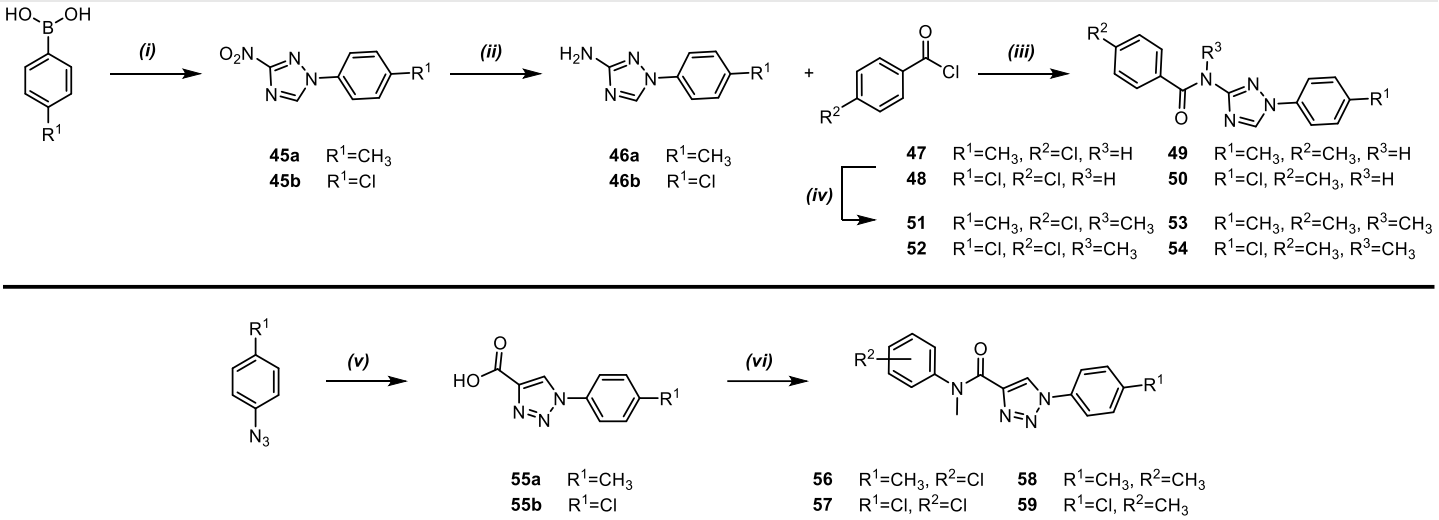
ID	R^1	R^2	EC_{50} (W2) (µM)	pEC_{50} ± SD (W2)	CC_{50} (HepG2) (µM)	LogP	LLE
20	4-Cl	Cl	0.519	6.28 ± 0.23	>10.0	2.93	3.36
22	4-CH_3		0.556	6.25 ± 0.26	>10.0	2.66	3.59
24	4-OCH_3		1.91	5.72 ± 0.29	>10.0	2.32	3.40
25	3-CH_3		>4.03	<5.39 ± 0.14	>10.0	2.66	2.73
6	3,4-CH_3		2.36	5.63 ± 0.14	>10.0	3.03	2.60
18	4-Cl	CH_3	1.68	5.77 ± 0.16	>10.0	2.70	3.07
26	4-CH_3		1.73	5.76 ± 0.16	>10.0	2.53	3.24
27	4-OCH_3		>4.11	<5.39 ± 0.13	>10.0	2.15	3.24
28	3-CH_3		>2.82	<5.55 ± 0.10	>10.0	2.53	3.02
29	3,4-CH_3		>6.93	<5.16 ± 0.28	>10.0	2.91	2.25
30	4-Cl	CH_2CH_3	0.612	6.21 ± 0.04	>10.0	3.06	3.16
31	4-CH_3		0.574	6.24 ± 0.17	>10.0	2.88	3.36
32	4-OCH_3		0.941	6.03 ± 0.06	>10.0	2.50	3.53
33	3-CH_3		>4.26	<5.37 ± 0.18	>10.0	2.88	2.44
34	3,4-CH_3		2.01	5.70 ± 0.02	>10.0	3.27	2.43
35	4-Cl	$CH(CH_3)_2$	0.847	6.07 ± 0.16	>10.0	3.37	2.70
36	4-CH_3		0.742	6.13 ± 0.22	>10.0	3.21	2.92
37	4-OCH_3		1.62	5.79 ± 0.16	>10.0	2.80	2.99
38	3-CH_3		>3.33	<5.48	>10.0	3.21	2.27
39	3,4-CH_3		>3.86	<5.41 ± 0.13	>10.0	3.60	1.81
40	4-Cl	OCH_3	>3.86	<5.41 ± 0.06	>10.0	2.32	3.10
41	4-CH_3		5.78	5.24 ± 0.03	>10.0	2.15	3.09
42	4-OCH_3		>10.0	<5.00	>10.0	1.74	3.26
43	3-CH_3		>5.77	<5.24 ± 0.34	>10.0	2.15	3.09
44	3,4-CH_3		>10.0	<5.00	>10.0	2.53	2.47

Overall, modifications at the molecule periphery did not produce an appreciable improvement in potency. Despite learning what changes were poorly tolerated, the triazole scaffold reached a potency plateau of 519 nM (**20**). This prompted a shift in the structure-activity relationship study towards scaffold-hopping.

Design and synthesis of scaffold hopping study

Alternative cores were selected and prioritized based upon three criteria. First, we selected solely heteroaromatic rings, as we hypothesized this would maintain any favorable interactions afforded by the triazole core. We also wished to maintain the relative size (five-membered) and bond angle of the current core. However, six-membered rings were also included to probe the size limitations of our binding pocket. These criteria led to the selection of thirteen alternative cores for the scaffold hopping studies, as well as two additional modifications. At minimum, two analogs were synthesized for each molecule core with the exception of the thiazole lactam, limited by synthetic accessibility. Of these thirteen scaffold modifications, three cores surpassed the triazole potency barrier (**20,** EC_{50} 519 nM): the 5-oxazole-2-carboxamides and the two pyridine carboxamides (**Table 5**).

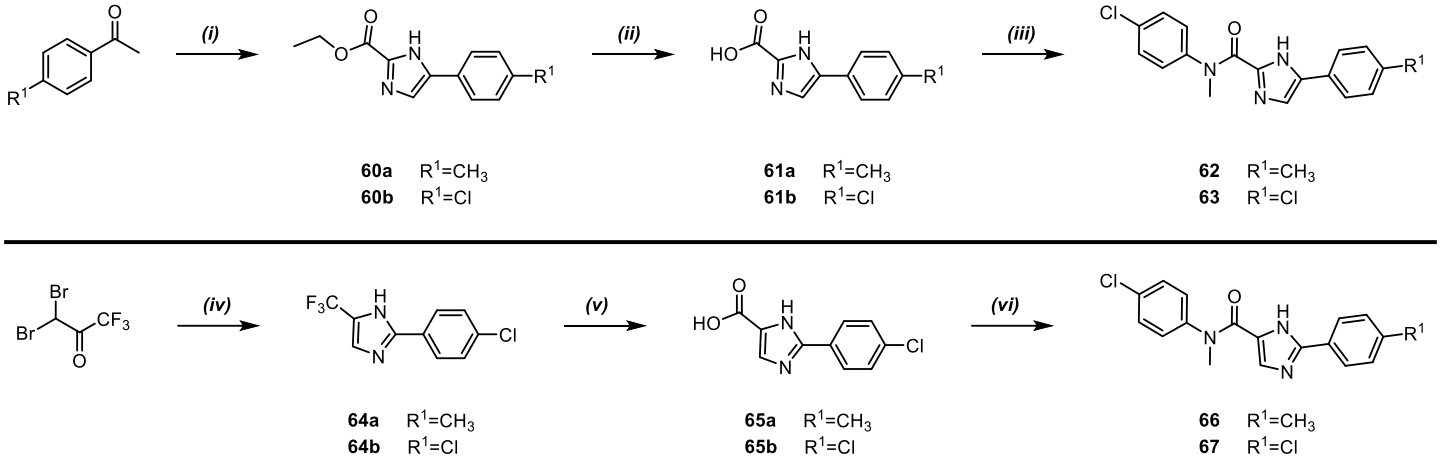
Scheme 2: Synthesis of Compounds 47-54 and 56-59[a]



[a]**Reagents and conditions:** ***(i)*** 3-nitro-1*H*-1,2,4-triazole, $Cu(OAc)_2$, anhydrous py/DCM, 30 °C, 12 h; ***(ii)*** Zn dust, sat. aq. NH_4Cl, acetone, 0 °C, then 23 °C, 2 h; ***(iii)*** anhydrous py/DCM, 0 °C, then 23 °C, 2 h; ***(iv)*** CH_3I, K_2CO_3, anhydrous DMF, 0 °C to 23 °C, 16 h; ***(v)*** propiolic acid, $CuSO_4$, NaAsc, *t*-BuOH/H_2O, 23 °C, 16 h; and ***(vi)*** $(COCl)_2$, anhydrous THF/DCM/DMF, 0 °C, then 23 °C 30 min *then* R_3R_2NH, NEt_3, anhydrous THF/DCM, 23 °C, 16 h.

The reversed amide (i.e., amine in closer proximity to the molecule core) (**Scheme 2**, **47**-**54**) was obtained by first performing a copper-catalyzed coupling in anhydrous pyridine and dichloromethane[17] to install the first periphery ring. Zinc dust reduced the nitro group to an amine[18], enabling *N*-acylation with an acid chloride to yield the amide that was then methylated using iodomethane in the presence of potassium carbonate[17]. The 1,2,3-triazole scaffold (**Scheme 2**, **56**-**59**) was formed through traditional Huisgen cycloaddition conditions with copper sulfate and sodium ascorbate. A final Schotten-Baumann amidation then afforded the final 1,2,3-triazoles.

Scheme 3: Synthesis of Compounds 62, 63, 66, and 67[a]



60a R^1=CH_3 **60b** R^1=Cl

61a R^1=CH_3 **61b** R^1=Cl

62 R^1=CH_3 **63** R^1=Cl

64a R^1=CH_3 **64b** R^1=Cl

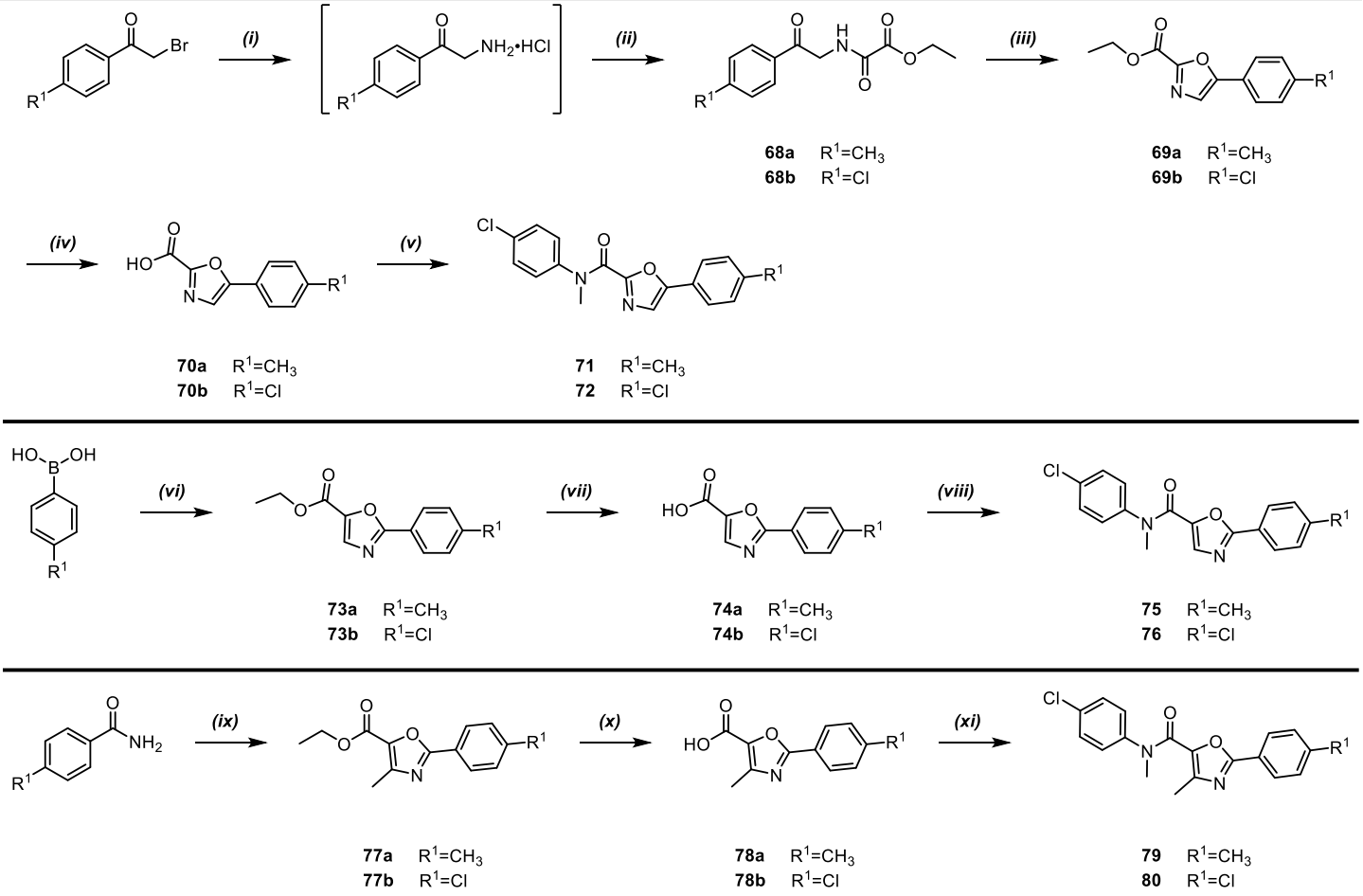
65a R^1=CH_3 **65b** R^1=Cl

66 R^1=CH_3 **67** R^1=Cl

[a]**Reagents and conditions:** ***(i)*** SeO_2, H_2O, anhydrous 1,4-dioxane, reflux, 7 h *then* ethyl 2-oxoacetate, NH_4OAc, CH_3CN/H_2O, 0 °C 30 min, then 23 °C, 2 h; ***(ii)*** NaOH, H_2O/EtOH, reflux, 24 h; ***(iii)*** $(COCl)_2$, anhydrous THF/DCM/DMF, 0 °C, then 23 °C 30 min *then* R_3R_2NH, NEt_3, anhydrous THF/DCM, 23 °C, 16 h; ***(iv)*** $NaOAc•3H_2O$, H_2O, 100 °C, 30 min *then* 4-R^1-benzaldehyde, NH_4OH, MeOH, 23 °C, 4 h; ***(v)*** NaOH, H_2O, 100 °C, 16 h; and ***(vi)*** $(COCl)_2$, anhydrous THF/DCM/DMF, 0 °C, then 23 °C 30 min *then* R_3R_2NH, NEt_3, anhydrous THF/DCM, 23 °C, 16 h.

The synthesis of 5-imidazole-2-carboxamides (**Scheme 3**, **62** and **63**) began by refluxing an acetophenone in the presence of selenium dioxide to afford the geminal diol at the terminal methyl (not shown). Due to the inherent instability of this intermediate, the material was used without further purification. A cyclization with polymerized ethyl 2-oxoacetate then afforded the imidazole core[19]. Hydrolysis of the ester with sodium hydroxide produced the carboxylic acid, enabling amidation via Schotten-Baumann conditions. The 2-imidazole-5-carboxamides (**Scheme 3**, **66** and **67**) were obtained through activation of 3,3-dibromo-1,1,1-trifluoropropan-2-one with sodium acetate, followed by subsequent cyclization with the corresponding aldehyde in the presence of ammonium acetate[20]. The trifluoromethyl imidazole was hydrolyzed to the carboxylic acid in refluxing basified water[20], allowing for the final amidation.

Scheme 4: Synthesis of Compounds 71, 72, 75, 76, 79, and 80[a]

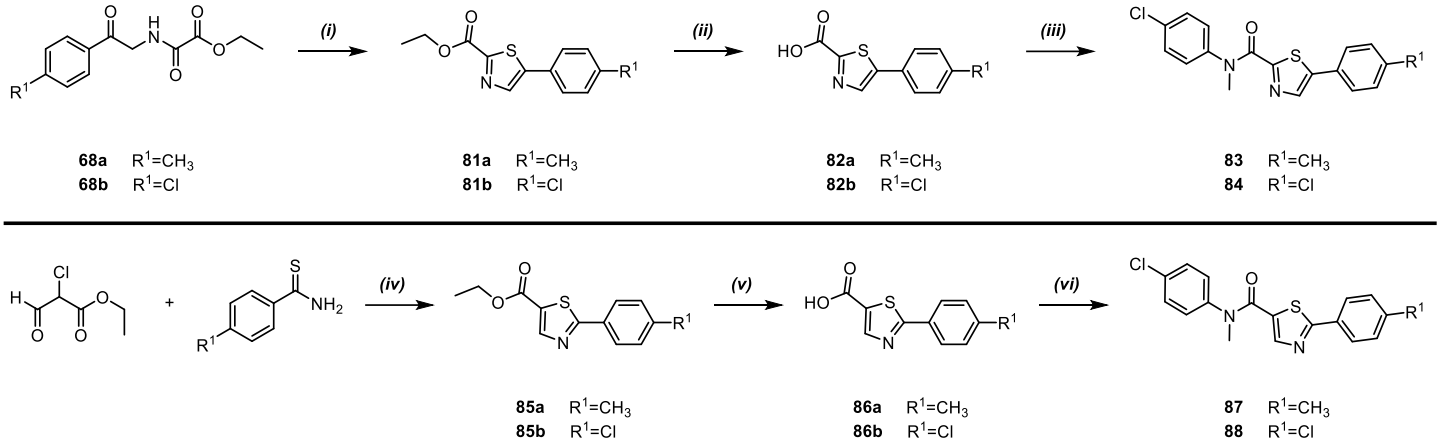


[a]**Reagents and conditions:** ***(i)*** 1,3,5,7-tetraazaadamantane, anhydrous DCM, 50 °C, 2 h *then* EtOH, conc. HCl, reflux, 2 h; ***(ii)*** ethyl 2-chloro-2-oxoacetate, NEt_3, anhydrous DCM, 0 °C to 23 °C, 16 h; ***(iii)*** $POCl_3$, reflux, 5 h; ***(iv)*** LiOH, THF/H_2O, 23 °C, 16 h; ***(v)*** $(COCl)_2$, anhydrous THF/DCM/DMF, 0 °C, then 23 °C 30 min *then* R_3R_2NH, NEt_3, anhydrous THF/DCM, 23 °C, 16 h; ***(vi)*** ethyl 2-chlorooxazole-5-carboxylate, $Pd(PPh_3)_4$, aq. Na_2CO_3, 1,4-dioxane, MW 150 °C, 5 min; ***(vii)*** LiOH•H_2O, THF/H_2O, 23 °C, 16 h; ***(viii)*** $(COCl)_2$, anhydrous THF/DCM/DMF, 0 °C, then 23 °C 30 min *then* R_3R_2NH, NEt_3, anhydrous THF/DCM, 23 °C, 16 h; ***(ix)*** ethyl 2-chloroacetoacetate, EtOH, 80 °C 2 h, then 110 °C, 14 h; ***(x)*** LiOH, THF/MeOH/H_2O, 23 °C, 12 h; and ***(xi)*** $(COCl)_2$, anhydrous THF/DCM/DMF, 0 °C, then 23 °C 30 min *then* R_3R_2NH, NEt_3, anhydrous THF/DCM, 23 °C, 16 h.

Synthesis of the 5-oxazole-2-carboxamides (**Scheme 4**, **71** and **72**) began with an alpha-bromo-acetophenone, where a Delepine reaction delivers the aminoacetophenone; these amines were utilized without further purification. This enables *N*-acylation with ethyl 2-chloro-2-oxoacetate[21] and the resulting chain is cyclized in refluxing phosphoryl chloride to afford the molecule core[22]. Hydrolysis with lithium hydroxide monohydrate then yields the carboxylic acid, enabling an amidation to afford the final product. The first periphery ring of the 2-oxazole-5-carboxamides (**Scheme 4**, **75** and **76**) was installed via a microwave-mediated Suzuki coupling[23]. Following hydrolysis with lithium hydroxide monohydrate, the carboxylic acid was used in a subsequent Schotten-Baumann amidation. The 4-methyloxazole-5-carboxamide (**Scheme 4**, **79** and **80**) scaffold is accessed

via stepwise heating of benzamide and ethyl 2-chloroacetoacetate in ethanol, first for 2 hours at 80 °C, then 110 °C for 14 hours[24]. The carboxylic acid is then afforded via hydrolysis with lithium hydroxide and the final product is achieved through a final amidation.

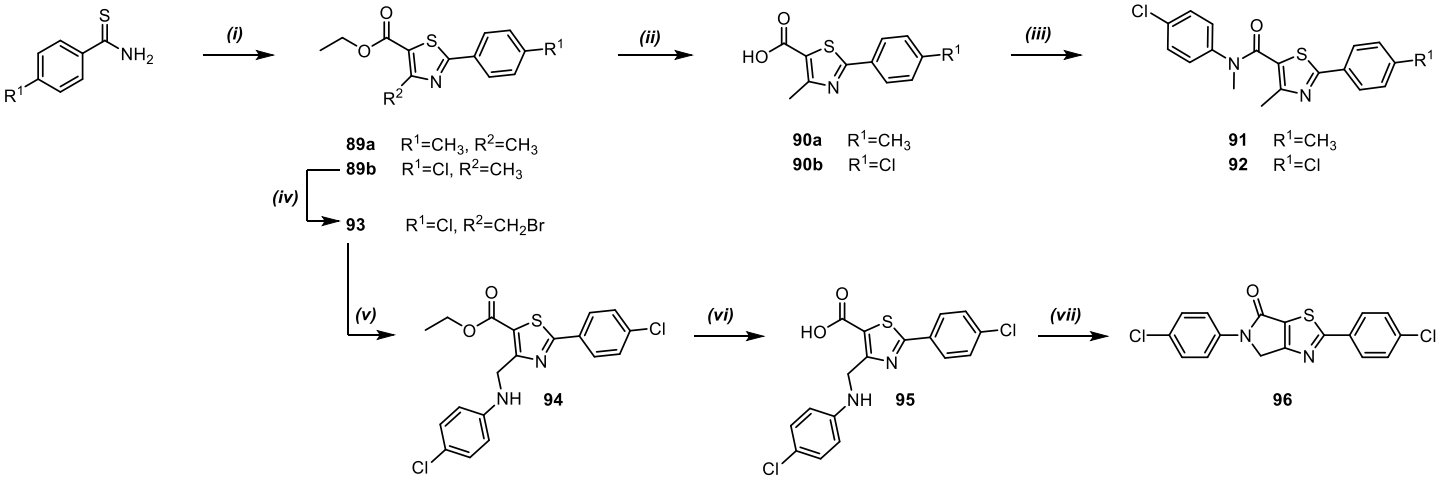
Scheme 5: Synthesis of Compounds 83, 84, 87, and 88[a]



[a]**Reagents and conditions:** ***(i)*** P_2S_5, anhydrous DCM, reflux, 5 h; ***(ii)*** LiOH, THF/H_2O, 23 °C, 16 h; ***(iii)*** $(COCl)_2$, anhydrous THF/DCM/DMF, 0 °C, then 23 °C 30 min *then* R_3R_2NH, NEt_3, anhydrous THF/DCM, 23 °C, 16 h; ***(iv)*** $MgSO_4$, anhydrous $PhCH_3$, 100 °C, 2 h; ***(v)*** LiOH•H_2O, THF/H_2O, 23 °C, 16 h; and ***(vi)*** $(COCl)_2$, anhydrous THF/DCM/DMF, 0 °C, then 23 °C 30 min *then* R_3R_2NH, NEt_3, anhydrous THF/DCM, 23 °C, 16 h.

The core of the 5-thiazole-2-carboxamides (**Scheme 5**, **83** and **84**) is afforded by refluxing intermediate **68a** or **68b** (synthesis described in **Scheme 4**) with phosphorus pentasulfide in anhydrous dichloromethane[21]. The carboxylic acid is accessed by hydrolysis with lithium hydroxide monohydrate and the final product is afforded via a Schotten-Baumann amidation. The synthesis towards the 2-thiazole-5-carboxamides (**Scheme 5**, **87** and **88**) begins with the thiazole-forming cyclization between a thiobenzamide and ethyl 2-chloro-2-formylacetate[25]. Hydrolysis with lithium hydroxide monohydrate affords the carboxylic acid for an amidation.

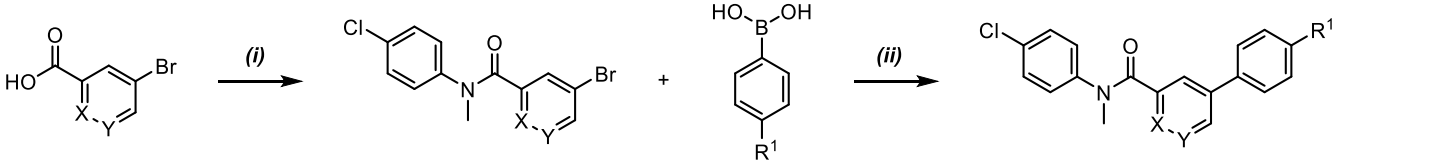
Scheme 6: Synthesis of Compounds 91, 92, and 96[a]



[a]**Reagents and conditions:** ***(i)*** ethyl 2-chloroacetoacetate, EtOH, reflux 4 h, then 23 °C, 16 h; ***(ii)*** LiOH, THF/MeOH/H_2O, 23 °C, 12 h; ***(iii)*** $(COCl)_2$, anhydrous THF/DCM/DMF, 0 °C, then 23 °C 30 min *then* R_3R_2NH, NEt_3, anhydrous THF/DCM, 23 °C, 16 h; ***(iv)*** NBS, AIBN, anhydrous CH_3CN, reflux, 2 h; ***(v)*** 4-chloroaniline, CH_3COOK, THF/H_2O, 23 °C 4 h, then 50 °C, 12 h; ***(vi)*** LiOH•H_2O, THF/H_2O, 23 °C, 2 h; and ***(vii)*** EDCI•HCl, anhydrous DCM/THF, 0 °C 1 h, then 23 °C, 23 h.

The thiazole core of the 4-methylthiazole-5-carboxamides (**Scheme 6**, **91** and **92**) is accessed by refluxing a thiobenzamide and ethyl 2-chloroacetoacetate in ethanol; cooling the solution to room temperature allows for the resulting precipitate to be isolated without further purification[26]. A subsequent hydrolysis with lithium hydroxide and amidation affords this class of final products. A thiazole lactam (**Scheme 6**, **96**) core was also explored, wherein intermediate **89b** is brominated with NBS and AIBN as a radical initiator[27]. This enables a substitution with 4-chloroaniline, installing the key amine functionality. Finally, hydrolysis with lithium hydroxide provides the carboxylic acid to enable an intramolecular amidation.

Scheme 7: Synthesis of Compounds 98-101[a]



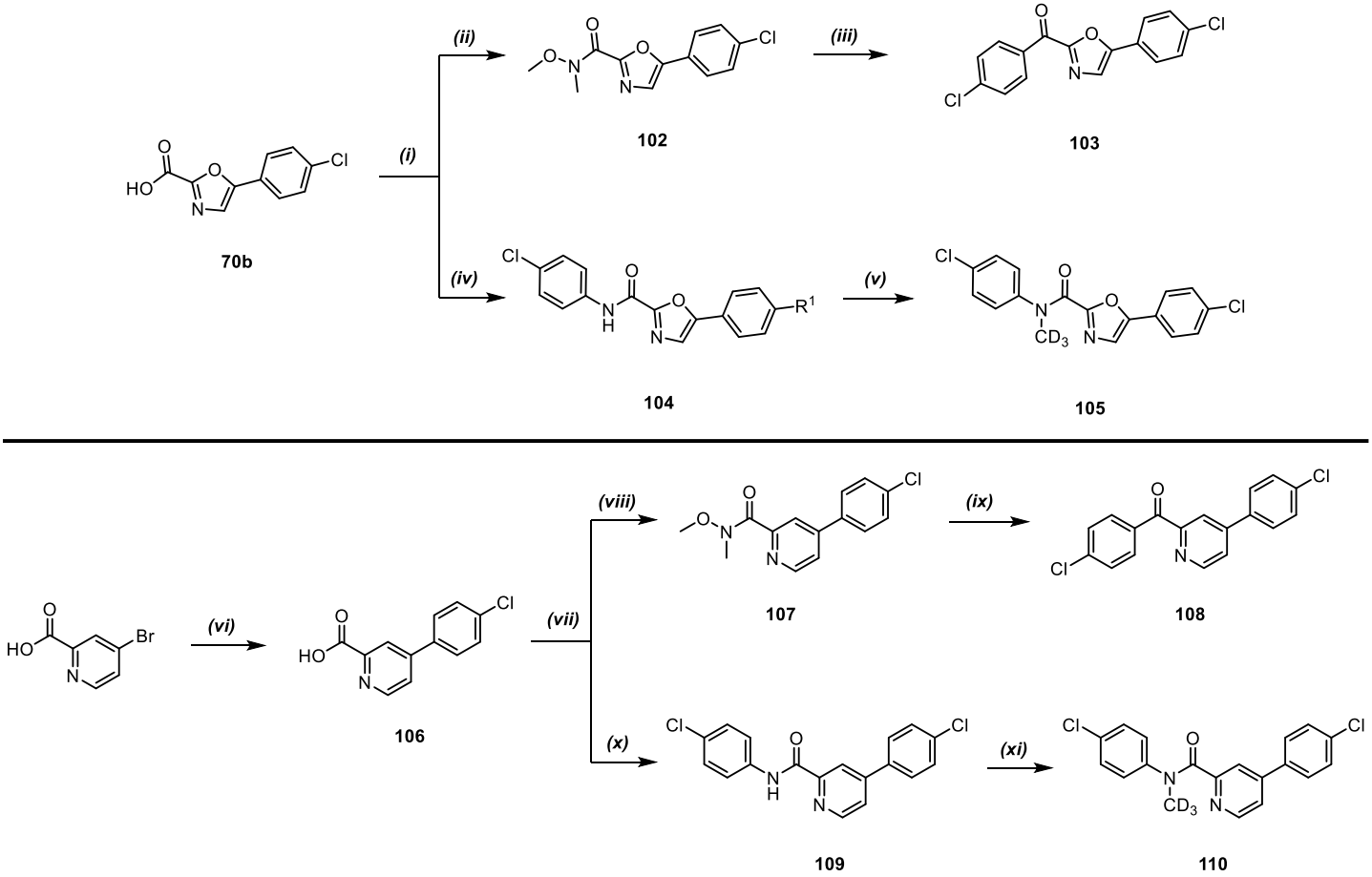
97a X=N, Y=CH
97b X=CH, Y=N

98 X=N, Y=CH, R^1=CH_3
99 X=N, Y=CH, R^1=Cl
100 X=CH, Y=N, R^1=CH_3
101 X=CH, Y=N, R^1=Cl

[a]**Reagents and conditions:** ***(i)*** $(COCl)_2$, anhydrous THF/DCM/DMF, 0 °C, then 23 °C 30 min *then* R_3R_2NH, NEt_3, anhydrous THF/DCM, 23 °C, 16 h; and ***(ii)*** $Pd(OAc)_2$, K_2CO_3, TBAB, H_2O, MW 150 °C, 5 min.

Both the 4-picolinamide (**Scheme 7**, **98** and **99**) and 5-nicotinamide (**Scheme 7**, **100** and **101**) syntheses begin with a Schotten-Baumann amidation and are followed with a microwave-mediated Suzuki coupling to afford the final products.

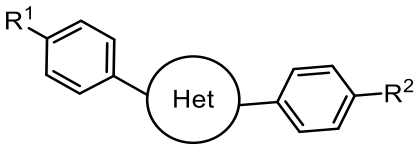
Scheme 8: Synthesis of Compounds 103, 105, 108, and 110[a]

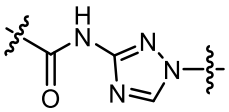
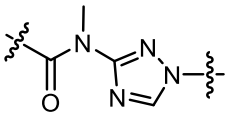
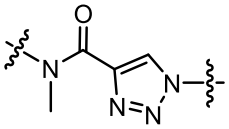
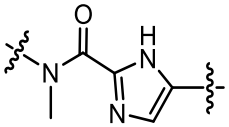
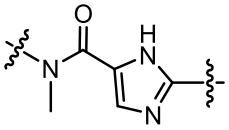
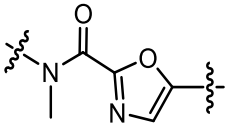
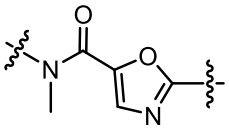
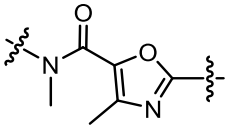


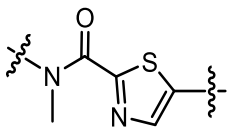
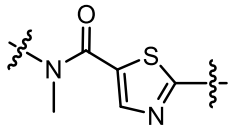
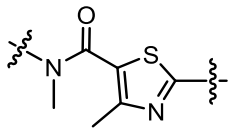
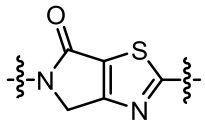
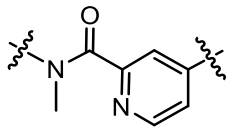
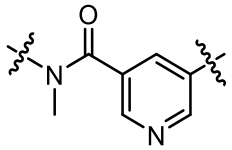
[a]**Reagents and conditions:** ***(i)*** $(COCl)_2$, anhydrous THF/DCM/DMF, 0 °C, then 23 °C, 30 min; ***(ii)*** *N,O*-dimethylhydroxylamine hydrochloride, NEt_3, anhydrous THF/DCM, 23 °C, 16 h; ***(iii)*** (4-chlorophenyl)magnesium bromide, anhydrous THF, 0 °C, then 23 °C, 3 h; ***(iv)*** 4-chloroaniline, NEt_3, anhydrous THF/DCM, 23 °C, 16 h; ***(v)*** CD_3I, K_2CO_3, anhydrous DMF, 0 °C to 23 °C, 12 h; ***(vi)*** $Pd(OAc)_2$, K_2CO_3, H_2O, MW 175 °C, 10 min; ***(vii)*** $(COCl)_2$, anhydrous THF/DCM/DMF, 0 °C, then 23 °C, 30 min; ***(viii)*** *N,O*-dimethylhydroxylamine hydrochloride, NEt_3, anhydrous THF/DCM, 23 °C, 16 h; ***(ix)*** (4-chlorophenyl)magnesium bromide, anhydrous THF, 0 °C, then 23 °C, 3 h; ***(x)*** 4-chloroaniline, NEt_3, anhydrous THF/DCM, 23 °C, 16 h; ***(xi)*** CD_3I, K_2CO_3, anhydrous DMF, 0 °C to 23 °C, 12 h.

Molecules, of both an oxazole and pyridine core, containing a ketone rather than an amide linkage (**Scheme 8**, **103** and **108**), were accessed by first preparing the Weinreb amide through a Schotten-Baumann amidation, then forming the ketone utilizing Grignard chemistry. Finally, deuteromethyl analogs (**Scheme 8**, **105** and **110**) were synthesized by first preparing the amide, then alkylating with iodomethane-d_3[17], facilitated by potassium carbonate.

Table 5: Alternative molecule cores explored via scaffold hopping study. EC_{50} and CC_{50} data represent geometric means for at least two independent experiments.



ID	Het	R^1	R^2	EC_{50} (W2) (μM)	pEC_{50} ± SD (W2)	CC_{50} (HepG2) (μM)
47		Cl	CH_3	>2.99	<5.52 ± 0.07	>10.0
48		Cl	Cl	3.08	5.51 ± 0.02	>10.0
49		CH_3	CH_3	2.49	5.60 ± 0.02	>10.0
50		CH_3	Cl	>10.0	<5.00	>10.0
51		Cl	CH_3	>1.80	<5.74 ± 0.38	>10.0
52		Cl	Cl	>1.52	<5.82 ± 0.19	>10.0
53		CH_3	CH_3	>3.38	<5.47 ± 0.01	>10.0
54		CH_3	Cl	4.24	5.37 ± 0.18	>10.0
56		Cl	CH_3	>10.0	<5.00	>10.0
57		Cl	Cl	>10.0	<5.00	>10.0
58		CH_3	CH_3	>10.0	<5.00	>10.0
59		CH_3	Cl	>10.0	<5.00	>10.0
62		Cl	CH_3	>10.0	<5.00	>10.0
63		Cl	Cl	>7.09	<5.15 ± 0.23	>10.0
66		Cl	CH_3	3.42	5.47 ± 0.10	>10.0
67		Cl	Cl	>2.26	<5.65 ± 0.24	>10.0
71		Cl	CH_3	0.672	6.17 ± 0.10	>10.0
72		Cl	Cl	0.170	6.77 ± 0.23	>10.0
75		Cl	CH_3	>10.0	<5.00	>10.0
76		Cl	Cl	>10.0	<5.00	>10.0
79		Cl	CH_3	>8.87	<5.05 ± 0.10	>10.0
80		Cl	Cl	>4.34	<5.36 ± 0.28	>10.0
83		Cl	CH_3	>10.0	<5.00	>10.0

84		Cl	Cl	>6.75	<5.17 ± 0.20	>10.0
87		Cl	CH_3	>10.0	<5.00	>10.0
88		Cl	Cl	>10.0	<5.00	>10.0
91		Cl	CH_3	>4.78	<5.32 ± 0.27	>10.0
92		Cl	Cl	>10.0	<5.00	>10.0
96		Cl	Cl	>10.0	<5.00	>10.0
98		Cl	CH_3	0.489	6.31 ± 0.09	>10.0
99		Cl	Cl	0.169	6.77 ± 0.15	>10.0
100		Cl	CH_3	0.131	6.88 ± 0.04	>10.0
101		Cl	Cl	0.435	6.36 ± 0.04	>10.0

Structure-activity and structure-property relationship studies of alternative molecule cores

The structure-activity relationship study revealed three scaffolds (5-oxazole-2-carboxamides, nicotinamides, picolinamides [**Table 5**]) with improved potency in comparison to the 1,2,4-triazoles. To identify the scaffold(s) with the best balance of activity profiles and physicochemical properties, select oxazoles and pyridines were profiled alongside select 1,2,4-triazoles for aqueous solubility, measured LogD, and metabolic stability ($CLint_{app}$ in both human liver microsomes [HLM] and rat hepatocytes [RH]) (**Table 6**).

Across all cores, bis-chlorinated molecules displayed poor aqueous solubilities and moderate intrinsic clearances in human liver microsomes. Though analogs containing one periphery methyl possessed improved solubilities (**100** and **26**), they suffered from extremely high microsomal clearances. The evaluated 5-nicotinamide (**100**), selected for its potency, had an extremely short half-life (under 10 minutes), likely due to oxidation of the aromatic methyl. To maintain the potency improvements thus far while preventing the introduction of further metabolic concerns, only the bis-chlorinated oxazole and picolinamide were advanced for further optimization.

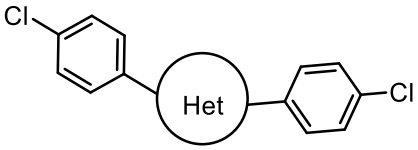
Table 6: Physicochemical properties of key SAR compounds. EC_{50} data represent geometric means for at least two independent experiments. Aqueous solubility (kinetic) and $LogD_{7.4}$ data represent means for two independent experiments.

ID	*Pf*ABS W2	Human liver microsomes		Rat hepatocytes		Aqueous solubility	$LogD_{7.4}$
	EC_{50} (nM)	$t_{1/2}$ (min)	$CLint_{app}$ (µL/min/mg)	$t_{1/2}$ (min)	$CLint_{app}$ (µL/min/10^6 cells)	pH 7.4 (µM)	
26	1730	11.1	125	<7.5	>92.4	19.1	3.15
22	556	33.8	41.1	<7.5	>92.4	4.4	3.36
20	519	43.5	31.9	<7.5	>92.4	3.2	3.57
72	170	14.1	98.6	<7.5	>92.4	4.2	4.91
100	131	6.1	228	<7.5	>92.4	12.8	4.32
99	169	41.3	33.5	<7.5	>92.4	<2.5	4.51

At this point in the hit expansion program, it was evident that metabolic stability was a limitation of this compound class, where amide dealkylation was suspected to be a metabolic concern. The likelihood for this *N*-dealkylation to occur (as predicted by MetaSite, **Figure S2**), in conjunction with the known loss of potency when an amide is not methylated, motivated the exploration of further amide modifications (**Scheme 8**) (**Table 7**). As investigated in the scaffold hopping study, simple reversal of the amide order resulted in a loss of potency (**51**-**54**), so this was not a viable option. A ketone linkage, rather than an amide, was evaluated (**103** and **108**), but it resulted in a complete loss of activity (EC_{50}'s >10.0 µM). Inspired by the recent success of deucravacitinib[28], a deuteromethyl was investigated as an isosteric replacement to improve metabolic stability. Given the increased bond strength of a carbon-deuterium bond (3 kJ/mol stronger than C-H[29]), it should be more difficult for a deuterium atom to be abstracted to initiate amide dealkylation. As shown in **Table 8**, with only a 29 nM loss of potency, the

deuteropyridine displayed a 2-fold improvement in stability in human liver microsomes (HLM $CLint_{app}$ 17.3 versus 33.5 µL/min/mg, **110** and **99**) and a 5-fold improvement in aqueous solubility. The metabolic stability of the oxazole only improved slightly (HLM $CLint_{app}$ 76.6 versus 98.6 µL/min/mg, **105** and **72**), but a 3-fold decrease in potency was observed. Thus, **110** and **72** were nominated as lead compounds for further evaluation.

Table 7: Alternative amide modifications. EC_{50} and CC_{50} data represent geometric means for at least two independent experiments.



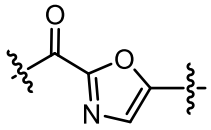
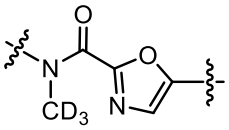
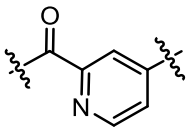
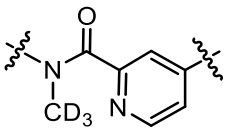
ID	Het	EC_{50} (W2) (nM)	pEC_{50} ± SD (W2)	CC_{50} (HepG2) (nM)
103		>10,000	<5.00	>10,000
105		388	6.41 ± 0.23	>10,000
108		>10,000	<5.00	>10,000
110		198	6.70 ± 0.15	>10,000

Table 8: Physicochemical properties of deuteromethyl amide replacements and their isotopologues. EC_{50} data represents geometric means for at least two independent experiments. Aqueous solubility (kinetic) and $LogD_{7.4}$ data represent means for two independent experiments.

ID	*Pf*ABS W2	Human liver microsomes		Rat hepatocytes		Aqueous solubility	$LogD_{7.4}$
	EC_{50} (nM)	$t_{1/2}$ (min)	$CLint_{app}$, app (µL/min/mg)	$t_{1/2}$ (min)	$CLint_{app}$, app (µL/min/10^6 cells)	pH 7.4 (µM)	
72	170	14.1	98.6	<7.5	>92.4	4.2	4.91
105	388	18.1	76.6	<7.5	>92.4	<2.5	4.64
99	169	41.3	33.5	<7.5	>92.4	<2.5	4.51
110	198	80.2	17.3	<7.5	>92.4	13.4	4.41

Additional biological analysis of APZ front-runners

Representative analogs were selected for additional biological profiling to gain insight into the mechanism of action of this compound class. As this series was originally discovered through a virtual high-throughput screen docking against *Pf*FNT, and *Pf*FNT inhibition results in lactate accumulation that in turn lowers intracellular pH, we utilized a previously reported assay to measure the cytosolic pH of the parasite in real time[30]. Parasites were saponin-lysed to remove the host red blood cell membrane but leave parasites intact. These are then loaded with the pH reactive dye BCECF-AM prior to treatment with test compounds. After testing three representative analogs, a pH decrease was not observed upon compound addition, suggesting this series acts by a different mechanism of action (**Figure S3**).

The most potent triazole (**20**) was then assayed alongside the lead oxazole (**72**) and deuteropyridine (**110**) against three additional *P. falciparum* strains with variable resistance profiles: TM90C2B (chloroquine, mefloquine, pyrimethamine, and atovaquone resistant), TM91C235 (chloroquine, mefloquine, and pyrimethamine resistant), and D6QHS3400 (artemisinin resistant) (**Table 9**). This was done both to assess if our compound series is susceptible to clinically relevant resistance mechanisms, but also in hopes to gain mechanistic insights. For the oxazole and deuteropyridine compounds, we observed comparable potencies to those seen against W2, suggesting that our compound class is interacting with a novel target (as they are not impacted by current resistance mechanisms). Further, the potency observed against TM90C2B is comparable to (**72**) or stronger than (**110**) potencies in the other assayed lines. This could imply that these compounds are acting upon a mitochondrial/energy related target. These results, as well as the target(s) of our compound series, are currently being investigated further.

Table 9: Assessment of key compounds against alternative *P. falciparum* lines. Values displayed are EC_{50} and pEC_{50} ± standard deviation. EC_{50} data represents geometric means for at least two independent experiments.

ID	W2	TM90C2B	TM91C235	D6QHS3400
20	519 nM	>3.69 μM	>4.81 μM	>4.74 μM
	6.28 ± 0.23	<5.43 ± 0.06	<5.32 ± 0.23	<5.32 ± 0.22
72	170 nM	168 nM	281 nM	840 nM
	6.77 ± 0.23	6.78 ± 0.03	6.55 ± 0.29	6.08 ± 0.12
110	198 nM	104 nM	199 nM	608 nM
	6.70 ± 0.15	6.98 ± 0.13	6.70 ± 0.22	6.22 ± 0.15

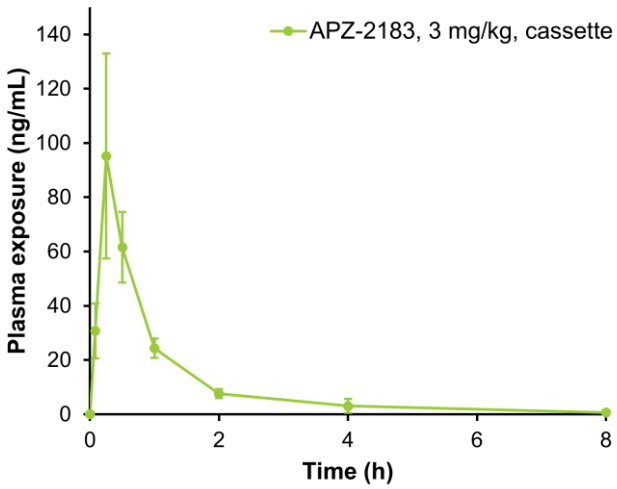
Pharmacokinetic analysis of APZ front-runners

Activity-driven optimization of this carboxamide series delivered several compounds that were in the low nanomolar range. Subsequent assessment of physicochemical and metabolic properties led to the selection of **72** and **110** for pharmacokinetic evaluation, as these compounds displayed the best balance of antimalarial

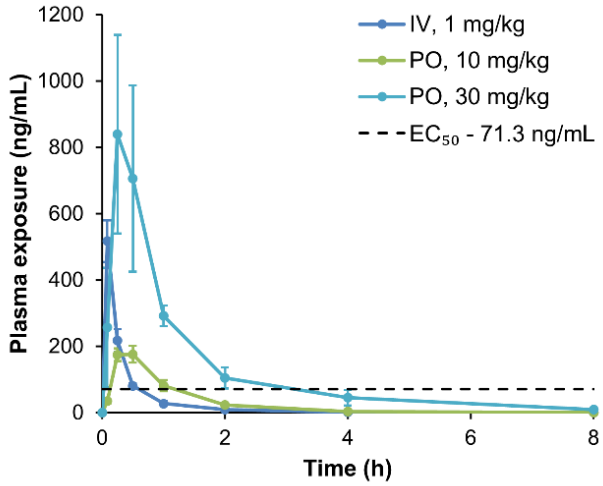
activity, physicochemical and ADME properties, and the absence of cytotoxicity. The oxazole (**72**) and deuteropyridine (**110**) were first profiled in a cassette dosing pharmacokinetic study via oral administration (PO, 3 mice, 3 mg/kg).

In the cassette study, the oxazole (**72**) was not detected, likely due to major stability issues (**Figure S4**). The deuteropyridine (**110**), by contrast, exhibited a half-life of 0.70 hours (**Table S5**) and a C_{max} of 96 ng/mL (**Figure 3a**), showing promise for further pharmacokinetic evaluation. In single-compound pharmacokinetic studies (IV, 3 mice, 1 mg/kg; PO, 3 mice, 10 mg/kg; and PO, 3 mice, 30 mg/kg) (**Figure 3b**), the plasma exposure showed some super-proportionality. However, as it was within a factor of 2 above a perfect proportionality from 10 to 30 mg/kg (0.63 h*µg/mL), it is thus likely within acceptable experimental variability rather than, for example, due to a clearance saturation event. At 30 mg/kg (PO), **110** displayed a half-life of 1.54 hours, a C_{max} of 843 ng/mL, and an oral bioavailability of 16.2% (**Figure 3c**). However, in line with *in vitro* clearance data in rat hepatocytes, we observed high clearance for **110**. The assessed doses were well tolerated; doses higher than 30 mg/kg were not explored.

(a)



(b)



(c)

Dose [mg/kg]	C_{max} [µg/mL]	t_{max} [h]	$t_{1/2}$ [h]	AUC_{inf} [h*µg/mL]	CL [mL/min/kg/]	% F	Vd_{ss} [L/kg]
1 (IV)	0.52 ± 0.08	–	0.69 ± 0.10	0.21 ± 0.04	81.2 ± 15.5	–	2.07 ± 0.31
10 (PO)	0.19 ± 0.01	0.33 ± 0.14	0.63 ± 0.10	0.21 ± 0.03	–	9.91 ± 1.53	–
30 (PO)	0.84 ± 0.36	0.33 ± 0.14	1.54 ± 0.50	1.02 ± 0.07	–	16.2 ± 0.93	–

Figure 3: Pharmacokinetic profiles of **110**. **(a)** Average and standard deviations of 3 replicates (3 mice) for 3 mg/kg oral administration in a cassette dosing protocol in 10% DMSO + 5% Tween 80 + 85% saline formulation. Significant data variation in average values due to data in one mouse; **(b)** Average and standard deviations of 3 replicates (3 mice per dataset) for single compound dosing at: 1 mg/kg (IV), 10 mg/kg (PO), and 30 mg/kg (PO) in 10% DMSO, 20% PEG400, 10% Solutol, and 60% Na_2HPO_4 solution (50 mM) with 0.5%

Tween 80 formulation. The EC_{50} (*Pf*ABS, strain W2) is displayed on the plot for reference; **(c)** Pharmacokinetic parameters of **110** after administration in a 10% DMSO, 20% PEG400, 10% Solutol, and 60% Na_2HPO_4 solution (50 mM) with 0.5% Tween 80 formulation.

Rate of killing assessments

We conducted a modified PRR assay[31] to evaluate the pharmacodynamic properties of **110**. In this experiment, we exposed *P. falciparum* 3D7 parasites to 10x EC_{50} of **110** for up to 5 days in 24-well plates. Every 24 hours, the compound was washed from a different 1 mL culture, the parasites were serially diluted in a 384-well microtiter plate, and surviving parasites were allowed to grow without compound pressure for 7 days. Parasite growth was then assessed using high-content imaging of Hoechst 33342-stain wells (see Experimental Section).

For controls, we used chloroquine as a fast-acting reference and pyrimethamine as a slow-to-moderate-acting reference[31] (**Figure 4**). Our results showed a reduction in viable parasites after 24 hours of exposure to **110**, with nearly complete parasite clearance (99.9%) occurring after 64.1–74.1 hours of continuous exposure (**Figure 4**, **Table 10**, **Figure S5**, **Table S6, Table S7**).

When compared to the controls, **110** exhibited a slow-to-moderate killing rate (average PRR 2.4 [1.7-3.7]) (**Table S6**) with a brief lag phase, similar to pyrimethamine (**Figure 4**, **Table 10**, **Figure S5**, **Table S6, Table S7**).

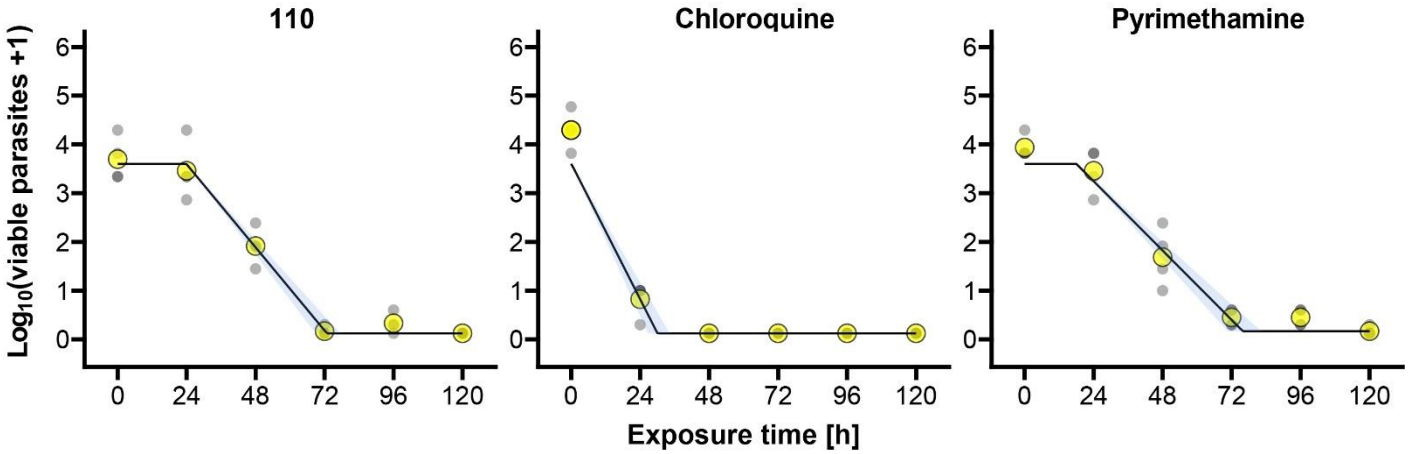


Figure 4: Miniaturized parasite reduction ratio (μPRR) assay. Using 24-well plates, 1 mL cultures of *P. falciparum* (strain 3D7) were treated with 10x EC_{50} of **110**, chloroquine, pyrimethamine for 0, 24, 48, 72, 96, or 120 h with daily media change. At each endpoint, the compound was washed off the culture and plated into four wells of a 384-well microtiter plate (with 10^4 parasites added at 0 h). Using automation, parasites were then plated in a 1:3 serial dilution series and allowed to grow for 7 days before detection using high-content imaging. The number of positive wells was used to calculate the starting number of parasites in each culture, enabling calculation of the reduction ratio (clearance over the first 48 h of treatment), 99.9% clearance time, and lag to clearance. One experiment is shown, two additional independent experiments are available in the Supporting Information.

Table 10: Key parameters from rate of killing assessment. Data for one experiment is shown. Data for two additional independent experiments are available in the Supporting Information.

Compound	Category	Lag phase [h]	99% PCT [h]	PRR	E_{max} [h^{-1}]
110	Intermediate with lag phase	24	66.1 [62.8 - 70.1]	3.4 [3.1 - 3.7]	0.20 [0.18 - 0.21]
Chloroquine	Fast	0	25.9 [23.1 - 29.5]	5.6 [4.9 - 6.3]	0.30 [0.27 - 0.33]
Pyrimethamine	Slow	18 [0 - 24]	68.6 [64.1 - 74.1]	2.8 [2.6 - 3.1]	0.17 [0.15 - 0.18]

Simulated human pharmacokinetic profiles

110 was profiled for a suite of additional ADME properties (**Table 11**, **Table 12**). Though the compound displayed moderate metabolic stability in human hepatocytes ($CLint_{app}$ HHep 34.4 µL/min/10^6 cells), high *in vitro* clearance was observed for both mouse and rat hepatocytes, in line with the *in vivo* clearance data. There is a 2-fold increase in clearance when comparing human liver microsomes ($CLint_{app}$ HLM 17.3 µL/min/mg, **Table 8**) and human hepatocytes ($CLint_{app}$ HHep 34.4 µL/min/10^6 cells, **Table 11**), suggesting that **110** is especially susceptible to phase II metabolism. Using the well-stirred model without any binding (plasma or microsome/hepatocyte) correction, the first value yields a scaled hepatic clearance of 7.04 mL/min/kg while the second yields a clearance of 11.9 mL/min/kg, both in plasma (adjusted using a blood to plasma ratio of 0.69, **Table 11**). The Extended Clearance Classification System also predicts that metabolic clearance is likely for our compound class given that **110** is a neutral permeable (**Table 12**) compound (Class 2)[32-34]. The observed plasma protein binding was high in human (99.8%), mouse (99.6%), and rat (94.4%) plasma, which can be attributed to the lipophilic nature ($LogD_{7.4}$ = 4.41) of this compound. However, the metabolic stability of the compound was poor in mouse and rat plasma, but moderate (86.6% plasma stability at 6 hours) in human plasma. Finally, as essentially no efflux in MDCK-MDR1 cells was observed for **110** (efflux ratio of 1.10), it is unlikely to be a substrate for the P-glycoprotein efflux transporter.

Table 11: Additional ADME parameters for **110**.

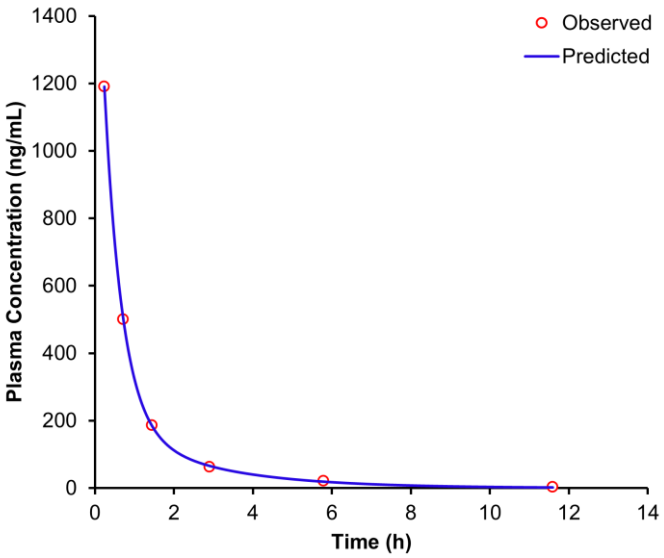
Hepatocytes, $CLint_{app}$ (µL/min/10^6 cells)			Blood to plasma ratio			RBC to plasma ratio		
Human	**Mouse**	**Rat**	**Human**	**Mouse**	**Rat**	**Human**	**Mouse**	**Rat**
34.4	>184.8	>92.4	0.69	0.76	0.83	0.32	0.46	0.62

Table 12: Additional ADME parameters for **110**.

% PPB			% plasma stability @ 6 h			MDCK-MDR1 permeability		
Human	**Mouse**	**Rat**	**Human**	**Mouse**	**Rat**	**A > B**	**B > A**	**Efflux ratio**
99.8	99.6	94.4	86.6	14.6	0.03	13.9	15.1	1.10

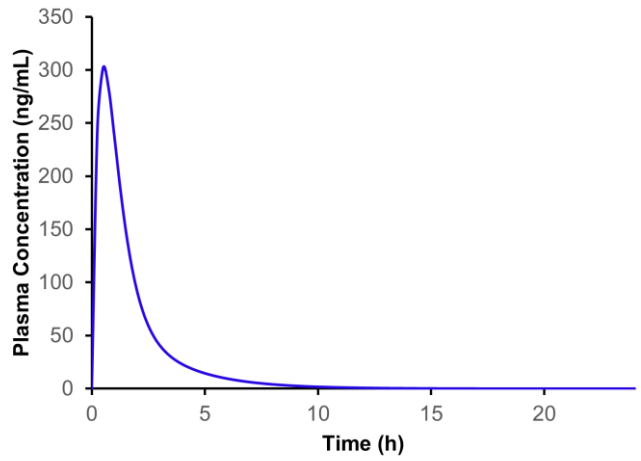
The aforementioned *in vitro* and pharmacokinetic murine data was utilized in the 1-species Wajima method (C_{ss}-MRT method)[35] for the prediction of a human pharmacokinetic profile. This was achieved via normalization (with murine C_{ss} and MRT, Mean Residence Time) to a dimensionless plot and back-transformation of the plot using human estimated C_{ss} and MRT. This step affords a predicted intravenous human plasma concentration-time profile (**Figure 5a**)[35]. From this predicted profile, an oral human plasma concentration-time profile[36] was simulated for both for single (**Figure 5b**) and repeated dosing (**Figure 5c**) at 300 mg. These data suggest that a 300 mg PO dose would achieve a C_{max} of 302 ng/mL and sustain a concentration at or above **110**'s EC_{50} (71.3 ng/mL or 198 nM) for 2.25 hours. Thus, no accumulation is predicted, and steady state is not reached.

(a)



Scaling parameters	
C_{ss} (1 mg/kg dose)	1098 ng/mL
CL (scaled, HHep)	11.9 mL/min/kg
$VD_{ss,\ estimated}$[a]	0.910 L/kg
MRT (VD_{ss}/CL)	1.27 h
Simulation parameters (human, 1 mg/kg, IV, 2 CA)	
α (IV fit)	2.22 h^{-1}
β (IV fit)	0.418 h^{-1}
k_{21} (IV fit)	0.617 h^{-1}
k_a (from 1/MAT)	1.96 h^{-1}
$V_{c,PO}$[b]	365720 mL
% F	10

(b)



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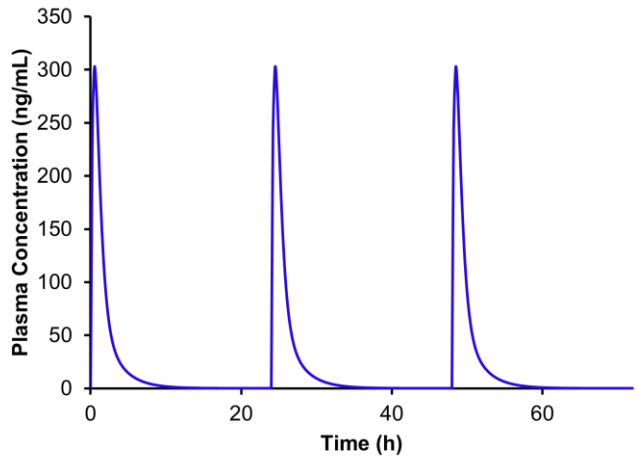

Figure 5: Predicted human pharmacokinetic profiles for **110**. **(a)** Predicted human plasma concentration-time profile, 1 mg/kg (IV). Parameters for the scaling of murine data to human estimations, as well as simulation parameters from the predicted human IV profile (*PK*Solver2.0, 2-compartment analysis[37]). These were used to simulate PO human plasma concentration-time profiles (PKMP, version 1.03.53). [a]Calculated via the Berelinni method[38]. [b]IV fit corrected for 70 kg average weight and F; **(b)** Predicted human plasma concentration-time profile, 300 mg single dose (PO); **(c)** Predicted human plasma concentration-time profile,

three once-daily 300 mg doses (PO). MAT derived from PO and IV MRT data in mouse and assumed to be equal to human.

110 qualifies as a good lead compound, as it displays acceptable potency (EC_{50} 198 nM), excellent selectivity (>10.0 μM, HepG2), acceptable physicochemical properties for a lead compound (aqueous solubility 13.4 μM, $CLint_{app}$ HLM 17.3 μL/min/mg), and a superior pharmacokinetic profile in comparison to **72**. However, several factors warrant further improvement before *in vivo* studies are initiated, such as the observed half-life in pharmacokinetic studies, *in vitro* and *in vivo* clearance in mice, and improvement of the predicted human dose of 300 mg (PO). These data justify further investigation and optimization of this compound class.

CONCLUSION

Through a molecular docking- and cheminformatics-driven virtual high throughput screen, a 1,2,4-triazole-3-carboxamide scaffold was identified as a novel antimalarial series with moderate potency and sup-optimal physicochemical properties. Structure-activity relationship studies found that only minor modifications are tolerated at the molecule periphery. An *N*-methyl carboxamide was found to be critical to activity, as the absence of this methyl group often resulted in a complete loss of potency, akin to a magic methyl. Numerous triazoles were synthesized with no major potency improvements, driving us to perform a scaffold-hopping study with 13 core modifications. In total, 33 molecules of alternative cores were synthesized. Ultimately, three cores (5-oxazole-2-carboxamides, 4-picolinamides, and 5-nicotinamides) had greater potency than the 1,2,4-triazoles.

After evaluation of physicochemical properties, the 5-oxazole-2-carboxamides and 4-picolinamides were prioritized for optimization of metabolic stability and aqueous solubility. Replacement of the *N*-methyl with a *N*-deuteromethyl improved both microsomal stability and aqueous solubility for the picolinamide scaffold. This compound, along with the most potent 5-oxazole-2-carboxamide, was advanced to cassette pharmacokinetic studies. As expected from *in vitro* data, the deuterated picolinamide outperformed the profiled oxazole and was nominated for further evaluation. The compound performed well in pharmacokinetic studies, displaying oral bioavailability (% F 16.2) and a moderate half-life at 30 mg/kg oral administration (1.54 hours). However, several parameters, such as the *in vivo* half-life and clearance, should be improved via further compound optimization before *in vivo* efficacy studies are initiated.

To assess whether the compounds evaluated herein were indeed *Pf*FNT inhibitors, we turned to a previously reported cytosolic pH assay[30]. A *Pf*FNT inhibitor should immediately yield a decrease in cytosolic pH upon administration to live trophozoites, but our compound series (**20**, **72**, **101**) did not display this effect. These data suggest the carboxamides are not *Pf*FNT inhibitors. Potent activities against several multi-drug-resistant lines (TM90C2B, TM91C235, and D6QHS3400) suggest this series is not cross-resistant with current antimalarial drugs and possibly is acting upon a novel target. We also evaluated the rate of killing of our compound series

through a modified parasite reduction ratio (PRR) assay[39]. **110** displayed a slow-to-intermediate rate of killing, similar to pyrimethamine.

Given the potent blood-stage *in vitro* activity profile, excellent selectivity, and acceptable physicochemical properties, **110** is a promising lead compound. This series shows promise for future structure-activity and structure-property relationship studies, as well as target deconvolution, which are ongoing.

EXPERIMENTAL SECTION

General Materials and Methods

Unless otherwise noted, all reagents and solvents were purchased from commercial sources and used without further purification. Tetrahydrofuran (THF) was distilled from benzophenone and sodium metal under a positive pressure argon atmosphere immediately before use. Column chromatography was carried out using Sorbtec silica gel 60 Å (particle size 40-63 μm) and analytical thin layer chromatography was performed on 0.25 mm silica gel 60 F254 precoated plates from EMD Millipore. Microwave reactions were performed in an Anton Paar Monowave 400. The identity of all title compounds was verified via ^{1}H NMR, ^{13}C NMR, and LRMS. Proton nuclear magnetic resonance (^{1}H NMR) and proton decoupled carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded at ambient temperature on a Bruker 500 or 700 MHz spectrometer or a Varian 400 or 500 MHz spectrometer. All ^{1}H NMR experiments are reported in δ units, parts per million (ppm) downfield of trimethyl silane (TMS) and were measured relative to the residual proton signals of chloroform (δ 7.26), methanol (δ 3.31), acetone (δ 2.05), and dimethylsulfoxide (δ 2.50). Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), multiplicity (bs = broad singlet, s = singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplets, ddt = doublet of doublet of triplets, t = triplet, tt = triplet of triplets, q = quartet, hept = heptet, m = multiplet), coupling constant (Hz), and integration. All ^{13}C NMR spectra are reported in δ units, parts per million (ppm) downfield of TMS, and were measured relative to the residual carbon signals of chloroform (δ 77.16 ppm), methanol (δ 49.00 ppm), acetone (δ 29.84), and dimethylsulfoxide (δ 39.52). Data for ^{13}C NMR are reported as follows: chemical shift (δ ppm), multiplicity where appropriate (d = doublet, q = quartet), and coupling constant (Hz). NMR data was analyzed by using MestReNova Software version 12.0.3-21384. The chemical purity of the title compounds was determined by LC-MS using an Agilent 1260 Infinity II HPLC coupled to an Agilent G6125B single quadrupole mass spectrometer with electrospray ionization. At a flow rate of 0.600 mL/min, samples were analyzed on an Agilent ZORBAX RRHT StableBond-C18 column (1.8 μm, 2.1 x 50 mm, part no: 827700-902) with the following HPLC method: 0 min 90/10 A/B, 3.5 min 10/90 A/B, 5.5 min 10/90 A/B, 6.0 min 90/10 A/B wherein A is water (+0.1% formic acid) and B is acetonitrile (+0.1% formic acid). All final compounds are >95% pure by HPLC analysis.

Antimalarial Potency Assays

Potencies against *P. falciparum* asexual blood stage parasites was determined as previously described[40]. Briefly, *P. falciparum* (strain W2[41], TM90C2B[42], TM91C235[43], or D6QHS3400[43] were cultured in RPMI 1640 (Gibco

31800-022) supplemented with 25 mM HEPES (Gibco 11344-041), 0.25% (w/v) $NaHCO_3$ (Gibco 25080-094), 10% inactivated human plasma (Interstate Blood Bank), 10 µg/mL gentamicin (Gibco 15610-072), and 2.5% hematocrit O+ human blood (Interstate Blood Bank) in T25 or T75 flasks in a 37 °C incubator at 5% CO_2 and 5% O_2.[44] Two days prior to starting an assay, a culture was synchronized with 5% D-sorbitol[45]. After 48 hours, cultures at >90% rings were adjusted to 2% parasitemia in 0.75% hematocrit and 40 µL were plated into each well of 384-well microtiter plates (Greiner Bio-One 781090) using a Biomek NX^P (Beckman Coulter). Test compounds were supplied as 10 mM solutions in DMSO that were spotted into conical bottom 384-well source microplates (Greiner Bio-One 784261) before being made into a 12-point, 1:3 dilution series in DMSO using a Biomek 4000 (Beckman Coulter). After seeding, a pin tool (V&P Scientific) affixed to a Biomek NX^P was used to transfer 40 nL from the source to the assay plate, thereby diluting all compounds in the series 1000-fold and making the highest dose 10 µM. Dihydroartemisinin (AvaChem Scientific lot OK1008) was used as the positive control and 0.1% DMSO (v/v) was used as the negative control. After 72 hours, plates were fixed and stained by adding 40 µL of 0.1% glutaraldehyde (Millipore-Sigma G7651) and 20 µg/mL Hoechst 33342 (Fisher H21492) to each well using a Biomek NX^P, resulting in a final concentration of 0.05% glutaraldehyde and 10 µg/mL Hoechst 33342 per well. Plates were stored at 4 °C overnight before imaging on an ImageXpress Micro Confocal (Molecular Devices) with a 4x objective and DAPI filter set. Net DNA signal from growing parasites was quantified using MetaXpress (Molecular Devices) and raw data was loaded into CDD Vault for normalization using

$$\%\ Inhibition = 100 \times \left(\frac{Raw\ Data - Average\ Negative\ Control}{Average\ Positive\ Control - Average\ Negative\ Control}\right)$$

and curve fitting using the Levenberg–Marquardt algorithm[46, 47].

Cytotoxicity Screens

Cytotoxicity against mammalian cells was determined as previously described[48]. Briefly, HepG2 cells (*Homo sapiens* hepatoblastoma, ATCC, cat HB-8065, RRID:CVCL_0027) were cultured in collagen-coated T75 flasks in media consisting of sugar-free DMEM (Gibco 11966-025) supplemented with 10% FBS (Corning 35-016-CV), 25 mM glucose (Millipore-Sigma 49163), 1 mM sodium pyruvate (Corning 25-000-CI), 1x penicillin-streptomycin-neomycin mix (Gibco, cat 15640-055), and 2 mM L-glutamine (Gibco 25030-081). Flasks were kept in an incubator at 37 °C and 5% CO_2. To start assays, TrnLE (Gibco 12605-028) was used to harvest cells before setting the density to 50 cells μL^{-1} in media supplemented with 10 mM galactose (Sigma G5388) instead of glucose. Cells were then seeded at 40 µL (2000 cells) $well^{-1}$ into collagen-coated 384 well plates (Greiner Bio-One, cat 781956) using a Biomek NX^P. Test compounds were plated into source plates as described above, but using puromycin as the positive control (Sigma, lot 131192). Assay plates were treated from source plates using a pin tool as described above. After 72 hours, plates were fixed and stained by dumping the well contents and adding 20 µL of 4% paraformaldehyde and 10 µg/mL Hoechst 33342 to all wells using a Biomek NX^P. Plates were imaged and analyzed as described above. Hepatic nuclei counts were loaded into CDD Vault for normalization and curve fitting as described above.

Determination of *In Vitro* DMPK Parameters

Experimental protocols for the determination of various DMPK parameters can be found in the Supporting Information. All experiments were performed by TCG LifeScience, Kolkata, India (contract research organization).

Pharmacokinetic Studies in Male CD-1 Mice

Pharmacokinetic studies were performed by TCG LifeScience (TCGLS), Kolkata, India. The animal facility is AAALAC accredited and TCGLS follows the guidelines of Committee for Control and Supervision of Experiments on Animals (CCSEA) and the Guide for the Care and Use of Laboratory Animals (Guide), NRC, 2011 for laboratory animals care and use. The entire facility is equipped with IVC system for housing of animals. All procedures to be carried out on live animals as part of this study will be subject to provisions of institutional animal ethics committee (IAEC) approvals. Animals were housed under 12 h/12 h light/dark cycle, 23 ± 3 °C temp, 50 ± 20% RH, and were allowed free access to food and water *ad libitum*. Animals were acclimatized to laboratory conditions for 5-7 days prior to use in the studies. Finally, animals were observed during the study period to ensure good health; all animals were in good health through the length of the studies.

Briefly, the plasma pharmacokinetics were determined in male CD-1 mice (6-8 weeks) in either a cassette dosing or single-compound dosing format. Following administration of compound (cassette: 3 mg/kg oral gavage; single-compound: 1 mg/kg intravenous, 10 or 30 mg/kg oral gavage), blood was collected (sampled via saphenous vein) from three mice (per study) at the following timepoints: 5 min, 15 min, 30 min, 1 h, 2 h, 4 h, 8 h, and 24 h. Approximately 40 µL blood sample was taken manually at each time points into K_2EDTA capillary tubes by piercing the saphenous vein of restrained, conscious animals with a needle. This sample was subsequently transferred into 0.5 mL eppendorf tubes and processed for plasma by centrifugation (4000 rpm, 10 min, 4 ºC) within half an hour of collection. Plasma samples were stored at -20 ºC until bioanalysis. Compound concentration was determined by LC-MS/MS (API6500 or AP4000 integrated to Shimadzu LC and CTC-PAL autosampler, YMC Triart C18 2.0 x 30 mm) after sample cleanup (70/30 acetonitrile/methanol deproteinization [1:6] and aqueous dilution [1:1]).

Miniaturized Parasite Reduction Ratio (µPRR) Assay

We assessed the number of parasites surviving compound treatment over time of exposure using a parasite reduction ratio (PRR) protocol modified from that previously described[31]. The PRR V2 as published uses 3 mL cultures of *P. falciparum* (strain NF54) parasites at 2% hematocrit and 0.5% parasitemia treated at 10x the EC_{50} of test or control compounds in 6-well plates. Media with compound is exchanged daily. At each timepoint, one well is collected, washed thrice to remove compound, resuspended in media, and serial diluted in a 96-well microtiter plate such that 10^5 parasites are added to the first well of the dilution series. After two weeks in culture, the number of dilutions containing parasites is determined using a standard hypoxanthine assay and the equation

$3^{(last\ dilution\ with\ growth-1)}$

is used to determine the starting number of parasites surviving treatment over the designated treatment time. Before starting our PRR assay, we determined the potency of **110**, chloroquine, and pyrimethamine against a subclone of *P. falciparum* (strain 3D7.c.2A6) in three independent experiments (3D7 is a subclone of NF54[49]). To increase throughput, we modified several steps resulting in a semi-automated, miniaturized, and expedited protocol. First, by using a 1 mL culture for each compound and timepoint in a 24-well plate (Costar 3524), less blood and media is required and at each collection timepoint an Eppendorf tube can hold the culture for washes (as opposed to a 15 mL conical tube needed for a 3 mL culture). Second, after washing thrice using a microcentrifuge, the pellets were resuspended in 1 mL media and 60 µL was added to four replicate wells in the first or thirteenth column of a 384-well plate (Greiner Bio-One 781090), allowing for up to 8 control or test conditions per 384-well plate. After loading, the remainder of the 384-well plate wells were filled with 40 µL culture media and blood (2% hematocrit) using a Biomek 4000 (Beckman Coulter) before 20 µL was taken from the first well and diluted down a 12-point series. Third, instead of letting parasites in the serial dilution grow out for 14 days prior to detection, we used high-content imaging of glutaraldehyde (0.05%) fixed, Hoechst-stained (10 µg/mL) wells as with our standard screening protocol (see above) to reliably quantify the number of growth-positive wells at 7 days post seeding, thereby removing the need for media change or detection with radiation. Following quantification, we used the previously reported R script (Version: 8.3.1 (21-09-2022)) script[31]) modified to account for one log less starting parasites in the 384-well format (10^4) to enable good curve fits used to calculate the lag phase, PRR ($\log_{10}$ drop of viable parasites within 48 h), 99.9% parasite clearance time (PCT; time to kill 99.9% of the initial parasites), and maximal killing rate (E_{max}) of **110** and the two control compounds.

Synthetic Chemistry

General Amidation Procedure (General Procedure A)

In a flame-dried round bottom flask under argon, the respective carboxylic acid (1 equiv) was dissolved in anhydrous dichloromethane (0.12 M), anhydrous tetrahydrofuran (0.91 M), and a catalytic amount of anhydrous *N,N*-dimethylformamide. The reaction mixture was then cooled to 0 °C and oxalyl chloride (3 equiv) was added slowly. Upon complete formation of the acid chloride intermediate, as monitored by LC-MS, the reaction mixture was concentrated *in vacuo*. Anhydrous dichloromethane and tetrahydrofuran were added back to the reaction mixture in their respective amounts, followed by the respective amine (3 equiv) and triethylamine (2 equiv). The reaction mixture was then stirred for 16 hours at room temperature. Upon reaction completion, the reaction mixture was diluted in dichloromethane and saturated aqueous sodium bicarbonate. The aqueous layer was extracted thrice with dichloromethane. The combined organic layers were dried over sodium sulfate and concentrated *in vacuo.* The crude product was purified by flash column chromatography to afford the title compound.

1-(4-chlorophenyl)-1*H*-1,2,4-triazole-3-carboxylic acid **(2a)**

In a round bottom flask, 4-chloroaniline (4.91 mmol, 1.11 equiv) was dissolved in water (1.40 M) and concentrated hydrochloric acid (14.8 mmol, 3.30 equiv). The reaction mixture was then cooled to 0 °C and a solution of sodium nitrite (4.91 mmol, 1.11 equiv) in water (9.40 M) was added dropwise. A solution of sodium acetate (30.9 mmol, 7 equiv) and ethyl isocyanoacetate (4.42 mmol, 1 equiv) in water (0.86 M) and methanol (8.60 M) was added to the reaction mixture very slowly, taking care to not allow the reaction mixture to rise above 5 °C. After 30 minutes at 0 °C, the reaction was warmed to room temperature and stirred for 16 hours. The resulting orange precipitate (intermediate **1a**) was isolated via vacuum filtration and carried into the next step without further purification.

In a round bottom flask, the crude ester (ethyl 1-(4-chlorophenyl)-1*H*-1,2,4-triazole-3-carboxylate) (4.42 mmol, 1 equiv) was dissolved in tetrahydrofuran (0.13 M) and water (0.40 M). Following addition of lithium hydroxide monohydrate (13.2 mmol, 3 equiv), the reaction mixture was stirred at room temperature for 16 hours. Upon complete consumption of the ester, the reaction mixture was basified to pH 12-13 with sodium hydroxide (3 M) and extracted thrice with dichloromethane. The aqueous layer was then acidified to pH 2-3 with hydrochloric acid (3 M). The resulting precipitate was isolated via vacuum filtration to afford the title compound as a light orange solid (37%, over 2 steps). ^{1}H NMR (400 MHz, CD_3OD) δ 9.20 (s, 1H), 7.90 (d, J = 8.8 Hz, 2H), 7.60 (d, J = 8.8 Hz, 2H); LRMS-ESI (*m/z*): $[M + H]^+$ 224.0.

1-(*p*-tolyl)-1*H*-1,2,4-triazole-3-carboxylic acid **(2b)**

Prepared as described for 1-(4-chlorophenyl)-1*H*-1,2,4-triazole-3-carboxylic acid from *p*-toluidine. An acid-base extraction afforded the title compound as a light orange solid (19%, over 2 steps). ^{1}H NMR (500 MHz, CD_3OD) δ 9.11 (s, 1H), 7.73 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.3 Hz, 2H), 2.42 (s, 3H); LRMS-ESI (*m/z*): $[M + H]^+$ 204.1.

1-(4-ethylphenyl)-1*H*-1,2,4-triazole-3-carboxylic acid (**2c**)

Prepared as described for 1-(4-chlorophenyl)-1*H*-1,2,4-triazole-3-carboxylic acid from 4-ethylaniline. An acid-base extraction afforded the title compound as an orange solid (24%, over 2 steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.71 (s, 1H), 7.67 (d, J = 8.3 Hz, 2H), 7.37 (d, J = 8.3 Hz, 2H), 2.74 (q, J = 7.6 Hz, 2H), 1.29 (t, J = 7.6 Hz, 3H); LRMS-ESI (*m/z*): $[M + H]^+$ 218.1.

1-(4-isopropylphenyl)-1*H*-1,2,4-triazole-3-carboxylic acid **(2d)**

Prepared as described for 1-(4-chlorophenyl)-1*H*-1,2,4-triazole-3-carboxylic acid from 4-isopropylaniline. An acid-base extraction afforded the title compound as a light tan solid (15%, over 2 steps). ^{1}H NMR (500 MHz, CD_3OD) δ 9.07 (s, 1H), 7.70 (d, J = 8.6 Hz, 2H), 7.37 (d, J = 8.6 Hz, 2H), 2.93 (hept, J = 6.9 Hz, 1H), 1.22 (d, J = 6.9 Hz, 6H); LRMS-ESI (*m/z*): $[M + H]^+$ 232.1.

1-(4-methoxyphenyl)-1*H*-1,2,4-triazole-3-carboxylic acid **(2e)**

Prepared as described for 1-(4-chlorophenyl)-1*H*-1,2,4-triazole-3-carboxylic acid from 4-methoxyaniline. An acid-base extraction afforded the title compound as a rust-colored solid (14%, over 2 steps). ^{1}H NMR (500 MHz, CD_3OD) δ 9.05 (s, 1H), 7.76 (d, *J* = 9.1 Hz, 2H), 7.11 (d, *J* = 9.1 Hz, 2H), 3.87 (s, 3H); LRMS-ESI (*m/z*): $[M + H]^+$ 220.1.

1-(4-chlorophenyl)-*N*-(4-ethylphenyl)-1*H*-1,2,4-triazole-3-carboxamide (3)

Prepared via General Procedure A from 1-(4-chlorophenyl)-1*H*-1,2,4-triazole-3-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a lustrous white solid (43%). mp 223-228 °C; R_f (40% EA/Hex) = 0.32; ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.92 (s, 1H), 8.59 (s, 1H), 7.74 (dt, *J* = 8.8, 2.9, 2.0 Hz, 2H), 7.65 (dt, *J* = 8.4, 2.7, 2.0, 2H), 7.52 (dt, *J* = 8.8, 2.9, 2.0 Hz, 2H), 7.25 – 7.16 (m, 2H), 2.65 (q, *J* = 7.6 Hz, 2H), 1.24 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 158.21, 156.22, 141.55, 141.11, 135.18, 135.01, 134.97, 130.24, 128.64, 121.68, 120.13, 28.53, 15.79; LRMS-ESI (*m/z*): $[M + H]^+$ 327.1.

1-(4-chlorophenyl)-*N*-(4-ethylphenyl)-*N*-methyl-1*H*-1,2,4-triazole-3-carboxamide (4)

Prepared via General Procedure A from 1-(4-chlorophenyl)-1*H*-1,2,4-triazole-3-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white pearlescent solid (87%). mp 197-199 °C; R_f (60% EA/Hex) = 0.20; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.40 (s, 4H), 7.11 (q, *J* = 7.9 Hz, 4H), 3.52 (s, 3H), 2.62 (q, *J* = 7.6 Hz, 2H), 1.21 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 161.38, 158.83, 143.52, 141.70, 140.53, 135.21, 134.21, 129.94, 128.62, 126.90, 121.18, 38.21, 28.52, 15.67; LRMS-ESI (*m/z*): $[M + H]^+$ 341.1.

1-(4-chlorophenyl)-*N*-(3,4-dimethylphenyl)-1*H*-1,2,4-triazole-3-carboxamide (5)

Prepared via General Procedure A from 1-(4-chlorophenyl)-1*H*-1,2,4-triazole-3-carboxylic acid and 3,4-dimethylaniline. The crude product was purified via recrystallization from ethyl acetate to afford the title compound as a white solid (57%). mp >260 °C; R_f (50% EA/Hex) = 0.38; ^{1}H NMR (700 MHz, $(CD_3)_2SO$) δ 10.32 (s, 1H), 9.51 (s, 1H), 8.00 (d, *J* = 8.2 Hz, 2H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.61 (s, 1H), 7.55 (d, *J* = 7.0 Hz, 1H), 7.11 (d, *J* = 7.9 Hz, 1H), 2.22 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (175 MHz, $(CD_3)_2SO$) δ 157.63, 156.76, 143.74, 136.27, 135.91, 135.33, 132.72, 132.01, 129.82, 129.52, 121.68, 121.58, 118.04, 19.66, 18.85; LRMS-ESI (*m/z*): $[M + H]^+$ 327.1.

1-(4-chlorophenyl)-*N*-(3,4-dimethylphenyl)-*N*-methyl-1*H*-1,2,4-triazole-3-carboxamide (6)

Prepared via General Procedure A from 1-(4-chlorophenyl)-1*H*-1,2,4-triazole-3-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white pearlescent solid (85%). mp 196-198 °C; R_f (60% EA/Hex) = 0.21; ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.52 – 7.29 (m, 4H), 7.06 – 6.93 (m, 2H), 6.87 (d, *J* = 6.3 Hz, 1H), 3.49 (s, 3H), 2.35 – 2.08 (m, 6H); ^{13}C

NMR (175 MHz, $CDCl_3$) δ 161.53, 159.01, 141.62, 140.48, 137.60, 135.83, 135.22, 134.16, 130.17, 129.95, 127.84, 124.30, 121.16, 38.21, 19.88, 19.45; LRMS-ESI (*m/z*): $[M + H]^+$ 341.1.

1-(4-chlorophenyl)-*N*-(4-nitrophenyl)-1*H*-1,2,4-triazole-3-carboxamide (7)

Prepared via General Procedure A from 1-(4-chlorophenyl)-1*H*-1,2,4-triazole-3-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a lustrous yellow solid (43%). mp >260 °C; R_f (70% EA/Hex) = 0.50; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 11.17 (s, 1H), 9.58 (s, 1H), 8.28 (d, *J* = 8.8 Hz, 2H), 8.16 (d, *J* = 8.8 Hz, 2H), 8.02 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 157.69, 157.01, 144.55, 144.15, 143.02, 135.31, 133.07, 129.97, 124.85, 121.84, 120.44; LRMS-ESI (*m/z*): $[M + H]^+$ 344.1.

1-(4-chlorophenyl)-*N*-methyl-*N*-(4-nitrophenyl)-1*H*-1,2,4-triazole-3-carboxamide (8)

Prepared via General Procedure A from 1-(4-chlorophenyl)-1*H*-1,2,4-triazole-3-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a yellow solid (73%). mp 178-179 °C; R_f (70% EA/Hex) = 0.24; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (s, 1H), 8.17 (d, *J* = 8.9 Hz, 2H), 7.49 (d, *J* = 8.8 Hz, 2H), 7.43 (d, *J* = 8.8 Hz, 2H), 7.35 (d, *J* = 8.8 Hz, 2H), 3.59 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 160.98, 158.21, 149.77, 146.10, 140.92, 134.91, 134.73, 130.15, 127.12, 124.73, 121.26, 38.21; LRMS-ESI (*m/z*): $[M + H]^+$ 358.1.

***N*-(4-acetylphenyl)-1-(4-chlorophenyl)-1*H*-1,2,4-triazole-3-carboxamide (9)**

Prepared via General Procedure A from 1-(4-chlorophenyl)-1*H*-1,2,4-triazole-3-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a tan solid (72%). mp >260 °C; R_f (70% EA/Hex) = 0.37; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 10.86 (bs, 1H), 9.55 (s, 1H), 8.05 – 7.95 (m, 6H), 7.70 (dt, *J* = 8.8, 3.2, 2.1 Hz, 2H), 2.56 (s, 3H); ^{13}C NMR (175 MHz, $(CD_3)_2SO$) δ 196.69, 157.37, 157.25, 143.96, 142.71, 135.28, 132.86, 132.43, 129.86, 129.28, 121.66, 119.83, 26.53; LRMS-ESI (*m/z*): $[M + H]^+$ 341.1.

***N*-(4-acetylphenyl)-1-(4-chlorophenyl)-*N*-methyl-1*H*-1,2,4-triazole-3-carboxamide (10)**

Prepared via General Procedure A from 1-(4-chlorophenyl)-1*H*-1,2,4-triazole-3-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a yellow solid (85%). mp 166-169 °C; R_f (80% EA/Hex) = 0.23; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.91 (d, *J* = 8.3 Hz, 2H), 7.48 (d, *J* = 8.5 Hz, 2H), 7.46 – 7.38 (m, 2H), 7.36 – 7.20 (m, 2H), 3.57 (s, 3H), 2.58 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 197.01, 161.15, 158.45, 148.15, 140.79, 135.49, 134.97, 134.43, 130.01, 129.42, 126.59, 121.17, 38.07, 26.70; LRMS-ESI (*m/z*): $[M + H]^+$ 355.1.

1-(4-chlorophenyl)-*N*-(3,4-dichlorophenyl)-1*H*-1,2,4-triazole-3-carboxamide (11)

Prepared via General Procedure A from 1-(4-chlorophenyl)-1*H*-1,2,4-triazole-3-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (37%). mp 254-258 °C; R_f (70% EA/Hex) = 0.59; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 10.90 (s, 1H), 9.56 (s, 1H), 8.23 (d, *J* = 1.6 Hz, 1H), 8.01 (d, *J* = 8.6 Hz, 2H), 7.88 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.71 (d, *J* = 8.6 Hz, 2H), 7.64 (d, *J* = 8.9 Hz, 1H); LRMS-ESI (*m/z*): $[M + H]^+$ 367.0 and 369.0.

1-(4-chlorophenyl)-*N*-(3,4-dichlorophenyl)-*N*-methyl-1*H*-1,2,4-triazole-3-carboxamide (12)

Prepared via General Procedure A from 1-(4-chlorophenyl)-1*H*-1,2,4-triazole-3-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a lustrous light yellow solid (74%). mp 176-178 °C; R_f (70% EA/Hex) = 0.31; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.63 – 7.28 (m, 6H), 7.20 – 6.92 (m, 1H), 3.50 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 160.93, 158.21, 143.37, 140.85, 135.03, 134.57, 132.97, 131.56, 130.82, 130.11, 129.14, 126.54, 121.25, 38.31; LRMS-ESI (*m/z*): $[M + H]^+$ 381.0 and 383.0.

1-(4-chlorophenyl)-*N*-(4-fluorophenyl)-1*H*-1,2,4-triazole-3-carboxamide (13)

Prepared via General Procedure A from 1-(4-chlorophenyl)-1*H*-1,2,4-triazole-3-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (85%). mp 224-225 °C; R_f (70% EA/Hex) = 0.58; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 10.63 (s, 1H), 9.53 (s, 1H), 8.00 (d, *J* = 8.8 Hz, 2H), 7.87 (dd, *J* = 9.0, 4.9 Hz, 2H), 7.70 (d, *J* = 8.8 Hz, 2H), 7.21 (t, *J* = 9.0 Hz, 2H); ^{13}C NMR (175 MHz, $(CD_3)_2SO$) δ 158.56 (d, CF, *J* = 240.9 Hz), 157.42, 156.95, 143.82, 135.29, 134.61 (d, ArF, *J* = 2.6 Hz), 132.77, 129.83, 122.47 (d, ArF, *J* = 8.0 Hz), 121.61, 115.26 (d, ArF, *J* = 22.3 Hz); LRMS-ESI (*m/z*): $[M + H]^+$ 317.1.

1-(4-chlorophenyl)-*N*-(4-fluorophenyl)-*N*-methyl-1*H*-1,2,4-triazole-3-carboxamide (14)

Prepared via General Procedure A from 1-(4-chlorophenyl)-1*H*-1,2,4-triazole-3-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white pearlescent solid (85%). mp 174-176 °C; R_f (70% EA/Hex) = 0.19; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.55 – 7.32 (m, 4H), 7.23 – 7.10 (m, 2H), 6.98 (t, *J* = 8.2 Hz, 2H), 3.51 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 161.56 (d, CF, *J* = 247.8 Hz), 161.32, 158.59, 140.61, 140.08, 135.09, 134.37, 130.04, 128.93 (d, ArF, *J* = 8.5 Hz), 121.14, 116.11 (d, ArF, *J* = 22.7 Hz), 38.31; LRMS-ESI (*m/z*): $[M + H]^+$ 331.1.

1-(4-chlorophenyl)-*N*-(4-(trifluoromethyl)phenyl)-1*H*-1,2,4-triazole-3-carboxamide (15)

Prepared via General Procedure A from 1-(4-chlorophenyl)-1*H*-1,2,4-triazole-3-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as

a light yellow solid (99%). mp 214-217 °C; R_f (40% EA/Hex) = 0.32; ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 10.03 (s, 1H), 9.28 (s, 1H), 8.18 (d, *J* = 8.3 Hz, 2H), 8.03 – 7.93 (m, 2H), 7.74 (d, *J* = 8.3 Hz, 2H), 7.69 – 7.51 (m, 2H); ^{13}C NMR (175 MHz, $(CD_3)_2CO$, N-inversion observed, all peaks reported) δ 158.41, 158.38, 157.87, 157.79, 144.09, 142.86, 142.76, 136.64, 134.56, 130.75, 126.91 (q, $ArCF_3$, *J* = 3.9 Hz), 126.06 (q, $\underline{C}CF_3$, *J* = 32.3 Hz), 125.30 (q, CF_3, *J* = 271.1 Hz), 122.55, 120.91, 120.82; LRMS-ESI (*m/z*): $[M + H]^+$ 367.1.

1-(4-chlorophenyl)-*N*-methyl-*N*-(4-(trifluoromethyl)phenyl)-1*H*-1,2,4-triazole-3-carboxamide (16)

Prepared via General Procedure A from 1-(4-chlorophenyl)-1*H*-1,2,4-triazole-3-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a light orange solid (82%). mp 173-176 °C; R_f (70 % EA/Hex) = 0.30; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.60 (d, *J* = 8.1 Hz, 2H), 7.41 (s, 4H), 7.32 (d, *J* = 8.1 Hz, 2H), 3.57 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 160.94, 158.22, 147.28, 140.84, 134.99, 134.52, 130.04, 129.31 (q, $\underline{C}CF_3$, *J* = 32.8 Hz), 127.26, 126.42 (q, $ArCF_3$, *J* = 3.7 Hz), 123.88 (q, CF_3, *J* = 272.1 Hz), 121.17, 38.23; LRMS-ESI (*m/z*): $[M + H]^+$ 381.1.

***N*-(4-chlorophenyl)-1-(*p*-tolyl)-1*H*-1,2,4-triazole-3-carboxamide (17)**

Prepared via General Procedure A from 1-(*p*-tolyl)-1*H*-1,2,4-triazole-3-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (10%). mp >260 °C; R_f (70% EA/Hex) = 0.74; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.98 (s, 1H), 8.56 (s, 1H), 7.71 (d, *J* = 8.8 Hz, 2H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.35 (t, *J* = 8.1 Hz, 4H), 2.44 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 157.55, 156.62, 141.62, 139.49, 136.10, 134.32, 130.56, 129.85, 129.33, 121.23, 120.47, 21.28; LRMS-ESI (*m/z*): $[M + H]^+$ 313.1.

***N*-(4-chlorophenyl)-*N*-methyl-1-(*p*-tolyl)-1*H*-1,2,4-triazole-3-carboxamide (18)**

Prepared via General Procedure A from 1-(*p*-tolyl)-1*H*-1,2,4-triazole-3-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (11%). mp 189-192 °C; R_f (70% EA/Hex) = 0.40; ^{1}H NMR (500 MHz, CD_3OD) δ 8.87 (bs, 1H), 7.43 (s, 2H), 7.36 (d, *J* = 6.9 Hz, 2H), 7.30 (d, *J* = 7.3 Hz, 2H), 7.25 (s, 2H), 3.51 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.50, 158.18, 142.78, 140.60, 138.84, 134.31, 132.98, 130.38, 129.39, 128.37, 119.99, 38.20, 21.17; LRMS-ESI (*m/z*): $[M + H]^+$ 327.1.

***N*,1-bis(4-chlorophenyl)-1*H*-1,2,4-triazole-3-carboxamide (19)**

Prepared via General Procedure A from 1-(4-chlorophenyl)-1*H*-1,2,4-triazole-3-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a tan solid (65%). mp >260 °C; R_f (50% EA/Hex) = 0.23; ^{1}H NMR (700 MHz, $(CD_3)_2SO$) δ 10.70 (s, 1H), 9.53 (s, 1H), 8.00 (dt, *J* = 5.1, 3.1, 2.1 Hz, 2H), 7.89 (dt, *J* = 5.1, 3.1, 2.1 Hz, 2H), 7.69 (dt, *J* = 5.3, 3.2, 2.1 Hz, 2H), 7.43

(dt, *J* = 5.3, 3.2, 2.1 Hz, 2H); ^{13}C NMR (175 MHz, $(CD_3)_2SO$) δ 157.31, 157.07, 143.86, 137.23, 135.27, 132.80, 129.82, 128.57, 127.83, 122.12, 121.62; LRMS-ESI (*m/z*): $[M + H]^+$ 333.0 and 335.0.

_N_,1-bis(4-chlorophenyl)-_N_-methyl-1_H_-1,2,4-triazole-3-carboxamide (20)

Prepared via General Procedure A from 1-(4-chlorophenyl)-1*H*-1,2,4-triazole-3-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (96%). mp 194-197 °C; R_f (60% EA/Hex) = 0.21; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.49 – 7.40 (m, 4H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.18 – 7.09 (m, 2H), 3.51 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 161.18, 158.52, 142.64, 140.68, 135.08, 134.44, 133.13, 130.07, 129.44, 128.42, 121.20, 38.16; LRMS-ESI (*m/z*): $[M + H]^+$ 347.1 and 349.1.

1-(4-chlorophenyl)-_N_-methyl-_N_-phenyl-1_H_-1,2,4-triazole-3-carboxamide (21)

Prepared via General Procedure A from 1-(4-chlorophenyl)-1*H*-1,2,4-triazole-3-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a light yellow solid (57%). mp 178-180 °C; R_f (60% EA/Hex) = 0.25; ^{1}H NMR (500 MHz, CD_3OD) δ 8.91 (s, 1H), 7.58 – 7.44 (m, 4H), 7.38 – 7.20 (m, 5H), 3.51 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 161.37, 158.77, 144.10, 140.58, 135.15, 134.26, 129.97, 129.23, 127.31, 127.03, 121.18, 38.15; LRMS-ESI (*m/z*): $[M + H]^+$ 313.1.

1-(4-chlorophenyl)-_N_-methyl-_N_-(_p_-tolyl)-1_H_-1,2,4-triazole-3-carboxamide (22)

Prepared via General Procedure A from 1-(4-chlorophenyl)-1*H*-1,2,4-triazole-3-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as an off-white solid (53%). mp 177-179 °C; R_f (60% EA/Hex) = 0.28; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.51 – 7.35 (m, 4H), 7.15 – 6.94 (m, 4H), 3.50 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 161.49, 158.91, 141.45, 140.50, 137.18, 135.19, 134.19, 129.95, 129.81, 126.79, 121.16, 38.17, 21.13; LRMS-ESI (*m/z*): $[M + H]^+$ 327.1.

_N_-(4-(_tert_-butyl)phenyl)-1-(4-chlorophenyl)-_N_-methyl-1_H_-1,2,4-triazole-3-carboxamide (23)

Prepared via General Procedure A from 1-(4-chlorophenyl)-1*H*-1,2,4-triazole-3-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (91%). mp 203-207 °C; R_f (70% EA/Hex) = 0.22; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.45 – 7.26 (m, 6H), 7.09 (d, *J* = 8.1 Hz, 2H), 3.51 (s, 3H), 1.29 (s, 9H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 161.20, 158.64, 150.40, 141.55, 140.60, 135.22, 134.22, 129.90, 126.58, 126.07, 121.18, 38.20, 34.70, 31.45; LRMS-ESI (*m/z*): $[M + H]^+$ 369.2.

1-(4-chlorophenyl)-_N_-(4-methoxyphenyl)-_N_-methyl-1_H_-1,2,4-triazole-3-carboxamide (24)

Prepared via General Procedure A from 1-(4-chlorophenyl)-1*H*-1,2,4-triazole-3-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a light yellow pearlescent solid (89%). mp 176-179 °C; R_f (80% EA/Hex) = 0.24; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.44 (q, *J* = 8.8 Hz, 4H), 7.11 (d, *J* = 8.7 Hz, 2H), 6.80 (d, *J* = 8.7 Hz, 2H), 3.77 (s, 3H), 3.49 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 161.60, 158.90, 158.63, 140.50, 136.83, 135.17, 134.16, 129.94, 128.29, 121.13, 114.31, 55.52, 38.31; LRMS-ESI (*m/z*): $[M + H]^+$ 343.1.

1-(4-chlorophenyl)-*N*-methyl-*N*-(*m*-tolyl)-1*H*-1,2,4-triazole-3-carboxamide (25)

Prepared via General Procedure A from 1-(4-chlorophenyl)-1*H*-1,2,4-triazole-3-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as an orange solid (45%). mp 147-149 °C; R_f (70% EA/Hex) = 0.32; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.42 (s, 4H), 7.22 – 7.10 (m, 1H), 7.04 (d, *J* = 7.2 Hz, 2H), 6.98 – 6.81 (m, 1H), 3.51 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 161.42, 158.85, 143.93, 140.57, 139.22, 135.19, 134.26, 129.98, 128.94, 128.08, 127.50, 124.11, 121.20, 38.16, 21.36; LRMS-ESI (*m/z*): $[M + H]^+$ 327.1.

***N*-methyl-*N*,1-di-*p*-tolyl-1*H*-1,2,4-triazole-3-carboxamide (26)**

Prepared via General Procedure A from 1-(*p*-tolyl)-1*H*-1,2,4-triazole-3-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white pearlescent solid (47%). mp 177-178 °C; R_f (60% EA/Hex) = 0.21; ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.17 – 6.98 (m, 4H), 3.51 (s, 3H), 2.38 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 161.83, 158.63, 141.65, 140.40, 138.62, 137.06, 134.44, 130.30, 129.81, 126.79, 119.98, 38.19, 21.17, 21.16; LRMS-ESI (*m/z*): $[M + H]^+$ 307.2.

***N*-(4-methoxyphenyl)-*N*-methyl-1-(*p*-tolyl)-1*H*-1,2,4-triazole-3-carboxamide (27)**

Prepared via General Procedure A from 1-(*p*-tolyl)-1*H*-1,2,4-triazole-3-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (25%). mp 150-152 °C; R_f (70% EA/Hex) = 0.29; ^{1}H NMR (500 MHz, CD_3OD, rotameric mixture, major form reported) δ 8.83 (s, 1H), 7.43 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 7.15 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 3.75 (s, 3H), 3.46 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (175 MHz, CD_3OD, rotameric mixture, major form reported) δ 163.66, 160.49, 158.78, 142.77, 140.02, 137.64, 135.63, 131.22, 129.48, 120.82, 115.32, 55.94, 38.42, 20.98; LRMS-ESI (*m/z*): $[M + H]^+$ 323.2.

***N*-methyl-*N*-(*m*-tolyl)-1-(*p*-tolyl)-1*H*-1,2,4-triazole-3-carboxamide (28)**

Prepared via General Procedure A from 1-(*p*-tolyl)-1*H*-1,2,4-triazole-3-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a lustrous

off-white solid (78%). mp 100-105 °C; R_f (90% EA/Hex) = 0.39; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 9.10 (bs, 1H), 7.75 – 7.38 (m, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.17 (t, *J* = 7.1 Hz, 1H), 7.09 (s, 1H), 7.03 (d, *J* = 7.1 Hz, 1H), 7.00 – 6.86 (m, 1H), 3.39 (s, 3H), 2.33 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 161.74, 158.53, 144.05, 140.46, 139.13, 138.63, 134.40, 130.28, 128.89, 127.95, 127.46, 124.05, 119.98, 38.11, 21.35, 21.13; LRMS-ESI (*m/z*): $[M + H]^+$ 307.2.

<u>*N*-(3,4-dimethylphenyl)-*N*-methyl-1-(*p*-tolyl)-1*H*-1,2,4-triazole-3-carboxamide (29)</u>

Prepared via General Procedure A from 1-(*p*-tolyl)-1*H*-1,2,4-triazole-3-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (11%). mp 144-147 °C; R_f(70% EA/Hex) = 0.36; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (bs, 1H), 7.45 – 7.30 (m, 2H), 7.24 (d, *J* = 7.0 Hz, 2H), 7.08 – 6.94 (m, 2H), 6.93 – 6.81 (m, 1H), 3.50 (s, 3H), 2.38 (s, 3H), 2.21 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.88, 158.74, 141.83, 140.42, 138.64, 137.57, 135.71, 134.50, 130.32, 130.20, 127.88, 124.32, 120.02, 38.22, 21.18, 19.91, 19.48; LRMS-ESI (*m/z*): $[M + H]^+$ 321.2.

<u>*N*-(4-chlorophenyl)-1-(4-ethylphenyl)-*N*-methyl-1*H*-1,2,4-triazole-3-carboxamide (30)</u>

Prepared via General Procedure A from 1-(4-ethylphenyl)-1*H*-1,2,4-triazole-3-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (62%). mp 154-156 °C; R_f (70% EA/Hex) = 0.29; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.46 – 7.34 (m, 2H), 7.28 (d, *J* = 7.6 Hz, 4H), 7.21 – 7.08 (m, 2H), 3.52 (s, 3H), 2.69 (q, *J* = 7.6 Hz, 2H), 1.25 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 161.50, 158.14, 145.15, 142.77, 140.63, 134.43, 132.96, 129.37, 129.21, 128.37, 120.07, 38.13, 28.52, 15.54; LRMS-ESI (*m/z*): $[M + H]^+$ 341.1.

<u>1-(4-ethylphenyl)-*N*-methyl-*N*-(*p*-tolyl)-1*H*-1,2,4-triazole-3-carboxamide (31)</u>

Prepared via General Procedure A from 1-(4-ethylphenyl)-1*H*-1,2,4-triazole-3-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a lustrous white solid (99%). mp 148-151 °C; R_f (60% EA/Hex) = 0.30; ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 8.79 (s, 1H), 7.57 (s, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 7.11 (s, 4H), 3.43 (s, 3H), 2.68 (q, *J* = 7.6 Hz, 2H), 2.26 (s, 3H), 1.22 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (175 MHz, $(CD_3)_2CO$) δ 162.52, 159.51, 145.30, 142.52, 142.11, 137.32, 135.76, 130.24, 129.84, 127.65, 120.53, 37.60, 28.87, 20.92, 15.91; LRMS-ESI (*m/z*): $[M + H]^+$ 321.1.

<u>1-(4-ethylphenyl)-*N*-(4-methoxyphenyl)-*N*-methyl-1*H*-1,2,4-triazole-3-carboxamide (32)</u>

Prepared via General Procedure A from 1-(4-ethylphenyl)-1*H*-1,2,4-triazole-3-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (28%). mp 124-126 °C; R_f (80% EA/Hex) = 0.51; ^{1}H NMR (500 MHz, $CDCl_3$, rotameric mixture, major form reported) δ 8.27 (s, 1H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.11 (d, *J* = 8.3 Hz, 2H), 6.79 (d, *J* = 8.3 Hz, 2H), 3.76 (s, 3H), 3.48 (s, 3H), 2.66 (q, *J* = 7.6 Hz, 2H), 1.23 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (175 MHz,

$CDCl_3$) δ 161.94, 158.56, 144.92, 140.42 (2 non-equivalent C), 137.01, 134.54, 129.12, 128.27, 120.02, 114.29, 55.53, 38.28, 28.50, 15.56; LRMS-ESI (*m/z*): $[M + H]^+$ 337.2.

1-(4-ethylphenyl)-*N*-methyl-*N*-(*m*-tolyl)-1*H*-1,2,4-triazole-3-carboxamide (33)

Prepared via General Procedure A from 1-(4-ethylphenyl)-1*H*-1,2,4-triazole-3-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a lustrous white solid (99%). mp 64-66 °C; R_f (60% EA/Hex) = 0.31; ^{1}H NMR (500 MHz, $(CD_3)_2CO$) 8.81 (s, 1H), 7.69 – 7.50 (m, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 7.16 (t, *J* = 7.3 Hz, 1H), 7.09 (s, 1H), 7.05 – 6.90 (m, 2H), 3.45 (s, 3H), 2.68 (q, *J* = 7.6 Hz, 2H), 2.26 (s, 3H), 1.22 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (175 MHz, $(CD_3)_2CO$) δ 162.47, 159.45, 145.30, 144.97, 142.16, 139.50, 135.75, 129.83, 129.46, 128.27 (2 non-equivalent C), 124.78, 120.56, 37.66, 28.86, 21.16, 15.90; LRMS-ESI (*m/z*): $[M + H]^+$ 321.2.

***N*-(3,4-dimethylphenyl)-1-(4-ethylphenyl)-*N*-methyl-1*H*-1,2,4-triazole-3-carboxamide (34)**

Prepared via General Procedure A from 1-(4-ethylphenyl)-1*H*-1,2,4-triazole-3-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (50%). mp 122-124 °C; R_f (70% EA/Hex) = 0.27; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 9.07 (s, 1H), 7.56 (s, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.14 – 6.94 (m, 2H), 6.86 (s, 1H), 3.37 (s, 3H), 2.64 (q, *J* = 7.6 Hz, 2H), 2.14 (s, 6H), 1.18 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 161.30, 157.86, 144.01, 142.00, 141.08, 136.86, 134.93, 134.22, 129.70, 128.99, 127.44, 123.92, 119.38, 37.22, 27.61, 19.25, 18.83, 15.46; LRMS-ESI (*m/z*): $[M + H]^+$ 335.2.

***N*-(4-chlorophenyl)-1-(4-isopropylphenyl)-*N*-methyl-1*H*-1,2,4-triazole-3-carboxamide (35)**

Prepared via General Procedure A from 1-(4-isopropylphenyl)-1*H*-1,2,4-triazole-3-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a light yellow solid (92%). mp 151-152 °C; R_f (70% EA/Hex) = 0.40; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.51 – 7.34 (m, 2H), 7.34 – 7.21 (m, 4H), 7.20 – 7.05 (m, 2H), 3.51 (s, 3H), 2.94 (hept, *J* = 6.9 Hz, 1H), 1.25 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 161.53, 158.15, 149.78, 142.78, 140.63, 134.47, 132.96, 129.38, 128.37, 127.82, 120.09, 38.14, 33.89, 23.97; LRMS-ESI (*m/z*): $[M + H]^+$ 355.1.

1-(4-isopropylphenyl)-*N*-methyl-*N*-(*p*-tolyl)-1*H*-1,2,4-triazole-3-carboxamide (36)

Prepared via General Procedure A from 1-(4-isopropylphenyl)-1*H*-1,2,4-triazole-3-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a lustrous light yellow solid (89%). mp 132-134 °C; R_f (50% EA/Hex) = 0.20; ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 8.79 (s, 1H), 7.76 – 7.43 (m, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.19 – 6.97 (m, 4H), 3.43 (s, 3H), 2.96 (hept, *J* = 6.9 Hz, 1H), 2.26 (s, 3H), 1.25 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (175 MHz, $(CD_3)_2CO$) δ 162.54, 159.50, 149.84, 142.50,

142.13, 137.31, 135.80, 130.23, 128.41, 127.64, 120.54, 37.60, 34.41, 24.13, 20.92; LRMS-ESI (*m/z*): $[M + H]^+$ 335.2.

1-(4-isopropylphenyl)-*N*-(4-methoxyphenyl)-*N*-methyl-1*H*-1,2,4-triazole-3-carboxamide (37)

Prepared via General Procedure A from 1-(4-isopropylphenyl)-1*H*-1,2,4-triazole-3-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a tan solid (84%). mp 105-107 °C; R_f (70% EA/Hex) = 0.29; ^{1}H NMR (500 MHz, $CDCl_3$, rotameric mixture, major form reported) δ 8.28 (s, 1H), 7.40 (d, *J* = 8.1 Hz, 2H), 7.28 (d, *J* = 8.6 Hz, 2H), 7.11 (d, *J* = 8.4 Hz, 2H), 6.80 (d, *J* = 8.4 Hz, 2H), 3.77 (s, 3H), 3.49 (s, 3H), 2.94 (hept, *J* = 6.9 Hz, 1H), 1.25 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 161.96, 158.55, 158.54, 149.52, 140.42, 136.99, 134.57, 128.25, 127.70, 120.01, 114.27, 55.51, 38.25, 33.85, 23.95; LRMS-ESI (*m/z*): $[M + H]^+$ 351.2.

1-(4-isopropylphenyl)-*N*-methyl-*N*-(*m*-tolyl)-1*H*-1,2,4-triazole-3-carboxamide (38)

Prepared via General Procedure A from 1-(4-isopropylphenyl)-1*H*-1,2,4-triazole-3-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a light orange solid (87%). mp 93-96 °C; R_f (70% EA/Hex) = 0.31; ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 8.81 (s, 1H), 7.66 – 7.49 (m, 2H), 7.38 (d, *J* = 8.2 Hz, 2H), 7.16 (t, *J* = 7.8 Hz, 1H), 7.09 (s, 1H), 7.05 – 6.94 (m, 2H), 3.45 (s, 3H), 2.96 (hept, *J* = 6.9 Hz, 1H), 2.26 (s, 3H), 1.24 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (175 MHz, $(CD_3)_2CO$) δ 162.47, 159.44, 149.83, 144.96, 142.17, 139.49, 135.79, 129.46, 128.39, 128.26 (2 non-equivalent C), 124.76, 120.57, 37.62, 34.40, 24.13, 21.16; LRMS-ESI (*m/z*): $[M + H]^+$ 335.2.

***N*-(3,4-dimethylphenyl)-1-(4-isopropylphenyl)-*N*-methyl-1*H*-1,2,4-triazole-3-carboxamide (39)**

Prepared via General Procedure A from 1-(4-isopropylphenyl)-1*H*-1,2,4-triazole-3-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a lustrous white solid (67%). mp 109-113 °C; R_f (70% EA/Hex) = 0.39; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.46 – 7.33 (m, 2H), 7.28 (d, *J* = 7.6 Hz, 2H), 7.07 – 6.79 (m, 3H), 3.49 (s, 3H), 2.93 (hept, *J* = 6.9 Hz, 1H), 2.31 – 2.10 (m, 6H), 1.25 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 161.88, 158.65, 149.52, 141.74, 140.42, 137.51, 135.66, 134.62, 130.13, 127.81, 127.70, 124.25, 120.06, 38.14, 33.86, 23.96, 19.86, 19.43; LRMS-ESI (*m/z*): $[M + H]^+$ 349.2.

***N*-(4-chlorophenyl)-1-(4-methoxyphenyl)-*N*-methyl-1*H*-1,2,4-triazole-3-carboxamide (40)**

Prepared via General Procedure A from 1-(4-methoxyphenyl)-1*H*-1,2,4-triazole-3-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as an off-white solid (31%). mp 143-145 °C; R_f (70% EA/Hex) = 0.28; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (bs, 1H), 7.45 – 7.33 (m, 2H), 7.32 – 7.25 (m, 2H), 7.19 – 7.08 (m, 2H), 6.95 (d, *J* = 8.7 Hz, 2H), 3.83 (s, 3H), 3.51 (s, 3H);

^{13}C NMR (175 MHz, $CDCl_3$) δ 161.53, 159.80, 158.10, 142.81, 140.60, 132.97, 130.00, 129.39, 128.38, 121.79, 114.93, 55.75, 38.17; LRMS-ESI (*m/z*): $[M + H]^+$ 343.1.

1-(4-methoxyphenyl)-*N*-methyl-*N*-(*p*-tolyl)-1*H*-1,2,4-triazole-3-carboxamide (41)

Prepared via General Procedure A from 1-(4-methoxyphenyl)-1*H*-1,2,4-triazole-3-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (63%). mp 129-134 °C; R_f (70% EA/Hex) = 0.25; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.48 – 7.30 (m, 2H), 7.07 (m, 4H), 6.93 (d, *J* = 8.0 Hz, 2H), 3.82 (s, 3H), 3.50 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 161.85, 159.67, 158.52, 141.64, 140.41, 137.03, 130.14, 129.80, 126.77, 121.75, 114.83, 55.73, 38.17, 21.15; LRMS-ESI (*m/z*): $[M + H]^+$ 323.2.

***N*,1-bis(4-methoxyphenyl)-*N*-methyl-1*H*-1,2,4-triazole-3-carboxamide (42)**

Prepared via General Procedure A from 1-(4-methoxyphenyl)-1*H*-1,2,4-triazole-3-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as an off-white solid (71%). mp 129-131 °C; R_f (70% EA/Hex) = 0.19; ^{1}H NMR (500 MHz, CD_3OD, rotameric mixture, major form reported) δ 8.76 (s, 1H), 7.46 (d, *J* = 8.7 Hz, 2H), 7.14 (d, *J* = 8.6 Hz, 2H), 7.00 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 3.82 (s, 3H), 3.75 (s, 3H), 3.46 (s, 3H); ^{13}C NMR (175 MHz, CD_3OD, rotameric mixture, major form reported) δ 163.75, 161.30, 160.49, 158.70, 142.69, 137.66, 131.22, 129.47, 122.63, 115.80, 115.32, 56.10, 55.95, 38.40; LRMS-ESI (*m/z*): $[M + H]^+$ 339.2.

1-(4-methoxyphenyl)-*N*-methyl-*N*-(*m*-tolyl)-1*H*-1,2,4-triazole-3-carboxamide *(*43)

Prepared via General Procedure A from 1-(4-methoxyphenyl)-1*H*-1,2,4-triazole-3-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a lustrous white solid (89%). mp 112-115 °C; R_f (80% EA/Hex) = 0.28; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 9.03 (s, 1H), 7.57 (s, 2H), 7.17 (t, *J* = 7.6 Hz, 1H), 7.12 – 7.04 (m, 3H), 7.03 (d, *J* = 7.6 Hz, 1H), 7.01 – 6.89 (m, 1H), 3.79 (s, 3H), 3.39 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 161.75, 159.65, 158.44, 144.06, 140.46, 139.11, 130.09, 128.87, 127.91, 127.42, 124.03, 121.76, 114.81, 55.69, 38.08, 21.34; LRMS-ESI (*m/z*): $[M + H]^+$ 323.2.

***N*-(3,4-dimethylphenyl)-1-(4-methoxyphenyl)-*N*-methyl-1*H*-1,2,4-triazole-3-carboxamide (44)**

Prepared via General Procedure A from 1-(4-methoxyphenyl)-1*H*-1,2,4-triazole-3-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (47%). mp 104-106 °C; R_f (10% EA/Hex) = 0.28; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.04 – 6.96 (m, 2H), 6.93 (d, *J* = 8.4 Hz, 2H), 6.91 – 6.83 (m, 1H), 3.83 (s, 3H), 3.49 (s, 3H), 2.21 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 161.89, 159.66, 158.63, 141.82, 140.40, 137.54, 135.67, 130.18, 130.16, 127.82, 124.27, 121.77, 114.83, 55.74, 38.20, 19.89, 19.46; LRMS-ESI (*m/z*): $[M + H]^+$ 337.2.

3-nitro-1-(*p*-tolyl)-1*H*-1,2,4-triazole **(45a)**

In a flame-dried round bottom flask under argon, 3-nitro-1*H*-1,2,4-triazole (13.2 mmol, 1 equiv) and *p*-tolylboronic acid (14.5 mmol, 1.10 equiv) were dissolved in anhydrous dichloromethane (0.17 M). Copper (II) acetate (19.7 mmol, 1.50 equiv) and anhydrous pyridine (26.3 mmol, 2 equiv) were then added and the reaction mixture was heated to 30 °C for 12 hours. Upon reaction completion via LCMS, the solids were removed by vacuum filtration and washed with dichloromethane. The filtrate was washed with water thrice. Brine was added to the combined aqueous layers, which was extracted with dichloromethane. The combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. The crude product was purified by flash column chromatography with hexanes/ethyl acetate, followed by recrystallization in hexanes to afford the title compound as a yellow solid (50%). R_f (30% EA/Hex) = 0.22; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 2.45 (s, 3H); LRMS-ESI (*m/z*): $[M + H]^+$ 205.0.

1-(4-chlorophenyl)-3-nitro-1*H*-1,2,4-triazole **(45b)**

Prepared as described for 3-nitro-1-(*p*-tolyl)-1*H*-1,2,4-triazole from (4-chlorophenyl)boronic acid. The crude product was purified via recrystallization in hexanes to afford the title compound as a lustrous white solid (39%). R_f (30% EA/Hex) = 0.30; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (s, 1H), 7.72 (dt, *J* = 5.0, 3.0, 1.8 Hz, 2H), 7.57 (dt, *J* = 5.0, 3.0, 1.8 Hz, 2H); LRMS-ESI (*m/z*): $[M + H]^+$ 225.0.

1-(*p*-tolyl)-1*H*-1,2,4-triazol-3-amine **(46a)**

In a round bottom flask, 3-nitro-1-(*p*-tolyl)-1*H*-1,2,4-triazole (6.61 mmol, 1 equiv) was dissolved in saturated ammonium chloride (0.37 M) and acetone (0.09 M). The reaction mixture was cooled to 0 °C and zinc dust (33.1 mmol, 5 equiv) was added. The reaction mixture was warmed to room temperature and stirred for 2 hours. Upon reaction completion via LCMS, the reaction mixture was diluted in water and dichloromethane and the aqueous layer was extracted thrice with dichloromethane. The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to afford the title compound as a light tan solid (56%). ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 8.75 (s, 1H), 7.59 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 8.3 Hz, 2H), 5.64 (s, 2H), 2.32 (s, 3H); LRMS-ESI (*m/z*): $[M + H]^+$ 175.1.

1-(4-chlorophenyl)-1*H*-1,2,4-triazol-3-amine **(46b)**

Prepared as described for 1-(*p*-tolyl)-1*H*-1,2,4-triazol-3-amine from 1-(4-chlorophenyl)-3-nitro-1*H*-1,2,4-triazole to afford the title compound as a tan solid (87%). ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 8.83 (s, 1H), 7.78 – 7.69 (m, 2H), 7.59 – 7.48 (m, 2H), 5.73 (s, 2H); LRMS-ESI (*m/z*): $[M + H]^+$ 195.0.

4-chloro-*N*-(1-(*p*-tolyl)-1*H*-1,2,4-triazol-3-yl)benzamide (47)

In a flame-dried round bottom flask under argon, 1-(*p*-tolyl)-1*H*-1,2,4-triazol-3-amine (1.15 mmol, 1 equiv) was dissolved in anhydrous dichloromethane (0.20 M) and anhydrous pyridine (3.44 mmol, 3 equiv). The flask was cooled to 0 °C and 4-chlorobenzoyl chloride (1.26 mmol, 2 equiv) was added. The reaction mixture was warmed to room temperature and stirred for 2 hours. Upon complete consumption of the amine, the reaction mixture was diluted in water and dichloromethane and the aqueous layer was extracted thrice with dichloromethane. The combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. The crude product was purified by flash column chromatography with hexanes/ethyl acetate, followed by recrystallization in hexanes to afford the title compound as a fluffy white solid (22%). mp 194-196 °C; R_f (50% EA/Hex) = 0.19; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 11.05 (s, 1H), 9.18 (s, 1H), 8.01 (d, *J* = 8.5 Hz, 2H), 7.73 (d, *J* = 8.3 Hz, 2H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.37 (d, *J* = 8.3 Hz, 2H), 2.36 (s, 3H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 164.29, 156.75, 141.68, 137.14, 136.89, 134.47, 132.37, 130.14, 129.86, 128.56, 118.90, 20.53; LRMS-ESI (*m/z*): $[M + H]^+$ 313.1.

4-chloro-*N*-(1-(4-chlorophenyl)-1*H*-1,2,4-triazol-3-yl)benzamide (48)

Prepared as described for 4-chloro-*N*-(1-(*p*-tolyl)-1*H*-1,2,4-triazol-3-yl)benzamide from 1-(4-chlorophenyl)-1*H*-1,2,4-triazol-3-amine and 4-chlorobenzoyl chloride. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a light yellow solid (20%). mp 188-190 °C; R_f (40% EA/Hex) = 0.17; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 11.12 (s, 1H), 9.27 (s, 1H), 8.02 (d, *J* = 8.5 Hz, 2H), 7.89 (d, *J* = 8.8 Hz, 2H), 7.65 (d, *J* = 8.8 Hz, 2H), 7.60 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 164.21, 157.08, 142.16, 136.94, 135.54, 132.31, 131.70, 129.89, 129.76, 128.57, 120.61; LRMS-ESI (*m/z*): $[M + H]^+$ 333.1 and 335.1.

4-methyl-*N*-(1-(*p*-tolyl)-1*H*-1,2,4-triazol-3-yl)benzamide (49)

Prepared as described for 4-chloro-*N*-(1-(*p*-tolyl)-1*H*-1,2,4-triazol-3-yl)benzamide from 1-(*p*-tolyl)-1*H*-1,2,4-triazol-3-amine and 4-methylbenzoyl chloride. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (25%). mp 189-194 °C; R_f (60% EA/Hex) = 0.15; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 10.84 (s, 1H), 9.18 (s, 1H), 7.91 (d, *J* = 7.8 Hz, 2H), 7.73 (d, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 7.8 Hz, 2H), 2.38 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 165.20, 156.96, 142.10, 141.61, 137.08, 134.51, 130.78, 130.14, 128.99, 127.95, 118.86, 21.04, 20.52; LRMS-ESI (*m/z*): $[M + H]^+$ 293.1.

***N*-(1-(4-chlorophenyl)-1*H*-1,2,4-triazol-3-yl)-4-methylbenzamide (50)**

Prepared as described for 4-chloro-*N*-(1-(*p*-tolyl)-1*H*-1,2,4-triazol-3-yl)benzamide from 1-(4-chlorophenyl)-1*H*-1,2,4-triazol-3-amine and 4-methylbenzoyl chloride. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a yellow solid (70%). mp 228-232 °C; R_f (60% EA/Hex) = 0.18; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 10.91 (s, 1H), 9.26 (s, 1H), 7.90 (t, *J* = 8.9 Hz, 4H),

7.65 (d, *J* = 8.6 Hz, 2H), 7.33 (d, *J* = 7.9 Hz, 2H), 2.38 (s, 3H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 165.11, 157.30, 142.15, 142.09, 135.57, 131.64, 130.73, 129.75, 129.00, 127.98, 120.57, 21.04; LRMS-ESI (*m/z*): $[M + H]^+$ 313.1.

4-chloro-*N*-methyl-*N*-(1-(*p*-tolyl)-1*H*-1,2,4-triazol-3-yl)benzamide (51)

In a flame-dried round bottom flask under argon, 4-chloro-*N*-(1-(*p*-tolyl)-1H-1,2,4-triazol-3-yl)benzamide (0.240 mmol, 1 equiv) was dissolved in anhydrous *N,N*-dimethylformamide (0.20 M). Potassium carbonate (0.480 mmol, 2 equiv) was added and the reaction mixture was cooled to 0 °C. After stirring for 15 minutes at 0 °C, iodomethane (0.480 mmol, 2 equiv) was added slowly. The reaction mixture was allowed to warm to room temperature and stirred for an additional 16 hours. Upon complete consumption of the amide starting material, the reaction mixture was diluted in ethyl acetate and transferred to a separatory funnel. The organic layer was washed with brine thrice, dried over sodium sulfate, and concentrated *in vacuo.* The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (52%). mp 86-88 °C; R_f (50% EA/Hex) = 0.37; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 9.09 (s, 1H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.36 (ddt, *J* = 10.8, 4.2, 2.2 Hz, 4H), 7.30 (d, *J* = 8.4 Hz, 2H), 3.43 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 168.72, 161.06, 142.25, 137.53, 134.90, 134.72, 134.03, 130.08, 129.56, 128.08, 118.85, 35.54, 20.47; LRMS-ESI (*m/z*): $[M + H]^+$ 327.1.

4-chloro-*N*-(1-(4-chlorophenyl)-1*H*-1,2,4-triazol-3-yl)-*N*-methylbenzamide (52)

Prepared as described for 4-chloro-*N*-methyl-*N*-(1-(*p*-tolyl)-1*H*-1,2,4-triazol-3-yl)benzamide from 4-chloro-*N*-(1-(4-chlorophenyl)-1*H*-1,2,4-triazol-3-yl)benzamide. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (62%). mp 95-98 °C; R_f (50% EA/Hex) = 0.21; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 9.17 (s, 1H), 7.68 (dt, *J* = 8.9, 2.9, 2.1 Hz, 2H), 7.59 (dt, *J* = 8.9, 2.9, 2.1 Hz, 2H), 7.37 (ddt, *J* = 10.7, 4.2, 1.9 Hz, 4H), 3.43 (s, 3H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 168.70, 161.36, 142.73, 135.09, 134.99, 134.62, 132.08, 129.73, 129.59, 128.12, 120.56, 35.55; LRMS-ESI (*m/z*): $[M + H]^+$ 347.1 and 349.1.

***N*,4-dimethyl-*N*-(1-(*p*-tolyl)-1*H*-1,2,4-triazol-3-yl)benzamide (53)**

Prepared as described for 4-chloro-*N*-methyl-*N*-(1-(*p*-tolyl)-1*H*-1,2,4-triazol-3-yl)benzamide from 4-methyl-*N*-(1-(*p*-tolyl)-1*H*-1,2,4-triazol-3-yl)benzamide. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a lustrous white solid (86%). mp 128-131 °C; R_f (50% EA/Hex) = 0.32; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 9.08 (s, 1H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.1 Hz, 2H), 7.10 (d, *J* = 8.1 Hz, 2H), 3.40 (s, 3H), 2.32 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 169.72, 161.50, 142.18, 140.11, 137.45, 134.08, 132.92, 130.07, 128.43, 127.82, 118.86, 35.74, 20.86, 20.46; LRMS-ESI (*m/z*): $[M + H]^+$ 307.2.

_N_-(1-(4-chlorophenyl)-1_H_-1,2,4-triazol-3-yl)-_N_,4-dimethylbenzamide (54)

Prepared as described for 4-chloro-*N*-methyl-*N*-(1-(*p*-tolyl)-1*H*-1,2,4-triazol-3-yl)benzamide from *N*-(1-(4-chlorophenyl)-1*H*-1,2,4-triazol-3-yl)-4-methylbenzamide. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (60%). mp 158-162 °C; R_f (50% EA/Hex) = 0.32; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 9.16 (s, 1H), 7.67 (dt, *J* = 8.9, 2.9, 2.1 Hz, 2H), 7.59 (dt, *J* = 8.9, 2.9, 2.1 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 3.41 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 169.72, 161.78, 142.67, 140.22, 135.14, 132.85, 132.02, 129.72, 128.48, 127.84, 120.57, 35.72, 20.88; LRMS-ESI (*m/z*): $[M + H]^+$ 327.1.

1-(*p*-tolyl)-1*H*-1,2,3-triazole-4-carboxylic acid **(55a)**

In a round bottom flask, copper (II) sulfate (0.467 mmol, 0.1 equiv) and sodium ascorbate (0.933 mmol, 0.2 equiv) were dissolved in water (1 M). 1-azido-4-methylbenzene (4.67 mmol, 1 equiv), *tert*-butanol (1 M), and propiolic acid (5.60 mmol, 1.2 equiv) were added to the flask, which was then sealed with a glass stopper and stirred at room temperature for 16 hours. The reaction was basified to pH 12-13 with sodium hydroxide (3 M) and extracted thrice with ethyl acetate. The aqueous layer was then acidified to pH 2-3 with hydrochloric acid (3 M) and extracted thrice with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to afford the title compound as a light orange solid (16%). ^{1}H NMR (500 MHz, CD_3OD) δ 9.00 (s, 1H), 7.76 (d, *J* = 8.2 Hz, 2H), 7.40 (d, *J* = 8.2 Hz, 2H), 2.4z3 (s, 3H); LRMS-ESI (*m/z*): $[M + H]^+$ 204.0.

1-(4-chlorophenyl)-1*H*-1,2,3-triazole-4-carboxylic acid **(55b)**

Prepared as described for 1-(*p*-tolyl)-1*H*-1,2,3-triazole-4-carboxylic acid from 1-azido-4-chlorobenzene. An acid-base extraction afforded the title compound as a white solid (22%). ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 9.41 (s, 1H), 8.01 (dt, *J* = 5.0, 3.0, 2.1 Hz, 2H), 7.68 (dt, *J* = 5.0, 3.0, 2.1 Hz, 2H); LRMS-ESI (*m/z*): $[M + H]^+$ 224.0.

_N_-(4-chlorophenyl)-_N_-methyl-1-(_p_-tolyl)-1_H_-1,2,3-triazole-4-carboxamide (56)

Prepared via General Procedure A from 1-(*p*-tolyl)-1*H*-1,2,3-triazole-4-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (72%). mp 146-148 °C; R_f (70% EA/Hex) = 0.56; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (bs, 1H), 7.53 (d, *J* = 7.1 Hz, 2H), 7.36 (d, *J* = 8.2 Hz, 2H), 7.30 (t, *J* = 8.2 Hz, 2H), 7.20 (d, *J* = 7.1 Hz, 2H), 3.53 (bs, 3H), 2.41 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 161.13, 144.04, 142.81, 139.53, 134.19, 133.40, 130.46, 129.70, 128.70, 125.12, 120.48, 38.83, 21.22; LRMS-ESI (*m/z*): $[M + H]^+$ 327.1.

_N_,1-bis(4-chlorophenyl)-_N_-methyl-1_H_-1,2,3-triazole-4-carboxamide (57)

Prepared via General Procedure A from 1-(4-chlorophenyl)-1*H*-1,2,3-triazole-4-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as

a lustrous white solid (82%). mp 162-165 °C; R_f (40% EA/Hex) = 0.32; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (bs, 1H), 7.62 (d, *J* = 6.9 Hz, 2H), 7.48 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.3 Hz, 2H), 7.19 (d, *J* = 6.3 Hz, 2H), 3.51 (bs, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 160.76, 144.31, 142.58, 135.09, 134.85, 133.40, 130.08, 129.63, 128.61, 125.09, 121.66, 38.75; LRMS-ESI (*m/z*): $[M + H]^+$ 347.1 and 349.1.

<u>*N*-methyl-*N*,1-di-*p*-tolyl-1*H*-1,2,3-triazole-4-carboxamide (58)</u>

Prepared via General Procedure A from 1-(*p*-tolyl)-1*H*-1,2,3-triazole-4-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (24%). mp 130-134 °C; R_f (50% EA/Hex) = 0.42; ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 8.31 (bs, 1H), 7.66 (d, *J* = 7.6 Hz, 2H), 7.37 (d, *J* = 8.1 Hz, 2H), 7.25 – 7.12 (m, 4H), 3.45 (s, 3H), 2.39 (bs, 3H), 2.32 (s, 3H); ^{13}C NMR (175 MHz, $(CD_3)_2CO$) δ 161.66, 144.93, 143.01, 139.86, 137.67, 135.37, 131.10, 130.57, 128.08, 125.40, 121.08, 38.49, 21.01, 20.97; LRMS-ESI (*m/z*): $[M + H]^+$ 307.2.

<u>1-(4-chlorophenyl)-*N*-methyl-*N*-(*p*-tolyl)-1*H*-1,2,3-triazole-4-carboxamide (59)</u>

Prepared via General Procedure A from 1-(4-chlorophenyl)-1*H*-1,2,3-triazole-4-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a lustrous white solid (68%). mp 176-179 °C; R_f (50% EA/Hex) = 0.40; ^{1}H NMR (700 MHz, $(CD_3)_2SO$) δ 8.89 (bs, 1H), 7.88 (d, *J* = 7.7 Hz, 2H), 7.65 (dt, *J* = 5.3, 3.0, 2.1 Hz, 2H), 7.23 (t, *J* = 7.7 Hz, 1H), 7.14 (s, 1H), 7.09 (d, *J* = 7.7 Hz, 1H), 7.03 (d, *J* = 6.9 Hz, 1H), 3.42 (bs, 3H), 2.28 (s, 3H); ^{13}C NMR (175 MHz, $(CD_3)_2SO$, N-inversion observed, all peaks reported) δ 160.46, 143.83, 143.69, 138.60, 134.85, 133.33, 129.87, 128.87, 127.74, 127.47, 125.52, 124.20, 121.89, 38.17, 20.81; LRMS-ESI (*m/z*): $[M + H]^+$ 327.1.

<u>ethyl 5-(*p*-tolyl)-1*H*-imidazole-2-carboxylate **(60a)**</u>

In a round bottom flask under argon, selenium dioxide (7.45 mmol, 2 equiv) was dissolved in anhydrous 1,4-dioxane (1 M). Water (7 drops) and 1-(*p*-tolyl)ethan-1-one (3.73 mmol, 1 equiv) were added and the flask was heated at reflux for 7 hours. Upon complete consumption of the acetophenone, the flask was cooled to room temperature. The reaction mixture was diluted in dichloromethane (0.25 M), filtered through a pad of celite, and the filtrate was concentrated *in vacuo*. This residue was diluted in water (0.53 M), heated at reflux for 10 minutes, then cooled to 0 °C. The resulting white precipitate was isolated via vacuum filtration and immediately carried into the next step without further purification due to product instability.

Polymerized ethyl 2-oxoacetate in 47% toluene (2.05 mL, 11.2 mmol, 3 equiv) was heated to 60 °C for 15 minutes, after which it was added dropwise to a stirring solution of ammonium acetate (11.2 mmol, 3 equiv) in water (1.54 M) and acetonitrile (0.77 M) at 0 °C. A solution of 2,2-dihydroxy-1-(*p*-tolyl)ethan-1-one (3.73 mmol, 1 equiv) in acetonitrile (0.77 M) was then added dropwise at 0 °C. After 30 minutes at 0 °C, the reaction mixture was warmed to room temperature and stirred for 2 hours. Upon complete diol consumption, the reaction mixture was concentrated *in vacuo.* This residue was diluted in water and extracted thrice with dichloromethane. The

combined organic layers were washed with brine, dried over sodium sulfate, and concentrated *in vacuo*. The crude product was purified by flash column chromatography with hexanes/ethyl acetate, followed by recrystallization from dichloromethane/hexanes to afford the title compound as a light yellow solid (36%). R_f (50% EA/Hex) = 0.24; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.85 (bs, 1H), 7.85 – 7.38 (m, 3H), 7.24 – 7.11 (m, 2H), 4.45 (q, *J* = 7.2 Hz, 2H), 2.37 (s, 3H), 1.41 (t, *J* = 7.2 Hz, 3H); LRMS-ESI (*m/z*): $[M + H]^+$ 231.1.

ethyl 5-(4-chlorophenyl)-1*H*-imidazole-2-carboxylate **(60b)**

Prepared as described for ethyl 5-(*p*-tolyl)-1*H*-imidazole-2-carboxylate from 1-(4-chlorophenyl)ethan-1-one. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a light yellow solid (44%, over 2 steps). R_f (70% EA/Hex) = 0.38; ^{1}H NMR (500 MHz, $CDCl_3$, tautomeric mixture, both forms reported) δ 10.54 (s, 0.3H), 10.37 (s, 0.7H), 7.78 (d, *J* = 8.5 Hz, 1.5H), 7.52 (d, *J* = 8.5 Hz, 0.5H), 7.50 (s, 0.25H), 7.46 (s, 0.75H), 7.42 (d, *J* = 8.5 Hz, 0.5H), 7.36 (d, *J* = 8.5 Hz, 1.5H), 4.53 – 4.42 (m, 2H), 1.44 (t, *J* = 7.1 Hz, 3H); LRMS-ESI (*m/z*): $[M + H]^+$ 251.1.

5-(*p*-tolyl)-1*H*-imidazole-2-carboxylic acid **(61a)**

In a round bottom flask, ethyl 5-(*p*-tolyl)-1*H*-imidazole-2-carboxylate (1.26 mmol, 1 equiv) was dissolved in ethanol (0.20 M), to which a solution of sodium hydroxide (6.30 mmol, 5 equiv) in water (0.20 M) was added slowly. The flask was heated at reflux for 24 hours. Upon complete consumption of the ester, the reaction mixture was acidified to pH 2-3 with hydrochloric acid (3 M) and extracted thrice with 3:1 chloroform:isopropanol. The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to afford the title compound as an off-white solid in quantitative yield. ^{1}H NMR (400 MHz, CD_3OD) δ 7.63 (s, 1H), 7.59 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 2.33 (s, 3H); LRMS-ESI (*m/z*): $[M + H]^+$ 203.1.

5-(4-chlorophenyl)-1*H*-imidazole-2-carboxylic acid **(61b)**

Prepared as described for 5-(*p*-tolyl)-1*H*-imidazole-2-carboxylic acid from ethyl 5-(4-chlorophenyl)-1*H*-imidazole-2-carboxylate. An acid-base extraction afforded the title compound as a white solid in quantitative yield. ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 7.90 (d, *J* = 8.3 Hz, 2H), 7.63 (s, 1H), 7.35 (d, *J* = 8.3 Hz, 2H); LRMS-ESI (*m/z*): $[M + H]^+$ 223.0.

***N*-(4-chlorophenyl)-*N*-methyl-5-(*p*-tolyl)-1*H*-imidazole-2-carboxamide (62)**

Prepared via General Procedure A from 5-(*p*-tolyl)-1*H*-imidazole-2-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (76%). mp 170-175 °C; R_f (40% EA/Hex) = 0.35; ^{1}H NMR (700 MHz, $(CD_3)_2CO$, tautomeric mixture, major form reported) δ 12.02 (bs, 1H), 7.60 (s, 1H), 7.51 (s, 2H), 7.44 (dt, *J* = 8.6, 2.8, 2.0 Hz, 2H), 7.38 (d, *J* = 8.2 Hz, 2H), 7.11 (d, *J* = 7.7 Hz, 2H), 3.65 (bs, 3H), 2.29 (s, 3H); ^{13}C NMR (175 MHz, $(CD_3)_2CO$, tautomeric mixture, major

form reported) δ 159.58, 144.94, 141.68, 136.98, 132.67, 132.57, 130.38, 129.91, 129.82, 129.61, 127.08, 125.54, 114.80, 39.14, 21.14; LRMS-ESI (*m/z*): $[M + H]^+$ 326.1.

<u>*N*,5-bis(4-chlorophenyl)-*N*-methyl-1*H*-imidazole-2-carboxamide (63)</u>

Prepared via General Procedure A from 5-(4-chlorophenyl)-1*H*-imidazole-2-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (65%). mp 198-202 °C; R_f (40% EA/Hex) = 0.29; ^{1}H NMR (500 MHz, $(CD_3)_2CO$, tautomeric mixture, major form reported) δ 12.09 (bs, 1H), 7.71 (s, 1H), 7.68 – 7.50 (m, 2H), 7.45 (dt, *J* = 8.6, 2.9, 2.0 Hz, 2H), 7.38 (d, *J* = 8.6 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 3.65 (bs, 3H); ^{13}C NMR (175 MHz, $(CD_3)_2CO$, tautomeric mixture, major form reported) δ 159.42, 144.85, 142.02, 141.46, 134.18, 132.79, 132.55, 129.95, 129.65, 129.26, 127.06, 115.78, 39.13; LRMS-ESI (*m/z*): $[M + H]^+$ 346.1 and 348.1.

<u>2-(*p*-tolyl)-5-(trifluoromethyl)-1*H*-imidazole **(64a)**</u>

In a 3-necked round bottom flask, sodium acetate trihydrate (5.29 mmol, 1.27 equiv) was dissolved in water (1.42 M), to which 3,3-dibromo-1,1,1-trifluoropropan-2-one (4.37 mmol, 1.05 equiv) was added. The flask was heated at 100 °C for 30 minutes then cooled to room temperature. A solution of 4-methylbenzaldehyde (4.16 mmol, 1 equiv) and ammonium hydroxide (4.54 mL) dissolved in methanol (0.94 M) was added to the reaction mixture. After 4 hours, the reaction was quenched with water and extracted thrice with dichloromethane. The combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (25%). R_f (30% EA/Hex) = 0.36; ^{1}H NMR (500 MHz, CD_3OD) δ 7.78 (d, *J* = 8.1 Hz, 2H), 7.62 – 7.56 (m, 1H), 7.29 (d, *J* = 8.1 Hz, 2H), 2.38 (s, 3H); LRMS-ESI (*m/z*): $[M + H]^+$ 227.1.

<u>2-(4-chlorophenyl)-5-(trifluoromethyl)-1*H*-imidazole **(64b)**</u>

Prepared as described for 2-(*p*-tolyl)-5-(trifluoromethyl)-1*H*-imidazole from 4-chlorobenzaldehyde. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (25%). R_f (30% EA/Hex) = 0.32; ^{1}H NMR (500 MHz, CD_3OD) δ 7.87 (dt, *J* = 4.7, 2.7, 2.0 Hz, 2H), 7.68 – 7.60 (m, 1H), 7.48 (dt, *J* = 4.7, 2.7, 2.0 Hz, 2H); LRMS-ESI (*m/z*): $[M + H]^+$ 247.0.

<u>2-(*p*-tolyl)-1*H*-imidazole-5-carboxylic acid **(65a)**</u>

In a round bottom flask, 2-(*p*-tolyl)-5-(trifluoromethyl)-1*H*-imidazole (0.831 mmol, 1 equiv) and sodium hydroxide pellets (4.27 mmol, 5.14 equiv) were dissolved in water (0.32 M). The flask was heated at 100 °C for 16 hours then cooled to room temperature. The reaction mixture was further diluted in water and extracted thrice with dichloromethane. The aqueous layer was then acidified to pH 2-3 with hydrochloric acid (3 M) and the resulting precipitate was isolated via vacuum filtration. The solids were dissolved in acetone and methanol and

concentrated *in vacuo* to afford the title compound as a light orange solid (76%). ^{1}H NMR (500 MHz, CD_3OD) δ 7.81 (d, *J* = 8.0 Hz, 2H), 7.74 (s, 1H), 7.30 (d, *J* = 8.0 Hz, 2H), 2.39 (s, 3H); LRMS-ESI (*m/z*): $[M + H]^+$ 203.1.

2-(4-chlorophenyl)-1*H*-imidazole-5-carboxylic acid **(65b)**

Prepared as described for 2-(*p*-tolyl)-1*H*-imidazole-5-carboxylic acid from 2-(4-chlorophenyl)-5-(trifluoromethyl)-1*H*-imidazole. An acid-base extraction afforded the title compound as a tan solid (64%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.93 (d, *J* = 8.7 Hz, 2H), 7.79 (s, 1H), 7.49 (d, *J* = 8.7 Hz, 2H); LRMS-ESI (*m/z*): $[M + H]^+$ 223.0.

***N*-(4-chlorophenyl)-*N*-methyl-2-(*p*-tolyl)-1*H*-imidazole-5-carboxamide (66)**

Prepared via General Procedure A from 2-(*p*-tolyl)-1*H*-imidazole-5-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate, followed by preparatory TLC to afford the title compound as a white solid (51%). mp 189-191 °C; R_f (50% EA/Hex) = 0.21; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.60 (bs, 1H), 7.86 (d, *J* = 7.9 Hz, 2H), 7.46 (d, *J* = 8.2 Hz, 2H), 7.32 – 7.24 (m, 2H), 7.21 (d, *J* = 7.9 Hz, 2H), 5.84 (s, 1H), 3.44 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 160.73, 148.66, 141.95, 139.70, 134.98, 134.28, 130.50, 129.52 (2 sets of non-equivalent C), 126.70, 126.06, 125.90, 38.54, 21.50; LRMS-ESI (*m/z*): $[M + H]^+$ 326.1.

***N*,2-bis(4-chlorophenyl)-*N*-methyl-1*H*-imidazole-5-carboxamide (67)**

Prepared via General Procedure A from 2-(4-chlorophenyl)-1*H*-imidazole-5-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate, followed by preparatory TLC to afford the title compound as a white solid (32%). mp 174-176 °C; R_f (50% EA/Hex) = 0.26; ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.10 (bs, 1H), 7.95 (d, *J* = 8.2 Hz, 2H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.36 (d, *J* = 8.2 Hz, 2H), 7.31 – 7.18 (m, 2H), 5.88 (s, 1H), 3.43 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 160.74, 147.67, 141.76, 135.51, 135.13, 134.55, 130.58, 129.39, 128.98, 128.04, 127.59, 126.35, 38.64; LRMS-ESI (*m/z*): $[M + H]^+$ 346.1 and 348.1.

ethyl 2-oxo-2-((2-oxo-2-(*p*-tolyl)ethyl)amino)acetate **(68a)**

In a flame-dried round bottom flask under argon, 2-bromo-1-(*p*-tolyl)ethan-1-one (2 mmol, 1 equiv) and 1,3,5,7-tetraazaadamantane (2 mmol, 1 equiv) were dissolved in anhydrous dichloromethane (0.13 M). The reaction mixture was heated to 50 °C for 2 hours and upon cooling to room temperature, a precipitate formed. This precipitate was isolated by vacuum filtration, washing the cake with dichloromethane and ethanol. The resulting white solids (urotropinium salt) were transferred to a round bottom flask, dissolved in ethanol (0.04 M) and concentrated hydrochloric acid (0.40 M), and heated to reflux for 2 hours. The reaction mixture was then concentrated to half *in vacuo* and the light-white precipitate was removed by vacuum filtration and washed with ethanol. The resulting filtrate was concentrated *in vacuo* and carried into the next step without further purification.

In a flame-dried round bottom flask under argon, 2-amino-1-(*p*-tolyl)ethan-1-one hydrochloride (2 mmol, 1 equiv) was dissolved in anhydrous dichloromethane (0.29 M) and triethylamine (6 mmol, 3 equiv) was added. Ethyl 2-chloro-2-oxoacetate (2 mmol, 1 equiv) was added at 0 °C. The reaction mixture was warmed to room temperature and stirred for 16 hours. Upon complete consumption of the amine, the reaction mixture was diluted in water and the aqueous layer was extracted thrice with dichloromethane. The combined organic layers were washed with water, brine, dried over sodium sulfate, and concentrated *in vacuo.* The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a light yellow solid (54%, over 2 steps). R_f (40% EA/Hex) = 0.36; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (bs, 1H), 7.89 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 4.83 – 4.76 (m, 2H), 4.40 (q, *J* = 7.2 Hz, 2H), 2.44 (s, 3H), 1.41 (t, *J* = 7.2 Hz, 3H); LRMS-ESI (*m/z*): $[M + H]^+$ 250.1.

ethyl 2-((2-(4-chlorophenyl)-2-oxoethyl)amino)-2-oxoacetate **(68b)**

Prepared as described for ethyl 2-oxo-2-((2-oxo-2-(*p*-tolyl)ethyl)amino)acetate from 2-bromo-1-(4-chlorophenyl)ethan-1-one. During the preparation of the 2-amino-1-(4-chlorophenyl)ethan-1-one salt, the isolated intermediate was the light-yellow precipitate formed following reflux in ethanol and concentrated hydrochloric acid. It was isolated via vacuum filtration (washing with ethanol) and carried into the next step without further purification, as described previously. The final crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (41%, over 2 steps). R_f (50% EA/Hex) = 0.28; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (bs, 1H), 7.94 (d, *J* = 8.1 Hz, 2H), 7.51 (d, *J* = 8.1 Hz, 2H), 4.83 – 4.78 (m, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H); LRMS-ESI (*m/z*): $[M + H]^+$ 270.0.

ethyl 5-(*p*-tolyl)oxazole-2-carboxylate **(69a)**

In a round bottom flask, ethyl 2-oxo-2-((2-oxo-2-(*p*-tolyl)ethyl)amino)acetate (0.802 mmol, 1 equiv) was dissolved in phosphoryl chloride (0.33 M) and heated to reflux for 5 hours. Upon reaction completion via LCMS, the reaction mixture was diluted in saturated sodium bicarbonate and dichloromethane. The aqueous layer was extracted thrice with dichloromethane. The combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. The crude product was purified by flash column chromatography with hexanes/ethyl acetate, followed by recrystallization from dichloromethane/hexanes to afford the title compound as a light yellow solid (86%). R_f (20% EA/Hex) = 0.22; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.2 Hz, 2H), 7.46 (s, 1H), 7.25 (d, *J* = 7.5 Hz, 2H), 4.48 (q, *J* = 7.1 Hz, 2H), 2.39 (s, 3H), 1.45 (t, *J* = 7.1 Hz, 3H); LRMS-ESI (*m/z*): $[M + H]^+$ 232.1.

ethyl 5-(4-chlorophenyl)oxazole-2-carboxylate **(69b)**

Prepared as described for ethyl 5-(*p*-tolyl)oxazole-2-carboxylate from ethyl 2-((2-(4-chlorophenyl)-2-oxoethyl)amino)-2-oxoacetate. The crude product was purified by flash column chromatography with hexanes/ethyl acetate, followed by recrystallization from dichloromethane/hexanes to afford the title compound as a lustrous tan solid (87%). R_f (20% EA/Hex) = 0.25; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (dt, *J* = 8.5, 2.6, 2.0

Hz, 2H), 7.51 (s, 1H), 7.44 (dt, *J* = 8.5, 2.6, 2.0 Hz, 2H), 4.50 (q, *J* = 7.1 Hz, 2H), 1.46 (t, *J* = 7.2 Hz, 3H); LRMS-ESI (*m/z*): $[M + H]^+$ 252.0.

5-(*p*-tolyl)oxazole-2-carboxylic acid **(70a)**

In a round bottom flask, ethyl 5-(*p*-tolyl)oxazole-2-carboxylate (0.650 mmol, 1 equiv) was dissolved in tetrahydrofuran (0.13 M) and water (0.40 M). Following addition of lithium hydroxide (1.30 mmol, 2 equiv), the reaction mixture was stirred at room temperature for 16 hours. Upon complete consumption of the ester, the reaction mixture was concentrated *in vacuo* to afford the title compound as an off-white solid in quantitative yield. ^{1}H NMR (500 MHz, CD_3OD) δ 7.68 (d, *J* = 7.8 Hz, 2H), 7.44 (s, 1H), 7.26 (d, *J* = 7.8 Hz, 2H), 2.36 (s, 3H); LRMS-ESI (*m/z*): $[M + H]^+$ 204.0.

5-(4-chlorophenyl)oxazole-2-carboxylic acid **(70b)**

Prepared as described for 5-(*p*-tolyl)oxazole-2-carboxylic acid from ethyl 5-(4-chlorophenyl)oxazole-2-carboxylate. The reaction mixture was concentrated *in vacuo* to afford the title compound as a white solid in quantitative yield. ^{1}H NMR (500 MHz, CD_3OD) δ 7.80 (dt, *J* = 8.6, 2.6, 2.0 Hz, 2H), 7.56 (s, 1H), 7.46 (dt, *J* = 8.6, 2.6, 2.0 Hz, 2H); LRMS-ESI (*m/z*): $[M + H]^+$ 224.0.

***N*-(4-chlorophenyl)-*N*-methyl-5-(*p*-tolyl)oxazole-2-carboxamide (71)**

Prepared via General Procedure A from 5-(*p*-tolyl)oxazole-2-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (90%). mp 126-132 °C; R_f (30% EA/Hex) = 0.36; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.3 Hz, 4H), 7.24 – 7.06 (m, 5H), 3.51 (bs, 3H), 2.37 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 156.87, 153.59, 152.65, 142.38, 139.73, 133.57, 129.78, 129.74, 128.08, 124.84, 124.23, 122.22, 38.68, 21.54; LRMS-ESI (*m/z*): $[M + H]^+$ 327.1.

***N*,5-bis(4-chlorophenyl)-*N*-methyloxazole-2-carboxamide (72)**

Prepared via General Procedure A from 5-(4-chlorophenyl)oxazole-2-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (82%). mp 139-141 °C; R_f (30% EA/Hex) = 0.30; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 7.75 (bs, 1H), 7.64 – 7.51 (m, 4H), 7.45 (d, *J* = 8.2 Hz, 2H), 7.37 (d, *J* = 8.2 Hz, 2H), 3.43 (bs, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 156.63, 154.01, 151.33, 142.21, 135.39, 133.68, 129.75, 129.38, 128.07, 126.08, 125.43, 123.09, 38.63; LRMS-ESI (*m/z*): $[M + H]^+$ 347.0 and 349.1.

ethyl 2-(*p*-tolyl)oxazole-5-carboxylate **(73a)**

In a microwave vial, while stirring, *p*-tolylboronic acid (1.37 mmol, 1.20 equiv), aqueous sodium carbonate (2 M), tetrakis(triphenylphosphine)palladium(0) (10 mol%), and ethyl 2-chlorooxazole-5-carboxylate (1.14 mmol, 1

equiv) were dissolved in 1,4-dioxane (0.14 M). Once well mixed, the reaction mixture was heated at 150 °C for 5 minutes in a microwave reactor (Anton Paar Monowave 400). Once cooled to 70 °C, the reaction mixture was filtered through a pad of celite and washed with water. The filtrate was transferred to a separatory funnel and the aqueous layer was extracted thrice with 3:1 chloroform:isopropanol. The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated *in vacuo*. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as an off-white solid (33%). R_f (10% EA/Hex) = 0.21; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.2 Hz, 2H), 7.81 (s, 1H), 7.28 (d, *J* = 8.1 Hz, 2H), 4.40 (q, *J* = 7.1 Hz, 2H), 2.41 (s, 3H), 1.40 (t, *J* = 7.1 Hz, 3H); LRMS-ESI (*m/z*): $[M + H]^+$ 232.1.

ethyl 2-(4-chlorophenyl)oxazole-5-carboxylate **(73b)**

Prepared as described for ethyl 2-(*p*-tolyl)oxazole-5-carboxylate from (4-chlorophenyl)boronic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (25%). R_f (10% EA/Hex) = 0.21; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.6 Hz, 2H), 7.83 (s, 1H), 7.47 (d, *J* = 8.6 Hz, 2H), 4.41 (q, *J* = 7.1 Hz, 3H), 1.41 (t, *J* = 7.1 Hz, 6H); LRMS-ESI (*m/z*): $[M + H]^+$ 252.0.

2-(*p*-tolyl)oxazole-5-carboxylic acid **(74a)**

In a round bottom flask, ethyl 2-(*p*-tolyl)oxazole-5-carboxylate (0.390 mmol, 1 equiv) was dissolved in tetrahydrofuran (0.24 M) and water (0.12 M). Following addition of lithium hydroxide monohydrate (0.468 mmol, 1.20 equiv), the reaction mixture was stirred at room temperature for 16 hours. Upon complete consumption of the ester, the reaction mixture was basified to pH 12-13 with sodium hydroxide (3 M) and extracted thrice with dichloromethane. The aqueous layer was then acidified to pH 2-3 with hydrochloric acid (3 M). The resulting precipitate was isolated via vacuum filtration to afford the title compound as an off-white solid (71%). ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 7.97 (s, 1H), 7.92 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 2.38 (s, 3H); LRMS-ESI (*m/z*): $[M + H]^+$ 204.0.

2-(4-chlorophenyl)oxazole-5-carboxylic acid **(74b)**

Prepared as described for 2-(*p*-tolyl)oxazole-5-carboxylic acid from ethyl 2-(4-chlorophenyl)oxazole-5-carboxylate. An acid-base extraction afforded the title compound as a white solid (69%). ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.13 – 7.99 (m, 3H), 7.66 (d, *J* = 8.5 Hz, 2H); LRMS-ESI (*m/z*): $[M + H]^+$ 224.0.

***N*-(4-chlorophenyl)-*N*-methyl-2-(*p*-tolyl)oxazole-5-carboxamide (75)**

Prepared via General Procedure A from 2-(*p*-tolyl)oxazole-5-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a pale-yellow solid (78%). mp 142-145 °C; R_f (50% EA/Hex) = 0.58; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.9 Hz, 2H), 7.45 (d, *J* = 8.5 Hz, 2H), 7.22 (t, *J* = 7.6 Hz, 4H), 6.86 (s, 1H), 3.44 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ

163.01, 157.77, 144.22, 142.05, 141.95, 134.55, 134.45, 130.15, 129.67, 129.08, 126.88, 123.76, 38.40, 21.69; LRMS-ESI (*m/z*): $[M + H]^+$ 327.1.

<u>*N*,2-bis(4-chlorophenyl)-*N*-methyloxazole-5-carboxamide (76)</u>

Prepared via General Procedure A from 2-(4-chlorophenyl)oxazole-5-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a yellow solid (88%). mp 163-166 °C; R_f (50% EA/Hex) = 0.50; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.2 Hz, 2H), 7.46 (d, *J* = 8.3 Hz, 2H), 7.39 (d, *J* = 8.3 Hz, 1H), 7.23 (d, *J* = 8.1 Hz, 1H), 6.85 (s, 1H), 3.45 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 161.73, 157.49, 144.64, 141.87, 137.63, 134.55, 134.45, 130.18, 129.29, 129.07, 128.11, 124.91, 38.39; LRMS-ESI (*m/z*): $[M + H]^+$ 347.0 and 349.0.

<u>ethyl 4-methyl-2-(*p*-tolyl)oxazole-5-carboxylate **(77a)**</u>

In a round bottom flask, ethyl 2-chloroacetoacetate (1.52 mmol, 1 equiv) and 4-methylbenzamide (4.56 mmol, 3 equiv) were dissolved in ethanol (1.20 M). The reaction mixture was heated to 80 °C for 2 hours, then heated at 110 °C for 14 hours. Upon complete consumption of the acetoacetate, the reaction mixture was cooled and the resulting precipitate was removed via vacuum filtration. The filtrate was diluted with ethyl acetate and basified to pH 10 with sodium hydroxide (1 M). The aqueous layer was extracted thrice with ethyl acetate and the combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. The resulting solids were washed with dichloromethane. The crude product, in the filtrate, was purified by flash column chromatography with hexanes/ethyl acetate, followed by recrystallization in dichloromethane/hexanes to afford the title compound as an off-white solid (27%). R_f (10% EA/Hex) = 0.27; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.2 Hz, 2H), 7.31 – 7.22 (m, 2H), 4.41 (q, *J* = 7.2 Hz, 2H), 2.53 (s, 3H), 2.41 (s, 3H), 1.42 (t, *J* = 7.2 Hz, 3H); LRMS-ESI (*m/z*): $[M + H]^+$ 246.1.

<u>ethyl 2-(4-chlorophenyl)-4-methyloxazole-5-carboxylate **(77b)**</u>

Prepared as described for ethyl 4-methyl-2-(*p*-tolyl)oxazole-5-carboxylate from 4-chlorobenzamide. The crude product was purified by flash column chromatography with hexanes/ethyl acetate, followed by recrystallization in dichloromethane/hexanes to afford the title compound as a light yellow solid (11%). R_f (10% EA/Hex) = 0.28; ^{1}H NMR (500 MHz, CD_3OD) δ 8.03 (d, *J* = 8.7 Hz, 2H), 7.54 (d, *J* = 8.7 Hz, 2H), 4.39 (q, *J* = 7.1 Hz, 2H), 2.49 (s, 3H), 1.40 (t, *J* = 7.1 Hz, 3H); LRMS-ESI (*m/z*): $[M + H]^+$ 266.0.

<u>4-methyl-2-(*p*-tolyl)oxazole-5-carboxylic acid **(78a)**</u>

In a round bottom flask, ethyl 4-methyl-2-(*p*-tolyl)oxazole-5-carboxylate (0.795 mmol, 1 equiv) was dissolved in tetrahydrofuran (1.20 M), methanol (1.20 M), and water (2.40 M). Following addition of lithium hydroxide (4.21 mmol, 5.30 equiv), the reaction mixture was stirred at room temperature for 12 hours. Upon completion consumption of ester, the reaction mixture was further basified to pH 12-13 with sodium hydroxide (3 M) and

extracted thrice with dichloromethane. The aqueous layer was then acidified to pH 2-3 with hydrochloric acid (3 M). The resulting precipitate was isolated via vacuum filtration to afford the title compound as a white solid (81%). ^{1}H NMR (500 MHz, CD_3OD) δ 7.96 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 2.50 (s, 3H), 2.41 (s, 3H); LRMS-ESI (*m/z*): $[M + H]^+$ 218.1.

2-(4-chlorophenyl)-4-methyloxazole-5-carboxylic acid **(78b)**

Prepared as described for 4-methyl-2-(*p*-tolyl)oxazole-5-carboxylic acid from ethyl 2-(4-chlorophenyl)-4-methyloxazole-5-carboxylate. An acid-base extraction afforded the title compound as a white solid (90%). ^{1}H NMR (500 MHz, CD_3OD) δ 8.07 (dt, *J* = 4.5, 2.4, 1.9 Hz, 2H), 7.51 (dt, *J* = 4.5, 2.4, 1.9 Hz, 2H), 2.49 (s, 3H); LRMS-ESI (*m/z*): $[M + H]^+$ 238.0.

***N*-(4-chlorophenyl)-*N*,4-dimethyl-2-(*p*-tolyl)oxazole-5-carboxamide (79)**

Prepared via General Procedure A from 4-methyl-2-(*p*-tolyl)oxazole-5-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a lustrous white solid (99%). mp 103-105 °C; R_f (30% EA/Hex) = 0.46; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.39 (dt, *J* = 8.6, 3.1, 2.1 Hz, 2H), 7.30 (d, *J* = 7.9 Hz, 2H), 7.17 (dt, *J* = 8.6, 3.1, 2.1 Hz, 2H), 7.14 (d, *J* = 7.9 Hz, 2H), 3.43 (s, 3H), 2.53 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 160.52, 159.03, 146.82, 142.99, 141.68, 138.76, 133.33, 129.64, 129.59, 128.43, 126.54, 123.73, 38.41, 21.63, 13.84; LRMS-ESI (*m/z*): $[M + H]^+$ 341.1.

***N*,2-bis(4-chlorophenyl)-*N*,4-dimethyloxazole-5-carboxamide (80)**

Prepared via General Procedure A from 2-(4-chlorophenyl)-4-methyloxazole-5-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a lustrous white solid (67%). mp 146-152 °C; R_f (30% EA/Hex) = 0.50; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.41 (dt, *J* = 8.5, 3.1, 2.1 Hz, 2H), 7.36 – 7.29 (m, 4H), 7.18 (dt, *J* = 8.5, 3.1, 2.1 Hz, 2H), 3.44 (s, 3H), 2.52 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 159.30, 158.82, 146.90, 142.89, 139.26, 137.41, 133.49, 129.70, 129.25, 128.48, 127.80, 124.96, 38.44, 13.82; LRMS-ESI (*m/z*): $[M + H]^+$ 361.1 and 363.1.

ethyl 5-(*p*-tolyl)thiazole-2-carboxylate **(81a)**

In a round bottom flask under argon, ethyl 2-oxo-2-((2-oxo-2-(*p*-tolyl)ethyl)amino)acetate (0.802 mmol, 1 equiv) was dissolved in anhydrous dichloromethane (0.38 M) and phosphorus pentasulfide (1.60 mmol, 2 equiv) was added. The reaction mixture was heated to reflux for 5 hours, then cooled to room temperature and quenched via the slow addition of water. The solution was transferred to a separatory funnel and the aqueous layer was extracted thrice with dichloromethane. The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated *in vacuo*. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a yellow solid (92%). R_f (20% EA/Hex) = 0.26; ^{1}H NMR

(500 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 4.48 (q, *J* = 7.1 Hz, 2H), 2.39 (s, 3H), 1.45 (t, *J* = 7.1 Hz, 3H); LRMS-ESI (*m/z*): $[M + H]^+$ 248.1.

ethyl 5-(4-chlorophenyl)thiazole-2-carboxylate **(81b)**

Prepared as described for ethyl 5-(*p*-tolyl)thiazole-2-carboxylate from ethyl 2-((2-(4-chlorophenyl)-2-oxoethyl)amino)-2-oxoacetate. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a yellow solid (77%). R_f (10% EA/Hex) = 0.13; ^1H NMR (500 MHz, CD_3OD) δ 8.29 (s, 1H), 7.70 (d, *J* = 8.5 Hz, 2H), 7.47 (d, *J* = 8.5 Hz, 2H), 4.45 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H); LRMS-ESI (*m/z*): $[M + H]^+$ 268.0.

5-(*p*-tolyl)thiazole-2-carboxylic acid **(82a)**

Prepared as described for 5-(*p*-tolyl)oxazole-2-carboxylic acid from ethyl 5-(*p*-tolyl)thiazole-2-carboxylate. An acid-base extraction afforded the title compound as a lustrous white solid (73%). ^1H NMR (500 MHz, CD_3OD) δ 8.01 (s, 1H), 7.53 (d, *J* = 8.1 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 2.36 (s, 3H); LRMS-ESI (*m/z*): $[M + H]^+$ 220.0.

5-(4-chlorophenyl)thiazole-2-carboxylic acid **(82b)**

Prepared as described for 5-(*p*-tolyl)oxazole-2-carboxylic acid from ethyl 5-(4-chlorophenyl)thiazole-2-carboxylate. An acid-base extraction afforded the title compound as a light yellow lustrous solid (42%). ^1H NMR (500 MHz, CD_3OD) δ 8.08 (s, 1H), 7.64 (dt, *J* = 8.6, 2.7, 2.0 Hz, 2H), 7.43 (dt, *J* = 8.6, 2.7, 2.0 Hz, 2H); LRMS-ESI (*m/z*): $[M + H]^+$ 240.0.

***N*-(4-chlorophenyl)-*N*-methyl-5-(*p*-tolyl)thiazole-2-carboxamide (83)**

Prepared via General Procedure A from 5-(*p*-tolyl)thiazole-2-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a light yellow solid (89%). mp 142-146 °C; R_f (30% EA/Hex) = 0.47; ^1H NMR (500 MHz, $CDCl_3$) δ 7.75 (bs, 1H), 7.43 (d, *J* = 7.7 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 7.24 – 7.12 (m, 4H), 3.56 (bs, 3H), 2.37 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 161.31, 161.03, 144.29, 142.93, 139.40, 138.58, 133.09, 130.00, 129.55, 128.33, 127.86, 127.02, 39.53, 21.40; LRMS-ESI (*m/z*): $[M + H]^+$ 343.1.

***N*,5-bis(4-chlorophenyl)-*N*-methylthiazole-2-carboxamide (84)**

Prepared via General Procedure A from 5-(4-chlorophenyl)thiazole-2-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a light pink solid (75%). mp 133-137 °C; R_f (20% EA/Hex) = 0.35; ^1H NMR (500 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.46 (d, *J* = 8.2 Hz, 2H), 7.40 – 7.29 (m, 4H), 7.17 (d, *J* = 6.4 Hz, 2H), 3.55 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 162.18, 160.75,

142.77, 139.24, 135.17, 133.22, 129.58, 129.55, 129.22, 128.29 (2 non-equivalent C), 39.54; LRMS-ESI (*m/z*): $[M + H]^+$ 363.0 and 365.0.

ethyl 2-(*p*-tolyl)thiazole-5-carboxylate **(85a)**

In a flame-dried round bottom flask under argon, 4-chlorothiobenzamide (1.98 mmol, 1 equiv) was dissolved in anhydrous toluene (0.30 M). Anhydrous magnesium sulfate (3.97 mmol, 2 equiv) and ethyl 2-chloro-2-formylacetate (3.97 mmol, 2 equiv) were added and the reaction mixture was heated to 100 °C for 2 hours. Upon complete consumption of the thioamide, the reaction mixture was cooled to room temperature. The resulting precipitate was isolated via vacuum filtration. The crude product was purified by flash column chromatography with hexanes/ethyl acetate, followed by recrystallization in dichloromethane/hexanes to afford the title compound as a lustrous white solid (77%). R_f (10% EA/Hex) = 0.34; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.88 (d, *J* = 8.2 Hz, 2H), 7.31 – 7.23 (m, 2H), 4.39 (q, *J* = 7.1 Hz, 2H), 2.41 (s, 3H), 1.40 (t, *J* = 7.1 Hz, 3H); LRMS-ESI (*m/z*): $[M + H]^+$ 248.1.

ethyl 2-(4-chlorophenyl)thiazole-5-carboxylate **(85b)**

Prepared as described for ethyl 2-(*p*-tolyl)thiazole-5-carboxylate from 4-methylbenzothioamide. The crude product was purified by flash column chromatography with hexanes/ethyl acetate, followed by recrystallization in dichloromethanes/hexanes to afford the title compound as a white fluffy solid (82%). R_f (10% EA/Hex) = 0.36; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.92 (d, *J* = 8.5 Hz, 2H), 7.45 (d, *J* = 8.5 Hz, 2H), 4.40 (q, *J* = 7.2 Hz, 2H), 1.40 (t, *J* = 7.2 Hz, 3H); LRMS-ESI (*m/z*): $[M + H]^+$ 268.0.

2-(*p*-tolyl)thiazole-5-carboxylic acid **(86a)**

In a round bottom flask, ethyl 2-(*p*-tolyl)thiazole-5-carboxylate (1.01 mmol, 1 equiv) was dissolved in tetrahydrofuran (0.13 M) and water (0.40 M). Following addition of lithium hydroxide monohydrate (3.03 mmol, 3 equiv), the reaction mixture was stirred at room temperature for 16 hours. Upon complete consumption of the ester, the reaction mixture was basified to pH 12-13 with sodium hydroxide (3 M) and extracted thrice with dichloromethane. The aqueous layer was then acidified to pH 2-3 with hydrochloric acid (3 M). The resulting precipitate was isolated via vacuum filtration to afford the title compound as a white solid (70%). ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 13.57 (bs, 1H), 8.37 (s, 1H), 7.89 (d, *J* = 8.1 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 2.36 (s, 3H); LRMS-ESI (*m/z*): $[M + H]^+$ 220.0.

2-(4-chlorophenyl)thiazole-5-carboxylic acid **(86b)**

Prepared as described for 2-(*p*-tolyl)thiazole-5-carboxylic acid from ethyl 2-(4-chlorophenyl)thiazole-5-carboxylate. An acid-base extraction afforded the title compound as a white solid (38%). ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 13.66 (bs, 1H), 8.41 (s, 1H), 8.01 (dt, *J* = 4.5, 2.7, 1.8 Hz, 2H), 7.59 (dt, *J* = 4.5, 2.7, 1.8 Hz, 2H); LRMS-ESI (*m/z*): $[M + H]^+$ 240.0.

***N*-(4-chlorophenyl)-*N*-methyl-2-(*p*-tolyl)thiazole-5-carboxamide (87)**

Prepared via General Procedure A from 2-(*p*-tolyl)thiazole-5-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a fluffy white solid (67%). mp 116-119 °C; R_f (30% EA/Hex) = 0.41; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 – 7.69 (m, 2H), 7.42 (dt, *J* = 8.6, 3.0, 2.0 Hz, 2H), 7.34 (s, 1H), 7.25 – 7.15 (m, 4H), 3.44 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 172.07, 161.41, 147.51, 142.19, 141.47, 134.70, 132.53, 130.45, 130.31, 129.83, 129.44, 126.70, 38.95, 21.59; LRMS-ESI (*m/z*): $[M + H]^+$ 343.1.

***N*,2-bis(4-chlorophenyl)-*N*-methylthiazole-5-carboxamide (88)**

Prepared via General Procedure A from 2-(4-chlorophenyl)thiazole-5-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (80%). mp 148-150 °C; R_f (30% EA/Hex) = 0.45; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (dt, *J* = 8.6, 2.5, 1.9 Hz, 2H), 7.43 (dt, *J* = 8.6, 3.0, 2.1 Hz, 2H), 7.37 (dt, *J* = 8.6, 2.5, 1.9 Hz, 2H), 7.35 (s, 1H), 7.21 (dt, *J* = 8.6, 3.0, 2.1 Hz, 2H), 3.44 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 170.41, 161.14, 147.60, 142.06, 137.06, 134.85, 133.40, 131.43, 130.53, 129.44, 129.42, 127.97, 38.99; LRMS-ESI (*m/z*): $[M + H]^+$ 363.0 and 365.0.

ethyl 4-methyl-2-(*p*-tolyl)thiazole-5-carboxylate **(89a)**

In a round bottom flask, 4-methylbenzothioamide (2.65 mmol, 1 equiv) was dissolved in ethanol (0.65 M) and ethyl 2-chloroacetoacetate (3.25 mmol, 1.23 equiv) was added. The reaction mixture was stirred for 4 hours at reflux, then allowed to cool to room temperature and stir for 16 hours. The resulting white precipitate was isolated via vacuum filtration and washed with ethanol (0 °C) to afford the title compound as a white solid (84%). R_f (30 % EA/Hex) = 0.72; ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 7.92 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 4.34 (q, *J* = 7.1 Hz, 2H), 2.70 (s, 3H), 2.40 (s, 3H), 1.36 (t, *J* = 7.1 Hz, 3H); LRMS-ESI (*m/z*): $[M + H]^+$ 262.1.

ethyl 2-(4-chlorophenyl)-4-methylthiazole-5-carboxylate **(89b)**

Prepared as described for ethyl 4-methyl-2-(*p*-tolyl)thiazole-5-carboxylate from 4-chlorobenzothiamide. Upon cooling the reaction mixture, the resulting yellow precipitate was isolated via vacuum filtration and washed with ethanol (0 °C) to afford the title compound as a yellow fluffy solid (81%). R_f (30% EA/Hex) = 0.80; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 4.36 (q, *J* = 7.1 Hz, 2H), 2.77 (s, 3H), 1.39 (t, *J* = 7.1 Hz, 3H); LRMS-ESI (*m/z*): $[M + H]^+$ 282.0.

4-methyl-2-(*p*-tolyl)thiazole-5-carboxylic acid **(90a)**

In a round bottom flask, ethyl 4-methyl-2-(*p*-tolyl)thiazole-5-carboxylate (0.383 mmol, 1 equiv) was dissolved in tetrahydrofuran (1 M), methanol (1.19 M), and water (2 M). Following slow addition of lithium hydroxide (2.03

mmol, 5.30 equiv), the reaction mixture was stirred for 12 hours at room temperature. The reaction mixture was concentrated to half *in vacuo*, diluted with water, and extracted thrice with dichloromethane. The aqueous layer was then acidified to pH 2-3 with hydrochloric acid (3 M) and extracted thrice with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to afford the title compound as a white solid (59%). ^{1}H NMR (500 MHz, CD_3OD) δ 7.86 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 7.9 Hz, 2H), 2.72 (s, 3H), 2.40 (s, 3H); LRMS-ESI (*m/z*): $[M + H]^+$ 234.0.

2-(4-chlorophenyl)-4-methylthiazole-5-carboxylic acid **(90b)**

Prepared as described for 4-methyl-2-(*p*-tolyl)thiazole-5-carboxylic acid from ethyl 2-(4-chlorophenyl)-4-methylthiazole-5-carboxylate. An acid-base extraction afforded the title compound as a white solid (80%). ^{1}H NMR (500 MHz, CD_3OD) δ 7.95 (dt, *J* = 8.6, 2.5, 1.8 Hz, 2H), 7.50 (dt, *J* = 8.6, 2.5, 1.9 Hz, 2H), 2.72 (s, 3H); LRMS-ESI (*m/z*): $[M + H]^+$ 254.0.

***N*-(4-chlorophenyl)-*N*,4-dimethyl-2-(*p*-tolyl)thiazole-5-carboxamide (91)**

Prepared via General Procedure A from 4-methyl-2-(*p*-tolyl)thiazole-5-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as an off-white oil (46%). R_f (30% EA/Hex) = 0.38; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.2 Hz, 2H), 7.29 (ddd, *J* = 8.7, 3.1, 2.0 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.09 (ddd, *J* = 8.7, 3.1, 2.0 Hz, 2H), 3.45 (s, 3H), 2.50 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.71, 163.66, 156.87, 142.50, 141.14, 133.36, 130.28, 129.82, 129.75, 128.53, 126.63, 124.00, 38.51, 21.58, 17.53; LRMS-ESI (*m/z*): $[M + H]^+$ 357.1.

***N*,2-bis(4-chlorophenyl)-*N*,4-dimethylthiazole-5-carboxamide (92)**

Prepared via General Procedure A from 2-(4-chlorophenyl)-4-methylthiazole-5-carboxylic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as an orange solid (94%). mp 111-113 °C; R_f (50% EA/Hex) = 0.65; ^{1}H NMR (500 MHz, CD_3OD) δ 7.76 (d, *J* = 8.1 Hz, 2H), 7.43 (d, *J* = 8.1 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 3.45 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (175 MHz, CD_3OD) δ 168.53, 164.80, 157.32, 143.56, 137.87, 134.70, 132.43, 130.75, 130.38, 130.01, 128.91, 126.27, 38.63, 17.10; LRMS-ESI (*m/z*): $[M + H]^+$ 377.0 and 379.0.

ethyl 4-(bromomethyl)-2-(4-chlorophenyl)thiazole-5-carboxylate **(93)**

In a flame-dried round bottom flask under argon, ethyl 2-(4-chlorophenyl)-4-methylthiazole-5-carboxylate (3.55 mmol, 1 equiv) was dissolved in anhydrous acetonitrile (0.25 M), to which *N*-bromosuccinimide (6.21 mmol, 1.75 equiv) and azobisisobutyronitrile (0.355 mmol, 0.10 equiv) were added. The flask was heated at reflux for 2 hours. Upon complete consumption of the ester starting material, the reaction mixture was concentrated *in vacuo*, diluted with water, and extracted thrice with dichloromethane. The combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. The crude product was purified by flash column chromatography

with hexanes/ethyl acetate to afford the title compound as a white solid (32%). R_f (30% EA/Hex) = 0.81; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (dt, *J* = 8.6, 2.5, 2.0 Hz, 2H), 7.44 (dt, *J* = 8.6, 2.4, 2.0 Hz, 2H), 4.98 (s, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H); LRMS-ESI (*m/z*): $[M + H]^+$ 359.9 and 361.9.

ethyl 2-(4-chlorophenyl)-4-(((4-chlorophenyl)amino)methyl)thiazole-5-carboxylate **(94)**

In a round bottom flask, 4-chloroaniline (0.499 mmol, 1.20 equiv) was dissolved in water (0.25 M) and tetrahydrofuran (0.25 M), to which potassium acetate (0.499 mmol, 1.20 equiv) was added. The reaction mixture was stirred for 5 minutes at room temperature, then ethyl 4-(bromomethyl)-2-(4-chlorophenyl)thiazole-5-carboxylate (0.416 mmol, 1 equiv) was added. The reaction mixture was stirred for 4 hours at room temperature, then 12 hours at 50 °C. Upon complete consumption of the bromo starting material, the reaction mixture was concentrated to half *in vacuo*, diluted with water, and extracted thrice with dichloromethane. The combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a yellow solid (97%). R_f (30% EA/Hex) = 0.77; ^{1}H NMR (500 MHz, $CDCl_3$, rotameric mixture, major form reported) δ 7.90 (dt, *J* = 8.6, 2.5, 1.9 Hz, 2H), 7.44 (dt, *J* = 8.6, 2.4, 1.9 Hz, 2H), 7.12 (dt, *J* = 8.8, 3.4, 2.1 Hz, 2H), 6.72 (dt, *J* = 8.8, 3.3, 2.1 Hz, 2H), 4.95 (s, 1H), 4.74 (s, 2H), 4.39 (q, *J* = 7.2 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H); LRMS-ESI (*m/z*): $[M + H]^+$ 407.0 and 409.0.

2-(4-chlorophenyl)-4-(((4-chlorophenyl)amino)methyl)thiazole-5-carboxylic acid **(95)**

In a round bottom flask, ethyl 2-(4-chlorophenyl)-4-(((4-chlorophenyl)amino)methyl)thiazole-5-carboxylate (0.491 mmol, 1 equiv) was dissolved in water (0.40 M) and tetrahydrofuran (0.13 M), to which lithium hydroxide monohydrate (1.47 mmol, 3 equiv) was added. The reaction mixture was stirred at room temperature for 2 hours, after which the reaction mixture was concentrated to half *in vacuo* and acidified to pH 2-3 with hydrochloric acid (3 M). The resulting precipitate was isolated via vacuum filtration to afford the title compound as a yellow-orange solid (97%). ^{1}H NMR (500 MHz, CD_3OD) δ 7.96 (d, *J* = 8.6 Hz, 2H), 7.47 (d, *J* = 8.6 Hz, 2H), 7.06 (d, *J* = 8.8 Hz, 2H), 6.75 (d, *J* = 8.9 Hz, 2H), 4.72 (s, 2H); LRMS-ESI (*m/z*): $[M + H]^+$ 379.0 and 381.0.

2,5-bis(4-chlorophenyl)-4,5-dihydro-6*H*-pyrrolo[3,4-*d*]thiazol-6-one (96)

In a round bottom flask, 2-(4-chlorophenyl)-4-(((4-chlorophenyl)amino)methyl)thiazole-5-carboxylic acid (0.264 mmol, 1 equiv) was dissolved in anhydrous dichloromethane (0.10 M) and anhydrous tetrahydrofuran (0.10 M). After cooling to 0 °C, EDCI•HCl (0.791 mmol, 3 equiv) was added and the reaction mixture was stirred for 1 hour at 0 °C. The reaction was then allowed to warm to room temperature and stir for 23 hours. The reaction mixture was concentrated *in vacuo*, diluted with water, and extracted thrice with dichloromethane. The combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a yellow solid (33%). mp >260 °C; R_f (20% EA/Hex) = 0.47; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 8.09 (d, *J* = 8.5 Hz, 2H), 7.87 (d, *J* = 8.9 Hz, 2H), 7.65 (d, *J* = 8.5 Hz, 2H), 7.50 (d, *J* = 8.9 Hz, 2H), 5.17 (s, 2H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 175.91, 167.91,

161.31, 138.41, 136.38, 131.14, 129.54, 128.74, 128.41, 127.96, 127.43, 120.88, 49.84; LRMS-ESI (*m/z*): $[M + H]^+$ 361.0 and 363.0.

4-chloro-*N*-(4-chlorophenyl)-*N*-methylpicolinamide **(97a)**

Prepared via General Procedure A from 4-bromopicolinic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as an off-white solid (68%). R_f (30% EA/Hex) = 0.27; ^{1}H NMR (500 MHz, CD_3OD) δ 8.26 (s, 1H), 7.61 (s, 1H), 7.38 (s, 1H), 7.26 (s, 2H), 7.15 (s, 2H), 3.46 (s, 3H); LRMS-ESI (*m/z*): $[M + H]^+$ 281.0. LCMS analysis indicates halogen exchange (Br → Cl) occurred based on observed mass and isotope pattern, similar to a previous report for a similar substrate[50].

5-bromo-*N*-(4-chlorophenyl)-*N*-methylnicotinamide **(97b)**

Prepared via General Procedure A from 5-bromonicotinic acid. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as an off-white solid (70%). R_f (50% EA/Hex) = 0.47; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (d, *J* = 1.9 Hz, 1H), 8.34 – 8.24 (m, 1H), 7.87 (t, *J* = 1.9 Hz, 1H), 7.27 (d, *J* = 8.3 Hz, 2H), 7.01 (d, *J* = 8.3 Hz, 2H), 3.48 (s, 3H); LRMS-ESI (*m/z*): $[M + H]^+$ 325.0 and 327.0.

***N*-(4-chlorophenyl)-*N*-methyl-4-(*p*-tolyl)picolinamide (98)**

In a microwave vial, while stirring, 4-chloro-*N*-(4-chlorophenyl)-*N*-methylpicolinamide (0.154 mmol, 1 equiv) and potassium carbonate (0.461 mmol, 3 equiv) were dissolved in water (0.50 M). Palladium (II) acetate (0.4 mol%), *p*-tolylboronic acid (0.184 mmol, 1.20 equiv), and tetrabutylammonium bromide (0.154 mmol, 1 equiv) were added. Once well mixed, the reaction mixture was heated at 150 °C for 5 minutes in a microwave reactor (Anton Paar Monowave 400). Once cooled to 70 °C, the reaction mixture was filtered through a pad of celite and washed with ethyl acetate and minimal water. The filtrate was extracted thrice with diethyl ether. The combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (49%). mp 123-130 °C; R_f (30% EA/Hex) = 0.13; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (bs, 1H), 7.78 (s, 1H), 7.48 (d, *J* = 6.9 Hz, 2H), 7.38 (s, 1H), 7.31 – 7.25 (m, 2H), 7.24 – 7.14 (m, 2H), 7.12 – 6.95 (m, 2H), 3.52 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 168.91, 154.38, 148.96, 148.91, 143.24, 139.75, 134.47, 132.20, 130.02, 129.27, 127.97, 126.87, 121.89, 121.65, 38.25, 21.34; LRMS-ESI (*m/z*): $[M + H]^+$ 337.1.

***N*,4-bis(4-chlorophenyl)-*N*-methylpicolinamide (99)**

Prepared as described for *N*-(4-chlorophenyl)-*N*-methyl-4-(*p*-tolyl)picolinamide from 4-chloro-*N*-(4-chlorophenyl)-*N*-methylpicolinamide. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (3%). mp 134-136 °C; R_f (70% EA/Hex) = 0.58; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (bs, 1H), 7.77 (s, 1H), 7.51 (d, *J* = 8.2 Hz, 2H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.36 (bs, 1H), 7.25 – 7.14 (m, 2H), 7.12 – 6.93 (m, 2H), 3.52 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 168.66,

154.63, 149.09, 147.91, 143.26, 135.94, 135.88, 132.35, 129.59, 129.35, 128.36, 128.04, 121.95, 121.80, 38.32; LRMS-ESI (*m/z*): $[M + H]^+$ 357.1 and 359.1.

<u>*N*-(4-chlorophenyl)-*N*-methyl-5-(*p*-tolyl)nicotinamide (100)</u>

Prepared as described for *N*-(4-chlorophenyl)-*N*-methyl-4-(*p*-tolyl)picolinamide from 5-bromo-*N*-(4-chlorophenyl)-*N*-methylnicotinamide. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (26%). mp 128-131 °C; R_f (50% EA/Hex) = 0.24; ^{1}H NMR (500 MHz, $CDCl_3$, rotameric mixture, major form reported) δ 8.71 (s, 1H), 8.41 (s, 1H), 7.82 (s, 1H), 7.31 (d, *J* = 7.8 Hz, 2H), 7.29 – 7.23 (m, 4H), 7.04 (d, *J* = 8.2 Hz, 2H), 3.52 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$, rotameric mixture, major form reported) δ 168.17, 149.05, 147.95, 142.96, 138.66, 136.01, 134.49, 133.98, 133.17, 131.32, 130.03, 129.95, 128.48, 127.03, 38.59, 21.30; LRMS-ESI (*m/z*): $[M + H]^+$ 337.1.

<u>*N*,5-bis(4-chlorophenyl)-*N*-methylnicotinamide (101)</u>

Prepared as described for *N*-(4-chlorophenyl)-*N*-methyl-4-(*p*-tolyl)picolinamide from 5-bromo-*N*-(4-chlorophenyl)-*N*-methylnicotinamide. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (70%). mp 110-113 °C; R_f (50% EA/Hex) = 0.19; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.43 (s, 1H), 7.81 (s, 1H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.3 Hz, 2H), 7.30 – 7.25 (m, 2H), 7.04 (d, *J* = 8.3 Hz, 2H), 3.52 (s, 3H); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 168.05, 149.13, 149.09, 144.43, 136.62, 134.99, 134.97, 134.79, 133.17, 132.91, 130.27, 130.10, 130.08, 129.53, 38.15; LRMS-ESI (*m/z*): $[M + H]^+$ 357.1 and 359.1.

<u>5-(4-chlorophenyl)-*N*-methoxy-*N*-methyloxazole-2-carboxamide **(102)**</u>

Prepared via General Procedure A from 5-(4-chlorophenyl)oxazole-2-carboxylic acid and *N,O*-dimethylhydroxylamine hydrochloride. The crude product was purified by flash column chromatography with hexanes/ethyl acetate, followed by recrystallization from dichloromethane/hexanes to afford the title compound as a lustrous yellow solid (56%). R_f (30% EA/Hex) = 0.15; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.2 Hz, 2H), 7.46 (s, 1H), 7.42 (d, *J* = 8.2 Hz, 2H), 3.91 (s, 3H), 3.48 (bs, 3H); LRMS-ESI (*m/z*): $[M + H]^+$ 267.1.

<u>(4-chlorophenyl)(5-(4-chlorophenyl)oxazol-2-yl)methanone (103)</u>

In a flame-dried round bottom flask under argon, 5-(4-chlorophenyl)-*N*-methoxy-*N*-methyloxazole-2-carboxamide (0.281 mmol, 1 equiv) was dissolved in anhydrous tetrahydrofuran (0.20 M). The flask was cooled to 0 °C and (4-chlorophenyl)magnesium bromide (1 M in anhydrous tetrahydrofuran) (0.844 mmol, 3 equiv) was added. The reaction mixture was warmed to room temperature and stirred for 3 hours. Upon complete consumption of the Weinreb amide, the reaction mixture was quenched via slow addition of water at 0 °C. This solution was transferred to a separatory funnel and the aqueous layer was extracted thrice with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated *in vacuo.*

The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a lustrous light yellow solid (63%). mp 186-189 °C; R_f (5% EA/Hex) = 0.23; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 8.40 (d, *J* = 8.2 Hz, 2H), 8.18 (s, 1H), 7.92 (d, *J* = 8.2 Hz, 2H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.64 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 176.79, 156.50, 152.42, 139.00, 134.66, 133.62, 132.31, 129.54, 128.75, 126.91, 125.61, 125.18; LRMS-ESI (*m/z*): $[M + H]^+$ 318.0 and 320.0.

N,5-bis(4-chlorophenyl)oxazole-2-carboxamide **(104)**

Prepared via General Procedure A from 5-(4-chlorophenyl)oxazole-2-carboxylic acid and 4-chloroaniline. The crude product was purified by flash column chromatography with hexanes/ethyl acetate, followed by recrystallization from dichloromethane to afford the title compound as a white solid (27%). R_f (30% EA/Hex) = 0.53; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.82 (s, 1H), 7.71 (d, *J* = 8.2 Hz, 2H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.47 – 7.41 (m, 3H), 7.36 (d, *J* = 8.4 Hz, 2H); LRMS-ESI (*m/z*): $[M + H]^+$ 333.0 and 335.0.

***N*,5-bis(4-chlorophenyl)-*N*-(methyl-d_3)oxazole-2-carboxamide (105)**

Prepared as described for 4-chloro-*N*-methyl-*N*-(1-(*p*-tolyl)-1*H*-1,2,4-triazol-3-yl)benzamide from *N*,5-bis(4-chlorophenyl)oxazole-2-carboxamide with iodomethane-d_3 in place of iodomethane. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a light yellow solid (64%). mp 140-142 °C; R_f (30% EA/Hex) = 0.24; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 7.75 (s, 1H), 7.67 – 7.56 (m, 2H), 7.54 (d, *J* = 8.2 Hz, 2H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 155.85, 153.75, 150.21, 142.16, 133.88, 131.83, 129.29, 129.17, 128.49, 126.11, 125.35, 123.88; LRMS-ESI (*m/z*): $[M + H]^+$ 350.1 and 352.1.

4-(4-chlorophenyl)picolinic acid **(106)**

In a microwave vial, while stirring, 4-bromopicolinic acid (4.95 mmol, 1 equiv) and potassium carbonate (14.9 mmol, 3 equiv) were dissolved in water (0.50 M). Palladium (II) acetate (1 mol%) and (4-chlorophenyl)boronic acid (9.90 mmol, 2 equiv) were added. Once well mixed, the reaction mixture was heated at 175 °C for 10 minutes in a microwave reactor (Anton Paar Monowave 400). Once cooled to 70 °C, the reaction mixture was filtered through a pad of celite and washed with ethyl acetate and minimal water. The filtrate was transferred to a separatory funnel, basified to pH 12-13 with sodium hydroxide (3 M), and extracted thrice with diethyl ether. The aqueous layer was then acidified to pH 2-3 with hydrochloric acid (3 M). The resulting precipitate was isolated via vacuum filtration to afford the title compound as a light yellow solid (30%). ^{1}H NMR (500 MHz, CD_3OD) δ 8.71 (d, *J* = 5.2 Hz, 1H), 8.43 (s, 1H), 7.94 (d, *J* = 5.2 Hz, 1H), 7.81 (d, *J* = 8.2 Hz, 2H), 7.55 (d, *J* = 8.2 Hz, 2H); LRMS-ESI (*m/z*): $[M + H]^+$ 234.0.

4-(4-chlorophenyl)-*N*-methoxy-*N*-methylpicolinamide **(107)**

Prepared via General Procedure A from 4-(4-chlorophenyl)picolinic acid and *N,O*-dimethylhydroxylamine hydrochloride. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to

afford the title compound as a white solid (62%). R_f (70% EA/Hex) = 0.23; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 (d, *J* = 5.1 Hz, 1H), 7.86 (s, 1H), 7.61 (dt, *J* = 8.5, 2.6, 2.1 Hz, 2H), 7.54 (dd, *J* = 5.1, 1.9 Hz, 1H), 7.47 (dt, *J* = 8.5, 2.6, 2.1 Hz, 2H), 3.80 (s, 3H), 3.44 (s, 3H); LRMS-ESI (*m/z*): $[M + H]^+$ 277.1.

(4-chlorophenyl)(4-(4-chlorophenyl)pyridin-2-yl)methanone (108)

Prepared as described for (4-chlorophenyl)(5-(4-chlorophenyl)oxazol-2-yl)methanone from 4-(4-chlorophenyl)-*N*-methoxy-*N*-methylpicolinamide. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a fluffy white solid (45%). R_f (20% EA/Hex) = 0.47; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.76 (d, *J* = 5.1 Hz, 1H), 8.29 – 8.24 (m, 1H), 8.10 (d, *J* = 8.5 Hz, 2H), 7.72 – 7.62 (m, 3H), 7.55 – 7.44 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.54, 155.51, 149.30, 148.68, 139.69, 136.11, 135.88, 134.69, 132.67, 129.71, 128.66, 128.50, 123.99, 122.45; LRMS-ESI (*m/z*): $[M + H]^+$ 328.0 and 330.0.

N,4-bis(4-chlorophenyl)picolinamide **(109)**

Prepared via General Procedure A from 4-(4-chlorophenyl)picolinic acid and 4-chloroaniline. The crude product was purified by flash column chromatography with hexanes/ethyl acetate, followed by recrystallization from dichloromethane to afford the title compound as a white solid (58%). R_f (30% EA/Hex) = 0.47; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.07 (s, 1H), 8.65 (d, *J* = 5.0 Hz, 1H), 8.49 (d, *J* = 1.3 Hz, 1H), 7.76 (d, *J* = 8.8 Hz, 2H), 7.70 – 7.61 (m, 3H), 7.50 (d, *J* = 8.6 Hz, 2H), 7.36 (d, *J* = 8.8 Hz, 2H); LRMS-ESI (*m/z*): $[M + H]^+$ 343.1 and 345.0.

***N*,4-bis(4-chlorophenyl)-*N*-(methyl-d_3)picolinamide (110)**

Prepared as described for 4-chloro-*N*-methyl-*N*-(1-(*p*-tolyl)-1*H*-1,2,4-triazol-3-yl)benzamide from *N*,4-bis(4-chlorophenyl)picolinamide with iodomethane-d_3 in place of iodomethane. The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (22%). mp 121-123 °C; R_f (40% EA/Hex) = 0.18; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.77 (s, 1H), 7.51 (d, *J* = 8.2 Hz, 2H), 7.45 (d, *J* = 8.5 Hz, 2H), 7.35 (s, 1H), 7.24 – 7.12 (m, 2H), 7.12 – 6.82 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.66, 154.64, 149.07, 147.88, 143.17, 135.93, 135.86, 132.30, 129.57, 129.32, 128.35, 127.99, 121.94, 121.78; LRMS-ESI (*m/z*): $[M + H]^+$ 360.1 and 362.1.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge.

Experimental protocols for *in vitro* DMPK assays, intracellular pH assay, and predicted human PK parameters and dose prediction; HPLC traces; synthetic characterization of additional compounds (yield, mp, R_f, ^1H, ^{13}C, LRMS); virtual high-throughput screen and down-selection details; SAR-by-catalog; MetaSite analysis of representative analogs; intracellular pH assay data; PK profile of **72**; outlier analysis of 110 half-life; μPRR results for three independent experiments; ^1H and ^{13}C NMR catalog (PDF)

Molecular SMILES strings of the compounds (CSV)

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M.C. performed virtual high-throughput screen; A.W. performed cheminformatics down-selection; S.M., A.A.R., C.A.C., W.E.L., G.N., A.A.M., and S.L.M. performed biological evaluation of all compounds; A.W. and R.M. designed analogs; A.W. designed syntheses; A.W., R.T., and M. P. synthesized and characterized compounds; S.M. designed and executed the μPRR assay; A.A.R. processed data for the μPRR assay; A.A.M. and S.M. designed and executed the intracellular pH assay; S.M. processed data for the intracellular pH assay; ADME and PK experiments were selected by R.M. and F.L. and executed by TCGLS; F.L. performed human PK and dose predictions; A.W. wrote the manuscript with contributions from R.T., R.M., A.A.R., S.M., and D.E.K. All authors have given approval of the final manuscript.

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Notes

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ABBREVIATIONS

ACT, artemisinin combination therapy; BCECF-AM, 2',7'-bis-(Carboxyethyl)-5(6')-carboxyfluorescein Acetoxymethyl Ester; CC_{50}, half-maximum cytotoxicity concentration; $CLint_{app}$, apparent intrinsic clearance; C_{max}, maximum concentration; C_{ss}, concentration at steady state; E_{max}, maximum killing rate; HHep, human

hepatocytes; HLM, human liver microsomes; IV, intravenous; LRMS, low-resolution mass spectrometry; MAT, mean absorption time; MRT, mean residence time; MW, microwave; PCT, parasite clearance time; *Pf*ABS, *Plasmodium falciparum* asexual blood stages; *Pf*FNT, *Plasmodium falciparum* formate nitrate transporter; PRR, parasite reduction ratio; RCF, relative centrifugal force; RH, rat hepatocytes; TCP, target candidate profiles; VD_{ss}, volume of distribution at steady state; vHTS, virtual high-throughput screen.

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