Article

Optimization of Physicochemical Properties for 4-Anilinoquinoline Inhibitors of Plasmodium falciparum Proliferation

Naimee Mehta, Lori Ferrins, Susan E. Leed, Richard J. Sciotti, and Michael P. Pollastri

ACS Infect. Dis., **Just Accepted Manuscript** • DOI: 10.1021/acsinfecdis.7b00212 • Publication Date (Web): 04 Jan 2018

Optimization of Physicochemical Properties for 4-Anilinoquinoline Inhibitors of *Plasmodium falciparum* Proliferation

Naimee Mehta,[a] *Lori Ferrins,*[a] *Susan E. Leed,*[b] *Richard J. Sciotti,*[b] *and Michael P. Pollastri.**[a]

[a]Northeastern University Department of Chemistry & Chemical Biology, 360 Huntington Avenue, Boston, MA 02115 USA. Tel: 617-373-2703; E-mail: m.pollastri@northeastern.edu

[b]Experimental Therapeutics, Walter Reed Army Institute for Research, 2460 Linden Lane, Silver Spring, MD, 20910

We recently reported the medicinal chemistry re-optimization of a known human tyrosine kinase inhibitor, lapatinib, against a variety of parasites responsible for numerous tropical diseases, including: human African trypanosomiasis (*Trypanosoma brucei*), Chagas disease (*T. cruzi*), Leishmaniasis (*Leishmania spp.*) and malaria (*Plasmodium falciparum*). Herein, we report our continuing efforts to optimize this series against *P. falciparum*. Through the design of a library of compounds focused on reducing the lipophilicity and molecular weight, followed by an SAR exploration, we have identified **NEU-1953** (**40**). This compound is a potent inhibitor of *P. falciparum* with an improved ADME profile over the previously reported compound, **NEU-961** (**3**).

Keywords: drug repurposing, tropical diseases, malaria, target class repurposing

In sub-Saharan Africa tropical diseases remain the dominant cause of disease burden. Malaria is caused by protozoan parasites of the genus *Plasmodium* and in 2015, it was responsible for 212 million new cases worldwide.[1] Eradication of malaria has proven challenging due to the complex life cycle of *Plasmodium* and the emergence of drug resistance.[2] The parasite is transmitted to the human host through the bite of an infected *Anopheles mosquito*, the injected sporozoites are taken up by the liver where they develop first into schizonts, and then into merozoites. It is these merozoites which are responsible for infection of red blood cells. The clinical signs of malaria arise due to this infection and consist of fever, chills, anemia and ultimately cerebral malaria.[3] Many current antimalarial therapies target the asexual blood stage of *Plasmodium*, in which the parasite replicates within erythrocytes.[4] However, in *P. vivax* and *P. ovale* a proportion of the parasites remain dormant in the hepatocytes for months to years, known as hypnozoites.[5] These parasites can then initiate a new cycle of asexual reproduction at a later stage causing further clinical symptoms.

In an effort to expedite the drug discovery process, we employed a target class repurposing approach,[6] wherein we screened known human tyrosine kinase inhibitors against a number of related pathogenic protozoan parasites: *Trypanosoma brucei* (human African trypanosomiasis), *T. cruzi* (Chagas disease), *Leishmania major* (leishmaniasis), and *P. falciparum*. We previously described the results of this screening and the subsequent discovery of **NEU-617** (**2**)[7] a potent anti-trypanosomal compound derived from the approved therapeutic lapatinib (**1**). We have since disclosed **NEU-961** (**3**),[8] a derivative of **2**, which is a highly potent growth inhibitor of *P. falciparum*.

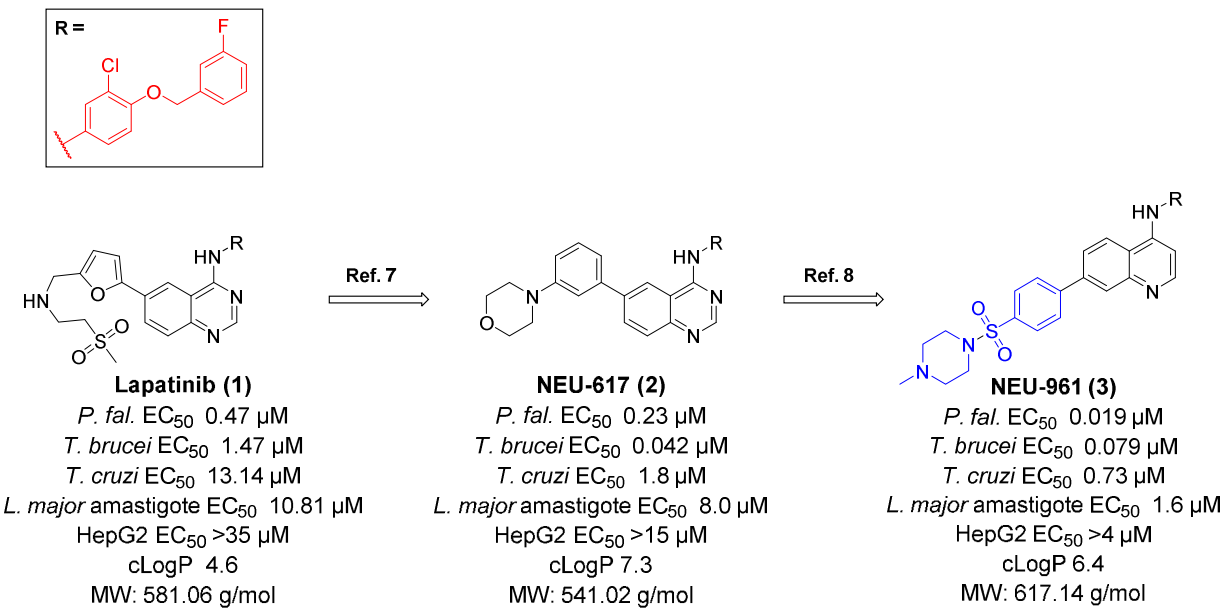


Figure 1. Progression from **1** to **2** was achieved through the implementation of a target class repurposing program.[7] Following scaffold exploration we arrived at the anilinoquinoline, **3** which showed significantly improved activity against *P. falciparum*.[8]

Clear limitations of **3** include its high molecular weight (MW) and lipophilicity, which may in part be responsible for its poor aqueous solubility. To move this chemical series towards more drug-like space and to lower the propensity for future toxicity issues, significant reductions in size and lipophilicity of the head group (red in **Figure 1**) were envisioned. We now report here our efforts to achieve improved properties while maintaining high potency by recapitulating sterics and electronics of this head group region of **3.** Simultaneously, we explored variations to the tail portion (blue in **Figure 1**) to reduce the lipophilicity and maintain potency against blood stage malaria.

Results

Since we previously observed that the structure-activity relationships (SAR) in the head group region (red in **Figure 1**) of the quinazoline core tolerated relatively large changes in size,[7] we

hypothesized that this region could be amenable to a reduction in size and lipophilicity without a loss of potency. We utilized an *in silico* design strategy to prioritize compounds for synthesis. Using a set of commercially available heterocyclic primary amines, we enumerated a virtual library of analogs of **3**, which was subsequently filtered on the basis of cLogP <5 and MW <500 g/mol, obtaining a sub-library of 84 quinolines.

In addition to improving size and lipophilicity, we hoped to recapitulate shape and electrostatic features of the R-group (**Figure 1**) that likely gave rise to its high potency. Using ROCS and EON (OpenEye Scientific Software),[9-10] a three-dimensional shape and electrostatics comparison was carried out between **3** and each member of the virtual library. Members of the conformer library were rank-ordered in terms of shape and electrostatics using the ET_Combo score. Fourteen compounds were chosen for synthesis considering computational scoring, calculated properties, and qualitative analysis of synthetic feasibility. **Figure 2** shows the comparison of the 246-membered virtual library (red) and the shaped library (blue). The average MW (487 g/mol) and cLogP (3.2; desirable range ≤ 3) of the selected analogs were substantially lower than those of **3** (MW 617 g/mol, cLogP 6.4).

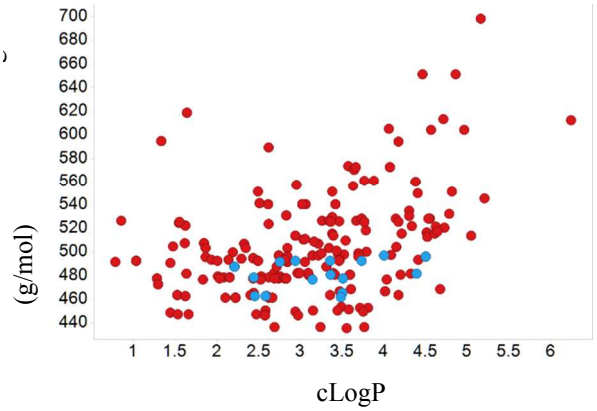
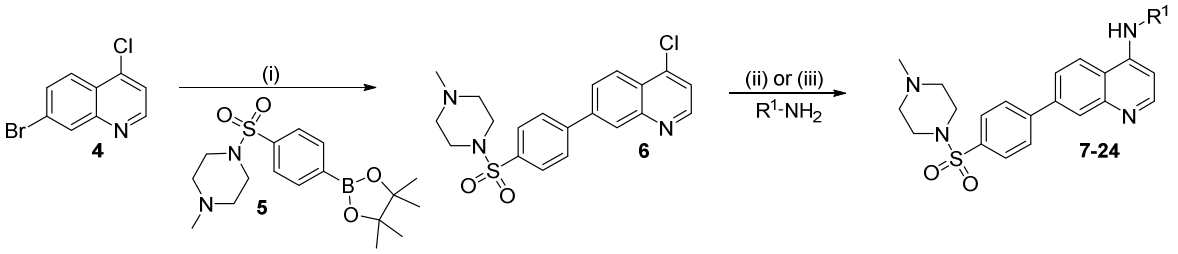


Figure 2. Comparison of all the compounds with variation around the R-group (see **Figure 1**) in the virtual library (red) with the shaped library (blue).

Synthesis of the library of substituted anilines started with Suzuki coupling of **4**[11] with boronic ester **5**,[7] which provided **6** in good yield. Installation of the primary aromatic amine occurred in reasonable yield under inert conditions with microwave irradiation (**Scheme 1**). In the case of electron deficient amines it was necessary to employ Buchwald-Hartwig conditions[12-13] to obtain the desired product in good yield following preparative HPLC purification.

Scheme 1. Synthesis of head group replacement analogs.



Reagents and conditions: (i) **5**, $Pd(OAc)_2$, triethylamine, 1:1 water:ethanol, 120 ^oC, 1h, microwave, 71%; (ii) Ar-NH_2, 4M HCl in dioxane, 2-propanol, 145 ^oC, 30min, microwave, 19-45%; (iii) Ar-NH_2, $Pd(OAc)_2$, Xantphos, KO^{t}Bu, xylene, 160 ^oC, 1 h, microwave, 24-45%.

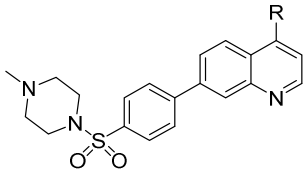
All synthesized compounds were tested for their antimalarial activity against three *P. falciparum* strains: D6 (chloroquine (CQ) sensitive, mefloquine (MQ) resistant), W2 (CQ resistant, MQ sensitive), and C235 (CQ, MQ and pyrimethamine resistant), and for their toxicity against mammalian cells (HepG2 cells). The SAR for the D6 strain will be discussed herein along with the toxicity data. The biological activity against the W2 and C235 cell lines is summarized in the **Supplementary Information, Table S1**.

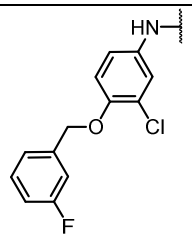
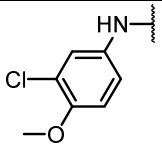
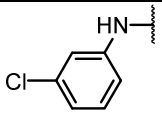
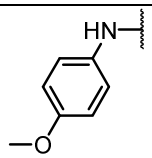
Most of the compounds tested exhibited activities within three-fold of that observed for D6, against both the W2 and C235 strains. Of the compounds tested 15% (8 out of 53 total compounds assayed; ID: **7**, **11**, **14**, **19**, **21**, **23-24**, **36**) did fall outside of the 3-fold range and were less potent against the W2 strain than the D6 strain. Further, 2% (1 out of 53 total compounds assayed; ID: **21**) of compounds fell outside the 3-fold range and were less potent against the C235 strain than the D6 strain. This suggests a lack of sensitivity to CQ resistance for the majority of compounds presented herein (see **Supplementary Information, Figure S2-S3**).

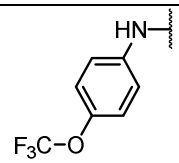
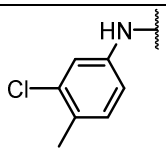
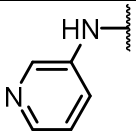
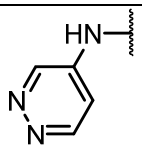
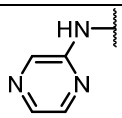
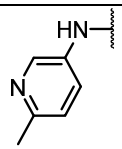
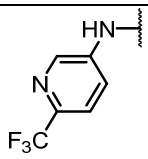
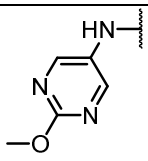
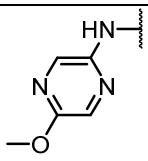
The screening results from this first round of analogs are shown in **Table 1**. Truncation of the halogenated benzyl ether head group of **3** to the 3-chloro-4-methoxyaniline (**7**; EC_{50}: 0.012 μM) led to an analog that was approximately equipotent and demonstrated a significant improvement in lipophilic ligand efficiency (LLE = pEC_{50} - cLogP, desired range ≥4).[14] However, removal of the 4-methoxy (**8**; EC_{50}: 0.20 μM) was detrimental to the potency, whilst removal of the 3-chloro (**9**; EC_{50}: 0.018 μM) led to a compound which was equipotent with **3** and showed a marked improvement in the selectivity versus HepG2 cells (SI: 1100), highlighting the importance of the 4-methoxy substituent. Substitution of the 4-methoxy by a 4-trifluoromethoxy (**10**) and the 3-chloro-4-methyl (**11**) was also tolerated. All the substituted aniline analogs had a lower cLogP and improved LLE as compared to **3**. The 3-pyridyl (**12**; EC_{50}: 0.13 μM) saw a 10-fold reduction in potency compared to **3**, the pyridazine (**13**; EC_{50}: 2.1 μM) highlighted the detrimental effect of the endocyclic nitrogen at the 4-position. Further substitution of the 3-pyridyl with a 4-methyl (**15**; EC_{50}: 0.022 μM) led to a three-fold improvement in potency, and a marked improvement in selectivity (SI: > 1300), while substitution with a 4-trifluoromethyl (**16**; EC_{50}: 0.16 μM) had no impact on potency. A trend is observed between **8** and **12**, and **11** and **15** where replacement of the 3-chloro with an endocyclic nitrogen atom yielded a boost in the selectivity for the parasite

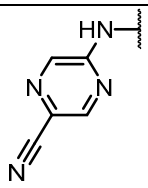
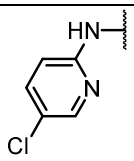
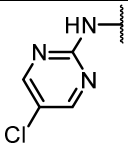
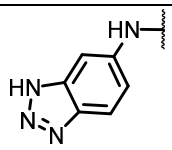
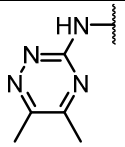
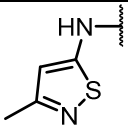
versus HepG2 cells. Replacement with other N-containing heterocycles such as the substituted pyrimidine, **17** (EC_{50}: 0.050 μM) and **21** (EC_{50}: 0.058 μM) was favorable, though pyrazines (**18** – **19**), 2-pyridyl (**20**) and the triazine (**23**) were less favored, the latter also showed greater overall toxicity which was of concern.

Table 1. Analogs of the head group on the 4-aminoquinoline series.



ID	R	*P. fal.* D6 EC_{50} (μM)[a]	HepG2 TC_{50} (μM)[b,c,d]	SI	cLogP	LLE
3		0.019	>4	>210	6.4	1.3
7		0.012	2.8	230	4.6	3.3
8		0.20	>5.5	>28	4.7	2.0
9		0.018	20	1100	3.9	3.8

10		0.085	7.1	84	5.5	1.5
11		0.064	>30	>470	5.2	2.0
12		0.13	>36	>280	2.9	4.0
13		2.1	>36	>17	1.9	3.8
14		0.20	>33	>170	2.3	4.4
15		0.022	>29	>1300	3.0	4.6
16		0.16	22	>140	4.2	2.6
17		0.050	21	420	2.7	4.6
18		0.13	>31	>240	2.7	4.2

19		0.12	>31	>260	2.5	3.6
20		0.25	10	40	4.1	2.5
21		0.058	>31	540	3.5	3.8
22		0.027	>28	>1000	3.5	4.2
23		0.16	>6	>38	2.2	4.7
24		0.11	>35	>320	3.4	3.6
Chloroquine		0.005	3.3	660		

[a] All r^2 values >0.9 unless noted otherwise

[b] n = 1 biological replicate made up of 2 technical replicates

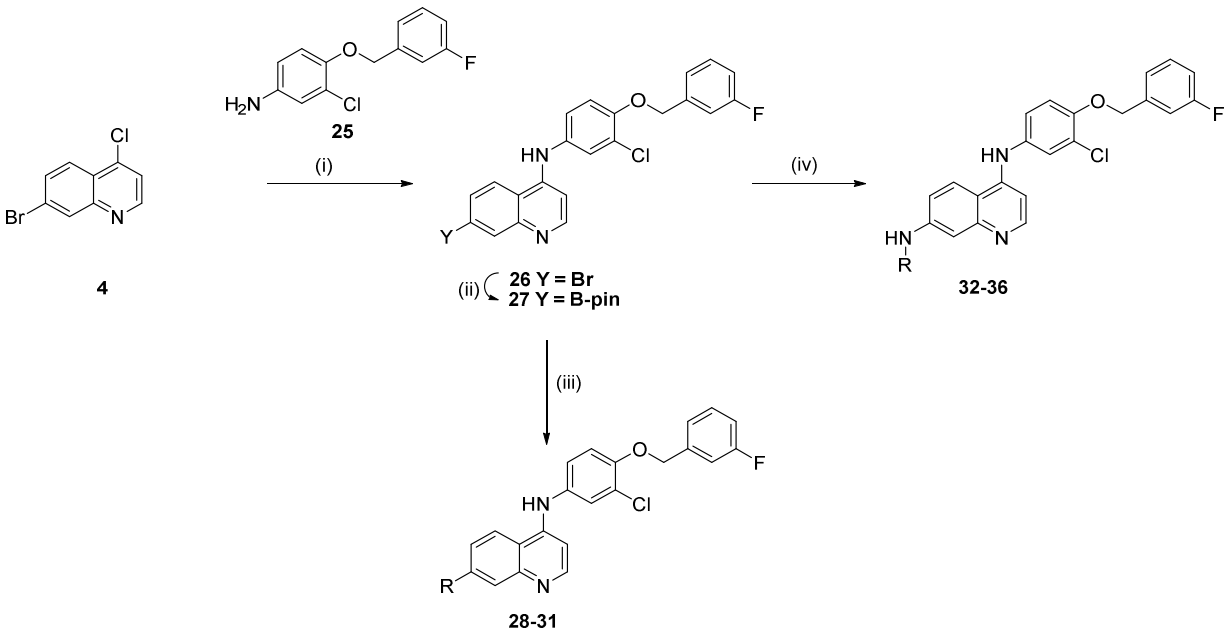
[c] concentration which is toxic to 50% of the cell population

[d] tested concentration ranges were determined based on compound solubility

Systematic exploration of the tail region was targeted next and could be readily achieved through **26**, which was synthesized from **4** and **25** as previously reported.[8] Miyaura coupling

followed by a Suzuki reaction led to the successful isolation of the desired products (**Scheme 2**). Alternatively, Buchwald-Hartwig coupling allowed the installation of aromatic amines. Simultaneously, we explored modifications to the tail region with the aim of reducing the lipophilicity of the series as compared to **3** (cLogP 6.4) (**Table 2**).

Scheme 2. Synthesis of linker replacement analogs.

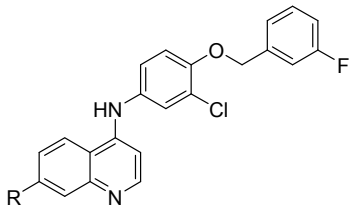


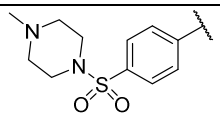
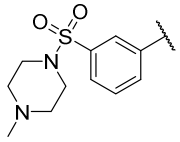
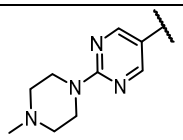
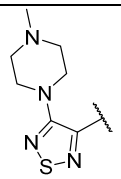
Reagents and conditions: (i) **25**, 2-propanol, 80 ^{o}C, 12 h, 90% (ii) B_2pin_2, $Pd(PPh_3)_4$, KOAc, dioxane, 120 ^{o}C, 2.5 h, microwave, 91%; (iii) Ar-Bpin or Ar-Br, $Pd(PPh_3)_4$, dioxane, 120 ^{o}C, 1h, microwave, 33-67%; (iv) Ar-NH_2, $Pd(OAc)_2$, XantPhos, Cs_2CO_3, dioxane, 160 ^{o}C 1h, microwave, 32-57%.

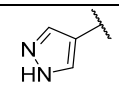
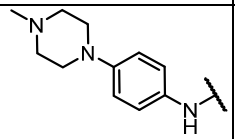
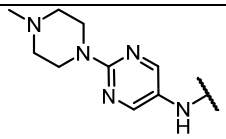
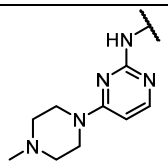
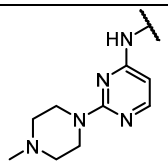
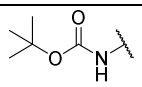
To determine whether there was a favored substitution pattern around the phenyl linker we investigated the *meta* (**28**) substituted analog and found it to be equipotent with **3**. Replacement of the phenyl sulfonamide with the pyrimidine (**29**) led to another equipotent compound (EC_{50}: 0.026 μM) that maintained excellent selectivity. The -NH linked analogs **32-35** all exhibited a

reduction in potency and decrease in the selectivity index, most markedly for **35** (SI: 19). The *tert*-butyl carbamate (**36**) similarly exhibited an almost three-fold drop in potency (EC_{50}: 0.050 μM) and a decrease in the SI (56). The 1,2,5-thiadiazole-linked *N*-methylpiperazine (**30**) led to a six-fold reduction in potency. In an effort to reduce the overall cLogP, the pyrazole (**31**) was tested and found to be equipotent to **3** with a SI of 100.

Table 2. Phenyl linker replacement analogs.



ID	R	*P. fal.* D6 EC_{50} (μM)[a]	HepG2 TC_{50} (μM)[b,c,d]	SI	cLogP	LLE
3		0.019	>4	>210	6.4	1.3
28		0.010	4.2	420	6.4	1.6
29		0.026	3.0	115	6.2	2.2
30		0.10	5.7	57	6.8	0.15

31		0.021	2.1	100	5.8	1.9
32		0.033	4.8	150	7.3	0.20
33		0.031	3.1	100	6.0	1.5
34		0.025	3.0	120	6.6	0.97
35		0.24	4.6	19	6.6	-0.020
36		0.050	2.8	56	6.8	0.51
Chloroquine		0.0050	3.3	660		

[a] All r^2 values >0.9

[b] n = 1 biological replicate made up of 2 technical replicates

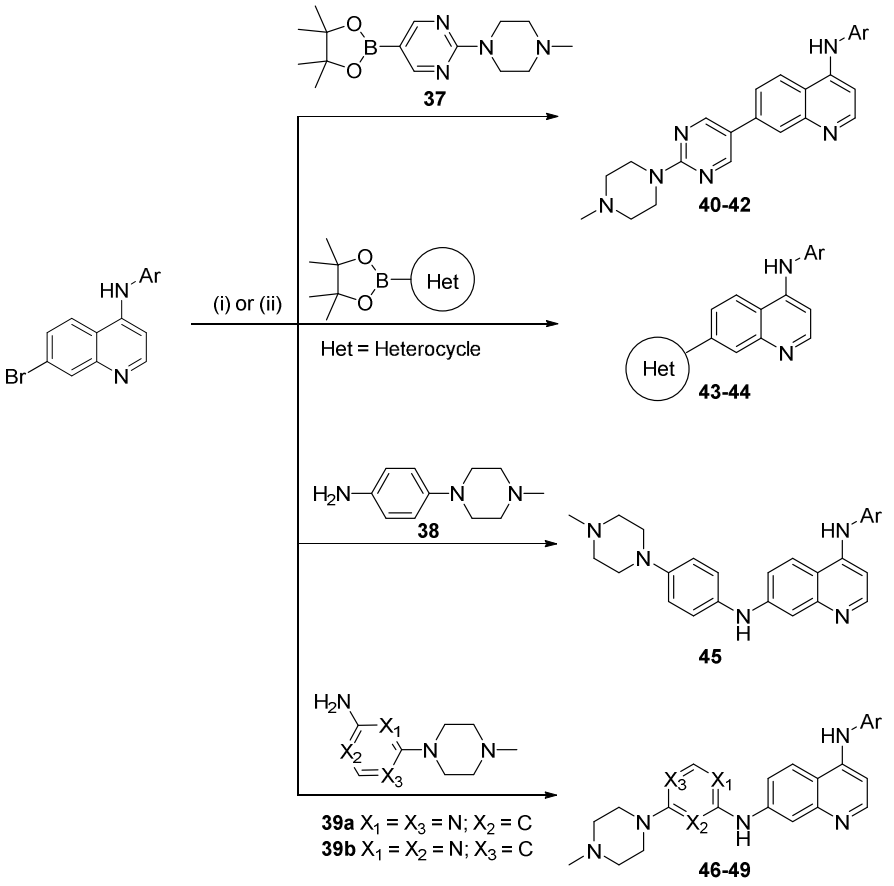
[c] concentration which is toxic to 50% of the cell population

[d] tested concentration ranges were determined based on compound solubility

A series of cross-over analogs was designed based upon the biological data and the ADME profile that was obtained for the head group and linker/tail replacement analogs shown in **Tables 1** and **2**. The head groups that were selected for further analysis included the 2-aminopyrazine (from compound **14**), 3-chloro-4-methoxyaniline (**7**), and the 5-aminobenzotriazole (**22**). The tail groups that were selected included the 2-(4-methylpiperazin-1-yl)pyrimidine (from compound

29), pyrazole (**31**), 4-(4-methylpiperazin-1-yl)aniline (**32**), 4-(4-methylpiperazin-1-yl)pyrimidin-2-amine (**34**), and 2-(4-methylpiperazin-1-yl)pyrimidin-4-amine (**35**). The synthesis of these analogs utilized the protocols summarized in **Scheme 3** and consisted of either a Buchwald-Hartwig or Suzuki coupling to obtain the desired product in reasonable to good yields.

Scheme 3. Synthesis of cross-over analogs, combining favorable head and tail/linker groups.

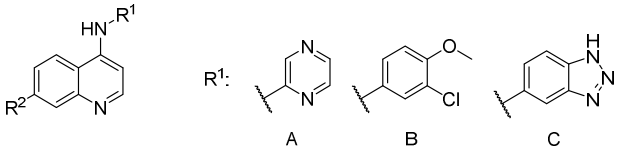


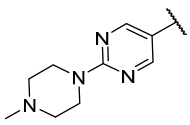
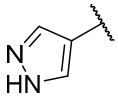
Reagents and conditions: (i) Ar-Bpin, $Pd(OAc)_2$, $Pd(PPh_3)_4$, dioxane, 120 ^oC, 1h, microwave, 21-63%; (ii) Ar-NH_2, $Pd(OAc)_2$, Xantphos, Cs_2CO_3, dioxane, 160 ^oC, 1h, microwave, 19-66%.

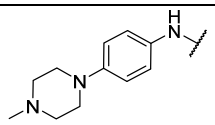
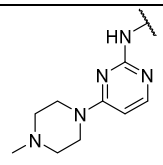
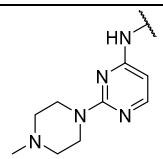
Clear trends in lipophilicity were observed across matched pairs with different headgroups (**Table 3**). Compounds with the 3-chloro-4-methoxyaniline head group (**B**; **41**, **44**, **47**, and **49**)

typically had an increased cLogP, decreased LLE, and decreased selectivity as compared to their matched pairs with other headgroups. While the incorporation of the 2-aminopyrazine head group (**A**) resulted in compounds with the highest LLE of the series (**40**, LLE = 5.5 and **46**, LLE = 4.8). The pyrimidine linker analogs (**40-42**) generally demonstrated an improvement in cLogP with no significant loss in potency. Replacement with the pyrazole (**43-44**) was generally unfavorable for activity though did lead to an improvement in the cLogP and LLE. In an attempt to improve the aqueous solubility of the series, analogs with an amine linking the tail to the quinoline core were synthesized (**45-49**) as it was thought that this would break up the planarity of the molecule. The amino-pyrimidine linked analogs (**46–49**) were largely equipotent and showed a boost in the selectivity when compared to **40-42** with the direct linkage.

Table 3. Biological assay data for cross-over series against *P. falciparum* and HepG2 cells.



ID	R^1	R^2	*P. fal.* D6 EC_{50} (μM)[a]	HepG2 TC_{50} (μM)[b,c,d]	SI	cLogP	LLE
40	A		0.026	>4	>150	2.1	5.5
41	B		0.035	>3	>86	4.4	3.1
42	C		0.093	21	230	3.1	3.8
43	A		0.94	4.5	4.8	1.6	4.4
44	B		0.25	23	92	3.9	2.6

45	A		0.13	17	540	3.1	3.8
46	A		0.054	22	410	2.4	4.8
47	B		0.099	7.6	77	4.7	2.2
48	A		0.18	21	120	2.5	4.3
49	B		0.078	4.7	60	4.7	2.3
Chloroquine			0.0050	3.3	660		

[a] All r^2 values >0.9

[b] n = 1 biological replicate made up of 2 technical replicates

[c] concentration which is toxic to 50% of the cell population

[d] tested concentration ranges were determined based on compound solubility

Analysis of the ADME data for the cross-over analogs is summarized in **Table 4** (for ADME data on all other compounds see **Supplementary Information, Table S3**). Incorporation of the -NH linker did, in some cases, lead to an increase in the aqueous solubility, and to an improvement in the overall ADME profile. For example, **45** exhibited the most significant improvement in aqueous solubility (810 μM; desired range > 10 μM) and had a lower plasma protein binding (88%; desired range < 95%) though this was also associated with a loss in potency (EC_{50}: 0.13 μM). While the cLogP and LLE were improved, the pyrazole replacement analogs (**43-44**) exhibited poor solubility, and **43** demonstrated high microsomal clearance. Despite the reduced selectivity observed with the 3-chloro-4-methoxy aniline head group (**B**), it tended to impart favorable metabolic stability to the analogs (**44**, **47**, **49**). Finally, **40** was potent against *P. falciparum* (EC_{50}: 0.026 μM), exhibited an improvement in aqueous solubility (44

μM), and a lower plasma protein binding (87%) compared with **3**, though microsomal stability was low in both humans and rats. Similarly, **7** was potent against *P. falciparum* (EC_{50}: 0.012 μM), exhibited an improvement in aqueous solubility (100 μM) though plasma protein binding (99%) and microsomal stability were still outside the desirable range (human: 47 μL/min/mg; rat: ≤ 27 μL/min/10^6). After considering the potency and ADME profile of all the analogs, **7** and **40** were identified as our most promising candidates to date.

Table 4. ADME data for cross-over analogs.

ID	Polar surface area (Å²)	Aqueous Solubility pH 7.4 (μM)	Human PPB (%)	Human Liver Microsome CLint (μL/min/mg)	Rat Hepatocyte CLint (μL/min/10^6)	$LogD_{7.4}$
3	75	0.3	> 99	140	20	nd
40	83	44	87	180	130	3.3
41	66	< 1	98	170	45	4.3
42	99	< 1	91	120	51	3.3
43	79	1.0	nd	130	5.0	2.6
44	63	2.0	97	8	5.0	3.5
45	69	810	88	nd	10	2.2
46	95	26	nd	nd	9.3	2.8
47	78	570	99	nd	7.2	3.3
48	95	2.0	nd	nd	nd	2.9
49	78	nd	nd	45	2.3	nd

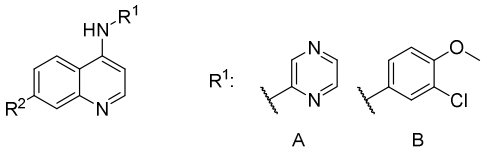
nd = not determined.

We note that overall, the aqueous solubility of this series does not correlate well with either cLogP or LogD (see **Supporting Information, Figure S1**). Despite this, we have made progress

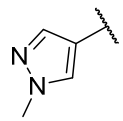
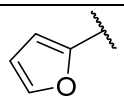
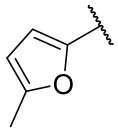
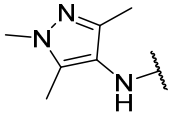
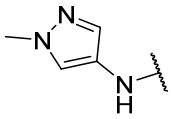
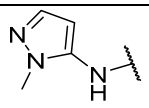
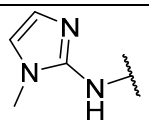
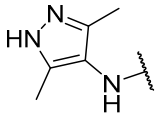
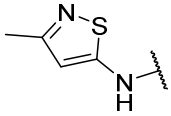
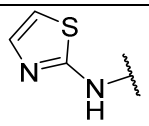
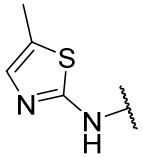
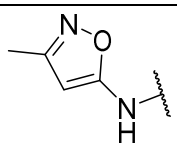
towards our goal of identifying potent compounds with improved aqueous solubility as exemplified by the fact that 21% (11 out of 53) of the compounds presented herein have aqueous solubility > 10 μM. Further efforts to fully understand the relationship between these properties is underway and will be presented in due course.

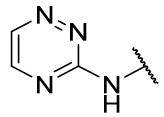
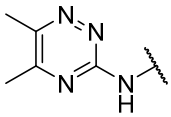
Given the ability to successfully modulate the ADME profile of the series seemed to reside with the tail region we explored additional heterocyclic and amine linked analogs (**Table 5**). No significant change in potency was observed upon capping the free -NH of the pyrazole with a methyl group (**50-51**), and insertion of an amine linker (**56**; EC_{50}: 0.40 μM) led to an equipotent compound. Replacement with the furan (**52**) led to a reduction in potency. A series of amine linked heterocycles was also trialed, including variously substituted pyrazoles (**55-59**), isothiazoles (**60**), thiazoles (**61-62**), isoxazoles (**63**) and triazines (**64-65**), in the hopes of recapitulating the boost in aqueous solubility observed with the cross-over analogs. In general, these compounds exhibited a loss of potency, with exception to **60**, and **62-63** which showed improved, potent activity and excellent selectivity. However, the ADME profile of these compounds (see **Supplementary Information, Table S3**) showed that they had poor aqueous solubility suggesting that this strategy could not be generally applied to the series to address the poor ADME profile.

Table 5. Biological assay data for further tail group replacement analogs against *P. falciparum*.



ID	R^1	R^2	*P. fal.*	HepG2 TC_{50}	SI	cLogP	LLE

			EC_{50} (μM)[a]	(μM)[b,c,d]			
50	A		0.50	40	80	1.8	4.5
51	B		0.16	>44	>280	4	2.8
52	A		0.30	>53	>180	2.4	4.1
53	A		1.0	>50	>50	2.6	3.4
54	B		0.10	>42	>420	4.9	2.1
55	A		1.2	>39	>33	1.9	4.0
56	A		0.40	29	73	1.6	4.8
57	A		0.60	35	58	1.7	4.5
58	A		0.86	>42	>49	2.0	4.1
59	A		6.8	>40	>5.9	1.8	3.4
60	A		0.031	>36	>1200	2.4	5.1
61	A		0.63	7.1	11	2.5	3.7
62	A		0.053	>40	>760	3.2	4.1
63	A		0.093	>48	>520	1.8	5.3

64	A		0.18	11	61	0.95	5.8
65	A		0.11	19	170	1.2	5.8
Chloroquine			0.0050	3.3	660		

[a] All r^2 values >0.9

[b] n = 1 biological replicate made up of 2 technical replicates

[c] concentration which is toxic to 50% of the cell population

[d] tested concentration ranges were determined based on compound solubility

In addition to demonstrating activity against blood-stage *Plasmodium*, it is useful to determine compound activity during the liver stage of the infection particularly for *P. vivax* and *P. ovale* malaria. It is during this stage that sporozoites develop into merozoites, which then invade and multiply in red blood cells;[3] compounds that target both the liver and blood stage of the infection are therefore more effective in preventing relapsing malaria and the symptomatic phase.[15] However, it is not critical to demonstrate activity in the hepatic stage for progression of promising compounds; most drugs that target bloodstream *Plasmodium* have little activity in the hepatic stage[16] and only primaquine is currently approved to eliminate hypnozoites.[17-18] Given this, a representative subset of our anilinoquinoline compounds were assessed in a *P. berghei* liver stage model (see **Supplementary Information, Table S2**). In general, the compounds exhibited low micromolar inhibition in the assay despite demonstrating nanomolar activity in the *P. falciparum* bloodstream form assays. It is important to acknowledge the differential activity that has been previously observed between human and murine models which could be due to differences in the humanized mouse model of *P. falciparum* and the normal mouse model for *P. berghei*.[16]

The exquisite human kinase selectivity of lapatinib (**1**) is attributed to the large, lipophilic head group. Compound **1** has previously demonstrated >300-fold selectivity versus numerous human kinases involved in cellular proliferation.[19] Given the structural modifications to the anilino head group presented herein, as well as modifications to other regions, we sought to assess the human kinase activity profile of **40** in a panel of human kinases (see **Supplementary Information, Figure S4**). At a test concentration of 5 μM, **40** showed significant inhibition of seven kinases largely belonging to the serine/threonine kinase family (Aurora A, MNK2 and MAP4K4) and the tyrosine kinase family (EGFR, Abl and KDR), which is unsurprising given the activity of **1**. In addition, **40** showed moderate to weak inhibition of 10 kinases, and insignificant inhibition of an additional 28 kinases.

Finally, **7** and **40** had the best combination of potency and aqueous solubility amongst all the members in the library and were tested in a modified Thompson *in vivo* infection model against *P. berghei*. This measures the parasite clearance and survivability of mice following administration of the compound on days 3 to 5 post-infection. Mice alive on day 31 with no parasitemia are considered cured. The mice in the study were given a single intraperitoneal dose of 160 mg/kg/day × 3 days and in both cases there was a reduction in parasitemia, but only mice treated with **7** experienced suppression of malaria and a life extension of 5 days compared to the control group. Hence, both **7** and **40** were suppressive and not curative of the *P. falciparum* infection. The poor *in vivo* efficacy is most likely due to the rapid clearance of **7** and **40**. Despite this, a positive impact was observed on the life span of infected mice, highlighting the promise of this series as anti-malarials.

Conclusion

We have previously observed that compounds bearing the large lipophilic head group of lapatinib have problematic physicochemical properties which are likely a result of the high MW and lipophilicity of the compounds in general. Given this, we designed a library of analogs which would mimic the key features of the head group while focusing on reducing the size and lipophilicity. These designs were further informed by shape and electrostatics similarity comparison to a known active, **3**. We also explored numerous tail region replacements and incorporated structural features that led to an improvement in the aqueous solubility of the series. Combining these features led us to the identification of **7** and **40**, potent inhibitors of bloodstream *P. falciparum*, with improved aqueous solubility over **3**. Progression of these compounds into an *in vivo* model demonstrated suppression of parasitemia, though neither were curative; it is likely that the metabolic instability of these analogs contributed to the outcome. Current efforts are centered upon further improving the overall ADME profile of this series with a focus on the microsomal stability, as well as further improvements to the aqueous solubility and plasma protein binding with an eye to identifying a lead compound for *P. falciparum*.

Experimental

General Chemistry Experimental

All starting materials were commercially procured and were used without further purification, unless specified. Reaction solvents were purified by passage through alumina columns on a purification system manufactured by Innovative Technology (Newburyport, MA). NMR spectra were obtained on Varian NMR systems, operating at 400 MHz or 500 MHz for ^{1}H acquisitions and at 126 MHz for ^{13}C acquisitions. LCMS analysis was performed using a Waters Alliance

reverse phase HPLC (columns Waters SunFire C18 4.6x50mm, 3.5μm or Waters SunFire C8 4.6x50mm, 3.5 μm), with single-wavelength UV–visible detector and LCT Premier time-of-flight mass spectrometer (electrospray ionization) or Waters Micromass ZQ detector (electrospray ionization). All final compounds were purified by preparative reverse phase HPLC (columns Waters Symmetry RP8 30 × 50 mm, 5 μm column or OBD RP18 30 × 50 mm, 5 μm), with a single-wavelength UV–visible detector and Waters Micromass ZQ (electrospray ionization). For further details regarding preparative HPLC and LCMS protocols, see Supporting Information. All final compounds have purities greater than 95% based upon LC/MS.

General library condition A:

In a dry 2mL microwave vial equipped with stir bar were combined **6** (0.018 g, 0.045 mmol), 0.067 mmol of amine and 4M hydrogen chloride in dioxane (0.017 mL, 0.067 mmol). The sealed vial was evacuated and backfilled three times with nitrogen followed by addition of 2-propanol (1 mL). The resultant mixture was stirred under nitrogen for 5 min. The vial was irradiated at 145 $^{\circ}$C for between 30 and 60 min; the reaction progress was monitored by LC-MS. The reaction was cooled to rt and filtered. The precipitate was sequentially washed with 2-propanol (5 mL) and DCM (5 mL) to afford final product. Further purification, if required, was carried out via preparative HPLC using a gradient 10-25% acetonitrile in water containing 0.1% formic acid to give the desired product.

General library condition B:

In a dry 2mL microwave vial equipped with stir bar was combined **6** (0.045 mmol), heterocyclic amine (0.067 mmol), palladium(II) acetate (2.5 mol%, 1.831 μmol), XantPhos (5

mol%, 3.57 μmol), and potassium tert-butoxide (0.089 mmol). The sealed vial was evacuated and backfilled three times with nitrogen followed by addition of xylene (1 mL). The contents was stirred under nitrogen for 5 min. The vial was irradiated at 160 °C for between 60 and 90 min; the reaction was monitored by LC-MS. The crude material was concentrated under reduced pressure. The solid was re-dissolved in ethyl acetate and filtered through a celite plug, which was washed sequentially with ethyl acetate (5mL) and methanol (5 mL) and concentrated. The crude material was solubilized in 1 mL DMSO and filtered through 17 mm cellulose syringe filter (0.45 μm). The crude product was purified via preparative HPLC using a gradient of 10-25% acetonitrile in water containing 0.1% formic acid to afford the desired product. HRMS data was collected using an Agilent Technologies 6520 Accurate-Mass Q-TOF MS system equipped with an IonSense DART SVP-100 ionization source.

General library condition C

In a dry 0.5-2 mL microwave vial were combined **26** (0.11 mmol), heterocyclic amine (0.13 mmol), palladium (II) acetate (10 mol%, 10.9 μmol), XantPhos (0.019 μmol), and cesium carbonate (0.218 mmol). The sealed vial was evacuated and backfilled three times with nitrogen followed by addition of dioxane (volume: 2 mL). The mixture was stirred under nitrogen for 5 min. The vial was irradiated at 140°C for 60-90 min; the reaction was monitored by LC-MS. Once the reaction was complete based on LC-MS the reaction mixture was concentrated under reduced pressure. The residue was partitioned between EtOAc and 2M NaOH. The aqueous layer was extracted twice with EtOAc (25 mL), the combined organic layers were washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The crude material was solubilized in 1 mL DMSO and filtered through a 17 mm cellulose syringe filter (0.45 μm). The crude product was

purified via preparative HPLC using a gradient 10-25% acetonitrile in water containing 0.1% formic acid to give the desired product.

General conditions D

In a 2mL microwave vial equipped with stir bar were appropriate bromide partner (1 eq), Ar-Bpin (1.2 eq), palladium (II) acetate (10 mol%), triethylamine (3 eq). 1:1 mixture of water and EtOH (1 mL) was added to the mixture and the sealed tube was irradiated at 120 °C for between 60 and 90 min. The reaction progress was monitored by LC-MS. Once the reaction was complete the crude material was filtered through a celite plug and washed with ethanol (10 mL). The filtrate was concentrated under vacuum. The crude material was solubilized in 1 mL DMSO and filtered through 17 mm cellulose syringe filter (0.45 μm). The crude material was purified via preparative HPLC using a 0-50% acetonitrile/water gradient containing 0.1% formic acid to give the desired product.

General library condition E

In a 2 mL microwave vial equipped with stir bar were appropriate bromide partner (50 mg, 1 eq), Ar-NH_2 (1.2 eq), palladium (II) acetate (10 mol %), XantPhos (11.1 mg, 0.019 mmol) cesium carbonate (71.2 mg, 0.21 mmol). The sealed vial was evacuated and backfilled three times with nitrogen followed by addition of anhydrous dioxane (2 mL). The contents were stirred under nitrogen for 5 min. The sealed vial was irradiated at 140 °C for 60-90 min. The reaction progress was monitored by LC-MS. Once the reaction was complete the crude was filtered through a celite plug and washed with dioxane (10 mL). The filtrate was concentrated under vacuum. The crude material was solubilized in 1 mL DMSO and filtered through 17 mm

cellulose syringe filter (0.45 μm). The crude material was purified via preparative HPLC using a 0-50% acetonitrile/water gradient containing 0.1% formic acid to give the desired product.

4-Chloro-7-(4-((4-methylpiperazin-1-yl)sulfonyl)phenyl)quinoline (**6**)

In a dry 20 mL microwave vial equipped with a stir bar was combined **4** (2.07 mmol), **5** (2.69 mmol), palladium(II) acetate (1 mol%, 0.027 mmol), triethylamine (6.21 mmol) and 1:1 mixture of water and ethanol (8 mL). The sealed vial was irradiated at 120 °C for 1 h. The crude material was filtered under vacuum and the precipitate was transferred to a conical flask. The precipitate was diluted with water (50 mL), and extracted with DCM (3 x 50 mL). The combined organic layers were washed with aq. NaOH (1M, 2 x 50 mL), water (50 mL), and brine (50 mL), dried over sodium sulfate and concentrated to afford **6** (584 mg, 1.45 mmol) as a pale white solid in 70% yield. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.93 (d, *J*=4.9 Hz, 1 H), 8.49 (d, *J*=2.0 Hz, 1 H), 8.35 (d, *J*=8.8 Hz, 1 H), 8.16 - 8.21 (m, 3 H), 7.87 - 7.90 (m, 2 H), 7.83 (d, *J*=4.4 Hz, 1 H), 2.96 (br. s., 4 H), 2.36 - 2.43 (m, 4 H), 2.16 ppm (br. s., 3 H). ESI-MS: *m/z* = 402.1 $(M + H)^+$.

***N*-(3-Chloro-4-methoxyphenyl)-7-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}quinolin-4-amine, formate salt** (**7**) Synthesized using general library condition A. Yield 42%

^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.46 - 8.50 (m, 2 H), 8.22 (d, *J*=2.0 Hz, 1 H), 8.20 (s, 1 H), 8.14 (d, *J*=8.3 Hz, 2 H), 7.94 (dd, *J*=8.8, 2.0 Hz, 1 H), 7.85 (d, *J*=8.8 Hz, 2 H), 7.43 (d, *J*=2.4 Hz, 1 H), 7.34 (dd, *J*=8.8, 2.4 Hz, 1 H), 7.22 (d, *J*=8.8 Hz, 1 H), 6.75 (d, *J*=5.4 Hz, 1 H), 3.87 (s, 3 H), 2.94 (br. s., 4 H), 2.37 (br. s., 4 H), 2.13 ppm (s, 3 H). ESI-MS: *m/z* = 523.1 $(M + H)^+$.

***N*-(3-Chlorophenyl)-7-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}quinolin-4-amine, bis-formate salt** (**8**) Synthesized using general library condition A. Yield 68%

^{1}H NMR (DMSO-d_6, 500 MHz) δ 9.17 (br. s., 1 H), 8.57 (d, *J*=5.4 Hz, 1 H), 8.48 (d, *J*=8.8 Hz, 1 H), 8.26 (d, *J*=1.5 Hz, 1 H), 8.22 (s, 2 H), 8.15 (d, *J*=8.3 Hz, 2 H), 7.98 (dd, *J*=8.8, 1.5 Hz, 1 H), 7.85 (d, *J*=8.3 Hz, 2 H), 7.39 - 7.44 (m, 2 H), 7.36 (d, *J*=7.8 Hz, 1 H), 7.15 (d, *J*=8.3 Hz, 1 H), 7.08 (d, *J*=5.4 Hz, 1 H), 2.94 (br. s., 4 H), 2.37 (br. s., 4 H), 2.13 ppm (s, 3 H). ESI-MS: *m/z* = 493.1 $(M + H)^+$.

***N*-(4-Methoxyphenyl)-7-(4-((4-methylpiperazin-1-yl)sulfonyl)phenyl)quinolin-4-amine, bis-formate salt** (**9**) Synthesized using general library condition A. Yield 56%

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.54 (d, *J*=8.8 Hz, 1 H), 8.43 (d, *J*=5.9 Hz, 1 H), 8.21 (d, *J*=2.0 Hz, 1 H), 8.13 - 8.15 (m, 2 H), 8.13 (s, 2 H), 7.94 (dd, *J*=9.0, 1.7 Hz, 1 H), 7.85 (d, *J*=8.3 Hz, 2 H), 7.30 (d, *J*=8.8 Hz, 2 H), 7.03 (d, *J*=8.8 Hz, 2 H), 6.65 (d, *J*=5.4 Hz, 1 H), 3.78 (s, 3 H), 2.94 (br. s., 4 H), 2.38 (br. s., 4 H), 2.14 ppm (s, 3 H). ESI-MS: *m/z* = 489.2 $(M + H)^+$.

7-(4-((4-Methylpiperazin-1-yl)sulfonyl)phenyl)-*N*-(4-(trifluoromethoxy)phenyl)quinolin-4-amine, bis-formate salt (**10**) Synthesized using general library condition A. Yield 56%

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.54 (d, *J*=5.4 Hz, 1 H), 8.50 (d, *J*=8.8 Hz, 1 H), 8.26 (d, *J*=2.0 Hz, 1 H), 8.14 (s, 2 H), 8.12 - 8.18 (m, 2 H), 7.97 (dd, *J*=8.8, 2.0 Hz, 1 H), 7.85 (d, *J*=8.3 Hz, 2 H), 7.45 - 7.51 (m, 2 H), 7.38 - 7.43 (m, 2 H), 7.02 (d, *J*=4.9 Hz, 1 H), 2.94 (br. s., 4 H), 2.37 (br. s., 4 H), 2.13 ppm (s, 3 H). ESI-MS: *m/z* = 543.2 $(M + H)^+$.

***N*-(3-Chloro-4-methylphenyl)-7-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}quinolin-4-amine, formate salt** (**11**) Synthesized using general library condition A. Yield 56%

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.53 (d, *J*=5.4 Hz, 1 H), 8.48 (d, *J*=8.8 Hz, 1 H), 8.24 (d, *J*=1.5 Hz, 1 H), 8.13 - 8.15 (m, 2 H), 8.15 (s, 1 H), 7.96 (dd, *J*=9.0, 1.7 Hz, 1 H), 7.85 (d, *J*=8.3 Hz, 2 H), 7.40 (d, *J*=2.0 Hz, 1 H), 7.38 (d, *J*=8.3 Hz, 1 H), 7.28 (dd, *J*=8.3, 2.0 Hz, 1 H), 6.96 (d, *J*=5.4 Hz, 1 H), 2.94 (br. s., 4 H), 2.90 - 3.00 (m, 4 H), 2.37 (br. s., 4 H), 2.33 (s, 3 H), 2.13 ppm (s, 3 H). ESI-MS: *m/z* = 507.1 $(M + H)^+$.

7-{4-[(4-Methylpiperazin-1-yl)sulfonyl]phenyl}-*N*-(pyridin-3-yl)quinolin-4-amine (**12**) Synthesized using general library condition A. Yield 19%

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.21 (br. s., 1 H), 8.65 (br. s., 1 H), 8.51 - 8.59 (m, 2 H), 8.40 (s, 1 H), 8.36 (d, *J*=3.9 Hz, 1 H), 8.28 (s, 1 H), 8.16 (d, *J*=8.8 Hz, 2 H), 8.00 (d, *J*=7.8 Hz, 1 H), 7.80 - 7.89 (m, 3 H), 7.46 (dd, *J*=7.8, 4.9 Hz, 1 H), 6.99 (d, *J*=4.9 Hz, 1 H), 2.96 (br. s., 4 H), 2.36 - 2.41 (m, 4 H), 2.15 ppm (s, 3 H). ESI-MS: *m/z* = 460.1 $(M + H)^+$.

7-{4-[(4-Methylpiperazin-1-yl)sulfonyl]phenyl}-*N*-(pyridazin-4-yl)quinolin-4-amine (**13**) Synthesized using general library condition A. Yield 37%

^{1}H NMR (500 MHz, METHANOL-d_4) δ 9.19 (d, *J*=4.4 Hz, 1 H), 9.10 (d, *J*=7.8 Hz, 1 H), 8.76 (d, *J*=2.9 Hz, 1 H), 8.56 (d, *J*=1.0 Hz, 1 H), 8.11 - 8.18 (m, 3 H), 8.06 (d, *J*=8.8 Hz, 1 H), 8.00 (d, *J*=8.3 Hz, 2 H), 7.85 (d, *J*=4.4 Hz, 1 H), 7.36 (dd, *J*=7.3, 2.9 Hz, 1 H), 2.98 - 3.21 (m, 4 H), 2.67 ppm (br. s, 3 H). ESI-MS: *m/z* = 461.1 $(M + H)^+$. *Four of the piperazine protons are coincidental with the methanol.

7-{4-[(4-Methylpiperazin-1-yl)sulfonyl]phenyl}-*N*-(pyrazin-2-yl)quinolin-4-amine, formate salt (**14**) Synthesized using general library condition B. Yield 29%

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.88 (br. s., 1 H), 8.78 (d, *J*=4.9 Hz, 1 H), 8.75 (s, 1 H), 8.65 (d, *J*=8.8 Hz, 1 H), 8.39 (d, *J*=4.9 Hz, 1 H), 8.34 (br. s., 2 H), 8.22 (s, 1 H), 8.19 (s, 1 H), 8.18 (d, *J*=5.9 Hz, 2 H), 8.06 (dd, *J*=8.8, 2.0 Hz, 1 H), 7.87 (d, *J*=8.8 Hz, 2 H), 2.96 (br. s., 4 H), 2.39 (br. s., 4 H), 2.15 ppm (s, 3 H). ESI-MS: *m/z* = 461.1 $(M + H)^+$.

7-(4-((4-Methylpiperazin-1-yl)sulfonyl)phenyl)-*N*-(6-methylpyridin-3-yl)quinolin-4-amine, formate salt (**15**) Synthesized using general library condition B. Yield 56%

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.55 (d, *J*=8.8 Hz, 1 H), 8.48 - 8.53 (m, 2 H), 8.25 (br. s., 1 H), 8.15 (d, *J*=7.8 Hz, 2 H), 8.12 (s, 1 H), 8.00 (d, *J*=8.8 Hz, 1 H), 7.86 (d, *J*=8.3 Hz, 2 H), 7.72 (dd, *J*=8.3, 2.9 Hz, 1 H), 7.33 (d, *J*=8.3 Hz, 1 H), 6.82 (d, *J*=5.4 Hz, 1 H), 2.97 (br. s., 4 H), 2.19 ppm (s, 3 H). ESI-MS: *m/z* = 474.2 $(M + H)^+$. *Four of the piperazine protons and the methyl are coincident with the DMSO.

7-(4-((4-Methylpiperazin-1-yl)sulfonyl)phenyl)-*N*-(6-(trifluoromethyl)pyridin-3-yl)quinolin-4-amine, formate salt (**16**) Synthesized using general library condition B. Yield 34%

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.56 (br. s., 1 H), 8.78 (br. s., 1 H), 8.68 (d, *J*=3.9 Hz, 1 H), 8.48 (d, *J*=8.8 Hz, 1 H), 8.32 (br. s., 1 H), 8.16 (d, *J*=8.3 Hz, 2 H), 8.15 (br. s., 1 H), 8.04 (d, *J*=8.3 Hz, 1 H), 7.96 (br. s., 1 H), 7.83 - 7.89 (m, 3 H), 7.33 (d, *J*=3.9 Hz, 1 H), 2.94 (br. s., 4 H), 2.37 (br. s., 4 H), 2.13 ppm (s, 3 H). ESI-MS: *m/z* = 528.2 $(M + H)^+$.

***N*-(2-Methoxypyrimidin-5-yl)-7-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}quinolin-4-amine, formate salt** (**17**) Synthesized using general library condition A. Yield 45%

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.68 (s, 2 H), 8.49 (d, *J*=9.3 Hz, 2 H), 8.45 (br. s, 1 H), 8.25 (s, 1 H), 8.15 (d, *J*=8.3 Hz, 2 H), 8.13 (s, 1 H), 7.99 (d, *J*=8.8 Hz, 1 H), 7.85 (d, *J*=8.3 Hz, 2 H), 6.66 (d, *J*=5.4 Hz, 1 H), 3.95 (s, 3 H), 2.94 (br. s., 4 H), 2.37 (br. s., 4 H), 2.13 ppm (s, 3 H). ESI-MS: *m/z* = 491.1 $(M + H)^+$.

***N*-(5-Methoxypyrazin-2-yl)-7-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}quinolin-4-amine, formate salt** (**18**) Synthesized using general library condition A. Yield 32%

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.62 (br. s., 1 H), 8.65 (d, *J*=5.4 Hz, 1 H), 8.62 (d, *J*=8.8 Hz, 1 H), 8.34 (d, *J*=1.0 Hz, 1 H), 8.29 (d, *J*=1.5 Hz, 1 H), 8.18 (s, 2 H), 8.17 (s, 1 H), 8.15 (d, *J*=1.5 Hz, 1 H), 8.02 (dd, *J*=8.8, 2.0 Hz, 1 H), 7.93 (d, *J*=5.4 Hz, 1 H), 7.87 (d, *J*=8.3 Hz, 2 H), 3.92 (s, 3 H), 2.96 (br. s., 4 H), 2.39 (br. s., 4 H), 2.15 ppm (s, 3 H). ESI-MS: *m/z* = 491.1 $(M + H)^+$.

5-[(7-{4-[(4-Methylpiperazin-1-yl)sulfonyl]phenyl}quinolin-4-yl)amino]pyrazine-2-carbonitrile, formate salt (**19**) Synthesized using general library condition B. Yield 23%

^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.88 (d, *J*=4.9 Hz, 1 H), 8.82 (s, 1 H), 8.73 (s, 1 H), 8.59 (d, *J*=8.8 Hz, 1 H), 8.39 (s, 1 H), 8.29 (d, *J*=5.4 Hz, 1 H), 8.25 (s, 1 H), 8.19 (d, *J*=8.3 Hz, 2 H), 8.10 (d, *J*=8.8 Hz, 1 H), 7.88 (d, *J*=8.3 Hz, 2 H), 2.96 (br. s., 4 H), 2.39 (br. s., 4 H), 2.15 ppm (s, 3 H). ESI-MS: *m/z* = 486.1 $(M + H)^+$.

***N*-(5-Chloropyridin-2-yl)-7-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}quinolin-4-amine** (**20**) Synthesized using general library condition B. Yield 32%

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.69 (br. s., 1 H), 8.74 (d, *J*=5.4 Hz, 1 H), 8.62 (d, *J*=8.8 Hz, 1 H), 8.37 (d, *J*=2.4 Hz, 1 H), 8.35 (d, *J*=5.4 Hz, 1 H), 8.32 (d, *J*=2.0 Hz, 1 H), 8.27 (s, 1 H), 8.17 (d, *J*=8.3 Hz, 2 H), 8.03 (dd, *J*=8.8, 1.5 Hz, 1 H), 7.87 (d, *J*=8.3 Hz, 2 H), 7.43 (d, *J*=8.8 Hz, 1 H), 2.96 (br. s., 4 H), 2.39 (br. s., 4 H), 2.15 ppm (s, 3 H). ESI-MS: *m/z* = 494.0 $(M + H)^+$.

***N*-(5-Chloropyrimidin-2-yl)-7-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}quinolin-4-amine, formate salt** (**21**) Synthesized using general library condition B. Yield 45%

^{1}H NMR (500 MHz, DMSO-d_6) δ 10.37 (s, 1 H), 8.84 (d, *J*=5.4 Hz, 1 H), 8.73 (s, 1 H), 8.58 (d, *J*=9.3 Hz, 1 H), 8.35 (d, *J*=1.5 Hz, 1 H), 8.26 (s, 1 H), 8.17 (d, *J*=8.8 Hz, 2 H), 8.17 (s, 1 H), 7.99 (dd, *J*=8.8, 2.0 Hz, 1 H), 7.86 (d, *J*=8.3 Hz, 2 H), 2.96 (br. s., 4 H), 2.39 (br. s., 4 H), 2.15 ppm (s, 3 H). ESI-MS: *m/z* = 495.1 $(M + H)^+$.

***N*-(1*H*-1,2,3-Benzotriazol-5-yl)-7-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}quinolin-4-amine, bis-formate salt** (**22**) Synthesized using general library condition A. Yield 32%.

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.56 (d, *J* = 8.8 Hz, 2H), 8.28 (s, 1H), 8.22 (s, 2H), 8.17 (d, *J* = 8.3 Hz, 2H), 8.00 (d, *J* = 8.8 Hz, 2H), 7.87 (d, *J* = 8.3 Hz, 2H), 7.75 (s, 1H), 7.48 (d, *J* = 8.8 Hz, 1H), 7.05 (d, *J* = 4.9 Hz, 1H), 2.96 (br. s., 4H), 2.39 (br. s., 4H), 2.15 (s, 3H). ESI-MS: *m/z* = 500.1 $(M + H)^+$.

***N*-(Dimethyl-1,2,4-triazin-3-yl)-7-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}quinolin-4-amine, 0.3 eq formate salt** (**23**) Synthesized using general library condition B. Yield 24%

^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.28 (br. s., 1 H), 8.83 (d, *J*=4.9 Hz, 1 H), 8.67 (d, *J*=8.8 Hz, 1 H), 8.35 (s, 1 H), 8.28 (d, *J*=4.9 Hz, 1 H), 8.22 (s, 0.3 H), 8.18 (d, *J*=8.3 Hz, 2 H), 7.98 (d,

J=8.8 Hz, 1 H), 7.86 (d, *J*=7.8 Hz, 2 H), 2.96 (br. s., 4 H), 2.57 (s, 3 H), 2.39 (br. s., 4 H), 2.15 ppm (s, 3 H). ESI-MS: *m/z* = 490.1 $(M + H)^+$. *One of the methyl peaks is coincidental with the DMSO.

***N*-(3-Methyl-1,2-thiazol-5-yl)-7-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}quinolin-4-amine** (**24**) Synthesized using general library condition A. Yield 28%

^{1}H NMR (500 MHz, DMSO-d_6) δ 10.38 (s, 1 H), 8.76 (d, *J*=5.4 Hz, 1 H), 8.56 (d, *J*=8.8 Hz, 1 H), 8.34 (s, 1 H), 8.18 (d, *J*=8.3 Hz, 2 H), 8.06 (d, *J*=7.3 Hz, 1 H), 7.87 (d, *J*=8.3 Hz, 2 H), 7.32 (d, *J*=5.4 Hz, 1 H), 7.09 (s, 1 H), 2.96 (br. s., 4 H), 2.35 – 2.43 (m, 7 H), 2.15 ppm (s, 3 H). ESI-MS: *m/z* = 480.1 $(M + H)^+$.

***N*-(3-Chloro-4-((3-fluorobenzyl)oxy)phenyl)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinolin-4-amine** (**27**) In a dry 2 mL microwave vial equipped with stir were combined **26**[8] (200 mg, 0.437 mmol), B_2pin_2 (144 mg, 0.568 mmol), $Pd(PPh_3)_4$ (15.15 mg, 0.013 mmol) and potassium acetate (129 mg, 1.311 mmol) in anhydrous dioxane (4 mL). The sealed vial was irradiated at 120 °C for 2.5 h. The solution was concentrated under vacuum and partitioned between EtOAc and sat. $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc (x3). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated under vacuum. The crude material was triturated with hexanes to afford the title compound as a magenta solid in 91% yield. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.93 (s, 1 H), 8.46 (d, *J*=5.4 Hz, 1 H), 8.32 (d, *J*=8.3 Hz, 1 H), 8.17 (s, 1 H), 7.70 (d, *J*=8.3 Hz, 1 H), 7.42 - 7.50 (m, 2 H), 7.25 - 7.34 (m, 4 H), 7.14 - 7.21 (m, 1 H), 6.80 (d, *J*=4.9 Hz, 1 H), 5.24 (s, 2 H), 1.30 - 1.37 ppm (m, 12 H). ESI-MS: m/z = 505.1 $(M + H)^+$.

***N*-(3-Chloro-4-((3-fluorobenzyl)oxy)phenyl)-7-(3-((4-methylpiperazin-1-yl)sulfonyl)phenyl)quinolin-4-amine, formate salt** (**28**) In a dry 2 mL microwave vial equipped with stir were combined **27** (20.0 mg, 0.004 mmol), 1-(3-bromophenyl)-4-methylpiperazine (9.7 mg, 0.030 mmol), $Pd(PPh_3)_4$ (4.5 mg, 3.9 μmol), and potassium carbonate (12.6 mg, 0.09 mmol). The sealed vial was evacuated and backfilled with nitrogen (x3). A 3:1 mixture of dioxane and water (total volume: 1.3 mL) was added to the mixture and the sealed tube was irradiated at 120 °C for 120 min. The contents were cooled to rt and filtered through a celite plug, washed with EtOAc (x2) and concentrated. The contents were partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc (x2). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated under vacuum. The crude material was purified via preparative HPLC using a 10-60% acetonitrile/water gradient. The final compound was isolated as a yellow solid in 57% yield. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.47-8.53 (m, 2H), 8.22 (d, *J*=7.3 Hz, 1H), 8.18 (d, *J*=1.5 Hz, 1H), 8.12 (s, 1H), 8.06 (s, 1H), 7.94 (dd, *J*=8.8, 1.5 Hz, 1H), 7.77-7.84 (m, 2H), 7.44-7.50 (m, 1H), 7.28-7.36 (m, 4H), 7.18 (td, *J*=8.5, 2.4 Hz, 1H), 6.77 (d, *J*=5.4 Hz, 1H), 5.26 (s, 2H), 2.98 (br. s., 4H), 2.40 (br. s., 4H), 2.14 ppm (s, 3H). ESI-MS: m/z = 617.2 $(M + H)^+$.

***N*-(3-Chloro-4-((3-fluorobenzyl)oxy)phenyl)-7-(2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)quinolin-4-amine** (**29**) In a 2 mL microwave vial equipped with stir bar was combined **26** (53.0 mg, 0.12 mmol), **37** (45.8 mg, 45.8 mmol), palladium (II) acetate (0.34 mg, 1.51 μmol), triethylamine (0.048 mL, 0.35 mmol). A 1:1 mixture of water and ethanol (1 mL) was added to the mixture and the sealed tube was irradiated at 120 °C for 1.5 h. The crude mixture was filtered

through a celite plug and was concentrated under vacuum. The crude material was then purified via a preparative HPLC using a 10-60% acetonitrile/water gradient. The final compound was isolated as a yellow solid in 33% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.94 (s, 2 H), 8.43 - 8.49 (m, 2 H), 8.14 (d, *J*=1.5 Hz, 1 H), 7.91 (d, *J*=8.8 Hz, 1 H), 7.45 - 7.53 (m, 2 H), 7.29 - 7.37 (m, 4 H), 7.20 (td, *J*=8.7, 2.2 Hz, 1 H), 6.74 (d, *J*=5.4 Hz, 1 H), 5.27 (s, 2 H), 3.78 - 3.96 (m, 4 H), 2.52 - 2.66 (m, 4 H), 2.35 ppm (br. s., 3 H). ESI-MS: m/z = 555.1 $(M + H)^+$.

***N*-(3-Chloro-4-((3-fluorobenzyl)oxy)phenyl)-7-(4-(4-methylpiperazin-1-yl)-1,2,5-thiadiazol-3-yl)quinolin-4-amine, formate salt** (**30**) In a dry 2 mL microwave vial equipped with stir were combined **27** (50.0 mg, 0.099 mmol), **60** (16.7 mg, 0.076 mmol), $Pd(PPh_3)_4$ (11.5 mg, 9.91 μmol), and potassium carbonate (31.6 mg, 0.23 mmol). The sealed vial was evacuated and backfilled with nitrogen (x3). A 3:1 mixture of dioxane and water (total volume: 1.3 mL) was added to the mixture and the sealed tube was irradiated at 120 °C for 120 min. The contents were cooled to rt and filtered through a celite plug, washed with EtOAc (x2) and concentrated. The contents were partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc (x2). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated under vacuum. The crude material was purified via silica gel chromatography using 0-20% MeOH in DCM. The final compound was isolated as a yellow solid in 51% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.51 (d, *J*=4.9 Hz, 1 H), 8.48 (d, *J*=8.8 Hz, 1 H), 8.41 (d, *J*=1.5 Hz, 1 H), 8.14 (s, 1 H), 8.00 (dd, *J*=8.8, 1.5 Hz, 1 H), 7.46 - 7.52 (m, 2 H), 7.29 - 7.37 (m, 4 H), 7.20 (td, *J*=8.7, 2.2 Hz, 1 H), 6.81 (d, *J*=5.4 Hz, 1 H), 5.27 (s, 2 H), 3.19 (br. s., 4 H), 2.26 ppm (s, 3 H). ESI-MS: m/z = 561.1 $(M + H)^+$. *Four of the piperazine protons are coincident with the residual solvent peak.

***N*-(3-Chloro-4-((3-fluorobenzyl)oxy)phenyl)-7-(1*H*-pyrazol-4-yl)quinolin-4-amine (31)**. In a 2 mL microwave vial were combined **26** (100 mg, 0.22 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (85 mg, 0.44 mmol), $Pd(PPh_3)_4$ (20.2 mg, 0.017 mmol), potassium carbonate (19.6 mg, 0.67 mmol). The sealed vial was evacuated and backfilled twice with nitrogen (x3). A 3:1 mixture of dioxane and water (volume: 1 mL:0.3 mL) was added to the mixture and the sealed tube was irradiated at 120 °C for 60 min. The contents were cooled to room temperature and filtered through a celite plug, washed with EtOAc twice and concentrated. The contents were partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc (x3). The combined organic layers were washed with 1N NaOH, brine, dried over sodium sulfate and concentrated under vacuum. The crude material was purified via silica gel chromatography using 0-20% MeOH in DCM. The final compound was isolated as a yellow solid in 67% yield. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 13.14 (br. s., 2H), 8.38-8.49 (m, 3H), 8.13 (br. s., 1H), 8.05 (d, *J*=1.0 Hz, 1H), 7.92 (d, *J*=8.3 Hz, 1H), 7.44-7.56 (m, 2H), 7.29-7.37 (m, 4H), 7.19 (td, *J*=8.7, 2.2 Hz, 1H), 6.67 (d, *J*=5.9 Hz, 1H), 5.27 ppm (s, 2H). ESI-MS: m/z = 445.1 $(M + H)^+$.

***N*^{4}-(3-Chloro-4-((3-fluorobenzyl)oxy)phenyl)-*N*^{7}-(4-(4-methylpiperazin-1-yl)phenyl)quinoline-4,7-diamine, bis-formate salt (32)** Synthesized using general library condition C. Yield 44%.

^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.51 (br. s., 1H), 8.22 (d, *J*=5.9 Hz, 1H), 8.19 (s, 1H), 8.17 (s, 2H), 7.45-7.53 (m, 2H), 7.29-7.38 (m, 4H), 7.12-7.24 (m, 5H), 6.99 (d, *J*=9.3 Hz, 2H), 6.49

(d, *J*=5.9 Hz, 1H), 5.28 (s, 2H), 3.08-3.16 (m, 4H), 2.25 ppm (s, 3H). ESI-MS: m/z = 568.1 $(M + H)^+$. *Four of the piperazine protons are coincident with the residual solvent peak.

N^4-(3-Chloro-4-((3-fluorobenzyl)oxy)phenyl)-N^7-(2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)quinoline-4,7-diamine (**33**) Synthesized using general library condition C. Yield 32%

^{1}H NMR (METHANOL-d_4, 500 MHz) δ 8.51 (br. s., 1H), 8.43 (s, 2H), 8.27 (d, *J*=9.3 Hz, 1H), 8.09 (d, *J*=6.8 Hz, 1H), 7.53 (d, *J*=2.0 Hz, 1H), 7.41-7.49 (m, 1H), 7.23-7.39 (m, 5H), 7.06 - 7.15 (m, 1H), 6.90 (s, 1H), 6.57 (d, *J*=6.8 Hz, 1H), 5.30 (s, 2H), 3.99 (br. s., 4H), 2.85 (d, *J*=4.4 Hz, 4H), 2.59 ppm (s, 3H). ESI-MS *m/z* = 570.0 $(M + H)^+$.

N^4-(3-Chloro-4-((3-fluorobenzyl)oxy)phenyl)-N^7-(4-(4-methylpiperazin-1-yl)pyrimidin-2-yl)quinoline-4,7-diamine, formate salt (**34**) Synthesized using general library condition C using **71**. Yield 35%

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.45 (s, 1 H), 8.41 (d, *J*=2.0 Hz, 1 H), 8.34 (d, *J*=5.9 Hz, 1 H), 8.20 (s, 1 H), 8.16 - 8.23 (m, 1 H), 8.06 (d, *J*=5.9 Hz, 1 H), 7.78 (dd, *J*=9.3, 2.0 Hz, 1 H), 7.46 - 7.53 (m, 1 H), 7.45 (d, *J*=2.0 Hz, 1 H), 7.26 - 7.38 (m, 4 H), 7.20 (td, *J*=8.5, 2.0 Hz, 1 H), 6.61 (d, *J*=5.4 Hz, 1 H), 6.37 (d, *J*=6.3 Hz, 1 H), 5.27 (s, 2 H), 3.67 (br. s., 4 H), 2.41 (t, *J*=4.6 Hz, 4 H), 2.24 ppm (s, 3 H). ESI-MS: m/z = 570.1 $(M + H)^+$.

N^4-(3-Chloro-4-((3-fluorobenzyl)oxy)phenyl)-N^7-(2-(4-methylpiperazin-1-yl)pyrimidin-4-yl)quinoline-4,7-diamine, bis-formate salt (**35**) Synthesized using general library condition C using **70**. Yield 35%

^{1}H NMR (DMSO-d_6, 500 MHz) δ 9.65 (s, 1H), 8.38 (d, *J*=5.4 Hz, 1H), 8.28 (d, *J*=9.3 Hz, 1H), 8.25 (d, *J*=2.0 Hz, 1H), 8.17 (s, 2H), 8.03 (d, *J*=5.4 Hz, 1H), 7.76 (dd, *J*=9.3, 2.0 Hz, 1H), 7.45-7.53 (m, 2H), 7.27-7.38 (m, 3H), 7.17-7.24 (m, 1H), 6.66 (d, *J*=5.4 Hz, 1H), 6.17 (d, *J*=5.4 Hz, 1H), 5.27 (s, 2H), 3.78 (br. s., 4H), 2.42 (t, *J*=4.6 Hz, 4H), 2.25 ppm (s, 3H). ESI-MS: m/z = 570.2 $(M + H)^+$.

***Tert*-butyl (4-((3-Chloro-4-((3-fluorobenzyl)oxy)phenyl)amino)quinolin-7-yl)carbamate** (**36**). In a dry 10 mL round-bottom flask equipped with stir-bar were combined tert-butyl carbamate (28.2 mg, 0.24 mmol), **7** (100 mg, 0.22 mmol), palladium(II) acetate (4.93 mg, 0.022 mmol), XantPhos (22.37 mg, 0.039 mmol), and cesium carbonate (142 mg, 0.44 mmol). Anhydrous 1,4-dioxane (2.5 mL) was added via a syringe and the mixture was refluxed for 4 h at 120 °C to give an orange mixture. The reaction was stopped and cooled to room temperature, diluted with water and extracted with EtOAc (2x). The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified via silica gel chromatography using 0-15% MeOH in EtOAc. The pre-packed silica cartridge was washed with 0.5% triethylamine in 100 mL EtOAc before loading the compound. The final compound was isolated as a pale-yellow solid in 57% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.65 (s, 1 H), 8.79 (br. s., 1 H), 8.33 (d, *J*=4.9 Hz, 1 H), 8.18 (d, *J*=9.3 Hz, 1 H), 7.98 (s, 1 H), 7.58 (dd, *J*=9.3, 1.5 Hz, 1 H), 7.46 (tdd, *J*=8.3, 8.3, 5.9, 2.0 Hz, 1 H), 7.41 (s, 1 H), 7.23 - 7.34 (m, 4 H), 7.17 (td, *J*=8.7, 2.2 Hz, 1 H), 6.61 (d, *J*=4.9 Hz, 1 H), 5.24 (s, 2 H), 1.50 ppm (s, 9 H). ESI-MS: m/z = 494.1 $(M + H)^+$.

7-(2-(4-Methylpiperazin-1-yl)pyrimidin-5-yl)-*N*-(pyrazin-2-yl)quinolin-4-amine (**40**). Synthesized using general library condition D. Yield 56%

^{1}H NMR (DMSO-d_6, 500MHz) δ 9.78 (s, 1H), 8.93 (s, 2H), 8.69-8.73 (m, 2H), 8.55 (d, *J*=8.8 Hz, 1H), 8.31 (d, *J*=4.9 Hz, 2H), 8.22 (d, *J*=1.5 Hz, 1H), 8.16 (d, *J*=2.4 Hz, 1H), 7.96 (dd, *J*=8.8, 2.0 Hz, 1H), 3.78-3.85 (m, 4H), 2.38 (t, *J*=4.9 Hz, 4H), 2.22 ppm (s, 3H). ^{13}C NMR (DMSO-d_6, 126 MHz) δ 160.7, 156.2, 151.7, 151.3, 149.2, 143.1, 141.0, 136.8, 136.1, 135.7, 124.7, 123.1, 123.1, 120.8, 119.1, 107.2, 54.4, 45.8, 43.4 ppm. ESI-MS: *m/z* = 399.2 $(M + H)^+$. HRMS (DART): calculated $C_{22}H_{23}N_8^+$, *m/z* = 399.2040; found, *m/z* = 399.2041.

***N*-(3-Chloro-4-methoxyphenyl)-7-(2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)quinolin-4-amine, formate salt** (**41**). Synthesized using general library condition D. Yield 63%

^{1}H NMR (DMSO-d_6, 500MHz) δ 8.90 (s, 2 H), 8.36-8.46 (m, 2 H), 8.14 (s, 1 H), 8.11 (d, *J*=1.5 Hz, 1 H), 7.85 (dd, *J*=8.8, 2.0 Hz, 1 H), 7.41 (d, *J*=2.4 Hz, 1 H), 7.32 (dd, *J*=8.8, 2.9 Hz, 1 H), 7.21 (d, *J*=8.8 Hz, 1 H), 6.70 (d, *J*=5.4 Hz, 1 H), 3.87 (s, 3 H), 3.77-3.84 (m, 4 H), 2.39 (t, *J*=4.6 Hz, 4 H), 2.23 ppm (s, 3 H). ESI-MS: *m/z* = 461.2 $(M + H)^+$.

***N*-(1*H*-Benzo[*d*][1,2,3]triazol-5-yl)-7-(2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)quinolin-4-amine, formate salt** (**42**). Synthesized using general library condition D. Yield 38%

^{1}H NMR (DMSO-d_6, 500MHz) δ 8.98 (s, 2 H), 8.61 (d, *J*=8.8 Hz, 1 H), 8.50 (d, *J*=5.9 Hz, 1 H), 8.17 (d, *J*=1.5 Hz, 1 H), 8.12 (s, 1 H), 8.03 (d, *J*=7.8 Hz, 2 H), 7.85 (br. s., 1 H), 7.49 (dd, *J*=8.8, 1.5 Hz, 1 H), 6.93 (d, *J*=5.9 Hz, 1 H), 3.98 (br. s., 4 H), 2.96 (br. s., 4 H), 2.61 ppm (s, 3 H). ESI-MS: *m/z* = 438.2 $(M + H)^+$.

***N*-(Pyrazin-2-yl)-7-(1*H*-pyrazol-4-yl)quinolin-4-amine, formate salt** (**43**). Synthesized using general library condition D. Yield 50%

^{1}H NMR (500 MHz, METHANOL-d_4) δ 8.68 (d, *J*=1.0 Hz, 1 H), 8.64 (d, *J*=5.9 Hz, 1 H), 8.54 (d, *J*=5.9 Hz, 1 H), 8.52 (d, *J*=9.3 Hz, 1 H), 8.41 (dd, *J*=2.4, 1.5 Hz, 1 H), 8.27 (s, 1 H), 8.26 (s, 1 H), 8.22 (s, 2 H), 8.11 (d, *J*=1.5 Hz, 1 H), 8.01 ppm (dd, *J*=8.8, 1.5 Hz, 1 H). ESI-MS: *m/z* = 289.2 $(M + H)^+$.

***N*-(3-Chloro-4-methoxyphenyl)-7-(1*H*-pyrazol-4-yl)quinolin-4-amine** (**44**). Synthesized using general library condition D. Yield 61%

^{1}H NMR (500 MHz, METHANOL-d_4) δ 8.46 (d, *J*=9.8 Hz, 1 H), 8.32 (d, *J*=6.8 Hz, 1 H), 8.24 (br. s., 2 H), 8.02 (d, *J*=9.3 Hz, 1 H), 8.01 (s, 1 H), 7.50 (d, *J*=2.4 Hz, 1 H), 7.38 (dd, *J*=8.8, 2.4 Hz, 1 H), 7.25 (d, *J*=8.8 Hz, 1 H), 6.74 (d, *J*=6.8 Hz, 1 H), 3.96 ppm (s, 3 H). ESI-MS: *m/z* = 351.1 $(M + H)^+$.

***N*^{7}-(4-(4-Methylpiperazin-1-yl)phenyl)-*N*^{4}-(pyrazin-2-yl)quinoline-4,7-diamine** (**45**). Synthesized using general library condition E. Yield 24%

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.58 (s, 1 H), 8.66 (s, 1 H), 8.48 (d, *J*=5.4 Hz, 1 H), 8.31 (s, 1 H), 8.28 (dd, *J*=2.4, 1.5 Hz, 1 H), 8.24 (d, *J*=9.3 Hz, 1 H), 8.13 (d, *J*=2.4 Hz, 1 H), 7.99 (d, *J*=4.9 Hz, 1 H), 7.27 (d, *J*=2.4 Hz, 1 H), 7.22 (dd, *J*=9.3, 2.0 Hz, 1 H), 7.16 (d, *J*=8.8 Hz, 2 H), 6.98 (d, *J*=9.3 Hz, 2 H), 3.07 - 3.15 (m, 4 H), 2.44 - 2.50 (m, 4 H), 2.24 ppm (s, 3 H). ESI-MS: *m/z* = 412.2 $(M + H)^+$.

***N*^{7}-(4-(4-Methylpiperazin-1-yl)pyrimidin-2-yl)-*N*^{4}-(pyrazin-2-yl)quinoline-4,7-diamine, bis-formate salt** (**46**). Synthesized using general library condition E. Yield 26%

^{1}H NMR (500 MHz, METHANOL-d_4) δ 8.74 (d, *J*=6.3 Hz, 2 H), 8.58 (d, *J*=6.3 Hz, 1 H), 8.48 (d, *J*=9.3 Hz, 2 H), 8.43 - 8.47 (m, 1 H), 8.34 (s, 2 H), 8.33 (d, *J*=2.0 Hz, 1 H), 8.14 (d, *J*=6.3 Hz, 1 H), 7.83 (dd, *J*=9.3, 1.5 Hz, 1 H), 6.46 (d, *J*=6.3 Hz, 1 H), 3.86 (br. s., 4 H), 2.82 (t, *J*=4.4 Hz, 4 H), 2.55 ppm (s, 3 H). ESI-MS: *m/z* = 414.2 $(M + H)^+$.

***N*^{4}-(3-Chloro-4-methoxyphenyl)-*N*^{7}-(4-(4-methylpiperazin-1-yl)pyrimidin-2-yl)quinoline-4,7-diamine, formate salt** (**47**). Synthesized using general library condition E. Yield 66%

^{1}H NMR (DMSO-d_6, 500MHz) δ 9.74 (s, 1H), 8.51 (d, *J*=2.0 Hz, 1H), 8.30-8.38 (m, 2H), 8.15 (s, 1H), 8.10 (d, *J*=6.3 Hz, 1H), 7.83 (dd, *J*=9.3, 1.5 Hz, 1H), 7.51 (d, *J*=2.4 Hz, 1H), 7.38 (dd, *J*=8.8, 2.4 Hz, 1H), 7.29 (d, *J*=9.3 Hz, 1H), 6.57 (d, *J*=6.3 Hz, 1H), 6.44 (d, *J*=6.3 Hz, 1H), 3.92 (s, 3H), 3.68 (br. s., 4H), 2.44 (t, *J*=4.9 Hz, 4H), 2.26 ppm (s, 3H). ESI-MS: *m/z* = 476.2 $(M + H)^+$.

***N*^{7}-(2-(4-Methylpiperazin-1-yl)pyrimidin-4-yl)-*N*^{4}-(pyrazin-2-yl)quinoline-4,7-diamine, bis-formate salt** (**48**). Synthesized using general library condition E. Yield 20%

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.70 (s, 1 H), 8.70 (s, 1 H), 8.63 (d, *J*=4.9 Hz, 1 H), 8.41 (d, *J*=9.3 Hz, 1 H), 8.36 (s, 1 H), 8.32 (br. s., 1 H), 8.19 (d, *J*=5.4 Hz, 1 H), 8.17 (d, *J*=2.4 Hz, 1 H), 8.15 (s, 2 H), 8.04 (d, *J*=5.9 Hz, 1 H), 7.85 (d, *J*=8.8 Hz, 1 H), 6.19 (d, *J*=5.9 Hz, 1 H), 3.82 (br. s., 4 H), 2.33 ppm (s, 3 H). ESI-MS: *m/z* = 414.2 $(M + H)^+$. *Four of the piperazine protons are coincident with residual solvent peak.

N^4-(3-Chloro-4-methoxyphenyl)-N^7-(2-(4-methylpiperazin-1-yl)pyrimidin-4-yl)quinoline-4,7-diamine, bis-formate salt (**49**). Synthesized using general library condition E. Yield 19%

^{1}H NMR (DMSO-d_6, 500MHz) δ 9.70 (s, 1H), 8.37 (d, *J*=5.9 Hz, 1H), 8.31 (d, *J*=9.3 Hz, 1H), 8.26 (d, *J*=2.0 Hz, 1H), 8.16 (s, 2H), 8.04 (d, *J*=5.9 Hz, 1H), 7.77 (dd, *J*=9.3, 2.0 Hz, 1H), 7.44 (d, *J*=2.4 Hz, 1H), 7.34 (dd, *J*=8.8, 2.4 Hz, 1H), 7.24 (d, *J*=9.3 Hz, 1H), 6.63 (d, *J*=5.4 Hz, 1H), 6.18 (d, *J*=5.4 Hz, 1H), 3.90 (s, 3H), 3.78 (br. s., 4H), 2.44 (d, *J*=4.4 Hz, 4H), 2.27 ppm (s, 3H). ESI-MS: *m/z* = 476.2 $(M + H)^+$.

7-(1-Methyl-1*H*-pyrazol-4-yl)-*N*-(pyrazin-2-yl)quinolin-4-amine (**50**). Synthesized using general library condition D. Yield 45%

^{1}H NMR (500 MHz, METHANOL-d_4) δ 8.62-8.67 (m, 2 H), 8.41-8.48 (m, 2 H), 8.38 (dd, *J*=2.4, 1.5 Hz, 1 H), 8.22 (s, 1 H), 8.20 (d, *J*=2.4 Hz, 1 H), 8.09 (d, *J*=1.5 Hz, 1 H), 8.05 (s, 1 H), 7.90 (dd, *J*=8.8, 1.5 Hz, 1 H), 4.01 ppm (s, 3 H). ESI-MS: *m/z* = 303.1 $(M + H)^+$.

***N*-(3-Chloro-4-methoxyphenyl)-7-(1-methyl-1*H*-pyrazol-4-yl)quinolin-4-amine** (**51**). Synthesized using general library condition D. Yield 34%

^{1}H NMR (500 MHz, METHANOL-d_4) δ 8.29 (d, *J*=5.4 Hz, 1 H), 8.22 (d, *J*=8.8 Hz, 1 H), 8.13 (s, 1 H), 7.93 (s, 1 H), 7.90 (s, 1 H), 7.70 (dd, *J*=8.8, 1.5 Hz, 1 H), 7.34 (d, *J*=2.4 Hz, 1 H), 7.25 (dd, *J*=8.3, 2.4 Hz, 1 H), 7.12 (d, *J*=8.8 Hz, 1 H), 6.64 (d, *J*=5.9 Hz, 1 H), 3.88 (s, 3 H), 3.84 ppm (s, 3 H). ESI-MS: *m/z* = 365.0 $(M + H)^+$.

7-(Furan-2-yl)-*N*-(pyrazin-2-yl)quinolin-4-amine (**52**). Synthesized using general library condition D. Yield 69%

^{1}H NMR (500 MHz, METHANOL-d_4) δ 8.49 - 8.53 (m, 2 H), 8.38 (d, *J*=5.9 Hz, 1 H), 8.36 (d, *J*=8.8 Hz, 1 H), 8.25 (dd, *J*=2.4, 1.5 Hz, 1 H), 8.12 (s, 1 H), 8.08 (dd, *J*=5.1, 2.2 Hz, 2 H), 7.88 (dd, *J*=9.0, 1.7 Hz, 1 H), 7.57 (d, *J*=1.5 Hz, 1 H), 6.97 (d, *J*=3.4 Hz, 1 H), 6.49 ppm (dd, *J*=3.2, 1.7 Hz, 1 H). ESI-MS: *m/z* = 289.0 $(M + H)^+$.

7-(5-Methylfuran-2-yl)-*N*-(pyrazin-2-yl)quinolin-4-amine (**53**). Synthesized using general library condition D. Yield 46%

^{1}H NMR (METHANOL-d_4, 500MHz) δ 8.63 (d, *J*=5.4 Hz, 1H), 8.60 (d, *J*=1.0 Hz, 1H), 8.40 (d, *J*=5.4 Hz, 1H), 8.37 (d, *J*=8.8 Hz, 1H), 8.34 (dd, *J*=2.7, 1.2 Hz, 1H), 8.15 (dd, *J*=9.8, 2.0 Hz, 2H), 7.90 (dd, *J*=8.8, 2.0 Hz, 1H), 6.91 (d, *J*=3.4 Hz, 1H), 6.21 (d, *J*=2.4 Hz, 1H), 2.42 ppm (s, 3H). ESI-MS: *m/z* = 303.1 $(M + H)^+$.

***N*-(3-Chloro-4-methoxyphenyl)-7-(5-methylfuran-2-yl)quinolin-4-amine** (**54**). Synthesized using general library condition D. Yield 40%

^{1}H NMR (500 MHz, METHANOL-d_4) δ 8.39 (d, *J* = 5.4 Hz, 1H), 8.30 (d, *J* = 8.8 Hz, 1H), 8.06 - 8.12 (m, 1H), 7.85 (d, *J* = 8.8 Hz, 1H), 7.43 (d, *J* = 2.4 Hz, 1H), 7.35 (d, *J* = 8.8 Hz, 1H), 7.21 (d, *J* = 9.3 Hz, 1H), 6.94 (d, *J* = 2.9 Hz, 1H), 6.75 (d, *J* = 5.4 Hz, 1H), 6.24 (d, *J* = 2.9 Hz, 1H), 3.95 (s, 3H), 2.44 ppm (s, 3H). ESI-MS: *m/z* = 365.0 $(M + H)^+$.

***N*^{4}-(Pyrazin-2-yl)-*N*^{7}-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)quinoline-4,7-diamine, formate salt** (**55**). Synthesized using general library condition E. Yield 30%

^{1}H NMR (500 MHz, METHANOL-d_4) δ 8.73 (d, *J*=1.0 Hz, 1 H), 8.47 (d, *J*=1.0 Hz, 1 H), 8.43 (d, *J*=9.8 Hz, 1 H), 8.41 (d, *J*=7.3 Hz, 1 H), 8.38 (d, *J*=2.4 Hz, 1 H), 8.33 (d, *J*=7.3 Hz, 2 H), 8.30

(br. s, 1 H), 7.30 (d, *J*=9.3 Hz, 1 H), 6.59 (br. s., 1 H), 3.79 (s, 3 H), 2.18 (s, 3 H), 2.09 ppm (s, 3 H). ESI-MS: *m/z* = 346.0 $(M + H)^+$.

N^7-(1-Methyl-1*H*-pyrazol-4-yl)-N^4-(pyrazin-2-yl)quinoline-4,7-diamine, formate salt (**56**). Synthesized using general library condition E. Yield 51%

^{1}H NMR (500 MHz, METHANOL-d_4) δ 8.70 (s, 1 H), 8.45 (d, *J*=8.8 Hz, 2 H), 8.36 - 8.40 (m, 2 H), 8.37 (s, 1 H), 8.34 (d, *J*=2.9 Hz, 1 H), 7.75 (s, 1 H), 7.55 (s, 1 H), 7.30 (dd, *J*=9.3, 2.0 Hz, 1 H), 7.05 (d, *J*=2.0 Hz, 1 H), 3.94 ppm (s, 3 H). ESI-MS: *m/z* = 318.0 $(M + H)^+$.

N^7-(1-Methyl-1*H*-pyrazol-5-yl)-N^4-(pyrazin-2-yl)quinoline-4,7-diamine, formate salt (**57**). Synthesized using general library condition E. Yield 51%

^{1}H NMR (500 MHz, METHANOL-d_4) δ 8.69 (d, *J*=1.0 Hz, 1 H), 8.46 (s, 1 H), 8.45 (d, *J*=2.4 Hz, 1 H), 8.43 - 8.44 (m, 1 H), 8.42 (d, *J*=6.3 Hz, 1 H), 8.39 - 8.41 (m, 1 H), 8.32 (d, *J*=2.9 Hz, 1 H), 7.56 (d, *J*=2.0 Hz, 1 H), 7.38 (dd, *J*=9.5, 2.2 Hz, 1 H), 7.08 (d, *J*=2.4 Hz, 1 H), 6.29 (d, *J*=2.0 Hz, 1 H), 3.77 ppm (s, 3 H). ESI-MS: *m/z* = 318.0 $(M + H)^+$.

N^7-(1-Methyl-1*H*-imidazol-2-yl)-N^4-(pyrazin-2-yl)quinoline-4,7-diamine, formate salt (**58**). Synthesized using general library condition E. Yield 26%

^{1}H NMR (500 MHz, METHANOL-d_4) δ 8.70 (d, *J*=1.0 Hz, 1 H), 8.47 (d, *J*=2.0 Hz, 1 H), 8.45 (d, *J*=2.4 Hz, 2 H), 8.44 (d, *J*=2.4 Hz, 1 H), 8.42 (s, 1 H), 8.33 (d, *J*=2.4 Hz, 1 H), 7.47 - 7.51 (m, 2 H), 7.05 (d, *J*=1.5 Hz, 1 H), 6.93 (d, *J*=1.0 Hz, 1 H), 3.64 ppm (s, 3 H). ESI-MS: *m/z* = 318.0 $(M + H)^+$.

***N*^{7}-(3,5-Dimethyl-1*H*-pyrazol-4-yl)-*N*^{4}-(pyrazin-2-yl)quinoline-4,7-diamine, formate salt** (**59**). Synthesized using general library condition E. Yield 18%

^{1}H NMR (METHANOL-d$_4$, 500MHz) δ 8.73 (d, *J*=5.4 Hz, 1H), 8.67 (s, 1H), 8.54-8.61 (m, 2H), 8.41 (br. s., 1H), 8.17 - 8.29 (s, 2H), 7.98 (s, 1H), 7.85 (d, *J*=8.8 Hz, 1H), 2.42 (s, 3H), 2.30 ppm (s, 3H). ESI-MS: *m/z* = 332.1 $(M + H)^+$.

***N*^{7}-(3-Methylisothiazol-5-yl)-*N*^{4}-(pyrazin-2-yl)quinoline-4,7-diamine, bis-formate salt** (**60**). Synthesized using general library condition E. Yield 33%

^{1}H NMR (METHANOL-d$_4$, 500MHz) δ 8.71 (s, 1 H), 8.59 (d, *J*=5.9 Hz, 1 H), 8.49 (d, *J*=9.3 Hz, 1 H), 8.36 - 8.41 (m, 2 H), 8.27 (d, *J*=2.4 Hz, 1 H), 8.18 (br. s., 2 H), 7.59 (d, *J*=2.4 Hz, 1 H), 7.44 (dd, *J*=9.3, 2.4 Hz, 1 H), 6.82 (s, 1 H), 2.40 ppm (s, 3 H). ESI-MS: *m/z* = 335.0 $(M + H)^+$.

***N*^{4}-(Pyrazin-2-yl)-*N*^{7}-(thiazol-2-yl)quinoline-4,7-diamine, bis-formate salt** (**61**). Synthesized using general library condition E. Yield 72%

^{1}H NMR (500 MHz, METHANOL-*d*$_4$) δ ppm 8.71 (d, *J*=2.4 Hz, 1 H), 8.69 (s, 1 H), 8.52 (d, *J*=6.3 Hz, 1 H), 8.45 - 8.49 (m, 3 H), 8.43 (br. s., 2 H), 8.30 (d, *J*=2.4 Hz, 1 H), 7.65 (dd, *J*=9.3, 2.4 Hz, 1 H), 7.40 (d, *J*=3.4 Hz, 1 H), 6.99 (d, *J*=3.9 Hz, 1 H). ESI-MS: *m/z* = 321.0 $(M + H)^+$.

***N*^{7}-(5-Methylthiazol-2-yl)-*N*^{4}-(pyrazin-2-yl)quinoline-4,7-diamine, formate salt** (**62**). Synthesized using general library condition E. Yield 51%

^{1}H NMR (METHANOL-d$_4$, 500MHz) δ 8.71 (s, 1H), 8.58 (d, *J* = 2.4 Hz, 1H), 8.55 (d, *J* = 5.9 Hz, 1H), 8.44 (d, *J* = 9.3 Hz, 1H), 8.38 (dd, *J* = 1.5, 2.4 Hz, 1H), 8.35 (d, *J* = 6.4 Hz, 1H), 8.30

(s, 1H), 8.25 (d, *J* = 2.4 Hz, 1H), 7.63 (dd, *J* = 1.95, 9.28 Hz, 1H), 7.05 (d, *J* = 0.98 Hz, 1H), 2.39 (s, 3H). ESI-MS: *m/z* = 335.0 $(M + H)^+$.

***N*^{7}-(3-Methylisoxazol-5-yl)-*N*^{4}-(pyrazin-2-yl)quinoline-4,7-diamine** (**63**). Synthesized using general library condition E. Yield 18%

^{1}H NMR (500 MHz, METHANOL-d_4) δ 8.66 (s, 1 H), 8.56 (d, *J*=5.9 Hz, 1 H), 8.47 (s, 1 H), 8.45 (s, 1 H), 8.44 (s, 1 H), 8.41 (d, *J*=1.0 Hz, 1 H), 8.38 (br. s., 1 H), 8.26 (d, *J*=2.4 Hz, 1 H), 7.74 (d, *J*=2.0 Hz, 1 H), 7.49 (dd, *J*=9.3, 2.0 Hz, 1 H), 5.76 (s, 1 H), 2.28 ppm (s, 3 H). ESI-MS: *m/z* = 319.1 $(M + H)^+$.

***N*^{4}-(Pyrazin-2-yl)-*N*^{7}-(1,2,4-triazin-3-yl)quinoline-4,7-diamine, formate salt** (**64**). Synthesized using general library condition E. Yield 50%

^{1}H NMR (METHANOL-d_4, 500MHz) δ 8.89 (d, *J*=2.0 Hz, 1H), 8.75 (d, *J*=2.0 Hz, 1H), 8.71 (s, 1H), 8.61 (d, *J*=5.9 Hz, 1H), 8.54 (d, *J*=2.0 Hz, 1H), 8.48 (d, *J*=8.8 Hz, 1H), 8.39 (d, *J*=5.9 Hz, 1H), 8.37 (s, 1H), 8.29 (br. s., 1H), 8.23 (d, *J*=2.4 Hz, 1H), 7.91 ppm (dd, *J*=8.8, 2.0 Hz, 1H). ESI-MS: *m/z* = 317.0 $(M + H)^+$.

***N*^{7}-(5,6-Dimethyl-1,2,4-triazin-3-yl)-*N*^{4}-(pyrazin-2-yl)quinoline-4,7-diamine, formate salt** (**65**). Synthesized using general library condition E. Yield 22%

^{1}H NMR (METHANOL-d_4, 500MHz) δ 8.88 (d, *J*=2.0 Hz, 1 H), 8.78 (s, 1 H), 8.66 (d, *J*=5.9 Hz, 1 H), 8.53 (d, *J*=9.3 Hz, 1 H), 8.44 (d, *J*=5.4 Hz, 2 H), 8.34 (s, 1 H), 8.31 (d, *J*=2.4 Hz, 1 H), 7.95 (dd, *J*=9.3, 2.0 Hz, 1 H), 2.61 ppm (s, 3 H). ESI-MS: *m/z* = 345.0 $(M + H)^+$. *The methyl is coincident with the residual solvent peak.

7-Bromo-*N*-(pyrazin-2-yl)quinolin-4-amine (66)

In a dry 20 mL vial equipped with stir bar were combined **4** (300 mg, 1.24 mmol) pyrazin-2-amine (294 mg, 3.09 mmol), NaH (173 mg, 4.33 mmol). The sealed vial was purged with nitrogen followed by drop wise addition of DMF (8 mL) under continuous stirring at 0 °C. The resulting yellow mixture was allowed to stir at rt for 4 h. The reaction mixture turned red over time. The reaction was quenched with ammonium chloride, observed a color change from red to yellowish orange. The aqueous layer was extracted with EtOAc (3x50 mL) and the combined organic layers were washed with brine, dried with sodium sulfate and concentrated under vacuum to afford the title compound as a white solid in 94% yield. The crude material was carried forward without further purification. ^{1}H NMR (DMSO-d_6, 500MHz) δ 9.84 (s, 1H), 8.71 (d, *J*=4.9 Hz, 1H), 8.69 (s, 1H), 8.45 (d, *J*=9.3 Hz, 1H), 8.36 (d, *J*=5.4 Hz, 1H), 8.31 (dd, *J*=2.4, 1.5 Hz, 1H), 8.16 (dd, *J*=13.2, 2.4 Hz, 2H), 7.78 ppm (dd, *J*=9.3, 2.0 Hz, 1H). ESI-MS: *m/z* = 301.0 $(M + H)^+$.

7-Bromo-*N*-(3-chloro-4-methoxyphenyl)quinolin-4-amine (67)

In a dry 20 mL vial equipped with stir bar were combined **4** (225 mg, 0.93 mmol), 3-chloro-4-methoxyaniline (219 mg, 1.3 mmol), 4M HCl in dioxane (0.348 mL, 1.392 mmol) drop wise followed by anhydrous dioxane (10 mL). The resultant murky solution was stirred under nitrogen for 5 min and heated at 85 °C for 12 h. Once the reaction was complete it was cooled to rt and filtered under vacuum. The precipitate was sequentially washed with dioxane and DCM. The precipitate was transferred to a separatory funnel, basified with 2N NaOH. Aqueous layer was extracted with EtOAc (2x50 mL). The combined organic layers were washed with water, brine,

dried over sodium sulfate and concentrated under vacuum. The crude material was purified via silica gel chromatography using 0-15% methanol in DCM to afford the title compound as a white solid in 70 % yield. ^{1}H NMR (DMSO-d_6, 500MHz) δ 9.00 (s, 1H), 8.42 (d, *J*=5.4 Hz, 1H), 8.30 (d, *J*=9.3 Hz, 1H), 8.03 (d, *J*=2.0 Hz, 1H), 7.66 (dd, *J*=8.8, 2.0 Hz, 1H), 7.40 (d, *J*=2.9 Hz, 1H), 7.31 (dd, *J*=8.8, 2.4 Hz, 1H), 7.21 (d, *J*=9.3 Hz, 1H), 6.72 (d, *J*=5.4 Hz, 1H), 3.87 ppm (s, 3H). ESI-MS *m/z* = 363.0 $(M + H)^+$.

_N_-(1_H_-Benzo[_d_][1,2,3]triazol-5-yl)-7-bromoquinolin-4-amine (68)

In a dry 20 mL round-bottomed flask equipped with stir bar were combined **4** (200 mg, 0.82 mmol), 1*H*-benzo[*d*][1,2,3]triazol-5-amine (166 mg, 1.2 mmol), 4M HCl in dioxane (0.30 mL, 1.2 mmol) drop wise followed by anhydrous dioxane (10 mL). The resultant murky yellow mixture was stirred under nitrogen and was refluxed for 4 h. The reaction was cooled to rt and filtered under vacuum. The precipitate was sequentially washed with dioxane and DCM. The precipitate was transferred to a separatory funnel, basified with 2N NaOH to pH 12 and the aqueous layer was extracted with EtOAc (2x50 mL). The combined organic layers were washed with water, brine, dried over sodium sulfate and concentrated under vacuum. The crude material was carried forward without further purification to afford the title compound as an orange solid in 28% yield and 85% purity. The material was telescoped without additional characterization. ESI-MS *m/z* = 340.1 $(M + H)^+$.

3-Chloro-4-(4-methylpiperazin-1-yl)-1,2,5-thiadiazole (69)

In a 10 mL round-bottomed flask equipped with stir bar and sealed with septa, 1-methylpiperazine (2.86 mL, 25.8 mmol) was suspended. It was stirred and heated to 110 °C. 3,4-

Dichloro-1,2,5-thiadiazole (0.61 mL, 6.45 mmol) was carefully added to the mixture dropwise over a period of 30 min and the resultant mixture was allowed to further stir at same temp for 2 hours The mixture turned yellow to red. Reaction was monitored by TLC (80:20, EtOAc:Hex). The reaction was stopped after two hours when no more SM was remaining based on TLC. The contents were cooled to rt, aqueous ammonium (20 mL) was added and the aqueous layer was extracted with DCM (5×20 mL). The combined organic layers were washed with water (2×10 mL) and dried over sodium sulfate. The solvent was removed under vacuum and the crude material was purified via silica gel chromatography using 0-20% MeOH in DCM to afford the title compound (1.28 g, 5.85 mmol) as a yellowish orange oil in 91% yield. ^{1}H NMR ($CDCl_3$-d, 500 MHz) δ 3.48 - 3.55 (m, 4 H), 2.53 - 2.61 (m, 4 H), 2.35 ppm (s, 3 H). ESI-MS: m/z = 219.1 $(M + H)^+$.

4-(4-Methylpiperazin-1-yl)pyrimidin-2-amine (**70**)

In a 5 mL microwave vial equipped with stir bar were combined 4-chloropyrimidin-2-amine (400 mg, 3.09 mmol) and 1-methylpiperazine (0.41 mL, 3.71 mmol) in ethanol (5 mL). The sealed vial was irradiated at 150 °C for 10 min. The solution was concentrated under vacuum and partitioned between dichloromethane and 10% aqueous K_2CO_3 solution. The aqueous layer was extracted twice with DCM and the combined organic layers were washed with brine, dried with sodium sulfate and concentrated under vacuum to afford the title compound as white crystals in 89% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.75 (d, J = 5.8 Hz, 1H), 6.01 (d, J = 5.8 Hz, 1H), 5.98 (s, 1H), 3.44 - 3.55 (m, 4H), 2.32 (t, J = 5.1 Hz, 4H), 2.20 (s, 3H). ESI-MS: *m/z* = 194.1 $(M + H)^+$.

2-(4-Methylpiperazin-1-yl) pyrimidin-4-amine (71)

In a 5 mL microwave vial equipped with stir bar were combined 2-chloropyrimidin-4-amine (400 mg, 3.09 mmol) and 1-methylpiperazine (0.41 mL, 3.71 mmol) in ethanol (5 mL). The sealed vial was irradiated at 150 °C for 10 min. The solution was concentrated under vacuum and partitioned between DCM and 10% aqueous K_2CO_3 solution. The aqueous layer was extracted twice with DCM and the combined organic layers were washed with brine, dried with sodium sulfate and concentrated under vacuum to afford the title compound as white crystals in 84% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.79 (d, J = 5.4 Hz, 1H), 6.64 (br. s., 2H), 5.85 (d, J = 5.4 Hz, 1H), 3.34 (s, 3H), 2.73 (br. s., 4H). ESI-MS: m/z = 194.1 $(M + H)^+$. *Four of the piperazine protons are coincident with the solvent.

SUPPORTING INFORMATION

The following material is available free of charge:

Biological assay protocols, computational chemistry procedure, compound activity against other *P. falciparum* strains, activity of compounds in a liver stage infection model, selected ADME data, a comparison of the activity of the compounds against the different *P. falciparum* strains, human kinase data for compound **40**, and SMILES strings for all compounds presented in this manuscript.

AUTHOR INFORMATION

Corresponding Author

Corresponding author: Michael P. Pollastri; m.pollastri@northeastern.edu

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

ACKNOWLEDGMENT

This work was funded by the National Institutes of Health (Grant R01AI082577, R56AI099476, R01AI124046, R21AI127594 to M.P.P). A free academic license to OpenEye Scientific Software and ChemAxon for their suites of programs is gratefully acknowledged. Dr. Adam B. Hall at the Mass Spectrometry Facility within the Barnett Institute of Chemical and Biological Analysis at Northeastern University. We are grateful to AstraZeneca for performing the *in vitro* ADME experiments tabulated in Table 4 and in the Supplementary Information. A free academic license to OpenEye Scientific Software and ChemAxon for their suites of programs is gratefully acknowledged.

ABBREVIATIONS

LLE, lipophilic ligand efficiency; PPB, plasma protein binding; CLint, intrinsic clearance; SI, selectivity index

REFERENCES

[1] World Health Organization (2016) World Malaria Report 2016, World Health Organization, France.
[2] Timothy, N. C. W. (2013) Discovering and Developing New Medicines for Malaria Control and Elimination, *Infectious Disorders - Drug Targets 13*, 292-302. DOI: 10.2174/18715265133666131129160156
[3] Wirth, D. F. (2002) The parasite genome: Biological revelations, *Nature 419*, 495-496. DOI: 10.1038/419495a
[4] Flannery, E. L., Chatterjee, A. K., and Winzeler, E. A. (2013) Antimalarial drug discovery – approaches and progress towards new medicines, *Nat Rev Micro 11*, 849-862. DOI: 10.1038/nrmicro3138
[5] Campo, B., Vandal, O., Wesche, D. L., and Burrows, J. N. (2015) Killing the hypnozoite – drug discovery approaches to prevent relapse in Plasmodium vivax, *Pathogens and Global Health 109*, 107-122. DOI: 10.1179/2047773215Y.0000000013

[6] Klug, D. M., Gelb, M. H., and Pollastri, M. P. (2016) Repurposing strategies for tropical disease drug discovery, *Bioorganic & Medicinal Chemistry Letters 26*, 2569-2576. DOI: 10.1016/j.bmcl.2016.03.103

[7] Patel, G., Karver, C. E., Behera, R., Guyett, P. J., Sullenberger, C., Edwards, P., Roncal, N. E., Mensa-Wilmot, K., and Pollastri, M. P. (2013) Kinase scaffold repurposing for neglected disease drug discovery: discovery of an efficacious, lapatinib-derived lead compound for trypanosomiasis, *J Med Chem 56*, 3820-3832. DOI: 10.1021/jm400349k

[8] Devine, W., Woodring, J. L., Swaminathan, U., Amata, E., Patel, G., Erath, J., Roncal, N. E., Lee, P. J., Leed, S. E., Rodriguez, A., Mensa-Wilmot, K., Sciotti, R. J., and Pollastri, M. P. (2015) Protozoan Parasite Growth Inhibitors Discovered by Cross-Screening Yield Potent Scaffolds for Lead Discovery, *J Med Chem 58*, 5522-5537. DOI: 10.1021/acs.jmedchem.5b00515

[9] Hawkins, P. C. D., Skillman, A. G., and Nicholls, A. (2007) Comparison of Shape-Matching and Docking as Virtual Screening Tools, *Journal of Medicinal Chemistry 50*, 74-82. DOI: 10.1021/jm0603365

[10] Hawkins, P. C. D., Skillman, A. G., Warren, G. L., Ellingson, B. A., and Stahl, M. T. (2010) Conformer Generation with OMEGA: Algorithm and Validation Using High Quality Structures from the Protein Databank and Cambridge Structural Database, *Journal of Chemical Information and Modeling 50*, 572-584. DOI: 10.1021/ci100031x

[11] Lin, L. S., Wiranowska-Stewart, M., Chudizio, T., and Stewart, W. E., 2nd. (1978) Characterization of the size and charge heterogeneities of human leukocyte interferon populations, *Archives of virology 56*, 269-272. DOI: 10.1007/BF01317857

[12] Fors, B. P., and Buchwald, S. L. (2010) A Multiligand Based Pd Catalyst for C−N Cross-Coupling Reactions, *Journal of the American Chemical Society 132*, 15914-15917. DOI: 10.1021/ja108074t

[13] Yin, J., and Buchwald, S. L. (2002) Pd-Catalyzed Intermolecular Amidation of Aryl Halides: The Discovery that Xantphos Can Be Trans-Chelating in a Palladium Complex, *Journal of the American Chemical Society 124*, 6043-6048. DOI: 10.1021/ja012610k

[14] Hopkins, A. L., Keseru, G. M., Leeson, P. D., Rees, D. C., and Reynolds, C. H. (2014) The role of ligand efficiency metrics in drug discovery, *Nat Rev Drug Discov 13*, 105-121. DOI: 10.1038/nrd4163

[15] da Cruz, F. P., Martin, C., Buchholz, K., Lafuente-Monasterio, M. J., Rodrigues, T., Sönnichsen, B., Moreira, R., Gamo, F.-J., Marti, M., Mota, M. M., Hannus, M., and Prudêncio, M. (2012) Drug Screen Targeted at Plasmodium Liver Stages Identifies a Potent Multistage Antimalarial Drug, *The Journal of Infectious Diseases 205*, 1278-1286. DOI: 10.1093/infdis/jis184

[16] Jiménez-Díaz, M. B., Ebert, D., Salinas, Y., Pradhan, A., Lehane, A. M., Myrand-Lapierre, M.-E., O'Loughlin, K. G., Shackleford, D. M., Justino de Almeida, M., Carrillo, A. K., Clark, J. A., Dennis, A. S. M., Diep, J., Deng, X., Duffy, S., Endsley, A. N., Fedewa, G., Guiguemde, W. A., Gómez, M. G., Holbrook, G., Horst, J., Kim, C. C., Liu, J., Lee, M. C. S., Matheny, A., Martínez, M. S., Miller, G., Rodríguez-Alejandre, A., Sanz, L., Sigal, M., Spillman, N. J., Stein, P. D., Wang, Z., Zhu, F., Waterson, D., Knapp, S., Shelat, A., Avery, V. M., Fidock, D. A., Gamo, F.-J., Charman, S. A., Mirsalis, J. C., Ma, H., Ferrer, S., Kirk, K., Angulo-Barturen, I., Kyle, D. E., DeRisi, J. L., Floyd, D. M., and Guy, R. K. (2014) (+)-SJ733, a clinical candidate for malaria that acts through ATP4 to induce rapid

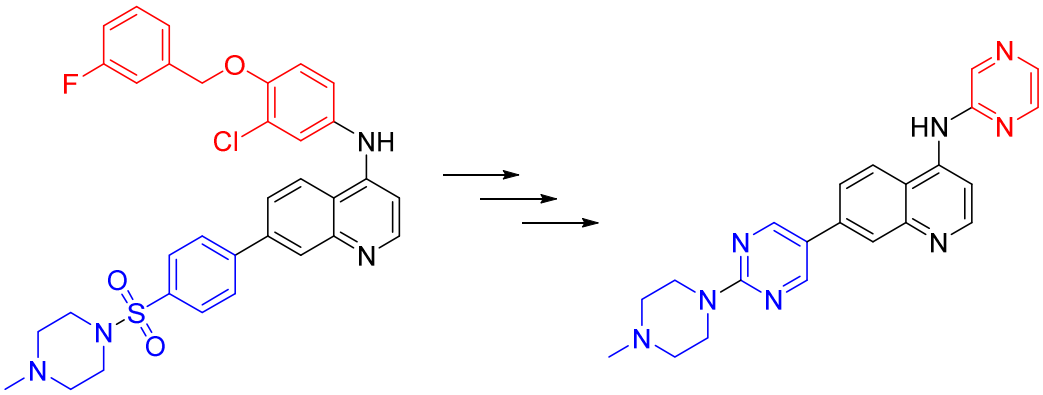
host-mediated clearance of Plasmodium, *Proceedings of the National Academy of Sciences 111*, E5455-E5462. DOI: 10.1073/pnas.1414221111

[17] Biamonte, M. A., Wanner, J., and Le Roch, K. G. (2013) Recent advances in malaria drug discovery, *Bioorganic & Medicinal Chemistry Letters 23*, 2829-2843. DOI: 10.1016/j.bmcl.2013.03.067

[18] Derbyshire, E. R., Prudêncio, M., Mota, M. M., and Clardy, J. (2012) Liver-stage malaria parasites vulnerable to diverse chemical scaffolds, *Proceedings of the National Academy of Sciences of the United States of America 109*, 8511-8516. DOI: 10.1073/pnas.1118370109

[19] Rusnak, D. W., Lackey, K., Affleck, K., Wood, E. R., Alligood, K. J., Rhodes, N., Keith, B. R., Murray, D. M., Knight, W. B., Mullin, R. J., and Gilmer, T. M. (2001) The Effects of the Novel, Reversible Epidermal Growth Factor Receptor/ErbB-2 Tyrosine Kinase Inhibitor, GW2016, on the Growth of Human Normal and Tumor-derived Cell Lines *in vitro* and *in vivo*, *Molecular Cancer Therapeutics 1*, 85-94.

Table of contents graphic



NEU-961 (Manuscript ID: 3)
P. fal. D6 EC_{50}: 19 nM
cLogP: 6.4
LLE: 1.2
Solubility: 0.3 µM

NEU-1953 (Manuscript ID: 40)
P. fal. D6 EC_{50}: 26 nM
cLogP: 2.1
LLE: 5.5
Solubility: 44 µM