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Synthesis and Pharmacological Evaluation of *N*-(3-(1*H*-Indol-4-yl)-5-(2-methoxyisonicotinoyl)phenyl)methanesulfonamide (LP-261), a Potent Antimitotic Agent

Rupa S. Shetty,* Younghee Lee, Bin Liu, Arifa Husain, Rhoda W. Joseph, Yixin Lu, David Nelson, John Mihelcic, Wenchun Chao, Kristofer K. Moffett, Andreas Schumacher,[†] Dietmar Flubacher,[†] Aleksandar Stojanovic,[†] Marina Bukhtiyarova, Ken Williams, Kyoung-Jin Lee, Alexander R. Ochman, Michael S. Saporito, William R. Moore, Gary A. Flynn, Bruce D. Dorsey, Eric B. Springman, Ted Fujimoto, and Martha J. Kelly

Ansaris, Four Valley Square, 512 East Township Line Road, Blue Bell, Pennsylvania 19401, United States.
[†]*Solvias AG, Klybeckstrasse 191, 4002 Basel, Switzerland. Phone: 41-61-686-61-61. Fax: 41-61-686-65-65.*

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The synthesis and optimization of a series of orally bioavailable 1-(1*H*-indol-4-yl)-3,5-disubstituted benzene analogues as antimitotic agents are described. A functionalized dibromobenzene intermediate was used as a key scaffold, which when modified by sequential Suzuki coupling and Buchwald–Hartwig amination provided a flexible entry to 1,3,5-trisubstituted phenyl compounds. A 1*H*-indol-4-yl moiety at the 1-position was determined to be a critical feature for optimal potency. The compounds have been shown to induce cell cycle arrest at the G2/M phase and demonstrate efficacy in both cell viability and cell proliferation assays. The primary site of action for these agents is revealed by their colchicine competitive inhibition of tubulin polymerization, and a computational model has been developed for the association of these compounds to tubulin. An optimized lead LP-261 significantly inhibits growth of a human non-small-cell lung tumor (NCI-H522) in a mouse xenograft model.

Introduction

Microtubules are highly dynamic noncovalent polymers formed by tubulin heterodimers consisting of α- and β-tubulin. They are major components of the cytoskeleton of all eukaryotic cells and play a vital role in maintenance of cell shape and cell signaling.[1] The elongation and shortening of the microtubules are critical to mitosis. Interference with the dynamics of microtubules blocks the cell cycle at the G2/M stage and leads to apoptosis. For this reason, targeting microtubule dynamics has been a successful strategy for chemotherapeutic agents.[2]

Antimitotic agents are often divided into two classes: one class that stabilizes microtubules and increases the mass of microtubules in the cells; the other class that destabilizes microtubules.[3] The well-characterized and clinically used taxanes and epothilones are examples of compounds that stabilize microtubules.

The majority of compounds that destabilize microtubules are characterized based on their binding site as those that bind at the *Vinca* or the colchicine site. A 4.1 Å resolution crystal structure of vinblastine, a *Vinca* alkaloid, bound to tubulin in complex with RB3 protein stathmin-like domain (RB3-SLD[a]) shows the molecule bound between the tubulin αβ heterodimers near the α-tubulin GTP binding site (1z2b.pdb).[4] Many other natural products such as the halichondrins and dolastatins have been found to bind at or near the *Vinca* binding site.[5]

*To whom correspondence should be addressed. Phone: 215-358-2037. Fax: 215-358-2030. E-mail: rshetty@ansarisbio.com.

[a] Abbreviations: WST-1, (4-[3-(4-iodophenyl)-2-(4-nitrophenyl)-2*H*-5-tetrazolino]-1,3-benzene disulfonate); MDR1, multidrug resistance 1; SLD, stathmin-like domain; NCI-ADR, National Cancer Institute adriamycin-resistant cell line; TIPS, triisopropylsilyl; TBAF, tetrabutylammonium fluoride; PMB, 4-methoxybenzyl.

Another natural product, **1** (colchicine),[6] destabilizes microtubules by binding to β-tubulin at the interface with α-tubulin within the heterodimer, a site distinct from the *Vinca* alkaloid binding site. A number of structurally diverse natural products and small molecules have been found to inhibit tubulin polymerization competitively with colchicine.[7] A pharmacophore model for colchicine site inhibitors has been proposed based on these ligands.[8] The crystal structures of tubulin complexed with a colchicine analogue,[9] **2** (ABT-751),[10] and two other colchicine competitive inhibitors have been reported.[11] The binding sites of these inhibitors overlap, although there are some differences in the pockets targeted by each compound. On the basis of these structures, it has been hypothesized that colchicine site inhibitors lock the tubulin complexes into a curved conformation and interfere with the adoption of a straight conformation that allows for microtubule assembly.[9,11]

The combretastatins, especially **3a** (CA4), represent another class of natural products that are colchicine competitive inhibitors of tubulin polymerization.[12] The combretastatins, and many of the other colchicine binding site inhibitors, exhibit potent vascular disrupting activity.[13] Colchicine, which is approved for the treatment of gout, has not been used as an anticancer agent, presumably because of its toxicity with prolonged exposures and high doses. There are no currently marketed colchicine competitive drugs, but a number of inhibitors are in clinical development, including **2**, the combretastatins **3b** (CA-4P)[14] and **3c** (AVE 8062),[15] 2-methoxyestradiol (2ME2),[16] and the more metabolically stable **4** (ENMD-1198),[16] **5** (NPI 2358),[17] and **6** (MPC-6827)[18] (Figure 1). Unlike the taxanes and *Vinca* alkaloids which in general require intravenous dosing, many of the colchicine competitive small molecules have the potential for good oral bioavailability.

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1: Colchicine

2: ABT-751

3a: R=OH Combrestestatin A-4 (CA4)
3b: R=OPO_3H_2 (CA-4P)
3c: AVE 8062

4: ENMD-1198

5: Plinabulin (NPI 2358)

6: Azixa(MPC-6827)

7

Figure 1

Scheme 1[a]

[a] Reagents and conditions: (a) KOH, benzyl alcohol, 4-methoxylbenzyl alcohol or methanol, Bu_4NBr, TMU; (b) HBr, Bu_4NBr; (c) NaH, DMF, TIPSCl or TBDPSCl; (d) pyridine-3-amine, $Pd_2(dba)_3$, BINAP, *t*-BuONa, toluene, 90 °C; (e) bis(pinacolato)diborane, $PdCl_2(dppf)$, KOAc, DMSO, 80 °C; (f) $Pd(PPh_3)_4$, 2 M aqueous Na_2CO_3, DME, 85 °C, or $PdCl_2(dppf)$, 2 M K_3PO_4, THF, 65 °C, or chloro(di-2-norbornylphosphino)(2-dimethylamino-1,1′-biphenyl-2-yl)palladium, 2 M K_3PO_4, 1,4-dioxane, 100 °C; (g) H_2, Pd/C or TFA, thioanisole, DIEA or $BF_3 \cdot OEt_2$, DMS, DCM, 0 °C.

The discovery that compound **7**, designed in house for a nuclear hormone receptor program, exhibited potent inhibition of mitosis at the G2/M stage led us to initiate an optimization effort around this structure. The results of that work are reported here, along with a proposed binding mode for the compounds on *β*-tubulin and the in vitro and in vivo activity of these compounds.

Chemistry

The 3-aryl substituted 5-(pyridine-3-ylamino)phenols **7**, **12**−**20** were synthesized as outlined in Scheme 1. The benzyloxy **9a**, 4-methoxybenzyloxy **9b**, and methoxyphenyl dibromide **9c** were synthesized from 3,5-dibromonitrobenzene according to the procedure reported by Effenberger et al.[19] The silyl ether analogues **9e** and **9f** were synthesized by cleavage of the methyl ether **9c**, followed by silylation of the resulting phenol as shown in Scheme 1. The symmetrical dibromides **9** were subjected to Buchwald−Hartwig amination conditions using 1 equiv of 3-aminopyridine to give the protected 3-bromo-5-(pyridine-3-ylamino)phenoxy compounds **10a**−**d**.[20] These reactions proceeded in about 60% yield for the benzyoxyl, 4-methoxybenzyloxy, and methoxy protected analogues. For analogue **10b**, the yield could be increased to 75% by heating the reaction mixture to 90 °C prior to the addition of the catalyst. The lower yield (45%) of the amination with the triisopropyl silyl (TIPS) protected phenol **9e** was due to the instability of the protecting group under the reaction conditions. No product **10e** was obtained when analogue **9f** was subjected to the same reaction conditions. The *tert*-butyldiphenylsilyl protected analogue **10e** was synthesized from **10b** by deprotection of the 4-methoxybenzyloxy group using trifluoroacetic acid in thiaanisole, followed by protection of the phenol using *tert*-butyldiphenylsilyl chloride in DMF. Suzuki coupling[21] of the bromides **10a**−**d** with an arylboronic acid or pinacol boronate followed by deprotection gave the 1,3,5-trisubstituted phenols. Alternatively, **10a**,**b**, and **10e** were converted to the pinacol boronates[22] **11a**−**c** which were

Scheme 2[a]

[a] Reagents and conditions: (a) $Pd(PPh_3)_4$, 2 M aqueous Na_2CO_3, DME, 85 °C; (b) **21a**, 2 M aqueous K_3PO_4, **22**, 1,4-dioxane, 100 °C (50%); (c) **21b**, 2 M aqueous K_3PO_4, **22**, 1, 4-dioxane, microwave, 130 °C (~75%); (d) H_2, Pd/C; (e) Pd/C, NH_4CO_2H, HCOOH, MeOH; (f) DDQ, DCM, 0 °C; (g) $BF_3 \cdot OEt_2$, DMS, DCM, 0 °C .

coupled with aryl bromides and deprotected to give the corresponding phenols.

The Suzuki coupling of 4-bromoindole to the pinacol boronate **11a** using catalytic amount of $Pd(PPh_3)_4$ as shown in Scheme 2 yielded only 35% of the coupled product. Better yields (50%) were obtained by coupling 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (**21a**) with bromide **10b** using chloro(di-2-norbornylphosphino)(2-dimethylamino-1,1′-biphenyl-2-yl)palladium (**22**) as a catalyst.[23] A 75% yield of **23c** along with small amounts of the deprotected indole **23b** was obtained by using 4-(4,4,5,5-tetramethyl-1,3,2-dioxoborolan-2-yl)-1-(triisopropylsilyl)-1*H*-indole (**21b**) in the reaction with **10b** and **22** under microwave conditions.

Unfortunately, no single method of deprotection worked for all the compounds of Schemes 1 and 2. While deprotection of the TIPS protected phenols proceeded to give the phenol cleanly, the lability of the TIPS group limited its use to reaction sequences with mild coupling conditions. Deprotection of compounds containing the sensitive indole moiety was especially challenging, and the results are summarized in Scheme 2. Hydrogenolysis of **23b** using Pd/C gave a low yield of **7** and required multiple additions of fresh catalyst, probably due to catalyst poisoning by the pyridine or by trace amounts of phosphines from previous steps. Transfer hydrogenolysis[24] of **23a** using ammonium formate and Pd/C proceeded in only 35% yield. Oxidative deprotection[25] of **23b** or **23c** using 2,3-dichloro-5,6-dicyanobenzoquinone failed to give the desired product. The $BF_3 \cdot OEt_2$/dimethyl sulfide system[26] proved to be the best condition for deprotection of the 4-methoxybenzyl group. A side product observed in the $BF_3 \cdot OEt_2$ deprotections of **23a** was **24**, which was formed by the acid catalyzed addition of the benzyl cation to the electron rich phenol. Addition of the cation scavenger to the reaction mixtures minimized formation of this side product. Thus, the best general method of making these compounds involved the use of the 4-methoxylbenzyl (PMB) protected phenols, which gave high yields in both the Buchwald–Hartwig amination and the $BF_3 \cdot OEt_2$/dimethyl sulfide mediated deprotection steps.

Compounds with replacements of the NH group linking the pyridine to the phenol were made as shown in Scheme 3. Methylation of the Buchwald–Hartwig amination product obtained from reacting key intermediate **9b** with 3-aminopyridine gave the N-methylated product **25**. Copper-catalyzed Ullmann ether synthesis with 3-hydroxypyridine afforded the ether linked bromide **27**.[27] The ketone **33** was synthesized by monolithiation of dibromide **9b** followed by reaction with 3-cyanopyridine, analogous to the method of Dickinson et al.[28] The bromides **25**, **27**, and **33** were then subjected to Suzuki coupling to introduce the TIPS protected indole. Deprotection of the 4-methoxybenzyl (PMB) group with $BF_3 \cdot OEt_2$/dimethyl sulfide followed by treatment with tetrabutylammonium fluoride (TBAF) yielded analogues **26**, **28**, and **34**. Suzuki reaction of the 1-bromo-3-iodo-5-(4-methoxybenzyloxy)benzene **9g** with **21b** gave intermediate **29** which was subjected to a second Suzuki reaction followed by deprotection to give analogue **32**. Lithiation of **29** followed by quenching with 3-pyridinecarboxaldehyde and subsequent deprotection provided methyl alcohol analogue **30**.

The des-hydroxylphenyl analogue **38** was synthesized from dibromobenzene as shown in Scheme 4. Introduction of 3-(*N*-acetylamino)pyridine via a Buchwald–Hartwig amination reaction using catalytic copper iodide[29] provided bromide **37**. Suzuki coupling followed by removal of the silyl protecting group and subsequent hydrolysis of the *N*-acetyl group under acidic conditions yielded **38**. Other phenol replacement analogues were synthesized (Scheme 4) from commercially available substituted phenyldibromides **39a–e** which under Buchwald–Hartwig amination conditions gave the aminopyridine intermediates **40a–e**. The bromide analogue **40e** was subjected to palladium catalyzed amidation conditions with acetamide to give **40f**. Installation of the TIPS protected indole group via the Suzuki reaction followed by desilylation using TBAF gave analogues **41–45**.

Tribromobenzene **39e** was used as the starting material for the synthesis of ketone analogues where the phenolic hydroxy moiety was replaced with a substituted amine. Scheme 5 shows the synthesis of the 3,5-dibromophenyl ketone intermediates. Tribromobenzene **39e** was monolithiated with *n*-BuLi and then reacted with either a nitrile or Weinreb amide **46a–d** to yield

Scheme 3[a]

[a] Reagents and conditions: (a) $Pd_2(dba)_3$, BINAP, *t*-BuONa, toluene, 90 °C; (b) MeI, NaH, DMF; (c) **21b**, **22**, 2 M aqueous K_3PO_4, 1,4-dioxane, 100 °C; (d) $BF_3 \cdot OEt_2$, DMS, DCM, 0 °C or TFA, DCM, DMS; (e) *n*-Bu_4NF, THF; (f) 3-hydroxypyridine, NaH, Cu_2O; (g) *n*-BuLi, ether,-76 °C, 3-pyridinecarboxaldehyde; (h) 3-pyridylboronic acid, $Pd(PPh_3)_4$, 2 M aqueous Na_2CO_3, DME, 85 °C; (i) *n*-BuLi, ether, −76 °C, 3-cyanopyridine.

Scheme 4[a]

[a] Reagents and conditions: (a) $Pd_2(dba)_3$, BINAP, NaO-*t*-Bu, toluene, 90 °C; (b) **21b**, **22**, 2 M aqueous K_3PO_4, 1,4-dioxane, 100 °C; (c) TFA, DMS, 6 N HCl; (d) acetamide, $Pd_2(dba)_3$, XantPhos, Cs_2CO_3, 1, 4-dioxane, 110 °C; (e) *n*-Bu_4NF, THF.

ketones **47a**,**b**,**d**,**f**.[28] The reaction yields with nitriles varied from very poor to good depending on the pyridine substituents, while the yields with the Weinreb amide were generally good. Functionalization of the chloro group on the pyridine of **47b**, **47d**, and **47f** by nucleophilic substitution with sodium methoxide or morpholine gave the substituted pyridines **47c**, **47e**, and **47g**, respectively.

Buchwald reaction of dibromide **47a** with benzyl carbamate provided the protected amine **48a** (Scheme 6), which on treatment with 12 M HCl gave the aniline **48b**. The amino group of **48b** was reacted with acetyl chloride, methyl chloroformate, or methylsulfonyl chloride to give the acetamide **48d**, methylcarbamate **48c**, and methyl sulfonamide **48e**, respectively. The *N*,*N*-dimethylurea **48f** was synthesized by first forming the

Scheme 5[a]

[a] Reagents and conditions: (a) *n*-BuLi, ether, −76 °C; (b) NaOMe, MeOH, 80 °C; (c) morpholine, 1,4-dioxane, 100 °C.

Scheme 6[a]

[a] Reagents and conditions: (a) benzyl carbamate, $Pd_2(dba)_3$, XantPhos, *t*-BuONa, 1,4-dioxane, 110 °C; (b) 12 N HCl, 80 °C, MeOH; (c) MeCOCl or $ClCO_2Me$ or $MeSO_2Cl$ or 4-nitrophenyl chloroformate and $NHMe_2$, pyridine or DIEA, DCM, 0 °C; (d) **21b**, **22**, 2 M aqueous K_3PO_4, 1,4-dioxane, 100 °C; (e) KOH, MeOH, reflux; (f) *n*-Bu_4NF, THF; (g) acetamide or methylcarbamate or methylsulfonamide, $Pd(PPh_3)_4$, XantPhos, *t*-BuONa, 1,4-dioxane, 110 °C; (h) acetamide or methylcarbamate or methylsulfonamide, CuI, Cs_2CO_3, *N*,*N*′-dimethylethylenediamine, 1,4-dioxane, 100 °C.

4-nitrophenylcarbamate, followed by reaction with dimethylamine to give the urea. Reaction of the bromides **48a**,**c**−**f** under Suzuki conditions with the TIPS protected indole pinacol boronic ester yielded **49a**,**c**−**f**. Treatment of **49a** with refluxing KOH in methanol resulted in hydrolysis of the benzylcarbamate as well as desilylation to give analogue **50**. Analogues **49c**−**f** were deprotected with TBAF in THF to give analogues **51**−**54**. Alternatively, the amine derivatives **55** can also be synthesized via a direct palladium or copper catalyzed reaction with acetamide, methyl carbamate, or methylsulfonamide to install the desired moiety. Installation of the amine derivative could be performed before or after the indole is in place as illustrated for compounds **57**−**62**.

The benzo[*d*]oxazole and oxazolo[4,5-*b*]pyridine analogues were synthesized as shown in Scheme 7 by reacting the 3,5-dibromobenzoic acid **63** with either 3-hydroxyaniline **64a** or 2-amino-3-hydroxypyridine **64b** in polyphosphoric acid to give the desired dibromo compounds **65a** and **65b**.[30] Buchwald coupling of **65a** with acetamide and **65b** with methylcarbamate gave intermediates **66a**−**b** respectively. The subsequent Suzuki

Scheme 7[a]

63; 64a: X=C; 64b: X=N; 65a: X=C; 65b: X=N; 66a: X=C, R_5=NHCOMe; 66b: X=N, R_5=$NHCO_2Me$; 67: X=C, R_5=NHCOMe; 68: X=N, R_5=$NHCO_2Me$

[a] Reagents and conditions: (a) polyphosphoric acid, 185 °C; (b) methyl carbamate or acetamide, $Pd_2(dba)_3$, XantPhos, *t*-BuONa, 1,4-dioxane, 110 °C; (c) **21b**, **22**, 2 M aqueous K_3PO_4, 1,4-dioxane, 100 °C; (d) *n*-Bu_4NF, THF.

Scheme 8[a]

69; 70; 71a: R_5= $NHSO_2Me$; 71b: R_5=NHCOMe; 72: R_5=$NHSO_2Me$, R=4-pyridyl; 73: R_5=NHCOMe, R=4-methoxy-3-pyridyl; 74: R_5=NHCOMe, R=3, 4-difluorophenyl

[a] Reagents and conditions: (a) DPPA, DIEA, *t*-BuOH, toluene 100 °C; (b) HCl, 1,4-dioxane; (c) methanesulfonyl chloride or acetic anhydride, pyridine, DCM, 0 °C; (d) arylboronic acid, $PdCl_2$(dppf), K_2CO_3, 1,4-dioxane-H_2O, 65 °C; (e) 1*H*-indol-4-ylboronic acid, $Pd(PPh_3)_4$, 2 M aqueous Na_2CO_3, toluene/ethanol, 100 °C or **21b**, **22**, 2 M aqueous K_3PO_4, 1,4-dioxane, 100 °C; (f) *n*-Bu_4NF, THF.

reaction with **21b** followed by deprotection of the TIPS group gave analogues **67** and **68**.

Analogues **72**–**74**, where the aromatic group is directly attached to the phenyl core, were synthesized as described in Scheme 8. The Curtius rearrangement of 5-bromo-3-iodobenzoic acid **69** followed by quenching with *tert*-butanol gave *tert*-butyl 3-bromo-5-iodophenylcarbamate, which on deprotection with HCl gave 3-bromo-5-iodoaniline **70**. Derivatization of the amine with acetyl anhydride or methanesulfonyl chloride in the presence of base provided intermediates **71a**,**b**. Via two sequential Suzuki reactions, the aryl group and indole moiety were introduced to give compounds **72**–**74**.

Results and Discussion

Biological Evaluation of Compounds in Cell Cycle Inhibition and Cell Viability Assays. The 3-(1*H*-indol-4-yl)-5-(pyridine-3-ylamino)phenol **7** was shown to be a potent inhibitor of cell viability in Jurkat and HeLa human cancer cell lines. Cell viability was determined using the 4-[3-(4-iodophenyl)-2-(4-nitrophenyl)-2*H*-5-tetrazolino]-1,3-benzene disulfonate (WST-1) colorimetric mitochondrial reduction assay. Flow cytometric analysis of cell-cycle status showed that MCF-7 cells treated with **7** became arrested in the G2/M phase of the cell cycle growth in a dose-dependent manner. Our initial efforts to optimize the activity of compound **7** focused on understanding the contributions of the indole moiety. As replacements to the indole, various small aryl groups were explored, including phenyl and various 5,6 and 6,6 bicyclic systems. The exploration of this region of the molecule is summarized in Table 1. The phenyl analogue **12** showed an approximately 140- to 20-fold loss in potency in Jurkat and HeLa cell viability assays and was inactive in the MCF-7 G2/M cell cycle block assay. The 4-substituted indazole **13** lost potency in both assays, while the 4-quinoline **15** and the 4-benzothiaxole **14** were inactive in both assays. While retaining some activity, the oxindole **17** was still less potent than **7**, and the ring-opened analogue **18** was inactive in both cell viability and G2/M block assays. N-Methylation of the 4-indole, analogue **16**, resulted in complete loss of activity in both the cell viability and G2/M cell cycle inhibition assays. These results clearly indicate that the indole with an unsubstituted N1 is a critical feature for potent activity. Many inhibitors of tubulin polymerization described in the literature contain an indole,[31] but with the exception of the complex marine natural product diazonamide A, none of these compounds have a 4-substituted indole. Methyl substitution in the 2-position of the 4-indolyl moiety was well tolerated as illustrated by analogue **20**, but substitution of a 3-chloro resulted in loss of activity as demonstrated by analogue **19**.

Next, we evaluated the effect of substitution on the amine linking the pyridine to the phenol, and also the effect of changing this amine group to other one atom linkers or eliminating it altogether (Table 2). Methylation of the amine resulted in compound **26** which retained activity in both cell viability and G2/M cell cycle inhibition assays. Ketone **34** and the directly linked pyridine **32** also maintained potency, with analogue **34** being more potent in the cell viability assays than in the cell cycle inhibition assay. The reduction of the ketone to the alcohol **30** resulted in loss of activity, as did changing to the ether linker in **28**. The central phenol of this series is very electron rich, which could be a potential metabolic liability.[32] The discovery that the amine can be replaced by the more electron withdrawing carbonyl or directly bound heteroaromatic group allowed us to reduce the electron density of this core. Much of the subsequent work focused on the analogues of these two subseries.

Modifications to the R_5 position, which are summarized in Table 3, were made in order to understand the importance of

Table 1. Effect of Replacing or Substituting the Indole on Cell Viability and G2/M Block Cell Cycle Inhibition

	R	Cell Viability Assay (WST-1) IC_{50} (μM) Jurkat	HeLa	Cell Cycle Inhibition G2/M Block IC_{50} (μ M) MCF-7		R	Cell Viability Assay (WST-1) IC_{50} (μ M) Jurkat	HeLa	Cell Cycle Inhibition G2/M Block IC_{50} (μ M) MCF-7
7		0.02	0.13	0.29	**16**		6.70	>10	>1.0
12		2.93	2.90	>1.0	**17**		0.65	0.28	1.82
13		0.59	2.29	>1.0	**18**		>10	>10	>1.0
14		3.30	1.40	>1.0	**19**		0.30	5.60	>1.0
15		>10	>10	>1.0	**20**		0.05	0.05	0.51

Table 2. Effect of Varying the Pyridyl Linker on Cell Viability and G2/M Block Cell Cycle Inhibition

compd	X	cell viability assay (WST-1), IC_{50} (μM) Jurkat	HeLa	cell cycle inhibition G2/M block IC_{50} (μM) MCF-7
7	−NH−	0.02	0.13	0.29
26	−N(Me)−	0.06	0.33	0.10
28	−O−	ND[a]	0.89	> 1.0
30	−CH(OH)−	> 3	ND[a]	> 1.0
32		0.04	ND[a]	0.02
34	−C(O)−	0.03	0.05	0.74

[a] ND: not determined.

Table 3. Effect of Varying R_5 Substituents on the G2/M Block Cell Cycle Inhibition in Jurkat and MCF-7 Cell Lines

compd	R_5	X	cell cycle inhibition G2/M block IC_{50} (μM) Jurkat	MCF-7
7	OH	−NH−	0.02	0.29
38	H	−NH−	2.0	> 3.0
41	Cl	−NH−	0.20	> 1.0
42	OMe	−NH−	> 0.1	> 10.0
43	Me	−NH−	> 3	> 1
44	CN	−NH−	0.16	0.67
45	NHCOMe	−NH−	0.12	0.15
34	OH	−C(O)−	0.03	0.74
50	NH_2	−C(O)−	1.30	0.86
51	$NHCO_2Me$	−C(O)−	0.01	0.08
52	NHCOMe	−C(O)−	0.02	0.12
53	$NHSO_2Me$	−C(O)−	0.02	0.07
54	$NHCONMe_2$	−C(O)−	1.60	0.99

the phenol group for activity and to find replacements for the phenol, which was susceptible to glucoronidation. Flow cytometry was used to evaluate the potency and effectiveness of the compounds to block mitosis by locking MCF-7 and Jurkat human tumor cells in the G2/M phase of cell cycle growth. The des-hydroxyl analogue **38** lost potency against both cell lines, as did the chloro **41** and methyl **43** analogues. Methylation of the hydroxyl group to give the methoxy analogue **42** resulted in complete loss in activity, indicating that the phenol was most likely acting as a hydrogen bond donor rather than an acceptor. The cyano analogue **44** showed a decrease in activity of 3- to 5-fold. Acetamide **45** lost some potency in the Jurkat cell line but was potent against the MCF-7 cell line. Aniline **50** was less potent than phenol **34** on the Jurkat cell line. Derivatization of the amine to the methylcarbamate **51**, acetamide **52**, and methylsulfonamide **53** resulted in improved potency in both Jurkat and MCF-7 cell lines. Increased size of the amine substituent resulted in loss of activity as evidenced by urea **54**.

Table 4. Effect of Various Aromatic Groups on Cell Cycle Inhibition in Multiple Cell Lines

				cell cycle inhibition G2/M block IC_{50} (μM)							
compd	R	R_5	X	MCF-7	U266	H522	Jurkat	SW- 620	H23	BXPC-3	PC-3
57	2-methoxy-3-pyridyl	NHCOMe	CO	0.03	0.02	0.03	0.03	0.05	0.05	0.03	0.06
58	3-methoxy-4-pyridyl	$NHSO_2Me$	CO	0.01	0.12	0.01	0.02	0.05	0.38	0.05	0.07
59	3-morpholino-4-pyridyl	$NHCO_2Me$	CO	0.03	0.12	0.01	0.01	0.03	0.03	0.01	0.02
60	3-chloro-5-methyl-4-pyridyl	$NHCO_2Me$	CO	0.11	0.02	0.12	0.03	0.13	0.10	0.06	0.08
61	3,5-di-methyl-4-pyridyl	$NHCO_2Me$	CO	0.05	0.03	0.06	1.28	0.04	0.01	0.04	0.03
62	3-methyl-5-morpholino-4-pyridyl	NHCOMe	CO	0.01	0.02	0.03	0.02	0.06	0.04	0.07	0.05
67	2- benzo[*d*]oxazole	NHCOMe		0.02	0.16	0.01	0.55	0.30	0.35	0.11	3.00
68	2-oxazolyl [4,5-*b*] pyridine	$NHCO_2Me$		0.18	0.03	0.13	0.03	0.03	0.10	0.06	0.05
72	4-pyridyl	$NHSO_2Me$		0.02	0.01	0.01	0.01	0.02	0.01	0.01	0.02
73	4-methoxy-3-pyridyl	NHCOMe		0.03	0.02	0.03	0.02	0.36	0.03	0.02	0.05
74	3,4-difluorophenyl	NHCOMe		0.03	0.01	0.01	< 0.01	0.04	0.02	0.02	0.10
1				ND[a]	0.01	0.014	0.017	0.014	0.013	0.016	0.033

[a] ND: not determined.

Table 5. Cell Proliferation Data

	cell proliferation IC_{50} (μM)				
compd	Jurkat	SW-620	A2780	HeLa	NCI-ADR MDR1
58	0.09	0.20	0.20	0.21	0.30
59	0.10	0.25	0.22	0.28	0.30
62	0.15	0.45	0.35	0.49	1.10
68	0.21	0.55	0.48	0.64	0.34
2	0.16	0.19	0.17	0.27	0.29
paclitaxel	0.01	0.03	0.01	0.02	13.00
cisplatin	0.60	13.00	0.65	4.40	6.90

Substituted 3- and 4-pyridyl ring systems were explored to improve potency and modulate physical properties. The results for the most potent compounds are summarized in Table 4. The 2-methoxy-3-pyridyl analogue **57** was more potent in the MCF-7 cell line than the unsubstituted analogue **52**. For the compounds with a ketone linker, it was found that 3-substituted 4-pyridyl analogues such as **58** (LP-261) and **59** and 3,5-disubstituted 4-pyridyl analogues such as **60**, **61**, and **62** were highly potent. Compounds were tested for G2/M cell cycle inhibition against a panel of eight tumor cell lines and exhibited a range of activity from 10 nM to 1.3 μM across the tested cell lines.

The carbonyl linker was replaced by a fused oxazole in the benzo[*d*]oxazole **67** and the oxazolo[4,5-*b*]pyridine **68** analogues. While retaining some activity, **67** was less potent in most cell lines, but **68** was reasonably potent.

Simple aryl substituents such as 4-pyridyl **72**, 4-methoxy-3-pyridyl **73**, and the 3,4-difluorophenyl **74** directly connected to the phenyl core resulted in highly potent compounds with low nanomolar activity across the majority of cell lines.

Selected analogues that showed potent G2/M block activity in multiple cell lines were tested in cell proliferation assays (Table 5). The compounds were less active in the cell proliferation assay when compared to the G2/M block. Across all cell lines the compounds showed comparable activity to **2** but were less active than paclitaxel. In contrast all selected compounds were substantially more active including **2** when compared to cisplatin. These compounds were also active against the paclitaxel resistant National Cancer Institute adriamycin-resistant multidrug resistance 1 (NCI-ADR MDR1) cell line which overexpresses P-glycoprotein, suggesting that the compounds will not be subject to multidrug resistant mechanisms.

Table 6. Inhibition of in Vitro Tubulin Polymerization (Microtubule Formation) and Colchicine Competition

		colchicine competition	
compd	anti-tubulin activity, EC_{50} (μM)	% inhibition at 30 μM	EC_{50} (μM)
7	4.1		
16	17		
51	4.5		
52	6.1		
58	5.0 ± 1.2	79	3.2 ± 0.78
59	4.60		
61	3.2		
72	2.2	77	
73	4.6		
74	2.1	81	
1	2.0 ± 0.50	79	3.70 ± 0
vincristine	2.50 ± 0.14	inactive	

In Vitro Tubulin Polymerization Assay. To further explore the mechanism of cell cycle inhibition, these compounds were evaluated in an in vitro tubulin polymerization assay. The results are summarized in Table 6. The initial lead compound **7** was shown to be a potent inhibitor of tubulin polymerization with an IC_{50} of 4 μM. Analogue **16**, which was significantly less active in the cell viability and G2/M cell cycle block assays, was also less potent at inhibiting tubulin polymerization. Analogues **51** and **52** and the substituted 4-pyridyl analogues **58**, **59**, and **61** all showed low micromolar potency in the tubulin polymerization assay. Analogues **72**, **73** and **74** with the aromatic group directly connected to the phenyl core were also found to be potent inhibitors of tubulin polymerization with IC_{50} values in the 2−4 μM range and thus comparable to the inhibitory activity of reference drugs colchicine and vincristine (2.0 and 2.5 μM, respectively). Overall, there is a good correlation between inhibition of tubulin polymerization and inhibition of tumor cell growth for all tested analogues; however, the IC_{50} values for the inhibition of tubulin formation are significantly higher compared to the IC_{50} values for inhibition of tumor cell

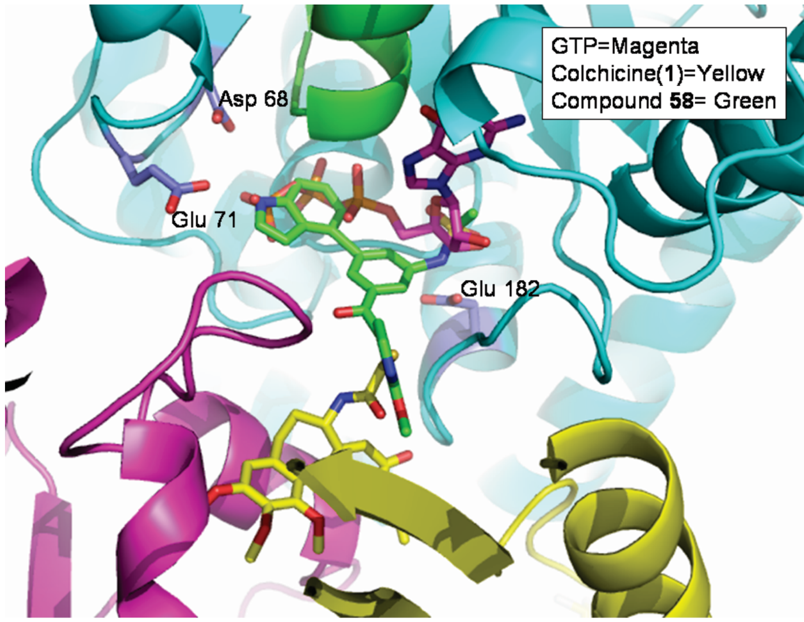

Figure 2. Proposed binding mode of **58** in tubulin structure 1SA0 generated by the Ansaris technology platform. Image was generated with the program PyMol.

growth. This appears to be a common characteristic of antimitotic drugs.[33] Various factors may contribute to this discrepancy including the fact that the in vitro tubulin polymerization assays are typically performed using a very high concentration of isolated tubulin.

Analogue **58** was assessed for its ability to compete with colchicine for binding to tubulin using [^{3}H]colchicine competition binding assay and was found to inhibit the binding with a potency similar to that of colchicine itself (Table 6). In addition analogues **72** and **74** were assessed for their ability to compete with [^{3}H]colchicine at 30 μM and showed similar inhibition as compound **58** and colchicine itself. In contrast, the *Vinca* alkaloid vincristine did not inhibit [^{3}H]colchicine binding to biotinylated tubulin. These results suggest that analogues **58**, **72**, and **74** inhibit tubulin polymerization by binding at or near the colchicine binding site.

Computational Model. We utilized our proprietary fragment-based screening technology platform[34] to develop a binding hypothesis for **58** bound to tubulin. Unlike docking programs such as GLIDE[35] that probe a specific region of the target protein with various orientations (poses) and conformations of the entire molecule of interest, our approach first identifies the high affinity poses of molecular fragments. We then connect these fragment poses together to construct a complete molecule. The tubulin structure 1SA0.pdb,[9] a 3.5 Å resolved X-ray structure, was used as the protein model for our simulations. Since the indole ring was established as a critical moiety for tubulin binding in this series, our initial focus was to find the high affinity sites for this fragment. The highest affinity indole poses involved a hydrogen bonding interaction between the indole NH and Glu71. A second high affinity pose with an interaction to Asp68 was also identified and only a minor change in the orientation of the indole ring is needed to flip the interacting NH between the two residues. The binding site identified by this method, which is a key region in the GTP site, appears to be the best location for the indole fragment. By use of the poses created by the Ansaris technology platform for other key fragments (acetophenone, methoxypyridine, and *N*-methylsulfonamide), compound **58** was readily constructed from the previously identified indole poses which involved hydrogen bonding to Glu71 and Asp68. Compounds **7**, **61**, and **74** were assembled in a similar manner. The putative binding pose for **58**, which spans both the GTP and the colchicines binding site, is depicted in Figure 2.

During the molecule build, a distribution of molecular poses were generated, from which one was selected as a representative for depiction in Figure 2. Figure 3 shows the actual distribution of molecule poses obtained for **58**.

Confirmation of this binding mode requires further biophysical studies; however, this proposed binding mode is consistent with the observed SAR. In this binding mode, the NH of the sulfonamide makes a hydrogen bond with Glu182 and explains the fact that hydrogen bond donors in the aryl ring 5 position increase potency. Methylation of the indole would prevent the hydrogen bond to Glu71 which accounts for the substantial loss in activity of the N-methylated analogue **26**. The molecule positioning in front of the GTP site would certainly prevent its binding, and while the compound only has a small overlap with colchicine, it appears large enough to prevent colchicine from occupying its binding site.

Oral Efficacy. This class of 4-aroylindole compounds displays modest to excellent oral bioavailability in rat PK studies. The original phenolic lead **7** was only 24% bioavailable in rats when dosed orally in a solution of ethanol/propylene glycol/10% Tween 80 in phosphate buffered saline (1:4:5) at a dose of 20 mg/kg. Not surprisingly, LC−MS analysis of the plasma showed extensive glucoronidation. However, when compounds **59**, **61**, **68**, **72**, and **74**, in which the phenol function is replaced by amide surrogates, were evaluated in rat PK in cassettes of three compounds each at 4 mg/kg, improved oral bioavailability ranging from 46% to 66% was observed. As a single compound dosed by oral gavage at 4 mg/kg in rat, administered as a solution formulation composed of 3:1 polyethylene glycol 400 and 100 mM citrate buffer, pH 3, compound **58** was 80% bioavailable (Table 7). Insignificant hepatic extraction in rats was indicated by a systemic clearance rate of 0.67 ± 0.43 (L/h)/kg, which is approximately 5-fold lower than the hepatic blood flow in rats (approximately 3.3 (L/h)/kg). The volume of distribution

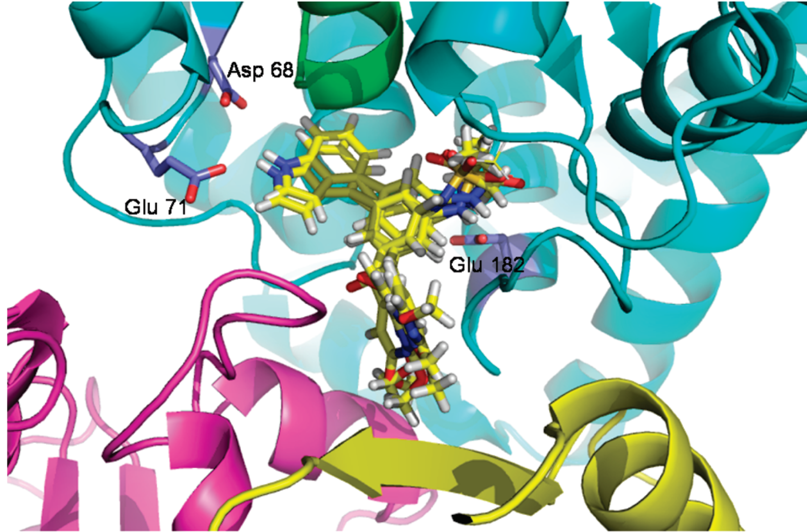

Figure 3. Distribution of molecule poses of **58** from molecule builds. Image was generated with the program PyMol.

Table 7. Pharmacokinetic Parameters of **58** after iv and po Administration (Mean ± SD, $N = 4$)

route	iv	po
dose (mg/kg)	2	4
AUC (μg·h/mL)	3.7 ± 1.6	5.9 ± 1.9
C_0 (μg/mL)	4.9 ± 3.4	
T_{max} (h)		2.0
C_{max} (μg/mL)		1.14 ± 0.43
half-life (h)	1.4 ± 0.2	1.4 ± 0.2
CL ((L/h)/kg)	0.67 ± 0.43	0.73 ± 0.31
V_{ss} (L/kg)	1.25 ± 1.13	
oral F (%)		80

(V_{ss}) was 1.25 ± 1.13 L/kg, which is approximately twice the body water of the rat (0.6 L/kg), suggesting that compound **58** is bound to tissues in the body. Finally, compound **58** displayed rapid adsorption by the oral route (T_{max} = 2.0 h) and the terminal half-life of 1.4 ± 0.2 h indicated a moderate rate of elimination.

In Vivo Efficacy of Compound 58 in NCI-H522 Xenografts. On the basis of its efficacy in a broad array of tumor cell lines and excellent oral bioavailability, **58** was selected for evaluation in a human tumor xenograft model in mice. Cultured NCI-H522 human non-small-cell lung tumors were implanted subcutaneously in NCr-*nu* mice with 10 animals per group, and the animals were treated with vehicle, **58**, or cisplatin, a drug known to inhibit NCI-H522 tumors in this model. Compound **58** was administered by oral gavage twice daily at doses of 15 and 50 mg/kg for 28 days. The results are shown in the Figure 4.

Significant inhibition of tumor growth was observed in the groups treated with **58** at doses of 50 mg/kg b.i.d. and cisplatin. Treatment with **58** at 50 mg/kg b.i.d. resulted in a mean tumor volume of 130 ± 190 mm^3 versus 3769 ± 1636 mm^3 in the vehicle treated group. This represents a 96% reduction in mean tumor volume, and the difference is statistically significant compared to the vehicle treated group ($P < 0.001$). Comparatively, cisplatin treatment reduced mean tumor volume by 98% to 63 ± 1 mm^3 ($P < 0.001$ compared to vehicle), which is the smallest measurable tumor size, and all tumors diminished in size during the study. Apparent partial inhibition of tumor growth was observed in the group treated with **58** at 15 mg/kg twice daily for 28 days (41% inhibition).

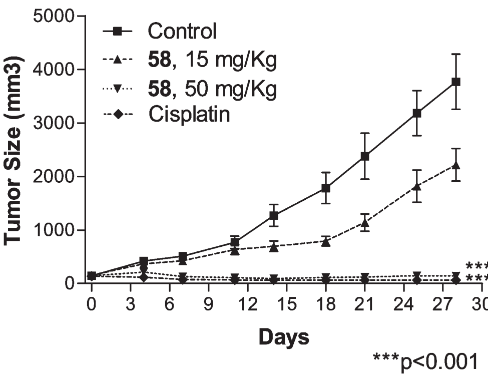

Figure 4. Inhibition of human H522 NSCL xenograft growth in vivo by **58**.

Overall, there were no significant changes in body weights for the **58** treated groups compared to the vehicle treated group. The cisplatin treated group initially exhibited weight loss that fully recovered by the end of the study.

Conclusion

In conclusion a novel series of 1-(1*H*-indol-4-yl)-3,5-disubstituted benzene analogues with potent antimitotic activity has been discovered. While the 4-indolyl substituent at the 1-position was found to be critical for potent activity against tumor cells in culture, the heteroaryl substituent at the 3-position can be either directly attached or attached via a linker such as the carbonyl group or the amino group. Placement of a hydrogen bond donor, such as hydroxyl, at the 5-position afforded potent analogues. Replacement of this phenolic hydroxyl group, which suffered from rapid glucoronidation, with an acylated or sulfonylated amine gave highly potent compounds with significantly improved oral bioavailability.

These compounds arrest cell division at the G2/M checkpoint in multiple cell lines and are highly potent in cell viability assays. The mechanism by which these agents induce G2/M block was shown to be colchicine-competitive inhibition of tubulin polymerization. Our fragment-based technology platform was used to develop a possible binding hypothesis that is consistent with the SAR of this series. The optimized lead compound **58** inhibits multiple cancer cell lines including an

MDR resistant line and inhibits tumor cell growth in a human non-small-cell lung mouse xenograft model. On the basis of these encouraging results, compound **58** was selected for further preclinical evaluation as a promising novel oral anticancer therapy.

Experimental Section

General Methods and Materials. All commercially available solvents and reagents were used without further purification. Anhydrous solvents were purchased from Sigma-Aldrich. Reactions that were air or moisture sensitive were carried out under an atmosphere of nitrogen. Microwave reactions were carried out in a CEM Discover unit. Flash chromatography was carried out using Selecto silica gel (30−63 μm) or with silica gel Flash+ cartridges on a Biotage Flash+ system. Thin layer chromatography (TLC) was performed on EMD silica gel 60 F254 plates using reagent grade solvents. Preparative TLC was performed on a 1000 μM Whatman Partisil PK6F silica gel 60 plate. ^{1}H and ^{13}C NMR spectra were obtained on a Varian Inova 400 MHz spectrometer. Compounds were analyzed for purity and molecular mass by analytical SFC using a Berger analytical SFC system (equipped with an automated column switching valve) with detection using an HP/Agilent DAD (190−300 nm) and a Waters Micromass ZQ (APCI mode). All compounds were ≥95% pure unless otherwise noted. Elution was by gradient using 5−55% MeOH in supercritical carbon dioxide over 5 min using Berger silica, amino, diol, pyridine, or cyano columns (column dimensions, 150 mm × 4.2 mm) at 2.5 mL/min. Purifications by preparative supercritical fluid chromatography were performed on a Berger preparative SFC system. Elution was by gradient using 5−55% MeOH in supercritical carbon dioxide over 5 min using Berger silica, amino, diol, pyridine, or cyano columns (all are 150 mm × 40 mm) at 50 mL/min.

3,5-Dibromo-1-benzyloxybenzene (9a). 1,3-Dibromo-5-nitrobenzene **8** (2.81 g, 10.0 mmol), freshly powdered KOH (1.00 g, 17.8 mmol), and *n*-Bu_4NBr (0.32 g, 1.00 mmol) were dissolved in tetramethylurea (TMU, 8 mL). Oxygen was bubbled through the reaction mixture for 5 min, and a solution of benzyl alcohol (1.30 g, 12.02 mmol) in TMU (2 mL) was added dropwise at room temperature over a period of 1 h. The mixture was stirred for 6 h at room temperature during which oxygen was bubbled through. The reaction mixture was poured on ice (30 g) and was extracted with *tert*-butyl methyl ether (2 × 50 mL). The combined organics were dried ($MgSO_4$) and concentrated to give the crude product which was purified by flash chromatography (120 g silica gel, EtOAc/heptane 1:4) to provide 3.15 g (92%) of **9a**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.29 (d, J = 2.8 Hz, 1H), 8.15 (dd, J = 4.7, 1.4 Hz, 1H), 7.36−7.22 (m, 6H), 7.11 (dd, J = 8.3, 4.7 Hz, 1H), 6.68 (dt, J = 3.8, 1.7 Hz, 2H), 6.48 (t, J = 2.1 Hz, 1H), 5.85 (s, 1H), 4.93 (s, 2H).

1,3-Dibromo-5-(4-methoxybenzyloxy)benzene (9b). Compound **9b** was synthesized from compound **8** in a similar manner as described for the preparation of **9a** using *p*-methoxybenzyl alcohol in 81% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (d, J = 8.6 Hz, 2H), 7.24 (s, 1H), 7.05 (d, J = 1.5 Hz, 2H), 6.91 (d, J = 8.6 Hz, 2H), 4.93 (s, 2H), 3.81 (s, 3H).

3,5-Dibromo-1-methoxybenzene (9c). Compound **9c** was synthesized from compound **8** in a similar manner as described for the preparation of **9a** using methanol in 84% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (t, J = 1.4 Hz, 1H), 6.98 (d, J = 1.5 Hz, 2H), 3.77 (s, 3H).

3,5-Dibromophenol (9d). 3,5-Dibromo-1-methoxybenzene **9c** (15.56 g, 58.5 mmol) and *n*-Bu_4NBr (1.0 g, 3.1 mmol) were suspended in 48% HBr (100 mL) and refluxed for 3 days. After cooling to room temperature, the reaction mixture was extracted with DCM (3 × 60 mL). The combined organic layers were washed with water (2 × 50 mL), dried ($MgSO_4$), and evaporated. The crude product was filtered over a pad of silica gel (EtOAc/heptane 10:1). After removal of the solvent, **9d** (14.23 g, 97%) was obtained as pale brown needles. ^{1}H NMR (400 MHz, acetone-d_6): δ 9.20 (s, 1H), 7.20 (s, 1H), 7.04 (s, 3H).

(3,5-Dibromophenoxy)triisopropylsilane (9e). Representative conditions for silyl protection of phenol were used. 3,5-Dibromophenol **9d** (23.07 g, 56.5 mmol) was dissolved in DMF (100 mL) under dry argon and cooled to 0 °C. Then 60% NaH (2.49 g, 62.3 mmol) was added in small portions over a period of 15 min. Stirring was continued for 15 min, followed by dropwise addition of triisopropylsilyl chloride (12.1 mL, 56.5 mmol). The mixture was warmed to room temperature and stirred for 20 h. The reaction mixture was diluted with *tert*-butyl methyl ether and washed with water and brine (2 × 50 mL each). The organic layer was dried ($MgSO_4$) and concentrated to give the crude product which was purified by flash chromatography on silica gel (500 g, EtOAc/heptane 1:1).to give (23.1 g, quant) of **9e** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (s, 1H), 6.96 (s, 2H), 1.30 − 1.18 (m, 3H), 1.09 (d, J = 7.2 Hz, 18H).

***N*-(3-Bromo-5-(4-methoxybenzyloxy)phenyl)pyridin-3-amine (10b).** Representative coupling conditions for Buchwald−Hartwig amination of protected 3,5-dibromophenols with 3-aminopyridine were used. An oven-dried flask was charged with (±)-BINAP (50 mg, 0.08 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ complex (28 mg, 0.027 mmol) and flushed with argon. Degassed toluene (2 mL) was added and the solution stirred for 10 min. The catalyst solution was added to a mixture of **9b** (2.00 g, 5.38 mmol), 3-aminopyridine (252 mg, 2.68 mmol), and *t*-BuONa (259 mg, 3.75 mmol) in degassed toluene (10 mL), and the mixture was heated to 90 °C for 24 h. The reaction mixture was cooled to room temperature. Brine (30 mL) and EtOAc (30 mL) were added, and the mixture was filtered over Hyflo. The aqueous layer was extracted with EtOAc (2 × 20 mL), and the organic layers were washed with brine (2 × 20 mL), dried (Na_2SO_4) and concentrated to give the crude product. Flash chromatography (silica gel, EtOAc/heptane 1:2 → 2:1) gave **10b** (636 mg, 62%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (d, J = 2.6 Hz, 1H), 8.21 (dd, J = 4.7, 1.1 Hz, 1H), 7.39 (ddd, J = 8.3, 2.6, 1.3 Hz, 1H), 7.30 (d, J = 8.6 Hz, 2H), 7.18 (dd, J = 8.3, 4.7 Hz, 1H), 6.90 (d, J = 8.6 Hz, 2H), 6.77 (t, J = 1.7 Hz, 1H), 6.72 (t, J = 1.8 Hz, 1H), 6.54 (t, J = 2.0 Hz, 1H), 5.88 (s, 1H), 4.91 (s, 2H), 3.80 (s, 3H).

***N*-(3-(4-Methoxybenzyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyridin-3-amine (11b).** Representative Suzuki-Miyura coupling conditions for synthesis of pinacol boronates were used. A round-bottom flask was charged with **10b** (623 mg, 1.62 mmol), bis(pinacolato)diboron (453 mg, 1.78 mmol), KOAc (477 mg, 4.86 mmol), and $PdCl_2(dppf) \cdot CH_2Cl_2$ complex (65 mg, 0.08 mmol). DMSO (10 mL) was added under argon, and the mixture was heated to 80 °C for 2 h. After completion of the reaction, the mixture was cooled to room temperature, filtered over Hyflo and the filter cake washed with EtOAc (2 × 5 mL). The filtrate was diluted with brine (100 mL) and the mixture extracted with EtOAc (3 × 15 mL). The combined organics were dried (Na_2SO_4) and concentrated under reduced pressure to give the crude material. Flash chromatography on silica gel (40 g, EtOAc/heptane 2:1 → 3:1) provided pure **11b** (640 mg, 91%) as an off white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (d, J = 2.3 Hz, 1H), 8.13 (d, J = 4.2 Hz, 1H), 7.39−7.30 (m, 3H), 7.14 (dd, J = 8.3, 4.7 Hz, 1H), 7.07 (dd, J = 8.7, 1.9 Hz, 2H), 6.89 (d, J = 8.6 Hz, 2H), 6.79 (t, J = 2.2 Hz, 1H), 5.83 (s, 1H), 4.98 (s, 2H), 3.80 (s, 3H), 1.32 (s, 12H). SFC-MS (APCI+), M + H found 433.3.

General Procedure A for the Suzuki Couplings Using Chloro-(di-2-norbornylphosphino)(2′-dimethylamino-1,1′-biphenyl-2-yl)-palladium (22) as Catalyst. *N*-(3-(1*H*-Indol-4-yl)-5-(4-methoxybenzyloxy)phenyl)pyridin-3-amine (23b). A 25 mL Schlenk flask was charged with **10b** (190 mg, 0.49 mmol) and **22** (11 mg, 0.02 mmol) in 1,4-dioxane (10 mL) under argon. A solution of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (**21b**, 92 mg, 0.38 mmol) in 1,4-dioxane (10 mL) followed by aqueous 2 M K_3PO_4 (0.57 mL, 1.14 mmol) was added, and the mixture was heated at reflux for 12 h. The reaction mixture was cooled, filtered over Hyflo and the filter cake washed with 1,4-dioxane (2 × 5 mL). The filtrate was concentrated in vacuo and the residue purified by flash chromatography

(silica gel, EtOAc/heptane 6:1 → 1:2) to provide *N*-(3-(1*H*-indol-4-yl)-5-(4-methoxybenzyloxy)phenyl)pyridine-3-amine **23b** (80 mg, 50%) as light brown solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60 (s, 1H), 8.40 (d, *J* = 2.6 Hz, 1H), 8.14 (d, *J* = 4.4 Hz, 1H), 7.45 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.35 (dd, *J* = 8.2, 3.4 Hz, 3H), 7.26−7.07 (m, 4H), 7.00−6.80 (m, 4H), 6.68 (dd, *J* = 11.0, 9.2 Hz, 2H), 5.99 (s, 1H), 5.01 (s, 2H), 3.80 (s, 3H). SFC-MS (APCI+), M + H found 422.7.

3-(1*H*-Indol-4-yl)-5-(pyridin-3-ylamino)phenol (7). *N*-(3-(1*H*-Indol-4-yl)-5-(4-methoxybenzyloxy)phenyl)pyridine-3-amine **23b** (35 mg, 0.083 mmol) was dissolved in dimethylsulfide (5 mL) and cooled to 0−5 °C, and $BF_3 \cdot OEt_2$(0.25 mL, 7.9 mmol) was added dropwise. The mixture was stirred for 10 min at 0−5 °C, quenched with saturated $NaHCO_3$ (5 mL), and extracted with EtOAc (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organics were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (silica gel, DCM/MeOH 10:1) to give **7** (15 mg, 60%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.18 (s, 1H), 9.36 (s, 1H), 8.36 (d, *J* = 2.7 Hz, 1H), 8.32 (s, 1H), 8.00 (dd, *J* = 4.6, 1.3 Hz, 1H), 7.48 (ddd, *J* = 8.4, 2.7, 1.4 Hz, 1H), 7.38−7.33 (m, 2H), 7.22 (dd, *J* = 8.3, 4.6 Hz, 1H), 7.11 (t, *J* = 7.7 Hz, 1H), 7.00 (d, *J* = 6.8 Hz, 1H), 6.78 (d, *J* = 1.6 Hz, 1H), 6.58 (t, *J* = 1.6 Hz, 1H), 6.55−6.51 (m, 2H). SFC-MS (APCI+), M + H found 302.7.

General Procedure B for the Suzuki Couplings Using $Pd(PPh_3)_4$ as Catalyst. 5-(Pyridin-3-ylamino)biphenyl-3-ol (12). A round-bottom flask was charged with **10a** (400 mg, 1.12 mmol) and $Pd(PPh_3)_4$ (38 mg, 0.034 mmol). 1,2-Dimethoxyethane (10 mL) was added under argon, and the mixture was stirred for 10 min at room temperature. A solution of phenylboronic acid (189 mg, 1.46 mmol) in ethanol (1.0 mL) and 2 M aqueous Na_2CO_3 (1.12 mL, 2.24 mmol) were added, and the mixture was heated at reflux overnight. After completion of the reaction, the mixture was cooled to room temperature, filtered over Hyflo and the filter cake washed with EtOAc (2 × 5 mL). The filtrate was concentrated under reduced pressure, and the oily residue was taken up in brine/EtOAc 1:1 (20 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (10 mL). The combined organics were dried (Na_2SO_4) and concentrated under reduced pressure to give the crude material (450 mg) which was flash chromatographed (silica gel 30 g, EtOAc/heptane 2:1) to give pure *N*-(5-(benzyloxy)biphenyl-3-yl)pyridin-3-amine (337 mg, 85%) as a yellow solid.

N-(5-(Benzyloxy)biphenyl-3-yl)pyridin-3-amine (170 mg, 0.48 mmol) was dissolved in THF (4 mL), and the flask was flushed with argon. Pd/C (50 mg) was added, and the argon was replaced by hydrogen (H_2 balloon). The mixture was stirred for 2 h, more Pd/C (150 mg) was added, and the mixture was stirred under H_2 for 48 h. The catalyst was filtered over Hyflo, the filter cake was washed with THF (2 × 5 mL). The filtrate was concentrated and flash chromatographed (silica gel 10 g, EtOAc/heptane 3:1) to give pure **12** (75 mg, 60%). ^{1}H NMR (400 MHz, acetone-d_6): δ 8.45 (d, *J* = 2.5 Hz, 1H), 8.41 (s, 1H), 8.09 (d, *J* = 4.5 Hz, 1H), 7.59 (d, *J* = 7.4 Hz, 4H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.34 (t, *J* = 7.3 Hz, 1H), 7.24 (dd, *J* = 8.2, 4.7 Hz, 1H), 6.89 (s, 1H), 6.70 (s, 1H), 6.67 (s, 1H). LC−MS (ES+), M + H found 263.11.

4-Bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazole. A solution of 4-bromo-1*H*-indazole (585 mg, 2.97 mmol) in dry DMF (5 mL) was cooled to 0 °C under argon. NaH (60% dispersion, 142 mg, 3.56 mmol) was added, and the suspension was stirred for 2 h at 0−5 °C. SEM chloride (265 μL, 3.86 mmol) was added at 0−5 °C, and the reaction mixture was left to warm to room temperature and stirred for 1 h. The mixture was cooled to 0 °C and quenched with water (15 mL) and was then extracted with isobutyl acetate (3 × 20 mL). The combined organics were dried (Na_2SO_4) and concentrated to provide the crude product as a mixture of isomers. Flash chromatography (silica gel, EtOAc/heptane 6:1) provided pure 4-bromo-1-((2-(trimethylsilyl)ethoxy)-methyl)-1*H*-indazole (770 mg, 75%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10 (d, *J* = 0.8 Hz, 1H), 7.59 (d, *J* = 8.2 Hz, 1H), 7.42 (dd, *J* = 7.4, 0.7 Hz, 1H), 7.36−7.30 (m, 1H), 5.79 (s, 2H), 3.73−3.49 (m, 2H), 0.95 (dd, *J* = 8.8, 7.7 Hz, 2H), −0.01 (d, *J* = 3.3 Hz, 9H).

3-(1*H*-Indazol-4-yl)-5-(pyridin-3-ylamino)phenol (13). *N*-(3-(4-Methoxybenzyloxy)-5-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazol-4-yl)phenyl)pyridin-3-amine was prepared from **11b** (472 mg, 1.09 mmol) and 4-bromo-1-((2-(trimethylsilyl)ethoxy)-methyl)-1*H*-indazole (370 mg, 0.84 mmol) using general Suzuki condition A. The Suzuki product (550 mg, 1.00 mmol) was dissolved in THF (3 mL) and ethylene diamine (0.67 mL, 10.0 mmol), and 1 M solution of TBAF in THF (3.0 mL, 3.0 mmol) was added. The reaction solution was heated at reflux for 7 days during which more TBAF solution (3xl.0 mL) was added. The reaction mixture was cooled, diluted with EtOAc (30 mL), and washed with 0.1 M HCl (20 mL). The layers were separated, and the aqueous layer was washed with EtOAc (2 × 29 mL). The combined organics were washed with saturated $NaHCO_3$ (20 mL), water (20 mL) and dried (Na_2SO_4). Concentration and filtration of the residue through a short plug of silica gel (EtOAc) provided the intermediate product (265 mg).

This intermediate was dissolved in dimethylsulfide (3.5 mL), and the solution was cooled to 0 °C. $BF_3 \cdot OEt_2$ (0.294 mL, 2.34 mmol) was added, and the mixture was stirred for 2 h at 0 °C and 2 h at room temperature. The reaction mixture was quenched with saturated $NaHCO_3$ solution (10 mL) and extracted with EtOAc (2 × 10 mL). The combined organics were dried (Na_2SO_4) and evaporated under reduced pressure. Silica gel chromatography of the crude material using THF/MeOH/NH_3 (97:2:1) gave product contaminated with BHT from the THF. The beige solid was taken up in TBME/heptane 1:1 (4 mL) and the suspension stirred at room temperature for 15 min. Filtration of the solid provided **13** (87 mg, 29%). ^{1}H NMR (400 MHz, acetone-d_6): δ 12.33 (s, 1H), 8.48 (d, *J* = 2.3 Hz, 1H), 8.46 (s, 1H), 8.19 (s, 1H), 8.10 (d, *J* = 4.7 Hz, 1H), 7.68 (s, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.42 (t, *J* = 7.7 Hz, 1H), 7.28−7.22 (m, 2H), 7.00 (s, 1H), 6.82 (s, 1H), 6.75 (s, 1H). LC−MS (ES+) M + H found 303.

Benzo[*b*]thiophen-4-yl Trifluoromethanesulfonate. Benzo[*b*]thiophen-4-ol (1.00 g, 6.66 mmol) was dissolved in dry CH_2Cl_2 (10 mL) under argon. Triethylamine (1.40 mL, 9.99 mmol) was added, and the reaction solution was cooled to 0−5 °C. A solution of trifluoromethanesulfonic acid anhydride (2.07 g, 7.32 mmol) in CH_2Cl_2 (2 mL) was added dropwise and the mixture was stirred at 0 °C for 10 min. Then 10% Na_2CO_3 solution (5 mL) was added, and the mixture was diluted with CH_2Cl_2 (10 mL) and water (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organics were washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated. Flash chromatography (silica gel, EtOAc/heptane 1:6) gave pure benzo[*b*]thiophen-4-yl trifluoromethanesulfonate (1.72 g, 87%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.91 (d, *J* = 7.9 Hz, 1H), 7.61 (d, *J* = 5.6 Hz, 1H), 7.49 (d, *J* = 5.6 Hz, 1H), 7.41 (t, *J* = 7.9 Hz, 1H), 7.34 (d, *J* = 7.6 Hz, 1H)

General Procedure C for the Suzuki Couplings Using $PdCl_2(dppf) \cdot CH_2Cl_2$ as Catalyst. *N*-(3-(Benzo[*b*]thiophen-4-yl)-5-(4-methoxybenzyloxy)phenyl)pyridine-3-amine. A 10 mL Schlenk flask was charged with **11b** (200 mg, 0.46 mmol), benzo[*b*]thiophen-4-yl trifluoromethanesulfonate (155 mg, 0.55 mmol), K_3PO_4 (195 mg, 0.92 mmol), and dry THF (4 mL). The mixture was degassed for 10 min with argon, and $PdCl_2(dppf) \cdot CH_2Cl_2$ complex (19 mg, 0.023 mmol) was added. The dark red mixture was heated at reflux for 6 h, cooled to room temperature, and diluted with EtOAc (20 mL) and saturated $NaHCO_3$ (20 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organics were washed with brine (20 mL), dried (Na_2SO_4), and concentrated to provide the crude product. Flash chromatography (silica gel, EtOAc/heptane 2:1) gave *N*-(3-(benzo[*b*]thiophen-4-yl)-5-(4-methoxybenzyloxy)phenyl)-pyridine-3-amine (198 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45 (d, *J* = 2.1 Hz, 1H), 8.16 (d, *J* = 4.4 Hz, 1H), 7.86 (d, *J* = 7.8 Hz, 1H), 7.50−7.44 (m, 1H), 7.42−7.31 (m, 6H), 7.17 (dd, *J* = 8.2, 4.7 Hz, 1H), 6.92 (d, *J* = 8.6 Hz, 2H), 6.81 (d, *J* = 12.5 Hz, 2H), 6.73 (d,

J = 1.8 Hz, 1H), 5.99 (s, 1H), 5.01 (s, 2H), 3.81 (d, J = 3.6 Hz, 3H). SFC-MS (APCI+), M + H found 439.1.

3-Benzo[*b*]thiophen-4-yl-5-(pyridine-3-ylamino)phenol (14). *N*-(3-(Benzo[*b*]thiophen-4-yl)-5-(4-methoxybenzyloxy)phenyl)pyridine-3-amine (35 mg, 0.08 mmol) was dissolved in CH_2Cl_2 (1 mL), and thioanisole (188 μL, 1.60 mmol) was added. The solution was cooled to 0 °C, and TFA (0.1 mL) was added. The reaction mixture was stirred at room temperature for 5 h and quenched with water (3 mL). Saturated $NaHCO_3$ solution was added until pH 7, and the mixture was extracted with CH_2Cl_2 (4 × 10 mL). The combined organics were washed with brine (5 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (silica gel, DCM/MeOH 95:5) provided **14** (17 mg, 58%). ^{1}H NMR (300 MHz, CD_3OD): δ 8.2 (d, 1H), 7.8 (d, 1H), 7.7 (d, 1H), 7.45 (d, 1H), 7.4 (2d, 2H), 7.2 (m, 2H), 7.1 (dd, 1H), 6.4 (s, 1H), 6.35 (s, 1H), 6.3 (s, 1H). LC−MS (ESI) M + H found 319. LC−MS indicated 87% purity.

3-(Pyridin-3-ylamino)-5-(quinolin-4-yl)phenol (15). *N*-(3-(4-Methoxybenzyloxy)-5-(quinolin-4-yl)phenyl)pyridin-3-amine was prepared from **11b** and 4-bromoquinoline using general Suzuki condition A in 98% yield. The PMB group was deprotected using the $BF_3 \cdot OEt_2$ conditions described for compound **7** to give **15** in 20% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.61 (s, 1H), 8.89 (d, J = 4.4 Hz, 1H), 8.44 (s, 1H), 8.36 (d, J = 2.3 Hz, 1H), 7.90−8.04 (m, 3H), 7.75 (dd, J = 8.4, 1.4 Hz, 1H), 7.60 (dd, J = 8.4, 1.4 Hz, 1H), 7.50 (d, J = 1.4 Hz, 1H), 7.42 (d, J = 4.4 Hz, 1H), 7.22 (dd, J = 8.2, 4.7 Hz, 1H), 6.65 (s, 1H), 6.59 (s, 1H), 6.43−6.34 (m, 1H). SFC-MS (APCI+), M + H found 314.8.

3-(1-Methyl-1*H*-indol-4-yl)-5-(pyridin-3-ylamino)phenol (16). *N*-(3-(4-Methoxybenzyloxy)-5-(1-methyl-1*H*-indol-4-yl)phenyl)-pyridin-3-amine was prepared from **10b** and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole using general Suzuki condition A in 53% yield. The PMB group was deprotected using the $BF_3 \cdot OEt_2$ conditions described for compound **7** to give **16** in 11.9% yield. ^{1}H NMR (400 MHz, CD_3OD): δ 8.32 (br s, 1H), 7.98 (br s, 1H), 7.70 (d, J = 8.6 Hz, 1H), 7.42−7.36 (m, 1H), 7.34 (d, J = 8.2 Hz, 1H), 7.21 (d, J = 7.2 Hz, 1H), 7.19−7.17 (m, 1H), 7.08 (dd, J = 7.2, 0.8 Hz, 1H), 6.91 (t, J = 1.7 Hz, 1H), 6.79−6.77 (m, 1H), 6.62 (t, J = 2.0 Hz, 1H), 6.59 (d, J = 3.1 Hz, 1H), 3.81 (s, 3H). SFC-MS (APCI+), M + H found 316.2.

4-(3-Hydroxy-5-(pyridin-3-ylamino)phenyl)-1,3-dihydroindol-2-one (17). 4-(3-(4-Methoxybenzyloxy)-5-(pyridin-3-ylamino)-phenyl)indolin-2-one was prepared from **11b** and 4-bromooxindole using general Suzuki condition A in 40% yield. The PMB group was deprotected using the $BF_3 \cdot OEt_2$ conditions described for compound **7** to give **17** in 30% yield. ^{1}H NMR (400 MHz, acetone-d_6): δ 9.47 (s, 1H), 8.60 (b s, 1H), 8.45 (d, J = 2.7 Hz, 1H), 8.09 (dd, J = 4.7, 1.4 Hz, 1H), 7.67 (s, 1H), 7.58 (ddd, J = 8.2, 2.8,1.4 Hz, 1H), 7.29−7.21 (m, 2H), 7.03 (dd, J = 7.8, 0.6 Hz, 1H), 6.89 (d, J = 7.6 Hz, 1H), 6.78 (t, J = 1.7 Hz, 1H), 6.69 (t, J = 2.0 Hz, 1H), 6.61 (t, J = 1.8 Hz, 1H), 3.56 (s, 2H). SFC-MS (APCI+), M + H found 318.8.

***N*-(3′-Hydroxy-5′-(pyridin-3-ylamino)biphenyl-3-yl)acetamide (18).** *N*-(3′-(4-Methoxybenzyloxy)-5′-(pyridine-3-ylamino)biphenyl-3-yl)acetamide was prepared from **10d** and 3-acetamidophenylboronic acid using general Suzuki condition B. To the Suzuki product (166 mg, 0.35 mmol) in THF (5 mL) at 0 °C was added 1 M TBAF in THF (0.39 mL, 0.39 mmol), and the mixture was stirred at room temperature for 30 min. The mixture was concentrated and crude was purified on a preparative SFC system to give **18** (31 mg, 27%). ^{1}H NMR (400 MHz, CD_3OD): δ 8.29 (dd, J = 2.8, 0.6 Hz, 1H), 7.96 (dd, J = 4.8, 1.4 Hz, 1H), 7.78 (t, J = 1.8 Hz, 1H), 7.58 (ddd, J = 8.4, 2.8, 1.4 Hz, 1H), 7.51−7.44 (m, 1H), 7.33 (t, J = 7.8 Hz, 1H), 7.30−7.23 (m, 2H), 6.83−6.77 (m, 1H), 6.65−6.60 (m, 1H), 6.58 (t, J = 2.1 Hz, 1H), 2.12 (s, 3H). SFC-MS (APCI+), M + H found 320.8.

3-Chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(triisopropylsilyl)-1*H*-indole. A 20 mL scintillation vial was charged with **21b** (100 mg, 0.250 mmol), *N*-chlorosuccinimde (35 mg, 0.262 mmol, 1.05 equiv), and anhydrous DMF (1.0 mL) under nitrogen. To the resulting solution is added 1 drop of TFA/DMF (10:1) via syringe. The contents of the vial are stirred at room temperature overnight. The DMF was reduced in volume in vacuo and the residue is taken up in EtOAc, washed with H_2O, brine, dried over $MgSO_4$, filtered, and concentrated to opaque foam (108 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, J = 8.1 Hz, 1H), 7.43 (d, J = 6.9 Hz, 1H), 7.22 (s, 1H), 7.15 (dd, J = 8.3, 7.1 Hz, 1H), 1.65 (dt, J = 15.0, 7.5 Hz, 3H), 1.42 (s, 12H), 1.11 (d, J = 7.5 Hz, 18H).

3-(3-Chloro-1*H*-indol-4-yl)-5-(pyridin-3-ylamino)phenol (19). 3-Chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(triisopropylsilyl)-1*H*-indole was coupled with **10d** using general Suzuki condition A, and the silyl groups were deprotected with 1 M TBAF to give **19** in 31% yield over two steps. ^{1}H NMR (400 MHz, CD_3OD): δ 8.31 (br s, 1H), 7.90 (br s, 1H), 7.59 (d, J = 8.2 Hz, 1H), 7.35 (d, J = 8.2 Hz, 1H), 7.24−7.18 (m, 2H), 7.15 (t, J = 7.7 Hz, 1H), 6.92 (d, J = 7.2 Hz, 1H), 6.66 (s, 1H), 6.59 (s, 1H), 6.50 (s, 1H). SFC-MS (APCI+), M + H found 336.7.

3-(2-Methyl-1*H*-indol-4-yl)-5-(pyridin-3-ylamino)phenol (20). 4-Hydroxy-2-methylindole (1.00 g, 6.79 mmol) and TEA (1.40 mL, 12.2 mmol) was taken up in dry CH_2Cl_2 (10 mL), and the solution was cooled to 0 °C. A solution of trifluoromethanesulfonic acid anhydride (1.23 mL, 7.47 mmol) in CH_2Cl_2 (2 mL) was added dropwise. The reaction mixture was stirred for 10 min at 0 °C and was diluted with $CHCl_3$ and extracted with saturated K_2CO_3. The organic layer was dried over K_2CO_3, filtered, and concentrated under reduced pressure. The residue was taken up in dry THF (3 mL), and NaH (60% dispersion, 360 mg, 9.00 mmol) was added portionwise. After the hydrogen evolution had ceased a solution of TBDMSCl (1.13 g, 7.50 mmol) in dry THF (2 mL) was added and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with CH_2Cl_2 (20 mL), washed with saturated NH_4Cl solution (10 mL), dried (Na_2SO_4), filtered, and concentrated to provide the crude product. Flash chromatography (silica gel, EtOAc/heptane 1:50) gave pure 1-(*tert*-butyldimethylsilyl)-2-methyl-1*H*-indol-4-yl trifluoromethanesulfonate (1.70 g, 64%). LC−MS (ES+) M + H found 394.

[3-[l-(*tert*-Butyldimethylsilanyl)-2-methyl-1*H*-indol-4-yl]-5-(4-methoxybenzyloxy)phenyl]pyridin-3-ylamine was prepared from **11b** and 1-(*tert*-butyldimethylsilyl)-2-methyl-1*H*-indol-4-yl trifluoromethanesulfonate using general procedure C for Suzuki coupling in 40% yield. The product (133 mg, 0.24 mmol) was deprotected using the $BF_3 \cdot OEt_2$ condition described for compound **7** to give **20** (57 mg, 59%) as a beige solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.99 (s, 1H), 9.32 (s, 1H), 8.35 (d, J = 2.5 Hz, 1H), 8.31 (s, 1H), 8.00 (dd, J = 4.5, 1.5 Hz, 1H), 7.48 (ddd, J = 8.4, 2.7,1.4 Hz, 1H), 7.24−7.19 (m, 2H), 7.01 (t, J = 7.6 Hz, 1H), 6.94 (d, J = 6.4 Hz, 1H), 6.76 (s, 1H), 6.56 (d, J = 1.4 Hz, 1H), 6.50 (t, J = 2.0 Hz, 1H), 6.25 (s, 1H), 2.36 (s, 3H). LC−MS (ES+) M + H found 316. LC−MS indicated 86% purity.

***N*-(3-Bromo-5-(4-methoxybenzyloxy)phenyl)-*N*-methylpyridin-3-amine (25).** To a suspension of KH (30% in mineral oil, 2.0 mmol, mineral oil washed with ether) in dry ether (20 mL) at 0 °C was added **10b** (385 mg, 1.0 mmol) in THF/ether (1:1, 10 mL), and the reaction mixture was stirred for 10 min at 0 °C. Iodomethane (74 μL, 1.2 mmol) was added, and the reaction mixture was stirred for 1 h at 0 °C. The reaction mixture was quenched with water and concentrated. The residue was dissolved in EtOAc, and the organic layer was washed with brine, dried, and concentrated. The crude product was passed through a short pad of silica gel using EtOAc/DCM (1:5) to give pure **25** (340 mg, 85%). ^{1}H NMR (400 MHz, CD_3OD): δ 8.39 (d, J = 2.8 Hz, 1H), 8.28 (dd, J = 4.8, 1.2 Hz, 1H), 7.36−7.32 (m, 1H), 7.29 (d, J = 8.4 Hz, 2H), 7.20 (dd, J = 8.4, 4.8 Hz, 1H), 6.89 (d, J = 8.4 Hz, 2H), 6.72 (t, J = 2.0 Hz, 1H), 6.68 (t, J = 2.0 Hz, 1H), 6.44 (t, J = 2.0 Hz, 1H), 4.89 (s, 2H), 3.80 (s, 3H), 3.28 (s, 3H). SFC-MS (APCI+), M + H found 399.0.

3-(1*H*-Indol-4-yl)-5-(methyl(pyridin-3-yl)amino)phenol (26). *N*-(3-(4-Methoxybenzyloxy)-5-(1-(triisopropylsilyl)-1*H*-indol-4-yl)phenyl)-*N*-methylpyridine-3-amine was prepared from **25** and **21b** using general Suzuki condition A in 57% yield. The crude Suzuki product was deprotected via a two-step protocol described for compound **13** to give **26** as a solid in 28% yield. ^{1}H NMR (400 MHz,

CD_3OD): δ 8.20 (d, J = 2.7 Hz, 1H), 7.95 (dd, J = 4.8, 1.3 Hz, 1H), 7.40 (ddd, J = 8.4, 2.9, 1.4 Hz, 1H), 7.34 (dt, J = 4.5, 2.7 Hz, 1H), 7.28−7.22 (m, 2H), 7.12 (t, J = 7.7 Hz, 1H), 7.03 (dd, J = 7.4, 1.0 Hz, 1H), 6.92 (dd, J = 2.3, 1.4 Hz, 1H), 6.90−6.89 (m, 1H), 6.57 (t, J = 2.1 Hz, 1H), 6.54 (dd, J = 3.3, 1.0 Hz, 1H), 3.33 (s, 3H). SFC-MS (APCI+), M + H found 315.4.

3-(3-Bromo-5-(4-methoxybenzyloxy)phenoxy)pyridine (27). A mixture of **9b** (250 mg, 0.672 mmol), 3-hydroxypyridine (128 mg, 1.34 mmol), and copper oxide (96 mg, 0.67 mmol) in collidine (3 mL) was treated with NaH (27 mg, 0.67 mmol) in a pressure tube. After 10 min the tube was sealed and the reaction mixture was heated to 210 °C overnight. The mixture was cooled and treated with EtOAc, aqueous NH_4OH and filtered through Celite. The phases were separated, and the aqueous phase was extracted with additional EtOAc. The combined organics were washed with brine, dried over Na_2SO_4, and concentrated. The product was chromatographed (silica gel, 33% EtOAc/hexane) to give **27** (66 mg, 25%). ^1H NMR (400 MHz, $CDCl_3$): δ 8.47 (s, 2H), 7.33−7.25 (m, 4H), 6.98−6.82 (m, 3H), 6.80−6.66 (m, 1H), 6.53 (t, J = 2.2 Hz, 1H), 4.92 (s, 2H), 3.80 (s, 3H).

3-(1*H*-Indol-4-yl)-5-(pyridin-3-yloxy)phenol (28). Compound **28** was prepared from **27** in a similar manner as described for the preparation of **26** in 15% yield over three steps. ^1H NMR (400 MHz, CD_3OD): δ 11.22 (s, 1H), 9.77 (s, 1H), 8.43 (d, J = 2.5 Hz, 1H), 8.36 (d, J = 3.5 Hz, 1H), 7.53 (ddd, J = 8.4, 2.7,1.3 Hz, 1H), 7.42 (dd, J = 8.4, 4.7 Hz, 1H), 7.36 (dd, J = 5.4, 2.4 Hz, 2H), 7.11 (t, J = 7.7 Hz, 1H), 7.00 (d, J = 7.0 Hz, 1H), 6.86 (s, 1H), 6.65 (s, 1H), 6.45 (s, 1H), 6.40 (t, J = 2.0 Hz, 1H). SFC-MS (APCI+), M + H found 303.26.

4-(3-Bromo-5-(4-methoxybenzyloxy)phenyl)-1-(triisopropylsilyl)-1*H*-indole (29). 3-Bromo-5-iodophenol (8.48 g, 28.37 mmol) was dissolved in DMF (50 mL) under dry argon and cooled to 0 °C. Then K_2CO_3 (3.92 g, 28.37 mmol) was added, followed by dropwise addition of 4-methoxybenzyl chloride (3.7 mL, 27.0 mmol). The mixture was slowly warmed to room temperature and stirred for 20 h. Additional 4-methoxybenzyl chloride (0.19 mL, 1.4 mmol) was added and stirred for another 24 h. The reaction mixture was diluted with *tert*-butyl methyl ether (300 mL) and water (150 mL). The layers were separated, and the aqueous one was extracted with additional *tert*-butylmethyl ether (2 × 150 mL). The combined organics were washed with water and brine (150 mL), dried (Na_2SO_4), and concentrated to give the crude product which was purified by flash chromatography (silica gel 330 g, EtOAc/heptane 1:9) to give 1-bromo-3-iodo-5-(4-methoxybenzyloxy)benzene (**9g**, 8.80 g, 59%) as a yellow oil.

A 1 L flask was charged with 1-bromo-3-iodo-5-(4-methoxybenzyloxy)benzene (17.44 g, 43.67 mmol), **21b** (18.30 g, 43.67 mmol) in EtOH (180 mL), toluene (180 mL), and under argon was added $Pd(PPh_3)_4$ (1.51 g, 1.31 mmol). A solution of Na_2CO_3 (9.26 g, 87.34 mmol) in water (92.6 mL) was added and the mixture heated to 90 °C and stirred for 14 h. The reaction mixture was cooled to room temperature, stirred with EtOAc (300 mL) and brine (200 mL), and filtered through a pad of Hyflo. The aqueous layer was extracted with additional EtOAc (2 × 300 mL). The combined organic layers were washed with water, brine (150 mL), dried over Na_2SO_4, filtered, and evaporated to dryness. Flash chromatography (silica gel 1 kg, EtOAc/heptane 1:19) gave **29** (22.5 g, 91%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, J = 8.2 Hz, 1H), 7.43 (s, 1H), 7.36 (d, J = 8.6 Hz, 2H), 7.27 (d, J = 3.3 Hz, 1H), 7.23 (s, 1H), 7.19 (t, J = 7.8 Hz, 1H), 7.14−7.11 (m, 2H), 6.94−6.90 (m, 2H), 6.70 (d, J = 3.0 Hz, 1H), 5.02 (s, 2H), 3.82 (s, 3H), 1.71 (dt, J = 15.0, 7.5 Hz, 3H), 1.14 (dd, J = 10.6, 8.0 Hz, 18H).

3-(Hydroxy(pyridin-3-yl)methyl)-5-(1*H*-indol-4-yl)phenol (30). To 0.298 g (0.529 mmol) of **29** in dry ether at −76 °C was added *n*-BuLi in hexane (1 M, 0.530 mL), and the resulting reaction mixture was stirred at −76 °C for 30 min. After slow addition of nicotinaldehyde (40 mg, 0.529 mmol) in ether, the reaction mixture was allowed to warm to room temperature. The reaction was quenched with saturated NH_4Cl and extracted with EtOAc. The organic phase was dried (Na_2SO_4) and concentrated. The crude product was purified by flash chromatography on silica gel to afford (3-(4-methoxybenzyloxy)-5-(1-(triisopropylsilyl)-1*H*-indol-4-yl)phenyl)(pyridin-3-yl)methanol (70 mg, 20%). This product was deprotected via a two-step protocol described for compound **13** to give **30** (7.5 mg, 20%). ^1H NMR (400 MHz, CD_3OD): δ 8.61 (s, 1H), 8.40 (d, J = 4.3 Hz, 1H), 7.87 (d, J = 7.9 Hz, 1H), 7.39 (dd, J = 7.9, 4.9 Hz, 1H), 7.34 (d, J = 8.1 Hz, 1H), 7.22 (d, J = 3.2 Hz, 1H), 7.17 (s, 1H), 7.12 (t, J = 7.7 Hz, 1H), 7.05−6.99 (m, 2H), 6.82 (s, 1H), 6.51 (d, J = 3.1 Hz, 1H), 5.84 (s, 1H). SFC-MS (APCI+), M + H found 317.1.

3-(1*H*-Indol-4-yl)-5-(pyridin-3-yl)phenol (32). To a 30 mL vial equipped with stir bar was added **29** (0.400 g, 0.71 mmol), 3-pyridinylboronic acid (0.096 g, 0.78 mmol), toluene (3 mL), ethanol (3 mL), 2 M Na_2CO_3 (0.71 mL), and n-Bu_4NBr (0.011 g, 0.035 mmol). The starting indole did not dissolve, so ethylene glycol dimethyl ether (3 mL) was added. Nitrogen was bubbled through the reaction mixture for 30 min, followed by addition of $Pd(PPh_3)_4$ (0.018 g, 0.022 mmol), and the mixture was heated to 100 °C for 18 h. The reaction mixture was cooled and filtered through Celite and washed with EtOAc. The solvent was removed under vacuum and the crude product was purified by preparative TLC (EtOAc/hexane, 30:70) to give 4-(3-(4-methoxybenzyloxy)-5-(pyridin-3-yl)phenyl)-1-(triisopropylsilyl)-1*H*-indole (0.184 g). This compound was deprotected using similar condition as described for compound **13** to give **32** in 20% yield. ^1H NMR (400 MHz, $CDCl_3$): δ 10.07 (d, J = 2.1 Hz, 1H), 9.74 (dd, J = 4.9, 1.3 Hz, 1H), 9.30 (dt, J = 4.9, 2.6 Hz, 1H), 8.70 (q, J = 4.3 Hz, 1H), 8.65−8.61 (m, 2H), 8.53 (d, J = 3.3 Hz, 1H), 8.45−8.36 (m, 3H), 8.29 (t, J = 1.9 Hz, 1H), 7.89 (d, J = 3.1 Hz, 1H). SFC-MS (APCI+), M + H found 287.1. SFC-MS indicated 94% purity.

(3-Bromo-5-(4-methoxybenzyloxy)phenyl)(pyridin-3-yl)methanone (33). In a flame-dried three-neck flask, **9b** (37.2 g, 100 mmol) was dissolved in 1 L of diethyl ether, and the solution was cooled to −75 °C. To the suspension was added *n*-BuLi (1.6 M in hexane, 62.5 mL, 100 mmol) in a fashion such that the temperature did not rise above −71 °C. The mixture was stirred for 30 min at −75 °C, and a solution of 3-cyanopyridine (10.4 g, 100 mmol) in diethyl ether (100 mL) was added slowly to maintain temperature below −70 °C. The mixture was stirred at −75 °C for 2 h and then slowly allowed to warm to −25 °C, when 2 N HCl (110 mL) was added. The reaction mixture was stirred for 20 min at room temperature, basified by addition of 1 N NaOH, and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated. The product was purified by chromatography (silica gel 700 g, CH_2Cl_2, to CH_2Cl_2/EtOAc 10:1, followed by neutral Alox A3 1000 g, heptane/EtOAc 10:1) to yield **33** (22.4 g, 56%). ^1H NMR (400 MHz, $CDCl_3$): δ 9.03−8.92 (m, 1H), 8.81 (dd, J = 4.9, 1.7 Hz, 1H), 8.13−7.94 (m, 1H), 7.47 (t, J = 1.5 Hz, 1H), 7.43 (ddd, J = 7.9, 4.9, 0.9 Hz, 1H), 7.36 (dd, J = 2.4, 1.7 Hz, 1H), 7.31 (ddd, J = 4.5, 3.9, 1.8 Hz, 3H), 6.94−6.87 (m, 2H), 5.01 (s, 2H), 3.81 (s, 3H).

(3-Hydroxy-5-(1*H*-indol-4-yl)phenyl)(pyridin-3-yl)methanone (34). (3-(4-Methoxybenzyloxy)-5-(1-(triisopropylsilyl)-1*H*-indol-4-yl)phenyl)(pyridin-3-yl)methanone was prepared from **33** and **21b** using general Suzuki condition A in 64% yield. The Suzuki product (80 mg, 0.14 mmol) was dissolved in DCM (1 mL), dimethylsulfide (1 mL), and TFA (2 mL). The resulting solution was stirred at room temperature for 2 h. DCM was added to the reaction mixture, followed by saturated $NaHCO_3$. The aqueous phase was adjusted to a pH 6 and then extracted with DCM twice. The organic phase was dried over Na_2SO_4, filtered, and concentrated to provide the crude product. The crude product was further purified by preparative TLC to give **34** (13 mg, 31%). ^1H NMR (400 MHz, CD_3OD): δ 8.97 (d, J = 2.0 Hz, 1H), 8.70 (dd, J = 4.8, 1.6 Hz, 1H), 8.21 (dt, J = 8.0, 2.0 Hz, 1H), 7.54−7.50 (m, 2H), 7.46−7.45 (m, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.27 (d, J = 3.2 Hz, 1H), 7.22 (t, J = 2.0 Hz, 1H), 7.17

(t, J = 8.0 Hz, 1H), 7.09 (d, J = 7.6 Hz, 1H), 6.61 (d, J = 3.2 Hz, 1H). SFC-MS (APCI+), M + H found 315.3.

***N*-(3-Bromophenyl)-*N*-(pyridin-3-yl)acetamide (37).** To a mixture of *N*-(3-pyridyl)acetamide **36** (272 mg, 2 mmol), CuI (powdered, 190 mg, 1.0 mmol), Cs_2CO_3 (651 mg, 2.0 mmol), 1,3-dibromobenzene **35** (2.3 g, 10.0 mmol) in 1,4-dioxane (10 mL) was added *N,N′*-dimethylethylenediamine (176 mg, 2 mmol). The reaction mixture was heated to 110 °C for 16 h. After cooling to room temperature, the reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated. The residue was extracted with DCM (5 mL), and the organic layer was washed with water (15 mL). The organic layer was dried, concentrated, and the residue was passed through a short pad of silica gel using DCM/MeOH (10:1) as eluent. The combined solution was concentrated under vacuum to give *N*-(3-bromophenyl)-*N*-(pyridin-3-yl)acetamide **37** (97 mg) in 16.7% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53−8.44 (m, 2H), 7.64−7.59 (m, 1H), 7.48−7.39 (m, 2H), 7.35−7.24 (m, 2H), 7.21−7.19 (m, 1H), 2.07 (s, 3H). SFC-MS (APCI+), M + H found 291.0.

***N*-(3-(1*H*-Indol-4-yl)phenyl)pyridin-3-amine (38).** *N*-(Pyridin-3-yl)-*N*-(3-(1-(triisopropylsilyl)-1*H*-indol-4-yl)phenyl)acetamide was prepared from *N*-(3-bromophenyl)-*N*-(pyridin-3-yl)acetamide **37** and **21b** using general Suzuki procedure A. The Suzuki product (15 mg, 0.03 mmol) was treated with 10% dimethylsulfide and 50% TFA in DCM (1 mL) for 10 min. The volatiles were evaporated with a stream of nitrogen and mild heating. The residue was purified by preparative SFC to obtain *N*-(3-(1*H*-indol-4-yl)phenyl)-*N*-(pyridin-3-yl)acetamide as an oil in 30% yield. To the oil (15 mg, 0.045 mmol) was added 6 N HCl (1 mL), and the solution was heated to 110 °C for 1 h in a sealed reaction tube. Volatiles were evaporated by blowing a gentle stream of nitrogen, and the residue was dissolved in H_2O and passed through a short pad of cotton filter. The clear solution was concentrated to give **38** (12.5 mg, 0.038 mmol) as the hydrochloride salt in 84.4% yield. ^{1}H NMR (400 MHz, D_2O): δ 8.15 (t, J = 4.6 Hz, 1H), 7.66 (s, 1H), 7.60 (s, 1H), 7.56−7.52 (2H), 7.46 (d, 4.8 Hz, 1H), 7.43−7.38 (4 H), 7.31 (d, J = 8.8 Hz, 1H), 7.07 (t, J = 7.0 Hz, 1H), 7.00 (d, J = 8.4 Hz, 1H). SFC-MS (APCI+), M + H found 286.3.

***N*-(3,5-Dibromophenyl)pyridin-3-amine (40e).** A vial with a septum cap was charged with 1,3,5-tribromobenzene **39e** (337 mg, 1.2 mmol), pyridin-3-amine (96 mg, 1.02 mmol), *t*-BuONa (112 mg, 2.02 mmol), and XantPhos (57 mg, 0.098 mmol). The atmosphere was flushed with nitrogen. Then 1,4-dioxane (6 mL) was added followed by $Pd_2(dba)_3$ (45 mg, 0.05 mmol). The atmosphere was again flushed with nitrogen and the mixture was heated to 110 °C. At 23 h, the reaction mixture was cooled, filtered through Celite, and the filter cake was eluted with EtOAc. Solvent was removed in vacuo and the residue was purified by flash column (3.8 cm × 12 cm, silica gel) using DCM:/MeOH (98:2) to give of *N*-(3,5-dibromophenyl)pyridin-3-amine (206.1 mg, 62%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (d, J = 2.0 Hz, 1H), 8.23 (d, J = 4.1 Hz, 1H), 7.44 (dd, J = 8.2, 1.0 Hz, 1H), 7.21 (dd, J = 8.0, 4.8 Hz, 1H), 7.16 (t, J = 1.4 Hz, 1H), 7.07 (d, J = 1.3 Hz, 2H), 6.45 (s, 1H). SFC-MS (APCI+), M + H found 306.1.

***N*-(3-Bromo-5-(pyridin-3-ylamino)phenyl)acetamide (40f).** The *N*-(3,5-dibromophenyl)pyridin-3-amine **40e** (150 mg, 0.44 mmol)), acetamide (36 mg, 0.62 mmol), and Cs_2CO_3 (204 mg, 0.44 mmol) were stirred together with 1,4-dioxane (2.5 mL), and the flask was flushed with argon. In a separate vial under argon was added $Pd_2(dba)_3$ (0.02 mmol) and XantPhos (0.03 mmol) to 1,4-dioxane (0.5 mL). The catalyst mixture was stirred at room temperature for 15 min, and this was added via syringe to the amine mixture which was heated at 110 °C for 4.5 h. The mixture was cooled and filtered through Celite, eluting with EtOAc. Then solvent was removed in vacuo. Purification by flash chromatography on silica gel using DCM/MeOH (95:5) gave **40f** (76.3 mg, 53%). ^{1}H NMR (400 MHz, acetone-d_6): δ 9.35 (s, 1H), 8.45 (d, J = 1.8 Hz, 1H), 8.15 (d, J = 4.2 Hz, 1H), 7.84 (s, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.46 (s, 2H), 7.26 (dd, J = 8.1, 4.6 Hz, 1H), 6.93 (s, 1H), 2.07 (s, 3H). SFC-MS (APCI+), M + H found 306.1.

***N*-(3-Chloro-5-(1*H*-indol-4-yl)phenyl)pyridin-3-amine (41).** *N*-(3-Bromo-5-chlorophenyl)pyridin-3-amine was prepared from 1,3-dibromo-5-chlorobenzene **39a** and pyridin-3-amine as described for preparation of **10b** in 30% yield. This material was reacted with **21b** using general Suzuki condition A (54%). The Suzuki product (54 mg, 0.11 mmol) in THF (3 mL) at 0 °C was treated with 1 M TBAF in THF (0.13 mL, 0.13 mmol) and stirred at room temperature for 30 min, the mixture was concentrated, and the crude product was purified on a preparative SFC system to give **41** (11 mg, 31%). ^{1}H NMR (400 MHz, CD_3OD): δ 8.35 (br s, 1H), 8.03 (d, J = 4.3 Hz, 1H), 7.63 (ddd, J = 8.3, 2.7,1.3 Hz, 1H), 7.39 (d, J = 8.2 Hz, 1H), 7.33−7.28 (m, 3H), 7.20−7.14 (m, 2H), 7.08−7.04 (m, 2H), 6.57 (d, J = 3.2 Hz, 1H). SFC-MS (APCI+), M + H found 320.1.

***N*-(3-(1*H*-Indol-4-yl)-5-methoxyphenyl)pyridin-3-amine (42).** *N*-(3-Bromo-5-methoxyphenyl)pyridin-3-amine was prepared from 1,3-dibromo-5-methoxybenzene **39b** and pyridin-3-amine as described for the preparation of **10b** in 50% yield. This material was converted to **42** as described for compound **41** in 19.4% yield over two steps. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.44 (d, J = 2.7 Hz, 1H), 8.34 (br s, 1H), 8.17 (dd, J = 4.7, 1.2 Hz, 1H), 7.50 (ddd, J = 8.2, 2.7, 1.4 Hz, 1H), 7.39 (d, J = 8.2 Hz, 1H), 7.27−7.23 (m, 2H), 7.19−7.15 (m, 2H), 6.98 (t, J = 1.7 Hz, 1H), 6.89 (dd, J = 2.2, 1.4 Hz, 1H), 6.73 (t, J = 2.1 Hz, 1H), 6.64 (t, J = 2.2 Hz, 1H), 5.81 (s, 1H), 3.84 (s, 3H). SFC-MS (APCI+), M + H found 316.4.

***N*-(3-(1*H*-Indol-4-yl)-5-methylphenyl)pyridin-3-amine (43).** *N*-(3-Bromo-5-methylphenyl)pyridin-3-amine was prepared from 1,3-dibromo-5-methylbenzene **39c** and pyridin-3-amine as described for preparation of **10b** in 31% yield. This material was converted to compound **43** as described for compound **41** in 24% yield. ^{1}H NMR (400 MHz, CD_3OD): δ 8.31 (s, 1H), 7.93 (d, J = 4.1 Hz, 1H), 7.56 (ddd, J = 8.4, 2.8, 1.3 Hz, 1H), 7.35 (d, J = 8.1 Hz, 1H), 7.29−7.19 (m, 3H), 7.09 (ddd, J = 11.3, 8.2, 4.2 Hz, 3H), 6.93 (s, 1H), 6.59 (dd, J = 3.2, 0.9 Hz, 1H), 2.38 (s, 3H). SFC-MS (APCI+), M + H found 300.8.

3-(1*H*-Indol-4-yl)-5-(pyridin-3-ylamino)benzonitrile (44). 3-Bromo-5-(pyridin-3-ylamino)benzonitrile was prepared from 3,5-dibromobenzonitrile **39d** and pyridin-3-amine as described for the preparation of **10b** in 62% yield. This material was converted to compound **44** as described for compound **41** in 9.7% yield over two steps. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.47 (s, 2H), 8.28 (d, J = 4.3 Hz, 1H), 7.55−7.49 (m, 3H), 7.44 (d, J = 8.2 Hz, 1H), 7.30−7.23 (m, 4H), 7.12 (dd, J = 7.3, 0.9 Hz, 1H), 6.63 (t, J = 2.5 Hz, 1H), 6.05 (s, 1H). SFC-MS (APCI+), M + H found 311.1.

***N*-(3-(1*H*-Indol-4-yl)-5-(pyridin-3-ylamino)phenyl)acetamide (45).** To a vial containing **40f** (0.109 g, 0.36 mmol) in toluene (0.7 mL), EtOH (0.7 mL), and H_2O (0.27 mL) was added Na_2CO_3 (0.076 g, 0.719 mmol) followed by *n*-Bu_4NBr (0.005 g, 0.02 mmol) and **21b** (0.158 g, 0.39 mmol). The vial was purged with nitrogen before and after addition of $Pd(Ph_3P)_4$ (0.020 g, 0.017 mol), capped, and heated at 110 °C for 18 h. The mixture was cooled, filtered through Celite, washed with MeOH. The solvent was removed in vacuo, giving a mixture of *N*-[3-(pyridin-3-ylamino)-5-(1-(triisopropylsilyl)-1*H*-indol-4-yl)phenyl)acetamide and *N*-(3-(1*H*-indol-4-yl)-5-(pyridin-3-ylamino)phenyl)acetamide. The mixture of Suzuki products (177 mg, 0.35 mmol) in THF (2 mL) at 0 °C was treated with 1 M TBAF in THF (0.5 mL, 0.5 mmol) and stirred at room temperature for 30 min The mixture was concentrated, and the crude product was purified on preparative SFC to give **45** (0.071 g, 58.7%). ^{1}H NMR (400 MHz, acetone-d_6): δ 10.41 (s, 1H), 9.28 (s, 1H), 8.51 (d, J = 2.5 Hz, 1H), 8.09 (dd, J = 4.6, 1.1 Hz, 1H), 7.77 (d, J = 17.0 Hz, 1H), 7.69 (s, 1H), 7.62 (ddd, J = 8.2, 2.7,1.3 Hz, 1H), 7.53 (s, 1H), 7.43 (d, J = 7.8 Hz, 1H), 7.38 (t, J = 2.8 Hz, 1H), 7.23 (q, J = 4.3 Hz, 1H), 7.20−7.17 (m, 2H), 7.16−7.11 (m, 1H), 6.76−6.72 (m, 1H), 2.11 (s, 3H). SFC-MS (APCI+), M + H found 343.2.

(3,5-Dibromophenyl)(pyridin-3-yl)methanone (47a). In a flame-dried three-neck flask under argon, 1,3,5-tribromobenzene **39e** (31.4 g, 100 mmol) was dissolved in 1 L of diethyl ether, and the

solution was cooled to −72 °C. To the resulting suspension was added a solution of *n*-BuLi (1.6 M in hexane, 62.5 mL, 100 mmol) slowly so that the temperature did not rise above −70 °C. The mixture was stirred for 30 min at −75 °C, and a solution of 3-cyanopyridine **46a** (10.4 g, 100 mmol) in diethyl ether (100 mL) was added slowly so that the temperature did not rise above −71 °C. The mixture was stirred at −75 °C for 60 min and slowly allowed to warm to −25 °C, when 2 N HCl (250 mL) was added and the mixture was stirred for 20 min at room temperature. The mixture was made basic by addition of 1 N NaOH. The product was extracted with EtOAc, and the combined organic layers were dried over Na_2SO_4. The product was purified by chromatography (silica gel,700 g) to yield **47a** (27.7 g, 81%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.97 (s, 1H), 8.85 (d, J = 4.0 Hz, 1H), 8.10 (dt, J = 7.9, 1.8 Hz, 1H), 7.92 (t, J = 1.6 Hz, 1H), 7.84 (d, J = 1.6 Hz, 2H), 7.49 (dd, J = 7.8, 4.9 Hz, 1H). SFC-MS (APCI+), M + H found 339.9.

(2-Chloropyridin-3-yl)(3,5-dibromophenyl)methanone (47b). Compound **47b** was prepared from 1,3,5-tribromobenzene **39e** and 2-chloronicotinonitrile **46b** in a similar manner as described for the preparation of compound **47a** in 20% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, J = 1.6 Hz, 2H), 8.00 (d, J = 8.1 Hz, 1H), 7.73 (d, J = 1.4 Hz, 1H), 7.68 (d, J = 8.1 Hz, 1H), 6.88 (d, J = 1.4 Hz, 1H). SFC-MS (APCI+), M + H found 376.

(3,5-Dibromophenyl)(2-methoxypyridin-3-yl)methanone (47c). To a 25 mL flask charged with anhydrous MeOH (4 mL) at 0 °C was added sodium (0.1 g, 5 mmol), and the reaction mixture was stirred for 30 min. To the solution of sodium methoxide was added **47b** (0.374 g, 1.0 mmol) in DMF (0.8 mL) and the reaction was heated to 80 °C for 5 h. The reaction mixture was cooled in an ice bath, slowly quenched with 4 N HCl, and concentrated under vacuum. The crude product was extracted with DCM (25 mL). The DCM layer was washed with saturated $NaHCO_3$, water, brine, and dried over Na_2SO_4. The organic layer was filtered, concentrated, and chromatographed on silica gel using 10% EtOAc in hexanes to give **47c** (0.16 g, 43%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (dd, J = 5.0, 1.9 Hz, 1H), 7.84 (t, J = 1.6 Hz, 1H), 7.79 (d, J = 1.6 Hz, 2H), 7.75 (dd, J = 7.3, 1.9 Hz, 1H), 7.03 (dd, J = 7.3, 5.0 Hz, 1H), 3.88 (s, 3H). SFC-MS (APCI+), M + H found 372.1.

(2-Chloropyridin-4-yl)(3,5-dibromophenyl)methanone (47d). Compound **47d** was prepared from 1,3,5-tribromobenzene **39e** and 2-chloroisonicotinonitrile **46c** in a similar manner as described for the preparation of compound **47a** in 75% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.61 (d, J = 5.0 Hz, 1H), 7.94 (d, J = 1.5 Hz, 1H), 7.82 (d, J = 1.6 Hz, 2H), 7.58 (s, 1H), 7.45 (d, J = 5.0 Hz, 1H), 1.57 (s, 1H). SFC-MS (APCI+), M + H found 376.1.

(3,5-Dibromophenyl)(2-morpholinopyridin-4-yl)methanone (47e). In a pressure tube **47d** (0.200 g, 0.53 mmol) was dissolved in 1,4-dioxane (1.0 mL), and morpholine (0.070 g, 0.80 mmol) was added. The mixture was subjected to microwave irradiation at 120 °C for 60 min. The reaction mixture was cooled and concentrated. The crude product was chromatographed on silica gel using hexane/EtOAc (1:1) to give **47e** (0.118 g, 52%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (d, J = 5.0 Hz, 1H), 7.89 (t, J = 1.6 Hz, 1H), 7.85 (d, J=1.6 Hz, 2H), 6.86 (s, 1H), 6.78 (d, J=5.0 Hz, 1H), 3.88−3.78 (m, 4H), 3.62−3.52 (m, 4H). SFC-MS (APCI+), M + H found 427.0.

2-Chloro-*N*-methoxy-6,*N*-dimethylisonicotinamide (46d). To 2-chloro-6-methylisonicotinic acid (0.500 g, 2.91 mmol) in a mixture of DCM (5.0 mL) and DMF (0.5 mL) was added HOBT (0.47 g, 3.5 mmol). The reaction mixture was stirred for 20 min at 0 °C followed by addition of EDCI (0.67 g, 3.5 mmol). The reaction mixture was slowly warmed to room temperature and stirred for 1 h. The reaction mixture was recooled to 0 °C. DIEA (0.750 g, 5.8 mmol) and *N*,*O*-dimethylhydroxylamine (0.340 g, 3.5 mmol) were added. The reaction mixture was stirred at room temperature for 16 h, then diluted with water and extracted with DCM (50 mL). The organic phase was washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was chromatographed on silica gel using 5:1 hexane/EtOAc to give 2-chloro-*N*-methoxy-6,*N*-dimethylisonicotinamide **46d** (360 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (s, 1H), 7.25 (s, 1H), 3.53 (s, 3H), 3.32 (s, 3H), 2.54 (s, 3H). SFC-MS (APCI+), M + H found 215.0

(2-Chloro-6-methylpyridin-4-yl)(3,5-dibromophenyl)methanone (47f). To 1,3,5-tribromobenzene **39e** (0.45 g, 1.4 mmol) in anhydrous ether (25.0 mL) at −78 °C was slowly added *n*-BuLi (0.57 mL, 1.4 mmol) so that the internal temperature was maintained below −70 °C. After the addition was complete, the mixture was stirred for 1 h at −78 °C. Then 2-chloro-*N*-methoxy-6,*N*-dimethylisonicotinamide **46d** (0.220 g, 1.1 mmol) in THF (2 mL) was added, again keeping the temperature below −70 °C. After the addition was complete, the mixture was allowed to stir at −25 °C for 45 min. Then saturated $NaHCO_3$ (100 mL) was added and the mixture was stirred at room temperature for 30 min. The phases were separated, and the aqueous phase was extracted with ether. The combined organic phases were dried with Na_2SO_4, the volatiles were removed in vacuo, and the crude product was chromatographed on silica gel using hexane/EtOAc (5:1) to give **47f** (330 mg, 77% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (t, J = 1.6 Hz, 1H), 7.81 (d, J = 1.6 Hz, 2H), 7.35 (s, 1H), 7.29 (s, 1H), 2.62 (s, 3H). SFC-MS (APCI+), M + H found 387.8.

Benzyl 3-Bromo-5-nicotinoylphenylcarbamate (48a). A 1 L four-neck flask equipped with a reflux condenser, a mechanical stirrer, and a thermometer was charged with **47a** (15.35 g, 45.0 mmol) and benzyl carbamate (16.33 g, 108.0 mmol). The flask was flushed with argon. Then Cs_2CO_3 (20.50 g, 63.0 mmol) and 1,4-dioxane (270 mL) were added, and the mixture was heated to an internal temperature of 80 °C. In a 100 mL Schlenk flask were placed together $Pd_2(dba)_3 \cdot CHCl_3$ complex (0.465 g, 0.9 mmol) and XantPhos (0.780 g, 1.35 mmol) in a toluene/1,4-dioxane mixture (1:4, 60 mL). The orange Pd catalyst suspension was stirred at room temperature for 20 min and then (10 mL) was added to the reaction mixture at 80 °C. The temperature was then raised to 105 °C, and a 10 mL portion of the catalyst suspension was added in 1 h intervals. After refluxing overnight the reaction mixture afforded a yellow solution and a brown precipitate. The reaction mixture was cooled to room temperature and the precipitate filtered and washed with EtOAc (3 × 50 mL). The yellow solution was evaporated to afford yellow brown oil. The crude was purified by chromatography (silica gel 900 g, toluene/DCM/EtOAc/HCOOH, 15/20/10/2) to yield a pale yellow oil. A further purification involved the precipitation of the product by dissolving the oil in a minimum of EtOAc and addition of hexane to yield **48a** (8.51 g, 46%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.98 (s, 1H), 8.82 (d, J = 4.0 Hz, 1H), 8.13 (dt, J = 7.9, 1.7 Hz, 1H), 7.99 (s, 1H), 7.67 (s, 1H), 7.58 (s, 1H), 7.47 (dd, J = 7.8, 4.9 Hz, 1H), 7.40−7.30 (m, 5H), 6.97 (s, 1H), 5.19 (s, 2H). LC−MS (ES+), M + H found 412.0.

(3-Amino-5-bromophenyl)(pyridin-3-yl)methanone (48b). A stirred slurry of **48a** (1 g, 2.43 mmol) in 12 N HCl (50 mL) was heated at 80 °C for 20 min. Methanol (10 mL) was added until the material went into solution. Starting material was consumed within 10 min of the addition of methanol. The material was neutralized with $NaHCO_3$ and extracted thrice with EtOAc (3 × 50 mL). The organics were combined, dried over Na_2SO_4, filtered and the solution was concentrated under reduced pressure, affording **48b** (0.63 g, 93%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.30 (s, 1H), 8.86 (d, J = 1.7 Hz, 1H), 8.82 (dd, J = 4.7, 1.2 Hz, 1H), 8.21 (s, 1H), 8.10 (d, J = 7.9 Hz, 1H), 7.83 (s, 1H), 7.58 (dd, J = 7.8, 4.9 Hz, 1H), 7.53 (s, 1H). LC−MS (ES+), M + CH_3CN found 317.9.

Methyl 3-Bromo-5-nicotinoylphenylcarbamate (48c). To a stirred solution of **48b** (0.20 g, 0.72 mmol) in DCM (5 mL) was added pyridine (0.58 mL) and methyl chloroformate (0.55 mL). The reaction mixture was heated to 60 °C for 20 min and diluted with DCM. The DCM layer was washed with saturated $NaHCO_3$, separated, dried over Na_2SO_4, and the volatiles were removed under reduced pressure to give **48c** (208 mg, 86% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.99 (s, 1H), 8.84 (s, 1H), 8.17−8.05 (m, 1H), 7.98 (s, 1H), 7.68 (d, J = 5.4 Hz, 1H), 7.59 (d, J = 1.5 Hz, 1H), 7.47 (d, J = 5.0 Hz, 1H), 6.80 (s, 1H), 3.79 (s, 3H). SFC-MS (APCI+), M + H found 335.0.

***N*-(3-Bromo-5-nicotinoylphenyl)acetamide (48d).** To **48b** (1.32 g, 3.6 mmol) in DCE (10 mL) and DIEA (1.0 mL) was added acetyl chloride (0.35 mL). The reaction mixture was stirred for 10 min, then poured into water and extracted twice with DCM. The organic phase was dried over Na_2SO_4, filtered, and concentrated to give 154 mg of **48d**, which was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.30 (s, 1H), 8.86 (d, J = 1.7 Hz, 1H), 8.82 (dd, J = 4.7, 1.2 Hz, 1H), 8.21 (s, 1H), 8.10 (d, J = 7.9 Hz, 1H), 7.83 (s, 1H), 7.58 (dd, J = 7.8, 4.9 Hz, 1H), 7.53 (s, 1H), 2.03 (s, 3H). SFC-MS (APCI+), M + H found 319.1.

***N*-(3-Bromo-5-nicotinoylphenyl)methanesulfonamide (48e).** To a stirred solution of **48b** (0.200 g, 0.72 mmol) in DCE (10 mL) was added pyridine (0.87 mL, 10.82 mmol), followed by methanesulfonyl chloride (0.56 mL, 7.2 mmol). The mixture was stirred at 80 °C for 2 h. The volatiles were removed under reduced pressure, affording material which was flash chromatographed using a gradient of EtOAc/hexane (25−100%) to give **48e** (0.150 g, 59%). ^{1}H NMR (400 MHz, CD_3OD): δ 8.89 (d, J = 1.4 Hz, 1H), 8.75 (dd, J = 4.8, 1.2 Hz, 1H), 8.15−8.11 (m, 1H), 7.65 (t, J = 1.7 Hz, 1H), 7.58 (s, 1H), 7.56−7.51 (m, 2H), 4.43 (s, 1H), 3.01 (s, 3H). SFC-MS (APCI+), M + H found 355.1.

3-(3-Bromo-5-nicotinoylphenyl)-1,1-dimethylurea (48f). To **48b** (0.2 g, 0.72 mmol) in DCM (5 mL) were added 4-nitrophenyl chloroformate (0.16 g, 0.79 mmol) and pyridine (0.12 mL). Additional DCM (10 mL) was added, and the mixture was stirred for 3 h at room temperature, at which time DIEA (0.15 mL, 0.866 mmol) and 2 N dimethylamine in THF (0.873 mL, 1.75 mmol) were added. The mixture was stirred at ambient temperature for 18 h and then diluted with DCM. The organic phase was washed with saturated $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated. The crude product was chromatographed to give **48f** (quantitative). ^{1}H NMR (400 MHz, CD_3OD): δ 8.90 (d, J = 1.5 Hz, 1H), 8.77 (dd, J = 4.9, 1.3 Hz, 1H), 8.19 (dt, J = 7.9, 1.8 Hz, 1H), 7.98 (dd, J = 3.9, 1.9 Hz, 1H), 7.83−7.77 (m, 1H), 7.60 (dd, J = 7.8, 5.0 Hz, 1H), 7.54 (d, J = 1.4 Hz, 1H), 2.98 (d, J = 11.2 Hz, 6H). SFC-MS (APCI+), M + H found 348.1.

(3-Amino-5-(1*H*-indol-4-yl)phenyl)(pyridin-3-yl)methanone (50). Benzyl 3-nicotinoyl-5-(1-(triisopropylsilyl)-1*H*-indol-4-yl)phenylcarbamate was prepared by Suzuki coupling of **48a** with **21b** using general procedure A to give **49a** in 74% yield. The Suzuki product **49a** (40 mg, 0.066 mmol) in 40% KOH in MeOH/H_2O (5 mL/5 mL) was brought to reflux for 2 h. After cooling to room temperature, the mixture was diluted with water and extracted with EtOAc. The organic layer was separated, dried, and concentrated. Purification on silica gel afforded **50** (11.9 mg, 57%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.01 (d, J = 1.6 Hz, 1H), 8.71 (dd, J = 4.8, 1.7 Hz, 1H), 8.29 (s, 1H), 8.09 (dt, J = 4.9, 2.6 Hz, 1H), 7.38−7.31 (m, 3H), 7.20−7.15 (m, 4H), 7.11−7.07 (m, 2H), 6.64−6.60 (m, 1H). SFC-MS (APCI+), M + H found 314.2.

[3-(1*H*-Indol-4-yl)-5-(pyridine-3-carbonyl)phenyl]carbamic Acid Methyl Ester (51). In a pressure tube **48c** (316 mg, 0.94 mmol), **21b** (0.377 mg, 0.94 mmol), and **22** (53 mg, 0.094 mmol) were dissolved in 1,4-dioxane (6 mL) under nitrogen. Aqueous 2 M K_3PO_4 (1 mL, 1.2 mmol) was added, and the mixture was heated at reflux overnight. The reaction mixture was filtered through Celite, and the solvent was removed in vacuo. The product was chromatographed to give **49c** (0.350 g, 70% yield).

To a stirred solution of **49c** (0.285 g, 0.54 mmol) in THF (10 mL) was added 1 M TBAF in THF (1.0 mL). The mixture was stirred for 10 min, poured into water, and was extracted with EtOAc. The organic phase was washed with saturated $NaHCO_3$, brine and dried over Na_2SO_4. The volatiles were removed under reduced pressure and the crude product was chromatographed using methanol/chloroform (1−5%) to give **51** in 78.1% yield. ^{1}H NMR (400 MHz, CD_3OD): δ 9.08 (s, 1H), 8.79 (d, J = 3.9 Hz, 1H), 8.43 (s, 1H), 8.16 (d, J = 7.8 Hz, 1H), 8.08 (s, 1H), 7.81 (s, 1H), 7.78 (s, 1H), 7.38−7.46 (m, 2H), 7.22−7.27 (m, 2H), 7.19 (d, J = 7.0 Hz, 1H), 7.01 (s, 1H), 6.72 (s, 1H), 3.79 (s, 3H). SFC-MS (APCI+), M + H found 372.3.

***N*-[3-(1*H*-Indol-4-yl)-5-(pyridine-3-carbonyl)phenyl]acetamide (52).** Compound **52** was synthesized from compound **48d** in a similar manner as described for the preparation of **51** in 21% yield for two steps. ^{1}H NMR (400 MHz, CD_3OD): δ 10.61 (s, 1H), 8.94 (s, 1H), 8.70 (s, 1H), 8.13−8.19 (m, 2H), 7.99 (s, 1H), 7.74 (s, 1H), 7.49 (s, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.25 (s, 1H), 7.13 (t, J = 7.7 Hz, 1H), 7.06 (d, J = 7.0 Hz, 1H), 6.62 (s, 1H), 2.12 (s, 3H). SFC-MS (APCI+), M + H found 356.9.

***N*-[3-(1*H*-Indol-4-yl)-5-(pyridine-3-carbonyl)phenyl]methanesulfonamide (53).** Compound **53** was synthesized from compound **48e** in a similar manner as described for the preparation of **51** in 13% yield for two steps. ^{1}H NMR (400 MHz, $CD_3OD/CDCl_3$): δ 8.97 (s, 1H), 8.71 (s, 1H), 8.14 (d, J = 7.8 Hz, 1H), 7.87 (t, J = 1.8 Hz, 1H), 7.78 (t, J = 1.5 Hz, 1H), 7.56 (t, J = 1.9 Hz, 1H), 7.44 (dd, J = 7.8, 4.9 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.22 (d, J = 3.1 Hz, 1H), 7.17 (t, J = 7.7 Hz, 1H), 7.09 (d, J = 7.3 Hz, 1H), 6.60 (d, J = 3.3 Hz, 1H), 3.00 (s, 3H). SFC-MS (APCI+), M + H found 392.2.

3-[3-(1*H*-Indol-4-yl)-5-(pyridine-3-carbonyl)phenyl]-1,1-dimethylurea (54). Compound **54** was synthesized from compound **48f** in a similar manner as described for the preparation of **51** in 31% yield for two steps. ^{1}H NMR (400 MHz, CD_3OD): δ 8.97 (s, 1H), 8.75 (d, J = 3.7 Hz, 1H), 8.25 (td, J = 7.9, 1.9 Hz, 1H), 8.09 (t, J = 1.9 Hz, 1H), 7.84 (t, J = 1.9 Hz, 1H), 7.73 (t, J = 1.6 Hz, 1H), 7.58 (dd, J = 7.8, 4.9 Hz, 1H), 7.39 (td, J = 8.0, 1.0 Hz, 1H), 7.28 (d, J = 3.1 Hz, 1H), 7.17 (t, J = 7.6 Hz, 1H), 7.12 (dd, J = 7.3, 1.1 Hz, 1H), 6.67 (dd, J = 3.1, 1.0 Hz, 1H), 3.02 (s, 6H). SFC-MS (APCI+), M + H found 385.2.

***N*-(3-(1*H*-Indol-4-yl)-5-(2-methoxypyridine-3-carbonyl)phenyl)-ethanamide (57).** In a pressure tube **47c** (204 mg, 0.55 mmol) and 1*H*-indol-4-ylboronic acid (0.092 g,) were treated with toluene (2.4 mL), EtOH (1.7 mL), H_2O (0.72 mL), and Na_2CO_3 (176 mg). The solution was degassed with a stream of nitrogen for 3 min, followed by addition of catalytic $Pd(PPh_3)_4$ and heating at 70 °C for 16 h. The mixture was filtered through Celite and washed with $CHCl_3$. The solution was concentrated, diluted with EtOAc (10 mL), and washed with water (7 mL). The organic layer was dried over Na_2SO_4, concentrated until only toluene was present, loaded on a silica gel column (1.4 cm i.d. × 3.4 cm), and eluted with EtOAC/hexane (1/3) to give (3-bromo-5-(1*H*-indol-4-yl)phenyl)-(2-methoxypyridin-3-yl)methanone (89 mg, 40% yield).

To the bromide (65 mg, 0.16 mmol), 1,4-dioxane (2 mL) in a pressure tube at 100 °C was added *N*,*N*′-dimethylethylenediamine (0.28 mmol) and copper(I) iodide (0.27 mmol). The mixture was cooled and treated with Cs_2CO_3 (0.38 mmol) and acetamide (3.1 mmol). The tube was sealed, and the mixture was stirred extremely vigorously and heated at 112 °C for 16 h. The reaction mixture was allowed to cool and was diluted with $CHCl_3$ (20 mL). The organic phase was washed with NH_4OH (3 × 10 mL, 10%). The combined aqueous layer was extracted with 20 mL of EtOAc. The crude product was chromatographed on silica gel using DCM/MeOH (10:1) to give to give **57** (16 mg, 25% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56 (s, 1H), 8.30−8.02 (m, 3H), 7.82 (s, 1H), 7.69 (s, 1H), 7.60 (d, J = 6.9 Hz, 1H), 7.24 (d, J = 7.9 Hz, 1H), 7.05 (dt, J = 20.8, 7.3 Hz, 3H), 6.92−6.72 (m, 1H), 6.56 (s, 1H), 3.81 (s, 3H), 2.03 (s, 3H). SFC-MS (APCI+), M + H found 386.1.

***N*-[3-Bromo-5-(2-chloropyridine-4-carbonyl)phenyl]methanesulfonamide.** To a microwave tube was added **47d** (0.250 g, 0.663 mmol), methanesulfonamide (0.063 g, 0.66 mmol), Cs_2CO_3 (0.304 g, 0.93 mmol), XantPhos (Strem, 0.007 g, 0.013 mmol), and anhydrous 1,4-dioxane (5.0 mL). The reaction mixture was flushed with argon. Then $Pd(PPh_3)_4$ (0.015 g, 0.013 mmol) was added. The vial was capped and heated at 110 °C for 18 h. The mixture was cooled, filtered through Celite, and eluted with EtOAc, and the filtrate was concentrated in vacuo. The crude product was redissolved in EtOAc, and the organic phase was washed with water, brine and dried over Na_2SO_4. The solution was filtered and concentrated. The crude product was chromatographed on silica gel using DCM/MeOH (10:1) to give *N*-[3-bromo-5-(2-chloropyridine-4-carbonyl)phenyl]methanesulfonamide (0.168 mg, 65% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.61 (d, J = 5.0 Hz, 1H), 7.67 (dd, J = 13.6, 1.5 Hz, 2H), 7.59 (s, 1H), 7.50 (dd, J = 19.3, 3.2 Hz, 2H), 3.10 (s, 3H).

***N*-[3-Bromo-5-(2-methoxypyridine-4-carbonyl)phenyl]methanesulfonamide.** To a mixture of *N*-[3-bromo-5-(2-chloropyridine-4-carbonyl)phenyl]methanesulfonamide (0.080 g, 0.21 mmol) and anhydrous MeOH (10.0 mL) in a pressure tube was added sodium (0.007 g, 0.21 mmol). The tube was sealed, and the mixture was heated at 80 °C for 18 h. The methanol was removed under vacuum, and water was added to the reaction mixture. The aqueous phase was extracted with EtOAc. The EtOAc layer was washed with water, brine and dried over Na_2SO_4. The solution was filtered and concentrated to give 0.035 g of *N*-[3-bromo-5-(2-methoxy-pyridine-4-carbonyl)phenyl]methanesulfonamide. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (d, J = 5.2 Hz, 1H), 7.68 (s, 2H), 7.52 (d, J = 1.5 Hz, 1H), 7.12 (d, J = 5.2 Hz, 1H), 6.96 (s, 1H), 6.68 (s, 1H), 3.99 (s, 3H), 3.09 (s, 3H).

***N*-[3-(1*H*-Indol-4-yl)-5-(2-methoxypyridine-4-carbonyl)phenyl]-methanesulfonamide (58).** Compound **58** was synthesized from compound *N*-[3-bromo-5-(2-methoxypyridine-4-carbonyl)phenyl]methanesulfonamide in a similar manner as described for the preparation of **51** in 73% yield. ^{1}H NMR (400 MHz, acetone-d_6): δ 10.49 (s, 1H), 8.96 (s, 1H), 8.38 (d, J = 5.1 Hz, 1H), 8.07 (t, J = 1.9 Hz, 1H), 7.90 (t, J = 1.6 Hz, 1H), 7.83 (t, J = 1.9 Hz, 1H), 7.51 (d, J = 7.8 Hz, 1H), 7.45 (t, J = 2.8 Hz, 1H), 7.30 (dd, J = 5.1, 1.3 Hz, 1H), 7.26−7.18 (m, 2H), 7.10 (s, 1H), 6.75−6.72 (m, 1H), 3.96 (s, 3H), 3.15 (s, 3H). HRMS calcd for $C_{22}H_{19}N_3O_4S$, 421.1096, found 421.1093.

Methyl 3-Bromo-5-(2-morpholinoisonicotinoyl)phenylcarbamate. (3,5-Dibromophenyl)-(2-morpholin-4-ylpyridin-4-yl)methanone **47e** was converted to methyl 3-bromo-5-(2-morpholinoisonicotinoyl))phenylcarbamate using a similar procedure as for the preparation of *N*-[3-bromo-5-(2-chloropyridine-4-carbonyl)phenyl]methanesulfonamide using methyl carbamate in place of methanesulfonamide in 56% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (d, J = 5.2 Hz, 1H), 7.94 (s, 1H), 7.70 (s, 1H), 7.62 (s, 1H), 6.93 (s, 1H), 6.85 (d, J = 4.8 Hz, 1H), 6.81−6.73 (m, 1H), 3.88−3.80 (m, 4H), 3.78 (s, 3H), 3.62 (bs, 4H).

[3-(1*H*-Indol-4-yl)-5-(2-morpholin-4-ylpyridine-4-carbonyl)-phenyl]carbamic Acid Methyl Ester (59). Compound **59** was synthesized from methyl 3-bromo-5-(2-morpholinoisonicotinoyl))phenylcarbamate in a similar manner as described for the preparation of **51** in 4% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (d, J = 5.3 Hz, 1H), 8.07 (t, J = 1.8 Hz, 1H), 7.95 (s, 1H), 7.76 (t, J = 1.6 Hz, 1H), 7.41 (d, J = 8.2 Hz, 1H), 7.29 (d, J = 3.3 Hz, 1H), 7.18 (t, J = 7.7 Hz, 1H), 7.10 (d, J = 7.4 Hz, 1H), 7.08 (s, 1H), 6.95 (dd, J = 5.1, 1.0 Hz, 1H), 6.62 (d, J = 3.1 Hz, 1H), 3.78 (t, J = 4.9 Hz, 4H), 3.75 (s, 3H), 3.54 (t, J = 4.9 Hz, 4H). SFC-MS (APCI+), M + H found 457.5.

Methyl 3-Bromo-5-(2-chloro-6-methylisonicotinoyl)phenylcarbamate. (2-Chloro-6-methylpyridin-4-yl)-(3,5-dibromophenyl)-methanone **(47f)** was converted to methyl 3-bromo-5-(2-chloro-6-methylisonicotinoyl)phenylcarbamate under the palladium catalyzed conditions described for *N*-[3-bromo-5-(2-chloropyridine-4-carbonyl)phenyl]methanesulfonamide using methyl carbamate in place of methanesulfonamide in 45.8% yield. ^{1}H NMR (400 MHz, acetone-d_6): δ 9.06 (s, 1H), 8.18 (d, J = 1.6 Hz, 1H), 7.92 (d, J = 1.3 Hz, 1H), 7.61 (d, J = 1.4 Hz, 1H), 7.51 (d, J = 5.7 Hz, 2H), 3.72 (d, J = 8.9 Hz, 3H), 2.59 (s, 3H).

Methyl 3-(2-Chloro-6-methylisonicotinoyl)-5-(1*H*-indol-4-yl)-phenylcarbamate (60). In a pressure tube methyl 3-bromo-5-(2-chloro-6-methylisonicotinoyl)phenylcarbamate (140 mg, 0.365 mmol), **21b** (0.146 g, 0.365 mmol), and **22** (53 mg, 0.094 mmol) were dissolved in dioxane (6 mL) under nitrogen. Aqueous 2 M K_3PO_4 (0.18 mL) was added, and the mixture was heated at reflux for 16 h. The reaction mixture was filtered through Celite, and the solvent was removed under vacuum. The product was chromatographed on silica gel using hexane/EtOAc (1:1) to give methyl 3-(2-chloro-6-methylisonicotinoyl)-5-(1-(triisopropylsilyl)-1*H*-indol-4-yl)-phenylcarbamate (0.120 g, 57% yield).

To the Suzuki product (0.05 g, 0.087 mmol) in THF (2.5 mL) was added of 1 M TBAF (0.17 mL), and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with water and extracted with EtOAc. The organic phase was washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was chromatographed on silica gel using DCM/MeOH (10:0.3) to give **60** (20 mg, 55% yield). ^{1}H NMR (400 MHz, acetone-d_6): δ 10.12 (s, 1H), 8.75 (s, 1H), 8.26 (s, 1H), 7.99 (s, 1H), 7.78 (t, J = 1.5 Hz, 1H), 7.64 (s, 1H), 7.50 (d, J = 6.1 Hz, 2H), 7.45 (d, J = 7.8 Hz, 1H), 7.34 (t, J = 2.8 Hz, 1H), 7.24−7.16 (m, 2H), 6.74−6.71 (m, 1H), 3.77 (s, 3H), 2.63 (s, 3H). SFC-MS (APCI+), M + H found 420.2.

Methyl 3-(2-Chloro-6-methylisonicotinoyl)-5-(1*H*-indol-4-yl)-phenylcarbamate (61). To methyl 3-(2-chloro-6-methylisonicotinoyl)-5-(1-(triisopropylsilyl)-1*H*-indol-4-yl)phenylcarbamate (0.100 g, 0.174 mmol) and anhydrous 1,4-dioxane (2.0 mL) in a pressure tube were added K_2CO_3 (0.034 g, 0.24 mmol) and methylboronic acid (0.015 g, 0.24 mmol). The reaction mixture was degassed with argon, and then $Pd(PPh_3)_4$ (0.006 g, 0.005 mmol) was added. The pressure tube was capped and heated at 110 °C for 18 h. The reaction mixture was diluted with water and extracted with EtOAc. The organic phase was washed with brine and dried over Na_2SO_4. The solution was filtered, concentrated, and the crude product was chromatographed on silica gel using DCM/MeOH (10:1) to give methyl 3-(2,6-dimethylisonicotinoyl)-5-(1-(triisopropylsilyl)-1*H*-indol-4-yl)phenylcarbamate (0.060 g, 60% yield). The silyl group was cleaved using 1 M TBAF to give **61** in 63% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.50 (s, 1H), 8.12 (s, 1H), 7.79−7.75 (m, 2H), 7.40 (d, J = 8.2 Hz, 1H), 7.29 (s, 2H), 7.27−7.22 (m, 2H), 7.17 (dd, J = 7.3, 0.9 Hz, 1H), 7.05 (s, 1H), 6.72 (s, 1H), 3.79 (s, 3H), 2.60 (s, 6H). SFC-MS (APCI+), M + 1 found 400.8.

(3-Bromo-5-(1*H*-indol-6-yl)phenyl)(2-chloro-6-methylpyridin-4-yl)methanone. In a pressure tube **47f** (425 mg, 1.09 mmol) and 1*H*-indol-4-ylboronic acid (0.193 g, 1.2 mmol) were suspended in toluene (5 mL), EtOH (3 mL), H_2O (1 mL), and Na_2CO_3 (347 mg, 3.2 mmol). The solution was degassed with a stream of nitrogen for 3 min followed by addition of $Pd(PPh_3)_4$ (0.063 g, 0.055 mmol) and heated at 70 °C for 16 h. The mixture was filtered through Celite and washed with $CHCl_3$. The filtrate was concentrated, extracted with EtOAc, and washed with water. The organic layer was dried over Na_2SO_4, concentrated, loaded on a silica gel column, and eluted with EtOAc/hexane (1:3) to give of (3-bromo-5-(1*H*-indol-6-yl)phenyl)(2-chloro-6-methylpyridin-4-yl)methanone (250 mg, 54% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (s, 1H), 8.12 (d, J = 1.6 Hz, 1H), 7.99 (s, 1H), 7.94 (d, J = 1.6 Hz, 1H), 7.47 (t, J = 4.0 Hz, 2H), 7.39 (s, 1H), 7.31 (dd, J = 8.8, 5.4 Hz, 2H), 7.17 (d, J = 7.2 Hz, 1H), 6.66 (s, 1H), 2.64 (s, 3H).

(3-Bromo-5-(1*H*-indol-6-yl)phenyl)(2-methyl-6-morpholinopyridin-4-yl)methanone. To the (3-bromo-5-(1*H*-indol-6-yl)phenyl)(2-chloro-6-methylpyridin-4-yl)methanone (0.1 g, 0.23 mmol) and 1,4-dioxane (1.0 mL) in a pressure tube was added the morpholine (1.0 mmol), and the reaction mixture was subjected to microwave at 120 °C for 3 h. The reaction mixture was cooled and concentrated. The crude product was chromatographed on silica gel using hexane/EtOAc (1:1) to give (3-bromo-5-(1*H*-indol-6-yl)phenyl)(2-methyl-6-morpholinopyridin-4-yl)methanone (45 mg, 40% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.51 (s, 1H), 7.93 (s, 3H), 7.42 (d, J = 6.9 Hz, 1H), 7.13 (s, 2H), 6.67 (d, J = 29.0 Hz, 4H), 3.78 (s, 4H), 3.53 (s, 4H), 2.46 (s, 3H).

***N*-(3-(1*H*-Indol-4-yl)-5-(2-methyl-6-morpholinoisonicotinoyl)-phenyl)acetamide (62).** The (3-bromo-5-(1*H*-indol-6-yl)phenyl)-(2-methyl-6-morpholinopyridin-4-yl)methanone (35 mg, 0.07 mmol) was dissolved in dioxane (2 mL), and the solution was transferred to a pressure tube. The mixture was heated at 100 °C and treated with *N*,*N*′-dimethylethylenediamine (0.35 mmol) and copper(I) iodide (0.12 mmol). The mixture was cooled and treated with Cs_2CO_3 (0.15 mmol) and acetamide (1.5 mmol). The tube was sealed, and the mixture was stirred extremely vigorously and heated at 112 °C for 16 h. The reaction mixture was allowed to cool, was diluted with $CHCl_3$ (20 mL), was washed with 10% NH_4OH (3 × 10 mL). The combined aqueous

layers were extracted with EtOAc (20 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by preparative SFC to give **62** in (0.019 g, 57%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42 (s, 1H), 8.24 (s, 1H), 7.84 (s, 2H), 7.59 (s, 1H), 7.40 (d, J = 7.9 Hz, 1H), 7.22 (d, J = 8.4 Hz, 1H), 7.16 (d, J = 7.2 Hz, 1H), 6.76 (d, J = 19.6 Hz, 3H), 3.79 (d, J = 4.3 Hz, 4H), 3.55 (d, J = 4.3 Hz, 4H), 2.46 (s, 3H), 2.19 (s, 3H). SFC-MS (APCI+), M + H found 455.4.

2-(3,5-Dibromophenyl)benzo[*d*]oxazole (65a). A mixture of 3,5-dibromobenzoic acid **63** (5.0 g, 17.3 mmol) and 2-aminophenol **64a** (1.91 g, 17.3 mmol) in polyphosporic acid (50 g) was heated at 185 °C for 16 h. The mixture was cooled, diluted with water, and then extracted with EtOAc. The organic layer was separated, and the aqueous layer was extracted twice with EtOAc. The combined organic phase was dried over $MgSO_4$, filtered and the residue purified by flash chromatography (silica gel, hexanes/EtOAc, 1:1) to give **65a** (5.73 g, 94%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (d, J = 2.0 Hz, 2H), 7.79 (t, J = 2.4 Hz, 1H), 7.78−7.75 (m, 1H), 7.59−7.56 (m, 1H), 7.41−7.35 (2H). SFC-MS (APCI+), M + H found 353.9.

***N*-(3-(Benzo[*d*]oxazol-2-yl)-5-bromophenyl)acetamide (66a).** To a pressure tube was added **65a** (0.700 g, 2.0 mmol), acetamide (0.10 g, 2.0 mmol), Cs_2CO_3 (1.0 g, 4.0 mmol), XantPhos (Strem, 0.08 g, 0.1 mmol), and anhydrous 1,4-dioxane (10.0 mL). The tube was flushed with argon, and then $Pd_2(dba)_3$ (0.1 g, 0.1 mmol) was added. The tube was capped and heated at 110 °C and monitored by SFC-MS. After 18 h, the mixture was cooled, filtered through Celite and the filter cake washed with EtOAc. The volatiles were removed in vacuo, and the crude product was redissolved in EtOAc. The organic phase was washed with water, brine and dried over Na_2SO_4. The solution was filtered, concentrated and the crude product was chromatographed on silica gel using DCM/MeOH (10:1) to give **66a** (0.281 mg, 40%). ^{1}H NMR (400 MHz, CD_3OD): δ 8.10 (d, J = 2.0 Hz, 2H), 7.98 (t, J = 2.0 Hz, 1H), 7.63 (m, 1H), 7.53 (m, 1H), 7.34−7.28 (2H), 2.09 (s, 3H). SFC-MS (APCI+), M + H found 331.1.

***N*-(3-(Benzo[*d*]oxazol-2-yl)-5-(1*H*-indol-4-yl)phenyl)acetamide (67).** *N*-(3-(Benzo[*d*]oxazol-2-yl)-5-bromophenyl)acetamide **66a** was converted to *N*-(3-(benzo[*d*]oxazol-2-yl)-5-(1*H*-indol-4-yl)-phenyl)acetamide **67** by the method described for the synthesis of compound **60** in 60.5% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.27 (s, 1H), 10.26 (s, 1H), 8.50 (s, 1H), 8.07 (s, 2H), 7.77−7.74 (2H), 7.41 (m, 1H), 7.39 (s, 1H), 7.38−7.33 (2H), 7.18−7.12 (2H), 6.59 (s, 1H), 2.06 (s, 3H). SFC-MS (APCI+), M + H found 368.6.

2-(3,5-Dibromophenyl)oxazolo[4,5-*b*]pyridine (65b). Compound **65b** was prepared from 3,5-dibromobenzoic acid **63** and 2-aminopyridin-3-ol **64b** in a similar manner as described for the preparation of **65a** in 47% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.57 (m, 1H), 8.33 (m, 2H), 7.84−7.80 (2H), 7.29 (m, 1H). SFC-MS (APCI+), M + H found 352.9.

Methyl 3-Bromo-5-(oxazolo[4,5-*b*]pyridin-2-yl)phenylcarbamate (66b). Compound **66b** was synthesized from compound **65b** and methylcarbamate in a similar manner as described for the preparation of **66a** in 40% yield. SFC-MS (APCI+), M + H found 348.1.

Methyl 3-(1*H*-Indol-4-yl)-5-(oxazolo[4,5-*b*]pyridin-2-yl)phenylcarbamate (68). Methyl 3-bromo-5-(oxazolo[4,5-*b*]pyridin-2-yl)-phenylcarbamate **66b** was converted to **68** by the method described for the synthesis of compound **60** in 31.8% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.34 (s, 1H), 10.09 (s, 1H), 8.54 (dd, J = 5.2, 1.2 Hz, 1H), 8.43 (s, 1H), 8.26 (dd, J = 8.0, 1.2 Hz, 1H), 8.13 (d, J = 1.2 Hz, 1H), 8.11 (s, 1H), 7.48−7.45 (3H), 7.23−7.16 (2H), 6.65 (m, 1H), 3.72 (s, 3H). SFC-MS (APCI+), M + H found 384.4.

3-Bromo-5-iodoaniline (70). To a stirred solution of 3-bromo-5-iodobenzoic acid **69** (5.0 g, 15 mmol) in methanol (30 mL) was added DIEA (2.9 mL, 16.8 mmol) and diphenylphosphorylazide (3.6 mL, 16.8 mmol). The reaction mixture was stirred for 12 h at room temperature and then quenched by addition of water (100 mL). The solid precipitate was filtered, washed with water, and dried to give 3-bromo-5-iodobenzoylazide (5.0 g, 96%).

To a stirred solution of 3-bromo-5-iodobenzoylazide (5.0 g, 14.0 mmol) in toluene (50 mL) was added *tert*-butanol (1.5 mL, 15.6 mmol). The reaction mixture was heated to reflux for 2 h, cooled to room temperature, and evaporated to dryness to afford 5.6 g (99% yield) of (3-bromo-5-iodophenyl)carbamic acid *tert*-butyl ester. The ester (5.6 g, 14 mmol) was dissolved in 1 M HCl in dioxane (35 mL, 141 mmol), stirred at room temperature for 12 h, and then cooled to 0 °C. Concentrated NaOH (50%) was added to the reaction mixture to give a pH of 14. Then water (100 mL) was added. The aqueous layer was extracted thrice with EtOAc (20 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified by silica gel chromatography to give **70** (2.8 g, 67%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 (m, 1H), 6.93 (m, 1H), 6.75 (m, 1H), 3.70 (bs, 2H). SFC-MS (APCI+), M + H found 297.9.

***N*-(3-Bromo-5-iodophenyl)methanesulfonamide (71a).** To a stirred solution of 3-bromo-5-iodoaniline **70** (1.0 g, 3.4 mmol) and pyridine (1.1 mL, 13.0 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added methylsulfonyl chloride (0.29 mL, 3.7 mmol). The reaction mixture was allowed to warm to room temperature and was stirred for 12 h. The reaction mixture was washed twice with 1 M HCl (5 mL) and brine (5 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated to give **71a** (1.23 g, 97%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (m, 1H), 7.47 (m, 1H), 7.35 (m, 1H), 6.52 (bs, 1H), 3.05 (s, 3H).

***N*-(3-Bromo-5-iodophenyl)acetamide (71b).** To a stirred solution of 3-bromo-5-iodoaniline **70** (0.60 g, 2.01 mmol) and pyridine (0.65 mL, 8.06 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added acetic anhydride (0.17 mL, 2.22 mmol). The reaction mixture was allowed to warm to room temperature and was stirred for 12 h. The reaction mixture was washed twice with 1 M HCl (5 mL) and brine (5 mL). The organic layer was dried over Na_2SO_4 and concentrated to give **71b** (0.71 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (t, J = 1.6 Hz, 1H), 7.64 (m, 1H), 7.42 (t, J = 1.6 Hz, 1H), 1.99 (s, 3H).

***N*-(3-Bromo-5-(pyridin-4-yl)phenyl)methanesulfonamide.** To a sealed tube were added *N*-(3-bromo-5-iodophenyl)methanesulfonamide **71a** (2.0 g, 5.30 mmol), pyridin-4-ylboronic acid (0.92 g, 7.4 mmol), 2 M aqueous Na_2CO_3 (8.0 mL, 16 mmol), and 1,4-dioxane (60 mL). A stream of nitrogen was passed through the mixture for 30 min. Then $PdCl_2(dppf)\cdot CH_2Cl_2$ (440 mg, 0.53 mmol) was added, and the tube was sealed and heated to 60 °C for 16 h. The reaction mixture was filtered through Celite, eluting with EtOAc. The filtrate was concentrated, and the residue was purified by silica gel column chromatography to give the desired product as an off white solid (1.5 g, 86%). ^{1}H NMR (400 MHz, CD_3OD): δ 8.59 (m, 2H), 7.67−7.64 (3H), 7.53 (m, 2H), 3.03 (s, 3H).

***N*-[3-(1*H*-Indol-4-yl)-5-pyridin-4-ylphenyl]methanesulfonamide (72).** To a sealed tube were added *N*-(3-bromo-5-(pyridin-4-yl)phenyl)methanesulfonamide (400 g, 1.22 mmol), 1*H*-indol-4-ylboronic acid (0.2 g, 1.22 mmol), 2 M aqueous Na_2CO_3 (2 mL, 4 mmol), toluene (4 mL), and EtOH (5 mL). A stream of nitrogen was passed through the mixture for 3 min. Then $Pd(PPh_3)_4$ (100 mg, 0.12 mmol) was added, and the tube was sealed and heated to 110 °C for 24 h. The reaction mixture was filtered through Celite and eluted with EtOAc. The filtrate was concentrated, and the residue was purified by silica gel chromatography to provide **72** (0.24 g, 54%). ^{1}H NMR (400 MHz, CD_3OD): δ 8.60 (dd, J = 4.8, 1.6 Hz, 2H), 7.75 (dd, J = 4.5, 1.7 Hz, 2H), 7.72 (dt, J = 5.2, 2.6 Hz, 2H), 7.57 (t, J = 1.9 Hz, 1H), 7.42 (d, J = 7.2 Hz, 1H), 7.32 (d, J = 3.1 Hz, 1H), 7.23−7.16 (m, 2H), 6.67 (d, J = 3.1 Hz, 1H), 3.04 (s, 3H). SFC-MS (APCI+), M + H found 364.4.

***N*-(3-Bromo-5-(6-methoxypyridin-3-yl)phenyl)acetamide.** *N*-(3-Bromo-5-(6-methoxypyridin-3-yl)phenyl)acetamide was synthesized from **71b** and 6-methoxypyridin-3-ylboronic acid in a similar manner as described for the synthesis of *N*-(3-bromo-5-(pyridin-4-yl)phenyl)methanesulfonamide in 87% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (s, J=2.4 Hz, 1H), 8.09 (bs, 1H), 7.69 (s, 1H), 7.65 (dd, J=8.8, 2.4 Hz, 1H), 7.55 (s, 1H), 7.31 (s, 1H), 6.74 (s, J=8.8 Hz,

1H), 3.93 (s, 3H), 2.16 (s, 3H). SFC-MS (APCI+), M + H found 321.2.

***N*-[3-(1*H*-Indol-4-yl)-5-(6-methoxypyridin-3-yl)phenyl]acetamide (73).** In a pressure tube *N*-(3-bromo-5-(6-methoxypyridin-3-yl)phenyl)acetamide (206 mg, 0.641 mmol), **21b** (0.384 g, 0.962 mmol), and **22** (35 mg, 0.064 mmol) were dissolved in dioxane (7 mL) under nitrogen. Aqueous 2 M K_3PO_4 (0.64 mL) was added, and the mixture was heated at reflux for 16 h. The reaction mixture was filtered through Celite and the solvent concentrated in vacuo. The product was chromatographed on silica gel using hexane/EtOAc (1:1) to give 0.298 g (90%) of coupled product. To the TIPS protected product (0.298 g, 0.087 mmol) in THF (6.0 mL) was added 1 M TBAF (0.64 mL), and the mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with water and extracted with EtOAc. The EtOAc layer was washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The crude was chromatographed on silica gel using 60% EtOAc in hexane to give **73** (132 mg, 63.7%). ^{1}H NMR (400 MHz, CD_3OD): δ 8.31 (d, J = 2.5 Hz, 1H), 7.83 (t, J = 1.7 Hz, 1H), 7.75 (dd, J = 8.7, 2.6 Hz, 1H), 7.69 (t, J = 1.9 Hz, 1H), 7.47 (t, J = 1.5 Hz, 1H), 7.35 (d, J = 7.8 Hz, 1H), 7.22 (d, J = 3.1 Hz, 1H), 7.14−7.06 (m, 2H), 6.67 (d, J = 8.6 Hz, 1H), 6.65 (d, J = 3.1 Hz, 1H), 3.82 (s, 3H), 2.09 (s, 3H). SFC-MS (APCI+), M + H found 358.4.

***N*-(5-Bromo-3′,4′-difluorobiphenyl-3-yl)acetamide.** To a pressure tube were added *N*-(3-bromo-5-iodophenyl)acetamide **71b** (2.5 g, 7.35 mmol), 3,4-difluorophenylboronic acid (1.22 g, 7.73 mmol), 2 M aqueous Na_2CO_3 (11 mL, 22 mmol), and dioxane (45 mL). A stream of nitrogen was passed through the mixture for 15 min. Then $PdCl_2(dppf)\cdot CH_2Cl_2$ (600 mg, 0.735 mmol) was added, and the tube was sealed and heated to 60 °C for 16 h. The reaction mixture was filtered through Celite, eluting with EtOAc. The filtrate was concentrated to a brown sludge. The residue was taken up in EtOAc, washed with H_2O, brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by column chromatography (3:1 hexanes/EtOAc) to give the desired product as a tan solid (88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (m, 2H), 7.37−7.15 (4H), 2.20 (s, 3H).

***N*-(3′,4′-Difluoro-5-(1*H*-indol-4-yl)biphenyl-3-yl)acetamide (74).** Compound **74** was prepared from *N*-(5-bromo-3′,4′-difluorobiphenyl-3-yl)acetamide in a similar manner as described for the preparation of **72** in 79% yield. ^{1}H NMR (400 MHz, CD_3OD): δ 7.87 (t, J = 1.6 Hz, 1H), 7.79 (t, J = 1.6 Hz, 1H), 7.57 (t, J = 1.6 Hz, 1H), 7.56−7.51 (m, 1H), 7.46−7.42 (m, 1H), 7.40−7.37 (m, 1H), 7.34−7.27 (m, 1H), 7.28 (d, J = 3.2 Hz, 1H), 7.17 (t, J = 7.2 Hz, 1H), 7.13 (dd, J = 7.2, 1.6 Hz, 1H), 6.66 (dd, J = 3.2, 0.8 Hz, 1H), 2.16 (s, 3H). SFC-MS (APCI+), M + H found 363.4.

Computational Model. The protein from the tubulin cocrystal X-ray structure PDB code 1SA0,[9] resolved to 3.5 Å, was prepared by protonating histidines and correcting serine, tyrosine, and threonine rotamers using an in-house algorithm.[34] The structure was then relaxed with 25−50 cycles of minimization using MacroModel.[36] A set of fragments, which included indole, acetophenone, 2-methoxypyridine, phenol, 3-aminopyridine, acetanilide, 1,2-difluorobenzene, benzaldehyde, 2,6-dimethylpyridine, and *N*-methylsulfonamide, was simulated against the protein using the grand canonical Monte Carlo simulation approach implemented using in-house developed software.[34] The fragment interaction positions were rank-ordered by the calculated free energy values. The highest affinity indole poses were identified, and the four inhibitors were assembled by automatically linking fragments in their computed positions, allowing some flexibility from standard bond lengths and bond angles. The fragments were linked sequentially starting from the distribution of the indole fragment.

Cell Viability Assay. Jurkat and HeLa cells were cultured in RPMI and EMEM media, respectively, containing 0.5% fetal calf serum. Cells were plated in a volume of 100 μL in a 96-well format. Test compounds were included in the culture media at concentrations ranging from 1 nM to 10 μM for a period of 48−72 h. Cell viability was determined using the WST-1 colorimetric mitochondrial reduction assay. Briefly, 10 μL of WST-1 reagent was included in the culture well for a period of 1−4 h. The WST-1 reaction was read on a multiwell spectrophotometer as the difference in the absorbance between 450 and 600 nm (baseline). Absorbance was proportional to the number of living cells in the culture well. Concentration response curves and IC_{50} values were calculated using GraphPAD Prism graphing and curve fitting program.

Cell Cycle Assay. MCF-7, Jurkat, U266, SW620, NCI-H522, NCI-H23, BxPC-3, and PC3 cell lines were purchased from American Type Culture Collection. Cells were maintained at 37 °C and 5% CO_2 in MEM (MCF-7), RPMI-1640 (Jurkat, U266, NCI-H522, NCI-H23, BxPC-3), L-15 (SW620), or F-12K (PC3). All cell culture media were supplemented with 10% (v/v) fetal bovine serum (FBS).

Cells were plated in 24-well plates at a volume of 1 mL/well at a density of 2×10^5 cells/mL and allowed to incubate overnight. FBS concentration was reduced to 0.5%, and cells were incubated for an additional 30 min. Following serum reduction, cells were incubated with various concentrations of test compound prepared in culture media containing 0.5% FBS from a 10 mM DMSO stock. After 24 h, cells were harvested for FACS analysis. Cells were fixed in 80% ethanol for 30 min at room temperature, and the nuclear DNA was stained with a solution of propidium iodide (PI)/RNase staining buffer. FACS analysis was done on a FACScalibur system with approximately 2000 events counted per condition. G1 and G2/M cell populations were measured and reported as a percentage of the total cell count.

Microtubule Polymerization Assay. The in vitro tubulin polymerization assay was conducted using tubulin polymerization assay kit (Cytoskeleton, Denver, CO) according to manufacturer recommendations. Colchicine **1** (95% pure) and vincristine (98% pure) were purchased from Sigma (St. Louis, MO). The final DMSO concentration in each assay well was 1%, and the final concentration series of each experimental tubulin inhibitor was 10, 5, 2.5, 1.25, and 0.6 μM.

Microtubule polymerization assays were performed using a Spectra Max Gemini XS microplate reader (Molecular Devices Corporation, Sunnyvale, CA) in a 96-well plate format. Tubulin polymerization was detected by measuring the absorbance (OD) of the solution at 340 nm once every minute over 60 min during the incubation at 37 °C.

Animals. Treatment of animals for in vivo studies was in accordance with study protocol and in adherence to regulations outlined in the USDA Animal Welfare Act (9CFR Parts 1, 2, and 3) and the conditions specified in the Guide for the Care and Use of Laboratory Animals (LAR Publication, 1996, National Academy Press).

In Vivo Pharmacokinetic Study. Sprague−Dawley rats were used to determine oral bioavailability and PK parameters of the free base form of **58** following oral and intravenous administration. Plasma concentration of **58** was determined by LC/MS/MS analysis, and PK parameters were calculated using a noncompartmental model. A solution of **58** in polyethylene gycol 400 (PEG) at 1.33 mg/mL was prepared. One volume of 100 mM citrate buffer, pH 3, was added to 3 volumes of 1.33 mg/mL solution of **58** in PEG to generate a final concentration of 1 mg/mL. The solution formulation of **58** was administered separately by bolus injection into a lateral tail vein and by oral gavage. All animals were surgically implanted with a catheter in a jugular vein using polyurethane tubing and housed individually. Blood sample was collected from four animals in each treatment group at 0 (predose), 0.0167, 0.083, 0.25, 0.5, 1, 2, 4, and 8 h for iv and 0 (predose), 0.083, 0.25, 0.5, 1, 2, 4, and 8 h for po. Calibration standards with **58** concentrations from 0.005 to 10 μg/mL were prepared by serial dilution in naive rat plasma. A portion (60 μL) of each calibration standard and experimental sample was combined with two volumes (120 μL) of acetonitrile containing an analytical internal standard. The mixture was centrifuged at 2000*g* at 4 °C for 30 min to extract the organic components. The supernatants containing the organic component for each sample were used for analysis.

Recovery of **58** by this method was greater than 85%, and the lower limit of quantitation was 0.005 μg/mL.

In Vivo Antitumor Activity. Cultured NCI-H522 tumors measuring 30−40 mm^3 were implanted subcutaneously into the thighs of athymic NCr-*nu* mice and allowed to grow to approximately 150 mm^3. Mice were assigned to groups by matching median tumor volume that ranged from 120 to 162 mm^3 in this study. The study lasted 28 days, and tumor was measured every third day during treatment phase. The compound was formulated as a free base, using 10 mg/mL **58** in DMSO/PG/TW/PBS (5:15:2:18 by volume) and was administered twice orally at 15 and 50 mg/kg. Vehicle was administered as the untreated control. Animals with tumors exceeding 4000 mm^3 or those exhibiting excessive morbidity were sacrificed immediately. Tumor volume for each individual animal was fitted to the exponential growth function using Prism software:

$$V_t = V_0 e^{Kt}$$

where V_t describes tumor volume at given time t, V_0 is starting tumor volume, and K is growth rate constant determined from the fitting.

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