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Protozoan Parasite Growth Inhibitors Discovered by Cross-Screening Yield Potent Scaffolds for Lead Discovery

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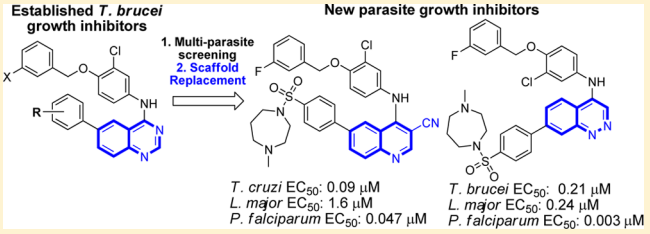
Supporting Information

ABSTRACT: Tropical protozoal infections are a significant cause of morbidity and mortality worldwide; four in particular (human African trypanosomiasis (HAT), Chagas disease, cutaneous leishmaniasis, and malaria) have an estimated combined burden of over 87 million disability-adjusted life years. New drugs are needed for each of these diseases. Building on the previous identification of NEU-617 (**1**) as a potent and nontoxic inhibitor of proliferation for the HAT pathogen (*Trypanosoma brucei*), we have now tested this class of analogs against other protozoal species: *T. cruzi* (Chagas disease), *Leishmania major* (cutaneous leishmaniasis), and *Plasmodium falciparum* (malaria). Based on hits identified in this screening campaign, we describe the preparation of several replacements for the quinazoline scaffold and report these inhibitors' biological activities against these parasites. In doing this, we have identified several potent proliferation inhibitors for each pathogen, such as 4-((3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-amino)-6-(4-((4-methyl-1,4-diazepan-1-yl)sulfonyl)phenyl)quinoline-3-carbonitrile (NEU-924, **83**) for *T. cruzi* and *N*-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-7-(4-((4-methyl-1,4-diazepan-1-yl)sulfonyl)phenyl)cinnolin-4-amine (NEU-1017, **68**) for *L. major* and *P. falciparum*.



INTRODUCTION

Several tropical diseases are caused by protozoan parasites transmitted by insects. Taken together, malaria (caused by *Plasmodium* species), human African trypanosomiasis (HAT, caused by *Trypanosoma brucei*), Chagas disease (caused by *T. cruzi*), and leishmaniasis (caused by *Leishmania* species) represent diseases with an estimated combined burden of over 87 million disability-adjusted life years.[1] While progress has certainly been made toward the discovery of new hits, much work remains to translate these hits into promising chemical lead series that may be advanced for drug development.

One pragmatic method for launching such programs is "target repurposing", wherein inhibitors of human homologues of essential parasite proteins are assessed for efficacy against parasite cells.[2] We have recently initiated the repurposing of a variety of kinase inhibitors for parasitic diseases[3−7] and have also described the use of established human phosphodiesterase inhibitors as starting points for lead discovery.[8]

We have described the discovery of NEU-617 (**1**), a derivative of the approved human cancer drug lapatinib (**2**), which acts as a potent, orally bioavailable growth inhibitor of *T. brucei* that showed a modest effect in a mouse model of bloodstream infection.[6] We also reported the association of lapatinib with four trypanosome protein kinases.[9] Based on the close phylogenetic relationship between the kinomes of the trypanosomatid parasites (*T. brucei*, *T. cruzi*, and *Leishmania major*),[10] we hypothesized that all the pathogens would be susceptible to these inhibitors. We have therefore tested **1**, along with the other analogs synthesized during the course of our hit-to-lead optimization program, against the two other kinetoplastid parasites. Based on our previous observation that related chemotypes show activity against *Plasmodium falciparum*,[11] we also screened this set of compounds against cultures of drug-sensitive and drug-resistant strains of malaria. In doing

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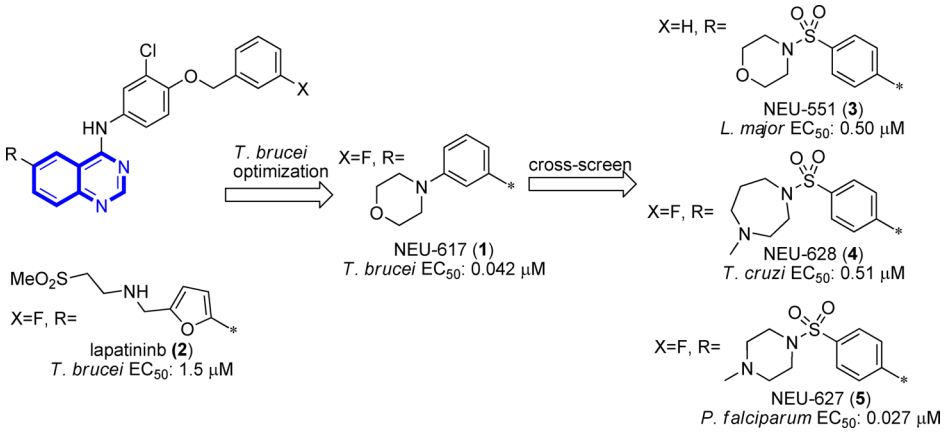
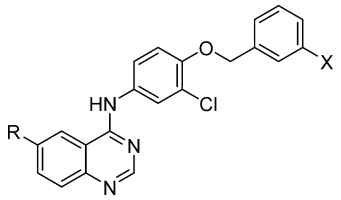
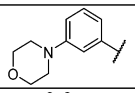
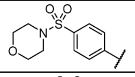
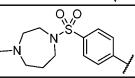
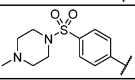


Figure 1. Program progression from **2** to four potent antiparasitic leads. The quinazoline scaffold is highlighted in blue.

Table 1. Potent Quinazolines Identified via Multiparasite Cross-Screening



Entry	R	X	*T. brucei* EC_{50} (μM)[a]	*T. cruzi* EC_{50} (μM)[a]	*L. major* EC_{50} (μM)[b]		*P.fal* D6 EC_{50} (μM)[b]	HepG2 TC_{50} (μM)
					Promast	*Amast*		
1		F	0.042	1.8	3.0	8.0	0.23	>15
3		H	1.4	(9.5)*	0.50	>15	0.26	>15
4		F	0.81	0.51	3.6	2.1	0.046	1.1
5		F	0.53	(60)*	2.8	1.6	0.027	>15
Control[c]			0.04	1.2	0.089	0.047	0.013	

[a]SEM values within 50%. *% inh at 10 μM. [b]r^2 values >0.75. [c]Control compounds: *T. brucei*, suramin; *T. cruzi*, benznidazole; *L. major*, amphotericin B; *P. falciparum*, chloroquine.

so, we noted differential structure−activity relationships for these compounds' growth inhibitory properties against each of the parasites, thus launching a multiparasite optimization campaign from the same lead series.

In this paper, we describe these cross-pathogen assay results and outline our evaluation of replacements for the quinazoline scaffold of **1** for each of the parasites. We posit that such a cross-screening approach can be a highly fruitful method for identification of new protozoan parasite growth inhibitors.

RESULTS

First, in order to ascertain antiparasitic activities of our 66 previously reported analogs,[6] we measured their growth inhibitory activities against *T. cruzi* (intracellular amastigotes), *L. major* (promastigote and intracellular amastigote life stages), and *P. falciparum* (D6, drug sensitive strain). The structures of the most potent compounds for each parasite are shown in Figure 1 and Table 1, and the complete set of screening data for these is tabulated in the Supporting Information (Tables S1−S7).

From these experiments, we observed that 15 morpholino-sulfonamide compounds were identified with activity against *L. major* promastigotes: seven of these were submicromolar inhibitors and two were also submicromolar against intracellular amastigotes (the most relevant life stage for human infections of leishmaniasis). The des-fluoro analog NEU-551 (**3**) showed the highest activity against promastigotes (EC_{50} = 0.50 μM). We initially tested compounds against *T. cruzi* at a single concentration and found that 32 compounds inhibited proliferation >65% at 10 μM concentrations; of these 32 compounds, the homopiperazinyl sulfonamide-substituted tail was preferred (NEU-628 (**4**), EC_{50} = 0.51 μM). The active compounds against *P. falciparum* (drug-sensitive D6 strain) all contained a basic nitrogen at the end of the tail group with NEU-627 (**5**) being the most potent with an EC_{50} of 27 nM. Though we note that the number of headgroup replacement analogs tested was far smaller and less diverse than the tail variations, the lapatinib headgroup 3-chloro-4-((3-fluorobenzyl)oxy)aniline showed optimal potency against all of the parasites, except for both *Leishmania* life stages.

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Previous efforts focused on the "head" (4-benzyloxyanilines) and "tail" (denoted as R in Figure 1) regions of lapatinib, while maintaining the central quinazoline scaffold (highlighted in blue in Figure 1). Thus, we planned a broader evaluation of other bicyclic aromatic replacements for the quinazoline scaffold that would test the important features of the chemotype for activity. These scaffold replacements were selected for exploration of the requisite nitrogen atom positioning in the heteroaromatic ring (see the heterocycle precursors highlighted in Figure 2,

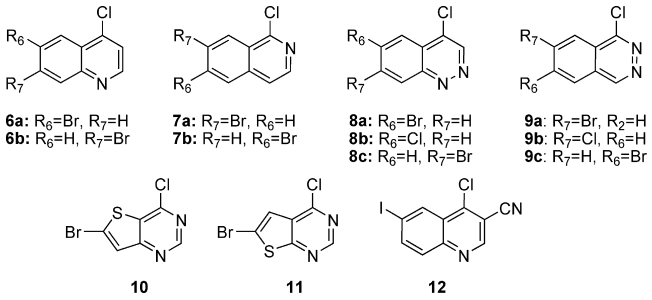


Figure 2. Quinazoline core replacements.

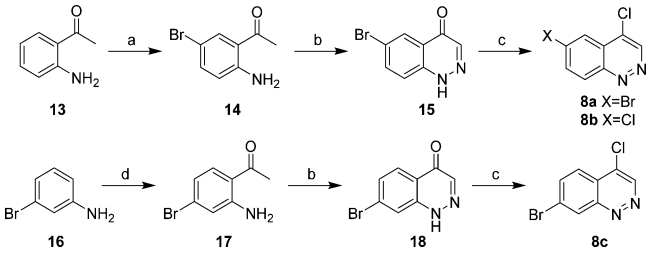
dihalides **6**–**9**). In addition, the cyanoquinoline and thienopyrimidine scaffolds (dihalides **10**–**12**) were selected in order to include other established tyrosine kinase inhibitor chemotypes.[12−15] For a matched exploration of these scaffolds, we elected to maintain the four permutations of head/tail combinations that displayed the most potency in each parasite (shown in Figure 1) in the new analogs that we prepared.

We first set out to synthesize the requisite dihalogenated scaffolds shown in Figure 2. The syntheses of 6- and 7-bromo-4-chloroquinolines **6a** and **6b** were carried out via the Gould–Jacobs sequence following previously reported protocols.[16] A complementary set of 1-aminoisoquinolines was devised to draw out essential interactions with either nitrogen of the quinazoline scaffold. Thus, **7a** and **7b** were synthesized utilizing known transformations.[17−19] The 6-bromo-4-chlorothienopyrimidines **10** and **11** were prepared as previously reported.[20−25] The requisite cyanoquinoline template **12** was prepared using established protocols similar to that of the 4-chloroquinolines.[26]

Though few examples of cinnoline or phthalazine based kinase inhibitors exist in the literature,[27−30] we opted to prepare analogues utilizing both heterocycles to test the required positioning of the two nitrogen atoms on the scaffold. Preparation of 6-bromo-4-chlorocinnoline **8a** commenced with the bromination of *o*-aminoacetophenone **13** followed by diazotization of the amine and *in situ* cyclization to the 6-bromocinnolin-4(1*H*)-one **15** (Scheme 1).[31,32] Chlorination in neat $POCl_3$ did not give the expected **8a** as the major product. Instead, we observed high conversion to 4,6-dichlorocinnoline **8b**. We hypothesized that this side reaction occurred via chloride displacement under the acidic conditions of the reaction (Scheme S1, see Supporting Information). A 10:1 product ratio of **8a** to **8b** could be achieved through the use of THF as solvent and 3 equiv of $POCl_3$. The regiomeric 7-bromo-4-chlorocinnoline **8c** was prepared in a similar fashion starting instead with the acylation of 3-bromoaniline **16** to 2-amino-4-bromoacetophenone **17**, followed by diazotization and chlorination.[33]

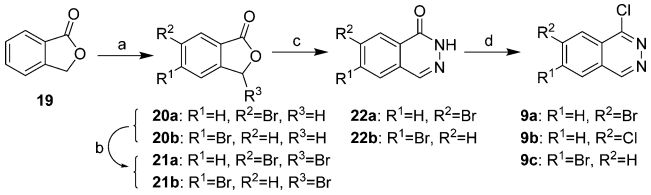
The 7-bromo-1-chlorophthalazine template **9a** was synthesized as shown in Scheme 2. Aryl bromination of phthalide **19** was carried out in acidic medium with NBS to produce a

Scheme 1. Synthesis of the Dihalocinnoline Core 8[a]



[a]Reagents and conditions: (a) NBS, CH_2Cl_2, −10 °C → 23 °C, o.n.; (b) $NaNO_2$, aq. HCl, H_2O, 75 °C, o.n.; (c) $POCl_3$, THF, reflux, 2 h; (d) (i) BCl_3, $(CH_2Cl)_2$, 0 °C; (ii) $AlCl_3$, CH_3CN, 80 °C, o.n.; (iii) aq. HCl, 80 °C, 30 min; (b) $NaNO_2$, aq. HCl, H_2O, 75 °C, o.n.; (c) $POCl_3$, THF, reflux, 2 h.

Scheme 2. Synthesis of the Dihalophthalazine Core 9[a]

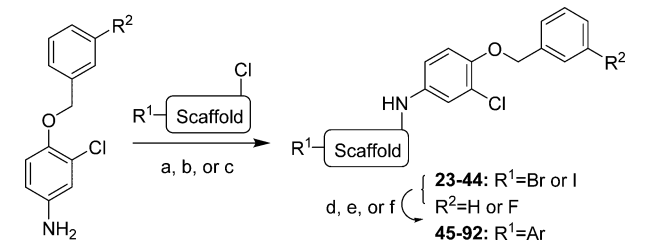


[a]Reagents and conditions: (a) NBS, H_2SO_4, CF_3CO_2H, 23 °C, 40 h; (b) NBS, AIBN, $CHCl_3$, reflux, 1 h; (c) N_2H_4, i-PrOH, reflux, 1.5 h; (d) $POCl_3$, CH_3CN, reflux, 3 h.

separable mixture of 4- and 6-bromophthalide **20**. Benzylic bromination was achieved using a modification of an established procedure,[34] and the resulting dibromides **21a,b** were converted to the corresponding bromophthalazinone **22** upon treatment with hydrazine. As with **15**, **22a** was converted to the dichlorinated side product **9b** on treatment with neat $POCl_3$, though dilution minimized this side reaction. Acetonitrile with 3 equiv of $POCl_3$ provided a >10:1 ratio of the desired chlorination product **9a**. The 6-bromo-1-chlorophthalazine scaffold **9c** could be synthesized in an identical manner starting with the commercially available 5-bromophthalide **20b**.

Amination of the dihalogenated quinoline, isoquinoline, cyanoquinoline, and thienopyrimidine scaffolds was carried out by applying methods similar to those we previously reported (Scheme 3).[6] However, low yields (~20%) resulted when these

Scheme 3. Head and Tail Group Attachments to Quinazoline Core Replacements[a]



[a]See Tables 2 and 3 for product structures. Reagents and conditions: (a) 1.1 equiv of amine, i-PrOH, reflux, o.n.; (b) 4 equiv of amine, toluene, reflux, 2.5 h; (c) 4 equiv of amine, toluene, 50 °C, o.n.; (d) ArBpin, Et_3N, $Pd(OAc)_2$, 1:1 H_2O/EtOH, MW, 120 °C, 1–3 h; (e) ArBpin, Et_3N, $PdCl_2(PPh_3)_2$, 1:1 H_2O/EtOH, MW, 120 °C, 1 h; (f) ArBpin, aq. Na_2CO_3, $Pd(PPh_3)_4$, 3:2 glyme/EtOH, N_2, 85 °C, 7–12 h.

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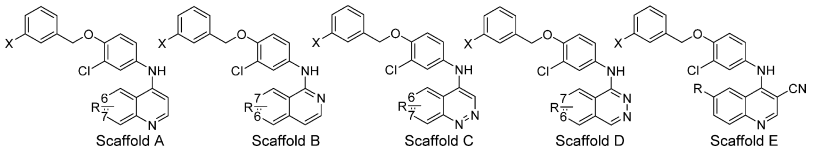
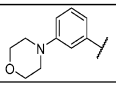
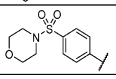
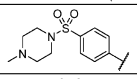
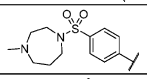
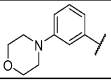
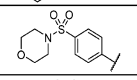
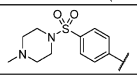
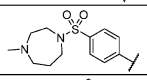
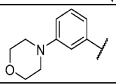
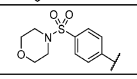
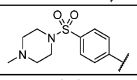
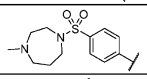
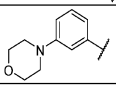
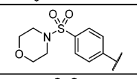
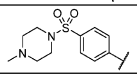
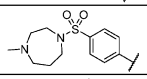
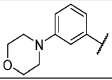
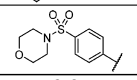
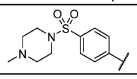
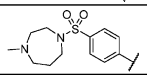
Table 2. Antiparasitic Activity of Quinoline, Isoquinoline, Cinnoline, Phthalazine, and 3-Cyanoquinoline Analogs



Entry	R	Scaff	Pos	X	*Tbb* EC_{50} (μM)[a]	*Tcr* EC_{50} (μM)[a]	*L. major* EC_{50} (μM)[e]		*P.fal* EC_{50} (μM)[e]	HepG2 TC_{50} (μM)[d]
							Promast	*Amast*		
45		A	6	F	1.0	6.6	0.9	4.0	0.035	10
46		A	7	F	1.2	2.7	1.4	3.7	0.061	>5
47		A	6	H	2.1	49	0.2	3.4	0.032	>5
48		A	7	H	0.24	3.5	>1.5	>1.5	0.016	>3
49		A	6	F	0.46	5.3	0.6[f]	2.0	>16	6.4
50		A	7	F	0.079	0.73[b]	1.0[f]	1.6[f]	0.019	>4
51		A	6	F	0.14	0.93	0.4	2.3	0.086	4.3
52		A	7	F	0.087	0.73[b]	0.4	0.89	0.094	5
53		B	7	F	(0.1)*	>50	>15	6.0[f]	2.6	>28
54		B	6	F	(12)*	>50	>15	2.2[f]	2.8	>28
55		B	7	H	>2.5	>50	>15	>15	0.87	>25
56		B	6	H	0.091	>50	>15	>3	3.4	>5
57		B	7	F	1.8	>50	>15	>15	0.04	>15
58		B	6	F	0.10	>50	2.7	>15	0.11	>15
59		B	7	F	0.73	4.7[c]	1.3	2.2	0.086	>15
60		B	6	F	0.39	33	0.44	4.4[f]	0.41	>15
61		C	6	F	1.1	>50	>15	>15	0.54	>15
62		C	7	F	0.89	45	9.8	>15	0.20	11
63		C	6	H	1.2	>50	>15	>15	0.82	>15
64		C	7	H	1.2	15	>15	>15	0.15	>11
65		C	6	F	0.98	>50	>15	1.9	0.13	>15
66		C	7	F	1.0	3.1	5.7	2.0	0.014	>15
67		C	6	F	0.58	2.2	4.1	1.06	0.027	7.3
68		C	7	F	0.21	49	6.4	0.24	0.003	15
69		D	7	F	0.29	>50	>15	1.7[f]	0.11	>15
70		D	6	F	1.4	>50	>15	2.2	0.24	>15
71		D	7	H	0.86	>50	>3.4	>4.0	0.54	>5.2
72		D	6	H	0.99	>50	>15	>15	0.11	>15
73		D	7	F	2.0	>50[d]	>3.2	>4.0	0.13	>5
74		D	6	F	1.2	18[d]	1.3[f]	>15	0.045	>15
75		D	7	F	0.62	17[d]	>15	5.6[f]	0.094	14
76		D	6	F	0.51	1.3[d]	0.41	1.1	0.029	3.4
77		E	-	F	(49)*	>50	>15	>15	0.48	>15
78		E	-	H	0.76	>50	>15	>15	0.97	>15
79		E	-	F	(15)*	>50	>15	>15	0.16	>15
80		E	-	H	(33)*	>50	>15	>15	0.28	>15
81		E	-	F	1.1	>50	>15	>15	0.082	>15
82		E	-	H	1.9	>50	4.1	>15	0.21	>15
83		E	-	F	0.35	0.09[b]	0.92	1.6	0.047	>15
84		E	-	H	0.43	0.95	1.6	2.3[f]	0.058	13

[a]All SEM values within 25% unless noted otherwise. *% inh at 5 μM. [b]SEM values within 40%. [c]SEM = 0.89. [d]n = 1. [e]All r^2 values >0.9 unless noted otherwise. [f]r^2 values >0.75.

conditions were applied to the cinnoline and phthalazine templates. Switching the solvent to toluene and using 4 equiv of amine improved yields to 54−78%. Suzuki couplings using the requisite boronates and 5−7 mol % $Pd(PPh_3)_4$ or 1 mol %

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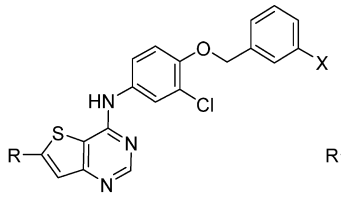
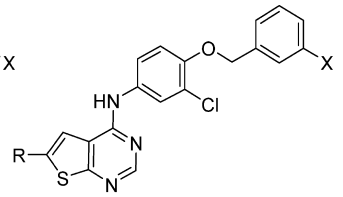
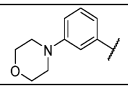
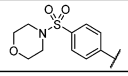
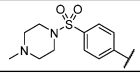
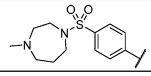
Table 3. Antiparasitic Activity of Thienopyrimidine Analogs



Scaffold F



Scaffold G

Entry	R	Scaff	X	*Tbb* EC_{50} (μM)[a]	*Tcr* EC_{50} (μM)[a]	*L. major* EC_{50} (μM)[c]		*Pfal* D6 EC_{50} (μM)[c]	*HepG2* TC_{50} (μM)[d]
						Promast	*Amast*		
85		F	F	(42)*	>50	>15	5.4[d]	0.86	>15
86		G	F	0.20	2.2	>15	2.6	0.52	>15
87		F	H	0.13	>50	>3	>3	0.62	>5
88		G	H	2.2	>50[b]	>15	>15	0.22	>15
89		F	F	0.63	5.5	3.4[c]	>15	0.021	>15
90		G	F	1.5	48[b]	>15	>15	0.043	>15
91		F	F	0.73	>50	0.32[c]	2.3	0.10	>15
92		G	F	0.42	15[b]	2.4[c]	1.9	0.10	>15

[a]All SEM values within 20% unless noted otherwise. *% inh at 5 μM. [b]n = 1. [c]All r^2 values >0.9 unless noted otherwise. [d]r^2 values >0.75

$Pd(OAc)_2$ provided the final analogs. Yields of the cinnoline or phthalazine products were drastically improved by switching to 2.5 mol % $PdCl_2(PPh_3)_2$ or 5 mol % $Pd(OAc)_2$ with extended reaction times. A higher catalyst loading of $Pd(OAc)_2$ was employed in lieu of $PdCl_2(PPh_3)_2$ in situations where the PPh_3O byproduct could not be separated from the products.

With this set of new analogs that are matched to the previously described antiparasitic agents,[6] we set out measuring these analogs' activities against *T. brucei*, *T. cruzi*, *L. major*, and *P. falciparum*, and counter-screened against host cells (NIH 3T3 and HepG2 cell lines) using assays that we previously reported.[7] The HepG2 data is summarized in Tables 2 and 3. A small number of compounds showed activity against NIH 3T3 cells; these are summarized in the Supporting Information, Table S8.

DISCUSSION AND CONCLUSIONS

Compound **1** remained the most potent *T. brucei* growth inhibitor among this set of analogs. A pair of quinoline-based compounds, **50** and **52**, each with a basic aliphatic amine on the tail group show double digit nanomolar potency (79 and 87 nM, respectively). The potency of these compounds seems to be driven by the aliphatic amine in the tail region rather than by the placement of nitrogen atoms in the scaffold, because the analogous isoquinoline analogue **58** is approximately equipotent (100 nM) to **50**.

The quinoline analogs **50**, **51**, and **52** displayed submicromolar potency against intracellular amastigotes of *T. cruzi*. Most other analogs showed a complete loss of activity, perhaps due to issues with penetration into both the host cell and the parasite. (With intracellular parasites, we note that compensating effects from interactions with host cell targets cannot be ruled out.) However, the 3-cyanoquinoline analogue **83**, shows a 5-fold improvement in potency over the matched original quinazoline analog **4**. In the headgroup region, the 3-fluoro substituent affords a 10-fold increase in potency over the matched des-fluoro analog (cf. **83** vs **84**). The quinoline **51** displayed a slight drop in potency compared with the quinazoline **4**, and the matched isoquinoline **59** is 10-fold less potent. Taken together with the cyanoquinoline analog **83**, this data demonstrates the apparent importance of two H-bond acceptor motifs in the scaffold.

In the case of *L. major*, **47** showed a 2.5-fold increase in potency from the matched quinazoline analogue **3** (0.20 versus 0.50 μM respectively) against the promastigote life stage of *L. major*. The corresponding isoquinoline compound **55** showed a complete loss in activity, reinforcing the essentiality of the N1 atom of the quinazoline. Interestingly, there was no activity observed against the amastigote life stage of the parasite for **47**. In contrast, the 7-substituted quinoline **52** displayed submicromolar potency against both life stages (0.40 μM against promastigotes and 0.89 μM versus amastigotes). Compared with the quinazoline compound **4**, the analogous cinnoline **68** displayed increased potency against amastigotes (0.24 μM) albeit with a significant decrease in potency against the promastigote form. This lack of correlation of compounds between promastigote and amastigote life stages of the parasite has been reported by us and others recently.[7,35] Other compounds displaying modest potency include **76** and **91**, both containing the *N*-methylhomopiperazinyl sulfonamide tail.

In *P. falciparum* cultures, three isoquinoline compounds with a basic amine at the terminus of the tail region showed modest potency highlighted by **57** being nearly equipotent to the parent quinazoline **5** (40 vs 27 nM). Though the matching quinoline **49** showed a complete loss in activity, its regioisomer **50** was slightly more active than **5** (EC_{50} = 19 nM). The four quinoline analogs without a basic amine on the tail group were within 2-fold of **5** with **48** being the most potent with an EC_{50} = 16 nM. Similarly, all four thienopyrimidine analogs with a basic tail group amine (**89**–**92**) were potent, within 4-fold of **5**. Among these compounds there was no preference for either thienopyridine isomer; the *N*-methylpiperazinyl tail group was 2.5- to 4-fold more potent than the *N*-methylhomopiperazinyl tail on each scaffold.

Among the phthalazines, **74** and **76**, both with a basic nitrogen on the tail and substituted at the 6-position (regiomeric to **5**) were equipotent to **5**. Also requiring a basic amine on the tail region, the cinnoline analogs with

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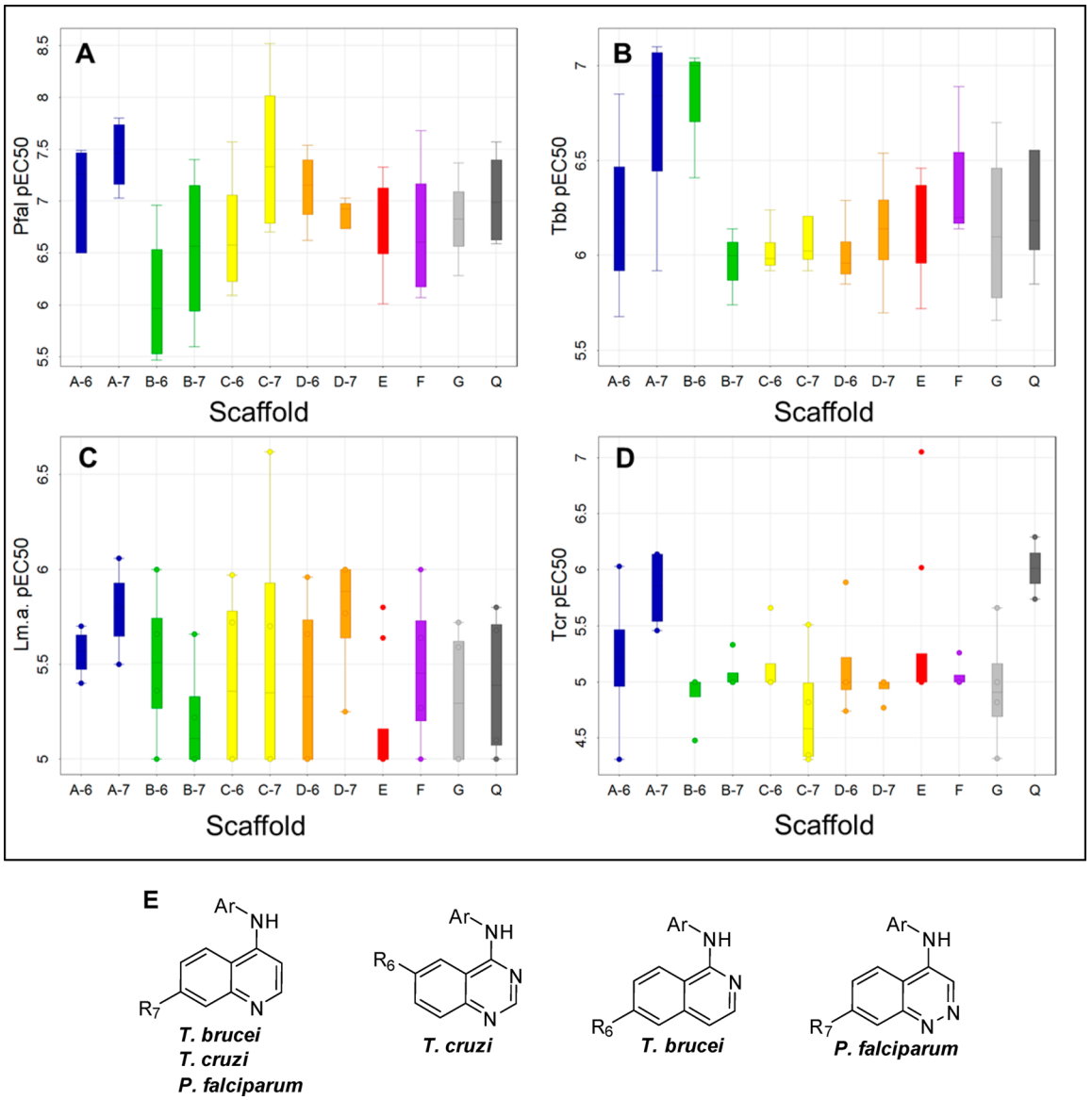

Figure 3. Bar chart showing range of potencies for each scaffold (as labeled in Tables 2 and 3) for (A) malaria, (B) *T. brucei*, (C) *L. major* (amastigotes), and (D) *T. cruzi*. Regiochemical information is shown by the suffix number (e.g., scaffold A-7 is the 7-substituted quinoline scaffold). Quinolines are shown in blue, isoquinolines in green, cinnolines in yellow, phthalazines in orange, cyanoquinolines in red, thieno[3,2-*d*]pyrimidines in purple, thieno[2,3-*d*]pyrimidines in light gray, and quinazolines in dark gray. (E) Summary of preferred scaffolds on a per-parasite basis.

piperazinyl and homopiperazinyl moieties (**65**−**68**) showed modest to high potency against *P. falciparum* D6 strain. Excitingly, the 7-substituted isomers (**66** and **68**) were highly potent antiplasmodial agents (14 and 3 nM, respectively).

Since we observed that the most potent compounds against *P. falciparum* were 4-aminoquinolines (similar to the prototypical antimalarial agent chloroquine), we tested them against drug resistant parasite strains W2 and C235. We were gratified to observe that all of the compounds tested are similarly active against drug resistant strains of *P. falciparum* (Table S9, Supporting Information), suggesting that despite the shared scaffold, these analogs likely display a mechanism of action or mechanism of resistance that differs from those of chloroquine.

Our studies demonstrate which of these scaffolds are the most promising for further optimization on a parasite-by-parasite basis. Figure 3 highlights the range of antiparasite potencies for each scaffold. By inspection, it is clear that the quinoline scaffold is significantly active across all four pathogens. We note that cinnoline (C) and quinoline (A) generally provide the most potent antiplasmodial agents, and the 7-position substitutions are slightly favored in both of these templates. For *T. brucei*, the 7-substituted quinolines and 6-substituted isoquinolines appear optimal (noting that, despite the differential numbering of the scaffolds, these two particular scaffolds present the same relative regiochemistry). Analogous diagrams for the other pathogens are also provided in Figure 3 (and a diagram for *Leishmania* promastigotes is in the Supporting Information (Figure S1). A summary of the preferred bicyclic scaffold for each parasite is shown in Figure 3E, noting that none appear to be markedly better than the others against *Leishmania* intracellular amastigotes.

For all parasites except for *T. brucei*, we also note a preference for tail substituents with a basic amine present. Considering only the most "potent" compounds ($EC_{50} \leq 0.1$ μM for the extracellular parasites *T. brucei* and *P. falciparum*; $EC_{50} \leq 1$ μM for the intracellular parasites *L. major* and *T.*

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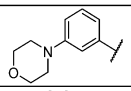
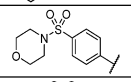
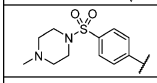
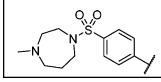
cruzi), we note that the *N*-methylpiperizine and *N*-methylhomopiperazine are preferred among analogs that were tested, over the less-basic morpholine or nonbasic morpholinosulfonamide substituents (Table 4). At this point, we cannot discern whether this is an effect that is mediated by the biological target(s) involved in proliferation inhibition, by parasite permeation, or by a combination of both; this will be a matter for further investigation.

Table 4. Summary of the Relative Prevalence of Each of the Four Tail Motifs among "Potent" Proliferation Inhibitors

R	*T. brucei*[a]	*T. cruzi*[b]	*L. major*[b]	*P. falciparum*[a]
	2/5 **40%**	0/6 **0%**	0/2 **0%**	2/28 **7.1%**
	1/5 **20%**	0/6 **0%**	0/2 **0%**	2/28 **7.1%**
	1/5 **20%**	1/6 **17%**	0/2 **0%**	11/28 **39.3%**
	1/5 **20%**	5/6 **83%**	2/2 **100%**	13/28 **46.4%**

[a]"Potent" compounds are $EC_{50} \leq 0.1$ μM. [b]"Potent" compounds are $EC_{50} \leq 1$ μM.

We have previously observed that molecules bearing these head and tail combinations possess problematic physicochemical properties, likely due to the molecular size and lipophilicity. The intent of the present work was to explore the central scaffold functionality, rather than to address these shortcomings. Nonetheless, we selected five representative compounds from among the most potent to be tested for their physicochemical properties (Table 5). Not unexpectedly, compounds tested were >99% plasma protein bound with limited thermodynamic aqueous solubility (<1 μM). Such properties are undoubtedly a result of the high molecular weights and clogP values; these issues remain the focus of ongoing efforts, which are now focused on specific scaffolds for each pathogen.

In summary, through a cross-parasite screening campaign of existing quinazoline *T. brucei* proliferation inhibitors, we uncovered new hits against three other protozoan parasites. Encouraged by that initial success, we focused on exploring the central heterocycle scaffold, an exercise that has uncovered additional highly potent compounds. Scaffold variations have revealed heteroatom positioning essential for activity within this chemotype, while variations to regiochemical attachment points have introduced a new set of regioisomers with multiparasite potency. Thus, we have established a new lead series for each of these protozoan parasites, which can be now advanced in parallel for drug discovery against four different parasitic diseases. With this in mind, further optimization of physicochemical properties and cellular selectivity of each is ongoing, with a specific focus on the "head" and "tail" regions. These results will be reported in due course.

EXPERIMENTAL SECTION

Chemical Synthesis. Unless otherwise noted, reagents were obtained from Sigma-Aldrich, Inc. (St. Louis, MO), Fisher Scientific, Frontier Scientific Services, Inc. (Newark, DE), or Matrix Scientific (Columbia, SC) and used as received. Boronic acids and esters and aniline reagents were purchased, except for those whose syntheses are listed in the Supporting Information. Reaction solvents were dried by passage through alumina columns on a purification system manufactured by Innovative Technology (Newburyport, MA). Microwave reactions were performed using a Biotage Initiatior-8 instrument. NMR spectra were obtained with Varian NMR systems, operating at 400 or 500 MHz for ^{1}H acquisitions as noted. LCMS analysis was performed using a Waters Alliance reverse-phase HPLC, with single-wavelength UV−visible detector and LCT Premier time-of-flight mass spectrometer (electrospray ionization). All newly synthesized compounds that were submitted for biological testing were deemed >95% pure by LCMS analysis (UV and ESI-MS detection) prior to submission for biological testing. Preparative LCMS was performed on a Waters Fraction Lynx system with a Waters MicroMass ZQ mass spectrometer (electrospray ionization) and a single-wavelength UV−visible detector, using acetonitrile/H_2O gradients with 0.1% formic acid. Fractions were collected on the basis of triggering using UV and mass detection. Yields reported for products obtained by preparative HPLC represent the amount of pure material isolated; impure fractions were not repurified.

*6-Bromo-4-chlorocinnoline (**8a**).* In a flame-dried 250 mL round-bottom flask were added 6-bromocinnolin-4(1*H*)-one (1.00 g, 4.44 mmol), anhydrous tetrahydrofuran (45 mL), and phosphorus oxychloride (1.25 mL, 13.41 mmol). The mixture was refluxed for 1 h at which point a deep green/blue solution had resulted. The solution was cooled to 0 °C and was quenched by the dropwise addition of sat. aq. $NaHCO_3$ (70 mL). The mixture was allowed to warm to room temperature and stir for an additional 1 h. Water (50 mL) was added, and the mixture was extracted with dichloromethane (3 × 100 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (50 mL), washed with brine (50 mL), dried over Na_2SO_4, concentrated on to silica, and purified by flash column chromatography using a gradient of 1−5% methanol in dichloromethane to yield an inseparable 10:1 mixture of **8a** and **8b** as a brown solid in 85% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.36 (s, 1 H), 8.43 (d, J = 8.8 Hz, 1 H), 8.36 (d, J = 2.0 Hz, 1 H), 7.98 (dd, J = 9.3, 2.0 Hz, 1 H). LCMS found 242.9 $[M + H]^+$.

*7-Bromo-4-chlorocinnoline (**8c**).* In a flame-dried 25 mL round-bottom flask were added 7-bromocinnolin-4(1*H*)-one (166 mg, 0.74 mmol), anhydrous tetrahydrofuran (7 mL), and phosphorus oxychloride (0.2 mL, 2.15 mmol). The mixture was refluxed for 1 h at which point a deep green/blue solution had resulted. The solution was

Table 5. Physicochemical Properties of Some of the Most Potent Antiparasitic Agents

compound	molecular weight	clogP	logD	plasma protein binding (% free)	solubility (uM)	Human liver microsomes median CL_{int} (μL/(min·mg))	male rat hepatocytes median CL_{int} (μL/(min·10^6 cells))
1	541	7.31	3.2	<1	<1	63.03	44.5
47	586	6.22	3.5	<1	<1	78.87	13.93
50	617	6.43	*a*	<1	*a*	142.7	20.24
68	632	5.51	*a*	<1	<1	99.32	36.72
83	656	6.35	*a*	<1	*a*	151.8	37.95

[a]Not determined.

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cooled to 0 °C and was quenched by the dropwise addition of sat. aq. $NaHCO_3$ (12 mL). The mixture was allowed to warm to room temperature and stir for an additional 1 h. Water (12 mL) was added, and the mixture was extracted with dichloromethane (3 × 25 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (20 mL), washed with brine (20 mL), and dried over Na_2SO_4 to yield **8c** as a dark brown solid in 92% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.39 (s, 1 H), 8.76 (d, J = 2.0 Hz, 1 H), 8.09 (d, J = 9.3 Hz, 1 H), 7.95 (dd, J = 9.0, 1.7 Hz, 1 H). LCMS found 242.9 $[M + H]^+$.

*7-Bromo-1-chlorophthalazine (**9a**).* In a flame-dried 25 mL round-bottom flask were added 7-bromophthalazin-1(2*H*)-one (205 mg, 0.91 mmol), anhydrous acetonitrile (9 mL), and phosphorus oxychloride (0.3 mL, 3.22 mmol). The mixture was refluxed for 2 h, then cooled to 0 °C, diluted with dichloromethane (20 mL), and quenched with a dropwise addition of sat. aq. $NaHCO_3$ (20 mL). The biphasic mixture was stirred vigorously and allowed to warm to room temperature. After 1 h, the layers were separated and the aqueous was extracted with dichloromethane (2 × 30 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (25 mL), washed with brine (20 mL), dried over Na_2SO_4, and concentrated to yield **9a** as an orange solid in 91% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.45 (s, 1 H), 8.49−8.51 (m, 1 H), 8.10 (dd, J = 8.8, 2.0 Hz, 1 H), 7.91 (d, J = 8.8 Hz, 1 H). LCMS found 242.9 $[M + H]^+$.

*6-Bromo-1-chlorophthalazine (**9c**).* In a flame-dried 50 mL round-bottom flask were added 6-bromophthalazin-1(2*H*)-one (402 mg, 1.78 mmol), anhydrous acetonitrile (18 mL), and phosphorus oxychloride (0.5 mL, 5.36 mmol). The mixture was refluxed for 2 h, then cooled to 0 °C, diluted with dichloromethane (40 mL), and quenched with a dropwise addition of sat. aq. $NaHCO_3$ (40 mL). The biphasic mixture was stirred vigorously and allowed to warm to room temperature. After 1 h, the layers were separated, and the aqueous was extracted with dichloromethane (2 × 50 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (40 mL), washed with brine (30 mL), dried over Na_2SO_4, and concentrated to yield **29c** as a yellow solid in 94% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.39 (s, 1 H), 8.17−8.21 (m, 2 H), 8.10 (dd, J = 8.8, 2.0 Hz, 1 H). LCMS found 242.9 $[M + H]^+$.

*6-Bromocinnolin-4(1H)-one (**15**).* In a 250 mL round-bottom flask were added 1-(2-amino-5-bromophenyl)ethanone (8.34 g, 39.0 mmol), water (30 mL), and conc. hydrochloric acid (30 mL, 987 mmol). The mixture was cooled to 0 °C in an ice bath and allowed to stir for 15 min until a suspension resulted. Aqueous sodium nitrite (2 M, 20 mL, 40.0 mmol) was then added dropwise with an addition funnel. The resulting solution was allowed to warm to room temperature over 1.5 h and was stirred at room temperature overnight, then refluxed for 6 h. The mixture was cooled to room temperature, water (200 mL) was added, and the mixture was extracted with ethyl acetate (3 × 200 mL). The combined organic layers were then washed with brine (50 mL), dried over sodium sulfate, filtered, and concentrated onto silica. The crude product was then purified by flash column chromatography using a gradient of 1−10% methanol in dichloromethane to yield **15** as a dark brown solid in 82% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 14.09 (br. s., 1 H), 8.09 (d, J = 2.2 Hz, 1 H), 7.92 (dd, J = 8.8, 2.2 Hz, 1 H), 7.79 (s, 1 H), 7.71 (d, J = 9.1 Hz, 1 H). LCMS found 224.9 $[M + H]^+$.

*7-Bromocinnolin-4(1H)-one (**18**).* In a 50 mL round-bottom flask were added 1-(2-amino-4-bromophenyl)ethanone (712 mg, 3.33 mmol), water (3 mL), and conc. hydrochloric acid (3 mL, 99 mmol). The mixture was cooled to 0 °C in an ice bath and allowed to stir for 15 min until a suspension resulted. Aqueous sodium nitrite (2 M, 1.84 mL, 3.68 mmol) was then added dropwise with an addition funnel. The resulting solution was allowed to warm to room temperature over 1.5 h and was stirred at room temperature overnight, then refluxed for 6 h. The mixture was cooled to room temperature, water (35 mL) was added, and the mixture was extracted with ethyl acetate (3 × 40 mL). The combined organic layers were then washed with brine (20 mL), dried over sodium sulfate, filtered, and concentrated onto silica. The crude product was then purified by flash column chromatography using a gradient of 20−50% ethyl acetate in hexanes, then ethyl acetate to yield **18** as a light brown solid in 26% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.49 (s, 1 H), 7.92 (d, J = 8.8 Hz, 1 H), 7.76 (s, 1 H), 7.73 (d, J = 2.0 Hz, 1 H), 7.53 (dd, J = 8.8, 2.0 Hz, 1 H). LCMS found 225.0 $[M + H]^+$.

*6-Bromoisobenzofuran-1(3H)-one (**20a**).* In a 100 mL round-bottom flask was dissolved isobenzofuran-1(3*H*)-one (4.01 g, 29.9 mmol) in trifluoroacetic acid (14 mL, 182 mmol) and sulfuric acid (6.5 mL, 122 mmol). *N*-Bromosuccinimide (7.95 g, 1.49 mmol) was added portionwise over 8 h, and the solution was stirred at room temperature for an additional 87 h. The solution was diluted with water (40 mL) and ethyl acetate (40 mL). The pH of the aqueous layer was neutralized with 1 M aq. NaOH and sat. aq. $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine (25 mL), dried over Na_2SO_4, and concentrated onto silica. The crude product was then purified by flash column chromatography using 10−20% ethyl acetate in hexanes to yield **20a** as white solid in 57% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, J = 1.5 Hz, 1 H), 7.77 (dd, J = 8.3, 1.5 Hz, 1 H), 7.40 (d, J = 8.3 Hz, 1 H), 5.27 (s, 2 H). LCMS found 212.9 $[M + H]^+$.

*3,6-Dibromoisobenzofuran-1(3H)-one (**21a**).* In a 50 mL round-bottom flask were added 6-bromoisobenzofuran-1(3*H*)-one (1.00 g, 4.69 mmol), *N*-bromosuccinimide (958 mg, 5.38 mmol), 2,2′-azobis(2-methylpropionitrile) (75 mg, 0.46 mmol), and chloroform (23 mL). The mixture was refluxed for 2.5 h, then cooled to room temperature and quenched with sat. aq. $NaHCO_3$ (25 mL). The organic layer was removed, washed with water (20 mL), washed with brine (15 mL), and concentrated onto silica. The crude product was purified by flash column chromatography using a gradient of 5−10% ethyl acetate in hexanes to yield **21a** as a white solid in 61% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, J = 1.5 Hz, 1 H), 7.90 (dd, J = 8.1, 1.7 Hz, 1 H), 7.52 (d, J = 8.3 Hz, 1 H), 7.37 (s, 1 H). GCMS found 289.9 $[M]^{+\bullet}$.

*3,5-Dibromoisobenzofuran-1(3H)-one (**21b**).* In a 25 mL round-bottom flask were added 5-bromoisobenzofuran-1(3*H*)-one (499 mg, 2.34 mmol), *N*-bromosuccinimide (421 mg, 2.37 mmol), 2,2′-azobis(2-methylpropionitrile) (38 mg, 0.23 mmol), and chloroform (10 mL). The mixture was refluxed for 2.5 h, then cooled to room temperature and quenched with sat. aq. $NaHCO_3$ (10 mL). The organic layer was removed, washed with water (10 mL), washed with brine (5 mL), and concentrated onto silica. The crude product was purified by flash column chromatography using 10% ethyl acetate in hexanes to yield **21b** as a white solid in 49% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74−7.83 (m, 3 H), 7.36 (s, 1 H). GCMS found 289.8 $[M]^{+\bullet}$.

*7-Bromophthalazin-1(2H)-one (**22a**).* In a 25 mL round-bottom flask was dissolved 3,6-dibromoisobenzofuran-1(3*H*)-one (143 mg, 0.49 mmol) in ethanol (5 mL). Hydrazine monohydrate (0.12 mL, 2.48 mmol) was then added via a syringe, and the solution was refluxed for 1.5 h. The solution was cooled to room temperature, and ice water (15 mL) was added to the reaction mixture. The precipitate was vacuum filtered and dried under a vacuum overnight to yield **22a** as a white solid in 56% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.82 (br. s., 1 H), 8.39 (s, 1 H), 8.30 (d, J = 2.0 Hz, 1 H), 8.11 (dd, J = 8.5, 2.2 Hz, 1 H), 7.90 (d, J = 8.3 Hz, 1 H). LCMS found 225.0 $[M + H]^+$.

*6-Bromophthalazin-1(2H)-one (**22b**).* In a 25 mL round-bottom flask was dissolved 3,5-dibromoisobenzofuran-1(3*H*)-one (302 mg, 1.04 mmol) in ethanol (10 mL). Hydrazine monohydrate (0.25 mL, 5.18 mmol) was then added via a syringe, and the solution was refluxed for 1.5 h. The solution was cooled to room temperature, and ice water (30 mL) was added to the reaction mixture. The precipitate was vacuum filtered and dried under a vacuum overnight to yield **22b** as a white solid in 73% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.78 (br. s., 1 H), 8.33 (s, 1 H), 8.23 (d, J = 2.0 Hz, 1 H), 8.12 (d, J = 8.3 Hz, 1 H), 8.00 (dd, J = 8.3, 2.0 Hz, 1 H). LCMS found 224.9 $[M + H]^+$.

General Procedure A for the Amination of 4-Chloro-6-iodoquinoline-3-carbonitrile and 4-Chlorothienopyrimidines. To a solution of the appropriate aryl chloride (1 equiv) in 2-propanol (0.15 M) was added 3-chloro-4-((3-fluorobenzyl)oxy)aniline or 4-(benzyloxy)-3-chloroaniline (1.1 equiv). The resulting mixture was refluxed

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overnight. The formed precipitate was collected by vacuum filtration to obtain the desired products.

General procedure B for the Amination of 4-Chloroquinolines and 1-Chloroisoquinolines. To a solution of the appropriate aryl chloride (1 equiv) in 2-propanol (0.15 M) was added 3-chloro-4-((3-fluorobenzyl)oxy)aniline or 4-(benzyloxy)-3-chloroaniline (1.1 equiv). The resulting mixture was refluxed overnight. The mixture was diluted with water, basified with 3 M aq. NaOH to pH 12, and extracted with dichloromethane (3×). The combined organic layers were washed with water, washed with brine, dried over Na_2SO_4, and concentrated. The crude products were purified by flash column chromatography to obtain the desired products.

General Procedure C for the Amination of 4-Chlorocinnolines. A solution of the appropriate 4-chlorocinnoline (1 equiv) and 3-chloro-4-((3-fluorobenzyl)oxy)aniline or 4-(benzyloxy)-3-chloroaniline (4 equiv) in toluene (0.1 M) was refluxed for 2.5 h and cooled to room temperature. Triethylamine (4 equiv) was added, and the mixture was returned to reflux for an additional 30 min. The mixture was cooled back to room temperature, and the formed yellow precipitate was vacuum filtered, washed with ethyl acetate, concentrated onto silica, and purified by flash column chromatography.

General Procedure D for the Amination of 1-Chlorophthalazines. A solution of the appropriate 1-chlorophthalazine (1 equiv) and 3-chloro-4-((3-fluorobenzyl)oxy)aniline or 4-(benzyloxy)-3-chloroaniline (4 equiv) in anhydrous toluene (0.2 M) was heated at 50 °C overnight. Water was added, and the mixture was neutralized with 1 M aq. NaOH and was extracted with 5% methanol in dichloromethane. The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated onto silica, and purified by flash column chromatography.

*6-Bromo-N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)quinolin-4-amine (**23**).* Synthesized by general procedure B. Flash column chromatography: 20−50% ethyl acetate in hexanes to yield **23** as a light brown solid in 90% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.99 (s, 1 H), 8.63 (s, 1 H), 8.46 (d, J = 5.4 Hz, 1 H), 7.80 (d, J = 1.5 Hz, 2 H), 7.43−7.51 (m, 2 H), 7.27−7.36 (m, 4 H), 7.19 (td, J = 8.7, 2.2 Hz, 1 H), 6.80 (d, J = 5.4 Hz, 1 H), 5.26 (s, 2 H). LCMS found 456.8 [M + H]$^+$.

*N-(4-(Benzyloxy)-3-chlorophenyl)-6-bromoquinolin-4-amine (**24**).* Synthesized by general procedure B. Flash column chromatography: 20−70% ethyl acetate in hexanes to yield **24** as a brown solid in 70% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.98 (s, 1 H), 8.63 (s, 1 H), 8.45 (d, J = 5.4 Hz, 1 H), 7.80 (s, 2 H), 7.50 (d, J = 7.3 Hz, 2 H), 7.39−7.46 (m, 3 H), 7.35 (t, J = 7.3 Hz, 1 H), 7.30 (s, 2 H), 6.79 (d, J = 5.4 Hz, 1 H), 5.23 (s, 2 H). LCMS found 439.2 [M + H]$^+$.

*7-Bromo-N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)quinolin-4-amine (**25**).* Synthesized by general procedure B. Flash column chromatography: 20−50% ethyl acetate in hexanes to yield **25** as a tan colored solid in 82% yield. ^{1}H NMR (399 MHz, DMSO-d_6) δ 9.05 (s, 1 H), 8.43 (d, J = 5.1 Hz, 1 H), 8.31 (d, J = 8.8 Hz, 1 H), 8.05 (d, J = 2.2 Hz, 1 H), 7.67 (dd, J = 8.8, 2.2 Hz, 1 H), 7.41−7.52 (m, 2 H), 7.25−7.37 (m, 4 H), 7.18 (td, J = 8.6, 2.6 Hz, 1 H), 6.76 (d, J = 5.9 Hz, 1 H), 5.25 (s, 2 H). LCMS found 456.8 [M + H]$^+$.

*N-(4-(Benzyloxy)-3-chlorophenyl)-7-bromoquinolin-4-amine (**26**).* Synthesized by general procedure B. Flash column chromatography: 20−50% ethyl acetate in hexanes to yield **26** as an off-white solid in 83% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.04 (s, 1 H), 8.43 (d, J = 4.9 Hz, 1 H), 8.31 (d, J = 9.3 Hz, 1 H), 8.05 (d, J = 2.0 Hz, 1 H), 7.67 (dd, J = 9.0, 2.2 Hz, 1 H), 7.49 (d, J = 6.8 Hz, 2 H), 7.39−7.46 (m, 3 H), 7.35 (t, J = 7.3 Hz, 1 H), 7.30 (s, 2 H), 6.75 (d, J = 5.4 Hz, 1 H), 5.23 (s, 2 H). LCMS found 439.2 [M + H]$^+$.

*7-Bromo-N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)isoquinolin-1-amine (**27**).* Synthesized by general procedure B. Flash column chromatography: 10−30% ethyl acetate in hexanes to yield **27** as a pale red-brown solid in 97% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.24 (s, 1 H), 8.80 (s, 1 H), 8.07 (d, J = 2.4 Hz, 1 H), 8.02 (d, J = 5.9 Hz, 1 H), 7.82 (dd, J = 8.8, 1.5 Hz, 1 H), 7.72−7.79 (m, 2 H), 7.41−7.49 (m, 1 H), 7.27−7.35 (m, 2 H), 7.13−7.23 (m, 3 H), 5.21 (s, 2 H). LCMS found 456.8 [M + H]$^+$.

*N-(4-(Benzyloxy)-3-chlorophenyl)-7-bromoisoquinolin-1-amine (**28**).* Synthesized by general procedure B. Flash column chromatography: 10−30% ethyl acetate in hexanes to yield **28** as a light red solid in 93% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.22 (s, 1 H), 8.80 (s, 1 H), 8.07 (d, J = 2.4 Hz, 1 H), 8.02 (d, J = 5.9 Hz, 1 H), 7.81 (dd, J = 8.8, 1.5 Hz, 1 H), 7.73−7.78 (m, 2 H), 7.48 (d, J = 7.3 Hz, 2 H), 7.40 (t, J = 7.6 Hz, 2 H), 7.33 (t, J = 7.3 Hz, 1 H), 7.21 (d, J = 8.8 Hz, 1 H), 7.15 (d, J = 5.9 Hz, 1 H), 5.18 (s, 2 H). LCMS found 439.2 [M + H]$^+$.

*6-Bromo-N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)isoquinolin-1-amine (**29**).* Synthesized by general procedure B. Flash column chromatography: 10−30% ethyl acetate in hexanes to yield **29** as a salmon colored solid in 91% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.27 (s, 1 H), 8.45 (d, J = 8.8 Hz, 1 H), 8.08 (dd, J = 12.0, 2.2 Hz, 2 H), 8.01 (d, J = 5.4 Hz, 1 H), 7.75 (ddd, J = 13.8, 9.2, 2.4 Hz, 2 H), 7.46 (m, J = 5.9 Hz, 1 H), 7.27−7.35 (m, 2 H), 7.10−7.23 (m, 3 H), 5.22 (s, 2 H). LCMS found 456.8 [M + H]$^+$.

*N-(4-(Benzyloxy)-3-chlorophenyl)-6-bromoisoquinolin-1-amine (**30**).* Synthesized by general procedure B. Flash column chromatography: 10−30% ethyl acetate in hexanes to yield **30** as a burnt orange solid in 81% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.24 (s, 1 H), 8.45 (d, J = 8.8 Hz, 1 H), 8.10 (d, J = 2.0 Hz, 1 H), 8.05 (d, J = 2.4 Hz, 1 H), 8.01 (d, J = 5.9 Hz, 1 H), 7.76 (dd, J = 9.0, 2.2 Hz, 1 H), 7.72 (dd, J = 8.8, 2.4 Hz, 1 H), 7.48 (d, J = 6.8 Hz, 2 H), 7.41 (t, J = 7.3 Hz, 2 H), 7.34 (t, J = 7.8 Hz, 1 H), 7.21 (d, J = 9.3 Hz, 1 H), 7.13 (d, J = 5.9 Hz, 1 H), 5.19 (s, 2 H). LCMS found 439.2 [M + H]$^+$.

*6-Bromo-N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)cinnolin-4-amine (**31**).* Synthesized by general procedure C. Flash column chromatography: 5% methanol in dichloromethane to yield an inseparable 10:1 mixture of **31** and dichloro side product as a vibrant yellow solid in 54% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.33 (s, 1 H), 8.78 (s, 1 H), 8.70 (d, J = 1.5 Hz, 1 H), 8.14 (d, J = 8.8 Hz, 1 H), 7.97 (dd, J = 9.3, 1.5 Hz, 1 H), 7.54 (d, J = 2.0 Hz, 1 H), 7.48 (td, J = 8.3, 6.3 Hz, 1 H), 7.40 (dd, J = 8.8, 2.4 Hz, 1 H), 7.30−7.37 (m, 3 H), 7.20 (td, J = 9.3, 2.0 Hz, 1 H), 5.29 (s, 2 H). LCMS found 458.0 [M + H]$^+$.

*N-(4-(Benzyloxy)-3-chlorophenyl)-6-bromocinnolin-4-amine (**32**).* Synthesized by general procedure C. Flash column chromatography: 5% methanol in dichloromethane to yield an inseparable 10:1 mixture of **32** and dichloro side product as a yellow solid in 68% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.32 (s, 1 H), 8.78 (s, 1 H), 8.71 (d, J = 2.0 Hz, 1 H), 8.14 (d, J = 9.3 Hz, 1 H), 7.97 (dd, J = 9.0, 1.7 Hz, 1 H), 7.47−7.55 (m, 3 H), 7.44 (t, J = 7.6 Hz, 2 H), 7.33−7.41 (m, 3 H), 5.26 (s, 2 H). LCMS found 439.9 [M + H]$^+$.

*7-Bromo-N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)cinnolin-4-amine (**33**).* Synthesized by general procedure C. Flash column chromatography: 5% methanol in dichloromethane to yield **33** as a brown solid in 55% yield with 84% purity. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.43 (s, 1 H), 8.76 (s, 1 H), 8.41 (d, J = 2.0 Hz, 1 H), 8.35 (d, J = 9.3 Hz, 1 H), 7.90 (dd, J = 9.0, 2.2 Hz, 1 H), 7.55 (d, J = 2.4 Hz, 1 H), 7.49 (m, J = 6.3 Hz, 1 H), 7.41 (dd, J = 8.8, 2.4 Hz, 1 H), 7.31−7.37 (m, 3 H), 7.20 (td, J = 8.4, 2.7 Hz, 1 H), 5.29 (s, 2 H). LCMS found 457.9 [M + H]$^+$.

*N-(4-(Benzyloxy)-3-chlorophenyl)-7-bromocinnolin-4-amine (**34**).* Synthesized by general procedure C. Flash column chromatography: 5% methanol in dichloromethane to yield **34** as a metallic bronze colored solid in 57% yield with 85% purity. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.42 (s, 1 H), 8.75 (s, 1 H), 8.41 (d, J = 2.0 Hz, 1 H), 8.35 (d, J = 8.8 Hz, 1 H), 7.90 (dd, J = 9.0, 2.2 Hz, 1 H), 7.54 (d, J = 2.4 Hz, 1 H), 7.51 (d, J = 7.3 Hz, 2 H), 7.43 (t, J = 7.6 Hz, 2 H), 7.40 (dd, J = 8.8, 2.4 Hz, 1 H), 7.33−7.38 (m, 2 H), 5.26 (s, 2 H). LCMS found 440.0 [M + H]$^+$.

*7-Bromo-N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)phthalazin-1-amine (**35**).* Synthesized by general procedure D. Flash column chromatography: 5−20% ethyl acetate in dichloromethane to yield **35** as a yellow solid in 69% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.21 (s, 1 H), 9.13 (s, 1 H), 8.87 (s, 1 H), 8.16 (d, J = 2.4 Hz, 1 H), 8.11 (dd, J = 8.8, 1.5 Hz, 1 H), 7.99 (d, J = 8.8 Hz, 1 H), 7.81 (dd, J = 8.8, 2.4 Hz, 1 H), 7.47 (td, J = 7.9, 6.1 Hz, 1 H), 7.29−7.36 (m, 2 H), 7.25 (d, J = 9.3 Hz, 1 H), 7.17 (td, J = 8.7, 2.2 Hz, 1 H), 5.24 (s, 2 H). LCMS found 457.9 [M + H]$^+$.

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*N-(4-(Benzyloxy)-3-chlorophenyl)-7-bromophthalazin-1-amine (**36**).* Synthesized by general procedure D. Flash column chromatography: 5−20% ethyl acetate in dichloromethane to yield **36** as a light greenish brown solid in 78% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.20 (s, 1 H), 9.14 (s, 1 H), 8.88 (s, 1 H), 8.15 (d, J = 2.4 Hz, 1 H), 8.13 (dd, J = 8.5, 1.7 Hz, 1 H), 8.00 (d, J = 8.8 Hz, 1 H), 7.80 (dd, J = 9.0, 2.7 Hz, 1 H), 7.50 (d, J = 7.3 Hz, 2 H), 7.42 (t, J = 7.6 Hz, 2 H), 7.35 (t, J = 7.3 Hz, 1 H), 7.27 (d, J = 8.8 Hz, 1 H), 5.21 (s, 2 H). LCMS found 440.0 $[M + H]^+$.

*6-Bromo-N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)phthalazin-1-amine (**37**).* Synthesized by general procedure D. Flash column chromatography: 5−20% ethyl acetate in dichloromethane to yield **37** as a light brown solid in 64% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.42 (s, 1 H), 9.09 (s, 1 H), 8.62 (d, J = 9.3 Hz, 1 H), 8.33 (d, J = 2.0 Hz, 1 H), 8.19 (d, J = 2.4 Hz, 1 H), 8.16 (dd, J = 9.0, 2.2 Hz, 1 H), 7.83 (dd, J = 8.8, 2.4 Hz, 1 H), 7.47 (td, J = 7.8, 5.9 Hz, 1 H), 7.32 (m, J = 7.3 Hz, 2 H), 7.25 (d, J = 9.3 Hz, 1 H), 7.17 (td, J = 8.5, 2.0 Hz, 1 H), 5.24 (s, 2 H). LCMS found 458.0 $[M + H]^+$.

*N-(4-(Benzyloxy)-3-chlorophenyl)-6-bromophthalazin-1-amine (**38**).* Synthesized by general procedure D. Flash column chromatography: 5−30% ethyl acetate in dichloromethane to yield **38** as a green-gray colored solid in 75% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.25 (s, 1 H), 9.09 (s, 1 H), 8.51 (d, J = 8.8 Hz, 1 H), 8.33 (d, J = 2.0 Hz, 1 H), 8.17 (dd, J = 8.8, 2.0 Hz, 1 H), 8.14 (d, J = 2.9 Hz, 1 H), 7.78 (dd, J = 9.0, 2.7 Hz, 1 H), 7.49 (d, J = 6.8 Hz, 2 H), 7.42 (t, J = 7.6 Hz, 2 H), 7.35 (t, J = 7.3 Hz, 1 H), 7.26 (d, J = 8.8 Hz, 1 H), 5.21 (s, 2 H). LCMS found 440.0 $[M + H]^+$.

*4-((3-Chloro-4-((3-fluorobenzyl)oxy)phenyl)amino)-6-iodoquinoline-3-carbonitrile (**39**).* Synthesized by general procedure A, collected as a yellow solid in 80% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.03 (s, 1H), 8.85 (br, s, 1H), 8.23 (d, J = 8.8 Hz, 1H), 7.73 (d, J = 8.8, 1H), 7.59 (d, J = 2.4, 1H), 7.45−7.50 (m, 1H), 7.30−7.39 (m, 4H), 7.18−7.22 (m, 1H), 5.30 (s, 2H). LCMS found 530.7 $[M + H]^+$.

*4-((4-(Benzyloxy)-3-chlorophenyl)amino)-6-iodoquinoline-3-carbonitrile (**40**).* Synthesized by general procedure A, collected as a yellow solid in 52% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.02 (s, 1H), 8.82 (br, s, 1H), 8.22 (d, J = 9.0 Hz, 1H), 7.72 (d, J = 8.5 Hz, 1H), 7.57 (s, 1H), 7.5 (d, J = 7.0 Hz, 2H), 7.43 (t, J = 7.5 Hz, 2H), 7.35 (m, 3H), 5.26 (s, 2H). LCMS found 512.7 $[M + H]^+$.

*6-Bromo-N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)thieno[3,2-d]pyrimidin-4-amine (**41**).* Synthesized by general procedure A as a light brown solid in 88% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.64 (s, 1 H), 8.71 (s, 1 H), 7.87 (d, J = 2.9 Hz, 1 H), 7.74 (s, 1 H), 7.57 (dd, J = 8.8, 2.2 Hz, 1 H), 7.47 (m, 1 H), 7.31 (m, 3 H), 7.19 (td, J = 8.1, 2.2 Hz, 1 H), 5.28 (s, 2 H). LCMS found 463.9, $[M + H]^+$.

*N-(4-(Benzyloxy)-3-chlorophenyl)-6-bromothieno[3,2-d]pyrimidin-4-amine (**42**).* Synthesized by general procedure A as a light brown solid in 74% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.71 (s, 1 H), 8.54 (s, 1 H), 7.89 (d, J = 2.0 Hz, 1 H), 7.68 (s, 1 H), 7.58 (dd, J = 8.8, 2.9 Hz, 1 H), 7.49 (d, J = 7.8 Hz, 2 H), 7.42 (t, J = 7.6 Hz, 2 H), 7.35 (t, J = 7.3 Hz, 1 H), 7.26 (d, J = 8.8 Hz, 1 H), 5.23 (s, 2 H). LCMS found 445.9, $[M + H]^+$.

*6-Bromo-N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)thieno[2,3-d]pyrimidin-4-amine (**43**).* Synthesized by general procedure A in 88% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.80 (s, 1H), 8.49 (s, 1H), 8.12 (s, 1H), 8.02 (d, J = 2.4 Hz, 1H), 7.67 (dd, J = 2.7, 9.03 Hz, 1H), 7.43−7.49 (m, 1H), 7.24−7.35 (m, 3H), 7.18 (dt, J = 2.4, 8.6 Hz, 1H), 5.24 (s, 2H). LCMS found 463.8 $[M + H]^+$.

*N-(4-(Benzyloxy)-3-chlorophenyl)-6-bromothieno[2,3-d]pyrimidin-4-amine (**44**).* Synthesized by general procedure A as a light brown solid in 63% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.94 (s, 1 H), 8.49 (s, 1 H), 8.19 (s, 1 H), 8.02 (d, J = 2.4 Hz, 1 H), 7.68 (dd, J = 8.8, 2.4 Hz, 1 H), 7.49 (m, 2 H), 7.41 (m, 2 H), 7.34 (m, 1 H), 7.27 (d, J = 9.3 Hz, 1 H), 5.21 (s, 2 H). LCMS found 445.9 $[M + H]^+$.

General Procedure A for Suzuki Couplings. In a 2−5 mL microwave vial equipped with a stir bar were added aryl bromide (1 equiv), boronic ester (1.3 equiv), 1:1 water/ethanol (0.04 M), triethylamine (3 equiv), and palladium(II) acetate (0.01 M in acetone, 1 mol %). The vial was sealed with a septum, and the contents were irradiated to and held at 120 °C with stirring for 1 h. The reaction mixture was cooled to room temperature, diluted with water (8 mL), and extracted with dichloromethane (3 × 8 mL). The combined organic layers were washed with aq. NaOH (1 M, 2 × 5 mL), water (5 mL), and brine (5 mL). The organic layer was then dried over Na_2SO_4 and concentrated onto silica. The crude product was purified by flash column chromatography.

General Procedure B for Suzuki Couplings. In a 2−5 mL microwave vial equipped with a stir bar were added aryl bromide (1 equiv), boronic ester (1.3 equiv), 1:1 water/ethanol (0.04 M), triethylamine (3 equiv), and bis(triphenylphosphine)palladium(II) chloride (2.5 mol %). The vial was sealed with a septum, and the contents were irradiated to and held at 120 °C with stirring for 1 h. The reaction mixture was cooled to room temperature, diluted with water (8 mL), and extracted with dichloromethane (3 × 8 mL). The combined organic layers were washed with aq. NaOH (1 M, 2 × 5 mL), water (5 mL), and brine (5 mL). The organic layer was then dried over Na_2SO_4 and concentrated on to silica. The crude product was purified by flash column chromatography.

General Procedure C for Suzuki Couplings. In a 2−5 mL microwave vial equipped with a stir bar were added aryl bromide (1 equiv), boronic ester (1.3 equiv), 1:1 water/ethanol (0.04 M), triethylamine (3 equiv), and palladium(II) acetate (5 mol %). The vial was sealed with a septum, and the contents were irradiated to and held at 120 °C with stirring for 3 h. The reaction mixture was cooled to room temperature, diluted with water (8 mL), and extracted with dichloromethane (3 × 8 mL). The combined organic layers were washed with aq. NaOH (1 M, 2 × 5 mL), water (5 mL), and brine (5 mL). The organic layer was then dried over Na_2SO_4 and concentrated on to silica. The crude product was purified by flash column chromatography.

General Procedure D for Suzuki Couplings. To a solution of the appropriate aryl iodide (1 equiv) in 3:2 dimethoxyethane/ethanol (0.05 M) were added the appropriate aryl boronic ester (1.1 equiv), aq. 2 M Na_2CO_3 (6 equiv), and $Pd(PPh_3)_4$ (5 mol %). The mixture was purged with nitrogen and heated at 85 °C for 7 h. The mixture was cooled to room temperature and filtered, and the filtrate was concentrated. The residue was dissolved in ethyl acetate, washed with water, washed with brine, dried over Na_2SO_4, and purified by flash column chromatography.

General Procedure E for Suzuki Couplings. To a solution of the appropriate aryl bromide (1 equiv) in 3:2 dimethoxyethane/ethanol (0.05 M) were added the appropriate aryl boronic ester (1.2 equiv), aq. 2 M Na_2CO_3 (6 equiv), and $Pd(PPh_3)_4$ (7 mol %). The mixture was heated at 85 °C for 12 h, then cooled to room temperature, and the solvents were removed under reduced pressure. The residue was purified by silica column chromatography (hexanes/ethyl acetate) and then by reverse phase chromatography (water/acetonitrile) unless otherwise mentioned.

*N-(3-Chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(3-morpholinophenyl)quinolin-4-amine (**45**).* Synthesized by general procedure A. Flash column chromatography: 2−5% methanol in dichloromethane, isolated as a yellow solid in 27% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.10 (br. s., 1 H), 8.61 (d, J = 2.0 Hz, 1 H), 8.43 (d, J = 5.4 Hz, 1 H), 8.04 (dd, J = 8.8, 2.0 Hz, 1 H), 7.92 (d, J = 8.8 Hz, 1 H), 7.45−7.52 (m, 2 H), 7.39 (t, J = 7.8 Hz, 1 H), 7.29−7.37 (m, 6 H), 7.20 (td, J = 8.8, 2.0 Hz, 1 H), 7.00 (dd, J = 8.1, 1.7 Hz, 1 H), 6.77 (d, J = 5.4 Hz, 1 H), 5.28 (s, 2 H), 3.75−3.81 (m, 4 H), 3.19−3.26 (m, 4 H). LCMS found 540.1 $[M + H]^+$.

*N-(3-Chloro-4-((3-fluorobenzyl)oxy)phenyl)-7-(3-morpholinophenyl)quinolin-4-amine (**46**).* Synthesized by general procedure A. Flash column chromatography: 2−5% methanol in dichloromethane, isolated as a yellow solid in 24% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.99 (br. s., 1 H), 8.47 (d, J = 5.4 Hz, 1 H), 8.41 (d, J = 8.8 Hz, 1 H), 8.12 (d, J = 2.0 Hz, 1 H), 7.88 (dd, J = 8.8, 1.5 Hz, 1 H), 7.45−7.51 (m, 2 H), 7.26−7.40 (m, 7 H), 7.20 (td, J = 8.8, 2.4 Hz, 1 H), 7.02 (dd, J = 8.3, 2.0 Hz, 1 H), 6.76 (d, J = 5.4 Hz, 1 H), 5.27 (s, 2 H), 3.74−3.82 (m, 4 H), 3.20−3.27 (m, 4 H). LCMS found 540.2 $[M + H]^+$.

*N-(4-(Benzyloxy)-3-chlorophenyl)-6-(4-(morpholinosulfonyl)-phenyl)quinolin-4-amine (**47**).* Synthesized by general procedure A.

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Flash column chromatography: 0−5% methanol in dichloromethane, isolated as a tan colored solid in 65% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.14 (s, 1 H), 8.78 (d, J = 2.0 Hz, 1 H), 8.47 (d, J = 5.4 Hz, 1 H), 8.17 (d, J = 8.8 Hz, 2 H), 8.11 (dd, J = 8.8, 2.0 Hz, 1 H), 7.98 (d, J = 8.8 Hz, 1 H), 7.88 (d, J = 8.3 Hz, 2 H), 7.51 (d, J = 7.3 Hz, 2 H), 7.48 (d, J = 1.5 Hz, 1 H), 7.43 (t, J = 7.6 Hz, 2 H), 7.32−7.39 (m, 3 H), 6.80 (d, J = 5.4 Hz, 1 H), 5.25 (s, 2 H), 3.61−3.70 (m, 4 H), 2.88−2.97 (m, 4 H). LCMS found 586.1 $[M + H]^+$.

*N-(4-(Benzyloxy)-3-chlorophenyl)-7-(4-(morpholinosulfonyl)-phenyl)quinolin-4-amine (**48**).* Synthesized by general procedure A. Flash column chromatography: 2−5% methanol in dichloromethane, isolated as a tan colored solid in 63% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.02 (s, 1 H), 8.50 (m, J = 5.4 Hz, 2 H), 8.25 (d, J = 1.5 Hz, 1 H), 8.18 (d, J = 8.8 Hz, 2 H), 7.97 (dd, J = 8.8, 1.5 Hz, 1 H), 7.87 (d, J = 8.3 Hz, 2 H), 7.51 (d, J = 7.3 Hz, 2 H), 7.47 (d, J = 2.0 Hz, 1 H), 7.44 (t, J = 7.6 Hz, 2 H), 7.36 (m, J = 6.8 Hz, 1 H), 7.30−7.34 (m, 2 H), 6.79 (d, J = 5.4 Hz, 1 H), 5.24 (s, 2 H), 3.62−3.70 (m, 4 H), 2.90−2.97 (m, 4 H). LCMS found 586.2 $[M + H]^+$.

*N-(3-Chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(4-((4-methylpiperazin-1-yl)sulfonyl)phenyl)quinolin-4-amine (**49**).* Synthesized by general procedure A. Flash column chromatography: 5−10% methanol in dichloromethane, isolated as a yellow solid in 40% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.19 (br. s., 1 H), 8.78 (d, J = 2.0 Hz, 1 H), 8.47 (d, J = 5.4 Hz, 1 H), 8.16 (d, J = 8.8 Hz, 2 H), 8.12 (dd, J = 8.8, 2.0 Hz, 1 H), 7.98 (d, J = 8.8 Hz, 1 H), 7.87 (d, J = 8.8 Hz, 2 H), 7.45−7.52 (m, 2 H), 7.30−7.38 (m, 4 H), 7.20 (td, J = 8.7, 2.7 Hz, 1 H), 6.81 (d, J = 5.4 Hz, 1 H), 5.28 (s, 2 H), 2.95 (br. s., 4 H), 2.35−2.43 (m, 4 H), 2.15 (s, 3 H). LCMS found 617.1 $[M + H]^+$.

*N-(3-Chloro-4-((3-fluorobenzyl)oxy)phenyl)-7-(4-((4-methylpiperazin-1-yl)sulfonyl)phenyl)quinolin-4-amine (**50**).* Synthesized by general procedure A. Flash column chromatography: 5−10% methanol in dichloromethane, isolated as a yellow solid in 33% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.10 (br. s., 1 H), 8.50 (d, J = 8.3 Hz, 2 H), 8.25 (d, J = 2.0 Hz, 1 H), 8.16 (d, J = 8.3 Hz, 2 H), 7.97 (dd, J = 8.8, 2.0 Hz, 1 H), 7.87 (d, J = 8.3 Hz, 2 H), 7.45−7.52 (m, 2 H), 7.29−7.38 (m, 4 H), 7.20 (td, J = 8.5, 2.0 Hz, 1 H), 6.80 (d, J = 5.4 Hz, 1 H), 5.28 (s, 2 H), 2.96 (br. s., 4 H), 2.40 (br. s., 4 H), 2.16 (s, 3 H). LCMS found 617.1 $[M + H]^+$.

*N-(3-Chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(4-((4-methyl-1,4-diazepan-1-yl)sulfonyl)phenyl)quinolin-4-amine (**51**).* Synthesized by general procedure A. Flash column chromatography: 5−20% methanol in dichloromethane. Then prep HPLC: 5−95% acetonitrile in water, isolated as a yellow solid in 10% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.77 (d, J = 2.0 Hz, 1 H), 8.46 (d, J = 5.4 Hz, 1 H), 8.27 (s, 1 H), 8.07−8.15 (m, 3 H), 7.97 (d, J = 8.8 Hz, 1 H), 7.92 (d, J = 8.3 Hz, 2 H), 7.45−7.52 (m, 2 H), 7.30−7.38 (m, 4 H), 7.20 (td, J = 8.5, 2.4 Hz, 1 H), 6.80 (d, J = 5.4 Hz, 1 H), 5.28 (s, 2 H), 3.36 (m, J = 5.2, 2.5, 2.5 Hz, 2 H), 3.33 (t, J = 6.3 Hz, 2 H), 2.53−2.57 (m, 2 H), 2.47 (m, J = 5.9 Hz, 2 H), 2.22 (s, 3 H), 1.74 (quin, J = 5.9 Hz, 2 H). LCMS found 631.2 $[M + H]^+$.

*N-(3-Chloro-4-((3-fluorobenzyl)oxy)phenyl)-7-(4-((4-methyl-1,4-diazepan-1-yl)sulfonyl)phenyl)quinolin-4-amine (**52**).* Synthesized by general procedure A. Flash column chromatography: 5−20% methanol in dichloromethane, isolated as a brown solid in 32% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.06 (s, 1 H), 8.47−8.52 (m, 2 H), 8.23 (d, J = 2.0 Hz, 1 H), 8.12 (d, J = 8.3 Hz, 2 H), 7.96 (dd, J = 8.8, 2.0 Hz, 1 H), 7.91 (d, J = 8.3 Hz, 2 H), 7.45−7.52 (m, 2 H), 7.29−7.37 (m, 4 H), 7.20 (td, J = 8.5, 2.4 Hz, 1 H), 6.79 (d, J = 4.9 Hz, 1 H), 5.27 (s, 2 H), 3.39 (m, J = 3.4 Hz, 2 H), 3.31−3.35 (m, 2 H), 2.63 (br. s., 2 H), 2.58 (br. s., 2 H), 2.29 (br. s., 3 H), 1.74−1.83 (m, 2 H). LCMS found 631.2 $[M + H]^+$.

*N-(3-Chloro-4-((3-fluorobenzyl)oxy)phenyl)-7-(3-morpholinophenyl)isoquinolin-1-amine (**53**).* Synthesized by general procedure A. Flash column chromatography: 30−50% ethyl acetate in hexanes, isolated as a biege solid in 59% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.27 (s, 1 H), 8.71 (s, 1 H), 8.06 (d, J = 2.4 Hz, 1 H), 8.03 (dd, J = 8.3, 1.5 Hz, 1 H), 7.98 (d, J = 5.4 Hz, 1 H), 7.88 (d, J = 8.8 Hz, 1 H), 7.76 (dd, J = 8.8, 2.4 Hz, 1 H), 7.47 (td, J = 8.1, 6.3 Hz, 1 H), 7.40 (t, J = 7.8 Hz, 1 H), 7.29−7.36 (m, 4 H), 7.23 (d, J = 9.3 Hz, 1 H), 7.15−7.21 (m, 2 H), 7.02 (dd, J = 8.3, 2.0 Hz, 1 H), 5.23 (s, 2 H), 3.75−3.82 (m, 4 H), 3.20−3.26 (m, 4 H). LCMS found 540.2 $[M + H]^+$.

*N-(3-Chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(3-morpholinophenyl)isoquinolin-1-amine (**54**).* Synthesized by general procedure A. Flash column chromatography: 30−50% ethyl acetate in hexanes, isolated as an orange solid in 81% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.21 (s, 1 H), 8.56 (d, J = 8.8 Hz, 1 H), 8.13 (d, J = 2.4 Hz, 1 H), 8.11 (d, J = 2.0 Hz, 1 H), 8.00 (d, J = 5.4 Hz, 1 H), 7.94 (dd, J = 8.8, 1.5 Hz, 1 H), 7.78 (dd, J = 8.8, 2.4 Hz, 1 H), 7.47 (td, J = 8.0, 6.3 Hz, 1 H), 7.35−7.41 (m, 2 H), 7.30−7.35 (m, 2 H), 7.28 (d, J = 7.8 Hz, 1 H), 7.20−7.25 (m, 2 H), 7.18 (td, J = 8.8, 2.4 Hz, 1 H), 7.03 (dd, J = 8.1, 2.2 Hz, 1 H), 5.23 (s, 2 H), 3.76−3.81 (m, 4 H), 3.21−3.25 (m, 4 H). LCMS found 540.2 $[M + H]^+$.

*N-(4-(Benzyloxy)-3-chlorophenyl)-7-(4-(morpholinosulfonyl)-phenyl)isoquinolin-1-amine (**55**).* Synthesized by general procedure A. Flash column chromatography: 20−50% ethyl acetate in hexanes, isolated as an orange solid in 55% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.35 (s, 1 H), 8.86 (s, 1 H), 8.18 (d, J = 8.8 Hz, 2 H), 8.12 (dd, J = 8.8, 1.5 Hz, 1 H), 8.04 (d, J = 2.4 Hz, 1 H), 8.03 (d, J = 5.9 Hz, 1 H), 7.96 (d, J = 8.3 Hz, 1 H), 7.90 (d, J = 8.3 Hz, 2 H), 7.76 (dd, J = 9.3, 2.9 Hz, 1 H), 7.50 (d, J = 6.8 Hz, 2 H), 7.42 (t, J = 7.3 Hz, 2 H), 7.35 (t, J = 7.3 Hz, 1 H), 7.25 (d, J = 9.3 Hz, 1 H), 7.22 (d, J = 5.9 Hz, 1 H), 5.21 (s, 2 H), 3.63−3.70 (m, 4 H), 2.90−2.96 (m, 4 H). LCMS found 586.1 $[M + H]^+$.

*N-(4-(Benzyloxy)-3-chlorophenyl)-6-(4-(morpholinosulfonyl)-phenyl)isoquinolin-1-amine (**56**).* Synthesized by general procedure A. Flash column chromatography: 30−50% ethyl acetate in hexanes, isolated as an orange solid in 81% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.26 (s, 1 H), 8.65 (d, J = 9.3 Hz, 1 H), 8.25 (d, J = 1.5 Hz, 1 H), 8.16 (d, J = 8.8 Hz, 2 H), 8.12 (d, J = 2.9 Hz, 1 H), 8.01−8.07 (m, 2 H), 7.88 (d, J = 8.3 Hz, 2 H), 7.78 (dd, J = 9.0, 2.7 Hz, 1 H), 7.50 (d, J = 6.8 Hz, 2 H), 7.42 (t, J = 7.3 Hz, 2 H), 7.35 (t, J = 7.3 Hz, 1 H), 7.27 (d, J = 5.9 Hz, 1 H), 7.23 (d, J = 9.3 Hz, 1 H), 5.20 (s, 1 H), 3.62−3.69 (m, 4 H), 2.89−2.97 (m, 4 H). LCMS found 586.1 $[M + H]^+$.

*N-(3-Chloro-4-((3-fluorobenzyl)oxy)phenyl)-7-(4-((4-methylpiperazin-1-yl)sulfonyl)phenyl)isoquinolin-1-amine (**57**).* Synthesized by general procedure A. Flash column chromatography: ethyl acetate, isolated as a cream colored solid in 53% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.11−8.14 (m, 2 H), 7.79−7.89 (m, 7 H), 7.54 (dd, J = 8.8, 2.4 Hz, 1 H), 7.36 (td, J = 7.8, 5.9 Hz, 1 H), 7.28 (s, 1 H), 7.21−7.27 (m, 2 H), 7.18 (d, J = 5.9 Hz, 1 H), 7.03 (td, J = 8.3, 2.4 Hz, 1 H), 6.97 (d, J = 8.8 Hz, 1 H), 5.15 (s, 2 H), 3.08 (br. s., 4 H), 2.49 (t, J = 4.6 Hz, 4 H), 2.28 (s, 3 H). LCMS found 617.2 $[M + H]^+$.

*N-(3-Chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(4-((4-methylpiperazin-1-yl)sulfonyl)phenyl)isoquinolin-1-amine (**58**).* Synthesized by general procedure A. Flash column chromatography: ethyl acetate, isolated as a pale orange solid in 52% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.14 (d, J = 5.9 Hz, 1 H), 8.02 (d, J = 8.8 Hz, 1 H), 7.95 (d, J = 2.0 Hz, 1 H), 7.83−7.91 (m, 5 H), 7.76 (dd, J = 8.5, 1.7 Hz, 1 H), 7.50 (dd, J = 8.8, 2.4 Hz, 1 H), 7.37 (td, J = 7.8, 5.9 Hz, 1 H), 7.22−7.27 (m, 2 H), 7.21 (d, J = 5.9 Hz, 1 H), 7.00−7.07 (m, 2 H), 6.98 (d, J = 8.8 Hz, 1 H), 5.16 (s, 2 H), 3.11 (br. s., 4 H), 2.52 (t, J = 4.6 Hz, 4 H), 2.29 (s, 3 H). LCMS found 617.2 $[M + H]^+$.

*N-(3-Chloro-4-((3-fluorobenzyl)oxy)phenyl)-7-(4-((4-methyl-1,4-diazepan-1-yl)sulfonyl)phenyl)isoquinolin-1-amine (**59**).* Synthesized by general procedure A. Flash column chromatography: 5% methanol in dichloromethane, isolated as an orange solid in 73% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.36 (s, 1 H), 8.85 (s, 1 H), 8.09−8.14 (m, 3 H), 8.05 (d, J = 2.4 Hz, 1 H), 8.02 (d, J = 5.9 Hz, 1 H), 7.91−7.97 (m, 3 H), 7.77 (dd, J = 8.8, 2.9 Hz, 1 H), 7.47 (td, J = 8.1, 6.3 Hz, 1 H), 7.29−7.36 (m, 2 H), 7.24 (d, J = 9.3 Hz, 1 H), 7.22 (d, J = 5.4 Hz, 1 H), 7.18 (td, J = 9.3, 2.0 Hz, 1 H), 5.24 (s, 2 H), 3.35−3.38 (m, 2 H), 3.31−3.35 (m, 2 H), 2.54−2.58 (m, 2 H), 2.47−2.49 (m, 2 H), 2.23 (s, 3 H), 1.75 (quin, J = 5.8 Hz, 2 H). LCMS found 631.1 $[M + H]^+$.

*N-(3-Chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(4-((4-methyl-1,4-diazepan-1-yl)sulfonyl)phenyl)isoquinolin-1-amine (**60**).* Synthesized by general procedure A. Flash column chromatography: 5% methanol in dichloromethane, isolated as a pale yellow solid in 68%

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yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.26 (s, 1 H), 8.64 (d, J = 8.8 Hz, 1 H), 8.23 (d, J = 1.5 Hz, 1 H), 8.13 (d, J = 2.4 Hz, 1 H), 8.10 (d, J = 8.3 Hz, 2 H), 8.00−8.06 (m, 2 H), 7.92 (d, J = 8.3 Hz, 2 H), 7.79 (dd, J = 9.0, 2.7 Hz, 1 H), 7.47 (td, J = 8.3, 6.3 Hz, 1 H), 7.29−7.35 (m, 2 H), 7.27 (d, J = 5.9 Hz, 1 H), 7.22 (d, J = 9.3 Hz, 1 H), 7.18 (td, J = 8.7, 2.7 Hz, 1 H), 5.23 (s, 2 H), 3.36 (m, J = 4.9, 2.4, 2.4 Hz, 2 H), 3.31−3.35 (m, 2 H), 2.53−2.58 (m, 2 H), 2.46−2.49 (m, 2 H), 2.23 (s, 3 H), 1.75 (quin, J = 5.8 Hz, 2 H). LCMS found 631.2 [M + H]$^+$.

*N-(3-Chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(3-morpholinophenyl)cinnolin-4-amine (**61**).* Synthesized by general procedure B. Flash column chromatography: 2−10% methanol in dichloromethane, isolated as a yellow solid in 67% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.76 (br. s., 1 H), 8.30 (s, 1 H), 8.26 (d, J = 4.9 Hz, 1 H), 7.95 (dd, J = 9.0, 1.2 Hz, 1 H), 7.48−7.59 (m, 1 H), 7.32−7.41 (m, 2 H), 7.29 (t, J = 7.8 Hz, 1 H), 7.17−7.24 (m, 2 H), 7.08−7.17 (m, 3 H), 7.02 (td, J = 8.4, 2.2 Hz, 1 H), 6.87−6.94 (m, 2 H), 5.13 (s, 2 H), 3.76−3.82 (m, 4 H), 3.09−3.16 (m, 4 H). LCMS found 541.1 [M + H]$^+$.

*N-(3-Chloro-4-((3-fluorobenzyl)oxy)phenyl)-7-(3-morpholinophenyl)cinnolin-4-amine (**62**).* Synthesized by general procedure B. Flash column chromatography: 2−8% methanol in dichloromethane, then 50−100% ethyl acetate in hexanes, isolated as a yellow solid in 38% yield. ^{1}H NMR (500 MHz, MeOH-d_4) δ 8.70 (br. s., 1 H), 8.36 (br. s., 1 H), 8.31 (d, J = 8.8 Hz, 1 H), 7.96 (d, J = 8.8 Hz, 1 H), 7.38−7.50 (m, 3 H), 7.23−7.35 (m, 5 H), 7.15 (d, J = 8.8 Hz, 1 H), 7.06 (m, J = 8.3, 2.0 Hz, 2 H), 5.24 (s, 2 H), 3.90−3.96 (m, 4 H), 3.27−3.32 (m, 4 H). LCMS found 541.1 [M + H]$^+$.

*N-(4-(Benzyloxy)-3-chlorophenyl)-6-(4-(morpholinosulfonyl)-phenyl)cinnolin-4-amine (**63**).* Synthesized by general procedure A. Flash column chromatography: 2% methanol and 18% acetone in dichloromethane, then 1% methanol in ethyl acetate, isolated as a yellow solid in 8% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.49 (br. s., 1 H), 8.82 (br. s., 2 H), 8.09−8.40 (m, 4 H), 7.91 (d, J = 7.8 Hz, 2 H), 7.48−7.60 (m, 3 H), 7.44 (t, J = 7.6 Hz, 3 H), 7.37 (t, J = 7.3 Hz, 2 H), 5.26 (s, 2 H), 3.61−3.70 (m, 4 H), 2.87−2.99 (m, 4 H). LCMS found 587.1 [M + H]$^+$.

*N-(4-(Benzyloxy)-3-chlorophenyl)-7-(4-(morpholinosulfonyl)-phenyl)cinnolin-4-amine (**64**).* Synthesized by general procedure B. Flash column chromatography: 2−8% methanol in dichloromethane, then 10−100% ethyl acetate in dichloromethane, isolated as a yellow solid in 71% yield. ^{1}H NMR (500 MHz, MeOH-d_4) δ 8.76 (br. s., 1 H), 8.48 (br. s., 1 H), 8.40 (d, J = 8.8 Hz, 1 H), 8.05 (d, J = 8.3 Hz, 2 H), 8.01 (d, J = 8.8 Hz, 1 H), 7.95 (d, J = 8.3 Hz, 2 H), 7.52 (d, J = 7.3 Hz, 2 H), 7.48 (br. s., 1 H), 7.43 (t, J = 7.6 Hz, 2 H), 7.36 (t, J = 7.3 Hz, 1 H), 7.30 (d, J = 8.8 Hz, 1 H), 7.17 (d, J = 8.8 Hz, 1 H), 5.25 (s, 2 H), 3.77−3.82 (m, 4 H), 3.07−3.12 (m, 4 H). LCMS found 587.1 [M + H]$^+$.

*N-(3-Chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(4-((4-methylpiperazin-1-yl)sulfonyl)phenyl)cinnolin-4-amine (**65**).* Synthesized by general procedure A. Flash column chromatography: 5−10% methanol in dichloromethane, then 10−30% methanol in ethyl acetate, isolated as a yellow solid in 15% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.81 (s, 1 H), 9.01 (s, 1 H), 8.82 (s, 1 H), 8.21−8.34 (m, 4 H), 7.88 (d, J = 8.3 Hz, 2 H), 7.61 (d, J = 2.0 Hz, 1 H), 7.43−7.53 (m, 2 H), 7.29−7.40 (m, 3 H), 7.20 (t, J = 8.8 Hz, 1 H), 5.29 (s, 2 H), 2.95 (br. s., 4 H), 2.37 (br. s., 4 H), 2.14 (s, 3 H). LCMS found 618.1 [M + H]$^+$.

*N-(3-Chloro-4-((3-fluorobenzyl)oxy)phenyl)-7-(4-((4-methylpiperazin-1-yl)sulfonyl)phenyl)cinnolin-4-amine (**66**).* Synthesized by general procedure B. Flash column chromatography: 5−10% methanol in dichloromethane, isolated as a yellow solid in 50% yield. ^{1}H NMR (500 MHz, MeOH-d_4) δ 8.74 (br. s., 1 H), 8.44 (br. s., 1 H), 8.39 (d, J = 8.8 Hz, 1 H), 7.93−8.04 (m, 5 H), 7.48 (br. s., 1 H), 7.42 (td, J = 8.1, 5.9 Hz, 1 H), 7.31 (d, J = 7.8 Hz, 2 H), 7.26 (d, J = 9.8 Hz, 1 H), 7.16 (d, J = 8.8 Hz, 1 H), 7.06 (td, J = 8.5, 2.0 Hz, 1 H), 5.25 (s, 2 H), 3.48−3.52 (m, 2 H), 3.46 (t, J = 6.3 Hz, 2 H), 2.73−2.77 (m, 2 H), 2.69−2.73 (m, 2 H), 2.40 (s, 3 H), 1.95 (dt, J = 11.4, 5.8 Hz, 2 H). LCMS found 618.1 [M + H]$^+$.

*N-(3-Chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(4-((4-methyl-1,4-diazepan-1-yl)sulfonyl)phenyl)cinnolin-4-amine (**67**).* Synthesized by general procedure B. Flash column chromatography: 2−10% methanol in dichloromethane, isolated as a yellow solid in 61% yield. ^{1}H NMR (500 MHz, 1:1 $CDCl_3$/CD_3OD) δ 8.77 (br. s., 1 H), 8.62 (s, 1 H), 8.31 (br. s., 1 H), 8.14 (d, J = 8.8 Hz, 1 H), 8.02 (d, J = 8.3 Hz, 2 H), 7.94 (d, J = 8.8 Hz, 2 H), 7.48 (br. s., 1 H), 7.38−7.45 (m, 2 H), 7.23−7.33 (m, 3 H), 7.16 (d, J = 8.8 Hz, 1 H), 7.06 (td, J = 8.4, 2.2 Hz, 1 H), 5.25 (s, 2 H), 3.47−3.50 (m, 2 H), 3.45 (t, J = 6.6 Hz, 2 H), 2.70−2.74 (m, 2 H), 2.66−2.70 (m, 2 H), 2.38 (s, 3 H), 1.89−1.96 (m, 2 H). LCMS found 632.1 [M + H]$^+$.

*N-(3-Chloro-4-((3-fluorobenzyl)oxy)phenyl)-7-(4-((4-methyl-1,4-diazepan-1-yl)sulfonyl)phenyl)cinnolin-4-amine (**68**).* Synthesized by general procedure B. Flash column chromatography: 5−15% methanol in dichloromethane, isolated as a yellow solid in 52% yield. ^{1}H NMR (500 MHz, MeOH-d_4) δ 8.74 (br. s., 1 H), 8.44 (br. s., 1 H), 8.39 (d, J = 8.8 Hz, 1 H), 7.93−8.04 (m, 5 H), 7.48 (br. s., 1 H), 7.42 (td, J = 8.1, 5.9 Hz, 1 H), 7.31 (d, J = 7.8 Hz, 2 H), 7.26 (d, J = 9.8 Hz, 1 H), 7.16 (d, J = 8.8 Hz, 1 H), 7.06 (td, J = 8.5, 2.0 Hz, 1 H), 5.25 (s, 2 H), 3.48−3.52 (m, 2 H), 3.46 (t, J = 6.3 Hz, 2 H), 2.73−2.77 (m, 2 H), 2.69−2.73 (m, 2 H), 2.40 (s, 3 H), 1.95 (dt, J = 11.4, 5.8 Hz, 2 H). LCMS found 632.1 [M + H]$^+$.

*N-(3-Chloro-4-((3-fluorobenzyl)oxy)phenyl)-7-(3-morpholinophenyl)phthalazin-1-amine (**69**).* Synthesized by general procedure C. Flash column chromatography: 40−80% ethyl acetate in hexanes, then prep HPLC 30−50% acetonitrile in water, isolated as a yellow solid in 9% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.27 (s, 1 H), 9.14 (s, 1 H), 8.78 (s, 1 H), 8.27 (dd, J = 8.3, 1.5 Hz, 1 H), 8.16 (d, J = 2.4 Hz, 1 H), 8.09 (d, J = 8.3 Hz, 1 H), 7.82 (dd, J = 9.0, 2.7 Hz, 1 H), 7.40−7.50 (m, 2 H), 7.39 (s, 1 H), 7.30−7.36 (m, 3 H), 7.27 (d, J = 8.8 Hz, 1 H), 7.18 (td, J = 8.7, 2.2 Hz, 1 H), 7.07 (dd, J = 8.3, 2.0 Hz, 1 H), 5.25 (s, 2 H), 3.76−3.82 (m, 4 H), 3.22−3.27 (m, 4 H). LCMS found 541.2 [M + H]$^+$.

*N-(3-Chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(3-morpholinophenyl)phthalazin-1-amine (**70**).* Synthesized by general procedure C. Flash column chromatography: 40−80% ethyl acetate in hexanes, then prep HPLC 30−50% acetonitrile in water, isolated as a pale yellow solid in 14% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.24 (s, 1 H), 9.16 (s, 1 H), 8.62 (d, J = 8.3 Hz, 1 H), 8.30−8.36 (m, 2 H), 8.21 (d, J = 2.4 Hz, 1 H), 7.84 (dd, J = 9.0, 2.7 Hz, 1 H), 7.47 (td, J = 7.8, 5.9 Hz, 1 H), 7.38−7.43 (m, 2 H), 7.29−7.36 (m, 3 H), 7.26 (d, J = 9.3 Hz, 1 H), 7.18 (td, J = 8.7, 2.2 Hz, 1 H), 7.06 (dd, J = 8.3, 2.0 Hz, 1 H), 5.25 (s, 2 H), 3.75−3.83 (m, 4 H), 3.21−3.28 (m, 4 H). LCMS found 541.2 [M + H]$^+$.

*N-(4-(Benzyloxy)-3-chlorophenyl)-7-(4-(morpholinosulfonyl)-phenyl)phthalazin-1-amine (**71**).* Synthesized by general procedure C. Flash column chromatography: 50−100% ethyl acetate in hexanes, then prep HPLC 30−50% acetonitrile in water, isolated as a yellow solid in 9% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.36 (s, 1 H), 9.18 (s, 1 H), 8.93 (s, 1 H), 8.36 (dd, J = 8.3, 1.5 Hz, 1 H), 8.20 (d, J = 8.3 Hz, 2 H), 8.17 (d, J = 8.3 Hz, 1 H), 8.15 (d, J = 2.9 Hz, 1 H), 7.94 (d, J = 8.3 Hz, 2 H), 7.82 (dd, J = 9.0, 2.7 Hz, 1 H), 7.50 (d, J = 7.3 Hz, 2 H), 7.42 (t, J = 7.6 Hz, 2 H), 7.35 (t, J = 7.3 Hz, 1 H), 7.30 (d, J = 9.3 Hz, 1 H), 5.22 (s, 2 H), 3.63−3.69 (m, 4 H), 2.90−2.98 (m, 4 H). LCMS found 587.2 [M + H]$^+$.

*N-(4-(Benzyloxy)-3-chlorophenyl)-6-(4-(morpholinosulfonyl)-phenyl)phthalazin-1-amine (**72**).* Synthesized by general procedure C. Flash column chromatography: 5−100% ethyl acetate in hexanes, then prep HPLC 30−50% acetonitrile in water, isolated as a yellow solid in 23% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.28 (s, 1 H), 9.19 (s, 1 H), 8.70 (d, J = 8.8 Hz, 1 H), 8.45 (d, J = 2.0 Hz, 1 H), 8.41 (dd, J = 8.5, 1.7 Hz, 1 H), 8.20 (d, J = 2.4 Hz, 1 H), 8.18 (d, J = 8.3 Hz, 2 H), 7.91 (d, J = 8.3 Hz, 2 H), 7.83 (dd, J = 8.8, 2.4 Hz, 1 H), 7.50 (d, J = 6.8 Hz, 2 H), 7.42 (t, J = 7.3 Hz, 2 H), 7.35 (t, J = 6.8 Hz, 1 H), 7.27 (d, J = 8.8 Hz, 1 H), 5.21 (s, 2 H), 3.63−3.69 (m, 4 H), 2.91−2.97 (m, 4 H). LCMS found 587.1 [M + H]$^+$.

*N-(3-Chloro-4-((3-fluorobenzyl)oxy)phenyl)-7-(4-((4-methylpiperazin-1-yl)sulfonyl)phenyl)phthalazin-1-amine, Formate Salt (**73**).* Synthesized by general procedure B. Flash column chromatography: 3−7% methanol in dichloromethane, then prep HPLC 5−95% acetonitrile in water, isolated as an orange solid in 39% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.32 (br. s., 1 H), 9.18 (s, 1 H), 8.91

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(s, 1 H), 8.35 (d, J = 7.3 Hz, 1 H), 8.12−8.21 (m, 6 H), 7.93 (d, J = 8.3 Hz, 2 H), 7.83 (d, J = 6.8 Hz, 1 H), 7.47 (td, J = 8.3, 6.3 Hz, 1 H), 7.30−7.36 (m, 2 H), 7.28 (d, J = 8.8 Hz, 1 H), 7.18 (td, J = 8.7, 2.2 Hz, 1 H), 5.25 (s, 2 H), 2.96 (br. s., 4 H), 2.35−2.43 (m, 4 H), 2.15 (s, 3 H). LCMS found 618.2 $[M + H]^+$.

*N-(3-Chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(4-((4-methylpiperazin-1-yl)sulfonyl)phenyl)phthalazin-1-amine, Formate Salt (**74**).* Synthesized by general procedure B. Flash column chromatography: 3−10% methanol in dichloromethane, then prep HPLC 5−95% acetonitrile in water, isolated as a dull yellow solid in 28% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.28 (s, 1 H), 9.20 (s, 1 H), 8.70 (d, J = 8.3 Hz, 1 H), 8.47 (d, J = 2.0 Hz, 1 H), 8.42 (dd, J = 8.5, 1.7 Hz, 1 H), 8.21 (d, J = 2.9 Hz, 1 H), 8.16−8.20 (m, 3 H), 7.91 (d, J = 8.3 Hz, 2 H), 7.84 (dd, J = 9.0, 2.7 Hz, 1 H), 7.48 (td, J = 8.3, 6.3 Hz, 1 H), 7.30−7.36 (m, 2 H), 7.27 (d, J = 9.3 Hz, 1 H), 7.18 (td, J = 8.7, 2.7 Hz, 1 H), 5.25 (s, 2 H), 2.96 (br. s., 4 H), 2.39 (t, J = 4.6 Hz, 4 H), 2.15 (s, 3 H). LCMS found 618.2 $[M + H]^+$.

*N-(3-Chloro-4-((3-fluorobenzyl)oxy)phenyl)-7-(4-((4-methyl-1,4-diazepan-1-yl)sulfonyl)phenyl)phthalazin-1-amine, Formate Salt (**75**).* Synthesized by general procedure B. Flash column chromatography: 5−10% methanol in dichloromethane, then prep HPLC 5−95% acetonitrile in water, isolated as an orange solid in 29% yield. ^{1}H NMR (500 MHz, MeOH-d_4) δ 8.94 (s, 1 H), 8.73 (s, 1 H), 8.25 (s, 2 H), 8.20 (dd, J = 8.5, 1.2 Hz, 1 H), 8.00−8.06 (m, 3 H), 7.95 (d, J = 8.3 Hz, 2 H), 7.88 (d, J = 2.4 Hz, 1 H), 7.59 (dd, J = 8.8, 2.4 Hz, 1 H), 7.38 (td, J = 8.1, 5.9 Hz, 1 H), 7.28 (d, J = 7.8 Hz, 1 H), 7.23 (d, J = 9.8 Hz, 1 H), 6.99−7.06 (m, 2 H), 5.18 (s, 2 H), 3.60−3.66 (m, 2 H), 3.47 (t, J = 6.6 Hz, 2 H), 3.22−3.28 (m, 4 H), 2.77 (s, 3 H), 2.14−2.21 (m, 2 H). LCMS found 632.2 $[M + H]^+$.

*N-(3-Chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(4-((4-methyl-1,4-diazepan-1-yl)sulfonyl)phenyl)phthalazin-1-amine, Formate Salt (**76**).* Synthesized by general procedure B. Flash column chromatography: 5−15% methanol in dichloromethane, then prep HPLC 5−95% acetonitrile in water, isolated as a light yellow solid in 29% yield. ^{1}H NMR (500 MHz, MeOH-d_4) δ 8.99 (s, 1 H), 8.51 (d, J = 8.3 Hz, 1 H), 8.25 (s, 1 H), 8.17−8.22 (m, 2 H), 7.97 (s, 4 H), 7.91 (d, J = 2.9 Hz, 1 H), 7.58−7.63 (m, 1 H), 7.39 (td, J = 7.8, 5.9 Hz, 1 H), 7.29 (d, J = 7.8 Hz, 1 H), 7.24 (d, J = 9.3 Hz, 1 H), 7.00−7.08 (m, 2 H), 5.20 (s, 2 H), 3.54−3.59 (m, 2 H), 3.47 (t, J = 6.6 Hz, 2 H), 2.97−3.04 (m, 4 H), 2.60 (s, 3 H), 2.06 (quin, J = 6.3 Hz, 2 H). LCMS found 632.2 $[M + H]^+$.

*4-((3-Chloro-4-((3-fluorobenzyl)oxy)phenyl)amino)-6-(3-morpholinophenyl)quinoline-3-carbonitrile (**77**).* Synthesized by general procedure D. Flash column chromatography: 0−30% methanol in dichloromethane, isolated as a yellow solid in 20% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (br, s, 1H), 8.73 (s, 1H), 8.55 (s, 1H), 8.18 (d, J = 8.8 Hz, 1H), 7.98 (d, J = 8.8 Hz, 1H), 7.55 (d, J = 2.4 Hz, 1H), 7.45−7.50 (m, 1H), 7.37−7.41 (m, 1H), 7.30−7.35 (m, 6H), 7.17−7.22 (m, 1H), 7.02 (d, J = 8.0 Hz, 1H), 5.29 (s, 2H), 3.76−3.79 (m, 4H), 3.20−3.23 (m, 4H). LCMS found 565.0 $[M + H]^+$.

*4-((4-(Benzyloxy)-3-chlorophenyl)amino)-6-(4-(morpholinosulfonyl)phenyl)quinoline-3-carbonitrile (**80**).* Synthesized by general procedure D. Flash column chromatography: 0−20% ethyl acetate in hexanes, isolated as a yellow solid in 50% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.99 (s, 1H), 8.87 (s, 1H), 8.55 (s, 1H), 8.24 (d, J = 8.8 Hz, 1H), 8.14 (d, J = 8.0 Hz, 2H), 8.01 (d, J = 8.8, 1H), 7.85 (d, J = 8.4 Hz, 2H), 7.46−7.51 (m, 3H), 7.39 (t, J = 7.2 Hz, 2H), 7.29−7.34 (m, 3H), 5.22 (s, 2H), 3.60−3.63 (m, 4H), 2.87−2.89 (m, 4H). LCMS found 611.1 $[M + H]^+$.

*4-((3-Chloro-4-((3-fluorobenzyl)oxy)phenyl)amino)-6-(4-((4-methylpiperazin-1-yl)sulfonyl)phenyl)quinoline-3-carbonitrile (**81**).* Synthesized by general procedure D. Flash column chromatography: 0−30% methanol in dichloromethane, isolated as a yellow solid in 16% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.01 (br, s, 1H), 8.89 (s, 1H), 8.59 (s, 1H), 8.27 (d, J = 8.8 Hz, 1H), 8.16 (d, J = 8.0 Hz, 2H), 8.05 (d, J = 8.8 Hz, 1H), 7.88 (d, J = 8.0 Hz, 2H), 7.55 (br, s, 1H), 7.45−7.70 (m, 1H), 7.31−7.35 (m 4H), 7.17−7.21 (m, 1H), 5.30 (s, 2H), 2.95 (br, s, 4H), 2.38 (br, 4H), 2.14 (s, 3H). LCMS found 642.1 $[M + H]^+$.

*4-((3-Chloro-4-((3-fluorobenzyl)oxy)phenyl)amino)-6-(4-((4-methyl-1,4-diazepan-1-yl)sulfonyl)phenyl)quinoline-3-carbonitrile (**83**).* Synthesized by general procedure D. Flash column chromatography: 0−30% methanol in dichloromethane, isolated as a yellow solid in 32% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.14 (d, J = 8.8 Hz, 1H), 8.08 (d, J = 2.4 Hz, 1H), 7.99 (dd, J = 8.8, 2.2 Hz, 1H), 7.80−7.82 (m, 2H), 7.66 (d, J = 8.8 Hz, 2H), 7.47 (s, 1H), 7.41 (d, J = 2 Hz, 1H), 7.36−7.39 (m, 1H), 7.23 (s, 1H), 7.19−7.20 (m, 1H), 7.17 (d, J = 2 Hz, 1H), 7.05 (dd, J = 8.0,2.4 Hz, 1H), 7.01 (d, J = 8.8 Hz, 1H), 5.19 (s, 2H), 3.36−3.40 (m, 4H), 2.56−2.62 (m, 4H), 2.33 (s, 3H), 1.81−1.85 (m, 2H). LCMS found 656.2 $[M + H]^+$.

*N-(3-Chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(3-morpholinophenyl)thieno[3,2-d]pyrimidin-4-amine (**85**).* Synthesized by general procedure E, isolated as a yellow solid in 12% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.68 (s, 1 H), 8.59 (s, 1 H), 8.01 (d, J = 2.4 Hz, 1 H), 7.94 (s, 1 H), 7.67 (dd, J = 8.8, 2.4 Hz, 1 H), 7.47 (m, 1 H), 7.40 (m, 1 H), 7.37 (d, J = 7.8 Hz, 1 H), 7.32 (m, 2 H), 7.25 (m, 2 H), 7.18 (td, J = 9.3, 2.4 Hz, 1 H), 7.08 (dd, J = 7.8, 2.4 Hz, 1 H), 5.25 (s, 2 H), 3.78 (m, 4 H), 3.23 (m, 4 H), LCMS found 547.0, $[M + H]^+$.

*N-(3-Chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(3-morpholinophenyl)thieno[2,3-d]pyrimidin-4-amine (**86**).* Synthesized by general procedure E, 39% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.64 (s, 1H), 8.49 (s, 1H), 8.18 (s, 1H), 8.05 (d, J = 2.93 Hz, 1H), 7.71 (dd, J = 2.44, 8.79 Hz, 1H), 7.44−7.50 (m, 1H), 7.13−7.41 (m, 7H), 7.04 (dd, J = 1.95, 8.30 Hz, 1H), 5.25 (s, 2H), 3.78 (t, J = 4.7 Hz, 4H), 3.21 (t, J = 4.7 Hz, 4H). LCMS found 547.0, $[M + H]^+$.

*N-(4-(Benzyloxy)-3-chlorophenyl)-6-(4-(morpholinosulfonyl)-phenyl)thieno[3,2-d]pyrimidin-4-amine (**87**).* Synthesized by general procedure E, isolated as a yellow solid in 8% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.61 (s, 1 H), 9.83 (s, 1 H), 8.15 (m, 3 H), 7.98 (s, 1 H), 7.88 (d, J = 8.8 Hz, 2 H), 7.65 (m, 1 H), 7.49 (m, 2 H), 7.42 (t, J = 7.3 Hz, 2 H), 7.35 (m, 1 H), 7.27 (d, J = 8.8 Hz, 1 H), 5.23 (s, 2 H), 3.65 (m, 4 H), 2.94 (m, 4 H). LCMS found 593.0, $[M + H]^+$.

*N-(4-(Benzyloxy)-3-chlorophenyl)-6-(4-(morpholinosulfonyl)-phenyl)thieno[2,3-d]pyrimidin-4-amine (**88**).* Synthesized by general procedure E, isolated as a yellow solid in 40% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.79 (s, 1 H), 8.52 (s, 1 H), 8.41 (s, 1 H), 8.03 (d, J = 2.0 Hz, 1 H), 7.97 (d, J = 8.3 Hz, 2 H), 7.88 (d, J = 8.3 Hz, 2 H), 7.68 (dd, J = 8.8, 2.4 Hz, 1 H), 7.49 (d, J = 7.8 Hz, 2 H), 7.42 (t, J = 7.6 Hz, 2 H), 7.35 (t, J = 7.3 Hz, 1 H), 7.29 (d, J = 9.3 Hz, 1 H), 5.22 (s, 2 H), 3.65 (m, 4 H), 2.94 (m, 4 H). LCMS found 593.0, $[M + H]^+$.

*N-(3-Chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(4-((4-methylpiperazin-1-yl)sulfonyl)phenyl)thieno[3,2-d]pyrimidin-4-amine (**89**).* Synthesized by general procedure E, isolated as a yellow solid in 36% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.84 (s, 1 H), 8.62 (s, 1 H), 8.14 (m, 3 H), 7.99 (d, J = 2.2 Hz, 1 H), 7.87 (d, J = 8.8 Hz, 2 H), 7.66 (dd, J = 9.2, 2.6 Hz, 1 H), 7.47 (m, 1 H), 7.32 (m, 2 H), 7.26 (d, J = 8.8 Hz, 1 H), 7.19 (td, J = 8.8, 2.2 Hz, 1 H), 5.26 (s, 2 H), 2.95 (m, 4 H), 2.38 (m, 4 H), 2.14 (s, 3 H). LCMS found 624.1, $[M + H]^+$.

*N-(3-Chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(4-((4-methylpiperazin-1-yl)sulfonyl)phenyl)thieno[2,3-d]pyrimidin-4-amine (**90**).* Synthesized by general procedure E, isolated as a yellow solid in 25% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.79 (s, 1 H), 8.52 (s, 1 H), 8.41 (s, 1 H), 8.05 (d, J = 2.4 Hz, 1 H), 7.95 (d, J = 8.3 Hz, 2 H), 7.87 (d, J = 8.3 Hz, 2 H), 7.69 (dd, J = 8.8, 2.4 Hz, 1 H), 7.47 (m, 1 H), 7.32 (m, 2 H), 7.28 (d, J = 8.8 Hz, 1 H), 7.18 (td, J = 8.5, 2.4 Hz, 1 H), 5.24 (s, 2 H), 2.95 (m, 4 H), 2.37 (m, 4 H), 2.14 (s, 3 H). LCMS found 624.1, $[M + H]^+$.

*N-(3-Chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(4-((4-methyl-1,4-diazepan-1-yl)sulfonyl)phenyl)thieno[3,2-d]pyrimidin-4-amine, Formic Acid Salt (**91**).* Synthesized by general procedure E, isolated as a pale yellow solid in 4% yield. The product was separated by silica column chromatography (dichloromethane/methanol) and purified by HPLC to obtain the formic acid salt. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.82 (s, 1 H), 8.61 (s, 1 H), 8.22 (s, 1 H), 8.06−8.13 (m, 3 H), 7.99 (d, J = 2.4 Hz, 1 H), 7.91 (d, J = 8.8 Hz, 2 H), 7.66 (dd, J = 9.0, 2.7 Hz, 1 H), 7.47 (td, J = 8.3, 6.3 Hz, 1 H), 7.29−7.36 (m, 2 H), 7.26 (d, J = 8.8 Hz, 1 H), 7.18 (td, J = 8.7, 2.2 Hz, 1 H), 5.26 (s, 2 H), 3.35 (dt, J = 5.1, 2.3 Hz, 2 H), 3.32 (t, J = 6.1 Hz, 2 H), 2.53−2.58 (m, 2

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H), 2.48 (d, J = 5.9 Hz, 2 H), 2.23 (s, 3 H), 1.74 (quin, J = 5.9 Hz, 2 H). LCMS found 638.0 $[M + H]^+$.

*N-(3-Chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(4-((4-methyl-1,4-diazepan-1-yl)sulfonyl)phenyl)thieno[2,3-d]pyrimidin-4-amine, Formic Acid Salt (**92**)*. Synthesized by general procedure E, isolated as a pale yellow solid in 10% yield. The product was separated by silica column chromatography (dichloromethane/methanol) and purified by HPLC to obtain the formic acid salt. ^{1}H NMR (500 MHz, $CDCl_3$/CD_3OD) δ ppm 8.46 (s, 1 H), 8.10 (s, 1 H), 7.89 (m, 5 H), 7.60 (m, 1 H), 7.39 (m, 1 H), 7.28 (d, J = 7.8 Hz, 1 H), 7.24 (d, J = 9.3 Hz, 1 H), 7.04 (m, 2 H), 5.20 (s, 2 H), 3.57 (m, 2 H), 3.45 (t, J = 6.6 Hz, 2 H), 3.05 (m, 4 H), 2.63 (s, 3 H), 2.08 (m, 2 H). LCMS found 638.1 $[M + H]^+$.

■ ASSOCIATED CONTENT

Supporting Information

Biological assay conditions, tabulation of the compounds with their Northeastern registry numbers and screening data, syntheses for custom boronic acids, and synthesis of intermediates and analogs previously reported. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jmedchem.5b00515. The screening data has been made freely available as a shared data set at www.collaborativedrug.com.

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Notes

The authors declare no competing financial interest.

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