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Kinase scaffold repurposing for neglected disease drug discovery: Discovery of an efficacious, lapatanib-derived lead compound for trypanosomiasis

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Abstract

Human African trypanosomiasis (HAT) is a neglected tropical disease caused by the protozoan parasite *Trypanosoma brucei*. Since drugs in use against HAT are toxic and require intravenous dosing, new drugs are needed. Initiating lead discovery campaigns by using chemical scaffolds from drugs approved for other indications can speed up drug discovery for neglected diseases. We demonstrated recently that the 4-anilinoquinazolines lapatinib (GW572016, **1**) and canertinib (CI-1033) kill *T. brucei* with low micromolar EC₅₀ values. We now report promising activity of analogs of **1**, which provided an excellent starting point for optimization of the chemotype. We report our compound optimization that has led to synthesis of several potent 4-anilinoquinazolines, including NEU621, **23a**, a highly potent, orally bioavailable inhibitor of trypanosome replication. At the cellular level, **23a** blocks duplication of the kinetoplast and arrests cytokinesis, making it a new tool for studying regulation of the trypanosome cell cycle.

Introduction

Neglected tropical diseases (NTDs) represent a significant global health burden, particularly in developing regions of the world. Estimates of as many as one in six in the world population (over 1 billion people) are infected by one or more NTD, with one in three people at risk.¹ These diseases are “neglected” since so few research dollars are invested in treating or preventing them, in comparison to those conditions primarily affecting the developed world. As a result, pragmatic and cost-effective approaches for identification of drug leads are needed in order to spawn the discovery of new drugs.

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Author contributions

MPP developed the medicinal chemistry strategy and contributed to compound designs. KM-W initiated the project. GP, CEK, PE, contributed to compound designs and performed chemical synthesis and characterization. RB, PG, and CS performed trypanosome assays, and NER performed the HepG2 assays.

Supporting Information.

Synthesis of selected boronates, and a tabulation of all the inhibitors, with their Northeastern registry numbers and screening data is in the Supporting Information, and the screening data has been made freely available as a shared data set at www.collaborativedrugdiscovery.com. Also included are biological assay details, data from pharmacokinetic and *in vivo* efficacy studies, plasma protein binding, and results from cell cycle analysis following inhibitor treatment. This supporting information is available free of charge via the Internet at <http://pubs.acs.org>.

One such approach is to “repurpose” classes of proven molecular targets with essential homologs in the pathogens that cause these NTDs.² For example, *Trypanosoma brucei* (which causes human African trypanosomiasis (HAT)), *T. cruzi* (Chagas’ disease), *Leishmania spp.* (causative agents for leishmaniasis) and *Plasmodium spp.* (malaria) all express kinases and phosphodiesterases (PDEs) that are involved in aspects of cellular signaling.^{3,4} Indeed, kinases and PDEs represent proven drug target classes in humans for a variety of indications, and, as such, a large amount of data related to medicinal chemistry, toxicology, and structural biology are available that can potentially inform new optimization programs against parasites. Furthermore, the clinical and pre-clinical chemical matter itself can sometimes represent a starting point for new antiparasitic approaches, an approach demonstrated by us⁵⁻⁷ and by others.^{8,9}

Following parasite transmission via an infected tsetse fly, a trypanosome bloodstream infection gives rise to flu-like symptoms that eventually subside. At this point, the parasites invade the central nervous system (CNS), where they establish an infection that leads to sleep disruption, coma and eventually death. Current drugs have less than optimal toxicity profiles, and the dosing regimens can be inconvenient, long, and costly. There is therefore a stated need for new HAT therapeutics that are orally administered, with minimal toxicity, and which are effective against both bloodstream and CNS forms of the disease. To that end, “hit” and “lead” criteria for HAT and other NTDs are clearly described.¹⁰

Kinase inhibitors have come to the fore as one of the principal enzyme target classes in drug discovery for a wide variety of indications, including cancer,¹¹ inflammation,^{12,13} diabetes,^{14,15} and CNS diseases.¹⁶ In particular, a number of tyrosine kinase inhibitors have been approved for clinical use.¹⁷ This list includes lapatinib (GW572016, Tykerb, **1**), an EGFR inhibitor that gained FDA approval in 2007.¹⁸

T. brucei expresses over 180 protein kinases,^{19,20} some of which (such as glycogen synthase kinase-3,²¹ phosphoinositol-3-kinases/TOR,⁷ and Aurora kinase 1⁶) have been targeted in drug discovery efforts already. There is unequivocal chemical data for protein Tyr phosphorylation in the parasite.^{22,23} However, trypanosomes do not express receptor tyrosine kinases (RTKs),⁴ and it is widely held that Tyr-phosphorylation must therefore be performed by dual-specificity enzymes (e.g., wee1) that act on Ser/Thr as well as Tyr residues.⁴ Intriguingly, based on bioinformatics analysis, enzymes with “EGFR-like” kinase domains are present in the parasite.²⁴ Further, inhibitors of human EGFR/HER2 (i.e., canertinib,²⁵ **1**,²⁶ and AEE788²⁷) kill *T. brucei* with EC₅₀ in the low micromolar range.²⁴

Transferrin is a growth factor that *T. brucei* acquires from its vertebrate host by receptor-mediated endocytosis.²⁸ We discovered that receptor-mediated endocytosis of Tf in the African trypanosome is stimulated by diacylglycerol (DAG).²⁹ In most eukaryotes, effects of DAG on signaling pathways are amplified by the Ser/Thr kinase protein kinase C, which binds to the lipid with its C1-domain. In trypanosomes, DAG signaling pathways have not been studied. To understand the pathway linking DAG and Tf endocytosis in the trypanosome, we tested the effect of inhibitors of Ser/Thr protein kinases (e.g., protein kinase C) or Tyr kinases on DAG-stimulated endocytosis of Tf. Unexpectedly, DAG-stimulated endocytosis of Tf was not blocked by a Ser/Thr protein kinase inhibitor, nor does the genome of *T. brucei* encode for a classic PKC. Instead, the pathway was inhibited by a Tyr kinase inhibitor Tyrphostin A47, a tyrosine mimic.³⁰ In a related study, we found that **1**, similar to Tyrphostin A47, inhibited endocytosis of transferrin.³¹

These data suggested to us that tyrosine kinase inhibitor drugs approved for treatment of non-parasite human diseases were worth testing as anti-trypanosomal agents. We have evaluated the trypanocidal properties of a panel of EGFR inhibitors provided by

GlaxoSmithKline (**Table 1**), and we describe the subsequent design and synthesis of novel analogs for a structure activity relationship study of a 6-phenyl 4-anilinoquinazoline scaffold, culminating in **23a**, a highly selective and potent inhibitor of trypanosome replication *in vitro*.

Results

We obtained nine quinazoline-based EGFR inhibitors (**1-9**, **Table 1**)^{18,32-34} from GlaxoSmithKline and screened them against cultures of *T. brucei brucei* Lister 427. The inhibitors demonstrated a four-fold range in potency (**Table 1**) within the limited scope in variation of the R¹ “tail” region of the scaffold. We noted the EC₅₀ of **1** (1.54 μM) to be four-fold more potent against *T. brucei* as compared to a HepG2 hepatocarcinoma cell line.³⁵ For comparison, we have also included in **Table 1** the published activities of three front-line HAT treatments (eflornithine, melarsoprol, and pentamidine), and of SCYX-7158, currently in clinical trials. The goal of our subsequent optimization efforts have dwelt on improvement of the potency of this chemotype for inhibition of *T. brucei* replication, and increasing the selectivity ratio over HepG2 cells.

Noting the effect of subtle tail-group changes on parasite growth inhibition, we first focused our attention on broader exploration of replacements for the furan-derived tail. This was achieved by a broad diversity scan utilizing Suzuki chemistry methodology using boronic acids or esters to enumerate a virtual library of analogs of **1** (**Scheme 1**). The structures in this 197-membered virtual library were clustered based on a maximum dissimilarity algorithm, and cluster centers were selected for synthesis (PipelinePilot, Scitegic, Inc).

In anticipation of the parallel synthesis, we prepared the iodoquinazoline **14** by the route shown in **Scheme 1**. Treatment of the commercially available anthranilic acid **11** with formamide proceeded in 70% yield, followed by chlorination with thionyl chloride to provide the chloroquinazoline **13** in 85% yield. This template was reacted with the requisite aniline (**17**, **Scheme 2**), which was prepared by a sequence of alkylation of the nitrophenol **15** with 3-fluorobenzyl bromide followed by nitro group reduction. With the required template **14** in hand, we prepared ten analogs (**10a-k**) from the selected boronates using standard Suzuki reaction conditions. The structures and biological activities for these compounds are summarized in **Table 2**. From this series of analogs we identified NEU369 (**10a**), which was approximately equipotent to **1** against *T. brucei* cells. Further testing of this compound and its analogs showed that, unlike **1**, it did not inhibit HepG2 cell growth (EC₅₀ > 15 μM) (**Table 3**).

Keeping the newly identified tail group present in **10a** (**Table 3**), we turned our attention to exploration of the aniline head group region of the molecule. Preparation of the requisite chloroquinazoline **19** (**Scheme 3**) was achieved by treatment of **12** with the required boronic acid using Suzuki conditions, followed by chlorination with thionyl chloride. This intermediate was reacted with a range of anilines (**Scheme 2**) to provide analogs **20** (**Table 3**).

This library was designed to explore the role of halogen substitutions on the terminal benzyl substituent (R¹) headgroup, testing positional isomers of fluoro substitutions and other potential halogen replacements such as methoxy and trifluoromethyl groups. These modifications produced insignificant changes in activity of the compounds against *T. brucei*. We prepared a few analogs to assess functional group tolerance at the R² position of the head group, replacing the chlorine atom of **1** with hydrogen and methoxy groups; these changes also resulted in very modest alterations in anti-trypanosomal activity. Interestingly, truncation of the molecule (**20a**) gave potency approximately equal to **10a**, translating to a

similar ligand efficiency value (LE of **10a**=0.14; **20a**=0.18).³⁶ Importantly, HepG2 cell toxicity was minimal with these modifications.

For the next round of analogs, we turned our attention back to further refinement of the tail group region of **1**, performing focused modifications of the 6-aryl position of the quinazoline ring that were designed to evaluate steric requirements, as well as the required adornment of polarity in this region of the inhibitor. These compounds (**10k-w**) were accessed from the corresponding boronic acids using the route shown in **Scheme 1**. The larger sulfonamide side chains showed some modest preference for *meta*-substitution (**Table 4**, entries 1-6), though the methyl sulfones (entries 11-12) showed preference for *para*-substituents. Comparing the sulfonamide substituents, morpholine was preferred over the other heterocyclics tested.

A more focused evaluation of linker and regiochemistry is shown in **Table 5**. Compounds were synthesized from **14** by reaction with the appropriate boronate ester **22**. In the case of the morpholinosulfonamides (entries 1-8), *meta*-substitution is consistently better than *para*; the most potent analog, NEU617 (**23a**), is directly linked to the aromatic ring. For piperidinosulfonamides (entries 9-16), the meta preference is less consistent, and none of these analogs show as potent growth inhibition as **23a**. When the tail contains a morpholine (entries 1-8), the linker has little impact on potency (except for **23a**, a clear outlier); all *meta*-substituted analogs are otherwise approximately equipotent. In cases where the morpholine moiety is at the *para*-position there is little difference resulting from linker variation.

With piperidine-substitution (entries 9-16), it appears that a modest preference exists for the *meta*-substituted amide, with a 6.7-fold loss of activity when moved to the *para* position (compare entries 13 and 14), though the importance of positional substitution is otherwise less for other examples, within ~2-fold in activity.

Lastly, we sequentially removed the head group substituents of **23a**. Removal of one (**23m**) or both (**23n**) halogens afforded an approximately 5-fold reduction in potency, and further truncation (**23o**) significantly reduced antiparasitic activity while restoring HepG2 potency (**Table 6**).

Noting its potency against *T. brucei* and selectivity over HepG2 cells (**Table 5**), we advanced **23a** into a mouse oral pharmacokinetic study. Mice were administered a single oral dose (40 mg/kg) of **23a**, and plasma and brain tissue drug levels were measured over 24 hours (Supporting Information **Figure S1** and **Table S6**). Though the CNS fraction was low (5%), the plasma levels were in excess of the EC₅₀ for >12 hours. We determined that **23a** was 99.6% plasma protein bound. However, since trypanosomes are noted for their ability to endocytose host plasma proteins,^{29,37,38} we believed that the oral exposure and *in vitro* potency warranted *in vivo* efficacy evaluation.

In a test of efficacy in a mouse model of HAT, mice were infected with *T. brucei brucei* CA427(10⁴ cells) and after 24 h, were administered a 40 mg/kg dose of **23a** once per day. No parasites were detected in the blood of the infected mice for 3 days whereas control mice had trypanosomes in their blood on day 2 post-infection. However drug-related toxicity was observed with **23a** in a multi-day regimen at the 40 mg/kg dose. These data point to a need to improve the pharmacokinetic properties of **23a** so that it can be more effective in the mouse model of HAT.

Nonetheless, inspired by these initial results, we adjusted the dosing regimen, opting to administer **23a** at 10 mg/kg twice per day (total dose of 20 mg/kg/day), either orally or

intraperitoneally (i.p.). The results are shown in **Figure 1A**. We noted three effects: First, i.p. treatment with **23a** delayed detection of trypanosomes in the blood of infected mice by 24 h. Whereas all control mice had trypanosomes in their blood on day 3, mice treated with **23a** all had parasites in their blood 24 h later, suggestive of either a significant reduction in replication rate (trypanosomes divide every 6 hours) or of parasite killing during this initial phase of infection. Second, on day 8 when all untreated mice had died, the mice dosed i.p. with **23a** were all alive (**Figure 1B**). In the oral administration experiment, mice died in the same time frame as control mice, suggesting insufficient drug exposure at this dosage. Third, i.p administration of **23a** led to better control of infection, leading to a doubling of mouse survival life span from 5 days in the control group to 9 days in **23a**-treated mice.

Although **23a** is structurally similar to **1**, the biological effects of the two compounds are different. Whereas **1** inhibited endocytosis of transferrin in the trypanosome³¹ in a manner similar to what we previously observed with tyrphostin,³⁰ **23a** had no effect on receptor-mediated endocytosis of transferrin. Instead, **23a** affected the cell cycle in ways not observed with **1** (**Figure 2**).

Trypanosomes possess two DNA-containing organelles (nucleus and kinetoplast (mitochondrial nucleoid)). The kinetoplast and nucleus can be tracked by microscopy during the cell cycle, which begins with trypanosomes harboring one nucleus (1N) and one kinetoplast (1K) (*i.e.*, 1K1N cells).^{39,40} A kinetoplast that is replicating its (DNA) (*i.e.*, kDNA) and increasing in the organelle's mass is observed as an elongated kinetoplast (1Ke). Fission (segregation) of 1Ke kinetoplasts into two daughter kinetoplasts (2K) inside the same cell is coincident with the nuclear S-phase, and produces 2K1N trypanosomes. Mitosis then occurs, yielding trypanosomes containing two kinetoplasts and two nuclei (2K2N). Following cell division each daughter trypanosome has a 1K1N1 configuration of the organelles.⁴¹

After a 7h incubation with **23a**, the chromosomal DNA profile of *T. brucei* was altered (**Figure 2A**); the fraction of cells with 2C-4C equivalents of DNA was reduced from 40 to 25%, whereas the proportion of cells with 4C DNA increased from 25% to 40% (**Figure 2B**). Single cell microscopy studies were performed to determine whether the changes in DNA per cell caused by **23a** (**Figure 2B**) were reflected in alterations in the number of DNA-containing organelles per cell (**Figure 2C**). Quantitation of the data obtained in **Figure 2C** revealed that **23a** reduced the number of cells containing one nucleus (*i.e.*, 1K1N, 1Ke1N) but selectively increased the fraction of a group of cells that are not normally detected in the absence of the drug; cells containing two nuclei and one kinetoplast (1K2N) (**Figure 2D**). This data is consistent with the increase in trypanosomes with 4C equivalent of DNA (**Figure 2B**). Thus, **23a** blocks duplication of the kinetoplast and arrests cytokinesis, without inhibiting division of the trypanosome nucleus.

Discussion and conclusions

While some efforts to find new anti-trypanosomal lead compounds involve screening of large compound libraries against cell cultures,⁴² these can be complemented with lead discovery programs that target important physiological pathways in the parasite. Further, since many of these pathways employ enzymes of functional similarity to drug targets in humans, a privileged set of starting compounds already exist that can represent useful starting points for lead discovery without massive drug screening initiatives.

In this report we have described the discovery of potent trypanocidal compounds that are based on established human EGFR inhibitor chemotypes. By starting with such “privileged” lead compounds, we have accelerated our anti-trypanosomal lead discovery program by

circumventing a need to run high-throughput screens. Indeed, in only a few optimization cycles we have identified a potent chemotype as a lead series for trypanosomiasis. Though compound **23a** has high calculated lipophilicity and molecular weight, its oral bioavailability lent the compound to further assessment in a mouse model of HAT, where we observed modest effects in controlling parasitemia, with concomitant life extension of infected mice. Since the pharmacokinetic experiments suggest acceptable plasma levels in mice following oral dosing, we hypothesize that the high plasma protein binding (99.6%) observed for **23a** is the cause of the lower-than-expected effect on *in vivo* parasite loads.

Trypanosome physiology analysis indicates that **23a** it acts via a mechanism different from **1** and tyrphostin. Work is in progress to identify the molecular targets of our lead compound series. Nonetheless, we note that utilization of cell replication assays has led to promising outcomes that are worthy of future lead optimization studies.

Besides working to reduce plasma protein binding, further optimization of **23a** is needed to improve predicted central nervous system exposure. A recent report by Wager *et al.* described an analysis that correlated compound properties to CNS exposure using data for both experimental and marketed drugs,⁴³ and devised a scoring paradigm for prediction of CNS exposure.⁴⁴ This protocol, termed multi-parameter optimization, or MPO, allows prediction of likely CNS exposure for a given compound based on how closely it meets desired property ranges for MW, cLogP, LogD, pKa, and TPSA with a maximal MPO score of 6.0, and compounds >4.0 predicted to be CNS-penetrant. As shown in **Table 7**, compound **23a** has significant shortcomings in terms of properties that have been shown relevant to CNS activity, particularly due to high calculated lipophilicity (cLogP, cLogD=7.1) and molecular weight (541 Da). Future efforts will be focused on reduction of molecular size and lipophilicity to improve the likelihood of CNS penetration, a pivotal requirement for any new therapeutic for HAT.

In summary, we have identified a potent trypanosomal growth inhibitor (**23a**) based on the 6-furanyl 4-anilinoquinazoline scaffold of **1**. The lead displays good selectivity over HepG2 cells, is orally bioavailable, and is modestly efficacious in a mouse model of HAT, such that it meets “Lead Criteria” as defined by The Special Programme for Research and Training in Tropical Diseases (TDR).¹⁰ Further optimization of this scaffold for increased effectiveness in the mouse model will be reported in due course. Our ability to (i) identify trypanosome replication inhibitors based on a basic biology principles using established kinase drug chemotypes, and (ii) perform rapid hit-to-lead medicinal chemistry supports our approach of re-optimizing existing drug scaffolds for anti-trypanosome lead discovery.

Experimental Section

Chemical synthesis

Unless otherwise noted, reagents were obtained from Sigma-Aldrich, Inc. (St. Louis, MO), or Frontier Scientific Services, Inc. (Newark, DE) and used as received. Boronic acids and aniline reagents were purchased, unless the synthesis is specifically described below. Reaction solvents were purified by passage through alumina columns on a purification system manufactured by Innovative Technology (Newburyport, MA). NMR spectra were obtained with Varian NMR systems, operating at 400 or 500 MHz for ¹H acquisitions as noted. LCMS analysis was performed using a Waters Alliance reverse-phase HPLC, with single-wavelength UV-visible detector and LCT Premier time-of-flight mass spectrometer (electrospray ionization). All newly synthesized compounds were that were submitted for biological testing were deemed >95% pure by LCMS analysis (UV and ESI-MS detection) prior to submission for biological testing. Preparative LCMS was performed on a Waters FractionLynx system with a Waters MicroMass ZQ mass spectrometer (electrospray

ionization) and a single-wavelength UV-visible detector, using acetonitrile/water gradients with 0.1% formic acid. Fractions were collected on the basis of triggering using UV and mass detection. Yields reported for products obtained by preparative HPLC represent the amount of pure material isolated; impure fractions were not repurified

4-chloro-6-iodoquinazoline hydrochloride (**13**).⁴⁵

Yield: 85%. ¹H NMR (500 MHz, DMSO-d₆) δ: 8.39 (d, *J* = 1.95 Hz, 1H), 8.29 (s, 1H), 8.13 (dd, *J* = 1.95, 8.30 Hz, 1H), 7.49 (d, *J* = 8.30 Hz, 1H). MS: *m/z* = 290.83 (M+H)⁺.

N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-iodoquinazolin-4-amine hydrochloride (**14**).⁴⁶

Yield: 84%. ¹H NMR (500 MHz, DMSO-d₆) δ: 11.21 (br. s., 1H), 9.16 (s, 1H), 8.92 (s, 1H), 8.34 (d, *J* = 8.79 Hz, 1H), 7.93 (d, *J* = 2.44 Hz, 1H), 7.64 - 7.68 (m, 2H), 7.46 - 7.51 (m, 1H), 7.30 - 7.37 (m, 2H), 7.20 (dt, *J* = 2.44, 8.79 Hz, 1H), 5.30 (s, 2H). MS: *m/z* = 505.85 (M+H)⁺.

Libraries of **10** were synthesized by Suzuki coupling of **14** with respective boronic acid/esters following **General procedure A**. Into glass vials was combined N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-iodoquinazolin-4-amine (**14**, 100 μM), boronic acids/esters (120 μmol) and tetrakis(triphenylphosphine)palladium(0) (7 μmol). To the reaction mixture was added 1,2-dimethoxyethane (2 mL), ethanol (1.33 mL) and a 2M aqueous solution of sodium carbonate (0.301 mL, 600 μM). The vials were capped and shaken at 80 °C for 18 h. The progress of the reaction was followed by LC-MS. Reaction mixture was evaporated to dryness. Crude products were purified using flash column chromatography, or by dissolving in DMSO and purifying by reverse phase HPLC using a gradient of 30-100% acetonitrile in water containing 0.1% formic acid.

N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(4-(morpholinosulfonyl)phenyl)quinazolin-4-amine (**10a**)

Yield: 48.1%. ¹H NMR (500 MHz, DMSO-d₆) δ: 10.00 (s, 1H), 8.92 (d, *J* = 1.46 Hz, 1H), 8.64 (s, 1H), 8.28 (dd, *J* = 1.95, 8.79 Hz, 1H), 8.17 (d, *J* = 8.79 Hz, 2H), 8.04 (d, *J* = 2.44 Hz, 1H), 7.92 (d, *J* = 8.79 Hz, 3H), 7.76 (dd, *J* = 2.45, 8.80 Hz, 1H), 7.46 - 7.50 (m, 1H), 7.30 - 7.36 (m, 3H), 7.19 - 7.23 (m, 1H), 5.28 (s, 2H), 3.66 - 3.68 (m, 4H), 2.93 - 2.95 (m, 4H). MS: *m/z* = 605.2 (M+H)⁺.

N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(4-methylnaphthalen-1-yl)quinazolin-4-amine, (**10b**)

Yielded 1 mg (2.6%) as a yellow film. ¹H NMR (400 MHz, DMSO-d₆) δ: 9.82 (s, 1H), 8.65 (s, 2H), 8.15 (d, *J* = 8.8 Hz, 1H), 8.03 (d, *J* = 2.2 Hz, 1H), 7.87-7.96 (m, 2H), 7.81 (d, *J* = 8.8 Hz, 1H), 7.71-7.76 (m, 1H), 7.63 (t, *J* = 8.0 Hz, 1H), 7.49-7.57 (m, 2H), 7.42-7.49 (m, 2H), 7.31 (t, *J* = 6.0 Hz, 2H), 7.25 (d, *J* = 8.8 Hz, 1H), 7.17 (t, *J* = 7.3 Hz, 1H), 5.24 (s, 2H), 2.74 (s, 3H). MS: *m/z* = 520.1 (M+H)⁺.

4-(4-((3-chloro-4-((3-fluorobenzyl)oxy)phenyl)amino)quinazolin-6-yl)-N-ethyl-2-fluorobenzamide (**10c**)

Yielded 1 mg (2.4%) as a yellow film. ¹H NMR (400 MHz, DMSO-d₆) δ: 9.98 (s, 1H), 8.87 (s, 1H), 8.58-8.61 (s, 1H), 8.35-8.42 (m, 1H), 8.26-8.34 (m, 1H), 8.01 (s, 1H), 7.87 (d, *J* = 4.4 Hz, 1H), 7.84 (m, 2H), 7.79 (d, *J* = 8.1 Hz, 1H), 7.70-7.76 (m, 1H), 7.47 (q, *J* = 7.3 Hz, 1H), 7.32 (dd, *J*_A = 13.2 Hz, *J*_B = 7.3 Hz, 3H), 7.18 (t, *J* = 8.8 Hz, 1H), 5.27 (s, 2H), 3.29 (q, *J* = 8.0 Hz, 2H), 1.14 (t, *J* = 7.0 Hz, 3H). MS: *m/z* = 545.2 (M+H)⁺.

***N*-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(3-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl)quinazolin-4-amine (10d)**

Obtained 1 mg (2.5% yield) as a yellow oil. ¹H NMR (400 MHz, DMSO-d₆) δ: 9.09-10.04 (brs, 1H), 8.88 (s, 1H), 8.61 (s, 1H), 8.42 (s, 1H), 8.37 (s, 1H), 8.26 (d, J = 8.8 Hz, 1H), 8.11 (d, J = 8.1 Hz, 1H), 8.0 (m, 2H), 7.89 (d, J = 8.8 Hz, 1H), 7.72-7.81 (m, 2H), 7.43-7.51 (m, 1H), 7.28-7.36 (m, 2H), 7.14-7.22 (m, 1H) 5.26 (s, 2H), 2.65 (s, 3H). MS: *m/z* = 538.1 (M+H)⁺.

3-(4-((3-chloro-4-((3-fluorobenzyl)oxy)phenyl)amino)quinazolin-6-yl)-*N*-cyclopropylbenzamide (10e)

Yielded 0.8 mg (2.0%) as a yellow film. ¹H NMR (400 MHz, DMSO-d₆) δ: 10.00 (s, 1H), 8.83 (s, 1H), 8.63 (d, J = 3.7 Hz, 1H), 8.59 (s, 1H), 8.35 (s, 1H), 8.26 (d, J = 5.1 Hz, 1H), 8.22 (s, 1H), 7.97-8.05 (m, 1H), 7.87 (t, J = 8.1 Hz, 2H), 7.74 (dd, J_A = 8.8 Hz, J_B = 2.0 Hz, 1H), 7.63 (t, J = 7.7 Hz, 1H), 7.43-7.52 (m, 1H), 7.25-7.35 (m, 2H), 7.17 (t, J = 8.0 Hz, 1H), 5.27 (s, 2H), 2.85-2.92 (m, 1H), 0.69-0.76 (m, 2H), 0.58-0.65 (m, 2H). MS: *m/z* = 539.2 (M+H)⁺.

***N*-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(quinolin-5-yl)quinazolin-4-amine (10f)**

Yielded 3.2 mg (8.4%) as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ: 9.81 (s, 1H), 8.98 (d, J = 2.9 Hz, 1H), 8.70 (s, 1H), 8.68 (s, 1H), 8.21-8.27 (m, 2H), 8.14 (d, J = 8.1 Hz, 1H), 8.03 (d, J = 2.2 Hz, 1H), 7.95-8.00 (m, 1H), 7.88-7.95 (m, 3H), 7.68-7.96 (m, 2H), 7.53-7.59 (dd, J_A = 8.4 Hz, J_B = 4.0 Hz, 1H), 7.46 (q, J = 8.0 Hz, 1H), 7.22-7.33 (m, 3H), 7.17 (t, J = 8.8 Hz, 1H), 5.23 (s, 2H). MS: *m/z* = 508.2 (M+H)⁺.

***N*-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(2-phenoxyphenyl)quinazolin-4-amine (10g)**

Yielded 1.4 mg (2.4%) as an orange oil. ¹H NMR (400 MHz, DMSO-d₆) δ: 9.85 (s, 1H), 8.65 (s, 1H), 8.58 (s, 1H), 8.01-8.06 (m, 2H), 7.72-7.78 (m, 2H), 7.67 (d, J = 6.6 Hz, 1H), 7.42-7.51 (m, 2H), 7.24-7.39 (m, 6H), 7.19 (t, J = 7.3 Hz, 1H), 7.00-7.09 (m, 2H), 6.94 (d, J = 8.1 Hz, 2H), 5.27 (s, 2H). MS: *m/z* = 548.1 (M+H)⁺.

6-(benzo[*b*]thiopen-2-yl)-*N*-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl) quinazolin-4-amine (10h)

Obtained 5.4 mg (14% yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ: 8.75 (s, 1H), 8.15 (t, J = 8.8 Hz, 1H), 8.03 (m, 1H), 7.96 (d, J = 8.8 Hz, 1H), 7.87 (d, J = 2.1 Hz, 2H), 7.82 (d, J = 7.3 Hz, 1H), 7.68 (s, 1H), 7.51-7.59 (m, 1H), 7.49 (s, 1H), 7.32-7.44 (m, 3H), 7.19-7.25 (m, 1H), 6.91-7.09 (m, 2H), 5.27 (s, 2H). MS: *m/z* = 512.0 (M+H)⁺.

4-(4-((3-chloro-4-((3-fluorobenzyl)oxy)phenyl)amino)quinazolin-6-yl)phenol (10i)

Yielded 1 mg (2.4%) as a yellow film. ¹H NMR (400 MHz, DMSO-d₆) δ: 10.09 (s, 1H), 8.98 (s, 1H), 8.63 (s, 2H), 8.45 (s, 1H), 8.42 (s, 1H), 8.05 (s, 1H), 7.96 (d, J = 8.8 Hz, 1H), 7.82 (d, J = 9.5 Hz, 1H), 7.43-7.51 (m, 2H), 7.27-7.36 (m, 2H), 7.14-7.22 (m, 1H), 6.66-6.72 (m, 2H), 5.27 (s, 2H). MS: *m/z* = 472.1 (M+H)⁺.

5-(4-((3-chloro-4-((3-fluorobenzyl)oxy)phenyl)amino)quinazolin-6-yl)pyrimidine-2,4(1*H*,3*H*)-dione (10j)

Yielded 2.6 mg (7.1%) as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ: 9.76-9.82 (brs, 1H), 8.47-8.59 (m, 2H), 8.30 (s, 1H), 8.04 (m, 2H), 7.81-7.88 (m, 1H), 7.71-7.80 (m, 2H), 7.59-7.67 (m, 1H), 7.43-7.50 (m, 1H), 7.31-7.36 (m, 1H), (m, 7.23-7.31 (m, 2H), 7.18 (t, J = 8.4 Hz, 1H), 5.26 (s, 2H). MS: *m/z* = 490.0 (M+H)⁺.

N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(3-(morpholinosulfonyl)phenyl)quinazolin-4-amine (10k)

Yield: 30.4%. ¹H NMR (500 MHz, DMSO-d₆) δ: 10.01 (s, 1H), 8.85 (d, *J* = 1.95 Hz, 1H), 8.63 (s, 1H), 8.24 - 8.27 (m, 2H), 8.12 (t, *J* = 1.71 Hz, 1H), 8.03 (d, *J* = 2.93 Hz, 1H), 7.86 - 7.92 (m, 2H), 7.80 - 7.85 (m, 1H), 7.73 (dd, *J* = 2.44, 8.79 Hz, 1H), 7.46 - 7.52 (m, 1H), 7.30 - 7.35 (m, 3H), 7.17 - 7.22 (m, 1H), 5.28 (s, 2H), 3.66 (t, *J* = 4.90 Hz, 4H), 2.95 (t, *J* = 4.40 Hz, 4H). MS: *m/z* = 605.1 (M+H)⁺.

N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(4-(piperidin-1-ylsulfonyl)phenyl)quinazolin-4-amine (10l)

Yield: 14.6%. ¹H NMR (500 MHz, DMSO-d₆) δ: 10.00 (s, 1H), 8.91 (d, *J* = 1.46 Hz, 1H), 8.64 (s, 1H), 8.27 (dd, *J* = 1.95, 8.30 Hz, 1H), 8.14 (d, *J* = 8.30 Hz, 2H), 8.04 (d, *J* = 2.93 Hz, 1H), 7.89 - 7.92 (m, 3H), 7.76 (dd, *J* = 2.69, 9.03 Hz, 1H), 7.46 - 7.51 (m, 1H), 7.31 - 7.36 (m, 3H), 7.20 (dt, *J* = 2.44, 8.55 Hz, 1H), 5.28 (s, 2H), 2.95 - 2.98 (m, 4H), 1.55 - 1.60 (m, 4H), 1.39 - 1.40 (m, 2H). MS: *m/z* = 603.2 (M+H)⁺.

N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(3-(piperidin-1-ylsulfonyl)phenyl)quinazolin-4-amine (10m)

Yield: 24.8%. ¹H NMR (500 MHz, DMSO-d₆) δ: 10.01 (s, 1H), 8.84 (d, *J* = 1.95 Hz, 1H), 8.62 (s, 1H), 8.24 (dd, *J* = 1.95, 8.79 Hz, 1H), 8.21 (d, *J* = 7.35 Hz, 1H), 8.11 (t, *J* = 1.71 Hz, 1H), 8.02 (d, *J* = 2.44 Hz, 1H), 7.90 (d, *J* = 8.30 Hz, 1H), 7.82 - 7.86 (m, 1H), 7.79 - 7.81 (m, 1H), 7.72 (dd, *J* = 2.69, 9.03 Hz, 1H), 7.45 - 7.51 (m, 1H), 7.29 - 7.36 (m, 3H), 7.19 (dt, *J* = 2.44, 8.55 Hz, 1H), 5.27 (s, 2H), 2.96 (t, *J* = 5.4 Hz, 4Hm, 4H), 1.52 - 1.60 (m, 4H), 1.33 - 1.40 (m, 2H). MS: *m/z* = 603.2 (M+H)⁺.

N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(4-(pyrrolidin-1-ylsulfonyl)phenyl)quinazolin-4-amine (10n)

Yield: 19.6%. ¹H NMR (500 MHz, DMSO-d₆) δ: 10.00 (s, 1H), 8.91 (d, *J* = 1.95 Hz, 1H), 8.63 (s, 1H), 8.27 (dd, *J* = 1.95, 8.79 Hz, 1H), 8.13 (d, *J* = 8.30 Hz, 2H), 8.03 (d, *J* = 2.44 Hz, 1H), 7.98 (d, *J* = 8.79 Hz, 2H), 7.90 (d, *J* = 8.79 Hz, 1H), 7.76 (dd, *J* = 2.44, 8.79 Hz, 1H), 7.45 - 7.52 (m, 1H), 7.29 - 7.36 (m, 3H), 7.20 (dt, *J* = 2.44, 8.55 Hz, 1H), 5.28 (s, 2H), 3.22 (t, *J* = 6.84 Hz, 4H), 1.66 - 1.72 (m, 4H). MS: *m/z* = 589.1 (M+H)⁺.

N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(3-(pyrrolidin-1-ylsulfonyl)phenyl)quinazolin-4-amine (10o)

Yield: 28.2%. ¹H NMR (500 MHz, DMSO-d₆) δ: 10.03 (s, 1H), 8.85 (d, *J* = 1.46 Hz, 1H), 8.62 (s, 1H), 8.26 (dd, *J* = 1.95, 8.79 Hz, 1H), 8.18 - 8.23 (m, 2H), 8.03 (d, *J* = 2.44 Hz, 1H), 7.88 - 7.93 (m, 2H), 7.81 - 7.87 (m, 1H), 7.73 (dd, *J* = 2.44, 8.79 Hz, 1H), 7.45 - 7.52 (m, 1H), 7.30 - 7.37 (m, 3H), 7.20 (dt, *J* = 2.44, 8.55 Hz, 1H), 5.28 (s, 2H), 3.23 (t, *J* = 6.84 Hz, 4H), 1.68 (td, *J* = 3.54, 6.59 Hz, 4H). MS: *m/z* = 589.2 (M+H)⁺.

N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(4-((4-methylpiperazin-1-yl)sulfonyl)phenyl)quinazolin-4-amine (10p)

Yield: 30.6%. ¹H NMR (500 MHz, DMSO-d₆) δ: 9.95 (s, 1H), 8.87 (d, *J* = 1.46 Hz, 1H), 8.59 (s, 1H), 8.23 (dd, *J* = 1.95, 8.79 Hz, 1H), 8.11 (d, *J* = 8.30 Hz, 2H), 7.99 (d, *J* = 2.44 Hz, 1H), 7.83 - 7.90 (m, 3H), 7.71 (dd, *J* = 2.69, 9.03 Hz, 1H), 7.40 - 7.47 (m, 1H), 7.25 - 7.32 (m, 3H), 7.15 (dt, *J* = 2.44, 8.55 Hz, 1H), 5.23 (s, 2H), 2.91 (br. s., 4H), 2.34 (br. s., 4H), 2.11 (s, 3H). MS: *m/z* = 618.2 (M+H)⁺.

N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(4-((4-methyl-1,4-diazepan-1-yl)sulfonyl)phenyl)quinazolin-4-amine (10q)

Yield: 42.8%. ¹H NMR (500 MHz, DMSO-d₆) δ: 10.00 (s, 1H), 8.91 (d, *J* = 1.95 Hz, 1H), 8.63 (s, 1H), 8.27 (dd, *J* = 1.95, 8.79 Hz, 1H), 8.12 (d, *J* = 8.80 Hz, 2H), 8.03 (d, *J* = 2.44 Hz, 1H), 7.96 (d, *J* = 8.30 Hz, 2H), 7.90 (d, *J* = 8.79 Hz, 1H), 7.76 (dd, *J* = 2.69, 9.03 Hz, 1H), 7.45 - 7.50 (m, 1H), 7.30 - 7.36 (m, 3H), 7.20 (dt, *J* = 2.44, 8.55 Hz, 1H), 5.28 (s, 2H), 3.37 - 3.39 (m, 2H), 3.34 (t, *J* = 6.10 Hz, 3H), 2.61 - 2.64 (m, 2H), 2.54 - 2.58 (m, 2H), 2.28 (s, 3H), 1.74 - 1.80 (m, 2H). MS: *m/z* = 632.2 (M+H)⁺.

N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(4-(thiomorpholin sulfonyl)phenyl)quinazolin-4-amine (10r)

Yield: 5.6%. ¹H NMR (500 MHz, DMSO-d₆) δ: 10.00 (s, 1H), 8.92 (d, *J* = 1.47 Hz, 1H), 8.64 (s, 1H), 8.28 (dd, *J* = 1.95, 8.79 Hz, 1H), 8.16 (d, *J* = 8.79 Hz, 2H), 8.04 (d, *J* = 2.44 Hz, 1H), 7.89 - 7.95 (m, 3H), 7.76 (dd, *J* = 2.45, 8.80 Hz, 1H), 7.46 - 7.52 (m, 1H), 7.30 - 7.37 (m, 3H), 7.20 (dt, *J* = 2.20, 8.67 Hz, 1H), 5.28 (s, 2H), 3.28 (t, *J* = 4.35 Hz, 4H), 2.71 (t, *J* = 5.35 Hz, 4H). MS: *m/z* = 621.2 (M+H)⁺.

N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(4-(piperazin-1-ylsulfonyl)phenyl)quinazolin-4-amine (10s)

To glass vials was weighed 46 mg of **14** (0.085 mmol) and tert-butyl 4-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)sulfonyl)piperazine-1-carboxylate (38.4 mg 0.085 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.006 mmol). To the reaction mixture was added 1,2-dimethoxyethane (0.4 mL), ethanol (0.3 mL) and a 2M aqueous solution of sodium carbonate (0.255 mL, 0.51 mmol). The vials were capped and shaken at 85 °C for 12, and progress of the reaction was monitored by LC-MS. The reaction mixture was evaporated to dryness, and the residue was dissolved in DMSO and purified by reverse phase HPLC using a gradient of 5-100% acetonitrile in water containing 0.1% formic acid providing the Boc-protected compound in 23.7% yield. ¹H NMR (500 MHz, DMSO-d₆) δ: 9.99 (s, 1H), 8.91 (d, *J* = 1.95 Hz, 1H), 8.64 (s, 1H), 8.28 (dd, *J* = 1.95, 8.79 Hz, 1H), 8.16 (d, *J* = 8.79 Hz, 2H), 8.04 (d, *J* = 2.44 Hz, 1H), 7.89 - 7.93 (m, 3H), 7.76 (dd, *J* = 2.44, 8.79 Hz, 1H), 7.46 - 7.52 (m, 1H), 7.30 - 7.36 (m, 3H), 7.20 (dt, *J* = 2.44, 8.79 Hz, 1H), 5.28 (s, 2H), 3.41 - 3.46 (m, 4H), 2.94 (t, *J* = 4.64 Hz, 4H), 1.34 (s, 9H). MS: *m/z* = 704.3 (M+H)⁺. To a solution of this compound (0.015 mmol) in 0.4 mL of dichloromethane was added trifluoroacetic acid (200 μmol, 0.154 mL). The reaction mixture was stirred for 12 h at 25 °C. Volatiles were removed *in vacuo*, and the crude product was triturated with hexanes to afford a crude solid that was purified via flash column chromatography (0-10% MeOH-DCM) to afford the desired compound **10t**. Yield: 78%. ¹H NMR (500 MHz, DMSO-d₆) δ: 9.01 (s, 1H), 8.80 (br. s., 1H), 8.59 (br. s., 2H), 8.39 (d, *J* = 7.81 Hz, 1H), 8.22 (d, *J* = 8.30 Hz, 2H), 7.92 - 8.03 (m, 4H), 7.72 (dd, *J* = 2.44, 8.79 Hz, 1H), 7.47 - 7.52 (m, 1H), 7.32 - 7.37 (m, 3H), 7.21 (dt, *J* = 2.20, 8.67 Hz, 1H), 5.31 (s, 2H), 3.25 (br. s., 4H), 3.18 (br. s., 4H). MS: *m/z* = 604.2 (M+H)⁺.

N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(4-(methylsulfonyl)phenyl)quinazolin-4-amine (10t)

Yield: 31.8%. ¹H NMR (500 MHz, DMSO-d₆) δ: 10.00 (s, 1H), 8.92 (d, *J* = 1.95 Hz, 1H), 8.64 (s, 1H), 8.29 (dd, *J* = 1.95, 8.79 Hz, 1H), 8.14 (d, *J* = 8.80 Hz, 2H), 8.11 (d, *J* = 8.30 Hz, 2H), 8.03 (d, *J* = 2.44 Hz, 1H), 7.92 (d, *J* = 8.79 Hz, 1H), 7.76 (dd, *J* = 2.44, 8.79 Hz, 1H), 7.45 - 7.53 (m, 1H), 7.31 - 7.37 (m, 3H), 7.20 (dt, *J* = 2.20, 8.42 Hz, 1H), 5.28 (s, 2H), 3.31 (s, 3H). MS: *m/z* = 534.1 (M+H)⁺.

N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(3-(methylsulfonyl)phenyl)quinazolin-4-amine (10u)

Yield: 34.9%. ^1H NMR (500 MHz, DMSO- d_6) δ : 10.02 (s, 1H), 8.88 (s, 1H), 8.63 (s, 1H), 8.38 (s, 1H), 8.30 (dd, J = 1.46, 8.79 Hz, 1H), 8.25 (d, J = 8.30 Hz, 1H), 7.99 - 8.06 (m, 2H), 7.92 (d, J = 8.79 Hz, 1H), 7.84 - 7.87 (m, 1H), 7.74 (dd, J = 2.44, 8.79 Hz, 1H), 7.45 - 7.53 (m, 1H), 7.30 - 7.36 (m, 3H), 7.20 (dt, J = 1.71, 8.67 Hz, 1H), 5.28 (s, 2H), 3.35 (s, 3H). MS: m/z = 534.2 (M+H) $^+$.

2-(4-((3-chloro-4-((3-fluorobenzyl)oxy)phenyl)amino)quinazolin-6-yl)-N,N-dimethylbenzenesulfonamide (10v)

Yield: 35%. ^1H NMR (500 MHz, DMSO- d_6) δ : 9.78 (s, 1H), 8.65 (s, 1H), 8.52 (d, J = 0.98 Hz, 1H), 8.06 (d, J = 2.44 Hz, 1H), 8.01 (dd, J = 0.98, 7.81 Hz, 1H), 7.83 (dt, J = 1.46, 9.03 Hz, 1H), 7.76 - 7.81 (m, 3H), 7.72 (dt, J = 1.22, 7.69 Hz, 1H), 7.54 (dd, J = 0.98, 7.81 Hz, 1H), 7.45 - 7.50 (m, 1H), 7.30 - 7.34 (m, 2H), 7.27 (d, J = 8.79 Hz, 1H), 7.19 (dt, J = 2.44, 8.55 Hz, 1H), 5.26 (s, 2H), 2.45 (s, 6H). MS: m/z = 563.2 (M+H) $^+$.

N-(tert-butyl)-2-(4-((3-chloro-4-((3-fluorobenzyl)oxy)phenyl)amino)quinazolin-6-yl)benzenesulfonamide (10w)

Yield: 12.5%. ^1H NMR (500 MHz, DMSO- d_6) δ : 9.79 (s, 1H), 8.64 (s, 1H), 8.53 (d, J = 1.95 Hz, 1H), 8.11 (dd, J = 1.22, 8.06 Hz, 1H), 8.05 (d, J = 2.44 Hz, 1H), 7.86 (dd, J = 1.71, 8.55 Hz, 1H), 7.70 - 7.79 (m, 3H), 7.63 - 7.67 (m, 1H), 7.45 - 7.50 (m, 2H), 7.30 - 7.35 (m, 2H), 7.27 (d, J = 9.28 Hz, 1H), 7.19 (dt, J = 2.44, 8.55 Hz, 1H), 6.90 (s, 1H), 5.26 (s, 2H), 1.04 (s, 9H). MS: m/z = 591.2 (M+H) $^+$.

N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(3-morpholinophenyl)quinazolin-4-amine (23a)

Yield: 38%. ^1H NMR (500 MHz, DMSO- d_6) δ : 9.90 (s, 1H), 8.76 (d, J = 1.95 Hz, 1H), 8.60 (s, 1H), 8.18 (dd, J = 1.71, 8.55 Hz, 1H), 8.04 (d, J = 2.93 Hz, 1H), 7.84 (d, J = 8.79 Hz, 1H), 7.76 (dd, J = 2.44, 8.79 Hz, 1H), 7.45 - 7.51 (m, 1H), 7.39 - 7.42 (m, 1H), 7.28 - 7.35 (m, 5H), 7.19 (dt, J = 2.44, 8.55 Hz, 1H), 7.03 (dd, J = 1.95, 8.30 Hz, 1H), 5.27 (s, 2H), 3.79 (t, J = 4.9 Hz, 4H), 3.24 (t, J = 4.86 Hz, 4H). MS: m/z = 541.2 (M+H) $^+$.

N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(4-morpholinophenyl)quinazolin-4-amine (23b)

Yield: 35.2%. ^1H NMR (500 MHz, DMSO- d_6) δ : 9.87 (s, 1H), 8.72 (d, J = 1.95 Hz, 1H), 8.55 (s, 1H), 8.16 (dd, J = 1.95, 8.79 Hz, 1H), 8.03 (d, J = 2.93 Hz, 1H), 7.78 - 7.82 (m, 3H), 7.76 (dd, J = 2.44, 8.79 Hz, 1H), 7.45 - 7.51 (m, 1H), 7.28 - 7.35 (m, 3H), 7.19 (dt, J = 2.69, 8.67 Hz, 1H), 7.11 (d, J = 8.79 Hz, 2H), 5.27 (s, 2H), 3.76 - 3.80 (m, 4H), 3.19 - 3.23 (m, 4H). MS: m/z = 541.04 (M+H) $^+$.

N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(3-(morpholinomethyl)phenyl)quinazolin-4-amine (23c)

Yield: 54.5%. ^1H NMR (500 MHz, DMSO- d_6) δ : 9.92 (s, 1H), 8.77 (s, 1H), 8.59 (s, 1H), 8.15 (d, J = 8.79 Hz, 1H), 8.03 (d, J = 1.95 Hz, 1H), 7.85 (d, J = 8.79 Hz, 1H), 7.72 - 7.80 (m, 3H), 7.43 - 7.54 (m, 2H), 7.39 (d, J = 7.32 Hz, 1H), 7.25 - 7.35 (m, 3H), 7.14 - 7.22 (m, 1H), 5.26 (s, 2H), 3.52-3.68 (m, 6H), 2.40 (br. s., 4H). MS: m/z = 554.3060 (M) $^+$.

N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(4-(morpholinomethyl)phenyl)quinazolin-4-amine (23d)

Yield: 36.8%. ^1H NMR (500 MHz, DMSO- d_6) δ : 9.92 (s, 1H), 8.80 (d, J = 1.95 Hz, 1H), 8.60 (s, 1H), 8.20 (dd, J = 1.95, 8.79 Hz, 1H), 8.04 (d, J = 2.44 Hz, 1H), 7.84 - 7.87 (m, 3H),

7.77 (dd, $J = 2.69, 9.03$ Hz, 1H), 7.46 - 7.54 (m, 3H), 7.28 - 7.36 (m, 3H), 7.20 (dt, $J = 1.95, 8.55$ Hz, 1H), 5.28 (s, 2H), 3.61 (t, $J = 4.64$ Hz, 4H), 3.56 (s, 2H), 2.40 (br. s., 4H). MS: $m/z = 555.2$ (M+H)⁺.

(3-(4-((3-chloro-4-((3-fluorobenzyl)oxy)phenyl)amino)quinazolin-6-yl)phenyl)(morpholino)methanone (23e)

Yield: 53.2%. ¹H NMR (500 MHz, DMSO- d_6) δ : 9.99 (br. s., 1H), 8.83 (d, $J = 1.46$ Hz, 1H), 8.61 (s, 1H), 8.23 (dd, $J = 1.46, 8.79$ Hz, 1H), 8.01 (d, $J = 2.44$ Hz, 1H), 7.97 (d, $J = 7.81$ Hz, 1H), 7.92 (s, 1H), 7.86 (d, $J = 8.79$ Hz, 1H), 7.73 (dd, $J = 2.44, 8.79$ Hz, 1H), 7.63 (t, $J = 7.81$ Hz, 1H), 7.47 (q, $J = 7.65$ Hz, 2H), 7.26 - 7.36 (m, 3H), 7.18 (dt, $J = 2.20, 8.67$ Hz, 1H), 5.26 (s, 2H), 3.20 - 3.78 (m, 8H). MS: $m/z = 568.2021$ (M)⁺.

(4-(4-((3-chloro-4-((3-fluorobenzyl)oxy)phenyl)amino)quinazolin-6-yl)phenyl)(morpholino)methanone (23f)

Yield: 58.9%. ¹H NMR (500 MHz, DMSO- d_6) δ : 9.93 (br. s., 1H), 8.84 (br. s., 1H), 8.60 (s, 1H), 8.21 (d, $J = 8.30$ Hz, 1H), 7.93 - 8.05 (m, 3H), 7.86 (d, $J = 8.30$ Hz, 1H), 7.76 (d, $J = 7.81$ Hz, 1H), 7.60 (d, $J = 7.81$ Hz, 2H), 7.43 - 7.51 (m, 1H), 7.26 - 7.36 (m, 3H), 7.18 (t, $J = 8.06$ Hz, 1H), 5.26 (s, 2H), 3.37 - 3.80 (m, 8H). MS: $m/z = 568.2183$ (M).

N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(3-(piperidin-1-yl)phenyl)quinazolin-4-amine (23g)

Yield: 21%. ¹H NMR (500 MHz, DMSO- d_6) δ : 9.90 (s, 1H), 8.74 (d, $J = 1.95$ Hz, 1H), 8.58 (s, 1H), 8.16 (dd, $J = 1.71, 8.55$ Hz, 1H), 8.03 (d, $J = 2.44$ Hz, 1H), 7.83 (d, $J = 8.79$ Hz, 1H), 7.75 (dd, $J = 2.44, 8.79$ Hz, 1H), 7.44 - 7.51 (m, 1H), 7.27 - 7.39 (m, 5H), 7.23 (d, $J = 7.81$ Hz, 1H), 7.19 (dt, $J = 2.44, 8.55$ Hz, 1H), 7.00 (dd, $J = 1.95, 8.30$ Hz, 1H), 5.27 (s, 2H), 3.23 - 3.27 (m, 4H), 1.64 - 1.69 (m, 4H), 1.53 - 1.59 (m, 2H). MS: $m/z = 539.16$ (M+H)⁺.

N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(4-(piperidin-1-yl)phenyl)quinazolin-4-amine (23h)

Yield: 41.4%. ¹H NMR (500 MHz, DMSO- d_6) δ : 9.87 (s, 1H), 8.69 (d, $J = 0.98$ Hz, 1H), 8.55 (s, 1H), 8.12 (dd, $J = 1.71, 8.55$ Hz, 1H), 8.03 (d, $J = 2.44$ Hz, 1H), 7.72 - 7.81 (m, 4H), 7.43 - 7.51 (m, 1H), 7.25 - 7.37 (m, 3H), 7.18 (dt, $J = 2.44, 8.55$ Hz, 1H), 7.06 (d, $J = 8.79$ Hz, 2H), 5.26 (s, 2H), 3.18 - 3.26 (m, 4H), 1.49 - 1.70 (m, 6H). MS: $m/z = 532.3831$ (M)⁺.

N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(3-(piperidin-1-ylmethyl)phenyl)quinazolin-4-amine (23i)

Yield: 66.7%. ¹H NMR (500 MHz, DMSO- d_6) δ : 9.91 (br. s., 1H), 8.81 (d, $J = 1.95$ Hz, 1H), 8.60 (s, 1H), 8.19 (dd, $J = 1.95, 8.79$ Hz, 1H), 8.01 (d, $J = 2.93$ Hz, 1H), 7.87 - 7.97 (m, 3H), 7.74 (dd, $J = 2.90, 9.25$ Hz, 1H), 7.63 (t, $J = 7.57$ Hz, 1H), 7.52 (d, $J = 7.32$ Hz, 1H), 7.46 (dt, $J = 6.35, 8.06$ Hz, 1H), 7.26 - 7.35 (m, 3H), 7.17 (dt, $J = 2.44, 8.55$ Hz, 1H), 5.25 (s, 2H), 4.22 (br. s., 2H), 3.00 (d, $J = 5.86$ Hz, 4H), 1.42 - 1.77 (m, 6H). MS: $m/z = 552.3265$ (M)⁺.

N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(4-(piperidin-1-ylmethyl)phenyl)quinazolin-4-amine (23j)

Yield: 52.3%. ¹H NMR (500 MHz, DMSO- d_6) δ : 9.89 (br. s., 1H), 8.80 (d, $J = 1.46$ Hz, 1H), 8.58 (s, 1H), 8.19 (dd, $J = 1.95, 8.79$ Hz, 1H), 8.01 (d, $J = 2.44$ Hz, 1H), 7.90 (d, $J = 8.30$ Hz, 2H), 7.85 (d, $J = 8.79$ Hz, 1H), 7.74 (dd, $J = 2.44, 8.79$ Hz, 1H), 7.56 (d, $J = 8.30$ Hz, 2H), 7.41 - 7.50 (m, 1H), 7.25 - 7.35 (m, 3H), 7.17 (dt, $J = 2.20, 8.67$ Hz, 1H), 5.25 (s, 2H), 3.93 (br. s., 2H), 2.74 (br. s., 4H), 1.56 - 1.69 (m, 4H), 1.45 (br. s., 2H). MS: $m/z = 552.3265$ (M)⁺.

(3-(4-((3-chloro-4-((3-fluorobenzyl)oxy)phenyl)amino)quinazolin-6-yl)phenyl)(piperidin-1-yl)methanone (23k)

Yield: 66.3%. ¹H NMR (500 MHz, DMSO-d₆) δ: 8.91 (s, 1H), 8.76 (br. s., 1H), 8.35 (d, *J* = 9.28 Hz, 1H), 7.96 - 8.00 (m, 2H), 7.87 - 7.93 (m, 2H), 7.70 (dd, *J* = 2.45, 8.80 Hz, 1H), 7.59 - 7.65 (m, 2H), 7.44 - 7.52 (m, 2H), 7.32 - 7.36 (m, 3H), 7.20 (dt, *J* = 2.44, 8.79 Hz, 1H), 5.30 (s, 2H), 3.65 (br. s., 3H), 1.41 - 1.70 (m, 7H). MS: *m/z* = 567.3 (M+H)⁺.

(4-(4-((3-chloro-4-((3-fluorobenzyl)oxy)phenyl)amino)quinazolin-6-yl)phenyl)(piperidin-1-yl)methanone (23l)

Yield: 73.3%. ¹H NMR (500 MHz, DMSO-d₆) δ: 9.93 (s, 1H), 8.83 (s, 1H), 8.59 (s, 1H), 8.21 (dd, *J* = 1.95, 8.30 Hz, 1H), 8.01 (d, *J* = 2.44 Hz, 1H), 7.93 (d, *J* = 8.30 Hz, 2H), 7.86 (d, *J* = 8.79 Hz, 1H), 7.74 (dd, *J* = 2.44, 8.79 Hz, 1H), 7.53 (d, *J* = 8.30 Hz, 3H), 7.43 - 7.49 (m, 1H), 7.27 - 7.34 (m, 3H), 7.17 (dt, *J* = 1.95, 8.55 Hz, 1H), 5.25 (s, 2H), 3.60 (br. s., 2H), 1.38 - 1.67 (m, 7H). MS: *m/z* = 567.3 (M+H)⁺.

N-(4-(benzyloxy)-3-chlorophenyl)-6-(3-morpholinophenyl)quinazolin-4-amine (23m)

Yield: 38%. ¹H NMR (500 MHz, DMSO-d₆) δ: 9.88 (s, 1H), 8.75 (d, *J* = 1.95 Hz, 1H), 8.58 (s, 1H), 8.18 (dd, *J* = 1.95, 8.79 Hz, 1H), 8.01 (d, *J* = 2.93 Hz, 1H), 7.84 (d, *J* = 8.30 Hz, 1H), 7.74 (dd, *J* = 2.69, 9.03 Hz, 1H), 7.50 (d, *J* = 7.32 Hz, 2H), 7.39 - 7.45 (m, 3H), 7.33 - 7.37 (m, 2H), 7.30 (d, *J* = 8.79 Hz, 2H), 7.03 (dd, *J* = 1.95, 8.30 Hz, 1H), 5.24 (s, 2H), 3.77 - 3.81 (m, 4H), 3.22 - 3.25 (m, 4H). MS: *m/z* = 523.07 (M+H)⁺.

N-(4-(benzyloxy)phenyl)-6-(3-morpholinophenyl)quinazolin-4-amine (23n)

Yield: 18%. ¹H NMR (500 MHz, DMSO-d₆) δ: 9.84 (s, 1H), 8.76 (d, *J* = 1.46 Hz, 1H), 8.51 (s, 1H), 8.16 (dd, *J* = 1.95, 8.79 Hz, 1H), 7.81 (d, *J* = 8.30 Hz, 1H), 7.68 (d, *J* = 9.30 Hz, 2H), 7.48 (d, *J* = 7.32 Hz, 2H), 7.38 - 7.43 (m, 3H), 7.28 - 7.37 (m, 3H), 7.07 (d, *J* = 8.80 Hz, 2H), 7.02 (dd, *J* = 1.95, 7.80 Hz, 1H), 5.14 (s, 2H), 3.78 (t, *J* = 4.87 Hz, 4H), 3.24 (t, *J* = 4.87 Hz, 4H). MS: *m/z* = 489.11 (M+H)⁺.

6-(3-morpholinophenyl)-N-phenylquinazolin-4-amine (23o)

Yield: 57.5%. ¹H NMR (500 MHz, DMSO-d₆) δ: 9.92 (s, 1H), 8.80 (d, *J* = 1.46 Hz, 1H), 8.58 (s, 1H), 8.19 (dd, *J* = 1.95, 8.79 Hz, 1H), 7.82 - 7.87 (m, 3H), 7.39 - 7.45 (m, 3H), 7.36 (d, *J* = 2.44 Hz, 1H), 7.30 - 7.33 (m, 1H), 7.15 - 7.18 (m, 1H), 7.03 (dd, *J* = 2.20, 8.06 Hz, 1H), 3.79 (t, *J* = 4.85 Hz, 4H), 3.24 (t, *J* = 4.85 Hz, 4H). MS: *m/z* = 383.06 (M+H)⁺.

Aniline synthesis

Anilines **17** were synthesized using **General procedure B**. In a 20 mL glass vial a solution of substituted 4-nitrophenol (1.5 mmol) in 5 mL acetonitrile was combined with potassium carbonate (3 mmol) and the appropriate benzyl bromide (1.5 mmol) at 25 °C. The reaction mixture was stirred at 50 °C for 12 h. After completion of the alkylation reaction, the reaction mixture was triturated with 10 mL of 10% MeOH/DCM and was filtered through a silica gel plug. The organic filtrate was evaporated and re-dissolved in 5 mL of MeOH:H₂O (5:1). To this solution was added Zinc (0.29 g, 4.5 mmol) followed by ammonium chloride (0.48 g, 9 mmol) at 25 °C. The temperature was raised to 50 °C and the stirring was continued 6 h. Progress of the reaction was followed by LC-MS. Upon completion of the reaction, 15 mL of DCM:MeOH (1:1) was added to the reaction mixture, inorganic residues were removed by filtration. The filtrate was evaporated and the residue was purified via flash chromatography (0-50% EtOAc/hexanes) to afford the desired substituted anilines.

4-(benzyloxy)-3-chloroaniline (17e)

Yield: 24.3%. ^1H NMR (500 MHz, CDCl_3) δ : 7.47 (d, $J = 7.32$ Hz, 2H), 7.37 - 7.41 (m, 2H), 7.30 - 7.35 (m, 1H), 6.81 (d, $J = 8.79$ Hz, 1H), 6.76 (d, $J = 2.93$ Hz, 1H), 6.51 (dd, $J = 2.69, 8.55$ Hz, 1H), 5.06 (s, 2H), 3.49 (br. s., 2H). MS: $m/z = 234.02$ ($\text{M}+\text{H}$) $^+$.

4-((3-bromobenzyl)oxy)-3-chloroaniline (17f)

Yield: 25%. ^1H NMR (500 MHz, CDCl_3) δ : 7.62 (s, 1H), 7.45 (d, $J = 8.30$ Hz, 1H), 7.39 (d, $J = 7.81$ Hz, 1H), 7.22 - 7.26 (m, 1H), 6.75 - 6.80 (m, 2H), 6.52 (dd, $J = 2.93, 8.79$ Hz, 1H), 5.01 (s, 2H), 3.52 (br. s., 2H). MS: $m/z = 311.89$ ($\text{M}+\text{H}$) $^+$.

3-chloro-4-((3-chlorobenzyl)oxy)aniline (17g)

Yield: 38%. ^1H NMR (500 MHz, CDCl_3) δ : 7.47 (s, 1H), 7.29 - 7.36 (m, 3H), 6.78 (d, $J = 8.30$ Hz, 1H), 6.75 (d, $J = 2.44$ Hz, 1H), 6.50 (dd, $J = 2.93, 8.79$ Hz, 1H), 5.01 (s, 2H), 3.52 (br. s., 2H). MS: $m/z = 267.96$ ($\text{M}+\text{H}$) $^+$.

3-chloro-4-((2,3-difluorobenzyl)oxy)aniline (17h)

Yield: 31%. ^1H NMR (500 MHz, CDCl_3) δ : 7.35 (t, $J = 6.59$ Hz, 1H), 7.07 - 7.16 (m, 2H), 6.83 (d, $J = 8.79$ Hz, 1H), 6.75 (d, $J = 2.93$ Hz, 1H), 6.52 (dd, $J = 2.69, 8.55$ Hz, 1H), 5.12 (s, 2H), 3.51 (br. s., 2H). MS: $m/z = 270.0$ ($\text{M}+\text{H}$) $^+$.

3-chloro-4-((2-fluorobenzyl)oxy)aniline (17i)

Yield: 37%. ^1H NMR (500 MHz, CDCl_3) δ : 7.58 (dt, $J = 1.71, 7.45$ Hz, 1H), 7.27 - 7.32 (m, 1H), 7.16 (dt, $J = 0.98, 7.57$ Hz, 1H), 7.04 - 7.08 (m, 1H), 6.83 (d, $J = 8.79$ Hz, 1H), 6.75 (d, $J = 2.93$ Hz, 1H), 6.51 (dd, $J = 2.69, 8.55$ Hz, 1H), 5.12 (s, 2H), 3.50 (br. s., 2H). MS: $m/z = 251.99$ ($\text{M}+\text{H}$) $^+$.

3-chloro-4-((4-fluorobenzyl)oxy)aniline (17j)

Yield: 22%. ^1H NMR (500 MHz, CDCl_3) δ : 7.40 - 7.44 (m, 2H), 7.03 - 7.10 (m, 2H), 6.78 (d, $J = 8.79$ Hz, 1H), 6.75 (d, $J = 2.44$ Hz, 1H), 6.50 (dd, $J = 2.93, 8.79$ Hz, 1H), 5.00 (s, 2H), 3.50 (br. s., 2H). MS: $m/z = 252.0$ ($\text{M}+\text{H}$) $^+$.

3-chloro-4-((3-methoxybenzyl)oxy)aniline (17k)

Yield: %. ^1H NMR (500 MHz, CDCl_3) δ : 7.27 - 7.32 (m, 1H), 7.01 - 7.05 (m, 2H), 6.86 (dd, $J = 2.69, 8.06$ Hz, 1H), 6.79 (d, $J = 8.79$ Hz, 1H), 6.74 (d, $J = 2.93$ Hz, 1H), 6.49 (dd, $J = 2.45, 8.80$ Hz, 1H), 5.04 (s, 2H), 3.83 (s, 3H), 3.44 (br. s., 2H). MS: $m/z = 264.01$ ($\text{M}+\text{H}$) $^+$.

3-chloro-4-((3-fluoro-4-(trifluoromethyl)benzyl)oxy)aniline (17l)

Yield: 35.2%. ^1H NMR (500 MHz, CDCl_3) δ : 7.60 (t, $J = 7.81$ Hz, 1H), 7.29 - 7.36 (m, 2H), 6.77 (d, $J = 4.39$ Hz, 1H), 6.76 (d, $J = 1.47$ Hz, 1H), 6.51 (dd, $J = 2.93, 8.79$ Hz, 1H), 5.06 (s, 2H), 3.54 (br. s., 2H). MS: $m/z = 319.93$ ($\text{M}+\text{H}$) $^+$.

3-chloro-4-((2,3,5-trifluorobenzyl)oxy)aniline (17m)

Yield: 22%. ^1H NMR (500 MHz, CDCl_3) δ : 7.13 - 7.18 (m, 1H), 6.85 - 6.93 (m, 1H), 6.81 (d, $J = 8.30$ Hz, 1H), 6.76 (d, $J = 2.93$ Hz, 1H), 6.53 (dd, $J = 2.93, 8.79$ Hz, 1H), 5.09 (s, 2H), 3.54 (br. s., 2H). MS: $m/z = 287.96$ ($\text{M}+\text{H}$) $^+$.

4-((3-fluorobenzyl)oxy)aniline (17n)

Yield: 28%. ¹H NMR (500 MHz, CDCl₃) δ: 7.34 (m, 1H), 7.14 - 7.21 (m, 2H), 7.01 (dt, *J* = 2.44, 8.55 Hz, 1H), 6.81 (d, *J* = 8.30 Hz, 2H), 6.64 (d, *J* = 8.30 Hz, 2H), 4.99 (s, 2H), 3.32 (br. s., 2H). MS: *m/z* = 218.07 (M+H)⁺.

4-((3-fluorobenzyl)oxy)-3-methoxyaniline (17o)

Yield: 7.52%. ¹H NMR (500 MHz, CDCl₃) δ: 7.28 - 7.33 (m, 1H), 7.14 - 7.21 (m, 2H), 6.97 (dt, *J* = 2.20, 8.67 Hz, 1H), 6.70 (d, *J* = 8.30 Hz, 1H), 6.32 (d, *J* = 2.93 Hz, 1H), 6.16 (dd, *J* = 2.69, 8.55 Hz, 1H), 5.02 (s, 2H), 3.84 (s, 3H), 3.51 (br. s., 2H). MS: *m/z* = 248.06 (M+H)⁺.

6-(4-(morpholinosulfonyl)phenyl)quinazolin-4(3H)-one (18)

A mixture of 6-iodoquinazolin-4(3H)-one (4.5 g, 16.54 mmol), (4-(morpholinosulfonyl)phenyl)boronic acid (4.93 g, 18.20 mmol), sodium carbonate (10.52 g, 99 mmol) and tetrakis(triphenylphosphine)palladium(0) (1.338 g, 1.158 mmol) were combined in a flask, and 400 mL of 1,2-dimethoxyethane was added, with ethanol (26.7 mL) and water (33.3 mL). The reaction mixture was heated with stirring at 80 °C for 30 h. The reaction progress was monitored by LC-MS. Upon completion of the reaction, the mixture was cooled to room temperature, and the product precipitated. Solids were collected by filtration, washed with cold water and air-dried, affording **18** (5.35 g, 14.40 mmol, 87 % yield). ¹H NMR (500 MHz, DMSO-*d*₆) δ: 12.40 (br. s., 1H), 8.44 (d, *J* = 2.44 Hz, 1H), 8.22 (dd, *J* = 2.20, 8.55 Hz, 1H), 8.16 (d, *J* = 3.42 Hz, 1H), 8.07 (d, *J* = 8.30 Hz, 2H), 7.84 (d, *J* = 8.30 Hz, 2H), 7.80 (d, *J* = 8.79 Hz, 1H), 3.64 (t, *J* = 4.65 Hz, 4H), 2.91 (t, *J* = 4.65 Hz, 4H). MS: *m/z* = 372.2 (M+H)⁺.

4-((4-(4-chloroquinazolin-6-yl)phenyl)sulfonyl)morpholine hydrochloride (19)

Thionyl chloride (9.83 mL, 135 mmol) was added slowly to 1.0 g of **18** (1 g, 2.69 mmol), followed by *N,N*-dimethylformamide (2.085 μL, 0.027 mmol). The reaction mixture was refluxed for 36 h, monitoring reaction progress with LC-MS. The volatile components were removed via distillation, providing **19** (1.12 g, 1.683 mmol, 80% pure, 78% yield), which was used for subsequent reactions without further purification. ¹H NMR (500 MHz, DMSO-*d*₆) δ: 8.45 (d, *J* = 1.95 Hz, 1H), 8.32 (s, 1H), 8.26 (dd, *J* = 2.20, 8.55 Hz, 1H), 8.07 (d, *J* = 8.79 Hz, 2H), 7.79 - 7.86 (m, 3H), 3.65 (t, *J* = 4.60 Hz, 4H), 2.92 (t, *J* = 4.65 Hz, 4H). MS: *m/z* = 390.04 (M+H)⁺.

6-(4-(morpholinosulfonyl)phenyl)-*N*-arylquinazolin-4-amine hydrochloride **20** were synthesized following **General procedure C**. To a solution of **19** (100 μmol) in *N,N*-dimethylformamide (0.5 mL) was added aryl amine (110 μmol) and the mixture was heated on a shaker plate at 80 °C for 12 h. After cooling the reaction mixture to room temperature, 0.5 mL of isopropanol was added. The resulting yellowish precipitate was filtered and washed with 2 mL of isopropanol, affording the amines **20**.

6-(4-(morpholinosulfonyl)phenyl)-*N*-phenylquinazolin-4-amine hydrochloride. (20a)

Yield: 50.8%. ¹H NMR (500 MHz, DMSO-*d*₆) δ: 11.51 (br. s., 1H), 9.20 (s, 1H), 8.93 (s, 1H), 8.50 (d, *J* = 8.79 Hz, 1H), 8.21 (d, *J* = 8.30 Hz, 2H), 8.01 (d, *J* = 8.30 Hz, 1H), 7.95 (d, *J* = 8.30 Hz, 2H), 7.75 (d, *J* = 8.30 Hz, 2H), 7.51 - 7.55 (m, 2H), 7.34 - 7.37 (m, 1H), 3.65 - 3.67 (br. m, 4H), 2.92 - 2.95 (br. m., 4H). MS: *m/z* = 447.2 (M+H)⁺.

6-(4-(morpholinosulfonyl)phenyl)-*N*-(*p*-tolyl)quinazolin-4-amine hydrochloride (20b)

Yield: 54.9%. ¹H NMR (500 MHz, DMSO-*d*₆) δ: 11.62 (br. s., 1H), 9.24 (s, 1H), 8.93 (s, 1H), 8.51 (d, *J* = 8.30 Hz, 1H), 8.22 (d, *J* = 8.30 Hz, 3H), 8.03 (d, *J* = 8.79 Hz, 1H), 7.95 (d,

$J = 8.79$ Hz, 2H), 7.63 (d, $J = 7.81$ Hz, 2H), 7.34 (d, $J = 7.81$ Hz, 2H), 3.67 (t, $J = 4.4$ Hz, 4H), 2.95 (t, $J = 4.4$ Hz, 4H), 2.38 (s, 3H). MS: $m/z = 496.2$ (M+H)⁺.

2-chloro-4-((6-(4-(morpholinosophonyl)phenyl)quinazolin-4-yl)amino)phenol hydrochloride (20c)

Yield: 52.7%. ¹H NMR (500 MHz, DMSO-d₆) δ : 11.60 (br. s., 1H), 10.55 (br. s., 1H), 9.22 (s, 1H), 8.96 (s, 1H), 8.51 (dd, $J = 1.47, 8.79$ Hz, 1H), 8.22 (d, $J = 8.30$ Hz, 2H), 8.02 (d, $J = 8.79$ Hz, 1H), 7.95 (d, $J = 8.30$ Hz, 2H), 7.81 (d, $J = 2.93$ Hz, 1H), 7.52 (dd, $J = 2.44, 8.79$ Hz, 1H), 7.12 (d, $J = 8.79$ Hz, 1H), 3.7 (t, $J = 4.40$ Hz, 4H), 2.95 (t, $J = 4.4$ Hz, 4H). MS: $m/z = 497.2$ (M+H)⁺.

N-(3-chloro-4-methoxyphenyl)-6-(4-(morpholinosophonyl)phenyl)quinazolin-4-amine hydrochloride (20d)

Yield: 43.4%. ¹H NMR (500 MHz, DMSO-d₆) δ : 11.34 (br. s., 1H), 9.14 (s, 1H), 8.94 (s, 1H), 8.49 (d, $J = 8.79$ Hz, 1H), 8.20 (d, $J = 8.79$ Hz, 2H), 8.00 (d, $J = 8.79$ Hz, 1H), 7.96 (d, $J = 8.30$ Hz, 2H), 7.93 (d, $J = 2.44$ Hz, 1H), 7.70 (dd, $J = 2.44, 8.79$ Hz, 1H), 7.31 (d, $J = 9.28$ Hz, 1H), 3.93 (s, 3H), 3.67 (t, $J = 4.6$ Hz, 4H), 2.95 (t, $J = 4.6$ Hz, 4H). MS: $m/z = 511.1$ (M+H)⁺.

N-(4-(benzyloxy)-3-chlorophenyl)-6-(4-(morpholinosophonyl)phenyl)quinazolin-4-amine hydrochloride (20e)

Yield: 70.1%. ¹H NMR (500 MHz, DMSO-d₆) δ : 11.49 (br. s., 1H), 9.18 (s, 1H), 8.95 (s, 1H), 8.50 (dd, $J = 1.71, 8.55$ Hz, 1H), 8.20 - 8.22 (m, 2H), 8.01 (d, $J = 8.79$ Hz, 1H), 7.93 - 7.96 (m, 3H), 7.68 (dd, $J = 2.69, 9.03$ Hz, 1H), 7.51 - 7.53 (m, 2H), 7.35 - 7.46 (m, 4H), 5.30 (s, 2H), 3.66 - 3.68 (t, $J = 4.9$ Hz, 4H), 2.5 (t, $J = 4.4$ Hz, 4H). MS: $m/z = 587.2$ (M+H)⁺.

N-(4-((3-bromobenzyl)oxy)-3-chlorophenyl)-6-(4-(morpholinosophonyl)phenyl)quinazolin-4-amine hydrochloride (20f)

Yield: 51.6%. ¹H NMR (500 MHz, DMSO-d₆) δ : 11.45 (br. s., 1H), 9.17 (s, 1H), 8.95 (s, 1H), 8.50 (d, $J = 8.79$ Hz, 1H), 8.21 (d, $J = 8.79$ Hz, 2H), 8.01 (d, $J = 8.30$ Hz, 1H), 7.94 - 7.97 (m, 3H), 7.72 (s, 1H), 7.69 (dd, $J = 2.69, 9.03$ Hz, 1H), 7.58 (d, $J = 7.81$ Hz, 1H), 7.52 (d, $J = 7.81$ Hz, 1H), 7.37 - 7.43 (m, 2H), 5.31 (s, 2H), 3.67 (t, $J = 4.4$ Hz, 4H), 2.95 (t, $J = 4.35$ Hz, 4H). MS: $m/z = 665.1$ (M+H)⁺.

N-(3-chloro-4-((3-chlorobenzyl)oxy)phenyl)-6-(4-(morpholinosophonyl)phenyl)quinazolin-4-amine hydrochloride (20g)

Yield: 49.1%. ¹H NMR (500 MHz, DMSO-d₆) δ : 11.54 (br. s., 1H), 9.19 (br. s., 1H), 8.96 (br. s., 1H), 8.50 (d, $J = 8.79$ Hz, 1H), 8.21 (d, $J = 8.30$ Hz, 2H), 7.98 - 8.08 (m, 1H), 7.94 - 7.96 (m, 3H), 7.69 (dd, $J = 2.44, 8.79$ Hz, 1H), 7.58 (br. s., 1H), 7.37 - 7.50 (m, 4H), 5.31 (br. s., 2H), 3.67 (br. s., 4H), 2.95 (br. s., 4H). MS: $m/z = 621.1$ (M+H)⁺.

N-(3-chloro-4-((2,3-difluorobenzyl)oxy)phenyl)-6-(4-(morpholinosophonyl)phenyl)quinazolin-4-amine hydrochloride (20h)

Yield: 53.3%. ¹H NMR (500 MHz, DMSO-d₆) δ : 11.58 (br. s., 1H), 9.22 (s, 1H), 8.97 (s, 1H), 8.51 (dd, $J = 1.46, 8.79$ Hz, 1H), 8.22 (d, $J = 8.30$ Hz, 2H), 8.03 (d, $J = 8.79$ Hz, 1H), 7.93 - 7.97 (m, 3H), 7.73 (dd, $J = 2.44, 8.79$ Hz, 1H), 7.43 - 7.53 (m, 3H), 7.28 - 7.34 (m, 1H), 5.38 (s, 2H), 3.67 (t, $J = 4.4$ Hz, 4H), 2.95 (t, $J = 4.6$ Hz, 4H). MS: $m/z = 623.2$ (M+H)⁺.

N-(3-chloro-4-((2-fluorobenzyl)oxy)phenyl)-6-(4-(morpholinosulfonyl)phenyl)quinazolin-4-amine hydrochloride (20i)

Yield: 41.2%. ¹H NMR (500 MHz, DMSO-d₆) δ: 11.32 (br. s., 1H), 9.12 (br. s., 1H), 8.93 (br. s., 1H), 8.47 (d, *J* = 8.79 Hz, 1H), 8.18 (d, *J* = 8.30 Hz, 2H), 7.98 (d, *J* = 8.79 Hz, 1H), 7.92 - 7.96 (m, 3H), 7.70 (dd, *J* = 2.44, 8.79 Hz, 1H), 7.60 - 7.63 (m, 1H), 7.43 - 7.46 (m, 2H), 7.25 - 7.32 (m, 2H), 5.31 (s, 2H), 3.65 (t, *J* = 4.6 Hz, 4H), 2.93 (t, *J* = 4.6 Hz, 4H). MS: *m/z* = 605.2 (M+H)⁺.

N-(3-chloro-4-((4-fluorobenzyl)oxy)phenyl)-6-(4-(morpholinosulfonyl)phenyl)quinazolin-4-amine hydrochloride (20j)

Yield: 67.1%. ¹H NMR (500 MHz, DMSO-d₆) δ: 11.66 (br. s., 1H), 9.24 (br. s., 1H), 8.97 (s, 1H), 8.52 (d, *J* = 8.79 Hz, 1H), 8.23 (d, *J* = 8.30 Hz, 2H), 8.03 (d, *J* = 8.79 Hz, 1H), 7.94 - 7.96 (m, 3H), 7.70 (dd, *J* = 2.44, 8.79 Hz, 1H), 7.55 - 7.58 (m, 2H), 7.41 (d, *J* = 8.79 Hz, 1H), 7.26 - 7.30 (m, 2H), 5.28 (s, 2H), 3.7 (t, *J* = 4.9 Hz, 4H), 2.95 (t, *J* = 4.6 Hz, 4H). MS: *m/z* = 605.2 (M+H)⁺.

N-(3-chloro-4-((3-methoxybenzyl)oxy)phenyl)-6-(4-(morpholinosulfonyl)phenyl)quinazolin-4-amine hydrochloride (20k)

Yield: 43.1%. ¹H NMR (500 MHz, DMSO-d₆) δ: 11.40 (br. s., 1H), 9.15 (s, 1H), 8.94 (s, 1H), 8.49 (d, *J* = 8.30 Hz, 1H), 8.20 (d, *J* = 8.30 Hz, 2H), 8.00 (d, *J* = 8.79 Hz, 1H), 7.93 - 7.97 (m, 3H), 7.68 (dd, *J* = 2.44, 8.79 Hz, 1H), 7.33 - 7.39 (m, 2H), 7.06 - 7.08 (m, 2H), 6.91 - 6.96 (m, 1H), 5.27 (s, 2H), 3.78 (s, 3H), 3.67 (t, *J* = 4.9 Hz, 4H), 2.95 (t, *J* = 4.4 Hz, 4H). MS: *m/z* = 617.2 (M+H)⁺.

N-(3-chloro-4-((3-fluoro-4-(trifluoromethyl)benzyl)oxy)phenyl)-6-(4-(morpholinosulfonyl)phenyl)quinazolin-4-amine hydrochloride (20l)

Yield: 40.9%. ¹H NMR (500 MHz, DMSO-d₆) δ: 11.74 (br. s., 1H), 9.29 (s, 1H), 8.98 (s, 1H), 8.52 (dd, *J* = 1.46, 8.79 Hz, 1H), 8.24 (d, *J* = 8.79 Hz, 2H), 8.05 (d, *J* = 8.79 Hz, 1H), 7.99 (d, *J* = 2.44 Hz, 1H), 7.95 (d, *J* = 8.30 Hz, 2H), 7.89 (t, *J* = 7.81 Hz, 1H), 7.72 (dd, *J* = 2.44, 8.79 Hz, 1H), 7.63 (d, *J* = 11.23 Hz, 1H), 7.55 (d, *J* = 7.81 Hz, 1H), 7.38 (d, *J* = 8.79 Hz, 1H), 5.43 (s, 2H), 3.67 (t, *J* = 4.4 Hz, 4H), 2.95 (t, *J* = 4.4 Hz, 4H). MS: *m/z* = 673.2 (M+H)⁺.

N-(3-chloro-4-((2,3,5-trifluorobenzyl)oxy)phenyl)-6-(4-(morpholinosulfonyl)phenyl)quinazolin-4-amine hydrochloride (20m)

Yield: 42%. ¹H NMR (500 MHz, DMSO-d₆) δ: 11.49 (br. s., 1H), 9.19 (s, 1H), 8.96 (s, 1H), 8.51 (d, *J* = 9.77 Hz, 1H), 8.21 (d, *J* = 8.30 Hz, 2H), 8.02 (d, *J* = 8.79 Hz, 1H), 7.95 - 7.98 (m, 3H), 7.73 (dd, *J* = 2.69, 9.03 Hz, 1H), 7.56 - 7.65 (m, 1H), 7.48 (d, *J* = 8.79 Hz, 1H), 7.34 - 7.36 (m, 1H), 5.38 (s, 2H), 3.67 (t, *J* = 4.9 Hz, 4H), 2.95 (t, *J* = 4.4 Hz, 4H). MS: *m/z* = 641.1 (M+H)⁺.

N-(4-((3-fluorobenzyl)oxy)phenyl)-6-(4-(morpholinosulfonyl)phenyl)quinazolin-4-amine (20n)

Yield: 45.8%. ¹H NMR (500 MHz, DMSO-d₆) δ: 11.40 (br. s., 1H), 9.15 (s, 1H), 8.88 (s, 1H), 8.49 (d, *J* = 8.79 Hz, 1H), 8.20 (d, *J* = 8.79 Hz, 2H), 7.92 - 8.02 (m, 3H), 7.65 (d, *J* = 9.30 Hz, 2H), 7.45 - 7.51 (m, 1H), 7.31 - 7.35 (m, 2H), 7.16 - 7.22 (m, 3H), 5.21 (s, 2H), 3.67 (t, *J* = 4.4 Hz, 4H), 2.95 (t, *J* = 4.4 Hz, 4H). MS: *m/z* = 571.2 (M+H)⁺.

N-(4-((3-fluorobenzyl)oxy)-3-methoxyphenyl)-6-(4-(morpholinofonyl)phenyl)quinazolin-4-amine (20o)

Yield: 18%. ¹H NMR (500 MHz, DMSO-d₆) δ: 11.32 (br. s., 1H), 9.14 (s, 1H), 8.90 (s, 1H), 8.49 (d, *J* = 8.30 Hz, 1H), 8.20 (d, *J* = 8.79 Hz, 2H), 7.99 (d, *J* = 8.79 Hz, 1H), 7.96 (d, *J* = 8.30 Hz, 2H), 7.45 - 7.50 (m, 1H), 7.41 (d, *J* = 2.44 Hz, 1H), 7.28 - 7.34 (m, 3H), 7.15 - 7.22 (m, 2H), 5.19 (s, 2H), 3.84 (s, 3H), 3.67 (t, *J* = 4.9 Hz, 4H), 2.95 (t, *J* = 4.4 Hz, 4H). MS: *m/z* = 601.1 (M+H)⁺.

Trypanosome replication assays

Bloodstream *T. brucei brucei* Lister 427 cells were seeded at a density of 2×10^3 cells/ml and cultured in HMI-9 medium⁴⁷ in a 24 well plate. Two microliters of DMSO (control) or different concentrations of drugs prepared from 200X DMSO stocks were added to the cultures. Cells were incubated at 37°C for 48 h, and counted with a hemocytometer. Drugs were initially tested at concentrations of 10 μM, 1 μM, 100 nM and 10 nM to determine the range of potency of each compound. Thereafter, a set of 5 concentrations centered around a dose that prevented replication of 50% of cells (compared to DMSO) was used to establish the EC₅₀. All experiments were repeated thrice in independent studies where each dose was administered in duplicate (total n = 6).

HepG2 Cell Toxicity assay

The 384 well MTT cytotoxicity assay is a modification of the MTT method described by Ferrari *et al.*⁴⁸ optimized for 384 well throughput, with modifications described in detail in the Supporting Information. The 50% inhibitory concentrations (IC₅₀) were generated for each toxicity dose response test using GraphPad Prism (GraphPad Software Inc., San Diego, CA) using the nonlinear regression (sigmoidal dose-response/variable slope) equation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

EGFR	epidermal growth factor receptor
EC₅₀	concentration at which cell growth is inhibited by 50%
FDA	food and drug administration
MTT	3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
PDE	phosphodiesterase

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^aReagents and conditions: (a) formamide, 170 °C, 4h, 70%; (b) thionyl chloride, DMF, 80 °C, 12h, 85%; (c) 3-chloro-4-((3-fluorobenzyl)oxy)aniline, 2-propanol, 80 °C, 12h, 85%; (d) Ar-B(OH)₂, Pd(PPh₃)₄, 2M Na₂CO₃, DME, EtOH, 80 °C, 12h.

Scheme 1.
Synthesis of analogs **10**.^a

^aReagents and conditions: (a) alkyl halide, K₂CO₃, acetonitrile, 50 °C, 12h; (b) Zn, NH₄Cl, MeOH, H₂O, 25-50 °C, 6h.

Scheme 2.
Synthesis of requisite aniline intermediates 17.^a

^aReagents and conditions: (a) (4-(morpholin-4-ylsulfonyl)phenyl)boronic acid, Pd(PPh₃)₄, 2M Na₂CO₃, DME, EtOH, 80 °C, 30h, 85%; (b) thionyl chloride, DMF, 80 °C, 36h, 66%; (c) Ar-NH₂, 2-propanol, 80 °C, 12h.

Scheme 3.
Synthesis of head group expansion set 20.^a

^aReagents and conditions: (a) bis(pinacolato)diboron, PdCl₂(dppf)-CH₂Cl₂, KOAc, 1,4-dioxane, 80 °C, 12h, 33-72%; (b) **14**, Pd(PPh₃)₄, 2M Na₂CO₃, DME, EtOH, 80 °C, 12h.

Scheme 4.
Synthesis of analogs 23.^a

Figure 1.

Assessment of **23a** in a mouse model of human African trypanosomiasis. Parasitemia was measured each day in untreated (U, red) and treated (T, blue) mice (20 mg/kg).

Figure 2.

Effects of **23a** on the cell cycle of the trypanosome. (A) **23a**-treated or control trypanosomes were analyzed by flow cytometry (10,000 events analyzed; see Methods section). Propidium iodide (PI) fluorescence is plotted against cell populations containing 2C or 4C equivalents of DNA. (B) Quantitation of DNA content per cell (calculated with FloJo software). (C) Microscopic analysis of **23a**-treated or untreated trypanosomes after staining with DNA-binding dye DAPI. N, nucleus; K, kinetoplast; DIC, differential interference contrast image. (D) Quantitation of organelle (nucleus (N) or kinetoplast (K)) distribution after **23a** treatment.

Table 1

Initial screening data of analogs of lapatinib **1**.

Compd	GSK Number	R ₁	R ₂	R ₃	Tbb EC ₅₀ (μM) ^{a,b}	
2	GW58337A		Cl	H	0.41	
3	GW601906A		Cl	F	0.43	
4	GW633460A		Cl	F	0.48	
5	GW616030X		Cl	F	0.52	
6	GW615311X		Cl	F	0.55	
7	GW580496A		Br	H	0.56

Compd	GSK Number	R ₁	R ₂	R ₃	Tbb EC ₅₀ (μM) ^{a,b}
8	GW576924A		F	F	0.60
9	GW616907X		Cl	F	1.51
1	lapatinib		Cl	F	1.54
	melarsoprol ⁴⁹				0.0063
	eflornithine ⁵⁰				16.4
	pentamidine ⁴⁹				0.0035
	SCYX-7158 ⁵¹				0.794

^a All EC₅₀ values are ± 7%.

^b Concentration giving 50% inhibition of growth of *T. brucei* brucei Lister 427 cells

Table 2*Trypanosoma brucei* growth inhibition data of diverse analogs **10a-10k**.

Compd	R ₁	Tbb EC ₅₀ (μM) ^{a,b}
10a		1.39
10b		2.27
10c		3.85
10d		4.21
10e		4.50
10f		4.53
10g		5.3

Compd	R ₁	Tbb EC ₅₀ (μM) ^{a,b}
10h		5.98
10i		6.45
10j		22.63

^a All EC₅₀ values are ± 7%.

^b Concentration giving 50% inhibition of growth of *T. brucei* Lister 427 cells

Table 3*T. brucei* growth inhibition data for headgroup variations of **10a**.

Compd	R ₁	R ₂	Tbb EC ₅₀ (μM) ^{a,b}	HepG2 IC ₅₀ (uM)
10a		Cl	1.39	>15
20a	H	H	1.44	> 3
20b	CH ₃	H	1.15	> 15
20c	OH	Cl	1.06	> 15
20d	OCH ₃	Cl	0.82	> 15
20e		Cl	1.35	> 15
20f		Cl	0.68	> 15
20g		Cl	0.66	> 15
20h		Cl	0.82	>15
20i		Cl	1.65	> 15
20j		Cl	1.34	> 15
20k		Cl	1.43	> 15

Compd	R ₁	R ₂	Tbb EC ₅₀ (μM) ^{a,b}	HepG2 IC ₅₀ (uM)
20l		Cl	0.54	> 15
20m		Cl	1.12	> 3
20n		H	0.65	> 15
20o		OCH ₃	1.88	> 15

^a All EC₅₀ values are ± 7%.

^b Concentration giving 50% inhibition of growth of *T. brucei brucei* Lister 427 cells

Table 4

T. brucei and HepG2 growth inhibition data for focused analogs of **10a**.

Entry	Compd	position	R ₁	Tbb EC ₅₀ (μM) ^{a,b}	HepG2 IC ₅₀ (nM)
1	10a	<i>p</i>		1.39	> 15
2	10k	<i>m</i>		0.33	> 15
3	10l	<i>p</i>		0.32	> 15
4	10m	<i>m</i>		0.46	> 15
5	10n	<i>p</i>		0.35	> 15

Entry	Compd	position	R ₁	Tbb EC ₅₀ (μM) ^{a,b}	HepG2 IC ₅₀ (nM)
6	10o	<i>m</i>		0.25	> 15
7	10p	<i>p</i>		0.53	> 15
8	10q	<i>p</i>		0.81	1.81
9	10r	<i>p</i>		0.47	> 15
10	10s	<i>p</i>		0.28	3.32
11	10t	<i>p</i>	CH ₃	0.90	> 15
12	10u	<i>m</i>	CH ₃	3.21	> 15
13	10v	<i>o</i>	N(CH ₃) ₂	1.04	> 15
14	10w	<i>o</i>	NHC(CH ₃) ₃	4.66	nd ^c

^aAll EC₅₀ values are ± 7%.

^bConcentration giving 50% inhibition of growth of *T. brucei* brucei Lister 427 cells.

^cNot determined.

Table 5

Growth inhibitory potency of regiochemical and linker analogs of **10**.

Entry	Compd	R	Regio	X	Tbb EC ₅₀ (μM) ^{a,b}	HepG2 IC ₅₀ (μM)
1	23a		m	--	0.042	>20
2	23b		p	--	1.91	9.6
3	23c		m	CH ₂	0.36	nd ^c
4	23d		p	CH ₂	0.99	12.9
5	23e		m	C=O	0.55	nd
6	23f		p	C=O	1.21	nd
7	10k		m	SO ₂	0.33	>20
8	10a		p	SO ₂	1.39	>20
9	23g		m	--	0.76	>15
10	23h		p	--	0.38	nd
11	23i		m	CH ₂	0.65	nd
12	23j		p	CH ₂	1.5	nd
13	23k		m	C=O	0.14	>6
14	23l		p	C=O	0.94	nd
15	10m		m	SO ₂	0.46	>20
16	10l		p	SO ₂	0.32	>20

^a All EC₅₀ values are ± 7%.^b Concentration giving 50% inhibition of growth of *T. brucei* brucei Lister 427 cells.^c Not determined.

Table 6

Headgroup truncation analogs of **23a**.

Compound	R ¹	R ²	Tbb EC ₅₀ (μM) ^{a,b}	HepG2 IC ₅₀ (μM)	LE
23a		Cl	0.042	>20	0.19
23m	OBn	Cl	0.23	>20	0.18
23n	OBn	H	0.18	>20	0.19
23o	H	H	11	7.02	0.17

^a All EC₅₀ values are ± 7%.^b Concentration giving 50% inhibition of growth of *T. brucei* brucei Lister 427 cells.

Table 7Desirable ranges for CNS penetration and the MPO scoring for **23a**.

Prop	Targeted Value	Properties of 23a	MPO Score
cLogP	3	7.1	0
cLogD	2	7.1	0
TPSA	40 < X 90	59.5	1.00
MW	360	541	0
HBD	0.5	1	0.8
pKa	8	3.05	1.0
MPO score			2.8