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Research paper

Discovery and optimization of a novel carboxamide scaffold with selective antimalarial activity

Alicia Wagner [a], Roger Trombley [a], Maris Podgurski [a], Anthony A. Ruberto [b], Meng Cui [c], Caitlin A. Cooper [b], William E. Long [b], Gia-Bao Nguyen [b], Adriana A. Marin [b], Sarah Lee Mai [b], Franco Lombardo [d], Steven P. Maher [b], Dennis E. Kyle [b], Roman Manetsch [a,c,e,*]

[a] Department of Chemistry and Chemical Biology, Northeastern University, Boston, 02115, Massachusetts, USA
[b] Center for Tropical and Emerging Global Diseases, University of Georgia, 500 DW Brooks Dr Ste 370, Athens, 30602, Georgia, USA
[c] Department of Pharmaceutical Sciences, Northeastern University, Boston, 02115, Massachusetts, USA
[d] CmaxDMPK LLC, P.O. Box 505549, Chelsea, 02150, Massachusetts, USA
[e] Center for Drug Discovery and Barnett Institute of Chemical and Biological Analysis, Northeastern University, Boston, 02115, Massachusetts, USA

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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, we have identified a 1,2,4-triazole-containing carboxamide scaffold that, through scaffold hopping efforts, resulted in a nanomolar potent deuterated picolinamide (**110**). The lead compound of this class (**110**) 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. Compound **110** also displayed activity against various *P. falciparum* isolates with different genetic backgrounds and a slow-to-moderate rate of killing (average parasite reduction ratio 2.4), making the series appealing for further development.

1. 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-aminoquinoline 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]. It is thus paramount to identify novel compounds that can be formulated into future combination therapies.

* Corresponding author. Department of Chemistry and Chemical Biology, Department of Pharmaceutical Sciences, Center for Drug Discovery, and Barnett Institute of Chemical and Biological Analysis, Northeastern University, Boston, MA, 02115, USA.
E-mail address: r.manetsch@northeastern.edu (R. Manetsch).

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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 micromolar 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 hit led to the identification of a lead compound that displays moderate oral bioavailability (%F 16.2), a half-life of 1.54 h, and approximately 3 h of coverage above the EC_{50} as assessed by a high dose oral administration pharmacokinetic study in mice. This lead also displays activity against *P. falciparum* isolates with different genetic backgrounds, and a slow-to-moderate rate of killing. Taken together, 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.

2. Results and discussion

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

This work began with a large-scale virtual high-throughput screen against *Plasmodium falciparum* formate nitrate transporter [11–14] (*Pf*FNT, PF3D7_0316600, PDB: 6VQR) [15] using Glide program version 2019-3 (Schrödinger, Inc.) [16] (Fig. S1). Ultimately, 39 structurally diverse *in silico* hits were purchased from Specs and tested in an *in vitro* 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, Fig. S2, Fig. S3). 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} < 10.0 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.

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

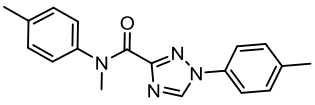
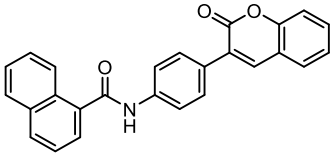
The triazole synthesis (Scheme 1) began with the *in situ* formation of a diazonium salt, followed by cyclization to form the 1,2,4-triazole core [17]. Hydrolysis with lithium hydroxide monohydrate afforded the carboxylic acid. The subsequent Schotten-Baumann amidation then yielded the final analogs (**3**–**44**).

2.3. Initial structure-activity relationship studies of triazoles

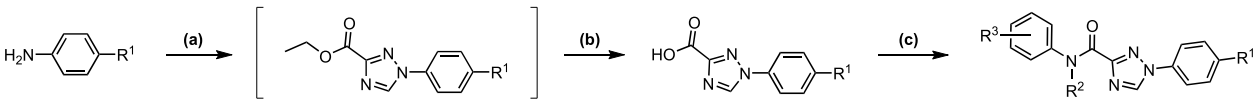
In the SAR-by-catalog of additional triazole cluster members, two matched pairs displayed an interesting trend: a tertiary, *N*-methyl amide displayed potency, but its secondary, H-substituted amide was inactive (EC_{50} > 10.0 μM) (Table S1). This prompted further investigation of the amide substitution 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 (EC_{50} > 10.0 μM) or less active by comparison, much like a magic methyl [18]. Many of the methylated analogs display EC_{50}'s > 1 μM, 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.

Next, the amide-adjacent ring (Table 3, R^1) was probed via Topliss scheme [19] and the Craig plot [20,21]. It was known from the hit resynthesis (Table S1) that 4-chloro (**20**) displayed greater potency than an unsubstituted ring (**21**), thus leading towards a 3,4-dichloro analog with a decrease in potency (**12**, EC_{50} 0.927 μM). The subsequent analogs, 4-trifluoromethyl (**16**, EC_{50} 3.79 μM) and 4-nitro (**8**, EC_{50} 2.28 μM), also did not yield a potency improvement. 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. Given the lack of success in applying Topliss scheme here, we attempted to utilize the Craig plot instead, sampling 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. Broadly, hydrophilic substituents were consistently less active, but weakly lipophilic substituents (e.g., Cl and CH_3) displayed moderate potencies. A sampling of aliphatic and heteroaromatic rings were also trialed, but few were active, and none more so than **20**

Table 1
Initial hits from virtual high-throughput screen.

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

[a] EC_{50} and CC_{50} data represents geometric means for at least two independent experiments; pEC_{50} and pCC_{50} data represents the respective means and standard deviations for these experiments. Where no standard deviation is reported, the standard deviation was zero.
[b] Puromycin (W2 – pEC_{50} ± SD = 7.20 ± 0.15; HepG2 – pCC_{50} ± SD = 6.19 ± 0.07) is the internal control for the *in vitro* antimalarial activity and cytotoxicity assays.



1a	R^1=Cl	**2a**	R^1=Cl	37%, 2 steps	**3-44 (below)**
1b	R^1=CH_3	**2b**	R^1=CH_3	19%, 2 steps	
1c	R^1=CH_2CH_3	**2c**	R^1=CH_2CH_3	24%, 2 steps	
1d	R^1=$CH(CH_3)_2$	**2d**	R^1=$CH(CH_3)_2$	15%, 2 steps	
1e	R^1=OCH_3	**2e**	R^1=OCH_3	14%, 2 steps	

3	R^1=Cl, R^2=H, R^3=4-CH_2CH_3	43%	**10**	R^1=Cl, R^2=CH_3, R^3=4-$COCH_3$	85%	**17**	R^1=CH_3, R^2=H, R^3=4-Cl	10%
4	R^1=CH_3, R^2=CH_3, R^3=4-CH_2CH_3	87%	**11**	R^1=Cl, R^2=H, R^3=3,4-di-Cl	37%	**18**	R^1=CH_3, R^2=CH_3, R^3=4-Cl	11%
5	R^1=Cl, R^2=H, R^3=3,4-CH_3	57%	**12**	R^1=Cl, R^2=CH_3, R^3=3,4-di-Cl	74%	**19**	R^1=Cl, R^2=H, R^3=4-Cl	65%
6	R^1=Cl, R^2=CH_3, R^3=3,4-di-CH_3	85%	**13**	R^1=Cl, R^2=H, R^3=4-F	85%	**20**	R^1=Cl, R^2=CH_3, R^3=4-Cl	96%
7	R^1=Cl, R^2=H, R^3=4-NO_2	43%	**14**	R^1=Cl, R^2=CH_3, R^3=4-F	85%	**21**	R^1=Cl, R^2=CH_3, R^3=H	57%
8	R^1=Cl, R^2=CH_3, R^3=4-NO_2	73%	**15**	R^1=Cl, R^2=H, R^3=4-CF_3	99%	**22**	R^1=Cl, R^2=CH_3, R^3=4-CH_3	53%
9	R^1=Cl, R^2=H, R^3=4-$COCH_3$	72%	**16**	R^1=Cl, R^2=CH_3, R^3=4-CF_3	82%	**23**	R^1=Cl, R^2=CH_3, R^3=4-$C(CH_3)_3$	91%
24	R^1=Cl, R^2=CH_3, R^3=4-OCH_3	88%	**31**	R^1=CH_2CH_3, R^2=CH_3, R^3=4-CH_3	99%	**38**	R^1=$CH(CH_3)_2$, R^2=CH_3, R^3=3-CH_3	87%
25	R^1=Cl, R^2=CH_3, R^3=3-CH_3	45%	**32**	R^1=CH_2CH_3, R^2=CH_3, R^3=4-OCH_3	28%	**39**	R^1=$CH(CH_3)_2$, R^2=CH_3, R^3=3,4-di-CH_3	67%
26	R^1=CH_3, R^2=CH_3, R^3=4-CH_3	47%	**33**	R^1=CH_2CH_3, R^2=CH_3, R^3=3-CH_3	99%	**40**	R^1=OCH_3, R^2=CH_3, R^3=4-Cl	31%
27	R^1=CH_3, R^2=CH_3, R^3=4-OCH_3	25%	**34**	R^1=CH_2CH_3, R^2=CH_3, R^3=3,4-di-CH_3	50%	**41**	R^1=OCH_3, R^2=CH_3, R^3=4-CH_3	63%
28	R^1=CH_3, R^2=CH_3, R^3=3-CH_3	78%	**35**	R^1=$CH(CH_3)_2$, R^2=CH_3, R^3=4-Cl	92%	**42**	R^1=OCH_3, R^2=CH_3, R^3=4-OCH_3	71%
29	R^1=CH_3, R^2=CH_3, R^3=3,4-di-CH_3	11%	**36**	R^1=$CH(CH_3)_2$, R^2=CH_3, R^3=4-CH_3	89%	**43**	R^1=OCH_3, R^2=CH_3, R^3=3-CH_3	89%
30	R^1=CH_2CH_3, R^2=CH_3, R^3=4-Cl	62%	**37**	R^1=$CH(CH_3)_2$, R^2=CH_3, R^3=4-OCH_3	84%	**44**	R^1=OCH_3, R^2=CH_3, R^3=3,4-di-CH_3	47%

Scheme 1. Synthesis of Compounds 3–44[a]

[a] **Reagents and conditions: (a)** 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; **(b)** LiOH•H_2O, THF/H_2O, 23 °C, 16 h; and **(c)** $(COCl)_2$, anhydrous THF/DCM/DMF, 0 °C, then 23 °C, 30 min *then* R^3R^2NH, NEt_3, anhydrous THF/DCM, 23 °C, 16 h.

(Table S4). This supports the finding from Table 1 that modifications about the amide-adjacent ring have only modest effects on potency.

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-di-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, cLogP, **30**–**39**).

2.4. Effect of compound **20** on the parasite's cytosolic pH

Given the potency enhancements observed in the series through peripheral modifications, we sought to explore the mechanism of action of this compound class. As this series originated from 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 [22]. To prepare the parasites, we performed saponin lysis to remove the host red blood cell membrane, leaving the parasites intact. These were then loaded with the pH-sensitive dye BCECF-AM before being treated with test compounds. When testing our most potent triazole (**20**, bis-chloro substituted), we did not observe a decrease in pH following compound treatment, suggesting that this series may operate through a mechanism distinct from *Pf*FNT inhibition (Fig. S4).

Despite this result, the novelty of this compound class—along with its moderate potency (**20**, EC_{50} 519 nM) and excellent selectivity—warranted further investigation. This prompted a shift in the structure-activity relationship study towards scaffold hopping in an attempt to further improve activity.

2.5. Design and synthesis of scaffold hopping study

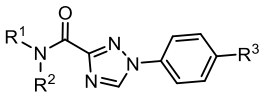
Alternative cores were selected and prioritized based upon three criteria. First, we selected solely heteroaromatic rings, as we hypothesized this would maintain any favorable interactions afforded by the triazole core. We also wished to maintain the relative size (five-membered) and bond angle of the 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.

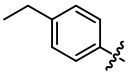
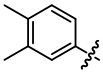
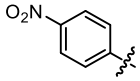
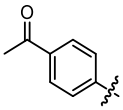
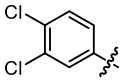
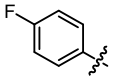
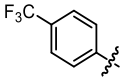
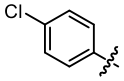
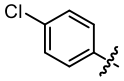
The reversed amide (i.e., amine nearer to the molecule core) (Scheme 2, **47**–**54**) was obtained by first performing a copper-catalyzed coupling in anhydrous pyridine and dichloromethane [23] to install the first periphery ring. The amine was afforded through a zinc-mediated nitro reduction [24], enabling *N*-acylation to yield the amide for methylation with iodomethane in the presence of potassium carbonate [23]. The 1,2,3-triazole scaffold (Scheme 2, **56**–**59**) was formed via a Huisgen cycloaddition with copper sulfate and sodium ascorbate. A final Schotten-Baumann amidation then afforded the final 1,2,3-triazoles.

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 [25]. 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 [26]. The trifluoromethyl imidazole was hydrolyzed to the carboxylic acid in refluxing basified water [26], allowing for the final amidation.

Synthesis of the 5-oxazole-2-carboxamides (Scheme 4, **71** and **72**) began with an alpha-bromo-acetophenone, where a Delepine reaction

Table 2
Investigation of amide substitution (H versus CH_3) and initial probing of phenyl substituents.



ID	R^1	R^2	R^3	EC_{50} (W2) [μM]	$pEC_{50} \pm SD$ (W2)	CC_{50} (HepG2) [μM]	$pCC_{50} \pm SD$ (HepG2)
3		H	Cl	>6.93	<5.16 ± 0.28	>10.0	<5.00
4		CH_3	Cl	>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	Cl	2.36	5.63 ± 0.14	>10.0	<5.00
7		H	Cl	>10.0	<5.00	>10.0	<5.00
8		CH_3	Cl	2.28	5.64 ± 0.10	>10.0	<5.00
9		H	Cl	>10.0	<5.00	>10.0	<5.00
10		CH_3	Cl	2.42	5.62 ± 0.08	>10.0	<5.00
11		H	Cl	>10.0	<5.00	>10.0	<5.00
12		CH_3	Cl	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	Cl	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	Cl	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	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	Cl	0.519	6.28 ± 0.23	>10.0	<5.00

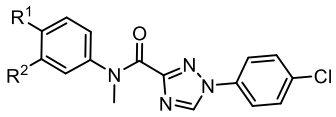
[a] EC_{50} and CC_{50} data represents geometric means for at least two independent experiments; pEC_{50} and pCC_{50} data represents the respective means and standard deviations for these experiments. Where no standard deviation is reported, the standard deviation was zero.
[b] Puromycin (W2 – $pEC_{50} \pm SD = 7.20 \pm 0.15$; HepG2 – $pCC_{50} \pm SD = 6.19 \pm 0.07$) is the internal control for the *in vitro* antimalarial activity and cytotoxicity assays.

delivers the aminoacetophenone; these amines were utilized without further purification. This enables *N*-acylation with ethyl 2-chloro-2-oxoacetate [27] and the resulting chain is cyclized in refluxing phosphoryl chloride to afford the molecule core [28]. Hydrolysis with lithium hydroxide 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 [29]. 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 h at 80 °C, then 110 °C for 14 h [30]. The carboxylic acid is then afforded via hydrolysis with lithium hydroxide and the final product is achieved through a final amidation.

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 [27]. 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 [31]. Hydrolysis with lithium hydroxide monohydrate affords the carboxylic acid for an amidation.

The thiazole core of the 4-methylthiazole-5-carboxamides (Scheme

Table 3
Investigation of amide-adjacent ring via the Topliss scheme.



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

[a] EC_{50} and CC_{50} data represents geometric means for at least two independent experiments; pEC_{50} and pCC_{50} data represents the respective means and standard deviations for these experiments. Where no standard deviation is reported, the standard deviation was zero.
[b] Puromycin (W2 – pEC_{50} ± SD = 7.20 ± 0.15; HepG2 – pCC_{50} ± SD = 6.19 ± 0.07) is the internal control for the *in vitro* antimalarial activity and cytotoxicity assays.

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 [32]. 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 [33]. 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.

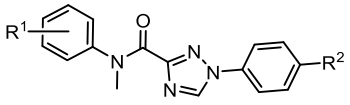
Both the 4-picolinamide (Scheme 7, **98** and **99**) and 5-nicotinamide (Scheme 7, **100** and **101**) syntheses begin with a Schotten-Baumann amidation and are followed with a microwave-mediated Suzuki coupling to afford the final products.

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 [23], facilitated by potassium carbonate.

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

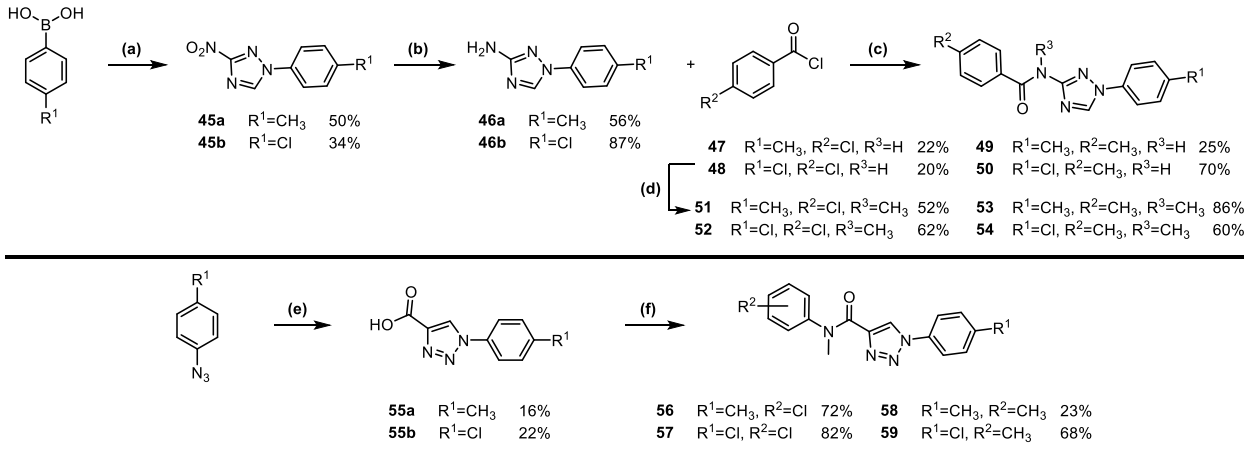
In the scaffold hopping study (Table 5), reversal of the amide order (e.g., amine closer to the molecule periphery) resulted in a global loss of potency (**47**–**54**). In contrast to the findings displayed in Table 2, though, the amide substitution is not significant; the H-substituted

Table 4
Investigation of *para*-substitutions at the triazole-adjacent ring.



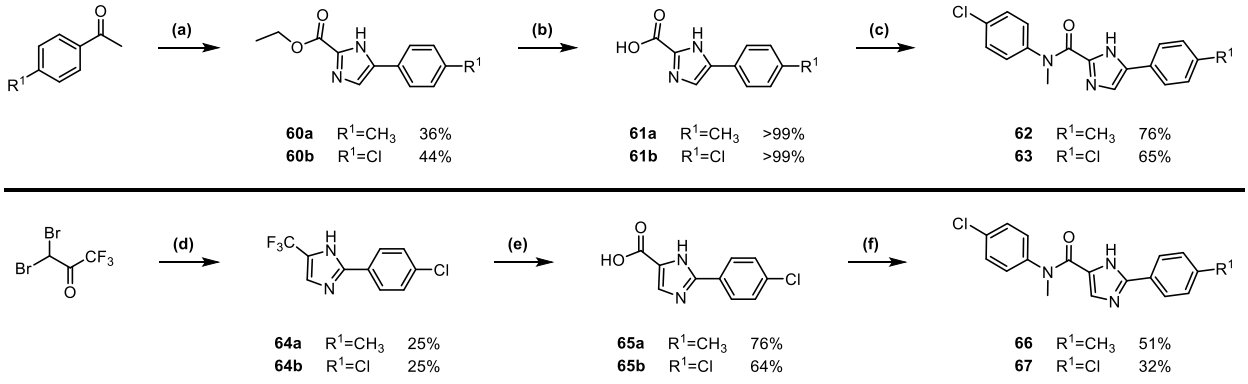
ID	R^1	R^2	EC_{50} (W2) [μM]	pEC_{50} ± SD (W2)	CC_{50} (HepG2) [μM]	pCC_{50} ± SD (HepG2)	cLogP	LLE[a]
20	4-Cl	Cl	0.519	6.28 ± 0.23	>10.0	<5.00	2.93	3.36
22	4-CH_3	Cl	0.556	6.25 ± 0.26	>10.0	<5.00	2.66	3.59
24	4-OCH_3	Cl	1.91	5.72 ± 0.29	>10.0	<5.00	2.32	3.40
25	3-CH_3	Cl	>4.03	<5.39 ± 0.14	>10.0	<5.00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

[a] EC_{50} and CC_{50} data represents geometric means for at least two independent experiments; pEC_{50} and pCC_{50} data represents the respective means and standard deviations for these experiments. Where no standard deviation is reported, the standard deviation was zero.
[b] Puromycin (W2 – pEC_{50} ± SD = 7.20 ± 0.15; HepG2 – pCC_{50} ± SD = 6.19 ± 0.07) is the internal control for the *in vitro* antimalarial activity and cytotoxicity assays.
[a] LLE = lipophilic ligand efficiency; LLE = pEC_{50}-cLogP (calculated via StarDrop, version 7.4.0.35635).



Scheme 2. Synthesis of Compounds 47–54 and 56–59[a]

[a] **Reagents and conditions: (a)** 3-nitro-1*H*-1,2,4-triazole, $Cu(OAc)_2$, anhydrous py/DCM, 30 °C, 12 h; **(b)** Zn dust, sat. aq. NH_4Cl, acetone, 0 °C, then 23 °C, 2 h; **(c)** anhydrous py/DCM, 0 °C, then 23 °C, 2 h; **(d)** CH_3I, K_2CO_3, anhydrous DMF, 0–23 °C, 16 h; **(e)** propiolic acid, $CuSO_4$, NaAsc, *t*-BuOH/H_2O, 23 °C, 16 h; and **(f)** $(COCl)_2$, anhydrous THF/DCM/DMF, 0 °C, then 23 °C, 30 min *then* R^3R^2NH, NEt_3, anhydrous THF/DCM, 23 °C, 16 h.



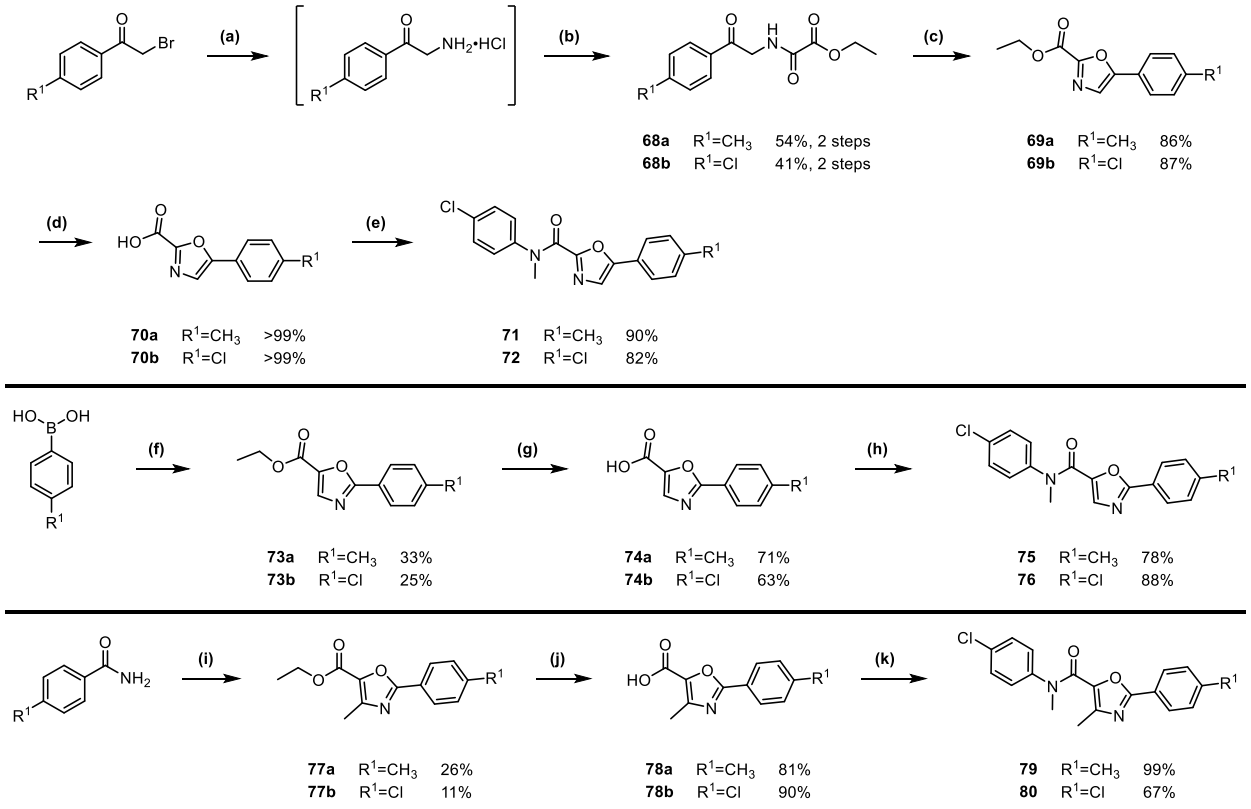
Scheme 3. Synthesis of Compounds 62, 63, 66, and 67[a]

[a] **Reagents and conditions: (a)** 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; **(b)** NaOH, H_2O/EtOH, reflux, 24 h; **(c)** $(COCl)_2$, anhydrous THF/DCM/DMF, 0 °C, then 23 °C, 30 min *then* R^3R^2NH, NEt_3, anhydrous THF/DCM, 23 °C, 16 h; **(d)** $NaOAc•3H_2O$, H_2O, 100 °C, 30 min *then* 4-R^1-benzaldehyde, NH_4OH, MeOH, 23 °C, 4 h; **(e)** NaOH, H_2O, 100 °C, 16 h; and **(f)** $(COCl)_2$, anhydrous THF/DCM/DMF, 0 °C, then 23 °C, 30 min *then* R^3R^2NH, NEt_3, anhydrous THF/DCM, 23 °C, 16 h.

(**47**–**50**) and the *N*-methyl (**51**–**54**) amides were all weakly active. Modifying the core to a 1,2,3-triazole (**56**–**59**) depletes activity, indicating that the 2-nitrogen of the 1,2,4-triazole is critical, perhaps due to a hydrogen bonding interaction. Both imidazole cores display poor potency, possibly due to the addition of a hydrogen bond donor (**62**, **63**, **66**, **67**). While the position of the nitrogen had a drastic effect on potency for the oxazoles (**71** versus **75**; **72** versus **76**), the analogous thiazoles displayed consistently weaker potencies (**83**, **84**, **87**, **88**). This may be attributed to modified bond angles and conformational changes resulting from sulfur's larger atomic radius. The addition of a methyl group to these cores provides weak potency improvements (**79**, **80**, **91**) to otherwise inactive molecules (**75**, **76**, **87**), perhaps due to conformational restrictions. Similarly, amide rigidification (**96**) also results in a loss of potency. An increase in ring size from the triazole, however, improves potency (**98**–**101**). In total, three scaffolds (5-oxazole-2-carboxamides **71** and **72**, nicotinamides **100** and **101**, picolinamides **98** and **99**) had greater potency than the 1,2,4-triazoles.

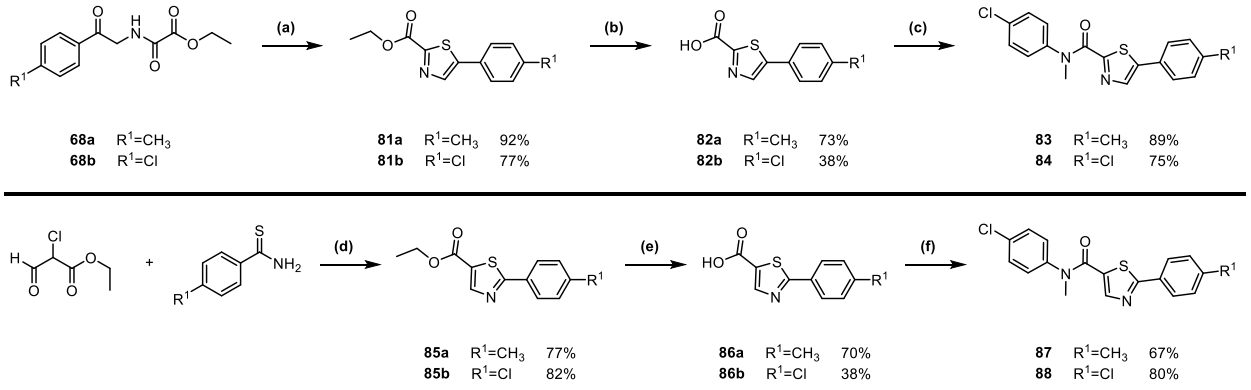
To identify the scaffold(s) with the best balance of activity profiles and physicochemical properties, select oxazoles and pyridines were profiled alongside select 1,2,4-triazoles for aqueous solubility, measured LogD, and metabolic stability ($CLint_{app}$ in both human liver microsomes [HLM] and rat 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 (nicotinamide **100** and triazole **26**), they suffered from extremely high microsomal clearances. The evaluated 5-nicotinamide (**100**), selected for its potency, had a very short half-life (under 10 min), 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.

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, Fig. S5), 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} > 10.0 μM). Inspired by the recent success of deucravacitinib [34], 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)[35], it should be



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

[a] **Reagents and conditions: (a)** 1,3,5,7-tetraazaadamantane, anhydrous DCM, 50 °C, 2 h *then* EtOH, conc. HCl, reflux, 2 h; **(b)** ethyl 2-chloro-2-oxoacetate, NEt_3, anhydrous DCM, 0 °C–23 °C, 16 h; **(c)** $POCl_3$, reflux, 5 h; **(d)** LiOH, THF/H_2O, 23 °C, 16 h; **(e)** $(COCl)_2$, anhydrous THF/DCM/DMF, 0 °C, then 23 °C, 30 min *then* R^3R^2NH, NEt_3, anhydrous THF/DCM, 23 °C, 16 h; **(f)** ethyl 2-chlorooxazole-5-carboxylate, $Pd(PPh_3)_4$, aq. Na_2CO_3, 1,4-dioxane, MW 150 °C, 5 min; **(g)** LiOH•H_2O, THF/H_2O, 23 °C, 16 h; **(h)** $(COCl)_2$, anhydrous THF/DCM/DMF, 0 °C, then 23 °C, 30 min *then* R^3R^2NH, NEt_3, anhydrous THF/DCM, 23 °C, 16 h; **(i)** ethyl 2-chloroacetoacetate, EtOH, 80 °C, 2 h, then 110 °C, 14 h; **(j)** LiOH, THF/MeOH/H_2O, 23 °C, 12 h; and **(k)** $(COCl)_2$, anhydrous THF/DCM/DMF, 0 °C, then 23 °C, 30 min *then* R^3R^2NH, NEt_3, anhydrous THF/DCM, 23 °C, 16 h.



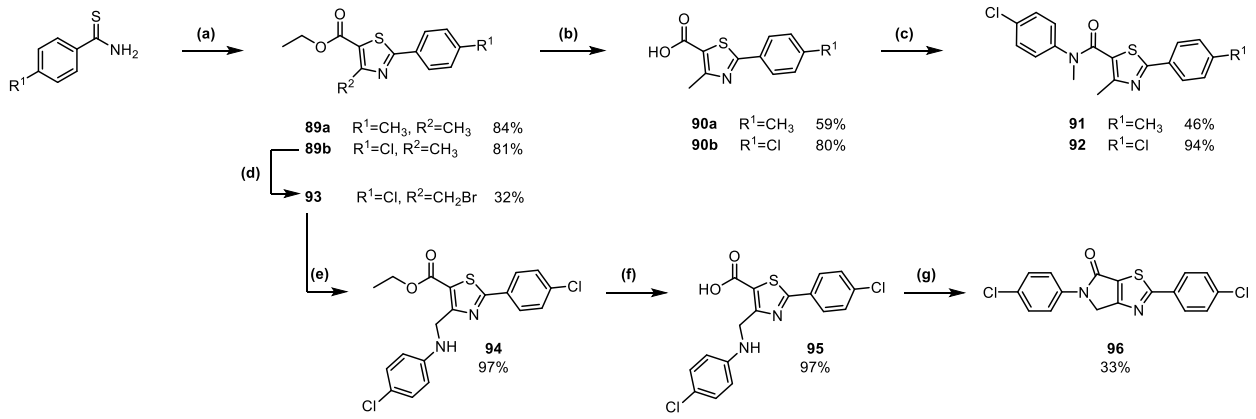
Scheme 5. Synthesis of Compounds 83, 84, 87, and 88[a]

[a] **Reagents and conditions: (a)** P_2S_5, anhydrous DCM, reflux, 5 h; **(b)** LiOH, THF/H_2O, 23 °C, 16 h; **(c)** $(COCl)_2$, anhydrous THF/DCM/DMF, 0 °C, then 23 °C, 30 min *then* R^3R^2NH, NEt_3, anhydrous THF/DCM, 23 °C, 16 h; **(d)** $MgSO_4$, anhydrous $PhCH_3$, 100 °C, 2 h; **(e)** LiOH•H_2O, THF/H_2O, 23 °C, 16 h; and **(f)** $(COCl)_2$, anhydrous THF/DCM/DMF, 0 °C, then 23 °C, 30 min *then* R^3R^2NH, NEt_3, anhydrous THF/DCM, 23 °C, 16 h.

more difficult for a deuterium atom to be abstracted to initiate amide dealkylation. As shown in Table 8, with a small loss of potency, the deuteromethyl pyridine 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, deuteromethyl pyridine **110** and oxazole **72** were nominated as front-runners for further evaluation.

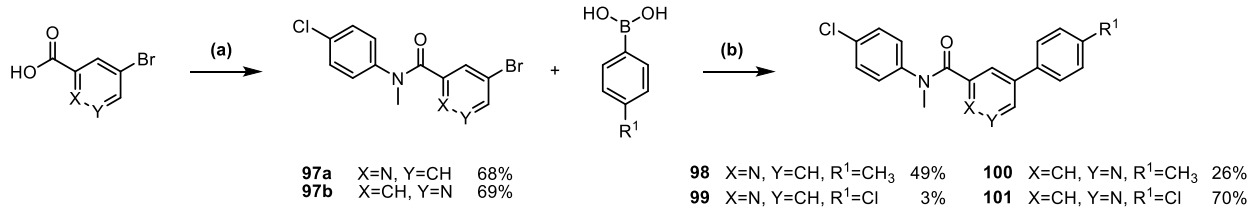
2.7. Pharmacokinetic analysis of front-runners *72* and *110*

The bis-chloro oxazole (**72**) and deuteromethyl pyridine (**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 (Fig. S6). The



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

[a] **Reagents and conditions: (a)** ethyl 2-chloroacetoacetate, EtOH, reflux 4 h, then 23 °C, 16 h; **(b)** LiOH, THF/MeOH/H_2O, 23 °C, 12 h; **(c)** $(COCl)_2$, anhydrous THF/DCM/DMF, 0 °C, then 23 °C, 30 min *then* R^3R^2NH, NEt_3, anhydrous THF/DCM, 23 °C, 16 h; **(d)** NBS, AIBN, anhydrous CH_3CN, reflux, 2 h; **(e)** 4-chloroaniline, CH_3COOK, THF/H_2O, 23 °C, 4 h, then 50 °C, 12 h; **(f)** LiOH•H_2O, THF/H_2O, 23 °C, 2 h; and **(g)** EDCI•HCl, anhydrous DCM/THF, 0 °C, 1 h, then 23 °C, 23 h.



Scheme 7. Synthesis of Compounds 98–101[a]

[a] **Reagents and conditions: (a)** $(COCl)_2$, 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 **(b)** Pd$(OAc)_2$, K_2CO_3, TBAB, H_2O, MW 150 °C, 5 min.

deuteromethyl pyridine (**110**), by contrast, exhibited a half-life of 0.70 h (Table S5) and a C_{max} of 96 ng/mL (Fig. 1a), 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) (Fig. 1b), the plasma exposure showed some super-proportionality. However, as AUC_{inf} 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 h, a C_{max} of 843 ng/mL, and an oral bioavailability of 16.2 % (Fig. 1c). 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.

2.8. Lead compound activity against additional P. falciparum isolates and rate of killing assessment

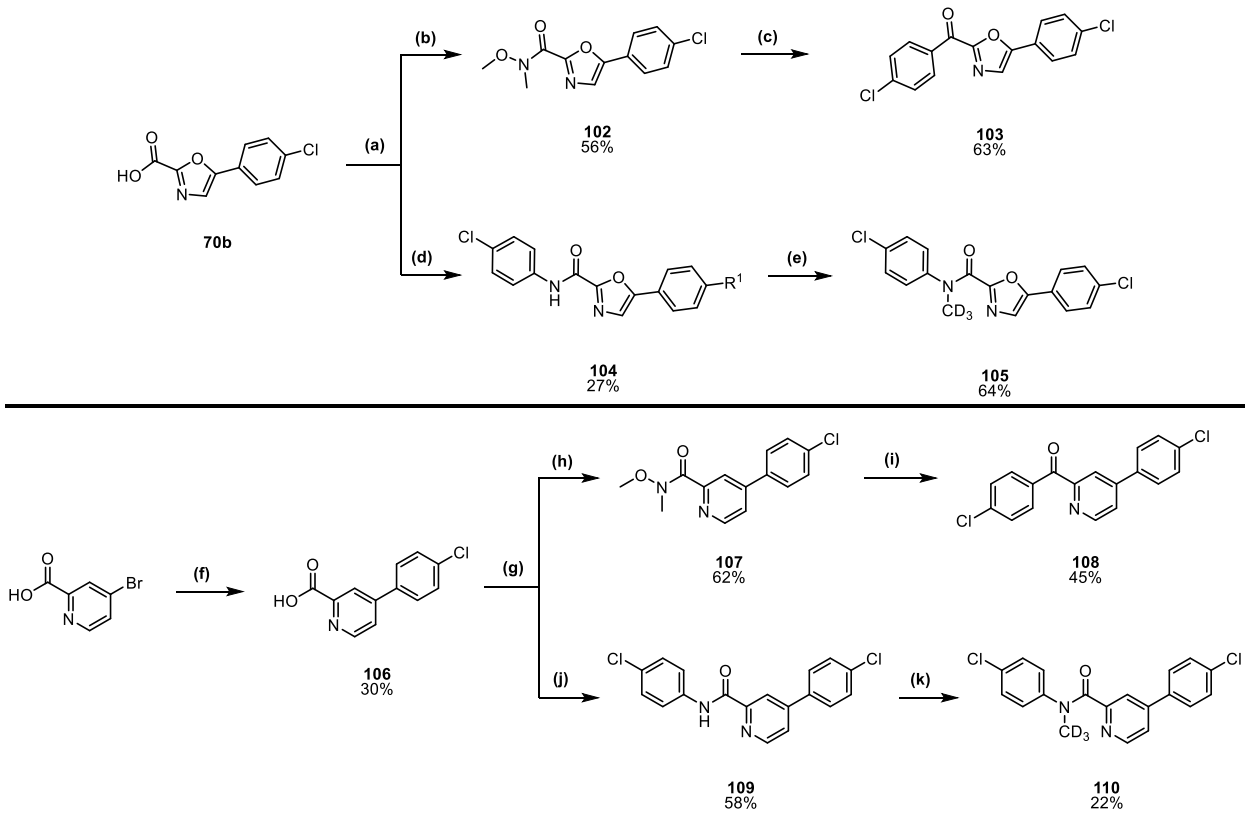
We evaluated the activity of lead compound **110** (deuteromethyl pyridine) against four additional *P. falciparum* isolates, including some with genetic backgrounds conferring resistance to common antimalarial drugs [36–39]. Compound **110** demonstrated nanomolar potency against each of the tested isolates (Table 9). Notably, we observed a slight decrease in potency in the chloroquine-sensitive isolates (D6 and 3D7) compared to the chloroquine-resistant isolates (W2, TM91C235, and TM90C2B). This is consistent with previous findings, as chloroquine resistance is often linked to reduced sensitivity to several antimalarials, such as amodiaquine, quinine, and mefloquine, and the observed decrease in potency for **110** falls within the same range.

To assess the pharmacodynamic properties of **110**, we conducted a parasite reduction ratio (PRR) assay [40] in a miniaturized format (see Experimental Section). In this assay, parasites were exposed to a concentration of **110** (10x EC_{50}) for up to 5 days. At 24-h intervals, the compound was washed from the culture, and parasites were serially diluted. Surviving parasites were then allowed to grow without compound pressure for 7 days, with growth assessed using high-content imaging of Hoechst 33342-stain wells (see Experimental Section). We included chloroquine as a fast-acting reference and pyrimethamine as a slow-to-moderate-acting reference [40] as controls (Fig. 2).

Our results showed a reduction in viable parasites after 24 h of exposure to the deuteromethyl pyridine **110**, with near-complete parasite clearance (99.9 %) achieved after 64.1–74.1 h of continuous exposure (Fig. 2, Table 10, Fig. S7, 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 the behavior of pyrimethamine (Fig. 2, Table 10, Fig. S7, Table S6, Table S7). In summary, these results suggest that compound **110** shows promising activity against a range of *P. falciparum* isolates, with a rate of killing comparable to that of slow-to-moderate-acting antimalarial agents. These findings highlight its potential as a therapeutic candidate, with efficacy across both resistant and sensitive parasite isolates.

2.9. Simulated human pharmacokinetic profiles of 110

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** might be susceptible to phase II metabolism. Using the well-stirred model without any binding (plasma or microsome/hepatocyte) correction, the first value yields a



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

[a] **Reagents and conditions: (a)** $(COCl)_2$, anhydrous THF/DCM/DMF, 0 °C, then 23 °C, 30 min; **(b)** *N,O*-dimethylhydroxylamine hydrochloride, NEt_3, anhydrous THF/DCM, 23 °C, 16 h; **(c)** (4-chlorophenyl)magnesium bromide, anhydrous THF, 0 °C, then 23 °C, 3 h; **(d)** 4-chloroaniline, NEt_3, anhydrous THF/DCM, 23 °C, 16 h; **(e)** CD_3I, K_2CO_3, anhydrous DMF, 0–23 °C, 12 h; **(f)** $Pd(OAc)_2$, K_2CO_3, H_2O, MW 175 °C, 10 min; **(g)** $(COCl)_2$, anhydrous THF/DCM/DMF, 0 °C, then 23 °C, 30 min; **(h)** *N,O*-dimethylhydroxylamine hydrochloride, NEt_3, anhydrous THF/DCM, 23 °C, 16 h; **(i)** (4-chlorophenyl)magnesium bromide, anhydrous THF, 0 °C, then 23 °C, 3 h; **(j)** 4-chloroaniline, NEt_3, anhydrous THF/DCM, 23 °C, 16 h; **(k)** CD_3I, K_2CO_3, anhydrous DMF, 0–23 °C, 12 h.

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) [41–43]. 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 h) 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.

The aforementioned *in vitro* and pharmacokinetic murine data was used in the 1-species Wajima method (C_{ss}-MRT method) [44] 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 IV human plasma concentration-time profile (Fig. 3a) [44]. From this profile, an oral human plasma concentration-time profile [45] was simulated for both for single (Fig. 3b) and repeated dosing (Fig. 3c) 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 h. Due to the rapid elimination of the compound, no accumulation is predicted, and no continuous coverage was achieved beyond 2.25 h.

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 but we concluded that the profile of **110** *in vivo* did not warrant investigation of efficacy *in vivo* due to the lack of a more extended EC_{50} coverage.

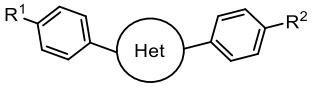
3. Conclusion

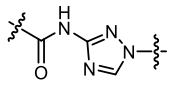
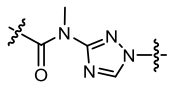
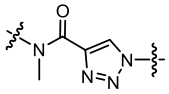
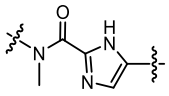
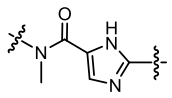
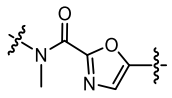
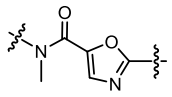
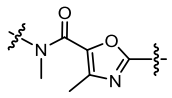
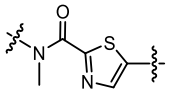
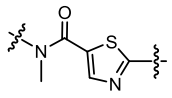
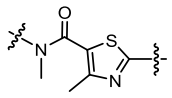
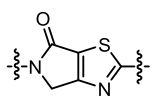
Through a molecular docking- and cheminformatics-driven virtual high throughput screen against *Pf*FNT, a 1,2,4-triazole-3-carboxamide scaffold was identified as a putative novel antimalarial series. Initially, this series had moderate potency and sub-optimal physicochemical properties. Structure-activity relationship studies revealed 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 [18].

We synthesized numerous triazoles 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-

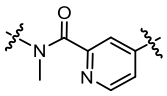
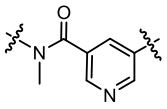
Table 5
Alternative molecule cores explored via scaffold hopping study.



ID	Het	R^1	R^2	EC_{50} (W2) [μM]	$pEC_{50} \pm SD$ (W2)	CC_{50} (HepG2) [μM]	$pCC_{50} \pm SD$ (HepG2)
47		Cl	CH_3	>2.99	<5.52 ± 0.07	>10.0	<5.00
48		Cl	Cl	3.08	5.51 ± 0.02	>10.0	<5.00
49		CH_3	CH_3	2.49	5.60 ± 0.02	>10.0	<5.00
50		CH_3	Cl	>10.0	<5.00	>10.0	<5.00
51		Cl	CH_3	>1.80	<5.74 ± 0.38	>10.0	<5.00
52		Cl	Cl	>1.52	<5.82 ± 0.19	>10.0	<5.00
53		CH_3	CH_3	>3.38	<5.47 ± 0.01	>10.0	<5.00
54		CH_3	Cl	4.24	5.37 ± 0.18	>10.0	<5.00
56		Cl	CH_3	>10.0	<5.00	>10.0	<5.00
57		Cl	Cl	>10.0	<5.00	>10.0	<5.00
58		CH_3	CH_3	>10.0	<5.00	>10.0	<5.00
59		CH_3	Cl	>10.0	<5.00	>10.0	<5.00
62		Cl	CH_3	>10.0	<5.00	>10.0	<5.00
63		Cl	Cl	>7.09	<5.15 ± 0.23	>10.0	<5.00
66		Cl	CH_3	3.42	5.47 ± 0.10	>10.0	<5.00
67		Cl	Cl	>2.26	<5.65 ± 0.24	>10.0	<5.00
71		Cl	CH_3	0.672	6.17 ± 0.10	>10.0	<5.00
72		Cl	Cl	0.170	6.77 ± 0.23	>10.0	<5.00
75		Cl	CH_3	>10.0	<5.00	>10.0	<5.00
76		Cl	Cl	>10.0	<5.00	>10.0	<5.00
79		Cl	CH_3	>8.87	<5.05 ± 0.10	>10.0	<5.00
80		Cl	Cl	>4.34	<5.36 ± 0.28	>10.0	<5.00
83		Cl	CH_3	>10.0	<5.00	>10.0	<5.00
84		Cl	Cl	>6.75	<5.17 ± 0.20	>10.0	<5.00
87		Cl	CH_3	>10.0	<5.00	>10.0	<5.00
88		Cl	Cl	>10.0	<5.00	>10.0	<5.00
91		Cl	CH_3	>4.78	<5.32 ± 0.27	>10.0	<5.00
92		Cl	Cl	>10.0	<5.00	>10.0	<5.00
96		Cl	Cl	>10.0	<5.00	>10.0	<5.00

(*continued on next page*)

Table 5 (*continued*)

ID	Het	R^1	R^2	EC_{50} (W2) [μM]	$pEC_{50} \pm SD$ (W2)	CC_{50} (HepG2) [μM]	$pCC_{50} \pm SD$ (HepG2)
98		Cl	CH_3	0.489	6.31 ± 0.09	>10.0	<5.00
99		Cl	Cl	0.169	6.77 ± 0.15	>10.0	<5.00
100		Cl	CH_3	0.131	6.88 ± 0.04	>10.0	<5.00
101		Cl	Cl	0.435	6.36 ± 0.04	>10.0	<5.00

[a] EC_{50} and CC_{50} data represents geometric means for at least two independent experiments; pEC_{50} and pCC_{50} data represents the respective means and standard deviations for these experiments. Where no standard deviation is reported, the standard deviation was zero.
[b] Puromycin (W2 – $pEC_{50} \pm SD = 7.20 \pm 0.15$; HepG2 – $pCC_{50} \pm SD = 6.19 \pm 0.07$) is the internal control for the *in vitro* antimalarial activity and cytotoxicity assays.

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 h). 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.

Early in the structure-activity relationship studies, we observed that, unlike other *Pf*FNT inhibitors [11–14], our most potent triazole compound (**20**) had no effect on the cytosolic pH of parasites. These findings suggest that the mode of action of this series is not linked to *Pf*FNT inhibition, as this phenomenon would be expected for compounds targeting this transporter.

Although the exact mechanism of action remains undetermined, compound **110** exhibits promising characteristics. It demonstrates potent blood-stage activity against various *P. falciparum* isolates *in vitro*, excellent selectivity, and favorable physicochemical and pharmacodynamic properties. Taken together, these attributes position compound **110** as a strong lead candidate for further development and optimization in the search for new antimalarial therapies.

Table 6
Physicochemical properties of key SAR compounds.

ID	Potency	Human liver microsomes		Rat hepatocytes		Aq. Sol.	$LogD_{7.4}$
	*Pf*ABS W2 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

[a] EC_{50} data represents geometric means for at least two independent experiments.
[b] Aq. Sol. = kinetic aqueous solubility; data represents means for two independent experiments.
[c] $LogD_{7.4}$ data represents means for two independent experiments.
[d] Puromycin (W2 – $pEC_{50} \pm SD = 7.20 \pm 0.15$) is the internal control for the *in vitro* antimalarial activity assay.

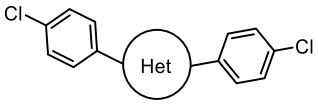
4. Experimental Section

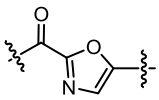
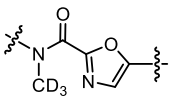
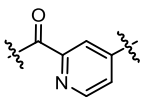
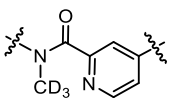
4.1. Antimalarial potency assays

Potencies against *P. falciparum* asexual blood stage parasites (strain W2)[36] was determined as previously described [48].

For testing of our lead compound, TM90C2B (chloroquine, mefloquine, pyrimethamine, and atovaquone resistant) [37], TM91C235 (chloroquine, mefloquine, and pyrimethamine resistant) [38], D6 (chloroquine, pyrimethamine, and atovaquone sensitive) [39], and 3D7 (a subclone of NF54 [49], chloroquine sensitive, sulfadoxine resistant)

Table 7
Alternative amide modifications.



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

[a] EC_{50} and CC_{50} data represents geometric means for at least two independent experiments; pEC_{50} and pCC_{50} data represents the respective means and standard deviations for these experiments. Where no standard deviation is reported, the standard deviation was zero.
[b] Puromycin (W2 – $pEC_{50} \pm SD = 7.20 \pm 0.15$; HepG2 – $pCC_{50} \pm SD = 6.19 \pm 0.07$) is the internal control for the *in vitro* antimalarial activity and cytotoxicity assays.

Table 8
Physicochemical properties of deuteromethyl amide replacements and their isotopologues.

ID	Potency	Human liver microsomes		Rat hepatocytes		Aq. Sol.	$LogD_{7.4}$
	*Pf*ABS W2 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]	
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

[a] EC_{50} data represents geometric means for at least two independent experiments.
[b] Aq. Sol. = kinetic aqueous solubility; data represents means for two independent experiments.
[c] $LogD_{7.4}$ data represents means for two independent experiments.
[d] Puromycin (W2 – pEC_{50} ± SD = 7.20 ± 0.15) is the internal control for the *in vitro* antimalarial activity assay.

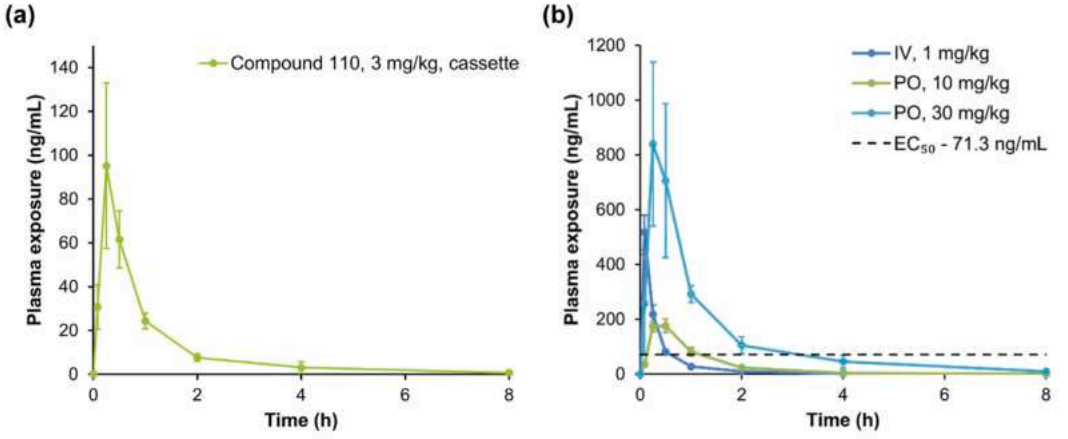
were also used. Briefly, parasites were cultured in RPMI 1640 (Gibco 31800-022) supplemented with 25 mM HEPES (Gibco 11344-041), 0.25 % (w/v) $NaHCO_3$ (Gibco 25080-094), 10 % inactivated human plasma (Interstate Blood Bank), 10 μg/mL gentamicin (Gibco 15610-072), and 2.5 % hematocrit O+ human blood (Interstate Blood Bank) in T25 or T75 flasks in a 37 °C incubator at 5 % CO_2 and 5 % O_2 [50]. Two days prior to starting an assay, a culture was synchronized with 5 % D-sorbitol [51]. After 48 h, 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 series 1000-fold and making the highest dose 10 μM. Puromycin (Sigma, lot 131192) was used as the positive control and 0.1 % DMSO (v/v) was used as the negative control. After 72 h, 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 4× 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 [52,53].

4.2. Cytotoxicity screens

Cytotoxicity against mammalian cells was determined as previously described [54]. 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



(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	–

Fig. 1. 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; and **(c)** Average and standard deviations of 3 replicates (3 mice) for various 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.

Table 9
Assessment of key compounds against various *P. falciparum* isolates.

ID	Activity	W2	C2B	C235	D6	3D7
72	EC_{50} [nM]	170	168	281	840	502
	pEC_{50} ± SD	6.77 ± 0.23	6.78 ± 0.03	6.55 ± 0.29	6.08 ± 0.12	6.30 ± 0.13
110	EC_{50} [nM]	198	104	199	608	588
	pEC_{50} ± SD	6.70 ± 0.15	6.98 ± 0.13	6.70 ± 0.22	6.22 ± 0.15	6.23 ± 0.10

[a] EC_{50} data represents geometric means for at least two independent experiments; pEC_{50} data represents the respective means and standard deviations for these experiments.
[b] Dihydroartemisinin (W2 – pEC_{50} ± SD = 9.38 ± 0.16; C2B – pEC_{50} ± SD = 9.75 ± 0.49; C235 – pEC_{50} ± SD = 8.53 ± 0.19; D6 – pEC_{50} ± SD = 8.81 ± 0.31; 3D7 – 9.18 ± 0.29) and atovaquone (W2 – pEC_{50} ± SD = 9.12 ± 0.13; C2B – pEC_{50} = >6.00; C235 – pEC_{50} ± SD = 8.71 ± 0.43; D6 – pEC_{50} ± SD = 9.22 ± 0.25; 3D7 – pEC_{50} ± SD = 9.07 ± 0.39) are the internal controls for the *in vitro* antimalarial activity assay. Where no standard deviation is reported, the standard deviation was zero.

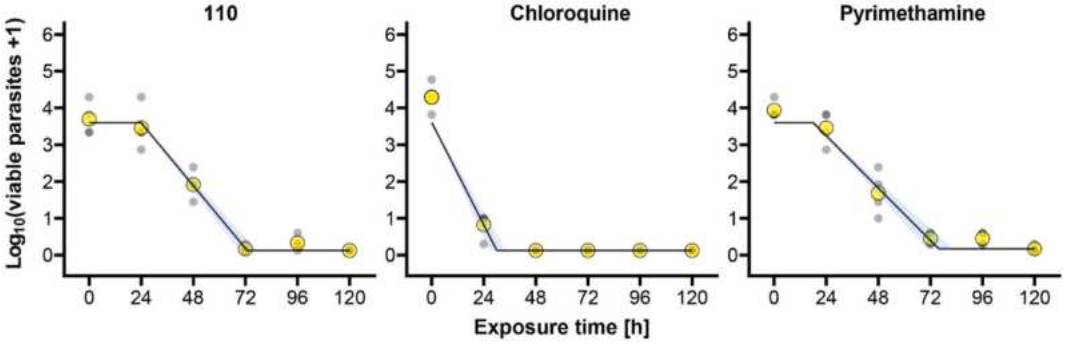


Fig. 2. Parasite clearance curves for compound **110** and fast-acting (chloroquine) and slow-to-moderate-acting (pyrimethamine) controls. Blue ribbons represent 95 % confidence intervals. One experiment is shown, two additional independent experiments are available in the Supporting Information. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

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
110	Intermediate with lag phase	24	66.1 [62.8–70.1]	3.4 [3.1–3.7]
Chloroquine	Fast	0	25.9 [23.1–29.5]	5.6 [4.9–6.3]
Pyrimethamine	Slow	18 [0–24]	68.6 [64.1–74.1]	2.8 [2.6–3.1]

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 h, 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.

4.3. 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).

4.4. 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

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 (P_{app})[a]		
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

[a] P_{app} = apparent permeability [x10−6 cm/s]; A = apical; B = basolateral.

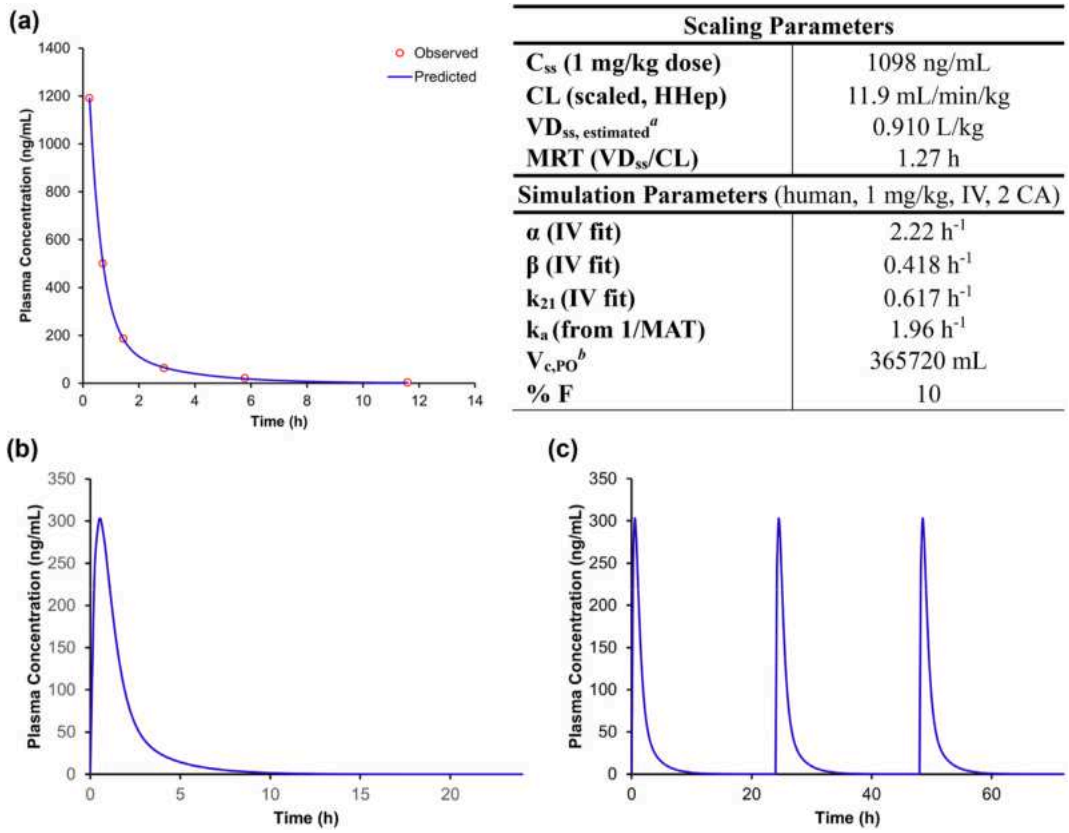


Fig. 3. Predicted human pharmacokinetic profiles for **110**. **(a)** Predicted human plasma concentration-time profile, 1 mg/kg (IV). Parameters for the scaling of murine data to human estimations, as well as simulation parameters from the predicted human IV profile (*PK*Solver2.0, 2-compartment analysis [46]). These were used to simulate PO human plasma concentration-time profiles (PKMP, version 1.03.53). [a]Calculated via the Berellini method [47]. [b]IV fit corrected for 70 kg average weight and F; **(b)** Predicted human plasma concentration-time profile, 300 mg single dose (PO); and **(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.

processed for plasma by centrifugation (4000 rpm, 10 min, 4 °C) within half an hour of collection. Plasma samples were stored at −20 °C until bioanalysis. Compound concentration was determined by LC-MS/MS (API6500 or AP4000 integrated to Shimadzu LC and CTC-PAL auto-sampler, YMC Triart C18 2.0 × 30 mm) after sample cleanup (70/30 acetonitrile/methanol deproteinization [1:6] and aqueous dilution [1:1]).

4.5. Miniaturized parasite reduction ratio 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 [40]. Briefly, 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 *P. falciparum* 3D7 in three independent experiments. 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 [40]) 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.

4.6. Synthetic methods

General. 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. Low resolution mass spectra (LRMS) were acquired on an Agilent G6125B single quadrupole mass spectrometer with electrospray ionization. High resolution mass spectra (HRMS) were acquired on a Waters Synapt G2-Si ESI/LC-MS. 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 × 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.

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 h 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.

4.6.1. 1-(4-chlorophenyl)-1H-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 min at 0 °C, the reaction was warmed to room temperature and stirred for 16 h. 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 h. 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 (733 mg, 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.

4.6.2. 1-(p-tolyl)-1H-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 (9.81 mmol, 1.11 equiv) and ethyl 2-isocyanoacetate (8.84 mmol, 1 equiv). An acid-base extraction afforded the title compound as a light orange solid (335 mg, 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.

4.6.3. 1-(4-ethylphenyl)-1H-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 (9.81 mmol, 1.11 equiv) and ethyl 2-isocyanoacetate (8.84 mmol, 1 equiv). An acid-base extraction afforded the title compound as an orange solid (467 mg, 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.

4.6.4. 1-(4-isopropylphenyl)-1H-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 (9.81 mmol, 1.11 equiv) and ethyl 2-isocyanoacetate (8.84 mmol, 1 equiv). An acid-base extraction afforded the title compound as a light tan solid (302 mg, 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.

4.6.5. 1-(4-methoxyphenyl)-1H-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 (9.81 mmol, 1.11 equiv) and ethyl 2-isocyanoacetate (8.84 mmol, 1 equiv). An acid-base extraction afforded the title compound as a rust-colored solid (272 mg, 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.

4.6.6. 1-(4-chlorophenyl)-N-(4-ethylphenyl)-1H-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 (0.134 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a lustrous white solid (18.9 mg, 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.

4.6.7. 1-(4-chlorophenyl)-N-(4-ethylphenyl)-N-methyl-1H-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 (0.134 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white pearlescent solid (39.8 mg, 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.

4.6.8. 1-(4-chlorophenyl)-N-(3,4-dimethylphenyl)-1H-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 (0.134 mmol). The crude product was purified via recrystallization from ethyl acetate to afford the title compound as a white solid (25.0 mg, 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.

4.6.9. 1-(4-chlorophenyl)-N-(3,4-dimethylphenyl)-N-methyl-1H-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 (0.134 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white pearlescent solid (39.0 mg, 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.

4.6.10. 1-(4-chlorophenyl)-N-(4-nitrophenyl)-1H-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 (0.112 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a lustrous yellow solid (16.6 mg, 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.

4.6.11. 1-(4-chlorophenyl)-N-methyl-N-(4-nitrophenyl)-1H-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 (0.134 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a yellow solid (35.0 mg, 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.

4.6.12. N-(4-acetylphenyl)-1-(4-chlorophenyl)-1H-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 (0.112 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a tan solid (27.4 mg, 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.

4.6.13. N-(4-acetylphenyl)-1-(4-chlorophenyl)-N-methyl-1H-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 (0.134 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a yellow solid (40.3 mg, 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.

4.6.14. 1-(4-chlorophenyl)-N-(3,4-dichlorophenyl)-1H-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 (0.134 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (18.1 mg, 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.

4.6.15. 1-(4-chlorophenyl)-N-(3,4-dichlorophenyl)-N-methyl-1H-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 (0.134 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a lustrous light yellow solid (37.8 mg, 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.

4.6.16. 1-(4-chlorophenyl)-N-(4-fluorophenyl)-1H-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 (0.134 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (36.3 mg, 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.

4.6.17. 1-(4-chlorophenyl)-N-(4-fluorophenyl)-N-methyl-1H-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 (0.134 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white pearlescent solid (37.6 mg, 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.

4.6.18. 1-(4-chlorophenyl)-N-(4-(trifluoromethyl)phenyl)-1H-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 (0.134 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a light yellow solid (48.7 mg, 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.

4.6.19. 1-(4-chlorophenyl)-N-methyl-N-(4-(trifluoromethyl)phenyl)-1H-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 (0.134 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a light orange solid (41.6 mg, 81 %). 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.

4.6.20. N-(4-chlorophenyl)-1-(p-tolyl)-1H-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 (0.148 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (4.6 mg, 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.

4.6.21. N-(4-chlorophenyl)-N-methyl-1-(p-tolyl)-1H-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 (0.148 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (5.3 mg, 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.

4.6.22. N,1-bis(4-chlorophenyl)-1H-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 (0.134 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a tan solid (29.2 mg, 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 = 8.8, 3.2, 2.1 Hz, 2H), 7.89 (dt, J = 8.8, 3.2, 2.1 Hz, 2H), 7.69 (dt, J = 8.8, 3.1, 2.2 Hz, 2H), 7.43 (dt, J = 8.8, 3.1, 2.2 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.

4.6.23. N,1-bis(4-chlorophenyl)-N-methyl-1H-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 (0.134 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (44.8 mg, 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; HRMS-ESI (*m/z*): [M+H]+ calcd for $C_{16}H_{13}Cl_2N_4O$ 347.0466, found 346.0470.

4.6.24. 1-(4-chlorophenyl)-N-methyl-N-phenyl-1H-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 (0.134 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a light yellow solid (23.9 mg, 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.

4.6.25. 1-(4-chlorophenyl)-N-methyl-N-(p-tolyl)-1H-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 (0.134 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as an off-white solid (23.4 mg, 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; HRMS-ESI (*m/z*): [M+H]+ calcd for $C_{17}H_{16}ClN_4O$ 327.1013, found 327.1013.

4.6.26. N-(4-(tert-butyl)phenyl)-1-(4-chlorophenyl)-N-methyl-1H-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 (0.134 mmol). The crude product was

purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (45.1 mg, 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.

4.6.27. 1-(4-chlorophenyl)-N-(4-methoxyphenyl)-N-methyl-1H-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 (0.103 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a light yellow pearlescent solid (31.0 mg, 88 %). 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.

4.6.28. 1-(4-chlorophenyl)-N-methyl-N-(m-tolyl)-1H-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 (0.134 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as an orange solid (19.7 mg, 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.

4.6.29. N-methyl-N,1-di-p-tolyl-1H-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 (0.148 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white pearlescent solid (21.1 mg, 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; HRMS-ESI (m/z): [M+H]+ calcd for $C_{18}H_{19}N_4O$ 307.1559, found 307.1565.

4.6.30. N-(4-methoxyphenyl)-N-methyl-1-(p-tolyl)-1H-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 (0.148 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (11.7 mg, 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.

4.6.31. N-methyl-N-(m-tolyl)-1-(p-tolyl)-1H-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 (0.246 mmol). 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.

4.6.32. N-(3,4-dimethylphenyl)-N-methyl-1-(p-tolyl)-1H-1,2,4-triazole-3-carboxamide (29)

Prepared via General Procedure A from 1-(*p*-tolyl)-1*H*-1,2,4-triazole-3-carboxylic acid (0.148 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (5.1 mg, 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.

4.6.33. N-(4-chlorophenyl)-1-(4-ethylphenyl)-N-methyl-1H-1,2,4-triazole-3-carboxamide (30)

Prepared via General Procedure A from 1-(4-ethylphenyl)-1*H*-1,2,4-triazole-3-carboxylic acid (0.092 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (19.5 mg, 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.

4.6.34. 1-(4-ethylphenyl)-N-methyl-N-(p-tolyl)-1H-1,2,4-triazole-3-carboxamide (31)

Prepared via General Procedure A from 1-(4-ethylphenyl)-1*H*-1,2,4-triazole-3-carboxylic acid (0.092 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a lustrous white solid (29.2 mg, 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.

4.6.35. 1-(4-ethylphenyl)-N-(4-methoxyphenyl)-N-methyl-1H-1,2,4-triazole-3-carboxamide (32)

Prepared via General Procedure A from 1-(4-ethylphenyl)-1*H*-1,2,4-triazole-3-carboxylic acid (0.092 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (8.7 mg, 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.

4.6.36. 1-(4-ethylphenyl)-N-methyl-N-(m-tolyl)-1H-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 (0.092 mmol). The crude product was purified

by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a lustrous white solid (29.4 mg, 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.

4.6.37. N-(3,4-dimethylphenyl)-1-(4-ethylphenyl)-N-methyl-1H-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 (0.230 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (38.5 mg, 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.

4.6.38. N-(4-chlorophenyl)-1-(4-isopropylphenyl)-N-methyl-1H-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 (0.130 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a light yellow solid (42.5 mg, 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.

4.6.39. 1-(4-isopropylphenyl)-N-methyl-N-(p-tolyl)-1H-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 (0.130 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a lustrous light yellow solid (38.4 mg, 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.

4.6.40. 1-(4-isopropylphenyl)-N-(4-methoxyphenyl)-N-methyl-1H-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 (0.130 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a tan solid (38.4 mg, 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.

4.6.41. 1-(4-isopropylphenyl)-N-methyl-N-(m-tolyl)-1H-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 (0.130 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a light orange solid (37.6 mg, 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.

4.6.42. N-(3,4-dimethylphenyl)-1-(4-isopropylphenyl)-N-methyl-1H-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 (0.130 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a lustrous white solid (30.2 mg, 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.

4.6.43. N-(4-chlorophenyl)-1-(4-methoxyphenyl)-N-methyl-1H-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 (0.137 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as an off-white solid (14.7 mg, 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.

4.6.44. 1-(4-methoxyphenyl)-N-methyl-N-(p-tolyl)-1H-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 (0.137 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (27.6 mg, 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.

4.6.45. N,1-bis(4-methoxyphenyl)-N-methyl-1H-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 (0.137 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as an off-white solid (32.8 mg, 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.

4.6.46. 1-(4-methoxyphenyl)-N-methyl-N-(m-tolyl)-1H-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 (0.228 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a lustrous white solid (65.5 mg, 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.

4.6.47. N-(3,4-dimethylphenyl)-1-(4-methoxyphenyl)-N-methyl-1H-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 (0.137 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (21.6 mg, 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.

4.6.48. 3-Nitro-1-(p-tolyl)-1H-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 h. Upon reaction completion via LC-MS, 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 (1.35 g, 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.

4.6.49. 1-(4-chlorophenyl)-3-nitro-1H-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 (14.5 mmol, 1.1 equiv) and 3-nitro-1*H*-1,2,4-triazole (13.2 mmol, 1 equiv). The crude product was purified via recrystallization in hexanes to afford the title compound as a lustrous white solid (990 mg, 34 %). R_f (30 % EA/Hex) = 0.30; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (s, 1H), 7.71 (dt, J = 8.8, 3.1, 1.9 Hz, 2H), 7.57 (dt, J = 8.8, 3.1, 1.9 Hz, 2H); LRMS-ESI (*m/z*): $[M + H]^+$ 225.0.

4.6.50. 1-(p-tolyl)-1H-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 h. Upon reaction completion via LC-MS, 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 (639 mg, 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.

4.6.50.1. 1-(4-chlorophenyl)-1H-1,2,4-triazol-3is used to determine the sta-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 (4.41 mmol) to afford the title compound as a tan solid (743 mg, 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.

4.6.51. 4-Chloro-N-(1-(p-tolyl)-1H-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 h. 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 (78.5 mg, 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.

4.6.52. 4-Chloro-N-(1-(4-chlorophenyl)-1H-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 (0.514 mmol) and 4-chlorobenzoyl chloride (1.03 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a light yellow solid (42.7 mg, 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; HRMS-ESI (*m/z*): [M+H]+ calcd for $C_{15}H_{11}Cl_2N_4O$ 333.0310, found 333.0307.

4.6.53. 4-Methyl-N-(1-(p-tolyl)-1H-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 (0.574 mmol) and 4-methylbenzoyl chloride (0.631 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (42.1 mg, 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.

4.6.54. N-(1-(4-chlorophenyl)-1H-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 (0.514 mmol) and 4-methylbenzoyl chloride (0.565 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a yellow solid (113 mg, 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.

4.6.55. 4-Chloro-N-methyl-N-(1-(p-tolyl)-1H-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 min 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 h. 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 (41.0 mg, 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.

4.6.56. 4-Chloro-N-(1-(4-chlorophenyl)-1H-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 (0.102 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (22.1 mg, 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; HRMS-ESI (*m/z*): [M+H]+ calcd for $C_{16}H_{13}Cl_2N_4O$ 347.0466, found 346.0468.

4.6.57. N,4-dimethyl-N-(1-(p-tolyl)-1H-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 (0.257 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a lustrous white solid (67.7 mg, 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.

4.6.58. N-(1-(4-chlorophenyl)-1H-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 (0.128 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (25.0 mg, 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.

4.6.59. 1-(p-tolyl)-1H-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 h. 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 (152 mg, 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.

4.6.60. 1-(4-chlorophenyl)-1H-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 (3.26 mmol). An acid-base extraction afforded the title compound as a white solid (162 mg, 22 %). ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 9.41 (s, 1H), 8.01 (dt, J = 8.9, 3.1, 2.1 Hz, 2H), 7.68 (dt, J = 8.9, 3.1, 2.1 Hz, 2H); LRMS-ESI (*m/z*): $[M + H]^+$ 224.0.

4.6.61. N-(4-chlorophenyl)-N-methyl-1-(p-tolyl)-1H-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 (0.148 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (34.9 mg, 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.

4.6.62. N,1-bis(4-chlorophenyl)-N-methyl-1H-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 (0.134 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a lustrous white solid (38.1 mg, 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; HRMS-ESI (*m/z*): [M+H]+ calcd for $C_{16}H_{13}Cl_2N_4O$ 347.0466, found 346.0468.

4.6.63. N-methyl-N,1-di-p-tolyl-1H-1,2,3-triazole-4-carboxamide (58)

Prepared via General Procedure A from 1-(*p*-tolyl)-1*H*-1,2,3-triazole-4-carboxylic acid (0.148 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (10.6 mg, 23 %). 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.

4.6.64. 1-(4-chlorophenyl)-N-methyl-N-(p-tolyl)-1H-1,2,3is used to determine the sta-triazole-4-carboxamide (59)

Prepared via General Procedure A from 1-(4-chlorophenyl)-1*H*-1,2,3-triazole-4-carboxylic acid (0.089 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to

afford the title compound as a lustrous white solid (20.0 mg, 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.

4.6.65. Ethyl 5-(p-tolyl)-1H-imidazole-2-carboxylate (60a)

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 h. 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 min, 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 min, 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 min at 0 °C, the reaction mixture was warmed to room temperature and stirred for 2 h. 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 (312 mg, 36 %, over 2 steps). 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.

4.6.66. Ethyl 5-(4-chlorophenyl)-1H-imidazole-2-carboxylate (60b)

Prepared as described for ethyl 5-(*p*-tolyl)-1*H*-imidazole-2-carboxylate from 1-(4-chlorophenyl)ethan-1-one (3.23 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a light yellow solid (358 mg, 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.

4.6.67. 5-(p-tolyl)-1H-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 h. 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.

4.6.68. 5-(4-chlorophenyl)-1H-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 (1.20 mmol). 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.

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

Prepared via General Procedure A from 5-(*p*-tolyl)-1*H*-imidazole-2-carboxylic acid (0.148 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (36.9 mg, 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.

4.6.70. N,5-bis(4-chlorophenyl)-N-methyl-1H-imidazole-2-carboxamide (63)

Prepared via General Procedure A from 5-(4-chlorophenyl)-1*H*-imidazole-2-carboxylic acid (0.135 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (30.5 mg, 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; HRMS-ESI (*m/z*): [M+H]+ calcd for $C_{17}H_{14}Cl_2N_3O$ 346.0514, found 346.0511.

4.6.71. 2-(p-tolyl)-5-(trifluoromethyl)-1H-imidazole (64a)

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 min 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 h, 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 (233 mg, 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.

4.6.72. 2-(4-chlorophenyl)-5-(trifluoromethyl)-1H-imidazole (64b)

Prepared as described for 2-(*p*-tolyl)-5-(trifluoromethyl)-1*H*-imidazole from 4-chlorobenzaldehyde (3.56 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (221 mg, 25 %). R_f (30 % EA/Hex) = 0.32; ^{1}H NMR (500 MHz, CD_3OD) δ 7.87 (dt, J = 8.6, 2.7, 2.1 Hz, 2H), 7.68–7.60 (m, 1H), 7.48 (dt, J = 8.6, 2.7, 2.1 Hz, 2H); LRMS-ESI (*m/z*): $[M + H]^+$ 247.0.

4.6.73. 2-(p-tolyl)-1H-imidazole-5-carboxylic acid (65a)

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 h 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 (141 mg, 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.

4.6.74. 2-(4-chlorophenyl)-1H-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 (0.770 mmol). An acid-base extraction afforded the title compound as a tan solid (110 mg, 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.

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

Prepared via General Procedure A from 2-(*p*-tolyl)-1*H*-imidazole-5-carboxylic acid (0.148 mmol). 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 (24.8 mg, 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.

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

Prepared via General Procedure A from 2-(4-chlorophenyl)-1*H*-imidazole-5-carboxylic acid (0.135 mmol). 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 (15.0 mg, 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; HRMS-ESI (*m/z*): [M+H]+ calcd for $C_{17}H_{14}Cl_2N_3O$ 346.0514, found 346.0518.

4.6.77. 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 h 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 h. 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 h. 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 (271 mg, 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.

4.6.78. 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 (12.85 mmol). 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 (2.15 g, 62 %, 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.

4.6.79. 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 h. Upon reaction completion via LC-MS, 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 (159 mg, 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.

4.6.80. 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 (2.41 mmol). 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 (530 mg, 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.

4.6.81. 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 h. 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.

4.6.82. 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 (1.99 mmol). 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.

4.6.83. 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 (0.246 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (72.0 mg, 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.

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

Prepared via General Procedure A from 5-(4-chlorophenyl)oxazole-2-carboxylic acid (0.447 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (128 mg, 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; HRMS-ESI (m/z): [M+H]+ calcd for $C_{17}H_{13}Cl_2N_2O_2$ 347.0354, found 347.0357.

4.6.85. 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 min 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 (86.1 mg, 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.

4.6.86. Ethyl 2-(4-chlorophenyl)oxazole-5-carboxylate (73b)

Prepared as described for ethyl 2-(*p*-tolyl)oxazole-5-carboxylate from (4-chlorophenyl)boronic acid (1.14 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (71.7 mg, 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.

4.6.87. 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 h. 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 (56.4 mg, 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.

4.6.88. 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 (0.282 mmol). An acid-base extraction afforded the title compound as a white solid (39.6 mg, 63 %). ^{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.

4.6.89. 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 (0.148 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a pale-yellow solid (37.7 mg, 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; HRMS-ESI (m/z): [M+H]+ calcd for $C_{18}H_{16}ClN_2O_2$ 327.0900, found 327.0903.

4.6.90. N,2-bis(4-chlorophenyl)-N-methyloxazole-5-carboxamide (76)

Prepared via General Procedure A from 2-(4-chlorophenyl)oxazole-5-carboxylic acid (0.112 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a yellow solid (34.2 mg, 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.

4.6.91. Ethyl 4-methyl-2-(p-tolyl)oxazole-5-carboxylate (77a)

In a round bottom flask, ethyl 2-chloroacetoacetate (3.04 mmol, 1 equiv) and 4-methylbenzamide (9.11 mmol, 3 equiv) were dissolved in ethanol (1.20 M). The reaction mixture was heated to 80 °C for 2 h, then heated at 110 °C for 14 h. 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 (197 mg, 26 %). 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.

4.6.92. Ethyl 2-(4-chlorophenyl)-4-methyloxazole-5-carboxylate (77b)

Prepared as described for ethyl 4-methyl-2-(*p*-tolyl)oxazole-5-carboxylate from 4-chlorobenzamide (36.5 mmol, 3 equiv) and ethyl 2-chloroacetoacetate (12.2 mmol, 1 equiv). 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 (361 mg, 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.

4.6.93. 4-Methyl-2-(p-tolyl)oxazole-5-carboxylic acid (78a)

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 h. 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 (140 mg, 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.

4.6.94. 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 (0.282 mmol). An acid-base extraction afforded the title compound as a white solid (60.6 mg, 90 %). ^{1}H NMR (500 MHz, CD_3OD) δ 8.07 (dt, J = 8.7, 2.5, 2.0 Hz, 2H), 7.51 (dt, J = 8.7, 2.5, 2.0 Hz, 2H), 2.49 (s, 3H); LRMS-ESI (m/z): $[M + H]^+$ 238.0.

4.6.95. 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 (0.138 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a lustrous white solid (47.0 mg, 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.

4.6.96. 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 (0.126 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a lustrous white solid (30.7 mg, 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; HRMS-ESI (m/z): [M+H]+ calcd for $C_{18}H_{15}Cl_2N_2O_2$ 361.0511, found 363.0511.

4.6.97. 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 h, 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 (182 mg, 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.

4.6.98. 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 (1.04 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a yellow solid (214 mg, 77 %). R_f (10 % EA/Hex) = 0.13; ^{1}H 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.

4.6.99. 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 (0.400 mmol). An acid-base extraction afforded the title compound as a lustrous white solid (63.8 mg, 73 %). ^{1}H 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.

4.6.100. 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 (0.784 mmol). An acid-base extraction afforded the title compound as a light yellow lustrous solid (71.2 mg, 38 %). ^{1}H 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.

4.6.101. 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 (0.137 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a light yellow solid (41.7 mg, 89 %). mp 142–146 °C; R_f (30 % EA/Hex) = 0.47; ^{1}H 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.

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

Prepared via General Procedure A from 5-(4-chlorophenyl)thiazole-2-carboxylic acid (0.125 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a light pink solid (34.2 mg, 75 %). mp 133–137 °C; R_f (20 % EA/Hex) = 0.35; ^{1}H 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; HRMS-ESI (m/z): [M+H]+ calcd for $C_{17}H_{13}Cl_2N_2OS$ 363.0126, found 363.0128.

4.6.103. 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 h. 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 (379 mg, 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.

4.6.104. Ethyl 2-(4-chlorophenyl)thiazole-5-carboxylate (85b)

Prepared as described for ethyl 2-(*p*-tolyl)thiazole-5-carboxylate from 4-methylbenzothioamide (1.75 mmol). 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 (385 mg, 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.

4.6.105. 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 h. 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 (156 mg, 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.

4.6.106. 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 (0.934 mmol). An acid-base extraction afforded the title compound as a white solid (84.6 mg, 38 %). ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 13.66 (bs, 1H), 8.41 (s, 1H), 8.01 (dt, $J = 8.6$, 2.7, 1.9 Hz, 2H), 7.59 (dt, $J = 8.6$, 2.7, 1.9 Hz, 2H); LRMS-ESI (*m/z*): $[M + H]^+$ 240.0.

4.6.107. 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 (0.137 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a fluffy white solid (31.4 mg, 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.

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

Prepared via General Procedure A from 2-(4-chlorophenyl)thiazole-5-carboxylic acid (0.125 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (36.2 mg, 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; HRMS-ESI (*m/z*): [M+H]+ calcd for $C_{17}H_{13}Cl_2N_2OS$ 363.0126, found 363.0127.

4.6.109. 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 h at reflux, then allowed to cool to room temperature and stir for 16 h. The resulting white precipitate was isolated via vacuum filtration and washed with ethanol (0 °C) to afford the title compound as a white solid (546 mg, 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.

4.6.110. 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 (14.6 mmol). 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 (3.16 g, 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.

4.6.111. 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 h 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 (52.4 mg, 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.

4.6.112. 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 (7.45 mmol). An acid-base extraction afforded the title compound as a white solid (1.52 g, 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.

4.6.113. 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 (0.129 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as an off-white oil (21.3 mg, 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.

4.6.114. 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 (0.296 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as an orange solid (104 mg, 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; HRMS-ESI (*m/z*): [M+H]+ calcd for $C_{18}H_{15}Cl_2N_2OS$ 377.0282, found 377.0284.

4.6.115. 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 h. 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 (411 mg, 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.

4.6.116. 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 min 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 h at room temperature, then 12 h 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 (164 mg, 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.

4.6.117. 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 h, 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 (180 mg, 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.

4.6.118. 2,5-bis(4-chlorophenyl)-4,5-dihydro-6H-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 h at 0 °C. The reaction was then allowed to warm to room temperature and stir for 23 h. 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 (31.0 mg, 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; HRMS-ESI (*m/z*): [M+H]+ calcd for $C_{17}H_{11}Cl_2N_2OS$ 360.9969, found 360.9967.

4.6.119. 4-Chloro-N-(4-chlorophenyl)-N-methylpicolinamide (97a)

Prepared via General Procedure A from 4-bromopicolinic acid (1.49 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as an off-white solid (283 mg, 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. LC-MS analysis indicates halogen exchange (Br → Cl) occurred based on observed mass and isotope pattern, similar to a previous report for a similar substrate [55].

4.6.120. 5-Bromo-N-(4-chlorophenyl)-N-methylnicotinamide (97b)

Prepared via General Procedure A from 5-bromonicotinic acid (1.49 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as an off-white solid (333 mg, 69 %). 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.

4.6.121. 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 min 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 (29.0 mg, 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.

4.6.122. 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 (0.178 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (1.96 mg, 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; HRMS-ESI (*m/z*): [M+H]+ calcd for $C_{19}H_{15}Cl_2N_2O$ 357.0561, found 337.0565.

4.6.123. N-(4-chlorophenyl)-N-methyl-5-(p-tolyl)nicotinamide (100)

Prepared as described for *N*-(4-chlorophenyl)-*N*-methyl-4-(*p*-tolyl) picolinamide from 5-bromo-*N*-(4-chlorophenyl)-*N*-methylnicotinamide (0.246 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (21.6 mg, 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; HRMS-ESI (*m/z*): [M+H]+ calcd for $C_{20}H_{18}ClN_2O$ 337.1108, found 337.1109.

4.6.124. N,5-bis(4-chlorophenyl)-N-methylnicotinamide (101)

Prepared as described for *N*-(4-chlorophenyl)-*N*-methyl-4-(*p*-tolyl) picolinamide from 5-bromo-*N*-(4-chlorophenyl)-*N*-methylnicotinamide (0.154 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (38.1 mg, 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.

4.6.125. 5-(4-chlorophenyl)-N-methoxy-N-methyloxazole-2-carboxamide (102)

Prepared via General Procedure A from 5-(4-chlorophenyl)oxazole-2-carboxylic acid (0.671 mmol, 1 equiv) and *N,O*-dimethylhydroxylamine hydrochloride (2.01 mmol, 3 equiv). 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 (101 mg, 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.

4.6.126. (4-chlorophenyl) (5-(4-chlorophenyl)oxazol-2-yl)methanone (103)

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 h. 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 (56.6 mg, 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.

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

Prepared via General Procedure A from 5-(4-chlorophenyl)oxazole-2-carboxylic acid (0.671 mmol, 1 equiv) and 4-chloroaniline (2.01 mmol, 3 equiv). 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 (61.0 mg, 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.

4.6.128. 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 (0.150 mmol, 1 equiv) with iodomethane-d_3 (0.300 mmol, 2 equiv) 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 (33.8 mg, 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; HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{10}D_3Cl_2N_2O_2$ 350.0542, found 350.0541.

4.6.129. 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 min 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 (342 mg, 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.

4.6.130. 4-(4-chlorophenyl)-N-methoxy-N-methylpicolinamide (107)

Prepared via General Procedure A from 4-(4-chlorophenyl)picolinic acid (0.600 mmol, 1 equiv) and *N,O*-dimethylhydroxylamine hydrochloride (1.80 mmol, 3 equiv). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a white solid (102 mg, 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.

4.6.131. (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 (0.325 mmol). The crude product was purified by flash column chromatography with hexanes/ethyl acetate to afford the title compound as a fluffy white solid (48.3 mg, 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.

4.6.132. N,4-bis(4-chlorophenyl)picolinamide (109)

Prepared via General Procedure A from 4-(4-chlorophenyl)picolinic acid (0.578 mmol, 1 equiv) and 4-chloroaniline (1.73 mmol, 3 equiv). 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 (115 mg, 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.

4.6.133. 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 (0.219 mmol, 1 equiv) with iodomethane-d_3 (0.437 mmol, 2 equiv) 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 (16.9 mg, 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; HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{19}H_{12}D_3Cl_2N_2O$ 360.0750, found 360.0749.

CRediT authorship contribution statement

Alicia Wagner: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Roger Trombley:** Methodology, Investigation, Formal analysis, Data curation. **Maris Podgurski:** Methodology, Formal analysis. **Anthony A. Ruberto:** Visualization, Validation, Investigation, Formal analysis, Data curation, Conceptualization. **Meng Cui:** Visualization, Software, Conceptualization. **Caitlin A. Cooper:** Formal analysis, Data curation. **William E. Long:** Formal analysis, Data curation. **Gia-Bao Nguyen:** Formal analysis, Data curation. **Adriana A. Marin:** Formal analysis, Data curation. **Sarah Lee Mai:** Formal analysis, Data curation. **Franco Lombardo:** Visualization, Investigation, Formal analysis, Conceptualization. **Steven P. Maher:** Writing – review & editing, Visualization, Validation, Supervision, Investigation, Formal analysis, Conceptualization. **Dennis E. Kyle:** Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Funding acquisition, Conceptualization. **Roman Manetsch:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Funding acquisition, Conceptualization.

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Declaration of competing interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejmech.2025.117572.

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.

Data availability

No data was used for the research described in the article.

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