Lead Optimization of 3,5-Disubstituted-7-Azaindoles for the Treatment of Human African Trypanosomiasis

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Abstract

Neglected tropical diseases such as human African trypanosomiasis (HAT) are prevalent primarily in tropical climates and among populations living in poverty. Historically, the lack of economic incentive to develop new treatments for these diseases has meant that existing therapeutics have serious shortcomings in terms of safety, efficacy, and administration, and better therapeutics are needed. We now report a series

of 3,5-disubstituted-7-azaindoles identified as growth inhibitors of *Trypanosoma brucei*, the parasite that causes HAT, through a high-throughput screen. We describe the hit-to-lead optimization of this series and the development and preclinical investigation of **29d**, a potent anti-trypanosomal compound with promising pharmacokinetic (PK) parameters. This compound was ultimately not progressed beyond *in vivo* PK studies due to its inability to penetrate the blood-brain barrier (BBB), critical for stage 2 HAT treatments.

Introduction

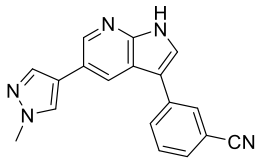
Human African trypanosomiasis (HAT) is designated by the World Health Organization as a neglected tropical disease (NTD), one of a group of 20 communicable diseases that are prevalent in tropical climates and disproportionately affect populations living in poverty.[1] HAT is caused by infection with either of two subspecies of the parasite *Trypanosoma brucei* (*T.b. gambiense* or *T.b. rhodesiense*), and is fatal if untreated.[2] The disease proceeds in two stages; in the first, patients exhibit milder, flu-like symptoms and thus often go undiagnosed. In the second, the parasite crosses the blood-brain barrier (BBB) and causes more serious neurological symptoms, such as the severe disruption of sleep patterns from which the disease takes the colloquial name "African sleeping sickness."[2] Historically, the treatments available for HAT have been sub-optimal in terms of efficacy, safety, and route of administration.[3] Recent advances include a combination therapy called NECT (nifurtimox-eflornithine combination therapy), which reduces the dose requirement for eflornithine, a repurposed cancer drug requiring hours-long intravenous infusions to administer, by combining it with nifurtimox, an oral treatment first used to treat Chagas disease (a related NTD).[3] Even more recently, the orally available drug fexinidazole has been approved to treat both stages of *T.b. gambiense* HAT and has been added to the WHO treatment guidelines;[4] and acoziborole, formerly known as SCYX-7158, has been advanced to Phase II/III clinical trials for HAT.[5, 6]

However, as with any infectious disease, resistance to current therapies may develop, and it is important to fill the pipeline with backup compounds. As much of the drug discovery for NTDs is done by academic laboratories with limited resources, repurposing strategies (including but not limited to drug repurposing)[7] are used to quickly identify chemical matter that may be suitable for further development. Such strategies take advantage of target function shared between human and parasite and assess compounds

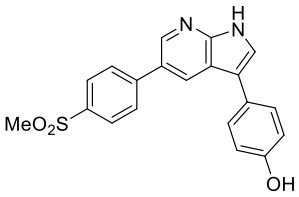
that were optimized against human targets as starting points for anti-parasitic agents. In this instance, we exploited the fact that trypanosomes are known to express essential kinases by repurposing compounds originally designed as inhibitors of human kinases.[8-10] A high-throughput screen (HTS) of over 40,000 kinase inhibitors, drawn largely from the published kinase inhibitor set (PKIS) and in-house GSK compounds, was undertaken and resulted in the identification of 797 compounds that showed *T. brucei* growth inhibition ($pEC_{50} > 6.0$) and 100× selectivity over HepG2 cells.[11] These hits were then clustered by structural similarity, and the most promising were selected for further optimization.

Due to a patient population that is likely to have limited access to health care facilities and the lack of effective therapeutics for stage 2 HAT, we sought a lead compound likely to be orally available and brain-penetrant. Therefore, in addition to potency against *T. brucei* and mammalian cell toxicity, physicochemical properties and metrics such as lipophilic ligand efficiency (LLE) and central nervous system multiparameter optimization (CNS-MPO) score were used to prioritize clusters for further optimization.[12, 13] One of the clusters identified through this HTS comprised a series of 3,5-disubstituted-7-azaindoles. **Table 1** highlights the properties of three compounds in this series: **NEU-1207**, **-1208**, and **-1209**. Both **NEU-1207** and **NEU-1208** display $pEC_{50} > 7.0$ against *T. brucei*; **NEU-1209** is ≥ 0.5 log units less potent. The longer aliphatic chain and primary amine of **NEU-1209** translate to sub-optimal physicochemical properties, such as high molecular weight and topological polar surface area (TPSA), and a low CNS-MPO score; however, the other two compounds had properties in acceptable ranges, and we felt the series warranted further investigation.

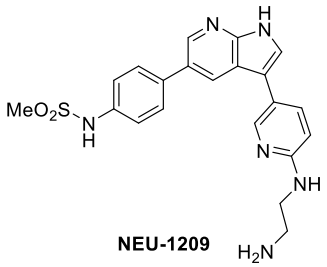
Table 1. Targeted versus measured and calculated values for properties of interest. *nd* = no data. Values highlighted in green meet or exceed targeted values; yellow highlighting indicates acceptable values, and red highlighting indicates values that are well outside the target. [†]Kinetic aqueous solubility.



NEU-1207



NEU-1208

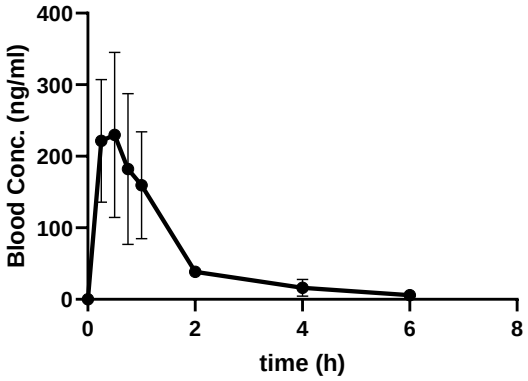


NEU-1209

	Targeted Value	NEU-1207	NEU-1208	NEU-1209
***T.b.b.* pEC_{50}**	≥7	7.0	7.2	6.5
HepG2 pTC_{50}	≤pEC_{50}-2	4.5	5.0	4.0
cLogP	≤3	2.6	2.8	2.2
TPSA (Å^2)	40<x≤90	70	83	130
MWt (Da)	≤360	300	360	420
LLE	≥4	4.4	4.4	4.3
CNS-MPO Score	≥4	5.4	4.9	3.1
Fast	Yes	Yes	Yes	No
Cidal	Yes	Yes	Yes	*nd*
Aq. Sol. (μM)	>10	2	18†	12†
PPB (%)	<95	95	*nd*	*nd*

In addition to these data, we also obtained pharmacokinetic (PK) data for **NEU-1207**. **Figure 1** shows the plasma concentration of this compound over time following a 5 mg/kg oral dose. The compound concentration was below the lower limit of quantitation after an average of 4.7 h *in vivo*, which is consistent with the high observed *in vitro* human liver microsome intrinsic clearance (HLM Cl_{int}) for this compound (190 μg/min/mg protein). Metabolism was therefore identified as a key liability of this series going forward. Given the data on the initial hits and the PK profile of **NEU-1207**, our major goals for the series were to maintain or improve potency against *T. brucei* while improving the ADME properties of **NEU-1207** (in particular, its clearance and solubility) in order to develop an effective, orally available HAT therapeutic.

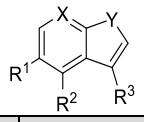
Figure 1. Plasma concentrations of **NEU-1207** over time after a 5 mg/kg oral dose.

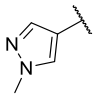
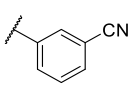


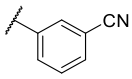
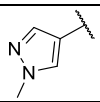
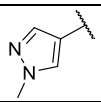
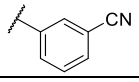
Results and Discussion

We first sought to establish structure-activity relationships (SAR) around the 7-azaindole core of the series. The biological activity of these analogs is shown in **Table 2** (preparation described in **Scheme S1-5**). Methylation (**1**) or tosylation (**2**) of the indole -NH resulted in a loss of activity against *T. brucei*, as did replacing the azaindole with a pyridofuran (**3**) or indole (**4**). These analogs demonstrated that the hydrogen bond donor/acceptor pair of the azaindole core was required for potency. The methylated-core analog **5**, which we anticipated might increase solubility by virtue of breaking the planarity of the molecule, maintained potency without any improvement in clearance or solubility. The substituents at the 3- and 5-positions of the core were interchangeable without sacrificing substantial activity (**6** vs **NEU-1207**), while removing either one (**7** and **8**) rendered the compound inactive.

Table 2. Biological activity of core replacement analogs. *nd* = no data. All pEC_{50} SD within ±0.17.

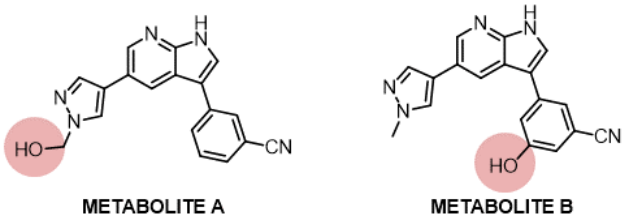


ID	X	Y	R^1	R^2	R^3	*T.b.b* pEC_{50}	MRC5 pTC_{50}	HLM Cl_{int} (µg/min/mg protein)	Aq. sol. (µM)
NEU-1207	N	NH		H		7.2	4.3	190	2
1	N	NMe		H		5.1	<4.3	180	3
2	N	NTs		H		5.7	<4.3	15	0.7
3	N	O		H		<4.3	<4.3	130	0.6
4	CH	NH		H		5.3	4.3	190	1.8
5	N	NH		Me		7.3	<4.3	210	0.6

6	N	NH		H		7.0	<4.3	300	*nd*
7	N	NH		H	H	4.7	<4.3	>300	299
8	N	NH	H	H		5.3	<4.3	*nd*	*nd*

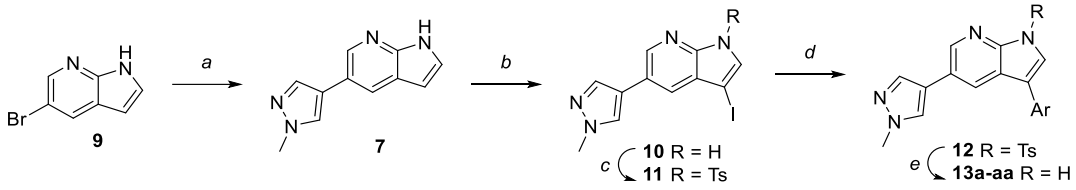
The HLM Cl_{int} of the core-replacement analogs was also assessed, but only compound **2** showed a significant reduction compared to **NEU-1207**. In order to better understand the high clearance of these compounds, predictive software was used to determine likely sites of metabolism. **Figure 2** shows the most likely metabolites for **NEU-1207** as predicted by MetaSite 5.0 (Molecular Discovery Ltd.): both are the products of oxidation at substituents on either the 3- or 5-position substituents of the 7-azaindole core, consistent with the clearance data presented in **Table 2**. We therefore focused further efforts on varying substituents at these positions.

Figure 2. Predicted metabolites of **NEU-1207** using MetaSite software.[14]



The synthesis of analogs varied at the 3-position is shown in **Scheme 1**. Maintaining the pyrazole at the 5-position, we employed a parallel-enabled synthetic route. The pyrazole was installed by reacting 5-bromo-7-azaindole **9** with 1-methyl-4-pyrazoleboronic acid pinacol ester under Suzuki conditions to afford intermediate **7**. This compound was iodinated using NIS and subsequently tosylated to afford intermediate **11**, which could then undergo a second Suzuki reaction with the desired boronic acid or ester to afford the protected products **12**. Under basic conditions, the tosyl group was removed to afford the final products **13a-aa**.

Scheme 1. Synthesis of 3-position analogs. Reagents and reaction conditions: *a*) 1-Methyl-4-pyrazoleboronic acid pinacol ester, K_2CO_3, $PdCl_2(dppf)\cdot CH_2Cl_2$, 3:1 dioxane:water, 85 °C, 4 h (93%). *b*) NIS, acetonitrile, 50 °C, 2 h (69%). *c*) Tosyl chloride, DMAP, TEA, DCM, rt, 12 h (89%). *d*) Aryl boronic acid or pinacol ester, K_2CO_3, $PdCl_2(dppf)\cdot CH_2Cl_2$, 3:1 dioxane:water, 120 °C, μw, 30 min (24-85%). *e*) NaOH (2M aq), dioxane, 150 °C, μw, 1-10 min (10-83%). Ar = aryl group.



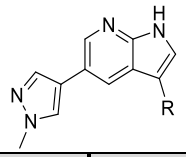
The *T. brucei* activity, *in vitro* clearance, and thermodynamic aqueous solubility of the aromatic benzonitrile replacements are shown in **Table 3**. Moving the nitrile to the 2- (**13a**) or 4- (**13b**) position of the benzene ring resulted in ~10-fold reduction in potency; an unsubstituted benzene ring (**13c**) was slightly more potent. 4-Chloro, -methyl, and -trifluoromethyl substituents (**13d-f, 13i**) were detrimental to anti-trypanosomal activity compared to the parent compound, while the methoxy group (**13g**) fared slightly better. A series of fluorinated analogs (**13j-o**), both with and without a nitrile group, maintained submicromolar potency, but only two of these compounds, the 3-fluoro (**13j**) and 3-cyano-5-fluoro (**13n**), were equipotent to **NEU-1207**. Although some of these compounds did show improved clearance over **NEU-1207**, all of them remain in the "high clearance" category (see Supporting Information, **Table S1**) and only a few were soluble at concentrations > 10 μM.

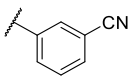
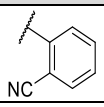
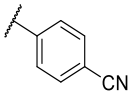
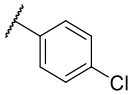
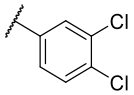
Further nitrile replacements included an amide (**13p**), carboxylic acid (**13q**), amine (**13r**), and nitro (**13t**) groups. Additionally, the 4-*N*,*N*-dimethylmethanamine (**13s**) and the 4-hydroxy (**13u**) substituents, both included in another azaindole-derived HTS cluster, were synthesized. Of these analogs, the amine and hydroxy substituents were equipotent to **NEU-1207**, and the nitro substituent showed an increase in potency (pEC_{50} 7.6). Although **13r** showed vastly improved solubility, the HLM Cl_{int} remained problematic, and both **13t** and **13u** showed signs of toxicity in mammalian cells (a known liability of nitrobenzenes and

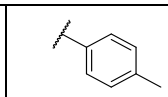
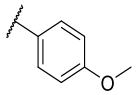
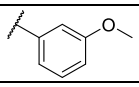
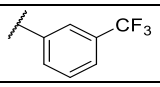
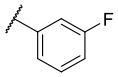
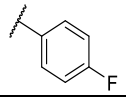
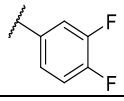
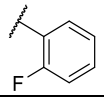
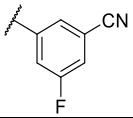
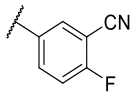
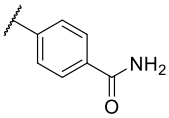
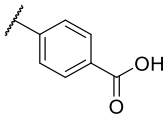
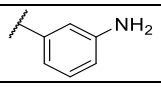
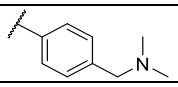
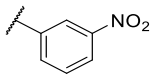
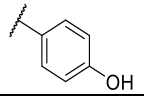
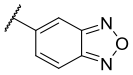
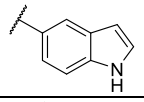
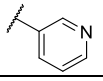
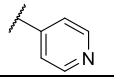
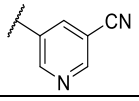
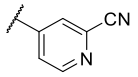
phenols; see Supporting Information, **Table S2**). The benzoxadiazole (**13v**) and indole (**13w**) were designed as bioisosteres of the nitro and hydroxy groups, respectively, in an attempt to recapitulate the improved potency and solubility of the parent compounds; however, both resulted in decreased activity against trypanosomes.

In a final attempt to improve the ADME properties by modification of the benzonitrile substituent, insertion of a heteroatom led to the 3-pyridyl (**13x**) and the 4-pyridyl (**13y**) analogs. Although these compounds did show a decrease in HLM Cl_{int} and an increase in solubility as compared to **NEU-1207**, they had lower anti-trypanosomal activity. Seeking additive SAR, we synthesized nitrile-substituted pyridyl groups (**13z-aa**), based on the previous SAR (cf **NEU-1207** vs **13c**). However, these analogs lost activity compared to the unsubstituted pyridyl compounds and the beneficial ADME properties were lost as well. Although **13y** showed the best combination of potency, clearance, and solubility, none of the aromatic groups installed at the 3-position had values within the desirable range for all three properties simultaneously.

Table 3. Biological activity, HLM Cl_{int}, and aqueous solubility of aromatic benzonitrile replacement analogs. *nd* = no data. All pEC_{50} SD within ±0.17.

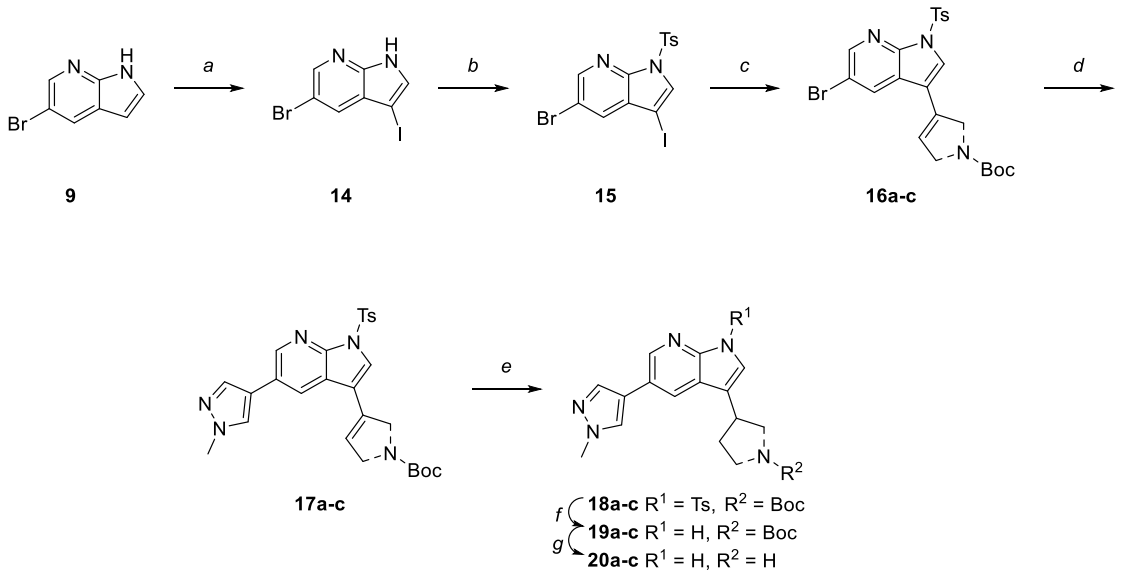


ID	R	*T.b.b* pEC_{50}	HLM Cl_{int} (µg/min/mg protein)	Aq. sol. (µM)	ID	R	*T.b.b* pEC_{50}	HLM Cl_{int} (µg/min/mg protein)	Aq. sol. (µM)
NEU-1207		7.2	190	2	**13a**		6.2	200	11
13b		6.0	51	2	**13c**		6.7	200	20
13d		5.8	57	0.8	**13e**		6.0	51	*nd*

13f		5.9	130	7	**13g**		6.8	180	5
13h		6.6	>300	18	**13i**		6.0	66	1
13j		7.1	110	3	**13k**		6.7	130	9
13l		6.3	90	5	**13m**		6.4	150	14
13n		6.9	91	0.5	**13o**		6.0	64	4
13p		6.6	14	3	**13q**		4.4	<3	850
13r		7.0	290	300	**13s**		5.7	*nd*	*nd*
13t		7.6	14	2	**13u**		7.2	50	<3
13v		6.5	88	0.3	**13w**		6.7	300	4
13x		6.7	90	97	**13y**		7.0	39	59
13z		6.0	150	17	**13aa**		5.6	190	2

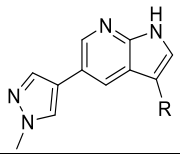
In addition to aromatic substituents, aliphatic groups were also installed at the 3-position. The synthesis of these analogs is shown in **Scheme 2**. The 5-bromo-7-azaindole starting material **9** was converted to the dihalide **14** and subsequently tosylated to afford intermediate **15**. A Suzuki reaction with 5- and 6-membered cyclic amine boronic acids produced the olefin compounds **16**, and a second Suzuki reaction to install the *N*-methylpyrazole at the 5-position afforded disubstituted intermediates **17**. The olefin was reduced via transfer hydrogenation using ammonium formate to produce intermediates **18**, which were subsequently deprotected to afford the final products **19a-c** and **20a-c**.

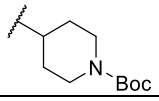
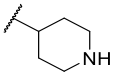
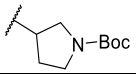
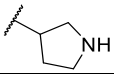
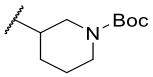
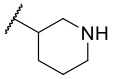
Scheme 2. Synthesis of aliphatic 3-position analogs. Reagents and reaction conditions: *a*) NIS, acetonitrile, 50 °C, 2h (83%). *b*) Tosyl chloride, Et_3N, DMAP, DCM, rt, 12 h (78%). *c*) Boronic ester, $PdCl_2(dppf)\cdot CH_2Cl_2$, K_2CO_3, 3:1 dioxane:water, 80 °C, 10 min, μw (56-73%). *d*) 1-Methyl-4-pyrazoleboronic acid pinacol ester, K_2CO_3, $PdCl_2(dppf)\cdot CH_2Cl_2$, 3:1 dioxane:water, 85 °C, 4 h (83-93%). *e*) NH_4COO, 10% Pd/C, EtOH, 85 °C, 1.5 h (59-68%). *f*) 2M aq. NaOH, dioxane, 150 °C, 15 min, μw (44-75%). *g*) HCl, dioxane, 1-3 h, rt (78-97%).



The biological activity, clearance, and solubility of analogs containing an aliphatic group at the 3-position are shown in **Table 4**. These compounds were designed to increase the Fsp^3, a known strategy to increase the solubility of highly aromatic, "flat" compounds.[15] None of these compounds displayed sub-micromolar activity against *T. brucei*, indicating that aromaticity in this position is essential for anti-trypanosomal activity. However, those compounds which possessed a basic amine showed a consistent and dramatic improvement in HLM Cl_{int} and aqueous solubility, the latter likely due to increased ionization at physiological pH.

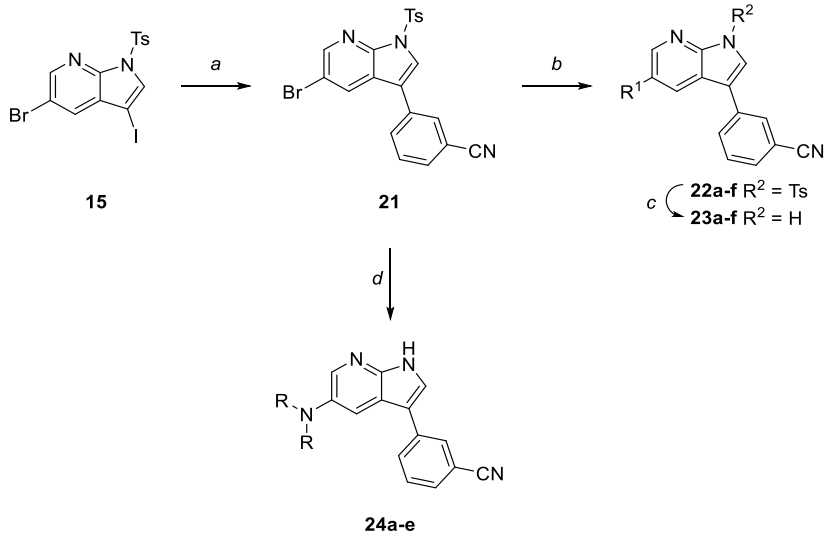
Table 4. Biological activity, HLM Cl_{int}, and aqueous solubility of aliphatic benzonitrile replacement analogs. All pEC_{50} SD within ±0.17.



ID	R	*T.b.b* pEC_{50}	HLM Cl_{int} (µg/min/ mg protein)	Aq. sol. (µM)	ID	R	*T.b.b* pEC_{50}	HLM Cl_{int} (µg/min/ mg protein)	Aq. sol. (µM)
19a		5.3	300	6	**20a**		5.1	3.0	770
19b		5.7	180	13	**20b**		5.2	<3.0	1000
19c		5.9	>300	17	**20c**		5.5	<3.0	1000

We next turned our attention to the pyrazole at the 5-position of the azaindole, also identified as a potential metabolic hotspot. Aromatic substituents were installed according to **Scheme 3** using the advanced intermediate **15**. Short reaction times in a microwave reactor enabled selective Suzuki coupling of the aryl iodide with (3-cyanophenyl)boronic acid to afford intermediate **21**. A second Suzuki reaction at the 5-position yielded intermediates **22**, which were detosylated to afford final products **23a-f**. Alternatively, intermediate **21** was subjected to palladium-mediated coupling conditions to afford 5-amino-substituted azaindoles **24**, where the tosyl group was deprotected under the reaction conditions. The synthesis of compounds **25-28** are presented in **Schemes S7-S8**.

Scheme 3. Synthesis of 5-position aromatic and cyclic amine analogs. Reagents and reaction conditions: *a*) (3-cyanophenyl)boronic acid, K_2CO_3, $PdCl_2(dppf)\cdot CH_2Cl_2$, 3:1 dioxane:water, 120 °C, µw, 5 min (60%). *b*) Aryl boronic acid or pinacol ester, K_2CO_3, $PdCl_2(dppf)\cdot CH_2Cl_2$, 3:1 dioxane:water, 85 °C, 4 h (31-84%). *c*) NaOH (2M aq), dioxane, 150 °C, µw, 1-10 min (10-83%). *d*) Amine, LiHMDS (1.0 M in THF), RuPhos, RuPhos Pd G1, 65 °C, 5 h (12-30%).

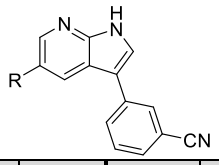


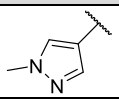
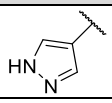
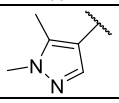
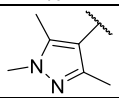
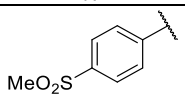
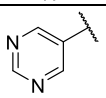
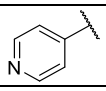
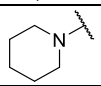
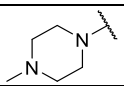
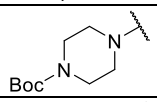
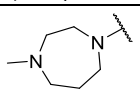
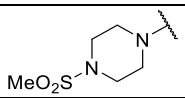
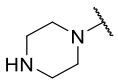
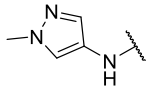
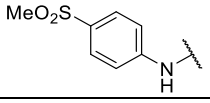
15 21 24a-e

The biological activity, clearance, and solubility data of the pyrazole replacement analogs are shown in **Table 5**. Many of the analogs with aromatic substituents (**23a-b**, **23d**, and **23f**), as well as compounds with an intervening *N* atom (**27**, **28**) were approximately equipotent with respect to **NEU-1207**, although the trisubstituted pyrazole (**23c**) and pyrimidine (**23e**) were almost 10-fold less potent. In general, aliphatic replacements of the pyrazole were inactive, except for the methylsulfonylpiperazine analog (**25**).

The clearance of pyrazoles **23a-c** remained quite high, whereas replacement with a methylsulfonyl benzene or pyrimidine significantly lowered the clearance, though poor aqueous solubility was still generally an issue with **23a** being the exception (aqueous solubility: 26 µM). In addition, most aliphatic substituents also had improved clearance over **NEU-1270**. Insertion of an intervening -NH resulted in improved solubility of compound **27**. This was thought to be due to the inclusion of an ionizable group, although **28** was no more soluble than its matched pair **23d**. Aliphatic substituents containing a basic nitrogen distal to the azaindole core (**24c**, **24e**, and **26**) resulted in significantly improved solubility; aliphatic substituents without this feature (**24a-b**) or those where the basicity of the distal nitrogen was attenuated by further substitution (**24d**, **25**) did not show similar improvement.

Table 5. Biological activity, HLM Cl_{int}, and aqueous solubility of aromatic and aliphatic pyrazole replacement analogs. *nd* = no data. All pEC_{50} SD within ±0.17.



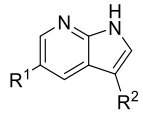
ID	R	*T.b.b* pEC_{50}	HLM Cl_{int} (µg/min/mg protein)	Aq. sol. (µM)	ID	R	*T.b.b* pEC_{50}	HLM Cl_{int} (µg/min/mg protein)	Aq. sol. (µM)
NEU-1207		7.2	190	2	**23a**		6.9	290	26
23b		7.3	250	2	**23c**		6.4	300	5.7
23d		7.2	30	1	**23e**		6.5	31	3
23f		7.3	160	0.2	**24a**		6.1	50	0.3
24b		5.4	300	4	**24c**		5.3	44	230
24d		5.9	94	12	**24e**		5.6	82	690
25		6.7	32	6.1	**26**		5.3	*nd*	240
27		7.2	15	31	**28**		7.0	33	2.1

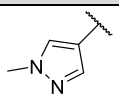
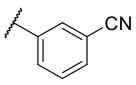
Finally, we explored a variety of substituted pyrazoles at the 5-position, including tetrahydropyran (**29a**), *N*-boc-piperidine (**29b**), and *N*-methyl piperidine (**29c**). The synthesis of these compounds is shown in **Scheme S9**. Of these, **29a** showed a significant (10-fold) improvement in potency, becoming the most potent compound to date for this series which was reflected in its high LLE. In addition, both **29a** and **29c** showed a significant reduction in HLM Cl_{int}, suggesting that the *N*-alkyl pyrazole moiety constitutes the major metabolic liability of this chemotype. This reduction in clearance represented a major step forward in resolving a critical issue for this series. However, all three of these substituted pyrazoles displayed poor solubility (<10 µM), prompting further optimization efforts.

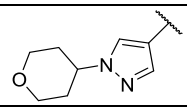
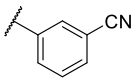
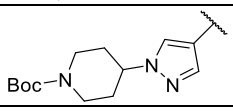
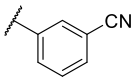
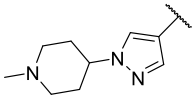
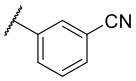
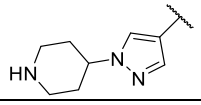
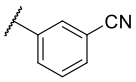
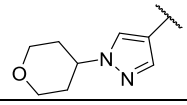
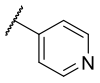
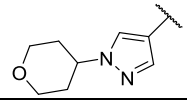
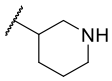
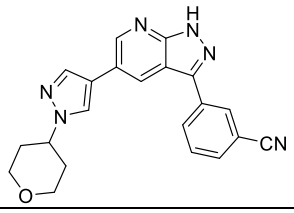
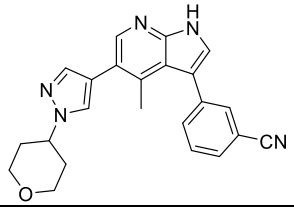
We sought to improve the solubility of **29a** using insights from the established SAR. Previously, both pyridyl and saturated groups at the 5-position had resulted in higher solubility. The synthesis of these compounds with the tetrahydropyran-substituted pyrazole in the 5-position is shown in **Schemes S10-S11**. In this case, inclusion of the pyridine (**30**) did not result in significant solubility improvement, and inclusion of a saturated group (**31**), while improving both solubility and HLM clearance, was significantly detrimental to potency, despite the presence of the THP-substituted pyrazole. Replacement of the tetrahydropyran moiety with a piperidinyl group (**29d**) to incorporate an additional H-bond donor resulted in a compound with the best combination of potency, solubility, and clearance thus far.

In a final effort to improve the ADME properties of **29a**, we returned to the strategy of making further modifications to the core (synthesis shown in **Scheme S12**). It was hypothesized that increasing the polarity of the azaindole may improve clearance and solubility; as such, the azaindole core was replaced with a pyrazolopyridine (**32**). Additionally, *ortho*-methylation is known to improve aqueous solubility of compounds,[16] and we had previously demonstrated that this change did not impact the potency of the series (cf. compound **5**). We reasoned that the installation of a methyl at the 4-position of **29d** (compound **33**) could increase aqueous solubility due to a steric clash with the tetrahydropyran that would twist the substituent out of plane. However, neither of these modifications produced the desired improvement in ADME properties.

Table 6. Biological activity, HLM Cl_{int}, and aqueous solubility of substituted pyrazoles and related analogs. All pEC_{50} SD within ±0.17.



ID	R^1	R^2	*T.b.b* pEC_{50}	LLE	HLM Cl_{int} (µg/min/mg protein)	Aq. sol. (µM)
NEU-1207			7.2	4.4	190	2

29a			8.1	5.3	46	0.6
29b			7.3	3.5	91	1.8
29c			7.7	4.9	17	3.8
29d			7.2	4.8	<3	25
30			7.0	5.3	29	5.9
31			5.0	3.6	<3	680
32			7.3	4.9	42	0.7
33			8.1	4.8	34	2

Given its combination of high potency, improved LLE, low clearance, and reasonable (>10 μM) solubility, we obtained additional data on compound **29d** (**Table 7**). In addition to its pEC_{50} of 7.2, this compound is non-toxic in MRC5 cells (see Supporting Information, **Table S2**), has an LLE of 4.8, and a CNS-MPO score of 4.4, indicating a likelihood of brain penetration. Additionally, it is stable in mouse plasma and its plasma protein binding is below the threshold of 95%. The major potential liabilities with this compound continue to be related to metabolism: although its HLM Cl_{int} is low, the clearance in rat hepatocytes and mouse liver microsomes (MLM) is higher, and this discrepancy could potentially pose issues when evaluating safety and efficacy in rodent animal models.

Table 7. Overall profile of **29d**.

	Targeted Value	29d
***T.b.b.* pEC_{50}**	≥7	7.2
Protein-binding adjusted *T.b.b.* EC_{50} (ng/mL)	--	256
MRC5 pTC_{50}	≤5	4.9
LLE	≥4	4.8
CNS-MPO Score	≥4	4.4
Aq. Sol. (μM)	>10	25
HLM Cl_{int} (μL/min/mg protein)	<9	<3
Rat Hepatocyte Cl_{int} (μL/min/10^6 cells)	<5	19
Mouse Plasma Stability $t_{1/2}$ (min)	--	>120
MLM $t_{1/2}$ (min)	>60	34
PPB	<95	91

Despite the concerns about rodent clearance, we felt that the potency of **29d** combined with its other, more favorable ADME properties, justified the progression of this compound to *in vivo* pharmacokinetic (PK) studies. Continuous sampling at a 10 mg/kg intraperitoneal (ip) dose showed an average C_{max} of 4413.3 ng/mL 1 h after dosing (**Fig. 3**). Calculation of the protein binding adjusted EC_{50} (EC_{50}/f_u, 256 ng/mL) reveals that exposure over the adjusted EC_{50} is maintained for ~8 h which is a marked improvement over **NEU-1207** (which, when accounting for PPB, did not achieve levels over the EC_{50} (378 ng/mL) for the duration of the study). However, as shown in **Table 8**, compound **29d** is not appreciably brain-penetrant. We sought to get a better understanding of the permeability and efflux of **29d** using a Caco-2 assay (see Supporting Information, **Table S3**), which revealed that **29d** had low permeability, and is likely a substrate for P-gp, or other active transporter. Given this information and the PK data, we concluded that the series was not likely to yield a compound appropriate for treating stage 2 HAT and did not undertake further optimization or pursue efficacy studies on compound **29d**.

Figure 3. Plasma concentration versus time profile of **29d** in mice (n=3) following a single 10 mg/kg ip dose. The blue dashed line shows the average concentration, and the shaded area represents the standard deviation.

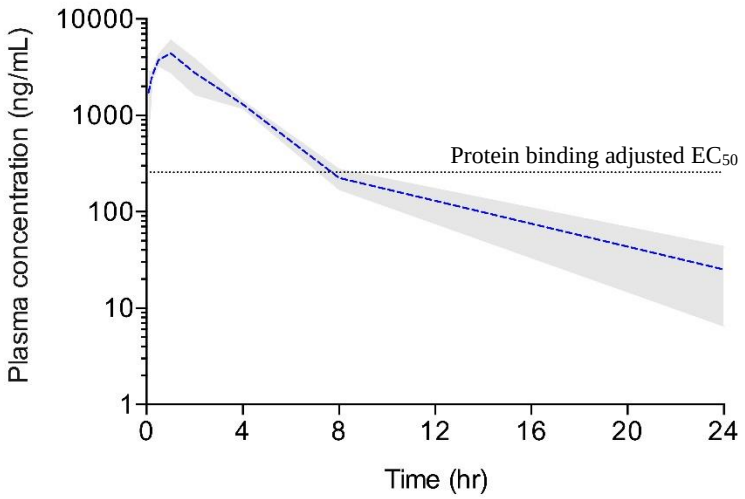


Table 8. Sparse sampling brain and plasma concentration of **29d** after a 10 mg/kg, ip dose. LLOQ = 9.77 ng/mL.

Time (h)	Mean plasma concentration (ng/mL)	Mean brain concentration (ng/mg)
0.5	3193.7	<LLOQ
4	426.3	0.22

It should be noted that a lack of CNS penetration was observed for another compound in this series (see Supporting Information, **Table S4**), which also had a high CNS-MPO score (>5; see Supporting Information, **Table S5**). Although unavailable to us at the time, we have since calculated a BBB score[17] for both compounds, according to which neither compound is predicted to penetrate the CNS (see Supporting Information, **Table S6**). The BBB score differs from the CNS-MPO score in the properties it takes into account, the functions used to assign T0 values to those properties, and the weight given to each, and higher sensitivity and specificity have been reported for the BBB score over the CNS-MPO score.[17]

For compound **29d**, the components that are most detrimental to the overall BBB score are the number of aromatic rings, which is not factored into the CNS-MPO score calculation, and the TPSA, which gives a T0 of 1 using the CNS-MPO calculator and a T0 of 0.43 using the BBB calculator. Thus, analysis of the BBB score of **29d** would suggest that a reduction in the number of aromatic rings and a reduction in the TPSA would improve its brain penetration, although it is unclear whether this would be effective if **29d** is indeed a P-gp substrate. One limitation of both metrics in our hands is the use of predicted pKa values, which can vary depending on the programs used to calculate them. Another is the general lack of guidance

for the physicochemical properties required for therapeutics that are *both* orally available and brain-penetrant, of great importance for stage 2 HAT therapeutics. However, it appears that the BBB score is a better predictor of brain penetration than the CNS-MPO score for this series, and may be of greater use for HAT drug discovery going forward.

Finally, as part of an ongoing cross-screening effort by our group, the compounds synthesized during this optimization campaign were screened against *T. cruzi*, *Leishmania donovani*, and *Schistosoma mansoni*; the causative parasites of Chagas disease, leishmaniasis, and schistosomiasis, respectively. Although compounds active against *T. brucei* are not assumed to have broad anti-parasitic activity, we have had some success with this approach as a way of generating new lead series against other pathogens by screening all compounds synthesized as part of our HAT medicinal chemistry campaigns against multiple parasites.[18] The data are presented in the Supporting Information (**Tables S7** and **S8).** None of the compounds in this series showed activity against *L. donovani*, and only one showed sub-micromolar activity against *T. cruzi*. To adjudicate the potency of compounds against adult *S. mansoni,* we employed a severity scoring system (0 – 4 (severest))[19-22] which encapsulates the many phenotypic changes (e.g., motility, density, shape, and inability to adhere to the bottom of the assay dish) that this parasite is capable of as a function of time and compound concentration.[23] At 10 μM for 48 h, compounds **1** and **13o** demonstrated modest activity whereby both yielded a severity score of 2.

Conclusions

Using a lead repurposing approach, we identified a series of 3,5-disubstituted-7-azaindoles with anti-trypanosomal activity through a HTS of human kinase inhibitors. Through a detailed SAR study, we identified **29d** that retained sub-micromolar activity against *T. brucei* while showing improved aqueous solubility and dramatically improved HLM Cl_{int} over the original HTS hit. This compound was progressed to *in vivo* PK studies and maintained a free plasma concentration greater than or equal to the EC_{50} for 4 hours after a 10 mg/kg ip dose. However, the low brain penetration of this series precluded it from progression as a HAT therapeutic, as the resulting low brain concentrations mean that the compounds would

not be effective in the target tissue for stage 2 of the disease. Similar limitations were observed for a related compound, and therefore work on the series discontinued for HAT. Cross-screening against *T. cruzi*, *L. donovani*, and *S. mansoni* did not result in potent inhibitors against any of these pathogens.

Experimental

***In Vitro* Biology.** In order to determine the *T. b. brucei* EC_{50} values, 4 μL per well from compound master plates was dispensed into a new plate, and 96 μL of HMI-9 per well was added to generate a 4% DMSO intermediate plate. Mid-log phase growth *T. b. brucei* was diluted to a working cell density of 2750 cells/mL, and 90 μL/well was dispensed into 96-well flat-bottom transparent assay plates (Nunc). From intermediate plates, 10 μL/well was added so that final cell concentration was 2500 cells/mL, and final top concentration of compounds was 40 μM in 0.4% DMSO per well. Assay plates were incubated for 72 h at 37 °C and 5% CO_2. Four hours prior to the end of the incubation, 20 μL of a 440 μM 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 EC_{50} 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. *In vivo* pharmacokinetics were evaluated in BALB/c mice (n=3). Each mouse received a 10 mg/kg dose of the test compound by intraperitoneal injection. Blood samples (50 μL) were be taken via retro-orbital bleeds at 0.083, 0.25, 0.5, 1, 2, 4, 8 and 24 hours post-dose. Plasma concentrations were determined using liquid chromatography with tandem mass spectrometry (LC-MS-MS).

Animal studies for **NEU-1207** 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, meanwhile the study for **29d** was conducted under animal use protocols approved by the University of California, San Diego Institutional Animal Care and Use Committee.

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, unless otherwise noted. ^{1}H 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 ($CDCl_3$: 7.26 [^{1}H]; DMSO-d_6: 2.50 [^{1}H]; Acetone-d_6: 2.05; or CD_3OD: 3.31 [^{1}H]). Data for ^{1}H 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 (For the synthesis of 5-(1-methyl-1*H*-pyrazol-4-yl)-3-aryl-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridines). Intermediate **11** (1.0 equiv), desired boronic acid or ester (2.5 equiv) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (10 mol%) were combined in a microwave vial that was purged with nitrogen and evacuated three times. Dioxane (0.26 M) and 2M K_2CO_3 (3.0 equiv) were added and the reaction mixture was degassed for ~10 minutes. The reaction was run in the microwave at 120 °C for 30 minutes. The reaction mixture was diluted with EtOAc, filtered through celite, and concentrated under reduced pressure, and the title compound was purified by the stated method to afford the title compounds.

General Procedure B (For the synthesis of 3-(5-aryl-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitriles). 3-(5-Bromo-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile (1 equiv), the desired boronic acid or ester (1.1 equiv), and $PdCl_2(dppf)\cdot CH_2Cl_2$ (0.1 equiv) were combined in a reaction vial that

was filled with nitrogen and evacuated three times. Dioxane (0.17 M) and 2M K_2CO_3 (5 equiv) were added and the reaction was degassed. The reaction was heated at 85 °C for ~4-5 h, then diluted with EtOAc, filtered through celite, and concentrated under reduced pressure. The crude material was purified by the stated method to afford the final compounds.

General Procedure C (For the synthesis of 3-(5-amino-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitriles). 3-(5-Bromo-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile (1 equiv), RuPhos (0.05 equiv), and RuPhos Pd G1 (0.05 equiv) were combined in a vial that was filled with nitrogen and evacuated three times. 1.0 M LiHMDS in THF (2.5 equiv) was added, followed by the addition of the desired amine (1.8 equiv). The reaction was heated at 65 °C for ~5 h, then quenched by the addition of 1M HCl, diluted with EtOAc and poured over sat. aq. $NaHCO_3$. 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 residue was purified by the stated method to afford the title compounds.

General Procedure D (For the synthesis of detosylated 3,5-disubstituted-1*H*-pyrrolo[2,3-*b*]pyridines). The tosylated azaindole starting material (1.0 equiv) was suspended in dioxane (0.10 M) and 2M NaOH (3.5-5.0 equiv) was added. The reaction was run in the microwave at 150 °C for the specified amount of time. The solvent was removed by rotovap and the crude material was purified by the stated method to afford the title compounds.

General Procedure E (For the synthesis of aryl 4,4,5,5-tetramethyl-1,3,2-dioxaborolanes). The desired aryl halide (1.0 equiv), bis(pinacolato)diboron (1.5 equiv), potassium acetate (3.5 equiv) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (0.05 equiv) were combined in a microwave vial that was filled with nitrogen and evacuated three times. Dry, degassed dioxane (0.13 M) was added and the reaction was run in the microwave (145 °C) for 30 mins. The reaction mixture was diluted with MeOH, filtered through celite, and concentrated. The crude material was purified by the stated method to afford the title compounds.

3-(1-Methyl-5-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile (1). 3-(5-(1-Methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile **NEU-1207** (58 mg, 0.194 mmol) was dissolved in dry DMF (0.30 ml, 0.65 M). The reaction was cooled to 0 °C and sodium hydride (81 mg,

0.387 mmol) was added. The reaction was stirred at 0 °C for ~1 h before the addition of methyl iodide (25 µl, 0.401 mmol). The reaction was allowed to warm to room temperature and stirred overnight. The reaction was diluted with EtOAc, poured over cold water, and extracted twice. The combined organic layers were washed once with brine, dried with sodium sulfate, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (0-10% MeOH:EtOAc) to afford the title compound as an off-white solid (41 mg, 97%). LCMS $[M+H]^+$ 314.16 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.60 (d, *J*=2.0 Hz, 1 H) 8.46 (d, *J*=2.0 Hz, 1 H) 8.28 (s, 1 H) 8.17 (s, 1 H) 8.11 - 8.14 (m, 2 H) 8.02 (s, 1 H) 7.69 (s, 1 H) 7.66 (d, *J*=7.8 Hz, 1 H) 3.89 (s, 3 H) 3.88 (s, 3 H).

3-(5-(1-Methyl-1*H*-pyrazol-4-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile (2). The title compound was prepared according to General Procedure A on a 199-mg scale using (3-cyanophenyl)boronic acid. The crude material was purified by flash chromatography (20-80% EtOAc:Hexanes) to afford the title compound as a light orange solid (135 mg, 71%). LCMS $[M+H]^+$ 454.16 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.70 (d, *J*=2.0 Hz, 1 H) 8.42 (d, *J*=2.0 Hz, 1 H) 8.40 (s, 1 H) 8.34 (t, *J*=1.5 Hz, 1 H) 8.31 (s, 1 H) 8.20 (dt, *J*=7.8, 1.5 Hz, 1 H) 8.06 (s, 1 H) 8.04 (d, *J*=3.4 Hz, 2 H) 7.85 (dt, *J*=7.8, 1.0 Hz, 1 H) 7.70 (t, *J*=7.8 Hz, 1 H) 7.44 (d, *J*=8.8 Hz, 2 H) 3.88 (s, 3 H) 2.35 (s, 3 H).

5-(1-Methyl-1*H*-pyrazol-4-yl)furo[2,3-*b*]pyridine (S2). 5-Bromofuro[2,3-*b*]pyridine **S1** (177 mg, 0.893 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (205 mg, 0.985 mmol), and $PdCl_2(dppf)\cdot CH_2Cl_2$ (37 mg, 0.045 mmol) were combined in a reaction vial that was filled with nitrogen and evacuated three times. Dioxane (5.2 ml, 0.17M) and 2M K_2CO_3 (1.3 ml, 2.60 mmol) were added and the reaction was degassed for 10 minutes. The reaction was heated at 85 °C for ~4.5 h. The reaction mixture was diluted with MeOH and filtered through celite. The filtrate was purified by flash chromatography (20-50% EtOAc:Hex) to afford the title compound as an off-white solid (140 mg, 79%). LCMS $[M+H]^+$ 199.95 m/z; ^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 8.46 (s, 1 H) 7.99 (d, *J*=2.0 Hz, 1 H) 7.79 (s, 1 H) 7.72 (d, *J*=2.0 Hz, 1 H) 7.67 (s, 1 H) 6.79 (d, *J*=2.4 Hz, 1 H) 3.99 (s, 3 H).

3-Bromo-5-(1-methyl-1*H*-pyrazol-4-yl)furo[2,3-*b*]pyridine (S3). 5-(1-Methyl-1*H*-pyrazol-4-yl)furo[2,3-*b*]pyridine **S2** (70 mg, 0.351 mmol) was dissolved in DCM (4.2 ml, 0.09 M) and cooled to 0

°C. Bromine (0.4 M in DCM, 0.95 ml, 0.380 mmol) was added dropwise to the reaction mixture. The reaction was stirred at 0 °C for 1 h. The reaction mixture was concentrated, redissolved in THF (~5 ml) and treated dropwise with 1M KOH in MeOH (~1 ml), upon which the reaction mixture turned cloudy. The reaction was stirred at room temperature for ~10 mins, then poured over water and 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 purified by flash chromatography (20-40% EtOAc:Hex) to afford the title compound as an off-white solid (34 mg, 35%). 278.04 m/z (^{79}Br), 279.99 m/z (^{81}Br); ^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 8.50 (d, *J*=2.0 Hz, 1 H) 7.93 (d, *J*=2.0 Hz, 1 H) 7.83 (s, 1 H) 7.77 (s, 1 H) 7.72 (s, 1 H) 4.00 (s, 3 H).

3-(5-(1-Methyl-1*H*-pyrazol-4-yl)furo[2,3-*b*]pyridin-3-yl)benzonitrile (3). 3-Bromo-5-(1-methyl-1*H*-pyrazol-4-yl)furo[2,3-*b*]pyridine **S3** (34 mg, 0.122 mmol), (3-cyanophenyl)boronic acid (26 mg, 0.176 mmol), and $PdCl_2(dppf)\cdot CH_2Cl_2$ (6 mg, 0.007 mmol) were combined in a microwave vial that was purged with nitrogen and evacuated three times. Dioxane (0.60 ml, 0.21 M) and 2M K_2CO_3 (0.30 ml, 0.600 mmol) were added and the reaction mixture was degassed for ~10 minutes. The reaction was run in the microwave (120 °C) for 5 minutes. The reaction mixture was diluted with EtOAc, filtered through celite, and concentrated under reduced pressure. The crude material was purified by flash chromatography (1% MeOH:DCM), then repurified by flash chromatography (30-50% EtOAc:hexanes) to afford the title compound as an off-white solid (59%). LCMS $[M+H]^+$ 301.15 m/z; ^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 8.53 (d, *J*=2.0 Hz, 1 H) 8.13 (d, *J*=2.4 Hz, 1 H) 7.95 (s, 1 H) 7.91 (s, 1 H) 7.86 (d, *J*=7.8 Hz, 1 H) 7.82 (s, 1 H) 7.73 (s, 1 H) 7.70 (d, *J*=7.8 Hz, 1 H) 7.63 (t, *J*=8.3 Hz, 1 H) 4.00 (s, 3 H).

5-(1-Methyl-1*H*-pyrazol-4-yl)-1*H*-indole (S5). 5-Bromo-1*H*-indole **S4** (251 mg, 1.28 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (293 mg, 1.41 mmol), and $PdCl_2(dppf)\cdot CH_2Cl_2$ (51 mg, 0.062 mmol) were combined in a reaction vial that was filled with nitrogen and evacuated three times. Dioxane (8.0 ml, 0.16 M) and 2M K_2CO_3 (2.0 ml, 4.00 mmol) were added and the reaction was degassed for 10 minutes. The reaction was run in the microwave (145 °C) for 30 minutes. The reaction mixture was diluted with EtOAc, filtered through celite, and concentrated under reduced

pressure. The crude material was purified by flash chromatography (10-40% EtOAc:Hex) to afford the title compound as an off-white solid (65 mg, 26%). LCMS $[M+H]^+$ 198.00 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.02 (br. s., 1 H) 8.01 (s, 1 H) 7.78 (s, 1 H) 7.68 - 7.71 (m, 1 H) 7.36 (d, *J*=8.3 Hz, 1 H) 7.31 (t, *J*=2.7 Hz, 1 H) 7.26 - 7.29 (m, 1 H) 6.38 (dd, *J*=2.7, 1.7 Hz, 1 H) 3.85 (s, 3 H).

3-Iodo-5-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-indole (S6). 5-(1-Methyl-1*H*-pyrazol-4-yl)-1*H*-indole **S5** (65 mg, 0.329 mmol) was dissolved in DCM (6.6 ml, 0.05 M) and KOH (10 mg, 0.178 mmol) was added. The reaction was stirred at room temperature for 30 minutes, after which NIS (76 mg, 0.338 mmol) was added. The reaction was stirred overnight at room temperature. The reaction mixture was quenched with $Na_2S_2O_3$ and extracted twice with DCM. The combined organic layers were dried with sodium sulfate and concentrated under reduced pressure to afford the title compound as a dark purple solid (97 mg, 91%). LCMS $[M+H]^+$ 324.02 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.46 - 11.51 (m, 1 H) 8.11 (s, 1 H) 7.82 (d, *J*=1.0 Hz, 1 H) 7.52 (d, *J*=2.4 Hz, 1 H) 7.35 - 7.40 (m, 3 H) 3.86 (s, 3 H).

3-Iodo-5-(1-methyl-1*H*-pyrazol-4-yl)-1-tosyl-1*H*-indole (S7). 3-Iodo-5-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-indole **S6** (97 mg, 0.300 mmol) was suspended in DCM (1.5 ml, 0.21 M) and TEA (0.15 ml, 1.08 mmol), DMAP (46 mg, 0.376 mmol) and 4-methylbenzenesulfonyl chloride (150 mg, 0.787 mmol) were added in that order. The reaction was stirred overnight at room temperature. The reaction was washed once with 1M HCl, once with sat. aq. $NaHCO_3$, 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 (50% EtOAc:Hex) to afford the title compound as a dark orange oil (102 mg, 71%). LCMS $[M+H]^+$ 477.98 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.21 (s, 1 H) 8.04 (s, 1 H) 7.89 - 7.93 (m, 3 H) 7.89 (s, 1 H) 7.62 (dd, *J*=8.8, 1.5 Hz, 1 H) 7.42 (d, *J*=1.5 Hz, 1 H) 7.40 (d, *J*=7.8 Hz, 2 H) 3.86 (s, 3 H) 2.32 (s, 3 H).

3-(5-(1-Methyl-1*H*-pyrazol-4-yl)-1-tosyl-1*H*-indol-3-yl)benzonitrile (S8). 3-Iodo-5-(1-methyl-1*H*-pyrazol-4-yl)-1-tosyl-1*H*-indole **S7** (100 mg, 0.210 mmol), (3-cyanophenyl)boronic acid (62 mg, 0.422 mmol), and $PdCl_2(dppf)\cdot CH_2Cl_2$ (20 mg, 0.025 mmol) were combined in a microwave vial that was purged with nitrogen and evacuated three times. Dioxane (0.85 ml, 0.25 M) and 2M K_2CO_3 (0.40 ml, 0.800 mmol) were added and the reaction mixture was degassed for ~10 minutes. The reaction was run in the microwave

(120 °C) for 30 minutes. The reaction mixture was diluted with EtOAc, filtered through celite, and concentrated under reduced pressure. The crude material was purified by flash chromatography (20-50% EtOAc:Hex) to afford the title compound as an orange solid (81 mg, 86%). LCMS $[M+H]^+$ 453.14 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.25 - 8.28 (m, 2 H) 8.19 (s, 1 H) 8.13 (dt, *J*=7.8, 1.5 Hz, 1 H) 7.98 (m, *J*=8.8, 3.4 Hz, 3 H) 7.93 (d, *J*=1.0 Hz, 1 H) 7.91 (d, *J*=1.0 Hz, 1 H) 7.85 (dt, *J*=7.8, 1.5 Hz, 1 H) 7.70 (t, *J*=7.8 Hz, 1 H) 7.62 (dd, *J*=8.8, 1.5 Hz, 1 H) 7.41 (d, *J*=7.8 Hz, 2 H) 3.85 (s, 3 H) 2.32 (s, 3 H).

3-(5-(1-Methyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-yl)benzonitrile (4). The title compound was prepared according to General Procedure D on an 81-mg scale using 3-(5-(1-methyl-1*H*-pyrazol-4-yl)-1-tosyl-1*H*-indol-3-yl)benzonitrile **S8**. The reaction was run for 1 h, and the crude material was purified by flash chromatography (5% EtOAc:DCM) to afford the title compound as an off-white solid (20 mg, 38%). LCMS $[M+H]^+$ 299.13 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.53 (br. s, 1 H) 8.09 - 8.14 (m, 3 H) 8.01 (s, 1 H) 7.85 - 7.88 (m, 2 H) 7.61 - 7.68 (m, 2 H) 7.44 (d, *J*=8.8 Hz, 1 H) 7.39 (dd, *J*=8.3, 2.0 Hz, 1 H) 3.87 (s, 3 H).

5-Bromo-3-iodo-4-methylpyridin-2-amine (S10). 5-Bromo-4-methylpyridin-2-amine **S9** (500 mg, 2.67 mmol) was dissolved in acetic acid (3.3 ml, 0.82 M) and N-iodosuccinimide (666 mg, 2.96 mmol) was added, followed by the addition of TFA (41 µL, 0.535 mmol). The reaction was stirred at 50 °C overnight. The reaction solution was poured over ice water and neutralized with 28% aqueous ammonia, upon which a light orange precipitate was observed and collected by vacuum filtration (washed with water) to afford the title compound as an orange solid (784 mg, 94%). LCMS $[M+H]^+$ 312.80 m/z (^{79}Br), 314.81 m/z (^{81}Br); ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.95 (s, 1 H) 6.24 (br. s., 2 H) 2.48 (s, 3 H).

5-Bromo-4-methyl-3-((trimethylsilyl)ethynyl)pyridin-2-amine (S11). 5-Bromo-3-iodopyridin-2-amine **S10** (784 mg, 2.51 mmol), copper iodide (26 mg, 0.137 mmol), and $PdCl_2(PPh_3)_2$ (37 mg, 0.053 mmol) were combined in a round bottom flask that was filled with nitrogen and evacuted three times. Degassed THF (3.0 ml, 0.84 M) was added, followed by the addition of degassed triethylamine (16.0 ml, 114.79 mmol) and TMS-acetylene (0.450 ml, 3.25 mmol). The reaction was run at room temperature overnight under nitrogen. The reaction mixture was diluted with EtOAc and washed 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% EtOAc:Hex) to afford the title compound as a tan solid (602 mg, 85%). LCMS $[M+H]^+$ 282.95 m/z (^{79}Br), 284.96 m/z (^{81}Br); ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.00 (s, 1 H) 6.26 (br. s., 2 H) 2.35 (s, 3 H) 0.25 (s, 9 H).

5-Bromo-4-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (S12). Potassium *tert*-butoxide (525 mg, 4.68 mmol) was dissolved in NMP (16.0 ml, 0.30 M) and heated to 80 °C. 5-Bromo-4-methyl-3-((trimethylsilyl)ethynyl)pyridin-2-amine **S11** (602 mg, 2.13 mmol) was dissolved in NMP (10 ml, 0.23 M) and added dropwise to the KOtBu solution. The reaction was stirred at 80 °C for 30 minutes. The reaction mixture was diluted with EtOAc and washed five times with water. 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% EtOAc:Hexanes) to afford the title compound as an off-white solid (236 mg, 53%). LCMS $[M+H]^+$ 210.84 m/z (^{79}Br), 212.86 m/z (^{81}Br); ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.79 (br. s., 1 H) 8.24 (s, 1 H) 7.48 (d, *J*=3.4 Hz, 1 H) 6.57 (t, *J*=2.7 Hz, 1 H) 2.54 (d, *J*=2.0 Hz, 3 H).

4-Methyl-5-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (S13). 5-Bromo-4-methyl-1*H*-pyrrolo[2,3-*b*]pyridine **S12** (236 mg, 1.12 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (258 mg, 1.24 mmol), and $PdCl_2(dppf)\cdot CH_2Cl_2$ (46 mg, 0.056 mmol) were combined in a reaction vial that was filled with nitrogen and evacuated three times. Dioxane (6.6 ml, 0.17 M) and 2M K_2CO_3 (1.7 ml, 3.40 mmol) were added and the reaction was degassed for 10 minutes. The reaction was heated at 85 °C for ~4 h. The reaction mixture was diluted with MeOH, filtered through celite, and concentrated under reduced pressure. The crude material was purified by flash chromatography (1-10% MeOH:DCM), then repurified by flash chromatography (100% EtOAc) to afford the title compound as a tan solid (152 mg, 64%). LCMS $[M+H]^+$ 212.99 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.54 (br. s., 1 H) 8.16 (s, 1 H) 7.93 (s, 1 H) 7.65 (s, 1 H) 7.40 (t, *J*=2.7 Hz, 1 H) 6.52 (dd, *J*=3.4, 2.0 Hz, 1 H) 3.90 (s, 3 H) 2.52 (s, 3 H).

3-Iodo-4-methyl-5-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (S14). 4-Methyl-5-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridine **S13** (152 mg, 0.716 mmol) was dissolved in acetonitrile (4.2 ml, 0.17 M) and N-iodosuccinimide (242 mg, 1.08 mmol) was added. The reaction was stirred at 50 °C for 2 h. Upon cooling to room temperature, a dark brown precipitate was observed and collected by vacuum filtration to afford the title compound as a dark brown solid (101 mg, 42%). LCMS $[M+H]^+$ 338.93 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.02 (br. s, 1 H) 8.16 (s, 1 H) 7.90 (s, 1 H) 7.65 (d, *J*=2.4 Hz, 1 H) 7.61 (s, 1 H) 3.90 (s, 3 H) 2.79 (s, 3 H).

3-Iodo-4-methyl-5-(1-methyl-1*H*-pyrazol-4-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine (S15). 3-Iodo-4-methyl-5-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridine **S14** (101 mg, 0.299 mmol) was suspended in DCM (1.6 ml, 0.19 M) and TEA (0.150 ml, 1.08 mmol), DMAP (46 mg, 0.377 mmol) and 4-methylbenzenesulfonyl chloride (142 mg, 0.745 mmol) were added in that order. The reaction was stirred overnight at room temperature. The reaction was washed once with 1M HCl, once with sat. aq. $NaHCO_3$, 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) to afford the title compound as an orange solid (37 mg, 25%). LCMS $[M+H]^+$ 492.90 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.30 (s, 1 H) 8.09 (s, 1 H) 8.00 (d, *J*=8.8 Hz, 2 H) 7.95 (s, 1 H) 7.64 (s, 1 H) 7.43 (d, *J*=8.3 Hz, 2 H) 3.89 (s, 3 H) 2.76 (s, 3 H) 2.35 (s, 3 H).

3-(4-Methyl-5-(1-methyl-1*H*-pyrazol-4-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile (S16). 3-Iodo-4-methyl-5-(1-methyl-1*H*-pyrazol-4-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine **S15** (37 mg, 0.075 mmol), (3-cyanophenyl)boronic acid (15 mg, 0.102 mmol), and $PdCl_2(dppf)\cdot CH_2Cl_2$ (7 mg, 0.009 mmol) were combined in a microwave vial that was purged with nitrogen and evacuated three times. Dioxane (0.40 ml, 0.21 M) and 2M K_2CO_3 (0.15 ml, 0.300 mmol) were added and the reaction mixture was degassed for ~10 minutes. The reaction was run in the microwave (120 °C) for 5 minutes. The reaction mixture was diluted with EtOAc, filtered through celite, and concentrated under reduced pressure. The crude material was purified by flash chromatography (50-100% EtOAc:Hexanes) to afford the title compound as a light yellow solid (25 mg, 71%). LCMS $[M+H]^+$ 468.03 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.34 (s, 1

H) 8.03 - 8.09 (m, 3 H) 7.98 (s, 1 H) 7.95 (s, 1 H) 7.90 (d, *J*=8.8 Hz, 2 H) 7.64 - 7.69 (m, 2 H) 7.45 (d, *J*=7.8 Hz, 2 H) 3.88 (s, 3 H) 2.36 (s, 3 H) 2.18 (s, 3 H).

3-(4-Methyl-5-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile (5). The title compound was prepared according to General Procedure D on a 25-mg scale using 3-(4-methyl-5-(1-methyl-1*H*-pyrazol-4-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile **S16**. The reaction was run for three minutes, and the crude material was purified by flash chromatography (1-5% MeOH:DCM), then repurified by flash chromatography (50-100% EtOAc:Hexanes) to afford the title compound as a beige solid (9 mg, 55%). LCMS $[M+H]^+$ 314.05 m/z; ^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 10.40 (br. s., 1 H) 8.32 (br. s., 1 H) 7.77 (s, 1 H) 7.72 (d, *J*=7.8 Hz, 1 H) 7.65 (d, *J*=7.8 Hz, 1 H) 7.61 (s, 1 H) 7.54 (t, *J*=7.8 Hz, 1 H) 7.48 (s, 1 H) 7.32 (s, 1 H) 4.01 (s, 3 H) 2.32 (s, 3 H).

5-Bromo-3-(1-methyl-1*H*-pyrazol-4-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine (S17). 5-Bromo-3-iodo-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine **15** (1502 mg, 0.318 mmol), (1-methyl-1*H*-pyrazol-4-yl)boronic acid (43 mg, 0.341 mmol), and $PdCl_2$(dppf)·CH_2Cl_2 (27 mg, 0.033 mmol) were combined in a microwave vial that was purged with nitrogen and evacuated three times. Dioxane (1.3 ml, 0.24 M) and 2M K_2CO_3 (0.50 ml, 1.00 mmol) were added and the reaction mixture was degassed for ~10 minutes. The reaction was run in the microwave (120 °C) for 15 minutes. The reaction mixture was diluted with EtOAc, filtered through celite, and concentrated under reduced pressure. The crude material was purified by flash chromatography (20-50% EtOAc:Hex) to afford the title compound as a tan solid (41 mg, 30%). LCMS $[M+H]^+$ 430.95 m/z (^{79}Br), 432.91 m/z (^{81}Br); ^{1}H NMR (399 MHz, DMSO-d_6) δ ppm 8.55 (d, *J*=2.9 Hz, 1 H) 8.48 - 8.53 (m, 1 H) 8.41 (s, 1 H) 8.24 (s, 1 H) 8.05 (s, 1 H) 7.94 - 8.01 (m, 2 H) 7.38 - 7.46 (m, 2 H) 3.88 (br. s., 3 H) 2.33 (br. s., 3 H).

3-(3-(1-Methyl-1*H*-pyrazol-4-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)benzonitrile (S18). 5-Bromo-3-(1-methyl-1*H*-pyrazol-4-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine **S17** (41 mg, 0.095 mmol), (3-cyanophenyl)boronic acid (24 mg, 0.163 mmol), and $PdCl_2$(dppf)·CH_2Cl_2 (9 mg, 0.011 mmol) were combined in a reaction vial that was filled with nitrogen and evacuated three times. Dioxane (0.6 ml, 0.17 M) and 2M K_2CO_3 (0.20 ml, 0.400 mmol) were added and the reaction was degassed for 10 minutes. The

reaction was run in the microwave (145 °C) for 5 minutes. The reaction was diluted with EtOAc, filtered through celite, and concentrated under reduced pressure. The crude material was purified by flash chromatography (50-100% EtOAc:Hex) to afford the title compound as a white solid (19 mg, 44%). LCMS $[M+H]^+$ 454.03 m/z; ^{1}H NMR (399 MHz, DMSO-d_6) δ ppm 8.77 (d, *J*=2.2 Hz, 1 H) 8.54 (d, *J*=2.2 Hz, 1 H) 8.46 (s, 1 H) 8.35 (s, 1 H) 8.23 (s, 1 H) 8.17 (d, *J*=7.3 Hz, 1 H) 8.12 (s, 1 H) 8.02 (d, *J*=8.1 Hz, 2 H) 7.89 (d, *J*=7.3 Hz, 1 H) 7.71 (t, *J*=8.1 Hz, 1 H) 7.43 (d, *J*=8.1 Hz, 2 H) 3.91 (s, 3 H) 2.34 (s, 3 H).

3-(3-(1-Methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)benzonitrile (6). The title compound was prepared according to General Procedure D on a 19-mg scale using 3-(3-(1-methyl-1*H*-pyrazol-4-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)benzonitrile **S18**. The reaction was run for two minutes, and the crude material was purified by flash chromatography (1-5% MeOH:DCM) to afford the title compound as a white solid (4 mg, 28%). LCMS $[M+H]^+$ 300.12 m/z; ^{1}H NMR (399 MHz, METHANOL-d_4) δ ppm 8.51 (d, *J*=1.5 Hz, 1 H) 8.42 (d, *J*=2.2 Hz, 1 H) 8.13 (d, *J*=1.5 Hz, 1 H) 8.09 (s, 1 H) 8.04 (dd, *J*=8.1, 1.5 Hz, 1 H) 7.86 (s, 1 H) 7.71 - 7.75 (m, 1 H) 7.68 (d, *J*=7.3 Hz, 1 H) 7.64 (s, 1 H) 3.97 (s, 3 H).

5-(1-Methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (7). 5-Bromo-1*H*-pyrrolo[2,3-*b*]pyridine **9** (686 mg, 3.48 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (800 mg, 3.84 mmol), and $PdCl_2$(dppf)·CH_2Cl_2 (147 mg, 0.180 mmol) were combined in a reaction vial that was filled with nitrogen and evacuated three times. Dioxane (20 ml, 0.17 M) and 2M K_2CO_3 (5.0 ml, 10.00 mmol) were added and the reaction was degassed for 10 minutes. The reaction was heated at 85 °C for ~4 h. The reaction mixture was diluted with EtOAc, filtered through celite, and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (1-10% MeOH:DCM) to afford the title compound as an orange solid (640 mg, 93%). LCMS $[M+H]^+$ 199.01 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.59 (br. s., 1 H) 8.45 (d, *J*=1.95 Hz, 1 H) 8.13 (s, 1 H) 8.08 (d, *J*=1.95 Hz, 1 H) 7.88 (s, 1 H) 7.44 (t, *J*=2.93 Hz, 1 H) 6.41 (dd, *J*=3.42, 1.95 Hz, 1 H) 3.87 (s, 3 H).

3-Iodo-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine (S20). 3-Iodo-1*H*-pyrrolo[2,3-*b*]pyridine **S19** (250 mg, 1.002 mmol) was suspended in DCM (10.0 ml, 0.10M) and TEA (0.35 ml, 2.51 mmol), DMAP (67 mg, 0.548 mmol) and 4-methylbenzenesulfonyl chloride (403 mg, 2.11 mmol) were added in that order. Upon the

addition of 4-methylbenzenesulfonyl chloride, the reaction mixture went from a cloudy suspension to a clear solution. The reaction was stirred overnight at room temperature. The reaction was washed once with 1M HCl, once with saturated aqueous $NaHCO_3$, and once with brine. The organic layer was dried with sodium sulfate and concentrated under reduced pressure to afford the title compound as an orange solid (311 mg, 76%). LCMS $[M+H]^+$ 398.97 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.41 (dd, *J*=4.9, 1.5 Hz, 1 H) 8.15 (s, 1 H) 8.02 (d, *J*=8.3 Hz, 2 H) 7.79 (dd, *J*=7.8, 1.5 Hz, 1 H) 7.42 (d, *J*=8.3 Hz, 2 H) 7.39 (dd, *J*=7.8, 4.9 Hz, 1 H) 2.34 (s, 3 H).

3-(1-Tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile (S21). 3-Iodo-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine **S20** (150 mg, 0.377 mmol), (3-cyanophenyl)boronic acid (140 mg, 0.953 mmol), and $PdCl_2(dppf)\cdot CH_2Cl_2$ (31 mg, 0.037 mmol) were combined in a microwave vial that was purged with nitrogen and evacuated three times. Dioxane (1.5 ml, 0.25 M) and 2M K_2CO_3 (0.55 ml, 1.10 mmol) were added and the reaction mixture was degassed for ~10 minutes. The reaction was run in the microwave (120 °C) for 30 minutes, then diluted with EtOAc, filtered through celite, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (20-40% EtOAc:Hex) to afford the title compound as an off-white solid (67 mg, 48%). LCMS $[M+H]^+$ 374.13 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.43 - 8.47 (m, 2 H) 8.40 (dd, *J*=8.3, 1.5 Hz, 1 H) 8.31 (s, 1 H) 8.14 (d, *J*=7.8 Hz, 1 H) 8.06 (d, *J*=8.8 Hz, 2 H) 7.84 (d, *J*=8.3 Hz, 1 H) 7.69 (t, *J*=7.8 Hz, 1 H) 7.43 (d, *J*=8.8 Hz, 2 H) 7.38 - 7.42 (m, 1 H) 2.34 (s, 3 H).

3-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile (8). The title compound was prepared according to General Procedure D on a 67-mg scale using 3-(1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile **S21**. The reaction was run for two minutes, and the crude material was purified by flash chromatography (1-5% MeOH:DCM) to afford the title compound as a white solid (18 mg, 45%). LCMS $[M+H]^+$ 220.03 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.09 (br. s., 1 H) 8.38 (d, *J*=8.3 Hz, 1 H) 8.30 (dd, *J*=4.6, 1.2 Hz, 1 H) 8.16 - 8.20 (m, 1 H) 8.06 - 8.13 (m, 2 H) 7.67 - 7.72 (m, 1 H) 7.63 (t, *J*=7.8 Hz, 1 H) 7.19 (dd, *J*=8.1, 4.6 Hz, 1 H).

3-Iodo-5-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (10). Intermediate **7** (640 mg, 3.23 mmol) was dissolved in acetonitrile (18 ml, 0.18 M) and *N*-iodosuccinimide (1.09 g, 4.84 mmol) was added.

The reaction was stirred at 50 °C for 2 h. Upon cooling to room temperature, a precipitate was observed and collected by vacuum filtration (washed with acetonitrile) to afford the title compound as a light brown solid (730 mg, 69%). LCMS $[M+H]^+$ 324.98 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.06 (br. s, 1 H) 8.51 (d, *J*=1.95 Hz, 1 H) 8.25 (s, 1 H) 7.96 (s, 1 H) 7.76 (d, *J*=2.44 Hz, 1 H) 7.69 (d, *J*=2.44 Hz, 1 H) 3.88 (s, 3 H).

3-Iodo-5-(1-methyl-1*H*-pyrazol-4-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine (11). Intermediate **10** (730 mg, 2.25 mmol) was suspended in DCM (37 ml, 0.06 M) and TEA (1.5 ml, 10.76 mmol), DMAP (227 mg, 1.86 mmol) and 4-methylbenzenesulfonyl chloride (1.06 g, 5.56 mmol) were added in that order. The reaction was stirred overnight at room temperature. The reaction was washed once with 1M HCl, once with sat. aq. $NaHCO_3$, 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 (0-100% EtOAc:Hex - 0-10% MeOH:DCM) to afford the title compound as a light orange solid (741 mg, 69%). LCMS $[M+H]^+$ 478.95 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.66 (d, *J*=1.95 Hz, 1 H) 8.33 (s, 1 H) 8.12 (s, 1 H) 7.98 - 8.04 (m, 3 H) 7.85 (d, *J*=2.44 Hz, 1 H) 7.43 (d, *J*=8.79 Hz, 2 H) 3.87 (s, 3 H) 2.34 (s, 3 H).

2-(5-(1-Methyl-1*H*-pyrazol-4-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile (12a). The title compound was prepared according to General Procedure A on a 75-mg scale using (2-cyanophenyl)boronic acid. The crude material was purified by flash chromatography (50-100% EtOAc:hexanes) to afford the title compound as a light orange solid (48 mg, 68%). LCMS $[M+H]^+$ 454.03 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.72 (d, *J*=1.95 Hz, 1 H) 8.29 (s, 1 H) 8.27 (s, 1 H) 8.16 (d, *J*=1.95 Hz, 1 H) 8.01 - 8.07 (m, 3 H) 7.98 (s, 1 H) 7.85 (d, *J*=3.91 Hz, 2 H) 7.64 (m, *J*=8.30, 4.20, 4.20 Hz, 1 H) 7.45 (d, *J*=7.81 Hz, 2 H) 3.85 (s, 3 H) 2.35 (s, 3 H).

3-(4-Fluorophenyl)-5-(1-methyl-1*H*-pyrazol-4-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine (12b). The title compound was prepared according to General Procedure A on a 65-mg scale using (4-fluorophenyl)boronic acid. The crude material was purified by flash chromatography (50-100% EtOAc:hexanes) to afford the title compound as a light orange solid (42 mg, 69%). LCMS $[M+H]^+$ 447.02 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.68 (d, *J*=1.95 Hz, 1 H) 8.33 (d, *J*=1.95 Hz, 1 H) 8.30 (s, 1 H) 8.19 (s, 1 H) 8.04 (d,

J=8.30 Hz, 2 H) 8.02 (s, 1 H) 7.84 - 7.90 (m, 2 H) 7.43 (d, *J*=7.81 Hz, 2 H) 7.30 - 7.36 (m, 2 H) 3.87 (s, 3 H) 2.34 (s, 3 H).

3-(3,4-Difluorophenyl)-5-(1-methyl-1*H*-pyrazol-4-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine (12c). The title compound was prepared according to General Procedure A on a 69-mg scale using (3,4-difluorophenyl)boronic acid. The crude material was purified by flash chromatography (50-100% EtOAc:hexanes) to afford the title compound as a light orange solid (42 mg, 62%). LCMS $[M+H]^+$ 465.05 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.69 (d, *J*=1.95 Hz, 1 H) 8.37 (d, *J*=1.95 Hz, 1 H) 8.32 (s, 1 H) 8.30 (s, 1 H) 8.02 - 8.07 (m, 3 H) 7.96 (qd, *J*=8.80, 2.00 Hz, 1 H) 7.68 - 7.73 (m, 1 H) 7.51 - 7.59 (m, 1 H) 7.44 (d, *J*=8.30 Hz, 2 H) 3.88 (s, 3 H) 2.35 (s, 3 H).

3-(2-Fluorophenyl)-5-(1-methyl-1*H*-pyrazol-4-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine (12d). The title compound was prepared according to General Procedure A on a 75-mg scale using (2-fluorophenyl)boronic acid. The crude material was purified by flash chromatography (50-100% EtOAc:Hexanes) to afford the title compound as an off-white solid (55 mg, 78%). LCMS $[M+H]^+$ 447.08 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.70 (d, *J*=1.95 Hz, 1 H) 8.28 (s, 1 H) 8.16 (t, *J*=1.95 Hz, 1 H) 8.11 (s, 1 H) 8.06 (d, *J*=8.30 Hz, 2 H) 7.99 (s, 1 H) 7.80 (td, *J*=7.69, 1.71 Hz, 1 H) 7.46 - 7.52 (m, 1 H) 7.45 (d, *J*=8.30 Hz, 2 H) 7.34 - 7.43 (m, 2 H) 3.86 (s, 3 H) 2.35 (s, 3 H).

3-Fluoro-5-(5-(1-methyl-1*H*-pyrazol-4-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile (12e). The title compound was prepared according to General Procedure A on a 75-mg scale using (3-cyano-5-fluorophenyl)boronic acid. The crude material was purified by flash chromatography (50-100% EtOAc:hexanes) to afford the title compound as an off-white solid (44 mg, 60%). LCMS $[M+H]^+$ 472.06 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.71 (d, *J*=1.95 Hz, 1 H) 8.49 (s, 1 H) 8.45 (d, *J*=2.44 Hz, 1 H) 8.32 (s, 1 H) 8.23 (s, 1 H) 8.12 (d, *J*=9.77 Hz, 1 H) 8.04 - 8.08 (m, 3 H) 7.87 (d, *J*=8.30 Hz, 1 H) 7.44 (d, *J*=8.79 Hz, 2 H) 3.88 (s, 3 H) 2.35 (s, 3 H).

2-Fluoro-5-(5-(1-methyl-1*H*-pyrazol-4-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile (12f). The title compound was prepared according to General Procedure A on a 74-mg scale using 2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile. The crude material was purified by flash

chromatography (50-100% EtOAc:Hexanes) to afford the title compound as an off-white solid (48 mg, 66%). LCMS $[M+H]^+$ 472.07 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.69 (d, *J*=1.95 Hz, 1 H) 8.43 (dd, *J*=6.35, 2.44 Hz, 1 H) 8.41 (d, *J*=1.95 Hz, 1 H) 8.39 (s, 1 H) 8.30 (s, 1 H) 8.26 (m, *J*=2.40, 2.40, 2.40, 2.40, 2.40, 2.40 Hz, 1 H) 8.03 - 8.07 (m, 3 H) 7.65 (t, *J*=9.03 Hz, 1 H) 7.44 (d, *J*=8.30 Hz, 2 H) 3.88 (s, 3 H) 2.34 (s, 3 H).

3-(5-(1-Methyl-1*H*-pyrazol-4-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)aniline (12g). Intermediate **11** (40 mg, 0.083 mmol), (3-aminophenyl)boronic acid (34 mg, 0.251 mmol), and $PdCl_2(dppf)\cdot CH_2Cl_2$ (6 mg, 0.007 mmol) were combined in a 8 ml vial. The vial was purged with nitrogen and evacuated three times. Dioxane (0.8 ml, 0.1 M) and 2 M aqueous K_2CO_3 (0.2 ml, 0.4 mmol) were added and the mixture was degassed for 10 minutes. The reaction was run at 100 °C for 4 h, then stopped, diluted with EtOAc, and filtered through celite. The crude material was purified by flash chromatography (50-100% EtOAc:hexanes, step gradient) to afford the title compound as a solid (5 mg, 14%). LCMS $[M+H]^+$ 290.16 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.66 (d, *J*=2.0 Hz, 1 H) 8.29 (d, *J*=2.0 Hz, 1 H) 8.27 (s, 1 H) 8.03 (d, *J*=8.8 Hz, 2 H) 8.00 (s, 2 H) 7.43 (d, *J*=8.3 Hz, 2 H) 7.14 (t, *J*=7.8 Hz, 1 H) 6.96 - 6.98 (m, 1 H) 6.89 - 6.93 (m, 1 H) 6.59 (dd, *J*=8.1, 2.2 Hz, 1 H) 5.18 - 5.23 (m, 2 H) 3.87 (s, 3 H) 2.34 (s, 3 H).

1-(4-bromophenyl)-*N*,*N*-dimethylmethanamine (S23). 1-Bromo-4-(bromomethyl)benzene **S22** (499 mg 2.00 mmol), was suspended in hexanes (2.0 ml, 1.0 M) and the reaction mixture was cooled to 0 °C. 2M Dimethylamine in THF (4.00 ml, 8.00 mmol) was added dropwise. The reaction mixture was left stirring overnight and allowed to warm to room temperature. A precipitate was observed and removed by filtration; the filtrate was concentrated to afford the title compound as an orange oil (350 mg, 82%). LCMS $[M+H]^+$ 213.93 m/z (^{79}Br), 215.93 m/z (^{81}Br); ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.50 (d, *J*=8.30 Hz, 2 H) 7.24 (d, *J*=8.30 Hz, 2 H) 3.34 (s, 2 H) 2.12 (s, 6 H).

***N*,*N*-Dimethyl-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanamine (S24).** The title compound was prepared according to General Procedure E on a 350-mg scale using 1-(4-bromophenyl)-*N*,*N*-dimethylmethanamine **S23**. The crude material was purified by flash chromatography (5-20% 5% NH_4OH/MeOH:DCM) to afford the title compound as a brown oil (176 mg, 41%). LCMS $[M+H]^+$ 262.22

m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.62 (d, *J*=8.30 Hz, 2 H) 7.30 (d, *J*=8.30 Hz, 2 H) 3.39 (s, 2 H) 2.12 (s, 6 H) 1.28 (s, 12 H).

***N*,*N*-Dimethyl-1-(4-(5-(1-methyl-1*H*-pyrazol-4-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl) phenyl)methanamine (12h).** The title compound was prepared according to General Procedure A on a 150-mg scale using *N*,*N*-dimethyl-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanamine **S24**. The crude material was purified by flash chromatography (50-100% EA:H - 0-20% MeOH:EA - 0-10% 5% NH_4OH/MeOH:DCM) to afford the title compound as a glassy brown solid (36 mg, 24%). LCMS $[M+H]^+$ 486.23 m/z; ^{1}H NMR (500 MHz, METHANOL-d_4) δ ppm 8.59 (d, *J*=1.95 Hz, 1 H) 8.29 (d, *J*=1.95 Hz, 1 H) 8.07 (s, 1 H) 8.05 (d, *J*=8.30 Hz, 2 H) 8.02 (s, 1 H) 7.90 (s, 1 H) 7.70 (d, *J*=8.30 Hz, 2 H) 7.48 (d, *J*=8.30 Hz, 2 H) 7.36 (d, *J*=8.79 Hz, 2 H) 3.94 (s, 3 H) 3.58 (s, 2 H) 2.37 (s, 3 H) 2.32 (s, 6 H).

5-(1-Methyl-1*H*-pyrazol-4-yl)-3-(3-nitrophenyl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine (12i). Intermediate **3-4** (38 mg, 0.08 mmol), (3-nitrophenyl)boronic acid (40 mg, 0.238 mmol), and $PdCl_2(dppf)\cdot CH_2Cl_2$ (6 mg, 0.007 mmol) were combined in a 8 ml vial. The vial was purged with nitrogen and evacuated three times. Dioxane (0.8 ml, 0.1 M) and 2 M aqueous K_2CO_3 (0.2 ml, 0.4 mmol) were added and the mixture was degassed for 10 minutes. The reaction was run at 100 °C for 4 h, then stopped, diluted with EtOAc, and filtered through celite. The crude material was purified by flash chromatography (30-80% EtOAc:hexanes, step gradient) to afford the title compound as a solid (30 mg, 80%). LCMS $[M+H]^+$ 320.12 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.71 (d, *J*=2.0 Hz, 1 H) 8.60 (t, *J*=2.4 Hz, 1 H) 8.48 (s, 1 H) 8.41 (d, *J*=2.0 Hz, 1 H) 8.28 - 8.32 (m, 2 H) 8.24 (dd, *J*=8.3, 1.5 Hz, 1 H) 8.08 (d, *J*=8.8 Hz, 2 H) 8.02 (s, 1 H) 7.80 (t, *J*=7.8 Hz, 1 H) 7.45 (d, *J*=8.3 Hz, 2 H) 3.87 (s, 3 H) 2.35 (s, 3 H).

4-(5-(1-Methyl-1*H*-pyrazol-4-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)phenol (12j). The title compound was prepared according to General Procedure A on a 100-mg scale using (4-hydroxyphenyl)boronic acid. The crude material was purified by flash chromatography (50-100% EtOAc:Hex) to afford the title compound as a tan solid (49 mg, 52%). LCMS $[M+H]^+$ 445.13 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.62 (br. s, 1 H) 8.65 (d, *J*=1.95 Hz, 1 H) 8.30 (s, 1 H) 8.28 (d, *J*=1.46 Hz, 1

H) 7.98 - 8.04 (m, 4 H) 7.61 (d, *J*=8.30 Hz, 2 H) 7.42 (d, *J*=8.30 Hz, 2 H) 6.89 (d, *J*=8.30 Hz, 2 H) 3.87 (s, 3 H) 2.34 (s, 3 H).

5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*c*][1,2,5]oxadiazole (S26). The title compound was prepared according to General Procedure E on a 100-mg scale using 5-chlorobenzo[*c*][1,2,5]oxadiazole **S25**. The dark brown crude material was carried forward without further purification.

*Does not ionize.

5-(5-(1-Methyl-1*H*-pyrazol-4-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzo[*c*][1,2,5]oxadiazole (12k). The title compound was prepared according to General Procedure A on a 151-mg scale using 5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*c*][1,2,5]oxadiazole **S26**. The crude material was purified by flash chromatography (20-60% EtOAc:hexanes) to afford the title compound as a white solid (109 mg, 73%). LCMS $[M+H]^+$ 471.02 m/z; ^{1}H NMR (399 MHz, DMSO-d_6) δ ppm 8.74 (d, *J*=2.20 Hz, 1 H) 8.63 (s, 1 H) 8.61 (d, *J*=2.20 Hz, 1 H) 8.53 (s, 1 H) 8.38 (s, 1 H) 8.21 (dd, *J*=9.53, 1.47 Hz, 1 H) 8.17 (d, *J*=8.79 Hz, 1 H) 8.06 - 8.12 (m, 3 H) 7.45 (d, *J*=8.79 Hz, 2 H) 3.89 (s, 3 H) 2.35 (s, 3 H).

3-(1*H*-Indol-5-yl)-5-(1-methyl-1*H*-pyrazol-4-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine (12l). The title compound was prepared according to General Procedure A on a 76-mg scale using (1*H*-indol-5-yl)boronic acid. The crude material was purified by flash chromatography (20-100% EtOAc:hexanes) to afford the title compound as a glassy orange solid (41 mg, 55%). LCMS $[M+H]^+$ 468.007 m/z; ^{1}H NMR (399 MHz, DMSO-d_6) δ ppm 11.21 (br. s., 1 H) 8.67 (d, *J*=1.47 Hz, 1 H) 8.34 (d, *J*=2.20 Hz, 1 H) 8.30 (s, 1 H) 8.05 (d, *J*=8.79 Hz, 2 H) 8.02 (s, 1 H) 8.01 (s, 1 H) 7.95 (s, 1 H) 7.46 - 7.56 (m, 2 H) 7.39 - 7.45 (m, 3 H) 6.52 (br. s., 1 H) 3.87 (s, 3 H) 2.34 (s, 3 H).

5-(1-Methyl-1*H*-pyrazol-4-yl)-3-(pyridin-4-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine (12m). The title compound was prepared according to General Procedure A using 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine. The crude material was carried forward without further purification. LCMS $[M+H]^+$ 430.11 m/z.

5-(5-(1-Methyl-1*H*-pyrazol-4-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)nicotinonitrile (12n). The title compound was prepared according to General Procedure A on a 75-mg scale using (5-cyanopyridin-3-

yl)boronic acid. The crude material was purified by flash chromatography (50-100% EtOAc:hexanes) to afford the title compound as a light orange solid (60 mg, 85%). LCMS $[M+H]^+$ 455.05 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.36 (t, *J*=2.20 Hz, 1 H) 9.03 (t, *J*=1.95 Hz, 1 H) 8.81 (q, *J*=2.28 Hz, 1 H) 8.72 (t, *J*=1.95 Hz, 1 H) 8.55 (d, *J*=1.95 Hz, 1 H) 8.50 (t, *J*=1.95 Hz, 1 H) 8.33 (d, *J*=0.98 Hz, 1 H) 8.04 - 8.08 (m, 3 H) 7.44 (d, *J*=8.30 Hz, 2 H) 3.88 (s, 3 H) 2.35 (s, 3 H).

4-(5-(1-Methyl-1*H*-pyrazol-4-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)picolinonitrile (12o). The title compound was prepared according to General Procedure A on a 100-mg scale using crude (2-cyanopyridin-4-yl)boronic acid **5-26**. The crude material was purified by flash chromatography (50-100% EtOAc:hexanes) to afford the title compound as a light yellow solid (34 mg, 36%). LCMS $[M+H]^+$ 455.12 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.80 (d, *J*=5.37 Hz, 1 H) 8.74 (s, 1 H) 8.73 (d, *J*=1.95 Hz, 1 H) 8.61 (s, 1 H) 8.57 (d, *J*=1.95 Hz, 1 H) 8.33 (s, 1 H) 8.27 (dd, *J*=5.86, 1.95 Hz, 1 H) 8.08 (s, 1 H) 8.06 (d, *J*=8.30 Hz, 2 H) 7.45 (d, *J*=8.30 Hz, 2 H) 3.89 (s, 3 H) 2.35 (s, 3 H).

5-(1-Methyl-1*H*-pyrazol-4-yl)-3-(2-methylpyridin-4-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine (12p). The title compound was prepared according to General Procedure A on a 75-mg scale using (2-methylpyridin-4-yl)boronic acid. The crude material was purified by flash chromatography (3% MeOH:DCM) to afford the title compound as a dark orange solid (47 mg, 68%). LCMS $[M+H]^+$ 444.16 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.70 (d, *J*=1.95 Hz, 1 H) 8.52 (d, *J*=5.37 Hz, 1 H) 8.46 (s, 1 H) 8.45 (d, *J*=1.95 Hz, 1 H) 8.33 (s, 1 H) 8.03 - 8.08 (m, 3 H) 7.74 (s, 1 H) 7.68 (d, *J*=5.86 Hz, 1 H) 7.44 (d, *J*=8.79 Hz, 2 H) 3.88 (s, 3 H) 2.56 (s, 3 H) 2.35 (s, 3 H).

2,6-Dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (S28). The title compound was prepared according to General Procedure E on a 150-mg scale using 4-bromo-2,6-dimethylpyridine **S28**. The dark brown crude material was carried forward without further purification. LCMS $[M+H]^+$ 151.78 m/z (boronic acid).

3-(2,6-Dimethylpyridin-4-yl)-5-(1-methyl-1*H*-pyrazol-4-yl)-1-tosyl-1*H*-pyrrolo[*2,3-b*]pyridine (12q). The title compound was prepared according to General Procedure A on a 75-mg scale using crude 2,6-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine **S28**. The crude material was purified by

flash chromatography (5% MeOH:DCM), then repurified by flash chromatography (10-100% EtOAc:DCM) to afford the title compound as a tan solid (43 mg, 60%). LCMS $[M+H]^+$ 458.14 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.69 (d, *J*=1.95 Hz, 1 H) 8.42 (d, *J*=1.46 Hz, 1 H) 8.41 (s, 1 H) 8.32 (s, 1 H) 8.05 (m, *J*=3.90, 3.90 Hz, 3 H) 7.52 (s, 2 H) 7.44 (d, *J*=8.30 Hz, 2 H) 3.88 (s, 3 H) 2.51 (s, 6 H) 2.35 (s, 3 H).

2-(5-(1-Methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile (13a). The title compound was prepared according to General Procedure D on a 48-mg scale using **12a**. The reaction was run for 5 minutes, and the crude material was purified by flash chromatography (1-5% MeOH:DCM), then by prep HPLC (70-5% water:ACN) to afford the title compound as a formate salt. The resulting solid was dissolved in MeOH and MP-carbonate was added. The suspension was stirred overnight at room temperature, then the solids were removed by filtration and the fitrate was concentrated to afford the title compound as a white solid (9 mg, 28%). LCMS $[M+H]^+$ 300.06 m/z; ^{1}H NMR (399 MHz, METHANOL-d_4) δ ppm 8.51 (d, *J*=2.20 Hz, 1 H) 8.22 (d, *J*=2.20 Hz, 1 H) 8.02 (s, 1 H) 7.84 - 7.89 (m, 2 H) 7.75 - 7.83 (m, 3 H) 7.49 (td, *J*=8.06, 1.47 Hz, 1 H) 3.94 (s, 3 H).

4-(5-(1-Methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile (13b). Intermediate **11** (90 mg, 0.188 mmol), (4-cyanophenyl)boronic acid (83 mg, 0.565 mmol), and $PdCl_2(dppf)\cdot CH_2Cl_2$ were combined in a microwave vial which was then purged with nitrogen and evacuated three times. Dioxane (1.9 ml, 0.1 M) and K_2CO_3 (0.565 ml, 1.1 mmol) were added and the mixture was then degassed for 10 minutes. The reaction was then run in the microwave for 30 minutes at 120 ºC. Aqueous 2M NaOH (0.3 ml, 0.6 mmol) was then added to the flask, and the solution was microwaved for 1.5 min at 150 °C. Additional 2M NaOH (0.1 ml, 0.2 mmol) was then added, and the reaction was microwaved for another 2.5 min at 150 °C. Crude product was then diluted with EtOAc, and filtered through celite using EtOAc to wash. The filtrate was purified by flash chromatography (50-100% EtOAc:hexanes) to afford the title compound as a solid (36 mg, 64%). LCMS $[M+H]^+$ 300.12 m/z, ^{1}H NMR (500 MHz, METHANOL-d_4) δ ppm 8.51 (d, *J*=2.0 Hz, 1 H) 8.46 (d, *J*=2.0 Hz, 1 H) 8.08 (s, 1 H) 7.94 (d, *J*=5.4 Hz, 2 H) 7.93 (s, 1 H) 7.87

(s, 1 H) 7.80 (d, *J*=8.3 Hz, 2 H) 3.96 (s, 3 H). *The -NH peak is too rapidly exchanging to be seen in the HNMR.

5-(1-methyl-1*H*-pyrazol-4-yl)-3-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine (13c). In a microwave tube, **10** (37.3 mg, 0.115 mmol) was added followed by phenylboronic acid (41.5 mg, 0.340 mmol) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (12.70 mg, 0.016 mmol). The tube was sealed and purged with nitrogen three times. 1,4-Dioxane (0.115 mL, 1 M), and a 2 M solution of potassium carbonate (0.517 mL, 1.035 mmol) were then added and the reaction mixture was degassed and run in the microwave for 30 minutes at 120 °C. The reaction was then concentrated, and EtOAc was added. This solution was then washed with water, followed by brine, and the organic layer was dried over sodium sulfate and concentrated. The crude product was purified by reverse phase chromatography (30-70% ACN/water gradient) to afford the title compound as a white solid (5 mg, 16%). LCMS $[M+H]^+$ 275.1; ^{1}H NMR (399 MHz, chloroform-*d*) δ ppm 3.99 (s, 3 H) 7.30 – 7.38 (m, 1 H) 7.45 – 7.55 (m, 3 H) 7.63 – 7.71 (m, 3 H) 7.82 (s, 1 H) 8.28 (s, 1 H) 8.52 (s, 1 H) 9.49 (br. s., 1 H).

3-(4-chlorophenyl)-5-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (13d). In a microwave tube, **10** (25 mg, 0.077 mmol) was added followed by (4-chlorophenyl)boronic acid (35.6 mg, 0.228 mmol) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (8.51 mg, 10.42 μmol). The tube was sealed and purged with nitrogen three times. 1,4-Dioxane (77 μL, 1 M), and a 2 M solution of potassium carbonate (0.347 mL, 0.695 mmol) were then added and the reaction mixture was degassed and run in the microwave for 30 minutes at 120 °C. The reaction was then concentrated, and EtOAc was added. This solution was then washed with water, followed by brine, and the organic layer was dried over sodium sulfate and concentrated. The crude product was purified by reverse phase chromatography (30-70% ACN/water gradient) to afford the title compound as a white solid (10 mg, 42%). LCMS $[M+H]^+$ 309.1; ^{1}H NMR (399 MHz, chloroform-*d*) δ ppm 4.00 (s, 3 H) 7.43 – 7.48 (m, 2 H) 7.50 (d, *J*=1.5 Hz, 1 H) 7.56 – 7.61 (m, 2 H) 7.68 (s, 1 H) 7.82 (s, 1 H) 8.21 (d, *J*= 1.5 Hz, 1 H) 8.52 (s, 1 H) 9.17 (br. s., 1 H).

3-(3,4-dichlorophenyl)-5-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (13e). In a microwave tube, **10** (25 mg,0.090 mmol) was added followed by (3,4-dichlorophenyl)boronic acid (19.7

mg, 0.103 mmol) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (7.51 mg, 9.2 μmol). The tube was sealed and purged with nitrogen three times. Tetrahydrofuran (0.626 mL, 0.144 M), and a 2 M solution of potassium carbonate (0.313 mL, 0.625 mmol, 6.93 eq) were then added and the reaction mixture was degassed and ran in the microwave for 30 minutes at 120 °C. The reaction was then concentrated, and EtOAc was added. This solution was then washed with water, followed by brine, and the organic layer was dried over sodium sulfate and concentrated. The crude product was purified by reverse phase chromatography (20-95% ACN/water gradient) to afford the title compound as a white solid (3.2 mg, 10%). LCMS $[M+H]^+$ 343.0; ^{1}H NMR (399 MHz, chloroform-*d*) δ ppm 4.01 (d, *J*=1.47 Hz, 3 H) 7.45 - 7.50 (m, 1 H) 7.53 – 7.59 (m, 2 H) 7.71 (d, *J*= 5.86 Hz, 2 H) 7.82 (s, 1 H) 8.19 (s, 1 H) 8.28 (s, 1 H) 8.46 (br. s., 1 H).

5-(1-methyl-1*H*-pyrazol-4-yl)-3-(*p*-tolyl)-1*H*-pyrrolo[2,3-*b*]pyridine (13f). In a microwave tube, **10** (70 mg, 0.253 mmol) was added followed by p-tolylboronic acid (37 mg, 0.275 mmol) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (21 mg, 0.026 mmol). The tube was sealed and purged with nitrogen three times. 1,4-Dioxane (1.754 mL, 0.144 M), and a 2 M solution of potassium carbonate (0.875 mL, 1.750 mmol) were then added and the reaction mixture was degassed and ran in the microwave for 30 minutes at 120 °C. The reaction was then concentrated, and EtOAc was added. This solution was then washed with water, followed by brine, and the organic layer was dried over sodium sulfate and concentrated. The crude product was purified by reverse phase chromatography (30-70% ACN/water gradient) to afford the title compound as a white solid (5.1 mg, 7%). LCMS [M+H]+ 289.0; 1H NMR (399 MHz, chloroform-*d*, D_2O) δ ppm 2.36 (s, 3 H) 3.93 (s, 3 H) 7.24 (d, *J*=8.1 Hz, 2 H) 7.43 (s, 1 H) 7.48 (d, *J*=8.1 Hz, 2 H) 7.61 (s, 1 H) 7.74 (s, 1 H) 8.23 (s, 1 H) 8.41 (br. s., 1 H).

3-(4-methoxyphenyl)-5-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (13g). In a microwave tube, **10** (21.30 mg, 0.066 mmol) was added followed by (4-methoxyphenyl)boronic acid (28.5 mg, 0.188 mmol, 2.85 eq) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (8 mg, 9.8 μmol, 0.149 eq). The tube was sealed and purged with nitrogen three times. 1,4-Dioxane (65.7 μL, 1 M), and a 2 M solution of potassium carbonate (0.284 mL, 0.567 mmol) were then added and the reaction mixture was degassed and ran in the microwave for 30 minutes at 120 °C. The reaction was then concentrated, and EtOAc was added. This solution was then

washed with water, followed by brine, and the organic layer was dried over sodium sulfate and concentrated. The crude product was purified by reverse phase chromatography (30-70% ACN/water gradient) to afford the title compound as a white solid (6.4 mg, 32%). LCMS $[M + H]^+$ 305.2; ^{1}H NMR (399 MHz, chloroform-*d*) δ ppm 3.89 (s, 3 H) 3.99 (s, 3 H) 7.05(d, *J*=8.8 Hz, 2 H) 7.44 (s, 1 H) 7.58 (d, *J*=8.1 Hz, 2 H) 7.68 (s, 1 H) 7.81 (s, 1 H) 8.25 (s, 1 H) 8.49 (br. s., 1 H) 9. 17 (br. s., 1 H).

3-(3-methoxyphenyl)-5-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (13h). In a microwave tube, **10** (30 mg, 0.108 mmol) was added followed by (3-methoxyphenyl)boronic acid (28.1 mg, 0.185 mmol), and $PdCl_2(dppf)\cdot CH_2Cl_2$ (9.02 mg, 0.011 mmol). The tube was sealed and purged with nitrogen three times. 1,4-Dioxane (0.752 mL, 0.144 M), and a 2 M solution of potassium carbonate (0.376 mL, 0.753 mmol) were then added and the reaction mixture was degassed and ran in the microwave for 30 minutes at 120 °C. The reaction was then concentrated, and EtOAc was added. This solution was then washed with water, followed by brine, and the organic layer was dried over sodium sulfate and concentrated. The crude product was purified by reverse phase chromatography (20-95% ACN/water gradient) to the title compound as a white solid (4.6 mg, 14%). LCMS $[M + H]^+$ 305.1; ^{1}H NMR (399 MHz, chloroform-*d*) δ ppm 3.87–3.95 (m, 3 H) 3.96 – 4.03 (m, 3 H) 6.90 (d, *J*=8.8 Hz, 1 H) 7.19 (d, *J*=1.5 Hz, 1 H) 7.25 (s, 1 H) 7.42 (t, *J*=8.1 Hz, 1 H) 7.53 (s, 1 H) 7.68 (s, 1 H) 7.81 (s, 1 H) 8.30 (s, 1 H) 8.50 (s, 1 H) 9.60 (br. s., 1 H).

5-(1-methyl-1*H*-pyrazol-4-yl)-3-(4-(trifluoromethyl)phenyl)-1*H*-pyrrolo[2,3-*b*]pyridine (13i). In a microwave tube, **10** (25.3 mg, 0.091 mmol) was added followed by (3-trifluoromethylphenyl)boronic acid (20 mg, 0.105 mmol) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (8.9 mg, 10.9 μmol). The tube was sealed and purged with nitrogen three times. 1,4-Dioxane (0.634 mL, 0.144 M), and a 2 M solution of potassium carbonate (0.313 mL, 0.626 mmol) were then added and the reaction mixture was degassed and ran in the microwave for 30 minutes at 120 °C. The reaction was then concentrated, and EtOAc was added. This solution was then washed with water, followed by brine, and the organic layer was dried over sodium sulfate and concentrated. The crude product was purified by reverse phase chromatography (20-90% ACN/water gradient) to afford the title compound as a white solid (4.9 mg, 15.7% yield). LCMS $[M + H]^+$ 343.1; ^{1}H

NMR (399 MHz, chloroform-*d*) δ ppm 4.01 (s, 3 H) 7.56 – 7.64 (m, 3 H) 7.69 (br. s., 1 H) 7.81 – 7.86 (m, 2 H) 7.88 (s, 1 H) 8.25 (s, 1 H) 8.52- 8.63 (m, 1 H) 9.50 – 9.63 (m, 1 H).

3-(3-luorophenyl)-5-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (13j). In a microwave tube, **10** (60 mg, 0.217 mmol) was added followed by (3-fluoromethylphenyl)boronic acid (33 mg, 0.236 mmol) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (18 mg, 0.022 mmol). The tube was sealed and purged with nitrogen three times. 1,4-Dioxane (1.504 mL, 0.144 M), and a 2 M solution of potassium carbonate (0.750 mL, 1.5 mmol) were then added and the reaction mixture was degassed and ran in the microwave for 30 minutes at 120 °C. The reaction was then concentrated, and EtOAc was added. This solution was then washed with water, followed by brine, and the organic layer was dried over sodium sulfate and concentrated. The crude product was purified by reverse phase chromatography (30-70% ACN/water gradient) to afford the title compound as a white solid (5.4 mg, 8.5% yield). LCMS $[M + H]^+$ 293.0; ^{1}H NMR (399 MHz, chloroform-*d*) δ ppm 4.01 (s, 3 H) 7.05 (t, *J*=7.7 Hz, 1 H) 7.34 (d, *J*=10.3 Hz, 1 H) 7.41 – 7.48 (m, 2 H) 7.58 (s, 1 H) 7.71 (br. s., 1 H) 7.83 (s, 1 H) 8.33 (s, 1 H) 8.62 (br. s., 1 H) 9.97 – 10.24 (m, 1 H).

3-(4-Fluorophenyl)-5-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (13k). The title compound was prepared according to General Procedure D on a 42-mg scale using **12b**. The reaction was run for 1.75 h, and the crude material was purified by flash chromatography (1-5% MeOH:DCM) to afford the title compound as a tan solid (11 mg, 39%). LCMS $[M+H]^+$ 293.17 m/z; ^{1}H NMR (500 MHz, METHANOL-d_4) δ ppm 8.45 (d, *J*=1.46 Hz, 1 H) 8.33 (d, *J*=1.95 Hz, 1 H) 8.03 (s, 1 H) 7.89 (d, *J*=0.98 Hz, 1 H) 7.67 - 7.72 (m, 2 H) 7.61 (s, 1 H) 7.15 - 7.21 (m, 2 H) 3.95 (s, 3 H).

3-(3,4-Difluorophenyl)-5-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (13l). The title compound was prepared according to General Procedure D on a 42-mg scale using **12c**. The reaction was run for 1.75 h, and the crude material was purified by flash chromatography (1-5% MeOH:DCM) to afford the title compound as a tan solid (17 mg, 59%). LCMS $[M+H]^+$ 311.14 m/z; ^{1}H NMR (500 MHz, METHANOL-d_4) δ ppm 8.47 (d, *J*=1.95 Hz, 1 H) 8.35 (d, *J*=1.95 Hz, 1 H) 8.06 (s, 1 H) 7.91 (s, 1 H) 7.68 (s, 1 H) 7.59 (ddd, *J*=11.96, 7.81, 2.20 Hz, 1 H) 7.48 - 7.54 (m, 1 H) 7.34 (m, *J*=10.50, 8.40, 8.40 Hz, 1 H) 3.94 - 3.99 (m, 3 H).

3-(2-Fluorophenyl)-5-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (13m). The title compound was prepared according to General Procedure D on a 55-mg scale using **12d**. The reaction was run for 6 minutes, and the crude material was purified by flash chromatography (1-5% MeOH:DCM) to afford the title compound as an off-white solid (23 mg, 64%). LCMS $[M+H]^+$ 293.11 m/z; ^{1}H NMR (399 MHz, DMSO-d_6) δ ppm 12.02 (br. s., 1 H) 8.54 (d, *J*=1.47 Hz, 1 H) 8.22 (s, 1 H) 8.18 (s, 1 H) 7.93 (s, 1 H) 7.74 - 7.81 (m, 2 H) 7.28 - 7.37 (m, 3 H) 3.87 (s, 3 H).

3-Fluoro-5-(5-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile (13n). The title compound was prepared according to General Procedure D on a 44-mg scale using **12e**. The reaction was run for 2 minutes, and the crude material was purified by flash chromatography (5% MeOH:DCM) to afford the title compound as a white solid (22 mg, 73%). LCMS $[M+H]^+$ 318.09 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.17 (s, 1 H) 8.56 (d, *J*=1.95 Hz, 1 H) 8.48 (d, *J*=1.46 Hz, 1 H) 8.29 (s, 1 H) 8.16 (s, 1 H) 8.11 (s, 1 H) 8.03 (s, 1 H) 8.01 (d, *J*=10.25 Hz, 1 H) 7.68 (d, *J*=8.30 Hz, 1 H) 3.90 (s, 3 H).

2-Fluoro-5-(5-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile (13o). The title compound was prepared according to General Procedure D on a 48-mg scale using **12f**. The reaction was run for 1 minute, and the crude material was purified by flash chromatography (1-10% MeOH:DCM, then 1-10% MeOH:EtOAc) to afford the title compound as a white solid (11 mg 34%). LCMS $[M+H]^+$ 318.09 m/z; ^{1}H NMR (399 MHz, DMSO-d_6) δ ppm 12.07 (br. s, 1 H) 8.55 (d, *J*=2.20 Hz, 1 H) 8.43 (d, *J*=1.47 Hz, 1 H) 8.28 (dd, *J*=5.13, 2.20 Hz, 1 H) 8.26 (s, 1 H) 8.16 - 8.23 (m, 1 H) 8.02 (d, *J*=2.20 Hz, 1 H) 8.01 (s, 1 H) 7.58 (t, *J*=9.53 Hz, 1 H) 3.89 (s, 3 H).

4-(5-(1-Methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzamide (13p). 4-(5-(1-Methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile **13b** (15 mg, 0.05 mmol) was put in a microwave vial and dissolved in dioxane (0.1 M, 0.5 ml). Aqueous 2 M NaOH was then added (0.25 ml, 0.5 mmol) and the reaction was run in the microwave at 150 °C for 40 mins. The crude material was purified by flash chromatography (4-1516% 5%NH4OH/MeOH:DCM) to afford the title compound as a solid (11 mg, 72%). LCMS $[M+H]^+$ 318.15 m/z, ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.54 (s, 1 H) 8.42 (s, 1 H) 8.26 (s, 1 H)

7.97 - 8.03 (m, 3 H) 7.96 (d, *J*=8.8 Hz, 2 H) 7.86 (d, *J*=7.8 Hz, 2 H) 7.32 (s, 1 H) 6.63 (s, 1 H) 3.89 (s, 3 H).

4-(5-(1-Methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzoic acid (13q). 4-(5-(1-Methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile **13b** (15 mg, 0.05 mmol) was put in a microwave vial and dissolved in dioxane (0.1 M, 0.5 ml). Aqueous 2M NaOH was then added (1 ml, 2 mmol). The reaction was run in the microwave at 150 °C for 30 mins. The crude material was purified by flash chromatography (4-15% 5%NH4OH/MeOH:DCM) to afford the title compound as a solid (16 mg, 100%). LCMS $[M+H]^+$ 319.13 m/z, ^{1}H NMR (500 MHz, METHANOL-d_4) δ ppm 8.48 - 8.50 (m, 1 H) 8.47 (d, *J*=2.0 Hz, 1 H) 8.12 (d, *J*=8.3 Hz, 2 H) 8.08 (s, 1 H) 7.93 (s, 1 H) 7.85 (d, *J*=8.8 Hz, 2 H) 7.82 (s, 1 H) 3.96 (s, 3 H). *The -NH and -OH peaks are too rapidly exchanging to be seen in the HNMR.

3-(5-(1-Methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)aniline (13r). The title compound was prepared according to General Procedure D on a 24-mg scale for 10 min using **12g**. The crude material was purified by flash chromatography (10% MeOH:DCM) to afford the title compound as a solid (5 mg, 32%). LCMS $[M+H]^+$ 290.19 m/z, ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.07 (d, *J*=2.4 Hz, 1 H) 8.04 (d, *J*=2.0 Hz, 1 H) 7.96 - 7.97 (m, 1 H) 7.76 (s, 1 H) 7.72 (s, 1 H) 7.47 - 7.49 (m, 1 H) 7.46 (s, 1 H) 7.11 (d, *J*=7.8 Hz, 2 H) 6.91 (t, *J*=7.6 Hz, 1 H) 6.83 (d, *J*=7.8 Hz, 1 H) 6.14 - 6.20 (m, 1 H) 3.86 (s, 3 H).

***N*,*N*-Dimethyl-1-(4-(5-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)phenyl)methanamine (13s).** The title compound was prepared according to General Procedure D on a 36-mg scale using **12h**. The reaction was run for 5 minutes, and the crude material was purified by flash chromatography (1-10% 10% NH_4OH/MeOH:DCM), then repurified by preparitive HPLC (99-5% water:ACN) to afford the title compound as a colorless oil (6 mg, 25%). LCMS $[M+H]^+$ 332.12 m/z; ^{1}H NMR (500 MHz, METHANOL-d_4) δ ppm 8.46 (d, *J*=1.95 Hz, 1 H) 8.39 (d, *J*=1.95 Hz, 1 H) 8.04 (s, 1 H) 7.89 (d, *J*=0.98 Hz, 1 H) 7.74 (d, *J*=8.30 Hz, 2 H) 7.69 (s, 1 H) 7.46 (d, *J*=8.30 Hz, 2 H) 3.95 (s, 3 H) 3.78 (s, 2 H) 2.48 (s, 6 H).

5-(1-Methyl-1*H*-pyrazol-4-yl)-3-(3-nitrophenyl)-1*H*-pyrrolo[2,3-*b*]pyridine (13t). The title compound was prepared according to General Procedure D on a 30-mg scale for 10 min using **12i**. The crude material

was purified by flash chromatography (3% MeOH:DCM) to afford the title compound as a solid (15 mg, 74%). LCMS $[M+H]^+$ 320.12 m/z, ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.13 (br. s, 1 H) 8.57 (d, *J*=2.0 Hz, 1 H) 8.49 (s, 1 H) 8.42 (d, *J*=2.0 Hz, 1 H) 8.27 (d, *J*=8.3 Hz, 1 H) 8.25 (s, 1 H) 8.14 (d, *J*=2.4 Hz, 1 H) 8.09 (dd, *J*=7.8, 2.0 Hz, 1 H) 7.98 - 7.99 (m, 1 H) 7.74 (t, *J*=8.1 Hz, 1 H) 3.89 (s, 3 H).

4-(5-(1-Methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)phenol (13u). The title compound was prepared according to General Procedure D on a 50-mg scale using **12j**. The reaction was run for 15 minutes, and the crude material was purified by flash chromatography (1-10% MeOH:DCM) to afford the title compound as a white solid (11 mg, 33%). LCMS $[M+H]^+$ 291.15 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.69 (br. s, 1 H) 9.34 (br. s, 1 H) 8.49 (d, *J*=1.95 Hz, 1 H) 8.28 (d, *J*=1.95 Hz, 1 H) 8.22 (s, 1 H) 7.94 (d, *J*=0.98 Hz, 1 H) 7.66 (d, *J*=2.44 Hz, 1 H) 7.55 (d, *J*=8.79 Hz, 2 H) 6.85 (d, *J*=8.30 Hz, 2 H) 3.88 (s, 3 H).

5-(5-(1-Methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzo[c][1,2,5] oxadiazole (13v). The title compound was prepared according to General Procedure D on a 109-mg scale using **12k**. The reaction was run for 5 minutes, and the crude reaction mixture was neutralized with acetic acid. A precipitate was observed and collected by vacuum filtration to afford the title compound as a yellow-green solid (37 mg, 50%). LCMS $[M+H]^+$ 317.11 m/z; ^{1}H NMR (399 MHz, DMSO-d_6) δ ppm 12.32 (br. s, 1 H) 8.65 (s, 1 H) 8.61 (d, *J*=1.47 Hz, 1 H) 8.35 (m, *J*=5.10 Hz, 3 H) 8.16 (d, *J*=9.53 Hz, 1 H) 8.06 - 8.10 (m, 2 H) 3.91 (s, 3 H).

3-(1*H*-indol-5-yl)-5-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (13w). The title compound was prepared according to General Procedure D on a 41-mg scale using **12l**. The reaction was run for 1 h, and the crude material was purified by flash chromatography (1-10% MeOH:DCM) to afford the title compound as a white solid (12 mg, 43%). LCMS $[M+H]^+$ 314.09 m/z; ^{1}H NMR (399 MHz, METHANOL-d_4) δ ppm 8.42 (br. s., 1 H) 8.37 (s, 1 H) 7.98 (s, 1 H) 7.85 (s, 1 H) 7.83 (s, 1 H) 7.53 (s, 1 H) 7.48 (d, *J*=8.79 Hz, 1 H) 7.42 (d, *J*=9.53 Hz, 1 H) 7.26 (d, *J*=2.93 Hz, 1 H) 6.51 (d, *J*=2.93 Hz, 1 H) 3.93 (s, 3 H).

5-(1-Methyl-1*H*-pyrazol-4-yl)-3-(pyridin-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (13x). Intermediate **11** (30 mg, 0.0627 mmol) was combined with pyridin-3-ylboronic acid and $PdCl_2(dppf)\cdot CH_2Cl_2$ (23 mg, 0.188

mmol) in a microwave vial which was purged with nitrogen and evacuated three times. Dioxane (0.6 ml, 0.1 M) and K_2CO_3 (0.25 ml, 0.5 mmol) were added and the mixture was degassed for 10 minutes. The reaction was run in the microwave for 40 min at 120 ºC. Aqueous NaOH (2 M, 0.3 ml, 0.6 mmol) added and the solution was then microwaved for 10 minutes at 150 C. The crude product was then diluted with EtOAc, and filtered through celite using EtOAc to wash. The filtrate was purified by flash chromatography (5% MeOH:DCM) to afford the title compound as a solid (13 mg, 73%). LCMS $[M+H]^+$ 276.14 m/z; ^{1}H NMR (500 MHz, METHANOL-d_4) δ ppm 8.91 (s, 1 H) 8.51 (d, *J*=2.0 Hz, 1 H) 8.45 (d, *J*=4.4 Hz, 1 H) 8.40 (d, *J*=2.4 Hz, 1 H) 8.21 (dt, *J*=8.3, 3.4 Hz, 1 H) 8.07 (s, 1 H) 7.92 (s, 1 H) 7.82 (s, 1 H) 7.54 (dd, *J*=7.8, 4.9 Hz, 1 H) 3.96 (s, 3 H). *The -NH peak is too rapidly exchanging to be seen in the HNMR.

5-(1-Methyl-1*H*-pyrazol-4-yl)-3-(pyridin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (13y). The title compound was prepared according to General Procedure D on a 40-mg scale for 20 min using crude **12m**. The crude material was purified by flash chromatography (1-10% MeOH:DCM) to afford the title compound as a solid (23 mg, 92%) LCMS $[M+H]^+$ 276.15 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.20 (s, 1 H) 8.57 (d, *J*=2.0 Hz, 1 H) 8.55 (d, *J*=6.3 Hz, 2 H) 8.51 (d, *J*=2.0 Hz, 1 H) 8.30 (s, 1 H) 8.21 (d, *J*=2.9 Hz, 1 H) 8.03 (d, *J*=1.0 Hz, 1 H) 7.83 (d, *J*=6.3 Hz, 2 H) 3.89 (s, 3 H).

5-(5-(1-Methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)nicotinonitrile (13z). The title compound was prepared according to General Procedure D on a 60-mg scale using **12n**. The reaction was run for 2 minutes, and the crude material was purified by flash chromatography (1-10% MeOH:DCM) to afford the title compound as a light pink solid (13 mg, 33%). LCMS $[M+H]^+$ 301.05 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.22 (br. s, 1 H) 9.33 (d, *J*=1.95 Hz, 1 H) 8.87 (d, *J*=1.95 Hz, 1 H) 8.68 (t, *J*=2.20 Hz, 1 H) 8.58 (d, *J*=1.46 Hz, 1 H) 8.53 (d, *J*=1.95 Hz, 1 H) 8.30 (s, 1 H) 8.19 (s, 1 H) 8.05 (s, 1 H) 3.89 (s, 3 H).

4-(5-(1-Methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)picolinonitrile (13aa). Intermediate **12o** (34 mg, 0.075 mmol) was dissolved in dioxane (1.5 ml, 0.05 M) and 2M aq. NaOH (0.10 ml, 0.200 mmol) was added. The reaction was stirred at 85 °C for 1 h. The reaction mixture was purified directly by flash chromatography (0-10% MeOH:EtOAc) to afford the title compound as an off-white solid (8 mg,

34%). LCMS $[M+H]^+$ 301.08 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.41 (br. s, 1 H) 8.68 (d, *J*=5.37 Hz, 1 H) 8.60 (s, 2 H) 8.46 (d, *J*=1.46 Hz, 1 H) 8.42 (s, 1 H) 8.31 (s, 1 H) 8.19 (dd, *J*=4.39, 1.95 Hz, 1 H) 8.06 (s, 1 H) 3.90 (s, 3 H).

5-(1-Methyl-1*H*-pyrazol-4-yl)-3-(2-methylpyridin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (13ab). The title compound was prepared according to General Procedure D on a 47-mg scale using **12p**. The reaction was run for 5 minutes, and the crude material was purified by flash chromatography (1-10% 5% NH_4OH/MeOH:DCM) to afford the title compound as a brown solid (19 mg, 60%). LCMS $[M+H]^+$ 290.16 m/z; ^{1}H NMR (500 MHz, METHANOL-d_4) δ ppm 8.45 (d, *J*=1.95 Hz, 1 H) 8.41 (d, *J*=1.95 Hz, 1 H) 8.36 (d, *J*=5.37 Hz, 1 H) 8.03 (s, 1 H) 7.91 (s, 1 H) 7.90 (s, 1 H) 7.60 (s, 1 H) 7.56 (dd, *J*=5.37, 1.46 Hz, 1 H) 3.94 (s, 3 H) 2.57 (s, 3 H).

3-(2,6-Dimethylpyridin-4-yl)-5-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (13ac). The title compound was prepared according to General Procedure D on a 43-mg scale using **12q**. The reaction was run for 5 minutes, and the crude material was purified by flash chromatography (1-10% MeOH:DCM) to afford the title compound as a tan solid (24 mg, 83%). LCMS $[M+H]^+$ 304.21 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.11 (br. s., 1 H) 8.55 (d, *J*=1.95 Hz, 1 H) 8.44 (d, *J*=1.95 Hz, 1 H) 8.27 (s, 1 H) 8.11 (s, 1 H) 8.02 (s, 1 H) 7.45 (s, 2 H) 3.90 (s, 3 H) 2.49 (s, 6 H).

5-Bromo-3-iodo-1*H*-pyrrolo[2,3-*b*]pyridine (14). 5-Bromo-1*H*-pyrrolo[2,3-*b*]pyridine **9** (1.01 g, 5.13 mmol) was dissolved in acetonitrile (30 ml, 0.17 M) and N-iodosuccinimide (1.71 g, 7.60 mmol) was added. The reaction was stirred at 50 °C for 2 h. Upon cooling to room temperature, a tan precipitate was observed and collected by vacuum filtration (washed with hexanes) to afford the title compound as a pale orange solid (1.38 g, 83%). LCMS $[M+H]^+$ 322.87 m/z (^{79}Br), 324.89 m/z (^{81}Br); ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.35 (br. s., 1 H) 8.32 (d, *J*=1.95 Hz, 1 H) 7.87 (d, *J*=2.93 Hz, 1 H) 7.80 (d, *J*=2.44 Hz, 1 H).

5-Bromo-3-iodo-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine (15). Intermediate **14** (1.38 g, 4.27 mmol) was suspended in DCM (20 ml, 0.21 M) and TEA (1.80 ml, 12.91 mmol), DMAP (646 mg, 5.29 mmol) and 4-methylbenzenesulfonyl chloride (2.05 g, 10.75 mmol) were added in that order. The reaction was stirred overnight at room temperature, then washed once with 1M HCl, once with sat. aq. $NaHCO_3$, 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 (0-50% EtOAc:Hex) to afford the title compound as a light orange solid (1.58 g, 78%). LCMS $[M+H]^+$ 476.90 m/z (^{79}Br), 478.92 m/z (^{81}Br); ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.51 (d, *J*=1.95 Hz, 1 H) 8.22 (s, 1 H) 7.97 - 8.04 (m, 3 H) 7.43 (d, *J*=8.79 Hz, 2 H) 2.34 (s, 3 H).

***tert*-Butyl 4-(5-bromo-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (16a).** Intermediate **15** (323 mg, 0.678 mmol), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (272 mg, 0.880 mmol), and $PdCl_2(dppf)\cdot CH_2Cl_2$ (28 mg, 0.034 mmol) were combined in a microwave vial that was purged with nitrogen and evacuated three times. Dioxane (3.2 ml, 0.21 M) and 2M K_2CO_3 (1.0 ml, 2.00 mmol) were added and the reaction mixture was degassed for ~10 minutes. The reaction was run in the microwave (80 °C) for 10 minutes. The reaction mixture was diluted with EtOAc, filtered through celite, and concentrated under reduced pressure. The crude material was purified by flash chromatography (0-20% EtOAc:Hex) to afford the title compound as an off-white solid (200 mg, 56%). LCMS $[M+H]^+$ 532.07 m/z (^{79}Br), 533.96 m/z (^{81}Br); ^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 8.46 (d, *J*=2.0 Hz, 1 H) 8.18 (d, *J*=2.0 Hz, 1 H) 8.05 (d, *J*=8.3 Hz, 2 H) 7.67 (s, 1 H) 7.29 (d, *J*=8.3 Hz, 2 H) 6.11 (br. s, 1 H) 4.13 (br. s., 2 H) 3.67 (t, *J*=5.4 Hz, 2 H) 2.52 (br. s., 2 H) 2.39 (s, 3 H) 1.51 (s, 9 H).

***tert*-Butyl 3-(5-bromo-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate (16b).** Intermediate **15** (200 mg, 0.419 mmol), *tert*-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate (160 mg, 0.232 mmol), and $PdCl_2(dppf)\cdot CH_2Cl_2$ (19 mg, 0.023 mmol) were combined in a microwave vial that was purged with nitrogen and evacuated three times. Dioxane (2.1 ml, 0.21 M) and 2M K_2CO_3 (0.65 ml, 1.30 mmol) were added and the reaction mixture was degassed for ~10 minutes. The reaction was run in the microwave (80 °C) for 15 minutes. The reaction mixture was diluted with EtOAc, filtered through celite, and concentrated under reduced pressure. The crude material was purified by flash chromatography (0-20% EtOAc:Hex) to afford the title compound as a yellow solid (159 mg, 73%). LCMS $[M+H]^+$ 518.09 m/z (^{79}Br), 520.10 m/z (^{81}Br); ^{1}H NMR (500 MHz,

DMSO-d_6) δ ppm 8.62 (d, *J*=8.8 Hz, 1 H) 8.52 (s, 1 H) 8.03 (s, 1 H) 8.00 (d, *J*=6.8 Hz, 2 H) 7.42 (d, *J*=7.3 Hz, 2 H) 6.58 (d, *J*=18.1 Hz, 1 H) 4.48 (br. s., 2 H) 4.22 (br. s., 2 H) 2.34 (s, 3 H) 1.47 (d, *J*=14.2 Hz, 9 H).

***tert*-Butyl 5-(5-bromo-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (16c)** Intermediate **15** (200 mg, 0.419 mmol), *tert*-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (169 mg, 0.546 mmol), and $PdCl_2(dppf)\cdot CH_2Cl_2$ (17 mg, 0.021 mmol) were combined in a microwave vial that was purged with nitrogen and evacuated three times. Dioxane (2.1 ml, 0.20 M) and 2M K_2CO_3 (0.65 ml, 1.30 mmol) were added and the reaction mixture was degassed for ~10 minutes. The reaction was run in the microwave (80 °C) for 15 minutes. The reaction mixture was diluted with EtOAc, filtered through celite, and concentrated under reduced pressure. The crude material was purified by flash chromatography (0-20% EtOAc:Hex) to afford the title compound as an off-white solid (158 mg, 71%). LCMS $[M+H]^+$ 532.13 m/z (^{79}Br), 534.09 m/z (^{81}Br); ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.51 (s, 1 H) 8.50 (s, 1 H) 8.00 (d, *J*=8.8 Hz, 2 H) 7.94 (br. s., 1 H) 7.42 (d, *J*=8.3 Hz, 2 H) 6.46 (s, 1 H) 4.22 (br. s., 2 H) 3.49 (br. s., 2 H) 2.34 (s, 3 H) 2.28 (br. s., 2 H) 1.45 (s, 9 H).

***tert*-Butyl 4-(5-(1-methyl-1*H*-pyrazol-4-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (17a).** *tert*-Butyl 4-(5-bromo-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate **16a** (200 mg, 0.376 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (95 mg, 0.456 mmol), and $PdCl_2(dppf)\cdot CH_2Cl_2$ (15 mg, 0.018 mmol) were combined in a reaction vial that was filled with nitrogen and evacuated three times. Dioxane (2.2 ml, 0.17 M) and 2M K_2CO_3 (0.55 ml, 1.10 mmol) were added and the reaction was degassed for 10 minutes. The reaction was heated at 85 °C for ~4 h, then the reaction mixture was diluted with EtOAc and filtered through celite. The filtrate was purified by flash chromatography (50% EtOAc:Hex) to afford the title compound as a light orange solid (169 mg, 85%). LCMS $[M+H]^+$ 534.27 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.64 (d, *J*=1.5 Hz, 1 H) 8.38 (d, *J*=2.0 Hz, 1 H) 8.31 (s, 1 H) 8.04 (s, 1 H) 7.98 (d, *J*=8.3 Hz, 2 H) 7.87 (s, 1 H) 7.41 (d, *J*=7.8 Hz, 2 H) 6.45 (s, 1 H) 4.08 (br. s, 2 H) 3.87 (s, 3 H) 3.52 - 3.61 (m, 2 H) 2.55 (br. s, 2 H) 2.33 (s, 3 H) 1.44 (s, 9 H).

***Tert*-Butyl 3-(5-(1-methyl-1*H*-pyrazol-4-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate (17b).** *tert*-Butyl 3-(5-bromo-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate **16b** (159 mg, 0.306 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (77 mg, 0.370 mmol), and $PdCl_2(dppf)\cdot CH_2Cl_2$ (14 mg, 0.017 mmol) were combined in a reaction vial that was filled with nitrogen and evacuated three times. Dioxane (1.8 ml, 0.17 M) and 2M K_2CO_3 (0.45 ml, 0.900 mmol) were added and the reaction was degassed for 10 minutes. The reaction was heated at 85 °C for ~4 h. The reaction mixture was diluted with EtOAc and filtered through celite. The filtrate was purified by flash chromatography (20-50% EtOAc:Hex) to afford the title compound as an off-white solid (132 mg, 83%). LCMS $[M+H]^+$ 520.17 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.67 (d, *J*=2.0 Hz, 1 H) 8.41 (dd, *J*=8.8, 2.0 Hz, 1 H) 8.34 (d, *J*=3.4 Hz, 1 H) 8.06 (d, *J*=2.4 Hz, 1 H) 8.01 (d, *J*=6.8 Hz, 2 H) 7.93 (s, 1 H) 7.42 (d, *J*=7.3 Hz, 2 H) 6.66 (d, *J*=24.9 Hz, 1 H) 4.50 (br. s., 2 H) 4.27 (br. s., 2 H) 3.88 (s, 3 H) 2.34 (s, 3 H) 1.48 (d, *J*=14.2 Hz, 9 H).

***tert*-Butyl 5-(5-(1-methyl-1*H*-pyrazol-4-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (17c)** *tert*-Butyl 5-(5-bromo-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate **16c** (158 mg, 0.297 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (75 mg, 0.360 mmol), and $PdCl_2(dppf)\cdot CH_2Cl_2$ (12 mg, 0.015 mmol) were combined in a reaction vial that was filled with nitrogen and evacuated three times. Dioxane (1.7 ml, 0.17 M) and 2M K_2CO_3 (0.50 ml, 1.00 mmol) were added and the reaction was degassed for 10 minutes. The reaction was heated at 85 °C for ~4 h. The reaction mixture was diluted with EtOAc and filtered through celite. The filtrate was purified by flash chromatography (20-50% EtOAc:Hexanes) to afford the title compound as an off-white solid (93%). LCMS $[M+H]^+$ 534.21 m/z, ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.63 (d, *J*=2.0 Hz, 1 H) 8.32 (s, 1 H) 8.28 (s, 1 H) 7.96 - 8.03 (m, 3 H) 7.82 (s, 1 H) 7.40 (d, *J*=8.3 Hz, 2 H) 6.54 (br. s., 1 H) 4.23 (br. s., 2 H) 3.85 (s, 3 H) 3.50 (br. s., 2 H) 2.28 - 2.34 (m, 5 H) 1.44 (s, 9 H).

***tert*-Butyl 4-(5-(1-methyl-1*H*-pyrazol-4-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)piper-idine-1-carboxylate (18a).** *tert*-Butyl 4-(5-(1-methyl-1*H*-pyrazol-4-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate **17a** (169 mg, 0.317 mmol) was dissolved in EtOH (6.3 ml, 0.05

M) and 10% wt Pd/C (35 mg, 0.033 mmol) was added. Ammonium formate (160 mg, 2.54 mmol) was added and the reaction was refluxed at 85 °C for 1.5 h. The reaction mixture was diluted with EtOAc and filtered through celite. Solids were removed from the filtrate by gravity filtration and the filtrate was concentrated under reduced pressure to afford the title compound as a tan solid (100 mg, 59%). LCMS $[M+H]^+$ 536.16 m/z; ^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 8.54 (s, 1 H) 8.07 (d, *J*=8.3 Hz, 2 H) 7.83 (s, 1 H) 7.75 (s, 1 H) 7.64 (s, 1 H) 7.46 (s, 1 H) 7.29 (s, 2 H) 4.19 - 4.33 (m, 2 H) 3.98 (s, 3 H) 2.88 (t, *J*=11.2 Hz, 2 H) 2.38 (s, 3 H) 1.99 (d, *J*=12.7 Hz, 2 H) 1.66 (qd, *J*=12.7, 4.4 Hz, 2 H) 1.50 (s, 9 H).

***tert*-Butyl 3-(5-(1-methyl-1*H*-pyrazol-4-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)pyrrolidine-1-carboxylate (18b).** Intermediate **17b** (132 mg, 0.254 mmol) was dissolved in EtOH (5.0 ml, 0.05 M) and 10% wt Pd/C (27 mg, 0.025 mmol) was added. Ammonium formate (126 mg, 2.00 mmol) was added and the reaction was refluxed at 85 °C for 1.5 h. The reaction mixture was diluted with EtOAc and filtered through celite. Solids were removed from the filtrate by gravity filtration and the filtrate was purified by flash chromatography (2% MeOH:DCM). However, separation was not achieved. Impure fractions containing the title compound were combined to afford a yellow oil (109 mg) which was taken forward without further purification. LCMS $[M+H]^+$ 522.18 m/z.

***tert*-Butyl 3-(5-(1-methyl-1*H*-pyrazol-4-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)piper-idine-1-carboxylate (18c).** Intermediate **17c** (147 mg, 0.275 mmol) was dissolved in EtOH (5.0 ml, 0.05 M) and 10% wt Pd/C (27 mg, 0.025 mmol) was added. Ammonium formate (119 mg, 1.89 mmol) was added and the reaction was refluxed at 85 °C for 1 h. The reaction mixture was diluted with EtOAc and filtered through celite. Solids were removed from the filtrate by gravity filtration and the filtrate was purified by flash chromatography (2% MeOH:DCM) to afford the title compound as a white solid (68%). LCMS $[M+H]^+$ 536.23 m/z; ^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 8.54 (s, 1 H) 8.06 (d, *J*=7.3 Hz, 2 H) 7.88 (br. s., 1 H) 7.75 (s, 1 H) 7.64 (s, 1 H) 7.51 (s, 1 H) 7.29 (s, 2 H) 4.04 - 4.14 (m, 1 H) 3.98 (s, 3 H) 2.91 (m, *J*=11.7 Hz, 3 H) 2.38 (s, 3 H) 2.16 (d, *J*=13.2 Hz, 1 H) 1.79 (d, *J*=12.2 Hz, 1 H) 1.60 - 1.73 (m, 3 H) 1.49 (s, 9 H).

***tert*-Butyl 4-(5-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)piperidine-1-carboxylate (19a).** The title compound was prepared according to General Procedure D on a 100-mg scale using **18a**. The reaction was run for 15 minutes, and the crude material was purified by flash chromatography (70-80% EtOAc:Hexanes) to afford the title compound as a white solid (53 mg, 75%). LCMS $[M+H]^+$ 382.19 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.30 (s, 1 H) 8.42 (d, *J*=2.0 Hz, 1 H) 8.16 (s, 1 H) 8.11 (d, *J*=2.0 Hz, 1 H) 7.89 (s, 1 H) 7.22 (d, *J*=2.0 Hz, 1 H) 3.98 - 4.16 (m, 2 H) 3.87 (s, 3 H) 2.80 - 3.00 (m, 3 H) 1.97 (d, *J*=13.7 Hz, 2 H) 1.47 - 1.58 (m, 2 H) 1.42 (s, 9 H).

***tert*-Butyl 3-(5-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)pyrrolidine-1-carboxylate (19b).** The title compound was prepared according to General Procedure D on a 109-mg scale using **18b**. The reaction was run for 15 minutes, and the crude material was purified by flash chromatography (2-5% MeOH:DCM, step gradient) to afford the title compound as a white solid (34 mg, 44%). LCMS $[M+H]^+$ 368.16 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.39 (br. s., 1 H) 8.45 (d, *J*=2.0 Hz, 1 H) 8.13 - 8.20 (m, 2 H) 7.92 (s, 1 H) 7.30 (br. s., 1 H) 3.87 (s, 3 H) 3.72 - 3.84 (m, 1 H) 3.43 - 3.63 (m, 2 H) 3.33 - 3.36 (m, 1 H) 3.16 - 3.28 (m, 1 H) 2.21 - 2.35 (m, 1 H) 1.99 - 2.14 (m, 1 H) 1.41 (d, *J*=11.7 Hz, 9 H).

***tert*-Butyl 3-(5-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)piperidine-1-carboxylate (19c).** The title compound was prepared according to General Procedure D on a 109-mg scale using **5-28c**. The reaction was run for 15 minutes, and the crude material was purified by flash chromatography (2-5% MeOH:DCM, step gradient) to afford the title compound as a white solid (38 mg, 54%). LCMS $[M+H]^+$ 382.19 m/z, ^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 8.70 - 8.82 (m, 1 H) 8.43 (s, 1 H) 8.00 - 8.09 (m, 1 H) 7.80 (s, 1 H) 7.67 (s, 1 H) 7.13 (s, 1 H) 4.27 - 4.45 (m, 1 H) 3.99 (s, 3 H) 2.97 - 3.08 (m, 1 H) 2.88 (br. s., 2 H) 2.16 - 2.22 (m, 1 H) 1.69 - 1.85 (m, 4 H) 1.50 (s, 9 H).

5-(1-Methyl-1*H*-pyrazol-4-yl)-3-(piperidin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (20a). *tert*-Butyl 4-(5-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)piperidine-1-carboxylate **19a** (48 mg, 0.125 mmol) was taken up in 4M HCl in dioxane (0.5 ml, 2.00 mmol). The reaction was stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure and the resulting white residue was dissolved in MeOH and stirred at room temperature with Si-carbonate overnight. The Si-

carbonate was removed by filtration and the filtrate was concentrated to afford the title compound as a light yellow solid (34 mg, 97%). LCMS $[M+H]^+$ 282.19 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.25 (br. s, 1 H) 8.42 (d, *J*=2.0 Hz, 1 H) 8.17 (s, 1 H) 8.11 (s, 1 H) 7.90 (s, 1 H) 7.17 (s, 1 H) 3.87 (s, 3 H) 3.05 (d, *J*=10.2 Hz, 2 H) 2.86 (t, *J*=13.2 Hz, 1 H) 2.67 (t, *J*=11.7 Hz, 2 H) 1.89 (d, *J*=13.7 Hz, 2 H) 1.52 - 1.66 (m, 2 H).

5-(1-Methyl-1*H*-pyrazol-4-yl)-3-(pyrrolidin-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridine hydrochloride (20b). *tert*-Butyl 3-(5-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)pyrrolidine-1-carboxylate **19b** (22 mg, 0.060 mmol) was taken up in 4M HCl in dioxane (0.1 ml, 0.400 mmol). The reaction was stirred at room temperature for 1 h, then stopped and concentrated under reduced pressure to afford the title compound as a tan solid (14 mg, 78%). LCMS $[M+H]^+$ 268.19 m/z; ^{1}H NMR (500 MHz, METHANOL-d_4) δ ppm 8.95 (d, *J*=1.5 Hz, 1 H) 8.68 (d, *J*=1.5 Hz, 1 H) 8.27 (s, 1 H) 8.06 (s, 1 H) 7.71 (s, 1 H) 3.99 (s, 3 H) 3.94 (q, *J*=8.8 Hz, 1 H) 3.87 (dd, *J*=11.2, 7.8 Hz, 1 H) 3.59 - 3.67 (m, 1 H) 3.47 (ddd, *J*=10.7, 9.3, 7.8 Hz, 1 H) 3.41 (t, *J*=10.2 Hz, 1 H) 2.64 (m, *J*=3.9 Hz, 1 H) 2.23 - 2.33 (m, 1 H).

*The -NH peaks are too rapidly exchanging to be seen in the HNMR in CD_3OD. 1.0 equiv. HCl salt confirmed by HNMR in DMSO-d_6.

5-(1-Methyl-1*H*-pyrazol-4-yl)-3-(piperidin-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (20c). *tert*-Butyl 3-(5-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)piperidine-1-carboxylate **19c** (34 mg, 0.089 mmol) was taken up in 4M HCl in dioxane (0.25 ml, 1.00 mmol). The reaction was stirred at room temperature for 3 h, after which the solvent was removed under reduced pressure. The resulting yellow solid was dissolved in MeOH and Si-carbonate was added. The mixture was stirred overnight at room temperature. The Si-carbonate was removed by filtration and the filtrate was concentrated to afford the title compound as an off-white solid (20 mg, 78%). LCMS $[M+H]^+$ 282.19 m/z; ^{1}H NMR (500 MHz, METHANOL-d_4) δ ppm 8.40 (d, *J*=2.0 Hz, 1 H) 8.19 (d, *J*=2.0 Hz, 1 H) 8.02 (s, 1 H) 7.88 (s, 1 H) 7.25 (s, 1 H) 3.96 (s, 3 H) 3.44 (d, *J*=12.7 Hz, 1 H) 3.27 (d, *J*=9.8 Hz, 1 H) 3.10 - 3.22 (m, 1 H) 2.87 (t, *J*=12.2 Hz, 2 H) 2.15 - 2.22 (m, 1 H) 1.93 - 1.99 (m, 1 H) 1.76 - 1.88 (m, 2 H).

3-(5-Bromo-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile (21). Intermediate **15** (575 mg, 1.21 mmol), (3-cyanophenyl)boronic acid (176 mg, 1.20 mmol), and $PdCl_2(dppf)\cdot CH_2Cl_2$ (88 mg, 0.108 mmol) were combined in a microwave vial that was purged with nitrogen and evacuated three times. Dioxane (8 ml, 0.15 M) and 2M K_2CO_3 (2.0ml, 4.00 mmol) were added and the reaction mixture was degassed for ~10 minutes. The reaction was run in the microwave (120 °C) for 5 minutes. The reaction mixture was diluted with EtOAc, filtered through celite, and concentrated under reduced pressure. The crude material was purified by flash chromatography (0-20% EtOAc:Hex) to afford the title compound as a light yellow solid (322 mg, 59%). LCMS $[M+H]^+$ 452.03 (^{79}Br), 454.04 (^{81}Br) m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.65 (d, *J*=1.95 Hz, 1 H) 8.55 (d, *J*=1.95 Hz, 1 H) 8.50 (s, 1 H) 8.33 (d, *J*=1.46 Hz, 1 H) 8.16 (dd, *J*=8.06, 1.22 Hz, 1 H) 8.04 (d, *J*=8.30 Hz, 2 H) 7.84 (dd, *J*=7.81, 0.98 Hz, 1 H) 7.68 (t, *J*=7.32 Hz, 1 H) 7.44 (d, *J*=7.81 Hz, 2 H) 2.35 (s, 3 H).

3-(5-(1,3-Dimethyl-1*H*-pyrazol-4-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile (22a). The title compound was prepared according to General Procedure B on a 76-mg scale using 1,3-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole. The crude material was purified by flash chromatography (20-100% EtOAc:hexanes) to afford the title compound as a light orange solid (57 mg, 72%). LCMS $[M+H]^+$ 468.06 m/z; ^{1}H NMR (399 MHz, DMSO-d_6) δ ppm 8.50 (d, *J*=1.6 Hz, 1 H) 8.43 (s, 1 H) 8.33 (s, 1 H) 8.26 (d, *J*=1.8 Hz, 1 H) 8.17 (d, *J*=6.6 Hz, 1 H) 8.07 (d, *J*=8.4 Hz, 2 H) 8.02 (s, 1 H) 7.84 (d, *J*=7.7 Hz, 1 H) 7.69 (t, *J*=8.0 Hz, 1 H) 7.44 (d, *J*=8.2 Hz, 2 H) 3.79 (s, 3 H) 2.35 (s, 3 H) 2.29 (s, 3 H).

3-(1-Tosyl-5-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile (22b). The title compound was prepared according to General Procedure B on a 101-mg scale using 1,3,5-trimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole. The crude material was purified by flash chromatography (20-70% EtOAc:Hex) to afford the title compound as a yellow solid (67 mg, 62%). LCMS $[M+H]^+$ 482.07 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.46 (s, 1 H) 8.34 (d, *J*=2.0 Hz, 1 H) 8.31 (s, 1 H) 8.18 (d, *J*=2.0 Hz, 1 H) 8.14 (d, *J*=7.8 Hz, 1 H) 8.10 (d, *J*=8.3 Hz, 2 H) 7.82 (d, *J*=7.8 Hz, 1 H) 7.67 (t, *J*=7.8 Hz, 1 H) 7.46 (d, *J*=8.3 Hz, 2 H) 3.71 (s, 3 H) 2.36 (s, 3 H) 2.19 (s, 3 H) 2.10 (s, 3 H).

3-(5-(4-(Methylsulfonyl)phenyl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile (22c). The title compound was prepared according to General Procedure B on a 30-mg scale using (4-(methylsulfonyl)phenyl)boronic acid. The crude material was purified by flash chromatography (20-70% EtOAc:Hexanes) to afford the title compound as a white solid (11 mg, 31%). LCMS $[M+H]^+$ 528.07 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.81 (d, *J*=1.5 Hz, 1 H) 8.63 (d, *J*=1.5 Hz, 1 H) 8.52 (s, 1 H) 8.41 (s, 1 H) 8.26 (d, *J*=6.8 Hz, 1 H) 8.07 - 8.13 (m, 4 H) 8.00 - 8.07 (m, 2 H) 7.86 (d, *J*=7.3 Hz, 1 H) 7.71 (t, *J*=7.8 Hz, 1 H) 7.46 (d, *J*=8.8 Hz, 2 H) 3.27 (s, 3 H) 2.36 (s, 3 H).

3-(5-(Pyrimidin-5-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile (22d). The title compound was prepared according to General Procedure B on a 74-mg scale using 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine. The crude material was purified by flash chromatography (20-100% EtOAc:Hex) to afford the title compound as an off-white solid (53 mg, 72%). LCMS $[M+H]^+$ 452.06 m/z; ^{1}H NMR (399 MHz, DMSO-d_6) δ ppm 9.29 (s, 2 H) 9.24 (s, 1 H) 8.85 (d, *J*=2.2 Hz, 1 H) 8.77 (d, *J*=2.2 Hz, 1 H) 8.55 (s, 1 H) 8.42 (s, 1 H) 8.28 (d, *J*=8.1 Hz, 1 H) 8.09 (d, *J*=8.8 Hz, 2 H) 7.86 (d, *J*=8.1 Hz, 1 H) 7.70 (t, *J*=8.1 Hz, 1 H) 7.46 (d, *J*=8.1 Hz, 2 H) 2.35 (s, 3 H).

3-(5-(Pyridin-4-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile (22e). The title compound was prepared according to General Procedure B on a 74-mg scale using 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine. The crude material was purified by flash chromatography to afford the title compound as an off-white solid (62 mg, 84%). LCMS $[M+H]^+$ 451.08 m/z; ^{1}H NMR (399 MHz, DMSO-d_6) δ ppm 8.86 (s, 1 H) 8.67 (m, *J*=5.9 Hz, 3 H) 8.52 (s, 1 H) 8.41 (s, 1 H) 8.26 (d, *J*=7.3 Hz, 1 H) 8.09 (d, *J*=8.1 Hz, 2 H) 7.84 - 7.91 (m, 3 H) 7.71 (t, *J*=8.1 Hz, 1 H) 7.46 (d, *J*=8.1 Hz, 2 H) 2.35 (s, 3 H).

3-(5-(1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile (23a). 3-(5-Bromo-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile (18 mg, 0.060 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (49 mg, 0.252 mmol), potassium carbonate (25 mg, 0.181 mmol) and palladium tetrakis (3 mg, 3 µmol) were combined in a microwave vial that was filled with nitrogen and evacuated three times. A 4:2:1 mixture of DME:EtOH:H2O (1.5 ml, 0.04M) was added and the reaction was degassed and run in the microwave (175 °C) for 15 minutes. The reaction mixture was diluted with MeOH, filtered through celite,

and concentrated under reduced pressure. The filtrate was purified by flash chromatography (1-10% 5% NH_4OH/MeOH:DCM) to afford the title compound as a white solid (13 mg, 76%). LCMS $[M+H]^+$ 286.09 m/z; ^{1}H NMR (399 MHz, DMSO-d_6) δ ppm 12.98 (br. s, 1 H) 12.06 (br. s., 1 H) 8.60 (d, *J*=1.5 Hz, 1 H) 8.48 (d, *J*=1.5 Hz, 1 H) 8.33 (br. s, 1 H) 8.22 (s, 1 H) 8.16 (dt, *J*=7.5, 1.7 Hz, 1 H) 8.02 - 8.12 (m, 2 H) 7.67 - 7.71 (m, 1 H) 7.64 (t, *J*=8.1 Hz, 1 H).

3-(5-(1,3-Dimethyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile (23b). The title compound was prepared according to General Procedure D on a 57-mg scale using 3-(5-(1,3-dimethyl-1*H*-pyrazol-4-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile. The reaction was run for 2 minutes, and the crude material was purified by flash chromatography (1-10% MeOH:DCM) to afford the title compound as an off-white solid (31 mg, 81%). LCMS $[M+H]^+$ 314.09 m/z; ^{1}H NMR (399 MHz, DMSO-d_6) δ ppm 12.11 (br. s., 1 H) 8.35 (br. s., 1 H) 8.27 (br. s., 1 H) 8.19 (br. s., 1 H) 8.12 (d, *J*=8.06 Hz, 1 H) 8.08 (br. s., 1 H) 7.97 (s, 1 H) 7.68 (d, *J*=7.33 Hz, 1 H) 7.64 (t, *J*=5.86 Hz, 1 H) 3.81 (s, 3 H) 2.31 (s, 3 H).

3-(5-(1,3,5-Trimethyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile (23c). The title compound was prepared according to General Procedure D on a 67-mg scale using 3-(1-tosyl-5-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile. The reaction was run for two minutes, and the crude material was purified by flash chromatography (5-10% MeOH:DCM) to afford the title compound as an off-white solid (17 mg, 36%). LCMS $[M+H]^+$ 328.10 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.14 (s, 1 H) 8.14 - 8.19 (m, 3 H) 8.07 - 8.12 (m, 2 H) 7.67 (d, *J*=7.8 Hz, 1 H) 7.61 (t, *J*=8.3 Hz, 1 H) 3.73 (s, 3 H) 2.22 (s, 3 H) 2.13 (s, 3 H).

3-(5-(4-(Methylsulfonyl)phenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile (23d). The title compound was prepared according to General Procedure D on an 11-mg scale using 3-(5-(4-(Methylsulfonyl)phenyl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile. The reaction was run for 2 minutes, and the crude material was purified by flash chromatography (2-10% MeOH:DCM) to afford the title compound as an off-white solid (7 mg, 89%). LCMS $[M+H]^+$ 374.03 m/z; ^{1}H NMR (399 MHz, DMSO-d_6) δ ppm 12.30 (br. s., 1 H) 8.69 (d, *J*=12.5 Hz, 1 H) 8.63 - 8.66 (m, 1 H) 8.28 (s, 1 H) 8.20 (d, *J*=7.3 Hz, 1 H) 8.16 (s, 1 H)

8.11 (d, *J*=8.8 Hz, 2 H) 8.03 (d, *J*=8.1 Hz, 2 H) 7.72 (d, *J*=8.1 Hz, 1 H) 7.65 (t, *J*=7.3 Hz, 1 H) 3.27 (s, 3 H).

3-(5-(pyrimidin-5-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile (23e). The title compound was prepared according to General Procedure D on a 53-mg scale using 3-(5-(pyrimidin-5-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile. The reaction was run for two minutes, then diluted with MeOH, upon which a precipitate was observed and removed by gravity filtration. The filtrate was purified by flash chromatography (5% MeOH:DCM) to afford the title compound as an off-white solid (17 mg, 47%). LCMS $[M+H]^+$ 298.03 m/z; ^{1}H NMR (399 MHz, DMSO-d_6) δ ppm 12.34 (br. s, 1 H) 9.31 (s, 2 H) 9.21 (s, 1 H) 8.77 (s, 1 H) 8.71 (s, 1 H) 8.30 (s, 1 H) 8.23 (d, *J*=8.1 Hz, 1 H) 8.19 (br. s., 1 H) 7.71 (d, *J*=7.3 Hz, 1 H) 7.65 (t, *J*=8.1 Hz, 1 H).

3-(5-(Pyridin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile (23f). The title compound was prepared according to General Procedure D on a 62-mg scale using 3-(5-(pyridin-4-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile. The reaction was run for two minutes, and the crude material was purified by flash chromatography (5% MeOH:DCM) to afford the title compound as an off-white solid (36 mg, 88%). LCMS $[M+H]^+$ 297.04 m/z; ^{1}H NMR (399 MHz, DMSO-d_6) δ ppm 12.34 (br. s., 1 H) 8.74 (s, 1 H) 8.69 (s, 1 H) 8.66 (d, *J*=5.1 Hz, 2 H) 8.29 (s, 1 H) 8.21 (d, *J*=8.1 Hz, 1 H) 8.17 (s, 1 H) 7.90 (d, *J*=5.9 Hz, 2 H) 7.72 (d, *J*=8.1 Hz, 1 H) 7.65 (t, *J*=7.3 Hz, 1 H).

3-(5-(Pyrrolidin-1-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile (24a). The title compound was prepared according to General Procedure C on a 153-mg scale using pyrrolidine. The crude material was purified by flash chromatography (50-100% EtOAc:Hexanes) to afford the title compound as a yellow solid (12 mg, 12%). LCMS $[M+H]^+$ 289.12 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.68 (br. s., 1 H) 8.11 (s, 1 H) 8.06 (d, *J*=6.8 Hz, 1 H) 7.91 (d, *J*=2.4 Hz, 1 H) 7.83 (d, *J*=2.4 Hz, 1 H) 7.59 - 7.66 (m, 2 H) 7.32 (s, 1 H) 3.29 - 3.32 (m, 4 H) 1.97 - 2.02 (m, 4 H).

3-(5-(Piperidin-1-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile (24b). The title compound was prepared according to General Procedure C on a 152-mg scale using piperidine. The crude material was purified by flash chromatography (50-100% EtOAc:Hexanes) to afford the title compound as a light orange

solid (20 mg, 19%). LCMS $[M+H]^+$ 303.10 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.84 (br. s, 1 H) 8.13 (d, *J*=2.0 Hz, 2 H) 8.06 (d, *J*=7.3 Hz, 1 H) 7.96 (d, *J*=2.4 Hz, 1 H) 7.76 (d, *J*=2.4 Hz, 1 H) 7.60 - 7.67 (m, 2 H) 3.11 (t, *J*=5.9 Hz, 4 H) 1.70 (quin, *J*=5.4 Hz, 4 H) 1.54 (quin, *J*=5.9 Hz, 2 H).

3-(5-(Piperidin-1-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile (24c). The title compound was prepared according to General Procedure C on a 95-mg scale using *N*-methylpiperazine. The crude material was purified by flash chromatography (5-10% MeOH:DCM) to afford the title compound as a light orange solid (12 mg, 18%). LCMS $[M+H]^+$ 318.15 m/z; ^{1}H NMR (500 MHz, METHANOL-d_4) δ ppm 8.13 (d, *J*=2.4 Hz, 1 H) 7.95 - 8.00 (m, 2 H) 7.85 (d, *J*=2.4 Hz, 1 H) 7.73 (s, 1 H) 7.57 - 7.63 (m, 2 H) 3.24 (br. t, *J*=4.9, 4.9 Hz, 4 H) 2.71 (br. t, *J*=4.9, 4.9 Hz, 4 H) 2.39 (s, 3 H).

***tert*-Butyl 4-(3-(3-cyanophenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)piperazine-1-carboxylate (24d).** The title compound was prepared according to General Procedure C on a 150-mg scale using *tert*-butyl piperazine-1-carboxylate; the reaction was run overnight. The crude material was purified by flash chromatography (20-100% EtOAc:Hexanes) to afford the title compound as a yellow solid (40 mg, 30%). LCMS $[M+H]^+$ 404.21 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.89 (br. s, 1 H) 8.16 (d, *J*=2.4 Hz, 1 H) 8.14 (t, *J*=1.7 Hz, 1 H) 8.08 (dt, *J*=8.1, 1.6 Hz, 1 H) 7.99 (d, *J*=2.9 Hz, 1 H) 7.83 (d, *J*=2.4 Hz, 1 H) 7.64 - 7.68 (m, 1 H) 7.62 (t, *J*=7.8 Hz, 1 H) 3.52 (m, *J*=4.9, 3.4 Hz, 4 H) 3.11 (br. t, *J*=4.9, 4.9 Hz, 4 H) 1.43 (s, 9 H).

3-(5-(4-Methyl-1,4-diazepan-1-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile (24e). The title compound was prepared according to General Procedure C on a 70-mg scale using 1-methyl-1,4-diazepane. The crude material was purified by flash chromatography (5-25% MeOH:DCM) to afford the title compound as a yellow solid (9 mg, 12%). LCMS $[M+H]^+$ 332.16 m/z; ^{1}H NMR (500 MHz, METHANOL-d_4) δ ppm 7.93 - 8.01 (m, 3 H) 7.67 (s, 1 H) 7.54 - 7.63 (m, 3 H) 3.69 (br. t, *J*=4.4, 4.4 Hz, 2 H) 3.55 (t, *J*=6.3 Hz, 2 H) 3.04 (br. t, *J*=4.4, 4.4 Hz, 2 H) 2.90 (br. t, *J*=4.9, 4.9 Hz, 1 H) 2.57 (s, 3 H) 2.15 (quint, *J*=11.1, 11.1, 11.1, 11.1, 5.9, 5.9 Hz, 2 H).

***tert*-Butyl 4-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)piperazine-1-carboxylate (S29).** 5-Bromo-1*H*-pyrrolo[2,3-*b*]pyridine **9** (250 mg, 1.27 mmol), 1-boc piperazine (286 mg, 1.54 mmol) RuPhos (30 mg, 0.064 mmol),

and RuPhos Pd G1 (51 mg, 0.062 mmol) were combined in a vial that was filled with nitrogen and evacuated three times. 1.0 M LiHMDS in THF (3.2 ml, 3.2 mmol) was added and the reaction was heated at 65 °C for ~5 h. The reaction was cooled to room temperature and quenched by the addition of 1M HCl, then diluted with EtOAc and poured over sat. aq. $NaHCO_3$. 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 residue was purified by flash chromatography (50-80% EtOAc:Hexanes) to afford the title compound as a light yellow solid (350 mg, 91%). LCMS $[M+H]^+$ 303.16 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.34 - 11.42 (m, 1 H) 8.06 (d, *J*=2.4 Hz, 1 H) 7.51 (d, *J*=2.4 Hz, 1 H) 7.37 (t, *J*=2.9 Hz, 1 H) 6.32 (dd, *J*=3.2, 1.7 Hz, 1 H) 3.49 (br. t, *J*=4.9, 4.9 Hz, 4 H) 3.01 (br. t, *J*=4.9, 4.9 Hz, 4 H) 1.43 (s, 9 H).

***tert*-Butyl 4-(3-iodo-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)piperazine-1-carboxylate (S30).** *tert*-Butyl 4-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)piperazine-1-carboxylate **S29** (350 mg, 1.16 mmol) was dissolved in acetonitrile (6.5 ml, 0.18 M) and N-iodosuccinimide (314 mg, 1.40 mmol) was added. The reaction was stirred at 50 °C for 2 h. The reaction was cooled to room temperature, diluted with EtOAc, and washed three times with water and once with brine. The organic layer was dried with sodium sulfate and concentrated under reduced pressure. The crude residue was purified by flash chromatography (50% EtOAc:Hexanes) to afford the title compound as a yellow solid (230 mg, 46%). LCMS $[M+H]^+$ 429.11 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.83 - 11.93 (m, 1 H) 8.12 (d, *J*=2.9 Hz, 1 H) 7.61 (d, *J*=2.9 Hz, 1 H) 7.13 (d, *J*=2.4 Hz, 1 H) 3.51 (br. s., 1 H) 3.07 (t, *J*=4.9 Hz, 4 H) 1.43 (s, 9 H).

***tert*-Butyl 4-(3-iodo-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)piperazine-1-carboxylate (S31).** *tert*-Butyl 4-(3-iodo-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)piperazine-1-carboxylate **S30** (230 mg, 0.537 mmol) was suspended in DCM (2.7 ml, 0.21 M) and TEA (0.30 ml, 2.15 mmol), DMAP (84 mg, 0.688 mmol) and 4-methylbenzenesulfonyl chloride (240 mg, 1.26 mmol) were added in that order. The reaction was stirred overnight at room temperature. The reaction was washed once with 1M HCl, once with sat. aq. $NaHCO_3$, and once with brine; the organic layer was dried with sodium sulfate and concentrated under reduced pressure. The crude residue was purified by flash chromatography (20% EtOAc:Hex) to afford the title

compound as an orange oil (138 mg, 44%). LCMS $[M+H]^+$ 583.04 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.22 (t, *J*=2.4 Hz, 1 H) 8.03 (d, *J*=2.4 Hz, 1 H) 7.95 (dd, *J*=8.5, 2.2 Hz, 2 H) 7.41 (d, *J*=6.8 Hz, 2 H) 7.13 (t, *J*=2.4 Hz, 1 H) 3.47 (br. s., 4 H) 3.14 (br. s., 4 H) 2.33 (s, 3 H) 1.42 (s, 9 H).

3-Iodo-5-(piperazin-1-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine (S32). *tert*-Butyl 4-(3-iodo-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)piperazine-1-carboxylate **S31** (138 mg, 0.237 mmol) was taken up in 4M HCl in dioxane (0.60 ml, 2.40 mmol) and the reaction was stirred at room temperature for 3 h. The solvent was removed under reduced pressure and the yellow residue (HCl salt) was dissolved in water and poured over 1 M NaOH. The aqueous layer (pH ~13-14) was extracted three times with DCM. The combined organic layers were dried with sodium sulfate and concentrated under reduced pressure to afford the title compound as a yellow oil (73 mg, 64%). LCMS $[M+H]^+$ 483.01 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.20 (d, *J*=2.9 Hz, 1 H) 8.01 (s, 1 H) 7.95 (d, *J*=8.3 Hz, 2 H) 7.41 (d, *J*=8.8 Hz, 2 H) 7.05 (d, *J*=2.9 Hz, 1 H) 3.08 (t, *J*=4.9 Hz, 4 H) 2.84 (t, *J*=5.4 Hz, 4 H) 2.34 (s, 3 H).

3-Iodo-5-(4-(methylsulfonyl)piperazin-1-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine (S33). 3-Iodo-5-(piperazin-1-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine **S32** (73 mg, 0.151) was dissolved in DCM (0.5 ml, 0.32 M) and TEA (42 µl, 0.301 mmol) was added. The reaction was stirred for 10 minutes at room temperature before the addition of methanesulfonyl chloride (14 µl, 0.181 mmol). The reaction was stirred overnight at room temperature. The reaction was quenched with water and extracted four times with DCM. 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 an orange solid (68 mg, 80%). LCMS $[M+H]^+$ 560.98 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.25 (d, *J*=2.4 Hz, 1 H) 8.04 (s, 1 H) 7.96 (d, *J*=8.3 Hz, 2 H) 7.41 (d, *J*=8.3 Hz, 2 H) 7.17 (d, *J*=2.9 Hz, 1 H) 3.28 - 3.32 (m, 4 H) 3.24 - 3.28 (m, 4 H) 2.93 (s, 3 H) 2.34 (s, 3 H).

3-(5-(4-(Methylsulfonyl)piperazin-1-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile (S34). 3-Iodo-5-(4-(methylsulfonyl)piperazin-1-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine **S33** (68 mg, 0.121 mmol), (3-cyanophenyl)boronic acid (36 mg, 0.245 mmol), and $PdCl_2(dppf)\cdot CH_2Cl_2$ (10 mg, 0.012 mmol) were combined in a microwave vial that was purged with nitrogen and evacuated three times. Dioxane (0.50 ml,

0.25 M) and 2M K_2CO_3 (0.20 ml, 0.400 mmol) were added and the reaction mixture was degassed for ~10 minutes. The reaction was run in the microwave (120 °C) for 5 minutes, then diluted with EtOAc, filtered through celite, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (50% EtOAc:Hex) to afford the title compound as a dull red glassy solid (41 mg, 63%). LCMS $[M+H]^+$ 536.10 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.31 (s, 1 H) 8.28 (s, 1 H) 8.28 (s, 1 H) 8.10 - 8.15 (m, 1 H) 8.01 (d, *J*=8.3 Hz, 2 H) 7.83 (d, *J*=7.8 Hz, 1 H) 7.76 (d, *J*=2.4 Hz, 1 H) 7.68 (t, *J*=7.8 Hz, 1 H) 7.42 (d, *J*=8.8 Hz, 2 H) 3.29 - 3.31 (m, 4 H) 3.26 (m, *J*=5.9 Hz, 4 H) 2.93 (s, 3 H) 2.34 (s, 3 H).

3-(5-(4-(Methylsulfonyl)piperazin-1-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile (25). The title compound was prepared according to General Procedure D on a 45-mg scale using 3-(5-(4-(methylsulfonyl)piperazin-1-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile **S34**. The reaction was run for 45 minutes, and the crude material was purified by flash chromatography (50-100% EtOAc:Hexanes) to afford the title compound as a white solid (15 mg, 53%). LCMS $[M+H]^+$ 382.13 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.92 (s, 1 H) 8.18 (d, *J*=2.4 Hz, 1 H) 8.15 (s, 1 H) 8.09 (d, *J*=7.8 Hz, 1 H) 8.00 (s, 1 H) 7.86 (d, *J*=2.0 Hz, 1 H) 7.66 (d, *J*=7.3 Hz, 1 H) 7.63 (t, *J*=7.8 Hz, 1 H) 3.29 - 3.32 (m, 4 H) 3.27 (m, *J*=5.9 Hz, 4 H) 2.95 (s, 3 H).

3-(5-(Piperazin-1-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile (26). *tert*-Butyl 4-(3-(3-cyanophenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)piperazine-1-carboxylate **24d** (40 mg, 0.099 mmol) was taken up in 4M HCl in dioxane (0.25 ml, 1.00 mmol) and the reaction was stirred at room temperature for 2 h. The solvent was removed under reduced pressure and the yellow residue (HCl salt) was dissolved in water and poured over sat. aq. $NaHCO_3$. The aqueous layer (pH ~8) was extracted three times with DCM. The pH of the aqueous layer was increased to ~13-14 by the addition of 1M NaOH and the aqueous layer was extracted once more with DCM. The combined organic layers were dried with sodium sulfate and concentrated under reduced pressure to afford the title compound as a yellow solid (19 mg, 62%). LCMS $[M+H]^+$ 304.17 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.84 (br. s., 1 H) 8.13 (d, *J*=2.0 Hz, 2 H) 8.05 - 8.09 (m, 1 H) 7.96 (d, *J*=2.4 Hz, 1 H) 7.74 (d, *J*=2.4 Hz, 1 H) 7.60 - 7.68 (m, 2 H) 3.30 (br. s., 1 H) 3.07 (br. t, *J*=4.4, 4.4 Hz, 4 H) 2.90 (m, *J*=4.9 Hz, 4 H).

3-(5-((1-Methyl-1*H*-pyrazol-4-yl)amino)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile (27). 3-(5-Bromo-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile **21** (151 mg, 0.334 mmol), BrettPhos (19 mg, 0.035 mmol), BrettPhos Pd G1 (32 mg, 0.040 mmol), and 4-amino-1-methylpyrazole (69 mg, 0.710 mmol) were combined in a vial that was filled with nitrogen and evacuated three times. 1.0 M LiHMDS in THF (0.800 ml, 0.800 mmol) was added and the reaction was heated at 65 °C overnight. The reaction was quenched by the addition of 1M HCl, then diluted with EtOAc and poured over sat. aq. $NaHCO_3$. 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 (20-100% EtOAc:Hex - 1-5% MeOH:EtOAc), then repurified by preparative HPLC (95-5% water:ACN) to afford the title compound (0.5 equiv formate salt) as a dark orange residue (5 mg, 8%). LCMS $[M+H]^+$ 315.19 m/z; ^{1}H NMR (500 MHz, METHANOL-d_4) δ ppm 8.46 - 8.65 (m, 0 H) 7.95 - 7.98 (m, 1 H) 7.93 - 7.95 (m, 1 H) 7.91 (dt, *J*=6.8, 2.0 Hz, 1 H) 7.71 (d, *J*=2.4 Hz, 1 H) 7.69 (s, 1 H) 7.54 - 7.61 (m, 3 H) 7.41 (d, *J*=1.0 Hz, 1 H) 3.88 (s, 3 H).

***N*-(4-(methylsulfonyl)phenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-amine (S35).** 5-Bromo-1*H*-pyrrolo[2,3-*b*]pyridine **9** (250 mg, 1.27 mmol), 4-(methylsulfonyl)aniline (264 mg, 1.54 mmol), BrettPhos (34 mg, 0.063 mmol), and BrettPhos Pd G1 (51 mg, 0.064 mmol) were combined in a vial that was filled with nitrogen and evacuated three times. 1.0 M LiHMDS in THF (3.2 ml, 3.2 mmol) was added and the reaction was heated at 65 °C for ~5 h. The reaction was quenched by the addition of 1M HCl, then diluted with EtOAc and poured over sat. aq. $NaHCO_3$. 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 (50-100% EtOAc:Hex) to afford the title compound as a light yellow solid (146 mg, 40%). LCMS $[M+H]^+$ 288.08 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.65 (br. s., 1 H) 8.69 (s, 1 H) 8.09 (d, *J*=2.4 Hz, 1 H) 7.82 (d, *J*=2.0 Hz, 1 H) 7.63 (d, *J*=8.8 Hz, 2 H) 7.49 (t, *J*=2.9 Hz, 1 H) 6.91 (d, *J*=8.8 Hz, 2 H) 6.43 (dd, *J*=3.2, 1.7 Hz, 1 H) 3.07 (s, 3 H).

3-Iodo-*N*-(4-(methylsulfonyl)phenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-amine (S36). N-(4-(methylsulfonyl)phenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-amine **S35** (146 mg, 0.508 mmol) was dissolved in acetonitrile (2.8 ml, 0.18 M) and N-iodosuccinimide (138 mg, 0.613 mmol) was added. The reaction was stirred at 50 °C for 5 h. Upon cooling, a dark brown precipitate was observed and collected by vacuum filtration to afford the title compound as a red-brown solid (110 mg, 52%). LCMS $[M+H]^+$ 413.99 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.13 (br. s., 1 H) 8.80 (s, 1 H) 8.15 (d, *J*=2.4 Hz, 1 H) 7.74 (d, *J*=2.4 Hz, 1 H) 7.67 (d, *J*=8.8 Hz, 2 H) 7.47 (d, *J*=2.0 Hz, 1 H) 6.97 (d, *J*=8.8 Hz, 2 H) 3.08 (s, 3 H).

3-Iodo-*N*-(4-(methylsulfonyl)phenyl)-1-tosyl-1*H*-pyrrolo[2,3-b]pyridin-5-amine (S37). 3-Iodo-N-(4-(methylsulfonyl)phenyl)-1*H*-pyrrolo[2,3-b]pyridin-5-amine **S36** (110 mg, 0.266 mmol) was suspended in DCM (1.3 ml, 0.21 M) and TEA (0.15 ml, 1.08 mmol), DMAP (43 mg, 0.352 mmol) and 4-methylbenzenesulfonyl chloride (129 mg, 0.677 mmol) were added in that order. The reaction was stirred overnight at room temperature. The reaction was washed once with 1M HCl, once with sat. aq. $NaHCO_3$, 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 (20-50% EtOAc:Hex) to afford the title compound as an off-white solid (66 mg, 44%). LCMS $[M+H]^+$ 567.90 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.03 (s, 1 H) 8.27 (d, *J*=2.4 Hz, 1 H) 8.13 (s, 1 H) 8.01 (d, *J*=8.3 Hz, 2 H) 7.71 (d, *J*=8.8 Hz, 2 H) 7.50 (d, *J*=2.4 Hz, 1 H) 7.44 (d, *J*=8.8 Hz, 2 H) 7.10 (d, *J*=8.8 Hz, 2 H) 3.11 (s, 3 H) 2.35 (s, 3 H).

3-(5-((4-(methylsulfonyl)phenyl)amino)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile (S38). 3-Iodo-N-(4-(methylsulfonyl)phenyl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-amine **S37** (65 mg, 0.114 mmol), (3-cyanophenyl)boronic acid (35 mg, 0.238 mmol), and $PdCl_2$(dppf)·CH_2Cl_2 (9 mg, 0.011 mmol) were combined in a microwave vial that was purged with nitrogen and evacuated three times. Dioxane (0.50 ml, 0.25 M) and 2M K_2CO_3 (0.20 ml, 0.400 mmol) were added and the reaction mixture was degassed for ~10 minutes. The reaction was run in the microwave (120 °C) for five minutes. The reaction mixture was diluted with EtOAc, filtered through celite, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (20-75% EtOAc:Hex) to afford the title compound as a dark orange solid (46 mg, 74%). LCMS $[M+H]^+$ 543.03 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.99 (s, 1 H) 8.42 (s, 1

H) 8.33 (d, *J*=2.4 Hz, 1 H) 8.29 (t, *J*=1.5 Hz, 1 H) 8.13 (d, *J*=2.4 Hz, 1 H) 8.11 (dt, *J*=8.3, 1.5 Hz, 1 H) 8.06 (d, *J*=8.3 Hz, 2 H) 7.82 (dt, *J*=7.8, 1.5 Hz, 1 H) 7.65 - 7.70 (m, 3 H) 7.45 (d, *J*=8.3 Hz, 2 H) 7.09 (d, *J*=8.8 Hz, 2 H) 3.09 (s, 3 H) 2.36 (s, 3 H).

3-(5-((4-(Methylsulfonyl)phenyl)amino)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile (28). The title compound was prepared according to General Procedure D on a 46-mg scale using 3-(5-((4-(methylsulfonyl)phenyl)amino)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile **S38**. The reaction was run for 80 minutes, and the crude material was purified by flash chromatography (50% EtOAc:Hexanes) to afford the title compound as a white solid (15 mg, 46%). LCMS $[M+H]^+$ 389.12 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.13 - 12.20 (m, 1 H) 8.79 (s, 1 H) 8.20 (dd, *J*=11.5, 2.2 Hz, 2 H) 8.16 (s, 1 H) 8.11 (s, 1 H) 8.06 (d, *J*=7.8 Hz, 1 H) 7.60 - 7.69 (m, 4 H) 6.97 (d, *J*=9.3 Hz, 2 H) 3.08 (s, 3 H).

Tetrahydro-2*H*-pyran-4-yl methanesulfonate (S40a). Tetrahydro-2*H*-pyran-4-ol **S39a** (0.500 ml, 5.24 mmol) was dissolved in DCM (9.0 ml, 0.60 M) and TEA (0.750 ml, 5.38 mmol) was added, followed by the addition of DMAP (128 mg, 1.05 mmol). The solution was cooled to 0 °C and MsCl (0.410 ml, 5.30 mmol) was added dropwise, upon which the reaction mixture turned opaque. The reaction was run at 0 °C for 4 h, after which water was added and the reaction was transferred to a separatory funnel. The organic layer was washed once with brine, dried with sodium sulfate, and concentrated under reduced pressure to afford the title compound as an off-white solid (770 mg, 82%). ^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 4.92 (spt, *J*=4.2 Hz, 1 H) 3.92 - 4.00 (m, 2 H) 3.56 (td, *J*=10.2, 8.8 Hz, 2 H) 3.05 (s, 3 H) 2.02 - 2.10 (m, 2 H) 1.84 - 1.95 (m, 2 H).

*Does not ionize.

***tert*-Butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate (S40b).** *tert*-Butyl 4-hydroxypiperidine-1-carboxylate **S39b** (2.00 g, 9.94 mmol) was dissolved in DCM (20 ml, 0.5 M) and the reaction mixture was cooled to 0-5. TEA (3.0 ml, 21.52 mmol) was slowly added followed by the slow addition of methane sulfonyl chloride (1.0 ml, 12.92 mmol). The reaction was stirred for 1 h at room temperature. The reaction mixture was purified by flash chromatography (10% EtOAc:Hexanes) to afford the title compound as a white solid (1.7g, 61%). LCMS $[M+H]^+$ 223.95 m/z (loss of *t*-Bu group); ^{1}H NMR (500 MHz, DMSO-d_6)

δ ppm 4.82 (tt, *J*=8.1, 3.8 Hz, 1 H) 3.60 (tt, *J*=5.9, 4.4 Hz, 2 H) 3.20 (s, 3 H) 3.12 - 3.19 (m, 2 H) 1.86 - 1.94 (m, 2 H) 1.60 (dtd, *J*=13.0, 8.8, 8.8, 4.1 Hz, 2 H) 1.40 (s, 9 H).

1-Methylpiperidin-4-yl methanesulfonate (S40c). 1-Methylpiperidin-4-ol **S39c** (0.500 ml, 4.25 mmol) was dissolved in DCM (7.0 ml, 0.60 M) and TEA (0.600 ml, 4.30 mmol) was added, followed by the addition of DMAP (103 mg, 0.843 mmol). The solution was cooled to 0 °C and MsCl (0.330 ml, 4.26 mmol) was added dropwise, upon which the reaction mixture turned opaque. The reaction was run at 0 °C for 5 h. Water was added and the reaction was transferred to a separatory funnel. The organic layer was washed once more with water, once with brine, dried with sodium sulfate, and concentrated under reduced pressure to afford the title compound as a yellow oil (444 mg, 54%). LCMS $[M+H]^+$ 193.97 m/z; ^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 4.75 (br. s., 1 H) 3.03 (s, 3 H) 2.67 (br. s., 2 H) 2.21 - 2.35 (m, 5 H) 1.99 - 2.07 (m, 2 H) 1.88 - 1.97 (m, 2 H).

4-Bromo-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazole (S41a). 4-bromo-1*H*-pyrazole (200 mg, 1.36 mmol) was dissolved in DMF (1.7 ml, 0.81 M) and cooled to 0 °C. NaH (165 mg, 4.13 mmol) was added portionwise and the reaction was stirred for 1 h at 0 °C. Tetrahydro-2*H*-pyran-4-yl methanesulfonate **S40a** (317 mg, 1.76 mmol) was added. The reaction was gradually heated to 100 °C and stirred overnight. The reaction mixture was quenched with water and extracted twice with EtOAc. The combined organic layers were washed with brine, dried with sodium sulfate and concentrated under reduced pressure. The product was purified by flash chromatography (2% 5%NH_4OH/MeOH:DCM) to afford the title compound as an off-white solid (191 mg, 61%). LCMS $[M+H]^+$ 230.93 m/z (^{79}Br), 232.92 m/z (^{81}Br); ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.06 (s, 1 H) 7.55 (s, 1 H) 4.39 (tt, *J*=10.6, 5.2 Hz, 1 H) 3.94 (d, *J*=12.7 Hz, 2 H) 3.44 (td, *J*=11.5, 2.9 Hz, 2 H) 1.85 - 1.98 (m, 4 H).

***tert*-Butyl 4-(4-bromo-1*H*-pyrazol-1-yl)piperidine-1-carboxylate (S41b).** 4-Bromo-1*H*-pyrazole (200 mg, 1.36 mmol) was dissolved in DMF (1.7 ml, 0.81 M) and cooled to 0 °C. NaH (166 mg, 4.15 mmol) was added portionwise and the reaction was stirred for 1 h at 0 °C. *tert*-Butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate **S40b** (497 mg, 1.78 mmol) was added and the reaction was gradually heated to 100 °C and stirred overnight. The reaction mixture was quenched with water and

extracted twice with EtOAc. The combined organic layers were washed with brine, dried with sodium sulfate and concentrated under reduced pressure. The product was purified by flash chromatography (0-50% EtOAc:Hex) to afford the title compound as a colorless oil (282 mg, 36%). LCMS $[M+H]^+$ 273.94 m/z (^{79}Br), 275.96 m/z (^{81}Br); ^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 7.47 (s, 1 H) 7.44 (s, 1 H) 4.16 - 4.41 (m, 3 H) 2.76 - 2.97 (m, 2 H) 2.10 (d, *J*=12.2 Hz, 2 H) 1.87 (qd, *J*=12.2, 3.9 Hz, 2 H) 1.47 (s, 9 H).

4-(4-Bromo-1*H*-pyrazol-1-yl)-1-methylpiperidine (S41c). 4-bromo-1*H*-pyrazole (200 mg, 1.36 mmol) was dissolved in dry DMF (1.7 ml, 0.81 M) and cooled to 0 °C. NaH (168 mg, 4.20 mmol) was added portionwise and the reaction was stirred for 1 h at 0 °C, after which 1-methylpiperidin-4-yl methanesulfonate **406c** (444 mg, 2.30 mmol) was dissolved in dry DMF (1.4 ml, 1.7 M) added. The reaction was gradually heated to 100 °C and stirred for two days. The reaction mixture was quenched with water and extracted twice with EtOAc. The combined organic layers were washed with brine, dried with sodium sulfate and concentrated under reduced pressure. The crude material was purified by flash chromatography (3% 5%NH_4OH/MeOH:DCM) to afford the title compound as an off-white solid (80 mg, 24%). LCMS $[M+H]^+$ 243.97 m/z (^{79}Br), 245.98 m/z (^{81}Br); ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.04 (s, 1 H) 7.53 (s, 1 H) 4.09 (dt, *J*=10.5, 5.0 Hz, 1 H) 2.82 (d, *J*=11.7 Hz, 2 H) 2.18 (s, 3 H) 1.96 - 2.07 (m, 2 H) 1.85 - 1.95 (m, 4 H).

3-(5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile (S42). The title compound was prepared according to General Procedure E on a 600-mg scale using 3-(5-bromo-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile **21**. The crude material was purified by flash chromatography (0-20% EtOAc:Hex), then repurified by flash chromatography (1% MeOH:DCM) to afford the title compound as a white solid (148 mg, 22%). LCMS $[M+H]^+$ 500.08 m/z; ^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 8.86 (s, 1 H) 8.40 (s, 1 H) 8.15 (d, *J*=8.3 Hz, 2 H) 7.92 (s, 1 H) 7.89 (s, 1 H) 7.85 (d, *J*=7.8 Hz, 1 H) 7.67 (d, *J*=7.8 Hz, 1 H) 7.61 (t, *J*=7.8 Hz, 1 H) 7.29 (d, *J*=8.3 Hz, 2 H) 2.39 (s, 3 H) 1.36 (s, 12 H).

3-(5-(1-(Tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazol-4-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile (S43a). 4-Bromo-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazole **S41a** (44 mg, 0.190 mmol) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (14 mg, 0.017 mmol) were combined in a reaction vial that was filled with nitrogen and evacuated three times. Crude 3-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile **S42** (84 mg, 0.168 mmol) was dissolved in dioxane (1.0 ml, 0.17 M) and added to the reaction mixture, followed by the addition of 2M K_2CO_3 (0.40 ml, 0.800 mmol). The reaction was degassed and run in the microwave (145 °C) for 5 minutes. The reaction mixture was diluted with EtOAc, filtered through celite, and concentrated under reduced pressure. The crude material was purified by flash chromatography (20-75% EtOAc:Hex) to afford the title compound as a pale yellow solid (37 mg, 43%). LCMS $[M+H]^+$ 524.07 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.72 (s, 1 H) 8.44 (m, *J*=6.3 Hz, 2 H) 8.40 (s, 1 H) 8.34 (s, 1 H) 8.19 (d, *J*=8.3 Hz, 1 H) 8.03 - 8.10 (m, 3 H) 7.86 (d, *J*=7.3 Hz, 1 H) 7.71 (t, *J*=8.3 Hz, 1 H) 7.44 (d, *J*=7.8 Hz, 2 H) 4.37 - 4.46 (m, 1 H) 3.97 (d, *J*=12.7 Hz, 2 H) 3.48 (t, *J*=10.7 Hz, 2 H) 2.35 (s, 3 H) 1.88 - 2.06 (m, 4 H).

***tert*-Butyl 4-(4-(3-(3-cyanophenyl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate (S43b).** *tert*-Butyl 4-(4-bromo-1*H*-pyrazol-1-yl)piperidine-1-carboxylate **S41b** (282 mg, 0.854 mmol) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (54 mg, 0.066 mmol) were combined in a reaction vial that was filled with nitrogen and evacuated three times. Crude 3-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile **S42** (332 mg, 0.665 mmol) was dissolved in dioxane (3.5 ml, 0.17 M) and added to the reaction mixture, followed by the additon of 2M K_2CO_3 (1.3 ml, 2.60 mmol). The reaction was degassed and run in the microwave (145 °C) for 25 minutes. The reaction mixture was diluted with EtOAc, filtered through celite, and concentrated under reduced pressure. The crude material was purified by flash chromatography (20-40-60% EtOAc:Hex, step gradient) to afford the title compound as a pale yellow solid (180 mg, 43%). LCMS $[M+H]^+$ 623.07 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.71 (d, *J*=1.5 Hz, 1 H) 8.44 (s, 1 H) 8.43 (d, *J*=1.5 Hz, 1 H) 8.40 (s, 1 H) 8.34 (s, 1 H) 8.18 (d, *J*=7.8 Hz, 1 H) 8.03 - 8.09 (m, 3 H) 7.85 (d, *J*=7.8 Hz, 1 H) 7.71 (t, *J*=8.3 Hz, 1 H) 7.43 (d, *J*=7.8 Hz, 2 H)

4.34 - 4.42 (m, 1 H) 4.02 (br. s, 2 H) 2.93 (br. s, 2 H) 2.34 (s, 3 H) 2.04 (d, *J*=10.7 Hz, 2 H) 1.79 (dd, *J*=12.2, 3.9 Hz, 2 H) 1.42 (s, 9 H).

3-(5-(1-(1-Methylpiperidin-4-yl)-1*H*-pyrazol-4-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile (S43c). 3-(5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile **S42** (64 mg, 0.128 mmol), 4-(4-bromo-1*H*-pyrazol-1-yl)-1-methylpiperidine **S41c** (40 mg, 0.164 mmol) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (11 mg, 0.013 mmol) were combined in a reaction vial that was filled with nitrogen and evacuated three times. Dioxane (1.0 ml, 0.17 M) was added to the reaction mixture, followed by the addition of 2M K2CO3 (0.30 ml, 0.600 mmol). The reaction was degassed and run in the microwave (145 °C) for 5 minutes. The reaction mixture was diluted with EtOAc, filtered through celite, and concentrated under reduced pressure. The product was purified by flash chromatography (1-10% MeOH:DCM) to afford the title compound as an orange residue (45 mg, 65%). LCMS $[M+H]^+$ 537.11 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.71 (s, 1 H) 8.43 (s, 2 H) 8.40 (s, 1 H) 8.34 (s, 1 H) 8.19 (d, *J*=7.3 Hz, 1 H) 8.02 - 8.09 (m, 3 H) 7.86 (d, *J*=7.8 Hz, 1 H) 7.71 (t, *J*=7.8 Hz, 1 H) 7.44 (d, *J*=8.3 Hz, 2 H) 4.05 - 4.17 (m, 1 H) 2.83 - 2.91 (m, 2 H) 2.35 (s, 3 H) 2.20 (s, 3 H) 1.96 - 2.07 (m, 6 H).

3-(5-(1-(Tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile (29a). The title compound was prepared according to General Procedure D on a 37-mg scale using 3-(5-(1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazol-4-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile **S43a**. The reaction was run for six minutes, and the crude material was purified by flash chromatography (1-10% MeOH:DCM) to afford the title compound as an off-white solid (13 mg, 49%). LCMS $[M+H]^+$ 370.10 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.07 (br. s., 1 H) 8.58 (d, *J*=1.5 Hz, 1 H) 8.46 (s, 1 H) 8.40 (s, 1 H) 8.21 (s, 1 H) 8.16 (d, *J*=7.8 Hz, 1 H) 8.06 (d, *J*=2.4 Hz, 1 H) 8.04 (s, 1 H) 7.70 (d, *J*=7.8 Hz, 1 H) 7.65 (t, *J*=7.8 Hz, 1 H) 4.43 (tquin, *J*=6.3, 6.3, 4.9, 4.9, 4.9, 4.9 Hz, 1 H) 3.99 (d, *J*=11.7 Hz, 2 H) 3.49 (td, *J*=10.7, 2.4 Hz, 2 H) 1.94 - 2.08 (m, 4 H).

***tert*-Butyl 4-(4-(3-(3-cyanophenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrazol-1-yl)piper-idine-1-carboxylate (29b).** The title compound was prepared according to General Procedure D on a 50-mg scale

using *tert*-butyl 4-(4-(3-(3-cyanophenyl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate **S43b**. The reaction was run for 10 minutes, and the crude material was purified by flash chromatography (3% 5% NH_4OH/MeOH:DCM) to afford the title compound as a light yellow solid (21 mg, 55%). LCMS $[M+H]^+$ 469.10 m/z; ^1H NMR (500 MHz, DMSO-d_6) δ ppm 12.07 (br. s., 1 H) 8.57 (d, *J*=1.5 Hz, 1 H) 8.46 (s, 1 H) 8.41 (s, 1 H) 8.21 (s, 1 H) 8.16 (d, *J*=7.3 Hz, 1 H) 8.06 (d, *J*=2.4 Hz, 1 H) 8.04 (s, 1 H) 7.69 (d, *J*=8.3 Hz, 1 H) 7.66 (t, *J*=7.8 Hz, 1 H) 4.34 - 4.44 (m, 1 H) 4.01 - 4.16 (m, 2 H) 2.81 - 3.06 (m, 2 H) 2.05 (d, *J*=10.7 Hz, 2 H) 1.83 (qd, *J*=14.2, 12.2 Hz, 2 H) 1.43 (s, 9 H).

3-(5-(1-(1-Methylpiperidin-4-yl)-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzo-nitrile (29c). The title compound was prepared according to General Procedure D on a 45-mg scale using 3-(5-(1-(1-methylpiperidin-4-yl)-1*H*-pyrazol-4-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile **S43c**. The reaction was run for five minutes, and the crude material was purified by flash chromatography (5-10% 5% NH_4OH/MeOH:DCM) to afford the title compound as an off-white solid (19 mg, 59%). LCMS $[M+H]^+$ 383.12 m/z; ^1H NMR (500 MHz, DMSO-d_6) δ ppm 12.06 (br. s., 1 H) 8.57 (d, *J*=1.5 Hz, 1 H) 8.45 (d, *J*=1.5 Hz, 1 H) 8.38 (s, 1 H) 8.21 (s, 1 H) 8.16 (d, *J*=7.8 Hz, 1 H) 8.06 (d, *J*=2.4 Hz, 1 H) 8.02 (s, 1 H) 7.69 (d, *J*=7.8 Hz, 1 H) 7.65 (t, *J*=7.8 Hz, 1 H) 4.13 (s, 1 H) 2.88 (d, *J*=10.7 Hz, 2 H) 2.22 (s, 3 H) 1.95 - 2.11 (m, 6 H).

5-Bromo-1-(4-(methylsulfonyl)phenyl)-3-(pyridin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (S44). Intermediate **15** (200 mg, 0.419 mmol), pyridin-4-ylboronic acid (52 mg, 0.423 mmol), and $PdCl_2(dppf)\cdot CH_2Cl_2$ (36 mg, 0.044 mmol) were combined in a microwave vial that was purged with nitrogen and evacuated three times. Dioxane (2.8 ml, 0.15 M) and 2M K_2CO_3 (0.70 ml, 1.40 mmol) were added and the reaction mixture was degassed for ~10 minutes. The reaction was run in the microwave (120 °C) for five minutes. The reaction mixture was diluted with EtOAc, filtered through celite, and concentrated under reduced pressure. The crude material was purified by flash chromatography (20-60% EtOAc:Hex) to afford the title compound as a light yellow solid (116 mg, 65%). LCMS $[M+H]^+$ 427.85 m/z (^{79}Br), 429.86 m/z (^{81}Br); ^1H

NMR (500 MHz, DMSO-d_6) δ ppm 8.67 (d, *J*=2.0 Hz, 1 H) 8.65 (d, *J*=5.9 Hz, 2 H) 8.61 (s, 1 H) 8.57 (d, *J*=2.0 Hz, 1 H) 8.06 (d, *J*=8.3 Hz, 2 H) 7.86 (d, *J*=5.9 Hz, 2 H) 7.45 (d, *J*=7.8 Hz, 2 H) 2.36 (s, 3 H).

1-(4-(Methylsulfonyl)phenyl)-3-(pyridin-4-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (S45). The title compound was prepared according to General Procedure E on a 115-mg scale using 5-bromo-3-(pyridin-4-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine **S44**. The resulting crude dark brown solid was used in the next reaction without further purification. LCMS $[M+H]^+$ 476.09 m/z.

1-(4-(Methylsulfonyl)phenyl)-3-(pyridin-4-yl)-5-(1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (S46). 4-Bromo-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazole **S41a** (50 mg, 0.216 mmol) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (23 mg, 0.028 mmol) were combined in a reaction vial that was filled with nitrogen and evacuated three times. Crude 3-(pyridin-4-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine **S45** (129 mg, 0.271 mmol) was dissolved in dioxane (1.6 ml, 0.17 M) and added to the reaction mixture, followed by the addition of 2M K_2CO_3 (0.60 ml, 1.20 mmol). The reaction was degassed and run in the microwave (145 °C) for 10 minutes. The reaction mixture was diluted with EtOAc/MeOH, filtered through celite, and concentrated under reduced pressure. The crude material was purified by flash chromatography (1-10% MeOH:EtOAc) to afford the title compound as a dark red residue (31 mg, 23%). LCMS $[M+H]^+$ 500.02 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.74 (d, *J*=2.0 Hz, 1 H) 8.67 (d, *J*=6.3 Hz, 2 H) 8.51 (s, 1 H) 8.50 (d, *J*=2.0 Hz, 1 H) 8.48 (s, 1 H) 8.09 (s, 1 H) 8.07 (d, *J*=8.3 Hz, 2 H) 7.90 (d, *J*=5.9 Hz, 2 H) 7.44 (d, *J*=8.3 Hz, 2 H) 4.38 - 4.47 (m, 1 H) 3.98 (d, *J*=10.2 Hz, 2 H) 3.93 (s, 3 H) 3.49 (td, *J*=11.7, 2.0 Hz, 2 H) 1.93 - 2.07 (m, 4 H).

3-(Pyridin-4-yl)-5-(1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (30). The title compound was prepared according to General Procedure D on a 31-mg scale using 3-(pyridin-4-yl)-5-(1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazol-4-yl)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine **S46**. The reaction was run for five minutes, and the crude material was purified by flash chromatography (5-10% 5% NH_4OH/MeOH:DCM) to afford the title compound as an orange solid (12 mg, 57%). LCMS $[M+H]^+$ 346.11 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.20 (br. s., 1 H) 8.60 (d, *J*=2.0 Hz, 1 H) 8.56 (d, *J*=5.9

Hz, 2 H) 8.53 (d, *J*=2.0 Hz, 1 H) 8.44 (s, 1 H) 8.21 (s, 1 H) 8.06 (s, 1 H) 7.83 (d, *J*=5.9 Hz, 2 H) 4.43 (spt, *J*=6.3 Hz, 1 H) 3.99 (d, *J*=11.2 Hz, 2 H) 3.50 (td, *J*=10.7, 2.4 Hz, 2 H) 1.96 - 2.08 (m, 4 H).

***tert*-Butyl 5-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosyl-1*H*-pyrrolo[2,3-b]pyridin-3-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (S47).** The title compound was prepared according to General Procedure E on a 320-mg scale using *tert*-butyl 5-(5-bromo-1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-3,6-dihydropyridine-1(2H)-carboxylate **16c**. The product was purified by flash chromatography (10-20% EtOAc:Hex) to afford the title compound as an off-white solid (156 mg, 45%). LCMS $[M+H]^+$ 580.1 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.30 (s, 12 H) 1.45 (s, 9 H) 2.28 - 2.32 (m, 2 H) 2.33 (s, 3 H) 3.49 (t, *J*=4.9 Hz, 2 H) 4.24 (br. s., 2 H) 6.37 (br. s, 1 H) 7.40 (d, *J*=8.3 Hz, 2 H) 7.89 - 7.93 (m, 1 H) 8.02 (d, *J*=8.3 Hz, 2 H) 8.32 - 8.36 (m, 1 H) 8.57 (s, 1 H)

tert-Butyl 5-(5-(1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazol-4-yl)-1-tosyl-1*H*-pyrrolo[2,3-b]pyridin-3-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (S48). *tert*-Butyl 5-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-3,6-dihydropyridine-1(2H)-carboxylate **S47** (156 mg, 0.269 mmol), 4-bromo-1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazole **S41a** (93 mg, 0.402 mmol) and PdCl2(dppf)·CH2Cl2 (22 mg, 0.027 mmol) were combined in a reaction vial that was filled with nitrogen and evacuated three times. Dioxane (1.6 ml, 0.17 M) was added to the reaction mixture, followed by the additon of 2M K2CO3 (0.4 ml, 0.800 mmol). The reaction was degassed and run in the microwave (145 °C, H abs) for 10 minutes. The reaction mixture was diluted with EtOAc, filtered through celite, and concentrated. The crude material was purified by flash chromatography (0-70% EtOAc:Hex) to afford the title compound as a dull orange solid (48 mg, 30%). LCMS $[M+H]^+$ 604.1 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.45 (s, 9 H) 1.91 - 2.07 (m, 4 H) 2.30 - 2.39 (m, 5 H) 3.44 - 3.57 (m, 4 H) 3.94 - 4.00 (m, 2 H) 4.25 (br. s., 2 H) 4.37 - 4.46 (m, 1 H) 6.56 (br. s, 1 H) 7.42 (d, *J*=7.8 Hz, 2 H) 7.84 (s, 1 H) 8.01 (d, *J*=8.3 Hz, 2 H) 8.05 (s, 1 H) 8.36 (s, 1 H) 8.44 (s, 1 H) 8.67 (d, *J*=2.0 Hz, 1 H).

***tert*-Butyl 3-(5-(1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazol-4-yl)-1-tosyl-1*H*-pyrrolo[2,3-b]pyridin-3-yl)piperidine-1-carboxylate (S49)**. *tert*-Butyl 5-(5-(1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazol-4-yl)-1-

tosyl-1*H*-pyrrolo[2,3-b]pyridin-3-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate **S48** (48 mg, 0.080 mmol) was dissolved in EtOH (1.6 ml, 0.05 M) and 10% wt Pd/C (8 mg, 0.008 mmol) was added. Ammonium formate (34 mg, 0.539 mmol) was added and the reaction was refluxed at 85 °C overnight. Additional catalyst (16 mg 5 wt% Pd/C, 0.008 mmol) was added and the reaction was monitored by LCMS. Upon completion, the reaction was stopped and cooled to room temperature. The reaction mixture was diluted with EtOAc, filtered through celite, and concentrated to afford the title compound as a yellow solid (46 mg, 95%). LCMS $[M+H]^+$ 606.1 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.40 (br. s, 9 H) 1.57 - 1.79 (m, 2 H) 1.88 - 2.09 (m, 6 H) 2.33 (s, 3 H) 2.88 - 3.08 (m, 2 H) 3.10 - 3.22 (m, 1 H) 3.48 (t, *J*=11.0 Hz, 2 H) 3.76 - 3.88 (m, 1 H) 3.97 (m, *J*=7.3 Hz, 3 H) 4.35 - 4.46 (m, 1 H) 7.41 (d, *J*=7.8 Hz, 2 H) 7.67 (s, 1 H) 7.96 (d, *J*=7.8 Hz, 2 H) 8.00 (s, 1 H) 8.21 - 8.26 (m, 1 H) 8.38 (s, 1 H) 8.63 (s, 1 H).

***tert*-Butyl 3-(5-(1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-b]pyridin-3-yl)piperidine-1-carboxylate (S50).** The title compound was prepared according to General Procedure D on a 46-mg scale using *tert*-butyl 3-(5-(1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl)-1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)piperidine-1-carboxylate **S49**. The reaction was run for 2 mins and the crude material was purified by flash chromatography (2-5% MeOH:DCM to afford the title compound as a pale yellow solid (17 mg, 51%). LCMS $[M+H]^+$ 452.2 m/z; ^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 1.50 (s, 9 H) 1.72 (m, *J*=10.7 Hz, 4 H) 2.06 - 2.26 (m, 6 H) 2.88 (t, *J*=12.0 Hz, 2 H) 2.96 - 3.09 (m, 1 H) 3.59 (td, *J*=11.5, 2.9 Hz, 2 H) 4.16 (d, *J*=11.7 Hz, 2 H) 4.42 (spt, *J*=5.4 Hz, 1 H) 7.13 (d, *J*=1.5 Hz, 1 H) 7.74 (s, 1 H) 7.83 (s, 1 H) 8.02 (br. s., 1 H) 8.46 (br. s., 1 H) 8.81 (br. s., 1 H).

3-(Piperidin-3-yl)-5-(1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-b]pyridine (31). *tert*-Butyl 3-(5-(1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl)-1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)piperidine-1-carboxylate **S50** (17 mg, 0.028 mmol) was dissolved in dioxane (0.300 ml, 0.10 M) and 4M HCl in dioxane (0.05 ml, 0.200 mmol) was added. The reaction was stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure and the resulting light yellow residue was dissolved in MeOH. Si-carbonate was added and the reaction was stirred at room temperature overnight. The Si-carbonate was filtered off and the filtrate was purified by flash chromatography (10-25% 5%

NH_4OH/MeOH:DCM, stepwise gradient) to afford the title compound as a white solid (9 mg, 72%). LCMS $[M+H]^+$ 352.1 m/z; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.77 (qd, *J*=7.8, 3.9 Hz, 1 H) 1.82 - 1.94 (m, 2 H) 1.94 - 2.10 (m, 5 H) 2.95 (td, *J*=12.1, 3.7 Hz, 1 H) 3.03 (t, *J*=12.2 Hz, 1 H) 3.23 - 3.32 (m, 3 H) 3.42 - 3.54 (m, 3 H) 3.98 (d, *J*=11.2 Hz, 2 H) 4.42 (spt, *J*=4.9 Hz, 1 H) 7.33 (s, 1 H) 7.95 (s, 1 H) 8.19 (s, 1 H) 8.31 (s, 1 H) 8.49 (d, *J*=1.5 Hz, 1 H) 11.51 (br. s., 1 H).

5-bromo-3-iodo-1H-pyrazolo[3,4-b]pyridine (S52a). 5-Bromo-1H-pyrazolo[3,4-b]pyridine **S51a** (300 mg, 1.51 mmol) was suspended in DCE (6.6 ml, 0.23 M) and NIS (511 mg, 2.27 mmol) was added. The reaction was refluxed at 80 °C overnight. An off-white precipitate was observed and collected by vacuum filtration (washed with DCE) to afford the title compound as an ivory solid (465 mg, 95%). LCMS $[M+H]^+$ 323.7 m/z (^{79}Br), 325.8 m/z (^{81}Br); ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.21 (d, *J*=1.1 Hz, 1 H) 8.65 (d, *J*=2.2 Hz, 1 H) 14.31 (s, 1 H).

5-Bromo-3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazolo[3,4-b]pyridine (S53a). 5-Bromo-3-iodo-1*H*-pyrazolo[3,4-b]pyridine **S52a** (465 mg, 1.44 mmol) was dissolved in DMF (3.7 ml, 0.039 M) and the reaction was cooled to 0 °C. NaH (178 mg, 4.45 mmol) was added and the reaction was stirred at 0 °C. After stirring for a few minutes, reaction mixture went from a cloudy off-white suspension to a bright orange solution. After 30 mins, 2-(trimethylsilyl)ethoxymethyl chloride (0.300 ml, 1.70 mmol) was added and the reaction turned bright yellow. The reaction was left stirring at 0 °C for another 2 h. The reaction was quenched with water and extracted three times with EtOAc. The combined organic layers were washed once with brine, dried with sodium sulfate, and concentrated. The crude material was dried under high vacuum overnight to afford the title compound as a beige solid (564 mg, 87%). LCMS $[M+H]^+$ 453.8 m/z (^{79}Br), 455.8 m/z (^{81}Br); ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm -0.13 - -0.10 (m, 9 H) 0.80 (t, *J*=7.8 Hz, 2 H) 3.58 (t, *J*=8.1 Hz, 2 H) 5.74 (s, 2 H) 8.28 (d, *J*=2.4 Hz, 1 H) 8.74 (d, *J*=2.4 Hz, 1 H).

3-(5-Bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazolo[3,4-b]pyridin-3-yl)benzonitrile (S54a). 5-Bromo-3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazolo[3,4-b]pyridine **S53a** (564 mg, 1.24 mmol), (3-cyanophenyl)boronic acid (184 mg, 1.25 mmol) and PdCl2(dppf)·CH2Cl2 (101 mg, 0.124 mmol) were combined in a microwave vial that was purged with nitrogen and evacuated three times.

Dioxane (7.0 ml, 0.18 M) was added, followed by the addition of 2M K_2CO_3 (1.5 ml, 3.00 mmol). The reaction mixture was degassed for ~10 minutes and the reaction was run in the microwave (80 °C, 15 mins). The reaction mixture was diluted with EtOAc, filtered through celite, and concentrated. The crude material was purified by flash chromatography (0-20% EtOAc:Hex) to afford the title compound as a light yellow solid (259 mg, 49%). LCMS $[M+H]^+$ 428.98 m/z (^{79}Br), 431.0 m/z (^{81}Br); ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm -0.11 (s, 9 H) 0.84 (t, *J*=7.8 Hz, 2 H) 3.66 (t, *J*=8.1 Hz, 2 H) 5.85 (s, 2 H) 7.75 (t, *J*=7.8 Hz, 1 H) 7.94 (d, *J*=7.8 Hz, 1 H) 8.39 (d, *J*=8.3 Hz, 1 H) 8.48 (s, 1 H) 8.77 (d, *J*=2.0 Hz, 1 H) 9.11 (d, *J*=2.0 Hz, 1 H).

3-(5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazolo[3,4-b]pyridin-3-yl)benzonitrile (S55a). The title compound was prepared according to General Procedure E on a 140-mg scale using 3-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazolo[3,4-b]pyridin-3-yl)benzonitrile **S54a**. The reaction was diluted with EtOAc, filtered through celite, and concentrated under reduced pressure. The crude material was purified by flash chromatography (10% EtOAc:Hex) to afford the title compound as a light yellow oil (96 mg, 61%). LCMS $[M+H]^+$ 477.0 m/z; ^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm -0.05 (s, 9 H) 0.97 (t, *J*=8.3 Hz, 2 H) 1.41 (s, 12 H) 3.71 (t, *J*=8.3 Hz, 2 H) 5.95 (s, 2 H) 7.66 (t, *J*=7.8 Hz, 1 H) 7.72 (d, *J*=7.8 Hz, 1 H) 8.29 (d, *J*=7.8 Hz, 1 H) 8.34 (s, 1 H) 8.73 (s, 1 H) 8.97 (s, 1 H).

3-(5-(1-(Tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazol-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazolo[3,4-b]pyridin-3-yl)benzonitrile (S56a). 3-(5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)benzonitrile **S55a** (96 mg, 0.201 mmol), 4-bromo-1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazole **S41a** (58 mg, 0.251 mmol) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (19 mg, 0.023 mmol) were combined in a reaction vial that was filled with nitrogen and evacuated three times. Dioxane (2.0 ml, 0.10 M) was added to the reaction mixture, followed by the addition of 2M K_2CO_3 (0.3 ml, 0.600 mmol). The reaction was degassed and run in the microwave (145 °C, H abs) for 10 minutes. The reaction mixture was diluted with EtOAc, filtered through celite, and concentrated. The crude material was purified by flash chromatography (20-60% EtOAc:Hex) to afford the

title compound as an orange oil (37 mg, 36%). LCMS $[M+H]^+$ 501.1 m/z; ^{1}H NMR (500 MHz, CHLOROFORM-*d*) d ppm -0.04 (s, 9 H) 0.98 (t, *J*=8.3 Hz, 2 H) 2.16 - 2.25 (m, 4 H) 3.60 (td, *J*=8.3, 3.9 Hz, 2 H) 3.74 (t, *J*=8.8 Hz, 2 H) 4.17 (d, *J*=11.2 Hz, 2 H) 4.39 - 4.50 (m, 1 H) 5.95 (s, 2 H) 7.66 (t, *J*=7.8 Hz, 1 H) 7.73 (d, *J*=7.8 Hz, 1 H) 7.82 (s, 1 H) 7.89 (s, 1 H) 8.27 (d, *J*=7.8 Hz, 1 H) 8.30 (s, 1 H) 8.30 (s, 1 H) 8.79 (d, *J*=2.0 Hz, 1 H).

3-(5-(1-(Tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazol-4-yl)-1*H*-pyrazolo[3,4-b]pyridin-3-yl)benzonitrile (32). To 3-(5-(1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazol-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazolo[3,4-b]pyridin-3-yl)benzonitrile **S56a** (37 mg, 0.074 mmol) was added 4 M HCl in dioxane (0.600 ml, 2.40 mmol). The reaction was stirred at room temperature for 3 days then at 50 °C overnight. The reaction was stopped and cooled to room temperature. The solvent was evaporated and the resulting yellow residue was redissolved in MeOH. Si-carbonate was added and the mixture was stirred overnight at room temperature. The Si-carbonate was filtered off and the filtrate was purified by flash chromatography (2-5% MeOH:DCM) to afford the title compound as a white solid (10 mg, 38%). LCMS $[M+H]^+$ 371.06 m/z64; ^{1}H NMR (500 MHz, DMSO-d6) δ ppm 14.02 (br. s., 1 H) 8.91 (d, J=1.6 Hz, 1 H) 8.75 (d, J=1.6 Hz, 1 H) 8.50 (s, 1 H) 8.46 (s, 1 H) 8.44 (d, J=8.2 Hz, 1 H) 8.15 (s, 1 H) 7.90 (d, J=7.7 Hz, 1 H) 7.76 (t, J=7.7 Hz, 1 H) 4.45 (tquin, J=6.6, 6.6, 4.9, 4.9, 4.9, 4.9 Hz, 1 H) 4.00 (d, J=13.7 Hz, 2 H) 3.51 (td, J=11.7, 1.9 Hz, 2 H) 1.94 - 2.09 (m, 4 H).

5-Bromo-3-iodo-4-methyl-1*H*-pyrrolo[2,3-b]pyridine (S52b). 5-Bromo-4-methyl-1*H*-pyrrolo[2,3-b]pyridine **S51b** (412 mg, 1.95 mmol) was dissolved in acetonitrile (12 ml, 0.17 M) and *N*-iodosuccinimide (690 mg, 3.07 mmol) was added. The reaction was stirred at 50 °C for two hours. The reaction was stopped and cooled to room temperature. Upon cooling, a tan precipitate was observed and collected by vacuum filtration (washed with hexanes) to afford the title compound as a dull orange solid (495 mg, 75%). LCMS $[M+H]^+$ 336.85 m/z (^{79}Br), 338.86 m/z (^{81}Br); ^{1}H NMR (500 MHz, CHLOROFORM-d) δ ppm 9.09 (br. s, 1 H) 8.38 (s, 1 H) 7.41 (d, J=2.0 Hz, 1 H) 2.95 (s, 3 H).

5-Bromo-3-iodo-4-methyl-1-tosyl-1*H*-pyrrolo[2,3-b]pyridine (S53b). 5-Bromo-3-iodo-4-methyl-1*H*-pyrrolo[2,3-b]pyridine **52b** (495 mg,1.47 mmol) was suspended in DCM (7.4 ml, 0.19 M) and TEA (0.60

ml, 4.30 mmol), DMAP (215 mg, 1.76 mmol) and 4-methylbenzenesulfonyl chloride (700 mg, 3.67 mmol) were added in that order. The reaction was stirred overnight at room temperature. The reaction was washed once with 1M HCl, once with sat. aq. $NaHCO_3$, and once with brine. The organic layer was dried with sodium sulfate and concentrated under reduced pressure. The product was purified by flash chromatography (0-20% EtOAc:Hex) to afford the title compound as a light orange solid (573 mg, 79%). LCMS $[M+H]^+$ 490.85 m/z (^{79}Br), 492.86 m/z (^{81}Br); ^1H NMR (500 MHz, CHLOROFORM-d) δ ppm 8.47 (s, 1 H) 8.05 (d, J=8.3 Hz, 2 H) 7.88 (s, 1 H) 7.30 (d, J=7.8 Hz, 2 H) 2.86 (s, 3 H) 2.39 (s, 3 H).

3-(5-Bromo-4-methyl-1-tosyl-1*H*-pyrrolo[2,3-b]pyridin-3-yl)benzonitrile (S54b). 5-Bromo-3-iodo-1-tosyl-1*H*-pyrrolo[2,3-b]pyridine **S53b** (573 mg, 1.20 mmol), (3-cyanophenyl)boronic acid (206 mg, 1.40 mmol), and $PdCl_2(dppf)\cdot CH_2Cl_2$ (95 mg, 0116 mmol) were combined in a microwave vial that was purged with nitrogen and evacuated three times. Dioxane (6.0 ml, 0.20 M) and 2M K_2CO_3 (1.8 ml, 3.60 mmol) were added and the reaction mixture was degassed for ~10 minutes. The reaction was run in the microwave (120 °C) for 5 minutes. The reaction mixture was diluted with EtOAc, filtered through celite, and concentrated. The product was purified by flash chromatography (0-50% EtOAc:Hex) to afford the title compound as a dull yellow solid (335 mg, 62%). LCMS $[M+H]^+$ 465.96 m/z (^{79}Br), 467.96 m/z (^{81}Br); ^1H NMR (500 MHz, CHLOROFORM-d) δ ppm 8.52 (s, 1 H) 8.12 (d, J=8.3 Hz, 2 H) 7.72 (d, J=7.8 Hz, 1 H) 7.68 (s, 2 H) 7.63 (d, J=7.8 Hz, 1 H) 7.57 (t, J=8.3 Hz, 1 H) 7.33 (d, J=8.3 Hz, 2 H) 2.41 (s, 3 H) 2.23 (s, 3 H).

3-(4-Methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosyl-1*H*-pyrrolo[2,3-b]pyridin-3-yl)benzonitrile (S55b). The title compound was prepared according to General Procedure E on a 335-mg scale using 3-(5-bromo-4-methyl-1-tosyl-1*H*-pyrrolo[2,3-b]pyridin-3-yl)benzonitrile **54b**. The crude material was purified by flash chromatography (20% EtOAc:Hex) to afford the title compound as a white solid (175 mg, 47%). LCMS $[M+H]^+$ 514.12 m/z; ^1H NMR (500 MHz, CHLOROFORM-d) δ ppm 8.76 (s, 1 H) 8.14 (d, J=8.3 Hz, 2 H) 7.69 (m, J=3.9, 2.0 Hz, 2 H) 7.61 - 7.66 (m, 2 H) 7.53 (t, J=7.8 Hz, 1 H) 7.29 (d, J=8.3 Hz, 2 H) 2.39 (s, 3 H) 2.37 (s, 3 H) 1.33 (s, 12 H).

3-(4-Methyl-5-(1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazol-4-yl)-1-tosyl-1*H*-pyrrolo[2,3-b]pyridin-3-yl)benzonitrile (S56b). 4-Bromo-1-(tetrahydro-2H-pyran-4-yl)-1*H*-pyrazole **S41a** (87 mg, 0.376 mmol) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (28 mg, 0.034 mmol) were combined in a reaction vial that was filled with nitrogen and evacuated three times. 3-(4-Methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)benzonitrile **S55b** (175 mg, 0.341 mmol) was dissolved in dioxane (2.0 ml, 0.17 M) and added to the reaction mixture, followed by the addition of 2M K2CO3 (0.70 ml, 01.40 mmol). The reaction was degassed and run in the microwave (145 °C) for 5 minutes. The reaction mixture was diluted with EtOAc, filtered through celite, and concentrated. The crude material was purified by flash chromatography (50-70% EtOAc:Hex, step gradient) to afford the title compound as a tan solid (69 mg, 38%). LCMS $[M+H]^+$ 538.05 m/z; ^{1}H NMR (500 MHz, DMSO-d6) δ ppm 8.38 (s, 1 H) 8.03 - 8.11 (m, 4 H) 7.98 (s, 1 H) 7.89 (d, J=7.3 Hz, 2 H) 7.70 (s, 1 H) 7.68 (t, J=7.8 Hz, 1 H) 7.44 (d, J=8.3 Hz, 2 H) 4.43 (spt, J=5.9 Hz, 1 H) 3.96 (d, J=10.2 Hz, 2 H) 3.43 - 3.51 (m, 2 H) 2.36 (s, 3 H) 2.19 (s, 3 H) 1.91 - 2.04 (m, 4 H).

3-(4-Methyl-5-(1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-b]pyridin-3-yl)benzonitrile (33). The title compound was prepared according to General Procedure D on a 69-mg scale using 3-(4-methyl-5-(1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazol-4-yl)-1-tosyl-1*H*-pyrrolo[2,3-b]pyridin-3-yl)benzonitrile **S56b.** The reaction was run for 5 minutes and the crude material was purified directly by flash chromatography (5% MeOH:DCM) to afford the title compound as an off-white solid (29 mg, 60%). LCMS $[M+H]^+$ 384.14 m/z; ^{1}H NMR (500 MHz, DMSO-d6) δ ppm 11.94 (br. s., 1 H) 8.24 (s, 1 H) 8.04 (s, 1 H) 7.92 (s, 1 H) 7.82 (d, J=7.8 Hz, 1 H) 7.78 (d, J=7.8 Hz, 1 H) 7.68 (s, 1 H) 7.62 (t, J=7.8 Hz, 1 H) 7.58 (s, 1 H) 4.44 (spt, J=6.3 Hz, 1 H) 3.98 (d, J=11.7 Hz, 2 H) 3.48 (t, J=11.0 Hz, 2 H) 2.31 (s, 3 H) 1.95 - 2.07 (m, 4 H).

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Abbreviations used

ADME, absorption distribution metabolism excretion; Clint, intrinsic clearance; Cmax, maximum concentration; CNS-MPO, central nervous system-multiparameter optimization; GSK, GlaxoSmithKline; HAT, human African trypanosomiasis; HLM, human liver microsomes; HTS, high-throughput screen; ip, intraperitoneal; LLE, lipophilic ligand efficiency; NECT, nifurtimox−eflornithine combination therapy; NTD, neglected tropical disease; PK, pharmacokinetic; PPB, plasma protein binding; SD, standard error of the mean; *T.b.b.*, *Trypanosoma brucei brucei*; TEA, triethylamine; t_{max}, time at which maximum concentration is achieved; TPSA, topological polar surface area; WHO, World Health Organization.

Supporting information

1. Supplementary biological and ADME data, experimental procedures, and characterization

2. Molecular formula strings

References

1. World Health Organization. Neglected Tropical Diseases. http://www.who.int/neglected_diseases/diseases/en/ (accessed 13 September 2016).

2. Buscher, P.; Cecchi, G.; Jamonneau, V.; Priotto, G., Human African Trypanosomiasis. *Lancet* **2017,** *390*, 2397-2409.

3. Becker, B.; Mehlhorn, H.; Andrews, P.; Thomas, H.; Eckert, J., Light and electron microscopic studies on the effect of praziquantel on Schistosoma mansoni, Dicrocoelium dendriticum, and Fasciola hepatica (Trematoda) in vitro. *Z Parasitenkd* **1980,** *63* (2), 113-28.
4. Fetterer, R. H.; Pax, R. A.; Bennett, J. L., Praziquantel, potassium and 2,4-dinitrophenol: analysis of their action on the musculature of Schistosoma mansoni. *Eur J Pharmacol* **1980,** *64* (1), 31-8.
5. Renganathan, E.; Cioli, D., An international initiative on praziquantel use. *Parasitol Today* **1998,** *14* (10), 390-1.
6. Drugs for Neglected Diseases Initiative. Acoziborole. https://dndi.org/research-development/portfolio/acoziborole/ (accessed April 10, 2021).
7. Klug, D. M.; Gelb, M. H.; Pollastri, M. P., Repurposing Strategies for Neglected Diseases. *Bioorg. Med. Chem. Lett.* **2016,** *26*, 2569-2575.
8. Merritt, C.; Silva, L. E.; Tanner, A. L.; Stuart, K.; Pollastri, M. P., Kinases as Druggable Targets in Trypanosomatid Protozoan Parasites. *Chem. Rev.* **2014,** *114*, 11280-11304.
9. Naula, C.; Parsons, M.; Mottram, J. C., Protein kinases as drug targets in trypanosomes and *Leishmania*. *Biochimica et Biophysica Acta* **2005,** *1754*, 151-159.
10. Hammarton, T. C.; Kramer, S.; Tetley, L.; Boshart, M.; Mottram, J. C., *Trypanosoma brucei* Polo-like Kinase is Essential for Basal Body Duplication, kDNA Segregation and Cytokinesis. *Mol. Microbiol.* **2007,** *65* (5), 1229-1249.
11. Diaz, R.; Luengo-Arratta, S.; Seixas, J. o. D.; Amata, E.; Devine, W.; Cordon-Obras, C.; Rojas-Barros, D. I.; Jimenez, E.; Ortega, F.; Crouch, S.; Colmenarejo, G.; Fiandor, J. M.; Martin, J. J.; Berlanga, M.; Gonzalez, S.; Manzano, P.; Navarro, M.; Pollastri, M. P., 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.
12. Shultz, M. D., The thermodynamic basis for the use of lipophilic efficiency (LipE) in enthalpic optimizations. *Bioorg Med Chem Lett* **2013,** *23*, 5992-6000.
13. Wager, T.; Hou, X.; Verhoest, P. R.; 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.
14. Cruciani, G.; Carosati, E.; De Boeck, B.; Ethirajulu, K.; Mackie, C.; Howe, T.; Vianello, R., MetaSite: Understanding metabolism in human cytochromes from the perspective of the chemist. *J. Med. Chem.* **2005,** *48*, 6970-6979.
15. Lovering, F.; Bikker, J.; Humblet, C., Escape from flatland: Increasing saturation as an approach to improving clinical success. *J. Med. Chem.* **2009,** *52*, 6752-6756.
16. Ishikawa, M.; Hashimoto, Y., Improvement in aqueous solubility in small molecule drug discovery programs by disruption of molecular planarity and symmetry. *J. Med. Chem.* **2011,** *54*, 1539-1554.
17. Gupta, M.; Lee, H. J.; Barden, C. J.; Weaver, D. F., The blood-brain barrier (BBB) score. *J. Med. Chem.* **2019,** *62*, 9824-9836.
18. Singh, B.; Bernatchez, J. A.; McCall, L.-I.; Calvet, C. M.; Ackermann, J.; Souza, J. M.; Thomas, D.; Silva, E. M.; Bachovchin, K. A.; Klug, D. M.; Jalani, H. B.; Bag, S.; Buskes, M. J.; Leed, S. E.; Roncal, N. E.; Penn, E. C.; Erath, J.; Rodriguez, A.; Sciotti, R. J.; Campbell, R. F.;

McKerrow, J. H.; Siqueira-Neto, J.; Ferrins, L.; Pollastri, M. P., Scaffold and parasite hopping: discovery of new protozoal proliferation inhibitors. *ACS Med. Chem. Lett.* **2020,** *11*, 249-257.
19. Probst, A.; Nguyen, T. N.; El-Sakkary, N.; Skinner, D.; Suzuki, B. M.; Buckner, F. S.; Gelb, M. H.; Caffrey, C. R.; Debnath, A., Bioactivity of Farnesyltransferase Inhibitors Against Entamoeba histolytica and Schistosoma mansoni. *Frontiers in Cellular and Infection Microbiology* **2019,** *9* (180).
20. Long, T.; Rojo-Arreola, L.; Shi, D.; El-Sakkary, N.; Jarnagin, K.; Rock, F.; Meewan, M.; Rascón, A. A., Jr.; Lin, L.; Cunningham, K. A.; Lemieux, G. A.; Podust, L.; Abagyan, R.; Ashrafi, K.; McKerrow, J. H.; Caffrey, C. R., Phenotypic, chemical and functional characterization of cyclic nucleotide phosphodiesterase 4 (PDE4) as a potential anthelmintic drug target. *PLOS Neglected Tropical Diseases* **2017,** *11* (7), e0005680.
21. Long, T.; Neitz, R. J.; Beasley, R.; Kalyanaraman, C.; Suzuki, B. M.; Jacobson, M. P.; Dissous, C.; McKerrow, J. H.; Drewry, D. H.; Zuercher, W. J.; Singh, R.; Caffrey, C. R., Structure-Bioactivity Relationship for Benzimidazole Thiophene Inhibitors of Polo-Like Kinase 1 (PLK1), a Potential Drug Target in Schistosoma mansoni. *PLOS Neglected Tropical Diseases* **2016,** *10* (1), e0004356.
22. Kyere-Davies, G.; Agyare, C.; Boakye, Y. D.; Suzuki, B. M.; Caffrey, C. R., Effect of Phenotypic Screening of Extracts and Fractions of Erythrophleum ivorense Leaf and Stem Bark on Immature and Adult Stages of Schistosoma mansoni. *Journal of Parasitology Research* **2018,** *2018*, 9431467.
23. Abdulla, M.-H.; Lim, K.-C.; Sajid, M.; McKerrow, J. H.; Caffrey, C. R., Schistosomiasis Mansoni: Novel Chemotherapy Using a Cysteine Protease Inhibitor. *PLOS Medicine* **2007,** *4* (1), e14.

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