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Discovery of Potent *Plasmodium falciparum* Protein Kinase 6 (PfPK6) Inhibitors with a Type II Inhibitor Pharmacophore

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Abstract

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

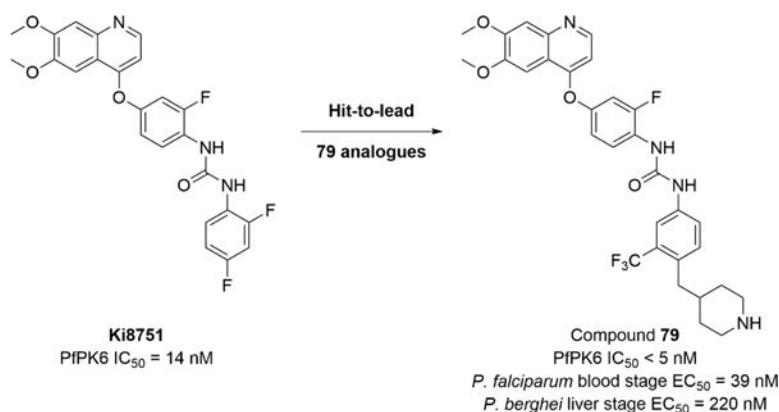
Appendix A. Supplementary Data

The following supporting data to this article is provided:

Activity of **Ki8751** on 97 human kinases determined using a thermal shift assay; compound pairs used for group efficiency analysis; correlation between predicted pK_a and %activity remaining on PfPK6; activity of compounds **45**, **67**, and **79** on 403 non-mutant kinases determined from DiscoverX KINOMEScan[®]; plot of Pf3D7 EC₅₀ values against PfPK6 IC₅₀ values; HepG2 cytotoxicity data determined using the CellTiter-Glo assay; supplemental methods for PK studies; NMR spectra and HPLC chromatograms (DOCX) Thermal Shift Assay results on 97 human kinases for **Ki8751**; pKa prediction of Ki8751 and analogues varying hinge-binder; KINOMEScan[®] results on 468 kinases for compounds **67**, **79**, **45** and **Ki8751** (XLSX) Molecular formula strings (CSV)

Malaria is a devastating disease that causes significant global morbidity and mortality. The rise of drug resistance against artemisinin-based combination therapy demonstrates the necessity to develop alternative antimalarials with novel mechanisms of action. We report the discovery of **Ki8751** as an inhibitor of essential kinase PfPK6. 79 derivatives were designed, synthesized and evaluated for PfPK6 inhibition and antiplasmodial activity. Using group efficiency analyses, we established the importance of key groups on the scaffold consistent with a type II inhibitor pharmacophore. We highlight modifications on the tail group that contribute to antiplasmodial activity, culminating in the discovery of compound **67**, a PfPK6 inhibitor ($IC_{50} = 13$ nM) active against the *P. falciparum* blood stage ($EC_{50} = 160$ nM), and compound **79**, a PfPK6 inhibitor ($IC_{50} < 5$ nM) with dual-stage antiplasmodial activity against *P. falciparum* blood stage ($EC_{50} = 39$ nM) and against *P. berghei* liver stage ($EC_{50} = 220$ nM).

Graphical Abstract



Keywords

Malaria; Antiplasmodial; *Plasmodium falciparum* Protein Kinase 6 (PfPK6); Kinase Inhibitor; Group Efficiency; Structure-Activity Relationship Study

Introduction

Malaria is a devastating infectious disease causing 241 million infections and 627,000 deaths worldwide in 2020¹. The causative agents of malaria are unicellular eukaryotic parasites from the *Plasmodium* genus. Of the five known species that infect humans, *P. falciparum* is associated with the bulk of malaria-associated morbidity and mortality^{1,2}. While there has been a favorable trend of declining mortality rates since the 2000s due to the effectiveness of artemisinin-based combination therapy (ACT), the frontline treatment for malaria globally, progress has stalled in recent years¹. Drug resistance remains a challenge in eliminating malaria. Ever since the first report of artemisinin resistance amongst *P. falciparum* strains isolated from Cambodia in 2009³, artemisinin resistance has reached high prevalence and is a worrying trend in the Greater Mekong Subregion of South East Asia¹. In the past two years, reports of independent emergence of artemisinin resistance in clinical isolates of parasites from Rwanda^{4,5} and Uganda⁶ may indicate the start of a foreboding trend in

Africa. This demonstrates the need to expand our arsenal of antimalarial treatments by the development of new drugs with novel mechanisms of action⁷.

Plasmodium protein kinases present an untapped opportunity for drug development^{8–10}. Of the 85–99 protein kinases identified from the *P. falciparum* genome^{11,12}, reverse genetics¹³ and saturation mutagenesis¹⁴ studies have identified 36 and 40 kinases, respectively, to be essential for *P. falciparum* asexual blood stage proliferation. Furthermore, kinases are well-established to be a druggable pharmacological target class, as evident from the 71 kinase inhibitors approved by the FDA for various indications up to May 2021¹⁵. With an abundance of literature on kinase inhibition to design inhibitors, knowledge of the specific scaffolds can be cautiously extrapolated for inhibition of *Plasmodium* kinases⁸. The *Plasmodium* kinome is significantly divergent from the human kinome, and many *Plasmodium* kinases have no clear human orthologue, hence the design of a selective *Plasmodium* kinase inhibitor should be possible^{10,11}. Moreover, no antimalarial drug currently in the market or in clinical trials is known to target any *Plasmodium* protein kinase⁷, while only a few investigational drugs, e.g. MMV390048¹⁶, target *P. falciparum* phosphatidylinositol-4-OH kinase (PfPI4K), a lipid kinase. We thus believe that there has been little or no selection pressure for resistance towards kinase inhibitors currently amongst the *Plasmodium* population. These factors combined support the hypothesis for targeting *Plasmodium* protein kinases.

Despite the attractiveness of *Plasmodium* protein kinases as drug targets, few kinases have been pharmacologically validated as targets. While inhibitors of PfPKG^{17–19} and PfCLK3²⁰ have shown promise as new antimalarial preclinical compounds, most other *Plasmodium* kinases have not had medicinal chemistry campaigns initiated against them. As a result, most *Plasmodium* kinases have no chemical probes or even tool compounds that could facilitate the investigation of their biological function or possible druggability. To bridge this gap, the overall goal of our research is to discover hits against lesser-studied *Plasmodium* kinases and develop them into lead compounds potent both against a specific kinase target and against *Plasmodium* proliferation. The molecules could support biological studies on kinase function as well as future drug development efforts.

In this report, we have focused on *P. falciparum* Protein Kinase 6 (PfPK6) (PlasmoDB ID: PF3D7_1337100), a kinase in the CMGC group²¹ genetically validated to be essential for blood stage proliferation of *P. falciparum*^{13,14}. The precise function of PfPK6 is not well defined, but it is postulated to be involved in the cell cycle of the *Plasmodium* parasite in a cyclin-independent manner by virtue of its homology with human CDK2 and its expression profile in late ring, trophozoites and early schizonts²¹. Two known inhibitors of PfPK6 are the purines roscovitine and olomoucine, which inhibit PfPK6 at biochemical IC₅₀s of 30 μM and 180 μM respectively²¹. A series of compounds based on the 1-(4-((2-aminopyrimidin-4-yl)(methyl)amino)phenyl)urea scaffold, labelled “Scaffold J”, have also been identified as PfPK6 inhibitors with biochemical IC₅₀s between 138 and 917 nM from the Tres Cantos Antimalarial Set (TCAMS)²² (Figure 1). To the best of our knowledge, these scaffolds were not subject to further development for PfPK6 inhibition. To discover hits against PfPK6, we have screened 110 kinase inhibitors against a panel of 11 *P. falciparum* kinases using the KinaseSeeker assay, an *in vitro* assay based on split-luciferase technology we had

previously developed for human kinases²³. Briefly, displacement of the chemical inducer of dimerization (CID) from the kinase active site by the test compound leads to disassembly of the split luciferase, which results in loss of luminescence. Using this assay, we found **Ki8751** to be a potent inhibitor of PfPK6 with an IC₅₀ of 14 nM (Luceome internal data). **Ki8751** was initially developed as a VEGFR2 inhibitor²⁴, with several other off-targets identified to be PDGFR α ²⁴, c-KIT²⁴, FGFR2²⁴, AXL²⁵, AURKB²⁶, AURKC²⁶, and ABL²⁷. Notably, these kinases belong either in the TK group or Aurora family of kinases.

Herein we report results from our early hit-to-lead medicinal chemistry project. We established a structure-activity-relationship (SAR) study of this scaffold, utilizing a group efficiency approach to guide SAR, and the discovery of **79**, a potent PfPK6 inhibitor with dual-stage antiplasmodial activity against the *P. falciparum* asexual blood stage and the *P. berghei* liver stage.

Results and Discussion

Preliminary Characterization and Group Efficiency.

Considering that known targets of **Ki8751** are in the TK group and Aurora family of kinases^{24–27}, it was especially intriguing to find **Ki8751** as a hit against PfPK6, a member of the CMGC group. To investigate the kinome-wide inhibitory potential of this scaffold, we screened **Ki8751** against 97 human kinases using a thermal shift assay (Figure S1 and Table S2). We found only three kinases (BRAF, LOK, ABL1) with a >10°C shift in melting point, and only seven kinases (PLK4, CHK2, EphA2, EphB3, SLK, CAMKK2, CLK1) with a 5–10°C shift in melting point. This suggests that **Ki8751** is not overly promiscuous across the kinome despite its ability to inhibit kinases from diverse groups, and is thus a suitable starting point for further hit-to-lead development.

To the best of our knowledge, **Ki8751** is the most potent PfPK6 inhibitor reported to date. With little known about the SAR on this series, we adopted a group efficiency (GE) approach to investigate which substituents on **Ki8751** contribute to its potency. GE is a metric commonly used in fragment-based drug discovery to determine which substituents are most efficient in enhancing binding energy per heavy atom²⁸. We hypothesized that through the comparison of the potencies of truncated analogues of **Ki8751**, we would be able to determine the efficiency of each group, and use this information to inform further optimization.

Removal of the 6-methoxy group (**1**) on the quinoline ring led to a 3-fold drop in potency against PfPK6 as compared to **Ki8751** (Table 1), whereas removal of the 7-methoxy group (**2**) led to a drastic 15-fold drop in potency. Removal of both methoxy groups (**3**) resulted in a 34-fold drop in potency relative to **Ki8751**. These results demonstrate that both methoxy groups are important for PfPK6 inhibition, and the 7-methoxy group is especially efficient, with a GE of 0.81 ± 0.04 (Figure 2 and Figure S2). Interestingly, removal of the annulated phenyl ring from the quinoline of **3** to give pyridine **4** led to a less than 2-fold difference in potency against PfPK6. This suggests that the annulated phenyl ring is a low-contributor to PfPK6 inhibition, which is reflected in the low GE of 0.08 ± 0.03 for the four atoms that comprise the annulated phenyl ring. Compounds **5** and **6**, where the pyridine of **4**

was removed, were completely inactive against PfPK6, suggesting that the pyridine ring of **Ki8751** is essential.

We next investigated the roles of the three fluorine atoms on **Ki8751**. Removal of either or both of the *ortho*- or *para*-substituted fluorine atom on the terminal “tail” phenyl ring (**7**, **8**, and **9**) yielded compounds with at least a 3-fold increase in potency as compared to **Ki8751**. Since the IC₅₀s determined for the most potent compounds approached the kinase concentration in the assay, it would not be prudent to quantitatively discriminate between IC₅₀ values less than ~5 nM. Nevertheless, our results show that both fluorine atoms on the tail phenyl ring were detrimental towards activity against PfPK6. In comparison with the SAR on VEGFR2 and PDGFR α reported, the removal of both fluorine atoms afforded a 3.5-fold increase in potency on VEGFR2 and no change in potency on PDGFR α .²⁴ While replacement of the fluorine atom on the middle ring of **Ki8751** with a hydrogen atom (**10**) led to a less than 2-fold difference in PfPK6 inhibition, the corresponding replacement on **9** to give **11** clearly decreased PfPK6 inhibition. We thus show that the fluorine atom in the middle ring is a modest contributor towards activity against PfPK6. In stark contrast, the removal of this fluorine atom did not change VEGFR2 potency and in fact increased PDGFR α potency 20-fold²⁴. To improve selectivity over PDGFR α , we believe that this fluorine atom should be retained on the molecule.

Removal of the entire tail phenyl ring (**12** and **13**) increased the IC₅₀ against PfPK6 by at least 2 orders of magnitude relative to **9**, which demonstrates the importance of the tail phenyl ring, with a GE of $>0.41 \pm 0.005$. Further removal of the carbonyl group of the urea (**14** and **15**) resulted in a complete loss of activity against PfPK6, which identifies the carbonyl group of **Ki8751** as a second essential pharmacophoric element. Removal of the entire urea (**16**) gave a compound with micromolar activity against PfPK6, and we thus determined the GE of the entire urea group to be 0.39 ± 0.02 .

While no crystal structure of PfPK6 is available, our results are consistent with a type II (DFG-out) binding mode to PfPK6. **Ki8751** contains the essential pharmacophoric elements of a type II inhibitor^{29–31}: a hydrogen bond acceptor to bind in the hinge region (the quinoline N1 atom), a hydrogen bond donor and acceptor pair 3–5 chemical bond lengths away (the urea) to bridge the cavity formed by the conserved α C-helix Glu and the DFG backbone NH, and lastly a hydrophobic group (the terminal phenyl ring) to occupy the back pocket created by the DFG-out flip. While it would be ideal to confirm the binding mode through structural studies, we were unable to perform docking studies in absence of a crystal structure of PfPK6. While structure prediction by AlphaFold is available, the structure predicted is of an active (DFG-in) state and is thus also unsuitable for docking. Future efforts to obtain a high-resolution crystal structure of PfPK6 in an inactive (DFG-out) state would be necessary to confirm this binding mode.

In summary, key contributors towards the potency of **Ki8751** have been identified as both methoxy groups on the quinoline ring, the pyridine component of the quinoline ring, the urea, and the terminal “tail” phenyl ring. Our strategy to improve the potency of this scaffold would be to replace the two underperforming groups (Figure 3). The first group is the

inefficient annulated phenyl ring on the pyridine, whereas the second group consists of the two fluorine atoms on the terminal phenyl ring detrimental for activity.

SAR of Hinge-Binding Region.

Based on an understanding of the type II pharmacophore, we hypothesize that the two methoxy groups are pointing towards the solvent-exposed region of the kinase ATP-binding pocket. Extension of the two methoxy groups to give a 6,7-bis(ethoxymethoxy)quinoline (**19**) demonstrated potency equivalent to **Ki8751** (Table 2). This is consistent with our hypothesis and shows that this region of the quinoline is amendable for attachment of solubilizing substituents. To better understand the potency-enhancing effect of the two methoxy groups, analogues where the two methoxy groups were cyclized to a 5-membered ring (**20**) or a 6-membered ring (**21**) were synthesized and screened. Surprisingly, both **20** and **21** were found to be approximately 40-to-50-fold less potent than **Ki8751**. Their potencies were comparable to the potency of **3**, where both methoxy groups were removed. This eliminates the possibility that the potency-enhancing effects of the two methoxy groups are due simply to their electron-donating effects, instead suggesting that specific interactions are formed between the methoxy groups and the residues surround the ATP-binding pocket. These results also suggest that, within the kinase pocket, the two methyl groups on the methoxy groups are either pointed away from each other in the plane of the quinoline ring, or pointed out of the plane of the quinoline ring, such that when constrained into the plane of the ring they lose their potency-enhancing effect. Our attempt at replacement of the highly-efficient 7-methoxy group with a 7-chloro group (**17**) was unsuccessful in maintaining its potency, demonstrating that the alkoxy groups at this position may be privileged groups for PfPK6 inhibition.

We have previously established that the pyridine component of the quinoline ring is essential for PfPK6 inhibition. We thus aim to investigate other heterocycles, maintaining the relative position of the N1 atom of the quinoline ring in **Ki8751**. Isosteric replacements of the quinoline with thieno[3,2-b]pyridine (**25**) was tolerated by PfPK6, but the thieno[2,3-b]pyridine isomer (**27**) was less preferred. We hypothesized that the efficiency of the annulated ring may be enhanced by the formation of an additional hydrogen bond with the carbonyl group of the outer hinge residue of the kinase (hinge.48, based on numbering in KLIFS³¹). Indeed, replacing the quinoline with a 7-azaindole (**29**) led to a 4-fold improvement in potency, but this was still an order of magnitude less potent than the 6,7-dimethoxyquinoline group of **Ki8751**.

We next investigated the effect of introduction of additional nitrogen atoms on the pyridine ring. Introduction of a nitrogen atom at the 2-position, forming a cinnoline (**24**), led to a complete loss of potency, possibly due to disruption of a CH–O weak hydrogen bond with the backbone carbonyl of the inner hinge residue (hinge.46, based on numbering in KLIFS³¹) well-recognized in kinase inhibitors^{32,33}. An alternate explanation would be the poorer hydrogen-bond accepting capability of the N1 atom in a cinnoline ring, as estimated by its lower pK_a³⁴. One consistent trend we have also observed was that addition of a 3-position nitrogen atom was generally detrimental towards PfPK6 inhibition. Introduction of a nitrogen atom at the 3-position of the quinoline, forming a quinazoline (**23**), or the

addition of a nitrile group at the same position (**18**) both led to a drastic drop in potency. In some kinases, a hydrogen bond acceptor at this position is known to form a hydrogen bond with either the gatekeeper residue or with a water molecule present, and a nitrile at this position may displace a water molecule the nitrogen atom is hydrogen bonded to³⁵, but this is evidently not applicable to PfPK6. Our results are consistent with the knowledge that the gatekeeper of PfPK6 is a Phe residue. Thus, this region of the ATP-binding site may be lipophilic and the lack of productive hydrogen bonding partners was expected. Interestingly, the 6,7-dimethoxyquinazoline (**22**), with an IC₅₀ of 19 nM, also possesses comparable potency to **Ki8751**. This observation further highlights the importance of the two methoxy groups for PfPK6 inhibition, which could almost fully compensate for the detrimental 3-position N atom. We also note that the 6,7-dimethoxyquinoline hinge-binding group led to a 2-fold change in potency in VEGFR2 and PDGFR α ²⁴, suggesting that selectivity for PfPK6 over the VEGFR2 and PDGFR α cannot be attained with this substitution. Similar to **23**, incorporation of a nitrogen atom at the equivalent positions of thieno[3,2-b]pyridine **25**, thieno[2,3-b]pyridine **27**, 7-azaindole **29** and pyridine **4**, to form compounds thieno[3,2-d]pyrimidine **26**, thieno[2,3-d]pyrimidine **28**, pyrrolo[2,3-d]pyrimidine **30**, and pyrimidine **31** respectively, was similarly detrimental towards activity against PfPK6.

Additionally, attempts at the removal of the annulated phenyl ring completely and replacing it with a chloro substituent (**32**, **33** and **34**) were found not to be tolerated by PfPK6, while addition of a benzylamino substituent on the 6-position of the pyrimidine (**35**) resulted in only a modest improvement in PfPK6 potency over **31**.

Our group has previously shown that the configuration of atoms on heterocycles bearing the hinge-binding N atom influences its pK_a, which is paramount for effective ligand-kinase molecular recognition³⁶. Using density functional theory (DFT)^{37–39}, we predicted the pK_a for each hinge-binding N atom on heterocycles tested (Table S3). As expected, we observed a general trend where increasing pK_a of the hinge-binding N atom is correlated with increasing potency against PfPK6 (Figure S3). This is exemplified by the electron-withdrawing 3-position nitrile group of **18**, which was predicted to decrease the pK_a of the hinge-binding N1 atom to 1.20, a notable decrease as compared to the quinoline group of **3**, with a predicted pK_a of 5.54. This offers another explanation to the decreased potency of **18**. There are a few outliers to this general trend, suggesting that the pK_a of the hinge-binding N atom is not the sole determinant of potency on PfPK6; interactions between the kinase active site residues and substituents on the heterocycle, such as the above-discussed two methoxy groups, also contribute to their activity. Nevertheless, our results show that the basicity of the hinge-binding N atom is an important contributor to PfPK6 inhibition.

To sum up the SAR for the hinge-binding region, we have observed modest improvements in potency as compared to quinoline **3** by attempting to replace the annulated phenyl ring. We have also found that incorporation of a 3-position nitrogen atom or nitrile group is disfavored. Comparing analogues varying the methoxy groups have also led us to conclude that the two methoxy groups are essential for activity and the specific 3-dimensional orientation of the methoxy groups are critical for PfPK6 inhibition. With this in mind, we find that the 6,7-dimethoxyquinoline group of **Ki8751** appears to be the optimal hinge binder for this chemotype, and would be used in our further optimization process.

Incorporation of CF₃ and Piperazines at the Tail Group.

When developing **Ki8751** for VEGFR2 inhibition, it was noted that substituents on the tail phenyl ring generally hardly had any influence on VEGFR2 inhibition, although only modest changes were attempted²⁴. To inform our decisions regarding suitable replacements of the two detrimental fluorine atoms on **Ki8751** for PfPK6 inhibition, we drew inspiration from three other type II inhibitors in our screen (Table 3). Compounds **36** and **37** were from the Kinase Chemogenomics Set (KCGS), a set of narrow-spectrum kinase inhibitors our group has developed and publicly-released⁴⁰, while compound **38** was a member of an internal library of type II inhibitors developed based on literature compounds^{41,42}. Compounds **36**, **37**, and **38** were active against PfPK6 with IC₅₀ values between 5–80 nM. These compounds also showed antiplasmodial activity against the asexual blood stage proliferation of *P. falciparum* 3D7 in a SYBR Green I-based fluorescence assay⁴³ with EC₅₀s between 390–500 nM. To benchmark the EC₅₀s we have obtained, we compared them to the EC₅₀s of known antimalarial drugs (none of which are known to be type II kinase inhibitors) we have measured here and previously reported using the same assay⁴⁴. Compounds **36–38** were at least an order of magnitude less potent than dihydroartemisinin (DHA) (EC₅₀ = 0.14 nM) (Table 3), pyrimethamine (EC₅₀ = 27 nM)⁴⁴ and quinacrine (EC₅₀ = 33 nM)⁴⁴, which is unsurprising considering these were unoptimized hits. Our assay results for DHA are consistent with literature values⁴⁵.

While these three type II inhibitors have different hinge-binding moieties and linker region to their tail group, they possess CF₃ (**36**, **38**) or piperazine substituents (**37**, **38**) on the tail group. The CF₃ substituent is found at the *meta*-position (relative to the urea or amide group of the linker) which we hypothesize to be binding in BP-III (using the KLIFS notation³¹). The piperazine may be found at the *meta*- or *para*-positions, linked with a methylene or carbonyl linker, which we hypothesize to bind in BP-V (using the KLIFS notation³¹). It is clear that these substituents are accepted by PfPK6. We thus took inspiration from these three compounds and incorporated the CF₃ and piperazine substituents onto the 1-phenyl-3-(4-(quinolin-4-yloxy)phenyl)urea scaffold of **Ki8751**. These analogues were then screened for both PfPK6 inhibition and antiplasmodial activity against *P. falciparum* asexual blood stage parasites (Table 4).

The incorporation of a CF₃ at the *meta*-position was successful and we obtained compounds with IC₅₀s < 5 nM against PfPK6 (**39**, **40**). Since these compounds have IC₅₀ values approaching the kinase concentration in the assay, we could not quantitatively compare their potency against PfPK6, and hence we elected to assess them by their antiplasmodial activity. In parasite assays, compound **39** was active against *P. falciparum* blood stage parasites with an EC₅₀ of 540 nM while **40** did not show any inhibition up to 5 μM, suggesting that the incorporation of an *ortho*-fluorine group is not preferred.

Incorporation of a piperazine with a methylene linker at the *para*-position afforded compound **41**, which was as potent as **Ki8751** on PfPK6 and possesses activity against the *P. falciparum* blood stage with an EC₅₀ of 580 nM. Shifting the piperazine to the *meta*-position (**42**) resulted in a less than 2-fold change in PfPK6 inhibition but loss of *P. falciparum* blood stage activity when tested at 1 μM. Replacement of the methylene with a carbonyl linker

to either the *para*- (**43**) or *meta*-positions (**44**) was less well-tolerated, with a 5-to-25-fold drop in activity against PfPK6 as compared to **41** and, consistent with the reduction in PfPK6 inhibitory potency, we did not observe antiparasmodial activity at 1 μ M for either of these compounds. It appears that the *para*-substituted piperazine with a methylene linker is preferred. The sensitivity of PfPK6 towards this linker merits further investigation (*vide infra*).

We next combined the *meta*-CF₃ group with the piperazine-containing analogues. It was striking to observe an additive effect of both groups on both PfPK6 inhibition as well as *P. falciparum* blood stage inhibition. Combining elements of compounds **39** and **41**, compound **45** saw an improvement of potency against PfPK6 by an order of magnitude relative to **41**, as well as improved potency against *P. falciparum* blood stage parasites from both **39** and **41** by 5-fold to an EC₅₀ of 110 nM. This one-order-of-magnitude improvement in PfPK6 inhibition was also observed upon addition of a *meta*-CF₃ group to the other piperazine-containing analogues (**46**, **47** and **48**, comparing with **42**, **43**, and **44**, respectively). **46** has also demonstrated antiparasmodial activity with an EC₅₀ of 410 nM, an improvement over **42**.

The antiparasmodial activity of compound **45** encouraged us to investigate its activity against the other ten *P. falciparum* kinases in our KinaseSeeker assay panel (Figure 4). Inhibition of four other *P. falciparum* kinases, PfCDPK5, PfGSK3, PfNEK3, and PfPKB with IC₅₀ values between 40 and 144 nM were observed. Of these targets, both PfCDPK5 and PfGSK3 have been determined to be essential for the asexual blood stage of *P. falciparum* through both reverse genetics and saturation mutagenesis studies^{13,14}, whereas PfNEK3 was shown to be non-essential¹³ or could be disrupted, albeit with a fitness penalty¹⁴. Interestingly, while the reverse genetics study found PfPKB to be essential¹³, the study using saturation mutagenesis found that it could be disrupted without fitness penalty¹⁴. Our results demonstrate that **45** likely exerts its antiparasmodial activity through inhibition of multiple essential *P. falciparum* kinases. Polypharmacology has many advantages for antimalarial drug development, as it reduces the likelihood of resistance, provides opportunities for multistage intervention, and may inhibit enzymes of bypass pathways that would otherwise be able to compensate for inhibition of a single target^{9,46}.

However, being able to inhibit five out of the 11 kinases in our *P. falciparum* kinase panel, across kinases from diverse groups and families, suggests that this compound may be promiscuous and has substantial risk of off-target effects in the human kinome. We thus screened compound **45** at 1 μ M against a panel of 468 kinases (403 non-mutant kinases) in the DiscoverX KINOMEScan[®] profiling service. As expected, **45** potently inhibited 134 non-mutant kinases with 1% control, with a selectivity score S₁ (1 μ M) of 0.33 (Table S4 and Figure S4). Additionally, from the DiscoverX KINOMEScan[®] profiling, we have found that **45** binds to PfCDPK1 (1.6% control at 1 μ M), another essential kinase for *P. falciparum* blood stage proliferation^{13,14} that **45** could possibly exert antiparasmodial activity through its inhibition. This finding demonstrates that the rules for improving inhibition against human kinases can be leveraged for inhibition against *Plasmodium* kinases, at least within this chemotype, adding to the body of evidence that *Plasmodium* kinases are a druggable target class⁹. However, like designing kinase inhibitors as treatments for other indications, selectivity between kinases still remains a significant challenge.

We evaluated **45** and other analogues active against *P. falciparum* blood stage proliferation for cytotoxicity against HepG2 cells, a human hepatoma cell line, using a commercially available CellTiter-Glo assay (Promega) (Table 8). This assay is a commonly used proxy for cytotoxicity against human cells, and has been previously used to evaluate cytotoxicity amongst the antimalarial hits from the TCAMS⁴⁷. **45** demonstrates only a modest cytotoxic effect against HepG2 cells with a cytotoxicity CC₅₀ of 1.00 μM. This only affords a suboptimal 9-fold window between the antiplasmodial EC₅₀ and the cytotoxicity CC₅₀. This is a promising start for optimization, where we aim to improve the cytotoxicity window of **45**.

SAR on the Tail Phenyl Ring.

In an attempt to discover compounds which are less promiscuous but still maintained activity against PfPK6 and against *P. falciparum* blood stage proliferation, we next investigated if the *meta*-CF₃ group of **39** and the *para*-piperazine group of **41** could be replaced with alternative substituents. We hypothesized that the additive effect on PfPK6 inhibition and inhibition of *P. falciparum* blood stage proliferation observed for the *meta*-CF₃ and *para*-piperazine would be similarly observed for the optimized substituents. Hence, we investigated these alternative substituents at the *meta*- and *para*-positions separately before combining the most promising *meta*- and *para*-position substituents onto the scaffold.

In the optimization of the *meta*-position substituent, we note that the introduction of *meta*-CF₃, chloro, methyl and methoxy groups have been attempted previously for VEGFR2 and PDGFR α inhibition^{24,48}. As compared to the unsubstituted tail phenyl ring, the *meta*-methyl and methoxy groups generally maintained potency, but the *meta*-CF₃ led to a 2.5-fold drop in PDGFR α inhibition⁴⁸ while the *meta*-chloro group led to a 7-to-8-fold drop in potency against both kinases²⁴. In attempts to replace the *meta*-CF₃ of **39** with halogens, nitrile, alkyl, and alkoxy groups of different sizes (**49–58**), we found this entire set of analogues to have IC₅₀ < 5 nM for PfPK6 inhibition. Under our assay conditions, we were unable to distinguish which, if any, substituent is preferred (Table 5). This suggests that this pocket of PfPK6 is non-discriminatory and tolerates both small aliphatic hydrophobic groups and groups containing hydrogen bond acceptors reasonably. The two substituents with a submicromolar EC₅₀ against the *P. falciparum* blood stage were the CF₃ (**39**) and OCF₃ (**57**) groups. Substitution of the CF₃ with a chloro (**49**), methyl (**51**) or tert-butyl substituent (**53**) led to a 4-to-6-fold drop in potency against *P. falciparum* blood stage parasites. Compounds with other substituents were inactive against *P. falciparum* blood stage parasites when screened at 1 μM. The finding that both the CF₃ and OCF₃ groups were the most promising substituents suggests that some unique property of the trifluoromethyl group is responsible for activity.

Removal of the methylene linker between the tail phenyl ring and the piperazine of **41** (compound **59**) led to a 30-fold drop in potency against PfPK6 (Table 6), suggesting that the linker atom is crucial to position the piperazine in a suitable orientation within the binding site. Surprisingly, the antiplasmodial activity of **59** was similar to **41**. To better understand which basic nitrogen atom of the piperazine group contributes to the activity of **41**, we first removed the tertiary amine distal to the tail phenyl ring by replacing the

N-methylpiperazine of **41** with a morpholine (**60**), piperidine (**61**), pyrrolidine (**62**), or diethylamine (**63**). These changes led to a 10-to-25-fold drop in potency against PfPK6, which informs us that the basic nitrogen distal to the tail phenyl ring is important for PfPK6 inhibition. In contrast, we observed a <2-fold change in antiplasmodial activity with the piperidine (**61**), pyrrolidine (**62**), and diethylamine (**63**) analogues, but the analogue with a morpholine (**60**) was inactive at 1 μM . Because the pK_a of the tertiary amine in **60** would be lower due to the electron-withdrawing oxygen of the morpholine, this suggests that having at least one sufficiently-basic nitrogen atom in this ring is important for inhibition of the *P. falciparum* blood stage.

When comparing compounds **41** and **43**, the reasons for a preference for a methylene linker over a carbonyl linker to the piperazine were not clear. Possible reasons include steric clash of the carbonyl oxygen atom with the kinase residues around the binding pocket, the incompatibility of hydrogen bond acceptors at this position, conformational restriction of the piperazine ring, or a change from a positively-charged tertiary amine to a neutral amide group. To deconvolute these factors, we replaced the piperazine in **41** with piperidine analogues with alternative linkers (**64–68**). While oxygen (**64**), N-methyl (**66**), and carbon linkers (**67**, **68**) were tolerated by PfPK6, the NH linker (**65**) was less preferred and led to a 12-fold decrease in inhibition. This suggests that the binding pocket of PfPK6 in the vicinity of this linker is hydrophobic and is unable to compensate for the loss of solvation energy of hydrophilic linkers upon ligand-target binding. Taken together, this suggests that the loss of potency against PfPK6 observed with the carbonyl linker previously (**43**) was due to the increase in polarity at this position. The argument for steric clash of the carbonyl oxygen atom was ruled out based on the acceptable potency with the similarly-sized N-methyl linker (**66**) while conformational restriction of the piperazine ring was shown to be tolerable in the case of the isosteric alkene linker (**68**). The antiplasmodial activity of **64**, **65** and **66** are within a 2-fold difference of **41**, whereas **67** and **68** possess an approximately 4-fold improvement in *P. falciparum* blood stage inhibitory activity, with EC_{50} s of 160 and 140 nM respectively. These analogues (**64–68**) also demonstrate that the basic amine proximal to the tail phenyl ring is neither essential for PfPK6 inhibition nor *P. falciparum* blood stage inhibition, as long as there is a second basic amine distal to the tail phenyl ring.

Finally, we have combined the *meta*- and *para*-position groups of most active compounds against the *P. falciparum* blood stage (Table 7). Gratifyingly, all compounds were active against PfPK6 and against *P. falciparum* blood stage proliferation. Compounds **69–74**, where either a CF_3 or a OCF_3 group was added to compounds **61–63**, saw an 8-to-26-fold improvement in PfPK6 inhibition but were equally potent with their parent compounds against the *P. falciparum* blood stage. In contrast to compounds **69–74**, an additive effect against both PfPK6 inhibition and *P. falciparum* blood stage inhibition was instead observed for the other compounds with a basic amine distal to the phenyl ring (**75–82**). All these compounds are extremely potent against PfPK6, with IC_{50} values < 5 nM. This approached the kinase concentration in the assay and thus we were unable to provide an exact measurement for the degree of improvement in PfPK6 activity. Nevertheless, at minimum, a 3-to-6-fold improvement in PfPK6 inhibition was observed in all cases. With the addition of a CF_3 group onto **64**, an 8-fold improvement in potency against *P. falciparum* blood stage

inhibition was additionally observed for **75**, affording a potent antimalarial with an EC₅₀ of 40 nM. The OCF₃ addition (**76**) afforded a more modest 4-fold improvement. Similarly, addition of a CF₃ group to **67** yielded **79**, which demonstrates potent antiplasmodial activity with an EC₅₀ of 39 nM, a 4-fold improvement over **67**. The OCF₃ analogue (**80**) only led to a 2-fold improvement. Addition of either a CF₃ or OCF₃ group to **68** afforded a 2-fold improvement in activity (**81**, **82**). Similarly, the addition of a CF₃ group to **66** gave a modest 2-fold improvement in antiplasmodial activity (**77**), but addition of an OCF₃ group only maintained potency (**78**). Overall, our hypothesis on additive effects between the *meta*- and *para*-position substituents was fruitful in finding compounds that possessed enhanced activity against PfPK6 and against *P. falciparum* blood stage parasites.

Characterization of **67**, **68**, **75**, and **79**.

With potent antimalarials (**75** and **79**) on hand, we next sought to measure the cytotoxicity of these compounds and evaluate if we have improved the therapeutic window compared to **45**. We screened compounds that have antiplasmodial effect for cytotoxicity of HepG2 cells using the CellTiter-Glo assay (Table S1), and found that compounds **75** and **79** exhibit cytotoxic effects with CC₅₀s values of 1.00 μM and 1.29 μM respectively (Table 8), demonstrating a 25-fold and 33-fold selectivity window, respectively, for antiplasmodial activity against the *P. falciparum* asexual blood stage over HepG2 cytotoxicity. In our cytotoxicity screen, two additional compounds stood out with a good balance of antiplasmodial activity and HepG2 cytotoxicity. Compound **67** and **68** have HepG2 cytotoxicity CC₅₀ values of 4.39 μM and 2.57 μM, respectively, while also having good antiplasmodial activity of 160 and 140 nM, respectively. This affords **67** a 27-fold therapeutic window and **68** an 18-fold therapeutic window. While **67** has a similar therapeutic window as compared to **75** and **79**, **68** has a slightly lower therapeutic window than **75** and **79**. Both **67** and **68** are still considerable improvements over **45**. Our results demonstrate that this scaffold has potential to be optimized for specificity against *Plasmodium* over human targets.

Ideally, an antimalarial drug would fulfill multiple target candidate profiles (TCPs) as outlined by the Medicines for Malaria Venture (MMV)⁴⁹. We thus investigated if our compounds demonstrate antiproliferative activity against other life stages of the *Plasmodium* life cycle. To this end, we tested **67**, **68**, **75**, and **79** for activity using a common liver stage model system. Specifically, compounds were tested for activity against *P. berghei* ANKA parasite load in HepG2 cells⁵⁰. Due to high sequence similarity between PfPK6 and *P. berghei* PK6 (81.9% similarity), we hypothesized that these compounds could demonstrate antiproliferative effects against *P. berghei*. As a counter-screen for host cell cytotoxicity, we screened these compounds in parallel in a cell viability assay in HepG2 cells with the CellTiter-Fluor assay. Our results from the CellTiter-Fluor assay generally agree with the results from our CellTiter-Glo assay, with **75** exhibiting a slightly greater cytotoxic response in the CellTiter-Fluor assay. For **67**, **68** and **75**, we observed some antiplasmodial effect against *P. berghei* liver stage, but with only a 1.4-, 1.9- and 1.9-fold difference between the *P. berghei* EC₅₀ and the CellTiter-Fluor CC₅₀ respectively. Therefore, they likely exert their antiplasmodial effect via host cell cytotoxicity. In contrast, compound **79** was observed to be active against *P. berghei* liver stage with an EC₅₀ of 0.22 μM (Table 8) and possesses a

5.9-fold window of selectivity between the *P. berghei* EC₅₀ and the CellTiter-Fluor CC₅₀, suggesting that its antiplasmodial activity may be attributed to parasite-specific toxicity. Compound **79** is thus a promising antiplasmodial lead compound with dual-stage activity against the *P. falciparum* blood stage and *P. berghei* liver stage.

We next obtained *in vitro* pharmacokinetic parameters for key compounds (Table 8). With our modifications to the tail group, **67** possesses the greatest solubility of the compounds tested (10.9 μ M), a noteworthy improvement over **Ki8751** (0.7 μ M) and **45** (2.1 μ M) but still leaves room for improvement. This increase in solubility came with a trade-off of decreased permeability. While the PAMPA assay we used does not fully model permeability into the parasite, the low permeability of these compounds of this series across lipid bilayers could be a factor for the disconnect between the *in vitro* kinase inhibitory activity and the activity against the parasite, especially considering that three membrane barriers (host cell membrane, parasitophorous vacuolar membrane, parasite plasma membrane) lay between the extracellular environment and the parasite cytoplasm. We hence envision that improvement in the permeability of compounds of this series during future optimization might be the key to improve cellular activity. Compounds **67**, **68**, **75**, and **79** also demonstrate good microsomal stability in human liver microsomes (88.6%–98.1% remaining after 30 min of incubation) and mouse liver microsomes (69.7%–88.9% remaining after 30 min of incubation). These pharmacokinetic data support further development of these compounds into novel antimalarial lead compounds, although future efforts would be required to address the permeability liabilities.

To establish the extent of possible off-targets in the human kinome, we screened compounds **67** and **79** in the DiscoverX KINOMEScan[®] profiling service. Compound **67** and **79** inhibited 22 and 97 non-mutant kinases with 1% control, respectively, with a selectivity score S_1 (1 μ M) of 0.055 and 0.24 respectively (Table S4, Figures S5 and S6). As a point of reference, we also profiled **Ki8751** in the DiscoverX KINOMEScan[®] profiling service and found **Ki8751** to inhibit 16 non-mutant kinases with 1% control, with a selectivity score S_1 (1 μ M) of 0.040 (Table S4, Figure S7). This demonstrates that **67** has maintained a similar degree of promiscuity of **Ki8751** in the human kinome, while being a considerable improvement over **45**. **79** also demonstrates a slight improvement over **45**.

From the KINOMEScan[®] profiling, PfCDPK1 was also identified as a target for **79** (1.1% control at 1 μ M) (Table 9), and thus PfCDPK1 may be one other target through which **79** may exert its potent antiplasmodial activity. To investigate alternative targets in the *Plasmodium* kinome that could contribute to the antimalarial efficacy of compounds **67**, **68**, **75**, and **79**, we screened them against the other ten *P. falciparum* kinases in our kinase panel in the KinaseSeeker assay (Table 9). Notably, consistent with our results from the DiscoverX KINOMEScan[®] profiling, **67** and **79** do not inhibit PfPK5 in both orthogonal assay formats. In our kinase panel, apart from PfPK6, **67** and **68** only weakly inhibits PfPKB, suggesting that their antiplasmodial activity is primarily exerted through inhibition of PfPK6, although this does not rule out inhibition of other targets beyond those screened by our efforts. On the other hand, compounds **75** and **79** demonstrate inhibition of PfCDPK5, PfGSK3, PfNEK3, and PfPKB, similar to **45**. The potency of **75** and **79** against the *P. falciparum* blood stage could thus be attributed to polypharmacology. We also acknowledge the possibility

that these compounds exert their antiplasmodial activity through other targets beyond those screened by our efforts. Further studies such as the evaluation of our compounds in inducible PfPK6 knockdown parasite lines or cellular thermal shift assays would be required to validate if PfPK6 is the primary target of these compounds in living parasites.

In general, we observe some disconnect between the SAR on PfPK6 inhibition and antiplasmodial activity for these analogues. This may be due to a multitude of factors. Low solubility could hinder detection of activity in cellular assays as poorly-soluble compounds could fail to achieve sufficient concentration for activity. Low permeability could result in insufficient intracellular concentration for target inhibition. The different physiochemical environment of PfPK6 and its binding partners in our *in vitro* kinase assay and in living parasites, which are not known, may be another factor for this disconnect. While we demonstrate that lead compound **67** primarily inhibits PfPK6 amongst the kinases screened, lead compound **79** additionally inhibits PfCDPK1, PfCDPK5, PfGSK3, PfNEK3, and PfPKB. It is possible that **67** and **79**, as well as other analogues in this series, target other kinases beyond those screened by our efforts and could have additional mechanisms of action. It is noteworthy that the most active compounds of this series against the *P. falciparum* blood stage have PfPK6 IC₅₀s < 5 nM (Figure S8), which suggests that PfPK6 is at least one of the targets they act upon. Possibly, different extents of compound retention within intracellular compartments may also play a role in the disconnect of SAR observed. A sufficiently-basic amine in these analogues may be important for retention of the compound inside acidic intracellular compartments of the parasite such as the digestive vacuole. pH-trapping was established to be important for the antimalarial drug chloroquine and analogues^{51–53}, which inhibits hemozoin formation within the digestive vacuole⁵⁴. Perhaps the targets of these compounds may be localized in or associated with the digestive vacuole. We speculate that pH-trapping may also allow for a slow release of the compound from within acidic intracellular compartments for sustained inhibition of its target(s) in live *P. falciparum* cells. Further experiments would be necessary to investigate these hypotheses.

Conclusions

In summary, we have synthesized 79 analogues based on the 1-phenyl-3-(4-(quinolin-4-yloxy)phenyl)urea scaffold of the initial hit **Ki8751**, focusing on diverse hinge-binding groups and tail groups, and we report the SAR of this scaffold on PfPK6 inhibition and inhibition of *P. falciparum* asexual blood stage parasites. Compound **67** was identified to be a potent PfPK6 inhibitor (IC₅₀ = 13 nM) active against the *P. falciparum* blood stage (EC₅₀ = 160 nM) while compound **79** was identified with excellent PfPK6 inhibition (IC₅₀ < 5 nM) and dual-stage antiplasmodial activity against *P. falciparum* at the blood stage (EC₅₀ = 39 nM) and against *P. berghei* in the liver stage (EC₅₀ = 0.22 μM). Both compounds were evaluated against other *P. falciparum* kinases. While **67** was found to primarily inhibit PfPK6, **79** likely exerts its antiplasmodial effects via polypharmacology. In conclusion, our results provide a good starting point for further lead optimization of compounds **67** and **79**. Further optimization would need to address key concerns found in this study regarding selectivity against human kinase targets, solubility and permeability, as well as demonstrate activity against *Plasmodium* in vivo, before these compounds could be considered suitable antimalarial drug candidates.

Chemistry

All synthetic procedures are described in detail in the Experimental Section. Truncated analogues of **Ki8751** were synthesized by a divergent synthetic strategy (Scheme 1). Nucleophilic aromatic substitution reactions with the appropriate phenol on 4-chloro-6,7-dimethoxyquinoline (**83**) under neutral or basic conditions afforded compounds **16**, **15**, and **84**. **15** was reacted with 2,4-difluoro-1-isocyanatobenzene to afford the urea **10**, and added to 1,1'-carbonyl diimidazole (CDI) and aniline to afford urea **11**. Reduction of the nitro group on **84** using iron and ammonium chloride in ethanol and water afforded **14** in good yields, which was then coupled with the appropriate aniline with CDI to form ureas **7**, **8**, and **9**. The experiments with CDI also revealed the highly-varied, substrate-dependent reactivity of the two aniline groups. We observed that **14** preferred to form its symmetrical urea by-product even when reacted with super-stoichiometric amounts of CDI, and low yields of the desired unsymmetrical urea were obtained after addition of the second aniline. Reactions of the latter anilines with CDI before addition of **14** were generally higher-yielding, although symmetrical urea by-products of both anilines were observed in most cases. Addition of acetyl chloride with DIPEA to **14** afforded **13** in excellent yields, while addition of aqueous sodium cyanate to **14** in acetic acid afforded the urea **12**, although trace amounts of **13** were also observed due to a side reaction with acetic acid.

We first attempted the synthesis of analogues varying the hinge-binding moiety by a tail-to-head strategy (Scheme 2), planning for diversification at the final step to expedite synthesis. Urea formation between **85** and **86** with 2,4-difluoro-1-isocyanatobenzene afforded **5** and **6** respectively. **5** was then subjected to nucleophilic aromatic substitution reactions under basic conditions with suitable aryl chlorides to afford **3**, **17**, **22**, and **26**, and with pyridine-4-yl triflate to afford **4**. Yields of these reactions were difficult to optimize as the urea group of **5** was unexpectedly labile under harsher reaction conditions. We thus adopted a head-to-tail synthetic strategy for the remaining compounds (Scheme 3). Refluxing **87** with aryl chlorides in *o*-xylene overnight afforded compounds **88-95**, in varying yields, depending on electrophilicity of the aryl chloride and ease of isolation. For less electrophilic aryl chlorides 4-chloro-1H-pyrrolo[2,3-b]pyridine and 4-chloro-7H-pyrrolo[2,3-d]pyrimidine, reaction with **87** under neat conditions in the microwave reactor or under basic conditions in NMP with 2,6-lutidine afforded **96** and **97** respectively in low yields. For more electron-deficient dichloropyrimidines, a milder reaction condition using potassium carbonate as a base in DMF with mild heating afforded **98** and **99** with minimal overreaction. Reduction of the nitro group using iron and ammonium chloride proceeded with moderate to excellent yields to afford anilines **100-105**, **108**, **109**, **111**, **112**, **115**, **116**. Anilines **106**, **107**, **110**, **113**, and **114** were obtained from nucleophilic aromatic substitution of **85** with the appropriate aryl chloride using potassium *tert*-butoxide as the base in DMF or DMA. These anilines were then coupled with 2,4-difluoroaniline using CDI to afford ureas **1**, **2**, **18-21**, **23-25**, **27-34**. An additional nucleophilic aromatic substitution reaction between the 6-chloropyrimidine group of **33** and benzyl amine under basic conditions in refluxing THF afforded **35** with moderate yields.

The majority of aryl chlorides used above were commercially available. The non-commercially available aryl chlorides **118**, **119**, **122**, **124**, and **127** were synthesized as described (Scheme 4). Removal of the methyl groups from **83** using boron tribromide in DCM afforded diphenol **117**, which reacted with diiodomethane and 1,2-dibromoethane to yield **118** and **119** respectively. Treatment of **120** with DMF-DMA afforded the formamidine intermediate, which was reacted with n-butyllithium-deprotonated acetonitrile to yield compound **121**. Condensation of **125** with formamide under refluxing conditions afforded **126**. **121**, **126**, and the commercially available **123** were subject to POCl_3 to form aryl chlorides **122**, **127** and **124**, respectively, suitable for the above nucleophilic aromatic substitution reactions.

To synthesize analogues with diverse tail group substituents, key intermediate **14** was coupled with the appropriate commercially available aniline using CDI to form ureas **40-43**, **45**, **49-60**, and **63** in poor-to-moderate yields (Scheme 5). In cases where the available aniline was available as a hydrochloride salt, one equivalent of DIPEA or Et_3N was additionally used for neutralization. **39** was synthesized by coupling **14** with 1-isocyanato-3-(trifluoromethyl)benzene.

With complex substituents where a suitable aniline or isocyanate was not commercially available, the appropriate aniline of the tail group was synthesized before coupling with **14** (Scheme 6). The coupling of acyl chloride **128** with 1-methylpiperazine followed by reduction of the nitro group using iron and ammonium chloride afforded **129**. The EDC-mediated amide coupling between 1-methylpiperazine and **130** followed by simultaneous reduction of both the nitro group and the resultant amide using LiAlH_4 yielded **131**. Similarly, EDC-mediated amide coupling of 1-methylpiperazine with **132** and **134** afforded anilines **133** and **135** respectively. **129**, **131**, **133**, and **135** were then reacted with CDI and **14** to yield **44**, **46**, **47**, and **48** respectively.

The potassium iodide-catalyzed substitution of the benzyl bromide group of **136** and **137** with piperidine, pyrrolidine or diethylamine using potassium carbonate as a base, followed by nitro reduction using iron and ammonium chloride afforded anilines **139-143**. The benzyl alcohol of aryl bromide **138** was converted to a mesylate using mesyl chloride and triethylamine in DCM, followed by one-pot substitution by piperidine, pyrrolidine or diethylamine. The aryl bromides were then converted to anilines **144-146** in excellent yields using a procedure modified from Lee *et al.*, 2001⁵⁵ using $\text{Pd}(\text{tBu}_3\text{P})_2$ as the catalyst and LiHMDS as the nitrogen source. The anilines **139**, **140**, **141**, **142**, **143**, **144**, **145**, and **146** were then successfully coupled with **14** to form ureas **61**, **62**, **69**, **71**, **73**, **70**, **72** and **74** respectively.

Nucleophilic aryl substitutions of aryl fluorides **147**, **148** and aryl chloride **149** with 1-methylpiperidin-4-ol, using potassium tert-butoxide as the base in DMSO at room temperature, and with 1-methylpiperidin-4-amine or N,1-dimethylpiperidin-4-amine using triethylamine as a base in DMSO at 90°C or 100°C were successful. The nitro groups of these substitution products were then reduced by iron and ammonium chloride to afford anilines **150-156**. Intriguingly, where there is a trifluoromethoxy group present *ortho* to the aryl chloride, a minor product was observed during the nucleophilic aromatic substitution

step, where displacement of the nitro group occurred instead of the chloro group. This minor product was only separable after the subsequent nitro reduction step. Anilines **150**, **151**, **152**, **153**, **154**, **155**, and **156** were then coupled with CDI and **14** to afford ureas **64**, **65**, **66**, **75**, **77**, **76**, and **78** respectively.

The synthesis of analogues with carbon linkers between the terminal phenyl ring and the piperidine ring required a different approach (Scheme 7). Heck coupling between **157** and **158** using Pd(dppf)Cl₂ and triethylamine in DMF heated at 100°C overnight afforded **159** as a minor product; the major product was not identified. Ester saponification proceeded with excellent yields to yield the corresponding benzoic acid, which was subjected to a one-pot microwave-assisted Curtius rearrangement using triethylamine and diphenylphosphoryl azide (DPPA), trapping the isocyanate using the aniline **14**, following the procedure by Kulkarni *et al.*, 2017⁵⁶, to yield **160** in excellent yields. **160** was subjected to 20% TFA in DCM to remove the Boc group, yielding **68**. Hydrogenation of the alkene of **68** afforded **67** in moderate yields.

Attempts at the analogous Heck coupling between **161** and **158** were unsuccessful, thus **165** was instead prepared by Suzuki coupling between **161** and **164**, using Pd₂(dba)₃ and Xphos as the catalytic system, potassium phosphate as the base, in 1,4-dioxane and water at 100°C for 1 h. Methylation of **162** with methyl iodide and potassium carbonate in DMSO afforded **163**, which was subjected to the same Suzuki coupling conditions to afford **166**. Hydrogenation of **165** and **166** yielded **167** and **168** in excellent yields. The methyl esters **165**, **166**, **167**, and **168** were saponified, next reacted with **14** in the abovementioned one-pot Curtius rearrangement, and finally subject to Boc deprotection by 20% TFA in DCM to afford **81**, **82**, **79** and **80** respectively in good yields.

Experimental Section

KinaseSeeker Assay.

Stock solutions of compounds were serially diluted in DMSO to make assay stocks. Prior to initiating a profiling campaign, the compounds were evaluated for false positive against split-luciferase. The compounds were then screened in duplicate against each of the kinases. For kinase assays, each Cfluc-Kinase was translated along with Fos-Nfluc using a cell-free system (cell lysate) at 30°C for 90 min. 24 µL aliquot of this lysate containing either 1 µL of DMSO (for no-inhibitor control) or compound solution in DMSO (final concentration: 1 µM) was incubated for 2 hours at room temperature in presence of a kinase specific probe. 80 µL of luciferin assay reagent was added to each solution and luminescence was immediately measured on a luminometer.

The % inhibition was calculated using the following equation:

$$\% \text{ Inhibition} = \frac{ALU_{control} - ALU_{sample}}{ALU_{control}} \times 100\%$$

***P. falciparum* Asexual Blood Stage Culture and Viability Assay.**

P. falciparum 3D7 parasites were continuously cultured in vitro in complete medium (10.44 g/L RPMI 1640 (ThermoFisher Scientific), 25 mM HEPES, pH 7.2 (ThermoFisher Scientific), 0.37 mM hypoxanthine (Sigma), 24 mM sodium bicarbonate (Sigma), 0.5% (wt/vol) AlbuMAX II (ThermoFisher Scientific), 25 µg/mL gentamicin (Sigma)) supplemented with freshly washed human erythrocytes (Gulf Coast Regional Blood Center, Houston, TX) approximately every 48 h. The parasite cultures were maintained at 2–10% parasitemia with 1% hematocrit at 37°C in a 3% O₂, 5% CO₂, 92% N₂ atmosphere. Highly synchronized cultures were generated by treatment with 25 volumes of 5% (wt/vol) D-sorbitol (Sigma) at 37°C for 10 min during the early ring stage.

Prior to the assays, *P. falciparum* 3D7 parasites were synchronized as described above and adjusted to 2% parasitemia and 2% hematocrit. Compounds were initially assayed for parasite inhibition at 1 µM. Dose response curves for select compounds were generated by dispensing 100 µL of the culture into each well of a 96-well black microplate (Corning), followed by administration of 1 µL serial diluted compounds in triplicate. Final compound concentrations ranged from 0 to 5 µM. Quinacrine at 125 nM was employed as the positive control and 0.5% DMSO as the negative control. Plates were incubated at 37°C in a 3% O₂, 5% CO₂, 92% N₂ atmosphere before and after drug administration. At 34 h post-reinvasion (i.e. 72 h after drug administration), 40 µL lysis solution (20 mM Tris-HCl, pH 7.5 (Fisher Chemical), 5 mM EDTA dipotassium salt dihydrate (Fisher Chemical), 0.16% (wt/vol) saponin (Sigma), 1.6% (vol/vol) Triton X-100 (Fisher Chemical)) containing fresh 10x SYBR Green I (ThermoFisher Scientific) was added to each well and incubated in the dark at room temperature for 24 h. The fluorescent signals were measured at 535 nm with excitation at 485 nm using an EnVision plate reader (PerkinElmer). Data was normalized to the negative and positive controls to obtain the relative percent parasite load. EC₅₀ values were determined by fitting data to a standard dose response equation (GraphPad Prism). The Z-factor ranged from 0.5–0.9.

***P. berghei* Liver Stage Parasite Load Assay and HepG2 CellTiter-Fluor Cytotoxicity Assay.**

HepG2 cells were maintained in Dulbecco's Modified Eagle Medium (DMEM) with L-glutamine (Gibco) supplemented with 10% heat-inactivated fetal bovine serum (HI-FBS) (v/v) (Sigma-Aldrich) and 1% antibiotic-antimycotic (Thermo Fisher Scientific) in a standard tissue culture incubator (37°C, 5% CO₂). *P. berghei* ANKA sporozoites used for liver stage experiments were isolated from freshly dissected salivary glands of infected mosquitoes (University of Georgia Sporocore). Dose response curves were generated for select compounds by assessing *P. berghei* parasite load in hepatocytes as previously described⁵⁰. Briefly, HepG2 (8,000 cells/well) were seeded into 384-well white microplates (Corning). After 24 hours, compounds (0–100 µM) were added (HP D300 Digital Dispenser) before infection with *P. berghei* ANKA sporozoites (4,000 spz/well). DMSO (1% v/v) was added as the negative control. All samples were evaluated in triplicate and had a final DMSO concentration of 1%. After 44 hours post-infection, HepG2 cell viability and parasite load were assessed using CellTiter-Fluor (Promega) and Bright-Glo (Promega) reagents, respectively, according to manufacturer's protocols. Relative fluorescence and luminescence signal was measured using an EnVision plate reader (PerkinElmer). The signal

intensity of each well was normalized to the negative control (1% DMSO) to assess relative viability. Dose response analysis was performed with GraphPad Prism.

HepG2 CellTiter-Glo Cytotoxicity Assay.

HepG2 cells were maintained in DMEM (Gibco) supplemented with 10% FBS, 1% NEAA, 1% L-glutamine. No antibiotics were used. Cells were plated at 4000 cells/well in 384-well plate (Costar) and incubated overnight (37°C, 5% CO₂) before adding compound. Compounds were added in quadruplicate and incubated for 48 hrs. DMSO percentage was constant across all concentrations of compound. Cell viability was measured using CellTiter-Glo2 (Promega) and luminescence signal was read on a GloMax plate reader (Promega). Dose response analysis was performed using GraphPad Prism.

DSF-based selectivity screening against a curated kinase library.

The assay was performed as previously described^{57,58}. Briefly, recombinant protein kinase domains at a concentration of 2 μ M were mixed with 10 μ M compound in a buffer containing 20 mM HEPES, pH 7.5, and 500 mM NaCl. SYPRO Orange (5000 \times , Invitrogen) was added as a fluorescence probe (1 μ L per mL). Subsequently, temperature-dependent protein unfolding profiles were measured using the QuantStudio™ 5 realtime PCR machine (Thermo Fisher). Excitation and emission filters were set to 465 nm and 590 nm, respectively. The temperature was raised with a step rate of 3°C per minute. Data points were analyzed with the internal software (Thermal Shift Software™ Version 1.4, Thermo Fisher) using the Boltzmann equation to determine the inflection point of the transition curve.

pK_a Calculation.

The pK_a value of PfPK6 inhibitors was simulated by the computational method proposed by one of the coauthors using the molecular electrostatic potential (MEP) on the acidic/basic nucleus and valence natural atomic orbital (NAO) energies as the equivalent descriptors^{37–39,59–61}. All calculations were carried out with Gaussian 16 package version C01⁶² with tight self-consistent-field convergence and ultrafine integration grids. The density functional theory B3LYP^{63,64} approximate exchange-correlation functional was employed for all calculations with Pople's 6–311+G(d) basis set⁶⁵. MEP and NAO descriptors were obtained by the natural population analysis⁶⁶ available from the Gaussian package. The reference pK_a values for structural analogues were from the reference⁶⁷.

General Chemistry Methods.

All reagents and solvents were used directly as received from commercial suppliers without further purification. Reactions were run under nitrogen or argon atmosphere unless otherwise noted. Solvents were degassed with argon for cross-coupling reactions. All microwave (μ W) reactions were carried out in a Biotage Initiator EXP US 400W microwave synthesizer. Thin-layer chromatography (TLC) analyses were performed using aluminum-backed 200 μ m pre-coated silica gel Sorbtech 254 nm-fluorescent TLC plates, and spots were visualized using UV light (254/365 nm). Flash chromatography was performed with RediSep 40–63 μ m irregular silica preppacked cartridges or RediSep 20–40 μ m spherical

C18-coated silica preppacked cartridges on Biotage Isolera One or Prime instruments, or with a Phenomenex Luna Phenyl-Hexyl (5 μm particle size, 100 \AA pore size, 75 \times 30 mm) column on an Agilent 1100 Series preparatory high-performance liquid chromatography (prep-HPLC) instrument equipped with an Agilent G1315B diode array detector measured at 220/254 nm.

Nuclear magnetic resonance (NMR) spectra were recorded in DMSO- d_6 , Methanol- d_4 , or CDCl_3 on Varian Inova 400 MHz, Bruker Avance 700 MHz or Bruker Avance 850 MHz instruments. Chemical shifts are reported in parts per million (ppm, δ), with residual solvent peaks referenced as the internal standard. Coupling constants are reported in Hz. Spin multiplicities are described as s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), p (pentet), and m (multiplet). Data were processed using MestReNova.

Yields are reported for pure material after isolation. All compounds tested for biological activity were 95% pure based on HPLC. High-resolution mass spectrometry samples were analyzed with a ThermoFisher Q Exactive HF-X (ThermoFisher, Bremen, Germany) mass spectrometer coupled with a Waters Acquity H-class liquid chromatograph system. Samples were introduced via a heated electrospray source (HESI) at a flow rate of 0.3 mL/min. Electrospray source conditions were set as: spray voltage 3.0 kV, sheath gas (nitrogen) 60 arb, auxiliary gas (nitrogen) 20 arb, sweep gas (nitrogen) 0 arb, nebulizer temperature 375 $^\circ\text{C}$, capillary temperature 380 $^\circ\text{C}$, RF funnel 45 V. The mass range was set to 150–2000 m/z. All measurements were recorded at a resolution setting of 120,000. Separations were conducted on a Waters Acquity UPLC BEH C18 column (2.1 \times 50 mm, 1.7 μm particle size). LC conditions were set at 95% water with 0.1% formic acid (A) ramped linearly over 5.0 mins to 100% acetonitrile with 0.1% formic acid (B) and held until 6.0 mins. At 7.0 mins the gradient was switched back to 95% A and allowed to re-equilibrate until 9.0 mins. Injection volume for all samples was 3 μL . Xcalibur (ThermoFisher, Bremen, Germany) was used to analyze the data. Solutions were analyzed at 0.1 mg/mL or less based on responsiveness to the ESI mechanism. Molecular formula assignments were determined with Molecular Formula Calculator (v 1.2.3). All observed species were singly charged, as verified by unit m/z separation between mass spectral peaks corresponding to the ^{12}C and $^{13}\text{C}^{12}\text{C}_{-1}$ isotope for each elemental composition.

Experimental Procedures in Scheme 1.

4-(3-fluorophenoxy)-6,7-dimethoxyquinoline (16).—A mixture of 4-chloro-6,7-dimethoxyquinoline (**83**) (50 mg, 0.22 mmol, 1 eq) and 3-fluorophenol (75 mg, 0.67 mmol, 3 eq) was heated at 170 $^\circ\text{C}$ for 20 min. The reaction mixture was cooled to rt, and saturated aqueous NaHCO_3 solution (20 mL) was added. The aqueous was extracted with EtOAc (30 mL \times 3). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 , filtered, concentrated onto Celite, and purified by flash chromatography (5–40% EtOAc in Hexanes on silica gel column) to afford **16** (23 mg, 34% yield) as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 8.52 (d, J = 5.2 Hz, 1H), 7.55 (td, J = 8.3, 6.8 Hz, 1H), 7.46 (s, 1H), 7.41 (s, 1H), 7.24 (dt, J = 10.0, 2.4 Hz, 1H), 7.18 (tdd, J = 8.5, 2.5, 0.9 Hz, 1H), 7.12 (ddd, J = 8.2, 2.5, 0.9 Hz, 1H), 6.60 (d, J = 5.2 Hz, 1H), 3.95 (s, 3H), 3.92 (s, 3H). ^{19}F NMR (376 MHz, DMSO- d_6) δ -110.22 (ddd, J = 9.6, 8.2, 6.9 Hz). ^{13}C NMR

(101 MHz, DMSO- d_6) δ 162.89 (d, J = 245.7 Hz), 158.92, 155.47 (d, J = 11.0 Hz), 152.65, 149.49, 148.89, 146.62, 131.73 (d, J = 9.6 Hz), 116.82 (d, J = 3.1 Hz), 115.32, 112.37 (d, J = 21.1 Hz), 108.61 (d, J = 24.1 Hz), 107.90, 104.15, 98.98, 55.76, 55.71. HRMS: calcd for $C_{17}H_{15}FNO_3$ [M + H]⁺ m/z, 300.1036; found m/z, 300.1021.

4-((6,7-dimethoxyquinolin-4-yl)oxy)aniline (15).—To a solution of 4-chloro-6,7-dimethoxyquinoline (**83**) (500 mg, 2.24 mmol, 1 eq) and 4-aminophenol (342 mg, 3.13 mmol, 1.4 eq) in DMF (10 mL) was added a suspension of sodium tert-butoxide (301 mg, 3.13 mmol, 1.4 eq) in DMF (10 mL) dropwise at 0°C. The reaction mixture was stirred at 110°C for 4 h. The reaction mixture was cooled to 0°C using an ice bath, water (60 mL) was added and stirred overnight. The solid was collected by filtration, washed with water, and dried. The crude material was dissolved in a mixture of DCM and MeOH, concentrated onto Celite and purified by flash chromatography (0–6% MeOH in DCM on silica gel column) to afford **15** (166 mg, 25% yield) as a yellow solid. ¹H NMR (400 MHz, DMSO- d_6) δ 8.42 (d, J = 5.2 Hz, 1H), 7.50 (s, 1H), 7.36 (s, 1H), 6.92 (d, J = 8.8 Hz, 2H), 6.66 (d, J = 8.7 Hz, 2H), 6.37 (d, J = 5.2 Hz, 1H), 5.15 (s, 2H), 3.93 (s, 3H), 3.93 (s, 3H). ¹³C NMR (101 MHz, DMSO- d_6) δ 160.95, 152.40, 149.10, 148.84, 146.65, 146.24, 143.40, 121.77, 115.00, 114.86, 107.79, 102.28, 99.19, 55.67, 55.65. HRMS: calcd for $C_{17}H_{17}N_2O_3$ [M + H]⁺ m/z, 297.1239; found m/z, 297.1224.

1-(4-((6,7-dimethoxyquinolin-4-yl)oxy)phenyl)-3-phenylurea (11).—To a solution of aniline (14 mg, 0.15 mmol, 1.3 eq) in DMSO (1 mL) was added 1,1'-carbonyldiimidazole (27 mg, 0.17 mmol, 1.4 eq). The reaction mixture was stirred at rt for 1 h, monitoring reaction progress by TLC. This was added to a solution of 4-((6,7-dimethoxyquinolin-4-yl)oxy)aniline (**15**) (35 mg, 0.12 mmol, 1 eq) in DMSO (1 mL). The reaction mixture was stirred at 50°C for 4 h, then cooled to rt. The crude reaction mixture was partitioned between EtOAc (15 mL) and water (15 mL). The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄, filtered, concentrated onto Celite, and purified by flash chromatography (0–3% MeOH in EtOAc on silica gel column) to afford **11** (35 mg, 71% yield) as a white solid. ¹H NMR (400 MHz, DMSO- d_6) δ 8.81 (s, 1H), 8.69 (s, 1H), 8.47 (d, J = 5.3 Hz, 1H), 7.63 – 7.56 (m, 2H), 7.52 (s, 1H), 7.50 – 7.44 (m, 2H), 7.39 (s, 1H), 7.29 (dd, J = 8.5, 7.3 Hz, 2H), 7.24 – 7.17 (m, 2H), 6.98 (t, J = 7.3 Hz, 1H), 6.44 (d, J = 5.2 Hz, 1H), 3.95 (s, 3H), 3.94 (s, 3H). ¹³C NMR (101 MHz, DMSO- d_6) δ 160.16, 152.58, 152.53, 149.28, 148.86, 148.13, 146.42, 139.65, 137.33, 128.81, 121.89, 121.56, 119.83, 118.25, 115.10, 107.85, 102.88, 99.12, 55.71, 55.69. HRMS: calcd for $C_{24}H_{22}N_3O_4$ [M + H]⁺ m/z, 416.1610; found m/z, 416.1591.

1-(2,4-difluorophenyl)-3-(4-((6,7-dimethoxyquinolin-4-yl)oxy)phenyl)urea (10).—To a solution of 4-((6,7-dimethoxyquinolin-4-yl)oxy)aniline (**15**) (60 mg, 0.20 mmol, 1 eq) in ethanol (0.6 mL) cooled to 0°C using an ice bath was added 2,4-difluoro-1-isocyanatobenzene (31 mg, 0.20 mmol, 1 eq) dropwise. The reaction mixture was warmed to rt and stirred at rt for 1 h. The reaction mixture was concentrated onto Celite and purified by flash chromatography (0–5% MeOH in EtOAc on silica gel column) to afford **10** (7.7 mg, 8% yield) as a white solid. ¹H NMR (400 MHz, DMSO- d_6) δ 9.16 (s, 1H), 8.54 (d, J = 2.3

Hz, 1H), 8.47 (d, $J = 5.2$ Hz, 1H), 8.08 (td, $J = 9.2, 6.1$ Hz, 1H), 7.62 – 7.55 (m, 2H), 7.52 (s, 1H), 7.39 (s, 1H), 7.32 (ddd, $J = 11.6, 8.9, 2.9$ Hz, 1H), 7.25 – 7.18 (m, 2H), 7.11 – 7.01 (m, 1H), 6.44 (d, $J = 5.2$ Hz, 1H), 3.95 (s, 3H), 3.94 (s, 3H). ^{19}F NMR (376 MHz, DMSO- d_6) δ –117.62 – –118.43 (m), –124.67 (t, $J = 10.8$ Hz). ^{13}C NMR (101 MHz, DMSO- d_6) δ 160.13, 156.88 (dd, $J = 241.7, 11.9$ Hz), 152.54, 152.37, 152.28 (dd, $J = 243.8, 12.3$ Hz), 149.30, 148.86, 148.34, 146.43, 137.02, 124.03 (dd, $J = 11.1, 3.5$ Hz), 122.10 (dd, $J = 9.1, 3.2$ Hz), 121.65, 119.80, 115.11, 111.91 – 110.58 (m), 107.85, 103.82 (dd, $J = 26.8, 23.8$ Hz), 102.92, 99.13, 55.72, 55.70. HRMS: calcd for $\text{C}_{24}\text{H}_{20}\text{F}_2\text{N}_3\text{O}_4$ [$\text{M} + \text{H}$] $^+$ m/z , 452.1422; found m/z , 452.1402.

4-(3-fluoro-4-nitrophenoxy)-6,7-dimethoxyquinoline (84).—A suspension of 4-chloro-6,7-dimethoxyquinoline (**83**) (2.50 g, 11.2 mmol, 1 eq) and 3-fluoro-4-nitrophenol (**87**) (3.16 g, 20.1 mmol, 1.8 eq) in *o*-xylene (24 mL) was stirred at 135°C for 16 h. The reaction mixture was cooled to rt. EtOAc (60 mL) was added and the mixture was stirred for 1 h at rt. The solid formed was collected by filtration, washed with EtOAc and dried. The solid was added to an aqueous NaOH solution (1 M, 60 mL) and stirred for 1 h at rt. The solids were collected by filtration, washed with water, and dried to afford **84** (2.936 g, 76% yield) as a light yellow solid. ^1H NMR (400 MHz, DMSO- d_6) δ 8.64 (d, $J = 5.1$ Hz, 1H), 8.27 (t, $J = 9.0$ Hz, 1H), 7.56 (dd, $J = 12.4, 2.6$ Hz, 1H), 7.46 (s, 1H), 7.33 (s, 1H), 7.20 (ddd, $J = 9.1, 2.6, 1.1$ Hz, 1H), 6.98 (d, $J = 5.1$ Hz, 1H), 3.96 (s, 3H), 3.88 (s, 3H). ^{19}F NMR (376 MHz, DMSO- d_6) δ –113.95 (dd, $J = 12.3, 8.9$ Hz). ^{13}C NMR (101 MHz, DMSO- d_6) δ 160.85 (d, $J = 11.3$ Hz), 156.82, 156.29 (d, $J = 263.3$ Hz), 152.88, 149.92, 148.90, 147.04, 133.14 (d, $J = 7.1$ Hz), 128.51 (d, $J = 1.8$ Hz), 115.81, 115.44 (d, $J = 3.4$ Hz), 109.34 (d, $J = 24.1$ Hz), 108.01, 107.03, 98.68, 55.81, 55.75.

4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluoroaniline (14).—A suspension of 4-(3-fluoro-4-nitrophenoxy)-6,7-dimethoxyquinoline (**84**) (2.90 g, 8.42 mmol, 1 eq), iron (2.35 g, 42.1 mmol, 5 eq), and ammonium chloride (3.60 g, 67.4 mmol, 8 eq) in ethanol (40 mL) and water (13 mL) was heated at 78°C for 5 h. The reaction mixture was cooled to rt and filtered through Celite. Solvent was removed from the filtrate and the residue was partitioned between DCM (100 mL) and aqueous NaOH solution (1 M, 100 mL). The aqueous layer was extracted with DCM (2 \times 100 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 , filtered, concentrated onto Celite, and purified by flash chromatography (0–10% MeOH in DCM on silica gel column) to afford **14** (2.064 g, 78% yield) as a light yellow solid. ^1H NMR (400 MHz, DMSO- d_6) δ 8.45 (d, $J = 5.3$ Hz, 1H), 7.48 (s, 1H), 7.37 (s, 1H), 7.05 (dd, $J = 12.1, 2.3$ Hz, 1H), 6.93 – 6.76 (m, 2H), 6.42 (d, $J = 5.2$ Hz, 1H), 5.20 (s, 2H), 3.94 (s, 3H), 3.93 (s, 3H). ^{19}F NMR (376 MHz, DMSO- d_6) δ –131.32 (dd, $J = 11.8, 8.9$ Hz). ^{13}C NMR (101 MHz, DMSO- d_6) δ 160.52, 152.46, 150.18 (d, $J = 239.8$ Hz), 149.19, 148.86, 146.31, 142.83 (d, $J = 9.3$ Hz), 134.45 (d, $J = 12.9$ Hz), 117.48 (d, $J = 3.1$ Hz), 116.43 (d, $J = 5.8$ Hz), 114.91, 109.15 (d, $J = 21.0$ Hz), 107.81, 102.49, 99.11, 55.69, 55.68. HRMS: calcd for $\text{C}_{17}\text{H}_{16}\text{FN}_2\text{O}_3$ [$\text{M} + \text{H}$] $^+$ m/z , 315.1145; found m/z , 315.1131.

1-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluorophenyl)-3-(2-fluorophenyl)urea (7).—To a solution of 4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluoroaniline (**14**) (60 mg,

0.19 mmol, 1 eq) in THF (1 mL) was added 1,1'-carbonyldiimidazole (40 mg, 0.25 mmol, 1.3 eq). The reaction mixture was stirred at rt for 2.5 h, followed by stirring at 45°C for 1.5 h, then 60°C for 1 h, monitoring reaction progress by TLC. A solution of 2-fluoroaniline (25 mg, 0.23 mmol, 1.2 eq) in THF (1 mL) was added. The reaction mixture was stirred at 45°C for 2 h, then cooled to rt. Water (10 mL) was added to precipitate a white solid. The solid was collected by filtration, washed with water and dried. The crude material was dissolved in a mixture of DCM and MeOH, concentrated onto Celite and purified by flash chromatography (0–10% MeOH in EtOAc on silica gel column) to afford **7** (4.4 mg, 5% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.29 (d, *J* = 2.4 Hz, 1H), 8.22 (d, *J* = 2.6 Hz, 1H), 7.67 (d, *J* = 5.2 Hz, 1H), 7.45 (t, *J* = 9.1 Hz, 1H), 7.35 (td, *J* = 8.2, 1.6 Hz, 1H), 6.67 (s, 1H), 6.58 (s, 1H), 6.53 (dd, *J* = 11.8, 2.7 Hz, 1H), 6.43 (ddd, *J* = 11.7, 8.1, 1.3 Hz, 1H), 6.33 (t, *J* = 7.8 Hz, 1H), 6.28 (ddd, *J* = 9.1, 2.6, 1.2 Hz, 1H), 6.25 – 6.16 (m, 1H), 5.72 (d, *J* = 5.2 Hz, 1H), 3.12 (s, 3H), 3.11 (s, 3H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ –125.74 (t, *J* = 10.7 Hz), –129.71 – –129.91 (m). ¹³C NMR (214 MHz, DMSO-*d*₆) δ 159.76, 152.74, 152.38 (d, *J* = 245.3 Hz), 152.19, 152.15 (d, *J* = 241.9 Hz), 149.52, 149.01, 148.54 (d, *J* = 10.2 Hz), 146.54, 127.36 (d, *J* = 10.1 Hz), 125.08 (d, *J* = 10.6 Hz), 124.71 (d, *J* = 3.7 Hz), 122.93 (d, *J* = 7.4 Hz), 121.77 (d, *J* = 2.9 Hz), 120.73, 117.24 (d, *J* = 3.1 Hz), 115.22, 115.18 (d, *J* = 19.9 Hz), 109.14 (d, *J* = 21.9 Hz), 107.89, 103.49, 99.16, 55.86, 55.84. HRMS: calcd for C₂₄H₂₀F₂N₃O₄ [M + H]⁺ *m/z*, 452.1422; found *m/z*, 452.1403.

1-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluorophenyl)-3-(4-fluorophenyl)urea (8).—To a solution of 4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluoroaniline (**14**) (60 mg, 0.19 mmol, 1 eq) in DMSO (1 mL) was added 1,1'-carbonyldiimidazole (40 mg, 0.25 mmol, 1.3 eq). The reaction mixture was stirred at rt for 2.5 h, followed by stirring at 45°C for 1.5 h, monitoring reaction progress by TLC. A solution of 4-fluoroaniline (25 mg, 0.23 mmol, 1.2 eq) in DMSO (1 mL) was added. The reaction mixture was stirred at 45°C for 3 h, then cooled to rt. Water (10 mL) was added to precipitate a white solid. The solid was collected by filtration, washed with water and dried. The crude material was dissolved in a mixture of DCM and MeOH, concentrated onto Celite and purified by flash chromatography (0–10% MeOH in EtOAc on silica gel column) to afford **8** (9.9 mg, 11% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.10 (s, 1H), 8.60 (d, *J* = 2.4 Hz, 1H), 8.49 (d, *J* = 5.2 Hz, 1H), 8.22 (t, *J* = 9.1 Hz, 1H), 7.56 – 7.43 (m, 3H), 7.40 (s, 1H), 7.34 (dd, *J* = 11.8, 2.7 Hz, 1H), 7.18 – 7.07 (m, 3H), 6.54 (d, *J* = 5.2 Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ –121.14 (ddd, *J* = 13.6, 8.9, 4.9 Hz), –125.79 (t, *J* = 10.6 Hz). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 159.63, 157.48 (d, *J* = 238.2 Hz), 152.59, 152.32, 152.31 (d, *J* = 244.3 Hz), 149.39, 148.88, 148.31 (d, *J* = 10.3 Hz), 146.49, 135.72 (d, *J* = 2.3 Hz), 125.16 (d, *J* = 10.7 Hz), 121.71 (d, *J* = 3.2 Hz), 119.90 (d, *J* = 7.6 Hz), 117.10, 115.42 (d, *J* = 22.2 Hz), 115.08, 109.02 (d, *J* = 21.9 Hz), 107.87, 103.32, 99.03, 55.74, 55.72. HRMS: calcd for C₂₄H₂₀F₂N₃O₄ [M + H]⁺ *m/z*, 452.1422; found *m/z*, 452.1403.

1-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluorophenyl)-3-phenylurea (9).—To a solution of aniline (14 mg, 0.15 mmol, 1.2 eq) in DMSO (1 mL) was added 1,1'-carbonyldiimidazole (27 mg, 0.17 mmol, 1.3 eq). The reaction mixture was stirred at rt for 1 h, monitoring reaction progress by TLC. This was added to a solution of 4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluoroaniline (**14**) (40 mg, 0.13 mmol, 1 eq) in DMSO (1

mL). The reaction mixture was stirred at 45°C for 3 h, followed by stirring at 60°C for 2 h, then cooled to rt. The crude reaction mixture was partitioned between EtOAc (15 mL) and water (15 mL). The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄, filtered, concentrated onto Celite, and purified by flash chromatography (0–4% MeOH in EtOAc on silica gel column) to afford **9** (18.5 mg, 34% yield) as a light purple solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.07 (s, 1H), 8.62 (d, *J* = 2.5 Hz, 1H), 8.49 (d, *J* = 5.2 Hz, 1H), 8.25 (t, *J* = 9.1 Hz, 1H), 7.49 (s, 1H), 7.47 (dd, *J* = 8.6, 1.2 Hz, 2H), 7.40 (s, 1H), 7.35 (dd, *J* = 11.8, 2.7 Hz, 1H), 7.30 (dd, *J* = 8.5, 7.3 Hz, 2H), 7.10 (ddd, *J* = 8.9, 2.7, 1.2 Hz, 1H), 7.00 (tt, *J* = 7.3, 1.2 Hz, 1H), 6.54 (d, *J* = 5.2 Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -125.93 (dd, *J* = 10.4, 9.5 Hz). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 160.09, 153.03, 152.67 (d, *J* = 244.4 Hz), 152.66, 149.82, 149.31, 148.66 (d, *J* = 10.4 Hz), 146.93, 139.83, 129.34, 125.67 (d, *J* = 10.6 Hz), 122.57, 122.02 (d, *J* = 2.8 Hz), 118.57, 117.55 (d, *J* = 3.1 Hz), 115.51, 109.45 (d, *J* = 22.1 Hz), 108.31, 103.74, 99.47, 56.18, 56.15. HRMS: calcd for C₂₄H₂₁FN₃O₄ [M + H]⁺ m/z, 434.1516; found m/z, 434.1498.

1-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluorophenyl)urea (12).—To a solution of 4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluoroaniline (**14**) (40 mg, 0.13 mmol, 1 eq) in acetic acid (0.25 mL) was added a solution of sodium cyanate (12 mg, 0.19 mmol, 1.5 eq) in water (0.2 mL). The reaction mixture was stirred at rt for 2 h, then concentrated under reduced pressure. Saturated aqueous NaHCO₃ solution was added, adjusting pH to 8. The solid formed was collected by filtration, washed with water and dried. The crude material was dissolved in a mixture of DCM and MeOH, concentrated onto Celite and purified by flash chromatography (0–6% MeOH in DCM on silica gel column) to afford **12** (28 mg, 61% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.48 (d, *J* = 5.3 Hz, 1H), 8.42 (d, *J* = 2.4 Hz, 1H), 8.23 (t, *J* = 9.2 Hz, 1H), 7.49 (s, 1H), 7.39 (s, 1H), 7.27 (dd, *J* = 11.9, 2.7 Hz, 1H), 7.03 (ddd, *J* = 8.9, 2.7, 1.3 Hz, 1H), 6.50 (d, *J* = 5.2 Hz, 1H), 6.21 (s, 2H), 3.94 (s, 3H), 3.93 (s, 3H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -126.54 (t, *J* = 10.9 Hz). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 159.77, 155.67, 152.56, 151.82 (d, *J* = 243.8 Hz), 149.34, 148.86, 147.45 (d, *J* = 10.4 Hz), 146.45, 126.08 (d, *J* = 10.6 Hz), 121.31 (d, *J* = 3.4 Hz), 116.98 (d, *J* = 3.1 Hz), 115.02, 108.84 (d, *J* = 22.2 Hz), 107.85, 103.13, 99.03, 55.72, 55.70. HRMS: calcd for C₁₈H₁₇FN₃O₄ [M + H]⁺ m/z, 358.1203; found m/z, 358.1186.

N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluorophenyl)acetamide (13).—To a solution of 4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluoroaniline (**14**) (25 mg, 0.080 mmol, 1 eq) and diisopropylethylamine (30 mg, 0.23 mmol, 2.9 eq) in 1,4-dioxane (0.5 mL) cooled to 0°C using an ice bath was added a solution of acetyl chloride (18 mg, 0.22 mmol, 2.8 eq) in 1,4-dioxane (0.5 mL). The reaction mixture was warmed to rt and stirred at rt for 2.5 h. The reaction mixture was concentrated onto Celite and purified by flash chromatography (0–3% MeOH in EtOAc on silica gel column) to afford **13** (26 mg, 92% yield) as a pink solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.81 (s, 1H), 8.50 (d, *J* = 5.2 Hz, 1H), 7.97 (t, *J* = 8.9 Hz, 1H), 7.47 (s, 1H), 7.40 (s, 1H), 7.32 (dd, *J* = 11.4, 2.7 Hz, 1H), 7.08 (ddd, *J* = 8.9, 2.7, 1.2 Hz, 1H), 6.56 (d, *J* = 5.2 Hz, 1H), 3.95 (s, 3H), 3.92 (s, 3H), 2.11 (s, 3H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -120.69 (dd, *J* = 10.3, 9.5 Hz). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 168.72, 159.30, 153.94 (d, *J* = 247.7 Hz), 152.62, 150.41 (d, *J* = 10.4 Hz), 149.43, 148.88,

146.54, 125.32, 123.76 (d, $J = 11.6$ Hz), 116.67 (d, $J = 3.4$ Hz), 115.16, 109.06 (d, $J = 22.7$ Hz), 107.88, 103.67, 99.00, 55.75, 55.71, 23.41. HRMS: calcd for $C_{19}H_{18}FN_2O_4$ $[M + H]^+$ m/z , 357.1251; found m/z , 357.1233.

Experimental Procedures in Scheme 2.

1-(2,4-difluorophenyl)-3-(2-fluoro-4-methoxyphenyl)urea (6).—To a solution of 2-fluoro-4-methoxyaniline (**86**) (70 mg, 0.50 mmol, 1 eq) in acetonitrile (0.8 mL) at room temperature was added 2,4-difluoro-1-isocyanatobenzene (77 mg, 0.50 mmol, 1 eq) dropwise. The resultant solution was stirred at room temperature for 30 minutes. Water (10 mL) was added and the solid was collected by filtration, washed with water and dried. The crude material was dissolved in a mixture of DCM and MeOH, concentrated onto Celite and purified by flash chromatography (10% EtOAc in Hexanes on silica gel column) to afford **6** (46 mg, 32% yield) as a white solid. 1H NMR (400 MHz, DMSO- d_6) δ 8.80 (d, $J = 1.8$ Hz, 1H), 8.69 (s, 1H), 8.10 (td, $J = 9.2, 6.1$ Hz, 1H), 7.89 (t, $J = 9.2$ Hz, 1H), 7.30 (ddd, $J = 11.7, 8.8, 2.9$ Hz, 1H), 7.04 (t, $J = 8.8$ Hz, 1H), 6.90 (dd, $J = 13.0, 2.8$ Hz, 1H), 6.75 (dd, $J = 8.6, 1.8$ Hz, 1H), 3.74 (s, 3H). ^{19}F NMR (376 MHz, DMSO- d_6) δ -118.16 – -119.01 (m), -125.08 (t, $J = 10.5$ Hz), -126.21 (t, $J = 10.9$ Hz). ^{13}C NMR (101 MHz, DMSO- d_6) δ 156.67 (dd, $J = 241.3, 11.8$ Hz), 155.33 (d, $J = 10.2$ Hz), 153.24 (d, $J = 242.2$ Hz), 152.35, 151.94 (dd, $J = 244.4, 11.7$ Hz), 124.12 (dd, $J = 10.7, 3.7$ Hz), 122.62 (d, $J = 3.1$ Hz), 121.66 (dd, $J = 9.2, 3.2$ Hz), 119.83 (d, $J = 11.3$ Hz), 111.02 (dd, $J = 21.6, 3.4$ Hz), 109.70 (d, $J = 2.9$ Hz), 103.76 (dd, $J = 27.0, 23.7$ Hz), 101.72 (d, $J = 22.9$ Hz), 55.62. HRMS: calcd for $C_{14}H_{12}F_3N_2O_2$ $[M + H]^+$ m/z , 297.0851; found m/z , 297.0842.

1-(2,4-difluorophenyl)-3-(2-fluoro-4-hydroxyphenyl)urea (5).—To a solution of 4-amino-3-fluorophenol (**85**) (250 mg, 1.97 mmol, 1 eq) in acetonitrile (0.8 mL) at room temperature was added 2,4-difluoro-1-isocyanatobenzene (305 mg, 1.97 mmol, 1 eq) dropwise. The resultant solution was stirred at room temperature for 30 minutes. Water (10 mL) was added and the solid was collected by filtration, washed with water and dried. The crude material was dissolved in a mixture of DCM and MeOH, concentrated onto Celite and purified by flash chromatography (0–80% EtOAc in Hexanes on silica gel column) to afford **5** (197 mg, 36% yield) as an off-white solid. 1H NMR (400 MHz, DMSO- d_6) δ 9.59 (s, 1H), 8.74 (d, $J = 2.3$ Hz, 1H), 8.55 (s, 1H), 8.14 – 8.04 (m, 1H), 7.71 (t, $J = 9.2$ Hz, 1H), 7.29 (ddd, $J = 11.7, 8.9, 2.9$ Hz, 1H), 7.03 (t, $J = 2.3$ Hz, 0H), 6.62 (dd, $J = 12.7, 2.6$ Hz, 1H), 6.56 (ddd, $J = 8.9, 2.7, 1.1$ Hz, 1H). ^{19}F NMR (376 MHz, DMSO- d_6) δ -118.50 – -118.65 (m), -125.18 (t, $J = 10.7$ Hz), -126.41 (dd, $J = 11.1, 10.5$ Hz). ^{13}C NMR (101 MHz, DMSO- d_6) δ 156.59 (dd, $J = 241.0, 11.5$ Hz), 153.80 (d, $J = 11.0$ Hz), 153.58 (d, $J = 241.8$ Hz), 152.46, 151.88 (dd, $J = 244.5, 12.4$ Hz), 124.24 (dd, $J = 10.6, 3.5$ Hz), 123.35 (d, $J = 3.2$ Hz), 121.57 (dd, $J = 9.1, 3.0$ Hz), 118.12 (d, $J = 11.4$ Hz), 110.99 (dd, $J = 21.8, 3.3$ Hz), 110.92 (d, $J = 3.0$ Hz), 103.72 (dd, $J = 26.9, 23.6$ Hz), 102.59 (d, $J = 21.7$ Hz). HRMS: calcd for $C_{13}H_{10}F_3N_2O_2$ $[M + H]^+$ m/z , 283.0694; found m/z , 283.0681.

1-(2,4-difluorophenyl)-3-(2-fluoro-4-(quinolin-4-yloxy)phenyl)urea (3).—To a solution of 1-(2,4-difluorophenyl)-3-(2-fluoro-4-hydroxyphenyl)urea (**5**) (85 mg, 0.30 mmol, 1.1 eq) and 4-chloroquinoline (45 mg, 0.28 mmol, 1 eq) in NMP (2 mL) was added DIPEA (71 mg, 0.55 mmol, 2 eq). The solution was heated at 90°C for 1.5 h. The reaction

mixture was cooled to rt and partitioned between EtOAc (30 mL) and water (20 mL). The aqueous layer was extracted with EtOAc (30 mL x 2). The combined organic extracts were washed with water, brine, dried over anhydrous Na₂SO₄, filtered, concentrated onto Celite, and purified by flash chromatography (10–70% EtOAc in Hexanes on silica gel column) to afford **3** (11 mg, 10% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.07 (d, *J* = 2.4 Hz, 1H), 9.00 (d, *J* = 2.3 Hz, 1H), 8.71 (d, *J* = 5.1 Hz, 1H), 8.34 – 8.23 (m, 2H), 8.13 (td, *J* = 9.2, 6.1 Hz, 1H), 8.04 (d, *J* = 8.5 Hz, 1H), 7.83 (ddd, *J* = 8.5, 6.8, 1.5 Hz, 1H), 7.67 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.40 (dd, *J* = 11.8, 2.7 Hz, 1H), 7.33 (ddd, *J* = 11.7, 8.9, 2.9 Hz, 1H), 7.14 (ddd, *J* = 9.0, 2.7, 1.3 Hz, 1H), 7.10 – 7.01 (m, 1H), 6.69 (d, *J* = 5.1 Hz, 1H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ –117.88 – –118.03 (m), –124.82 (t, *J* = 10.1 Hz), –125.61 (t, *J* = 10.5 Hz). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 160.88, 156.87 (dd, *J* = 241.5, 11.6 Hz), 152.25 (d, *J* = 244.7 Hz), 152.12, 152.07 (dd, *J* = 244.8, 12.3 Hz), 151.49, 149.24, 148.17 (d, *J* = 10.5 Hz), 130.31, 128.82, 126.45, 125.19 (d, *J* = 10.7 Hz), 123.87 (dd, *J* = 10.8, 3.5 Hz), 121.79 (dd, *J* = 9.1, 3.0 Hz), 121.62 (d, *J* = 2.9 Hz), 121.43, 120.52, 117.17 (d, *J* = 3.3 Hz), 111.12 (dd, *J* = 21.5, 3.5 Hz), 109.11 (d, *J* = 22.1 Hz), 104.43, 103.85 (dd, *J* = 26.9, 23.6 Hz). HRMS: calcd for C₂₂H₁₅F₃N₃O₂ [M + H]⁺ m/z, 410.1116; found m/z, 410.1098.

1-(2,4-difluorophenyl)-3-(2-fluoro-4-(pyridin-4-yloxy)phenyl)urea (4).—To a solution of 1-(2,4-difluorophenyl)-3-(2-fluoro-4-hydroxyphenyl)urea (**5**) (48 mg, 0.17 mmol, 1.1 eq) and pyridin-4-yl trifluoromethanesulfonate (35 mg, 0.15 mmol, 1 eq) in DMF (1 mL) was added DIPEA (40 mg, 0.31 mmol, 2 eq). The solution was irradiated in a microwave reactor at 130°C for 3 h. The reaction mixture was cooled to rt and partitioned between EtOAc (30 mL) and water (20 mL). The aqueous layer was extracted with EtOAc (30 mL x 2). The combined organic extracts were washed with water, brine, dried over anhydrous Na₂SO₄, filtered, concentrated onto Celite, and purified by flash chromatography (0–80% EtOAc in Hexanes on silica gel column) to afford **4** (3.3 mg, 6% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.04 (s, 1H), 8.99 (s, 1H), 8.49 – 8.44 (m, 2H), 8.21 (t, *J* = 9.1 Hz, 1H), 8.12 (td, *J* = 9.3, 6.1 Hz, 1H), 7.33 (ddd, *J* = 11.7, 8.9, 2.9 Hz, 1H), 7.26 (dd, *J* = 11.9, 2.7 Hz, 1H), 7.09 – 7.04 (m, 1H), 7.04 – 6.99 (m, 1H), 6.97 – 6.93 (m, 2H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ –117.97 (tdd, *J* = 8.9, 6.0, 3.6 Hz), –124.79 (t, *J* = 9.6 Hz), –125.59 (t, *J* = 10.5 Hz). ¹³C NMR (214 MHz, DMSO-*d*₆) δ 151.12, 143.95 (dd, *J* = 242.4, 12.0 Hz), 139.33 (d, *J* = 245.1 Hz), 139.19, 139.17 (dd, *J* = 245.1, 12.1 Hz), 138.53, 135.01 (d, *J* = 10.1 Hz), 111.93 (d, *J* = 10.9 Hz), 110.82 (dd, *J* = 10.8, 3.2 Hz), 108.96 (dd, *J* = 8.3, 3.3 Hz), 108.81 (dd, *J* = 5.8, 1.4 Hz), 103.92 (d, *J* = 2.9 Hz), 98.90, 98.15 (dd, *J* = 21.5, 3.2 Hz), 95.86 (d, *J* = 21.9 Hz), 90.87 (dd, *J* = 26.8, 23.6 Hz). HRMS: calcd for C₁₈H₁₃F₃N₃O₂ [M + H]⁺ m/z, 360.0960; found m/z, 360.0944.

1-(4-((7-chloroquinolin-4-yl)oxy)-2-fluorophenyl)-3-(2,4-difluorophenyl)urea (17).—To a solution of 1-(2,4-difluorophenyl)-3-(2-fluoro-4-hydroxyphenyl)urea (**5**) (71 mg, 0.25 mmol, 1.1 eq) and 4,7-dichloroquinoline (45 mg, 0.23 mmol, 1 eq) in DMF (2 mL) was added DIPEA (59 mg, 0.45 mmol, 2 eq). The solution was heated at 120°C for 18 h. The reaction mixture was cooled to rt and partitioned between EtOAc (30 mL) and water (20 mL). The aqueous layer was extracted with EtOAc (30 mL x 2). The combined organic extracts were washed with water, brine, dried over anhydrous Na₂SO₄, filtered, concentrated onto Celite, and purified by flash chromatography (0–80% EtOAc in Hexanes on silica

gel column) to afford **17** (3.4 mg, 3% yield) as an off-white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 9.08 (dd, J = 29.9, 1.6 Hz, 1H), 9.00 (d, J = 1.5 Hz, 1H), 8.74 (d, J = 5.2 Hz, 1H), 8.33 (d, J = 8.9 Hz, 1H), 8.27 (t, J = 9.1 Hz, 1H), 8.17 – 8.08 (m, 2H), 7.70 (dd, J = 8.9, 2.2 Hz, 1H), 7.42 (dd, J = 11.8, 2.7 Hz, 1H), 7.33 (ddd, J = 11.7, 8.8, 2.9 Hz, 1H), 7.16 (dt, J = 8.8, 1.5 Hz, 1H), 7.07 (t, J = 8.9 Hz, 1H), 6.72 (d, J = 5.2 Hz, 1H). ^{19}F NMR (376 MHz, DMSO- d_6) δ -117.92 (tdd, J = 8.9, 6.1, 3.6 Hz), -124.79 (t, J = 10.5 Hz), -125.53 (t, J = 10.6 Hz). ^{13}C NMR (214 MHz, DMSO- d_6) δ 161.17, 157.01 (dd, J = 241.4, 11.5 Hz), 153.13, 152.33 (d, J = 245.2 Hz), 152.22, 152.21 (dd, J = 244.6, 12.2 Hz), 149.70, 147.94 (d, J = 10.1 Hz), 135.11, 127.51, 127.15, 125.45 (d, J = 10.3 Hz), 123.91 (d, J = 2.8 Hz), 123.86, 121.99 (dd, J = 9.0, 2.4 Hz), 121.76 (d, J = 1.8 Hz), 119.28, 117.31, 111.21 (dd, J = 21.4, 3.0 Hz), 109.25 (d, J = 22.2 Hz), 104.87, 103.94 (dd, J = 26.8, 23.7 Hz). HRMS: calcd for $\text{C}_{22}\text{H}_{14}\text{ClF}_3\text{N}_3\text{O}_2$ $[\text{M} + \text{H}]^+$ m/z , 444.0727; found m/z , 444.0708.

1-(2,4-difluorophenyl)-3-(4-((6,7-dimethoxyquinazolin-4-yl)oxy)-2-fluorophenyl)urea (22).—To a solution of 1-(2,4-

difluorophenyl)-3-(2-fluoro-4-hydroxyphenyl)urea (**5**) (62 mg, 0.22 mmol, 1.1 eq) and 4-chloro-6,7-dimethoxyquinazoline (45 mg, 0.20 mmol, 1 eq) in DMF (2 mL) was added DIPEA (52 mg, 0.40 mmol, 2 eq). The solution was heated at 110°C for 18 h. The reaction mixture was cooled to rt and partitioned between EtOAc (30 mL) and water (20 mL). The aqueous layer was extracted with EtOAc (30 mL x 2). The combined organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4 , filtered, concentrated onto Celite, and purified by flash chromatography (10–100% EtOAc in Hexanes on silica gel column) to afford **22** (6.7 mg, 7% yield) as an off-white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 9.02 (d, J = 2.3 Hz, 1H), 8.99 (d, J = 2.2 Hz, 1H), 8.57 (s, 1H), 8.20 (t, J = 9.1 Hz, 1H), 8.14 (td, J = 9.2, 6.1 Hz, 1H), 7.55 (s, 1H), 7.43 – 7.38 (m, 2H), 7.33 (ddd, J = 11.6, 8.8, 2.8 Hz, 1H), 7.14 (d, J = 8.7 Hz, 1H), 7.10 – 7.02 (m, 1H), 3.99 (s, 3H), 3.98 (s, 3H). ^{19}F NMR (376 MHz, DMSO- d_6) δ -117.52 – -119.07 (m), -124.83 (t, J = 10.2 Hz), -126.88 (t, J = 10.6 Hz). ^{13}C NMR (214 MHz, DMSO- d_6) δ 165.14, 157.40 (dd, J = 242.2, 11.6 Hz), 156.23, 152.68, 152.65 (dd, J = 245.5, 12.4 Hz), 152.53, 152.48 (d, J = 244.0 Hz), 150.51, 149.12, 147.29 (d, J = 10.9 Hz), 125.16 (d, J = 10.8 Hz), 124.04 (dd, J = 10.3, 3.2 Hz), 122.58 (dd, J = 8.5, 2.4 Hz), 121.77 (d, J = 2.4 Hz), 118.57 (d, J = 2.6 Hz), 111.50 (dd, J = 21.8, 3.4 Hz), 110.54 (d, J = 22.1 Hz), 110.04, 106.90, 104.20 (dd, J = 27.0, 23.4 Hz), 101.08, 56.55, 56.39. HRMS: calcd for $\text{C}_{23}\text{H}_{18}\text{F}_3\text{N}_4\text{O}_4$ $[\text{M} + \text{H}]^+$ m/z , 471.1280; found m/z , 471.1262.

1-(2,4-difluorophenyl)-3-(2-fluoro-4-(thieno[3,2-d]pyrimidin-4-

yl)oxy)phenyl)urea (26).—To a solution of 1-(2,4-difluorophenyl)-3-(2-fluoro-4-hydroxyphenyl)urea (**5**) (64 mg, 0.23 mmol, 1.1 eq) and 4-chloro-6,7-dimethoxyquinazoline (35 mg, 0.21 mmol, 1 eq) in DMF (1.5 mL) was added DIPEA (53 mg, 0.41 mmol, 2 eq). The solution was heated at 120°C for 18 h. The reaction mixture was cooled to rt and partitioned between EtOAc (30 mL) and water (20 mL). The aqueous layer was extracted with EtOAc (30 mL x 2). The combined organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4 , filtered, concentrated onto Celite, and purified by flash chromatography (0–50% EtOAc in Hexanes on silica gel column) to afford **26** (4.4 mg, 5% yield) as an orange-brown solid. ^1H NMR (400 MHz, DMSO- d_6) δ 9.04 (d, J = 2.4 Hz, 1H), 8.99 (d, J = 2.2 Hz, 1H), 8.73 (s, 1H), 8.49 (d, J = 5.4 Hz, 1H), 8.20 (t, J = 9.1 Hz, 1H), 8.13

(td, $J = 9.2, 6.1$ Hz, 1H), 7.69 (d, $J = 5.4$ Hz, 1H), 7.45 (dd, $J = 11.8, 2.7$ Hz, 1H), 7.33 (ddd, $J = 11.6, 8.8, 2.9$ Hz, 1H), 7.17 (dq, $J = 9.0, 1.2$ Hz, 1H), 7.07 (t, $J = 8.8$ Hz, 1H). ^{19}F NMR (376 MHz, DMSO- d_6) δ -116.75 – -120.17 (m), -124.82 (t, $J = 10.4$ Hz), -126.65 (dd, $J = 11.8, 9.2$ Hz). ^{13}C NMR (101 MHz, DMSO- d_6) δ 163.60, 163.19, 154.11, 152.14, 152.06 (dd, $J = 244.6, 11.7$ Hz), 151.85 (d, $J = 243.7$ Hz), 146.02 (d, $J = 10.6$ Hz), 137.44, 125.36 (d, $J = 10.7$ Hz), 124.29, 123.89 (d, $J = 7.0$ Hz), 121.78 (d, $J = 10.7$ Hz), 121.00, 118.15 (d, $J = 3.3$ Hz), 116.81, 111.10 (d, $J = 21.9$ Hz), 110.18 (d, $J = 22.6$ Hz), 103.84. (only one doublet of the dd was observed at 158.06 ppm (d, $J = 11.2$ Hz), the other doublet was not observed due to signal to noise). HRMS: calcd for $\text{C}_{19}\text{H}_{12}\text{F}_3\text{N}_4\text{O}_2\text{S}$ [$\text{M} + \text{H}$] $^+$ m/z , 417.0633; found m/z , 417.0616.

Experimental Procedures in Schemes 3 and 4.

4-(3-fluoro-4-nitrophenoxy)-7-methoxyquinoline (88).—A suspension of 4-chloro-7-methoxyquinoline (250 mg, 1.29 mmol, 1 eq) and 3-fluoro-4-nitrophenol (**87**) (406 mg, 2.58 mmol, 2 eq) in *o*-xylene (3.5 mL) was stirred at 135°C for 16 h. The reaction mixture was cooled to rt. EtOAc (15 mL) was added and the mixture was stirred for 1 h at rt. The solid formed was collected by filtration, washed with EtOAc and dried. The solid was added to an aqueous NaOH solution (1 M, 20 mL) and stirred for 1 h at rt. The solids were collected by filtration, washed with water, and dried under vacuum to afford **88** (265 mg, 65% yield) as a light yellow solid. ^1H NMR (400 MHz, DMSO- d_6) δ 8.78 (d, $J = 5.1$ Hz, 1H), 8.27 (t, $J = 8.9$ Hz, 1H), 8.03 (d, $J = 9.2$ Hz, 1H), 7.59 (dd, $J = 12.3, 2.6$ Hz, 1H), 7.48 (d, $J = 2.5$ Hz, 1H), 7.31 (dd, $J = 9.2, 2.5$ Hz, 1H), 7.21 (ddd, $J = 9.2, 2.7, 1.2$ Hz, 1H), 6.98 (d, $J = 5.1$ Hz, 1H), 3.95 (s, 3H). ^{19}F NMR (376 MHz, DMSO- d_6) δ -113.92 (dd, $J = 12.3, 8.8$ Hz).

2-fluoro-4-((7-methoxyquinolin-4-yl)oxy)aniline (100).—A suspension of 4-(3-fluoro-4-nitrophenoxy)-7-methoxyquinoline (**88**) (263 mg, 0.84 mmol, 1 eq), iron (234 mg, 4.2 mmol, 5 eq), and ammonium chloride (358 mg, 6.7 mmol, 8 eq) in ethanol (4.5 mL) and water (15 mL) was heated at 78°C for 6 h. The reaction mixture was cooled to rt and filtered through Celite. Solvent was removed from the filtrate and the residue was partitioned between DCM (30 mL) and aqueous NaOH solution (1 M, 30 mL). The aqueous layer was extracted with DCM (2 \times 30 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 , filtered, concentrated onto Celite, and purified by flash chromatography (0–6% MeOH in DCM on silica gel column) to afford **100** (203 mg, 85% yield) as an orange solid. ^1H NMR (400 MHz, DMSO- d_6) δ 8.58 (d, $J = 5.2$ Hz, 1H), 8.18 (d, $J = 9.1$ Hz, 1H), 7.38 (d, $J = 2.5$ Hz, 1H), 7.26 (dd, $J = 9.2, 2.6$ Hz, 1H), 7.07 (dd, $J = 12.2, 2.1$ Hz, 1H), 6.96 – 6.78 (m, 2H), 6.43 (d, $J = 5.2$ Hz, 1H), 5.20 (s, 2H), 3.93 (s, 3H). ^{19}F NMR (376 MHz, DMSO- d_6) δ -131.33 (dd, $J = 11.9, 8.5$ Hz). ^{13}C NMR (214 MHz, DMSO- d_6) δ 162.14, 160.94, 151.71, 150.81, 150.26 (d, $J = 239.8$ Hz), 142.75 (d, $J = 9.5$ Hz), 134.67 (d, $J = 12.5$ Hz), 122.99, 118.75, 117.50 (d, $J = 2.9$ Hz), 116.56 (d, $J = 5.6$ Hz), 115.13, 109.17 (d, $J = 21.0$ Hz), 107.07, 102.26, 55.61.

1-(2,4-difluorophenyl)-3-(2-fluoro-4-((7-methoxyquinolin-4-yl)oxy)phenyl)urea (1).—To a solution of 2-fluoro-4-((7-methoxyquinolin-4-yl)oxy)aniline (**100**) (50 mg, 0.18 mmol, 1 eq) in ethanol (0.5 mL) cooled to 0°C using an ice bath was added 2,4-difluoro-1-isocyanatobenzene (27 mg, 0.18 mmol, 1 eq) dropwise. The reaction mixture was warmed

to rt and stirred at rt for 1 h. The reaction mixture was concentrated onto Celite and purified by flash chromatography (0–3% MeOH in DCM on silica gel column) to afford **1** (24 mg, 31% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.06 (d, *J* = 2.4 Hz, 1H), 8.99 (d, *J* = 2.3 Hz, 1H), 8.63 (d, *J* = 5.2 Hz, 1H), 8.25 (t, *J* = 9.1 Hz, 1H), 8.18 (d, *J* = 9.1 Hz, 1H), 8.13 (td, *J* = 9.2, 6.1 Hz, 1H), 7.41 (d, *J* = 2.6 Hz, 1H), 7.40 – 7.26 (m, 3H), 7.15 – 7.09 (m, 1H), 7.06 (t, *J* = 8.1 Hz, 1H), 3.94 (s, 3H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ –117.92 – –118.01 (m), –124.83 (t, *J* = 9.7 Hz), –125.67 (t, *J* = 10.7 Hz). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 160.90, 160.81, 156.90 (dd, *J* = 241.6, 11.5 Hz), 152.27 (d, *J* = 244.6 Hz), 152.15, 152.10 (dd, *J* = 245.0, 12.2 Hz), 151.88, 151.30, 148.27 (d, *J* = 10.3 Hz), 125.11 (d, *J* = 10.8 Hz), 123.89 (dd, *J* = 10.7, 3.5 Hz), 122.78, 121.83 (dd, *J* = 9.1, 2.6 Hz), 121.64 (d, *J* = 2.8 Hz), 118.85, 117.13 (d, *J* = 3.2 Hz), 115.16, 111.14 (dd, *J* = 21.6, 3.5 Hz), 109.07 (d, *J* = 22.1 Hz), 107.43, 103.87 (dd, *J* = 27.1, 23.6 Hz), 102.95, 55.55. HRMS: calcd for C₂₃H₁₇F₃N₃O₃ [M + H]⁺ *m/z*, 440.1222; found *m/z*, 440.1204.

4-(3-fluoro-4-nitrophenoxy)-6-methoxyquinoline hydrochloride (89).—A suspension of 4-chloro-6-methoxyquinoline (250 mg, 1.25 mmol, 1 eq) and 3-fluoro-4-nitrophenol (**87**) (406 mg, 2.58 mmol, 2 eq) in *o*-xylene (3.5 mL) was stirred at 135°C for 16 h. The reaction mixture was cooled to rt. EtOAc (15 mL) was added and the mixture was stirred for 1 h at rt. The solid formed was collected by filtration, washed with EtOAc and dried. The solid was added to an aqueous NaOH solution (1 M, 20 mL) and stirred for 1 h at rt. The solids were collected by filtration, washed with water, and dried. The residue was then transferred to an aqueous HCl solution (2 M, 5 mL) and the aqueous solution was decanted. EtOAc was added to the remaining residue, and decanted. The remaining residue was dried under vacuum to afford **89** (83 mg, 20% yield) as a light brown solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.97 (d, *J* = 6.1 Hz, 1H), 8.41 (t, *J* = 8.9 Hz, 1H), 8.28 (d, *J* = 9.3 Hz, 1H), 7.90 – 7.75 (m, 2H), 7.69 (d, *J* = 2.7 Hz, 1H), 7.57 – 7.43 (m, 1H), 7.33 (d, *J* = 6.1 Hz, 1H), 3.99 (s, 3H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ –113.59 (dd, *J* = 11.9, 8.6 Hz).

2-fluoro-4-((6-methoxyquinolin-4-yl)oxy)aniline (101).—A suspension of 4-(3-fluoro-4-nitrophenoxy)-6-methoxyquinoline (**89**) (83 mg, 0.26 mmol, 1 eq), iron (74 mg, 1.3 mmol, 5 eq), and ammonium chloride (110 mg, 2.1 mmol, 8 eq) in ethanol (1.5 mL) and water (0.5 mL) was heated at 78°C for 5 h. The reaction mixture was cooled to rt and filtered through Celite. Solvent was removed from the filtrate and the residue was partitioned between DCM (30 mL) and aqueous NaOH solution (1 M, 30 mL). The aqueous layer was extracted with DCM (2 × 30 mL). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄, filtered, concentrated onto Celite, and purified by flash chromatography (0–6% MeOH in DCM on silica gel column) to afford **101** (55 mg, 73% yield) as a yellow solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.38 (d, *J* = 5.3 Hz, 1H), 7.84 (d, *J* = 9.3 Hz, 1H), 7.57 (d, *J* = 2.8 Hz, 1H), 7.37 (dd, *J* = 9.2, 2.8 Hz, 1H), 6.98 – 6.87 (m, 2H), 6.80 (ddd, *J* = 8.6, 2.6, 1.2 Hz, 1H), 6.53 (d, *J* = 5.3 Hz, 1H), 3.89 (s, 3H). ¹⁹F NMR (376 MHz, Methanol-*d*₄) δ –132.99 (t, *J* = 10.7 Hz).

1-(2,4-difluorophenyl)-3-(2-fluoro-4-((6-methoxyquinolin-4-yl)oxy)phenyl)urea (2).—To a solution of 2-fluoro-4-((6-methoxyquinolin-4-yl)oxy)aniline (**101**) (53 mg, 0.19 mmol, 1 eq) in ethanol (0.55 mL) cooled to 0°C using an ice bath was added 2,4-difluoro-1-

isocyanatobenzene (29 mg, 0.19 mmol, 1 eq) dropwise. The reaction mixture was warmed to rt and stirred at rt for 1 h. The reaction mixture was concentrated onto Celite and purified by flash chromatography (0–10% MeOH in DCM on silica gel column) to afford **2** (40 mg, 49% yield) as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 9.07 (d, J = 2.4 Hz, 1H), 9.00 (d, J = 2.2 Hz, 1H), 8.56 (d, J = 5.1 Hz, 1H), 8.27 (t, J = 9.1 Hz, 1H), 8.13 (td, J = 9.2, 6.1 Hz, 1H), 7.95 (d, J = 9.2 Hz, 1H), 7.55 (d, J = 2.9 Hz, 1H), 7.47 (dd, J = 9.2, 2.9 Hz, 1H), 7.38 (dd, J = 11.8, 2.7 Hz, 1H), 7.33 (ddd, J = 11.7, 8.5, 2.5 Hz, 1H), 7.13 (ddd, J = 9.1, 2.7, 1.3 Hz, 1H), 7.10 – 7.03 (m, 1H), 6.66 (d, J = 5.1 Hz, 1H), 3.93 (s, 3H). ^{19}F NMR (376 MHz, DMSO- d_6) δ –117.96 (tdd, J = 8.9, 6.0, 3.6 Hz), –124.81 (t, J = 10.7 Hz), –125.67 (t, J = 10.6 Hz). ^{13}C NMR (101 MHz, DMSO- d_6) δ 159.96, 157.35, 156.87 (dd, J = 241.1, 11.6 Hz), 152.23 (d, J = 244.7 Hz), 152.12, 152.07 (dd, J = 245.2, 11.8 Hz), 148.73, 148.28 (d, J = 10.4 Hz), 145.27, 130.53, 125.10 (d, J = 10.7 Hz), 123.87 (dd, J = 10.7, 3.8 Hz), 122.63, 121.80 (dd, J = 9.1, 3.0 Hz), 121.58 (d, J = 2.6 Hz), 121.33, 117.19 (d, J = 2.9 Hz), 111.12 (dd, J = 21.5, 3.6 Hz), 109.11 (d, J = 22.0 Hz), 104.76, 103.85 (dd, J = 26.9, 23.9 Hz), 99.13, 55.60. HRMS: calcd for $\text{C}_{23}\text{H}_{17}\text{F}_3\text{N}_3\text{O}_3$ [$\text{M} + \text{H}$] $^+$ m/z , 440.1222; found m/z , 440.1214.

4-oxo-1,4-dihydroquinoline-3-carbonitrile (121).—To a solution of methyl 2-aminobenzoate (**120**) (200 mg, 1.3 mmol, 1 eq) in DMF (1.5 mL) was added N,N-dimethylformamide dimethyl acetal (473 mg, 4.0 mmol, 3 eq). The reaction mixture was refluxed at 150°C for 3 h, then cooled to rt. Repeatedly, toluene was added and volatiles were removed *in vacuo* until the crude formamidine was obtained as a dark purple liquid. Separately, to a degassed round-bottom-flask with anhydrous THF (2 mL) cooled to –78°C using a dry-ice/acetone bath was added n-butyllithium (2.5 M in hexanes, 1.3 mL, 2.5 eq), a solution of anhydrous MeCN (136 mg, 0.17 mL, 2.5 eq) in anhydrous THF (2.6 mL) dropwise, and the crude formamidine dissolved in anhydrous THF (2.6 mL) dropwise. The reaction mixture was stirred at –78°C for 1 h, then quenched by dropwise addition of water (0.5 mL) and acetic acid (0.3 mL), warmed to rt and concentrated *in vacuo*. Water was added, and the solids were collected by filtration, washed with water and chloroform, and dried *in vacuo* to afford **121** (180 mg, 80% yield) as an off-white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 12.81 (s, 1H), 8.74 (s, 1H), 8.13 (dd, J = 8.1, 1.5 Hz, 1H), 7.78 (ddd, J = 8.5, 7.0, 1.5 Hz, 1H), 7.64 (d, J = 8.3 Hz, 1H), 7.48 (ddd, J = 8.1, 7.1, 1.1 Hz, 1H). ^{13}C NMR (214 MHz, DMSO- d_6) δ 177.66, 149.81, 142.21, 136.49, 128.74, 128.23, 128.14, 122.36, 119.93, 96.68.

4-chloroquinoline-3-carbonitrile (122).—A mixture of 4-oxo-1,4-dihydroquinoline-3-carbonitrile (**121**) (175 mg, 1.03 mmol, 1 eq) in phosphoryl trichloride (2 mL) was refluxed at 100°C for 2 h. The reaction was cooled to rt, and concentrated *in vacuo*. The mixture was then cooled to 0°C using an ice bath. Water (20 mL) and dichloromethane (20 mL) was carefully added to the mixture while stirring, followed by careful addition of solid potassium carbonate until the pH was between 8–9. The mixture was left to stir for 30 min at rt. The organic layer was separated, washed with water, then brine, dried over anhydrous Na_2SO_4 , filtered, and concentrated *in vacuo* to give **122** (185 mg, 95% yield) as a light brown solid. ^1H NMR (400 MHz, DMSO- d_6) δ 9.21 (s, 1H), 8.34 (dd, J = 8.5, 1.4 Hz, 1H), 8.21 (dd, J = 8.5, 1.2 Hz, 1H), 8.08 (ddd, J = 8.5, 6.9, 1.4 Hz, 1H), 7.93 (ddd, J = 8.3, 6.9, 1.2 Hz, 1H).

^{13}C NMR (214 MHz, DMSO- d_6) δ 174.50, 146.64, 139.14, 133.30, 125.56, 125.13, 125.00, 119.26, 116.83, 93.55.

4-(3-fluoro-4-nitrophenoxy)quinoline-3-carbonitrile (90).—A suspension of 4-chloroquinoline-3-carbonitrile (**122**) (175 mg, 0.928 mmol, 1 eq) and 3-fluoro-4-nitrophenol (**87**) (262 mg, 1.67 mmol, 1.8 eq) in *o*-xylene (2.3 mL) was stirred at 135°C for 40 h. The reaction mixture was cooled to rt. EtOAc (15 mL) was added and the mixture was stirred for 1 h at rt. The solid formed was collected by filtration, washed with EtOAc and dried. The solid was added to an aqueous NaOH solution (1 M, 20 mL) and stirred for 1 h at rt. The solids were collected by filtration, washed with water, and dried under vacuum. The crude material was dissolved in a mixture of DCM and MeOH, concentrated onto Celite and purified by flash chromatography (0–35% EtOAc in Hexanes on silica gel column) to afford **90** (118 mg, 41% yield) as a light yellow-brown solid. ^1H NMR (400 MHz, DMSO- d_6) δ 9.27 (s, 1H), 8.29–8.20 (m, 2H), 8.10–8.01 (m, 2H), 7.79 (ddd, J = 8.3, 6.9, 1.2 Hz, 1H), 7.62 (dd, J = 12.3, 2.7 Hz, 1H), 7.22 (ddd, J = 9.3, 2.7, 1.2 Hz, 1H). ^{19}F NMR (376 MHz, DMSO- d_6) δ -113.55 (dd, J = 12.4, 8.7 Hz). ^{13}C NMR (214 MHz, DMSO- d_6) δ 161.20 (d, J = 11.0 Hz), 160.21, 156.31 (d, J = 263.6 Hz), 151.74, 150.76, 133.83, 133.21 (d, J = 7.1 Hz), 129.73, 129.14, 128.73, 122.28, 120.52, 114.01, 113.35 (d, J = 3.2 Hz), 107.26 (d, J = 25.3 Hz), 98.88.

4-(4-amino-3-fluorophenoxy)quinoline-3-carbonitrile (102).—A suspension of 4-(3-fluoro-4-nitrophenoxy)quinoline-3-carbonitrile (**90**) (113 mg, 0.365 mmol, 1 eq), iron (102 mg, 1.83 mmol, 5 eq), and ammonium chloride (156 mg, 2.92 mmol, 8 eq) in ethanol (1.0 mL) and water (0.35 mL) was heated at 31°C for 4 h. The reaction mixture was cooled to rt and filtered through Celite. The filtrate was concentrated onto Celite, and purified by flash chromatography (0–40% EtOAc in Hexanes on silica gel column) to afford **102** (59 mg, 58% yield) as a yellow-brown solid. ^1H NMR (400 MHz, DMSO- d_6) δ 8.97 (s, 1H), 8.28–8.24 (m, 1H), 8.12 (dt, J = 8.5, 1.0 Hz, 1H), 7.99 (ddd, J = 8.4, 6.9, 1.5 Hz, 1H), 7.75 (ddd, J = 8.3, 6.9, 1.2 Hz, 1H), 7.15 (dd, J = 11.8, 2.7 Hz, 1H), 6.88–6.75 (m, 2H), 5.21 (s, 2H). ^{19}F NMR (376 MHz, DMSO- d_6) δ -131.65 (dd, J = 11.9, 9.7 Hz). ^{13}C NMR (214 MHz, DMSO- d_6) δ 163.43, 152.49, 150.02 (d, J = 239.8 Hz), 149.92, 145.01 (d, J = 9.7 Hz), 134.84 (d, J = 13.2 Hz), 133.26, 129.18, 128.16, 122.73, 120.44, 116.08 (d, J = 5.7 Hz), 115.78 (d, J = 3.0 Hz), 114.24, 107.83 (d, J = 22.4 Hz), 93.91.

1-(4-((3-cyanoquinolin-4-yl)oxy)-2-fluorophenyl)-3-(2,4-difluorophenyl)urea (18).—To a solution of 2,4-difluoroaniline (28 mg, 0.21 mmol, 2 eq) in DCM (1 mL) cooled to 0°C using an ice bath was added 1,1'-carbonyldiimidazole (39 mg, 0.24 mmol, 2.25 eq). The reaction mixture was stirred at 0°C for 30 min, monitoring reaction progress by TLC. This was added to a solution of 4-(4-amino-3-fluorophenoxy)quinoline-3-carbonitrile (**102**) (30 mg, 0.11 mmol, 1 eq) in DCM (0.5 mL). The reaction mixture was stirred at 35°C for 4 h, then cooled to rt. The crude reaction mixture was partitioned between EtOAc (15 mL) and water (15 mL). The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 , filtered, concentrated onto Celite, and purified by flash chromatography (0–40% EtOAc in Hexanes on silica gel column) to afford **18** (18.3 mg, 40% yield) as a light yellow solid. ^1H NMR

(400 MHz, DMSO- d_6) δ 9.09 (s, 1H), 9.02 (d, J = 2.4 Hz, 1H), 8.96 (d, J = 2.2 Hz, 1H), 8.23 – 8.14 (m, 3H), 8.10 (td, J = 9.2, 6.1 Hz, 1H), 8.02 (ddd, J = 8.5, 7.0, 1.4 Hz, 1H), 7.77 (ddd, J = 8.2, 6.9, 1.2 Hz, 1H), 7.41 (dd, J = 11.8, 2.8 Hz, 1H), 7.32 (ddd, J = 11.6, 8.9, 2.9 Hz, 1H), 7.11 – 7.01 (m, 2H). ^{19}F NMR (376 MHz, DMSO- d_6) δ -117.74 – -118.49 (m), -124.75 – -124.85 (m), -125.84 (ddt, J = 11.0, 9.3, 1.6 Hz). ^{13}C NMR (214 MHz, DMSO- d_6) δ 162.27, 156.89 (dd, J = 241.5, 11.6 Hz), 152.16, 152.15 (d, J = 244.8 Hz), 152.10 (dd, J = 245.0, 12.2 Hz), 152.09, 150.57 (d, J = 10.3 Hz), 150.29, 133.47, 129.40, 128.51, 124.79 (d, J = 10.5 Hz), 123.83 (dd, J = 10.8, 3.6 Hz), 122.61, 121.86 (dd, J = 9.1, 2.4 Hz), 121.37 (d, J = 2.2 Hz), 120.65, 114.43 (d, J = 3.2 Hz), 114.20, 111.10 (dd, J = 21.7, 3.5 Hz), 106.84 (d, J = 23.4 Hz), 103.84 (dd, J = 27.0, 23.6 Hz), 95.97. HRMS: calcd for $\text{C}_{23}\text{H}_{14}\text{F}_3\text{N}_4\text{O}_2$ [M + H] $^+$ m/z , 435.1069; found m/z , 435.1059.

4-(3-fluoro-4-nitrophenoxy)-6,7-bis(2-methoxyethoxy)quinoline (91).—A suspension of 4-chloro-6,7-bis(2-methoxyethoxy)quinoline (350 mg, 1.12 mmol, 1 eq) and 3-fluoro-4-nitrophenol (**87**) (353 mg, 2.25 mmol, 2 eq) in *o*-xylene (2.8 mL) was stirred at 135°C for 14 h. The reaction mixture was cooled to rt. EtOAc (10 mL) was added and the mixture was stirred for 1 h at rt. The solid formed was collected by filtration, washed with EtOAc and dried. The solid was added to an aqueous NaOH solution (1 M, 15 mL) and stirred for 1 h at rt. The solids were collected by filtration, washed with water, and dried under vacuum to afford **91** (290 mg, 60% yield) as a light yellow solid. ^1H NMR (400 MHz, DMSO- d_6) δ 8.64 (d, J = 5.1 Hz, 1H), 8.27 (t, J = 9.0 Hz, 1H), 7.55 (dd, J = 12.4, 2.6 Hz, 1H), 7.49 (s, 1H), 7.37 (s, 1H), 7.18 (ddd, J = 9.2, 2.7, 1.1 Hz, 1H), 6.98 (d, J = 5.1 Hz, 1H), 4.34 – 4.28 (m, 2H), 4.25 – 4.18 (m, 2H), 3.80 – 3.73 (m, 2H), 3.72 – 3.69 (m, 2H), 3.36 (s, 3H), 3.32 (s, 3H). ^{19}F NMR (376 MHz, DMSO- d_6) δ -114.00 (dd, J = 12.4, 8.8 Hz). ^{13}C NMR (214 MHz, DMSO- d_6) δ 160.92 (d, J = 11.2 Hz), 156.75, 156.27 (d, J = 263.3 Hz), 152.18, 149.19, 149.05, 146.99, 133.13 (d, J = 6.9 Hz), 128.52, 115.87, 115.35 (d, J = 3.0 Hz), 109.27 (d, J = 24.1 Hz), 109.09, 107.24, 100.12, 70.07, 68.17, 68.11, 58.35, 58.30. (1 aliphatic carbon was not observed, probably due to overlap at the extraordinarily intense peak at 70.07 ppm).

4-((6,7-bis(2-methoxyethoxy)quinolin-4-yl)oxy)-2-fluoroaniline (103).—A suspension of 4-(3-fluoro-4-nitrophenoxy)-6,7-bis(2-methoxyethoxy)quinoline (**91**). (274 mg, 0.634 mmol, 1 eq), iron (177 mg, 3.17 mmol, 5 eq), and ammonium chloride (271 mg, 5.07 mmol, 8 eq) in ethanol (1.7 mL) and water (0.55 mL) was heated at 31°C for 4 h. The reaction mixture was cooled to rt and filtered through Celite. The filtrate was concentrated onto Celite, and purified by flash chromatography (0–10% MeOH in DCM on silica gel column) to afford **103** (226 mg, 89% yield) as a light yellow solid. ^1H NMR (400 MHz, DMSO- d_6) δ 8.53 (d, J = 5.6 Hz, 1H), 7.58 (s, 1H), 7.45 (s, 1H), 7.13 – 7.02 (m, 1H), 6.94 – 6.81 (m, 2H), 6.54 (d, J = 5.6 Hz, 1H), 5.32 (br s, 2H), 4.34 – 4.26 (m, 4H), 3.81 – 3.72 (m, 4H), 3.36 (s, 3H), 3.35 (s, 3H). ^{19}F NMR (376 MHz, DMSO- d_6) δ -131.12 – -131.28 (m). ^{13}C NMR (214 MHz, DMSO- d_6) δ 161.91, 152.63, 150.12 (d, J = 240.2 Hz), 148.92, 147.51, 143.91, 142.46 (d, J = 9.1 Hz), 134.74 (d, J = 12.5 Hz), 117.42 (d, J = 3.2 Hz), 116.41 (d, J = 5.9 Hz), 115.02, 109.10 (d, J = 21.3 Hz), 106.82, 102.66, 100.74, 70.10, 70.04, 68.24, 68.19, 58.38, 58.33.

1-(4-((6,7-bis(2-methoxyethoxy)quinolin-4-yl)oxy)-2-fluorophenyl)-3-(2,4-difluorophenyl)urea (19).—To a solution of 2,4-difluoroaniline (32 mg, 0.25 mmol, 2 eq) in DCM (1.2 mL) cooled to 0°C using an ice bath was added 1,1'-carbonyldiimidazole (51 mg, 0.31 mmol, 2.5 eq). The reaction mixture was stirred at 0°C for 30 min. This was added to a solution of 4-((6,7-bis(2-methoxyethoxy)quinolin-4-yl)oxy)-2-fluoroaniline (**103**) (55 mg, 0.13 mmol, 1 eq) in DCM (0.7 mL). The reaction mixture was stirred at 40°C for 2.5 h. Separately, another solution of 2,4-difluoroaniline (22 mg, 0.17 mmol, 1.4 eq) in DCM (0.8 mL) cooled to 0°C was added 1,1'-carbonyldiimidazole (34 mg, 0.21 mmol, 1.7 eq) and stirred at 0°C for 30 min, followed by addition to the former reaction mixture. The reaction mixture was stirred at 40°C for 1 h, then cooled to rt. The crude reaction mixture was partitioned between EtOAc (15 mL) and water (15 mL). The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄, filtered, concentrated onto Celite, and purified by flash chromatography (50–100% EtOAc in Hexanes on silica gel column) to afford **19** (45 mg, 64% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.05 (d, *J* = 2.4 Hz, 1H), 8.99 (d, *J* = 2.3 Hz, 1H), 8.49 (d, *J* = 5.2 Hz, 1H), 8.25 (t, *J* = 9.1 Hz, 1H), 8.13 (td, *J* = 9.2, 6.1 Hz, 1H), 7.52 (s, 1H), 7.43 (s, 1H), 7.40 – 7.26 (m, 2H), 7.18 – 6.98 (m, 2H), 6.54 (d, *J* = 5.2 Hz, 1H), 4.32 – 4.24 (m, 4H), 3.79 – 3.72 (m, 4H), 3.36 (s, 3H), 3.35 (s, 3H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -117.97 (tdd, *J* = 8.9, 6.1, 3.6 Hz), -124.78 – -124.86 (m), -125.75 (t, *J* = 10.6 Hz). ¹³C NMR (214 MHz, DMSO-*d*₆) δ 159.57, 156.87 (dd, *J* = 241.6, 11.8 Hz), 152.22 (d, *J* = 244.5 Hz), 152.12, 152.07 (dd, *J* = 244.8, 12.3 Hz), 151.89, 148.97, 148.66, 148.44 (d, *J* = 10.4 Hz), 146.45, 124.94 (d, *J* = 10.8 Hz), 123.87 (dd, *J* = 10.9, 3.8 Hz), 121.80 (dd, *J* = 9.0, 2.4 Hz), 121.57, 117.08 (d, *J* = 3.1 Hz), 115.15, 111.10 (dd, *J* = 21.8, 3.3 Hz), 109.05, 108.95, 103.84 (dd, *J* = 26.9, 23.6 Hz), 103.39, 100.44, 70.14, 70.12, 68.12, 68.00, 58.36, 58.33. HRMS: calcd for C₂₈H₂₇F₃N₃O₆ [M + H]⁺ *m/z*, 558.1852; found *m/z*, 558.1842.

4-chloroquinoline-6,7-diol (117).—To a solution of 4-chloro-6,7-dimethoxyquinoline (**83**) (1.40 g, 6.26 mmol, 1 eq) in DCM (45 mL) cooled to 0°C using an ice bath was added boron tribromide (4.23 g, 16.9 mL, 2.7 eq) dissolved in DCM (15 mL) dropwise. The solution was stirred at 0°C for 2 h, then allowed to warm slowly to rt and stir for 16 h. Water (70 mL) was added to quench the reaction and the pH was adjusted to pH 6 by addition of solid NaOH. 23 mmol, 1 eq) in DCM (1.1 mL). The reaction mixture was stirred at 40°C for 2.5 h, then cooled to rt. The aqueous layer was extracted with EtOAc (100 mL x 3). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄ and filtered. The solvent was removed in vacuo to afford **117** (520 mg, 42% yield) as a bright yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.33 (s, 2H), 8.48 (d, *J* = 4.9 Hz, 1H), 7.42 (d, *J* = 4.8 Hz, 1H), 7.37 (s, 1H), 7.30 (s, 1H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 151.16, 148.79, 146.65, 145.19, 138.28, 120.84, 118.54, 111.00, 104.51.

8-chloro-[1,3]dioxolo[4,5-*g*]quinoline (118).—To a solution of 4-chloroquinoline-6,7-diol (**117**) (342 mg, 1.75 mmol, 1 eq) in DMF (12 mL) was added potassium carbonate (906 mg, 6.56 mmol, 3.75 eq) and diiodomethane (1.87 g, 6.99 mmol, 4 eq). The reaction mixture was stirred at 60°C for 2 h, then cooled to rt. The crude reaction mixture was partitioned between EtOAc (60 mL) and water (60 mL). The aqueous layer was extracted with EtOAc

(60 mL x 2). The combined organic extracts were washed with water, brine, dried over anhydrous Na₂SO₄, filtered, concentrated onto Celite, and purified by flash chromatography (10–50% EtOAc on Hexanes on silica gel column to afford **118** (193 mg, 53% yield) as a light green solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.59 (d, *J* = 4.9 Hz, 1H), 7.57 (d, *J* = 4.8 Hz, 1H), 7.48 (s, 1H), 7.43 (s, 1H), 6.28 (s, 2H). ¹³C NMR (214 MHz, DMSO-*d*₆) δ 151.36, 149.12, 147.97, 147.13, 139.57, 122.59, 119.91, 105.50, 102.67, 98.74.

8-(3-fluoro-4-nitrophenoxy)-[1,3]dioxolo[4,5-g]quinoline (92).—A suspension of 8-chloro-[1,3]dioxolo[4,5-g]quinoline (**118**) (190 mg, 0.92 mmol, 1 eq) and 3-fluoro-4-nitrophenol (**87**) (288 mg, 1.83 mmol, 2 eq) in *o*-xylene (2.3 mL) was stirred at 135°C for 16 h. The reaction mixture was cooled to rt. EtOAc (20 mL) was added and the mixture was stirred for 1 h at rt. Aqueous NaOH solution (1 M, 20 mL) was added. The aqueous layer was extracted with EtOAc (30 mL x 2). The combined organic extracts were washed with aqueous NaOH (1 M), brine, dried over anhydrous Na₂SO₄, filtered, concentrated onto Celite, and purified by flash chromatography (10–60% EtOAc on Hexanes on silica gel column to afford **92** (228 mg, 76% yield) as a beige solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.64 (d, *J* = 5.1 Hz, 1H), 8.25 (t, *J* = 9.0 Hz, 1H), 7.50 (dd, *J* = 12.4, 2.6 Hz, 1H), 7.45 (s, 1H), 7.36 (s, 1H), 7.13 (ddd, *J* = 9.2, 2.6, 1.1 Hz, 1H), 7.05 (d, *J* = 5.1 Hz, 1H), 6.24 (s, 2H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -113.95 (dd, *J* = 12.7, 8.9 Hz). ¹³C NMR (214 MHz, DMSO-*d*₆) δ 161.04 (d, *J* = 10.9 Hz), 157.09, 156.29 (d, *J* = 263.3 Hz), 151.32, 149.17, 148.33, 148.26, 133.04 (d, *J* = 6.7 Hz), 128.54, 117.49, 114.93 (d, *J* = 3.2 Hz), 108.90 (d, *J* = 24.2 Hz), 108.18, 105.40, 102.41, 96.42.

4-([1,3]dioxolo[4,5-g]quinolin-8-yloxy)-2-fluoroaniline (104).—A suspension of 8-(3-fluoro-4-nitrophenoxy)-[1,3]dioxolo[4,5-g]quinoline (**92**) (225 mg, 0.68 mmol, 1 eq), iron (189 mg, 3.4 mmol, 5 eq), and ammonium chloride (290 mg, 5.4 mmol, 8 eq) in ethanol (1.8 mL) and water (0.6 mL) was heated at 60°C for 3 h. The reaction mixture was cooled to rt and filtered through Celite. Solvent was removed from the filtrate and the residue was partitioned between DCM (30 mL) and aqueous NaOH solution (1 M, 30 mL). The aqueous layer was extracted with DCM (2 x 30 mL). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄, filtered, concentrated onto Celite, and purified by flash chromatography (0–5% MeOH in DCM on silica gel column) to afford **104** (190 mg, 94% yield) as a beige solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.43 (d, *J* = 5.3 Hz, 1H), 7.51 (s, 1H), 7.34 (s, 1H), 7.03 (dd, *J* = 11.8, 2.5 Hz, 1H), 6.89 – 6.75 (m, 2H), 6.46 (d, *J* = 5.2 Hz, 1H), 6.22 (s, 2H), 5.19 (s, 2H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -131.34 (dd, *J* = 11.8, 9.5 Hz). ¹³C NMR (214 MHz, DMSO-*d*₆) δ 160.98, 150.82, 150.16 (d, *J* = 239.8 Hz), 149.02, 147.51, 147.43, 142.89 (d, *J* = 9.3 Hz), 134.44 (d, *J* = 12.7 Hz), 117.33 (d, *J* = 3.0 Hz), 116.41 (d, *J* = 5.8 Hz), 116.38, 109.02 (d, *J* = 21.0 Hz), 105.12, 103.04, 102.08, 96.77.

1-(4-([1,3]dioxolo[4,5-g]quinolin-8-yloxy)-2-fluorophenyl)-3-(2,4-difluorophenyl)urea (20).—To a solution of 1,1'-carbonyldiimidazole (65 mg, 0.40 mmol, 3 eq) in DCM (0.6 mL) cooled to 0°C using an ice bath was added a solution of 2,4-difluoroaniline (52 mg, 0.40 mmol, 3 eq) in DCM (0.6 mL) dropwise. The reaction mixture was stirred at 0°C for 30 min, monitoring reaction progress by TLC. This was added to a solution of 4-([1,3]dioxolo[4,5-g]quinolin-8-yloxy)-2-

fluoroaniline (**104**) (40 mg, 0.13 mmol, 1 eq) in DCM (0.7 mL). The reaction mixture was stirred at 40°C for 3 h, then cooled to rt. The crude reaction mixture was partitioned between EtOAc (15 mL) and water (15 mL). The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄, filtered, concentrated onto Celite, and purified by flash chromatography (20–80% EtOAc in Hexanes on silica gel column) to afford **20** (41 mg, 67% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.05 (s, 1H), 9.00 (s, 1H), 8.49 (d, *J* = 5.2 Hz, 1H), 8.23 (t, *J* = 9.1 Hz, 1H), 8.12 (td, *J* = 9.2, 6.1 Hz, 1H), 7.51 (s, 1H), 7.38 (s, 1H), 7.41 – 7.23 (m, 2H), 7.12 – 6.91 (m, 2H), 6.59 (d, *J* = 5.3 Hz, 1H), 6.24 (s, 2H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ –117.98 (tdd, *J* = 8.9, 6.1, 3.7 Hz), –124.80 (t, *J* = 9.8 Hz), –125.67 (t, *J* = 10.4 Hz). ¹³C NMR (214 MHz, DMSO-*d*₆) δ 159.99, 156.86 (dd, *J* = 241.8, 11.5 Hz), 152.26 (d, *J* = 244.6 Hz), 152.13, 152.07 (dd, *J* = 244.9, 12.1 Hz), 150.97, 149.03, 148.54 (d, *J* = 10.1 Hz), 147.72, 147.65, 124.89 (d, *J* = 10.5 Hz), 123.88 (dd, *J* = 10.9, 3.4 Hz), 121.80 (dd, *J* = 8.7, 2.4 Hz), 121.64 (d, *J* = 2.6 Hz), 116.84 (d, *J* = 2.9 Hz), 116.62, 111.09 (dd, *J* = 21.4, 3.6 Hz), 108.81 (d, *J* = 22.0 Hz), 105.19, 104.06, 103.83 (dd, *J* = 26.8, 23.4 Hz), 102.17, 96.70. HRMS: calcd for C₂₃H₁₅F₃N₃O₄ [M + H]⁺ *m/z*, 454.1015; found *m/z*, 454.1004.

9-chloro-2,3-dihydro-[1,4]dioxino[2,3-g]quinoline (119).—To a solution of 4-chloroquinoline-6,7-diol (**117**) (311 mg, 1.59 mmol, 1 eq) in DMF (17 mL) was added potassium carbonate (1.21 g, 8.75 mmol, 5.5 eq) and 1,2-dibromoethane (2.24 g, 11.9 mmol, 7.5 eq). The reaction mixture was stirred at 60°C for 2 h, then cooled to rt. The crude reaction mixture was partitioned between EtOAc (100 mL) and water (100 mL). The aqueous layer was extracted with EtOAc (100 mL x 2). The combined organic extracts were washed with water, brine, dried over anhydrous Na₂SO₄, filtered, concentrated onto Celite, and purified by flash chromatography (10–50% EtOAc on Hexanes on silica gel column) to afford **119** (234 mg, 66% yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 8.58 (d, *J* = 4.7 Hz, 1H), 7.62 (s, 1H), 7.55 (s, 1H), 7.32 (d, *J* = 4.7 Hz, 1H), 4.40 (s, 4H). ¹³C NMR (214 MHz, CDCl₃) δ 148.43, 147.69, 145.78, 145.41, 140.88, 122.77, 119.69, 114.78, 109.13, 64.56, 64.56.

9-(3-fluoro-4-nitrophenoxy)-2,3-dihydro-[1,4]dioxino[2,3-g]quinoline (93).—9-chloro-2,3-dihydro-[1,4]dioxino[2,3-g]quinoline (**119**) (234 mg, 1.06 mmol, 1 eq) and 3-fluoro-4-nitrophenol (**87**) (333 mg, 2.12 mmol, 2 eq) in *o*-xylene (2.6 mL) was stirred at 135°C for 16 h. The reaction mixture was cooled to rt. EtOAc (20 mL) was added and the mixture was stirred for 1 h at rt. Aqueous NaOH solution (1 M, 20 mL) was added. The aqueous layer was extracted with EtOAc (30 mL x 2). The combined organic extracts were washed with aqueous NaOH (1 M), brine, dried over anhydrous Na₂SO₄, filtered, concentrated onto Celite, and purified by flash chromatography (10–60% EtOAc on Hexanes on silica gel column) to afford **93** (78 mg, 22% yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.65 (d, *J* = 5.0 Hz, 1H), 8.25 (t, *J* = 9.0 Hz, 1H), 7.52 (dd, *J* = 12.4, 2.6 Hz, 1H), 7.49 (s, 1H), 7.39 (s, 1H), 7.14 (ddd, *J* = 9.2, 2.6, 1.2 Hz, 1H), 6.99 (d, *J* = 5.0 Hz, 1H), 4.43 – 4.36 (m, 4H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ –113.92 (dd, *J* = 12.4, 8.8 Hz). ¹³C NMR (214 MHz, DMSO-*d*₆) δ 160.95 (d, *J* = 11.3 Hz), 156.72, 156.28 (d, *J* = 263.6 Hz), 149.76, 147.56, 146.34, 144.72, 133.11 (d, *J* = 6.9 Hz), 128.56, 116.59, 115.04 (d, *J* = 2.9 Hz), 113.69, 109.01 (d, *J* = 24.1 Hz), 107.44, 105.39, 64.30, 64.25.

4-((2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-9-yl)oxy)-2-fluoroaniline (105).—A suspension of 9-(3-fluoro-4-nitrophenoxy)-2,3-dihydro-[1,4]dioxino[2,3-g]quinoline (**93**) (73 mg, 0.21 mmol, 1 eq), iron (59 mg, 1.1 mmol, 5 eq), and ammonium chloride (91 mg, 1.7 mmol, 8 eq) in ethanol (0.6 mL) and water (0.2 mL) was heated at 45°C for 4 h. The reaction mixture was cooled to rt and filtered through Celite. Solvent was removed from the filtrate and the residue was partitioned between DCM (30 mL) and aqueous NaOH solution (1 M, 30 mL). The aqueous layer was extracted with DCM (2 × 30 mL). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄, filtered, concentrated onto Celite, and purified by flash chromatography (0–5% MeOH in DCM on silica gel column) to afford **105** (47 mg, 71% yield) as a light purple solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.44 (d, *J* = 5.1 Hz, 1H), 7.55 (s, 1H), 7.38 (s, 1H), 7.03 (dd, *J* = 11.8, 2.5 Hz, 1H), 6.91 – 6.76 (m, 2H), 6.39 (d, *J* = 5.2 Hz, 1H), 5.19 (s, 2H), 4.42 – 4.37 (m, 4H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ –131.36 (dd, *J* = 11.9, 9.3 Hz). ¹³C NMR (214 MHz, DMSO-*d*₆) δ 160.61, 150.16 (d, *J* = 239.8 Hz), 149.67, 147.11, 145.71, 143.94, 142.84 (d, *J* = 9.3 Hz), 134.45 (d, *J* = 13.1 Hz), 117.33 (d, *J* = 3.0 Hz), 116.40 (d, *J* = 5.5 Hz), 115.88, 113.28, 109.02 (d, *J* = 21.0 Hz), 105.77, 102.21, 64.31, 64.20.

1-(2,4-difluorophenyl)-3-(4-((2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-9-yl)oxy)-2-fluorophenyl)urea (21).—To a solution of 1,1'-carbonyldiimidazole (65 mg, 0.40 mmol, 3 eq) in DCM (0.6 mL) cooled to 0°C using an ice bath was added a solution of 2,4-difluoroaniline (52 mg, 0.40 mmol, 3 eq) in DCM (0.6 mL) dropwise. The reaction mixture was stirred at 0°C for 30 min, monitoring reaction progress by TLC. This was added to a solution of 4-((2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-9-yl)oxy)-2-fluoroaniline (**105**) (43 mg, 0.13 mmol, 1 eq) in DCM (0.7 mL). The reaction mixture was stirred at 40°C for 3 h, then cooled to rt. The crude reaction mixture was partitioned between EtOAc (15 mL) and water (15 mL). The aqueous layer was extracted with EtOAc (20 mL × 2). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄, filtered, concentrated onto Celite, and purified by flash chromatography (20–80% EtOAc in Hexanes on silica gel column) to afford **21** (39 mg, 62% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.06 (d, *J* = 2.2 Hz, 1H), 9.00 (d, *J* = 2.1 Hz, 1H), 8.49 (d, *J* = 5.1 Hz, 1H), 8.23 (t, *J* = 9.1 Hz, 1H), 8.12 (td, *J* = 9.2, 6.1 Hz, 1H), 7.55 (s, 1H), 7.41 (s, 1H), 7.38 – 7.28 (m, 2H), 7.10 – 7.02 (m, 2H), 6.52 (d, *J* = 5.1 Hz, 1H), 4.42 – 4.38 (m, 4H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ –117.98 (tdd, *J* = 8.9, 6.1, 3.6 Hz), –124.80 (t, *J* = 10.0 Hz), –125.67 (t, *J* = 10.7 Hz). ¹³C NMR (214 MHz, DMSO-*d*₆) δ 159.62, 156.86 (dd, *J* = 241.8, 11.6 Hz), 152.25 (d, *J* = 244.5 Hz), 152.13, 152.07 (dd, *J* = 244.9, 12.2 Hz), 149.66, 148.48 (d, *J* = 10.3 Hz), 147.24, 145.87, 144.14, 124.92 (d, *J* = 10.4 Hz), 123.88 (dd, *J* = 10.8, 3.5 Hz), 121.81 (dd, *J* = 8.9, 2.6 Hz), 121.63 (d, *J* = 2.4 Hz), 116.88 (d, *J* = 3.1 Hz), 116.02, 113.38, 111.09 (dd, *J* = 21.6, 3.6 Hz), 108.84 (d, *J* = 21.9 Hz), 105.70, 103.83 (dd, *J* = 27.1, 23.5 Hz), 103.23, 64.31, 64.22. HRMS: calcd for C₂₄H₁₇F₃N₃O₄ [M + H]⁺ m/z, 468.1171; found m/z, 468.1160.

2-fluoro-4-(quinazolin-4-yloxy)aniline (106).—To a solution of 4-chloroquinazoline (350 mg, 2.13 mmol, 1 eq) and 4-amino-3-fluorophenol (**85**) (378 mg, 2.98 mmol, 1.4 eq) in DMF (8 mL) cooled to 0°C was added potassium tert-butoxide (334 mg, 2.98 mmol, 1.4 eq). The reaction mixture was stirred at 110°C for 4 h, then cooled to rt. The reaction

mixture was partitioned between DCM (50 mL) and water (50 mL). The aqueous layer was extracted with DCM (50 mL x 2). The combined organic extracts were washed with water, brine, dried over anhydrous Na₂SO₄, filtered, concentrated onto Celite, and purified by flash chromatography (0–6% MeOH in DCM on silica gel column) to afford **106** (58 mg, 11% yield) as a light brown solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.72 (s, 1H), 8.33 (ddd, *J* = 8.2, 1.4, 0.7 Hz, 1H), 8.05 – 7.95 (m, 2H), 7.76 (ddd, *J* = 8.2, 6.7, 1.5 Hz, 1H), 7.11 (dd, *J* = 11.9, 2.4 Hz, 1H), 6.95 – 6.78 (m, 2H), 5.15 (s, 2H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ –132.56 (dd, *J* = 11.9, 9.3 Hz).

1-(2,4-difluorophenyl)-3-(2-fluoro-4-(quinazolin-4-yloxy)phenyl)urea (23).—To a solution of 2-fluoro-4-(quinazolin-4-yloxy)aniline (**106**) (50 mg, 0.20 mmol, 1 eq) in ethanol (0.5 mL) cooled to 0°C using an ice bath was added 2,4-difluoro-1-isocyanatobenzene (30 mg, 0.20 mmol, 1 eq) dropwise. The reaction mixture was warmed to rt and stirred at rt for 30 min. The reaction mixture was concentrated onto Celite and purified by flash chromatography (0–10% MeOH in EtOAc on silica gel column then 0–100% EtOAc in Hexanes on silica gel) to afford **23** (13.7 mg, 17% yield) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.04 (s, 1H), 9.00 (s, 1H), 8.76 (s, 1H), 8.40 – 8.36 (m, 1H), 8.21 (t, *J* = 9.5 Hz, 1H), 8.16 – 8.11 (m, 1H), 8.10 – 7.99 (m, 2H), 7.80 (q, *J* = 6.4 Hz, 1H), 7.51 – 7.40 (m, 1H), 7.40 – 7.28 (m, 1H), 7.24 – 7.14 (m, 1H), 7.14 – 7.02 (m, 1H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ –118.43 – –118.57 (m), –125.31 (t, *J* = 10.7 Hz), –127.16 – –127.26 (m). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 166.44, 156.91 (dd, *J* = 241.5, 11.8 Hz), 153.88, 152.21, 152.12 (dd, *J* = 244.9, 12.3 Hz), 152.00 (d, *J* = 243.6 Hz), 151.19, 146.59 (d, *J* = 10.7 Hz), 134.79, 128.23, 127.58, 125.20 (d, *J* = 10.7 Hz), 123.92 (dd, *J* = 10.8, 3.5 Hz), 123.44, 121.86 (dd, *J* = 9.0, 3.1 Hz), 121.14, 118.19 (d, *J* = 3.3 Hz), 115.54, 111.15 (dd, *J* = 21.5, 3.6 Hz), 110.23 (d, *J* = 22.3 Hz), 103.88 (dd, *J* = 27.0, 23.7 Hz). HRMS: calcd for C₂₁H₁₄F₃N₄O₂ [M + H]⁺ m/z, 411.1069; found m/z, 411.1060.

4-chlorocinnoline (124).—To a suspension of cinnolin-4-ol (**123**) (200 mg, 1.37 mmol, 1 eq) in anhydrous THF (14 mL) was added phosphoryl trichloride (629 mg, 4.11 mmol, 3 eq). The reaction mixture was refluxed at 66°C for 1 h, then cooled to 0°C using an ice bath. Saturated NaHCO₃ solution (24 mL) was added dropwise and the reaction mixture was allowed to warm to rt and stirred at rt for 1 h. The reaction mixture was partitioned between DCM (50 mL) and water (50 mL). The aqueous layer was extracted with DCM (50 mL x 2). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄, filtered, concentrated in vacuo to afford **124** (193 mg, 86% yield) as a brown solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.60 (s, 1H), 8.62 – 8.53 (m, 1H), 8.28 – 8.19 (m, 1H), 8.14 – 8.02 (m, 2H).

4-(cinnolin-4-yloxy)-2-fluoroaniline (107).—To a solution of 4-chlorocinnoline (**124**) (190 mg, 1.15 mmol, 1 eq) and 4-amino-3-fluorophenol (**85**) (205 mg, 1.62 mmol, 1.4 eq) in DMF (3.8 mL) cooled to 0°C was added potassium tert-butoxide (181 mg, 1.62 mmol, 1.4 eq). The reaction mixture was stirred at 110°C for 4 h, then cooled to rt. Water (60 mL) was added and the solid formed was collected by filtration, washed with water and dried. The crude material was dissolved in a mixture of DCM and MeOH, concentrated onto Celite and purified by flash chromatography (0–8% MeOH in DCM on silica gel column) to afford

107 (100 mg, 34% yield) as a yellow-orange solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.64 (s, 1H), 8.46 (dt, $J = 8.5, 1.0$ Hz, 1H), 8.33 (ddd, $J = 8.3, 1.4, 0.7$ Hz, 1H), 8.01 (ddd, $J = 8.5, 6.8, 1.4$ Hz, 1H), 7.92 (ddd, $J = 8.2, 6.9, 1.2$ Hz, 1H), 7.20 (dd, $J = 11.8, 2.5$ Hz, 1H), 6.99 – 6.85 (m, 2H), 5.29 (s, 2H). ^{19}F NMR (376 MHz, $\text{DMSO}-d_6$) δ –130.95 (dd, $J = 12.0, 9.6$ Hz). ^{13}C NMR (214 MHz, $\text{DMSO}-d_6$) δ 152.94, 150.53, 150.22 (d, $J = 240.4$ Hz), 142.20 (d, $J = 9.5$ Hz), 135.08 (d, $J = 12.9$ Hz), 131.72, 131.45, 130.89, 128.45, 120.75, 117.85, 117.16 (d, $J = 3.0$ Hz), 116.58 (d, $J = 5.6$ Hz), 108.93 (d, $J = 21.3$ Hz).

1-(4-(cinnolin-4-yloxy)-2-fluorophenyl)-3-(2,4-difluorophenyl)urea (24).—To a solution of 4-(cinnolin-4-yloxy)-2-fluoroaniline (**107**) (98 mg, 0.38 mmol, 1 eq) in ethanol (1 mL) cooled to 0°C using an ice bath was added 2,4-difluoro-1-isocyanatobenzene (60 mg, 0.38 mmol, 1 eq) dropwise. The reaction mixture was warmed to rt and stirred at rt for 1 h. The reaction mixture was concentrated onto Celite and purified by flash chromatography (0–10% MeOH in DCM on silica gel column then 0–10% MeOH in EtOAc on silica gel) to afford **24** (10.1 mg, 6% yield) as a beige solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.11 (d, $J = 2.4$ Hz, 1H), 9.03 (d, $J = 2.2$ Hz, 1H), 8.78 (s, 1H), 8.49 (dt, $J = 8.6, 1.0$ Hz, 1H), 8.34 (d, $J = 7.9$ Hz, 1H), 8.30 (t, $J = 9.1$ Hz, 1H), 8.13 (td, $J = 9.2, 6.1$ Hz, 1H), 8.04 (ddd, $J = 8.5, 6.9, 1.4$ Hz, 1H), 7.94 (ddd, $J = 8.2, 6.8, 1.2$ Hz, 1H), 7.50 (dd, $J = 11.7, 2.7$ Hz, 1H), 7.34 (ddd, $J = 11.7, 8.9, 2.9$ Hz, 1H), 7.21 (ddd, $J = 9.3, 2.5, 1.3$ Hz, 1H), 7.07 (tq, $J = 8.7, 1.8$ Hz, 1H). ^{19}F NMR (376 MHz, $\text{DMSO}-d_6$) δ –117.90 (tdd, $J = 8.9, 6.1, 3.7$ Hz), –124.72 (t, $J = 10.6$ Hz), –125.27 (t, $J = 10.6$ Hz). ^{13}C NMR (101 MHz, $\text{DMSO}-d_6$) δ 156.90 (dd, $J = 241.3, 11.9$ Hz), 152.21 (d, $J = 245.1$ Hz), 152.12, 152.11 (dd, $J = 244.8, 12.8$ Hz), 152.11, 150.69, 147.64 (d, $J = 10.6$ Hz), 131.97, 131.74, 131.05, 128.53, 125.62 (d, $J = 10.7$ Hz), 123.84 (dd, $J = 10.8, 3.6$ Hz), 121.86 (dd, $J = 9.1, 2.9$ Hz), 121.58 (d, $J = 3.1$ Hz), 120.65, 117.93, 116.85 (d, $J = 3.3$ Hz), 111.12 (dd, $J = 21.9, 3.7$ Hz), 108.90 (d, $J = 22.5$ Hz), 103.86 (dd, $J = 26.8, 23.6$ Hz). HRMS: calcd for $\text{C}_{21}\text{H}_{14}\text{F}_3\text{N}_4\text{O}_2$ [$\text{M} + \text{H}$] $^+$ m/z , 411.1069; found m/z , 411.1058.

7-(3-fluoro-4-nitrophenoxy)thieno[3,2-b]pyridine hydrochloride (94).—A suspension of 7-chlorothieno[3,2-b]pyridine (300 mg, 1.77 mmol, 1 eq) and 3-fluoro-4-nitrophenol (**87**) (556 mg, 3.54 mmol, 2 eq) in *o*-xylene (4 mL) was stirred at 135°C for 16 h. The reaction mixture was cooled to rt. EtOAc (15 mL) was added and the mixture was stirred for 1 h at rt. The solid formed was collected by filtration, washed with EtOAc and dried. The solid was added to an aqueous NaOH solution (1 M, 20 mL) and stirred for 1 h at rt. The solids were collected by filtration, acidified with HCl solution (2 M, 20 mL). The solids formed were washed with water, then EtOAc and dried under vacuum to afford **94** (104 mg, 18% yield) as a brown solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.77 (dd, $J = 5.8, 1.1$ Hz, 1H), 8.37 (dd, $J = 5.5, 1.5$ Hz, 1H), 8.33 (t, $J = 8.9$ Hz, 1H), 7.77 – 7.71 (m, 2H), 7.37 (ddd, $J = 9.0, 2.5, 1.2$ Hz, 1H), 7.19 (d, $J = 5.7$ Hz, 1H). ^{19}F NMR (376 MHz, $\text{DMSO}-d_6$) δ –113.73 (dd, $J = 12.2, 8.8$ Hz).

2-fluoro-4-(thieno[3,2-b]pyridin-7-yloxy)aniline (108).—A suspension of 7-(3-fluoro-4-nitrophenoxy)thieno[3,2-b]pyridine hydrochloride (**94**) (100 mg, 0.306 mmol, 1 eq), iron (85.5 mg, 1.53 mmol, 5 eq), and ammonium chloride (131 mg, 2.45 mmol, 8 eq) in ethanol (2 mL) and water (0.65 mL) was heated at 78°C for 5 h. The reaction mixture

was cooled to rt and filtered through Celite. Solvent was removed from the filtrate and the residue was partitioned between DCM (30 mL) and aqueous NaOH solution (1M, 30 mL). The aqueous layer was extracted with DCM (2 × 30 mL). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄, filtered, concentrated onto Celite, and purified by flash chromatography (0–5% MeOH in DCM on silica gel column) to afford **108** (63 mg, 79% yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.48 (d, *J* = 5.4 Hz, 1H), 8.12 (d, *J* = 5.4 Hz, 1H), 7.57 (d, *J* = 5.4 Hz, 1H), 7.14 – 7.02 (m, 1H), 6.91 – 6.79 (m, 2H), 6.59 (d, *J* = 5.4 Hz, 1H), 5.24 (s, 2H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ –131.27 – –131.39 (m).

1-(2,4-difluorophenyl)-3-(2-fluoro-4-(thieno[3,2-b]pyridin-7-yloxy)phenyl)urea (25).—To a solution of 2-fluoro-4-(thieno[3,2-b]pyridin-7-yloxy)aniline (**108**) (60 mg, 0.23 mmol, 1 eq) in ethanol (0.6 mL) cooled to 0°C using an ice bath was added 2,4-difluoro-1-isocyanatobenzene (36 mg, 0.23 mmol, 1 eq) dropwise. The reaction mixture was warmed to rt and stirred at rt for 45 min. The reaction mixture was concentrated onto Celite and purified by flash chromatography (0–10% MeOH in DCM on silica gel column) to afford **25** (55 mg, 58% yield) as a light yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.09 (d, *J* = 2.4 Hz, 1H), 9.02 (d, *J* = 2.3 Hz, 1H), 8.54 (d, *J* = 5.4 Hz, 1H), 8.25 (t, *J* = 9.1 Hz, 1H), 8.17 (d, *J* = 5.4 Hz, 1H), 8.13 (td, *J* = 9.2, 6.1 Hz, 1H), 7.61 (d, *J* = 5.4 Hz, 1H), 7.41 (dd, *J* = 11.7, 2.7 Hz, 1H), 7.33 (ddd, *J* = 11.6, 8.9, 2.9 Hz, 1H), 7.14 (ddd, *J* = 9.1, 2.8, 1.3 Hz, 1H), 7.10 – 7.03 (m, 1H), 6.72 (d, *J* = 5.4 Hz, 1H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ –117.26 – –118.41 (m), –124.76 (t, *J* = 10.4 Hz), –125.61 (t, *J* = 10.5 Hz). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 159.59, 158.64, 156.88 (dd, *J* = 241.5, 11.5 Hz), 152.10, 152.08 (dd, *J* = 245.0, 12.2 Hz), 152.07 (d, *J* = 244.8 Hz), 149.38, 147.46 (d, *J* = 10.3 Hz), 132.29, 125.44 (d, *J* = 10.6 Hz), 124.82, 123.84 (dd, *J* = 10.7, 3.5 Hz), 121.81 (dd, *J* = 9.0, 2.9 Hz), 121.51, 121.42 (d, *J* = 2.9 Hz), 117.13 (d, *J* = 3.4 Hz), 111.11 (dd, *J* = 21.6, 3.5 Hz), 109.09 (d, *J* = 22.2 Hz), 104.30, 104.14 – 103.53 (m). HRMS: calcd for C₂₀H₁₃F₃N₃O₂S [M + H]⁺ m/z, 416.0681; found m/z, 416.0671.

4-(3-fluoro-4-nitrophenoxy)thieno[2,3-b]pyridine (95).—A suspension of 4-chlorothieno[2,3-b]pyridine (350 mg, 2.06 mmol, 1 eq) and 3-fluoro-4-nitrophenol (**87**) (583 mg, 3.71 mmol, 1.8 eq) in *o*-xylene (4.5 mL) was stirred at 135°C for 60 h. The reaction mixture was cooled to rt and partitioned between EtOAc (50 mL) and aqueous NaOH solution (1 M, 50 mL). The aqueous layer was extracted with EtOAc (50 mL x 2). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄, filtered, concentrated into celite, and purified by flash chromatography (0–35% EtOAc in Hexanes on silica gel column) to afford **95** (267 mg, 45% yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.57 (d, *J* = 5.3 Hz, 1H), 8.27 (t, *J* = 9.0 Hz, 1H), 7.93 (d, *J* = 6.1 Hz, 1H), 7.58 (dd, *J* = 12.4, 2.6 Hz, 1H), 7.40 (d, *J* = 6.1 Hz, 1H), 7.21 (ddd, *J* = 9.2, 2.6, 1.2 Hz, 1H), 7.12 (d, *J* = 5.3 Hz, 1H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ –113.86 (dd, *J* = 12.3, 8.8 Hz). ¹³C NMR (214 MHz, DMSO-*d*₆) δ 163.74, 160.32 (d, *J* = 10.9 Hz), 156.47, 156.26 (d, *J* = 263.7 Hz), 148.79, 128.57, 128.15, 124.24, 117.82, 115.47 (d, *J* = 3.2 Hz), 109.39 (d, *J* = 24.1 Hz), 108.53. (missing aromatic carbon is probably due to overlap at the intense peak at 128.15 ppm.)

2-fluoro-4-(thieno[2,3-b]pyridin-4-yloxy)aniline (109).—A suspension of 4-(3-fluoro-4-nitrophenoxy)thieno[2,3-b]pyridine (**95**) (264 mg, 0.909 mmol, 1 eq), iron (254 mg, 4.55 mmol, 5 eq), and ammonium chloride (389 mg, 7.28 mmol, 8 eq) in ethanol (2.7 mL) and water (0.9 mL) was heated at 31°C for 4 h. The reaction mixture was cooled to rt and filtered through Celite. The filtrate was concentrated onto Celite, and purified by flash chromatography (0–40% EtOAc in Hexanes on silica gel column) to afford **109** (184 mg, 78% yield) as an orange solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.37 (d, *J* = 5.5 Hz, 1H), 7.82 (d, *J* = 6.0 Hz, 1H), 7.50 (d, *J* = 6.0 Hz, 1H), 7.11 – 7.03 (m, 1H), 6.92 – 6.78 (m, 2H), 6.56 (d, *J* = 5.4 Hz, 1H), 5.21 (s, 2H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ –131.24 (dd, *J* = 11.9, 8.2 Hz). ¹³C NMR (214 MHz, DMSO-*d*₆) δ 163.04, 160.39, 150.13 (d, *J* = 239.8 Hz), 148.57, 142.57 (d, *J* = 9.3 Hz), 134.62 (d, *J* = 12.6 Hz), 126.30, 122.94, 118.15, 117.28 (d, *J* = 3.3 Hz), 116.41 (d, *J* = 6.0 Hz), 108.98 (d, *J* = 21.0 Hz), 104.27.

1-(2,4-difluorophenyl)-3-(2-fluoro-4-(thieno[2,3-b]pyridin-4-yloxy)phenyl)urea (27).—To a solution of 2,4-difluoroaniline (39 mg, 0.30 mmol, 1.3 eq) in DMSO (1.2 mL) was added 1,1'-carbonyldiimidazole (56 mg, 0.35 mmol, 1.5 eq). The reaction mixture was stirred at rt for 2 h, monitoring reaction progress by TLC. This was added to a solution of 2-fluoro-4-(thieno[2,3-b]pyridin-4-yloxy)aniline (**109**) (60 mg, 0.23 mmol, 1 eq) in DMSO (1.2 mL). The reaction mixture was stirred at 40°C for 3 h, then cooled to rt. The crude reaction mixture was partitioned between EtOAc (15 mL) and water (15 mL). The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄, filtered, concentrated onto Celite, and purified by flash chromatography (0–40% EtOAc in Hexanes on silica gel column) to afford **27** (23 mg, 24% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.06 (d, *J* = 2.5 Hz, 1H), 8.99 (d, *J* = 2.3 Hz, 1H), 8.43 (d, *J* = 5.4 Hz, 1H), 8.25 (t, *J* = 9.1 Hz, 1H), 8.13 (td, *J* = 9.2, 6.1 Hz, 1H), 7.86 (d, *J* = 6.0 Hz, 1H), 7.51 (d, *J* = 6.0 Hz, 1H), 7.45 – 7.25 (m, 2H), 7.19 – 7.03 (m, 2H), 6.69 (d, *J* = 5.5 Hz, 1H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ –117.70 – –118.08 (m), –124.82 (t, *J* = 10.8 Hz), –125.60 (t, *J* = 10.6 Hz). ¹³C NMR (214 MHz, DMSO-*d*₆) δ 163.22, 159.39, 158.07 – 156.03 (m), 152.19 (d, *J* = 244.9 Hz), 152.10, 152.06 (dd, *J* = 245.0, 12.3 Hz), 148.62, 148.08 (d, *J* = 10.3 Hz), 126.77, 125.14 (d, *J* = 10.7 Hz), 123.85 (dd, *J* = 10.8, 3.3 Hz), 123.21, 121.79 (dd, *J* = 9.0, 2.3 Hz), 121.56 (d, *J* = 2.8 Hz), 118.06, 116.92 (d, *J* = 3.1 Hz), 111.11 (dd, *J* = 21.4, 3.4 Hz), 108.89 (d, *J* = 22.0 Hz), 105.08, 103.84 (dd, *J* = 27.1, 23.4 Hz). HRMS: calcd for C₂₀H₁₃F₃N₃O₂S [M + H]⁺ m/z, 416.0681; found m/z, 416.0670.

thieno[2,3-d]pyrimidin-4(1H)-one (126).—A solution of methyl 2-aminothiophene-3-carboxylate (**125**) (1.0 g, 6.3 mmol, 1 eq) in formamide (5 mL, 127 mmol, 20 eq) was stirred at 160°C for 24 h, then cooled to rt. Water was added, and the solid formed was collected by filtration, washed with water, and dried *in vacuo* to afford **126** (507 mg, 52% yield) as a brown solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.12 (s, 1H), 7.58 (d, *J* = 5.8 Hz, 1H), 7.39 (d, *J* = 5.8 Hz, 1H). ¹³C NMR (214 MHz, DMSO-*d*₆) δ 164.26, 157.54, 145.63, 124.64, 123.88, 121.66.

4-chlorothieno[2,3-d]pyrimidine (127).—A solution of thieno[2,3-d]pyrimidin-4(1H)-one (**126**) (627 mg, 4.123 mmol) in phosphoryl trichloride (6 mL) was refluxed at 100°C

for 2 h. The reaction mixture was cooled to rt and an ice-cold saturated aqueous NaHCO₃ solution was added dropwise. The solid was collected by filtration, washed with water and dried. The crude material was dissolved in a mixture of DCM and MeOH, concentrated onto Celite and purified by flash chromatography (0–25% EtOAc in Hexanes on silica gel column) to afford **127** (349 mg, 50% yield) as an off-white solid. ¹H NMR (400 MHz, CDCl₃) δ 8.87 (s, 1H), 7.64 (d, *J* = 6.1 Hz, 1H), 7.46 (d, *J* = 6.1 Hz, 1H).

2-fluoro-4-(thieno[2,3-d]pyrimidin-4-yloxy)aniline (110).—To a solution of 4-chlorothieno[2,3-d]pyrimidine (**127**) (340 mg, 1.99 mmol, 1 eq) and 4-amino-3-fluorophenol (**85**) (355 mg, 2.79 mmol, 1.4 eq) in DMF (1.5 mL) cooled to 0°C was added a solution of potassium tert-butoxide (313 mg, 2.79 mmol, 1.4 eq) in DMF (5 mL) dropwise. The reaction mixture was stirred at 110°C for 4 h, then cooled to rt. Water (100 mL) was added. The solid formed was collected by filtration, washed with water and dried. The crude material was dissolved in a mixture of DCM and MeOH, concentrated onto Celite and purified by flash chromatography (0–5% MeOH in DCM on silica gel column then 0–60% EtOAc in Hexanes on silica gel column) to afford **110** (238 mg, 46% yield) as a light brown solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.61 (s, 1H), 7.94 (d, *J* = 5.9 Hz, 1H), 7.61 (d, *J* = 5.9 Hz, 1H), 7.17 – 7.04 (m, 1H), 6.88 – 6.75 (m, 2H), 5.14 (s, 2H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ –132.50 (dd, *J* = 11.9, 8.6 Hz). ¹³C NMR (214 MHz, DMSO-*d*₆) δ 168.88, 163.59, 153.05, 149.95 (d, *J* = 238.9 Hz), 141.34 (d, *J* = 9.8 Hz), 134.32 (d, *J* = 12.9 Hz), 127.22, 118.55, 118.54, 117.93 (d, *J* = 3.1 Hz), 115.90 (d, *J* = 5.4 Hz), 109.80 (d, *J* = 21.6 Hz).

1-(2,4-difluorophenyl)-3-(2-fluoro-4-(thieno[2,3-d]pyrimidin-4-yloxy)phenyl)urea (28).—To a solution of 2-fluoro-4-(thieno[2,3-d]pyrimidin-4-yloxy)aniline (**110**) (92 mg, 0.352 mmol, 1 eq) in ethanol (1.0 mL) cooled to 0°C using an ice bath was added 2,4-difluoro-1-isocyanatobenzene (55 mg, 0.35 mmol, 1 eq) dropwise. The reaction mixture was warmed to rt and stirred at rt for 1.5 h. 2,4-difluoro-1-isocyanatobenzene (55 mg, 0.35 mmol, 1 eq) was added dropwise and the reaction mixture was stirred at rt for 45 min. The reaction mixture was concentrated onto Celite and purified by flash chromatography (0–8% MeOH in DCM on silica gel column then 30–100% MeCN in water with 0.1% formic acid on C18 column) to afford **28** (7.9 mg, 5% yield) as a light pink solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.05 (d, *J* = 2.1 Hz, 1H), 9.00 (s, 1H), 8.64 (s, 1H), 8.19 (t, *J* = 9.1 Hz, 1H), 8.13 (td, *J* = 9.2, 6.1 Hz, 1H), 7.98 (d, *J* = 6.0 Hz, 1H), 7.67 (d, *J* = 6.0 Hz, 1H), 7.41 (dd, *J* = 11.8, 2.6 Hz, 1H), 7.33 (ddd, *J* = 11.7, 8.9, 2.9 Hz, 1H), 7.15 (ddd, *J* = 9.0, 2.7, 1.3 Hz, 1H), 7.12 – 7.03 (m, 1H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ –117.61 – –118.37 (m), –124.76 (t, *J* = 9.3 Hz), –126.61 (t, *J* = 10.4 Hz). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 169.08, 163.11, 156.86 (dd, *J* = 242.2, 11.5 Hz), 152.93, 152.16, 152.07 (dd, *J* = 244.9, 12.0 Hz), 151.93 (d, *J* = 243.8 Hz), 146.38 (d, *J* = 10.9 Hz), 127.54, 125.15 (d, *J* = 10.8 Hz), 123.90 (dd, *J* = 10.7, 3.7 Hz), 121.80 (dd, *J* = 9.1, 2.9 Hz), 121.10 (d, *J* = 2.7 Hz), 118.54, 118.46, 118.06 (d, *J* = 3.3 Hz), 111.11 (dd, *J* = 21.9, 3.7 Hz), 110.10 (d, *J* = 22.4 Hz), 103.84 (dd, *J* = 26.8, 23.5 Hz). HRMS: calcd for C₁₉H₁₂F₃N₄O₂S [M + H]⁺ m/z, 417.0633; found m/z, 417.0624.

4-(3-fluoro-4-nitrophenoxy)-1H-pyrrolo[2,3-b]pyridine (96).—In a microwave vial charged with a stir bar was added 4-chloro-1H-pyrrolo[2,3-b]pyridine (500 mg, 3.28 mmol,

1 eq) and 3-fluoro-4-nitrophenol (**87**) (618 mg, 3.93 mmol, 1.2 eq). The microwave vial was sealed and irradiated at 150°C for 20 min. The crude material was dissolved in EtOAc (3 mL) and was partitioned between EtOAc (50 mL) and aqueous NaOH solution (1 M, 50 mL). The aqueous layer was extracted with EtOAc (50 mL x 2). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄, filtered, concentrated onto Celite, and purified by flash chromatography (0–5% MeOH in DCM on silica gel column then 0–50% EtOAc in Hexanes on silica gel column) to afford **96** (103 mg, 12% yield) as a light yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.96 (s, 1H), 8.33 – 8.13 (m, 2H), 7.47 (dd, *J* = 3.5, 2.5 Hz, 1H), 7.40 (dd, *J* = 12.6, 2.6 Hz, 1H), 7.06 (ddd, *J* = 9.2, 2.6, 1.2 Hz, 1H), 6.86 (d, *J* = 5.3 Hz, 1H), 6.21 (dd, *J* = 3.5, 1.9 Hz, 1H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ –114.11 (dd, *J* = 12.6, 8.9 Hz). ¹³C NMR (214 MHz, DMSO-*d*₆) δ 161.36 (d, *J* = 11.2 Hz), 156.29 (d, *J* = 263.2 Hz), 153.56, 151.47, 144.39, 132.54 (d, *J* = 7.0 Hz), 128.41, 126.26, 114.34 (d, *J* = 3.1 Hz), 111.15, 108.16 (d, *J* = 24.1 Hz), 105.50, 96.75.

4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)-2-fluoroaniline (111).—A suspension of 4-(3-fluoro-4-nitrophenoxy)-1H-pyrrolo[2,3-b]pyridine (**96**) (105 mg, 0.384 mmol, 1 eq), iron (107 mg, 1.92 mmol, 5 eq), and ammonium chloride (164 mg, 3.07 mmol, 8 eq) in ethanol (1 mL) and water (0.3 mL) was heated at 31°C for 4 h. The reaction mixture was cooled to rt and filtered through Celite. The filtrate was concentrated onto Celite, and purified by flash chromatography (20–70% EtOAc in Hexanes on silica gel column) to afford **111** (83 mg, 88% yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.84 (s, 1H), 7.21 (d, *J* = 5.5 Hz, 1H), 6.50 (dd, *J* = 3.5, 2.5 Hz, 1H), 6.15 (dd, *J* = 11.9, 2.5 Hz, 1H), 6.06 – 5.90 (m, 2H), 5.51 (d, *J* = 5.4 Hz, 1H), 5.38 (dd, *J* = 3.5, 2.0 Hz, 1H), 4.31 (s, 2H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ –131.62 (dd, *J* = 12.1, 9.6 Hz). ¹³C NMR (214 MHz, DMSO-*d*₆) δ 158.19, 151.02, 150.10 (d, *J* = 239.6 Hz), 144.17, 143.68 (d, *J* = 8.9 Hz), 134.01 (d, *J* = 13.0 Hz), 124.32, 117.13 (d, *J* = 3.1 Hz), 116.30 (d, *J* = 5.5 Hz), 109.65, 108.78 (d, *J* = 20.9 Hz), 101.12, 97.11.

1-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)-2-fluorophenyl)-3-(2,4-difluorophenyl)urea (29).—To a solution of 2,4-difluoroaniline (59 mg, 0.45 mmol, 2 eq) in DCM (2.2 mL) cooled to 0°C was added 1,1'-carbonyldiimidazole (92 mg, 0.57 mmol, 2.5 eq). The reaction mixture was stirred at 0°C for 30 min. This was added to a solution of 4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)-2-fluoroaniline (**111**) (60 mg, 0.23 mmol, 1 eq) in DCM (1.1 mL). The reaction mixture was stirred at 40°C for 2.5 h, then cooled to rt. The crude reaction mixture was partitioned between EtOAc (15 mL) and water (15 mL). The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄, filtered, concentrated onto Celite, and purified by flash chromatography (0–60% EtOAc on Hexanes on silica gel column then 20–50% MeCN in water with 0.1% formic acid on C18 column) to afford **29** (3.3 mg, 4% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.76 (s, 1H), 9.08 (s, 1H), 9.05 (s, 1H), 8.29 – 8.01 (m, 3H), 7.37 (s, 1H), 7.32 (t, *J* = 10.2 Hz, 1H), 7.24 (d, *J* = 11.8 Hz, 1H), 7.14 – 6.96 (m, 2H), 6.47 (d, *J* = 5.4 Hz, 1H), 6.22 (s, 1H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ –115.96 – –119.80 (m), –124.65 (t, *J* = 10.3 Hz), –125.77 (t, *J* = 11.0 Hz). ¹³C NMR (214 MHz, DMSO-*d*₆) δ 156.95, 156.85 (dd, *J* = 241.6, 11.6 Hz), 152.28 (d, *J* = 244.4 Hz), 152.19, 152.11 (dd, *J* = 245.0, 12.1 Hz), 151.15,

149.31 (d, $J = 10.0$ Hz), 144.23, 124.85, 124.34 (d, $J = 10.6$ Hz), 123.92 (dd, $J = 10.7, 3.3$ Hz), 121.87 (dd, $J = 8.7, 2.6$ Hz), 121.65 (d, $J = 2.1$ Hz), 116.41 (d, $J = 3.0$ Hz), 111.08 (dd, $J = 21.6, 3.5$ Hz), 110.06, 108.33 (d, $J = 22.1$ Hz), 103.83 (dd, $J = 26.7, 23.5$ Hz), 102.18, 97.01. HRMS: calcd for $C_{20}H_{14}F_3N_4O_2$ [M + H]⁺ m/z, 399.1069; found m/z, 399.1059.

4-(3-fluoro-4-nitrophenoxy)-7H-pyrrolo[2,3-d]pyrimidine (97).—To a solution of 4-chloro-7H-pyrrolo[2,3-d]pyrimidine (405 mg, 2.64 mmol, 1 eq) and 3-fluoro-4-nitrophenol (**87**) (539 mg, 3.43 mmol, 1.3 eq) in N-methyl-2-pyrrolidone (1.5 mL) was added 2,6-lutidine (339 mg, 3.16 mmol, 1.2 eq). The reaction mixture was stirred at 130°C for 22 h, then cooled to rt and poured into ice water (30 mL). The solid was collected by filtration, washed with water and diethyl ether, then re-suspended in isopropanol (5 mL) and collected by filtration, washed with isopropanol and dried under vacuum to afford **97** (202 mg, 28% yield) as a light grey solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.38 (s, 1H), 8.39 (s, 1H), 8.28 (t, $J = 8.9$ Hz, 1H), 7.72 (dd, $J = 12.4, 2.5$ Hz, 1H), 7.57 (dd, $J = 3.5, 2.4$ Hz, 1H), 7.40 (ddd, $J = 9.1, 2.5, 1.2$ Hz, 1H), 6.62 (dd, $J = 3.5, 1.8$ Hz, 1H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -115.28 (dd, $J = 12.5, 8.8$ Hz). ¹³C NMR (214 MHz, DMSO-*d*₆) δ 160.30, 158.24 (d, $J = 11.0$ Hz), 155.76 (d, $J = 262.4$ Hz), 154.11, 150.03, 134.04 (d, $J = 7.5$ Hz), 127.80, 126.44, 118.67 (d, $J = 3.4$ Hz), 112.20 (d, $J = 23.5$ Hz), 105.17, 98.01.

4-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)-2-fluoroaniline (112).—A suspension of 4-(3-fluoro-4-nitrophenoxy)-7H-pyrrolo[2,3-d]pyrimidine (**97**) (80 mg, 0.29 mmol, 1 eq), iron (81 mg, 1.5 mmol, 5 eq), and ammonium chloride (120 mg, 2.3 mmol, 8 eq) in ethanol (0.9 mL) and water (0.3 mL) was heated at 78°C for 5 h. The reaction mixture was cooled to rt and filtered through Celite. The filtrate was concentrated onto Celite, and purified by flash chromatography (0–60% EtOAc in Hexanes on silica gel column) to afford **112** (62 mg, 87% yield) as a light pink solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.15 (s, 1H), 8.28 (s, 1H), 7.42 (d, $J = 3.5$ Hz, 1H), 7.14 – 6.96 (m, 1H), 6.85 – 6.75 (m, 2H), 6.35 (d, $J = 3.4$ Hz, 1H), 5.09 (s, 2H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -131.17 – -138.43 (m). ¹³C NMR (214 MHz, DMSO-*d*₆) δ 162.08, 153.46, 150.20, 149.94 (d, $J = 238.3$ Hz), 142.03 (d, $J = 9.5$ Hz), 134.03 (d, $J = 12.6$ Hz), 124.96, 117.98 (d, $J = 3.2$ Hz), 115.84 (d, $J = 5.5$ Hz), 109.79 (d, $J = 21.1$ Hz), 104.39, 98.08.

1-(4-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)-2-fluorophenyl)-3-(2,4-difluorophenyl)urea (30).—To a solution of 4-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)-2-fluoroaniline (**112**) (58 mg, 0.24 mmol, 1 eq) in ethanol (0.7 mL) cooled to 0°C using an ice bath was added 2,4-difluoro-1-isocyanatobenzene (37 mg, 0.24 mmol, 1 eq) dropwise. The reaction mixture was warmed to rt and stirred at rt for 1 h. 2,4-difluoro-1-isocyanatobenzene (48 mg, 0.31 mmol, 1.3 eq) was added over the course of 1.5 h portionwise. The reaction mixture was stirred at rt for another 1 h. The reaction mixture was concentrated onto Celite and purified by flash chromatography (0–100% EtOAc in Hexanes on silica gel column then 100% MeCN in water with 0.1% formic acid on C18 column) to afford **30** (33 mg, 35% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.24 (s, 1H), 9.02 (d, $J = 2.3$ Hz, 1H), 9.00 (d, $J = 1.3$ Hz, 1H), 8.32 (s, 1H), 8.19 – 8.09 (m, 2H), 7.48 (dd, $J = 3.6, 1.6$ Hz, 1H), 7.39 – 7.27 (m, 2H), 7.15 – 7.02 (m, 2H), 6.50 (d, $J = 3.5$ Hz, 1H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -117.46 – -118.53 (m), -124.82 (t, J

= 10.2 Hz), -126.82 (t, J = 10.6 Hz). ^{13}C NMR (101 MHz, DMSO- d_6) δ 161.48, 156.83 (dd, J = 241.3, 11.3 Hz), 153.57, 152.19, 152.05 (dd, J = 241.3, 12.3 Hz), 152.02 (d, J = 243.3 Hz), 150.08, 147.16 (d, J = 10.7 Hz), 125.38, 124.65 (d, J = 10.6 Hz), 123.94 (dd, J = 10.6, 3.5 Hz), 121.79 (dd, J = 9.0, 2.9 Hz), 121.16 (d, J = 2.6 Hz), 118.03 (d, J = 3.2 Hz), 111.10 (dd, J = 21.1, 3.5 Hz), 110.01 (d, J = 22.0 Hz), 104.54, 103.83 (dd, J = 26.7, 23.7 Hz), 97.96. HRMS: calcd for $\text{C}_{19}\text{H}_{13}\text{F}_3\text{N}_5\text{O}_2$ [$\text{M} + \text{H}$] $^+$ m/z , 400.1021; found m/z , 400.1013.

2-fluoro-4-(pyrimidin-4-yloxy)aniline (113).—To a solution of 4-chloropyrimidine hydrochloride (250 mg, 1.66 mmol, 1 eq) and 4-amino-3-fluorophenol (**85**) (295 mg, 2.32 mmol, 1.4 eq) in DMF (10 mL) cooled to 0°C using an ice bath was added a suspension of potassium tert-butoxide (446 mg, 3.97 mmol, 2.4 eq) in DMF (5 mL) dropwise. The reaction mixture was stirred at 110°C for 4 h. The reaction mixture was cooled to 0°C using an ice bath, water (50 mL) was added. The aqueous layer was extracted with DCM (50 mL x 3). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 , filtered, concentrated onto Celite, and purified by flash chromatography (0–5% MeOH in DCM on silica gel column) to afford **113** (183 mg, 54% yield) as a beige solid. ^1H NMR (400 MHz, DMSO- d_6) δ 8.75 (dd, J = 1.2, 0.6 Hz, 1H), 8.63 (dd, J = 5.8, 0.7 Hz, 1H), 7.03 (dd, J = 5.8, 1.2 Hz, 1H), 6.99 (dd, J = 11.9, 2.4 Hz, 1H), 6.84 – 6.74 (m, 2H), 5.13 (s, 2H). ^{19}F NMR (376 MHz, DMSO- d_6) δ -132.21 (dd, J = 12.0, 9.5 Hz). ^{13}C NMR (101 MHz, DMSO- d_6) δ 169.20, 158.93, 158.40, 149.92 (d, J = 239.1 Hz), 141.15 (d, J = 9.6 Hz), 134.44 (d, J = 13.0 Hz), 117.64 (d, J = 3.2 Hz), 115.93 (d, J = 5.7 Hz), 109.45 (d, J = 21.3 Hz), 108.07.

1-(2,4-difluorophenyl)-3-(2-fluoro-4-(pyrimidin-4-yloxy)phenyl)urea (31).—To a solution of 2-fluoro-4-(pyrimidin-4-yloxy)aniline (**113**) (64 mg, 0.31 mmol, 1 eq) in ethanol (0.8 mL) cooled to 0°C using an ice bath was added 2,4-difluoro-1-isocyanatobenzene (49 mg, 0.31 mmol, 1 eq) dropwise. The reaction mixture was warmed to rt and stirred at rt for 1 h. The reaction mixture was concentrated onto Celite and purified by flash chromatography (0–8% MeOH in DCM on silica gel column then 0–80% EtOAc in Hexanes on silica gel column) to afford **31** (18.1 mg, 16% yield) as an off-white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 9.01 (s, 1H), 8.98 (s, 1H), 8.78 (dd, J = 1.2, 0.6 Hz, 1H), 8.69 (dd, J = 5.8, 0.6 Hz, 1H), 8.17 (t, J = 9.1 Hz, 1H), 8.12 (td, J = 9.2, 6.1 Hz, 1H), 7.41 – 7.27 (m, 2H), 7.16 (dd, J = 5.8, 1.2 Hz, 1H), 7.09 – 7.01 (m, 2H). ^{19}F NMR (376 MHz, DMSO- d_6) δ -118.02 (tdd, J = 8.8, 5.8, 3.5 Hz), -124.85 (t, J = 10.7 Hz), -126.49 (t, J = 10.7 Hz). ^{13}C NMR (101 MHz, DMSO- d_6) δ 168.64, 159.21, 158.36, 156.87 (dd, J = 241.3, 11.8 Hz), 152.15, 152.07 (dd, J = 244.9, 12.2 Hz), 152.02 (d, J = 243.7 Hz), 146.41 (d, J = 10.6 Hz), 125.07 (d, J = 10.7 Hz), 123.90 (dd, J = 10.7, 3.6 Hz), 121.80 (dd, J = 9.1, 3.0 Hz), 121.26 (d, J = 2.8 Hz), 117.82 (d, J = 3.3 Hz), 111.12 (dd, J = 21.7, 3.5 Hz), 109.81 (d, J = 22.2 Hz), 108.56, 103.85 (dd, J = 27.0, 23.6 Hz). HRMS: calcd for $\text{C}_{17}\text{H}_{12}\text{F}_3\text{N}_4\text{O}_2$ [$\text{M} + \text{H}$] $^+$ m/z , 361.0912; found m/z , 361.0902.

4-((2-chloropyridin-4-yl)oxy)-2-fluoroaniline (114).—To a solution of 4-amino-3-fluorophenol (**85**) (1.00 g, 7.9 mmol, 1.17 eq) in DMA (13.5 mL) was added potassium tert-butoxide (910 mg, 8.1 mmol, 1.2 eq) and stirred at rt for 30 min. 2,4-dichloropyridine (1.00 g, 6.76 mmol, 1 eq) was added and the reaction mixture was stirred at 80°C for 16 h.

The reaction mixture was partitioned between EtOAc (100 mL) and water (100 mL). The aqueous layer was extracted with EtOAc (100 mL x 2). The combined organic extracts were washed with water, brine, dried over anhydrous Na₂SO₄, filtered, concentrated onto Celite, and purified by flash chromatography (0–35% EtOAc in Hexanes on silica gel column) to afford **114** (940 mg, 58% yield) as a light yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.25 (dd, *J* = 5.7, 0.6 Hz, 1H), 7.02 (dd, *J* = 11.8, 2.5 Hz, 1H), 6.93 – 6.88 (m, 2H), 6.87 – 6.75 (m, 2H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ –131.09 (dd, *J* = 12.0, 9.7 Hz). ¹³C NMR (214 MHz, DMSO-*d*₆) δ 166.99, 151.46, 151.15, 150.06 (d, *J* = 240.0 Hz), 141.95 (d, *J* = 9.3 Hz), 134.84 (d, *J* = 13.0 Hz), 117.17 (d, *J* = 3.1 Hz), 116.40 (d, *J* = 5.6 Hz), 111.16, 111.02, 108.89 (d, *J* = 21.1 Hz).

1-(4-((2-chloropyridin-4-yl)oxy)-2-fluorophenyl)-3-(2,4-difluorophenyl)urea (32).

—To a solution of 1,1'-carbonyldiimidazole (469 mg, 2.89 mmol, 2.5 eq) in DCM (5 mL) cooled to 0°C using an ice bath was added 2,4-difluoroaniline (299 mg, 2.31 mmol, 2 eq) in DCM (7 mL) dropwise over 10 min. The reaction mixture was stirred at 0°C for 30 min, monitoring reaction progress by TLC. This was added to a solution of 4-((2-chloropyridin-4-yl)oxy)-2-fluoroaniline (**114**) (300 mg, 1.16 mmol, 1 eq) in DCM (3 mL). The reaction mixture was stirred at 40°C for 2 h. Separately, to another solution of 1,1'-carbonyldiimidazole (469 mg, 2.89 mmol, 2.5 eq) in DCM (5 mL) cooled to 0°C using an ice bath was added 2,4-difluoroaniline (299 mg, 2.31 mmol, 2 eq) in DCM (5 mL) dropwise and stirred at 0°C for 10 min. The reaction mixtures were combined and stirred at 40°C for 2 h. The crude reaction mixture was partitioned between EtOAc (60 mL) and water (50 mL). The aqueous layer was extracted with EtOAc (50 mL x 2). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄, filtered, concentrated onto Celite, and purified by flash chromatography (5–30% EtOAc in Hexanes on silica gel column) to afford **32** (285 mg, 63% yield) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.05 (d, *J* = 2.4 Hz, 1H), 8.99 (d, *J* = 2.2 Hz, 1H), 8.30 (d, *J* = 5.8 Hz, 1H), 8.23 (t, *J* = 9.1 Hz, 1H), 8.12 (td, *J* = 9.3, 6.1 Hz, 1H), 7.32 (dtd, *J* = 11.7, 4.4, 2.9 Hz, 2H), 7.12 – 7.02 (m, 3H), 6.98 (dd, *J* = 5.7, 2.3 Hz, 1H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ –117.77 – –118.13 (m), –124.81 (t, *J* = 10.9 Hz), –125.39 (t, *J* = 10.5 Hz). ¹³C NMR (214 MHz, DMSO-*d*₆) δ 166.13, 156.88 (dd, *J* = 241.7, 11.5 Hz), 152.15 (d, *J* = 245.8 Hz), 152.08, 152.07 (dd, *J* = 245.0, 12.2 Hz), 151.59, 151.32, 147.34 (d, *J* = 10.4 Hz), 125.46 (d, *J* = 10.7 Hz), 123.83 (dd, *J* = 10.9, 3.5 Hz), 121.79 (dd, *J* = 9.2, 2.2 Hz), 121.57 (d, *J* = 2.8 Hz), 116.98 (d, *J* = 3.3 Hz), 111.62, 111.57, 111.11 (dd, *J* = 21.8, 3.3 Hz), 108.97 (d, *J* = 22.0 Hz), 103.84 (dd, *J* = 26.8, 23.6 Hz). HRMS: calcd for C₁₈H₁₂ClF₃N₃O₂ [M + H]⁺ m/z, 394.0570; found m/z, 394.0561.

4-chloro-6-(3-fluoro-4-nitrophenoxy)pyrimidine (98).—To a solution of 4,6-dichloropyrimidine (500 mg, 3.36 mmol, 1 eq) and 3-fluoro-4-nitrophenol (**87**) (527 mg, 3.36 mmol, 1 eq) in DMF (11 mL) was added potassium carbonate (464 mg, 3.36 mmol, 1 eq). The reaction mixture was stirred at 70°C for 16 h, then cooled to rt and was partitioned between EtOAc (60 mL) and water (60 mL). The aqueous layer was extracted with EtOAc (60 mL x 2). The combined organic extracts were washed with water, brine, dried over anhydrous Na₂SO₄, filtered, concentrated onto Celite, and purified by flash chromatography (0–35% EtOAc in Hexanes on silica gel column) to afford **98** (554 mg, 61% yield) as a light

yellow solid. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 8.73 (d, J = 0.9 Hz, 1H), 8.30 (t, J = 8.9 Hz, 1H), 7.72 (dd, J = 12.1, 2.5 Hz, 1H), 7.63 (d, J = 0.9 Hz, 1H), 7.40 (ddd, J = 9.1, 2.5, 1.3 Hz, 2H). ^{19}F NMR (376 MHz, $\text{DMSO-}d_6$) δ -114.92 (dd, J = 12.1, 8.7 Hz). ^{13}C NMR (214 MHz, $\text{DMSO-}d_6$) δ 168.84, 161.44, 158.52, 156.94 (d, J = 11.0 Hz), 155.54 (d, J = 263.1 Hz), 134.60 (d, J = 7.0 Hz), 127.90, 118.59 (d, J = 3.4 Hz), 112.28 (d, J = 24.0 Hz), 109.11.

4-((6-chloropyrimidin-4-yl)oxy)-2-fluoroaniline (115).—A suspension of 4-chloro-6-(3-fluoro-4-nitrophenoxy)pyrimidine (**98**) (365 mg, 1.35 mmol, 1 eq), iron (378 mg, 6.77 mmol, 5 eq), and ammonium chloride (579 mg, 10.8 mmol, 8 eq) in ethanol (4 mL) and water (1.35 mL) was heated at 31 °C for 4 h. The reaction mixture was cooled to rt and filtered through Celite. The filtrate was concentrated onto Celite, and purified by flash chromatography (0–40% EtOAc in Hexanes on silica gel column) to afford **115** (307 mg, 95% yield) as a beige solid. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 8.64 (d, J = 0.9 Hz, 1H), 7.25 (d, J = 0.9 Hz, 1H), 7.07 – 6.97 (m, 1H), 6.89 – 6.72 (m, 2H), 5.17 (s, 2H). ^{19}F NMR (376 MHz, $\text{DMSO-}d_6$) δ -132.12 (dd, J = 11.9, 8.1 Hz). ^{13}C NMR (214 MHz, $\text{DMSO-}d_6$) δ 170.54, 160.77, 158.61, 149.86 (d, J = 239.1 Hz), 140.99 (d, J = 9.5 Hz), 134.67 (d, J = 12.8 Hz), 117.50 (d, J = 3.3 Hz), 115.90 (d, J = 5.7 Hz), 109.34 (d, J = 21.4 Hz), 107.62.

1-(4-((6-chloropyrimidin-4-yl)oxy)-2-fluorophenyl)-3-(2,4-difluorophenyl)urea (33).—To a solution of 4-((6-chloropyrimidin-4-yl)oxy)-2-fluoroaniline (**115**) (448 mg, 1.87 mmol, 1 eq) in ethanol (4.5 mL) was added 2,4-difluoro-1-isocyanatobenzene (1.45 g, 9.35 mmol, 5 eq) portionwise over 10 h while stirring at rt, monitoring reaction progress by TLC. The reaction mixture was stirred at rt for 14 h, then concentrated onto Celite, and purified by flash chromatography (0–30% EtOAc in Hexanes on silica gel column then 25%–100% DCM in Hexanes followed by 0–10% MeOH in DCM on silica gel column) to afford **33** (81 mg, 11% yield) as a white solid. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 9.03 (d, J = 2.3 Hz, 1H), 8.99 (d, J = 2.2 Hz, 1H), 8.67 (d, J = 0.9 Hz, 1H), 8.22 – 8.08 (m, 2H), 7.42 (d, J = 0.9 Hz, 1H), 7.34 (dd, J = 11.7, 2.7 Hz, 1H), 7.32 (dd, J = 11.5, 2.9 Hz, 1H), 7.11 – 7.02 (m, 2H). ^{19}F NMR (376 MHz, $\text{DMSO-}d_6$) δ -117.98 (tdd, J = 8.9, 6.1, 3.6 Hz), -124.82 (t, J = 10.9 Hz), -126.34 (t, J = 10.8 Hz). ^{13}C NMR (214 MHz, $\text{DMSO-}d_6$) δ 169.95, 160.95, 158.56, 156.86 (dd, J = 241.6, 11.2 Hz), 152.12, 152.06 (dd, J = 245.4, 12.2 Hz), 151.93 (d, J = 244.4 Hz), 146.18 (d, J = 10.2 Hz), 125.36 (d, J = 10.9 Hz), 124.30 – 123.34 (m), 121.78 (dd, J = 9.1, 2.5 Hz), 121.17, 117.89 – 117.04 (m), 111.22 – 110.62 (m), 109.69 (d, J = 22.4 Hz), 108.13, 103.84 (dd, J = 27.2, 23.6 Hz). HRMS: calcd for $\text{C}_{17}\text{H}_{11}\text{ClF}_3\text{N}_4\text{O}_2$ [$\text{M} + \text{H}$] $^+$ m/z , 395.0523; found m/z , 395.0512.

2-chloro-4-(3-fluoro-4-nitrophenoxy)pyrimidine (99).—To a solution of 2,4-dichloropyrimidine (800 mg, 5.37 mmol, 1 eq) and 3-fluoro-4-nitrophenol (**87**) (844 mg, 5.37 mmol, 1 eq) in DMF (15 mL) was added potassium carbonate (742 mg, 5.37 mmol, 1 eq). The reaction mixture was stirred at 70 °C for 16 h, then cooled to rt and was partitioned between EtOAc (60 mL) and water (60 mL). The aqueous layer was extracted with EtOAc (60 mL x 2). The combined organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4 , filtered, concentrated onto Celite, and purified by flash chromatography (20–100% DCM in Hexanes on silica gel column) to afford **99** (788 mg, 54% yield) as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 8.73 (d, J = 5.7 Hz, 1H), 8.31 (t, J = 8.9

Hz, 1H), 7.75 (dt, $J = 12.0, 2.1$ Hz, 1H), 7.43 (ddd, $J = 9.1, 2.5, 1.3$ Hz, 1H), 7.37 (dd, $J = 5.7, 1.1$ Hz, 1H). ^{19}F NMR (376 MHz, DMSO- d_6) δ -114.62 – -114.74 (m). ^{13}C NMR (214 MHz, DMSO- d_6) δ 168.87, 162.15, 158.75, 156.51 (d, $J = 11.4$ Hz), 155.51 (d, $J = 263.2$ Hz), 134.72 (d, $J = 6.9$ Hz), 127.95, 118.53 (d, $J = 3.5$ Hz), 112.20 (d, $J = 23.8$ Hz), 108.36.

4-((2-chloropyrimidin-4-yl)oxy)-2-fluoroaniline (116).—A suspension of 2-chloro-4-(3-fluoro-4-nitrophenoxy)pyrimidine (**99**) (770 mg, 2.86 mmol, 1 eq), iron (798 mg, 14.3 mmol, 5 eq), and ammonium chloride (1.22 g, 22.8 mmol, 8 eq) in ethanol (7.5 mL) and water (2.5 mL) was heated at 40°C for 5 h. The reaction mixture was cooled to rt and filtered through Celite. The filtrate was concentrated onto Celite, and purified by flash chromatography (0–40% EtOAc in Hexanes on silica gel column) to afford **116** (625 mg, 91% yield) as a yellow solid. ^1H NMR (400 MHz, DMSO- d_6) δ 8.57 (d, $J = 5.8$ Hz, 1H), 7.12 – 6.97 (m, 2H), 6.87 – 6.76 (m, 2H), 5.21 (s, 2H). ^{19}F NMR (376 MHz, DMSO- d_6) δ -128.17 – -134.17 (m). ^{13}C NMR (214 MHz, DMSO- d_6) δ 170.73, 161.32, 159.05, 149.83 (d, $J = 239.5$ Hz), 140.73 (d, $J = 9.5$ Hz), 134.82 (d, $J = 12.8$ Hz), 117.44 (d, $J = 3.1$ Hz), 115.96 (d, $J = 5.5$ Hz), 109.25 (d, $J = 21.7$ Hz), 107.13.

1-(4-((2-chloropyrimidin-4-yl)oxy)-2-fluorophenyl)-3-(2,4-difluorophenyl)urea (34).—To a solution of 1,1'-carbonyldiimidazole (761 mg, 4.69 mmol, 2.25 eq) in DCM (10 mL) cooled to 0°C using an ice bath was added 2,4-difluoroaniline (539 mg, 4.17 mmol, 2 eq) in DCM (10 mL) dropwise over 10 min. The reaction mixture was stirred at 0°C for 50 min, monitoring reaction progress by TLC. This was added to a solution of 4-((2-chloropyrimidin-4-yl)oxy)-2-fluoroaniline (**116**) (500 mg, 2.09 mmol, 1 eq) in DCM (5 mL). The reaction mixture was stirred at 40°C for 3 h. The crude reaction mixture was partitioned between EtOAc (60 mL) and water (50 mL). The aqueous layer was extracted with EtOAc (50 mL x 2). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 , filtered, concentrated onto Celite, and purified by flash chromatography (5–35% EtOAc in Hexanes on silica gel column) to afford **34** (443 mg, 54% yield) as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 9.04 (d, $J = 2.3$ Hz, 1H), 9.00 (d, $J = 2.1$ Hz, 1H), 8.63 (d, $J = 5.7$ Hz, 1H), 8.20 (t, $J = 9.1$ Hz, 1H), 8.12 (td, $J = 9.2, 6.1$ Hz, 1H), 7.44 – 7.29 (m, 2H), 7.19 (d, $J = 5.7$ Hz, 1H), 7.14 – 6.99 (m, 2H). ^{19}F NMR (376 MHz, DMSO- d_6) δ -117.96 (tdd, $J = 8.9, 6.1, 3.6$ Hz), -124.81 (t, $J = 10.2$ Hz), -126.15 (t, $J = 10.6$ Hz). ^{13}C NMR (214 MHz, DMSO- d_6) δ 170.08, 161.54, 158.95, 156.87 (dd, $J = 241.7, 11.5$ Hz), 152.11, 152.06 (dd, $J = 245.1, 12.3$ Hz), 151.88 (d, $J = 244.3$ Hz), 145.83 (d, $J = 10.3$ Hz), 125.55 (d, $J = 10.3$ Hz), 123.85 (dd, $J = 11.0, 3.5$ Hz), 121.79 (dd, $J = 8.7, 2.8$ Hz), 121.18 (d, $J = 2.5$ Hz), 117.62 (d, $J = 3.1$ Hz), 111.10 (dd, $J = 21.6, 3.4$ Hz), 109.60 (d, $J = 22.5$ Hz), 107.58, 103.84 (dd, $J = 26.7, 23.5$ Hz). HRMS: calcd for $\text{C}_{17}\text{H}_{11}\text{ClF}_3\text{N}_4\text{O}_2$ [$\text{M} + \text{H}$] $^+$ m/z, 395.0523; found m/z, 395.0515.

1-(4-((6-(benzylamino)pyrimidin-4-yl)oxy)-2-fluorophenyl)-3-(2,4-difluorophenyl)urea (35).—To a solution of 1-(4-((6-chloropyrimidin-4-yl)oxy)-2-fluorophenyl)-3-(2,4-difluorophenyl)urea (**33**) (61 mg, 0.15 mmol, 1 eq) in THF (0.6 mL) was added triethylamine (23 mg, 1.5 eq, 0.23 mmol) and benzylamine (100 mg, 0.93 mmol, 6 eq). The reaction mixture was stirred at 66°C for 10 h, then concentrated onto Celite, and purified by flash chromatography (0–4% MeOH

in DCM on silica gel column then 25–100% MeCN in water with 0.1% formic acid on C18 column) to afford **35** (37 mg, 52% yield) as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 8.99 (s, 1H), 8.98 (s, 1H), 8.20–8.06 (m, 3H), 7.90 (s, 1H), 7.38–7.28 (m, 5H), 7.27–7.22 (m, 1H), 7.18 (d, J = 10.7 Hz, 1H), 7.05 (t, J = 8.7 Hz, 1H), 6.95 (d, J = 8.4 Hz, 1H), 5.87 (s, 1H), 4.50 (s, 2H). ^{19}F NMR (376 MHz, DMSO- d_6) δ -118.02 – -118.12 (m), -124.83 (t, J = 9.7 Hz), -126.57. ^{13}C NMR (214 MHz, DMSO- d_6) δ 168.79, 164.59, 158.09, 156.81 (dd, J = 241.5, 11.6 Hz), 152.15, 152.04 (d, J = 243.9 Hz), 152.04 (dd, J = 244.9, 12.2 Hz), 147.31 (d, J = 10.3 Hz), 139.55, 128.35, 127.22, 126.85, 124.44 (d, J = 11.7 Hz), 123.92 (dd, J = 10.8, 3.7 Hz), 121.76 (dd, J = 9.0, 2.0 Hz), 121.30, 117.62 (d, J = 2.4 Hz), 111.08 (dd, J = 21.6, 3.4 Hz), 109.54 (d, J = 21.8 Hz), 103.82 (dd, J = 27.1, 23.5 Hz), 87.21, 43.64. HRMS: calc for $\text{C}_{24}\text{H}_{19}\text{F}_3\text{N}_5\text{O}_2$ $[\text{M} + \text{H}]^+$ m/z , 466.1491; found m/z , 466.1482.

Experimental Procedures in Schemes 5 and 6.

1-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluorophenyl)-3-(3-(trifluoromethyl)phenyl)urea (**39**).—

To a solution of 4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluoroaniline (**14**) (80 mg, 0.25 mmol, 1 eq) in DCM (0.3 mL) and ethanol (0.6 mL) was added 1-isocyanato-3-(trifluoromethyl)benzene (144 mg, 0.75 mmol, 3 eq). The reaction mixture was stirred at rt for 16 h, then concentrated onto Celite, and purified by flash chromatography (1–5% MeOH in DCM on silica gel column) to afford **39** (75 mg, 58% yield) as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 9.42 (s, 1H), 8.72 (d, J = 2.3 Hz, 1H), 8.50 (d, J = 5.3 Hz, 1H), 8.21 (t, J = 9.1 Hz, 1H), 8.04 (d, J = 2.2 Hz, 1H), 7.59–7.51 (m, 2H), 7.49 (s, 1H), 7.41 (s, 1H), 7.39–7.31 (m, 2H), 7.11 (ddd, J = 8.9, 2.8, 1.3 Hz, 1H), 6.55 (d, J = 5.2 Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H). ^{19}F NMR (376 MHz, DMSO- d_6) δ -61.35 (s, 3F), -125.21 (t, J = 10.6 Hz, 1F). ^{13}C NMR (214 MHz, DMSO- d_6) δ 159.58, 152.62 (d, J = 244.8 Hz), 152.62, 152.28, 149.41, 148.87, 148.77 (d, J = 10.2 Hz), 146.52, 140.28, 130.06, 129.63 (q, J = 31.5 Hz), 124.75 (d, J = 10.8 Hz), 124.19 (q, J = 271.8 Hz), 122.20 (d, J = 2.2 Hz), 121.79, 118.39 (q, J = 3.6 Hz), 117.09 (d, J = 3.1 Hz), 115.11, 114.04 (q, J = 3.9 Hz), 109.05 (d, J = 21.9 Hz), 107.87, 103.39, 99.04, 55.74, 55.72. HRMS: calcd for $\text{C}_{25}\text{H}_{20}\text{F}_4\text{N}_3\text{O}_4$ $[\text{M} + \text{H}]^+$ m/z , 502.1390; found m/z , 502.1380.

1-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluorophenyl)-3-(2-fluoro-5-(trifluoromethyl)phenyl)urea (**40**).—

To a solution of 2-fluoro-5-(trifluoromethyl)aniline (51 mg, 0.29 mmol, 1.2 eq) in DMSO (1 mL) was added 1,1'-carbonyldiimidazole (50 mg, 0.31 mmol, 1.3 eq). The reaction mixture was stirred at rt for 1 h then warmed to 40°C and stirred for 2.5 h, monitoring reaction progress by TLC. This was added to a solution of 4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluoroaniline (**14**) (75 mg, 0.24 mmol, 1 eq) in DMSO (1 mL). The reaction mixture was stirred at 60°C for 3 h, then cooled to rt. The crude reaction mixture was partitioned between EtOAc (15 mL) and water (15 mL). The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4 , filtered, concentrated onto Celite, and purified by flash chromatography (40–100% EtOAc in Hexanes on silica gel column) to afford **40** (47 mg, 38% yield) as a light pink solid. ^1H NMR (400 MHz, DMSO- d_6) δ 9.38 (d, J = 2.8 Hz, 1H), 9.23 (d, J = 2.3 Hz, 1H), 8.65 (dd, J = 7.2, 2.3 Hz, 1H), 8.50 (d, J = 5.2 Hz, 1H), 8.27 (t, J = 9.1 Hz, 1H), 7.52 (dd, J = 10.8, 8.7 Hz, 1H), 7.49 (s, 1H), 7.44–7.40 (m, 1H), 7.41 (s, 1H), 7.38 (dd, J = 11.8, 2.7 Hz, 1H), 7.12

(ddd, $J = 9.0, 2.8, 1.2$ Hz, 1H), 6.55 (d, $J = 5.2$ Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H). ^{19}F NMR (376 MHz, DMSO- d_6) δ -60.74 (s, 3F), -123.98 (t, $J = 8.3$ Hz, 1F), -125.46 (t, $J = 10.7$ Hz, 1F). ^{13}C NMR (214 MHz, DMSO- d_6) δ 159.55, 153.47 (d, $J = 247.8$ Hz), 152.61, 152.37 (d, $J = 245.1$ Hz), 152.00, 149.41, 148.87, 148.76 (d, $J = 10.2$ Hz), 146.51, 128.50 (d, $J = 11.3$ Hz), 125.42 (qd, $J = 31.9, 2.2$ Hz), 124.55 (d, $J = 10.8$ Hz), 123.90 (q, $J = 271.8$ Hz), 121.84 (d, $J = 2.5$ Hz), 119.55 (dq, $J = 7.7, 3.9$ Hz), 117.13 (d, $J = 3.1$ Hz), 116.57 (dq, $J = 4.0, 3.2$ Hz), 116.17 (d, $J = 20.4$ Hz), 115.10, 109.07 (d, $J = 21.9$ Hz), 107.87, 103.40, 99.03, 55.74, 55.72. HRMS: calcd for $\text{C}_{25}\text{H}_{19}\text{F}_5\text{N}_3\text{O}_4$ [M + H] $^+$ m/z, 520.1296; found m/z, 520.1287.

1-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluorophenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)phenyl)urea (41).—To a solution

of 4-((4-methylpiperazin-1-yl)methyl)aniline (55 mg, 0.27 mmol, 1.2 eq) in DMSO (1 mL) was added 1,1'-carbonyldiimidazole (47 mg, 0.29 mmol, 1.3 eq). The reaction mixture was stirred at rt for 2 h, monitoring reaction progress by TLC. This was added to a solution of 4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluoroaniline (**14**) (70 mg, 0.22 mmol, 1 eq) in DMSO (1 mL). The reaction mixture was stirred at 60°C for 2 h, then cooled to rt. The crude reaction mixture was partitioned between EtOAc (15 mL) and water (15 mL). The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 , filtered, concentrated onto Celite, and purified by flash chromatography (5–15% MeOH in DCM on silica gel column) to afford **41** (55 mg, 45% yield) as an off-white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 9.21 (s, 1H), 8.68 (d, $J = 2.5$ Hz, 1H), 8.49 (d, $J = 5.2$ Hz, 1H), 8.24 (t, $J = 9.1$ Hz, 1H), 7.49 (s, 1H), 7.44–7.39 (m, 3H), 7.34 (dd, $J = 11.8, 2.7$ Hz, 1H), 7.21 (d, $J = 8.5$ Hz, 2H), 7.09 (ddd, $J = 9.0, 2.7, 1.3$ Hz, 1H), 6.54 (d, $J = 5.2$ Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.40 (s, 2H), 2.38 (br s, 8H), 2.21 (s, 3H). ^{19}F NMR (376 MHz, DMSO- d_6) δ -125.74 (t, $J = 10.7$ Hz). ^{13}C NMR (101 MHz, DMSO- d_6) δ 160.11, 153.03, 152.77, 152.70 (d, $J = 244.6$ Hz), 149.82, 149.32, 148.61 (d, $J = 10.3$ Hz), 146.93, 138.79, 132.01, 129.89, 125.75 (d, $J = 10.6$ Hz), 122.07 (d, $J = 2.8$ Hz), 118.36, 117.50 (d, $J = 2.9$ Hz), 115.52, 109.44 (d, $J = 22.2$ Hz), 108.31, 103.74, 99.49, 61.95, 56.18, 56.16, 54.91, 52.52, 45.78. HRMS: calcd for $\text{C}_{30}\text{H}_{33}\text{FN}_5\text{O}_4$ [M + H] $^+$ m/z, 546.2517; found m/z, 546.2511.

1-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluorophenyl)-3-(3-((4-methylpiperazin-1-yl)methyl)phenyl)urea diformate (42).—To

a solution of 3-((4-methylpiperazin-1-yl)methyl)aniline (55 mg, 0.27 mmol, 1.2 eq) in DMSO (1 mL) was added 1,1'-carbonyldiimidazole (47 mg, 0.29 mmol, 1.2 eq). The reaction mixture was stirred at rt for 2 h, monitoring reaction progress by TLC. This was added to a solution of 4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluoroaniline (**14**) (70 mg, 0.22 mmol, 1 eq) in DMSO (1 mL). The reaction mixture was stirred at 60°C for 2 h, then cooled to rt. The crude reaction mixture was partitioned between EtOAc (15 mL) and water (15 mL). The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4 , filtered, concentrated onto Celite, and purified by flash chromatography (5–15% MeOH in DCM on silica gel column then 10% MeCN in water with 0.1% formic acid on C18 column) to afford **42** (78 mg, 55% yield) as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 9.13 (s, 1H), 8.63 (d, $J = 2.6$ Hz, 1H), 8.50 (d, $J = 5.2$ Hz, 1H),

8.24 (t, $J = 9.1$ Hz, 1H), 8.16 (s, 2H), 7.49 (s, 1H), 7.43 (t, $J = 1.9$ Hz, 1H), 7.40 (s, 1H), 7.36 (d, $J = 2.5$ Hz, 1H), 7.35 – 7.31 (m, 1H), 7.24 (t, $J = 7.8$ Hz, 1H), 7.10 (ddd, $J = 9.3, 2.5, 1.3$ Hz, 1H), 6.92 (d, $J = 7.5$ Hz, 1H), 6.54 (d, $J = 5.2$ Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.44 (s, 2H), 2.42 (br s, 8H), 2.23 (s, 3H). ^{19}F NMR (376 MHz, DMSO- d_6) δ -125.80 (t, $J = 10.9$ Hz). ^{13}C NMR (101 MHz, DMSO- d_6) δ 163.52, 159.65, 152.59, 152.33 (d, $J = 244.5$ Hz), 152.25, 149.39, 148.86, 148.28 (d, $J = 10.3$ Hz), 146.49, 139.43, 138.76, 128.67, 125.23 (d, $J = 10.5$ Hz), 122.65, 121.75 (d, $J = 3.0$ Hz), 118.43, 117.07 (d, $J = 3.2$ Hz), 116.84, 115.08, 109.01 (d, $J = 22.1$ Hz), 107.86, 103.31, 99.03, 61.87, 55.73, 55.71, 54.19, 51.78, 44.89. HRMS: calcd for $\text{C}_{30}\text{H}_{34}\text{FN}_5\text{O}_4$ $[\text{M} + 2\text{H}]^{2+}$ m/z , 273.6298; found m/z , 273.6284.

1-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluorophenyl)-3-(4-(4-methylpiperazine-1-carbonyl)phenyl)urea (43).—To a

solution of (4-aminophenyl)(4-methylpiperazin-1-yl)methanone (59 mg, 0.27 mmol, 1.2 eq) in DMSO (1 mL) was added 1,1'-carbonyldiimidazole (47 mg, 0.29 mmol, 1.3 eq). The reaction mixture was stirred at rt for 2 h, monitoring reaction progress by TLC. This was added to a solution of 4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluoroaniline (**14**) (70 mg, 0.22 mmol, 1 eq) in DMSO (1 mL). The reaction mixture was stirred at 60°C for 2 h, then cooled to rt. The crude reaction mixture was partitioned between EtOAc (15 mL) and water (15 mL). The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4 , filtered, concentrated onto Celite, and purified by flash chromatography (1–12% MeOH in DCM on silica gel column) to afford **43** (57 mg, 45% yield) as an off-white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 9.33 (s, 1H), 8.71 (d, $J = 2.5$ Hz, 1H), 8.50 (d, $J = 5.3$ Hz, 1H), 8.24 (t, $J = 9.1$ Hz, 1H), 7.55 – 7.51 (m, 2H), 7.49 (s, 1H), 7.40 (s, 1H), 7.38 – 7.33 (m, 3H), 7.11 (ddd, $J = 8.9, 2.8, 1.3$ Hz, 1H), 6.55 (d, $J = 5.2$ Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.49 (br s, 4H), 2.32 (br s, 4H), 2.20 (s, 3H). ^{19}F NMR (376 MHz, DMSO- d_6) δ -125.57 (t, $J = 10.6$ Hz). ^{13}C NMR (214 MHz, DMSO- d_6) δ 168.87, 159.61, 152.60, 152.38 (d, $J = 244.5$ Hz), 152.14, 149.40, 148.88, 148.47 (d, $J = 9.7$ Hz), 146.50, 140.70, 129.13, 128.28, 125.01 (d, $J = 10.2$ Hz), 121.77, 117.45, 117.20 – 116.90 (m), 115.09, 109.04 (d, $J = 22.1$ Hz), 107.87, 103.35, 99.04, 55.74, 55.72, 55.67 (br s), 54.49 (br s), 45.60. HRMS: calcd for $\text{C}_{30}\text{H}_{31}\text{FN}_5\text{O}_5$ $[\text{M} + \text{H}]^+$ m/z , 560.2309; found m/z , 560.2303.

(4-methylpiperazin-1-yl)(3-nitrophenyl)methanone (169).—To a solution of 3-nitrobenzoyl chloride (**128**) (335 mg, 1.81 mmol, 1 eq) in THF (2.25 mL) was added 1-methylpiperazine (181 mg, 1.81 mmol, 1 eq). The reaction mixture was stirred at rt for 30 min, then partitioned between EtOAc (30 mL) and aqueous NaOH solution (1 M, 30 mL). The aqueous layer was extracted with EtOAc (30 mL x 2). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 , and filtered to afford **169** (243 mg, 54% yield) as an orange liquid. ^1H NMR (400 MHz, DMSO- d_6) δ 8.30 (ddd, $J = 8.2, 2.4, 1.1$ Hz, 1H), 8.18 (t, $J = 1.9$ Hz, 1H), 7.85 (dt, $J = 7.7, 1.3$ Hz, 1H), 7.74 (t, $J = 7.9$ Hz, 1H), 3.64 (s, 2H), 3.30 (s, 2H), 2.38 (s, 2H), 2.27 (s, 2H), 2.20 (s, 3H). ^{13}C NMR (214 MHz, DMSO- d_6) δ 166.70, 147.70, 137.44, 133.35, 130.29, 124.24, 121.79, 54.55 (br s), 54.05 (br s), 47.04 (br s), 45.54, 41.57 (br s).

(3-aminophenyl)(4-methylpiperazin-1-yl)methanone (129).—A suspension of (4-methylpiperazin-1-yl)(3-nitrophenyl)methanone (**169**) (240 mg, 0.96 mmol, 1 eq), iron (269 mg, 4.82 mmol, 5 eq), and ammonium chloride (412 mg, 7.71 mmol, 8 eq) in ethanol (3 mL) and water (1 mL) was stirred at 31°C for 4 h then warmed to 40°C and stirred for 1 h. The reaction mixture was cooled to rt and filtered through Celite. The filtrate was concentrated onto Celite, and purified by flash chromatography (3–10% MeOH in DCM on silica gel column) to afford **129** (142 mg, 67% yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.04 (t, *J* = 7.7 Hz, 1H), 6.59 (ddd, *J* = 8.1, 2.3, 1.0 Hz, 1H), 6.52 (t, *J* = 1.9 Hz, 1H), 6.43 (dt, *J* = 7.4, 1.3 Hz, 1H), 5.24 (s, 2H), 3.54 (br s, 2H), 3.35 (br s, 2H), 2.29 (br s, 4H), 2.19 (s, 3H). ¹³C NMR (214 MHz, DMSO-*d*₆) δ 172.75, 151.86, 139.75, 131.97, 117.78, 116.86, 115.05, 57.90 (br s), 57.46 (br s), 50.02 (br s), 48.69, 44.34 (br s).

1-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluorophenyl)-3-(3-(4-methylpiperazine-1-carbonyl)phenyl)urea (44).—To a solution of (3-aminophenyl)(4-methylpiperazin-1-yl)methanone (**129**) (59 mg, 0.27 mmol, 1.2 eq) in DMSO (1 mL) was added 1,1'-carbonyldiimidazole (47 mg, 0.29 mmol, 1.3 eq). The reaction mixture was stirred at rt for 2 h, monitoring reaction progress by TLC. This was added to a solution of 4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluoroaniline (**14**) (70 mg, 0.22 mmol, 1 eq) in DMSO (1 mL). The reaction mixture was stirred at 60°C for 2 h, then cooled to rt. The crude reaction mixture was partitioned between EtOAc (15 mL) and water (15 mL). The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic extracts were washed with water, brine, dried over anhydrous Na₂SO₄, filtered, concentrated onto Celite, and purified by flash chromatography (1–12% MeOH in DCM on silica gel column) to afford **44** (58 mg, 47% yield) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.26 (s, 1H), 8.68 (d, *J* = 2.5 Hz, 1H), 8.50 (d, *J* = 5.2 Hz, 1H), 8.22 (t, *J* = 9.1 Hz, 1H), 7.58 (t, *J* = 1.9 Hz, 1H), 7.49 (s, 1H), 7.46–7.40 (m, 2H), 7.39–7.32 (m, 2H), 7.11 (ddd, *J* = 8.9, 2.8, 1.3 Hz, 1H), 6.99 (dt, *J* = 7.5, 1.4 Hz, 1H), 6.55 (d, *J* = 5.2 Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.61 (br s, 2H), 3.36 (br s, 2H), 2.33 (br s, 4H), 2.20 (s, 3H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ –125.49 (t, *J* = 10.5 Hz). ¹³C NMR (214 MHz, DMSO-*d*₆) δ 168.79, 159.61, 152.60, 152.43 (d, *J* = 244.8 Hz), 152.25, 149.40, 148.87, 148.49 (d, *J* = 9.6 Hz), 146.50, 139.50, 136.62, 129.08, 125.00 (d, *J* = 10.8 Hz), 121.88, 120.41, 118.99, 117.10, 116.31, 115.09, 109.02 (d, *J* = 22.1 Hz), 107.87, 103.35, 99.03, 55.73, 55.71, 54.75 (br s), 54.26 (br s), 47.02 (br s), 45.58, 41.38 (br s). HRMS: calcd for C₃₀H₃₁FN₅O₅ [M + H]⁺ m/z, 560.2309; found m/z, 560.2302.

1-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluorophenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea diformate (45).—To a solution of 4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)aniline (79 mg, 0.29 mmol, 1.3 eq) in DMSO (1.3 mL) was added 1,1'-carbonyldiimidazole (65 mg, 0.40 mmol, 1.8 eq). The reaction mixture was stirred at rt for 3 h, monitoring reaction progress by TLC. This was added to a solution of 4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluoroaniline (**14**) (70 mg, 0.22 mmol, 1 eq) in DMSO (1 mL). The reaction mixture was stirred at 60°C for 2 h, then cooled to rt. The crude reaction mixture was partitioned between EtOAc (15 mL) and water (15 mL). The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic extracts were washed

with water, brine, dried over anhydrous Na₂SO₄, filtered, concentrated onto Celite, and purified by flash chromatography (3–15% MeOH in DCM on silica gel column then 8–15% MeCN in water with 0.1% formic acid on C18 column) to afford **45** (66 mg, 42% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.63 (s, 1H), 8.91 (s, 1H), 8.50 (d, *J* = 5.3 Hz, 1H), 8.26 – 8.14 (m, 3H), 8.00 (s, 1H), 7.69 – 7.55 (m, 2H), 7.49 (s, 1H), 7.40 (s, 1H), 7.38 – 7.31 (m, 1H), 7.16 – 7.04 (m, 1H), 6.54 (d, *J* = 5.3 Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.55 (s, 2H), 2.55 (br s, 4H), 2.44 (br s, 4H), 2.31 (s, 3H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ –58.03 (s, 3F), –124.88 (t, *J* = 10.7 Hz, 1F). ¹³C NMR (214 MHz, DMSO-*d*₆) δ 163.51, 159.58, 152.67 (d, *J* = 245.1 Hz), 152.60, 152.37, 149.40, 148.86, 148.72 (d, *J* = 10.1 Hz), 146.50, 138.73, 131.52, 130.01, 127.65 (q, *J* = 29.6 Hz), 124.85 (d, *J* = 10.8 Hz), 124.35 (q, *J* = 274.2 Hz), 122.32 (d, *J* = 2.2 Hz), 121.51, 117.05 (d, *J* = 3.2 Hz), 115.10, 114.92 (q, *J* = 6.1 Hz), 109.04 (d, *J* = 22.0 Hz), 107.86, 103.37, 99.03, 57.20, 55.73, 55.71, 54.27, 51.94, 44.90. HRMS: calcd for C₃₁H₃₃F₄N₅O₄ [M + 2H]²⁺ *m/z*, 307.6234; found *m/z*, 307.6220.

(4-methylpiperazin-1-yl)(3-nitro-5-(trifluoromethyl)phenyl)methanone (170).—

To a solution of 3-nitro-5-(trifluoromethyl)benzoic acid (**130**) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (856 mg, 4.47 mmol, 1.5 eq) in DCM (6 mL) was added 1-methylpiperazine (358 mg, 3.57 mmol, 1.2 eq). The reaction mixture was stirred at rt for 18 h, then was partitioned between DCM (50 mL) and saturated aqueous NaHCO₃ solution (50 mL). The aqueous layer was extracted with DCM (50 mL x 2). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄, filtered, concentrated onto Celite, and purified by flash chromatography (0–4% MeOH in DCM on silica gel column) to afford **170** (744 mg, 79% yield) as a yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.55 (t, *J* = 2.1 Hz, 1H), 8.48 (t, *J* = 1.8 Hz, 1H), 8.26 (t, *J* = 1.7 Hz, 1H), 3.65 (s, 2H), 3.29 (s, 2H), 2.40 (s, 2H), 2.27 (s, 2H), 2.20 (s, 3H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ –61.30. ¹³C NMR (214 MHz, DMSO-*d*₆) δ 165.28, 148.22, 139.03, 130.70 (q, *J* = 33.7 Hz), 129.80 (q, *J* = 3.7 Hz), 125.70, 122.74 (q, *J* = 273.2 Hz), 121.15 (q, *J* = 3.9 Hz), 54.35, 53.87, 46.96, 45.53, 41.64.

3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)aniline (131).—To a solution of lithium aluminium hydride (299 mg, 7.9 mmol, 10 eq) in THF (8.5 mL) was added a solution of (4-methylpiperazin-1-yl)(3-nitro-5-(trifluoromethyl)phenyl)methanone (**170**) (250 mg, 0.79 mmol, 1 eq) in THF (1.5 mL). The reaction mixture was stirred at 66°C for 5 h, then cooled to 0°C using an ice bath. Water (0.3 mL) was added dropwise to the reaction mixture, followed by aqueous NaOH solution (15%, 0.3 mL) then water (0.9 mL). The reaction mixture was warmed to rt and stirred at rt for 2 h and the resultant grey suspension was filtered through Celite. The filtrate was concentrated onto Celite and purified by flash chromatography (1–20% MeOH in DCM on silica gel column) to afford **131** (60 mg, 28% yield) as a light yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 6.76 (s, 1H), 6.71 (s, 1H), 6.68 (s, 1H), 5.52 (s, 2H), 3.35 (s, 2H), 2.33 (br s, 8H), 2.14 (s, 3H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ –61.31.

1-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluorophenyl)-3-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)urea (46).—

To a solution of 3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)aniline (**131**) (55

mg, 0.20 mmol, 1 eq) in DMSO (1 mL) was added 1,1'-carbonyldiimidazole (59 mg, 0.36 mmol, 1.8 eq). The reaction mixture was stirred at rt for 2 h then warmed to 40°C and stirred for 1 h, monitoring reaction progress by TLC. This was added to a solution of 4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluoroaniline (**14**) (89 mg, 0.28 mmol, 1.4 eq) in DMSO (1 mL). The reaction mixture was stirred at 60°C for 2 h, then cooled to rt. The crude reaction mixture was partitioned between EtOAc (15 mL) and water (15 mL). The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic extracts were washed with water, brine, dried over anhydrous Na₂SO₄, filtered, concentrated onto Celite, and purified by flash chromatography (1–15% MeOH in DCM on silica gel column) to afford **46** (71 mg, 58% yield) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.48 (s, 1H), 8.68 (d, *J* = 2.4 Hz, 1H), 8.50 (d, *J* = 5.2 Hz, 1H), 8.20 (t, *J* = 9.1 Hz, 1H), 7.93 (t, *J* = 2.0 Hz, 1H), 7.51 (s, 1H), 7.49 (s, 1H), 7.40 (s, 1H), 7.36 (dd, *J* = 11.7, 2.7 Hz, 1H), 7.23 (s, 1H), 7.10 (ddd, *J* = 9.0, 2.8, 1.3 Hz, 1H), 6.55 (d, *J* = 5.2 Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.52 (s, 2H), 2.39 (br s, 4H), 2.35 (br s, 4H), 2.16 (s, 3H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -61.26 (s, 3F), -125.21 (t, *J* = 10.5 Hz, 1F). ¹³C NMR (214 MHz, DMSO-*d*₆) δ 159.57, 152.61 (d, *J* = 245.1 Hz), 152.60, 152.25, 149.40, 148.86, 148.76 (d, *J* = 10.2 Hz), 146.51, 140.99, 140.30, 129.53 (q, *J* = 31.2 Hz), 124.74 (d, *J* = 10.6 Hz), 124.21 (q, *J* = 272.4 Hz), 122.21 (d, *J* = 2.0 Hz), 121.52, 118.33 (q, *J* = 3.5 Hz), 117.07 (d, *J* = 3.1 Hz), 115.10, 112.69 (q, *J* = 3.9 Hz), 109.04 (d, *J* = 22.1 Hz), 107.87, 103.38, 99.03, 61.19, 55.73, 55.71, 54.71, 52.46, 45.70. HRMS: calcd for C₃₁H₃₂F₄N₅O₄ [M + H]⁺ *m/z*, 614.2390; found *m/z*, 614.2381.

(4-amino-2-(trifluoromethyl)phenyl)(4-methylpiperazin-1-yl)methanone (133).—

To a solution of 4-amino-2-(trifluoromethyl)benzoic acid (**132**) (250 mg, 1.2 mmol, 1 eq) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (350 mg, 1.8 mmol, 1.5 eq) in DCM (2.4 mL) was added 1-methylpiperazine (134 mg, 1.3 mmol, 1.1 eq). The reaction mixture was stirred at rt for 18 h, then was partitioned between DCM (30 mL) and saturated aqueous NaHCO₃ solution (30 mL). The aqueous layer was extracted with DCM (30 mL x 2). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄, filtered, concentrated onto Celite, and purified by flash chromatography (0–10% MeOH in DCM on silica gel column) to afford **133** (216 mg, 62% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.01 (d, *J* = 8.3 Hz, 1H), 6.88 (d, *J* = 2.3 Hz, 1H), 6.78 (dd, *J* = 8.4, 2.3 Hz, 1H), 5.77 (s, 2H), 3.56 (br s, 2H), 3.13 (br s, 1H), 3.08 (br s, 1H), 2.36 – 2.09 (m, 7H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -58.80. ¹³C NMR (214 MHz, DMSO-*d*₆) δ 170.31, 152.62, 131.61, 129.52 (q, *J* = 30.7 Hz), 127.11 (q, *J* = 273.8 Hz), 124.23 (q, *J* = 2.2 Hz), 119.57, 113.40 (q, *J* = 5.0 Hz), 57.40, 57.26, 49.77, 48.75, 44.16.

1-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluorophenyl)-3-(4-(4-methylpiperazine-1-carbonyl)-3-(trifluoromethyl)phenyl)urea (47).—

To a solution of (4-amino-2-(trifluoromethyl)phenyl)(4-methylpiperazin-1-yl)methanone (**133**) (90 mg, 0.31 mmol, 1.4 eq) in DMSO (1.3 mL) was added 1,1'-carbonyldiimidazole (54 mg, 0.33 mmol, 1.5 eq). The reaction mixture was stirred at rt for 2 h, then warmed to 40°C and stirred for 1 h, monitoring reaction progress by TLC. This was added to a solution of 4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluoroaniline (**14**) (70 mg, 0.22 mmol, 1 eq) in DMSO (1 mL). The reaction mixture was stirred at 60°C for 2 h, then cooled to rt. The crude reaction mixture was partitioned between EtOAc

(15 mL) and water (15 mL). The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic extracts were washed with water, brine, dried over anhydrous Na₂SO₄, filtered, concentrated onto Celite, and purified by flash chromatography (1–20% MeOH in DCM on silica gel column) to afford **47** (26 mg, 19% yield) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.56 (s, 1H), 8.77 (d, *J* = 2.4 Hz, 1H), 8.50 (d, *J* = 5.2 Hz, 1H), 8.19 (t, *J* = 9.1 Hz, 1H), 8.08 (d, *J* = 2.1 Hz, 1H), 7.62 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.49 (s, 1H), 7.41 (s, 1H), 7.39 – 7.34 (m, 2H), 7.11 (ddd, *J* = 8.9, 2.8, 1.2 Hz, 1H), 6.55 (d, *J* = 5.2 Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.70 – 3.56 (m, 2H), 3.21 – 2.94 (m, 2H), 2.45 – 2.12 (m, 7H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ –58.84 (s, 3F), –124.95 (t, *J* = 10.6 Hz, 1F). ¹³C NMR (214 MHz, DMSO-*d*₆) δ 166.10, 159.55, 152.73 (d, *J* = 245.4 Hz), 152.62, 152.24, 149.42, 148.94 (d, *J* = 10.3 Hz), 148.88, 146.52, 140.35, 128.46, 128.01, 126.04 (q, *J* = 29.6 Hz), 124.60 (d, *J* = 10.8 Hz), 123.62 (q, *J* = 274.9 Hz), 122.39, 121.51, 117.10, 115.11, 115.09, 109.08 (d, *J* = 22.5 Hz), 107.88, 103.42, 99.03, 55.75, 55.72, 54.14, 54.02, 46.55, 45.55, 41.02. HRMS: calcd for C₃₁H₃₀F₄N₅O₅ [M + H]⁺ *m/z*, 628.2183; found *m/z*, 628.2175.

(3-amino-5-(trifluoromethyl)phenyl)(4-methylpiperazin-1-yl)methanone (135).—

To a solution of 3-amino-5-(trifluoromethyl)benzoic acid (**134**) (250 mg, 1.2 mmol, 1 eq) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (350 mg, 1.8 mmol, 1.5 eq) in DCM (2.4 mL) was added 1-methylpiperazine (134 mg, 1.3 mmol, 1.1 eq). The reaction mixture was stirred at rt for 18 h, then was partitioned between DCM (30 mL) and saturated aqueous NaHCO₃ solution (30 mL). The aqueous layer was extracted with DCM (30 mL x 2). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄, filtered, concentrated onto Celite, and purified by flash chromatography (1–12% MeOH in EtOAc on silica gel column) to afford **135** (161 mg, 46% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 6.89 (t, *J* = 2.0 Hz, 1H), 6.76 (t, *J* = 1.8 Hz, 1H), 6.69 (s, 1H), 5.79 (s, 2H), 3.57 (br s, 2H), 3.29 (br s, 2H), 2.32 (br s, 2H), 2.28 (br s, 2H), 2.19 (s, 3H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ –61.63. ¹³C NMR (214 MHz, DMSO-*d*₆) δ 168.12, 149.63, 137.74, 129.96 (q, *J* = 31.3 Hz), 124.13 (q, *J* = 272.4 Hz), 115.01, 110.10 (q, *J* = 3.7 Hz), 109.46 (q, *J* = 4.2, 3.7 Hz), 54.71 (br s), 54.21 (br s), 46.95 (br s), 45.59, 41.39 (br s).

1-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluorophenyl)-3-(3-(4-methylpiperazine-1-carbonyl)-5-(trifluoromethyl)phenyl)urea formate (48).—

To a solution of (3-amino-5-(trifluoromethyl)phenyl)(4-methylpiperazin-1-yl)methanone (**135**) (80 mg, 0.28 mmol, 1.25 eq) in DMSO (1.2 mL) was added 1,1'-carbonyldiimidazole (54 mg, 0.33 mmol, 1.5 eq). The reaction mixture was stirred at rt for 2 h, monitoring reaction progress by TLC. This was added to a solution of 4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluoroaniline (**14**) (70 mg, 0.22 mmol, 1 eq) in DMSO (1 mL). The reaction mixture was stirred at 60°C for 2 h, then cooled to rt. The crude reaction mixture was partitioned between EtOAc (15 mL) and water (15 mL). The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic extracts were washed with water, brine, dried over anhydrous Na₂SO₄, filtered, concentrated onto Celite, and purified by flash chromatography (1–12% MeOH in DCM on silica gel column then 8–20% MeCN in water with 0.1% formic acid on C18 column) to afford **48** (38 mg, 26% yield) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.70 (s, 1H), 8.93 (s, 1H), 8.50 (d, *J* = 5.2 Hz, 1H), 8.19 – 8.10 (m, 2H), 8.01 (s, 1H), 7.66 (s, 1H), 7.49 (s, 1H), 7.41 (s, 1H), 7.36 (dd, *J* = 11.6, 2.7 Hz, 1H), 7.31

(s, 1H), 7.16 – 7.08 (m, 1H), 6.55 (d, $J = 5.2$ Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.63 (br s, 2H), 3.33 (br s, 2H), 2.39 (br s, 2H), 2.32 (br s, 2H), 2.21 (s, 3H). ^{19}F NMR (376 MHz, DMSO- d_6) δ -61.47 (s, 3F), -124.36 (t, $J = 10.4$ Hz, 1F). ^{13}C NMR (214 MHz, DMSO- d_6) δ 167.24, 163.40, 159.52, 152.97 (d, $J = 245.2$ Hz), 152.61, 152.37, 149.41, 149.10 (d, $J = 10.9$ Hz), 148.86, 140.63, 137.78, 129.92 (q, $J = 32.5$ Hz), 124.52 (d, $J = 10.9$ Hz), 123.76 (q, $J = 273.2$ Hz), 122.80, 119.76, 117.04, 116.56, 115.12, 114.92, 109.08 (d, $J = 22.6$ Hz), 107.87, 103.44, 99.03, 55.74, 55.71, 54.58 (br s), 54.07 (br s), 46.96 (br s), 45.49, 41.47 (br s). HRMS: calcd for $\text{C}_{31}\text{H}_{31}\text{F}_4\text{N}_5\text{O}_5$ [$\text{M} + 2\text{H}$] $^{2+}$ m/z , 314.6131; found m/z , 314.6117.

1-(3-chlorophenyl)-3-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluorophenyl)urea (49).—

To a solution of 3-chloroaniline (24 mg, 0.19 mmol, 1.2 eq) in DMSO (1 mL) was added 1,1'-carbonyldiimidazole (34 mg, 0.21 mmol, 1.3 eq). The reaction mixture was stirred at rt for 1 h, monitoring reaction progress by TLC. This was added to a solution of 4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluoroaniline (**14**) (50 mg, 0.16 mmol, 1 eq) in DMSO (0.8 mL). The reaction mixture was stirred at 60°C for 4 h, then cooled to rt. The crude reaction mixture was partitioned between EtOAc (15 mL) and water (15 mL). The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4 , filtered, concentrated onto Celite, and purified by flash chromatography (20–100% EtOAc in Hexanes on silica gel column then 1–4% MeOH in DCM on silica gel column) to afford **49** (24 mg, 32% yield) as a light orange solid. ^1H NMR (400 MHz, DMSO- d_6) δ 9.26 (s, 1H), 8.68 (d, $J = 2.4$ Hz, 1H), 8.50 (d, $J = 5.2$ Hz, 1H), 8.20 (t, $J = 9.1$ Hz, 1H), 7.74 (t, $J = 2.0$ Hz, 1H), 7.49 (s, 1H), 7.40 (s, 1H), 7.35 (dd, $J = 11.8, 2.7$ Hz, 1H), 7.33 (t, $J = 8.0$ Hz, 1H), 7.26 (ddd, $J = 8.2, 2.1, 1.1$ Hz, 1H), 7.11 (ddd, $J = 9.0, 2.8, 1.3$ Hz, 1H), 7.05 (ddd, $J = 7.8, 2.1, 1.1$ Hz, 1H), 6.55 (d, $J = 5.2$ Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H). ^{19}F NMR (376 MHz, DMSO- d_6) δ -125.38 (t, $J = 10.6$ Hz). ^{13}C NMR (214 MHz, DMSO- d_6) δ 159.63, 152.64, 152.52 (d, $J = 245.0$ Hz), 152.15, 149.43, 148.87, 148.65 (d, $J = 10.6$ Hz), 146.47, 140.94, 133.31, 130.55, 124.85 (d, $J = 10.7$ Hz), 122.01 (d, $J = 2.8$ Hz), 121.80, 117.52, 117.12 (d, $J = 2.5$ Hz), 116.64, 115.11, 109.06 (d, $J = 22.3$ Hz), 107.84, 103.40, 99.06, 55.76, 55.74. HRMS: calcd for $\text{C}_{24}\text{H}_{20}\text{ClFN}_3\text{O}_4$ [$\text{M} + \text{H}$] $^+$ m/z , 468.1126; found m/z , 468.1115.

1-(3-bromophenyl)-3-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluorophenyl)urea (50).—

To a solution of 3-bromoaniline (33 mg, 0.19 mmol, 1.2 eq) in DMSO (1 mL) was added 1,1'-carbonyldiimidazole (34 mg, 0.21 mmol, 1.3 eq). The reaction mixture was stirred at rt for 30 min, monitoring reaction progress by TLC. This was added to a solution of 4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluoroaniline (**14**) (50 mg, 0.16 mmol, 1 eq) in DMSO (0.8 mL). The reaction mixture was stirred at 60°C for 5 h, then cooled to rt. The crude reaction mixture was partitioned between EtOAc (15 mL) and water (15 mL). The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4 , filtered, concentrated onto Celite, and purified by flash chromatography (20–70% EtOAc in Hexanes on silica gel column) to afford **50** (17 mg, 21% yield) as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 9.25 (s, 1H), 8.69 (d, $J = 2.5$ Hz, 1H), 8.49 (s, 0H), 8.20 (t, $J = 9.1$ Hz, 1H), 7.49 (s, 1H), 7.40 (s, 1H), 7.38 – 7.33 (m, 1H), 7.30 (dt, $J = 8.2, 1.7$ Hz, 1H), 7.26 (t, $J = 7.8$ Hz, 1H), 7.18 (dt, $J = 7.5, 1.7$ Hz, 1H), 7.11 (ddd, $J = 8.9, 2.8, 1.3$ Hz, 1H), 6.55 (d, $J = 5.2$ Hz, 1H), 3.95 (s,

3H), 3.93 (s, 3H). ^{19}F NMR (376 MHz, DMSO- d_6) δ -125.36 (t, J = 10.6 Hz). ^{13}C NMR (214 MHz, DMSO- d_6) δ 159.57, 152.60, 152.50 (d, J = 244.7 Hz), 152.11, 149.40, 148.87, 148.63 (d, J = 10.3 Hz), 146.50, 141.07, 130.83, 124.83 (d, J = 10.3 Hz), 124.67, 121.98 (d, J = 2.0 Hz), 121.81, 120.35, 117.09 (d, J = 3.0 Hz), 117.00, 115.09, 109.04 (d, J = 21.9 Hz), 107.87, 103.38, 99.03, 55.74, 55.71. HRMS: calcd for $\text{C}_{24}\text{H}_{20}\text{BrFN}_3\text{O}_4$ [$\text{M} + \text{H}$] $^+$ m/z , 512.0621; found m/z , 512.0611.

1-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluorophenyl)-3-(m-tolyl)urea (51).—To a solution of m-toluidine hydrochloride (27 mg, 0.19 mmol, 1.2 eq) in DMSO (1 mL) was added DIPEA (25 mg, 0.19 mmol, 1.2 eq) and 1,1'-carbonyldiimidazole (34 mg, 0.21 mmol, 1.3 eq). The reaction mixture was stirred at rt for 45 min, monitoring reaction progress by TLC. This was added to a solution of 4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluoroaniline (**14**) (50 mg, 0.16 mmol, 1 eq) in DMSO (0.8 mL). The reaction mixture was stirred at 60°C for 4 h, then cooled to rt. The crude reaction mixture was partitioned between EtOAc (15 mL) and water (15 mL). The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4 , filtered, concentrated onto Celite, and purified by flash chromatography (20–75% EtOAc in Hexanes on silica gel column) to afford **51** (25 mg, 35% yield) as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 9.00 (s, 1H), 8.61 (d, J = 2.5 Hz, 1H), 8.49 (d, J = 5.2 Hz, 1H), 8.25 (t, J = 9.1 Hz, 1H), 7.49 (s, 1H), 7.40 (s, 1H), 7.34 (dd, J = 11.8, 2.7 Hz, 1H), 7.31 (t, J = 1.9 Hz, 1H), 7.27 – 7.22 (m, 1H), 7.18 (t, J = 7.7 Hz, 1H), 7.09 (ddd, J = 8.9, 2.8, 1.3 Hz, 1H), 6.82 (dt, J = 7.4, 1.7 Hz, 1H), 6.54 (d, J = 5.2 Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 2.29 (s, 3H). ^{19}F NMR (376 MHz, DMSO- d_6) δ -125.95 (t, J = 10.6 Hz). ^{13}C NMR (214 MHz, DMSO- d_6) δ 159.64, 152.59, 152.21 (d, J = 244.1 Hz), 152.20, 149.38, 148.87, 148.19 (d, J = 10.2 Hz), 146.49, 139.31, 138.08, 128.73, 125.26 (d, J = 10.3 Hz), 122.86, 121.54 (d, J = 2.6 Hz), 118.65, 117.08 (d, J = 3.0 Hz), 115.32, 115.08, 108.99 (d, J = 22.0 Hz), 107.87, 103.31, 99.04, 55.73, 55.71, 21.22. HRMS: calcd for $\text{C}_{25}\text{H}_{23}\text{FN}_3\text{O}_4$ [$\text{M} + \text{H}$] $^+$ m/z , 448.1673; found m/z , 448.1661.

1-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluorophenyl)-3-(3-isopropylphenyl)urea (52).—To a solution of 3-isopropylaniline (26 mg, 0.19 mmol, 1.2 eq) in DMSO (1 mL) was added 1,1'-carbonyldiimidazole (34 mg, 0.21 mmol, 1.3 eq). The reaction mixture was stirred at rt for 20 min, monitoring reaction progress by TLC. This was added to a solution of 4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluoroaniline (**14**) (50 mg, 0.16 mmol, 1 eq) in DMSO (0.8 mL). The reaction mixture was stirred at 60°C for 4 h then cooled to rt. The crude reaction mixture was partitioned between EtOAc (15 mL) and water (15 mL). The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4 , filtered, concentrated onto Celite, and purified by flash chromatography (20–70% EtOAc in Hexanes on silica gel column) to afford **52** (39 mg, 52% yield) as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 9.03 (s, 1H), 8.59 (d, J = 2.5 Hz, 1H), 8.50 (d, J = 5.3 Hz, 1H), 8.25 (t, J = 9.1 Hz, 1H), 7.50 (s, 1H), 7.40 (s, 1H), 7.37 – 7.31 (m, 2H), 7.27 (ddd, J = 8.1, 2.2, 1.2 Hz, 1H), 7.21 (t, J = 7.7 Hz, 1H), 7.09 (ddd, J = 9.0, 2.7, 1.2 Hz, 1H), 6.88 (dt, J = 7.4, 1.5 Hz, 1H), 6.54 (d, J = 5.3 Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 2.86 (hept, J = 7.0 Hz, 1H), 1.20 (d, J = 6.9 Hz, 6H). ^{19}F NMR (376 MHz, DMSO-

d_6) δ -125.97 (t, J = 10.6 Hz). ^{13}C NMR (214 MHz, DMSO- d_6) δ 159.65, 152.59, 152.24, 152.23 (d, J = 244.4 Hz), 149.38, 149.14, 148.87, 148.20 (d, J = 10.2 Hz), 146.49, 139.36, 128.79, 125.26 (d, J = 10.6 Hz), 121.62 (d, J = 1.9 Hz), 120.22, 117.09 (d, J = 3.0 Hz), 116.08, 115.74, 115.07, 108.99 (d, J = 21.9 Hz), 107.87, 103.29, 99.03, 55.73, 55.71, 33.47, 23.86. HRMS: calcd for $\text{C}_{27}\text{H}_{27}\text{FN}_3\text{O}_4$ $[\text{M} + \text{H}]^+$ m/z , 476.1986; found m/z , 476.1973.

1-(3-(tert-butyl)phenyl)-3-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluorophenyl)urea (53).—To a solution of 3-(tert-butyl)aniline

(28 mg, 0.19 mmol, 1.2 eq) in DMSO (1 mL) was added 1,1'-carbonyldiimidazole (34 mg, 0.21 mmol, 1.3 eq). The reaction mixture was stirred at rt for 30 min, monitoring reaction progress by TLC. This was added to a solution of 4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluoroaniline (**14**) (50 mg, 0.16 mmol, 1 eq) in DMSO (0.8 mL). The reaction mixture was stirred at 60°C for 5 h, then cooled to rt. The crude reaction mixture was partitioned between EtOAc (15 mL) and water (15 mL). The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4 , filtered, concentrated onto Celite, and purified by flash chromatography (20–75% EtOAc in Hexanes on silica gel column) to afford **53** (42 mg, 54% yield) as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 9.05 (s, 1H), 8.57 (d, J = 2.5 Hz, 1H), 8.49 (d, J = 5.3 Hz, 1H), 8.25 (t, J = 9.1 Hz, 1H), 7.50 (s, 1H), 7.47 (t, J = 2.0 Hz, 1H), 7.40 (s, 1H), 7.34 (dd, J = 11.8, 2.7 Hz, 1H), 7.30 (ddd, J = 8.1, 2.1, 1.1 Hz, 1H), 7.22 (t, J = 7.9 Hz, 1H), 7.09 (ddd, J = 9.1, 2.8, 1.3 Hz, 1H), 7.04 (ddd, J = 7.8, 1.9, 1.1 Hz, 1H), 6.54 (d, J = 5.2 Hz, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 1.28 (s, 9H). ^{19}F NMR (376 MHz, DMSO- d_6) δ -126.01 (t, J = 10.4 Hz). ^{13}C NMR (214 MHz, DMSO- d_6) δ 159.66, 152.59, 152.27, 152.23 (d, J = 244.3 Hz), 151.39, 149.38, 148.87, 148.18 (d, J = 10.3 Hz), 146.49, 139.12, 128.54, 125.27 (d, J = 10.4 Hz), 121.66 (d, J = 2.6 Hz), 119.16, 117.10 (d, J = 3.0 Hz), 115.40, 115.11, 115.07, 108.99 (d, J = 22.2 Hz), 107.87, 103.28, 99.03, 55.73, 55.71, 34.40, 31.10. HRMS: calcd for $\text{C}_{28}\text{H}_{29}\text{FN}_3\text{O}_4$ $[\text{M} + \text{H}]^+$ m/z , 490.2142; found m/z , 490.2129.

1-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluorophenyl)-3-(3-methoxyphenyl)urea (54).—To a solution of 3-methoxyaniline (24 mg, 0.19 mmol,

1.2 eq) in DMSO (1 mL) was added 1,1'-carbonyldiimidazole (34 mg, 0.21 mmol, 1.3 eq). The reaction mixture was stirred at rt for 5 min. This was added to a solution of 4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluoroaniline (**14**) (50 mg, 0.16 mmol, 1 eq) in DMSO (0.8 mL). The reaction mixture was stirred at 60°C for 4 h, then cooled to rt. The crude reaction mixture was partitioned between EtOAc (15 mL) and water (15 mL). The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4 , filtered, concentrated onto Celite, and purified by flash chromatography (20–70% EtOAc in Hexanes on silica gel column) to afford **54** (11 mg, 15% yield) as an off-white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 9.09 (s, 1H), 8.61 (d, J = 2.5 Hz, 1H), 8.49 (d, J = 5.2 Hz, 1H), 8.24 (t, J = 9.1 Hz, 1H), 7.49 (s, 1H), 7.40 (s, 1H), 7.35 (dd, J = 11.8, 2.7 Hz, 1H), 7.24 – 7.16 (m, 2H), 7.10 (ddd, J = 8.9, 2.8, 1.3 Hz, 1H), 6.93 (ddd, J = 8.1, 2.0, 0.9 Hz, 1H), 6.58 (ddd, J = 8.3, 2.5, 0.9 Hz, 1H), 6.54 (d, J = 5.3 Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.74 (s, 3H). ^{19}F NMR (376 MHz, DMSO- d_6) δ -125.85 (t, J = 10.5 Hz). ^{13}C NMR (214 MHz, DMSO- d_6) δ 159.74, 159.63, 152.59, 152.27 (d, J = 244.4 Hz), 152.16, 149.38, 148.87, 148.29 (d, J = 10.5 Hz), 146.49, 140.60,

129.67, 125.14 (d, $J = 10.6$ Hz), 121.68 (d, $J = 2.6$ Hz), 117.10 (d, $J = 2.3$ Hz), 115.07, 110.43, 109.00 (d, $J = 21.8$ Hz), 107.87, 107.53, 103.90, 103.30, 99.03, 55.73, 55.71, 54.94. HRMS: calcd for $C_{25}H_{23}FN_3O_5$ $[M + H]^+$ m/z , 464.1622; found m/z , 464.1611.

1-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluorophenyl)-3-(3-

isopropoxyphenyl)urea (55).—To a solution of 3-isopropoxyaniline (29 mg, 0.19 mmol, 1.2 eq) in DMSO (1 mL) was added 1,1'-carbonyldiimidazole (34 mg, 0.21 mmol, 1.3 eq). The reaction mixture was stirred at rt for 20 min, monitoring reaction progress by TLC. This was added to a solution of 4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluoroaniline (**14**) (50 mg, 0.16 mmol, 1 eq) in DMSO (0.8 mL). The reaction mixture was stirred at 60°C for 4 h, then cooled to rt. The crude reaction mixture was partitioned between EtOAc (15 mL) and water (15 mL). The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4 , filtered, concentrated onto Celite, and purified by flash chromatography (20–70% EtOAc in Hexanes on silica gel column) to afford **55** (38 mg, 47% yield) as a white solid. 1H NMR (400 MHz, $DMSO-d_6$) δ 9.05 (s, 1H), 8.61 (d, $J = 2.5$ Hz, 1H), 8.49 (d, $J = 5.2$ Hz, 1H), 8.24 (t, $J = 9.1$ Hz, 1H), 7.49 (s, 1H), 7.40 (s, 1H), 7.34 (dd, $J = 11.8, 2.7$ Hz, 1H), 7.21 – 7.14 (m, 2H), 7.10 (ddd, $J = 9.0, 2.7, 1.3$ Hz, 1H), 6.88 (ddd, $J = 8.2, 1.9, 0.9$ Hz, 1H), 6.57 – 6.52 (m, 2H), 4.56 (hept, $J = 6.0$ Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 1.28 (s, 3H), 1.26 (s, 3H). ^{19}F NMR (376 MHz, $DMSO-d_6$) δ –125.84 (t, $J = 10.6$ Hz). ^{13}C NMR (214 MHz, $DMSO-d_6$) δ 159.64, 157.93, 152.59, 152.27 (d, $J = 244.4$ Hz), 152.18, 149.38, 148.87, 148.27 (d, $J = 10.3$ Hz), 146.49, 140.62, 129.65, 125.16 (d, $J = 10.3$ Hz), 121.66 (d, $J = 2.4$ Hz), 117.10 (d, $J = 3.1$ Hz), 115.07, 110.26, 109.29, 109.00 (d, $J = 22.1$ Hz), 107.87, 105.56, 103.30, 99.03, 69.09, 55.73, 55.71, 21.86. HRMS: calcd for $C_{27}H_{27}FN_3O_5$ $[M + H]^+$ m/z , 492.1935; found m/z , 492.1920.

1-(3-(difluoromethoxy)phenyl)-3-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-

fluorophenyl)urea (56).—To a solution of 3-(difluoromethoxy)aniline (30 mg, 0.19 mmol, 1.2 eq) in DMSO (1 mL) was added 1,1'-carbonyldiimidazole (34 mg, 0.19 mmol, 1.2 eq). The reaction mixture was stirred at rt for 10 min, monitoring reaction progress by TLC. This was added to a solution of 4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluoroaniline (**14**) (50 mg, 0.16 mmol, 1 eq) in DMSO (0.8 mL). The reaction mixture was stirred at 60°C for 4 h, then cooled to rt. The crude reaction mixture was partitioned between EtOAc (15 mL) and water (15 mL). The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4 , filtered, concentrated onto Celite, and purified by flash chromatography (20–70% EtOAc in Hexanes on silica gel column) to afford **56** (19 mg, 24% yield) as a white solid. 1H NMR (400 MHz, $DMSO-d_6$) δ 9.28 (s, 1H), 8.67 (d, $J = 2.5$ Hz, 1H), 8.50 (d, $J = 5.2$ Hz, 1H), 8.22 (t, $J = 9.1$ Hz, 1H), 7.52 – 7.47 (m, 2H), 7.40 (s, 1H), 7.38 – 7.29 (m, 2H), 7.21 (t, $J = 74.1$ Hz, 1H), 7.19 (ddd, $J = 8.3, 2.1, 1.0$ Hz, 1H), 7.11 (ddd, $J = 9.0, 2.9, 1.3$ Hz, 1H), 6.80 (dd, $J = 8.3, 2.4$ Hz, 1H), 6.55 (d, $J = 5.2$ Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H). ^{19}F NMR (376 MHz, $DMSO-d_6$) δ –81.53 (d, $J = 74.2$ Hz, 2F), –125.51 (t, $J = 10.7$ Hz, 1F). ^{13}C NMR (214 MHz, $DMSO-d_6$) δ 159.59, 152.60, 152.44 (d, $J = 244.9$ Hz), 152.14, 151.42 (t, $J = 3.2$ Hz), 149.39, 148.87, 148.56 (d, $J = 10.3$ Hz), 146.50, 140.99, 130.25, 124.89 (d, $J = 10.7$ Hz), 121.92 (d, $J = 2.6$ Hz), 117.10 (d, $J = 3.2$ Hz), 116.39 (t, $J = 256.3$

Hz), 115.08, 114.69, 111.91, 109.03 (d, $J = 21.8$ Hz), 108.34, 107.87, 103.35, 99.03, 55.74, 55.71. HRMS: calcd for $C_{25}H_{21}F_3N_3O_5$ [M + H]⁺ m/z, 500.1433; found m/z, 500.1425.

1-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluorophenyl)-3-(3-(trifluoromethoxy)phenyl)urea (57).—

To a solution of 3-(trifluoromethoxy)aniline (34 mg, 0.19 mmol, 1.2 eq) in DMSO (1 mL) was added 1,1'-carbonyldiimidazole (34 mg, 0.21 mmol, 1.3 eq). The reaction mixture was stirred at rt for 20 min, monitoring reaction progress by TLC. This was added to a solution of 4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluoroaniline (**14**) (50 mg, 0.16 mmol, 1 eq) in DMSO (0.8 mL). The reaction mixture was stirred at 60°C for 4 h, then cooled to rt. The crude reaction mixture was partitioned between EtOAc (15 mL) and water (15 mL). The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4 , filtered, concentrated onto Celite, and purified by flash chromatography (20–70% EtOAc in Hexanes on silica gel column) to afford **57** (17 mg, 21% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.37 (s, 1H), 8.69 (d, $J = 2.4$ Hz, 1H), 8.50 (d, $J = 5.2$ Hz, 1H), 8.20 (t, $J = 9.1$ Hz, 1H), 7.73 (s, 1H), 7.49 (s, 1H), 7.42 (t, $J = 8.2$ Hz, 1H), 7.41 (s, 1H), 7.36 (dd, $J = 11.8, 2.7$ Hz, 1H), 7.28 (ddd, $J = 8.3, 2.1, 0.9$ Hz, 1H), 7.11 (ddd, $J = 8.8, 2.8, 1.3$ Hz, 1H), 6.97 (ddt, $J = 8.1, 2.1, 1.0$ Hz, 1H), 6.55 (d, $J = 5.2$ Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -56.62 (s, 3F), -125.33 (t, $J = 10.5$ Hz, 1F). ¹³C NMR (214 MHz, DMSO-*d*₆) δ 159.57, 152.60, 152.54 (d, $J = 244.6$ Hz), 152.16, 149.40, 148.87, 148.76 (q, $J = 1.6$ Hz), 148.70 (d, $J = 10.5$ Hz), 146.50, 141.17, 130.54, 124.76 (d, $J = 10.8$ Hz), 122.10 (d, $J = 2.3$ Hz), 120.10 (q, $J = 256.2$ Hz), 117.10 (d, $J = 2.4$ Hz), 116.77, 115.09, 113.99, 110.09, 109.04 (d, $J = 21.9$ Hz), 107.87, 103.37, 99.03, 55.74, 55.72. HRMS: calcd for $C_{25}H_{20}F_4N_3O_5$ [M + H]⁺ m/z, 518.1339; found m/z, 518.1327.

1-(3-cyanophenyl)-3-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluorophenyl)urea (58).—

To a solution of 3-aminobenzonitrile (23 mg, 0.19 mmol, 1.2 eq) in DMSO (1 mL) was added 1,1'-carbonyldiimidazole (34 mg, 0.21 mmol, 1.3 eq). The reaction mixture was stirred at rt for 15 min, monitoring reaction progress by TLC. This was added to a solution of 4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluoroaniline (**14**) (50 mg, 0.16 mmol, 1 eq) in DMSO (0.8 mL). The reaction mixture was stirred at 60°C for 4 h, then cooled to rt. To achieve complete conversion, additional 1,1'-carbonyldiimidazole (68 mg, 0.42 mmol, 2.6 eq) and a solution of 3-aminobenzonitrile (23 mg, 0.19 mmol, 1.2 eq) in DMSO (0.5 mL) was added to the reaction mixture. The reaction mixture was stirred at 60°C for 18 h, then cooled to rt. The crude reaction mixture was partitioned between EtOAc (15 mL) and water (15 mL). The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4 , filtered, concentrated onto Celite, and purified by flash chromatography (20–75% EtOAc in Hexanes on silica gel column) to afford **58** (20 mg, 28% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.41 (s, 1H), 8.78 (d, $J = 2.4$ Hz, 1H), 8.50 (d, $J = 5.2$ Hz, 1H), 8.20 (t, $J = 9.1$ Hz, 1H), 8.00 (t, $J = 1.9$ Hz, 1H), 7.68 (ddd, $J = 8.5, 2.2, 1.2$ Hz, 1H), 7.52 (t, $J = 7.9$ Hz, 1H), 7.51 – 7.42 (m, 2H), 7.41 (s, 1H), 7.36 (dd, $J = 11.7, 2.7$ Hz, 1H), 7.12 (ddd, $J = 9.0, 2.7, 1.4$ Hz, 1H), 6.55 (d, $J = 5.2$ Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -125.13 (t, $J = 10.6$ Hz). ¹³C NMR (214 MHz, DMSO-*d*₆) δ 159.55, 152.61 (d, $J = 245.0$ Hz), 152.60, 152.20, 149.40, 148.87, 148.80 (d, $J = 10.4$ Hz), 146.51, 140.31, 130.31,

125.64, 124.68 (d, $J = 10.9$ Hz), 122.85, 122.15 (d, $J = 2.2$ Hz), 120.70, 118.82, 117.10 (d, $J = 2.9$ Hz), 115.10, 111.71, 109.06 (d, $J = 22.4$ Hz), 107.87, 103.41, 99.03, 55.74, 55.72. HRMS: calcd for $C_{25}H_{20}FN_4O_4$ $[M + H]^+$ m/z , 459.1469; found m/z , 459.1459.

1-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluorophenyl)-3-(4-(4-methylpiperazin-1-yl)phenyl)urea (59).—To a solution

of 4-(4-methylpiperazin-1-yl)aniline (37 mg, 0.19 mmol, 1.2 eq) in DMSO (1 mL) was added 1,1'-carbonyldiimidazole (34 mg, 0.21 mmol, 1.3 eq). The reaction mixture was stirred at rt for 2 h, monitoring reaction progress by TLC. This was added to a solution of 4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluoroaniline (**14**) (50 mg, 0.16 mmol, 1 eq) in DMSO (0.8 mL). The reaction mixture was stirred at 60°C for 3 h, then cooled to rt. The crude reaction mixture was partitioned between EtOAc (15 mL) and water (15 mL). The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4 , filtered, concentrated onto Celite, and purified by flash chromatography (0–15% MeOH in DCM on silica gel column) to afford **59** (31.4 mg, 19% yield) as a light yellow solid. 1H NMR (400 MHz, DMSO- d_6) δ 8.83 (s, 1H), 8.52 (d, $J = 2.6$ Hz, 1H), 8.49 (d, $J = 5.2$ Hz, 1H), 8.25 (t, $J = 9.1$ Hz, 1H), 7.49 (s, 1H), 7.40 (s, 1H), 7.35 – 7.24 (m, 3H), 7.08 (ddd, $J = 8.8, 2.8, 1.2$ Hz, 1H), 6.96 – 6.84 (m, 2H), 6.53 (d, $J = 5.2$ Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.05 (t, $J = 5.0$ Hz, 4H), 2.44 (t, $J = 5.0$ Hz, 4H), 2.21 (s, 3H). ^{19}F NMR (376 MHz, DMSO- d_6) δ -126.20 (t, $J = 10.7$ Hz). ^{13}C NMR (214 MHz, DMSO- d_6) δ 159.69, 152.59, 152.35, 152.09 (d, $J = 243.9$ Hz), 149.38, 148.88, 147.94 (d, $J = 10.5$ Hz), 146.69, 146.48, 131.31, 125.52 (d, $J = 10.4$ Hz), 121.39 (d, $J = 3.2$ Hz), 119.55, 117.09 (d, $J = 3.1$ Hz), 116.15, 115.07, 108.96 (d, $J = 21.9$ Hz), 107.86, 103.26, 99.05, 55.74, 55.72, 54.69, 48.80, 45.79. HRMS: calcd for $C_{29}H_{31}FN_5O_4$ $[M + H]^+$ m/z , 532.2360; found m/z , 532.2353.

1-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluorophenyl)-3-(4-(morpholinomethyl)phenyl)urea (60).—To a solution

of 4-(morpholinomethyl)aniline (39 mg, 0.20 mmol, 1.4 eq) in DMSO (1 mL) was added 1,1'-carbonyldiimidazole (35 mg, 0.21 mmol, 1.5 eq). The reaction mixture was stirred at rt for 1 h, monitoring reaction progress by TLC. This was added to a solution of 4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluoroaniline (**14**) (45 mg, 0.14 mmol, 1 eq) in DMSO (0.7 mL). The reaction mixture was stirred at 60°C for 2.5 h, then cooled to rt. The crude reaction mixture was partitioned between EtOAc (15 mL) and water (15 mL). The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4 , filtered, concentrated onto Celite, and purified by flash chromatography (1–10% MeOH in DCM on silica gel column) to afford **60** (28.3 mg, 37% yield) as a white solid. 1H NMR (850 MHz, DMSO- d_6) δ 9.09 (s, 1H), 8.64 (d, $J = 2.6$ Hz, 1H), 8.49 (d, $J = 5.2$ Hz, 1H), 8.24 (t, $J = 9.1$ Hz, 1H), 7.49 (s, 1H), 7.43 – 7.41 (m, 2H), 7.40 (s, 1H), 7.34 (dd, $J = 11.7, 2.7$ Hz, 1H), 7.24 – 7.19 (m, 2H), 7.09 (ddd, $J = 8.9, 2.7, 1.1$ Hz, 1H), 6.54 (d, $J = 5.2$ Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.56 (t, $J = 4.7$ Hz, 4H), 3.39 (s, 2H), 2.33 (br s, 4H). ^{19}F NMR (376 MHz, DMSO- d_6) δ -125.90 (t, $J = 10.6$ Hz). ^{13}C NMR (214 MHz, DMSO- d_6) δ 159.64, 152.58, 152.23, 152.22 (d, $J = 244.4$ Hz), 149.38, 148.86, 148.19 (d, $J = 10.1$ Hz), 146.48, 138.26, 131.36, 129.52, 125.26 (d, $J = 10.4$ Hz), 121.56 (d, $J = 2.6$ Hz), 117.97, 117.09 (d, $J =$

3.2 Hz), 115.07, 108.99 (d, $J = 21.9$ Hz), 107.86, 103.30, 99.03, 66.20, 62.01, 55.73, 55.71, 53.10. HRMS: calcd for $C_{29}H_{30}FN_4O_5$ [$M + H$] $^+$ m/z , 533.2200; found m/z , 533.2194.

1-(4-nitrobenzyl)piperidine (171).—To a solution of 1-(bromomethyl)-4-nitrobenzene (**136**) (500 mg, 2.3 mmol, 1 eq) in MeCN (5 mL) was added potassium carbonate (640 mg, 4.6 mmol, 2 eq), potassium iodide (38 mg, 0.23 mmol, 0.1 eq), and piperidine (217 mg, 2.6 mmol, 1.1 eq). The reaction mixture was stirred at rt for 3 h, then partitioned between EtOAc (50 mL) and water (50 mL). The aqueous layer was extracted with EtOAc (50 mL x 2). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 , and filtered to afford **171** (470 mg, 92% yield) as an orange oil. 1H NMR (400 MHz, DMSO- d_6) δ 8.28 – 8.11 (m, 2H), 7.67 – 7.47 (m, 2H), 3.55 (s, 2H), 2.33 (t, $J = 5.3$ Hz, 4H), 1.50 (p, $J = 5.4$ Hz, 4H), 1.39 (q, $J = 6.0$ Hz, 2H). ^{13}C NMR (101 MHz, DMSO- d_6) δ 147.27 (br s), 146.49, 129.60, 123.33, 61.84, 53.95, 25.55, 23.85.

4-(piperidin-1-ylmethyl)aniline (139).—A suspension of 1-(4-nitrobenzyl)piperidine (**171**) (467 mg, 2.1 mmol, 1 eq), iron (593 mg, 10.6 mmol, 5 eq), and ammonium chloride (908 mg, 17.0 mmol, 8 eq) in ethanol (6.3 mL) and water (2.1 mL) was heated at 45°C for 5 h. The reaction mixture was cooled to rt and filtered through Celite. Solvent was removed from the filtrate and the residue was partitioned between EtOAc (30 mL) and aqueous NaOH solution (1 M, 30 mL). The aqueous layer was extracted with EtOAc (30 mL x 2). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 , filtered, concentrated onto Celite, and purified by flash chromatography (0–15% MeOH in DCM on silica gel column) to afford **139** (385 mg, 95% yield) as a yellow-orange solid. 1H NMR (400 MHz, DMSO- d_6) δ 7.01 – 6.82 (m, 2H), 6.62 – 6.38 (m, 2H), 4.90 (s, 2H), 3.20 (s, 2H), 2.24 (t, $J = 6.0$ Hz, 4H), 1.45 (p, $J = 5.5$ Hz, 4H), 1.35 (q, $J = 9.3, 4.4$ Hz, 2H). ^{13}C NMR (101 MHz, DMSO- d_6) δ 147.41, 129.70, 125.28, 113.58, 62.79, 53.71, 25.57, 24.18.

1-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluorophenyl)-3-(4-(piperidin-1-ylmethyl)phenyl)urea bis(2,2,2-trifluoroacetate) (61).—To a solution of 4-(piperidin-1-ylmethyl)aniline (**139**) (35 mg, 0.19 mmol, 1.3 eq) in DMSO (1 mL) was added 1,1'-carbonyldiimidazole (37 mg, 0.23 mmol, 1.6 eq). The reaction mixture was stirred at rt for 1 h, monitoring reaction progress by TLC. This was added to a solution of 4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluoroaniline (**14**) (45 mg, 0.14 mmol, 1 eq) in DMSO (0.7 mL). The reaction mixture was stirred at 60°C for 2 h, then cooled to rt. The crude reaction mixture was partitioned between EtOAc (15 mL) and water (15 mL). The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4 , filtered, concentrated onto Celite, and purified by flash chromatography (0–12% MeOH in DCM on silica gel column then 10–100% MeOH in water with 0.05% TFA on reverse-phase column in prep-HPLC) to afford **61** (29.7 mg, 27% yield) as a light grey solid. 1H NMR (850 MHz, DMSO- d_6) δ 9.45 (s, 1H), 9.39 (s, 1H), 8.91 (d, $J = 2.9$ Hz, 1H), 8.78 (d, $J = 6.3$ Hz, 1H), 8.30 (t, $J = 9.0$ Hz, 1H), 7.69 (s, 1H), 7.60 – 7.53 (m, 3H), 7.50 (dd, $J = 11.4, 2.7$ Hz, 1H), 7.42 (dd, $J = 8.8, 2.2$ Hz, 2H), 7.25 – 7.21 (m, 1H), 6.89 (d, $J = 6.2$ Hz, 1H), 4.22 (d, $J = 5.1$ Hz, 2H), 4.03 (s, 3H), 4.02 (s, 4H), 3.32 (d, $J = 12.2$ Hz, 2H), 2.89 – 2.80 (m, 2H), 1.82 (dt, $J = 15.1, 3.4$ Hz, 2H), 1.69 (dt, $J = 13.3, 3.7$ Hz, 1H), 1.66 – 1.57 (m, 2H), 1.35 (qt, $J = 12.7, 3.8$

Hz, 1H). ^{19}F NMR (376 MHz, $\text{DMSO}-d_6$) δ -73.96 (s, 6H), -124.80 (t, J = 10.0 Hz, 1H). ^{13}C NMR (214 MHz, $\text{DMSO}-d_6$) δ 163.98 (br s), 158.17 (q, J = 32.7 Hz), 155.30, 152.33 (d, J = 245.3 Hz), 152.17, 150.75, 147.08 (d, J = 8.8 Hz), 144.63 (br s), 140.58, 132.13, 126.13 (d, J = 9.8 Hz), 122.88, 121.87 (d, J = 2.1 Hz), 118.08, 117.36 (d, J = 2.6 Hz), 116.76 (q, J = 297.9 Hz), 115.27, 109.36 (d, J = 22.7 Hz), 103.49, 99.98, 58.73, 56.42, 56.30, 51.54, 22.37, 21.33. (two expected aromatic singlets are not observed, probably due to overlap or signal-to-noise.) HRMS: calcd for $\text{C}_{30}\text{H}_{32}\text{FN}_4\text{O}_4$ [$\text{M} + \text{H}$] $^+$ m/z , 531.2408; found m/z , 531.2400.

1-(4-nitrobenzyl)pyrrolidine (172).—To a solution of 1-(bromomethyl)-4-nitrobenzene (**136**) (500 mg, 2.3 mmol, 1 eq) in MeCN (5 mL) was added potassium carbonate (640 mg, 4.6 mmol, 2 eq), potassium iodide (38 mg, 0.23 mmol, 0.1 eq), and pyrrolidine (181 mg, 2.6 mmol, 1.1 eq). The reaction mixture was stirred at rt for 3 h, then partitioned between EtOAc (50 mL) and water (50 mL). The aqueous layer was extracted with EtOAc (50 mL x 2). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 , and filtered to afford **172** (259 mg, 54% yield) as a yellow-orange oil. ^1H NMR (850 MHz, $\text{DMSO}-d_6$) δ 8.22 – 8.15 (m, 2H), 7.64 – 7.53 (m, 2H), 3.72 (s, 2H), 2.46 (t, J = 6.0 Hz, 4H), 1.71 (p, J = 3.1 Hz, 4H). ^{13}C NMR (214 MHz, $\text{DMSO}-d_6$) δ 146.46, 129.42, 123.38, 58.70, 53.52, 23.19. (missing carbon signal is likely due to overlap at the extraordinarily intense peak at 123.38 ppm.)

4-(pyrrolidin-1-ylmethyl)aniline (140).—A suspension of 1-(4-nitrobenzyl)pyrrolidine (**172**) (255 mg, 1.2 mmol, 1 eq), iron (346 mg, 6.2 mmol, 5 eq), and ammonium chloride (530 mg, 9.9 mmol, 8 eq) in ethanol (3.75 mL) and water (1.25 mL) was heated at 45°C for 7 h. The reaction mixture was cooled to rt and filtered through Celite. Solvent was removed from the filtrate and the residue was partitioned between EtOAc (30 mL) and aqueous NaOH solution (1 M, 30 mL). The aqueous layer was extracted with EtOAc (30 mL x 2). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 , filtered, concentrated onto Celite, and purified by flash chromatography (1–15% MeOH in DCM on silica gel column) to afford **140** (218 mg, 100% yield) as a yellow-orange solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.04 – 6.83 (m, 2H), 6.54 – 6.42 (m, 2H), 4.90 (s, 2H), 3.36 (s, 2H), 2.41 – 2.29 (m, 4H), 1.65 (p, J = 3.0 Hz, 4H). ^{13}C NMR (101 MHz, $\text{DMSO}-d_6$) δ 147.37, 129.30, 126.28, 113.62, 59.37, 53.29, 23.04.

1-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluorophenyl)-3-(4-(pyrrolidin-1-ylmethyl)phenyl)urea (62).—To a solution of 4-(pyrrolidin-1-ylmethyl)aniline (**140**) (36 mg, 0.21 mmol, 1.3 eq) in DMSO (1 mL) was added 1,1'-carbonyldiimidazole (44 mg, 0.27 mmol, 1.7 eq). The reaction mixture was stirred at rt for 1 h, monitoring reaction progress by TLC. This was added to a solution of 4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluoroaniline (**14**) (50 mg, 0.16 mmol, 1 eq) in DMSO (0.8 mL). The reaction mixture was stirred at 60°C for 4 h, then cooled to rt. The crude reaction mixture was partitioned between EtOAc (15 mL) and water (15 mL). The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4 , filtered, concentrated onto Celite, and purified by flash chromatography (1–15% MeOH in DCM on silica gel column) to afford **62** (51 mg, 63% yield) as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-$

d_6) δ 9.05 (s, 1H), 8.61 (d, J = 2.6 Hz, 1H), 8.49 (d, J = 5.2 Hz, 1H), 8.25 (t, J = 9.1 Hz, 1H), 7.49 (s, 1H), 7.40 (dd, J = 6.3, 2.2 Hz, 3H), 7.34 (dd, J = 11.8, 2.7 Hz, 1H), 7.25 – 7.18 (m, 2H), 7.09 (ddd, J = 8.9, 2.8, 1.3 Hz, 1H), 6.54 (d, J = 5.2 Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.50 (s, 2H), 2.44 – 2.33 (m, 4H), 1.68 (p, J = 3.0 Hz, 4H). ^{19}F NMR (376 MHz, DMSO- d_6) δ –125.98 (t, J = 10.7 Hz). ^{13}C NMR (214 MHz, DMSO- d_6) δ 159.65, 152.59, 152.23, 152.20 (d, J = 244.3 Hz), 149.38, 148.87, 148.16 (d, J = 10.2 Hz), 146.49, 137.98, 133.20, 128.99, 125.29 (d, J = 10.6 Hz), 121.52 (d, J = 2.6 Hz), 117.96, 117.09 (d, J = 3.0 Hz), 115.07, 108.98 (d, J = 21.9 Hz), 107.87, 103.30, 99.04, 59.14, 55.73, 55.71, 53.40, 23.09. HRMS: calcd for $\text{C}_{29}\text{H}_{30}\text{FN}_4\text{O}_4$ $[\text{M} + \text{H}]^+$ m/z , 517.2251; found m/z , 517.2244.

1-(4-((diethylamino)methyl)phenyl)-3-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluorophenyl)urea (63).—To a solution of 4-((diethylamino)methyl)aniline hydrochloride (44 mg, 0.21 mmol, 1.3 eq) in DMSO (1 mL) was added triethylamine (21 mg, 0.21 mmol, 1.3 eq) and 1,1'-carbonyldiimidazole (44 mg, 0.27 mmol, 1.7 eq). The reaction mixture was stirred at rt for 1 h, monitoring reaction progress by TLC. This was added to a solution of 4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluoroaniline (**14**) (50 mg, 0.16 mmol, 1 eq) in DMSO (0.8 mL). The reaction mixture was stirred at 60°C for 2 h, then cooled to rt. The crude reaction mixture was partitioned between EtOAc (15 mL) and water (15 mL). The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4 , filtered, concentrated onto Celite, and purified by flash chromatography (1–12% MeOH in DCM on silica gel column) to afford **63** (50 mg, 60% yield) as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 9.04 (s, 1H), 8.61 (d, J = 2.6 Hz, 1H), 8.49 (d, J = 5.2 Hz, 1H), 8.25 (t, J = 9.1 Hz, 1H), 7.49 (s, 1H), 7.43 – 7.37 (m, 3H), 7.34 (dd, J = 11.8, 2.7 Hz, 1H), 7.25 – 7.18 (m, 2H), 7.09 (ddd, J = 9.0, 2.8, 1.3 Hz, 1H), 6.54 (d, J = 5.2 Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.46 (s, 2H), 2.44 (q, J = 7.1 Hz, 4H), 0.97 (t, J = 7.1 Hz, 6H). ^{19}F NMR (376 MHz, DMSO- d_6) δ –126.01 (t, J = 10.6 Hz). ^{13}C NMR (214 MHz, DMSO- d_6) δ 159.65, 152.59, 152.23, 152.18 (d, J = 244.4 Hz), 149.38, 148.87, 148.15 (d, J = 10.1 Hz), 146.48, 137.89, 133.51, 129.06, 125.30 (d, J = 10.3 Hz), 121.50 (d, J = 1.9 Hz), 117.97, 117.09 (d, J = 3.1 Hz), 115.07, 108.98 (d, J = 22.2 Hz), 107.86, 103.29, 99.03, 56.38, 55.73, 55.71, 45.95, 11.64. HRMS: calcd for $\text{C}_{29}\text{H}_{32}\text{FN}_4\text{O}_4$ $[\text{M} + \text{H}]^+$ m/z , 519.2408; found m/z , 519.2400.

1-methyl-4-(4-nitrophenoxy)piperidine (173).—To a solution of 1-fluoro-4-nitrobenzene (**147**) (404 mg, 2.9 mmol, 1.1 eq) in DMSO (10 mL) in a water bath was added 1-methylpiperidin-4-ol (300 mg, 2.6 mmol, 1 eq) and potassium tert-butoxide (351 mg, 3.1 mmol, 1.2 eq) portionwise. The reaction mixture was stirred at rt for 16 h, then poured into ice water. The solid precipitated was collected by filtration, washed with water and dried under vacuum to afford **173** (219 mg, 36% yield) as a yellow solid. ^1H NMR (400 MHz, DMSO- d_6) δ 8.21 – 8.14 (m, 2H), 7.20 – 7.12 (m, 2H), 4.58 (tt, J = 8.2, 4.0 Hz, 1H), 2.65 – 2.55 (m, 2H), 2.22 – 2.14 (m, 5H), 2.01 – 1.89 (m, 2H), 1.66 (dtd, J = 12.7, 8.8, 3.7 Hz, 2H). ^{13}C NMR (101 MHz, DMSO- d_6) δ 162.73, 140.55, 125.96, 115.84, 73.10, 52.20, 45.78, 30.31.

4-((1-methylpiperidin-4-yl)oxy)aniline (150).—A suspension of 1-methyl-4-(4-nitrophenoxy)piperidine (**173**) (215 mg, 0.91 mmol, 1 eq), iron (254 mg, 4.6 mmol, 5 eq),

and ammonium chloride (389 mg, 7.3 mmol, 8 eq) in ethanol (2.7 mL) and water (0.9 mL) was heated at 45°C for 4 h. The reaction mixture was cooled to rt and filtered through Celite. Solvent was removed from the filtrate and the residue was partitioned between EtOAc (30 mL) and aqueous NaOH solution (1 M, 30 mL). The aqueous layer was extracted with EtOAc (30 mL x2). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄, filtered, concentrated onto Celite, and purified by flash chromatography (0–15% MeOH in DCM on silica gel column) to afford **173** (152 mg, 81% yield) as a yellow-orange solid. ¹H NMR (850 MHz, DMSO-*d*₆) δ 6.70 – 6.53 (m, 2H), 6.53 – 6.37 (m, 2H), 4.60 (s, 2H), 4.03 (tt, *J* = 8.8, 4.1 Hz, 1H), 2.61 – 2.57 (m, 2H), 2.16 (s, 3H), 2.10 (t, *J* = 10.9 Hz, 2H), 1.86 – 1.80 (m, 2H), 1.55 (dtd, *J* = 12.9, 8.9, 3.6 Hz, 2H). ¹³C NMR (214 MHz, DMSO-*d*₆) δ 147.98, 142.79, 117.77, 114.90, 73.06 (br s), 52.51, 45.80, 30.81.

1-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluorophenyl)-3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)urea (64).—To a solution

of 4-((1-methylpiperidin-4-yl)oxy)aniline (**150**) (43 mg, 0.21 mmol, 1.3 eq) in DMSO (1 mL) was added 1,1'-carbonyldiimidazole (44 mg, 0.27 mmol, 1.7 eq). The reaction mixture was stirred at rt for 1 h, monitoring reaction progress by TLC. This was added to a solution of 4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluoroaniline (**14**) (50 mg, 0.16 mmol, 1 eq) in DMSO (0.8 mL). The reaction mixture was stirred at 60°C for 3 h, then cooled to rt. The crude reaction mixture was partitioned between EtOAc (15 mL) and water (15 mL). The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic extracts were washed with water, brine, dried over anhydrous Na₂SO₄, filtered, concentrated onto Celite, and purified by flash chromatography (1–15% MeOH in DCM on silica gel column) to afford **64** (57 mg, 66% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.89 (s, 1H), 8.54 (d, *J* = 2.6 Hz, 1H), 8.49 (d, *J* = 5.2 Hz, 1H), 8.24 (t, *J* = 9.1 Hz, 1H), 7.49 (s, 1H), 7.40 (s, 1H), 7.37 – 7.30 (m, 3H), 7.09 (ddd, *J* = 8.9, 2.7, 1.3 Hz, 1H), 6.96 – 6.85 (m, 2H), 6.53 (d, *J* = 5.2 Hz, 1H), 4.26 (tt, *J* = 8.4, 3.8 Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 2.67 – 2.57 (m, 2H), 2.20 – 2.09 (m, 5H), 1.90 (d, *J* = 12.5 Hz, 2H), 1.60 (dtd, *J* = 12.7, 9.0, 3.6 Hz, 2H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ –126.12 (t, *J* = 10.7 Hz). ¹³C NMR (214 MHz, DMSO-*d*₆) δ 159.68, 152.59, 152.36, 152.34, 152.14 (d, *J* = 244.3 Hz), 149.38, 148.87, 148.03 (d, *J* = 10.0 Hz), 146.48, 132.51, 125.43 (d, *J* = 10.6 Hz), 121.45 (d, *J* = 2.5 Hz), 119.94, 117.09 (d, *J* = 3.1 Hz), 116.47, 115.07, 108.97 (d, *J* = 22.2 Hz), 107.86, 103.27, 99.04, 72.37 (br s), 55.73, 55.71, 52.45, 45.85, 30.68. HRMS: calcd for C₃₀H₃₂FN₄O₅ [M + H]⁺ m/z, 547.2357; found m/z, 547.2348.

1-methyl-N-(4-nitrophenyl)piperidin-4-amine (174).—To a solution of 1-fluoro-4-nitrobenzene (**147**) (435 mg, 3.1 mmol, 1 eq) in DMSO (6 mL) was added triethylamine (936 mg, 9.3 mmol, 3 eq) and 1-methylpiperidin-4-amine (387 mg, 3.4 mmol, 1.1 eq). The reaction mixture was stirred at 90°C for 16 h, then cooled to rt. The crude reaction mixture was partitioned between EtOAc (50 mL) and water (50 mL). The aqueous layer was extracted with EtOAc (50 mL x 2). The combined organic extracts were washed with water, brine, dried over anhydrous Na₂SO₄, filtered, concentrated onto Celite, and purified by flash chromatography (0–10% MeOH in DCM on silica gel column) to afford **174** (596 mg, 82% yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.00 – 7.94 (m, 2H), 7.18 (d, *J* = 7.7 Hz, 1H), 6.70 – 6.60 (m, 2H), 3.43 – 3.24 (m, 1H), 2.73 (dt, *J* = 12.6, 3.5 Hz, 2H), 2.16

(s, 3H), 2.01 (td, $J = 11.5, 2.5$ Hz, 2H), 1.92 – 1.80 (m, 2H), 1.51 – 1.36 (m, 2H). ^{13}C NMR (214 MHz, DMSO- d_6) δ 153.71, 135.37, 126.33, 111.03 (br s), 53.91, 48.64, 45.97, 31.29.

N¹-(1-methylpiperidin-4-yl)benzene-1,4-diamine (151).—A suspension of 1-methyl-N-(4-nitrophenyl)piperidin-4-amine (**174**) (384 mg, 1.6 mmol, 1 eq), iron (456 mg, 8.2 mmol, 5 eq), and ammonium chloride (698 mg, 13.1 mmol, 8 eq) in ethanol (4.8 mL) and water (1.6 mL) was heated at 60°C for 7 h, then cooled to rt. Additional iron (912 mg, 16.4 mmol, 10 eq) and ammonium chloride (1.40 g, 26.2 mmol, 16 eq) were added and the reaction mixture was stirred at 78°C for 26 h. The reaction mixture was cooled to rt and filtered through Celite. Solvent was removed from the filtrate and the residue was partitioned between EtOAc (50 mL) and aqueous NaOH solution (1 M, 50 mL). The aqueous layer was extracted with EtOAc (50 mL x2). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄, filtered, concentrated onto Celite, and purified by flash chromatography (5–15% MeOH in DCM on silica gel column) to afford **151** (177 mg, 53% yield) as a dull rose solid, which was stored under vacuum or under an argon atmosphere to prevent oxidation by atmospheric oxygen. ^1H NMR (850 MHz, DMSO- d_6) δ 6.41 – 6.38 (m, 2H), 6.38 – 6.35 (m, 2H), 4.36 (s, 1H), 4.23 (s, 2H), 2.97 (tt, $J = 10.2, 3.7$ Hz, 1H), 2.70 (d, $J = 10.9$ Hz, 2H), 2.14 (s, 3H), 1.94 (t, $J = 10.9$ Hz, 2H), 1.83 – 1.80 (m, 2H), 1.33 – 1.26 (m, 2H). ^{13}C NMR (214 MHz, DMSO- d_6) δ 139.08, 138.92, 115.48, 114.55, 54.37, 49.82 (br s), 46.01, 32.05.

1-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluorophenyl)-3-(4-((1-methylpiperidin-4-yl)amino)phenyl)urea (65).—To a solution of N¹-(1-methylpiperidin-4-yl)benzene-1,4-diamine (**151**) (42 mg, 0.21 mmol, 1.3 eq) in DMSO (1 mL) was added 1,1'-carbonyldiimidazole (44 mg, 0.27 mmol, 1.7 eq). The reaction mixture was stirred at rt for 1 h, monitoring reaction progress by TLC. This was added to a solution of 4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluoroaniline (**14**) (50 mg, 0.16 mmol, 1 eq) in DMSO (0.8 mL). The reaction mixture was stirred at 60°C for 5 h, then cooled to rt. The crude reaction mixture was partitioned between EtOAc (15 mL) and water (15 mL). The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic extracts were washed with water, brine, dried over anhydrous Na₂SO₄, filtered, concentrated onto Celite, and purified by flash chromatography (1–18% MeOH in DCM on silica gel column then 10–100% MeOH in water with 0.05% TFA on reverse-phase column on prep-HPLC) to afford the desired compound as a tris-(2,2,2-trifluoroacetate) salt. The salt was partitioned between EtOAc (15 mL) and saturated aqueous NaHCO₃ solution (15 mL). The aqueous layer was extracted with EtOAc (15 mL x 2). The combined organic extracts were washed with saturated aqueous NaHCO₃ solution, water, brine, dried over anhydrous Na₂SO₄, filtered, and dried under vacuum to afford **65** (30 mg, 34% yield) as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 8.60 (s, 1H), 8.49 (d, $J = 5.2$ Hz, 1H), 8.44 (d, $J = 2.6$ Hz, 1H), 8.25 (t, $J = 9.1$ Hz, 1H), 7.49 (s, 1H), 7.40 (s, 1H), 7.31 (dd, $J = 11.9, 2.7$ Hz, 1H), 7.18 – 7.10 (m, 2H), 7.07 (ddd, $J = 8.9, 2.8, 1.3$ Hz, 1H), 6.54 (d, $J = 6.2$ Hz, 2H), 6.52 (d, $J = 2.5$ Hz, 1H), 5.16 (d, $J = 8.2$ Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.17 – 3.02 (m, 1H), 2.72 (d, $J = 11.5$ Hz, 2H), 2.16 (s, 3H), 1.99 (t, $J = 11.3$ Hz, 2H), 1.86 (d, $J = 12.4$ Hz, 2H), 1.45 – 1.28 (m, 2H). ^{19}F NMR (376 MHz, DMSO- d_6) δ –126.48 (t, $J = 10.8$ Hz). ^{13}C NMR (214 MHz, DMSO- d_6) δ 159.72, 152.57, 152.49,

151.95 (d, $J = 243.7$ Hz), 149.36, 148.87, 147.70 (d, $J = 10.0$ Hz), 146.47, 143.84, 127.95, 125.73 (d, $J = 10.5$ Hz), 121.19 (d, $J = 2.5$ Hz), 120.72, 117.07 (d, $J = 3.1$ Hz), 115.05, 112.78, 108.92 (d, $J = 21.8$ Hz), 107.86, 103.21, 99.04, 55.73, 55.71, 54.27, 48.93, 46.01, 31.79. HRMS: calcd for $C_{30}H_{33}FN_5O_4$ $[M + H]^+$ m/z , 546.2517; found m/z , 546.2511.

N,1-dimethyl-N-(4-nitrophenyl)piperidin-4-amine (175).—To a solution of 1-fluoro-4-nitrobenzene (**147**) (400 mg, 2.8 mmol, 1 eq) in DMSO (5.7 mL) was added triethylamine (717 mg, 7.1 mmol, 2.5 eq) and N,1-dimethylpiperidin-4-amine (400 mg, 3.1 mmol, 1.1 eq). The reaction mixture was stirred at 90°C for 16 h, then cooled to rt. The crude reaction mixture was partitioned between EtOAc (50 mL) and water (50 mL). The aqueous layer was extracted with EtOAc (50 mL x 2). The combined organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4 , filtered, concentrated onto Celite, and purified by flash chromatography (0–10% MeOH in DCM on silica gel column) to afford **175** (536 mg, 76% yield) as a yellow solid. 1H NMR (400 MHz, DMSO- d_6) δ 8.15 – 7.84 (m, 2H), 7.03 – 6.65 (m, 2H), 3.80 (tt, $J = 11.7, 4.0$ Hz, 1H), 2.89 (s, 3H), 2.87 – 2.78 (m, 2H), 2.18 (s, 3H), 2.05 (td, $J = 11.8, 2.4$ Hz, 2H), 1.80 (qd, $J = 12.1, 3.9$ Hz, 2H), 1.65 – 1.53 (m, 2H). ^{13}C NMR (214 MHz, DMSO- d_6) δ 154.08, 135.53, 125.92, 111.08, 55.17, 54.55, 45.84, 31.43, 28.45.

N¹-methyl-N¹-(1-methylpiperidin-4-yl)benzene-1,4-diamine (152).—A suspension of N,1-dimethyl-N-(4-nitrophenyl)piperidin-4-amine (**175**) (221 mg, 0.89 mmol, 1 eq), iron (346 mg, 6.2 mmol, 7 eq), and ammonium chloride (474 mg, 8.9 mmol, 10 eq) in ethanol (2.7 mL) and water (0.9 mL) was heated at 78°C for 16 h. The reaction mixture was cooled to rt and filtered through Celite. Solvent was removed from the filtrate and the residue was partitioned between EtOAc (40 mL) and aqueous NaOH solution (1 M, 40 mL). The aqueous layer was extracted with EtOAc (50 mL x 2). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 , filtered, concentrated onto Celite, and purified by flash chromatography (5–15% MeOH in DCM on silica gel column) to afford **152** (177 mg, 91% yield) as a brown oil, which was stored under vacuum or under an argon atmosphere to prevent oxidation by atmospheric oxygen. 1H NMR (400 MHz, DMSO- d_6) δ 6.68 – 6.59 (m, 2H), 6.53 – 6.42 (m, 2H), 4.50 (s, 2H), 3.17 – 2.99 (m, 1H), 2.84 – 2.71 (m, 2H), 2.54 (s, 3H), 2.12 (s, 3H), 1.97 – 1.81 (m, 2H), 1.60 – 1.45 (m, 4H). ^{13}C NMR (214 MHz, DMSO- d_6) δ 141.56, 141.41, 118.83, 114.83, 58.54, 55.06, 45.91, 33.87, 28.39.

1-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluorophenyl)-3-(4-(methyl(1-methylpiperidin-4-yl)amino)phenyl)urea (66).—To a solution of N¹-methyl-N¹-(1-methylpiperidin-4-yl)benzene-1,4-diamine (**152**) (45 mg, 0.21 mmol, 1.3 eq) in DMSO (1 mL) was added 1,1'-carbonyldiimidazole (44 mg, 0.27 mmol, 1.7 eq). The reaction mixture was stirred at rt for 1 h, monitoring reaction progress by TLC. This was added to a solution of 4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluoroaniline (**14**) (50 mg, 0.16 mmol, 1 eq) in DMSO (0.8 mL). The reaction mixture was stirred at 60°C for 3 h, then cooled to rt. The crude reaction mixture was partitioned between EtOAc (15 mL) and water (15 mL). The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4 , filtered, concentrated onto Celite, and purified by flash chromatography (3–15% MeOH in DCM on

silica gel column) to afford **66** (62 mg, 69% yield) as a light grey solid. ^1H NMR (400 MHz, DMSO- d_6) δ 8.77 (s, 1H), 8.51 (d, J = 2.6 Hz, 1H), 8.49 (d, J = 5.3 Hz, 1H), 8.25 (t, J = 9.1 Hz, 1H), 7.49 (s, 1H), 7.40 (s, 1H), 7.32 (dd, J = 11.8, 2.7 Hz, 1H), 7.29 – 7.24 (m, 2H), 7.08 (ddd, J = 9.1, 2.7, 1.3 Hz, 1H), 6.82 – 6.74 (m, 2H), 6.53 (d, J = 5.2 Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 2.87 – 2.74 (m, 3H), 2.67 (s, 3H), 2.16 (s, 3H), 1.97 (td, J = 11.7, 2.4 Hz, 2H), 1.69 (qd, J = 12.1, 3.9 Hz, 2H), 1.58 – 1.48 (m, 2H). ^{19}F NMR (376 MHz, DMSO- d_6) δ –126.32 (t, J = 10.7 Hz). ^{13}C NMR (214 MHz, DMSO- d_6) δ 159.71, 152.58, 152.42, 152.02 (d, J = 243.7 Hz), 149.37, 148.87, 147.81 (d, J = 10.1 Hz), 146.47, 145.86, 129.29, 125.64 (d, J = 10.7 Hz), 121.31 (d, J = 2.7 Hz), 120.11, 117.07 (d, J = 3.1 Hz), 115.06, 114.47, 108.94 (d, J = 21.8 Hz), 107.86, 103.23, 99.04, 56.37, 55.73, 55.71, 55.09, 45.93, 31.60, 28.27. HRMS: calcd for $\text{C}_{31}\text{H}_{35}\text{FN}_5\text{O}_4$ [M + H] $^+$ m/z , 560.2673; found m/z , 560.2665.

1-(4-nitro-2-(trifluoromethyl)benzyl)piperidine (177).—To a solution of 1-(bromomethyl)-4-nitro-2-(trifluoromethyl)benzene (**137**) (250 mg, 0.88 mmol, 1 eq) in acetonitrile (1.8 mL) was added potassium carbonate (243 mg, 1.8 mmol, 2 eq), potassium iodide (15 mg, 0.088 mmol, 0.1 eq), and piperidine (90 mg, 1.1 mmol, 1.2 eq). The reaction mixture was stirred at rt for 1.5 h. The crude reaction mixture was partitioned between EtOAc (40 mL) and water (40 mL). The aqueous layer was extracted with EtOAc (40 mL x 2). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 , filtered, concentrated onto Celite, and purified by flash chromatography (0–15% EtOAc in Hexanes on silica gel column) to afford **177** (233 mg, 92% yield) as a yellow liquid. ^1H NMR (400 MHz, DMSO- d_6) δ 7.70 (dd, J = 8.6, 2.4 Hz, 1H), 7.59 (d, J = 2.4 Hz, 1H), 7.29 (d, J = 8.6 Hz, 1H), 2.86 (s, 2H), 1.56 (t, J = 5.0 Hz, 4H), 0.72 (p, J = 5.6 Hz, 4H), 0.60 (p, J = 5.7 Hz, 2H). ^{19}F NMR (376 MHz, DMSO- d_6) δ –58.97. ^{13}C NMR (214 MHz, DMSO- d_6) δ 146.19, 145.99, 132.02, 127.99 (q, J = 31.4 Hz), 127.20, 123.20 (q, J = 274.7 Hz), 120.99 (q, J = 6.2 Hz), 58.03, 54.09, 25.56, 23.66.

4-(piperidin-1-ylmethyl)-3-(trifluoromethyl)aniline (141).—A suspension of 1-(4-nitro-2-(trifluoromethyl)benzyl)piperidine (**177**) (233 mg, 0.81 mmol, 1 eq), iron (226 mg, 4.0 mmol, 5 eq), and ammonium chloride (346 mg, 6.5 mmol, 8 eq) in ethanol (2.4 mL) and water (0.8 mL) was heated at 40°C for 3 h. The reaction mixture was cooled to rt and filtered through Celite. Solvent was removed from the filtrate and the residue was partitioned between EtOAc (30 mL) and aqueous NaOH solution (1 M, 30 mL). The aqueous layer was extracted with EtOAc (30 mL x 2). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 , filtered, concentrated onto Celite, and purified by flash chromatography (0–10% MeOH in DCM on silica gel column) to afford **141** (196 mg, 94% yield) as a yellow liquid. ^1H NMR (400 MHz, DMSO- d_6) δ 7.30 (d, J = 8.3 Hz, 1H), 6.84 (d, J = 2.4 Hz, 1H), 6.75 (dd, J = 8.4, 2.4 Hz, 1H), 5.39 (s, 2H), 3.34 (s, 2H), 2.28 (t, J = 5.3 Hz, 4H), 1.47 (p, J = 5.4 Hz, 4H), 1.43 – 1.32 (m, 2H). ^{19}F NMR (376 MHz, DMSO- d_6) δ –57.85. ^{13}C NMR (214 MHz, DMSO- d_6) δ 147.65, 131.60, 127.68 (q, J = 28.8 Hz), 124.77 (q, J = 274.2 Hz), 123.32, 116.90, 110.21 (q, J = 5.8 Hz), 58.27, 53.99, 25.63, 24.04.

1-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluorophenyl)-3-(4-(piperidin-1-ylmethyl)-3-(trifluoromethyl)phenyl)urea (69).—To a solution of 4-(piperidin-1-ylmethyl)-3-(trifluoromethyl)aniline (**141**) (53 mg, 0.21

mmol, 1.3 eq) in DMSO (1 mL) was added 1,1'-carbonyldiimidazole (44 mg, 0.27 mmol, 0.16 eq). The reaction mixture was stirred at rt for 30 min, monitoring reaction progress by TLC. This was added to a solution of 4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluoroaniline (**14**) (50 mg, 0.16 mmol, 1 eq) in DMSO (0.8 mL). The reaction mixture was stirred at 60°C for 3 h, then cooled to rt. The crude reaction mixture was partitioned between EtOAc (15 mL) and water (15 mL). The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic extracts were washed with water, brine, dried over anhydrous Na₂SO₄, filtered, concentrated onto Celite, and purified by flash chromatography (1–10% MeOH in DCM on silica gel column) to afford **69** (30 mg, 32% yield) as a light pink solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.36 (s, 1H), 8.67 (d, *J* = 2.4 Hz, 1H), 8.50 (d, *J* = 5.2 Hz, 1H), 8.21 (t, *J* = 9.1 Hz, 1H), 7.99 (d, *J* = 2.2 Hz, 1H), 7.67 (d, *J* = 8.5 Hz, 1H), 7.55 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.49 (s, 1H), 7.40 (s, 1H), 7.35 (dd, *J* = 11.7, 2.7 Hz, 1H), 7.10 (ddd, *J* = 9.0, 2.8, 1.3 Hz, 1H), 6.55 (d, *J* = 5.2 Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.49 (s, 2H), 2.33 (t, *J* = 5.4 Hz, 4H), 1.51 (p, *J* = 5.5 Hz, 4H), 1.46 – 1.36 (m, 2H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ –58.10 (s, 3F), –125.40 (t, *J* = 10.6 Hz, 1F). ¹³C NMR (214 MHz, DMSO-*d*₆) δ 159.71, 152.63, 152.52 (d, *J* = 244.7 Hz), 152.32, 149.42, 148.96, 148.57 (d, *J* = 10.3 Hz), 146.53, 138.43, 131.34, 130.97, 127.54 (q, *J* = 29.6 Hz), 124.97 (d, *J* = 10.7 Hz), 124.45 (q, *J* = 274.0 Hz), 122.02, 121.62, 117.27 (d, *J* = 3.2 Hz), 115.09, 114.81 (q, *J* = 5.8 Hz), 109.22 (d, *J* = 22.2 Hz), 107.89, 103.33, 99.03, 58.14, 55.80, 55.77, 54.16, 25.69, 23.99. HRMS: calcd for C₃₁H₃₁F₄N₄O₄ [M + H]⁺ *m/z*, 599.2281; found *m/z*, 599.2272.

1-(4-bromo-2-(trifluoromethoxy)benzyl)piperidine (178).—To a solution of (4-bromo-2-(trifluoromethoxy)phenyl)methanol (**138**) (300 mg, 1.1 mmol, 1 eq) in DCM (7.4 mL) was added triethylamine (224 mg, 2.2 mmol, 2 eq). The reaction solution was cooled to 0°C using an ice bath and methanesulfonyl chloride (165 mg, 1.4 mmol, 1.3 eq) was added dropwise. The reaction mixture was warmed slowly to rt and stirred at rt for 2 h. Triethylamine (112 mg, 1.1 mmol, 1 eq) and pyrrolidine (315 mg, 4.4 mmol, 4 eq) were added. The reaction mixture was stirred at rt for 16 h, then concentrated onto Celite, and purified by flash chromatography (0–15% EtOAc in Hexanes on silica gel column) to afford **178** (333 mg, 89% yield) as a colorless liquid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.61 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.56 (dq, *J* = 2.0, 1.4 Hz, 1H), 7.51 (d, *J* = 8.3 Hz, 1H), 3.43 (s, 2H), 2.32 (t, *J* = 5.3 Hz, 4H), 1.48 (p, *J* = 5.5 Hz, 4H), 1.37 (p, *J* = 5.6 Hz, 2H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ –56.23. ¹³C NMR (101 MHz, DMSO-*d*₆) δ 147.22 (q, *J* = 1.4 Hz), 132.70, 131.24, 130.57, 123.71 (q, *J* = 1.2 Hz), 120.03 (q, *J* = 257.4 Hz), 119.94, 55.60, 53.83, 25.55, 23.77.

4-(piperidin-1-ylmethyl)-3-(trifluoromethoxy)aniline (144).—To a solution of 1-(4-bromo-2-(trifluoromethoxy)benzyl)piperidine (**178**) (328 mg, 0.97 mmol, 1 eq) in toluene (2.4 mL) was added bis(tri-*tert*-butylphosphine)palladium(0) (50 mg, 0.10 mmol, 0.1 eq) and lithium bis(trimethylsilyl)amide (1.5 M in THF, 0.97 mL, 1.5 mmol, 1.5 eq). The reaction mixture was stirred at rt for 16 h, then aqueous HCl (1 M, 2 mL) was added. The reaction mixture was stirred at rt for 10 min, then partitioned between EtOAc (20 mL) and aqueous NaOH (1 M, 15 mL). The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄, filtered, concentrated in vacuo, and purified by flash chromatography (1–10% MeOH in DCM on

silica gel column) to afford **144** (233 mg, 87% yield) as a yellow liquid. ^1H NMR (400 MHz, DMSO- d_6) δ 7.08 (d, J = 8.1 Hz, 1H), 6.57 – 6.43 (m, 2H), 5.39 (s, 2H), 3.26 (2H), 2.27 (br s, 4H), 1.45 (p, J = 5.4 Hz, 4H), 1.40 – 1.33 (m, 2H). ^{19}F NMR (376 MHz, DMSO- d_6) δ -55.49. ^{13}C NMR (214 MHz, DMSO- d_6) δ 149.27, 148.01, 131.75, 120.23 (q, J = 255.3 Hz), 116.64, 112.49, 104.78, 55.97, 53.65, 25.57, 24.00.

1-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluorophenyl)-3-(4-(piperidin-1-ylmethyl)-3-(trifluoromethoxy)phenyl)urea (70).—To a solution of 4-(piperidin-1-ylmethyl)-3-(trifluoromethoxy)aniline (**144**) (68 mg, 0.25 mmol, 1.3 eq) in DMSO (1.3 mL) was added 1,1'-carbonyldiimidazole (53 mg, 0.32 mmol, 1.7 eq). The reaction mixture was stirred at rt for 45 min, monitoring reaction progress by TLC. This was added to a solution of 4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluoroaniline (**14**) (60 mg, 0.19 mmol, 1 eq) in DMSO (1 mL). The reaction mixture was stirred at 60°C for 3 h, then cooled to rt. The crude reaction mixture was partitioned between EtOAc (15 mL) and water (15 mL). The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4 , filtered, concentrated onto Celite, and purified by flash chromatography (1–12% MeOH in DCM on silica gel column then 10–100% MeOH in water with 0.05% TFA on reverse-phase column on prep-HPLC). Fractions containing the desired product were concentrated in vacuo, then partitioned between EtOAc (15 mL) and saturated aqueous NaHCO_3 solution (15 mL). The aqueous layer was extracted with EtOAc (15 mL x 2). The combined organic extracts were washed with saturated aqueous NaHCO_3 solution, water, brine, dried over anhydrous Na_2SO_4 , filtered, and dried under vacuum to afford **70** (42 mg, 35% yield) as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 9.35 (s, 1H), 8.66 (d, J = 2.4 Hz, 1H), 8.50 (d, J = 5.2 Hz, 1H), 8.21 (t, J = 9.1 Hz, 1H), 7.75 (p, J = 1.7 Hz, 1H), 7.49 (s, 1H), 7.43 (d, J = 8.4 Hz, 1H), 7.40 (s, 1H), 7.35 (dd, J = 11.7, 2.7 Hz, 1H), 7.23 (dd, J = 8.4, 2.1 Hz, 1H), 7.10 (ddd, J = 9.0, 2.8, 1.3 Hz, 1H), 6.54 (d, J = 5.2 Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.41 (s, 2H), 2.33 (br s, 4H), 1.49 (p, J = 5.4 Hz, 4H), 1.38 (td, J = 9.8, 4.2 Hz, 2H). ^{19}F NMR (376 MHz, DMSO- d_6) δ -55.79 (s, 3F), -125.46 (t, J = 10.7 Hz, 1F). ^{13}C NMR (214 MHz, DMSO- d_6) δ 159.58, 152.60, 152.49 (d, J = 244.6 Hz), 152.17, 149.40, 148.85, 148.62 (d, J = 10.2 Hz), 147.21, 146.50, 139.60, 131.44, 124.82 (d, J = 10.4 Hz), 124.13 (br s), 122.05 (d, J = 2.3 Hz), 120.22 (q, J = 256.2 Hz), 117.10 (d, J = 3.1 Hz), 116.62, 115.08, 109.67, 109.03 (d, J = 22.1 Hz), 107.87, 103.34, 99.02, 55.79, 55.73, 55.71, 53.78, 25.56, 23.88. HRMS: calcd for $\text{C}_{31}\text{H}_{31}\text{F}_4\text{N}_4\text{O}_5$ [$\text{M} + \text{H}$] $^+$ m/z , 615.2231; found m/z , 615.2226.

1-(4-nitro-2-(trifluoromethyl)benzyl)pyrrolidine (179).—To a solution of 1-(bromomethyl)-4-nitro-2-(trifluoromethyl)benzene (**137**) (250 mg, 0.88 mmol, 1 eq) in acetonitrile (1.8 mL) was added potassium carbonate (243 mg, 1.8 mmol, 2 eq), potassium iodide (15 mg, 0.088 mmol, 0.1 eq), and pyrrolidine (75 mg, 1.1 mmol, 1.2 eq). The reaction mixture was stirred at rt for 1.5 h. The crude reaction mixture was partitioned between EtOAc (40 mL) and water (40 mL). The aqueous layer was extracted with EtOAc (40 mL x 2). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 , filtered, concentrated onto Celite, and purified by flash chromatography (0–20% EtOAc in Hexanes on silica gel column) to afford **179** (187 mg, 78% yield) as a yellow liquid. ^1H NMR (400 MHz, DMSO- d_6) δ 8.50 (dd, J = 8.6, 2.4 Hz, 1H), 8.40 (d, J = 2.4 Hz, 1H), 8.09

(d, $J = 8.6$ Hz, 1H), 3.86 (s, 2H), 2.54 – 2.51 (m, 4H), 1.80 – 1.69 (m, 4H). ^{19}F NMR (376 MHz, DMSO- d_6) δ –59.02. ^{13}C NMR (214 MHz, DMSO- d_6) δ 146.14, 132.10, 127.54 (q, $J = 31.7$ Hz), 127.26, 123.20 (q, $J = 274.7$ Hz), 120.95 (q, $J = 6.0$ Hz), 55.05, 53.60, 23.29. (missing aromatic carbon peak is probably due to overlap at 146.14 ppm.)

4-(pyrrolidin-1-ylmethyl)-3-(trifluoromethyl)aniline (142).—A suspension of 1-(4-nitro-2-(trifluoromethyl)benzyl)pyrrolidine (**179**). (184 mg, 0.67 mmol, 1 eq), iron (187 mg, 3.4 mmol, 5 eq), and ammonium chloride (287 mg, 5.4 mmol, 8 eq) in ethanol (2 mL) and water (0.65 mL) was heated at 40°C for 3 h. The reaction mixture was cooled to rt and filtered through Celite. Solvent was removed from the filtrate and the residue was partitioned between EtOAc (30 mL) and aqueous NaOH solution (1 M, 30 mL). The aqueous layer was extracted with EtOAc (30 mL x2). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 , filtered, concentrated onto Celite, and purified by flash chromatography (1–10% MeOH in DCM on silica gel column) to afford **142** (149 mg, 91% yield) as a yellow liquid. ^1H NMR (400 MHz, DMSO- d_6) δ 7.31 (d, $J = 8.3$ Hz, 1H), 6.84 (d, $J = 2.4$ Hz, 1H), 6.75 (dd, $J = 8.3, 2.4$ Hz, 1H), 5.39 (s, 2H), 3.52 (s, 2H), 2.41 (t, $J = 5.9$ Hz, 4H), 1.73 – 1.63 (m, 4H). ^{19}F NMR (376 MHz, DMSO- d_6) δ –57.88. ^{13}C NMR (214 MHz, DMSO- d_6) δ 147.61, 131.56, 127.22 (q, $J = 28.5, 27.8$ Hz), 124.78 (q, $J = 274.1$ Hz), 123.93, 116.90, 110.19 (q, $J = 5.9$ Hz), 55.09, 53.52, 23.13.

1-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluorophenyl)-3-(4-(pyrrolidin-1-ylmethyl)-3-(trifluoromethyl)phenyl)urea (71).—To a solution of 4-(pyrrolidin-1-ylmethyl)-3-(trifluoromethyl)aniline (**142**) (51 mg, 0.21 mmol, 1.3 eq) in DMSO (1 mL) was added 1,1'-carbonyldiimidazole (52 mg, 0.32 mmol, 2 eq). The reaction mixture was stirred at rt for 45 min, monitoring reaction progress by TLC. This was added to a solution of 4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluoroaniline (**14**) (50 mg, 0.16 mmol, 1 eq) in DMSO (0.8 mL). The reaction mixture was stirred at 60°C for 3 h, then cooled to rt. The crude reaction mixture was partitioned between EtOAc (15 mL) and water (15 mL). The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4 , filtered, concentrated onto Celite, and purified by flash chromatography (1–12% MeOH in DCM on silica gel column then 10–100% MeOH in water with 0.05% TFA on reverse-phase column on prep-HPLC). Fractions containing the desired product were concentrated in vacuo, then partitioned between EtOAc (15 mL) and saturated aqueous NaHCO_3 solution (15 mL). The aqueous layer was extracted with EtOAc (15 mL x 2). The combined organic extracts were washed with saturated aqueous NaHCO_3 solution, water, brine, dried over anhydrous Na_2SO_4 , filtered, and dried under vacuum to afford **71** (40 mg, 43% yield) as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 9.36 (s, 1H), 8.67 (d, $J = 2.4$ Hz, 1H), 8.50 (d, $J = 5.2$ Hz, 1H), 8.21 (t, $J = 9.1$ Hz, 1H), 7.98 (d, $J = 2.3$ Hz, 1H), 7.66 (d, $J = 8.5$ Hz, 1H), 7.56 (dd, $J = 8.5, 2.3$ Hz, 1H), 7.49 (s, 1H), 7.41 (s, 1H), 7.35 (dd, $J = 11.7, 2.7$ Hz, 1H), 7.10 (ddd, $J = 8.9, 2.8, 1.3$ Hz, 1H), 6.55 (d, $J = 5.2$ Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.68 (s, 2H), 2.46 (d, $J = 6.0$ Hz, 4H), 1.76 – 1.68 (m, 4H). ^{19}F NMR (376 MHz, DMSO- d_6) δ –58.12 (s, 3F), –125.38 (t, $J = 10.4$ Hz, 1F). ^{13}C NMR (214 MHz, DMSO- d_6) δ 159.71, 152.63, 152.54 (d, $J = 244.8$ Hz), 152.32, 149.42, 148.95, 148.59 (d, $J = 10.2$ Hz), 146.53, 138.41, 131.40, 127.09 (q, $J = 29.0, 28.4$ Hz),

124.96 (d, $J = 10.5$ Hz), 124.45 (q, $J = 274.1$ Hz), 122.05, 121.62, 117.27 (d, $J = 3.0$ Hz), 115.10, 114.78 (q, $J = 5.5$ Hz), 109.22 (d, $J = 21.9$ Hz), 107.89, 103.33, 99.03, 55.80, 55.77, 55.04, 53.69, 23.25. (missing aromatic carbon is probably due to overlap of signals at 131.40 ppm) HRMS: calcd for $C_{30}H_{29}F_4N_4O_4$ $[M + H]^+$ m/z , 585.2125; found m/z 585.2115.

1-(4-bromo-2-(trifluoromethoxy)benzyl)pyrrolidine (180).—To a solution of (4-bromo-2-(trifluoromethoxy)phenyl)methanol (**138**) (300 mg, 1.1 mmol, 1 eq) in DCM (7.4 mL) was added triethylamine (224 mg, 2.2 mmol, 2 eq). The reaction solution was cooled to 0°C using an ice bath and methanesulfonyl chloride (165 mg, 1.4 mmol, 1.3 eq) was added dropwise. The reaction mixture was warmed slowly to rt and stirred at rt for 2 h. Triethylamine (112 mg, 1.1 mmol, 1 eq) and pyrrolidine (315 mg, 4.4 mmol, 4 eq) were added. The reaction mixture was stirred at rt for 16 h, then concentrated onto Celite, and purified by flash chromatography (0–15% EtOAc in Hexanes on silica gel column) to afford **180** (310 mg, 86% yield) as a colorless liquid. 1H NMR (400 MHz, DMSO- d_6) δ 7.60 (dd, $J = 8.3, 1.9$ Hz, 1H), 7.56 (dq, $J = 1.9, 1.5$ Hz, 1H), 7.53 (d, $J = 8.3$ Hz, 1H), 3.60 (s, 2H), 2.46–2.41 (m, 4H), 1.69 (p, $J = 3.0$ Hz, 4H). ^{19}F NMR (376 MHz, DMSO- d_6) δ –56.34 (d, $J = 1.3$ Hz). ^{13}C NMR (101 MHz, DMSO- d_6) δ 146.76 (q, $J = 1.6$ Hz), 132.63, 131.80, 130.62, 123.65 (q, $J = 1.4$ Hz), 120.03 (q, $J = 257.5$ Hz), 119.87, 53.40, 52.37, 23.16.

4-(pyrrolidin-1-ylmethyl)-3-(trifluoromethoxy)aniline (145).—To a solution of 1-(4-bromo-2-(trifluoromethoxy)benzyl)pyrrolidine (**180**) (303 mg, 0.94 mmol, 1 eq) in toluene (2.3 mL) was added bis(tri-*tert*-butylphosphine)palladium(0) (48 mg, 0.09 mmol, 0.1 eq) and lithium bis(trimethylsilyl)amide (1.5 M in THF, 0.94 mL, 1.4 mmol, 1.5 eq). The reaction mixture was stirred at rt for 16 h, then aqueous HCl (1 M, 2 mL) was added. The reaction mixture was stirred at rt for 10 min, then partitioned between EtOAc (20 mL) and aqueous NaOH (1 M, 15 mL). The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 , filtered, concentrated in vacuo, and purified by flash chromatography (1–10% MeOH in DCM on silica gel column) to afford **145** (147 mg, 60% yield) as a yellow liquid. 1H NMR (400 MHz, DMSO- d_6) δ 7.10 (d, $J = 8.2$ Hz, 1H), 6.54–6.45 (m, 2H), 5.39 (s, 2H), 3.43 (s, 2H), 2.39 (t, $J = 5.7$ Hz, 4H), 1.72–1.60 (m, 4H). ^{19}F NMR (376 MHz, DMSO- d_6) δ –55.61. ^{13}C NMR (214 MHz, DMSO- d_6) δ 149.24, 147.55, 131.58, 120.23 (q, $J = 255.4$ Hz), 117.37 (br s), 112.55, 104.75, 53.23, 52.46, 23.05.

1-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluorophenyl)-3-(4-(pyrrolidin-1-ylmethyl)-3-(trifluoromethoxy)phenyl)urea (72).—To a solution of 4-(pyrrolidin-1-ylmethyl)-3-(trifluoromethoxy)aniline (**145**) (65 mg, 0.25 mmol, 1.3 eq) in DMSO (1.3 mL) was added 1,1'-carbonyldiimidazole (53 mg, 0.32 mmol, 1.7 eq). The reaction mixture was stirred at rt for 45 min, monitoring reaction progress by TLC. This was added to a solution of 4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluoroaniline (**14**) (60 mg, 0.19 mmol, 1 eq) in DMSO (1 mL). The reaction mixture was stirred at 60°C for 3 h, then cooled to rt. The crude reaction mixture was partitioned between EtOAc (15 mL) and water (15 mL). The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4 , filtered, concentrated onto Celite, and purified by flash chromatography

(1–12% MeOH in DCM on silica gel column then 10–100% MeOH in water with 0.05% TFA on reverse-phase column on prep-HPLC). Fractions containing the desired product were concentrated in vacuo, then partitioned between EtOAc (15 mL) and saturated aqueous NaHCO₃ solution (15 mL). The aqueous layer was extracted with EtOAc (15 mL x 2). The combined organic extracts were washed with saturated aqueous NaHCO₃ solution, water, brine, dried over anhydrous Na₂SO₄, filtered, and dried under vacuum to afford **72** (38 mg, 33% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.36 (s, 1H), 8.66 (d, *J* = 2.5 Hz, 1H), 8.50 (d, *J* = 5.2 Hz, 1H), 8.21 (t, *J* = 9.1 Hz, 1H), 7.75 (t, *J* = 1.8 Hz, 1H), 7.49 (s, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.41 (s, 1H), 7.35 (dd, *J* = 11.7, 2.7 Hz, 1H), 7.24 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.10 (ddd, *J* = 9.3, 2.7, 1.4 Hz, 1H), 6.54 (d, *J* = 5.2 Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.58 (s, 2H), 2.45 (t, *J* = 5.6 Hz, 4H), 1.77 – 1.64 (m, 4H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ –55.89 (s, 3F), –125.42 (t, *J* = 10.6 Hz, 1F). ¹³C NMR (214 MHz, DMSO-*d*₆) δ 159.58, 152.60, 152.50 (d, *J* = 244.6 Hz), 152.18, 149.40, 148.86, 148.63 (d, *J* = 10.1 Hz), 146.75, 146.50, 139.59 (br s), 131.35 (br s), 124.81 (d, *J* = 10.4 Hz), 124.81 (br s), 122.07 (d, *J* = 2.0 Hz), 120.22 (q, *J* = 256.4 Hz), 117.09 (d, *J* = 3.1 Hz), 116.66, 115.09, 109.62, 109.03 (d, *J* = 22.1 Hz), 107.87, 103.34, 99.02, 55.73, 55.71, 53.38, 52.41 (br s), 23.12. HRMS: calcd for C₃₀H₂₉F₄N₄O₅ [M + H]⁺ m/z, 601.2074; found m/z, 601.2070.

N-ethyl-N-(4-nitro-2-(trifluoromethyl)benzyl)ethanamine (181).—To a solution of 1-(bromomethyl)-4-nitro-2-(trifluoromethyl)benzene (**137**) (250 mg, 0.88 mmol, 1 eq) in acetonitrile (1.8 mL) was added potassium carbonate (243 mg, 1.8 mmol, 2 eq), potassium iodide (15 mg, 0.088 mmol, 0.1 eq), and diethylamine (77.3 mg, 1.0 mmol, 1.2 eq). The reaction mixture was stirred at rt for 3 h, then another portion of diethylamine (77.3 mg, 1.0 mmol, 1.2 eq) was added. The reaction mixture was stirred at 50°C for 4 h, then another portion of diethylamine (77.3 mg, 1.0 mmol, 1.2 eq) was added to drive reaction to completion. The reaction mixture was stirred at 50°C for 16 h, then cooled to rt. The crude reaction mixture was partitioned between EtOAc (40 mL) and water (40 mL). The aqueous layer was extracted with EtOAc (40 mL x 2). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄, filtered, concentrated onto Celite, and purified by flash chromatography (0–25% EtOAc in Hexanes on silica gel column) to afford **181** (154 mg, 64% yield) as a yellow liquid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.51 (dd, *J* = 8.7, 2.4 Hz, 1H), 8.39 (d, *J* = 2.4 Hz, 1H), 8.17 (d, *J* = 8.6 Hz, 1H), 3.78 (s, 2H), 2.53 (t, *J* = 7.1 Hz, 4H), 0.98 (t, *J* = 7.1 Hz, 6H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ –59.18. ¹³C NMR (214 MHz, DMSO-*d*₆) δ 147.66, 146.10, 131.98, 127.60 (q, *J* = 31.4 Hz), 127.14, 123.25 (q, *J* = 274.3 Hz), 120.88 (q, *J* = 6.2 Hz), 53.11, 46.97, 11.79.

4-((diethylamino)methyl)-3-(trifluoromethyl)aniline (143).—A suspension of N-ethyl-N-(4-nitro-2-(trifluoromethyl)benzyl)ethanamine (**181**) (151 mg, 0.55 mmol, 1 eq), iron (214 mg, 3.8 mmol, 7 eq), and ammonium chloride (292 mg, 5.5 mmol, 10 eq) in ethanol (1.7 mL) and water (0.55 mL) was heated at 50°C for 3 h. The reaction mixture was cooled to rt and filtered through Celite. Solvent was removed from the filtrate and the residue was partitioned between EtOAc (30 mL) and aqueous NaOH solution (1 M, 30 mL). The aqueous layer was extracted with EtOAc (30 mL x 2). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄, filtered, concentrated onto Celite, and purified by flash chromatography (0–10% MeOH in DCM on silica gel column) to

afford **143** (89 mg, 66% yield) as a yellow oil. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 7.37 (d, J = 8.4 Hz, 1H), 6.84 (d, J = 2.4 Hz, 1H), 6.75 (dd, J = 8.5, 2.4 Hz, 1H), 5.38 (s, 2H), 3.45 (s, 2H), 2.42 (q, J = 7.1 Hz, 4H), 0.94 (t, J = 7.1 Hz, 6H). ^{19}F NMR (376 MHz, $\text{DMSO-}d_6$) δ -58.06. ^{13}C NMR (214 MHz, $\text{DMSO-}d_6$) δ 147.51, 131.46, 127.39 (q, J = 29.2 Hz), 124.81 (q, J = 274.1 Hz), 124.61, 116.94, 110.19 (q, J = 5.8 Hz), 52.85, 46.25, 11.66.

1-(4-((diethylamino)methyl)-3-(trifluoromethyl)phenyl)-3-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluorophenyl)urea (73).—To a

solution of 4-((diethylamino)methyl)-3-(trifluoromethyl)aniline (**143**) (51 mg, 0.21 mmol, 1.3 eq) in DMSO (1 mL) was added 1,1'-carbonyldiimidazole (44 mg, 0.27 mmol, 1.7 eq). The reaction mixture was stirred at 40°C for 1 h, monitoring reaction progress by TLC. This was added to a solution of 4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluoroaniline (**14**) (50 mg, 0.16 mmol, 1 eq) in DMSO (0.8 mL). The reaction mixture was stirred at 60°C for 3 h, then cooled to rt. The crude reaction mixture was partitioned between EtOAc (15 mL) and water (15 mL). The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4 , filtered, concentrated onto Celite, and purified by flash chromatography (1–12% MeOH in DCM on silica gel column then 10–100% MeOH in water with 0.05% TFA on reverse-phase column on prep-HPLC). Fractions containing the desired product were concentrated in vacuo, then partitioned between EtOAc (15 mL) and saturated aqueous NaHCO_3 solution (15 mL). The aqueous layer was extracted with EtOAc (15 mL x 2). The combined organic extracts were washed with saturated aqueous NaHCO_3 solution, water, brine, dried over anhydrous Na_2SO_4 , filtered, and dried under vacuum to afford **73** (14 mg, 15% yield) as a white solid. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 9.35 (s, 1H), 8.67 (d, J = 2.5 Hz, 1H), 8.50 (d, J = 5.2 Hz, 1H), 8.21 (t, J = 9.1 Hz, 1H), 7.99 (d, J = 2.3 Hz, 1H), 7.74 (d, J = 8.5 Hz, 1H), 7.59 – 7.51 (m, 1H), 7.49 (s, 1H), 7.40 (s, 1H), 7.35 (dd, J = 11.7, 2.7 Hz, 1H), 7.14 – 7.07 (m, 1H), 6.55 (d, J = 5.2 Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.60 (s, 2H), 2.47 (q, J = 7.0 Hz, 4H), 0.97 (t, J = 7.1 Hz, 6H). ^{19}F NMR (376 MHz, $\text{DMSO-}d_6$) δ -58.32 (s, 3F), -125.42 (t, J = 10.8 Hz, 1F). ^{13}C NMR (214 MHz, $\text{DMSO-}d_6$) δ 159.58, 152.60, 152.51 (d, J = 244.7 Hz), 152.27, 149.40, 148.86, 148.62 (d, J = 10.2 Hz), 146.50, 138.23, 132.33, 131.19, 127.18 (q, J = 29.5 Hz), 124.85 (d, J = 10.7 Hz), 124.42 (q, J = 274.2 Hz), 122.04 (d, J = 2.5 Hz), 121.55, 117.09 (d, J = 3.0 Hz), 115.09, 114.76 (q, J = 6.5, 6.0 Hz), 109.04 (d, J = 22.0 Hz), 107.87, 103.36, 99.03, 55.73, 55.71, 52.83, 46.55, 11.73. HRMS: calcd for $\text{C}_{30}\text{H}_{31}\text{F}_4\text{N}_4\text{O}_4$ [$\text{M} + \text{H}$] $^+$ m/z, 587.2281; found m/z, 587.2271.

N-(4-bromo-2-(trifluoromethoxy)benzyl)-N-ethylethanamine (182).—To a solution of (4-bromo-2-(trifluoromethoxy)phenyl)methanol (**138**) (250 mg, 0.92 mmol, 1 eq) in DCM (6 mL) was added triethylamine (187 mg, 1.8 mmol, 2 eq). The reaction solution was cooled to 0°C using an ice bath and methanesulfonyl chloride (137 mg, 1.2 mmol, 1.3 eq) was added dropwise. The reaction mixture was warmed slowly to rt and stirred at rt for 2 h. Triethylamine (93 mg, 0.92 mmol, 1 eq) and diethylamine (337 mg, 4.6 mmol, 5 eq) were added. The reaction mixture was stirred at rt for 16 h, then concentrated onto Celite, and purified by flash chromatography (0–15% EtOAc in Hexanes on silica gel column) to afford **182** (226 mg, 75% yield) as a colorless liquid. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 7.61 (dd, J = 8.3, 1.9 Hz, 1H), 7.58 – 7.53 (m, 2H), 3.52 (s, 2H), 2.45 (q, J = 7.1 Hz, 4H), 0.96 (t, J

= 7.1 Hz, 6H). ^{19}F NMR (376 MHz, DMSO- d_6) δ -56.29. ^{13}C NMR (176 MHz, DMSO- d_6) δ 147.10, 132.72, 132.66, 130.52, 123.63, 120.07 (q, J = 257.5 Hz), 119.76, 50.31, 46.50, 11.70.

4-((diethylamino)methyl)-3-(trifluoromethoxy)aniline (146).—To a solution of N-(4-bromo-2-(trifluoromethoxy)benzyl)-N-ethylethanamine (**182**) (103 mg, 0.32 mmol, 1 eq) in toluene (0.8 mL) was added bis(tri-tert-butylphosphine)palladium(0) (16 mg, 0.03 mmol, 0.1 eq) and lithium bis(trimethylsilyl)amide (1.5 M in THF, 0.32 mL, 0.47 mmol, 1.5 eq). The reaction mixture was stirred at rt for 16 h, then aqueous HCl (1 M, 2 mL) was added. The reaction mixture was stirred at rt for 10 min, then partitioned between EtOAc (20 mL) and aqueous NaOH (1 M, 15 mL). The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 , filtered, concentrated in vacuo, and purified by flash chromatography (1–10% MeOH in DCM on silica gel column) to afford **146** (69 mg, 83% yield) as a yellow liquid. ^1H NMR (400 MHz, DMSO- d_6) δ 7.11 (d, J = 8.2 Hz, 1H), 6.53 – 6.46 (m, 2H), 5.38 (s, 2H), 3.37 (s, 2H), 2.41 (q, J = 7.1 Hz, 4H), 0.95 (t, J = 7.1 Hz, 6H). ^{19}F NMR (376 MHz, DMSO- d_6) δ -55.57 (d, J = 1.8 Hz). ^{13}C NMR (214 MHz, DMSO- d_6) δ 149.34, 148.03, 131.87, 120.33 (q, J = 255.2 Hz), 112.53, 104.85, 50.26, 46.00, 11.59. (missing aromatic carbon peak is probably due to overlap at 112.53 ppm.)

1-(4-((diethylamino)methyl)-3-(trifluoromethoxy)phenyl)-3-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluorophenyl)urea (74).—To a solution of 4-((diethylamino)methyl)-3-(trifluoromethoxy)aniline (**146**) (66 mg, 0.25 mmol, 1.3 eq) in DMSO (1.3 mL) was added 1,1'-carbonyldiimidazole (53 mg, 0.33 mmol, 1.7 eq). The reaction mixture was stirred at rt for 45 min, monitoring reaction progress by TLC. This was added to a solution of 4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluoroaniline (**14**) (61 mg, 0.19 mmol, 1 eq) in DMSO (1 mL). The reaction mixture was stirred at 60°C for 4 h, then cooled to rt. The crude reaction mixture was partitioned between EtOAc (15 mL) and water (15 mL). The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4 , filtered, concentrated onto Celite, and purified by flash chromatography (1–12% MeOH in DCM on silica gel column then 10–100% MeOH in water with 0.05% TFA on reverse-phase column on prep-HPLC). Fractions containing the desired product were concentrated in vacuo, then partitioned between EtOAc (15 mL) and saturated aqueous NaHCO_3 solution (15 mL). The aqueous layer was extracted with EtOAc (15 mL x 2). The combined organic extracts were washed with saturated aqueous NaHCO_3 solution, water, brine, dried over anhydrous Na_2SO_4 , filtered, and dried under vacuum to afford **74** (31 mg, 27% yield) as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 9.39 (s, 1H), 8.68 (s, 1H), 8.50 (d, J = 5.2 Hz, 1H), 8.21 (t, J = 9.1 Hz, 1H), 7.76 (s, 1H), 7.49 (s, 1H), 7.47 (d, J = 8.4 Hz, 1H), 7.41 (s, 1H), 7.35 (dd, J = 11.7, 2.7 Hz, 1H), 7.23 (dd, J = 8.6, 2.1 Hz, 1H), 7.10 (ddd, J = 9.0, 2.7, 1.3 Hz, 1H), 6.54 (d, J = 5.2 Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.51 (s, 2H), 2.46 (br s, 4H), 0.98 (t, J = 7.3 Hz, 6H). ^{19}F NMR (376 MHz, DMSO- d_6) δ -55.84 (s, 3F), -125.42 (t, J = 10.8 Hz, 1F). ^{13}C NMR (214 MHz, DMSO- d_6) δ 159.58, 152.60, 152.50 (d, J = 244.8 Hz), 152.19, 149.39, 148.85, 148.61 (d, J = 9.9 Hz), 147.11 (br s), 146.49, 139.47 (br s), 131.40 (br s), 125.40 (br s), 124.82 (d, J = 10.5

(br s), 122.06, 120.24 (q, $J = 256.5$ Hz), 117.09 (d, $J = 3.1$ Hz), 116.56, 115.08, 109.64 (br s), 109.03 (d, $J = 22.1$ Hz), 107.86, 103.34, 99.02, 55.73, 55.71, 50.28 (br s), 46.28, 11.67 (br s). HRMS: calcd for $C_{30}H_{31}F_4N_4O_5$ [$M + H$] $^+$ m/z , 603.2231; found m/z , 603.2229.

1-methyl-4-(4-nitro-2-(trifluoromethyl)phenoxy)piperidine (183).—To a solution of 1-fluoro-4-nitro-2-(trifluoromethyl)benzene (**148**) (629 mg, 3.0 mmol, 1.1 eq) in DMSO (10 mL) in a water bath was added 1-methylpiperidin-4-ol (315 mg, 2.7 mmol, 1 eq) and potassium tert-butoxide (368 mg, 3.3 mmol, 1.2 eq) portionwise. The reaction mixture was stirred at rt for 16 h, then was partitioned between EtOAc (60 mL) and water (60 mL). The aqueous layer was extracted with EtOAc (60 mL x 2). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 , filtered, concentrated onto Celite, and purified by flash chromatography (2–10% MeOH in DCM on silica gel column) to afford **183** (485 mg, 58% yield) as an orange solid. 1H NMR (400 MHz, DMSO- d_6) δ 8.47 (dd, $J = 9.3, 2.9$ Hz, 1H), 8.37 (d, $J = 2.8$ Hz, 1H), 7.56 (d, $J = 9.3$ Hz, 1H), 4.87 (tt, $J = 6.8, 3.5$ Hz, 1H), 2.49 – 2.41 (m, 2H), 2.39 – 2.25 (m, 2H), 2.17 (s, 3H), 1.95 (ddt, $J = 12.1, 7.7, 3.7$ Hz, 2H), 1.74 (dtd, $J = 13.6, 7.0, 3.5$ Hz, 2H). ^{19}F NMR (376 MHz, DMSO- d_6) δ –61.97. ^{13}C NMR (214 MHz, DMSO- d_6) δ 160.08, 139.70, 129.93, 123.17 (q, $J = 5.3$ Hz), 122.52 (q, $J = 272.2$ Hz), 117.90 (q, $J = 31.5$ Hz), 115.21, 73.72, 51.24, 45.86, 29.76.

4-((1-methylpiperidin-4-yl)oxy)-3-(trifluoromethyl)aniline (153).—A suspension of 1-methyl-4-(4-nitro-2-(trifluoromethyl)phenoxy)piperidine (**183**) (473 mg, 1.6 mmol, 1 eq), iron (434 mg, 7.8 mmol, 5 eq), and ammonium chloride (665 mg, 12.4 mmol, 8 eq) in ethanol (4.65 mL) and water (1.55 mL) was heated at 45°C for 16 h. The reaction mixture was cooled to rt and filtered through Celite. Solvent was removed from the filtrate and the residue was partitioned between EtOAc (50 mL) and aqueous NaOH solution (1 M, 50 mL). The aqueous layer was extracted with EtOAc (50 mL x2). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 , filtered, concentrated onto Celite, and purified by flash chromatography (3–15% MeOH in DCM on silica gel column) to afford **153** (379 mg, 89% yield) as a yellow solid, which was stored under vacuum or under an argon atmosphere to prevent oxidation by atmospheric oxygen. 1H NMR (400 MHz, DMSO- d_6) δ 6.97 (d, $J = 8.8$ Hz, 1H), 6.80 (d, $J = 2.8$ Hz, 1H), 6.75 (dd, $J = 8.8, 2.8$ Hz, 1H), 5.01 (s, 2H), 4.27 (tt, $J = 8.0, 3.8$ Hz, 1H), 2.59 – 2.52 (m, 2H), 2.21 – 2.07 (m, 5H), 1.96 – 1.77 (m, 2H), 1.61 (dtd, $J = 12.3, 8.3, 3.5$ Hz, 2H). ^{19}F NMR (376 MHz, DMSO- d_6) δ –60.05. ^{13}C NMR (214 MHz, DMSO- d_6) δ 145.35, 142.41, 123.98 (q, $J = 272.5$ Hz), 118.65 (q, $J = 29.3$ Hz), 118.52, 117.15, 111.42 (q, $J = 5.3$ Hz), 73.02 (br s), 52.04, 45.83, 30.50.

1-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluorophenyl)-3-(4-((1-methylpiperidin-4-yl)oxy)-3-(trifluoromethyl)phenyl)urea (75).—To a solution of 4-((1-methylpiperidin-4-yl)oxy)-3-(trifluoromethyl)aniline (**153**) (57 mg, 0.21 mmol, 1.3 eq) in DMSO (1 mL) was added 1,1'-carbonyldiimidazole (44 mg, 0.27 mmol, 1.7 eq). The reaction mixture was stirred at rt for 1 h, monitoring reaction progress by TLC. This was added to a solution of 4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluoroaniline (**14**) (50 mg, 0.16 mmol, 1 eq) in DMSO (0.8 mL). The reaction mixture was stirred at 60°C for 3 h, then cooled to rt. The crude reaction mixture was partitioned between EtOAc

(15 mL) and water (15 mL). The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic extracts were washed with water, brine, dried over anhydrous Na₂SO₄, filtered, concentrated onto Celite, and purified by flash chromatography (1–20% MeOH in DCM on silica gel column then 10–100% MeOH in water with 0.05% TFA on reverse-phase column on prep-HPLC). Fractions containing the desired product were concentrated in vacuo, then partitioned between EtOAc (15 mL) and saturated aqueous NaHCO₃ solution (15 mL). The aqueous layer was extracted with EtOAc (15 mL x 2). The combined organic extracts were washed with saturated aqueous NaHCO₃ solution, water, brine, dried over anhydrous Na₂SO₄, filtered, and dried under vacuum to afford **75** (36 mg, 37% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.16 (s, 1H), 8.60 (d, *J* = 2.3 Hz, 1H), 8.50 (d, *J* = 5.2 Hz, 1H), 8.20 (t, *J* = 9.1 Hz, 1H), 7.85 (d, *J* = 2.7 Hz, 1H), 7.52 (dd, *J* = 9.0, 2.7 Hz, 1H), 7.49 (s, 1H), 7.40 (s, 1H), 7.34 (dd, *J* = 11.7, 2.7 Hz, 1H), 7.26 (d, *J* = 9.1 Hz, 1H), 7.09 (ddd, *J* = 9.0, 2.7, 1.3 Hz, 1H), 6.54 (d, *J* = 5.2 Hz, 1H), 4.52 (tt, *J* = 7.5, 3.6 Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 2.54 (dd, *J* = 9.4, 5.7 Hz, 2H), 2.27 – 2.19 (m, 2H), 2.17 (s, 3H), 1.90 (tt, *J* = 10.7, 3.5 Hz, 2H), 1.74 – 1.61 (m, 2H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ –60.62 (s, 3F), –125.49 (t, *J* = 10.5 Hz, 1F). ¹³C NMR (214 MHz, DMSO-*d*₆) δ 159.60, 152.59, 152.45 (d, *J* = 244.6 Hz), 152.42, 149.95, 149.38, 148.85, 148.46 (d, *J* = 10.3 Hz), 146.49, 132.14, 125.02 (d, *J* = 10.7 Hz), 123.75, 123.63 (q, *J* = 272.5 Hz), 121.99 (d, *J* = 2.5 Hz), 117.92 (q, *J* = 29.5 Hz), 117.06 (d, *J* = 3.1 Hz), 116.83 (q, *J* = 5.2 Hz), 115.79, 115.08, 109.01 (d, *J* = 21.9 Hz), 107.86, 103.32, 99.02, 72.45 (br s), 55.73, 55.70, 51.72, 45.87, 30.19. HRMS: calcd for C₃₁H₃₁F₄N₄O₅ [M + H]⁺ m/z, 615.2231; found m/z, 615.2219.

1-methyl-4-(4-nitro-2-(trifluoromethoxy)phenoxy)piperidine (184).—To a solution of 1-chloro-4-nitro-2-(trifluoromethoxy)benzene (**149**) (300 mg, 1.24 mmol, 1 eq) in DMSO (5 mL) in a water bath was added 1-methylpiperidin-4-ol (143 mg, 1.24 mmol, 1 eq) and potassium tert-butoxide (167 mg, 1.2 mmol) portionwise. The reaction mixture was stirred at rt for 18 h, then was partitioned between EtOAc (30 mL) and aqueous NaOH (1M, 30 mL). The aqueous layer was extracted with EtOAc (30 mL x 2). The combined organic extracts were washed with water, brine, dried over anhydrous Na₂SO₄, filtered, concentrated onto Celite, and purified by flash chromatography (2–10% MeOH in DCM on silica gel column) to afford **184** (111 mg, 28% yield) as a brown solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.26 (dd, *J* = 9.2, 2.8 Hz, 1H), 8.23 – 8.21 (m, 1H), 7.55 (d, *J* = 9.4 Hz, 1H), 4.76 (tt, *J* = 7.4, 3.9 Hz, 1H), 2.55 – 2.51 (m, 2H), 2.27 (ddd, *J* = 11.4, 8.0, 3.3 Hz, 2H), 2.17 (s, 3H), 2.01 – 1.91 (m, 2H), 1.71 (dtd, *J* = 12.1, 7.9, 3.7 Hz, 2H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ –57.37. ¹³C NMR (176 MHz, DMSO-*d*₆) δ 155.40, 139.79, 136.51, 124.99, 120.10 (q, *J* = 258.2 Hz), 119.44, 115.22, 73.95 (br s), 51.60, 45.82, 29.93.

4-((1-methylpiperidin-4-yl)oxy)-3-(trifluoromethoxy)aniline (155).—A suspension of 1-methyl-4-(4-nitro-2-(trifluoromethoxy)phenoxy)piperidine (**184**) (108 mg, 0.34 mmol, 1 eq), iron (94 mg, 1.7 mmol, 5 eq), and ammonium chloride (144 mg, 2.7 mmol, 8 eq) in ethanol (1 mL) and water (0.35 mL) was heated at 60°C for 3 h. The reaction mixture was cooled to rt and filtered through Celite. Solvent was removed from the filtrate and the residue was partitioned between DCM (30 mL) and aqueous NaOH solution (1 M, 30 mL). The aqueous layer was extracted with DCM (30 mL x2). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄, filtered, concentrated onto Celite,

and purified by flash chromatography (3–12% MeOH in DCM on silica gel column) to afford **155** (87 mg, 90% yield) as a yellow oil, which was stored under vacuum or under an argon atmosphere to prevent oxidation by atmospheric oxygen. ¹H NMR (400 MHz, DMSO-*d*₆) δ 6.91 (d, *J* = 8.7 Hz, 1H), 6.52 (dq, *J* = 2.8, 1.4 Hz, 1H), 6.48 (dd, *J* = 8.7, 2.7 Hz, 1H), 5.04 (s, 2H), 4.05 (tt, *J* = 7.8, 3.8 Hz, 1H), 2.59 – 2.52 (m, 2H), 2.14 (s, 3H), 2.14 – 2.06 (m, 2H), 1.90 – 1.76 (m, 2H), 1.59 (dtd, *J* = 12.4, 8.4, 3.6 Hz, 2H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ –56.40. ¹³C NMR (214 MHz, DMSO-*d*₆) δ 144.11, 139.49, 139.17, 120.32 (q, *J* = 255.5 Hz), 119.82, 113.23, 107.70, 74.64 (br s), 52.24 (br s), 45.96, 30.73.

1-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluorophenyl)-3-(4-((1-methylpiperidin-4-yl)oxy)-3-(trifluoromethoxy)phenyl)urea (76).—To

a solution of 4-((1-methylpiperidin-4-yl)oxy)-3-(trifluoromethoxy)aniline (**155**) (86 mg, 0.30 mmol, 1.3 eq) in DMSO (1.5 mL) was added 1,1'-carbonyldiimidazole (63 mg, 0.39 mmol, 1.7 eq). The reaction mixture was stirred at rt for 45 min, monitoring reaction progress by TLC. This was added to a solution of 4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluoroaniline (**14**) (72 mg, 0.23 mmol, 1 eq) in DMSO (1 mL). The reaction mixture was stirred at 60°C for 3 h, then cooled to rt. The crude reaction mixture was partitioned between EtOAc (15 mL) and water (15 mL). The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic extracts were washed with water, brine, dried over anhydrous Na₂SO₄, filtered, concentrated onto Celite, and purified by flash chromatography (1–15% MeOH in DCM on silica gel column then 10–100% MeOH in water with 0.05% TFA on reverse-phase column on prep-HPLC). Fractions containing the desired product were concentrated in vacuo, then partitioned between EtOAc (15 mL) and saturated aqueous NaHCO₃ solution (15 mL). The aqueous layer was extracted with EtOAc (15 mL x 2). The combined organic extracts were washed with saturated aqueous NaHCO₃ solution, water, brine, dried over anhydrous Na₂SO₄, filtered, and dried under vacuum to afford **76** (81 mg, 56% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.15 (s, 1H), 8.59 (d, *J* = 2.5 Hz, 1H), 8.49 (d, *J* = 5.2 Hz, 1H), 8.20 (t, *J* = 9.1 Hz, 1H), 7.68 (q, *J* = 1.4 Hz, 1H), 7.49 (s, 1H), 7.40 (s, 1H), 7.34 (dd, *J* = 11.8, 2.7 Hz, 1H), 7.22 (d, *J* = 1.5 Hz, 2H), 7.09 (ddd, *J* = 8.9, 2.8, 1.3 Hz, 1H), 6.54 (d, *J* = 5.2 Hz, 1H), 4.36 (tt, *J* = 7.6, 3.5 Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 2.60 – 2.52 (m, 2H), 2.24 – 2.15 (m, 5H), 1.93 – 1.82 (m, 2H), 1.65 (dtd, *J* = 12.1, 8.0, 3.6 Hz, 2H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ –56.76 (s, 3F), –125.57 (dd, *J* = 12.2, 9.1 Hz, 1F). ¹³C NMR (214 MHz, DMSO-*d*₆) δ 159.61, 152.59, 152.43 (d, *J* = 244.6 Hz), 152.29, 149.39, 148.86, 148.47 (d, *J* = 10.3 Hz), 146.49, 144.20, 137.90, 133.10, 124.99 (d, *J* = 10.6 Hz), 121.97 (d, *J* = 2.0 Hz), 120.28 (q, *J* = 255.8 Hz), 118.08, 117.40, 117.08 (d, *J* = 3.0 Hz), 115.08, 113.17, 109.01 (d, *J* = 22.1 Hz), 107.87, 103.32, 99.03, 73.48 (br s), 55.73, 55.71, 51.96, 45.87, 30.40. HRMS: calcd for C₃₁H₃₁F₄N₄O₆ [M + H]⁺ m/z, 631.2180; found m/z, 631.2169.

N,1-dimethyl-N-(4-nitro-2-(trifluoromethyl)phenyl)piperidin-4-amine (185).—To a solution of 1-fluoro-4-nitro-2-(trifluoromethyl)benzene (**148**) (500 mg, 2.4 mmol, 1 eq) in DMSO (4.8 mL) was added triethylamine (605 mg, 6.0 mmol, 2.5 eq) and N,1-dimethylpiperidin-4-amine (337 mg, 2.6 mmol, 1.1 eq). The reaction mixture was stirred at 90°C for 20 h, then cooled to rt. The crude reaction mixture was partitioned between EtOAc (50 mL) and water (50 mL). The aqueous layer was extracted with EtOAc (50 mL

x 2). The combined organic extracts were washed with water, brine, dried over anhydrous Na₂SO₄, filtered, concentrated onto Celite, and purified by flash chromatography (2–10% MeOH in DCM on silica gel column) to afford **185** (567 mg, 75% yield) as a reddish orange oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.37 (d, *J* = 2.8 Hz, 1H), 8.33 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.53 (d, *J* = 9.2 Hz, 1H), 3.23 (tt, *J* = 11.0, 4.0 Hz, 1H), 2.82 – 2.76 (m, 5H), 2.14 (s, 3H), 1.88 (td, *J* = 11.7, 2.5 Hz, 2H), 1.72 (qd, *J* = 11.8, 3.7 Hz, 2H), 1.66 – 1.59 (m, 2H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ –57.84. ¹³C NMR (214 MHz, DMSO-*d*₆) δ 156.85, 140.18, 127.80, 124.42 (q, *J* = 5.9 Hz), 123.87, 123.33 (q, *J* = 273.3 Hz), 120.64 (q, *J* = 30.8 Hz), 60.92, 54.48, 45.72, 36.28, 28.55.

N¹-methyl-N¹-(1-methylpiperidin-4-yl)-2-(trifluoromethyl)benzene-1,4-diamine (154).—A suspension of N,1-dimethyl-N-(4-nitro-2-(trifluoromethyl)phenyl)piperidin-4-amine (**185**) (561 mg, 1.8 mmol, 1 eq), iron (691 mg, 12.4 mmol, 7 eq), and ammonium chloride (946 mg, 17.7 mmol, 10 eq) in ethanol (5.25 mL) and water (1.75 mL) was heated at 78°C for 16 h. The reaction mixture was cooled to rt and filtered through Celite. Solvent was removed from the filtrate and the residue was partitioned between DCM (30 mL) and aqueous NaOH solution (1 M, 30 mL). The aqueous layer was extracted with DCM (30 mL x 2). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄, filtered, concentrated onto Celite, and purified by flash chromatography (5–15% MeOH in DCM on silica gel column) to afford **154** (371 mg, 73% yield) as a reddish oil, which was stored under vacuum or under an argon atmosphere to prevent oxidation by atmospheric oxygen. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.18 (d, *J* = 8.5 Hz, 1H), 6.79 (d, *J* = 2.7 Hz, 1H), 6.76 (dd, *J* = 8.5, 2.7 Hz, 1H), 5.31 (s, 2H), 2.70 (d, *J* = 11.3 Hz, 2H), 2.56 (t, *J* = 9.9 Hz, 1H), 2.46 (s, 3H), 2.09 (s, 3H), 1.75 (td, *J* = 12.0, 2.3 Hz, 2H), 1.62 (d, *J* = 12.3 Hz, 2H), 1.30 (qd, *J* = 12.2, 3.8 Hz, 2H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ –58.66. ¹³C NMR (214 MHz, DMSO-*d*₆) δ 146.24, 139.65, 127.61 (q, *J* = 27.3 Hz), 127.18, 124.19 (q, *J* = 273.3 Hz), 117.80, 110.46 (q, *J* = 5.5 Hz), 60.19, 54.45, 45.81, 41.23, 30.09.

1-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluorophenyl)-3-(4-(methyl(1-methylpiperidin-4-yl)amino)-3-(trifluoromethyl)phenyl)urea (77).—To a solution of N¹-methyl-N¹-(1-methylpiperidin-4-yl)-2-(trifluoromethyl)benzene-1,4-diamine (**154**) (59 mg, 0.21 mmol, 1.3 eq) in DMSO (1 mL) was added 1,1'-carbonyldiimidazole (44 mg, 0.27 mmol, 1.7 eq). The reaction mixture was stirred at rt for 1 h, monitoring reaction progress by TLC. This was added to a solution of 4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluoroaniline (**14**) (50 mg, 0.16 mmol, 1 eq) in DMSO (0.8 mL). The reaction mixture was stirred at 60°C for 3 h, then cooled to rt. The crude reaction mixture was partitioned between EtOAc (15 mL) and water (15 mL). The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic extracts were washed with water, brine, dried over anhydrous Na₂SO₄, filtered, concentrated onto Celite, and purified by flash chromatography (1–18% MeOH in DCM on silica gel column then 10–100% MeOH in water with 0.05% TFA on reverse-phase column on prep-HPLC). Fractions containing the desired product were concentrated in vacuo, then partitioned between EtOAc (15 mL) and saturated aqueous NaHCO₃ solution (15 mL). The aqueous layer was extracted with EtOAc (15 mL x 2). The combined organic extracts were washed with saturated aqueous NaHCO₃ solution, water, brine, dried over anhydrous Na₂SO₄, filtered, and dried under vacuum to afford **77**

(31 mg, 31% yield) as a white solid. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 9.34 (s, 1H), 8.66 (d, $J = 2.4$ Hz, 1H), 8.50 (d, $J = 5.3$ Hz, 1H), 8.21 (t, $J = 9.1$ Hz, 1H), 7.91 (d, $J = 2.5$ Hz, 1H), 7.58 (dd, $J = 8.8, 2.6$ Hz, 1H), 7.50 (d, $J = 9.5$ Hz, 2H), 7.41 (s, 1H), 7.34 (dd, $J = 11.7, 2.7$ Hz, 1H), 7.10 (ddd, $J = 8.9, 2.8, 1.3$ Hz, 1H), 6.55 (d, $J = 5.2$ Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 2.72 (t, $J = 10.2$ Hz, 3H), 2.54 (s, 3H), 2.12 (s, 3H), 1.81 (t, $J = 11.7$ Hz, 2H), 1.65 (d, $J = 11.6$ Hz, 2H), 1.38 (qd, $J = 12.0, 3.8$ Hz, 2H). ^{19}F NMR (376 MHz, $\text{DMSO-}d_6$) δ -58.77 (s, 3F), -125.39 (t, $J = 10.6$ Hz, 1F). ^{13}C NMR (214 MHz, $\text{DMSO-}d_6$) δ 159.59, 152.59, 152.49 (d, $J = 245.1$ Hz), 152.28, 149.39, 148.86, 148.59 (d, $J = 10.2$ Hz), 146.50, 145.97, 136.67, 127.49, 127.40 (q, $J = 27.2$ Hz), 124.89 (d, $J = 10.6$ Hz), 123.82 (q, $J = 273.3$ Hz), 122.62, 122.03 (d, $J = 2.4$ Hz), 117.09 (d, $J = 3.2$ Hz), 115.71 (q, $J = 5.6$ Hz), 115.08, 109.03 (d, $J = 22.0$ Hz), 107.87, 103.34, 99.02, 60.02, 55.73, 55.71, 54.32, 45.71, 40.78, 29.83. HRMS: calcd for $\text{C}_{32}\text{H}_{34}\text{F}_4\text{N}_5\text{O}_4$ $[\text{M} + \text{H}]^+$ m/z , 628.2547; found m/z , 628.2535.

N,1-dimethyl-N-(4-nitro-2-(trifluoromethoxy)phenyl)piperidin-4-amine (186).—

To a solution of 1-chloro-4-nitro-2-(trifluoromethoxy)benzene (**149**) (300 mg, 1.24 mmol, 1 eq) in DMSO (2.5 mL) was added N,1-dimethylpiperidin-4-amine (510 mg, 4.0 mmol, 3.2 eq) and potassium phosphate (527 mg, 2.48 mmol, 2 eq). The reaction mixture was stirred at 100°C for 18 h, then cooled to rt. The crude reaction mixture was partitioned between EtOAc (30 mL) and water (30 mL). The aqueous layer was extracted with EtOAc (30 mL x 2). The combined organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4 , filtered, concentrated onto Celite, and purified by flash chromatography (2–10% MeOH in DCM on silica gel column) to afford **186** (198 mg, 48% yield) as a yellow-brown solid. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 8.11 (dd, $J = 9.3, 2.7$ Hz, 1H), 8.04 (dq, $J = 2.7, 1.3$ Hz, 1H), 7.21 (d, $J = 9.3$ Hz, 1H), 3.53 (tt, $J = 11.2, 3.9$ Hz, 1H), 2.91 – 2.81 (m, 5H), 2.17 (s, 3H), 2.01 – 1.80 (m, 4H), 1.62 – 1.49 (m, 2H). ^{19}F NMR (376 MHz, $\text{DMSO-}d_6$) δ -57.18. ^{13}C NMR (214 MHz, $\text{DMSO-}d_6$) δ 150.46, 137.63, 136.32, 124.23, 120.22 (q, $J = 258.1$ Hz), 119.32, 118.70, 59.51, 54.72, 45.76, 33.41, 28.41.

N¹-methyl-N¹-(1-methylpiperidin-4-yl)-2-(trifluoromethoxy)benzene-1,4-diamine (156).—

A suspension of N,1-dimethyl-N-(4-nitro-2-(trifluoromethoxy)phenyl)piperidin-4-amine (**186**). (194 mg, 0.58 mmol, 1 eq), iron (261 mg, 4.6 mmol, 8 eq), and ammonium chloride (313 mg, 5.8 mmol, 10 eq) in ethanol (1.8 mL) and water (0.6 mL) was heated at 60°C for 24 h. The reaction mixture was cooled to rt and filtered through Celite. Solvent was removed from the filtrate and the residue was partitioned between DCM (30 mL) and aqueous NaOH solution (1 M, 30 mL). The aqueous layer was extracted with DCM (30 mL x 2). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 , filtered, concentrated onto Celite, and purified by flash chromatography (3–12% MeOH in DCM on silica gel column) to afford **156** (113 mg, 64% yield) as an orange oil, which was stored under vacuum or under an argon atmosphere to prevent oxidation by atmospheric oxygen. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 7.04 – 6.90 (m, 1H), 6.56 – 6.42 (m, 2H), 5.16 (s, 2H), 2.78 – 2.70 (m, 2H), 2.63 (tt, $J = 11.1, 4.1$ Hz, 1H), 2.52 (s, 3H), 2.10 (s, 3H), 1.78 (td, $J = 11.7, 2.4$ Hz, 2H), 1.64 – 1.53 (m, 2H), 1.43 (qd, $J = 11.9, 3.8$ Hz, 2H). ^{19}F NMR (376 MHz, $\text{DMSO-}d_6$) δ -55.41. ^{13}C NMR (214 MHz, $\text{DMSO-}d_6$) δ 146.19, 144.66, 132.92, 125.82, 120.34 (q, $J = 255.2$ Hz), 112.83, 106.42, 60.25, 54.84, 46.05, 37.16, 28.99.

1-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluorophenyl)-3-(4-(methyl(1-methylpiperidin-4-yl)amino)-3-(trifluoromethoxy)phenyl)urea (78).—To a solution of N¹-methyl-N¹-(1-methylpiperidin-4-yl)-2-(trifluoromethoxy)benzene-1,4-diamine (**156**) (55 mg, 0.18 mmol, 1.3 eq) in DMSO (0.9 mL) was added 1,1'-carbonyldiimidazole (39 mg, 0.24 mmol, 1.7 eq). The reaction mixture was stirred at rt for 45 min, monitoring reaction progress by TLC. This was added to a solution of 4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluoroaniline (**14**) (44 mg, 0.14 mmol, 1 eq) in DMSO (0.7 mL). The reaction mixture was stirred at 60°C for 3 h, then cooled to rt. The crude reaction mixture was partitioned between EtOAc (15 mL) and water (15 mL). The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic extracts were washed with water, brine, dried over anhydrous Na₂SO₄, filtered, concentrated onto Celite, and purified by flash chromatography (3–15% MeOH in DCM on silica gel column then 10–100% MeOH in water with 0.05% TFA on reverse-phase column on prep-HPLC). Fractions containing the desired product were concentrated in vacuo, then partitioned between EtOAc (15 mL) and saturated aqueous NaHCO₃ solution (15 mL). The aqueous layer was extracted with EtOAc (15 mL x 2). The combined organic extracts were washed with saturated aqueous NaHCO₃ solution, water, brine, dried over anhydrous Na₂SO₄, filtered, and dried under vacuum to afford **78** (40 mg, 44% yield) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 9.19 (s, 1H), 8.60 (d, J = 2.5 Hz, 1H), 8.49 (d, J = 5.2 Hz, 1H), 8.21 (t, J = 9.1 Hz, 1H), 7.66 (s, 1H), 7.49 (s, 1H), 7.40 (s, 1H), 7.34 (dd, J = 11.7, 2.7 Hz, 1H), 7.23 – 7.13 (m, 2H), 7.09 (dt, J = 8.9, 1.8 Hz, 1H), 6.54 (d, J = 5.2 Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 2.89 (tt, J = 10.6, 4.7 Hz, 1H), 2.78 (d, J = 11.3 Hz, 2H), 2.61 (s, 3H), 2.12 (s, 3H), 1.83 (td, J = 11.2, 3.4 Hz, 2H), 1.68 – 1.51 (m, 4H). ¹⁹F NMR (376 MHz, DMSO-d₆) δ -55.86 (s, 3F), -125.64 (t, J = 10.4 Hz, 1F). ¹³C NMR (214 MHz, DMSO-d₆) δ 159.73, 152.62, 152.40 (d, J = 244.5 Hz), 152.28, 149.41, 148.95, 148.36 (d, J = 10.3 Hz), 146.52, 142.22, 139.31, 134.72, 125.12 (d, J = 10.6 Hz), 123.51, 121.87 (d, J = 2.7 Hz), 120.25 (q, J = 256.2 Hz), 117.31, 117.28 (d, J = 2.4 Hz), 115.07, 111.75, 109.20 (d, J = 21.9 Hz), 107.89, 103.27, 99.03, 59.95, 55.79, 55.76, 54.90, 45.90, 34.76, 28.39. HRMS: calcd for C₃₂H₃₄F₄N₅O₅ [M + H]⁺ m/z, 644.2496; found m/z, 644.2485.

Experimental Procedures in Scheme 7.

tert-butyl 4-(4-(methoxycarbonyl)benzylidene)piperidine-1-carboxylate (159).—To a solution of methyl 4-bromobenzoate (**157**) (700 mg, 3.26 mmol, 1 eq) and tert-butyl 4-methylenepiperidine-1-carboxylate (**158**) (963 mg, 4.88 mmol, 1.5 eq) in DMF (6.5 mL) was added triethylamine (988 mg, 9.77 mmol, 3 eq) and [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (238 mg, 0.33 mmol, 0.1 eq). The reaction mixture was stirred at 100°C for 16 h. The reaction mixture was cooled to rt and filtered through Celite. The filtrate was portioned between EtOAc (50 mL) and water (50 mL), and the organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered, concentrated onto Celite, and purified by flash chromatography (0–20% EtOAc in Hexanes on silica gel column) to afford **159** (199 mg, 18% yield) as a light green solid. ¹H NMR (400 MHz, DMSO-d₆) δ 7.91 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.3 Hz, 2H), 6.43 (s, 1H), 3.84 (s, 3H), 3.42 (t, J = 5.8 Hz, 2H), 3.35 (t, J = 5.9 Hz, 2H), 2.42 (t, J = 5.8 Hz, 2H), 2.31 (t, J = 5.5 Hz, 2H), 1.41 (s, 9H). ¹³C NMR (214 MHz, DMSO-d₆) δ 166.01, 153.77, 141.94, 140.87, 129.15, 128.97, 127.31, 123.34, 78.81, 52.04, 44.78 (*), 43.78 (*), 35.66

(br s), 28.89 (br s), 28.06. (*not observed on 1D ^{13}C spectrum, peaks were confirmed by (^1H - ^{13}C)-HSQC. 1D spectrum shows three very broad singlets at this region probably reflecting chemical exchange)

4-((1-(tert-butoxycarbonyl)piperidin-4-ylidene)methyl)benzoic acid (176).—To a solution of tert-butyl 4-(4-(methoxycarbonyl)benzylidene)piperidine-1-carboxylate (**159**) (194 mg, 0.58 mmol, 1 eq) in THF (3.6 mL) and water (0.90 mL) was added lithium hydroxide (42 mg, 1.8 mmol, 3 eq). The reaction mixture was stirred at 50°C for 6 h. The reaction mixture was cooled to rt and THF was removed in vacuo, then the reaction mixture was acidified to pH 2 using aqueous HCl (2 M). The solid formed was collected by filtration, washed with water and dried to afford **176** (165 mg, 89% yield) as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 12.89 (s, 1H), 7.97 – 7.83 (m, 2H), 7.34 (d, J = 8.3 Hz, 2H), 6.43 (s, 1H), 3.42 (t, J = 5.8 Hz, 2H), 3.35 (t, J = 5.9 Hz, 2H), 2.42 (t, J = 5.9 Hz, 2H), 2.31 (t, J = 5.7 Hz, 2H), 1.41 (s, 9H). ^{13}C NMR (214 MHz, DMSO- d_6) δ 167.10, 153.78, 141.47, 140.52, 129.31, 128.80, 123.47, 78.81, 44.59 (*), 43.63 (*), 35.68 (br s), 28.86 (br s), 28.08. (*not observed on 1D ^{13}C spectrum, peaks were confirmed by (^1H - ^{13}C)-HSQC. 1D spectrum shows three very broad singlets at this region probably reflecting chemical exchange) (missing aromatic carbon signal is likely due to overlap of peaks)

tert-butyl 4-(4-(3-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluorophenyl)ureido)benzylidene)piperidine-1-carboxylate (160).—In a microwave vial was added 4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluoroaniline (**14**) (107 mg, 0.34 mmol, 1 eq), 4-((1-(tert-butoxycarbonyl)piperidin-4-ylidene)methyl)benzoic acid (**176**) (180 mg, 0.51 mmol, 1.5 eq), toluene (0.75 mL) and triethylamine (103 mg, 1.02 mmol, 3 eq). The suspension was sonicated until fine particles were obtained, then diphenylphosphoryl azide (140 mg, 0.51 mmol, 1.5 eq) was added and the reaction mixture was irradiated at 100°C for 10 min. The reaction mixture was partitioned between EtOAc (30 mL) and water (20 mL). The aqueous layer was extracted with EtOAc (30 mL x 2). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 , filtered, concentrated onto Celite, and purified by flash chromatography (40–100% EtOAc in Hexanes on silica gel column) to afford **160** (176 mg, 82% yield) as a beige solid. ^1H NMR (400 MHz, DMSO- d_6) δ 9.12 (d, J = 2.8 Hz, 1H), 8.64 (s, 1H), 8.49 (d, J = 5.2 Hz, 1H), 8.25 (t, J = 9.2 Hz, 1H), 7.49 (s, 1H), 7.44 (d, J = 8.4 Hz, 2H), 7.40 (s, 1H), 7.35 (dd, J = 11.8, 2.7 Hz, 1H), 7.17 (d, J = 8.4 Hz, 2H), 7.10 (dd, J = 9.1, 2.7 Hz, 1H), 6.54 (d, J = 5.2 Hz, 1H), 6.31 (s, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.46 – 3.38 (m, 2H), 3.37 – 3.34 (m, 2H), 2.42 (d, J = 6.1 Hz, 2H), 2.27 (t, J = 5.7 Hz, 2H), 1.42 (s, 9H). ^{19}F NMR (376 MHz, DMSO- d_6) δ -125.88 (t, J = 10.6 Hz). ^{13}C NMR (214 MHz, DMSO- d_6) δ 159.64, 153.81, 152.59, 152.24 (d, J = 244.5 Hz), 152.17, 149.38, 148.87, 148.24 (d, J = 10.3 Hz), 146.49, 137.67, 136.96, 130.86, 129.29, 125.22 (d, J = 10.4 Hz), 123.77, 121.58 (d, J = 2.5 Hz), 117.91, 117.11 (d, J = 3.0 Hz), 115.07, 109.00 (d, J = 22.2 Hz), 107.87, 103.30, 99.03, 78.74, 55.73, 55.71, 44.83 (*), 43.64 (*), 35.61 (br s), 28.81 (br s), 28.09. (*not observed on 1D ^{13}C spectrum, peaks were confirmed by (^1H - ^{13}C)-HSQC. 1D spectrum shows three very broad singlets at this region probably reflecting chemical exchange) HRMS: calcd for $\text{C}_{35}\text{H}_{38}\text{FN}_4\text{O}_6$ [$\text{M} + \text{H}$] $^+$ m/z, 629.2775; found m/z, 629.2766.

1-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluorophenyl)-3-(4-(piperidin-4-ylidenemethyl)phenyl)urea (68).—To a solution of tert-butyl 4-(4-(3-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluorophenyl)ureido)benzylidene)piperidine-1-carboxylate (**160**) (144 mg, 0.23 mmol) in DCM (2 mL) was added TFA (0.5 mL). The reaction mixture was stirred at rt for 1 h, then concentrated in vacuo, and purified by flash chromatography (10–100% MeOH in water with 0.1% TFA on C18 column). Fractions containing the desired product were concentrated in vacuo, then partitioned between EtOAc (15 mL) and saturated aqueous NaHCO₃ solution (15 mL). The aqueous layer was extracted with EtOAc (15 mL x 2). The combined organic extracts were washed with saturated aqueous NaHCO₃ solution, water, brine, dried over anhydrous Na₂SO₄, filtered, and dried under vacuum to afford **68** (96 mg, 79% yield) as a light yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.12 (s, 1H), 8.65 (s, 1H), 8.49 (d, *J* = 5.2 Hz, 1H), 8.25 (t, *J* = 9.1 Hz, 1H), 7.49 (s, 1H), 7.42 (d, *J* = 8.7 Hz, 2H), 7.40 (s, 1H), 7.34 (dd, *J* = 11.8, 2.7 Hz, 1H), 7.14 (d, *J* = 8.6 Hz, 2H), 7.10 (ddd, *J* = 9.1, 2.8, 1.3 Hz, 1H), 6.54 (d, *J* = 5.2 Hz, 1H), 6.18 (s, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 2.77 (t, *J* = 5.6 Hz, 2H), 2.69 (t, *J* = 5.6 Hz, 2H), 2.35 (t, *J* = 5.7 Hz, 2H), 2.21 (t, *J* = 5.6 Hz, 2H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -125.87 (t, *J* = 10.3 Hz). ¹³C NMR (214 MHz, DMSO-*d*₆) δ 159.65, 152.59, 152.23 (d, *J* = 244.4 Hz), 152.19, 149.38, 148.87, 148.20 (d, *J* = 10.2 Hz), 146.49, 139.70, 137.38, 131.31, 129.23, 125.26 (d, *J* = 10.5 Hz), 121.90, 121.57 (d, *J* = 2.9 Hz), 117.90, 117.10 (d, *J* = 3.0 Hz), 115.08, 109.00 (d, *J* = 21.9 Hz), 107.87, 103.30, 99.04, 55.73, 55.71, 48.13, 47.26, 37.74, 30.63. HRMS: calcd for C₃₀H₃₀FN₄O₄ [M + H]⁺ m/z, 529.2251; found m/z, 529.2245.

1-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluorophenyl)-3-(4-(piperidin-4-ylmethyl)phenyl)urea (67).—To a solution of 1-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluorophenyl)-3-(4-(piperidin-4-ylidenemethyl)phenyl)urea (**68**) (76 mg, 0.14 mmol, 1 eq) in methanol (1.4 mL) was added palladium on carbon (10% Pd by wt, 15 mg, 0.1 eq). The solution was purged with argon, then hydrogen gas. The reaction mixture was stirred under hydrogen atmosphere at rt for 18 h, then filtered through Celite. The filtrate was concentrated onto Celite and purified by flash chromatography (10–100% MeOH in water with 0.1% TFA on reverse-phase column in prep-HPLC). Fractions containing the desired product were concentrated in vacuo, then partitioned between EtOAc (15 mL) and saturated aqueous NaHCO₃ solution (15 mL). The aqueous layer was extracted with EtOAc (15 mL x 2). The combined organic extracts were washed with saturated aqueous NaHCO₃ solution, water, brine, dried over anhydrous Na₂SO₄, filtered, and dried under vacuum to afford **67** (42 mg, 55% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.06 (s, 1H), 8.64 (d, *J* = 2.6 Hz, 1H), 8.49 (d, *J* = 5.2 Hz, 1H), 8.24 (t, *J* = 9.1 Hz, 1H), 7.49 (s, 1H), 7.40 (s, 1H), 7.38 – 7.30 (m, 3H), 7.12 – 7.04 (m, 3H), 6.54 (d, *J* = 5.2 Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 2.94 (dt, *J* = 12.3, 3.2 Hz, 2H), 2.44 (td, *J* = 10.9, 9.7, 2.6 Hz, 4H), 1.60 – 1.47 (m, 3H), 1.06 (qd, *J* = 12.0, 4.0 Hz, 2H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -125.91 (t, *J* = 10.6 Hz). ¹³C NMR (214 MHz, DMSO-*d*₆) δ 159.66, 152.59, 152.27, 152.20 (d, *J* = 244.4 Hz), 149.38, 148.87, 148.12 (d, *J* = 10.2 Hz), 146.48, 137.17, 133.88, 129.37, 125.34 (d, *J* = 10.3 Hz), 121.53 (d, *J* = 2.4 Hz), 118.12, 117.08 (d, *J* = 3.2 Hz), 115.07, 108.99 (d, *J* = 21.9 Hz), 107.86, 103.29, 99.04, 55.73, 55.71, 45.61, 42.23, 37.63, 32.12. HRMS: calcd for C₃₀H₃₂FN₄O₄ [M + H]⁺ m/z, 531.2408; found m/z, 531.2401.

tert-butyl 4-(4-(methoxycarbonyl)-2-(trifluoromethyl)benzylidene)piperidine-1-carboxylate (165).—To a solution of methyl 4-bromo-3-(trifluoromethyl)benzoate (**161**) (250 mg, 0.88 mmol, 1 eq) and tert-butyl 4-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methylene)piperidine-1-carboxylate (**164**) (286 mg, 0.88 mmol, 1 eq) in 1,4-dioxane (5.7 mL) and water (0.6 mL) was added tris(dibenzylideneacetone)dipalladium(0) (61 mg, 0.066 mmol, 0.075 eq), Xphos (63 mg, 0.13 mmol, 0.15 eq) and potassium phosphate (281 mg, 1.3 mmol, 1.5 eq). The reaction mixture was stirred at 100°C for 1 h, then cooled to rt and partitioned between EtOAc (30 mL) and water (20 mL). The aqueous layer was extracted with EtOAc (30 mL x 2). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄, and filtered. The filtrate was exposed to atmosphere for 2 days to oxidize an otherwise difficult-to-separate impurity, then concentrated onto Celite, and purified by flash chromatography (0–12% EtOAc in Hexanes on silica gel column) to afford **165** (238 mg, 67% yield) as a light yellow liquid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.24 – 8.13 (m, 2H), 7.53 (d, *J* = 7.6 Hz, 1H), 6.52 (s, 1H), 3.90 (s, 3H), 3.42 (t, *J* = 5.8 Hz, 2H), 3.30 (t, *J* = 5.8 Hz, 2H), 2.33 (t, *J* = 5.8 Hz, 2H), 2.17 (t, *J* = 5.8 Hz, 2H), 1.41 (s, 9H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ –59.91. ¹³C NMR (214 MHz, DMSO-*d*₆) δ 165.01, 153.81, 142.97, 140.52, 132.82, 132.64, 128.41, 127.56 (q, *J* = 30.0 Hz), 126.23 (q, *J* = 6.4, 4.9 Hz), 123.74 (q, *J* = 273.8 Hz), 119.49, 79.00, 52.68, 44.94 (*), 44.06 (*), 35.71 (br s), 29.09 (br s), 28.11. (*not observed on 1D ¹³C spectrum, peaks were confirmed by (¹H-¹³C)-HSQC. 1D spectrum shows three very broad singlets at this region probably reflecting chemical exchange)

tert-butyl 4-(4-(methoxycarbonyl)-2-(trifluoromethyl)benzyl)piperidine-1-carboxylate (167).—To a solution of tert-butyl 4-(4-(methoxycarbonyl)-2-(trifluoromethyl)benzylidene)piperidine-1-carboxylate (**165**) (235 mg, 0.59 mmol, 1 eq) in methanol (3.9 mL) was added palladium on carbon (10% Pd by wt, 63 mg, 0.1 eq). The solution was purged with argon, then hydrogen gas. The reaction mixture was stirred under hydrogen atmosphere at rt for 24 h, then filtered through Celite. The filtrate was concentrated onto Celite and purified by flash chromatography (0–15% EtOAc in Hexanes on silica gel column) to afford **167** (203 mg, 86% yield) as a colorless liquid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.20 – 8.12 (m, 2H), 7.66 (d, *J* = 7.9 Hz, 1H), 4.00 – 3.85 (m, 5H), 2.75 (d, *J* = 7.2 Hz, 2H), 2.62 (s, 3H), 1.78 (dt, *J* = 14.5, 7.1, 3.8 Hz, 1H), 1.52 (dd, *J* = 13.3, 2.9 Hz, 1H), 1.38 (s, 9H), 1.10 (qd, *J* = 12.4, 4.2 Hz, 2H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ –58.10. ¹³C NMR (214 MHz, DMSO-*d*₆) δ 165.09, 153.82, 144.32, 133.05, 132.64, 128.10, 127.89 (q, *J* = 29.8 Hz), 126.45 (q, *J* = 5.7 Hz), 124.08 (q, *J* = 274.1 Hz), 78.58, 52.63, 43.89 (br s), 42.90 (br s), 38.54, 37.09, 31.68 (br s), 31.47 (br s), 28.15.

4-((1-(tert-butoxycarbonyl)piperidin-4-yl)methyl)-3-(trifluoromethyl)benzoic acid (187).—To a solution of tert-butyl 4-(4-(methoxycarbonyl)-2-(trifluoromethyl)benzyl)piperidine-1-carboxylate (**167**) (200 mg, 0.50 mmol, 1 eq) in THF (3.2 mL) and water (0.8 mL) was added lithium hydroxide (36 mg, 1.5 mmol, 3 eq). The reaction mixture was stirred at 50°C for 4 h then cooled to rt. THF was removed in vacuo and the solution was acidified to pH 2 using aqueous HCl (1 M). The solid was collected by filtration, washed with water and dried in vacuo to afford **187** (173 mg, 90% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.16 (d, *J* = 1.7 Hz, 1H), 8.08 (dd, *J* =

8.0, 1.7 Hz, 1H), 7.52 (d, J = 8.0 Hz, 1H), 3.92 (d, J = 13.2 Hz, 2H), 2.71 (d, J = 7.1 Hz, 2H), 2.62 (br s, 2H), 1.83 – 1.68 (m, 1H), 1.52 (d, J = 13.0 Hz, 2H), 1.38 (s, 9H), 1.08 (qd, J = 12.3, 4.3 Hz, 2H). ^{19}F NMR (376 MHz, DMSO- d_6) δ -57.76. ^{13}C NMR (214 MHz, DMSO- d_6) δ 166.44, 153.79, 141.72 (br s), 133.02 (br s), 132.51, 132.13, 127.12 (q, J = 29.7, 29.0 Hz), 126.47 (q, J = 6.1 Hz), 124.46 (q, J = 274.0 Hz), 78.47, 43.88 (br s), 42.96 (br s), 38.45, 37.04, 31.59 (br s), 28.10. (missing aliphatic carbon peak is probably due to overlap at 31.59 ppm.)

1-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluorophenyl)-3-(4-(piperidin-4-ylmethyl)-3-(trifluoromethyl)phenyl)urea (79).—In a microwave vial was added 4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluoroaniline (**14**) (38 mg, 0.12 mmol, 1 eq), 4-((1-(tert-butoxycarbonyl)piperidin-4-yl)methyl)-3-(trifluoromethyl)benzoic acid (**187**) (65 mg, 0.17 mmol, 1.4 eq), toluene (0.8 mL) and triethylamine (36 mg, 0.36 mmol, 3 eq). The suspension was sonicated until fine particles were obtained, then diphenylphosphoryl azide (46 mg, 0.17 mmol, 1.4 eq) was added and the reaction mixture was irradiated at 100°C for 10 min. The reaction mixture was partitioned between EtOAc (20 mL) and water (15 mL). The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 , filtered, concentrated onto Celite, and purified by flash chromatography (50–100% EtOAc in Hexanes on silica gel column). Solvent was removed in vacuo from fractions containing the desired Boc-protected product. The solid was redissolved in DCM (2 mL) and TFA (0.5 mL) was added. The reaction solution was stirred at rt for 1 h, then concentrated in vacuo and purified by flash chromatography (10–100% MeOH in water with 0.05% TFA on reverse-phase column on prep-HPLC). Fractions containing the desired product were concentrated in vacuo, then partitioned between EtOAc (15 mL) and saturated aqueous NaHCO_3 solution (15 mL). The aqueous layer was extracted with EtOAc (15 mL x 2). The combined organic extracts were washed with saturated aqueous NaHCO_3 solution, water, brine, dried over anhydrous Na_2SO_4 , filtered, and dried under vacuum to afford **79** (45 mg, 63% yield) as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 9.43 (s, 1H), 8.74 (s, 1H), 8.50 (d, J = 5.2 Hz, 1H), 8.20 (t, J = 9.1 Hz, 1H), 7.96 (d, J = 2.3 Hz, 1H), 7.53 (dd, J = 8.5, 2.3 Hz, 1H), 7.49 (s, 1H), 7.40 (s, 1H), 7.38 – 7.32 (m, 2H), 7.10 (dt, J = 8.9, 1.8 Hz, 1H), 6.54 (d, J = 5.2 Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 2.92 (d, J = 12.0 Hz, 2H), 2.58 (d, J = 7.0 Hz, 2H), 2.45 – 2.35 (m, 2H), 1.67 – 1.57 (m, 1H), 1.49 (d, J = 12.6 Hz, 2H), 1.09 (qd, J = 12.0, 3.9 Hz, 2H). ^{19}F NMR (376 MHz, DMSO- d_6) δ -57.78 (s, 3F), -125.22 (t, J = 10.2 Hz, 1F). ^{13}C NMR (214 MHz, DMSO- d_6) δ 159.71, 152.62, 152.57 (d, J = 244.9 Hz), 152.39, 149.41, 148.95, 148.56 (d, J = 10.1 Hz), 146.53, 137.86, 132.72, 131.84, 127.63 (q, J = 28.9 Hz), 125.01 (d, J = 10.6 Hz), 124.60 (q, J = 274.1 Hz), 122.11, 121.47, 117.25 (d, J = 3.0 Hz), 115.09, 115.02 (q, J = 6.0 Hz), 109.22 (d, J = 21.8 Hz), 107.89, 103.32, 99.03, 55.80, 55.76, 45.98, 38.74, 37.70, 32.74. HRMS: calcd for $\text{C}_{31}\text{H}_{31}\text{F}_4\text{N}_4\text{O}_4$ [$\text{M} + \text{H}$] $^+$ m/z , 599.2281; found m/z , 599.2273.

4-((1-(tert-butoxycarbonyl)piperidin-4-ylidene)methyl)-3-(trifluoromethyl)benzoic acid (188).—To a solution of tert-butyl 4-(4-(methoxycarbonyl)-2-(trifluoromethyl)benzylidene)piperidine-1-carboxylate (**165**) (179 mg, 0.45 mmol, 1 eq) in THF (2.8 mL) and water (0.7 mL) was added lithium hydroxide (32 mg, 1.3 mmol, 3 eq). The reaction mixture was

stirred at 50°C for 4 h then cooled to rt. THF was removed in vacuo and the solution was acidified to pH 2 using aqueous HCl (1 M). The solid was collected by filtration, washed with water and dried in vacuo to afford **188** (153 mg, 88% yield) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.18 (d, *J* = 1.7 Hz, 1H), 8.14 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 6.51 (s, 1H), 3.42 (t, *J* = 5.8 Hz, 2H), 3.30 (t, *J* = 5.9 Hz, 2H), 2.36 – 2.28 (m, 2H), 2.17 (t, *J* = 5.9 Hz, 2H), 1.41 (s, 9H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ –59.81 (d, *J* = 2.4 Hz). ¹³C NMR (214 MHz, DMSO-*d*₆) δ 166.02, 153.78, 142.44, 139.75, 132.80, 132.28, 130.24 (br s), 127.32 (q, *J* = 29.6 Hz), 126.28 (q, *J* = 5.2 Hz), 123.84 (q, *J* = 273.8 Hz), 119.62, 78.91, 44.92 (*), 43.86 (*), 35.47 (br s), 29.19 (br s), 28.06. (*not observed on 1D ¹³C spectrum, peaks were confirmed by (¹H-¹³C)-HSQC. 1D spectrum shows three very broad singlets at this region probably reflecting chemical exchange)

1-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluorophenyl)-3-(4-(piperidin-4-ylidenemethyl)-3-(trifluoromethyl)phenyl)urea (81).—In a microwave vial was added 4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluoroaniline (**14**) (35 mg, 0.11 mmol, 1 eq), 4-((1-(tert-butoxycarbonyl)piperidin-4-ylidene)methyl)-3-(trifluoromethyl)benzoic acid (**188**) (55 mg, 0.14 mmol, 1.3 eq), toluene (0.75 mL) and triethylamine (33 mg, 0.33 mmol, 3 eq). The suspension was sonicated until fine particles were obtained, then diphenylphosphoryl azide (39 mg, 0.14 mmol, 1.3 eq) was added and the reaction mixture was irradiated at 100°C for 10 min. The reaction mixture was partitioned between EtOAc (20 mL) and water (15 mL). The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄, filtered, concentrated onto Celite, and purified by flash chromatography (50–100% EtOAc in Hexanes on silica gel column). Solvent was removed in vacuo from fractions containing the desired Boc-protected product. The solid was redissolved in DCM (2 mL) and TFA (0.5 mL) was added. The reaction solution was stirred at rt for 1 h, then concentrated in vacuo and purified by flash chromatography (10–100% MeOH in water with 0.05% TFA on reverse-phase column on prep-HPLC). Fractions containing the desired product were concentrated in vacuo, then partitioned between EtOAc (15 mL) and saturated aqueous NaHCO₃ solution (15 mL). The aqueous layer was extracted with EtOAc (15 mL x 2). The combined organic extracts were washed with saturated aqueous NaHCO₃ solution, water, brine, dried over anhydrous Na₂SO₄, filtered, and dried under vacuum to afford **81** (41 mg, 63% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.44 (s, 1H), 8.73 (d, *J* = 2.4 Hz, 1H), 8.50 (d, *J* = 5.2 Hz, 1H), 8.21 (t, *J* = 9.1 Hz, 1H), 8.01 (d, *J* = 2.3 Hz, 1H), 7.53 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.49 (s, 1H), 7.40 (s, 1H), 7.35 (dd, *J* = 11.7, 2.7 Hz, 1H), 7.24 (d, *J* = 8.4 Hz, 1H), 7.10 (ddd, *J* = 8.9, 2.8, 1.3 Hz, 1H), 6.55 (d, *J* = 5.2 Hz, 1H), 6.29 (s, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 2.78 (t, *J* = 5.5 Hz, 2H), 2.66 (t, *J* = 5.6 Hz, 2H), 2.24 (t, *J* = 5.6 Hz, 2H), 2.12 (t, *J* = 5.7 Hz, 2H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ –59.65 (d, *J* = 2.5 Hz, 3F), –125.25 (t, *J* = 10.5 Hz, 1F). ¹³C NMR (214 MHz, DMSO-*d*₆) δ 159.70, 152.62, 152.58 (d, *J* = 245.0 Hz), 152.33, 149.42, 148.95, 148.61 (d, *J* = 10.4 Hz), 146.53, 142.68, 138.27, 132.55, 129.32, 127.51 (q, *J* = 28.4 Hz), 124.95 (d, *J* = 10.5 Hz), 124.26 (q, *J* = 273.9 Hz), 122.11, 121.14, 118.10, 117.26 (d, *J* = 3.3 Hz), 115.09, 114.89 (q, *J* = 6.0 Hz), 109.23 (d, *J* = 22.1 Hz), 107.89, 103.33, 99.03, 55.79, 55.76, 48.19, 47.35, 37.50, 30.94. HRMS: calcd for C₃₁H₂₉F₄N₄O₄ [M + H]⁺ m/z, 597.2125; found m/z, 597.2116.

methyl 4-iodo-3-(trifluoromethoxy)benzoate (163).—To a solution of 4-iodo-3-(trifluoromethoxy)benzoic acid (**162**) (500 mg, 1.5 mmol, 1 eq) in DMSO (10 mL) was added potassium carbonate (416 mg, 3.0 mmol, 2 eq) and iodomethane (321 mg, 2.3 mmol, 1.5 eq). The reaction mixture was stirred at rt for 6 h, then partitioned between EtOAc (80 mL) and water (80 mL). The aqueous layer was extracted with EtOAc (80 mL x 2). The combined organic extracts were washed with water, brine, dried over anhydrous Na₂SO₄, filtered, concentrated in vacuo to afford **163** (495 mg, 95% yield) as a light orange liquid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.18 (d, *J* = 8.2 Hz, 1H), 7.81 (dq, *J* = 1.8, 1.4 Hz, 1H), 7.70 (dd, *J* = 8.2, 1.8 Hz, 1H), 3.88 (s, 3H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -56.19 (d, *J* = 1.4 Hz). ¹³C NMR (176 MHz, DMSO-*d*₆) δ 164.65, 148.80, 141.05, 131.67, 129.35, 121.05, 120.05 (q, *J* = 257.6 Hz), 98.20, 52.75.

tert-butyl 4-(4-(methoxycarbonyl)-2-(trifluoromethoxy)benzylidene)piperidine-1-carboxylate (166).—To a solution of methyl 4-iodo-3-(trifluoromethoxy)benzoate (**163**) (490 mg, 1.4 mmol, 1 eq) and tert-butyl 4-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methylene)piperidine-1-carboxylate (**164**) (458 mg, 1.4 mmol, 1 eq) in 1,4-dioxane (9 mL) and water (1 mL) was added tris(dibenzylideneacetone)dipalladium(0) (130 mg, 0.14 mmol, 0.1 eq), Xphos (135 mg, 0.28 mmol, 0.2 eq) and potassium phosphate (451 mg, 2.1 mmol, 1.5 eq). The reaction mixture was stirred at 100°C for 1 h, then cooled to rt and partitioned between EtOAc (40 mL) and water (30 mL). The aqueous layer was extracted with EtOAc (40 mL x 2). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄, filtered, concentrated onto Celite, and purified by flash chromatography (0–12% EtOAc in Hexanes on silica gel column) to afford **166** (490 mg, 83% yield) as an orange-brown liquid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.94 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.82 (dq, *J* = 3.0, 1.4 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 6.37 (s, 1H), 3.88 (s, 3H), 3.42 (t, *J* = 5.7 Hz, 2H), 3.33 (t, *J* = 5.7 Hz, 2H), 2.34 (t, *J* = 5.8 Hz, 2H), 2.25 (t, *J* = 5.9 Hz, 2H), 1.41 (s, 9H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -56.41 (d, *J* = 5.4 Hz). ¹³C NMR (214 MHz, DMSO-*d*₆) δ 164.84, 153.77, 145.84, 143.57, 135.36, 132.03, 129.70, 127.97, 121.44, 120.12 (q, *J* = 257.5 Hz), 116.92, 78.93, 52.59, 44.91 (*), 43.94 (*), 35.55 (br s), 29.23 (br s), 28.06. (*not observed on 1D ¹³C spectrum, peaks were confirmed by (¹H-¹³C)-HSQC. 1D spectrum shows three very broad singlets at this region probably reflecting chemical exchange)

tert-butyl 4-(4-(methoxycarbonyl)-2-(trifluoromethoxy)benzyl)piperidine-1-carboxylate (168).—To a solution of tert-butyl 4-(4-(methoxycarbonyl)-2-(trifluoromethoxy)benzylidene)piperidine-1-carboxylate (**166**) (239 mg, 0.58 mmol, 1 eq) in methanol (3.8 mL) was added palladium on carbon (10% Pd by wt, 61 mg, 0.1 eq). The solution was purged with argon, then hydrogen gas. The reaction mixture was stirred under hydrogen atmosphere at rt for 24 h, then filtered through Celite. The filtrate was concentrated onto Celite and purified by flash chromatography (0–15% EtOAc in Hexanes on silica gel column) to afford **168** (211 mg, 88% yield) as a light yellow liquid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.91 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.79 (dq, *J* = 1.8, 1.3 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 3.87 (s, 5H), 2.65 (d, *J* = 7.2 Hz, 2H), 2.62 (br s, 2H), 1.73 (ttt, *J* = 11.8, 7.2, 3.1 Hz, 1H), 1.50 (d, *J* = 14.1 Hz, 2H), 1.38 (s, 9H), 1.06 (qd, *J* = 12.3, 4.2 Hz, 2H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -56.04 (d, *J* = 8.7 Hz). ¹³C NMR (214 MHz, DMSO-*d*₆) δ

165.00, 153.82, 146.93, 138.27, 132.70, 129.54, 127.89, 120.51, 120.18 (q, $J = 257.8$ Hz), 78.56, 52.64, 43.81 (br s), 42.82 (br s), 36.23, 35.97, 31.54 (br s), 31.35 (br s), 28.14.

4-((1-(tert-butoxycarbonyl)piperidin-4-yl)methyl)-3-(trifluoromethoxy)benzoic acid (189).—To a solution of tert-butyl 4-(4-(methoxycarbonyl)-2-

(trifluoromethoxy)benzyl)piperidine-1-carboxylate (**168**) (208 mg, 0.50 mmol, 1 eq) in THF (3.2 mL) and water (0.8 mL) was added lithium hydroxide (36 mg, 1.5 mmol, 3 eq). The reaction mixture was stirred at 50°C for 4 h then cooled to rt. THF was removed in vacuo and the solution was acidified to pH 2 using aqueous HCl (1 M). The solid was collected by filtration, washed with water and dried in vacuo to afford **189** (184 mg, 92% yield) as a gray solid. ^1H NMR (400 MHz, DMSO- d_6) δ 7.87 (dd, $J = 7.9, 1.6$ Hz, 1H), 7.77 (dq, $J = 1.7, 1.6$ Hz, 1H), 7.52 (d, $J = 8.0$ Hz, 1H), 3.90 (d, $J = 13.2$ Hz, 2H), 2.72 – 2.60 (m, 4H), 1.80 – 1.65 (m, 1H), 1.50 (dd, $J = 13.3, 2.0$ Hz, 2H), 1.38 (s, 9H), 1.06 (qd, $J = 12.4, 4.2$ Hz, 2H). ^{19}F NMR (376 MHz, DMSO- d_6) δ –55.98 (d, $J = 1.6$ Hz). ^{13}C NMR (214 MHz, DMSO- d_6) δ 166.04, 153.79, 146.84, 137.26, 132.29, 131.38 (br s), 127.83, 120.44, 120.16 (q, $J = 256.9$ Hz), 78.49, 43.78 (br s), 42.82 (br s), 36.17, 35.89, 31.41 (br s), 28.09. (missing aliphatic carbon peak is probably due to overlap at 31.41 ppm.)

1-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluorophenyl)-3-(4-(piperidin-4-ylmethyl)-3-(trifluoromethoxy)phenyl)urea (80).—In a microwave vial

was added 4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluoroaniline (**14**) (36 mg, 0.12 mmol, 1 eq), 4-((1-(tert-butoxycarbonyl)piperidin-4-yl)methyl)-3-(trifluoromethoxy)benzoic acid (**189**) (70 mg, 0.17 mmol, 1.5 eq), toluene (0.8 mL) and triethylamine (35 mg, 0.35 mmol, 3 eq). The suspension was sonicated until fine particles were obtained, then diphenylphosphoryl azide (48 mg, 0.17 mmol, 1.5 eq) was added and the reaction mixture was irradiated at 100°C for 10 min. The reaction mixture was partitioned between EtOAc (20 mL) and water (15 mL). The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 , filtered, concentrated onto Celite, and purified by flash chromatography (40–100% EtOAc in Hexanes on silica gel column). Solvent was removed in vacuo from fractions containing the desired Boc-protected product. The solid was redissolved in DCM (2 mL) and TFA (0.5 mL) was added. The reaction solution was stirred at rt for 1 h, then concentrated in vacuo and purified by flash chromatography (10–100% MeOH in water with 0.05% TFA on reverse-phase column on prep-HPLC). Fractions containing the desired product were concentrated in vacuo, then partitioned between EtOAc (15 mL) and saturated aqueous NaHCO_3 solution (15 mL). The aqueous layer was extracted with EtOAc (15 mL x 2). The combined organic extracts were washed with saturated aqueous NaHCO_3 solution, water, brine, dried over anhydrous Na_2SO_4 , filtered, and dried under vacuum to afford **80** (50 mg, 71% yield) as a white solid. ^1H NMR (850 MHz, DMSO- d_6) δ 9.51 (s, 1H), 8.82 (s, 1H), 8.49 (d, $J = 5.2$ Hz, 1H), 8.20 (t, $J = 9.0$ Hz, 1H), 7.75 (s, 1H), 7.49 (s, 1H), 7.40 (s, 1H), 7.37 (dd, $J = 11.6, 2.7$ Hz, 1H), 7.26 (d, $J = 8.3$ Hz, 1H), 7.19 (dd, $J = 8.3, 2.2$ Hz, 1H), 7.10 (dd, $J = 8.4, 2.4$ Hz, 1H), 6.53 (d, $J = 5.2$ Hz, 1H), 3.94 (s, 3H), 3.93 (s, 3H), 2.92 (dt, $J = 12.4, 3.4$ Hz, 2H), 2.47 (d, $J = 7.2$ Hz, 2H), 2.40 (td, $J = 12.2, 2.6$ Hz, 2H), 1.60 – 1.53 (m, 1H), 1.48 (d, $J = 11.7$ Hz, 2H), 1.07 (qd, $J = 12.2, 4.0$ Hz, 2H). ^{19}F NMR (376 MHz, DMSO- d_6) δ –55.68 (s, 3F), –125.21 (t, $J = 10.9$ Hz,

1F). ^{13}C NMR (214 MHz, $\text{DMSO-}d_6$) δ 159.72, 152.62, 152.57 (d, J = 244.8 Hz), 152.33, 149.41, 148.95, 148.53 (d, J = 10.2 Hz), 147.10, 146.53, 139.04, 131.96, 125.43, 125.01 (d, J = 10.6 Hz), 122.14, 120.29 (q, J = 256.3 Hz), 117.25 (d, J = 2.0 Hz), 116.62, 115.08, 109.54, 109.21 (d, J = 21.9 Hz), 107.89, 103.30, 99.03, 55.79, 55.76, 45.78, 36.89, 36.16, 32.40. HRMS: calcd for $\text{C}_{31}\text{H}_{31}\text{F}_4\text{N}_4\text{O}_5$ [$\text{M} + \text{H}$] $^+$ m/z , 615.2231; found m/z , 615.2228.

4-((1-(tert-butoxycarbonyl)piperidin-4-ylidene)methyl)-3-(trifluoromethoxy)benzoic acid (190).—To a solution

of tert-butyl 4-(4-(methoxycarbonyl)-2-(trifluoromethoxy)benzylidene)piperidine-1-carboxylate (**166**) (226 mg, 0.54 mmol, 1 eq) in THF (3.4 mL) and water (0.85 mL) was added lithium hydroxide (39 mg, 1.6 mmol, 3 eq). The reaction mixture was stirred at 50°C for 4 h then cooled to rt. THF was removed in vacuo and the solution was acidified to pH 2 using aqueous HCl (1 M). The solid was collected by filtration, washed with water and dried in vacuo to afford **190** (205 mg, 94% yield) as a black solid. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 7.90 (dd, J = 7.9, 1.6 Hz, 1H), 7.80 (dq, J = 1.6, 1.3 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 6.36 (s, 1H), 3.42 (t, J = 5.8 Hz, 2H), 3.32 (t, J = 5.9 Hz, 2H), 2.37 – 2.29 (m, 2H), 2.25 (t, J = 5.9 Hz, 2H), 1.41 (s, 9H). ^{19}F NMR (376 MHz, $\text{DMSO-}d_6$) δ –56.35 (d, J = 1.3 Hz). ^{13}C NMR (214 MHz, $\text{DMSO-}d_6$) δ 165.95, 153.78, 145.81, 143.11, 134.51, 131.79 (br s), 131.72, 128.00, 121.43, 120.15 (q, J = 256.9 Hz), 117.09, 78.92, 44.81 (*), 43.78 (*), 35.57 (br s), 29.27 (br s), 28.07. (*not observed on 1D ^{13}C spectrum, peaks were confirmed by ($^1\text{H-}^{13}\text{C}$)-HSQC. 1D spectrum shows three very broad singlets at this region probably reflecting chemical exchange)

1-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluorophenyl)-3-(4-(piperidin-4-ylidenemethyl)-3-(trifluoromethoxy)phenyl)urea (82).—In a microwave

vial was added 4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-fluoroaniline (**14**) (38 mg, 0.12 mmol, 1 eq), 4-((1-(tert-butoxycarbonyl)piperidin-4-ylidene)methyl)-3-(trifluoromethoxy)benzoic acid (**190**) (68 mg, 0.17 mmol, 1.4 eq), toluene (0.8 mL) and triethylamine (37 mg, 0.36 mmol, 3 eq). The suspension was sonicated until fine particles were obtained, then diphenylphosphoryl azide (47 mg, 0.17 mmol, 1.4 eq) was added and the reaction mixture was irradiated at 100°C for 10 min. The reaction mixture was partitioned between EtOAc (20 mL) and water (15 mL). The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 , filtered, concentrated onto Celite, and purified by flash chromatography (50–100% EtOAc in Hexanes on silica gel column). Solvent was removed in vacuo from fractions containing the desired Boc-protected product. The solid was redissolved in DCM (2 mL) and TFA (0.5 mL) was added. The reaction solution was stirred at rt for 1 h, then concentrated in vacuo and purified by flash chromatography (10–100% MeOH in water with 0.05% TFA on reverse-phase column on prep-HPLC). Fractions containing the desired product were concentrated in vacuo, then partitioned between EtOAc (15 mL) and saturated aqueous NaHCO_3 solution (15 mL). The aqueous layer was extracted with EtOAc (15 mL x 2). The combined organic extracts were washed with saturated aqueous NaHCO_3 solution, water, brine, dried over anhydrous Na_2SO_4 , filtered, and dried under vacuum to afford **82** (51 mg, 69% yield) as a white solid. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 9.42 (s, 1H), 8.71 (s, 1H), 8.50 (d, J = 5.2 Hz, 1H), 8.20 (t, J = 9.1 Hz, 1H), 7.78 – 7.74 (m, 1H), 7.49

(s, 1H), 7.40 (s, 1H), 7.35 (dd, $J = 11.7, 2.7$ Hz, 1H), 7.23 (d, $J = 1.2$ Hz, 2H), 7.14 – 7.07 (m, 1H), 6.54 (d, $J = 5.2$ Hz, 1H), 6.11 (s, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 2.77 (t, $J = 5.5$ Hz, 2H), 2.67 (t, $J = 5.6$ Hz, 2H), 2.23 (t, $J = 5.5$ Hz, 2H), 2.19 (t, $J = 5.4$ Hz, 2H). ^{19}F NMR (376 MHz, DMSO- d_6) δ -56.06 (s, 3F), -125.32 (t, $J = 10.7$ Hz, 1F). ^{13}C NMR (214 MHz, DMSO- d_6) δ 159.71, 152.62, 152.55 (d, $J = 244.8$ Hz), 152.24, 149.42, 148.95, 148.58 (d, $J = 10.2$ Hz), 146.53, 146.19, 143.04, 139.35, 131.63, 124.94 (d, $J = 10.8$ Hz), 123.98, 122.09 (d, $J = 2.7$ Hz), 120.29 (q, $J = 256.2$ Hz), 117.27 (d, $J = 3.1$ Hz), 116.57, 115.42, 115.08, 110.36, 109.22 (d, $J = 21.9$ Hz), 107.89, 103.31, 99.03, 55.80, 55.76, 48.28, 47.31, 37.67, 31.09. HRMS: calcd for $\text{C}_{31}\text{H}_{29}\text{F}_4\text{N}_4\text{O}_5$ $[\text{M} + \text{H}]^+$ m/z , 613.2074; found m/z , 613.2068.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

Data will be made available on request.

Abbreviations Used

ABL	tyrosine-protein kinase ABL1
ACT	artemisinin-based combination therapy
ATP	adenosine triphosphate
AURKB	aurora kinase B
AURKC	aurora kinase C
AXL	tyrosine-protein kinase receptor UFO
CDI	1,1'-carbonyl diimidazole
CDK2	cyclin-dependent kinase 2
c-KIT	mast/stem cell growth factor receptor Kit
CID	chemical inducer of dimerization
DCM	dichloromethane

DFT	density functional theory
DHA	dihydroartemisinin
DIPEA	diisopropylethylamine
DMA	dimethylacetamide
DMF	dimethylformamide
DMF-DMA	N,N-dimethylformamide dimethyl acetal
DMSO	dimethylsulfoxide
DPPA	diphenylphosphoryl azide
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
FDA	United States Food and Drug Administration
FGFR2	fibroblast growth factor receptor 2
GE	group efficiency
KCGS	Kinase Chemogenomics Set
LiHMDS	lithium bis(trimethylsilyl)amide
MEP	molecular electrostatic potential
MMV	Medicines for Malaria Venture
NAO	natural atomic orbital
NMP	N-methylpyrrolidone
PDGFRα	platelet-derived growth factor receptor alpha
PfCDPK1	<i>P. falciparum</i> calcium-dependent protein kinase 1
PfCDPK5	<i>P. falciparum</i> calcium-dependent protein kinase 5
PfCLK3	<i>P. falciparum</i> cyclin-dependent-like kinase CLK3
PfGSK3	<i>P. falciparum</i> glycogen synthase kinase 3
PfNEK3	<i>P. falciparum</i> NIMA related kinase 3
PfPI4K	<i>P. falciparum</i> phosphatidylinositol 4-kinase beta
PfPK5	<i>P. falciparum</i> Protein Kinase 5
PfPK6	<i>P. falciparum</i> Protein Kinase 6
PfPKB	<i>P. falciparum</i> RAC-beta serine/threonine protein kinase
PfPKG	<i>P. falciparum</i> cGMP-dependent protein kinase

SAR	structure-activity-relationship
TCAMS	Tres Cantos Antimalarial Set
TCP	target candidate profile
TFA	trifluoroacetic acid
THF	tetrahydrofuran
VEGFR2	vascular endothelial growth factor receptor

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- **Ki8751**, a type II human VEGFR2 inhibitor, was discovered to be a PfPK6 inhibitor
- 79 analogues were designed, synthesized, and screened for PfPK6 inhibition
- Top analogues were screened for antiplasmodial activity
- **67** inhibits PfPK6 and is active against *P. falciparum* asexual blood stage
- **79** inhibits PfPK6 and is active against *Plasmodium* liver and asexual blood stages

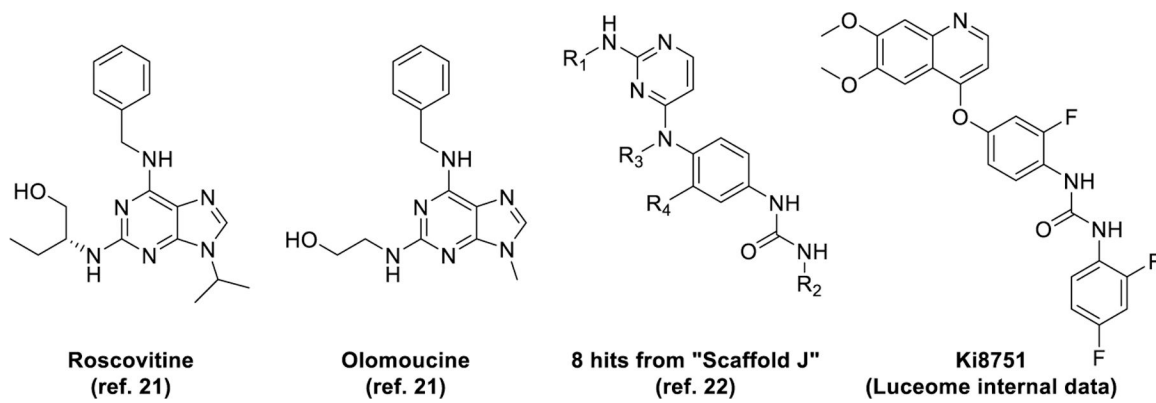


Figure 1.
Known inhibitors of PfPK6.

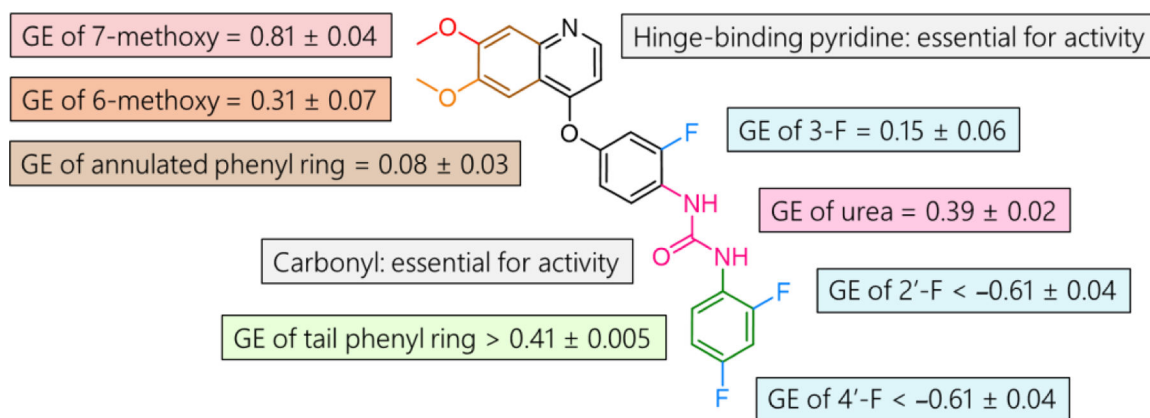


Figure 2. Group Efficiency (GE) Analysis of Ki8751 on Pfk6 inhibition^a

^aGE = $\frac{G}{\text{no. of heavy atoms}}$

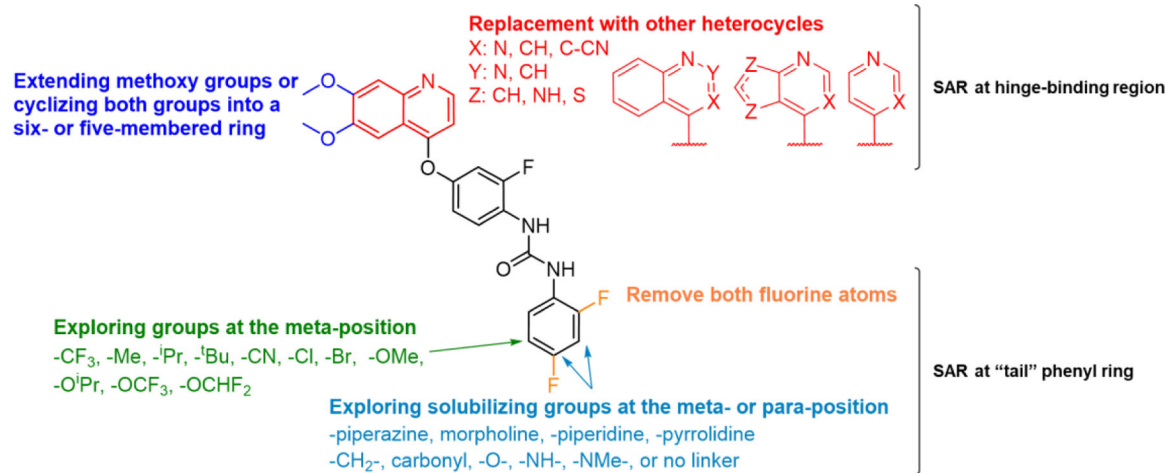
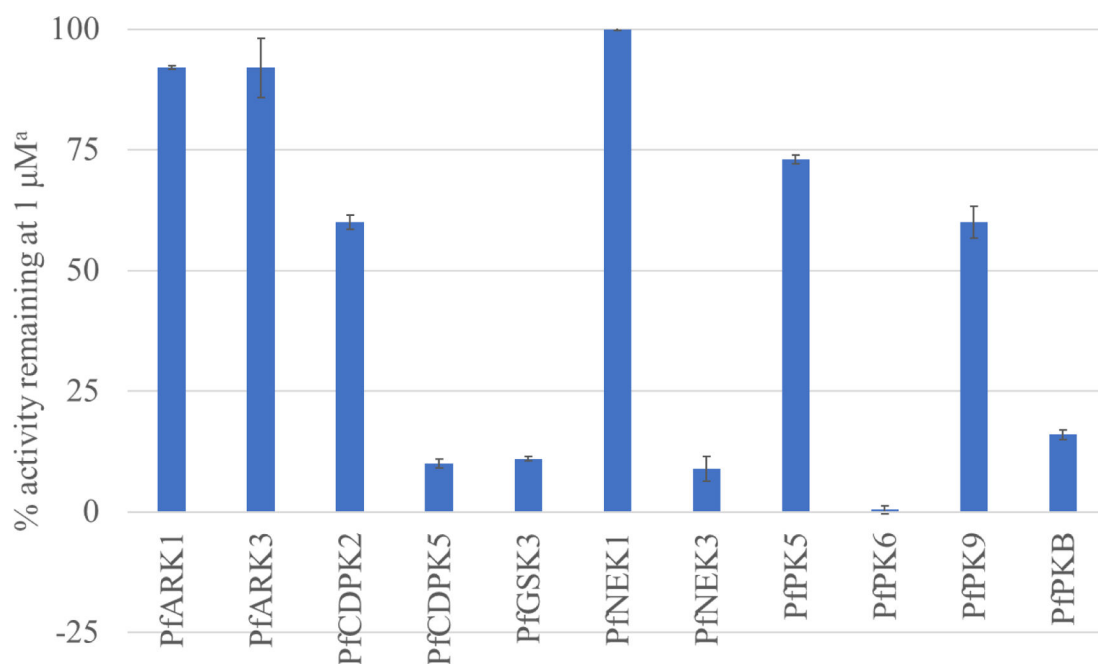


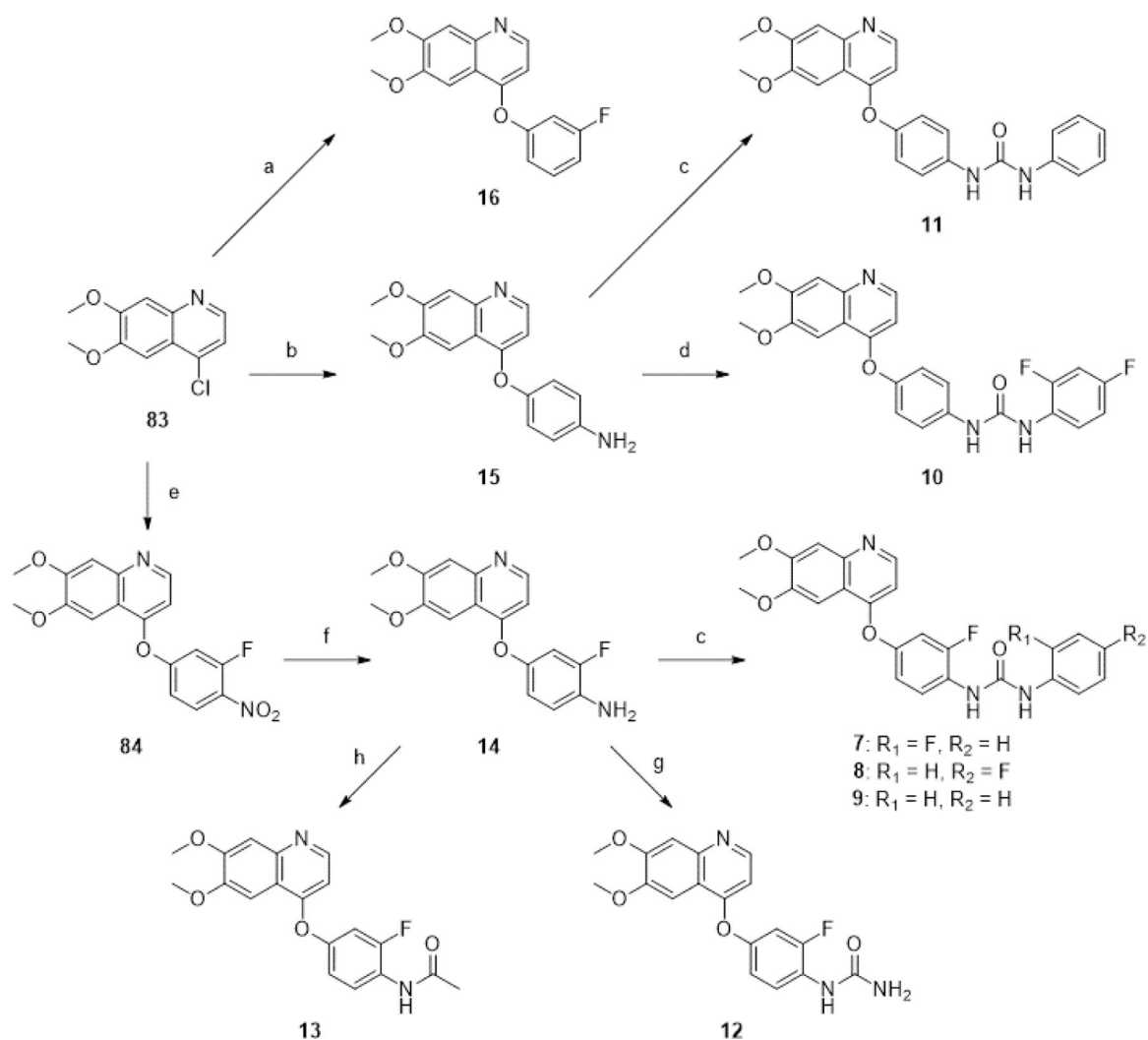
Figure 3.
SAR Plan



Kinase IC ₅₀ (nM) ^b	n.d.	n.d.	n.d.	76 ± 11	144 ± 7	n.d.	40 ± 5	n.d.	1.9 ± 0.1 ^c	n.d.	116 ± 14
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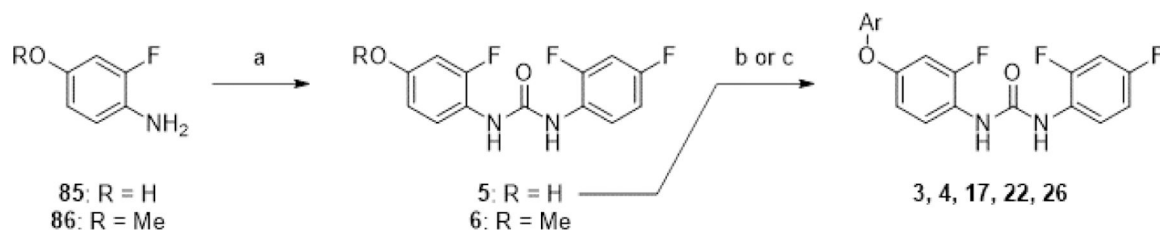
Figure 4. Inhibition of compound 45 on the *P. falciparum* Kinase Panel

^aResults presented as mean ± s.d. values from experiments using the KinaseSeeker assay performed in duplicate. ^bIC₅₀ values were determined using the KinaseSeeker assay with 5-fold dilutions, presented as mean ± s.e.m. values of two experiments performed in duplicate. ^cIC₅₀ values approach the kinase concentration in the assay. IC₅₀s < 5 nM treated as equipotent. n.d. = not determined.

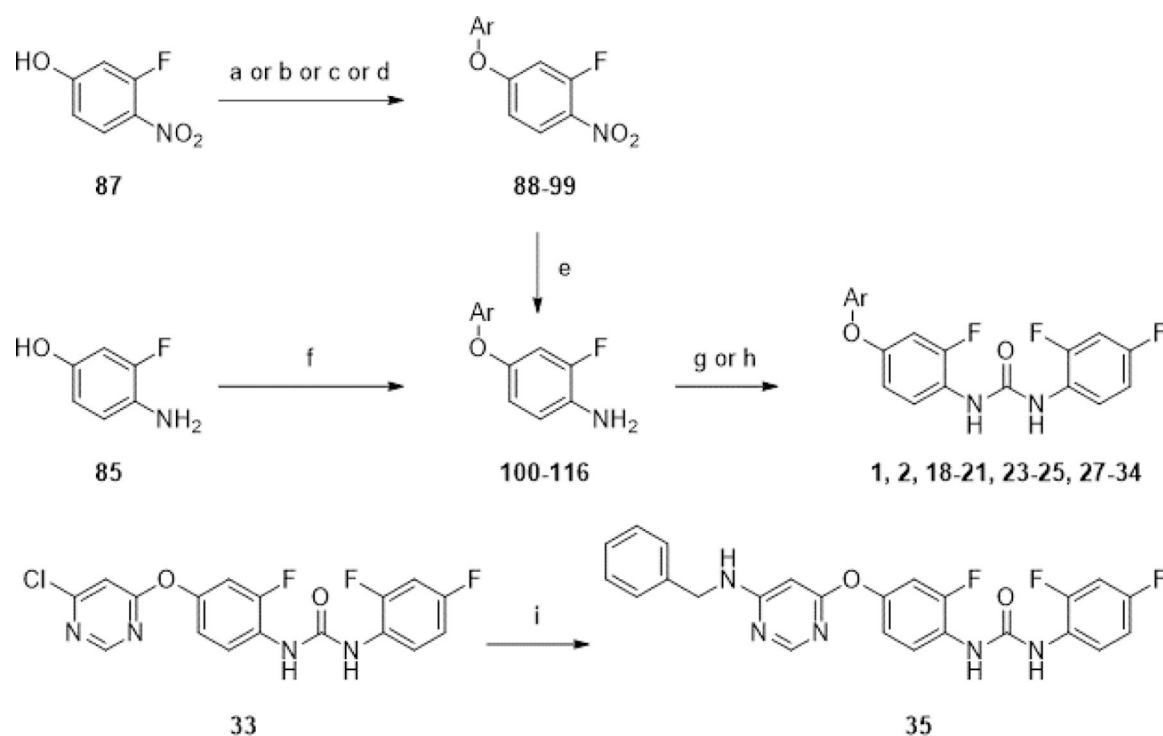


Scheme 1. Synthesis of truncated analogues of Ki8751^a

^aReagents and conditions: (a) 3-fluorophenol, neat, 170°C, 20 min, 34%; (b) 4-aminophenol, NaO^tBu, DMF, 0–110°C, 4 h, 25%; (c) 2-fluoroaniline, 4-fluoroaniline or aniline, CDI, THF or DMSO, rt, [1–2.5 h], then [45–50°C], [1.5–4 h], [7 (5%), 8 (11%), 9 (34%), 11 (71%)]; (d) 2,4-difluoro-1-isocyanatobenzene, EtOH, 0°C-rt, 1 h, 8%; (e) 3-fluoro-4-nitrophenol (87), *o*-xylene, 135°C, 16 h, 76%; (f) Fe, NH₄Cl, EtOH/H₂O (3:1), 78°C, 5 h, 78%; (g) NaOCN, AcOH/H₂O (5:4), rt, 2 h, 61%; (h) acetyl chloride, DIPEA, 1,4-dioxane, 0°C-rt, 2.5 h, 92%.

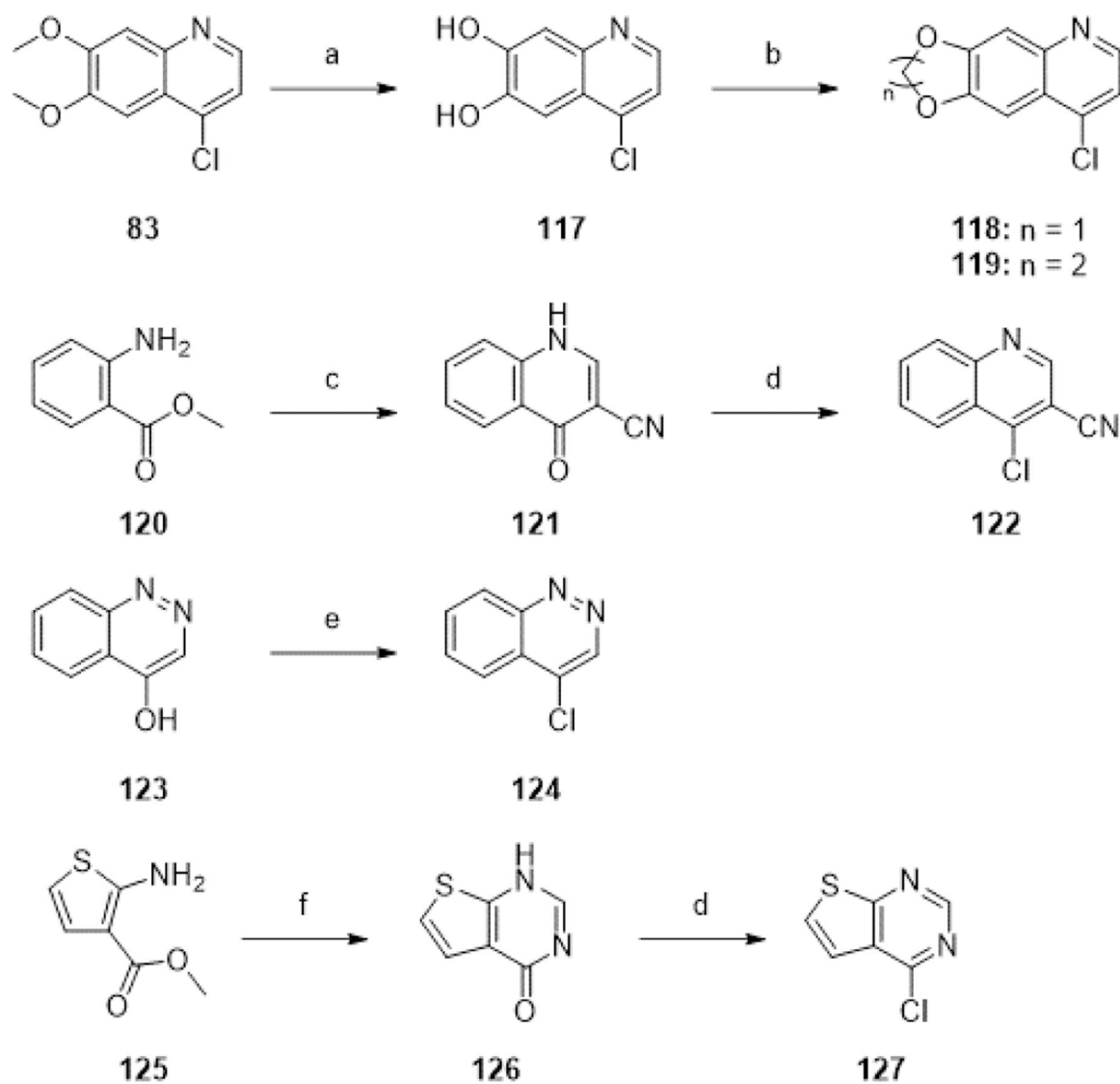
**Scheme 2. Tail-to-head synthesis of analogues varying hinge-binding group^a**

^aReagents and conditions: (a) 2,4-difluoro-1-isocyanatobenzene, MeCN, rt, 30 min, 32–36%; (b) ArCl or ArOTf, DIPEA, NMP or DMF, [90–120°C], [1.5–18 h], 3–10%; (c) (for **4**) pyridin-4-yl trifluoromethanesulfonate, DIPEA, DMF, μ W, 130°C, 3 h, 6%.



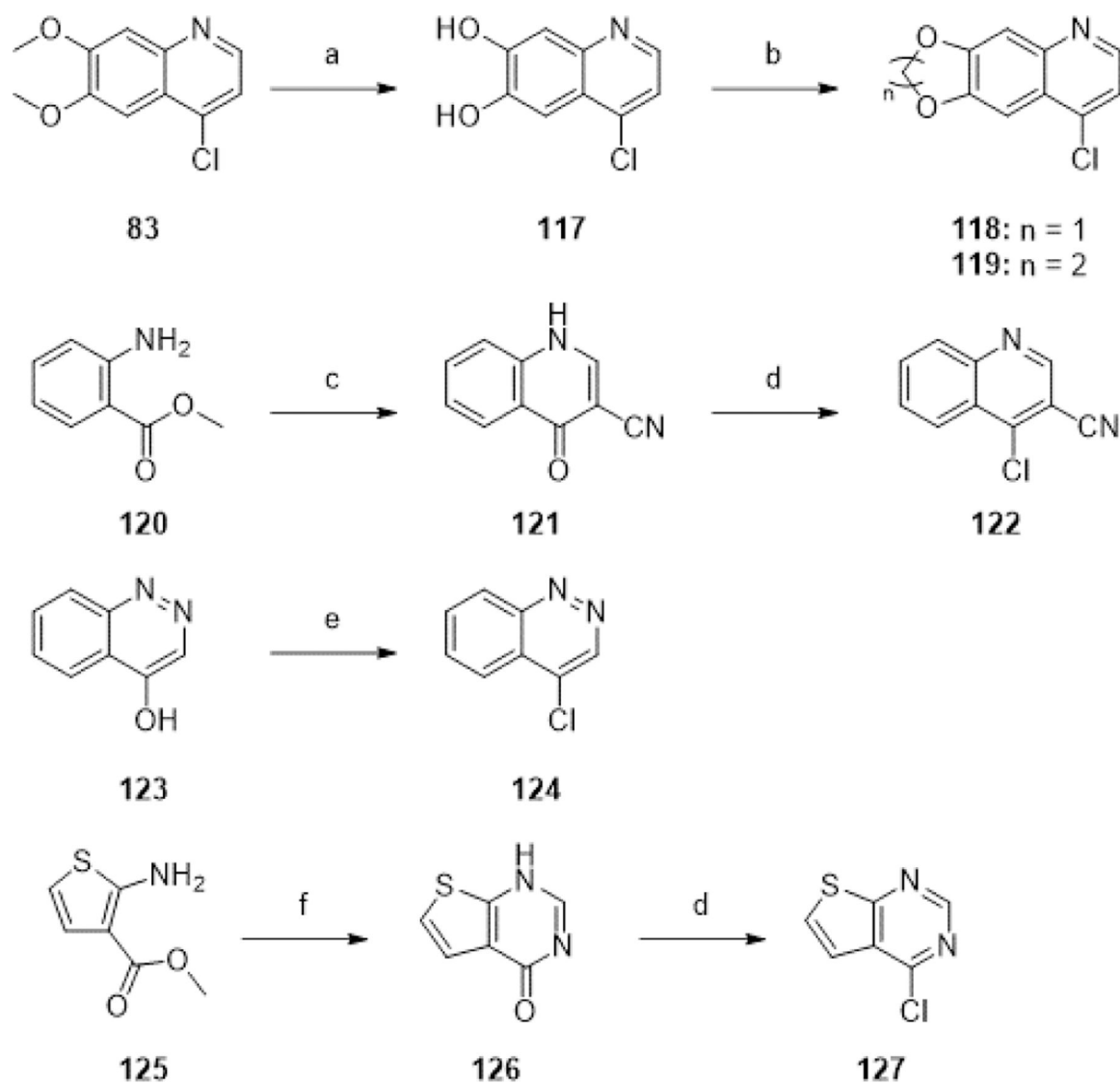
Scheme 3. Head-to-tail synthesis of analogues varying hinge-binding group^a

^aReagents and conditions: (a) ArCl, *o*-xylene, 135°C, [14–60 h], 18–76%; (b) (for **96**) 4-chloro-1H-pyrrolo[2,3-b]pyridine, neat, μ W, 150°C, 20 min, 12%; (c) (for **97**) 4-chloro-7H-pyrrolo[2,3-d]pyrimidine, 2,6-lutidine, NMP, 130°C, 22 h, 28%; (d) (for **98** and **99**) 4,6-dichloropyrimidine or 2,4-dichloropyrimidine, K₂CO₃, DMF, 70°C, 16 h, 54–61%; (e) Fe, NH₄Cl, EtOH/H₂O (3:1), [31–78°C], [2–6 h], 58–95%; (f) ArCl, KO^tBu, DMF or DMA, [0–110°C or rt–80°C], [4–16 h], 11–58%; (g) 2,4-difluoro-1-isocyanatobenzene, EtOH, 0°C–rt, [0.5–24 h], 5–58%; (h) 2,4-difluoroaniline, CDI, DCM or DMSO, 0°C or rt, [0.5–2 h], then [35–40°C], [2.5–4 h], 4–67%; (i) benzylamine, Et₃N, THF, 66°C, 10 h, 52%.



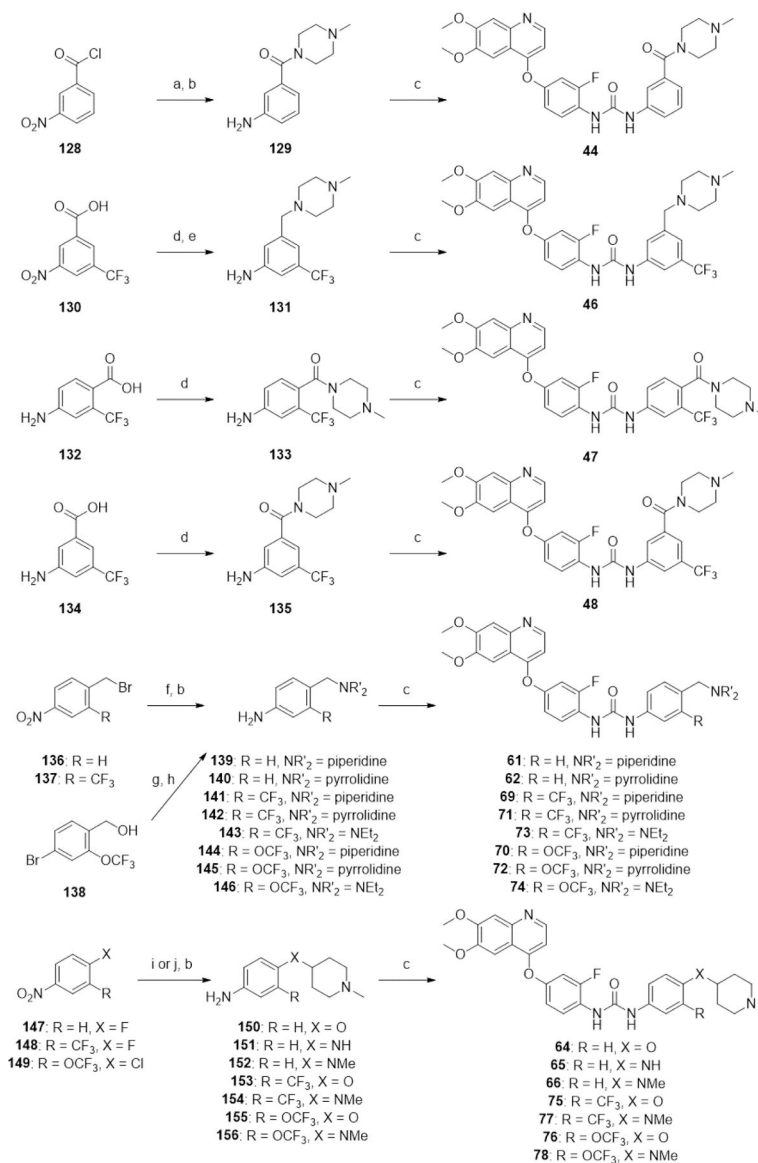
Scheme 4. Preparation of aryl chlorides 118, 119, 122, 124, 127^a

^aReagents and conditions: (a) BBr_3 , DCM, 0°C -rt, 18 h, 42%; (b) diiodomethane or 1,2-dibromoethane, K_2CO_3 , DMF, 60°C , 2 h, 53–66%; (c) (i) DMF-DMA, DMF, 150°C , 3 h, (ii) MeCN, $^n\text{BuLi}$, THF, -78°C , 1 h, 80% (over two steps); (d) POCl_3 , neat, 100°C , 2 h, 50–95%; (e) POCl_3 , THF, 66°C , 1 h, 86%; (f) formamide, neat, 160°C , 24 h, 52%.



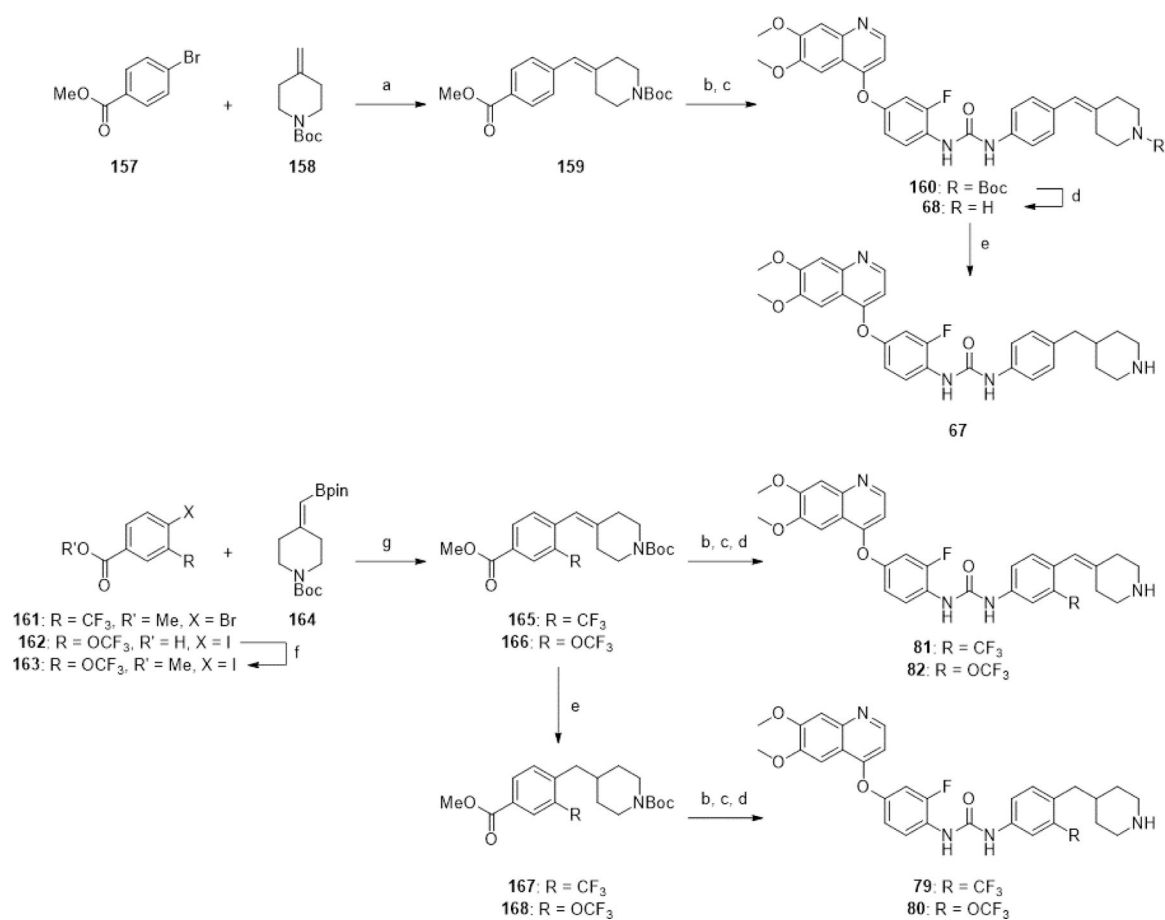
Scheme 5. One-step diversification at the tail group^a

^aReagents and conditions: (a) ArNH₂, CDI, DMSO, [rt or rt-40°C], [5 min-3.5 h], then 60°C, [2-5 h], 15-55%; (b) (for **39**) 1-isocyanato-3-(trifluoromethyl)benzene, EtOH/DCM (2:1), rt, 16 h, 58%; (c) (for **51**) m-toluidine hydrochloride, DIPEA, CDI, DMSO, rt, 45 min, then 60 °C, 4 h, 35%; (d) (for **63**) 4-((diethylamino)methyl)aniline hydrochloride, Et₃N, CDI, DMSO, rt, 1 h, then 60 °C, 2 h, 60%.



Scheme 6. Synthesis of tail group anilines and urea formation^a

^aReagents and conditions: (a) 1-methylpiperazine, THF, 54%; (b) Fe, NH₄Cl, EtOH/H₂O (3:1), [31–78°C], [5–24 h], 53–100%; (c) **14**, CDI, DMSO, [rt–40°C], [0.5–3 h], then 60°C, [2–5 h], 15–69%; (d) 1-methylpiperazine, EDC, DCM, rt, 18 h, 46–79%; (e) LiAlH₄, THF, 66°C, 5 h, 28%; (f) piperidine, pyrrolidine, or Et₂NH, KI, K₂CO₃, MeCN, rt, [1.5–3 h], 54–92%; (g) (i) MsCl, Et₃N, DCM, 0°C–rt, 2 h, (ii) piperidine, pyrrolidine, or Et₂NH, Et₃N, rt, 16 h, 75–89% (over two steps); (h) (i) LiHMDS, Pd(^tBu₃P)₂, toluene, rt, 16 h, (ii) HCl (aq), rt, 10 min, 60–87% (over two steps); (i) 1-methylpiperidin-4-ol, KO^tBu, DMSO, rt, 16 h, 28–58%; (j) 1-methylpiperidin-4-amine or N,1-dimethylpiperidin-4-amine, Et₃N, DMSO, [90–100°C], [16–20 h], 48–82%.

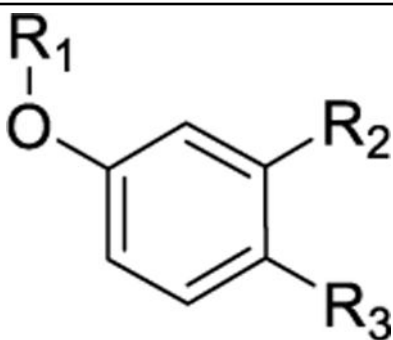

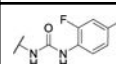

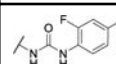

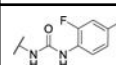

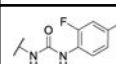

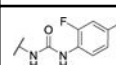
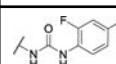
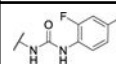

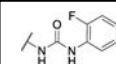

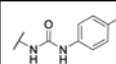

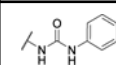

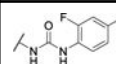


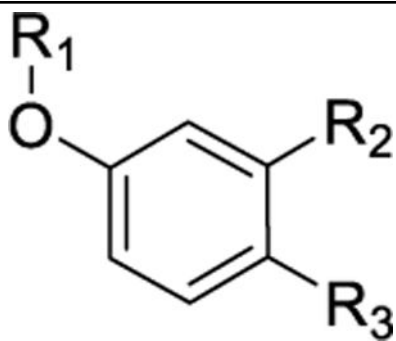
Scheme 7. Synthesis of compounds **67**, **68**, **79–82**^a

^aReagents and conditions: (a) Et₃N, Pd(dppf)Cl₂, DMF, 100°C, 16 h, 18%; (b) LiOH, THF/H₂O (4:1), 50°C, [4–6 h], 88–94%; (c) **14**, DPPA, Et₃N, toluene, μ W, 100°C, 10 min, [**160** (82%)]; (d) TFA/DCM (1:4), rt, 1 h, [**68** (79%), **79** (63% over two steps), **80** (71% over two steps), **81** (63% over two steps), **82** (69% over two steps)]; (e) H₂, Pd/C, MeOH, rt, [18–24 h], 55–88%; (f) MeI, K₂CO₃, DMSO, rt, 6 h, 95%; (g) Pd₂(dba)₃, Xphos, K₃PO₄, 1,4-dioxane/H₂O (9:1), 100°C, 1 h, 67–83%.

Table 1.

Truncated Analogues of Ki8751

					
Compound	R ₁	R ₂	R ₃	PfPK6 activity remaining at 1 μM (%) ^a	PfPK6 IC ₅₀ (nM) ^b
Ki8751		F		n.d.	14 ± 1
1		F		11	40 ± 9
2		F		24	216 ± 21
3		F		40	470 ± 80
4		F		50	830 ± 90
5	H	F		100	n.d.
6	Me	F		100	n.d.
7		F		1	1.3 ± 0.13 ^c
8		F		1	2.0 ± 0.12 ^c
9		F		1	1.3 ± 0.24 ^c
10		H		6	18 ± 1.3



Compound	R ₁	R ₂	R ₃	PfPK6 activity remaining at 1 μM (%) ^a	PfPK6 IC ₅₀ (nM) ^b
11		H		4	9.0 ± 0.5
12		F		28	310 ± 15
13		F		26	240 ± 13
14		F	NH ₂	100	n.d.
15		H	NH ₂	95	n.d.
16		F	H	84	4290 ± 420

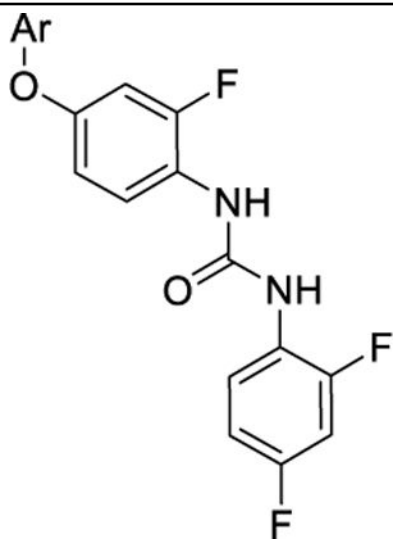
^aResults presented as mean values from experiments using the KinaseSeeker assay performed in duplicate. Variability between individual values is less than 10%.

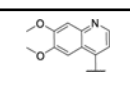
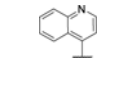
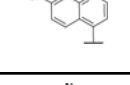
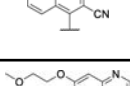
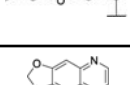
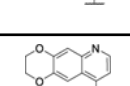
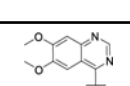
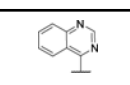

^bIC₅₀ values were determined using the KinaseSeeker assay with 5-fold dilutions, presented as mean ± s.e.m. values of two experiments performed in duplicate.

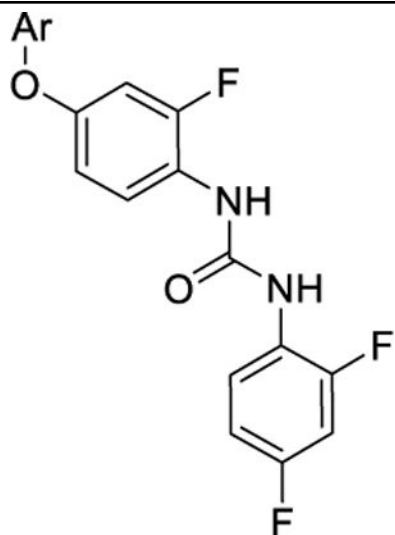
^cIC₅₀ values approach the kinase concentration in the assay. IC₅₀s < 5 nM treated as equipotent. n.d. = not determined.

Table 2.

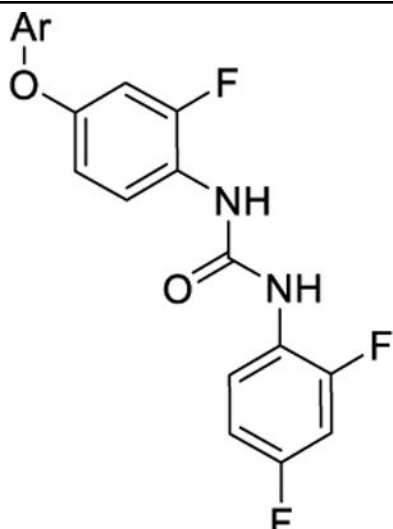


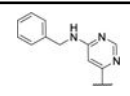
SAR of Hinge-Binding Heterocycles



Compound	Ar	PfPK6 activity remaining at 1 μ M (%) ^a	PfPK6 IC ₅₀ (nM) ^b
Ki8751		n.d.	14 \pm 1
3		40	470 \pm 80
17		38	510 \pm 160
18		86	n.d.
19		2	10 \pm 0.5
20		28	680 \pm 240
21		30	540 \pm 80
22		6	19 \pm 2
23		83	n.d.



Compound	Ar	Pfk6 activity remaining at 1 μ M (%) ^a	Pfk6 IC ₅₀ (nM) ^b
24		100	n.d.
25		34	327 \pm 17
26		61	1970 \pm 240
27		43	800 \pm 100
28		80	n.d.
29		14	124 \pm 12
30		54	n.d.
4		50	830 \pm 9
31		84	n.d.
32		92	n.d.

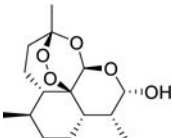
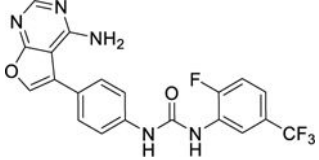
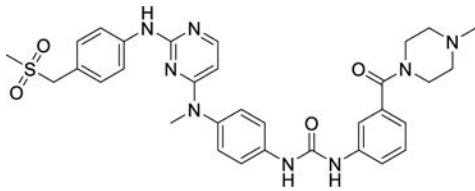
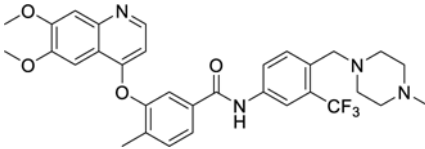
			
Compound	Ar	PfPK6 activity remaining at 1 μ M (%) ^a	PfPK6 IC ₅₀ (nM) ^b
33		96	n.d.
34		98	n.d.
35		60	n.d.

^aResults presented as mean values from experiments using the KinaseSeeker assay performed in duplicate. Variability between individual values is less than 10%.

^bIC₅₀ values were determined using the KinaseSeeker assay with 5-fold dilutions, presented as mean \pm s.e.m. values of two experiments performed in duplicate. n.d. = not determined.

Table 3.

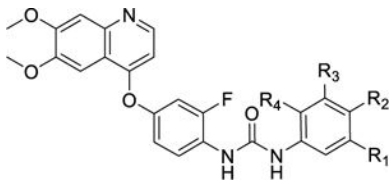
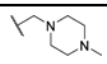
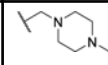
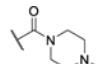
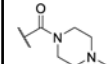
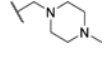
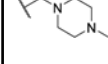
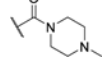
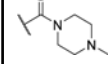
Other inhibitors with a Type II pharmacophore benchmarked against dihydroartemisinin (DHA)

Compound	Structure	PfPK6 IC ₅₀ (nM) ^a	Pf3D7 blood stage EC ₅₀ (nM) ^b
DHA		n.d.	0.14 ± 0.04
36		5.3 ± 0.2	500 ± 68
37		8.5 ± 0.2	390 ± 10
38		76 ± 4	410 ± 28

^aIC₅₀ values were determined using the KinaseSeeker assay with 5-fold dilutions, presented as mean ± s.e.m. values of two experiments performed in duplicate.

^bEC₅₀ values were determined using the SYBR Green I-based assay with 2-fold dilutions, presented as mean ± s.e.m. values performed in triplicate. n.d. = not determined

Table 4.Incorporating CF₃ and piperazines to tail group of Ki8751

						
Compound	R ₁	R ₂	R ₃	R ₄	PPK6 IC ₅₀ (nM) ^a	<i>Pf</i> 3D7 blood stage EC ₅₀ (nM) ^b
Ki8751	H	F	H	F	14 ± 1	n.d.
39	CF ₃	H	H	H	0.84 ± 0.04 ^c	540 ± 24
40	CF ₃	H	H	F	1.2 ± 0.07 ^c	Inactive ^d
41	H		H	H	13 ± 0.5	580 ± 65
42	H	H		H	23 ± 1	Inactive ^e
43	H		H	H	321 ± 21	Inactive ^e
44	H	H		H	68 ± 3	Inactive ^e
45	CF ₃		H	H	1.9 ± 0.1 ^c	110 ± 4
46	CF ₃	H		H	0.81 ± 0.02 ^c	410 ± 23
47	CF ₃		H	H	21 ± 1	Inactive ^e
48	CF ₃	H		H	0.29 ± 0.02 ^c	Inactive ^e

^aIC₅₀ values were determined using the KinaseSeeker assay with 5-fold dilutions, presented as mean ± s.e.m. values of two experiments performed in duplicate.

^bEC₅₀ values were determined using the SYBR Green I-based assay with 2-fold dilutions, presented as mean ± s.e.m. values performed in triplicate.

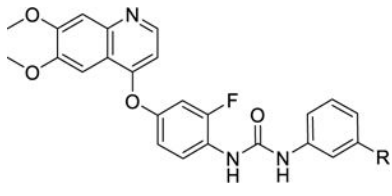
^cIC₅₀ values approach the kinase concentration in the assay. IC₅₀s < 5 nM treated as equipotent.

^dNo inhibition when tested up to 5 μM in two experiments, testing in dose-response manner.

^eNo inhibition when tested in triplicate at a single concentration of 1 μM. n.d. = not determined.

Table 5.

SAR of the meta-position substituent at the tail group



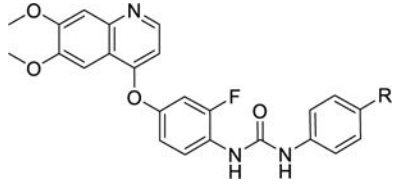
Compound	R	PfPK6 IC ₅₀ (nM) ^a	<i>Pf</i> 3D7 blood stage EC ₅₀ (nM) ^b
39	CF ₃	0.84 ± 0.04 ^c	540 ± 24
49	Cl	1.0 ± 0.08 ^c	2190 ± 201
50	Br	1.1 ± 0.03 ^c	Inactive ^d
51	Me	1.2 ± 0.07 ^c	3010 ± 234
52	ⁱ Pr	1.1 ± 0.07 ^c	Inactive ^d
53	^t Bu	2.1 ± 0.08 ^c	2520 ± 106
54	OMe	1.7 ± 0.13 ^c	Inactive ^d
55	O ⁱ Pr	1.5 ± 0.12 ^c	Inactive ^d
56	OCHF ₂	0.44 ± 0.05 ^c	Inactive ^d
57	OCF ₃	1.2 ± 0.06 ^c	800 ± 15
58	CN	1.8 ± 0.07 ^c	Inactive ^d

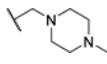
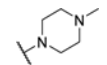
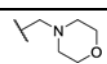
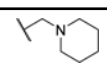
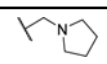
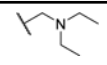
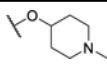
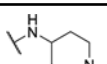
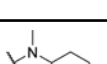
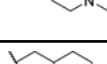
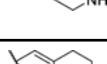
^aIC₅₀ values were determined using the KinaseSeeker assay with 5-fold dilutions, presented as mean ± s.e.m. values of two experiments performed in duplicate.

^bEC₅₀ values were determined using the SYBR Green I-based assay with 2-fold dilutions, presented as mean ± s.e.m. values performed in triplicate.

^cIC₅₀ values approach the kinase concentration in the assay. IC₅₀s < 5 nM treated as equipotent.

^dNo inhibition when tested in triplicate at a single concentration of 1 μM.

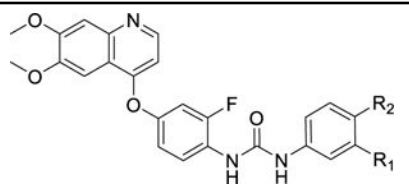
Table 6.SAR of the *para*-position substituent at the tail group
















Compound	R	PPK6 IC ₅₀ (nM) ^a	<i>Pf</i> 3D7 blood stage EC ₅₀ (nM) ^b
41		13 ± 0.5	580 ± 65
59		390 ± 30	630 ± 13
60		135 ± 8	Inactive ^c
61		310 ± 13	250 ± 7
62		220 ± 40	270 ± 41
63		138 ± 14	320 ± 13
64		26 ± 2	330 ± 11
65		150 ± 30	660 ± 15
66		17 ± 3	330 ± 5
67		13 ± 0.9	160 ± 2
68		29 ± 3	140 ± 4

^aIC₅₀ values were determined using the KinaseSeeker assay with 5-fold dilutions, presented as mean ± s.e.m. values of two experiments performed in duplicate.

^bEC₅₀ values were determined using the SYBR Green I-based assay with 2-fold dilutions, presented as mean ± s.e.m. values performed in triplicate.

^cNo inhibition when tested in triplicate at a single concentration of 1 μM.

Table 7.SAR combining optimal *meta*- and *para*-position substituents


Compound	R ₁	R ₂	PfPK6 IC ₅₀ (nM) ^a	Pf3D7 blood stage EC ₅₀ (nM) ^b
69	CF ₃		12 ± 1	490 ± 15
70	OCF ₃		14 ± 2	310 ± 14
71	CF ₃		27 ± 3	330 ± 13
72	OCF ₃		12 ± 1	230 ± 5
73	CF ₃		8.1 ± 0.8	300 ± 3
74	OCF ₃		14 ± 2	270 ± 7
75	CF ₃		1.9 ± 0.09 ^c	40 ± 0.7
76	OCF ₃		3.1 ± 0.1 ^c	75 ± 1.8
77	CF ₃		1.9 ± 0.1 ^c	150 ± 12
78	OCF ₃		1.8 ± 0.1 ^c	250 ± 11
79	CF ₃		1.6 ± 0.3 ^c	39 ± 0.3
80	OCF ₃		2.8 ± 0.3 ^c	82 ± 0.4
81	CF ₃		2.0 ± 0.2 ^c	84 ± 1.6
82	OCF ₃		2.7 ± 0.2 ^c	84 ± 0.3

^aIC₅₀ values were determined using the KinaseSeeker assay with 5-fold dilutions, presented as mean ± s.e.m. values of two experiments performed in duplicate.

^bEC₅₀ values were determined using the SYBR Green I-based assay with 2-fold dilutions, presented as mean ± s.e.m. values performed in triplicate.

^cIC₅₀ values approach the kinase concentration in the assay. IC₅₀s < 5 nM treated as equipotent.

Table 8.

Antiparasitic Effect on *P. berghei* Liver Stage Parasite Load, HepG2 Cytotoxicity, and Pharmacokinetic Parameters of Key Compounds

Compound	HepG2 cytotoxicity CellTiter-Glo CC ₅₀ (μM) ^a	<i>P. berghei</i> liver stage EC ₅₀ (μM) ^b	HepG2 cytotoxicity CellTiter-Fluor CC ₅₀ (μM) ^c	Solubility (μM) ^d	PAMPA P _{app} (10 ⁻⁶ cm/s) ^e	Human Liver Microsomal Stability (% remaining after 30 min) ^f	Mouse Liver Microsomal Stability (% remaining after 30 min) ^f
Ki8751	n.d.	n.d.	n.d.	0.7	24.2	n.d.	n.d.
45	1.00 ± 0.24	n.d.	n.d.	2.1	2.57	n.d.	n.d.
67	4.39 ± 0.17	inactive ^g	3.29 ± 0.28	10.9	<0.669 ^h	95.9	85.8
68	2.57 ± 0.05	inactive ^g	6.62 ± 1.32	7.4	<0.709 ^h	88.6	86.7
75	1.00 ± 1.00	inactive ^g	0.41 ± 0.18	1.5	<0.513 ^h	88.6	69.7
79	1.29 ± 1.34	0.22 ± 0.05	1.29 ± 0.49	2.1	0.734	98.1	88.9

^aCC₅₀ values were presented as mean ± s.d. values from 2–3 experiments using the CellTiter-Glo assay, each performed in quadruplicate.

^bEC₅₀ values were presented as mean ± s.d. values from two experiments, each performed in triplicate.

^cCC₅₀ values were presented as mean ± s.d. values from two experiments using the CellTiter-Fluor assay, each performed in triplicate.

^dKinetic solubility analysis was carried out in phosphate buffered saline solution (PBS) at pH 7.4 from 10 mM DMSO stock solutions.

^ePermeability analysis was performed using a chamber separated by an immobilized artificial phospholipid membrane layer into a donor and an acceptor well.

^fMicrosomal stability analysis were performed using a test compound concentration of 5 μM, microsomal protein concentration of 0.5 mg/mL, NADPH concentration of 7–9 mM.

^gEC₅₀ not reported because we observed a <5-fold difference between observed EC₅₀ and cytotoxicity in host HepG2 cells using the CellTiter-Fluor assay.

^hBelow limit of quantitation in acceptor well. n.d. = not determined.

Table 9.Inhibition of compound 67, 68, 75, and 79 on other *P. falciparum* kinases

	% Activity remaining at 1 μ M (IC ₅₀) ^a											% control at 1 μ M ^b	
	PfARK1	PfARK3	PfCDPK2	PfCDPK5	PfGSK3	PfNEK1	PfNEK3	PfPK5	PfPK6	PfPK9	PfPKB	PfCDPK1	PfPK5
67	97	100	88	91	97	100	82	97	2 (13 nM)	99	30	51	84
68	98	100	96	98	100	100	84	100	1 (29 nM)	100	38	n.d.	n.d.
75	94	97	78	25	30	100	6	94	0 (1.9 nM) ^c	79	20	n.d.	n.d.
79	100	87	64	27	34	100	7	94	1 (1.6 nM) ^c	89	21	1.1	80

^aResults presented as mean values from experiments using the KinaseSeeker assay performed in duplicate. Variability between individual values is less than 10%. IC₅₀ values were determined using the KinaseSeeker assay with 5-fold dilutions, presented as mean values of two experiments performed in duplicate.

^bResults from DiscoverX KINOMEScan[®] profiling service.

^cIC₅₀ values approach the kinase concentration in the assay. IC₅₀s < 5 nM treated as equipotent. n.d. = not determined.