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Hit-to-lead optimization of benzoxazepinoindazoles as human African trypanosomiasis therapeutics

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Abstract

Human African trypanosomiasis (HAT) is a neglected tropical disease caused by infection with either of two subspecies of the parasite *Trypanosoma brucei*. Due to a lack of economic incentive to develop new drugs, current treatments have severe limitations in terms of safety, efficacy, and ease of administration. In an effort to develop new HAT therapeutics, we report the structure-activity relationships around *T. brucei* for a series of benzoxazepinoindazoles previously identified through a high-throughput screen of human kinase inhibitors, and the subsequent *in vivo* experiments for HAT. We identified compound **18**, which showed an improved kinase selectivity profile and acceptable pharmacokinetic parameters, as a promising lead. Although treatment with **18** cured 60% of mice in a systemic model of HAT, the compound was unable to clear parasitemia in a CNS model of the disease. We also report the results of cross-screening these compounds against *T. cruzi*, *L. donovani* and *S. mansoni*.

Graphical Abstract

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Supporting Information Available

1. MS Word document containing: Supplemental biological and ADME data, supplemental synthetic schemes, HPLC chromatograms, cell and whole-organism assay protocols, and ADME experiment protocols.
2. MS Excel document containing: SMILES strings for final compounds with biological activity.



Introduction

Human African trypanosomiasis (HAT) is a parasitic infection caused by two subspecies of the organism *Trypanosoma brucei* (*T.b. gambiense* and *T.b. rhodesiense*). Prevalent in sub-Saharan Africa, HAT is one of 20 neglected tropical diseases (NTDs) designated by the World Health Organization.¹ The disease proceeds in two stages. In the first stage, the parasite is present in the blood and lymph and causes mild, flu-like symptoms.² A transition to stage 2 occurs when the parasite crosses the blood-brain barrier; this results in more severe symptoms such as disrupted sleeping patterns and mood fluctuation.² There are five compounds currently in use for the treatment of HAT: pentamidine, suramin, melarsoprol, and an eflornithine/nifurtimox combination therapy, referred to as NECT. These treatments are reasonably efficacious but cause a variety of adverse effects and can be challenging to administer.² Recent developments include the approval of fexinidazole as an oral treatment for HAT in the Democratic Republic of Congo, and the progression of acoziborole to Phase II/III clinical trials.³ However, given the attrition rate of compounds in clinical trials and the possibility that *T. brucei* could develop resistance to current drugs, we believe it is prudent to continue to seed the drug discovery pipeline for HAT.

As part of our ongoing NTD drug discovery efforts, we employed a lead repurposing strategy to find new chemical matter to use as a starting point for HAT therapeutics. Lead repurposing entails the screening of sets of targeted chemical matter based on homology between humans and parasites.⁴ As there are many examples of kinase essentiality in *T. brucei*,⁵ we undertook a high-throughput screen (HTS) of human kinase inhibitors against *T.b. brucei* cultures.⁶ A set of 42,444 known human kinase inhibitors were screened against *T.b. brucei* at 4 μM; those that showed >50% inhibition of parasite growth were progressed to dose-response assays against *T.b. brucei* and HepG2 cells. This screening process yielded 797 compounds with a *T.b. brucei* pEC₅₀ >6 that were >100x selective against HepG2 cells. These compounds were grouped by structural similarity into 59 clusters and 53 singletons.

One of the overall most promising clusters to emerge from this HTS comprised a series of substituted benzoxazepinoindazoles (BOXIs). Structural features of note are highlighted in Table 1 and include an aromatic “head” (red), the oxazepinoindazole “core” (blue) and an appended heterocyclic “tail” (yellow). The average potency of compounds in this cluster is a pEC₅₀ of 7.6, and the three hits highlighted in Table 1 (**NEU-1117**, **-1118**, and **-1119**) all have pEC₅₀ >8 while maintaining a good margin of selectivity against mammalian cells. The physicochemical properties of these compounds are also promising: topological polar surface area (TPSA) and molecular weight fall well within the targeted range for lead

compounds, and while the cLogP and LogD of these compounds are on average higher than desired, the lipophilic ligand efficiencies (LLEs)⁷ are high.

Additional parameters were also calculated or measured with the end goal of producing a HAT drug in mind. Central nervous system multiparameter optimization (CNS-MPO)⁸ scores were calculated for the HTS hits in order to provide an indication of whether they were likely to be brain-penetrant, essential for any treatment of stage 2 HAT. On average, the CNS-MPO scores of these compounds are consistent with likely blood-brain barrier penetration. The rate of action and trypanosome cidality of hits were also assessed; fast-acting, trypanocidal compounds are preferred to develop an effective treatment. Most compounds in this cluster are fast-acting and cidal, including **NEU-1117** and **NEU-1118**, though which structural features gave rise to this property was not yet understood.

Despite their promising characteristics, these compounds were not without room for optimization; Table 1 highlights some challenges to be overcome in this cluster of compounds. In particular, *in vitro* absorption, distribution, metabolism, and excretion (ADME) properties, such as aqueous solubility and plasma protein binding (PPB), were outside of the desired range. As our end goal is to develop an orally available HAT therapeutic, it was essential that these properties be improved. Additionally, a representative compound was selected for assessment against a panel of human kinases. Given the cluster's origin as human kinase inhibitors, it is perhaps unsurprising that this compound, **NEU-1328**, is a potent (<100 nM) inhibitor of at least five human kinases (Table S1). Our overall goal, therefore, was to improve the ADME properties of BOXIs while maintaining their potency and favorable physicochemical properties, and to assess how these changes impacted human kinase selectivity.

Results

Initial SAR studies focused on exploring the effect of various nitrogen-containing heterocyclic tails coupled to the BOXI core. The synthesis of such compounds is shown in Scheme 1. Synthesis began with the conversion of 4-bromo-2,6-difluorobenzoic acid **1** to the acid chloride **2**; this intermediate was coupled with 2-aminophenol to produce amide **3**. The benzoxazepine ring was then formed upon treatment with potassium carbonate. Compound **4** was converted to the thioamide **5** using Lawesson's reagent, which then yielded benzoxazepinoindazole **6** upon treatment with hydrazine. Protection with acetic anhydride and subsequent borylation gave boronic ester **8**, which was then coupled via a Suzuki reaction with the desired aryl halide to yield compounds **9b-s**. Analog **9a** was synthesized using 2,6-difluorobenzoic acid and following steps *a-e*.

The biological activity data of the initial tail replacement analogs is shown in Table 2. Of these, the 2-aminopyrimidine motif remained the best option in terms of potency. Excising the tail altogether (**9a**) led to a drop in potency of ~2 log units; although notably, this compound still retained sub-micromolar activity. Removal of the -NH₂ of the tail group resulted in a compound (**9b**) that was more than 10-fold less active than **NEU-1119**. Analogs where the 2-aminopyrimidine was replaced with other aminopyrimidines (**9c**, **9d**),

aminopyridines (**9e**, **9f**) or a phenyl ring (**9g**) all lost 1–2 log units of potency compared to NEU-1119.

Small substitutions at the 6-position of the pyrimidine, such as the ethyl of **9h**, the cyclopropyl of **9i**, the methylamine of **9j**, and the ethylamine of **9k** were well-tolerated, with only a slight loss in potency as compared to the original hits. Bulkier amines such as the isopropylamine, aniline, and methylaniline of **9l**, **9m**, and **9n**, respectively, were also tolerated from a potency standpoint but showed signs of toxicity in mammalian cells. Tertiary amines at the 6-position, including a dimethylamine (**9o**), morpholine (**9p**), pyrrolidine (**9q**), piperidine (**9r**), and *N*-methylpiperazine (**9s**), were not tolerated and consistently showed a drop in potency by 1–2 log units as compared to the primary amines or the unsubstituted 2-aminopyrimidine. In general, compounds that were active at sub-micromolar concentrations maintained LLEs between 3 and 4. Moving forward, analogs were primarily synthesized with an unsubstituted 2-aminopyrimidine as the “tail” group with the idea that, once an improved core was identified, it could be matched with other “tails” identified in this early SAR exploration if necessary.

The importance of each potential hydrogen bond donor on the 2-aminopyrimidine-substituted core was explored by systematically installing methyl groups at each position. These compounds were synthesized in a manner similar to the other BOXIs in the series (Scheme S1–S2). Methylation of the benzoxazepine nitrogen (**15**), as well as *bis*-methylation of the aminopyrimidine (**19**) resulted in complete loss of activity; however, methyl groups on the indazole nitrogen (**18**), as well as mono-methylation of the aminopyrimidine **20** were reasonably well-tolerated.

All analogs with a $pEC_{50} > 6$ were assessed in a speed-to-kill assay.⁶ Figure 1 shows the rate of action profile of three slow-acting compounds (**9a**, **9b**, and **9f**) and three fast-acting compounds (**9j**, **9l**, and **18**), where fast-acting compounds are defined as those that reach a $pEC_{50} > 6$ in less than 18 h of incubation time. Although all six analogs eventually reached a $pEC_{50} > 6.5$, slow-acting compounds required incubation times of up to 72 h. Interestingly, all fast-acting compounds were analogs that retained the benzoxazepine core and 2-aminopyrimidine tail, while slow-acting compounds were analogs where the 2-aminopyrimidine was either removed or changed to a different heterocycle altogether. These data illustrate the importance of the 2-aminopyrimidine motif to producing not only potent, but fast-acting analogs, and this tail group was prioritized moving forward.

Additionally, we assessed the *in vitro* ADME parameters of these compounds. The properties of tail replacement and methylated analogs for which ADME data was available are shown in Table 4. As was typical for all analogs synthesized as this point in the campaign, these compounds show moderate to high clogP and high logD, as well as low solubility and high PPB. In addition, we observed moderate-to-high microsomal and hepatocyte clearance. With this in mind, despite the high LLE of the BOXI analogs, we felt that further reduction of the lipophilicity would serve the overall goal of developing a potent analog with a good ADME profile. Thus, considering metabolic stability and lipophilicity, we turned our attention to the benzoxazepine core as the next site of modification.

Initial analogs targeted a truncated oxazepinoindazole core, the synthesis of which is shown in Scheme 2. Reaction of **2** with PMB-ethanolamine facilitated cyclization to the desired amide **21**; direct deprotection of the oxazepine ring allowed the use of Lawesson's reagent to convert amide **23** to thioamide **24**. Subsequent transformations proceeded in an analogous manner to those required to make the benzoxazepine core, with thioamide **24** converted to oxazepinoindazole **25** using hydrazine. This reaction was followed by acetylation and conversion of the bromide **26** to the boronic ester **27** through a Miyaura borylation using bis(pinacolato)diboron. Finally, a Suzuki reaction of this intermediate with the requisite chloropyrimidines yielded the desired products **28a-b**.

We also explored truncation to substituted indazoles and aminoindazoles (Scheme 3). The aminoindazole core was constructed from (4-cyano-3-fluorophenyl)boronic acid **29**, which was subjected to a Suzuki reaction with the desired aryl chlorides to form biaryl compounds **30**. These intermediates were then reacted with hydrazine to form final compounds **31a-c**. To synthesize indazole analogs, 4-bromoindazole was subjected to the same Miyaura and Suzuki conditions as previously described to provide final compounds **34a-c**. The syntheses of other core or headgroup replacement analogs, such as **40** and **49**, were completed in an analogous route to that described in Scheme 1, and are described in detail in Scheme S3–S4.

The biological activity and ADME properties of these core replacement analogs are presented in Table 5 (additional ADME data in Table S2). Systematic truncation of the benzoxazepine core to an oxazepinoindazole (**28a-b**), aminoindazole (**31a-c**), or indazole (**34a-c**) core uniformly resulted in a loss in potency of ~3 log units. However, these analogs were much more soluble than the original hits. Interestingly, despite their low potency, they also retained LLEs of around 4, suggesting that the lipophilic benzoxazepine group is contributing to potency in proportion to its lipophilicity. Excision of the indazole ring, as in compound **49**, also led to a drop in potency, but without a corresponding lowering of clogP or boost in solubility.

Given the importance of the full BOXI core to potency and its detrimental effect on solubility, we sought to replace the benzene “headgroup” of this core with other features that would improve solubility while filling the space occupied by the aromatic ring. We hypothesized that increased sp³ content or more polarity might increase solubility without a loss in potency. However, while analogs with either a saturated cyclopentane ring (**49**) or a heterocyclic pyridine (**50**) did indeed retain sub-100 nM activity, we did not observe an increase in solubility. Interestingly, the methoxy-substituted aminoindazole **51** retained sub-micromolar potency with solubility of >100 μM; its reduced clogP also translated into an LLE of 5.2.

Capitalizing on the reasonable potency and excellent solubility of **51**, we pursued a series substituted aminoindazoles, the synthesis of which is shown in Scheme 4. Starting with 4-bromo-2,6-difluorobenzonitrile **52**, desired alkoxybenzonitriles **53** were synthesized by substitution with the corresponding alcohol. The indazole ring was closed using hydrazine to produce **54**, then reacted with acetic anhydride to yield the protected indazoles **55**. Miyaura borylation of the core and subsequent Suzuki coupling with 2-amino-4-chloropyrimidine

gave the final ring-opened products **57a-j**. The syntheses of compounds **63** and **68** are presented in Scheme S5–S6.

The biological activity of these compounds is shown in Table 6. Although we were able to slightly improve upon the potency of **51** by introducing bulkier alkoxy substituents at R¹ (**57a-f**), the LLE either remained the same or dropped, suggesting that more lipophilic substituents such as the *t*-butyl or phenyl were, on balance, making the compound more lipophilic without a corresponding boost in potency. Furthermore, the phenyl substituent **57e** introduced some toxicity to mammalian cells.

We hypothesized that some potency could be gained by introducing substituents containing a hydrogen bond acceptor which could interact with the aminoindazole. This potential intramolecular hydrogen bond could position the substituent in such a way as to mimic the orientation of the benzene ring of the full BOXI core. Compounds **57g-j** were synthesized in order to test this hypothesis; unfortunately, none of these analogs showed increased activity. However, they displayed some of the best overall ADME data of the series (Table S2). Finally, compounds with a phenyl- (**63**) or benzyl- (**68**) substituted amine were tested; these compounds displayed potency in the micromolar range and did not show significant improvement in ADME profile.

At this point, we assessed the overall profile of several promising compounds. Table 7 represents a heat map of an original HTS hit, **NEU-1117**, as well as three analogs, **18**, **49**, and **57a**. Values highlighted in green meet or exceed targeted values; yellow highlighting indicates mid-range values, and red highlighting indicates values that are well outside the targeted range. All three compounds show an improved overall profile over **NEU-1117**. Compounds **18** and **49** both maintain high potency against *T.b. brucei* and are less toxic against MRC5 cells than **NEU-1117**, although **49** is highly cleared in both rat hepatocytes and human liver microsomes. These limitations were deemed sufficient to preclude **49** from further assessment. Compound **57a**, although approximately 1.5 log units less potent than **NEU-1117**, nevertheless, exhibits excellent ADME properties including high aqueous solubility, low clearance, and low PPB. Based on these data, we selected **18** and **57a** for progression to pharmacokinetic (PK) studies.

The results of the mouse PK studies of **18** and **57a** are shown below. Figure 2 shows PK results for two separate experiments: the green line represents blood concentration over time, while the red and blue dots represent sparse sampling of blood and brain concentrations. Parameters calculated from these curves, including C_{max}, t_{max}, and t_{1/2}, are presented in Table 8. Both compounds are cleared from the blood within 4 h after injection, although **18** has a slightly longer half-life. Additionally, both compounds achieve a C_{max} >30× their *T.b. brucei* EC₅₀. Of the two compounds, **18** demonstrates higher brain penetration and maintains its blood/brain ratio for 4 h.

Because the compounds included in the HTS were designed as human kinase inhibitors, and a compound in this cluster had known human kinase activity, we also assessed the activity of both **18** and **57a** against a panel of 46 human kinases at a 1 μM concentration; Figure 3 shows the percent inhibition of each kinase for both compounds. In general, **18** is a much

more selective compound than **57a**, inhibiting only three kinases >50% (Syk, MAP4K4, and JAK3), and two additional kinases (PKA and IRAK4) when the cutoff is lowered to 30% inhibition. In contrast, at 1 μ M **57a** is a potent inhibitor of 19 kinases included in the panel and a moderate inhibitor of an additional nine (Table S3).

Given its superior brain penetration and more selective kinase panel results as compared to **57a**, compound **18** was progressed to an *in vivo* efficacy model of blood-stage HAT. Infected mice with *T. brucei brucei* STIB795 were treated with **18** once daily at 30 mg/kg intraperitoneally (IP) for five days; the results are shown in Figure 4. Compared to vehicle control mice, which did not survive past day 5, all of the mice treated with **18** survived up to day 23, and 60% of mice were cured of infection (undetectable parasitemia on day 30). Furthermore, **18** is a fast-acting, trypanocidal compound: 80% of treated mice had undetectable parasitemia 24 h after treatment began (Table S6).

Based on the promising results of this experiment, compound **18** was further progressed to a CNS efficacy model to assess its potential as a stage 2 HAT therapeutic. Mice infected with *T. brucei brucei* GVR35 were divided into three groups: **control** (Berenil 40 mg/kg pretreatment + vehicle), **Treatment 1** (Berenil 40 mg/kg pretreatment + 25 mg/kg BID **18**), and **Treatment 2** (25 mg/kg BID **18**). Berenil®, an anti-trypanosomal therapeutic used in livestock, was administered to control and Treatment 1 groups on day 18 to clear blood stage parasitemia. Compound **18** was administered to Treatment 1 and 2 groups on day 21–25, while vehicle was administered to the control group.

Figure 5 shows the relative survival and relative survival means of the three groups. Treatment with **18** in combination with Berenil did not significantly extend life expectancy over the control group, and the Treatment 2 group (**18** alone) showed a lower relapse mean than either the control or Treatment 1 groups. In addition, toxicity was observed when dosing **18** at 50 mg/kg QD with 50% of animals experiencing inflammation after dosing, which resolved with time, and 50% of animals dying within 30 minutes of treatment. For these reasons, **18** was not progressed for further evaluation.

In addition to assessing *T. brucei* activity, we cross-screened selected compounds against other parasites, including *Trypanosoma cruzi* (the causative agent of Chagas disease), *Leishmania donovani* (one of the causative agents of leishmaniasis) and *Schistosoma mansoni* (a trematode flatworm and a causative agent of schistosomiasis). The detailed activity data for *T. cruzi* and *L. donovani* are presented in Table S4. Although only **9o** showed a modest activity against *L. donovani* intracellular amastigotes with an acceptable selectivity over host cells, two compounds (**NEU-1117** and **18**) had pEC₅₀ >7.0 against *T. cruzi*, and three additional analogs (**9j**, **9k**, and **20**) had pEC₅₀ ~ 6.0. Further work is ongoing to elaborate the SAR of this series and assess its potential as anti-*T. cruzi* agents. Overall, the data highlight the importance of the fully elaborated BOXI core and the 2-aminopyrimidine moiety for activity.

The data for four of the BOXIs vs. adult *S. mansoni* are presented in Table S5. When these compounds were screened at 10 μ M over 48 h against *S. mansoni* adults, a variety of phenotypic responses and associated severity scores were elicited (Table S5). Thus, **9c**, at

the earliest observation time point of 3 h, induced uncoordinated muscular activity and an inability of the oral and ventral suckers to adhere to the substratum, which decreased over time; **9d** produced a pronounced and sustained flaccid paralysis at 3 h that was reversible upon removal of the compound; **63** elicited an uncoordinated response at 3 h that was then replaced by decreased motility, darkening and an inability of the oral and ventral suckers to adhere to the substratum; finally, **31c** was inactive. Investigations into the anti-schistosomal activity of other molecules in this series is continuing.

Discussion and Conclusion

Through a lead repurposing approach, we have evaluated a series of benzoxazepinoindazoles and related compounds as potential HAT therapeutics. Detailed structure-activity and structure-property relationships were established that enabled us to select two compounds, **18** and **57a**, for further evaluation. Given its high potency, favorable PK profile, and improved selectivity against human kinases, **18** was assessed for *in vivo* efficacy. Promising results were obtained with **18** in the systemic *T. brucei* infection model. This, coupled with a high brain-blood ratio in pharmacokinetic experiments, led to the progression of **18** into the CNS model, though it was not successful in clearing parasitemia and toxicity was observed. Further investigation to understand these findings is ongoing. In addition, several BOXIs have been identified as potent inhibitors of *T. cruzi*, the causative agent of Chagas disease, and *S. mansoni*, the causative agent of Schistosomiasis. Investigation of this class of compounds as anti-Chagas agents and their potential as schistosomiasis therapeutics is likewise ongoing.

Experimental Section

In vitro Biology.

In order to determine the *T. b. brucei* EC₅₀ values, 4 μ L per well from compound master plates were dispensed into a new plate and 96 μ L of HMI-9 per well were added to generate a 4% DMSO intermediate plate. Mid-log phase growth *T. b. brucei* was diluted to a working cell density of 2,750 cells/mL and 90 μ L/well dispensed into 96-well flat-bottom transparent assay plates (Nunc®). Ten μ L/well from intermediate plates were added so final cell concentration was 2,500 cell/mL, and final top concentration of compounds was 40 μ M in 0.4% DMSO per well. Assay plates were incubated for 72 h at 37 °C and 5% CO₂. Four hours prior to the end of the incubation, 20 μ L of a 440 μ M resazurin solution in prewarmed HMI-9 was added to each well and incubated for another 4 h. Fluorescence was then measured in an Infinite F200 plate reader (Tecan®) at 550 nm (excitation filter) and 590 nm (emission filter). A four-parameter equation was employed to fit the dose-response curves and determine EC₅₀ using the SigmaPlot® 13.0 software. Assays were performed in duplicate at least twice, to achieve a minimal n=2 per dose response.

Pharmacokinetics Protocols.

Animals and ethical statement: All animal studies were ethically reviewed and carried out in accordance with European Directive 2010/63/EEC and the GSK Policy on the Care, Welfare and Treatment of Animals. Compound was administered intraperitoneally (IP) to

two groups of female NMRI mice (Group 1 n=3; Group 2 n=6) supplied by Charles River (Germany) Ltd. The compound was prepared in 1% (v/v) DMSO:99% (v/v) 20% (w/v) sulfobutyl ether-beta-cyclodextrin (SBE- β -CD/Captisol®, used as a solubilizing agent) in water and the dosing volume was 10 mL/kg for a total dose of 10 mg/kg. Food and tap water were available *ad libitum*. Following IP dosing, Group 1 blood samples were collected from the tail vein into capillary tubes containing K2EDTA at the following time-points: 0.0833, 0.25, 0.5, 1, 2, 4, 6, 8 and 24 h.

In order to obtain simultaneous blood and brain samples, Group 2 mice were placed under terminal anaesthetic (isoflurane) and blood samples (0.3 mL) collected from the retro-orbital sinus into K2EDTA tubes at 0.5 h (n= 3) and 4 h (n=3) after compound administration. Immediately following blood sample collection, death was confirmed by cervical dislocation and the brain removed. Aliquots of each blood sample were diluted in an equal volume of water. Mouse brain samples were weighed, water was added at a 1/2 (w/v) ratio (brain/water), and then homogenized. Both blood and brain samples were stored –80 °C until analysis.

Diluted blood and brain homogenates were processed under standard liquid-liquid extraction procedures using CAN containing an internal standard (Nifedipine) and analysed by LC-MS/MS. Non-compartmental analysis was performed using the Phoenix pharmacokinetic software version 1.4 (Certara) and C_{max} , t_{max} , AUClast, AUC, and $t_{1/2}$ were estimated.

***In vivo* Efficacy Experiment Protocols.**

Animals and ethical statement: All procedures were approved by ethical committee of Institute of Parasitology and Biomedicine Lopez-Neyra (Spanish National Research Council, CSIC), code MNC.2/2015. This Institute has joined the Agreement on Transparency in Animal Experimentation, promoted by the Confederation of Scientific Societies of Spain (COSCE), with the collaboration of the European Association for Animal Research released on September 20, 2016. The Animal Experimentation Unit is under the control of the competent authority, registered in the national register as Center of Breeding and User of experimental animals code ES-18021000022, according with the European and Spanish regulations. Female NMRI mice (Charles River Laboratories) were provided with sterilized water and commercial pellets *ad libitum* and maintained under the standard conditions in a conventional room at 20–24 °C with a 12/12-h light/dark cycle. Compound **18** solution for treatment was resuspended in vehicle: 5 % DMSO in 20 % Captisol® sulfobutyl ether β -cyclodextrin that improves solubility and stability for drug dosing.

Blood-stage efficacy model.—Infection was performed by i.p. injection of 10^4 bloodstream forms in 0.2 mL TDB glucose of *T. brucei brucei* (STIB795) from a cryopreserved stock. Three days later, 9 infected animals with confirmed parasitemia were divided into two groups: **control** (infected mice treated with vehicle, n=4) and **treated** (infected mice treated with 30 mg/kg/day of **18**, n=5). For treatment, both control and **18** were heated at 50 °C for 10 min to solubilize. Control and drug-treated mice received a 0.2 mL i.p. injection at the 3rd day from infection during 5 consecutive days. Parasitemia was individually checked by direct microscopic counting of parasites in a Neubauer chamber using 2 μ L of blood from infected mice tail, diluted in 100 μ L of TDB glucose. Parasitaemia

of all mice were periodically checked by tail blood examination up to day 31th. The day of death was recorded.

CNS efficacy model.—Infection was performed by i.p. injection of $2 \cdot 10^4$ bloodstream forms in 0.2 mL TDB glucose of *T. brucei brucei* (GVR25 strain) from a cryopreserved stock. Fourteen days later, 13 infected animals with confirmed parasitemia were divided into three equal groups: **control** (infected mice pretreated with a single dose of 40 mg/kg diminazene aceturate -Berenil®- and treated with vehicle BID, n=5); **treatment 1** (infected mice pretreated with 40 mg/kg Berenil® + 25 mg/kg /day BID **11**, n=4) and **treatment 2** (infected mice just treated with 25 mg/kg /day BID **18**, n=4): the total concentration of **18** administered to mice was 50 /mg/kg/day. For treatment, vehicle and **18** were heated at 50 °C for 10 min to solubilize. Mice received a 0.2 mL i.p. injection of vehicle or **18** at the 21th day from infection during 5 consecutive days. Parasitemia was individually checked by direct microscopic counting of parasites in a Neubauer chamber using 2 µL of blood from infected mice tail, diluted in 100 µL of TDB glucose. Parasitaemia of all mice were checked twice a week by tail blood examination and thereafter mice with parasitaemia relapses were euthanized and the day of parasitaemia relapse was recorded. Results are expressed as percentage of accumulative mortality and in Mean Survival Days (MSD).

General Chemistry.

Reagents purchased were used as received, unless otherwise noted. Purification of intermediates and final compounds was performed using silica gel chromatography using the Biotage® Isolera™ One flash purification system. When required, preparative HPLC was conducted for final compounds on Waters FractionLynx system using acetonitrile/water and 0.1% formic acid gradient and collected based on UV monitoring at 254 nm. LCMS analysis was performed using a Waters Alliance reverse phase HPLC (columns Waters SunFire C18 4.6 × 50 mm, 3.5 µm, or Waters SunFire C8 4.6 × 50 mm, 3.5 µm), using a multi-wavelength photodiode array detector from 210 nm to 600 nm and Waters Micromass ZQ detector (electrospray ionization). All compounds tested had a purity of > 95% as measured by LCMS. ¹H NMR spectra were obtained with Varian NMR systems, operating at either 400 or 500 MHz at room temperature, using solvents from Cambridge Isotope Laboratories. Chemical shifts (δ, ppm) are reported relative to the solvent peak (CDCl₃: 7.26 [¹H]; DMSO-*d*₆: 2.50 [¹H]; Acetone-*d*₆: 2.05; or CD₃OD: 3.31 [¹H]). Data for ¹H NMR spectra are reported as follows: chemical shift (ppm), multiplicity (s for singlet, d for doublet, t for triplet, dd for doublet of doublet, m for multiplet), coupling constant (Hz), and integration. Compounds obtained from GSK in-house library were not resynthesized unless otherwise noted.

General Procedure A.

Desired boronate, desired aryl halide (1.5 equiv.), and potassium carbonate (3.5 equiv.) were suspended in 3:1 dioxane:water (0.08 M), and the reaction vial was degassed for ~10 minutes. Pd(PPh₃)₄ (5 mol%) was added and the reaction was run under nitrogen at 100 °C until completion as indicated by LCMS analysis (~4 h). The reaction mixture was diluted with EtOAc or MeOH, filtered through celite, and concentrated under reduced pressure. The resulting crude residue was purified by the stated method to afford the desired product.

General Procedure B.

The desired alcohol (1.2 equiv.) was dissolved in THF (0.64 M) and 1 M LHMDS in THF (1.2 equiv.) was added dropwise. The reaction was stirred at room temperature for ~1 h, then cooled to 0 °C. 4-Bromo-2,6-difluorobenzonitrile **52** was added and the reaction was allowed to warm to room temperature and stirred until completion by TLC. The reaction mixture was diluted with EtOAc, poured over water, and extracted three times. The combined organic layers were washed once with brine, dried with sodium sulfate and rotovapped. The crude material was purified by the stated method to afford the title compound.

General Procedure C.

The desired 4-bromo-2-alkoxy-6-fluorobenzonitrile **53** was dissolved in ethanol (0.10 M) and hydrazine monohydrate (10 equiv.) was added. The reaction was refluxed overnight at 95 °C. The reaction was cooled to room temperature and the solvent was removed under reduced pressure. The crude material was purified by the stated method to afford the title compound.

General Procedure D.

The desired 6-bromo-4-alkoxy-1*H*-indazol-3-amine **54** was dissolved in pyridine (0.09 M) and acetic anhydride (3.5 equiv.) was added. The reaction was refluxed at 100 °C for ~4 h. The reaction mixture was diluted with DCM and extracted three times with 1M HCl. The combined aqueous layers were extracted once with DCM, and the combined organic layers were washed once with water, once with brine, dried with sodium sulfate, and concentrated under reduced pressure. The crude material was purified by the stated method to afford the title compound.

General Procedure E.

The desired protected 6-bromo-4-alkoxy-1*H*-indazol-3-amines **55** (1.0 equiv.), potassium acetate (3.5 equiv.), bis(pinacolato)diboron (1.5 equiv.), and PdCl₂(dppf)·CH₂Cl₂ (0.5 equiv.) were combined in a reaction vial that was filled with nitrogen and evacuated three times. Dry, degassed dioxane (0.10 M) was added and the reaction was run in the microwave (145 °C) for 0.5 h. The reaction mixture was diluted with EtOAc, filtered through celite, and concentrated under reduced pressure. The crude material was either taken forward without further purification or purified by the stated method and used as a mixture of mono- and di-protected boronic acid and ester **56**.

Potassium carbonate (3.0 equiv.), 2-amino-4-chloropyrimidine (1.2 equiv.), and PdCl₂(dppf)·CH₂Cl₂ (0.5 equiv.) were combined in a microwave vial that was filled with nitrogen and evacuated three times. The requisite boronic ester **56** or mixture of mono- and di-protected boronic acid and ester was dissolved in 3:1 dioxane:water (0.10 M) and added to the reaction mixture. The reaction was degassed for ~10 minutes and run in the microwave (150 °C) for 0.5–1.5 h. The reaction mixture was diluted with MeOH, filtered through celite, and concentrated under reduced pressure. The resulting crude residue was purified by the stated method to afford the desired product.

4-Bromo-2,6-difluorobenzoyl chloride (2).

4-Bromo-2,6-difluorobenzoic acid **1** (3.00, 12.66 mmol) was suspended in thionyl chloride (15 ml, 207 mmol) and the reaction was refluxed at 75 °C for approximately 4 h. Excess thionyl chloride was removed by distillation as the product was azeotroped with toluene three times, affording the title compound as a yellow oil which was used in the next reaction without further purification.

4-Bromo-2,6-difluoro-N-(2-hydroxyphenyl)benzamide (3).

2-Aminophenol (1.38 g, 12.65 mmol) was dissolved in DCM (30 ml, 0.42 M), and TEA (3.5 ml, 25.11 mmol) was added. Compound **2** (3.23 g, 12.64 mmol) was dissolved in DCM (15 ml, 0.22 M), and this solution was added to the reaction mixture dropwise at 0 °C. The reaction was allowed to warm to room temperature and stirred overnight. After pouring the reaction mixture over 1M HCl, the title compound was isolated by vacuum filtration as an off-white solid (3.62 g, 87%). LCMS [M+H]⁺ 327.95 m/z (⁷⁹Br), 329.96 m/z (⁸¹Br); ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 10.03 (s, 1 H) 9.88 (br. s., 1 H) 7.88 (dd, *J*=8.1, 1.2 Hz, 1 H) 7.60 (d, *J*=7.3 Hz, 2 H) 6.97 – 7.03 (m, 1 H) 6.91 (dd, *J*=8.1, 1.2 Hz, 1 H) 6.78 – 6.84 (m, 1 H).

3-Bromo-1-fluorodibenzo[*b,f*][1,4]oxazepin-11(10*H*)-one (4).

Compound **3** (3.62 g, 11.04 mmol) was dissolved in DMF (30 ml, 0.37 M) and potassium carbonate (3.05 g, 22.06 mmol) was added. The reaction was stirred at room temperature for two days and was then poured over water. The title compound was isolated by vacuum filtration as an off-white solid (2.44 g, 72%). LCMS [M+H]⁺ 307.99 m/z (⁷⁹Br), 309.96 m/z (⁸¹Br); ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 10.74 (br. s., 1 H) 7.61 (s, 1 H) 7.57 (dd, *J*=9.8, 1.5 Hz, 1 H) 7.37 – 7.41 (m, 1 H) 7.22 (dd, *J*=8.3, 1.5 Hz, 1 H) 7.14 – 7.19 (m, 2 H).

3-Bromo-1-fluorodibenzo[*b,f*][1,4]oxazepine-11(10*H*)-thione (5).

Compound **4** (2.44 g, 7.91 mmol) was suspended in toluene (160 ml, 0.05M) and Lawesson's reagent (3.49 g, 8.63 mmol) was added. The reaction was refluxed at 100 °C overnight. Upon cooling to room temperature, a yellow precipitate was observed and collected by vacuum filtration to afford the title compound as a yellow solid (1.75 g) which was carried forward without further purification. LCMS [M+H]⁺ 323.93 m/z (⁷⁹Br), 325.95 m/z (⁸¹Br).

4-Bromo-2,11-dihydrobenzo[2,3][1,4]oxazepino[5,6,7-*cd*]indazole (6).

Compound **5** (1.00 g, 3.09 mmol) was suspended in dioxane (10 ml, 0.3 M) and hydrazine monohydrate (0.30 ml, 6.11 mmol) was added. The reaction was refluxed for 3 h at 85 °C. After cooling to room temperature, the reaction mixture was diluted with DCM and concentrated under reduced pressure. The residue was purified by flash chromatography (0–5% MeOH:DCM) to afford the title compound as an off-white solid (833 mg, 89%). LCMS [M+H]⁺ 301.97 m/z (⁷⁹Br), 303.99 m/z (⁸¹Br); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 12.29 (s, 1 H) 9.52 (s, 1 H) 7.31 (d, *J*=1.5 Hz, 1 H) 7.26 (dd, *J*=8.1, 1.5 Hz, 1 H) 7.23 (dd, *J*=8.1, 1.5 Hz, 1 H) 7.04 – 7.09 (m, 1 H) 6.85 – 6.91 (m, 2 H).

1-(4-Bromobenzo[2,3][1,4]oxazepino[5,6,7-*cd*]indazol-11(2*H*)-yl)ethan-1-one and 1-(4-bromobenzo[2,3][1,4]oxazepino[5,6,7-*cd*]indazol-2(11*H*)-yl)ethan-1-one (7).

Acetic anhydride (12.0 ml, 127.18 mmol) was added to **6** (833 mg, 2.76 mmol) and the reaction was refluxed at 100 °C for ~3 h. Upon cooling to room temperature, a bright yellow precipitate was observed and collected by vacuum filtration to afford the title compounds as a mixture of isomers. (Bright yellow solid, 885 mg, 93%). LCMS [M+H]⁺ 343.99 m/z (⁷⁹Br), 345.96 m/z (⁸¹Br).

1-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[2,3][1,4]oxazepino[5,6,7-*cd*]indazol-11(2*H*)-yl)ethan-1-one (8).

Compound **7** (401 mg, 1.17 mmol), potassium acetate (405 mg, 4.13 mmol), bis(pinacolato)diboron (443 mg, 1.74 mmol), and PdCl₂(dppf)·CH₂Cl₂ (46 mg, 0.06 mmol) were combined in a reaction vial that was filled with nitrogen and evacuated three times. Dry, degassed dioxane (8.0 ml, 0.15 M) was added and the reaction was run in the microwave (145 °C) for 1 h. The reaction mixture was then diluted with EtOAc, filtered through celite, and concentrated under reduced pressure. The residue was purified by flash chromatography (0–50% EtOAc:hexanes) to afford the title compound as an off-white solid (297 mg, 65%). LCMS [M+H]⁺ 392.13 m/z; ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 10.03 (s, 1 H) 8.25 (s, 1 H) 7.27 (dd, *J*=7.6, 3.2 Hz, 2 H) 7.26 (s, 1 H) 7.11 (t, *J*=7.6 Hz, 1 H) 6.98 (t, *J*=7.3 Hz, 1 H) 2.62 (s, 3 H) 1.34 (s, 12 H).

4-(Pyrimidin-4-yl)-2,11-dihydrobenzo[2,3][1,4]oxazepino[5,6,7-*cd*]indazole (9b).

The title compound was prepared according to General Procedure A on a 40-mg scale using **8** and 4-chloropyrimidine-HCl. Upon cooling to room temperature, a precipitate was observed and collected by vacuum filtration. The precipitate was suspended in DME (0.75 ml, 0.06 M) and concentrated HCl (0.25 ml, 3.00 mmol) was added. This suspension was stirred at 85 °C for ~1 h, then cooled to room temperature. The resulting precipitate was collected to afford the title compound as an orange solid (12 mg, 40%). LCMS [M+H]⁺ 302.09 m/z; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 12.55 (br. s., 1 H) 9.59 (s, 1 H) 9.28 (s, 1 H) 8.89 (d, *J*=5.9 Hz, 1 H) 8.24 (dd, *J*=5.1, 1.5 Hz, 1 H) 8.00 (s, 1 H) 7.58 (s, 1 H) 7.29 (dd, *J*=8.1, 1.5 Hz, 2 H) 7.08 (t, *J*=7.7 Hz, 1 H) 6.90 (t, *J*=6.6 Hz, 1 H).

6-(2,11-Dihydrobenzo[2,3][1,4]oxazepino[5,6,7-*cd*]indazol-4-yl)pyrimidin-4-amine (9c).

The title compound was prepared according to General Procedure A on a 41-mg scale using **8** and 4-amino-6-chloropyrimidine. The crude material was purified preparative HPLC (5–50% water:acetonitrile) to afford the title compound as a yellow solid (15 mg, 45%). LCMS [M+H]⁺ 317.11 m/z; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 12.36 (s, 1 H) 9.52 (s, 1 H) 8.46 (s, 1 H) 7.74 (s, 1 H) 7.23 – 7.32 (m, 3 H) 7.06 (t, *J*=7.3 Hz, 1 H) 6.99 (s, 1 H) 6.92 (s, 2 H) 6.89 (t, *J*=8.1 Hz, 1 H).

2-(2,11-Dihydrobenzo[2,3][1,4]oxazepino[5,6,7-*cd*]indazol-4-yl)pyrimidin-4-amine (9d).

The title compound was prepared according to General Procedure A on a 41-mg scale using **8** and 4-amino-2-chloropyrimidine. The crude material was purified by preparative HPLC (5–50% acetonitrile:water) to afford the title compound as a yellow solid (17 mg, 51%).

LCMS [M+H]⁺ 317.11 m/z; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 12.32 (s, 1 H) 9.49 (s, 1 H) 8.20 (d, *J*=5.9 Hz, 1 H) 8.07 (s, 1 H) 7.71 (s, 1 H) 7.28 (d, *J*=8.1 Hz, 2 H) 7.06 (t, *J*=6.6 Hz, 1 H) 6.96 (br. s., 2 H) 6.88 (t, *J*=7.3 Hz, 1 H) 6.39 (d, *J*=5.9 Hz, 1 H).

6-(2,11-Dihydrobenzo[2,3][1,4]oxazepino[5,6,7-*cd*]indazol-4-yl)pyridin-2-amine formate (9e).

The title compound was prepared according to General Procedure A on a 75-mg scale using **8** and 2-amino-6-chloropyridine. The crude material was purified by flash chromatography (50% EtOAc:hexanes – 33%/33%/33% EtOAc:hexanes:acetone – 33% EtOAc:acetone), further purified by flash chromatography (10% MeOH:DCM), and finally purified by preparative HPLC (5–95% acetonitrile:water to afford the title compound as a colorless solid (45 mg, 74%). LCMS [M+H]⁺ 315.99 m/z; ¹H NMR (399 MHz, DMSO-*d*₆) δ ppm 12.23 (s, 1 H) 9.48 (s, 1 H) 8.15 (s, 1 H) 7.70 (s, 1 H) 7.47 (t, *J*=8.1 Hz, 1 H) 7.38 (s, 1 H) 7.27 (d, *J*=8.1 Hz, 2 H) 7.15 (d, *J*=7.3 Hz, 1 H) 7.05 (t, *J*=7.0 Hz, 1 H) 6.88 (t, *J*=8.1 Hz, 1 H) 6.44 (d, *J*=8.1 Hz, 1 H) 6.06 (s, 2 H).

2-(2,11-Dihydrobenzo[2,3][1,4]oxazepino[5,6,7-*cd*]indazol-4-yl)pyridin-4-amine (9f).

The title compound was prepared according to General Procedure A on a 51-mg scale using **8** and 4-amino-2-bromopyridine. The crude material was dissolved in MeOH (2.0 ml, 0.10 M) and potassium carbonate (54 mg, 0.391 mmol) was added before stirring at room temperature for ~1 h. The reaction mixture was diluted with EtOAc and washed with water; the aqueous layer was then extracted twice with EtOAc. The combined organic layers were concentrated under reduced pressure and purified by flash chromatography (3–20% MeOH:1% TEA/DCM) to afford the title compound as a dark gold solid (4.8 mg, 8%). LCMS [M+H]⁺ 315.99 m/z; ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 12.67 (s, 1 H) 9.65 (s, 1 H) 8.14 (d, *J*=6.8 Hz, 1 H) 7.96 (br. s., 2 H) 7.54 (s, 1 H) 7.25 – 7.34 (m, 2 H) 7.18 (d, *J*=2.0 Hz, 1 H) 7.07 – 7.13 (m, 2 H) 6.91 (t, *J*=8.3 Hz, 1 H) 6.83 (d, *J*=8.3 Hz, 1 H).

4-Phenyl-2,11-dihydrobenzo[2,3][1,4]oxazepino[5,6,7-*cd*]indazole (9g).

The title compound was prepared according to General Procedure A on a 40-mg scale using **8** and chlorobenzene. The crude material was purified by flash chromatography (40% EtOAc:hexanes) to afford the title compound as a tan solid (14 mg, 46%). LCMS [M+H]⁺ 300.06 m/z; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 12.23 (s, 1 H) 9.48 (s, 1 H) 7.75 (d, *J*=7.3 Hz, 2 H) 7.49 (t, *J*=7.3 Hz, 2 H) 7.40 (d, *J*=7.3 Hz, 1 H) 7.24 – 7.32 (m, 3 H) 7.06 (t, *J*=8.1 Hz, 1 H) 7.01 (s, 1 H) 6.88 (dd, *J*=8.1, 6.60 Hz, 1 H).

6-(2,11-Dihydrobenzo[2,3][1,4]oxazepino[5,6,7-*cd*]indazol-4-yl)-*N*⁴-methylpyrimidine-2,4-diamine formate (9j).

The title compound was prepared according to General Procedure a on a 50-mg scale using **8** and 6-chloro-*N*⁴-methylpyrimidine-2,4-diamine. The crude material was purified by flash chromatography (20–100% EtOAc:hexanes – 0–20% MeOH:EtOAc), then repurified by preparative HPLC (5–95% acetonitrile:water) to afford the formate salt of the title compound as a solid (6 mg, 13%). LCMS [M+H]⁺ 346.09 m/z; ¹H NMR (500 MHz, METHANOL-*d*₄) δ ppm 8.47 (br. s., 1 H) 7.46 (br. s., 1 H) 7.26 (d, *J*=7.81 Hz, 1 H) 7.16 (d, *J*=8.30 Hz, 1 H) 7.01 – 7.11 (m, 2 H) 6.91 (t, *J*=7.81 Hz, 1 H) 6.34 (s, 1 H) 3.00 (s, 3 H).

6-(2,11-Dihydrobenzo[2,3][1,4]oxazepino[5,6,7-*cd*]indazol-4-yl)-N⁴-ethylpyrimidine-2,4-diamine (9k).

The title compound was prepared according to General Procedure A on a 40-mg scale using **8** and 6-chloro-*N*⁴-ethylpyrimidine-2,4-diamine. The crude material was purified by flash chromatography (0–20% MeOH:DCM) to afford the title compound as a solid (20 mg, 50%). LCMS [M+H]⁺ 360.39 m/z; ¹H NMR (500 MHz, METHANOL-*d*₄) δ ppm 7.52 (s, 1 H) 7.26 (dd, *J*=7.8, 1.5 Hz, 1 H) 7.10 – 7.17 (m, 2 H) 7.03 (td, *J*=7.6, 1.5 Hz, 1 H) 6.89 (td, *J*=7.8, 1.5 Hz, 1 H) 6.26 (s, 1 H) 3.40 (q, *J*=7.2 Hz, 2 H) 1.24 (t, *J*=7.3 Hz, 3 H).

6-(2,11-Dihydrobenzo[2,3][1,4]oxazepino[5,6,7-*cd*]indazol-4-yl)-*N*⁴-isopropylpyrimidine-2,4-diamine formate (9l).

The title compound was prepared according to General Procedure A on a 50-mg scale **8** and using 6-chloro-*N*⁴-isopropylpyrimidine-2,4-diamine. The crude material was purified by flash chromatography (20–100% EtOAc:hexanes – 0–20% MeOH:DCM), then repurified by preparative HPLC (5–95% acetonitrile:water) to afford the formate salt of the title compound as a solid (8 mg, 17%). LCMS [M+H]⁺ 374.09 m/z; ¹H NMR (500 MHz, METHANOL-*d*₄) δ ppm 8.50 (s, 1 H) 7.46 (s, 1 H) 7.27 (dd, *J*=8.8, 1.46 Hz, 1 H) 7.17 (dd, *J*=8.3, 1.5 Hz, 1 H) 7.03 – 7.10 (m, 2 H) 6.92 (t, *J*=6.4 Hz, 1 H) 6.31 (s, 1 H) 4.21 – 4.39 (m, 1 H) 1.27 (d, *J*=6.8 Hz, 6 H).

6-(2,11-Dihydrobenzo[2,3][1,4]oxazepino[5,6,7-*cd*]indazol-4-yl)-*N*⁴,*N*⁴-dimethylpyrimidine-2,4-diamine (9o).

The title compound was prepared according to General Procedure A on a 35-mg scale using **8** and 6-chloro-*N*⁴,*N*⁴-dimethylpyrimidine-2,4-diamine. The crude material was purified by flash chromatography (4–20% MeOH:DCM) to afford the title compound as a solid (16 mg, 35%). LCMS [M+H]⁺ 360.39 m/z; ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 12.35 (s, 1 H) 9.53 (s, 1 H) 7.79 (s, 1 H) 7.41 (s, 1 H) 7.24 – 7.31 (m, 2 H) 7.06 (td, *J*=6.8, 1.5 Hz, 1 H) 6.90 (td, *J*=7.8, 1.5 Hz, 1 H) 6.55 (s, 1 H) 6.25 (br. s, 2 H) 3.11 (s, 6 H).

4-(2,11-Dihydrobenzo[2,3][1,4]oxazepino[5,6,7-*cd*]indazol-4-yl)-6-morpholinopyrimidin-2-amine (9p).

The title compound was prepared according to General Procedure A on a 50-mg scale using **8** and 4-chloro-6-morpholinopyrimidin-2-amine. The crude material was purified by flash chromatography (4–20% MeOH:DCM), then re-purified by preparative HPLC (5–95% acetonitrile:water) to afford the title compound as a solid (5 mg, 10%). LCMS [M+H]⁺ 402.09 m/z; ¹H NMR (500 MHz, Acetone) δ ppm 11.42 (br. s, 1 H) 8.52 (s, 1 H) 7.91 (d, *J*=1.0 Hz, 1 H) 7.49 (d, *J*=1.0 Hz, 1 H) 7.33 (ddd, *J*=13.7, 7.8, 1.5 Hz, 2 H) 7.09 (ddd, *J*=8.3, 7.1, 1.7 Hz, 1 H) 6.93 (td, *J*=7.3, 2.0 Hz, 1 H) 6.71 (s, 1 H) 5.69 (br. s., 2 H) 3.70 – 3.76 (m, 4 H) 3.66 – 3.70 (m, 4 H).

4-(2,11-Dihydrobenzo[2,3][1,4]oxazepino[5,6,7-*cd*]indazol-4-yl)-6-(pyrrolidin-1-yl)pyrimidin-2-amine formate (9q).

The title compound was prepared according to General Procedure A on a 50-mg scale using **8** and 4-chloro-6-(pyrrolidin-1-yl)pyrimidin-2-amine. The crude material was purified by

flash chromatography (4–20% MeOH:DCM), then re-purified by preparative HPLC (5–95% acetonitrile:water) to afford the formate salt of the title compound as a solid (9 mg, 18%). LCMS [M+H]⁺ 386.09 m/z; ¹H NMR (500 MHz, Acetone-*d*₆) δ ppm 11.38 (br. s, 1 H) 8.50 (s, 1 H) 8.12 (s, 1 H) 7.88 (s, 1 H) 7.48 (d, *J*=0.98 Hz, 1 H) 7.34 (t, *J*=7.81 Hz, 2 H) 7.08 (t, *J*=7.32 Hz, 1 H) 6.94 (t, *J*=6.84 Hz, 1 H) 6.39 (s, 1 H) 5.53 (br. s., 2 H) 3.52 (t, *J*=5.37 Hz, 4 H) 2.00 (br. s., 4 H).

4-(2,11-Dihydrobenzo[2,3][1,4]oxazepino[5,6,7-*cd*]indazol-4-yl)-6-(piperidin-1-yl)pyrimidin-2-amine formate (9r).

The title compound was prepared according to General Procedure A on a 50-mg scale using **8** and 4-chloro-6-(piperidin-1-yl)pyrimidin-2-amine. The crude material was purified by flash chromatography (20–100% EtOAc:hexanes – 0–20% MeOH:EtOAc), then repurified by preparative HPLC (5–95% acetonitrile:water) to afford the formate salt of the title compound as a solid (7 mg, 14%). LCMS [M+H]⁺ 400.13 m/z; ¹H NMR (500 MHz, METHANOL-*d*₄) δ ppm 8.48 – 8.52 (m, 1 H) 7.52 (s, 1 H) 7.28 (dd, *J*=8.8, 1.46 Hz, 1 H) 7.14 – 7.19 (m, 2 H) 7.06 (td, *J*=7.3, 1.5 Hz, 1 H) 6.91 (td, *J*=7.3, 2.0 Hz, 1 H) 6.62 (s, 1 H) 3.80 (t, *J*=5.4 Hz, 4 H) 1.73 – 1.79 (m, 1 H) 1.63 – 1.71 (m, 4 H).

4-(2,11-Dihydrobenzo[2,3][1,4]oxazepino[5,6,7-*cd*]indazol-4-yl)-6-(4-methylpiperazin-1-yl)pyrimidin-2-amine (9s).

The title compound was prepared according to General Procedure A on a 20-mg scale using **8** and 4-chloro-6-(4-methylpiperazin-1-yl)pyrimidin-2-amine. The crude material was purified by flash chromatography (0–60% 10% NH₄OH in MeOH:DCM) to afford the title compound as a solid (7 mg, 19%). LCMS [M+H]⁺ 415.47 m/z; ¹H NMR (500 MHz, METHANOL-*d*₄) δ ppm 7.58 (s, 1 H) 7.27 (dd, *J*=7.8, 1.5 Hz, 1 H) 7.23 (s, 1 H) 7.16 (dd, *J*=8.8, 1.5 Hz, 1 H) 7.06 (td, *J*=8.3, 1.5 Hz, 1 H) 6.92 (td, *J*=8.8, 1.5 Hz, 1 H) 6.55 (s, 1 H) 3.76 (t, *J*=4.9 Hz, 4 H) 2.54 (t, *J*=4.9 Hz, 4 H) 2.36 (s, 3 H).

3-Bromo-1-fluoro-10-methyldibenzo[*b,f*][1,4]oxazepin-11(10*H*)-one (10).

Compound **4** (482 mg, 1.56 mmol) was dissolved in dry DMF (6 ml, 0.27 M). Sodium hydride (129 mg, 3.23 mmol) was added and the reaction was stirred for 30 min at room temperature. Methyl iodide (0.15 mL, 2.41 mmol) was added dropwise at 0 °C and the reaction was stirred for an additional 4 h, warming to room temperature. The reaction was quenched with saturated aqueous ammonium chloride and extracted three times with EtOAc. The combined organic layers were washed once with water and once with brine, dried with sodium sulfate, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (10–20% EtOAc:hexanes) to afford the title compound as a white solid (267 mg, 53%). LCMS [M+H]⁺ 321.98 m/z (⁷⁹Br), 323.99 m/z (⁸¹Br); ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.62 (s, 1 H) 7.51 – 7.59 (m, 2 H) 7.43 (d, *J*=8.3 Hz, 1 H) 7.33 (dd, *J*=7.8 Hz, 1 H) 7.26 (dd, *J*=7.8 Hz, 1 H) 3.49 (s, 3 H).

3-Bromo-1-fluoro-10-methyldibenzo[*b,f*][1,4]oxazepine-11(10*H*)-thione (11).

Compound **10** (280 mg, 0.869 mmol) was dissolved in toluene (3.5 ml, 0.25 M) and phosphorus pentasulfide (291 mg, 1.31 mmol) was added. The reaction was refluxed at 100

°C overnight, then additional phosphorus pentasulfide (256 mg, 1.15 mmol) was added. The reaction continued to reflux at 100 °C for an additional 24 h. The reaction was cooled to room temperature and the solvent was removed under reduced pressure. The crude residue was purified by flash chromatography (0–25% methyl *tert*-butyl ether:hexanes) to afford the title compound as a yellow solid (200 mg, 68%). LCMS [M+H]⁺ 337.94 m/z (⁷⁹Br), 339.93 m/z (⁸¹Br); ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.66 (dd, *J*=7.3, 2.0 Hz, 1 H) 7.58 (t, *J*=1.7 Hz, 1 H) 7.52 (dd, *J*=10.0, 2.0 Hz, 1 H) 7.44 – 7.48 (m, 1 H) 7.32 – 7.40 (m, 2 H) 3.93 (s, 3 H).

4-Bromo-11-methyl-2,11-dihydrobenzo[2,3][1,4]oxazepino[5,6,7-*cd*]indazole (12).

Compound **11** (200 mg, 0.620 mmol) was suspended in dioxane (3.1 mL, 0.2 M) and hydrazine monohydrate (0.06 mL, 1.22 mmol) was added. The reaction was refluxed for 3 h at 85 °C. After cooling to room temperature, the solvent was removed under reduced pressure. The resulting crude residue was purified by flash chromatography (20–30% EtOAc:hexanes) to afford the title compound as an orange solid (125 mg, 63%). LCMS [M+H]⁺ 315.93 m/z (⁷⁹Br), 317.92 m/z (⁸¹Br); ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 12.36 (s, 1 H) 7.31 – 7.35 (m, 3 H) 7.26 (td, *J*=7.8, 1.5 Hz, 1 H) 7.08 (td, *J*=6.8, 1.5 Hz, 1 H) 6.91 (d, *J*=1.0 Hz, 1 H) 3.45 (s, 3 H).

1-(4-Bromo-11-methylbenzo[2,3][1,4]oxazepino[5,6,7-*cd*]indazol-2(11*H*)-yl)ethan-1-one (13).

Acetic anhydride (1.1 mL, 11.64 mmol) was added to **12** (125 mg, 0.395 mmol). The reaction was refluxed at 100 °C for 3 h, then cooled to room temperature. Upon cooling, a white precipitate was observed and collected by vacuum filtration (washed with water) to afford the title compound as a white solid (126 mg, 89%). LCMS [M+H]⁺ 357.96 m/z (⁷⁹Br), 359.93 m/z (⁸¹Br); ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.08 (s, 1 H) 7.42 (d, *J*=7.8 Hz, 1 H) 7.39 (s, 1 H) 7.36 (d, *J*=7.8 Hz, 1 H) 7.32 (t, *J*=7.3 Hz, 1 H) 7.18 (t, *J*=8.3 Hz, 1 H) 3.52 (s, 3 H) 2.63 (s, 3 H).

1-(11-Methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[2,3][1,4]oxazepino [5,6,7-*cd*]indazol-2(11*H*)-yl)ethan-1-one (14).

Compound **13** (95 mg, 0.265 mmol), potassium acetate (92 mg, 0.937 mmol), bis(pinacolato)diboron (102 mg, 0.402 mmol), and PdCl₂(dppf) (12 mg, 14.7 μmol) were combined in a reaction vial that was filled with nitrogen and evacuated three times. Dry, degassed dioxane (2.2 mL, 0.12 M) was added and the reaction was run in the microwave (145 °C) for 1 h. The reaction mixture was diluted with EtOAc and filtered through Celite®, and the crude residue was purified by flash chromatography (0–20% EtOAc:hexanes) to afford the title compound as an off-white solid (90 mg, 83%). LCMS [M+H]⁺ 406.09 m/z; ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.24 (s, 1 H) 7.38 – 7.43 (m, 2 H) 7.26 – 7.32 (m, 2 H) 7.16 (td, *J*=7.6, 1.5 Hz, 1 H) 3.53 (s, 3 H) 2.64 (s, 3 H) 1.16 (s, 12 H).

4-(11-Methyl-2,11-dihydrobenzo[2,3][1,4]oxazepino[5,6,7-*cd*]indazol-4-yl)pyrimidin-2-amine (15).

The title compound was prepared according to General Procedure A on a 54-mg scale using **14** and 2-amino-4-chloropyrimidine. The crude material was purified twice by flash

chromatography (20–100% EtOAc:DCM - 0–5% MeOH:EtOAc, then 1–5% 1% NH₄OH/MeOH:EtOAc) and once by preparative HPLC (5–95% water:acetonitrile) to afford the title compound as a yellow solid (4 mg, 10%). LCMS [M+H]⁺ 331.07 m/z; ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 12.45 (s, 1 H) 8.32 (d, *J*=5.4 Hz, 1 H) 7.82 (s, 1 H) 7.45 (s, 1 H) 7.32 – 7.38 (m, 2 H) 7.25 (t, *J*=7.3 Hz, 1 H) 7.22 (d, *J*=5.4 Hz, 1 H) 7.08 (t, *J*=8.3 Hz, 1 H) 6.73 (s, 2 H) 3.48 (s, 3 H).

4-Bromo-2-methyl-2,11-dihydrobenzo[2,3][1,4]oxazepino[5,6,7-*cd*]indazole (16).

Compound **5** (199 mg, 0.614 mmol) was suspended in dioxane (2.5 mL, 0.25 M) and methyl hydrazine (0.10 mL, 1.90 mmol) was added. The reaction was refluxed for 4 h at 85 °C, then stopped and cooled to room temperature. Upon cooling, a precipitate was observed and collected by vacuum filtration (washed with water) to afford the title compound as an off-white solid (83 mg, 43%). LCMS [M+H]⁺ 315.95 m/z (⁷⁹Br), 317.96 m/z (⁸¹Br); ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 9.56 (s, 1 H) 7.55 (s, 1 H) 7.21 – 7.25 (m, 2 H) 7.07 (ddd, *J*=8.2, 7.0, 1.5 Hz, 1 H) 6.86 – 6.91 (m, 2 H) 3.87 (s, 3 H).

2-Methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,11-dihydrobenzo[2,3][1,4]oxazepino[5,6,7-*cd*]indazole (17).

Compound **S6** (83 mg, 0.262 mmol), potassium acetate (91 mg, 0.927 mmol), bis(pinacolato)diboron (101 mg, 0.398 mmol), and PdCl₂(dppf)·CH₂Cl₂ (12 mg, 0.015 mmol) were combined in a reaction vial that was filled with nitrogen and evacuated three times. Dry, degassed dioxane (2.7 mL, 0.15 M) was added and the reaction was run in the microwave (140 °C) for 30 min. The reaction was diluted with EtOAc, filtered through celite, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (20–60% EtOAc:hexanes) to afford the title compound as a yellow solid (60 mg, 63%). LCMS [M+H]⁺ 364.18 m/z; ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 9.49 (s, 1 H) 7.49 (s, 1 H) 7.25 (d, *J*=7.8 Hz, 2 H) 7.05 (td, *J*=8.3, 1.5 Hz, 1 H) 6.93 (s, 1 H) 6.87 (td, *J*=8.3, 1.5 Hz, 1 H) 3.92 (s, 3 H) 1.33 (s, 12 H).

4-(2-Methyl-2,11-dihydrobenzo[2,3][1,4]oxazepino[5,6,7-*cd*]indazol-4-yl)pyrimidin-2-amine (18).

The title compound was prepared according to General Procedure A on a 60-mg scale using **17** and 2-amino-4-chloropyrimidine. The crude material was purified by flash chromatography (0–100% EtOAc:hexanes - 0–10% MeOH:EtOAc), then by preparative HPLC (95–30% water:acetonitrile) to afford the title compound as a yellow solid (6 mg, 10%). LCMS [M+H]⁺ 331.12 m/z; ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 9.55 (s, 1 H) 8.35 (d, *J*=5.4 Hz, 1 H) 7.95 (s, 1 H) 7.50 (s, 1 H) 7.30 (d, *J*=4.9 Hz, 1 H) 7.24 – 7.29 (m, 2 H) 7.06 (t, *J*=7.8 Hz, 1 H) 6.89 (t, *J*=7.81 Hz, 1 H) 6.73 (s, 2 H) 3.96 (s, 3 H).

4-(2,11-Dihydrobenzo[2,3][1,4]oxazepino[5,6,7-*cd*]indazol-4-yl)-*N,N*-dimethylpyrimidin-2-amine (19).

The title compound was prepared according to General Procedure A on a 100-mg scale using **8** and 4-chloro-*N,N*-dimethylpyrimidin-2-amine. The crude material was purified by flash chromatography (0–100% EtOAc:hexanes), then repurified by preparative HPLC (95–

5% water:acetonitrile) to afford the final compound as a yellow solid (7 mg, 8%). LCMS [M+H]⁺ 345.00 m/z; ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 12.38 (s, 1 H) 9.55 (s, 1 H) 8.43 (d, *J*=4.9 Hz, 1 H) 7.90 (d, *J*=1.0 Hz, 1 H) 7.49 (d, *J*=1.0 Hz, 1 H) 7.25 – 7.32 (m, 3 H) 7.07 (td, *J*=8.3, 1.5 Hz, 1 H) 6.89 (td, *J*=8.3, 1.5 Hz, 1 H) 3.23 (s, 6 H).

4-(2,11-Dihydrobenzo[2,3][1,4]oxazepino[5,6,7-*cd*]indazol-4-yl)-*N*-methylpyrimidin-2-amine (20).

The title compound was prepared according to General Procedure B on a 75-mg scale using **8** and 4-bromo-*N*-methylpyrimidin-2-amine. The crude material was purified by flash chromatography (70% EtOAc:hexanes) to afford the title compound as a yellow solid (13 mg, 21%). LCMS [M+H]⁺ 331.12 m/z; ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 12.38 (s, 1 H) 9.53 (s, 1 H) 8.36 (s, 1 H) 7.87 (s, 1 H) 7.47 (s, 1 H) 7.28 (dd, *J*=7.8, 1.5 Hz, 2 H) 7.24 (d, *J*=4.9 Hz, 1 H) 7.13 – 7.20 (m, 1 H) 7.06 (td, *J*=8.8, 7.3 Hz, 1 H) 6.88 (td, *J*=9.3, 6.3 Hz, 1 H) 2.90 (br. s., 3 H).

4-Bromo-2,6-difluoro-*N*-(2-hydroxyethyl)-*N*-(4-methoxybenzyl)benzamide (21).

2-((4Methoxybenzyl)amino)ethan-1-ol (2.32 g, 12.8 mmol) was dissolved in DCM (30 ml, 0.43 M) and TEA (3.80 ml, 27.3 mmol) was added. Compound **2** (2.83 g, 11.1 mmol) was dissolved in DCM (15 ml, 0.74 M) and this solution was added to the reaction mixture dropwise at 0 °C. The reaction was allowed to warm to room temperature and stirred overnight. The reaction mixture was diluted with DCM and washed once with 1M HCl, once with water, and once with brine. The organic layer was dried with sodium sulfate and concentrated under reduced pressure. The title compound was isolated by flash chromatography (20–50% EtOAc:hexanes) as a yellow oil (3.81 g, 86%). LCMS [M+H]⁺ 399.86 m/z (⁷⁹Br), 401.90 m/z (⁸¹Br).

8-Bromo-6-fluoro-4-(4-methoxybenzyl)-3,4-dihydrobenzo[*f*][1,4]oxazepin-5(2*H*)-one (22).

Sodium hydride (766 mg, 19.2 mmol) was suspended in dry DMF (50 ml, 0.38 M). Compound **14** (3.81 g, 9.53 mmol) was dissolved in dry DMF (50 ml, 0.19 M) and added slowly to the sodium hydride suspension. The reaction was stirred at room temperature overnight. The reaction mixture was diluted with DCM and washed three times with saturate aqueous NaHCO₃, once with water, and once with brine. The organic layer was dried with sodium sulfate and concentrated under reduced pressure to afford the title compound as a solid (3.06 g, 84%). LCMS [M+H]⁺ 379.99 m/z (⁷⁹Br), 381.99 m/z (⁸¹Br); ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.46 (dd, *J*=9.3, 2.0 Hz, 1 H) 7.29 (d, *J*=8.3 Hz, 2 H) 7.19 (d, *J*=1.5 Hz, 1 H) 6.93 (d, *J*=8.3 Hz, 2 H) 4.66 (s, 2 H) 4.11 (t, *J*=5.6 Hz, 2 H) 3.74 (s, 3 H) 3.50 (t, *J*=5.6 Hz, 2 H).

8-Bromo-6-fluoro-3,4-dihydrobenzo[*f*][1,4]oxazepin-5(2*H*)-one (23).

Compound **22** (1.65 g, 4.33 mmol) was taken up in 3:1 acetonitrile:water (48 ml, 0.09 M) and cerium ammonium nitrate (7.13 g, 13.0 mmol) was added, upon which the reaction mixture turned orange. The reaction was stirred at room temperature and monitored by LCMS. After ~3 h, the reaction mixture was diluted with water and extracted three times with EtOAc. The combined organic layers were washed once with sat. aq. NaHCO₃ and

once with brine. The combined organic layers were dried with sodium sulfate and concentrated under reduced pressure. The crude residue was purified by flash chromatography (20–80% EtOAc:hexanes) to afford the final product as a solid (410 mg, 36%). LCMS [M+H]⁺ 259.96 m/z (⁷⁹Br), 261.96 m/z (⁸¹Br); ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.56 (br. s., 1 H) 7.43 (dd, *J*=9.5, 1.71 Hz, 1 H) 7.20 (t, *J*=1.7 Hz, 1 H) 4.21 (t, *J*=5.6 Hz, 2 H) 3.26 (q, *J*=5.5 Hz, 2 H).

8-Bromo-6-fluoro-3,4-dihydrobenzo[*f*][1,4]oxazepine-5(2*H*)-thione (24).

Compound **23** (410 mg, 1.58 mmol) was suspended in toluene (30 ml, 0.05 M) and Lawesson's reagent (702 mg, 1.74 mmol) was added. The reaction was refluxed overnight at 100 °C. The reaction mixture was concentrated under reduced pressure to a yellow residue, which was then purified by flash chromatography (0–50% EtOAc:hexanes) to afford the title compound as a solid (245 mg, 56%). LCMS [M+H]⁺ 275.94 m/z (⁷⁹Br), 277.96 m/z (⁸¹Br); ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 10.93 (br. s., 1 H) 7.47 (dd, *J*=9.3, 1.95 Hz, 1 H) 7.22 (t, *J*=1.5 Hz, 1 H) 4.27 (t, *J*=5.9 Hz, 2 H) 3.42 (q, *J*=5.9 Hz, 2 H).

4-Bromo-2,7,8,9-tetrahydro-[1,4]oxazepino[5,6,7-*cd*]indazole (25).

Compound **24** (245 mg, 0.887 mmol) was dissolved in dioxane (3.0 ml, 0.30 M) and hydrazine monohydrate (0.10 ml, 2.0 mmol) was added. The reaction was refluxed at 85 °C for 3 h. The reaction mixture was concentrated under reduced pressure, leaving an orange residue. The product was purified by flash chromatography (0–5% MeOH:DCM) to afford the title compound as a solid (214 mg, 95%). LCMS [M+H]⁺ 253.96 m/z (⁷⁹Br), 255.99 m/z (⁸¹Br); ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 11.75 (s, 1 H) 6.99 (d, *J*=1.5 Hz, 1 H) 6.46 (br. s., 1 H) 6.45 (d, *J*=1.5 Hz, 1 H) 4.32 – 4.40 (m, 2 H) 3.39 – 3.45 (m, 2 H).

1-(4-Bromo-8,9-dihydro-[1,4]oxazepino[5,6,7-*cd*]indazol-2(7*H*)-yl)ethan-1-one (26).

Acetic anhydride (2.5 ml, 27 mmol) was added to **25** (214 mg, 0.842 mmol) and the reaction was refluxed at 100 °C. After ~3 h, the reaction was cooled further to 0 °C and the title compound was isolated as a yellow solid by vacuum filtration (151 mg, 60%). LCMS [M+H]⁺ 295.99 m/z (⁷⁹Br), 297.96 m/z (⁸¹Br); ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.99 (d, *J*=1.5 Hz, 1 H) 7.45 (br. s., 1 H) 6.99 (d, *J*=1.5 Hz, 1 H) 4.41 – 4.45 (m, 2 H) 3.51 – 3.55 (m, 2 H) 3.32 (s, 3 H).

1-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-8,9-dihydro-[1,4]oxazepino[5,6,7-*cd*]indazol-2(7*H*)-yl)ethan-1-one (27).

Compound **26** (151 mg, 0.510 mmol), potassium acetate (175 mg, 1.78 mmol), bis(pinacolato)diboron (193 mg, 0.760 mmol), and PdCl₂(dppf) (20 mg, 0.06 mmol) were combined in a reaction vial that was filled with nitrogen and evacuated three times. Dry, degassed dioxane (3.4 ml, 0.15 M) was added and the reaction was run in the microwave (145 °C) for 1 h. The reaction mixture was then diluted with EtOAc, filtered through celite, and concentrated under reduced pressure. The crude material was purified by flash chromatography (20–75% EtOAc:hexanes) to afford the title compound as a solid (139 mg, 79%). LCMS [M+H]⁺ 344.12 m/z; ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.18 (s, 1 H)

7.40 (br. s., 1 H) 6.97 (s, 1 H) 4.38 – 4.43 (m, 2 H) 3.53 (m, $J=4.9$ Hz, 2 H) 2.51 (s, 3 H) 1.31 (s, 12 H).

6-(2,7,8,9-Tetrahydro-[1,4]oxazepino[5,6,7-cd]indazol-4-yl)pyrimidine-2,4-diamine (28a).

The title compound was prepared according to General Procedure A on a 29-mg scale using **27** and 2,6-diamino-4-chloropyrimidine. The crude material was purified by flash chromatography (3–10% 15% NH_4OH in $\text{MeOH}:\text{DCM}$), then re-purified by preparative HPLC (5–95% acetonitrile:water) to afford the title compound as a solid (8 mg, 33%). LCMS $[\text{M}+\text{H}]^+$ 284.12 m/z; ^1H NMR (500 MHz, Acetone) δ ppm 11.10 (br. s, 1 H) 8.14 (s, 1 H) 7.60 (s, 1 H) 6.97 (d, $J=1.0$ Hz, 1 H) 6.41 (s, 1 H) 5.97 (br. s, 2 H) 5.68 (br. s, 2 H) 4.41 – 4.47 (m, 2 H) 3.60 (m, $J=6.3$ Hz, 2 H).

6-(2,7,8,9-Tetrahydro-[1,4]oxazepino[5,6,7-cd]indazol-4-yl)pyrimidin-4-amine (28b).

The title compound was prepared according to General Procedure A on a 29-mg scale using **27** and 4-amino-6-chloropyrimidine. The crude material was purified by flash chromatography (3–10% $\text{MeOH}:\text{DCM}$), then re-purified by preparative HPLC (5–95% acetonitrile:water) to afford the title compound as a solid (3 mg, 12%). LCMS $[\text{M}+\text{H}]^+$ 269.11 m/z; ^1H NMR (500 MHz, Acetone) δ ppm 11.03 (br. s, 1 H) 8.47 (s, 1 H) 7.67 (s, 1 H) 7.04 (s, 2 H) 6.21 (br. s, 2 H) 5.71 (br. s, 1 H) 4.44 – 4.48 (m, 2 H) 3.59 – 3.63 (m, 2 H).

4-(2,6-Diaminopyrimidin-4-yl)-2-fluorobenzonitrile (30a).

(4-Cyano-3-fluorophenyl)boronic acid **29** (75 mg, 0.46 mmol) and 6-chloropyrimidin-2,4-diamine (67 mg, 0.46 mmol) were combined in a reaction vial and dissolved in dioxane (3.0 mL, 0.15 M), followed by the addition of saturated aqueous NaHCO_3 (0.75 mL). The reaction vial was purged with nitrogen for 10 min and $\text{Pd}(\text{PPh}_3)_4$ (28 mg, 0.024 mmol) was added. The reaction was run at 95 °C for 3 h. Upon completion, the reaction mixture was diluted with EtOAc, filtered through Celite®, and concentrated *in vacuo*. The crude material was purified by flash chromatography (0–7% $\text{MeOH}:\text{DCM}$) to afford the title compound as a yellow solid (75 mg, 72%). LCMS $[\text{M}+\text{H}]^+$ 230.03 m/z; ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 8.00 (t, $J=7.3$ Hz, 1 H) 7.95 (d, $J=11.2$ Hz, 1 H) 7.88 (dd, $J=8.8, 1.47$ Hz, 1 H) 6.54 (br. s., 2 H) 6.29 (s, 1 H) 6.12 (s, 2 H).

4-(6-Aminopyrimidin-4-yl)-2-fluorobenzonitrile (30b).

(4-Cyano-3-fluorophenyl)boronic acid **29** (75 mg, 0.46 mmol) and 6-chloropyrimidin-4-amine (60 mg, 0.46 mmol) were combined in a reaction vial and dissolved in dioxane (3.0 mL, 0.15 M), followed by the addition of saturated aqueous NaHCO_3 (0.75 mL). The reaction vial was purged with nitrogen for 10 min and $\text{Pd}(\text{PPh}_3)_4$ (27 mg, 0.023 mmol) was added. The reaction was run at 95 °C for 3 h. Upon completion, the reaction mixture was diluted with EtOAc, filtered through celite, and concentrated *in vacuo*. The crude material was purified by flash chromatography (70–100% EtOAc:hexanes) to afford the title compound as an off-white solid (42 mg, 43%). LCMS $[\text{M}+\text{H}]^+$ 214.95 m/z; ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 8.49 (s, 1 H) 8.02 – 8.09 (m, 2 H) 7.98 (d, $J=7.8$ Hz, 1 H) 7.13 (s, 2 H) 6.99 (s, 1 H).

4-(2-Aminopyrimidin-4-yl)-2-fluorobenzonitrile (30c).

(4-Cyano-3-fluorophenyl)boronic acid **29** (75 mg, 0.46 mmol) and 4-chloropyrimidin-2-amine (59 mg, 0.46 mmol) were combined in a reaction vial and dissolved in dioxane (3.0 mL, 0.15 M), followed by the addition of saturated aqueous NaHCO₃ (0.75 mL). The reaction vial was purged with nitrogen for 10 min and Pd(PPh₃)₄ (27 mg, 0.023 mmol) was added. The reaction was run at 95 °C for 3 h. Upon completion, the reaction mixture was diluted with EtOAc, filtered through Celite®, and concentrated *in vacuo*. The crude material was purified by flash chromatography (0–50% EtOAc:hexanes) to afford the title compound as an off-white solid (93 mg, 97%). LCMS [M+H]⁺ 215.01 m/z; ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.42 (d, *J*=5.4 Hz, 1 H) 8.17 (d, *J*=11.7 Hz, 1 H) 8.11 (s, 2 H) 7.29 (d, *J*=4.9 Hz, 1 H) 6.88 (s, 2 H).

6-(3-Amino-1*H*-indazol-6-yl)pyrimidine-2,4-diamine (31a).

Compound **30a** (50 mg, 0.218 mmol) was suspended in EtOH (3.7 mL, 0.06 M) and hydrazine monohydrate (0.900 mL, 18.33 mmol) was added. The reaction was run overnight at 95 °C. Upon cooling, an off-white precipitate was observed and collected by vacuum filtration to afford the title compound as an off-white solid (29 mg, 55%). LCMS [M+H]⁺ 242.05 m/z; ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 11.51 (s, 1 H) 7.81 (s, 1 H) 7.69 (d, *J*=8.3 Hz, 1 H) 7.39 (d, *J*=8.8 Hz, 1 H) 6.33 (br. s., 2 H) 6.24 (s, 1 H) 5.95 (br. s., 2 H) 5.37 (s, 2 H).

6-(6-Aminopyrimidin-4-yl)-1*H*-indazol-3-amine (31b).

Compound **30b** (42 mg, 0.196 mmol) was suspended in EtOH (3.3 mL, 0.06 M) and hydrazine monohydrate (0.800 mL, 16.30 mmol) was added. The reaction was run overnight at 95 °C. Upon cooling, a yellow precipitate was observed and collected by vacuum filtration to afford the title compound as a yellow solid (25 mg, 57%). LCMS [M+H]⁺ 227.01 m/z; ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 11.58 (s, 1 H) 8.44 (d, *J*=1.0 Hz, 1 H) 7.88 (s, 1 H) 7.75 (d, *J*=8.3 Hz, 1 H) 7.48 (dd, *J*=8.6, 1.22 Hz, 1 H) 6.92 (d, *J*=1.0 Hz, 1 H) 6.89 (s, 2 H) 5.42 (br. s., 2 H).

6-(2-Aminopyrimidin-4-yl)-1*H*-indazol-3-amine (31c).

Compound **30c** (50 mg, 0.233 mmol) was suspended in EtOH (3.7 mL, 0.06 M) and hydrazine monohydrate (0.900 mL, 18.33 mmol) was added. The reaction was run overnight at 95 °C. Upon cooling, a yellow precipitate was observed and collected by vacuum filtration to afford the title compound as a yellow solid (44 mg, 83%). LCMS [M+H]⁺ 227.03 m/z; ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 11.62 (s, 1 H) 8.29 (d, *J*=4.9 Hz, 1 H) 7.98 (s, 1 H) 7.76 (d, *J*=8.3 Hz, 1 H) 7.58 (dd, *J*=8.6, 1.22 Hz, 1 H) 7.16 (d, *J*=5.4 Hz, 1 H) 6.66 (s, 2 H) 5.44 (br. s., 2 H).

6-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazole (33).

4-Bromoindazole **32** (251 mg, 1.27 mmol), bis(pinacolato)diboron (480 mg, 1.89 mmol), potassium acetate (433 mg, 4.41 mmol) and PdCl₂(dppf)·CH₂Cl₂ (53 mg, 0.065 mmol) were combined in a microwave vial that was filled with nitrogen and evacuated three times. Dry, degassed dioxane (10 mL, 0.13 M) was added and the reaction was run in the microwave

(145 °C) for 3 h. The reaction was diluted with EtOAc, filtered through celite, and concentrated under reduced pressure. The crude material was purified by flash chromatography (20–50% EtOAc:hexanes) to afford the title compound as a solid (183 mg, 59%). LCMS [M+H]⁺ 245.11 m/z; ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 13.16 (s, 1 H) 8.09 (s, 1 H) 7.86 (s, 1 H) 7.75 (d, *J*=7.8 Hz, 1 H) 7.36 (d, *J*=7.8 Hz, 1 H) 1.32 (s, 12 H).

6-(1*H*-Indazol-6-yl)pyrimidine-2,4-diamine (34a).

The title compound was prepared according to General Procedure A on a 54-mg scale using **33** and 2,6-diamino-4-chloropyrimidine. The crude material was purified by flash chromatography (0–10% 10% NH₄OH in MeOH:DCM) to afford the title compound as a solid (16 mg, 43%). LCMS [M+H]⁺ 227.08 m/z; ¹H NMR (399 MHz, DMSO-*d*₆) δ ppm 8.11 (s, 1 H) 8.09 (s, 1 H) 7.79 (d, *J*=8.8 Hz, 1 H) 7.61 (d, *J*=9.5 Hz, 1 H) 6.38 (br. s., 2 H) 6.29 (s, 1 H) 6.00 (br. s., 2 H).

6-(1*H*-Indazol-6-yl)pyrimidin-4-amine (34b).

The title compound was prepared according to General Procedure A on a 66-mg scale using **33** and 4-amino-6-chloropyrimidine. The crude material was purified by flash chromatography (1–10% MeOH:DCM) to afford the title compound as a solid (16 mg, 28%). LCMS [M+H]⁺ 212.00 m/z; ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 13.25 (s, 1 H) 8.46 (s, 1 H) 8.18 (s, 1 H) 8.12 (s, 1 H) 7.85 (d, *J*=8.3 Hz, 1 H) 7.70 (dd, *J*=8.6, 1.2 Hz, 1 H) 6.97 (s, 1 H) 6.92 (s, 2 H).

4-(1*H*-Indazol-6-yl)pyrimidin-2-amine (34c).

The title compound was prepared according to General Procedure A on a 44-mg scale using **33** and 2-amino-4-chloropyrimidine. The crude material was purified by flash chromatography (0–10% 10% NH₄OH in MeOH:DCM) to afford the title compound as a solid. (16 mg, 43%). LCMS [M+H]⁺ 212.00 m/z; ¹H NMR (399 MHz, DMSO-*d*₆) δ ppm 8.32 (d, *J*=5.1 Hz, 1 H) 8.27 (s, 1 H) 8.13 (s, 1 H) 8.05 (d, *J*=2.2 Hz, 1 H) 7.79 – 7.88 (m, 2 H) 7.21 (d, *J*=5.1 Hz, 1 H) 6.70 (s, 2 H).

4-Bromo-2-fluorobenzoyl chloride (36).

To **35** (1.00 g, 4.57 mmol) was added thionyl chloride (3.3 mL, 45.5 mmol). The reaction was refluxed at 75 °C for 5 h. Excess thionyl chloride was removed by distillation and the product was azeotroped with toluene three times to afford the title compound as a tan solid which was used in the next reaction without further purification.

4-Bromo-2-fluoro-*N*-(2-hydroxyphenyl)benzamide (37).

2-Aminophenol (253 mg, 2.32 mmol) was dissolved in DCM (6.0 mL) and TEA (0.400 mL, 2.87 mmol) was added. Compound **36** (500 mg, 2.11 mmol) was dissolved in DCM (3.0 mL) and this solution was added to the reaction mixture dropwise at 0 °C. The reaction was allowed to warm to room temperature and stirred overnight. Upon the addition of 1M HCl, an off-white precipitate was observed; this was collected by vacuum filtration to afford the title compound as an off-white solid (341 mg, 52%). LCMS [M+H]⁺ 310.03 (⁷⁹Br) m/z, 311.99 (⁸¹Br); ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 10.04 (s, 1 H) 9.47 (d, *J*=7.3 Hz, 1 H)

8.01 (d, $J=7.8$ Hz, 1 H) 7.81 (t, $J=8.3$ Hz, 1 H) 7.76 (dd, $J=10.7, 1.5$ Hz, 1 H) 7.59 (dd, $J=8.3, 1.5$ Hz, 1 H) 7.00 (td, $J=8.8, 1.0$ Hz, 1 H) 6.92 (d, $J=7.8$ Hz, 1 H) 6.83 (t, $J=7.8$ Hz, 1 H).

3-Bromodibenzo[*b,f*][1,4]oxazepin-11(10*H*)-one (38).

Compound **37** (219 mg, 0.938 mmol) was dissolved in DMF (7.2 mL, 0.13 M) and cesium carbonate (457 mg, 1.40 mmol) was added. The reaction was stirred at 50 °C overnight. The reaction was stopped and cooled to room temperature. Upon addition of water, a gray precipitate was observed; this was collected by vacuum filtration and washed with water to afford the title compound as a gray solid (244 mg, 90%). LCMS [M+H]⁺ 290.03 m/z (⁷⁹Br), 219.99 (⁸¹Br) m/z; ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 10.62 (s, 1 H) 7.67 – 7.72 (m, 2 H) 7.54 (dd, $J=8.3, 2.0$ Hz, 1 H) 7.37 (dd, $J=7.3, 1.5$ Hz, 1 H) 7.13 – 7.23 (m, 3 H).

3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)dibenzo[*b,f*][1,4]oxazepin-11(10*H*)-one (39).

Compound **38** (244 mg, 0.841 mmol), potassium acetate (290 mg, 2.95 mmol), bis(pinacolato)diboron (322 mg, 1.23 mmol), and PdCl₂(dppf)·CH₂Cl₂ (33 mg, 0.040 mmol) were combined in a reaction vial that was filled with nitrogen and evacuated three times. Dry, degassed dioxane (9.5 mL, 0.09 M) was added and the reaction was run in the microwave (145 °C) for 30 min. The reaction was diluted with EtOAc, filtered through Celite®, and concentrated under reduced pressure. The crude material was purified by flash chromatography (20–30% EtOAc:hexanes) to afford the title compound as a tan solid (250 mg, 88%). LCMS [M+H]⁺ 338.16 m/z; ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 10.59 (s, 1 H) 7.78 (d, $J=7.3$ Hz, 1 H) 7.53 – 7.59 (m, 2 H) 7.41 (d, $J=7.8$ Hz, 1 H) 7.10 – 7.20 (m, 3 H) 1.30 (s, 12 H).

3-(2-Aminopyrimidin-4-yl)dibenzo[*b,f*][1,4]oxazepin-11(10*H*)-one (40).

Compound **39** (76 mg, 0.225 mmol), K₂CO₃ (94 mg, 0.680 mmol), and 2-amino-4-chloropyrimidine (48 mg, 0.370 mmol) were combined in a reaction vial and 3:1 dioxane:water (2.2 mL, 0.10 M) was added. The reaction was degassed for 10 min and Pd(PPh₃)₄ (15 mg, 0.013 mmol) was added. The reaction was refluxed at 100 °C for 3 h, then cooled to room temperature and stirred overnight. The reaction mixture was diluted with EtOAc and the crude material was purified by flash chromatography (50–100% EtOAc:hexanes), then repurified by preparative HPLC (5–95% water:ACN) to afford the title compound as a white solid (4 mg, 6%). LCMS [M+H]⁺ 305.11 m/z; ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 10.63 (s, 1 H) 8.54 (s, 1 H) 8.38 (d, $J=5.4$ Hz, 1 H) 8.02 (d, $J=1.5$ Hz, 1 H) 7.99 (dd, $J=7.3, 2.0$ Hz, 1 H) 7.88 (d, $J=8.3$ Hz, 1 H) 7.37 (d, $J=6.8$ Hz, 1 H) 7.13 – 7.25 (m, 4 H) 6.82 (s, 1 H).

(1*R*,2*R*)-2-((4-Methoxybenzyl)amino)cyclopentan-1-ol (41).

4-Methoxybenzaldehyde (0.46 mL, 3.78 mmol) was dissolved in DCM (14.5 mL, 0.26 M) and (1*R*,2*R*)-2-aminocyclohexan-1-ol hydrochloride (701 mg, 5.09 mmol), TEA (1.0 mL, 7.17 mmol), and acetic acid (0.43 mL, 7.52 mmol) were added in that order. The reaction was stirred at room temperature for 30 min. NaHB(OAc)₃ (1.47 g, 6.94 mmol) was added and the reaction was stirred at room temperature overnight. The reaction was diluted with

DCM and washed twice with 1M NaOH, once with water, and once with brine. The organic layer was dried with sodium sulfate and concentrated under reduced pressure. The crude material was purified by flash chromatography (20–100% EtOAc:hexanes - 0–20% DCM:EtOAc) to afford the title compound as an off-white solid (417 mg, 37%). LCMS [M+H]⁺ 222.16 m/z; ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.22 (d, *J*=8.8 Hz, 2 H) 6.86 (d, *J*=8.3 Hz, 2 H) 4.47 (d, *J*=4.4 Hz, 1 H) 3.73 – 3.77 (m, 1 H) 3.72 (s, 3 H) 3.61 (q, *J*=13.2 Hz, 2 H) 2.72 (q, *J*=6.3 Hz, 1 H) 1.91 (br. s, 1 H) 1.79 (spt, *J*=6.3 Hz, 2 H) 1.50 – 1.61 (m, 2 H) 1.34 – 1.42 (m, 1 H) 1.26 (sxt, *J*=12.7 Hz, 1 H).

4-Bromo-2,6-difluoro-*N*-((1*R*,2*R*)-2-hydroxycyclopentyl)-*N*-(4-methoxybenzyl)benzamide (42).

Compound **41** (417 mg, 1.88 mmol) was dissolved in DCM (4.4 mL) and TEA (0.40 mL, 2.87 mmol) was added. Compound **2** (526 mg, 2.06 mmol) was dissolved in another DCM (2.2 mL) and this solution was added to the reaction mixture dropwise at 0 °C. The reaction was allowed to warm to room temperature and stirred overnight. The reaction mixture was diluted with DCM and washed once with 1M HCl, once with water, and once with brine. The combined organic layers were dried with sodium sulfate and concentrated under reduced pressure. The crude material was purified by flash chromatography (20–50% EtOAc:hexanes) to afford the title compound as an orange oil (764 mg) which was used without further purification. LCMS [M+H]⁺ 440.13 m/z (⁷⁹Br), 442.15 m/z (⁸¹Br); ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.61 (d, *J*=7.3 Hz, 2 H) 7.25 (d, *J*=8.8 Hz, 2 H) 6.88 (d, *J*=8.8 Hz, 2 H) 4.78 (q, *J*=4.9 Hz, 2 H) 3.94 (quin, *J*=7.8 Hz, 1 H) 3.73 (s, 3 H) 3.59 (q, *J*=8.3 Hz, 1 H) 1.55 – 1.78 (m, 3 H) 1.38 – 1.54 (m, 3 H) 1.26 (td, *J*=7.8, 4.9 Hz, 1 H).

(3*aR*,10*aR*)-6-Bromo-8-fluoro-10-(4-methoxybenzyl)-1,2,3,3*a*,10,10*a*-hexahydro-9*H*-benzo[*f*]cyclopenta[*b*][1,4]oxazepin-9-one (43).

Compound **42** (764 mg, 1.74 mmol) was dissolved in DMF (12.5 mL, 0.14 M) and cesium carbonate (849 mg, 2.61 mmol) was added. The reaction was stirred at room temperature overnight. The reaction temperature was then increased to 50 °C and the reaction was heated another 24 h. The reaction was stopped and cooled to room temperature. The reaction mixture was diluted with EtOAc and washed three times with water. The combined aqueous layers were extracted once with EtOAc, and the combined organic layers were washed once with brine, dried with sodium sulfate, and concentrated under reduced pressure to afford the title compound as a yellow oil (614 mg, 84%). LCMS [M+H]⁺ 420.06 m/z (⁷⁹Br), 422.04 m/z (⁸¹Br); ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.38 (dd, *J*=9.8, 2.0 Hz, 1 H) 7.22 (d, *J*=8.3 Hz, 2 H) 7.07 (s, 1 H) 6.88 – 6.93 (m, 2 H) 4.69 (s, 2 H) 4.51 (q, *J*=9.0 Hz, 1 H) 4.09 (ddd, *J*=11.5, 9.8, 7.6 Hz, 1 H) 3.73 (s, 3 H) 1.84 – 1.91 (m, 1 H) 1.75 – 1.84 (m, 1 H) 1.67 – 1.75 (m, 1 H) 1.54 – 1.66 (m, 2 H) 1.44 – 1.54 (m, 1 H).

(3*aR*,10*aR*)-6-Bromo-8-fluoro-1,2,3,3*a*,10,10*a*-hexahydro-9*H*-benzo[*f*]cyclopenta[*b*][1,4]oxazepin-9-one (44).

To **43** (614 mg, 1.46 mmol) was added TFA (1.1 mL, 14.37 mmol). The reaction was run in the microwave (140 °C) for 30 min. The reaction mixture was then diluted with EtOAc and poured over sat. aq. NaHCO₃. The aqueous layer was extracted three times with EtOAc, and

the combined organic layers were washed once with brine, dried with sodium sulfate, and concentrated under reduced pressure. The crude material was purified by flash chromatography (20–50% EtOAc:hexanes) to afford the title compound as a pale yellow solid (337 mg, 77%). LCMS [M+H]⁺ 300.02 m/z (⁷⁹Br), 302.03 m/z (⁸¹Br); ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.57 (d, *J*=5.4 Hz, 1 H) 7.21 (dd, *J*=10.3, 2.0 Hz, 1 H) 7.02 (t, *J*=1.7 Hz, 1 H) 4.52 (q, *J*=8.0 Hz, 1 H) 3.66 – 3.77 (m, 1 H) 2.06 – 2.16 (m, 1 H) 1.96 (m, *J*=7.8 Hz, 1 H) 1.62 – 1.77 (m, 4 H).

(3a*R*,10a*R*)-6-Bromo-8-fluoro-1,2,3,3a,10,10a-hexahydro-9*H*-benzo[*f*]cyclopenta[*b*][1,4]oxazepine-9-thione (45).

Compound **44** (287 mg, 0.956 mmol) was suspended in toluene (19 mL, 0.05 M) and Lawesson's reagent (777 mg, 1.92 mmol) was added. The reaction was refluxed at 100 °C overnight. The reaction was stopped and cooled to room temperature and the crude material was purified by flash chromatography (20–50% EtOAc:hexanes) to afford the title compound as a yellow solid (171 mg) which was used in next reaction without further purification. LCMS [M+H]⁺ 315.99 m/z (⁷⁹Br), 318.03 m/z (⁸¹Br); ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 11.07 (d, *J*=5.4 Hz, 1 H) 7.33 (dd, *J*=9.8, 2.0 Hz, 1 H) 7.03 (t, *J*=1.5 Hz, 1 H) 4.61 (q, *J*=9.8 Hz, 1 H) 3.95 (quint, *J*=10.3, 10.3, 10.3, 10.3, 8.3, 8.3 Hz, 1 H) 1.91 – 1.97 (m, 1 H) 1.75 – 1.90 (m, 2 H) 1.62 – 1.71 (m, 2 H) 1.51 – 1.61 (m, 1 H).

(6a*R*,9a*R*)-4-Bromo-6a,7,8,9,9a,10-hexahydro-2*H*-cyclopenta[2,3][1,4]oxazepino[5,6,7-*cd*]indazole (46).

Compound **45** (171 mg, 0.540 mmol) was suspended in dioxane (1.8 mL, 0.30 M), and hydrazine monohydrate (0.15 mL, 3.06 mmol) was added. The reaction was refluxed for 3 h at 85 °C. The reaction mixture was concentrated under reduced pressure and the crude material was purified by flash chromatography (50–80% EtOAc:hexanes) to afford the title compound as a tan solid (149 mg, 94%). LCMS [M+H]⁺ 294.09 m/z (⁷⁹Br), 296.06 m/z (⁸¹Br); ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 11.80 (s, 1 H) 6.99 (d, *J*=1.5 Hz, 1 H) 6.58 (s, 1 H) 6.45 (d, *J*=1.5 Hz, 1 H) 4.31 (q, *J*=6.8 Hz, 1 H) 3.48 (q, *J*=8.8 Hz, 1 H) 2.29 (m, *J*=8.3, 8.3, 6.3, 6.3, 6.3 Hz, 1 H) 2.18 (m, *J*=7.8 Hz, 1 H) 1.90 (sxt, *J*=7.3 Hz, 1 H) 1.75 – 1.84 (m, 1 H) 1.61 – 1.75 (m, 2 H).

1-((6a*R*,9a*R*)-4-Bromo-6a,7,8,9,9a,10-hexahydro-2*H*-cyclopenta[2,3][1,4]oxazepino[5,6,7-*cd*]indazol-2-yl)ethan-1-one (47).

Acetic anhydride (2.7 mL, 28.56 mmol) was added to **46** (130 mg, 0.442 mmol), upon which the reaction mixture turned bright yellow, and the reaction was refluxed at 100 °C for 3 h. The reaction was kept at room temperature for an additional 12 h, after which a yellow precipitate was observed and collected by vacuum filtration (washed with water) to afford the title compound as a yellow solid (89 mg, 60%). LCMS [M+H]⁺ 336.06 m/z (⁷⁹Br), 338.08 m/z (⁸¹Br); ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.03 (d, *J*=1.5 Hz, 1 H) 7.63 (s, 1 H) 6.99 (d, *J*=1.5 Hz, 1 H) 4.38 (q, *J*=8.3 Hz, 1 H) 3.62 (q, *J*=8.8 Hz, 1 H) 2.51 (s, 3 H) 2.27 – 2.39 (m, 1 H) 2.16 – 2.25 (m, 1 H) 1.87 – 1.98 (m, 1 H) 1.77 – 1.85 (m, 1 H) 1.60 – 1.76 (m, 2 H).

1-((6aR,9aR)-4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-6a,7,8,9,9a,10-hexahydro-2H-cyclopenta[2,3][1,4]oxazepino[5,6,7-cd]indazol-2-yl)ethan-1-one (48).

Compound **47** (79 mg, 0.235 mmol), potassium acetate (81 mg, 0.825 mmol), bis(pinacolato)diboron (93 mg, 0.366 mmol), and PdCl₂(dppf)·CH₂Cl₂ (10 mg, 12.3 μmol) were combined in a reaction vial that was filled with nitrogen and evacuated three times. Dry, degassed dioxane (2.6 mL, 0.09 M) was added and the reaction was run in the microwave (145 °C) for 20 min. The reaction was diluted with MeOH, filtered through Celite®, and concentrated under reduced pressure. The crude material was purified by flash chromatography (20–50% EtOAc:hexanes) to afford the title compound as an off-white solid (56 mg, 62%). LCMS [M+H]⁺ 384.26 m/z; ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.20 (s, 1 H) 7.58 (s, 1 H) 6.97 (s, 1 H) 4.33 (q, *J*=7.8 Hz, 1 H) 3.61 (q, *J*=8.3 Hz, 1 H) 2.27 – 2.38 (m, 1 H) 2.17 – 2.26 (m, 1 H) 1.88 – 1.97 (m, 1 H) 1.78 – 1.88 (m, 1 H) 1.61 – 1.77 (m, 2 H) 1.34 (s, 3 H) 1.31 (s, 12 H).

1-((6aR,9aR)-4-(2-Aminopyrimidin-4-yl)-6a,7,8,9,9a,10-hexahydro-2H-cyclopenta[2,3][1,4]oxazepino[5,6,7-cd]indazol-2-yl)ethan-1-one (49).

Compound **48** (56 mg, 0.164 mmol), K₂CO₃ (70 mg, 0.507 mmol), and 2-amino-4-chloropyrimidine (34 mg, 0.262 mmol) were combined in a reaction vial and 3:1 dioxane:water (1.6 mL, 0.10 M) was added. The reaction was degassed for 10 min and PdCl₂(dppf)·CH₂Cl₂ (8 mg, 0.010 mmol) was added. The reaction was refluxed at 100 °C overnight. The reaction mixture was diluted with MeOH, filtered through Celite®, and concentrated under reduced pressure. The crude material was purified by flash chromatography (1–15% 10% NH₄OH/MeOH:DCM), then repurified by flash chromatography (0–10% MeOH:EtOAc) to afford the title compound as a yellow solid (25 mg, 56%). LCMS [M+H]⁺ 309.17 m/z; ¹H NMR (500 MHz, METHANOL-*d*₄) δ ppm 8.28 (d, *J*=5.9 Hz, 1 H) 7.64 (s, 1 H) 7.25 (d, *J*=5.9 Hz, 1 H) 7.12 (s, 1 H) 4.36 – 4.48 (m, 1 H) 3.66 (q, *J*=8.8 Hz, 1 H) 2.27 – 2.46 (m, 2 H) 2.02 – 2.12 (m, 1 H) 1.89 – 1.98 (m, 1 H) 1.73 – 1.88 (m, 2 H).

4-Bromo-2-ethoxy-6-fluorobenzonitrile (53a).

The title compound was prepared according to General Procedure B on a 302-mg scale using EtOH. The reaction was stirred at room temperature overnight, then heated to 50 °C for another 24 h. The crude material was purified by flash chromatography (0–20% EtOAc:hexanes) to afford the title compound as a white solid (280 mg, 83%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.48 (d, *J*=8.8 Hz, 1 H) 7.40 (s, 1 H) 4.26 (q, *J*=7.3 Hz, 2 H) 1.36 (t, *J*=7.0 Hz, 3 H).

*Compound does not ionize.

4-Bromo-2-(*tert*-butoxy)-6-fluorobenzonitrile (53b).

The title compound was prepared according to General Procedure B on a 300-mg scale using *tert*-butanol. The reaction was stirred at room temperature overnight, then heated to 50 °C for another 24 h. The crude material was purified by flash chromatography (0–20%

EtOAc:hexanes) to afford the title compound as a yellow oil (258 mg, 69%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.60 (d, *J*=8.8 Hz, 1 H) 7.40 (s, 1 H) 1.45 (s, 9 H).

*Compound does not ionize.

4-Bromo-2-cyclobutoxy-6-fluorobenzonitrile (53c).

The title compound was prepared according to General Procedure B on a 300-mg scale using cyclobutanol. The reaction was stirred at room temperature overnight, then heated to 50 °C for another 24 h. The crude material was purified by flash chromatography (0–20% EtOAc:Hexanes) to afford the title compound as a yellow oil (259 mg, 70%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.48 (d, *J*=9.5 Hz, 1 H) 7.18 (s, 1 H) 4.96 (quin, *J*=7.0 Hz, 1 H) 2.46 (br. s., 2 H) 2.09 (quin, *J*=10.3 Hz, 2 H) 1.82 (q, *J*=10.3 Hz, 1 H) 1.63 (tq, *J*=10.3, 8.8 Hz, 1 H).

*Compound does not ionize.

4-Bromo-2-fluoro-6-((tetrahydrofuran-3-yl)oxy)benzonitrile (53d).

The title compound was prepared according to General Procedure B on a 204-mg scale using tetrahydrofuran-3-ol. The reaction was stirred at room temperature for two days and the crude material was purified by flash chromatography (0–30% EtOAc:hexanes) to afford the title compound as a white solid (183 mg, 68%). ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.50 (dd, *J*=8.8, 1.5 Hz, 1 H) 7.43 (s, 1 H) 5.32 (t, *J*=5.1 Hz, 1 H) 3.82 – 3.92 (m, 3 H) 3.77 (td, *J*=8.3, 4.4 Hz, 1 H) 2.28 (sxt, *J*=7.3 Hz, 1 H) 1.95 – 2.04 (m, 1 H).

*Compound does not ionize.

4-Bromo-2-fluoro-6-((tetrahydro-2H-pyran-4-yl)oxy)benzonitrile (53e).

The title compound was prepared according to General Procedure B on a 51-mg scale using tetrahydro-2H-pyran-4-ol. The reaction mixture was stirred at room temperature overnight and the crude material was purified by flash chromatography (20–30% EtOAc:hexanes) to afford the title compound as an off-white solid (37 mg, 53%). ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.57 (s, 1 H) 7.47 (dd, *J*=8.8, 1.5 Hz, 1 H) 4.94 (tt, *J*=8.2, 4.0 Hz, 1 H) 3.79 – 3.89 (m, 2 H) 3.52 (ddd, *J*=11.5, 8.5, 2.9 Hz, 2 H) 1.93 – 2.05 (m, 2 H) 1.63 (dtd, *J*=12.9, 8.6, 8.6, 3.7 Hz, 2 H).

*Compound does not ionize.

4-Bromo-2-fluoro-6-((tetrahydro-2H-pyran-3-yl)oxy)benzonitrile (53f).

The title compound was prepared according to General Procedure B on a 200-mg scale using tetrahydro-2H-pyran-3-ol. The reaction was stirred at room temperature overnight and the crude material was purified by flash chromatography (0–20% EtOAc:hexanes) to afford the title compound as a yellow solid (143 mg, 52%). ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.53 (s, 1 H) 7.47 (dd, *J*=8.8, 1.5 Hz, 1 H) 4.74 (m, *J*=2.4 Hz, 1 H) 3.75 (dd, *J*=12.0, 2.2 Hz, 1 H) 3.53 – 3.65 (m, 3 H) 1.94 – 2.05 (m, 1 H) 1.72 – 1.87 (m, 2 H) 1.49 – 1.58 (m, 1 H).

*Compound does not ionize.

4-Bromo-2-fluoro-6-(oxetan-3-yloxy)benzotrile (53g).

The title compound was prepared according to General Procedure B on a 200-mg scale using oxetan-3-ol. The reaction was stirred at room temperature for two days and the crude material was purified by flash chromatography (0–50% EtOAc:hexanes) to afford the title compound as a beige solid (121 mg, 49%). ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.55 (dd, *J*=8.8, 1.5 Hz, 1 H) 7.07 (s, 1 H) 5.52 (quin, *J*=5.4 Hz, 1 H) 4.97 (t, *J*=6.8 Hz, 2 H) 4.58 (dd, *J*=7.6, 4.6 Hz, 2 H).

*Compound does not ionize.

6-Bromo-4-ethoxy-1*H*-indazol-3-amine (54a).

The title compound was prepared according to General Procedure C on a 280-mg scale using **53a**. The crude material was purified by flash chromatography (0–60% EtOAc:hexanes) to afford the title compound as a yellow solid (240 mg, 82%). LCMS [M+H]⁺ 256.00 m/z (⁷⁹Br), 258.01 m/z (⁸¹Br); ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 11.51 (s, 1 H) 6.96 (d, *J*=1.0 Hz, 1 H) 6.43 (s, 1 H) 5.02 (s, 2 H) 4.13 (q, *J*=7.0 Hz, 2 H) 1.40 (t, *J*=6.8 Hz, 3 H).

6-Bromo-4-(*tert*-butoxy)-1*H*-indazol-3-amine (54b).

The title compound was prepared according to General Procedure C on a 258-mg scale using **53b**. The crude material was purified by flash chromatography (0–50% EtOAc:hexanes) to afford the title compound as a red solid (230 mg, 85%). LCMS [M+H]⁺ 284.08 m/z (⁷⁹Br), 286.03 m/z (⁸¹Br); ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 11.53 (s, 1 H) 7.03 (s, 1 H) 6.55 (s, 1 H) 4.96 (s, 2 H) 1.45 – 1.48 (m, 9 H).

6-Bromo-4-cyclobutoxy-1*H*-indazol-3-amine (54c).

The title compound was prepared according to General Procedure C on a 259-mg scale using **53c**. The crude material was purified by flash chromatography (0–50% EtOAc:hexanes) to afford the title compound as a light yellow solid (236 mg, 87%). LCMS [M+H]⁺ 282.07 m/z (⁷⁹Br), 284.04 m/z (⁸¹Br); ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 11.51 (s, 1 H) 6.95 (s, 1 H) 6.25 (s, 1 H) 5.04 (s, 2 H) 4.83 (quin, *J*=7.1 Hz, 1 H) 2.41 – 2.49 (m, 2 H) 2.16 (ddd, *J*=9.8, 7.3, 2.4 Hz, 2 H) 1.82 (q, *J*=10.7 Hz, 1 H) 1.67 (sxt, *J*=10.3 Hz, 1 H).

6-Bromo-4-((tetrahydrofuran-3-yl)oxy)-1*H*-indazol-3-amine (54d).

The title compound was prepared according to General Procedure C on a 143-mg scale using **53d**. The crude material was purified by flash chromatography (50–100% EtOAc:hexanes) to afford the title compound as an off-white solid (130 mg, 68%). LCMS [M+H]⁺ 297.94 m/z (⁷⁹Br), 299.92 m/z (⁸¹Br); ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 11.54 (s, 1 H) 6.98 (d, *J*=1.0 Hz, 1 H) 6.42 (s, 1 H) 5.15 (br. s., 1 H) 5.02 (s, 2 H) 3.92 (d, *J*=2.9 Hz, 2 H) 3.88 (q, *J*=7.3 Hz, 1 H) 3.77 (td, *J*=8.3, 4.4 Hz, 1 H) 2.25 (m, *J*=7.3 Hz, 1 H) 2.11 (dt, *J*=13.3, 6.3 Hz, 1 H)

6-Bromo-4-((tetrahydro-2H-pyran-4-yl)oxy)-1H-indazol-3-amine (54e).

The title compound was prepared according to General Procedure C on a 111-mg scale using **53e**. The crude material was purified by flash chromatography (50–100% EtOAc:hexanes) to afford the title compound as a tan solid (104 mg, 90%). LCMS [M+H]⁺ 311.92 m/z (⁷⁹Br), 313.93 m/z (⁸¹Br); ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 11.52 (s, 1 H) 6.95 (d, *J*=1.0 Hz, 1 H) 6.57 (s, 1 H) 5.03 (s, 2 H) 4.77 (tt, *J*=8.2, 4.3 Hz, 1 H) 3.81 – 3.89 (m, 2 H) 3.53 (m, *J*=2.9 Hz, 2 H) 2.00 (m, *J*=12.2 Hz, 2 H) 1.66 – 1.76 (m, 2 H).

6-Bromo-4-((tetrahydro-2H-pyran-3-yl)oxy)-1H-indazol-3-amine (54f).

The title compound was prepared according to General Procedure C on a 143-mg scale using 4-bromo-2-fluoro-6-((tetrahydro-2H-pyran-3-yl)oxy)benzotrile **53f**. The crude material was purified by flash chromatography (40–70% EtOAc:hexanes) to afford the title compound as a beige solid (123 mg, 82%). LCMS [M+H]⁺ 311.98 m/z (⁷⁹Br), 313.99 m/z (⁸¹Br); ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 11.52 (br. s., 1 H) 6.96 (d, *J*=1.0 Hz, 1 H) 6.54 (s, 1 H) 5.07 (s, 2 H) 4.59 (tt, *J*=3.9, 2.4 Hz, 1 H) 3.77 (dd, *J*=10.7, 2.0 Hz, 1 H) 3.55 – 3.72 (m, 3 H) 1.94 – 2.02 (m, 1 H) 1.83 – 1.90 (m, 1 H) 1.78 (dtd, *J*=17.3, 8.8, 8.8, 4.6 Hz, 1 H) 1.53 (m, *J*=10.1, 3.0, 3.0 Hz, 1 H).

6-Bromo-4-(oxetan-3-yloxy)-1H-indazol-3-amine (54g).

The title compound was prepared according to General Procedure C on a 121-mg scale using 4-bromo-2-fluoro-6-(oxetan-3-yloxy)benzotrile **53g**. The crude material was purified by flash chromatography (100% EtOAc) to afford the title compound as a beige solid (82 mg, 65%). LCMS [M+H]⁺ 283.96 m/z (⁷⁹Br), 285.97 m/z (⁸¹Br); ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 11.58 (s, 1 H) 7.01 (d, *J*=1.0 Hz, 1 H) 6.06 (s, 1 H) 5.39 (quin, *J*=5.4 Hz, 1 H) 5.20 (s, 2 H) 4.95 (t, *J*=6.8 Hz, 2 H) 4.70 (dd, *J*=7.1, 5.1 Hz, 2 H).

1-(3-Amino-6-bromo-4-ethoxy-1H-indazol-1-yl)ethan-1-one (55a).

The title compound was prepared according to General Procedure D on a 240-mg scale using 6-bromo-4-ethoxy-1H-indazol-3-amine **54a**. The crude material was purified by flash chromatography (0–50% EtOAc:hexanes) to afford the title compound as a light yellow solid (65 mg, 23%). LCMS [M+H]⁺ 298.03 m/z (⁷⁹Br), 300.01 m/z (⁸¹Br). ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.92 (d, *J*=1.5 Hz, 1 H) 7.00 (d, *J*=1.0 Hz, 1 H) 5.99 (s, 2 H) 4.23 (q, *J*=7.2 Hz, 2 H) 2.49 (s, 3 H) 1.41 (t, *J*=7.1 Hz, 3 H).

1-(3-Amino-6-bromo-4-(tert-butoxy)-1H-indazol-1-yl)ethan-1-one (55b).

The title compound was prepared according to General Procedure D on a 205-mg scale using **54b**. The crude material was purified by flash chromatography (0–50% EtOAc:hexanes) to afford the title compound as an orange solid (92 mg, 39%). LCMS [M+H]⁺ 326.03 m/z (⁷⁹Br), 328.04 m/z (⁸¹Br). ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.00 (d, *J*=1.5 Hz, 1 H) 7.07 (d, *J*=1.5 Hz, 1 H) 5.89 (s, 2 H) 2.50 (s, 3 H) 1.51 (s, 9 H).

1-(3-Amino-6-bromo-4-cyclobutoxy-1H-indazol-1-yl)ethan-1-one (55c).

The title compound was prepared according to General Procedure D on a 236-mg scale using **54c**. The crude material was purified by flash chromatography (0–50%

EtOAc:hexanes) to afford the title compound as an off-white solid (65 mg, 24%). LCMS [M+H]⁺ 324.03 m/z (⁷⁹Br), 326.02 m/z (⁸¹Br). ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.92 (d, *J*=1.5 Hz, 1 H) 6.81 (d, *J*=1.0 Hz, 1 H) 6.03 (s, 2 H) 4.93 (quin, *J*=7.1 Hz, 1 H) 2.49 (s, 3 H) 2.41 – 2.48 (m, 2 H) 2.23 (quint, *J*=9.7, 9.7, 9.7, 9.7, 2.3, 2.3 Hz, 1 H) 1.82 (qt, *J*=10.3, 2.4 Hz, 1 H) 1.66 (qt, *J*=10.7, 8.3 Hz, 1 H).

1-(3-Amino-6-bromo-4-((tetrahydrofuran-3-yl)oxy)-1*H*-indazol-1-yl)ethan-1-one and *N*-(1-acetyl-6-bromo-4-((tetrahydrofuran-3-yl)oxy)-1*H*-indazol-3-yl)acetamide (55d).

The title compound was prepared according the General Procedure D on a 130-mg scale using 6-bromo-4-((tetrahydrofuran-3-yl)oxy)-1*H*-indazol-3-amine **54d**. The crude material was not purified but taken forward as a mixture of mono- and di-acetylated products (170 mg orange solid). LCMS [M+H]⁺ 339.94 m/z (⁷⁹Br mono-aceylated), 341.81 m/z (⁸¹Br mono-aceylated), 381.88 m/z (⁷⁹Br di-aceylated), 383.89 m/z (⁸¹Br di-aceylated).

1-(3-Amino-6-bromo-4-((tetrahydro-2*H*-pyran-4-yl)oxy)-1*H*-indazol-1-yl)ethan-1-one and *N*-(1-acetyl-6-bromo-4-((tetrahydro-2*H*-pyran-4-yl)oxy)-1*H*-indazol-3-yl)acetamide (55e).

The title compound was prepared according the General Procedure D on a 104-mg scale using 6-bromo-4-((tetrahydro-2*H*-pyran-4-yl)oxy)-1*H*-indazol-3-amine **54e**. The crude material was not purified but taken forward as a mixture of mono- and di-acetylated products (148 mg orange solid). LCMS [M+H]⁺ 353.92 m/z (⁷⁹Br mono-aceylated), 355.93 m/z (⁸¹Br mono-aceylated), 395.92 m/z (⁷⁹Br di-aceylated), 397.87 m/z (⁸¹Br di-aceylated).

1-(3-Amino-6-bromo-4-((tetrahydro-2*H*-pyran-3-yl)oxy)-1*H*-indazol-1-yl)ethan-1-one and *N*-(1-acetyl-6-bromo-4-((tetrahydro-2*H*-pyran-3-yl)oxy)-1*H*-indazol-3-yl)acetamide (55f).

The title compound was prepared according the General Procedure D on a 104-mg scale using 6-bromo-4-((tetrahydro-2*H*-pyran-3-yl)oxy)-1*H*-indazol-3-amine **54f**. The crude material was not purified but taken forward as a mixture of mono- and di-acetylated products (147 mg orange solid). LCMS [M+H]⁺ 353.98 m/z (⁷⁹Br mono-aceylated), 356.00 m/z (⁸¹Br mono-aceylated), 395.98 m/z (⁷⁹Br di-aceylated), 398.00 m/z (⁸¹Br di-aceylated).

1-(3-Amino-6-bromo-4-(oxetan-3-yloxy)-1*H*-indazol-1-yl)ethan-1-one and *N*-(1-acetyl-6-bromo-4-(oxetan-3-yloxy)-1*H*-indazol-3-yl)acetamide (55g).

The title compound was prepared according the General Procedure D on an 82-mg scale using 6-bromo-4-(oxetan-3-yloxy)-1*H*-indazol-3-amine **54g**. The crude material was not purified but taken forward as a mixture of mono- and di-acetylated products (84 mg yellow solid). LCMS [M+H]⁺ 325.96 m/z (⁷⁹Br mono-aceylated), 327.97 m/z (⁸¹Br mono-aceylated), 367.96 m/z (⁷⁹Br di-aceylated), 369.91 m/z (⁸¹Br di-aceylated).

6-(2-Aminopyrimidin-4-yl)-4-ethoxy-1*H*-indazol-3-amine formate (57a).

The title compound was prepared according to General Procedure E on a 348-mg scale using **55a**. The crude material of the Miyaura reaction was taken forward without further purification. The crude residue of the Suzuki reaction was purified by flash chromatography (20–100% EtOAc:hexanes – 0–10% MeOH:DCM), then repurified by preparative HPLC (5–50% ACN:water) to afford the formate salt of the title compound as an orange solid (18 mg,

6%). LCMS $[M+H]^+$ 271.17 m/z; 1H NMR (500 MHz, DMSO- d_6) δ ppm 11.67 (br. s., 1 H) 8.52 (s, 1 H) 8.28 (d, $J=5.4$ Hz, 1 H) 7.52 (s, 1 H) 7.14 (d, $J=5.4$ Hz, 1 H) 6.96 (s, 1 H) 6.64 (s, 2 H) 5.03 (s, 2 H) 4.21 (q, $J=7.2$ Hz, 2 H) 1.45 (t, $J=7.1$ Hz, 3 H).

6-(2-Aminopyrimidin-4-yl)-4-(*tert*-butoxy)-1*H*-indazol-3-amine (57c).

The title compound was prepared according to General Procedure E on a 92-mg scale using **55b**. The product of the Miyaura reaction was isolated by flash chromatography (20% EtOAc:hexanes) to afford 1-(3-amino-4-(*tert*-butoxy)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazol-1-yl)ethan-1-one **56a** as an off-white solid (73 mg, 69%). LCMS $[M+H]^+$ 374.19 m/z; 1H NMR (500 MHz, DMSO- d_6) δ ppm 8.19 (s, 1 H) 7.12 (s, 1 H) 5.89 (s, 2 H) 2.50 (s, 3 H) 1.48 (s, 9 H) 1.32 (s, 12 H).

The crude residue of the Suzuki reaction was purified by flash chromatography (5% MeOH:DCM), then repurified by preparative HPLC (5–50% acetonitrile:water) to afford the title compound as a brown solid (8 mg, 14%). LCMS $[M+H]^+$ 299.19 m/z; 1H NMR (500 MHz, DMSO- d_6) δ ppm 11.68 (s, 1 H) 8.28 (d, $J=5.4$ Hz, 1 H) 7.58 (d, $J=1.0$ Hz, 1 H) 7.13 (d, $J=1.0$ Hz, 1 H) 7.09 (d, $J=5.4$ Hz, 1 H) 6.64 (s, 2 H) 4.97 (s, 2 H) 1.50 (s, 9 H).

6-(2-Aminopyrimidin-4-yl)-4-cyclobutoxy-1*H*-indazol-3-amine formate (57d).

The title compound was prepared according to General Procedure E on a 65-mg scale using **55c**. The product of the Miyaura reaction was isolated by flash chromatography (20% EtOAc:hexanes) to afford 1-(3-amino-4-cyclobutoxy-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazol-1-yl)ethan-1-one **56b** as an off-white solid (52 mg, 71%). LCMS $[M+H]^+$ 372.18 m/z; 1H NMR (500 MHz, DMSO- d_6) δ ppm 8.11 (s, 1 H) 6.79 (s, 1 H) 6.00 (s, 2 H) 4.91 (quin, $J=7.1$ Hz, 1 H) 2.50 (s, 3 H) 2.38 – 2.47 (m, 2 H) 2.17 – 2.29 (m, 2 H) 1.83 (q, $J=10.7$ Hz, 1 H) 1.72 (q, $J=9.8$ Hz, 1 H) 1.32 (s, 12 H).

The crude residue of the Suzuki reaction was purified by flash chromatography (5% MeOH:DCM), then repurified by preparative HPLC (5–50% ACN:water) to afford the title compound as a brown solid (5 mg, 12%). LCMS $[M+H]^+$ 297.18 m/z; 1H NMR (500 MHz, DMSO- d_6) δ ppm 11.66 (s, 1 H) 8.52 (s, 1 H) 8.28 (d, $J=4.9$ Hz, 1 H) 7.52 (s, 1 H) 7.11 (d, $J=5.4$ Hz, 1 H) 6.80 (s, 1 H) 6.64 (s, 2 H) 5.04 (s, 2 H) 4.91 (quin, $J=7.3$ Hz, 1 H) 2.53 (m, $J=9.8$ Hz, 2 H) 2.21 (quint, $J=10.3, 10.3, 10.3, 10.3, 2.4, 2.4$ Hz, 2 H) 1.84 (q, $J=10.3$ Hz, 1 H) 1.71 (quin, $J=10.7$ Hz, 1 H).

6-(2-Aminopyrimidin-4-yl)-4-((tetrahydrofuran-3-yl)oxy)-1*H*-indazol-3-amine (57g).

The title compound was prepared according to General Procedure E on a 150-mg scale **55d**. The crude Miyaura reaction mixture was run through a pad of silica using 100% EtOAc as the eluent to afford a mixture of mono-, bi- and tri-acetylated boronic acid and ester which was taken forward to the Suzuki reaction without further purification. The crude residue of the Suzuki reaction was purified by flash chromatography (5–10% 5% NH_4OH /MeOH:DCM, step gradient) to afford a mixture of the title compound and the acetylated product. This crude material was suspended in MeOH (10 mL, 0.04 M) and 12M HCl (1 mL, 12 mmol) was added, upon which the reaction mixture went from a cloudy suspension to a clear solution. The mixture was refluxed at 65 °C overnight. The solvent was removed

under reduced pressure and the resulting residue was redissolved in EtOAc. The reaction mixture was poured over saturated aqueous NaHCO₃ and the aqueous layer was extracted four times with EtOAc. The combined organic layers were washed once with brine, dried with sodium sulfate, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (10% 5% NH₄OH/MeOH:EtOAc) to afford the title compound as a yellow solid (26 mg, 19%). LCMS [M+H]⁺ 313.05 m/z; ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 11.67 (s, 1 H) 8.29 (d, *J*=5.4 Hz, 1 H) 7.56 (s, 1 H) 7.16 (d, *J*=4.9 Hz, 1 H) 6.91 (s, 1 H) 6.64 (s, 2 H) 5.25 (br. s., 1 H) 5.03 (s, 2 H) 3.94 – 4.00 (m, 2 H) 3.91 (q, *J*=7.8 Hz, 1 H) 3.80 (sxt, *J*=4.4 Hz, 1 H) 2.30 (quin, *J*=6.8 Hz, 1 H) 2.13 – 2.21 (m, 1 H).

6-(2-Aminopyrimidin-4-yl)-4-((tetrahydro-2H-pyran-4-yl)oxy)-1H-indazol-3-amine (57h).

The title compound was prepared according to General Procedure E on a 120-mg scale using **55e**. The crude Miyaura reaction mixture was run through a pad of silica using 100% EtOAc as the eluent to afford a mixture of mono-, bi- and tri-acetylated boronic acid and ester which was taken forward to the Suzuki reaction without further purification. The crude residue of the Suzuki reaction was purified by flash chromatography (1–10% 5% NH₄OH/MeOH:EtOAc) to afford a mixture of the title compound and the acetylated product. This crude material was suspended in MeOH (10 mL, 0.04 M) and 12M HCl (1 mL, 12 mmol) was added, upon which the reaction mixture went from a cloudy suspension to a clear solution. The mixture was refluxed at 65 °C overnight, then concentrated under reduced pressure. The resulting residue was redissolved in EtOAc. The reaction mixture was poured over saturated aqueous NaHCO₃ and the aqueous layer was extracted four times with EtOAc. The combined organic layers were washed once with brine, dried with sodium sulfate, and concentrated under reduced pressure. The crude material was repurified by flash chromatography (3% 5% NH₄OH/MeOH:EtOAc) to afford the title compound as a yellow-green solid (26 mg, 24%). LCMS [M+H]⁺ 327.09 m/z; ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 11.65 (s, 1 H) 8.29 (d, *J*=5.4 Hz, 1 H) 7.54 (s, 1 H) 7.16 (d, *J*=5.4 Hz, 1 H) 7.02 (s, 1 H) 6.64 (s, 2 H) 5.03 (s, 2 H) 4.87 (m, *J*=3.9 Hz, 1 H) 3.82 – 3.93 (m, 2 H) 3.57 (td, *J*=8.8, 2.4 Hz, 2 H) 2.02 – 2.11 (m, 2 H) 1.76 (m, *J*=8.8 Hz, 2 H).

6-(2-Aminopyrimidin-4-yl)-4-((tetrahydro-2H-pyran-3-yl)oxy)-1H-indazol-3-amine (57i).

The title compound was prepared according to General Procedure E on a 140-mg scale using **55f**. The crude Miyaura reaction mixture was run through a pad of silica using 100% EtOAc as the eluent to afford a mixture of mono-, bi- and tri-acetylated boronic acid and ester which was taken forward to the Suzuki reaction without further purification. The crude residue of the Suzuki reaction was purified by flash chromatography (1–10% 5% NH₄OH/MeOH:EtOAc) to afford a mixture of the title compound and the acetylated product. This crude material was suspended in MeOH (10 mL, 0.04 M) and 12M HCl (1 mL, 12 mmol) was added, upon which the reaction mixture went from a cloudy suspension to a clear solution. The mixture was refluxed at 65 °C overnight. The solvent was removed under reduced pressure and the resulting residue was redissolved in EtOAc. The reaction mixture was poured over saturated aqueous NaHCO₃ and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed once with brine, dried with sodium sulfate, and concentrated under reduced pressure. The crude material was then purified by flash chromatography (5% 5% NH₄OH/MeOH:EtOAc) to afford the title compound as a

yellow solid (12 mg, 9%). LCMS [M+H]⁺ 327.09 m/z; ¹H NMR (500 MHz, METHANOL-*d*₄) δ ppm 8.27 (d, *J*=4.9 Hz, 1 H) 7.51 (s, 1 H) 7.12 (d, *J*=5.4 Hz, 1 H) 7.09 (s, 1 H) 4.66 – 4.72 (m, 1 H) 3.94 (dd, *J*=10.7, 2.0 Hz, 1 H) 3.84 (dd, *J*=14.6, 5.4 Hz, 1 H) 3.74 – 3.80 (m, 1 H) 3.71 (m, *J*=8.1, 3.2 Hz, 1 H) 2.03 – 2.15 (m, 2 H) 1.97 (m, *J*=8.7, 4.2, 4.2 Hz, 1 H) 1.58 – 1.67 (m, 1 H).

6-(2-Aminopyrimidin-4-yl)-4-(oxetan-3-yloxy)-1*H*-indazol-3-amine (57j).

The title compound was prepared according to General Procedure E on an 84-mg scale using 1-(3-amino-6-bromo-4-(oxetan-3-yloxy)-1*H*-indazol-1-yl)ethan-1-one **55g**. The crude Miyaura reaction mixture was run through a pad of silica using 100% EtOAc as the eluent to afford a mixture of mono-, bi- and tri-acetylated boronic acid and ester which was taken forward to the Suzuki reaction without further purification. The crude residue of the Suzuki reaction was purified by flash chromatography (1-5-10% 5% NH₄OH/MeOH:EtOAc, step gradient) to afford the title compound as a yellow solid (20 mg, 26%). LCMS [M+H]⁺ 299.07 m/z; ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 11.72 (s, 1 H) 8.28 (d, *J*=5.4 Hz, 1 H) 7.59 (s, 1 H) 7.13 (d, *J*=4.9 Hz, 1 H) 6.64 (s, 2 H) 6.55 (s, 1 H) 5.48 (quin, *J*=5.1 Hz, 1 H) 5.18 (s, 2 H) 5.01 (t, *J*=6.8 Hz, 2 H) 4.75 (dd, *J*=7.3, 4.9 Hz, 1 H).

4-Bromo-2-fluoro-*N*-phenylbenzamide (58).

Aniline (0.200 ml, 2.19 mmol) was dissolved in 6.0 ml DCM and TEA (0.400 ml, 2.87 mmol) was added. Compound **36** (500 mg, 2.11 mmol) was dissolved in another 3.0 ml DCM and this solution was added to the reaction mixture dropwise at 0 °C. The reaction was allowed to warm to room temperature and stirred overnight. The reaction was diluted with DCM and washed once with 1M HCl, once with water, and once with brine. The combined organic layers were dried with sodium sulfate and concentrated under reduced pressure to afford the title compound as an off-white solid (485 mg, 78%). LCMS [M+H]⁺ 294.03 m/z (⁷⁹Br), 295.99 m/z (⁸¹Br); ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 10.45 (s, 1 H) 7.75 (dd, *J*=9.8, 2.0 Hz, 1 H) 7.70 (d, *J*=7.8 Hz, 2 H) 7.63 (t, *J*=8.3 Hz, 1 H) 7.57 (dd, *J*=7.3, 1.5 Hz, 1 H) 7.36 (t, *J*=7.8 Hz, 2 H) 7.12 (t, *J*=7.6 Hz, 1 H).

4-Bromo-2-fluoro-*N*-phenylbenzothioamide (59).

Compound **58** (365 mg, 1.24 mmol) was suspended in toluene (25 ml, 0.05M) and Lawesson's reagent (1.01 g, 2.50 mmol) was added. The reaction was refluxed at 100 °C overnight. Upon cooling to room temperature, a pale yellow precipitate was observed and removed by vacuum filtration (washed with hexanes). The filtrate was purified by flash chromatography (5–20% EtOAc:hexanes) to afford the title compound as a yellow solid (283 mg, 74%). LCMS [M+H]⁺ 310.02 m/z (⁷⁹Br), 311.99 m/z (⁸¹Br); ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 12.11 (s, 1 H) 7.91 (d, *J*=7.8 Hz, 2 H) 7.69 (dd, *J*=9.8, 2.0 Hz, 1 H) 7.57 (t, *J*=7.3 Hz, 1 H) 7.51 (dd, *J*=6.3, 2.0 Hz, 1 H) 7.45 (t, *J*=7.8 Hz, 2 H) 7.29 (t, *J*=7.3 Hz, 1 H).

6-Bromo-*N*-phenyl-1*H*-indazol-3-amine (60).

Compound **59** (266 mg, 0.858 mmol) was suspended in dioxane (2.5 ml, 0.34 M) and hydrazine monohydrate (0.25 ml, 5.09 mmol) was added. The reaction was refluxed

overnight at 85 °C. The reaction was diluted with MeOH and purified directly by flash chromatography (0–50% EtOAc:hexanes) to afford the title compound as a yellow solid (174 mg, 70%). LCMS [M+H]⁺ 288.06 m/z (⁷⁹Br), 290.03 m/z (⁸¹Br); ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 12.11 (s, 1 H) 8.93 (s, 1 H) 7.93 (d, *J*=8.8 Hz, 1 H) 7.66 (d, *J*=7.8 Hz, 2 H) 7.58 (s, 1 H) 7.26 (t, *J*=7.8 Hz, 2 H) 7.17 (dd, *J*=9.0, 1.2 Hz, 1 H) 6.81 (t, *J*=7.3 Hz, 1 H).

1-(6-Bromo-3-(phenylamino)-1*H*-indazol-1-yl)ethan-1-one (61).

Acetic anhydride (1.50 ml, 15.9 mmol) was added to **60** (156 mg, 0.541 mmol) and the reaction was refluxed at 100 °C for ~3.5 h (reaction mixture turns bright yellow as acetic anhydride is added). Upon cooling to room temperature, an off-white precipitate was observed and collected by vacuum filtration (washed with water) to afford the title compound as a white solid (134 mg, 75%). LCMS [M+H]⁺ 330.03 m/z (⁷⁹Br), 332.06 m/z (⁸¹Br); ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 9.57 (s, 1 H) 8.46 (s, 1 H) 8.18 (d, *J*=8.3 Hz, 1 H) 7.83 (d, *J*=8.8 Hz, 2 H) 7.65 (dd, *J*=8.5, 1.7 Hz, 1 H) 7.37 (t, *J*=7.3 Hz, 2 H) 6.95 – 7.01 (m, 1 H) 2.67 (s, 3 H).

1-(3-(phenylamino)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazol-1-yl)ethan-1-one (62).

Compound **61** (115 mg, 0.348 mmol), potassium acetate (119 mg, 1.21 mmol), bis(pinacolato)diboron (132 mg, 0.520 mmol), and PdCl₂(dppf)·CH₂Cl₂ (14 mg, 17.14 μmol) were combined in a reaction vial that was filled with nitrogen and evacuated three times. Dry, degassed dioxane (3.9 ml, 0.09 M) was added and the reaction was run in the microwave (145 °C, N abs) for 30 minutes. The reaction was diluted with EtOAc and filtered through celite. The crude material was purified by flash chromatography (20–50% EtOAc:hexanes) to afford the title compound as a white solid (112 mg, 85%). LCMS [M+H]⁺ 378.22 m/z; ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 9.55 (s, 1 H) 8.65 (s, 1 H) 8.24 (d, *J*=7.8 Hz, 1 H) 7.85 (d, *J*=7.3 Hz, 2 H) 7.72 (d, *J*=7.8 Hz, 1 H) 7.37 (t, *J*=8.1 Hz, 2 H) 6.97 (t, *J*=7.3 Hz, 1 H) 2.68 (s, 3 H) 1.35 (s, 12 H).

6-(2-aminopyrimidin-4-yl)-*N*-phenyl-2*H*-indazol-3-amine (63).

Compound **62** (75 mg, 0.199 mmol), K₂CO₃ (97 mg, 0.702 mmol), and 2-amino-4-chloropyrimidine (54 mg, 0.417 mmol) were combined in a reaction vial and 3:1 dioxane:water (2.0 ml, 0.10 M) was added. The reaction was degassed for ~10 minutes and PdCl₂(dppf)·CH₂Cl₂ (8 mg, 0.011 mmol) was added. The reaction was refluxed at 100 °C overnight. The reaction was diluted with MeOH and filtered through celite and the crude material was purified by flash chromatography (50–100% EtOAc:hexanes) to afford the title compound as a light orange solid (19 mg, 32%). LCMS [M+H]⁺ 303.14 m/z; ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 12.24 (s, 1 H) 8.93 (s, 1 H) 8.33 (d, *J*=5.4 Hz, 1 H) 8.11 (s, 1 H) 8.04 (d, *J*=8.8 Hz, 1 H) 7.73 (dd, *J*=8.8, 1.5 Hz, 1 H) 7.68 (d, *J*=7.8 Hz, 2 H) 7.26 (dd, *J*=8.5, 7.6 Hz, 2 H) 7.21 (d, *J*=5.4 Hz, 1 H) 6.81 (t, *J*=7.3 Hz, 1 H) 6.69 (s, 2 H).

4-(2-Chloropyrimidin-4-yl)-2-fluorobenzonitrile (64).

Compound **29** (400 mg, 2.43 mmol), 2,4-dichloropyrimidine (444 mg, 2.98 mmol), potassium carbonate (1.01 g, 7.31 mmol), and PdCl₂(dppf) (91 mg, 0.124 mmol) were

combined in a microwave vial that was filled with nitrogen and evacuated three times. 3:1 Dioxane:water (16 ml, 0.15 M) was added and the reaction was degassed for ~10 min. The reaction was run in the microwave (145 °C, H abs) for 30 min. The reaction mixture was diluted with EtOAc, filtered through celite, and concentrated under reduced pressure. The crude material was purified by flash chromatography (0–50% EtOAc:Hex) to afford the title compound as an off-white solid (308 mg, 54%). LCMS [M+H]⁺ 233.96 m/z (³⁵Cl), 235.93 m/z (³⁷Cl); ¹H NMR (399 MHz, DMSO-*d*₆) δ ppm 8.98 (d, *J*=5.1 Hz, 1 H) 8.29 – 8.35 (m, 2 H) 8.24 (d, *J*=8.8 Hz, 1 H) 8.17 (dd, *J*=8.1, 6.6 Hz, 1 H).

4-(2-(Bis(4-methoxybenzyl)amino)pyrimidin-4-yl)-2-fluorobenzonitrile (65).

Compound **64** (308 mg, 1.32 mmol) was suspended in MeOH (6.6 ml, 0.20 M) and bis(4-methoxybenzyl)amine (409 mg, 1.59 mmol) was added, followed by the addition of Hunig's base (0.7 m, 4.02 mmol). The reaction was refluxed for 36 hrs at 65 °C. The reaction was concentrated under reduced pressure and redissolved in DCM. The organic layer was washed once with 1M HCl, once with water, and once with brine, then dried with sodium sulfate and concentrated under reduced pressure. The crude material was purified by flash chromatography (20–50% EtOAc:Hex) to afford the title compound as a yellow solid (301 mg, 50%). LCMS [M+H]⁺ 455.21 m/z; ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.58 (d, *J*=4.9 Hz, 1 H) 8.18 (d, *J*=10.7 Hz, 1 H) 8.15 (dd, *J*=8.3, 1.0 Hz, 1 H) 8.07 (m, *J*=6.8 Hz, 1 H) 7.40 (d, *J*=5.4 Hz, 1 H) 7.21 (d, *J*=8.3 Hz, 4 H) 6.87 (d, *J*=8.8 Hz, 4 H) 4.81 (br. s., 4 H) 3.71 (s, 6 H).

6-(2-(Bis(4-methoxybenzyl)amino)pyrimidin-4-yl)-1*H*-indazol-3-amine (66).

Compound **65** (301 mg, 0.662 mmol) was suspended in ethanol (11.0 ml, 0.06M) and hydrazine monohydrate (1.0 ml, 20.37 mmol) was added. The reaction was run overnight at 95 °C, then left standing overnight. A bright yellow precipitate was observed and collected by vacuum filtration to afford the title compound as a bright yellow solid (124 mg, 40%). LCMS [M+H]⁺ 467.15 m/z; ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 11.59 (s, 1 H) 8.45 (d, *J*=5.4 Hz, 1 H) 8.03 (s, 1 H) 7.76 (d, *J*=8.3 Hz, 1 H) 7.64 (d, *J*=8.8 Hz, 1 H) 7.29 (d, *J*=5.4 Hz, 1 H) 7.24 (br. s., 4 H) 6.89 (d, *J*=8.8 Hz, 4 H) 5.43 (s, 2 H) 4.81 (br. s., 4 H) 3.72 (s, 6 H).

N-benzyl-6-(2-(bis(4-methoxybenzyl)amino)pyrimidin-4-yl)-1*H*-indazol-3-amine (67).

Benzal-dehyde (0.06 ml, 0.588 mmol) was dissolved in DCM (1.9 ml, 0.31 M) and compound **66** (197 mg, 0.422 mmol), and acetic acid (50 μl, 0.874 mmol) were added in that order. Upon addition of acetic acid, the reaction mixture went from cloudy yellow to clear yellow. The reaction was stirred at room temperature for ~40 minutes, after which NaHB(OAc)₃ (313 mg, 1.48 mmol) was added. The reaction was stirred overnight at room temperature. The reaction was diluted with DCM and washed twice with 3M NaOH, once with water, and once with brine. The organic layer was dried with sodium sulfate and concentrated under reduced pressure. The crude material was purified three times by flash chromatography (0–50% EtOAc:Hex, then 1–10% MeOH:DCM, then 0–20% EtOAc:DCM) to afford the title compound as a pale yellow solid (77 mg, 33%). LCMS [M+H]⁺ 557.12 m/z; ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 11.63 (s, 1 H) 8.46 (d, *J*=5.4 Hz, 1 H) 8.05 (s, 1

H) 7.84 (d, $J=8.3$ Hz, 1 H) 7.65 (d, $J=8.8$ Hz, 1 H) 7.41 (d, $J=6.8$ Hz, 2 H) 7.28 – 7.33 (m, 3 H) 7.18 – 7.27 (m, 5 H) 6.88 (d, $J=8.8$ Hz, 4 H) 6.65 (t, $J=6.1$ Hz, 1 H) 4.82 (br. s., 4 H) 4.48 (d, $J=5.9$ Hz, 2 H) 3.72 (s, 6 H).

6-(2-aminopyrimidin-4-yl)-N-benzyl-2H-indazol-3-amine (68).

To compound **67** (77 mg, 0.138 mmol) was added TFA (0.3 ml, 3.92 mmol). The reaction was run overnight at 95 °C. The reaction mixture was diluted with MeOH and purified by preparative HPLC (5–50% water:acetonitrile), then repurified by flash chromatography (20% EtOAc:Hex - 0–5% MeOH:DCM) to afford the title compound as a yellow solid (9.6 mg, 22%). LCMS $[M+H]^+$ 317.11 m/z; ^1H NMR (500 MHz, METHANOL- d_4) δ ppm 8.29 (d, $J=5.4$ Hz, 1 H) 8.00 (s, 1 H) 7.80 (d, $J=8.3$ Hz, 1 H) 7.63 (dd, $J=8.5, 1.2$ Hz, 1 H) 7.44 (d, $J=6.8$ Hz, 2 H) 7.31 (dd, $J=7.6$ Hz, 2 H) 7.23 (t, $J=7.3$ Hz, 1 H) 7.17 (d, $J=5.4$ Hz, 1 H) 4.56 (s, 2 H).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations used

| | |
|-------------------------|---------------------------------------------|
| BID | twice daily |
| BOXI | benzoxazepinoindazole |
| Cl_{int} | intrinsic clearance |
| C_{max} | maximum concentration |
| CNS-MPO | CNS-multiparameter optimization |
| GSK | GlaxoSmithKline |
| HAT | human African trypanosomiasis |
| HLM | human liver microsomes |
| NECT | nifurtimox-eflornithine combination therapy |
| NTD | neglected tropical disease |
| PPB | plasma protein binding |

| | |
|------------------------------|-------------------------------------------------|
| QD | once daily |
| SD | standard error of the mean |
| <i>T.b.b.</i> | <i>Trypanosoma brucei brucei</i> |
| TEA | triethylamine |
| t_{\max} | time at which maximum concentration is achieved |
| TPSA | topological polar surface area |

References

1. World Health Organization. Neglected Tropical Diseases. http://www.who.int/neglected_diseases/diseases/en/ (accessed November 24, 2015).
2. Buscher P; Cecchi G; Jamonneau V; Priotto G, Human African trypanosomiasis. Lancet 2017, 390, 2397–2409. [PubMed: 28673422]
3. (a) Drugs for Neglected Diseases Initiative. Fexinidazole (HAT). <http://www.dndi.org/diseases-projects/portfolio/fexinidazole/> (accessed February 13, 2018); (b) Mesu VKBKM; Kalonji WM; Bardonneau C; Mordt OV; Blesson S; Simon F; Delhomme S; Bernhard S; Kuziena W; Lubaki J-PF; Vuvu SL; Ngima PN; Mbembo HM; Ilunga M; Bonama AK; Heradi JA; Solomo JLL; Mandula G; Badibabi LK; Dama FR; Lukula PK; Tete DN; Lumbala C; Scherrer B; Strub-Wourgaft N; Tarral A, Oral fexinidazole for late-stage African *Trypanosoma brucei gambiense* trypanosomiasis; a pivotal multicentre, randomised, non-inferiority trial. Lancet 2017, 391 (10116), 144–154; [PubMed: 29113731] (c) Drugs for Neglected Diseases Initiative. Acoziborole. <http://www.dndi.org/diseasesprojects/portfolio/scyx-7158/> (accessed February 13, 2017).
4. Klug DM; Gelb MH; Pollastri MP, Repurposing strategies for neglected diseases. Bioorg. Med. Chem. Lett 2016, 26, 2569–2575. [PubMed: 27080183]
5. Merritt C; Silva LE; Tanner AL; Stuart K; Pollastri MP, Kinases as druggable targets in trypanosomatid protozoan parasites. Chem. Rev 2014, 114, 11280–11304. [PubMed: 26443079]
6. Diaz R; Luengo-Arratta S; Seixas J. o. D.; Amata E; Devine W; Cordon-Obras C; Rojas-Barros DI; Jimenez E; Ortega F; Crouch S; Colmenarejo G; Fiandor JM; Martin JJ; Berlanga M; Gonzalez S; Manzano P; Navarro M; Pollastri MP, Identification and characterization of hundreds of potent and selective inhibitors of *Trypanosoma brucei* growth from a kinase-targeted library screening campaign. PLoS Negl. Trop. Dis 2014, 8 (10), e3253. [PubMed: 25340575]
7. Shultz MD, The thermodynamic basis for the use of lipophilic efficiency (LipE) in enthalpic optimizations. Bioorg Med Chem Lett 2013, 23, 5992–6000. [PubMed: 24054120]
8. Wager T; Hou X; Verhoest PR; Villalobos A, Moving beyond rules: The development of a central nervous system multiparameter optimization (CNS MPO) approach to enable alignment of druglike properties. ACS Chem. Neurosci 2010, 1, 435–449. [PubMed: 22778837]

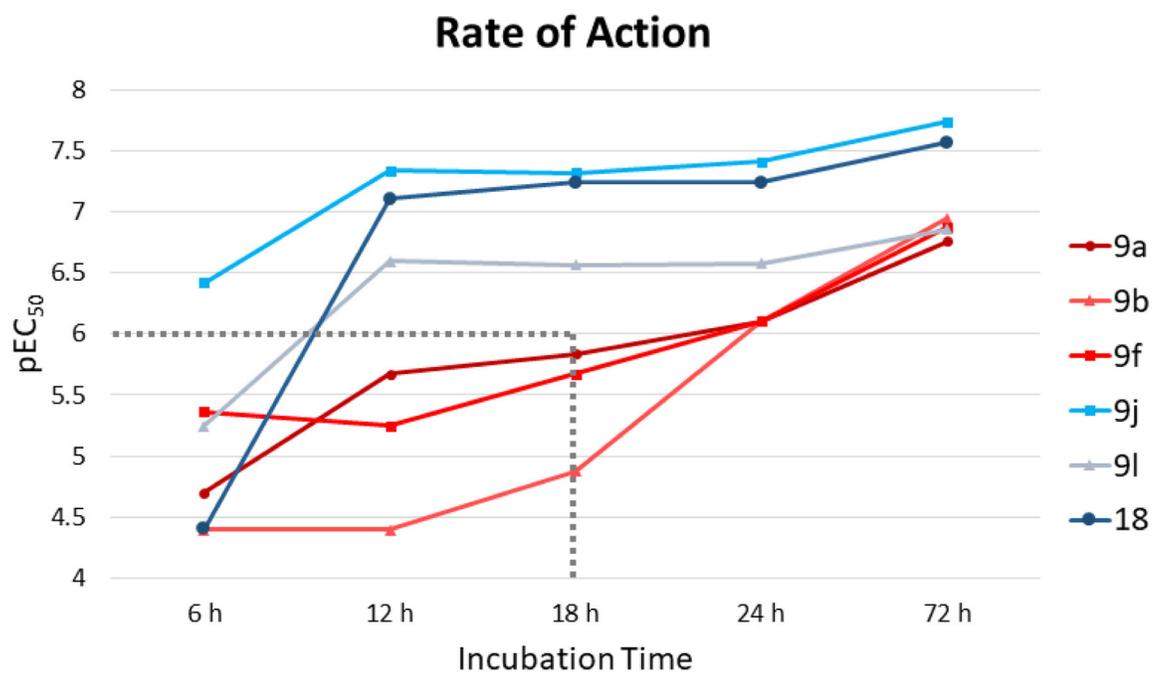


Figure 1. Rate of action of selected analogs. Slow-acting compounds **9a**, **9b**, and **9f** are represented in red and fast-acting compounds **9j**, **9l**, and **18** are represented in blue. Dotted gray lines show the cutoff of pEC₅₀ of 6 at 18 h incubation time.

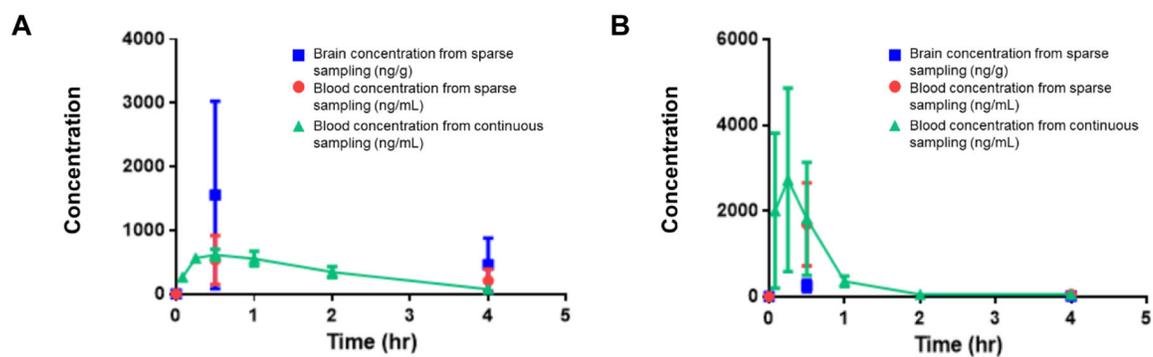


Figure 2.
Brain and blood concentrations of (A) **18** and (B) **57a** over time after a 10 mg/kg intraperitoneal dose.

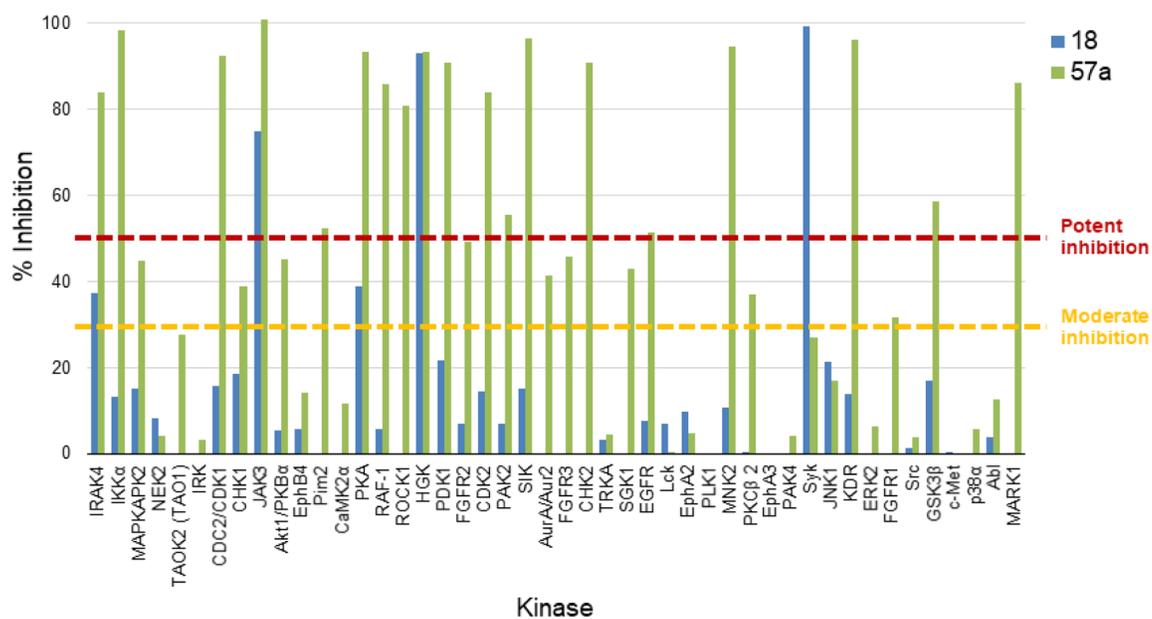


Figure 3. Percent inhibition of a human kinase panel for **18** (blue) and **57a** (green). Compounds were tested at a 1 μ M concentration.

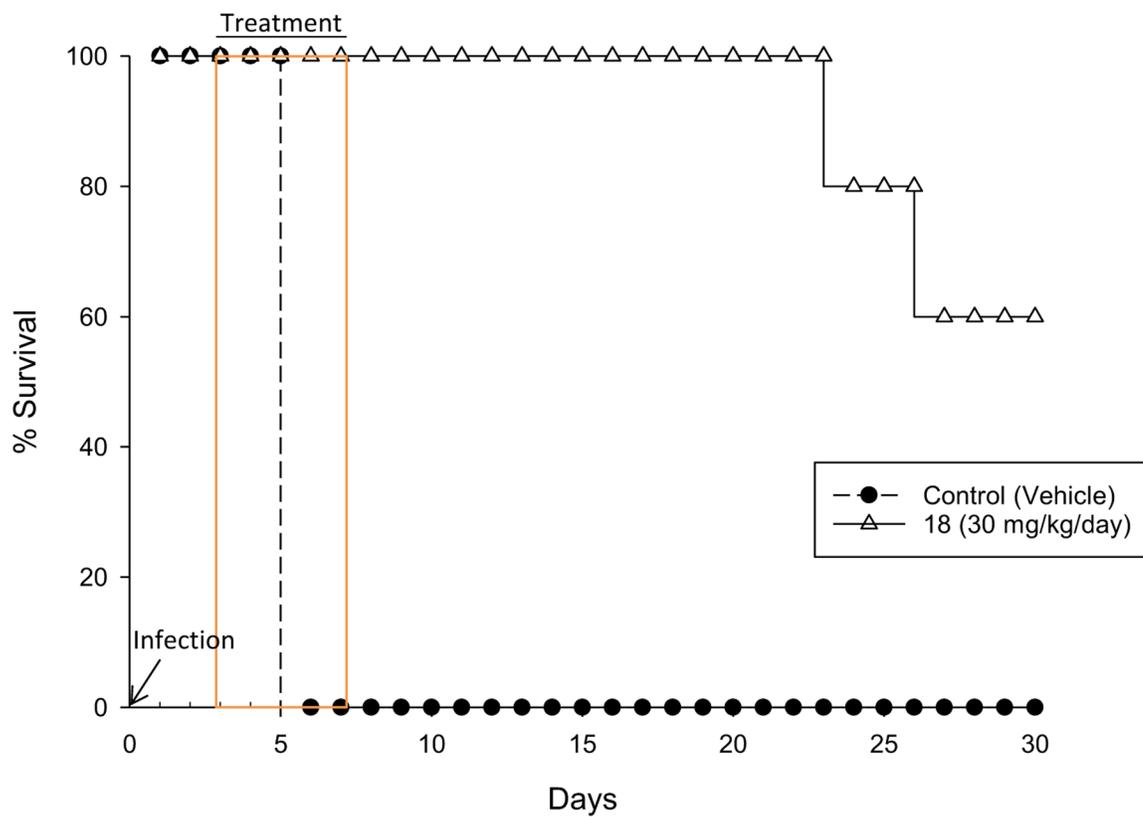


Figure 4. Efficacy model results. Control mice are represented by closed circles and mice treated with 30 mg/kg/day **18** (IP dosing) are represented by open triangles.

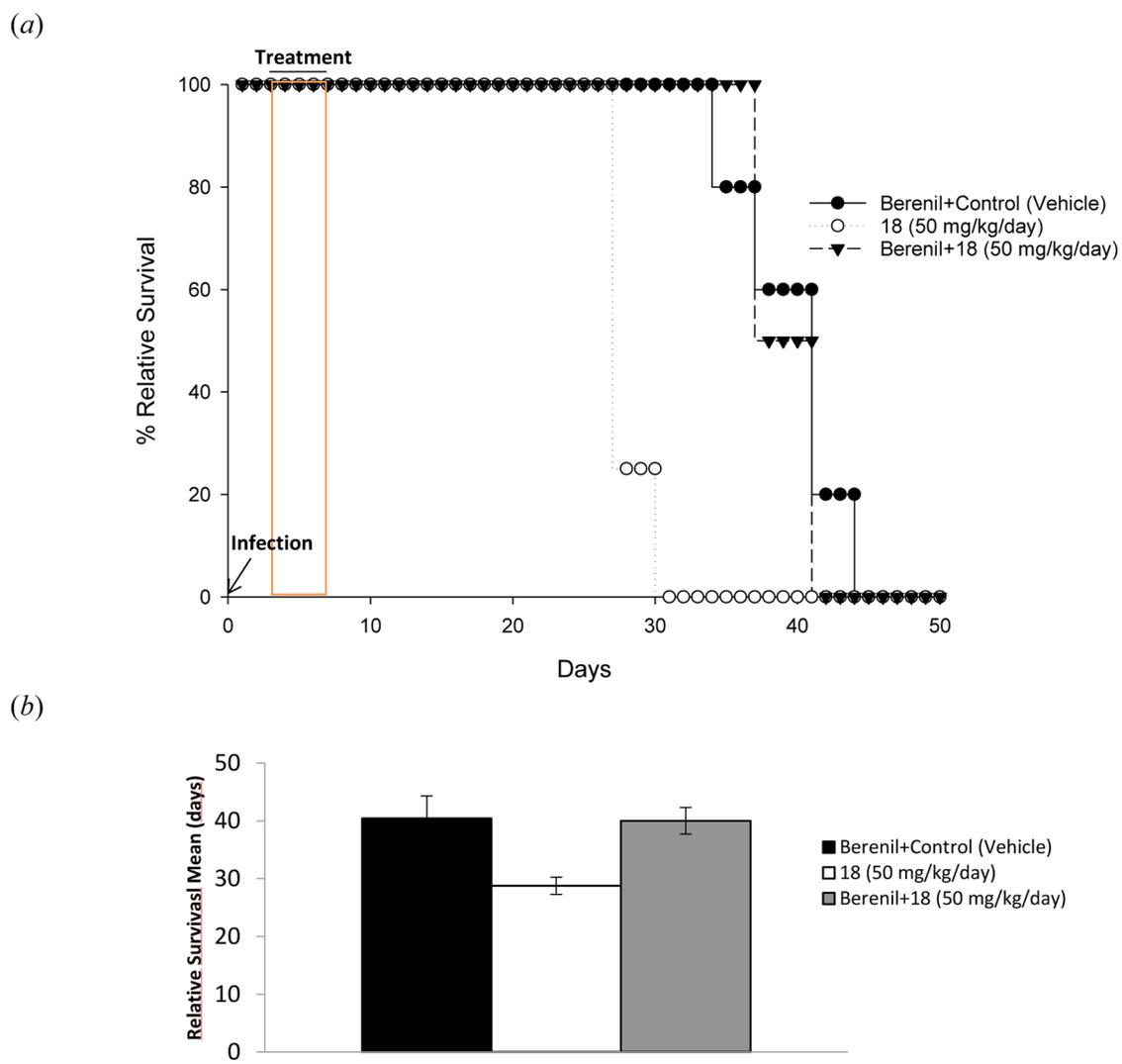
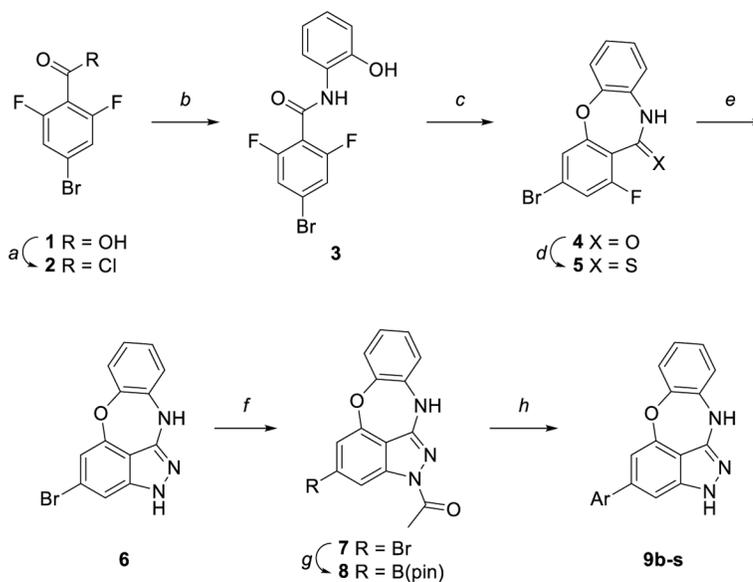
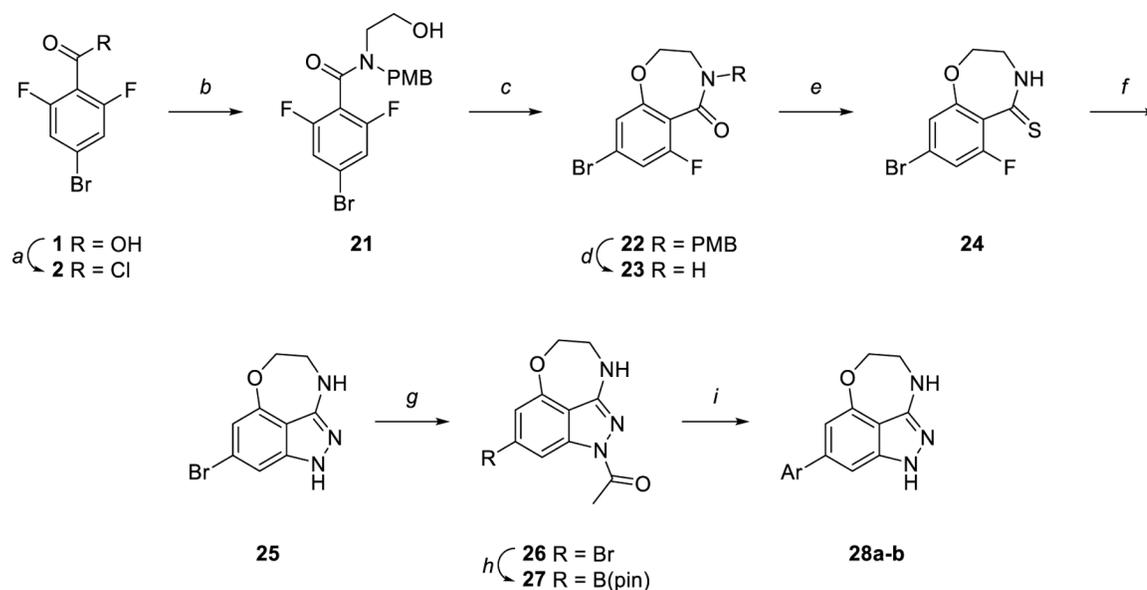


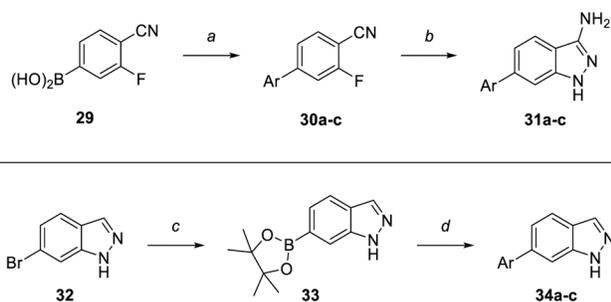
Figure 5. CNS efficacy model results. (a) Relative survival of control mice (closed circles), Treatment 1 mice (closed triangles) and Treatment 2 mice (open circles). (b) Relative survival mean of the control (black), Treatment 1 (white), and Treatment 2 (gray) groups.

**Scheme 1.**

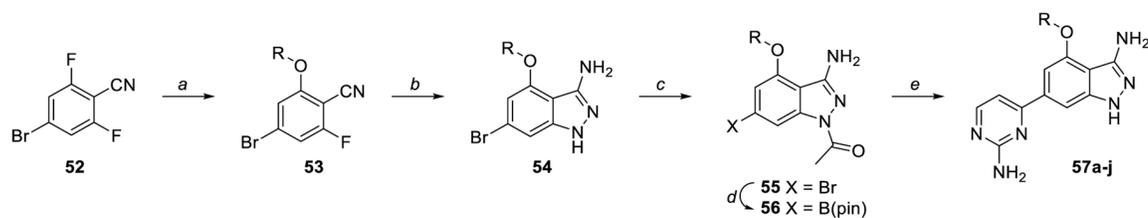
Synthesis of compounds **9a-s**. Reagents and reaction conditions: *a*) SOCl_2 , 75 °C, 4 h (quant.). *b*) 2-aminophenol, TEA, DCM, 0 °C to rt, 12 h (87%). *c*) K_2CO_3 , DMF, rt, 36 h (72%). *d*) Lawesson's reagent, toluene, 100 °C, 12 h (68%). *e*) Hydrazine, dioxane, 85 °C, 3 h (89%). *f*) Acetic anhydride, 100 °C, 3 h (93%). *g*) $\text{B}_2(\text{pin})_2$, KOAc, $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$, dioxane, 145 °C, μw , 1 h (65%). *h*) Aryl halide, K_2CO_3 , $\text{Pd}(\text{PPh}_3)_4$, 3:1 dioxane:water, 100 °C, 4 h (10–74%).

**Scheme 2.**

Synthesis of oxazepinoindazole core. Reagents and reaction conditions: *a*) SOCl_2 , 75°C , 4 h (quant.). *b*) 2-((4-Methoxy-benzyl)amino)ethan-1-ol or ethanolamine, TEA, DCM, 0°C to rt, 12 h (54%). *c*) NaH, DMF, rt, 12 h (96%). *d*) CAN, 3:1 acetonitrile:water, rt, 3 h (36%). *e*) Lawesson's reagent, toluene, 100°C , 12 h (56%). *f*) Hydrazine, dioxane, 85°C , 3 h (95%). *g*) Acetic anhydride, 100°C , 3 h (60%). *h*) $\text{B}_2(\text{pin})_2$, KOAc, $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$, dioxane, 145°C , μw , 1 h (79%). *i*) Aryl halide, K_2CO_3 , $\text{Pd}(\text{PPh}_3)_4$, 3:1 dioxane:water, 100°C , 4 h (12–34%).

**Scheme 3.**

Synthesis of indazoles and aminoindazoles. Reagents and reaction conditions: *a*) Aryl halide, NaHCO₃ (sat. aq.), Pd(PPh₃)₄, dioxane, 95 °C, 3 h (43–97%). *b*) Hydrazine, EtOH, 95 °C, 12 h (71–87%). *c*) B₂(pin)₂, KOAc, PdCl₂(dppf)·CH₂Cl₂, dioxane, 145 °C, μw, 30 min – 1.5 h. *d*) Aryl halide, K₂CO₃, PdCl₂(dppf)·CH₂Cl₂, 3:1 dioxane:water, 150 °C, μw 30 min, (6–26%). Where no yield is reported, crude material was progressed without further purification.

**Scheme 4.**

Synthesis of ring-opened analogs. Reagents and reaction conditions: *a*) Alcohol, LHMDS (1 M in THF), THF, 0 °C to rt, 2 days (55–86%). *b*) Hydrazine, ethanol, 95 °C, 12 h (71–87%). *c*) Boc₂O, DMAP, DCM, rt, 12 h (75%); or Ac₂O, pyridine, 100 °C, 3.5 h (24–75%). *d*) B₂(pin)₂, KOAc, PdCl₂(dppf)·CH₂Cl₂, dioxane, 145 °C, μw, 30 min – 1.5 h. *e*) Aryl halide, K₂CO₃, PdCl₂(dppf)·CH₂Cl₂, 3:1 dioxane:water, 150 °C, μw 30 min, (6–26%). Where no yield is reported, crude material was progressed without further purification.

Table 1.

Targeted, cluster average, and individual cluster member values for properties of interest. Values highlighted in green meet or exceed targeted values; yellow highlighting indicates mid-range values, and red highlighting indicates values that are well outside the targeted value. *nd* = no data.

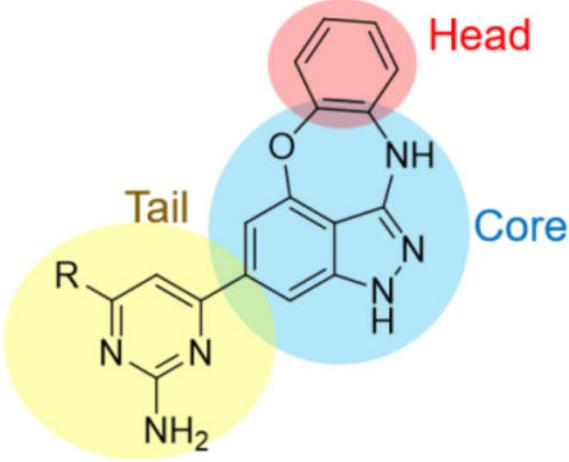
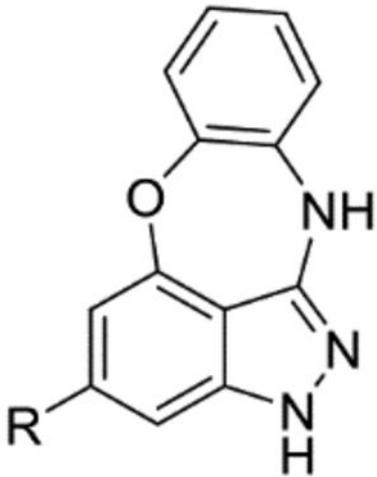
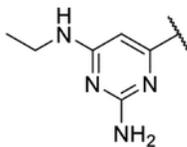
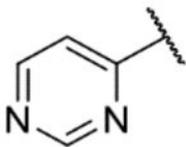
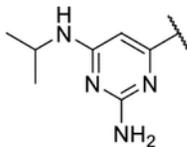
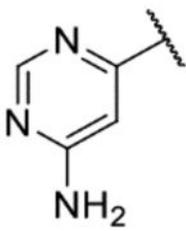
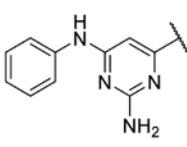
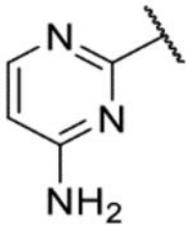
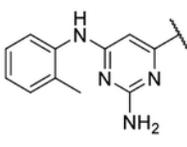
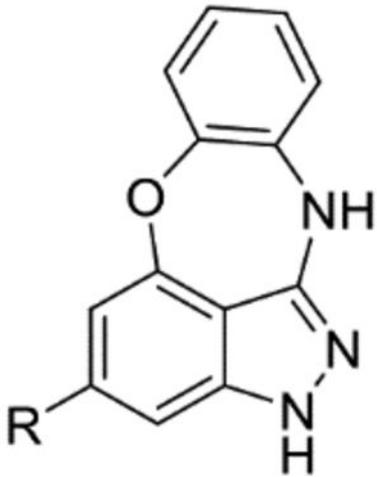
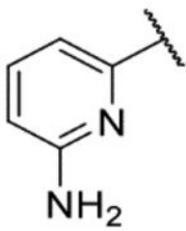
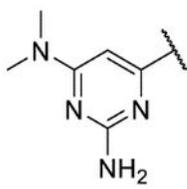
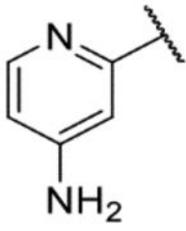
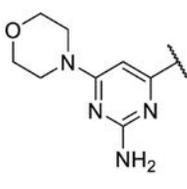
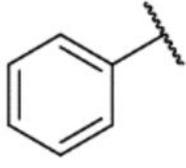
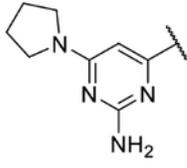
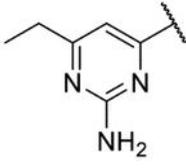
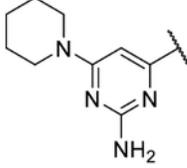
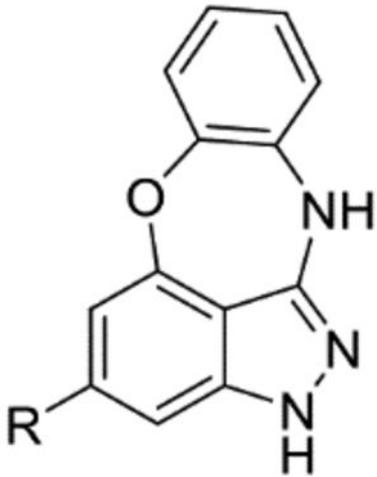
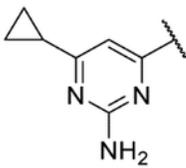
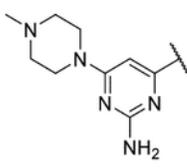
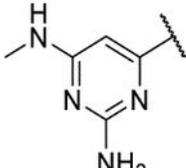
| |  | | | | |
|---------------------------------|-----------------------------------------------------------------------------------|-----------------|--------------------------------------|---------------------|-----------|
| | Targeted Value | Cluster Average | NEU-1117 | NEU-1118 | NEU-1119 |
| | | | R = CH ₂ OCH ₃ | R = NH ₂ | R = H |
| <i>T.b.b.</i> pEC ₅₀ | 7 | 7.6 | 8.1 | 8.9 | 8.4 |
| HepG2 pTC ₅₀ | pEC ₅₀ -2 | 4.8 | 5.1 | 5.5 | 4.0 |
| cLogP | 3 | 3.9 | 2.2 | 3.7 | 3.7 |
| TPSA (Å ²) | 40 < x < 90 | 106 | 110 | 130 | 100 |
| MW (Da) | 360 | 332 | 360 | 330 | 320 |
| LLE | 4 | 3.7 | 5.8 | 5.2 | 4.7 |
| CNS-MPO Score | 4 | 3.9 | 4.4 | 3.9 | 4.5 |
| Fast | Yes | 85% | Yes | Yes | Yes |
| Cidal | Yes | 69% | Yes | Yes | No |
| Aq. Sol. (μM) | >10 | -- | 11 | 4 | 8 |
| PPB (%) | <95 | -- | 98 | 97 | <i>nd</i> |

Table 2.

Biological activity and LLE of tail replacement analogs.

|  | | | | | | | | | |
|------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------|-------------------|-----|-----------------|---------------------------------------------------------------------------------------|-----------------------------------|-------------------|------|
| ID | R | <i>T.bb.</i> pEC ₅₀ | pTC ₅₀ | LLE | ID | R | <i>T.bb.</i> pEC ₅₀ | pTC ₅₀ | LLE |
| 9a | H | 6.2 | 4.0 | 2.1 | 9k |  | 7.8 | 4.6 [†] | 5.1 |
| 9b |  | 6.9 | <4.3 [†] | 4.2 | 9l |  | 6.9 | <4.3 [†] | 3.7 |
| 9c |  | 7.2 | 4.8 | 3.5 | 9m [*] |  | 7.2 | 5.0 | 0.85 |
| 9d |  | 6.6 | <4.3 [†] | 3.5 | 9n [*] |  | 7.5 | 5.3 | 0.66 |

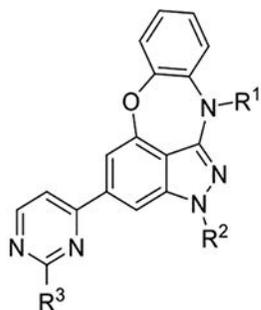
| | |  | | | | | | | |
|----|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|-------------------|-----|----|---------------------------------------------------------------------------------------|------------------------------------|-------------------|------|
| ID | R | <i>T.b.b.</i> pEC ₅₀ | pTC ₅₀ | LLE | ID | R | <i>T.b.b.</i> pEC ₅₀ | pTC ₅₀ | LLE |
| 9e |  | 6.7 | <4.3 [†] | 3.6 | 9o |  | 6.3 | 4.8 [†] | 3.2 |
| 9f |  | 6.9 | nd | 4.8 | 9p |  | 6.3 | <4.3 [†] | 3.4 |
| 9g |  | 5.7 | <4.3 [†] | 1.5 | 9q |  | 6.1 | 4.7 [†] | 2.7 |
| 9h |  | 7.9 | 4.8 | 3.2 | 9r |  | 4.8 | <4.3 [†] | 0.91 |

| | | | |  | | | | | |
|-----|-------------------------------------------------------------------------------------|------------------------------------|-------------------|------------------------------------------------------------------------------------|----|-------------------------------------------------------------------------------------|------------------------------------|-------------------|-----|
| ID | R | <i>T.b.b.</i> pEC ₅₀ | pTC ₅₀ | LLE | ID | R | <i>T.b.b.</i> pEC ₅₀ | pTC ₅₀ | LLE |
| 9i* |  | 7.7 | 4.6 | 3.1 | 9s |  | 5.7 | <4.3 [†] | 2.3 |
| 9j |  | 7.7 | 5.3 | 3.2 | | | | | |

* HTS hit, not resynthesized.

Data obtained against MRC5 cells are indicated with †; otherwise, HepG2 data is presented.

All SD within ± 0.20.

Table 3.Biological activity of *N*-methylated analogs. All SD within ± 0.08 .

| ID | R ¹ | R ² | R ³ | <i>T.b.b.</i> pEC ₅₀ | MRC 5 pTC ₅₀ | LLE |
|-----------|-----------------|-----------------|----------------------------------|------------------------------------|-------------------------------|-----|
| 15 | CH ₃ | H | NH ₂ | 5.1 | <4.3 | 2.3 |
| 18 | H | CH ₃ | NH ₂ | 7.6 | <4.3 | 4.9 |
| 19 | H | H | N(CH ₃) ₂ | 5.3 | <4.3 | 1.9 |
| 20 | H | H | NHCH ₃ | 7.0 | <4.3 | 3.8 |

Table 4.

ADME properties of selected analogs.

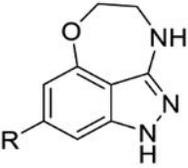
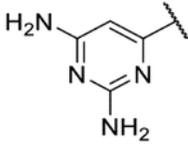
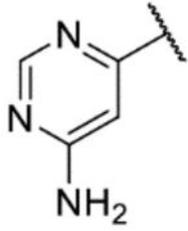
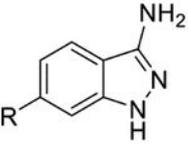
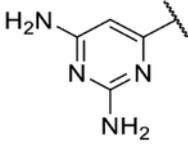
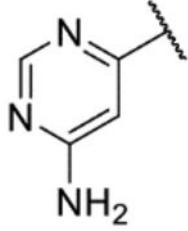
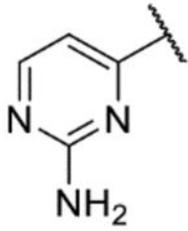
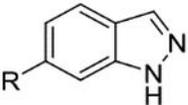
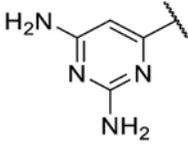
| ID | <i>T.b.b.</i> PEC ₅₀ | cLogP | LogD | Aq. sol. (μM) | PPB (%) | HLM Cl _{int} (μg/min/mg protein) | Rat Hepatocyte Cl _{int} (μg/min/10 ⁶ cells) |
|----|---------------------------------|-------|------|---------------|---------|-------------------------------------------|-----------------------------------------------------------------|
| 9a | 6.2 | 2.9 | 4.1 | 19 | >99 | 7.6 | 47 |
| 9b | 6.9 | 3.0 | 3.5 | <1 | >96 | 130 | 68 |
| 9c | 7.2 | 2.8 | 3.8 | 0.6 | >99 | 52 | 73 |
| 9d | 6.6 | 3.4 | 4.1 | 4 | >99 | 34 | 56 |
| 9e | 6.7 | 3.5 | 3.7 | 9 | >81 | 99 | 220 |
| 9j | 7.7 | 2.9 | >4.2 | 2 | >95 | 9.5 | 45 |
| 9k | 7.8 | 3.3 | 4.6 | 2 | >99 | 9 | 26 |
| 9l | 6.9 | 3.7 | 4.9 | 9 | >99 | 6.7 | 32 |
| 9o | 6.3 | 3.6 | >4.4 | 0.4 | >99 | 63 | 44 |
| 9r | 4.8 | 4.4 | 4.6 | 0.3 | >99 | 17 | 25 |
| 9s | 5.7 | 3.4 | 3.4 | 26 | 97* | 41 | 16 |
| 18 | 7.6 | 2.7 | >4.3 | 3 | nd | 110 | 12 |
| 19 | 5.3 | 3.8 | >3.9 | 0.7 | <99 | 51 | 29 |
| 20 | 7.0 | 3.2 | 3.8 | 1.9 | 99 | 55 | 45 |

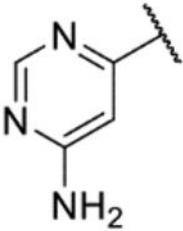
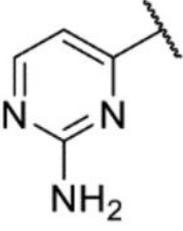
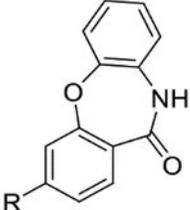
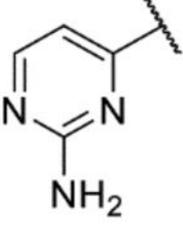
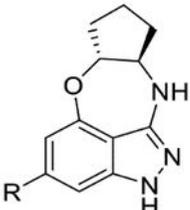
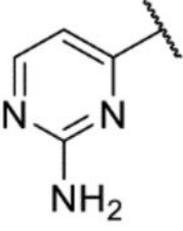
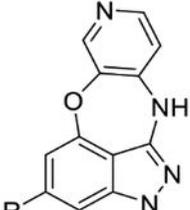
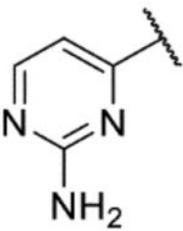
* Predicted PPB.

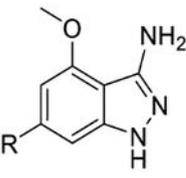
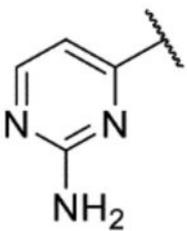
nd = no data.

Table 5.

Biological activity and selected ADME data for headgroup truncation and replacement analogs.

| ID | Core | R | <i>T.b.b.</i> pEC ₅₀ | MRC5 pTC ₅₀ | LLE | Aq. sol. (μM) | cLogP |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|---------------------------------|------------------------|-----|---------------|-------|
| 28a |  |  | 4.8 | <4.3 | 4.1 | 65 | 0.61 |
| 28b | |  | 5.4 | <4.3 | 4.7 | <i>nd</i> | 0.76 |
| 31a |  |  | 4.8 | <4.3 | 4.2 | 58 | 0.64 |
| 31b | |  | 4.8 | <4.3 | 4.0 | 5 | 0.79 |
| 31c | |  | 5.5 | <4.3 | 4.6 | <13 | 0.87 |
| 34a |  |  | 5.3 | <4.3 | 3.9 | 660 | 1.4 |

| ID | Core | R | <i>T.b.b.</i> pEC ₅₀ | MRC5 pTC ₅₀ | LLE | Aq. sol. (μM) | cLogP |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|---------------------------------|------------------------|-----|---------------|-------|
| 34b | |  | 4.3 | <4.3 | 2.8 | 332 | 1.5 |
| 34c | |  | 5.2 | <4.3 | 3.6 | 215 | 1.6 |
| 40 |  |  | 5.9 | <4.3 | 3.4 | 0.3 | 2.6 |
| 49 |  |  | 7.1 | <4.3 | 5.3 | 13 | 1.8 |
| 50* |  |  | 8.2 | 5.9 | 5.1 | 10 | 1.4 |

| ID | Core | R | <i>T.b.b.</i> pEC ₅₀ | MRC5 pTC ₅₀ | LLE | Aq. sol. (μM) | cLogP |
|-----------------|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|---------------------------------|------------------------|-----|---------------|-------|
| 51 [*] |  |  | 6.2 | 4.0 | 5.2 | >100 | 0.71 |

[†] Kinetic aqueous solubility.

^{*} Compound and data provided by GSK; HepG2 toxicity and kinetic aqueous solubility.

All SD within ± 0.19.

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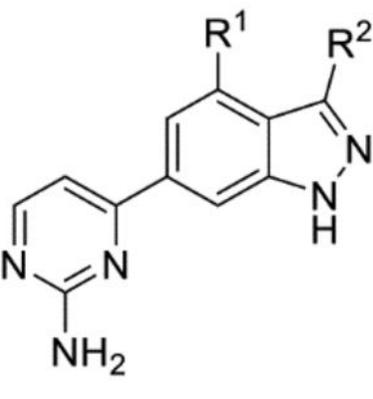
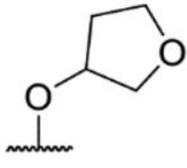
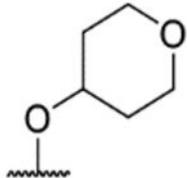
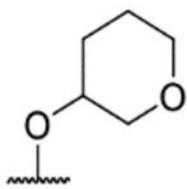
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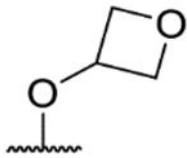
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Table 6.

Biological activity and selected ADME data for ring-opened analogs.

| | |  | | | | | |
|------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|---------------------------------|------------------------|-----|---------------|-------|
| ID | R ¹ | R ² | <i>T.b.b.</i> pEC ₅₀ | MRC5 pTC ₅₀ | LLE | Aq. sol. (μM) | cLogP |
| 31c | -H | -NH ₂ | 5.5 | <4.3 | 4.4 | <13 | 0.87 |
| 51 | -OMe | -NH ₂ | 6.2 | <4.3 | 5.2 | 196 | 0.71 |
| 57a | -OEt | -NH ₂ | 6.4 | 5.0 | 5.3 | 861 | 1.1 |
| 57b* | -OiPr | -NH ₂ | 6.4 | 5.0 | 4.9 | 354 | 1.5 |
| 57c | -OtBu | -NH ₂ | 6.2 | 4.6 | 4.4 | 68 | 1.8 |
| 57d | -OcyBu | -NH ₂ | 6.6 | 5.0 | 5.0 | <i>nd</i> | 1.6 |
| 57e* | -OPh | -NH ₂ | 5.7 | 5.7 | 3.3 | 117 | 2.4 |
| 57f* | -OBn | -NH ₂ | 5.9 | 5.0 | 3.4 | 85 | 2.4 |
| 57g |  | -NH ₂ | 5.5 | <4.3 | 4.9 | 751 | 0.62 |
| 57h |  | -NH ₂ | 5.8 | <4.3 | 5.1 | 770 | 0.68 |
| 57i |  | -NH ₂ | 6.1 | <4.3 | 5.0 | 1000 | 1.13 |

| ID | R ¹ | R ² | <i>T.b.b.</i> pEC ₅₀ | MRC5 pTC ₅₀ | LLE | Aq. sol. (μM) | cLogP |
|-----|-----------------------------------------------------------------------------------|------------------|---------------------------------|------------------------|-----|---------------|-------|
| 57j |  | -NH ₂ | 5.7 | <4.3 | 5.1 | 383 | 0.56 |
| 63 | -H | -NHPh | 5.4 | <4.3 | 2.1 | 3 | 3.1 |
| 68 | -H | -NHbn | 6.1 | <4.3 | 2.2 | 17 | 2.9 |

* Compound and data provided by GSK; HepG2 toxicity and kinetic aqueous solubility.

All SD within ± 0.16.

Table 7.Heat maps of **NEU-1117**, **18**, **49**, and **57a**.

| | Targeted Value | NEU-1117 | 18 | 49 | 57a |
|-----------------------------------------------------------------|----------------|----------|--------|-------|-------|
| <i>T.b.b.</i> pEC ₅₀ | >7.5 | 8.1 | 7.6 | 7.1 | 6.4 |
| MRC5 pTC ₅₀ | <5 | 5.1 | 4.3 | 4.3 | 4.3 |
| MW | 360 | 360.4 | 330.34 | 308.3 | 270.3 |
| cLogP | 3 | 2.6 | 2.7 | 2.0 | 1.1 |
| LogD (7.4) | 2 | >4 | >4.3 | 2.8 | 1.7 |
| LLE | 4 | 5.5 | 4.9 | 5.1 | 5.3 |
| MPO Score | 4 | 3.9 | 3.9 | 4.2 | 4.1 |
| Aq. sol. (μM) | >10 | 1 | 3 | 13 | 861 |
| HLM Cl _{int} (μg/min/mg protein) | <9 | 23.6 | 108 | nd* | 25 |
| Rat Hepatocyte Cl _{int} (μg/min/10 ⁶ cells) | <5 | 41.4 | 12.4 | 52 | 20.3 |
| PPB (%) | 95 | >99 | nd | 88 | 89 |

nd = no data.

* Compound was cleared too rapidly for detection.

Table 8.PK parameters for **18** and **57a**.

| ID | <i>T.b.b.</i> EC ₅₀ (ng/mL) | C _{max} (ng/mL) | t _{max} (h) | t _{1/2} (h) | Brain/blood ratio (t = 0.5 h) | Brain/blood ratio (t = 4 h) |
|------------|----------------------------------------|--------------------------|----------------------|----------------------|-------------------------------|-----------------------------|
| 18 | 8.9 | 615 ± 85.8 | 0.25–0.5 | 1.06 ± 0.235 | 2.39 ± 1.12 | 2.12 ± 0.52 |
| 57a | 96.2 | 3603 ± 636 | 0.25–0.5 | 0.893 ± 0.500 | 0.155 ± 0.021 | 0.214 |

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