Supporting Information

Discovery of Potent and Selective 7-Azaindole Isoindolinone-Based PI3Kγ Inhibitors

Dillon H. Miles, Xuelei Yan, Rhiannon Thomas-Tran, Jeremy Fournier, Ehesan U. Sharif, Samuel L. Drew, Guillaume Mata, Kenneth V. Lawson, Elaine Ginn, Kent Wong, Divyank Soni, Puja Dhanota, Stefan G. Shaqfeh, Cesar Meleza, Ada Chen, Amber T. Pham, Timothy Park, Debbie Swinarski, Jesus Banuelos, Ulrike Schindler, Matthew J. Walters, Nigel P. Walker, Xiaoning Zhao, Stephen W. Young, Jie Chen, Lixia Jin, Manmohan Reddy Leleti, Jay P. Powers, and Jenna L. Jeffrey*

Arcus Biosciences, Inc., Hayward, CA 94545, United States

Table of Contents

Biological Experimentals

Determination of Biochemical PI3K Isoform Inhibition

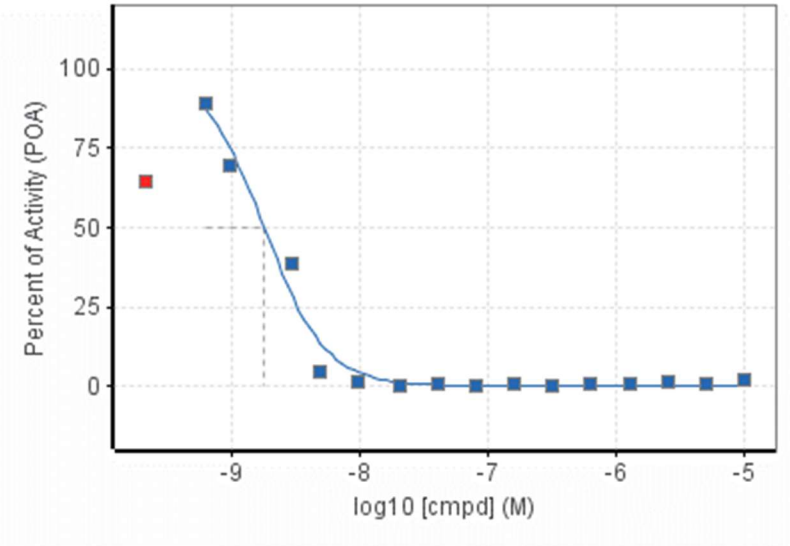
Compounds were evaluated to determine the potency with which they inhibited the kinase activity of the Class I PI3K subunits p110α/p85α (Promega, catalog # V1721), p110β/p85α (Promega, catalog # V1751), p120γ (Promega, catalog # V1761) and p110δ/p85α (Promega, catalog # V1771). Activity was determined as a function of adenosine diphosphate (ADP) generated from adenosine triphosphate (ATP) consumed during the phosphorylation of phosphatidylinositol-4,5-bisphosphate (PIP2) (Promega, catalog # V1701) to yield phosphatidylinositol-3,4,5-trisphosphate (PIP3). ADP levels in the assay mixture at the end of the reaction were quantitated using ADP Glo (Promega, catalog # V9103) according to the manufacturer's recommended protocol. On the day of the assay, compounds were solubilized in DMSO and dispensed into a 384-well white Opti-plate (PerkinElmer, catalog # 6007290) to generate a 14 point 1:2 titration. Enzyme was prepared for each of the PI3K subunits in 100 mM HEPES, pH 7.4, 100 mM NaCl, 6 mM $MgCl_2$ and 0.05% BSA. p110α/p85α was prepared at 2 nM (2x), p110β/p85α was prepared at 7 nM (2x), p120γ was prepared at 8 nM (2x) and p110δ/p85α was prepared at 2 nM (2x). Five microliters of 2x enzyme dilution of each PI3K subunit were added to a 384-well white Opti-plate pre-dispensed with compound and allowed to incubate for 1 h at r.t. A substrate mix containing 0.1 mg/mL (2x) of PIP2 and 50 μM (2x) ATP (Promega, catalog # V915) was prepared in 25 mM HEPES and 0.5 mM EGTA. Reactions were initiated by addition of 5 μL of 2x substrate mix to each well of the plates containing the various PI3K isoforms and allowed to proceed for 60 min at r.t. Ten microliters of ADP Glo reagent 1 were added to the wells of each plate and allowed to incubate at r.t. for 45 min according to the manufacturer's directions. Following incubation, 20 μL of ADP Glo reagent 2 were added to each plate and allowed to incubate for an additional 45 min. Luminescent signal, generated by ADP Glo, was quantified by reading on a PerkinElmer Envision multimode reader. Compound potencies (IC_{50} values) were determined using a standard 4-parameter fit non-linear regression fit.

Comparison of in-house vs. literature PI3Kγ biochemical IC_{50} values:

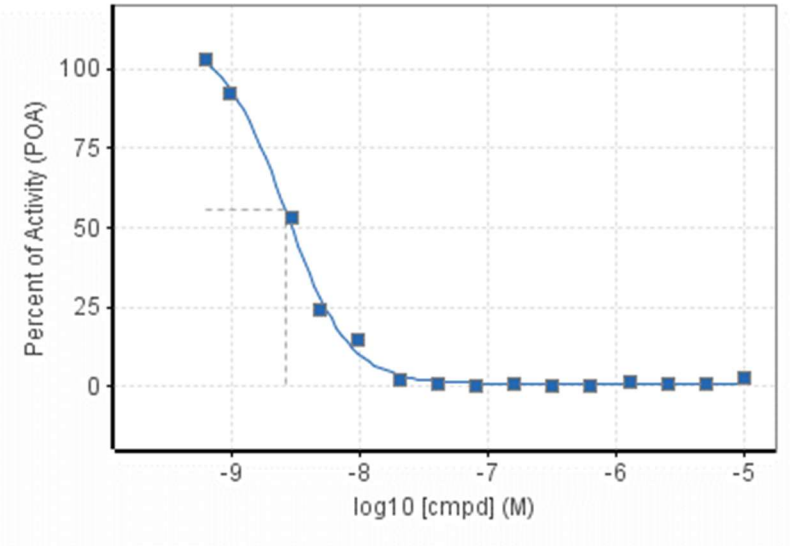
Compound	In-house	Literature	Differences of note from in-house assay
1	2 ± 1 nM	16 nM	[PI3Kγ] = 40 nM; [ATP] = 3 mM; [PIP2] = 500 µM
2	--	18 nM	[PI3Kγ] = 30 nM; [ATP] = 1 µM; [PIP2] = 10 µM
3	4 ± 1 nM	0.63 nM	[PI3Kγ] = 1.2 nM; [ATP] = 20 µM; [PIP2] = 80 µM

Representative Dose-Response Curves for Selected Compounds:

Inhibition of PI3Kγ by compound **28**:



Inhibition of PI3Kγ by compound **64**:



Determination of Cellular PI3Kγ Inhibition

The day prior to assay, THP-1 cells (ATCC, catalog # TIB-202) were seeded at a density of $1x10^6$ cells per mL in serum-free DMEM in a T175 flask (Thermo Fisher, catalog # 12-562-000) and incubated overnight at 5% CO_2 and 37 °C. On the day of experiment, a 14 point, 1:2 titration of test compound was pre-dispensed into 384-well Opti-plates (PerkinElmer, catalog # 6007290). Twenty microliters of serum-starved THP-1 cells were added to the compound plate in serum-free DMEM at a density of $9x10^6$ cells per mL. Final assay conditions comprised $1.8x10^5$ THP-1 cells per well with test compounds in 2% DMSO across a concentration range from 4 nM to 30 µM. Following a 60-minute incubation with test compound at 37 °C and 5% CO_2, THP-1 cells were stimulated with 25 nM rhMCP-1 (R&D Systems, catalog # 279-MC-010) for 2 min at 37 °C. PI3Kγ-stimulated phosphorylation of endogenous AKT Serine residue 473 in THP-1 cells was measured using an AlphaLISA SureFire Ultra AKT 1/2/3 (pS473) Assay Kit (PerkinElmer, catalog # ALSU-PAKT-B50K) according to the manufacturer's recommended protocol. Briefly, 10 µL of 4x lysis buffer were added to cells after stimulation. Following a 60-minute incubation at r.t., 10 µL of cell lysate were transferred to a fresh 384-well Opti-plate to which 5 µL of AlphaLisa acceptor beads and 5 µL of AlphaLisa donor beads had been added. After a further 120-minute incubation at r.t. in the dark, AlphaLisa signal was assessed using an Envision 2102 Multilabel Reader. PI3Kγ activity was evaluated as a correlate of endogenous AKT phosphorylation levels. Percentage maximum activity in each test well was calculated based on DMSO (100% activity) and positive control treated cell wells (0% activity). The potencies (IC_{50} values) of test compounds were determined using a standard 4-parameter fit non-linear regression fit.

Comparison of in-house vs. literature PI3Kγ cellular IC_{50} values:

Compound	In-house	Literature	Differences of note from in-house assay
1	20 ± 20 nM	1.2 nM	RAW 264.7 cells; stimulated with C5a
2	--	773 nM	RAW 264.7 cells; stimulated with C5a
3	90 ± 30 nM	6.3 nM	RAW264 cells; HTRF® detection of p-AKT; stimulated with C5a

ADME Experimentals

In Vitro CYP Inhibition Assay

Test compounds were evaluated *in vitro* for their potential to inhibit major human drug metabolizing enzymes of the cytochrome P450 family. The test compounds were incubated separately over a concentration range of 0−40 μM with 0.1 mg/mL human liver microsomal protein suspension in 0.1 M potassium phosphate buffer at pH 7.4, 1 mM NADPH, and a probe substrate (Phenacetin for CYP1A2, Diclofenac for CYP2C9, S-mephenytoin for CYP2C19, dextromethorphan for CYP2D6, and midazolam for CYP3A4). Each substrate was incubated at 37 °C for 5−20 min as defined by the previous assay validation. Samples for each substrate were collected and pooled with samples from other substrate incubations for determination of product formation by LC-MS/MS. IC_{50} values were calculated using a variable slope (4-parameter) model. Furafylline (1A2), sulfaphenazole (2C9), (+)-N-3-Benzylnirvanol (2C19), quinidine (2D6), and ketoconazole (3A4) were used as reference controls.

In Vitro Hepatocyte-Based Intrinsic Clearance Assay

A 50-donor pool of cryopreserved human hepatocytes was thawed in prewarmed 37 °C thawing medium (BioIVT), centrifuged, and resuspended in incubation medium (BioIVT). The number of viable cells was determined by the Trypan blue exclusion method. The cells were diluted to 2 million viable cells/mL (viability >80%) and seeded into round-bottom 96-well plates (50 μL/well). The test compounds were dissolved in DMSO and further diluted in 50% acetonitrile, with a final concentration of 0.01% DMSO and 0.1% acetonitrile. Incubation was performed at a final concentration of 1 million cells/mL and 0.5 μM test compound, with agitation at a frequency of 1100 rpm in a 37 °C, 5/95% CO_2/air incubator. At different time points, 100 μL samples were taken and mixed with 300 μL of ice-cold acetonitrile to stop the enzymatic reaction. After centrifugation at 4200 rpm, the supernatant was analyzed by LC-MS/MS.

In Vivo Rat Measurements

Pharmacokinetic properties in male SD rats (weight between 200 and 250 g) were determined following intravenous (IV) administration at a dose of 0.25 mg/kg. For IV dosing (n = 2 each group), rats were catheterized in jugular and femoral vein. Compounds were formulated in DMAC : EtOH : PG (31.6 : 36.8 : 31.6) for IV. Rats were not fasted during these studies. Blood was sampled at 0 (predose), 0.083, 0.25, 0.5, 1, 2, 4, 6 and 8 h following IV dosing. Plasma was isolated by centrifugation, and all samples were frozen at −80 °C. Calibration standards and QCs were prepared by the addition of known concentrations of compound to blank rat plasma to provide a calibration range of 0.5−5000 ng/mL. Then, 50 μL plasma samples or calibration standard was added to 150 μL of internal standard solution in acetonitrile. Samples were vortex mixed and centrifuged at 4200 rpm for 10 min at 4 °C. Supernatant (80 μL) was transferred to a 96 well injection plate containing 160 μL of water, mixed, and analyzed by LC-MS/MS. A bioanalytical method was developed for the quantification of compound in rat plasma. Method development and sample analysis was conducted using an API 6500 LC-MS/MS (Applied Biosystems, Foster City, CA) equipped with Shimadzu Nexera X2 UHPLC system (Shimadzu Scientific Instruments, Maryland, MD). One μL of the samples was analyzed using a C18 reversed-phase column (Phenomenex Kinetex C18, 1.7 μm, 2.1 mm × 50.0 mm) (Phenomenex, Torrance, CA) interfaced to a Turbo Spray ionization source. Mobile phase consisted of A: water with 0.1% formic acid and B: acetonitrile with 0.1% formic acid. The flow rate was 0.5 mL/min and the gradient was 30% A to 100% B over 1.5 min and then 100% B for 1 min. Multiple reaction monitoring (MRM) transition (478.0/346.0 for internal standard) in positive ion mode was used.

Tabulated Pharmacokinetic Data for Compounds Tested *In Vivo*:

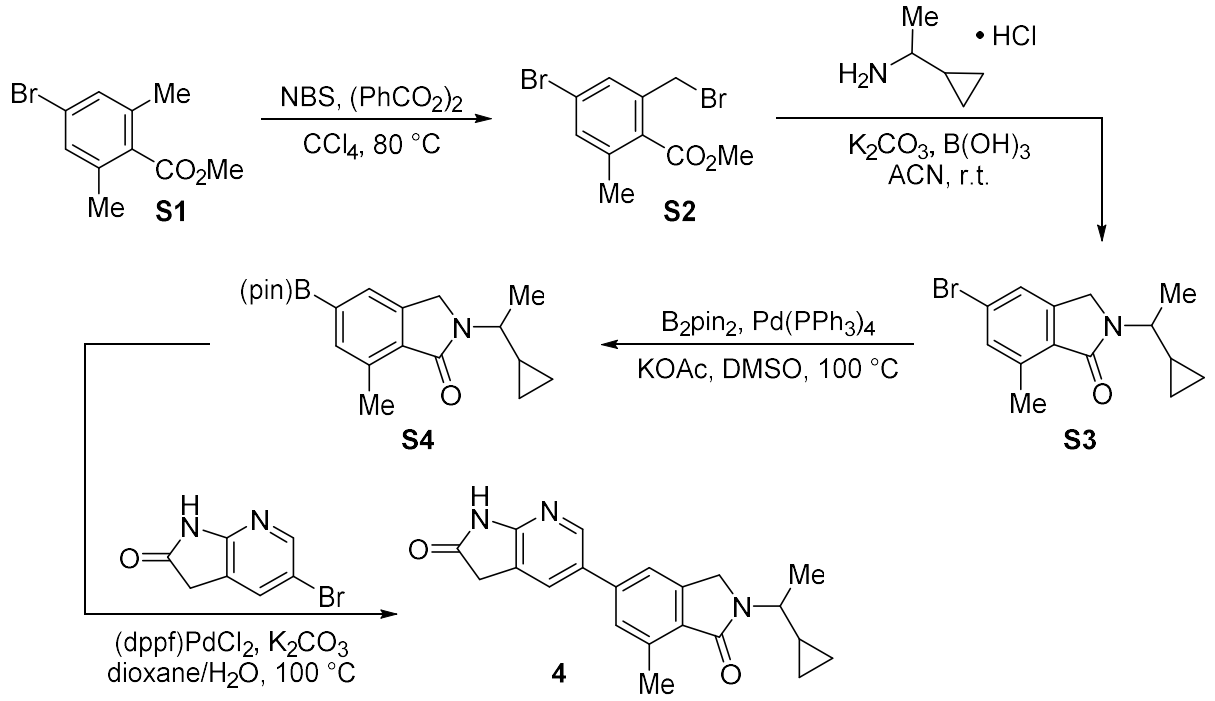
Cmpd.	$CL_{int, human}$ ($\mu L/min/10^6$ cells)	$CL_{int, rat}$ ($\mu L/min/10^6$ cells)	CL (L/hr/kg)	V_{ss} (L/kg)	Terminal $t_{1/2}$ (hr)	AUC_{INF} (hr*ng/mL)
20	60	7.1	2.7	6.6	2.4	95
25	24	54	11	3.0	0.4	23
29	< 1.2	2.0	6.9	3.1	0.5	36
55	9.4	23	6.0	6.2	1.0	107
58	2.3	4.7	4.5	4.3	1.1	56
60	1.8	< 1.2	28	21	0.8	14
62	8.0	23	1.8	0.3	1.0	142
64	1.7	16	1.8	1.0	2.2	137

Chemistry Experimentals

General Considerations

All reactions were performed using a Teflon-coated magnetic stir bar at the indicated temperature and were conducted under an inert atmosphere when stated. All chemicals were used as received. (*S*)-1-Cyclopropylethylamine was purchased from Sigma-Aldrich (catalog # 727245, ≥98.5% enantiomeric excess). (*R*)-1-Cyclopropylethylamine was purchased from Sigma-Aldrich (catalog # 727261, ≥98.5% enantiomeric excess). (*S*)-1-(4-Fluorophenyl)ethanamine was purchased from Alfa Aesar (catalog # AAL1912103, 99% enantiomeric excess). (2*S*)-1-Methoxy-2-propanamine was purchased from Alfa Aesar (catalog # AAL1632503, ≥96% enantiomeric excess). (1*S*)-1-cyclopropylpropan-1-amine was purchased from AP Bioscience (catalog # 7169515, 97% purity). Reactions were monitored by TLC (silica gel 60 with fluorescence F254, visualized with a short wave/long wave UV lamp) and/or LCMS (Agilent 1100 series LCMS with UV detection at 254 nm using a binary solvent system [0.1% TFA in MeCN/0.1% TFA in H_2O] using either of the following columns: Agilent Eclipse Plus C18 [3.5 µm, 4.6 mm i.d. x 100 mm] or Aeris Widepore C4 [3.6 µm, 2.1 mm i.d. x 50 mm]). Flash chromatography was conducted on silica gel using an automated system (CombiFlash RF+ manufactured by Teledyne ISCO), with detection wavelengths of 254 and 280 nm. Reverse phase preparative HPLC was conducted on an Agilent 1260 Infinity series HPLC. Samples were eluted using a binary solvent system (0.1% TFA in MeCN/0.1% TFA in H_2O) with gradient elution on a Gemini C18 110 Å column (21.2 mm i.d. x 250 mm) with detection at 254 nm. Final compounds obtained through preparative HPLC were concentrated through lyophilization. All reported yields are isolated yields. All assayed compounds were purified to ≥95% purity as determined by LCMS (Agilent 1100 series LCMS with UV detection at 254 nm using a binary solvent system [0.1% TFA in MeCN/0.1% TFA in H_2O] using either of the following columns: Agilent Eclipse Plus C18 column [3.5 µm, 4.6 mm i.d. x 100 mm] or Aeris Widepore C4 column [3.6 µm, 2.1 mm i.d. x 50 mm]). ^{1}H and ^{13}C NMR spectra were recorded on a Varian 400 MHz NMR spectrometer equipped with an Oxford AS400 magnet. Chemical shifts (δ) are reported as parts per million (ppm) relative to residual undeuterated solvent as an internal reference. The abbreviations s, br. s, d, t, q, dd, dt, ddd, and m stand for singlet, broad singlet, doublet, triplet, quartet, doublet of doublets, doublet of triplets, doublet of doublet of doublets, and multiplet, respectively. Room temperature (r.t.) is defined as 23 °C.

2-(1-Cyclopropylethyl)-7-methyl-5-{2-oxo-1*H*,2*H*,3*H*-pyrrolo[2,3-*b*]pyridin-5-yl}-2,3-dihydro-1*H*-isoindol-1-one (**4**)



To a solution of methyl 4-bromo-2,6-dimethylbenzoate (**S1**) (20.0 g, 82.3 mmol) in CCl_4 (330 mL) was added NBS (16.8 mg, 94.6 mmol) followed by benzoyl peroxide (1.99 g, 8.23 mmol). The mixture was heated to 80 °C overnight. After cooling to r.t., the reaction was filtered and the filter cake was washed with CCl_4. The filtrate was concentrated under reduced pressure to provide **S2** which was used directly in the next step without further purification.

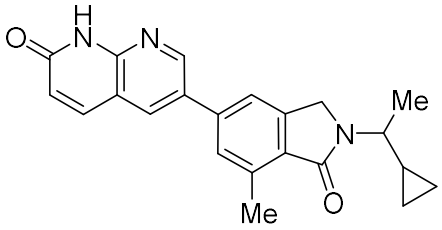
A suspension of crude **S2** (79 mmol), 1-cyclopropylethanamine hydrochloride (24.2 g, 199 mmol), potassium carbonate (38.2 g, 277 mmol), and boric acid (976 mg, 15.8 mmol) in acetonitrile (316 mL) was heated to 80°C overnight. After cooling to r.t., the reaction was diluted with EtOAc and washed with water, 10% citric acid, saturated $NaHCO_3$, and brine. The organics were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography (SiO_2, 10-40% EA/Hex) afforded **S3** as an off-white solid (15.6 g, 67%). ESI MS $[M+H]^+$ for $C_{14}H_{16}BrNO$, calcd. 294.0, found 294.0.

A flask charged with **S3** (6.4 g, 22 mmol), bis(pinacolato)diboron (8.30 g, 32.7 mmol), potassium acetate (8.99 g, 91.6 mmol) and $Pd(PPh_3)_4$ (1.76 g, 1.53 mmol) was evacuated and backfilled with nitrogen (2x) then degassed DMSO (109 mL) was added and the mixture was heated to 100 °C for

4 hours. After cooling to r.t., the reaction was diluted with EtOAc and washed with water (3x) and brine. The organics were dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by column chromatography (SiO_2, 0 → 30% EtOAc/hexanes) to afford **S4** as an off-white solid (5.4 g, 72% yield).

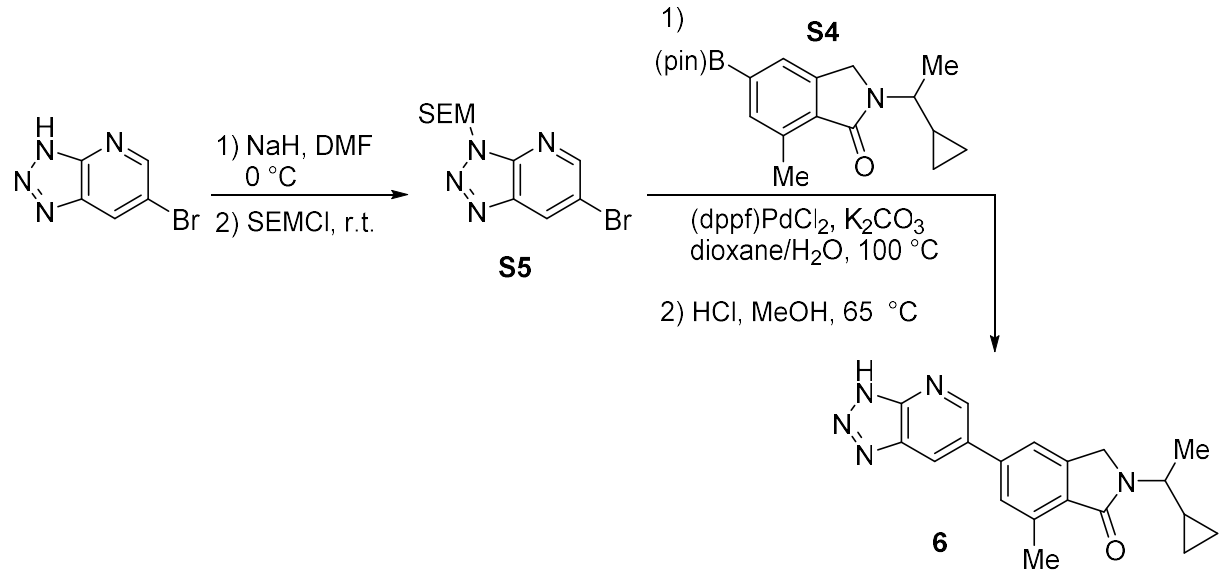
To a mixture of **S4** (171 mg, 0.442 mmol), 5-bromo-1,3-dihydropyrrolo[2,3-*b*]pyridin-2-one (107 mg, 0.502 mmol), (dppf)$PdCl_2$ (18 mg, 0.025 mmol), and K_2CO_3 (138 mg, 1.00 mmol) under nitrogen was added degassed dioxane (2.0 mL) and degassed H_2O (0.5 mL). The reaction mixture was stirred at reflux for 14 h, cooled, and diluted with brine (20 mL). The solids were collected by filtration, washed with water, dried and purified by column chromatography (hexanes/EtOAc), 0-70% gradient (30 min) to afford **4** as an off-white solid (35 mg, 20%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.87 (s, 1H), 8.42 – 8.37 (m, 1H), 7.77 – 7.70 (m, 1H), 7.41 (dd, *J* = 1.6, 0.8 Hz, 1H), 7.33 (m, 1H), 4.61 – 4.35 (m, 2H), 3.77 (dq, *J* = 9.4, 6.8 Hz, 1H), 3.68 – 3.65 (m, 2H), 2.79 (s, 3H), 1.35 (d, *J* = 6.8 Hz, 3H), 1.09 – 0.96 (m, 1H), 0.70 – 0.58 (m, 1H), 0.51 – 0.31 (m, 3H). ESI MS $[M+H]^+$ for $C_{21}H_{22}N_3O_2$, calcd. 348.2, found 348.2.

6-[2-(1-Cyclopropylethyl)-7-methyl-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl]-1,2-dihydro-1,8-naphthyridin-2-one (**5**)



5 was prepared in a similar manner to **4**. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 11.15 (br. s, 1H), 8.91 (d, *J* = 2.3 Hz, 1H), 8.12 (d, *J* = 2.3 Hz, 1H), 7.81 (d, *J* = 9.6 Hz, 1H), 7.54 – 7.48 (m, 1H), 7.46 – 7.40 (m, 1H), 6.81 (d, *J* = 9.5 Hz, 1H), 4.66 – 4.38 (m, 2H), 3.85 – 3.68 (m, 1H), 2.82 (s, 3H), 1.37 (d, *J* = 6.8 Hz, 3H), 1.11 – 0.98 (m, 1H), 0.70 – 0.61 (m, 1H), 0.54 – 0.31 (m, 3H). ESI MS $[M+H]^+$ for $C_{22}H_{22}N_3O_2$, calcd. 360.2, found 360.2.

2-(1-Cyclopropylethyl)-7-methyl-5-{3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-6-yl}-2,3-dihydro-1*H*-isoindol-1-one (**6**)

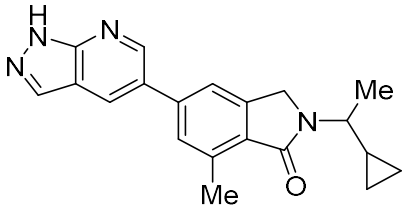


To a mixture of 6-bromo-1*H*-1,2,3-triazolo[4,5-*b*]pyridine (604 mg, 3.04 mmol) and DMF (7.6 mL) at 0 °C was added NaH (243 mg, 6.07 mmol, 60% wt. in oil). The reaction mixture was stirred at 0 °C for 10 min and SEMCl (913 µL, 5.16 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 10 min, stirred at r.t. for 1 h, and quenched with water. The mixture was diluted with EtOAc (100 mL), washed with brine (4 x 100 mL), dried over Na_2SO_4, and concentrated. The crude material was purified by column chromatography (hexanes/EtOAc), 0-30% gradient (30 min) to afford **S5** as a colorless oil (610 mg, 61%, presumed mixture of N1 and N3 isomers).

To a mixture of **S5** (610 mg, 1.85 mmol), **S4** (632 mg, 1.85 mmol), (dppf)$PdCl_2$ (68 mg, 0.093 mmol), and K_2CO_3 (512 mg, 3.70 mmol) under nitrogen was added degassed 4:1 dioxane/H_2O (9.3 mL). The reaction mixture was stirred at 100 °C for 2 h, cooled, diluted with H_2O (10 mL), and extracted with EtOAc (2 x 20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated. The crude material was purified by column chromatography (hexanes/EtOAc), 0-50% gradient (30 min) to afford the intermediate as a light orange oil (843 mg). 3 M HCl in MeOH (3.7 mL) was added. The reaction mixture was stirred at 65 °C for 30 min, cooled, diluted with H_2O (20 mL), neutralized with sat. $NaHCO_{3(aq)}$, and extracted with 4:1 CH_2Cl_2/IPA (2 x 100 mL). The combined organic phases were dried over Na_2SO_4 and concentrated. A portion of the crude material (250 mg) was recrystallized from hot EtOH (6.2 mL) to afford **6** as a white solid (112 mg,

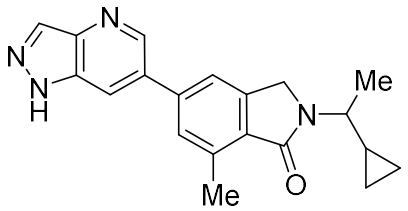
18%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.08 (d, J = 2.1 Hz, 1H), 8.72 (br. s, 1H), 7.86 (s, 1H), 7.73 (s, 1H), 4.56 (s, 2H), 3.65 – 3.53 (m, 1H), 2.71 (s, 3H), 1.30 (d, J = 6.8 Hz, 3H), 1.21 – 1.10 (m, 1H), 0.64 – 0.54 (m, 1H), 0.47 – 0.35 (m, 2H), 0.29 – 0.20 (m, 1H) [exchangeable triazole NH proton not observed]. ESI MS $[M+H]^+$ for $C_{19}H_{20}N_5O$, calcd. 334.2, found 334.2.

2-(1-Cyclopropylethyl)-7-methyl-5-{1*H*-pyrazolo[3,4-*b*]pyridin-5-yl}-2,3-dihydro-1*H*-isoindol-1-one ((±)-**7**)



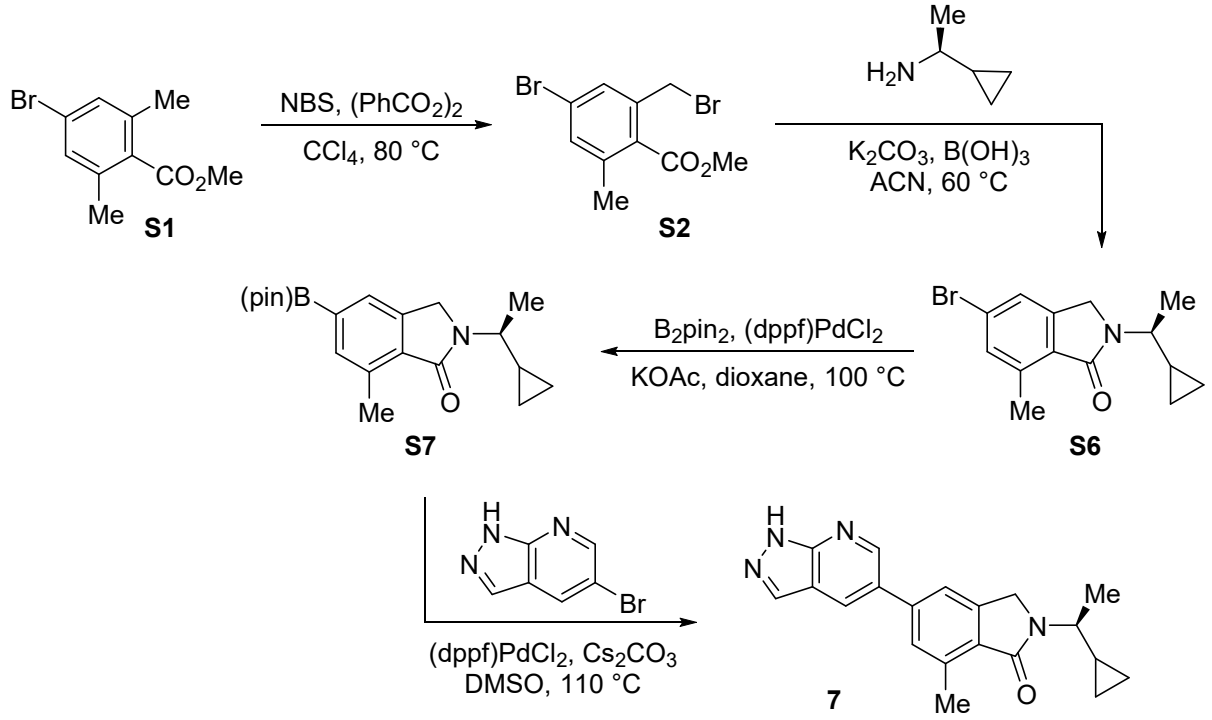
7 was prepared in a similar manner to **6**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.79 (br. s, 1H), 8.89 (d, J = 2.2 Hz, 1H), 8.55 (d, J = 2.2 Hz, 1H), 8.23 (s, 1H), 7.77 (s, 1H), 7.63 (s, 1H), 4.55 (s, 2H), 3.64 – 3.53 (m, 1H), 2.69 (s, 3H), 1.29 (d, J = 6.8 Hz, 3H), 1.20 – 1.10 (m, 1H), 0.62 – 0.54 (m, 1H), 0.46 – 0.34 (m, 2H), 0.27 – 0.21 (m, 1H). ESI MS $[M+H]^+$ for $C_{20}H_{21}N_4O$, calcd. 333.2, found 333.2.

2-(1-Cyclopropylethyl)-7-methyl-5-{1*H*-pyrazolo[4,3-*b*]pyridin-6-yl}-2,3-dihydro-1*H*-isoindol-1-one (**8**)



8 was prepared in a similar manner to **6**. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 11.15 (br. s, 1H), 8.86 (d, J = 1.9 Hz, 1H), 8.37 (d, J = 1.0 Hz, 1H), 8.01 (dd, J = 1.9, 1.1 Hz, 1H), 7.54 – 7.51 (m, 1H), 7.49 – 7.40 (m, 1H), 4.66 – 4.42 (m, 2H), 3.79 (dq, J = 9.5, 6.8 Hz, 1H), 2.82 (s, 3H), 1.36 (d, J = 6.8 Hz, 3H), 1.09 – 0.97 (m, 1H), 0.71 – 0.59 (m, 1H), 0.52 – 0.30 (m, 3H). ESI MS $[M+H]^+$ for $C_{20}H_{21}N_4O$, calcd. 333.2, found 333.2.

2-[(1*S*)-1-Cyclopropylethyl]-7-methyl-5-{1*H*-pyrazolo[3,4-*b*]pyridin-5-yl}-2,3-dihydro-1*H*-isoindol-1-one (**7**)



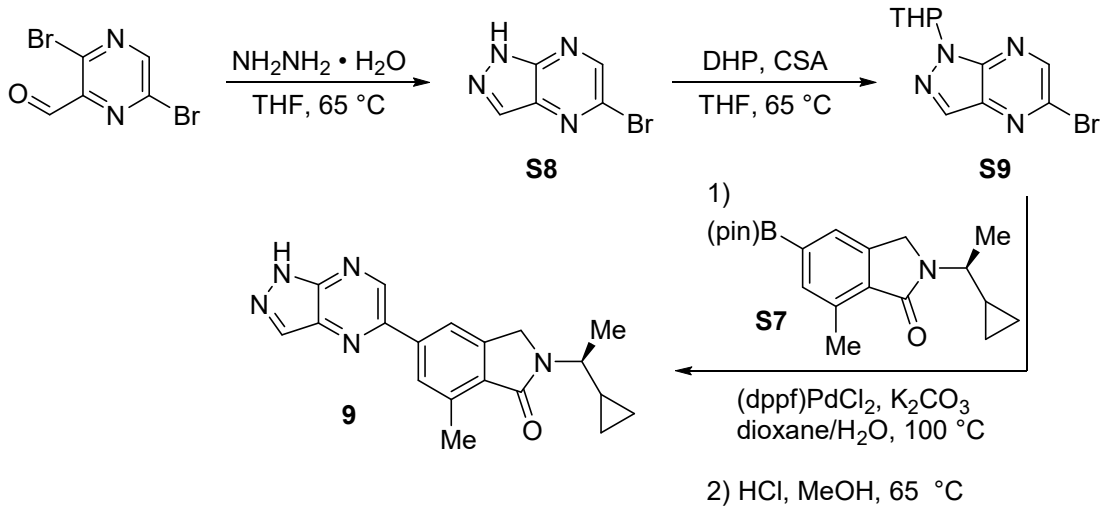
A mixture of methyl 4-bromo-2,6-dimethylbenzoate (**S1**) (24.7 g, 102 mmol), *N*-bromosuccinimide (20.8 g, 117 mmol), benzoyl peroxide (3.28 g, 10.2 mmol, 75% wt. in H_2O), and CCl_4 (400 mL) was stirred at 80 °C for 20 h. The reaction mixture was cooled, filtered to remove solids, and concentrated *in vacuo* to afford crude **S2** (102 mmol) which was used directly in the next step.

To a mixture of crude **S2** and ACN (400 mL) at r.t. was added (*S*)-1-cyclopropylethylamine (13.0 g, 153 mmol) [≥98.5% enantiomeric excess], $B(OH)_3$ (6.30 g, 102 mmol), and K_2CO_3 (42.3 g, 306 mmol), The reaction mixture was stirred at 60 °C for 2 h, cooled, filtered to remove solids, and concentrated. The crude material was purified by column chromatography (SiO_2, 0 to 20% EtOAc in hexanes) to afford **S6** as an off-white solid (15.8 g, 53%).

To a mixture of **S6** (1.00 g, 3.40 mmol), B_2pin_2 (863 mg, 3.40 mmol), $(dppf)PdCl_2$ (124 mg, 0.170 mmol), and KOAc (667 mg, 6.80 mmol) under nitrogen was added degassed dioxane (17 mL). The reaction mixture was stirred at 100 °C for 4 h, cooled, and concentrated. The crude material was purified by column chromatography (hexanes/EtOAc), 0-30% gradient (20 min) to afford **S7** as an off-white solid (1.09 g, 94%).

To a mixture of **S7** (256 mg, 0.750 mmol), 5-bromo-1*H*-pyrazolo[3,4-*b*]pyridine (149 mg, 0.750 mmol), (dppf)$PdCl_2$ (27 mg, 0.038 mmol), and Cs_2CO_3 (489 mg, 1.50 mmol) under nitrogen was added degassed DMSO (2.5 mL). The reaction mixture was stirred at 110 °C for 14 h, cooled, and diluted with water (20 mL). The solids were collected by filtration, agitated with EtOAc (20 mL), and filtered. The filtrate was passed through a short plug of silica and concentrated. The crude material was purified by reversed-phase HPLC (H_2O/ACN+0.1%TFA), 5-95% gradient (45 min) to afford (*S*)-**7** as a white solid (5 mg, 1%, TFA salt). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.78 (br. s, 1H), 8.89 (d, *J* = 2.2 Hz, 1H), 8.55 (dd, *J* = 2.2, 0.6 Hz, 1H), 8.23 (d, *J* = 1.4 Hz, 1H), 7.77 (s, 1H), 7.63 (s, 1H), 4.55 (s, 2H), 3.64 – 3.54 (m, 1H), 2.69 (s, 3H), 1.29 (d, *J* = 6.8 Hz, 3H), 1.20 – 1.09 (m, 1H), 0.62 – 0.53 (m, 1H), 0.46 – 0.35 (m, 2H), 0.28 – 0.21 (m, 1H). ESI MS $[M+H]^+$ for $C_{20}H_{21}N_4O$, calcd. 333.2, found 333.2.

2-[(1*S*)-1-Cyclopropylethyl]-7-methyl-5-{1*H*-pyrazolo[3,4-*b*]pyrazin-5-yl}-2,3-dihydro-1*H*-isoindol-1-one (**9**)

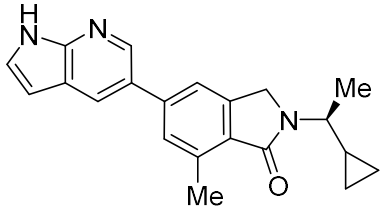


To a mixture of 3,6-dibromo-2-pyrazinecarboxaldehyde (1.14 g, 4.29 mmol) and THF (107 mL) at r.t. was added hydrazine monohydrate (2.08 mL, 42.9 mmol). The reaction mixture was stirred at r.t. for 2 h, stirred at 65 °C for 6 h, cooled, concentrated, and triturated with H_2O (100 mL). The solids were collected by filtration, washing with H_2O, and dried. The crude material was purified by column chromatography (CH_2Cl_2/EtOAc), 0-50% gradient (25 min) to afford **S8** as a white solid (440 mg, 51%).

A mixture of **S8** (199 mg, 1.00 mmol), 3,4-dihydro-2*H*-pyran (424 µL, 5.00 mmol), camphorsulfonic acid (46 mg, 0.20 mmol), and THF (2 mL) was stirred at 65 °C for 1 h, cooled, neutralized with sat. $NaHCO_{3(aq)}$ (3 mL), and extracted with EtOAc (2 x 3 mL). The combined organic phases were dried over Na_2SO_4 and concentrated. The crude material was purified by column chromatography (hexanes/EtOAc), 0-25% gradient (20 min) to afford **S9** as a light-yellow oil (295 mg, >100%).

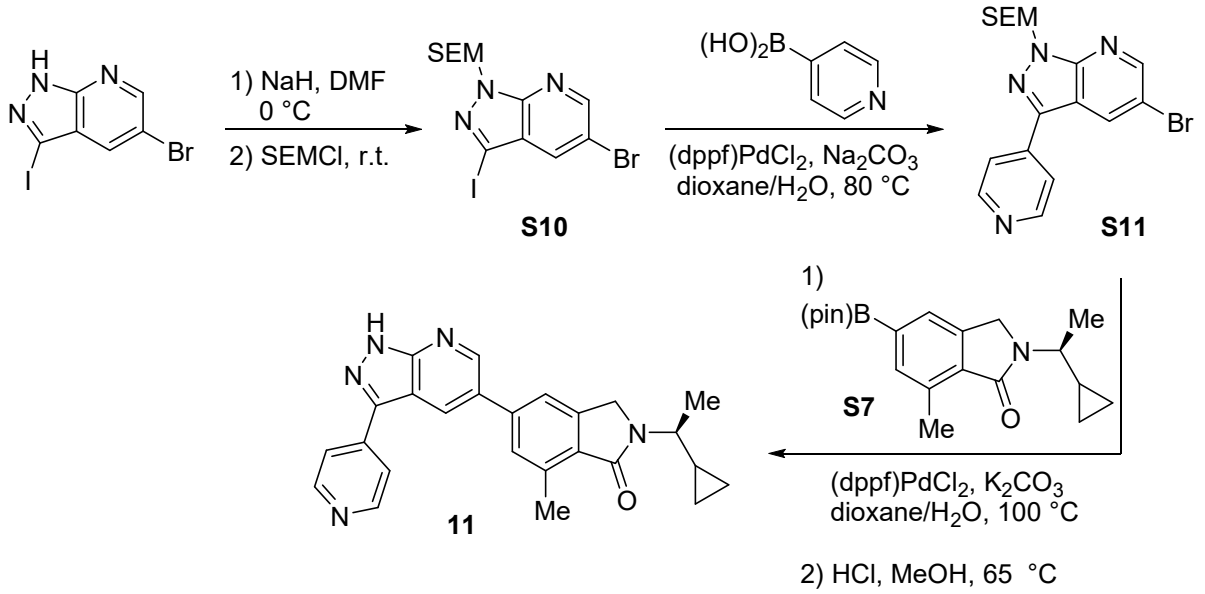
To a mixture of **S9** (283 mg, 1.00 mmol), **S7** (341 mg, 1.00 mmol), (dppf)$PdCl_2$ (37 mg, 0.050 mmol), and K_2CO_3 (276 mg, 2.00 mmol) under nitrogen was added degassed 4:1 dioxane/H_2O (5.0 mL). The reaction mixture was stirred at 100 °C for 2 h, cooled, diluted with H_2O (5.0 mL), and extracted with EtOAc (2 x 20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated. The crude material was purified by column chromatography (hexanes/EtOAc), 0-100% gradient (30 min) to afford the intermediate. 3 M HCl in MeOH (4.0 mL) was added. The reaction mixture was stirred at 60 °C for 1.5 h, cooled, and diluted with MTBE (20 mL). The solids were collected by filtration, washing with MTBE, and dried to afford **9** as a white solid (172 mg, 47%, HCl salt). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.28 (s, 1H), 8.53 (s, 1H), 8.20 (s, 1H), 8.07 (s, 1H), 4.58 (s, 2H), 3.65 – 3.54 (m, 1H), 2.72 (s, 3H), 1.30 (d, J = 6.8 Hz, 3H), 1.21 – 1.09 (m, 1H), 0.62 – 0.54 (m, 1H), 0.47 – 0.35 (m, 2H), 0.29 – 0.22 (m, 1H) [exchangeable indazole NH proton not observed]. ESI MS $[M+H]^+$ for $C_{19}H_{20}N_5O$, calcd. 334.2, found 334.2.

2-[(*1S*)-1-Cyclopropylethyl]-7-methyl-5-{1*H*-pyrrolo[2,3-*b*]pyridin-5-yl}-2,3-dihydro-1*H*-isoindol-1-one (**10**)



10 was prepared in a similar manner to **6**. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.11 (br. s, 1H), 8.57 (dd, J = 2.2, 0.4 Hz, 1H), 8.16 (dd, J = 2.1, 0.8 Hz, 1H), 7.57 – 7.48 (m, 1H), 7.47 – 7.43 (m, 1H), 7.43 – 7.33 (m, 1H), 6.59 (dd, J = 3.6, 2.0 Hz, 1H), 4.66 – 4.36 (m, 2H), 3.78 (dq, J = 9.5, 6.9 Hz, 1H), 2.81 (s, 3H), 1.36 (d, J = 6.8 Hz, 3H), 1.12 – 0.98 (m, 1H), 0.70 – 0.59 (m, 1H), 0.52 – 0.30 (m, 3H). ESI MS $[M+H]^+$ for $C_{21}H_{22}N_3O$, calcd. 332.2, found 332.2.

2-[(1*S*)-1-Cyclopropylethyl]-7-methyl-5-[3-(pyridin-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]-2,3-dihydro-1*H*-isoindol-1-one (**11**)



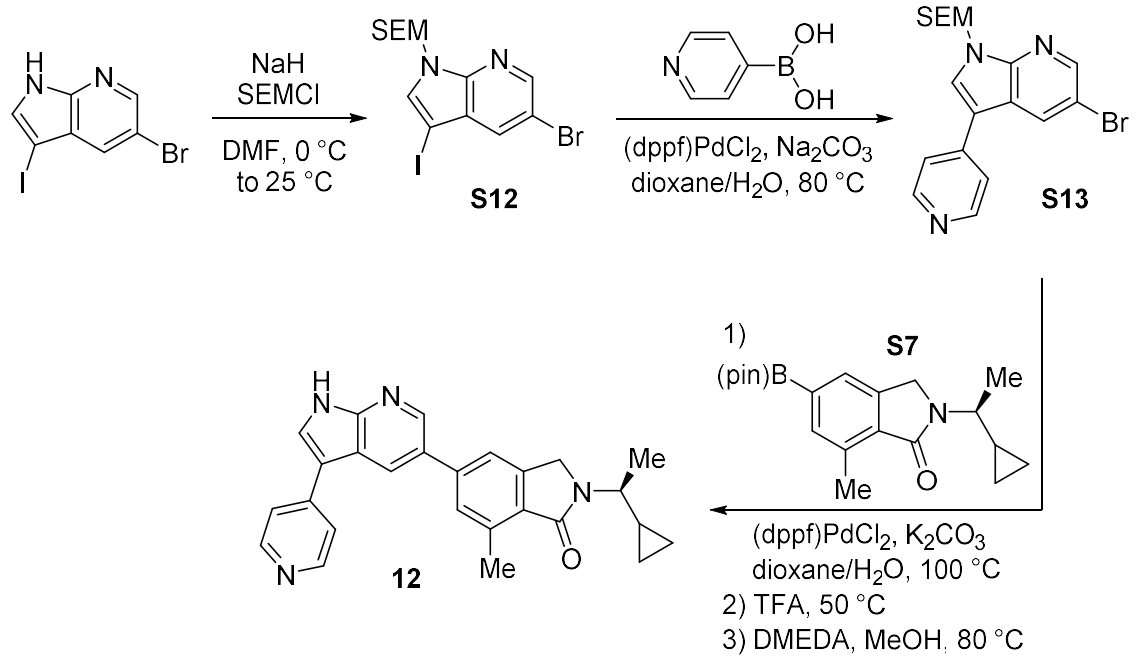
To a mixture of 5-bromo-3-iodo-1*H*-pyrazolo[3,4-*b*]pyridine (5.01 g, 15.5 mmol) and DMF (39 mL) at 0 °C was added NaH (1.24 mg, 30.9 mmol, 60% wt. in oil) portionwise. The reaction mixture was stirred at 0 °C for 10 min and SEMCl (4.65 mL, 26.3 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 10 min, stirred at r.t. for 1 h, and quenched with water. The mixture was diluted with EtOAc (250 mL), washed with brine (4 x 200 mL), dried over Na_2SO_4, and concentrated. The crude material was purified by column chromatography (hexanes/EtOAc), 0-20% gradient (30 min) to afford **S10** as a colorless oil (4.82 g, 68%).

To a mixture of **S10** (908 mg, 2.00 mmol), 4-pyridinylboronic acid (246 mg, 2.00 mmol), (dppf)$PdCl_2$ (73 mg, 0.10 mmol), and Na_2CO_3 (424 mg, 4.00 mmol) under nitrogen was added degassed 4:1 dioxane/H_2O (10 mL). The reaction mixture was stirred at 80 °C for 2 h, cooled, diluted with H_2O (10 mL), and extracted with EtOAc (2 x 20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated. The crude material was purified by column chromatography (hexanes/EtOAc), 0-50% gradient (30 min) to afford **S11** as an off-white solid (464 mg, 57%).

To a mixture of **S11** (203 mg, 0.500 mmol), **S7** (171 mg, 0.500 mmol), (dppf)$PdCl_2$ (18 mg, 0.025 mmol), and K_2CO_3 (138 mg, 1.00 mmol) under nitrogen was added degassed 4:1 dioxane/H_2O (2.5 mL). The reaction mixture was stirred at 100 °C for 1 h, cooled, diluted with H_2O (10 mL),

and extracted with EtOAc (2 x 20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated. The crude material was purified by column chromatography (hexanes/EtOAc), 0-100% gradient (30 min) to afford the intermediate as a white solid (234 mg). 3 M HCl in MeOH (2.5 mL) was added. The reaction mixture was stirred at 65 °C for 18 h, cooled, diluted with H_2O (10 mL), neutralized with sat. $NaHCO_{3(aq)}$ (20 mL), and extracted with CH_2Cl_2 (2 x 100 mL). The combined organic phases were dried over Na_2SO_4 and concentrated. The crude material was purified by column chromatography (hexanes/EtOAc), 50-100% gradient (30 min) to afford **11** as a white solid (23 mg, 11%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.98 (d, J = 2.1 Hz, 1H), 8.91 (d, J = 2.1 Hz, 1H), 8.74 (d, J = 6.1 Hz, 2H), 8.14 (d, J = 6.2 Hz, 2H), 7.90 (s, 1H), 7.76 (s, 1H), 4.57 (s, 2H), 3.66 – 3.54 (m, 1H), 2.72 (s, 3H), 1.30 (d, J = 6.8 Hz, 3H), 1.20 – 1.11 (m, 1H), 0.63 – 0.54 (m, 1H), 0.46 – 0.36 (m, 2H), 0.29 – 0.21 (m, 1H) [exchangeable indazole NH proton not observed]. ESI MS $[M+H]^+$ for $C_{25}H_{24}N_5O$, calcd. 410.2, found 410.2.

2-[(*1S*)-1-Cyclopropylethyl]-7-methyl-5-[3-(pyridin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl]-2,3-dihydro-1*H*-isoindol-1-one (**12**)



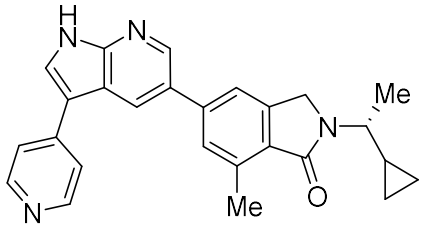
NaH (500 mg, 12.4 mmol, 2.0 equiv, 60% dispersion in mineral oil) was added to a suspension of 5-bromo-3-iodo-1*H*-pyrrolo[2,3-*b*]pyridine (2.00 g, 6.19 mmol, 1.0 equiv) in dry DMF (16.0 mL) at 0 °C. The reaction mixture was stirred 10 min. at 0 °C, then SEMCl (1.86 mL, 10.5 mmol, 1.69

equiv) was added dropwise. The reaction mixture was allowed to warm to 25 °C and then stirred at 25 °C for 1 h. Upon complete conversion, as judged by TLC analysis, the reaction mixture was cooled to 0 °C, diluted with EtOAc, and quenched by dropwise addition of water. The aqueous phase was separated and extracted with EtOAc (3x). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. The crude product was purified by flash column chromatography (SiO_2, 30:1 hexanes/EtOAc) to afford **S12** as an off-white oil (1.81 g, 64% yield).

A degassed mixture of **S12** (307 mg, 0.677 mmol, 1.0 equiv), pyridine-4-boronic acid (81.5 mg, 0.663 mmol, 0.98 equiv), (dppf)$PdCl_2$ (49.5 mg, 0.068 mmol, 10 mol %), 2 M aqueous Na_2CO_3 (0.68 mL, 1.4 mmol, 2.0 equiv), and dioxane (3.8 mL) was stirred at 80 °C under a nitrogen atmosphere for 3 h. After cooling to 25 °C, the reaction mixture was diluted with EtOAc, filtered over Celite, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, CH_2Cl_2/EtOAc gradient) to afford **S13** as a colorless oil (77.2 mg, 29% yield).

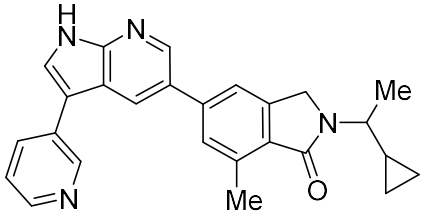
A degassed mixture of **S13** (77.2 mg, 0.191 mmol, 1.0 equiv), **S7** (65.0 mg, 0.191 mmol, 1.0 equiv), (dppf)$PdCl_2$ (14 mg, 0.019 mmol, 10 mol %), 2 M aqueous K_2CO_3 (0.24 mL, 0.48 mmol, 2.5 equiv), and dioxane (2.4 mL) was stirred at 100 °C under a nitrogen atmosphere for 12 h. After cooling to 25 °C, the reaction mixture was diluted with EtOAc, filtered over Celite, and concentrated under reduced pressure. The resulting residue was treated with 9:1 TFA/H_2O (1 mL), stirred at 50 °C for 2 h, then concentrated under reduced pressure. The resulting oil was dissolved in MeOH (3 mL), treated with DMEDA (0.2 mL, 1.9 mmol, 10 equiv), and stirred at 80 °C for 1 h. Upon complete SEM deprotection, as judged by LCMS analysis, the reaction mixture was concentrated *in vacuo*. The crude material was purified by flash column chromatography (SiO_2, 0 to 5% gradient of MeOH/CH_2Cl_2) to afford **12** (25 mg, 32% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.36 (br. s, 1H), 8.64 (d, J = 2.1 Hz, 1H), 8.61 (d, J = 2.1 Hz, 1H), 8.56 (d, J = 1.6 Hz, 1H), 8.55 (d, J = 1.7 Hz, 1H), 8.27 (s, 1H), 7.84 (d, J = 1.6 Hz, 1H), 7.83 (d, J = 1.7 Hz, 1H), 7.81 (s, 1H), 7.67 (s, 1H), 4.54 (s, 2H), 3.65 – 3.50 (m, 1H), 2.69 (s, 3H), 1.27 (d, J = 6.9 Hz, 3H), 1.19 – 1.07 (m, 1H), 0.62 – 0.52 (m, 1H), 0.45 – 0.32 (m, 2H), 0.27 – 0.18 (m, 1H). ESI MS $[M+H]^+$ for $C_{26}H_{25}N_4O$, calcd. 409.2, found 409.2.

2-[(*1R*)-1-Cyclopropylethyl]-7-methyl-5-[3-(pyridin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl]-2,3-dihydro-1*H*-isoindol-1-one ((*R*)-**12**)



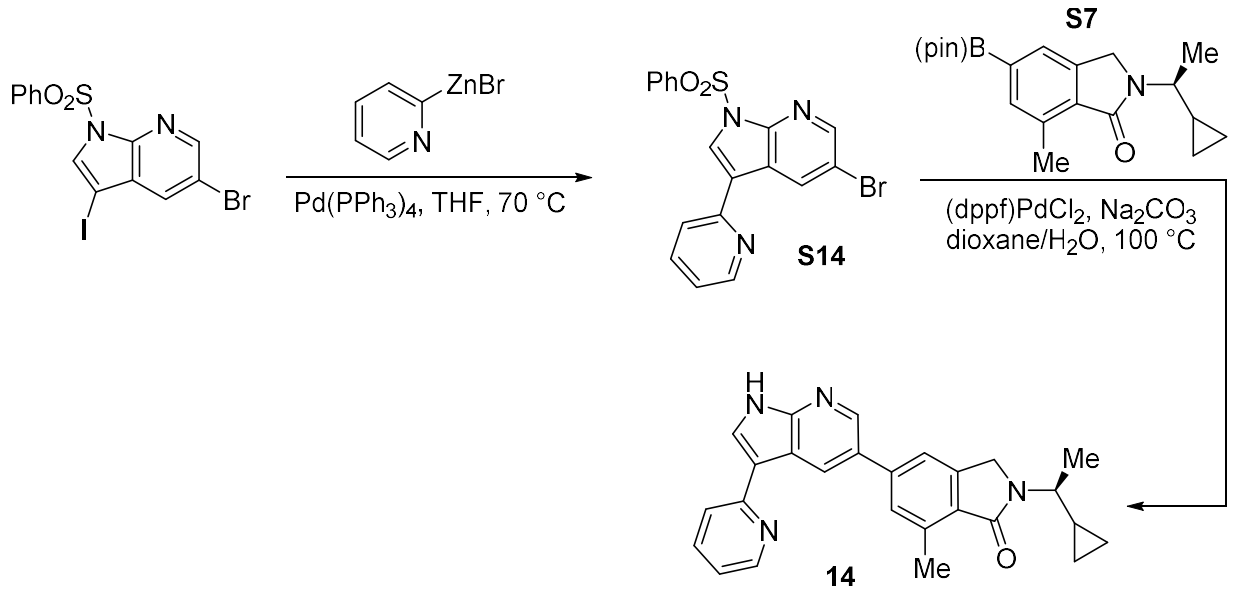
(*R*)-**12** was prepared in a similar manner to **12** using the enantiomer of **S7**, prepared from (*R*)-1-cyclopropylethylamine (≥98.5% enantiomeric excess). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.35 (br. s, 1H), 8.65 – 8.59 (m, 2H), 8.58 – 8.53 (m, 2H), 8.26 (s, 1H), 7.85 – 7.82 (m, 2H), 7.82 – 7.80 (m, 1H), 7.67 – 7.64 (m, 1H), 4.53 (s, 2H), 3.63 – 3.49 (m, 1H), 2.68 (s, 3H), 1.27 (d, *J* = 6.8 Hz, 3H), 1.19 – 1.03 (m, 1H), 0.61 – 0.49 (m, 1H), 0.46 – 0.30 (m, 2H), 0.27 – 0.12 (m, 1H). ESI MS $[M+H]^+$ for $C_{26}H_{25}N_4O$, calcd. 409.2, found 409.2.

2-(1-Cyclopropylethyl)-7-methyl-5-[3-(pyridin-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl]-2,3-dihydro-1*H*-isoindol-1-one (**13**)



13 was prepared in a similar manner to **12** using 3-pyridylboronic acid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.54 (br. s, 1H), 9.00 (dd, *J* = 2.3, 0.9 Hz, 1H), 8.66 (d, *J* = 2.1 Hz, 1H), 8.59 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.39 (d, *J* = 2.1 Hz, 1H), 7.97 (ddd, *J* = 7.9, 2.3, 1.6 Hz, 1H), 7.64 (d, *J* = 2.5 Hz, 1H), 7.53 (s, 1H), 7.46 (s, 1H), 7.43 (ddd, *J* = 7.8, 4.8, 0.9 Hz, 1H), 4.68 – 4.38 (m, 2H), 3.84 – 3.70 (m, 1H), 2.82 (s, 3H), 1.37 (d, *J* = 6.8 Hz, 3H), 1.11 – 0.98 (m, 1H), 0.71 – 0.59 (m, 1H), 0.53 – 0.33 (m, 3H). ESI MS $[M+H]^+$ for $C_{26}H_{25}N_4O$, calcd. 409.2, found 409.2.

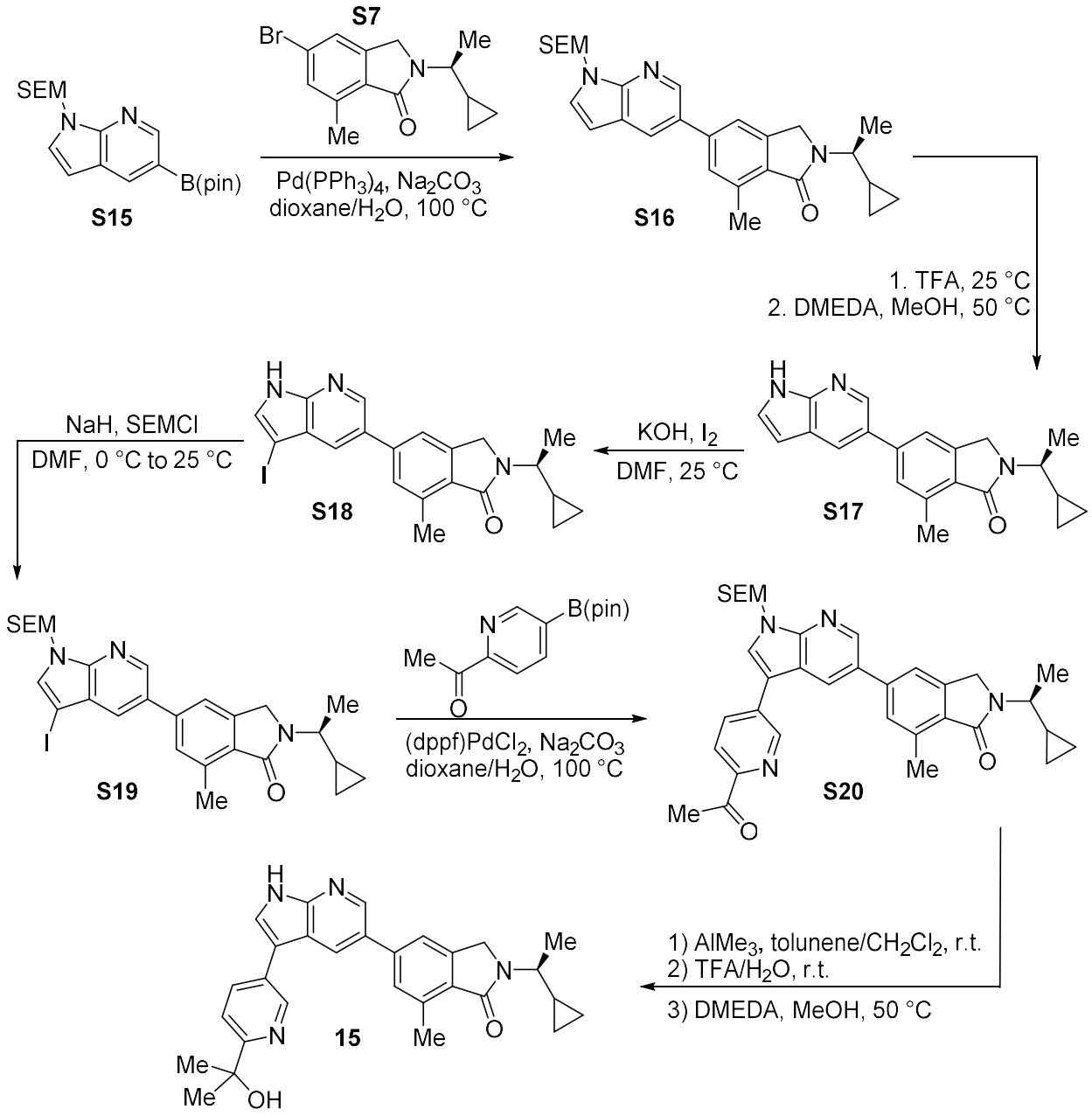
2-[(1*S*)-1-Cyclopropylethyl]-7-methyl-5-[3-(pyridin-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl]-2,3-dihydro-1*H*-isoindol-1-one (**14**)



A mixture of 5-bromo-3-iodo-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine (200 mg, 0.43 mmol), 2-pyridylzinc bromide (950 µL, 0.48 mmol), $Pd(PPh_3)_4$ (50 mg, 0.43 mmol), and THF (4.3 mL) was stirred at 70 °C under a nitrogen atmosphere until reaction completion. The mixture was cooled, diluted with H_2O, extracted with EtOAc, dried over Na_2SO_4, and concentrated. The crude material was purified by flash column chromatography (SiO_2, 0-30% gradient of EtOAc/hexanes), which provided **S14** (58 mg, 33%).

A mixture of **S7** (57 mg, 0.17 mmol), **S14** (58 mg, 0.14 mmol), $(dppf)PdCl_2$ (10 mg, 0.014 mmol), 1 M aqueous Na_2CO_3 (0.56 mL, 0.56 mmol), and dioxane (1.4 mL) was stirred at 100 °C under a nitrogen atmosphere for 16 h. diluted with brine, extracted with EtOAc, dried over Na_2SO_4, and concentrated. The crude material was purified by reversed-phase HPLC (H_2O/ACN+0.1% TFA) to afford **14** as a white solid (10 mg, 17%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.40 (s, 1H), 8.95 (d, J = 2.2 Hz, 1H), 8.67 (d, J = 5.2 Hz, 1H), 8.64 (d, J = 2.2 Hz, 1H), 8.38 (d, J = 2.8 Hz, 1H), 8.08 (d, J = 8.1 Hz, 1H), 7.97 (m, 1H), 7.75 (s, 1H), 7.61 (s, 1H), 7.33 (m, 1H), 4.55 (s, 2H), 3.58 (m, 1H), 2.69 (s, 3H), 1.28 (d, J = 6.8 Hz, 3H), 1.13 (m, 1H), 0.57 (m, 1H), 0.42 – 0.34 (m, 2H), 0.22 (m, 1H). ESI MS $[M+H]^+$ for $C_{26}H_{25}N_4O$, calcd. 409.2, found 409.2.

2-[(*1S*)-1-Cyclopropylethyl]-5-{3-[6-(2-hydroxypropan-2-yl)pyridin-3-yl]-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl}-7-methyl-2,3-dihydro-1*H*-isoindol-1-one (**15**)



To a mixture of **S7** (1.04 g, 3.54 mmol), **S15**[1] (1.32 g, 3.53 mmol), $Pd(PPh_3)_4$ (283 mg, 0.245 mmol) under nitrogen was added degassed 2 M $Na_2CO_{3(aq)}$ (4 mL), and degassed dioxane (12 mL). The reaction mixture was stirred at 100 °C for 2 h, cooled, and concentrated. The crude material was purified by column chromatography (hexanes/EtOAc), 30-100% gradient to afford **S16** (1.1 g, 67%).

S16 (2.10 g, 4.55 mmol, 1.0 equiv) was dissolved in TFA (10 mL) and the solution was stirred at 25 °C for 1 h, then concentrated under reduced pressure. The resulting oil was suspended in MeOH (10 mL), treated with DMEDA (4.9 mL, 46 mmol, 10 equiv), and the mixture was stirred at 50 °C for 1 h. Upon complete SEM deprotection, as judged by LCMS analysis, the reaction mixture was concentrated *in vacuo*. The crude material was partitioned between water and EtOAc. The aqueous phase was further extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure to obtain crude **S17** which was used in the next step.

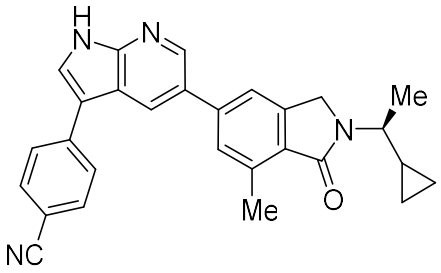
To a mixture of crude **S17** (4.55 mmol assumed), KOH (667 mg, 11.9 mmol, 2.6 equiv), and DMF (9.5 mL) at r.t. was added a solution of I_2 (1.33 g, 5.23 mmol, 1.15 equiv) in a minimal amount of DMF. The reaction mixture was stirred at r.t. for 45 min and poured into ice water containing 1% ammonia and 0.2% sodium disulfite, causing precipitation of a beige solid. The solid was collected by vacuum filtration, rinsed several times with water, azeotroped with PhMe (2x), and dried *in vacuo* to afford **S18** as a beige solid (1.22 g, 59%, two steps).

To a suspension of **S18** (1.22 g, 2.67 mmol, 1.0 equiv) in dry DMF (6.84 mL) at 0 °C was added NaH (60% dispersion in mineral oil, 213 mg, 5.33 mmol, 2.0 equiv). The reaction mixture was stirred at 0 °C for 10 min and SEMCl (0.80 mL, 4.5 mmol, 1.7 equiv) was added dropwise. The reaction mixture stirred at 25 °C for 1 h, cooled to 0 °C, and quenched with H_2O (1 mL). The mixture was partitioned between EtOAc and water. The aqueous phase was extracted with EtOAc (2x) and the combined organic extracts were washed with water (2x), brine (1x), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, hexanes/EtOAc gradient) afforded **S19** as an off-white solid (1.20 g, 76%).

A mixture of **S19** (105 mg, 0.179 mmol), 1-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridinyl]-ethanone (48 mg, 0.19 mmol), (dppf)$PdCl_2$ (14 mg, 0.019 mmol), 2 M aqueous Na_2CO_3 (0.19 mL, 0.38 mmol), and dioxane (1.9 mL) was stirred at 100 °C under a nitrogen atmosphere for 2 h. After cooling, the reaction mixture was diluted with H_2O and extracted with EtOAc (2x). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. The crude material was purified by column chromatography (0 to 100% gradient of EtOAc and hexanes) to afford **S20**.

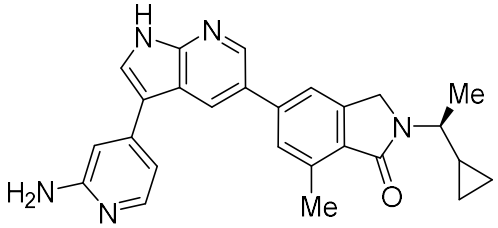
To a solution of **S20** (87.7 mg, 0.151 mmol, 1.0 equiv) in CH_2Cl_2 (1.5 mL) at 25 °C was added a 2 M solution of $AlMe_3$ in PhMe (0.45 mL, 0.91 mmol, 6.0 equiv) dropwise. The resulting solution was stirred under N_2 for 1 h. Upon completion, the solution was cooled to 0 °C and the reaction was quenched by dropwise addition of 30% aqueous NaOH solution. The crude product was extracted with CH_2Cl_2 (2x) and the combined extracts were dried over Na_2SO_4, filtered and concentrated. The resulting residue was treated with 9:1 TFA/H_2O (1.0 mL) and stirred at 25 °C for 1 h. The resulting mixture was then concentrated under reduced pressure. The resulting oil was dissolved in MeOH (3 mL) and treated with DMEDA (0.16 mL, 1.51 mmol, 10 equiv). The solution was stirred at 50 °C for 1 h. Upon complete SEM deprotection, as judged by LCMS analysis, the reaction mixture was concentrated *in vacuo*. The crude material was purified by flash column chromatography (silica, 0-5% gradient of MeOH/CH_2Cl_2) to afford **15** as a white solid (5.0 mg, 7%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.22 (br. s, 1H), 8.88 (dd, *J* = 2.2, 0.9 Hz, 1H), 8.67 (dd, *J* = 2.1, 0.4 Hz, 1H), 8.39 (dd, *J* = 2.1, 0.6 Hz, 1H), 7.99 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.66 (d, *J* = 2.5 Hz, 1H), 7.55 – 7.52 (m, 1H), 7.51 (dd, *J* = 8.2, 0.9 Hz, 1H), 7.48 – 7.46 (m, 1H), 4.92 (s, 1H), 4.63 – 4.39 (m, 2H), 3.79 (dq, *J* = 9.3, 6.8 Hz, 1H), 2.82 (s, 3H), 1.62 (s, 6H), 1.37 (d, *J* = 6.8 Hz, 3H), 1.11 – 0.97 (m, 1H), 0.72 – 0.58 (m, 1H), 0.54 – 0.32 (m, 3H). ESI MS $[M+H]^+$ for $C_{29}H_{31}N_4O_2$, calcd. 467.2, found 467.2.

4-(5-{2-[(1*S*)-1-Cyclopropylethyl]-7-methyl-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl}-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile (**16**)



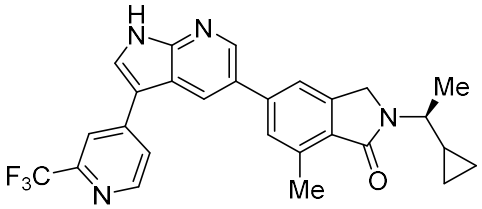
16 was prepared in a similar manner to **15** using 4-cyanophenylboronic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.34 (d, *J* = 2.8 Hz, 1H), 8.64 (d, *J* = 2.1 Hz, 1H), 8.56 (d, *J* = 2.1 Hz, 1H), 8.20 (d, *J* = 2.8 Hz, 1H), 8.05 – 8.01 (m, 2H), 7.89 – 7.84 (m, 2H), 7.80 (s, 1H), 7.65 (s, 1H), 4.54 (s, 2H), 3.57 (m, 1H), 2.68 (s, 3H), 1.28 (d, *J* = 6.8 Hz, 3H), 1.14 (m, 1H), 0.56 (m, 1H), 0.43 – 0.34 (m, 2H), 0.23 (m, 1H). ESI MS $[M+H]^+$ for $C_{28}H_{25}N_4O$, calcd. 433.2, found 433.2.

5-[3-(2-Aminopyridin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl]-2-[(*1S*)-1-cyclopropylethyl]-7-methyl-2,3-dihydro-1*H*-isoindol-1-one (**17**)



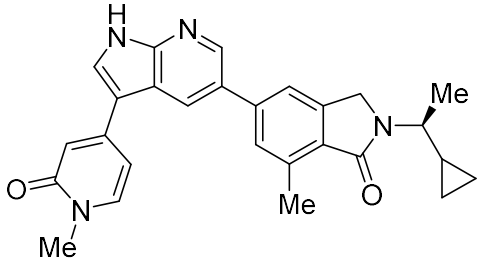
17 was prepared in a similar manner to **12** using (2-aminopyridin-4-yl)boronic acid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.69 (br. s, 1H), 8.63 (d, *J* = 2.1 Hz, 1H), 8.41 (d, *J* = 2.1 Hz, 1H), 8.14 (dd, *J* = 5.4, 0.7 Hz, 1H), 7.70 (s, 1H), 7.51 (s, 1H), 7.45 (s, 1H), 6.97 (dd, *J* = 5.4, 1.5 Hz, 1H), 6.80 (s, 1H), 4.69 (s, 2H), 4.64 – 4.36 (m, 2H), 3.79 (dq, *J* = 9.5, 6.8 Hz, 1H), 2.83 (s, 3H), 1.36 (d, *J* = 6.8 Hz, 3H), 1.12 – 0.96 (m, 1H), 0.70 – 0.60 (m, 1H), 0.51 – 0.34 (m, 3H). ESI MS $[M+H]^+$ for $C_{26}H_{26}N_5O$, calcd. 424.2, found 424.2.

2-[(1*S*)-1-Cyclopropylethyl]-7-methyl-5-{3-[2-(trifluoromethyl)pyridin-4-yl]-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl}-2,3-dihydro-1*H*-isoindol-1-one (**18**)



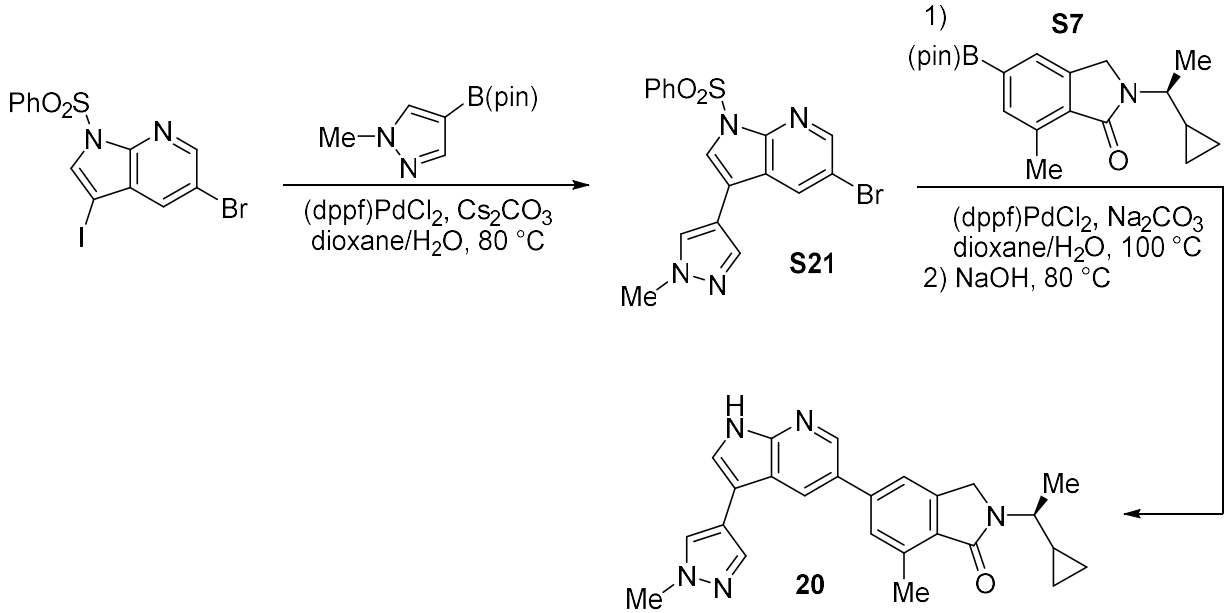
18 was prepared in a similar manner to **15** using 2-trifluoromethylpyridine-4-boronic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.54 (s, 1H), 8.74 (d, *J* = 5.1 Hz, 1H), 8.67 - 8.64 (m, 2H), 8.53 (d, *J* = 2.9 Hz, 1H), 8.25 - 8.20 (m, 2H), 7.81 (s, 1H), 7.67 (s, 1H), 4.54 (s, 2H), 3.57 (m, 1H), 2.69 (s, 3H), 1.28 (d, *J* = 6.8 Hz, 3H), 1.13 (m, 1H), 0.56 (m, 1H), 0.45 – 0.33 (m, 2H), 0.23 (m, 1H). ESI MS $[M+H]^+$ for $C_{27}H_{24}F_3N_4O$, calcd. 477.2, found 477.2.

2-[(1*S*)-1-Cyclopropylethyl]-7-methyl-5-[3-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl]-2,3-dihydro-1*H*-isoindol-1-one (**19**)



19 was prepared in a similar manner to **15** using 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2(1*H*)-pyridinone. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.38 (s, 1H), 8.62 (d, J = 2.1 Hz, 1H), 8.46 (d, J = 2.1 Hz, 1H), 8.22 (d, J = 2.8 Hz, 1H), 7.78 (s, 1H), 7.70 (d, J = 7.1 Hz, 1H), 7.63 (s, 1H), 6.80 (d, J = 2.1 Hz, 1H), 6.73 (dd, J = 7.1, 2.1 Hz, 1H), 4.55 (s, 2H), 3.57 (m, 1H), 3.43 (s, 3H), 2.68 (s, 3H), 1.27 (d, J = 6.8 Hz, 3H), 1.12 (m, 1H), 0.56 (m, 1H), 0.42 – 0.35 (m, 2H), 0.22 (m, 1H). ESI MS $[M+H]^+$ for $C_{27}H_{27}N_4O_2$, calcd. 439.2, found 439.2.

2-[(*1S*)-1-Cyclopropylethyl]-7-methyl-5-[3-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl]-2,3-dihydro-1*H*-isoindol-1-one (**20**)

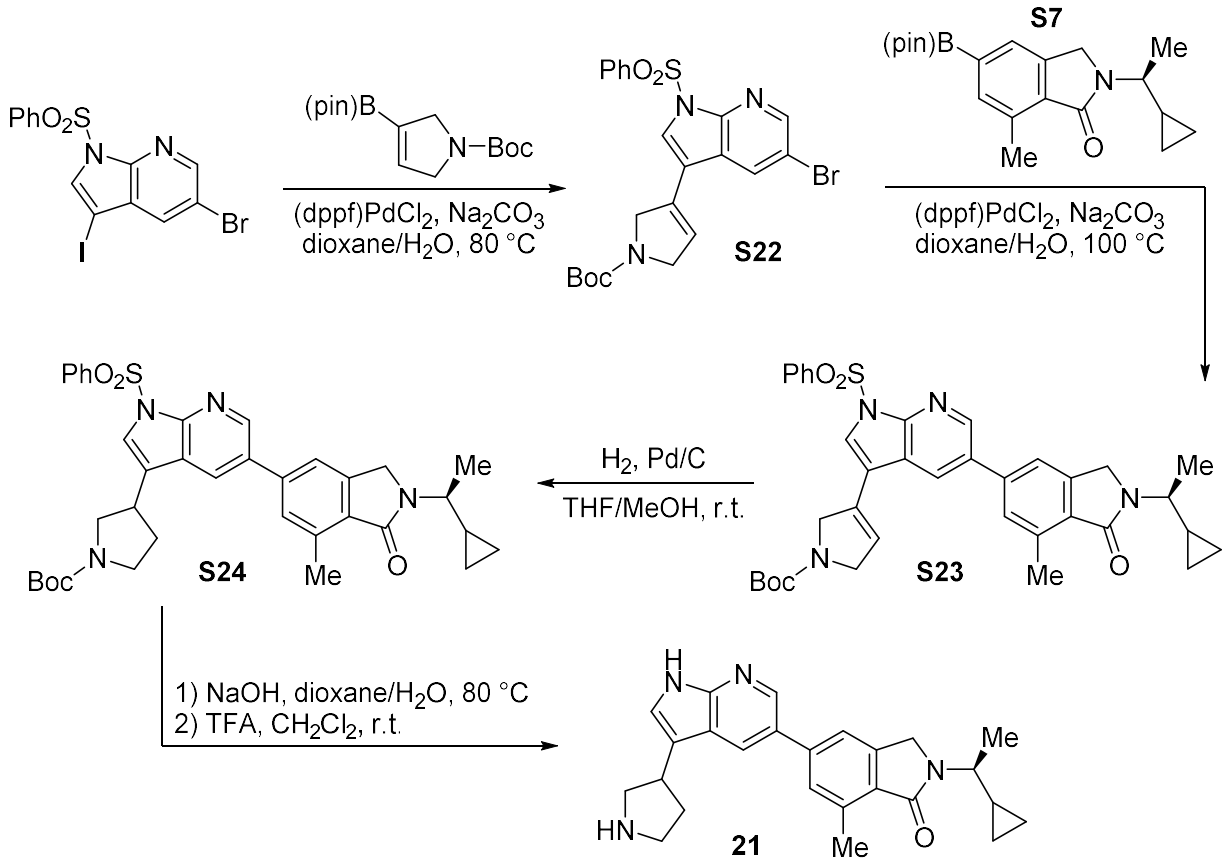


A mixture of 5-bromo-3-iodo-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine (5.00 g, 10.8 mmol, 1.0 equiv), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (2.25 g, 10.8 mmol, 1.0 equiv), (dppf)$PdCl_2$ (790 mg, 1.08 mmol, 10 mol %), Cs_2CO_3 (8.79 g, 27.0 mmol, 2.5

equiv), and 3:1 dioxane/H_2O (60 mL) was stirred at 80 °C under a nitrogen atmosphere for 3 h. Upon complete conversion, as judged by LCMS analysis, the reaction mixture was cooled to 25 °C, diluted with EtOAc, filtered over Celite and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica gel, 0 to 40% gradient of 1:1 hexanes/CH_2Cl_2 and EtOAc), which provided **S21** as a white solid (2.34 g, 52% yield).

A mixture of **S7** (61.4 mg, 0.180 mmol, 1.1 equiv), **S21** (68.3 mg, 0.164 mmol, 1.0 equiv), (dppf)$PdCl_2$ (12 mg, 0.016 mmol, 10 mol %), 2 M aqueous Na_2CO_3 (0.16 mL, 0.33 mmol, 2.0 equiv), and dioxane (1.6 mL) was stirred at 100 °C under a nitrogen atmosphere for 2 h. After cooling the reaction mixture, 6 N aqueous NaOH (0.33 mL, 1.97 mmol, 12 equiv) was added and the resulting mixture was stirred at 80 °C for 1 h. Upon complete conversion, as judged by LCMS analysis, the reaction mixture was cooled to 25 °C and diluted with EtOAc. The organic phase was separated, washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude material was purified by flash column chromatography (SiO_2, 0-5% gradient of MeOH/CH_2Cl_2) to afford **20** as a white solid (14 mg, 21%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.34 (br. s, 1H), 8.61 (d, *J* = 2.1 Hz, 1H), 8.24 (d, *J* = 2.1 Hz, 1H), 7.81 (d, *J* = 0.8 Hz, 1H), 7.67 (d, *J* = 0.7 Hz, 1H), 7.53 (s, 1H), 7.49 (d, *J* = 2.4 Hz, 1H), 7.46 (s, 1H), 4.71 – 4.33 (m, 2H), 4.01 (s, 3H), 3.87 – 3.72 (m, 1H), 2.82 (s, 3H), 1.36 (d, *J* = 6.8 Hz, 3H), 1.11 – 0.97 (m, 1H), 0.72 – 0.58 (m, 1H), 0.52 – 0.29 (m, 3H). ESI MS $[M+H]^+$ for $C_{25}H_{26}N_5O$, calcd. 412.2, found 412.2.

2-[(1*S*)-1-Cyclopropylethyl]-7-methyl-5-[3-(pyrrolidin-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl]-2,3-dihydro-1*H*-isoindol-1-one (**21**)



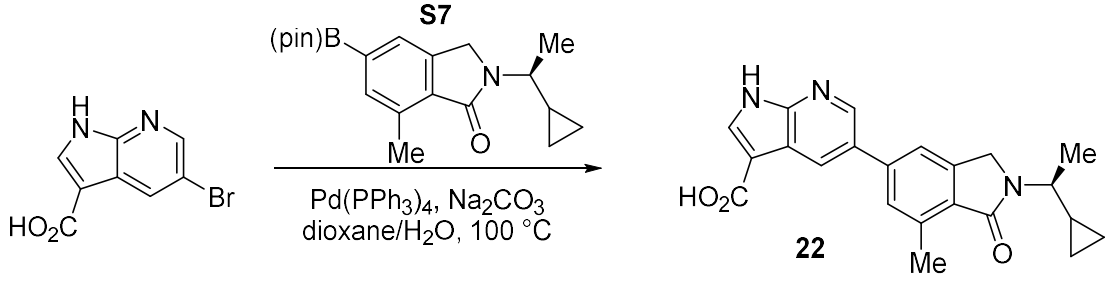
To a mixture of 5-bromo-3-iodo-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine (750 mg, 1.62 mmol), *tert*-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate (478 mg, 1.62 mmol), and (dppf)$PdCl_2$ (119 mg, 0.162 mmol) under nitrogen was added degassed 2 M $Na_2CO_{3(aq)}$ (2.43 mL, 4.86 mmol) and degassed dioxane (6.5 mL). The reaction mixture was stirred at 80 °C for 1.5 h, cooled, filtered through celite, and concentrated. The crude material was purified by column chromatography (hexanes/EtOAc), 0-50% gradient to afford **S22** (603 mg, 74%).

To a mixture of **S22** (400 mg, 0.793 mmol), **S7** (325 mg, 0.952 mmol), and (dppf)$PdCl_2$ (58 mg, 0.079 mmol) under nitrogen was added degassed 2 M $Na_2CO_{3(aq)}$ (1.2 mL, 2.4 mmol) and degassed dioxane (3.2 mL). The reaction mixture was stirred at 100 °C for 3 h, cooled, filtered through celite, and concentrated. The crude material was purified by column chromatography (hexanes/EtOAc), 0-70% gradient to afford **S23** (521 mg, >100%).

A mixture of **S23** (100 mg, 0.156 mmol), Pd/C (100 mg, 10% wt.), and 2:1 MeOH/THF (8 mL) was stirred under hydrogen at r.t. for 3 h, filtered through celite, and concentrated to afford **S24** (97 mg, 97%).

To a mixture of **S24** (97 mg, 0.15 mmol) and dioxane (1.5 mL) was added 6 M $NaOH_{(aq)}$ (152 µL, 0.912 mmol). The reaction mixture was heated to 80 °C for 2.5 h, cooled, and concentrated. The residue was dissolved in 10:1 CH_2Cl_2/TFA (1.5 mL) and stirred at r.t. for 30 min. The crude material was purified by reversed-phase HPLC (H_2O/ACN+0.1% TFA), 5-95% gradient (35 min) to afford **21** (50 mg, 64%, TFA salt). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.73 (d, J = 2.5 Hz, 1H), 8.95 (br. s, 1H), 8.59 (d, J = 2.1 Hz, 1H), 8.35 (dd, J = 2.2, 0.6 Hz, 1H), 7.79 – 7.73 (m, 1H), 7.61 (dd, J = 1.7, 0.9 Hz, 1H), 7.53 (d, J = 2.5 Hz, 1H), 4.53 (s, 2H), 3.71 (td, J = 13.4, 11.3, 6.7 Hz, 2H), 3.59 (dq, J = 9.3, 6.8 Hz, 1H), 3.48 – 3.40 (m, 1H), 3.36 – 3.20 (m, 2H), 2.70 (s, 3H), 2.50 – 2.41 (m, 1H), 2.10 (dq, J = 12.7, 8.8 Hz, 1H), 1.29 (d, J = 6.8 Hz, 3H), 1.20 – 1.07 (m, 1H), 0.65 – 0.53 (m, 1H), 0.47 – 0.33 (m, 2H), 0.29 – 0.19 (m, 1H). ESI MS $[M+H]^+$ for $C_{25}H_{29}N_4O$; calcd. 401.2, found 401.2.

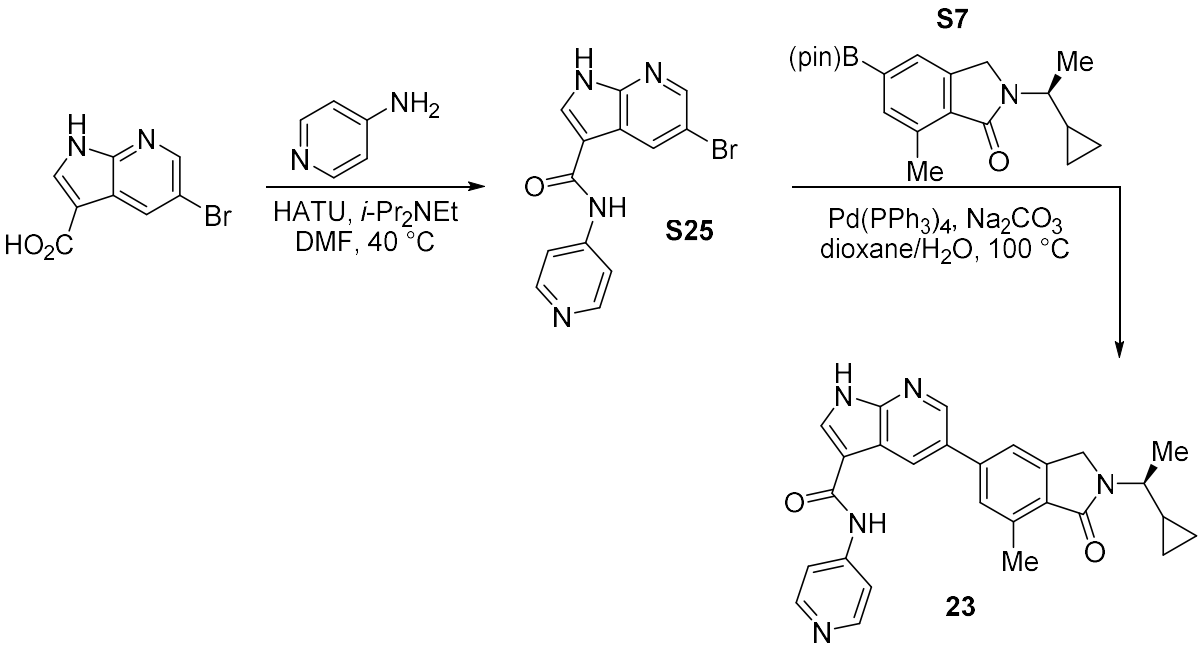
5-{2-[(1*S*)-1-Cyclopropylethyl]-7-methyl-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl}-1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxylic acid (**22**)



To a mixture of 5-bromo-1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxylic acid (50 mg, 0.21 mmol), **S7** (62 mg, 0.21 mmol), $Pd(PPh_3)_4$ (25 mg, 0.021 mmol) under nitrogen was added degassed 2 M $Na_2CO_{3(aq)}$ (0.5 mL) and degassed dioxane (1.5 mL). The reaction mixture was stirred at reflux for 2 h, cooled, and concentrated. The crude material was purified by column chromatography (CH_2Cl_2/MeOH), 0-20% gradient (30 min) and reversed-phase HPLC (H_2O/ACN+0.1%TFA), 5-95% gradient (45 min) to afford **22**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.54 (s, 1H), 8.64 (d, J = 2.3 Hz, 1H), 8.52 (d, J = 2.3 Hz, 1H), 8.20 (d, J = 3.0 Hz, 1H), 7.71 (s, 1H), 7.56 (s, 1H), 4.54 (s,

2H), 3.57 (dd, *J* = 6.8, 9.2 Hz, 1H), 2.68 (s, 3H), 1.27 (d, *J* = 6.8 Hz, 3H), 1.17 – 1.06 (m, 1H), 0.61 – 0.51 (m, 1H), 0.38 (dtt, *J* = 5.2, 9.6, 14.5 Hz, 2H), 0.27 – 0.17 (m, 1H) [exchangeable carboxylic acid proton not observed]. ESI MS $[M+H]^+$ for $C_{22}H_{22}N_3O_3$, calcd. 376.1, found 376.1.

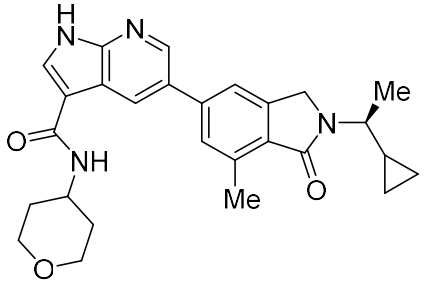
5-{2-[(1*S*)-1-Cyclopropylethyl]-7-methyl-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl}-*N*-(pyridin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxamide (**23**)



A mixture of 5-bromo-1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxylic acid (320 mg, 1.33 mmol), *i*-Pr_2NEt (486 mg, 3.95 mmol), and DMF (4 mL) was stirred at 40 °C for 15 min after which 4-aminopyridine (164 mg, 1.73 mmol) was added. The reaction mixture was stirred at 40 °C for 4 h, cooled to r.t., quenched with sat. $NaHCO_{3(aq)}$, extracted with 10% MeOH in CH_2Cl_2, and concentrated. The crude material was purified by column chromatography (CH_2Cl_2/MeOH), 0-20% gradient to afford **S25** (58 mg, 14%).

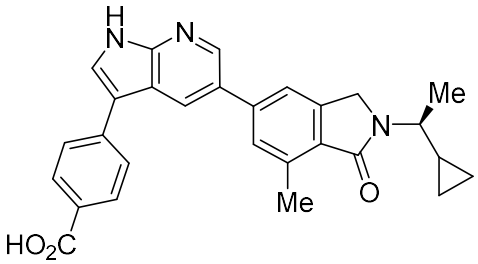
23 was then prepared in a similar manner to **22** using **S25** and **S7**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.79 (d, *J* = 3.2 Hz, 1H), 11.11 (s, 1H), 8.76 – 8.60 (m, 4H), 8.27 – 8.21 (m, 2H), 7.77 – 7.71 (m, 1H), 7.58 (d, *J* = 1.5 Hz, 1H), 4.55 (s, 2H), 3.64 – 3.51 (m, 2H), 2.69 (d, *J* = 0.8 Hz, 3H), 1.28 (d, *J* = 6.8 Hz, 3H), 1.18 – 1.05 (m, 1H), 0.64 – 0.51 (m, 1H), 0.46 – 0.32 (m, 2H), 0.28 – 0.18 (m, 1H). ESI MS $[M+H]^+$ for $C_{27}H_{26}N_5O_2$, calcd. 452.2, found 452.1.

5-{2-[(1*S*)-1-Cyclopropylethyl]-7-methyl-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl}-*N*-(oxan-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxamide (**24**)



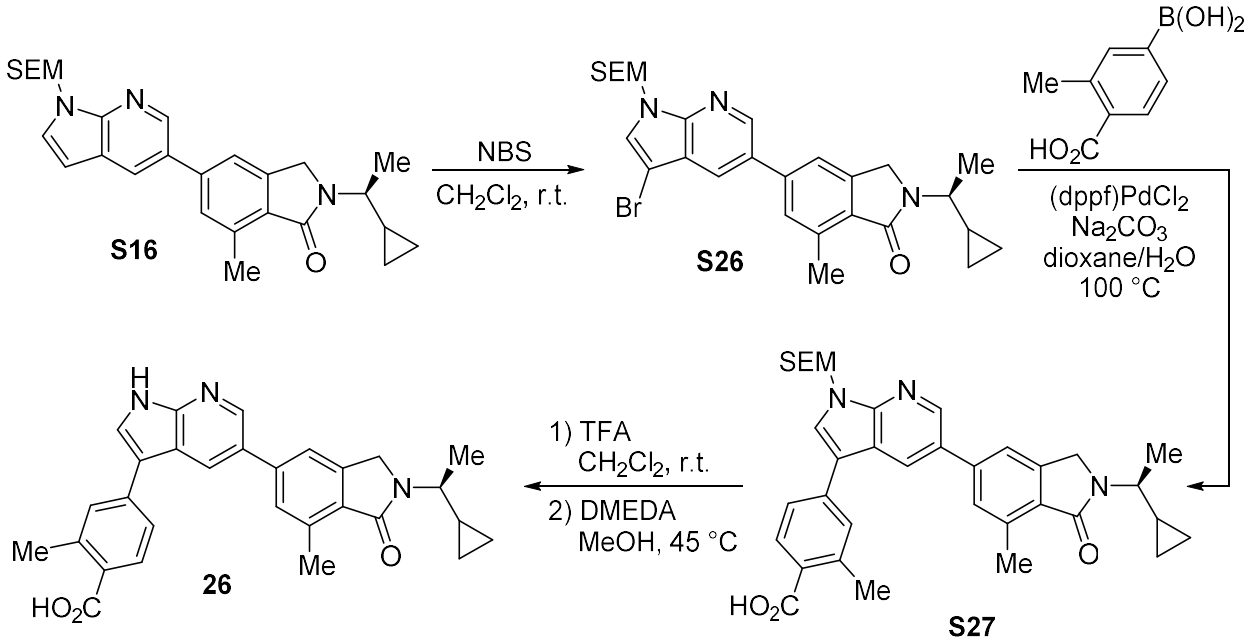
24 was prepared in a similar manner to **23** using 4-aminotetrahydropyran. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.20 (d, J = 2.9 Hz, 1H), 8.72 – 8.67 (m, 1H), 8.60 (d, J = 2.3 Hz, 1H), 8.24 (d, J = 2.9 Hz, 1H), 7.93 (d, J = 7.6 Hz, 1H), 7.69 (s, 1H), 7.54 (s, 1H), 4.53 (s, 2H), 4.03 – 3.94 (m, 1H), 3.88 (m, 2H), 3.63 – 3.50 (m, 1H), 3.38 (td, J = 2.1, 11.7 Hz, 2H), 2.68 (s, 3H), 1.79 (dd, J = 3.2, 12.8 Hz, 2H), 1.55 (qd, J = 4.4, 11.8 Hz, 2H), 1.27 (d, J = 6.8 Hz, 3H), 1.11 (m, 1H), 0.61 – 0.51 (m, 1H), 0.45 – 0.31 (m, 2H), 0.27 – 0.17 (m, 1H). ESI MS $[M+H]^+$ for $C_{27}H_{31}N_4O_3$, calcd. 459.2, found 459.2.

4-(5-{2-[(1*S*)-1-Cyclopropylethyl]-7-methyl-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl}-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzoic acid (**25**)



25 was prepared in a similar manner to **20** using 4-(methoxycarbonyl)phenylboronic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.24 (d, J = 2.8 Hz, 1H), 8.63 (d, J = 2.1 Hz, 1H), 8.56 (d, J = 2.0 Hz, 1H), 8.11 (d, J = 2.8 Hz, 1H), 8.03 – 7.97 (m, 2H), 7.96 – 7.91 (m, 2H), 7.80 (s, 1H), 7.65 (s, 1H), 4.54 (d, 2H), 3.57 (dd, J = 9.2, 6.8 Hz, 1H), 2.68 (s, 3H), 1.27 (d, J = 6.8 Hz, 3H), 1.16 – 1.07 (m, 1H), 0.61 – 0.51 (m, 1H), 0.43 – 0.32 (m, 2H), 0.25 – 0.20 (m, 1H) [exchangeable carboxylic acid proton not observed]. ESI MS $[M+H]^+$ for $C_{28}H_{26}N_3O_3$, calcd. 452.2, found 452.2.

4-(5-{2-[(1*S*)-1-Cyclopropylethyl]-7-methyl-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl}-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2-methylbenzoic acid (**26**)



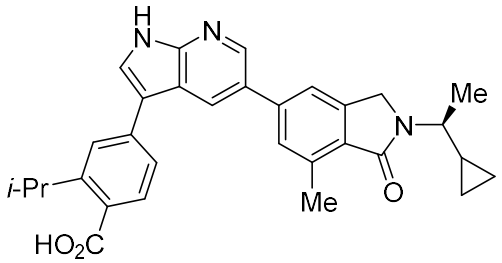
To a solution of **S16** (1.1 g, 2.4 mmol) in CH_2Cl_2 (10 mL) at r.t. under nitrogen was added NBS (0.47 g, 2.6 mmol). The reaction mixture was stirred at r.t. for 1 h and concentrated. The crude material was purified by column chromatography (hexanes/EtOAc), 30-100% gradient to afford **S26** (1.0 g, 78%).

To a mixture of **S26** (75 mg, 0.14 mmol), 4-borono-2-methylbenzoic acid (31 mg, 0.17 mmol), (dppf)$PdCl_2$ (11 mg, 0.014 mmol) under nitrogen was added degassed 2 M $Na_2CO_{3(aq)}$ (1 mL), and degassed dioxane (3 mL). The reaction mixture was stirred at 100 °C for 2 h, cooled, and concentrated. The crude material was purified by column chromatography (hexanes/EtOAc), 20-70% gradient to afford **S27** which was used directly in the next step.

A mixture of **S27** (0.14 mmol, assumed) and 1:1 TFA/ CH_2Cl_2 was stirred at r.t. for 1 h and concentrated. The residue was dissolved in MeOH and DMEDA (153 µL, 1.40 mmol) was added. The reaction mixture was stirred at 45 °C for 30 min, cooled and concentrated. The crude material was purified by reversed-phase HPLC (H_2O/ACN+0.1% TFA) to afford **26**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.20 (d, J = 2.7 Hz, 1H), 8.61 (d, J = 2.1 Hz, 1H), 8.53 (d, J = 2.1 Hz, 1H), 8.07 (d, J = 2.7 Hz, 1H), 7.93 (d, J = 8.1 Hz, 1H), 7.81 – 7.68 (m, 3H), 7.64 (d, J = 1.3 Hz, 1H), 4.54 (s, 2H), 3.61 – 3.51 (m, 1H), 2.68 (s, 3H), 2.61 (s, 3H), 1.27 (d, J = 6.8 Hz, 3H), 1.12 (ddt, J = 4.6,

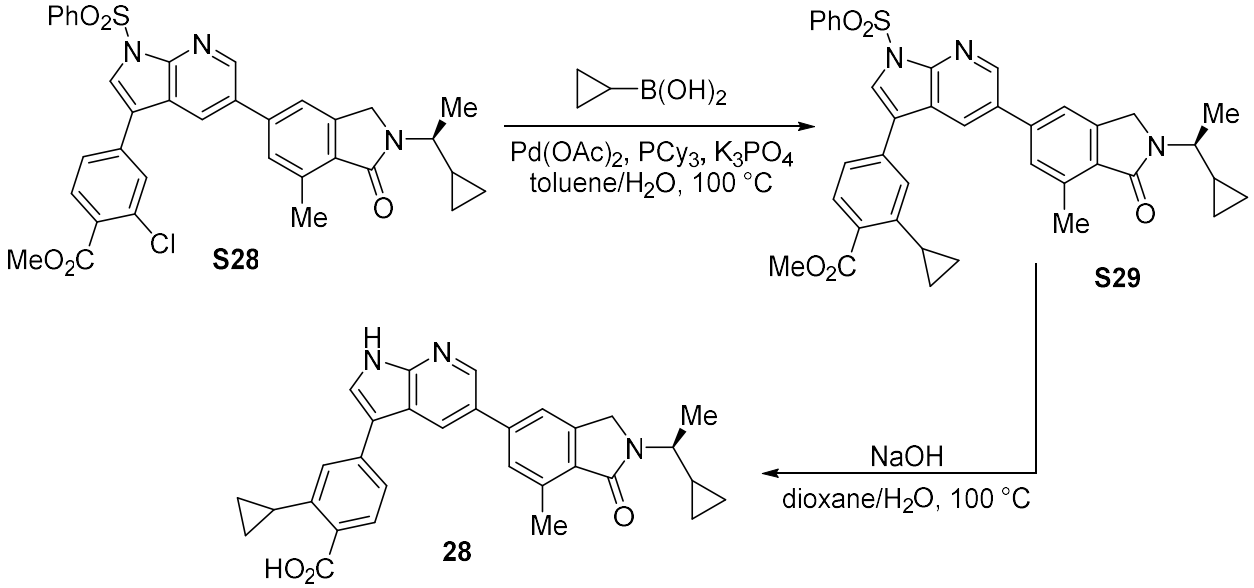
8.2, 13.0 Hz, 1H), 0.61 – 0.51 (m, 1H), 0.46 – 0.31 (m, 2H), 0.27 – 0.17 (m, 1H) [exchangeable carboxylic acid proton not observed]. ESI MS $[M+H]^+$ for $C_{29}H_{28}N_3O_3$, calcd. 466.2, found 466.1.

4-(5-{2-[(1*S*)-1-Cyclopropylethyl]-7-methyl-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl}-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2-(propan-2-yl)benzoic acid (**27**)



27 was prepared in a similar manner to **26** using 2-isopropyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (d, J = 2.1 Hz, 1H), 8.48 (d, J = 2.1 Hz, 1H), 8.10 (d, J = 2.7 Hz, 1H), 7.85 – 7.76 (m, 3H), 7.72 (dd, J = 1.8, 8.1 Hz, 1H), 7.64 (d, J = 1.3 Hz, 1H), 4.55 (s, 2H), 3.88 (h, J = 6.9 Hz, 1H), 3.65 – 3.53 (m, 1H), 2.78 – 2.61 (s, 3H), 1.29 (m, 9H), 1.20 – 1.11 (m, 1H), 0.63 – 0.52 (m, 1H), 0.47 – 0.33 (m, 2H), 0.29 – 0.19 (m, 1H) [exchangeable carboxylic acid and azaindole protons not observed]. ESI MS $[M+H]^+$ for $C_{31}H_{32}N_3O_3$, calcd. 494.2, found 494.1.

2-Cyclopropyl-4-(5-{2-[(1*S*)-1-cyclopropylethyl]-7-methyl-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl}-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzoic acid (**28**)



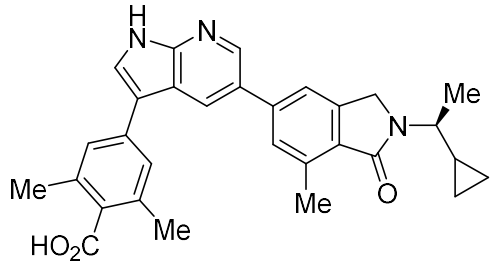
S28 was prepared in a similar manner to **20** using 4-borono-2-chlorobenzoic acid.

To a mixture of **S28** (100 mg, 0.156 mmol), cyclopropylboronic acid (40.3 mg, 0.469 mmol), $Pd(OAc)_2$ (1.8 mg, 0.0080 mmol), PCy_3 (4.5 mg, 0.016 mmol), K_3PO_4 (116 mg, 0.546 mmol) under nitrogen was added degassed toluene (800 µL) and degassed water (40 µL). The reaction mixture was stirred at 100 °C for 16 h., cooled, filtered though celite, and concentrated. The crude material was purified by column chromatography (hexanes/EtOAc), 0-60% gradient to afford **S29** (97 mg, 96%).

To a mixture of **S29** (97 mg, 0.150 mmol) and dioxane (1.5 mL) at r.t. was added 6 M $NaOH_{(aq)}$ (750 µL). The reaction mixture was stirred at 100 °C for 4 h, cooled, acidified with 1 M $HCl_{(aq)}$, and extracted with EtOAc. The organic phase was concentrated and the crude material purified by column chromatography (CH_2Cl_2/MeOH), 0-10% gradient to afford **28** (42 mg, 57%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.76 (s, 1H), 12.20 (d, J = 2.7 Hz, 1H), 8.63 (d, J = 2.1 Hz, 1H), 8.46 (d, J = 2.1 Hz, 1H), 8.10 (d, J = 2.7 Hz, 1H), 7.86 (d, J = 8.1 Hz, 1H), 7.78 (d, J = 1.5 Hz, 1H), 7.73 – 7.61 (m, 2H), 7.27 (d, J = 1.8 Hz, 1H), 4.55 (s, 2H), 3.65 – 3.53 (m, 1H), 2.85 (tt, J = 8.5, 5.3 Hz, 1H), 2.69 (s, 3H), 1.29 (d, J = 6.8 Hz, 3H), 1.14 (tt, J = 7.9, 3.8 Hz, 1H), 1.05 – 0.93 (m, 2H), 0.93 – 0.80 (m, 2H), 0.63 – 0.52 (m, 1H), 0.40 (dtt, J = 14.2, 9.1, 5.1 Hz, 2H), 0.29 – 0.19 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.0, 167.4, 148.9, 145.0, 143.3, 142.4, 141.4, 138.3,

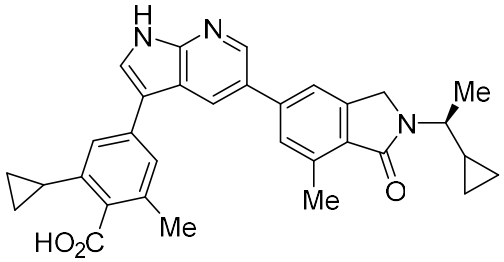
136.6, 130.8, 128.7, 128.6, 128.5, 128.4, 126.1, 125.8, 123.0, 122.2, 119.5, 117.3, 114.0, 51.3, 45.2, 18.2, 16.9, 15.7, 12.8, 9.5, 4.0, 3.3. ESI MS $[M+H]^+$ for $C_{31}H_{30}N_3O_3$; calcd. 492.2, found 492.2.

4-(5-{2-[(1*S*)-1-Cyclopropylethyl]-7-methyl-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl}-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2,6-dimethylbenzoic acid (**29**)



29 was prepared in a similar manner to **26** using methyl 4-borono-2,6-dimethyl-benzoate. 6 M $NaOH_{(aq)}$/dioxane at 100 °C was used for saponification of the hindered methyl ester. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.11 (d, J = 2.7 Hz, 1H), 8.61 (d, J = 2.1 Hz, 1H), 8.49 (d, J = 2.2 Hz, 1H), 7.95 (d, J = 2.7 Hz, 1H), 7.78 (s, 1H), 7.63 (s, 1H), 7.48 (d, J = 0.8 Hz, 2H), 4.55 (s, 2H), 3.59 (dd, J = 9.3, 6.8 Hz, 1H), 2.69 (s, 3H), 2.37 (s, 6H), 1.29 (d, J = 6.8 Hz, 3H), 1.20 – 1.08 (m, 1H), 0.58 (dq, J = 8.8, 4.3, 3.3 Hz, 1H), 0.40 (ddt, J = 14.4, 9.2, 5.2 Hz, 2H), 0.24 (p, J = 4.9, 4.4 Hz, 1H). ESI MS $[M+H]^+$ for $C_{30}H_{30}N_3O_3$; calcd. 480.2, found 480.2.

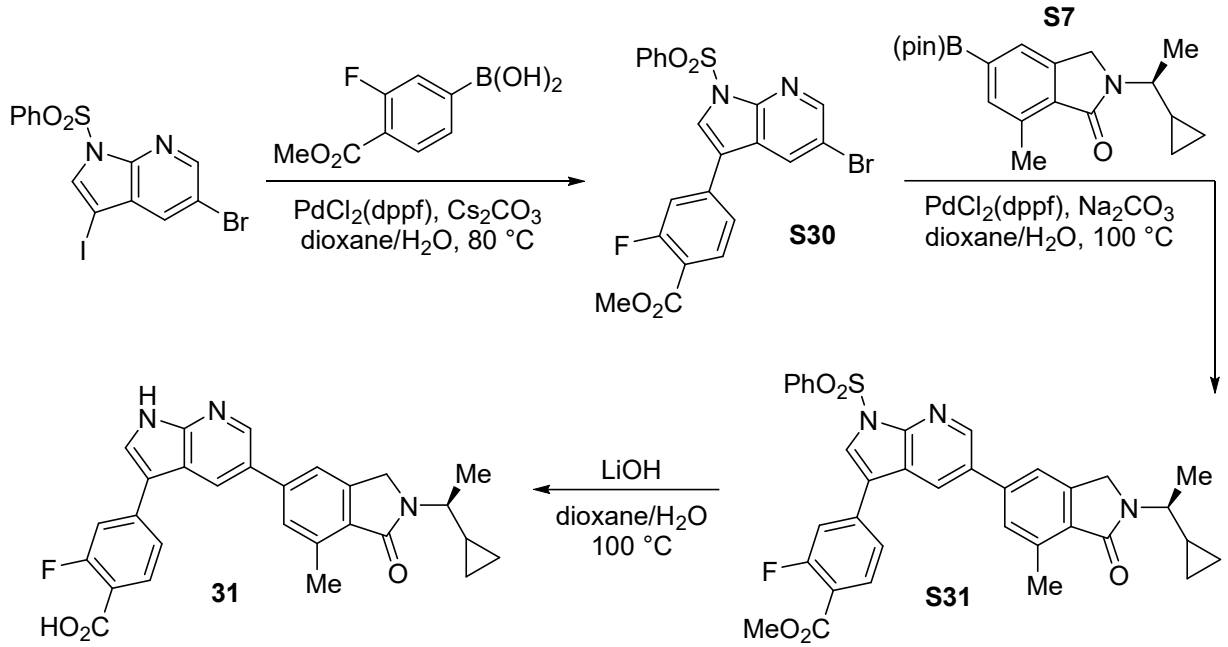
2-Cyclopropyl-4-(5-{2-[(1*S*)-1-cyclopropylethyl]-7-methyl-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl}-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-6-methylbenzoic acid (**30**)



30 was prepared in a similar manner to **28** using methyl 4-bromo-2-chloro-6-methylbenzoate. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.09 (d, J = 2.7 Hz, 1H), 8.60 (d, J = 2.1 Hz, 1H), 8.40 (d, J = 2.1 Hz, 1H), 7.96 (d, J = 2.7 Hz, 1H), 7.76 (d, J = 1.4 Hz, 1H), 7.61 (s, 1H), 7.45 (d, J = 1.5 Hz, 1H),

7.07 (d, *J* = 1.5 Hz, 1H), 4.55 (s, 2H), 3.64 – 3.55 (m, 1H), 2.69 (s, 3H), 2.36 (s, 3H), 1.99 (ddd, *J* = 13.6, 8.5, 5.2 Hz, 1H), 1.29 (d, *J* = 6.8 Hz, 3H), 1.14 (tt, *J* = 8.2, 3.6 Hz, 1H), 0.99 – 0.90 (m, 2H), 0.84 – 0.75 (m, 2H), 0.58 (dq, *J* = 9.1, 4.4, 3.5 Hz, 1H), 0.40 (ddt, *J* = 14.6, 9.3, 5.2 Hz, 2H), 0.25 (dd, *J* = 9.3, 4.8 Hz, 1H). ESI MS $[M+H]^+$ for $C_{32}H_{32}N_3O_3$; calcd. 506.2, found 506.1.

4-(5-{2-[(1*S*)-1-Cyclopropylethyl]-7-methyl-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl}-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2-fluorobenzoic acid (**31**)



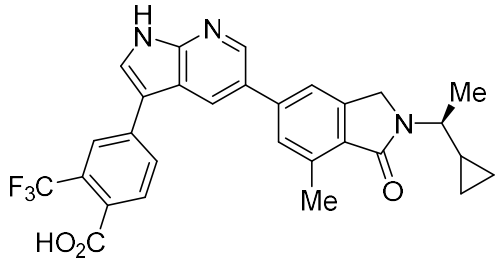
A mixture of 5-bromo-3-iodo-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine (2.34 g, 5.05 mmol, 1.0 equiv), methyl 4-borono-2-fluoro-1-benzoate (1.00 g, 5.05 mmol, 1.0 equiv), (dppf)$PdCl_2$ (366 mg, 0.500 mmol, 10 mol %), Cs_2CO_3 (4.11 g, 12.6 mmol, 2.5 equiv), and 3:1 dioxane/H_2O (28 mL) was stirred at 80 °C under a nitrogen atmosphere for 3 h. Upon complete conversion, as judged by LCMS analysis, the reaction mixture was cooled to 25 °C, diluted with EtOAc, filtered over Celite and concentrated *in vacuo*. The crude material. was purified by flash column chromatography (silica gel, hexanes/EtOAc gradient) to afford **S30**.

A mixture of **S7** (293 mg, 0.858 mmol, 1.0 equiv), **S30** (420 mg, 0.858 mmol, 1.0 equiv), (dppf)$PdCl_2$ (63 mg, 0.086 mmol, 10 mol %), 2 M aqueous Na_2CO_3 (0.86 mL, 1.7 mmol, 2.0 equiv), and dioxane (8.6 mL) was stirred at 100 °C under a nitrogen atmosphere for 2 h. Upon complete conversion, as judged by LCMS analysis, the reaction mixture was cooled to 25 °C and

diluted with EtOAc. The organic phase was separated, washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude material was purified by flash column chromatography (silica gel, hexanes/EtOAc gradient) to afford **S31**.

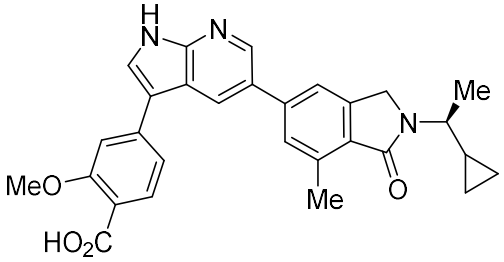
A mixture of **S31** (90.1 mg, 0.144 mmol, 1.0 equiv) and 3 N aq. LiOH (0.48 mL, 1.44 mmol, 10 equiv) in dioxane (1 mL) stirred at 100 °C for 3 h. After cooling to 25 °C, the reaction mixture was neutralized with AcOH and diluted with EtOAc. The organic phase was concentrated under reduced pressure and the resulting residue was purified by reversed-phase HPLC (10-90% gradient of ACN/H_2O with 0.1% TFA) to afford **31** as an off-white solid (16 mg, 19%, TFA salt). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.72 – 8.66 (m, 1H), 8.64 (s, 1H), 7.94 (s, 1H), 7.75 (s, 1H), 7.71 (dd, J = 7.9, 1.6 Hz, 1H), 7.64 – 7.58 (m, 2H), 7.53 (t, J = 7.6 Hz, 1H), 4.71 – 4.56 (m, 2H), 3.72 – 3.60 (m, 1H), 2.76 (s, 3H), 1.40 (d, J = 6.8 Hz, 3H), 1.23 – 1.09 (m, 1H), 0.73 – 0.63 (m, 1H), 0.54 – 0.46 (m, 1H), 0.46 – 0.38 (m, 1H), 0.38 – 0.29 (m, 1H). ESI MS $[M+H]^+$ for $C_{28}H_{25}FN_3O_3$, calcd. 470.2, found 470.2.

4-(5-{2-[(1*S*)-1-Cyclopropylethyl]-7-methyl-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl}-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2-(trifluoromethyl)benzoic acid (**32**)



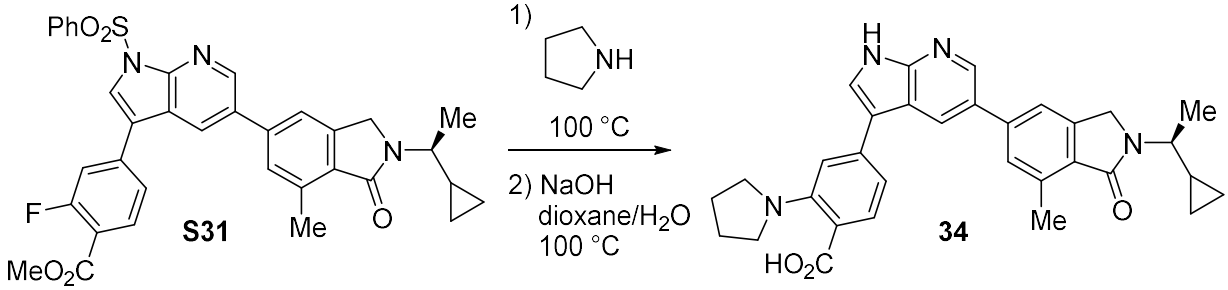
32 was prepared in a similar manner to **26** using methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethyl)benzoate. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.37 (d, J = 2.8 Hz, 1H), 8.66 (d, J = 2.1 Hz, 1H), 8.55 (d, J = 2.1 Hz, 1H), 8.31 – 8.20 (m, 2H), 8.14 (d, J = 1.7 Hz, 1H), 7.95 (d, J = 8.1 Hz, 1H), 7.80 (s, 1H), 7.65 (d, J = 1.4 Hz, 1H), 4.55 (s, 2H), 3.65 – 3.53 (m, 1H), 2.70 (d, J = 0.7 Hz, 3H), 1.29 (d, J = 6.8 Hz, 3H), 1.16 – 1.08 (m, 1H), 0.58 (dq, J = 8.8, 4.4, 3.4 Hz, 1H), 0.47 – 0.33 (m, 2H), 0.24 (p, J = 5.2, 4.6 Hz, 1H). ESI MS $[M+H]^+$ for $C_{29}H_{25}F_3N_3O_3$; calcd. 520.2, found 520.0.

4-(5-{2-[(1*S*)-1-Cyclopropylethyl]-7-methyl-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl}-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2-methoxybenzoic acid (**33**)



33 was prepared in a similar manner to **26** using 3-methoxy-4-methoxycarbonylphenylboronic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.23 (d, J = 2.8 Hz, 1H), 8.63 (d, J = 2.1 Hz, 1H), 8.55 – 8.51 (d, J = 2.1 Hz, 1H), 8.13 (d, J = 2.7 Hz, 1H), 7.80 – 7.76 (m, 2H), 7.64 (s, 1H), 7.46 (dd, J = 8.0, 1.6 Hz, 1H), 7.41 (d, J = 1.5 Hz, 1H), 4.53 (s, 2H), 3.92 (s, 3H), 3.62 – 3.51 (m, 1H), 2.68 (s, 3H), 1.27 (d, J = 6.8 Hz, 3H), 1.17 – 1.06 (m, 1H), 0.60 – 0.51 (m, 1H), 0.44 – 0.30 (m, 2H), 0.27 – 0.17 (m, 1H) [exchangeable carboxylic acid proton not observed]. ESI MS $[M+H]^+$ for $C_{29}H_{28}N_3O_4$, calcd. 482.2, found 482.2.

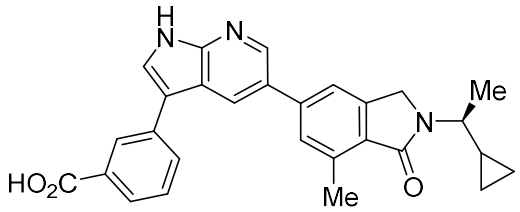
4-(5-{2-[(*1S*)-1-Cyclopropylethyl]-7-methyl-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl}-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2-(pyrrolidin-1-yl)benzoic acid (**34**)



A mixture of **S31** (138 mg, 0.22 mmol) and pyrrolidine (0.3 mL) was stirred at 100 °C in a sealed vial for 2 h. The reaction mixture was cooled and diluted with water. The resulting precipitate was collected by vacuum filtration and rinsed with water. The solid was dissolved in dioxane (0.5 mL) and 6 N aqueous NaOH (0.5 mL) was added. The mixture was stirred at 100 °C for 3 h. Upon complete conversion, as judged by LCMS analysis, the reaction mixture was cooled to 25 °C, neutralized with AcOH, and extracted with EtOAc. The organic phase was separated, washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude material was purified by

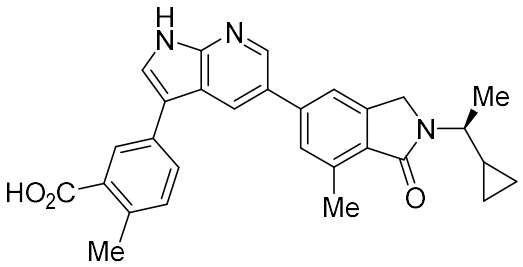
reversed-phase HPLC (0-90% gradient of ACN/H_2O with 0.1% TFA) to afford **34** as a white solid (12 mg, 23%, TFA salt). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.66 – 8.62 (m, 2H), 8.32 (d, J = 8.2 Hz, 1H), 8.14 – 8.11 (m, 2H), 8.07 (dd, J = 8.2, 1.6 Hz, 1H), 7.76 – 7.72 (m, 1H), 7.63 – 7.59 (m, 1H), 4.73 – 4.54 (m, 2H), 3.96 – 3.82 (m, 4H), 3.74 – 3.59 (m, 1H), 2.76 (s, 3H), 2.44 – 2.33 (m, 4H), 1.40 (d, J = 6.8 Hz, 3H), 1.23 – 1.11 (m, 1H), 0.73 – 0.65 (m, 1H), 0.56 – 0.47 (m, 1H), 0.47 – 0.39 (m, 1H), 0.38 – 0.29 (m, 1H). ESI MS $[M+H]^+$ for $C_{32}H_{33}N_4O_3$, calcd. 521.2, found 521.2.

3-(5-{2-[(1*S*)-1-Cyclopropylethyl]-7-methyl-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl}-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzoic acid (**35**)



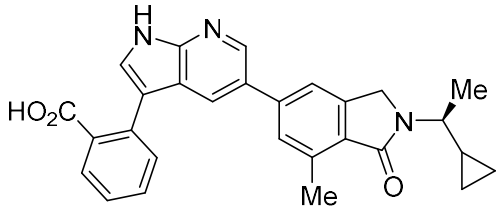
35 was prepared in a similar manner to **31** using 3-(methoxycarbonyl)phenylboronic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.16 (d, J = 2.7 Hz, 1H), 8.61 (d, J = 2.1 Hz, 1H), 8.44 (d, J = 2.1 Hz, 1H), 8.24 (t, J = 1.9 Hz, 1H), 8.05 (ddd, J = 7.7, 1.9, 1.1 Hz, 1H), 8.03 (d, J = 2.6 Hz, 1H), 7.83 (ddd, J = 7.8, 1.6, 1.2 Hz, 1H), 7.76 (s, 1H), 7.62 – 7.57 (m, 2H), 4.53 (s, 2H), 3.59 – 3.52 (m, 1H), 2.67 (s, 3H), 1.27 (d, J = 6.8 Hz, 3H), 1.17 – 1.08 (m, 1H), 0.60 – 0.52 (m, 1H), 0.43 – 0.32 (m, 2H), 0.25 – 0.19 (m, 1H) [exchangeable carboxylic acid proton not observed]. ESI MS $[M+H]^+$ for $C_{28}H_{26}N_3O_3$, calcd. 452.2, found 452.2.

5-(5-{2-[(1*S*)-1-Cyclopropylethyl]-7-methyl-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl}-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2-methylbenzoic acid (**36**)



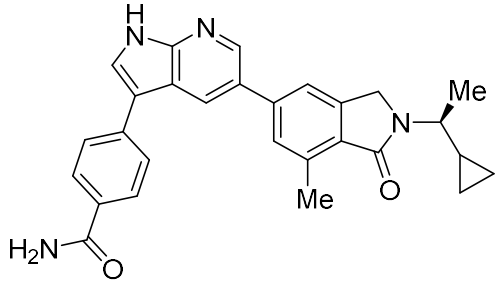
36 was prepared in a similar manner to **26** using 5-borono-2-methylbenzoic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.09 (d, J = 2.7 Hz, 1H), 8.60 (d, J = 2.1 Hz, 1H), 8.42 (d, J = 2.1 Hz, 1H), 8.12 (d, J = 2.1 Hz, 1H), 7.95 (d, J = 2.6 Hz, 1H), 7.86 (dd, J = 2.1, 7.8 Hz, 1H), 7.74 (s, 1H), 7.60 (s, 1H), 7.38 (d, J = 7.9 Hz, 1H), 4.53 (s, 2H), 3.57 (m, 1H), 2.67 (s, 3H), 2.54 (s, 3H), 1.27 (d, J = 6.8 Hz, 3H), 1.18 – 1.06 (m, 1H), 0.60 – 0.51 (m, 1H), 0.44 – 0.31 (m, 2H), 0.27 – 0.17 (m, 1H) [exchangeable carboxylic acid proton not observed]. ESI MS $[M+H]^+$ for $C_{29}H28N_3O_3$, calcd. 466.2, found 466.1.

2-(5-{2-[(*1S*)-1-Cyclopropylethyl]-7-methyl-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl}-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzoic acid (**37**)



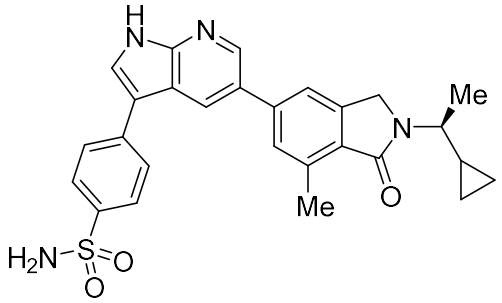
37 was prepared in a similar manner to **26** using 2-(methoxycarbonyl)phenylboronic acid. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.62 (d, J = 2.0 Hz, 1H), 8.30 (d, J = 2.0 Hz, 1H), 7.93 (ddd, J = 7.8, 1.4, 0.6 Hz, 1H), 7.72 – 7.45 (m, 6H), 4.67 – 4.53 (m, 2H), 3.72 – 3.58 (m, 1H), 2.73 (s, 3H), 1.39 (d, J = 6.8 Hz, 3H), 1.22 – 1.09 (m, 1H), 0.73 – 0.62 (m, 1H), 0.55 – 0.46 (m, 1H), 0.46 – 0.37 (m, 1H), 0.37 – 0.27 (m, 1H). ESI MS $[M+H]^+$ for $C_{28}H_{26}N_3O_3$, calcd. 452.2, found 452.2.

4-(5-{2-[(1*S*)-1-Cyclopropylethyl]-7-methyl-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl}-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzamide (**38**)



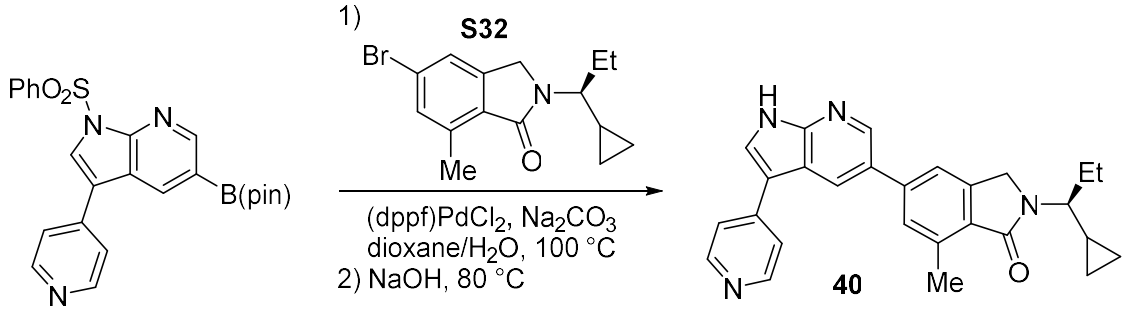
38 was prepared in a similar manner to **26** using 4-carbamoylphenylboronic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.19 (d, J = 2.7 Hz, 1H), 8.62 (d, J = 2.1 Hz, 1H), 8.53 (d, J = 2.1 Hz, 1H), 8.07 (d, J = 2.7 Hz, 1H), 8.02 – 7.94 (m, 3H), 7.92 – 7.83 (m, 2H), 7.82 – 7.77 (m, 1H), 7.65 (dd, J = 0.9, 1.6 Hz, 1H), 7.31 (s, 1H), 4.54 (d, J = 36.1 Hz, 2H), 3.63 – 3.51 (m, 1H), 2.68 (s, 3H), 1.27 (d, J = 6.8 Hz, 3H), 1.12 (ddt, J = 4.6, 8.1, 13.0 Hz, 1H), 0.56 (ddd, J = 4.5, 8.1, 9.4 Hz, 1H), 0.38 (ddp, J = 5.1, 9.4, 14.4 Hz, 2H), 0.27 – 0.17 (m, 1H). ESI MS $[M+H]^+$ for $C_{28}H_{27}N_4O_2$, calcd. 451.2, found 451.2.

4-(5-{2-[(1*S*)-1-Cyclopropylethyl]-7-methyl-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl}-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzene-1-sulfonamide (**39**)



39 was prepared in a similar manner to **26** using 4-aminosulfonylphenylboronic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.27 (d, J = 2.8 Hz, 1H), 8.65 (d, J = 2.1 Hz, 1H), 8.57 (d, J = 2.1 Hz, 1H), 8.13 (d, J = 2.7 Hz, 1H), 8.01 (d, J = 8.7 Hz, 2H), 7.89 (d, J = 8.6 Hz, 2H), 7.82 (s, 1H), 7.67 (s, 1H), 7.36 (s, 2H), 4.56 (s, 2H), 3.65 – 3.55 (m, 1H), 2.70 (s, 3H), 1.30 (d, J = 6.8 Hz, 3H), 1.20 – 1.09 (m, 1H), 0.63 – 0.54 (m, 1H), 0.47 – 0.35 (m, 2H), 0.29 – 0.20 (m, 1H). ESI MS $[M+H]^+$ for $C_{27}H_{27}N_4O_3S$, calcd. 487.2, found 487.0.

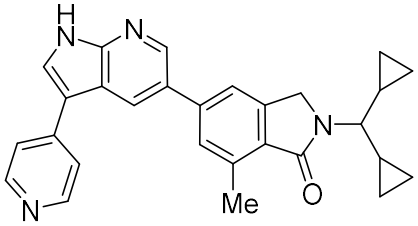
2-[(*1S*)-1-Cyclopropylpropyl]-7-methyl-5-[3-(pyridin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl]-2,3-dihydro-1*H*-isoindol-1-one (**40**)



S32 was prepared in a similar manner to **S6** using (1*S*)-1-cyclopropylpropan-1-amine.

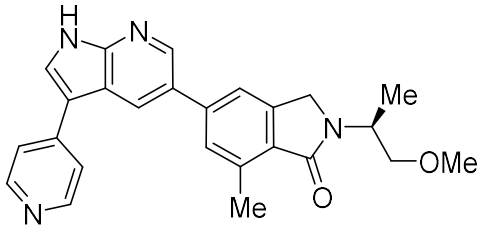
A mixture of **S32** (68.0 mg, 0.217 mmol, 1.0 equiv), 1-(phenylsulfonyl)-3-(4-pyridinyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridine[2] (100 mg, 0.217 mmol, 1.0 equiv), (dppf)$PdCl_2$ (16 mg, 0.022 mmol, 10 mol %), 2 M aqueous Na_2CO_3 (0.20 mL, 0.40 mmol, 2.0 equiv), and dioxane (2.2 mL) was stirred at 100 °C under a nitrogen atmosphere for 2 h. After cooling the reaction mixture, 6 N aqueous NaOH (0.43 mL, 2.60 mmol, 12 equiv) was added and the resulting mixture was stirred at 80 °C for 1 h. Upon complete conversion, as judged by LCMS analysis, the reaction mixture was cooled to 25 °C and diluted with EtOAc. The organic phase was separated, washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude material was purified by reversed-phase HPLC (10-90% gradient of ACN/H_2O with 0.1% TFA) to afford **40** as a white solid (30 mg, 26%, TFA salt). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.81 (d, J = 2.0 Hz, 1H), 8.73 (d, J = 2.0 Hz, 1H), 8.67 (d, J = 6.4 Hz, 2H), 8.60 (s, 1H), 8.47 (d, J = 6.8 Hz, 2H), 7.79 (s, 1H), 7.67 (s, 1H), 4.71 – 4.42 (m, 2H), 3.45 (td, J = 9.7, 5.5 Hz, 1H), 2.79 (s, 3H), 1.99 – 1.73 (m, 2H), 1.21 – 1.06 (m, 1H), 0.94 (t, J = 7.4 Hz, 3H), 0.78 – 0.65 (m, 1H), 0.53 – 0.41 (m, 2H), 0.34 – 0.19 (m, 1H). ESI MS $[M+H]^+$ for $C_{27}H_{27}N_4O$, calcd. 423.2, found 423.2.

2-(Dicyclopropylmethyl)-7-methyl-5-[3-(pyridin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl]-2,3-dihydro-1*H*-isoindol-1-one (**41**)



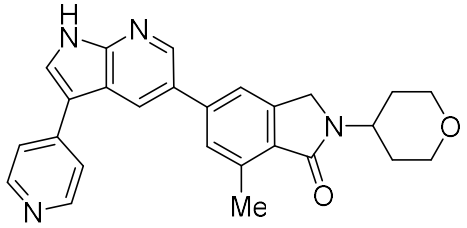
41 was prepared in a similar manner to **40** using dicyclopropylmethanamine. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.63 (br. s, 1H), 8.73 – 8.63 (m, 3H), 8.47 (d, J = 1.9 Hz, 1H), 7.82 – 7.78 (m, 1H), 7.66 – 7.58 (m, 2H), 7.56 (s, 1H), 7.48 (s, 1H), 4.64 (s, 2H), 3.24 (t, J = 8.9 Hz, 1H), 2.84 (s, 3H), 1.18 – 1.05 (m, 2H), 0.74 – 0.61 (m, 2H), 0.57 – 0.48 (m, 2H), 0.47 – 0.35 (m, 4H). ESI MS $[M+H]^+$ for $C_{28}H_{27}N_4O$, calcd. 435.2, found 435.2.

2-[(*2S*)-1-Methoxypropan-2-yl]-7-methyl-5-[3-(pyridin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl]-2,3-dihydro-1*H*-isoindol-1-one (**42**)



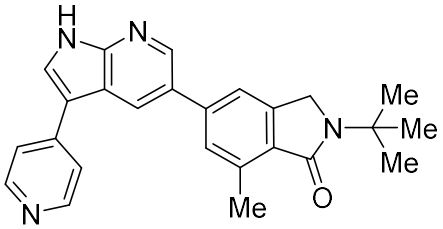
42 was prepared in a similar manner to **40** using (2*S*)-1-methoxy-2-propanamine (≥96% enantiomeric excess). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.78 (d, *J* = 2.0 Hz, 1H), 8.70 (d, *J* = 2.0 Hz, 1H), 8.68 – 8.65 (m, 2H), 8.59 (s, 1H), 8.49 – 8.41 (m, 2H), 7.75 (s, 1H), 7.64 (s, 1H), 4.69 – 4.59 (m, 1H), 4.59 – 4.46 (m, 2H), 3.72 – 3.50 (m, 2H), 3.38 (s, 3H), 2.77 (s, 3H), 1.33 (d, *J* = 7.0 Hz, 3H). ESI MS $[M+H]^+$ for $C_{25}H_{25}N_4O_2$, calcd. 413.2, found 413.2.

7-Methyl-2-(oxan-4-yl)-5-[3-(pyridin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl]-2,3-dihydro-1*H*-isoindol-1-one (**43**)



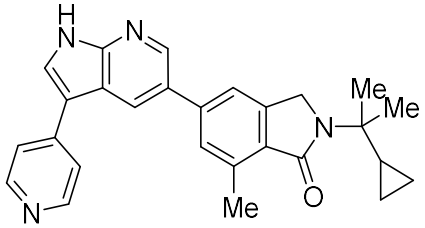
43 was prepared in a similar manner to **40** using tetrahydro-2*H*-pyran-4-amine. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.72 (br. s, 1H), 8.75 – 8.58 (m, 3H), 8.44 (d, *J* = 2.0 Hz, 1H), 7.77 (d, *J* = 2.5 Hz, 1H), 7.64 – 7.57 (m, 1H), 7.54 (s, 2H), 7.48 (s, 1H), 4.59 – 4.48 (m, 1H), 4.42 (s, 2H), 4.11 (dd, *J* = 11.6, 4.4 Hz, 2H), 3.59 (td, *J* = 11.8, 2.2 Hz, 2H), 2.84 (s, 3H), 2.00 – 1.73 (m, 4H). ESI MS $[M+H]^+$ for $C_{26}H_{25}N_4O_2$, calcd. 425.2, found 425.2.

2-*tert*-Butyl-7-methyl-5-[3-(pyridin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl]-2,3-dihydro-1*H*-isoindol-1-one (**44**)



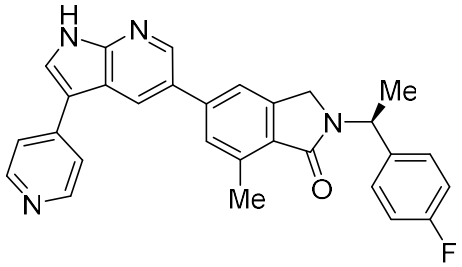
44 was prepared in a similar manner to **40** using *tert*-butylamine. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.79 (d, *J* = 2.0 Hz, 1H), 8.71 (d, *J* = 2.0 Hz, 1H), 8.66 (d, *J* = 7.1 Hz, 2H), 8.60 (s, 1H), 8.46 (d, *J* = 7.1 Hz, 2H), 7.72 (s, 1H), 7.63 (s, 1H), 4.64 (s, 2H), 2.76 (s, 3H), 1.61 (s, 9H). ESI MS $[M+H]^+$ for $C_{25}H_{25}N_4O$, calcd. 397.2, found 397.2.

2-(2-Cyclopropylpropan-2-yl)-7-methyl-5-[3-(pyridin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl]-2,3-dihydro-1*H*-isoindol-1-one (**45**)



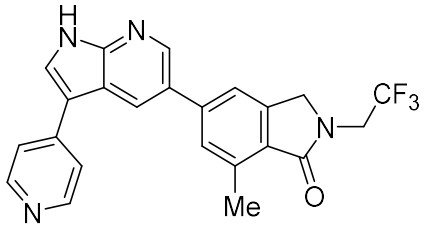
45 was prepared in a similar manner to **40** using 2-cyclopropylpropan-2-amine hydrochloride. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.79 (d, J = 2.0 Hz, 1H), 8.71 (d, J = 2.0 Hz, 1H), 8.66 (d, J = 7.1 Hz, 2H), 8.59 (s, 1H), 8.46 (d, J = 7.1 Hz, 2H), 7.75 – 7.70 (m, 1H), 7.65 – 7.61 (m, 1H), 4.75 (s, 2H), 2.76 (s, 3H), 1.55 (tt, J = 7.8, 6.0 Hz, 1H), 1.50 (s, 6H), 0.63 – 0.52 (m, 4H). ESI MS $[M+H]^+$ for $C_{27}H_{27}N_4O$, calcd. 423.2, found 423.2.

2-[(*1S*)-1-(4-Fluorophenyl)ethyl]-7-methyl-5-[3-(pyridin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl]-2,3-dihydro-1*H*-isoindol-1-one (**46**)



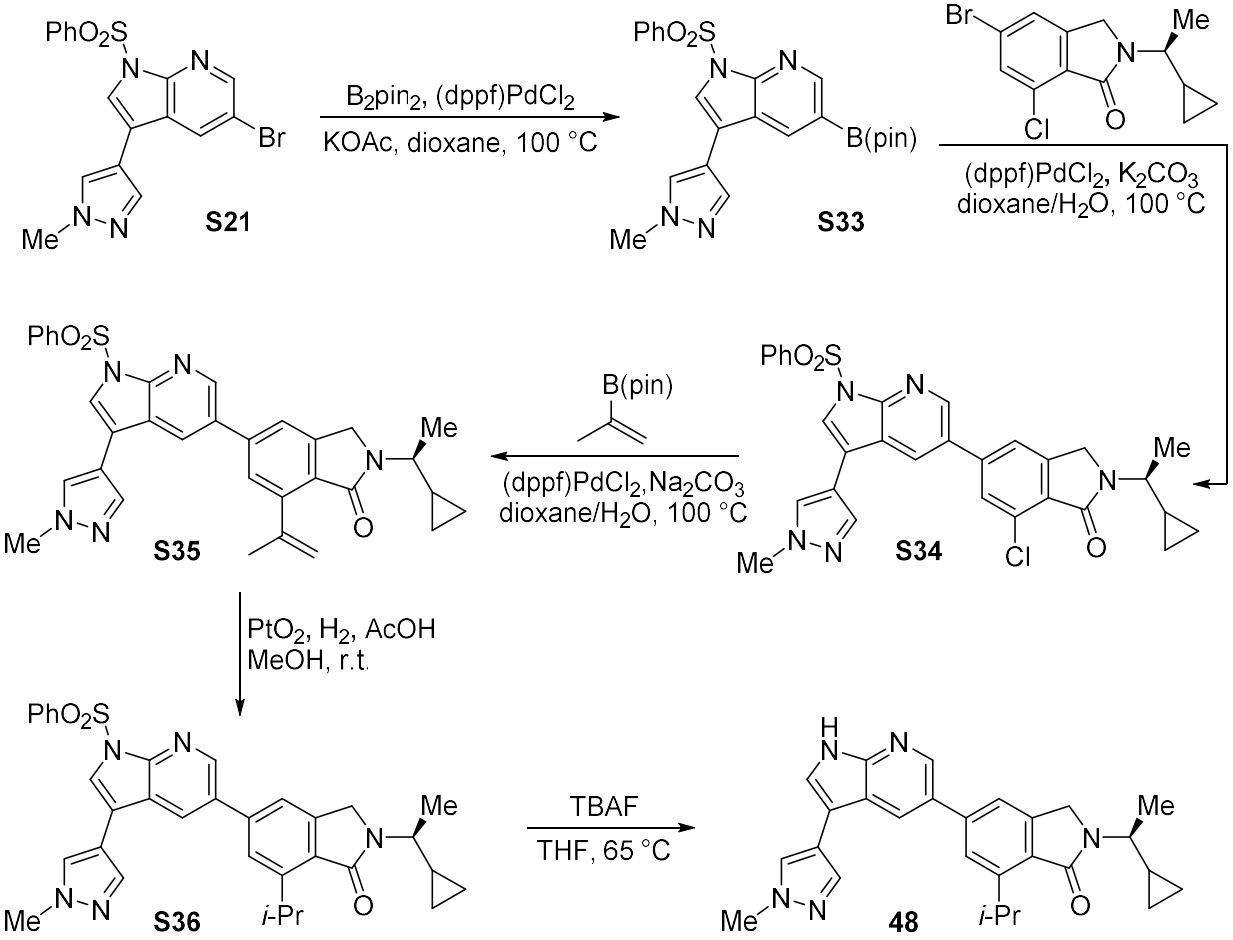
46 was prepared in a similar manner to **40** using (*S*)-1-(4-fluorophenyl)ethanamine [99% enantiomeric excess]. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.76 (d, J = 2.0 Hz, 1H), 8.69 (d, J = 2.0 Hz, 1H), 8.65 (d, J = 7.1 Hz, 2H), 8.57 (s, 1H), 8.43 (d, J = 7.1 Hz, 2H), 7.71 (s, 1H), 7.66 (s, 1H), 7.43 (ddd, J = 9.0, 5.3, 0.7 Hz, 2H), 7.11 (t, J = 8.8 Hz, 2H), 5.68 (q, J = 7.0 Hz, 1H), 4.35 (dd, J = 169.3, 17.8 Hz, 2H), 2.80 (s, 3H), 1.73 (d, J = 7.1 Hz, 3H). ^{19}F NMR (376 MHz, Methanol-d_4) δ -117.10. ESI MS $[M+H]^+$ for $C_{29}H_{24}FN_4O$, calcd. 463.2, found 463.2.

7-Methyl-5-[3-(pyridin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl]-2-(2,2,2-trifluoroethyl)-2,3-dihydro-1*H*-isoindol-1-one (**47**)



47 was prepared in a similar manner to **40** using 2,2,2-trifluoroethan-1-amine hydrochloride. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.95 (s, 1H), 8.80 (d, *J* = 2.1 Hz, 1H), 8.78 – 8.72 (m, 4H), 8.39 (d, J = 6.6 Hz, 2H), 7.91 (s, 1H), 7.78 (s, 1H), 4.65 (s, 2H), 4.41 (q, *J* = 9.7 Hz, 2H), 2.74 (s, 3H). ESI MS $[M+H]^+$ for $C_{23}H_{18}F_3N_4O$, calcd. 423.1, found 423.2.

2-[(1*S*)-1-cyclopropylethyl]-5-[3-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl]-7-(propan-2-yl)-2,3-dihydro-1*H*-isoindol-1-one (**48**)



A mixture of **S21** (1.56 g, 3.74 mmol, 1.0 equiv), B_2pin_2 (1.33 g, 5.23 mmol, 1.4 equiv), KOAc (1.47 g, 15.0 mmol, 4.0 equiv), and (dppf)$PdCl_2$ (271 mg, 0.37 mmol, 10 mol %) in dioxane (12.5 mL) was stirred at 100 °C under a nitrogen atmosphere for 2 h. The reaction mixture was cooled to 25 °C, diluted with EtOAc, filtered over Celite and concentrated *in vacuo*. The crude product was dissolved in CH_2Cl_2 and filtered over a plug of silica gel, rinsing several times with CH_2Cl_2 and then EtOAc, and the filtrate was concentrated under reduced pressure. The resulting solid was triturated with MeOH and dried *in vacuo* to afford **S33** as a white solid (1.41 g, 81% yield).

To a mixture of 5-bromo-7-chloro-2-[(1*S*)-l-cyclopropylethyl]-2,3-dihydro-1*H*-isoindol-1-one[3] (626 mg, 2.0 mmol), **S33** (928 mg, 2.0 mmol), (dppf)$PdCl_2$ (146.3 mg, 0. 2 mmol), and K_2CO_3 (276.4 mg, 2. 0 mmol) under nitrogen was added degassed dioxane (8.0 mL) and degassed H_2O (2.0 mL). The reaction mixture was stirred at 100 °C for 14 h, cooled, and diluted with brine (50

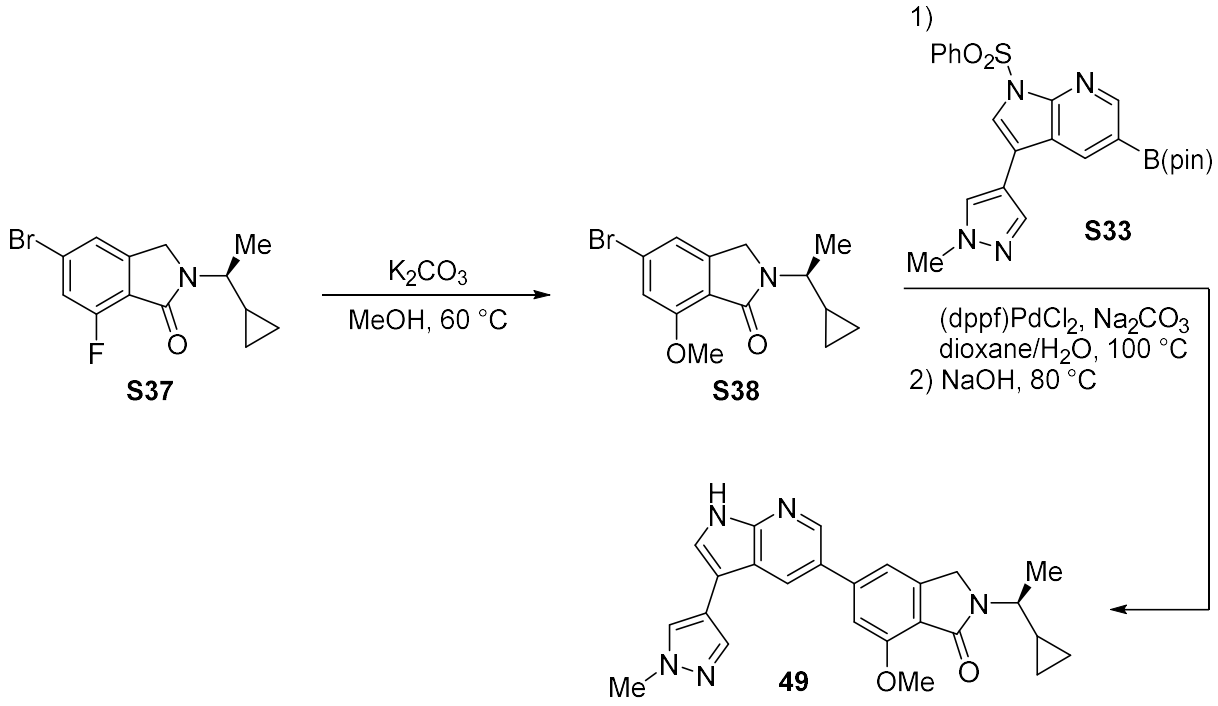
mL). The solids were collected by filtration, washed with water, dried, and purified by column chromatography (hexanes/EtOAc), 0-100% gradient (30 min) to afford **S34** as an off-white solid (790 mg, 69%).

To a mixture of **S34** (200 mg, 0.350 mol) and (dppf)$PdCl_2$ (26 mg, 0.36 mmol) under nitrogen was added 2-isopropenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (198 µL, 1.05 mmol), degassed 2 M $Na_2CO_{3(aq)}$ (525 µL, 1.05 mmol), and degassed dioxane (3.5 mL). The reaction mixture was stirred at 100 °C for 5 h, cooled, charged with additional 2-isopropenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (198 µL, 1.05 mmol) and (dppf)$PdCl_2$ (26 mg, 0.36 mmol), stirred at 100 °C for 17 h, cooled, filtered through celite, and concentrated. The crude material was purified by column chromatography (hexanes/EtOAc), 50-100% gradient to afford **S35** (60 mg, 30%).

A mixture of **S35** (60 mg, 0.104 mmol), PtO_2 (6.0 mg, 0.26 mmol), AcOH (100 µL), and MeOH (2.0 mL) was stirred under hydrogen at r.t. for 24 h, filtered through celite, and concentrated to afford crude **S36**.

A mixture of **S36** (60 mg assumed, 0.104 mmol), TBAF (208 µL, 0.208 mmol, 1 M in THF), and THF (4.2 mL) was stirred at 65 °C for 5 h. The mixture was cooled and concentrated. The crude material was purified by reversed-phase HPLC (H_2O/ACN+0.1% TFA), 5-95% gradient (35 min) to afford **48** (15 mg, 26%, two steps, TFA salt). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.84 (d, J = 2.6 Hz, 1H), 8.59 (d, J = 2.1 Hz, 1H), 8.42 – 8.37 (m, 1H), 8.21 (d, J = 0.8 Hz, 1H), 7.91 (d, J = 0.8 Hz, 1H), 7.77 (dd, J = 17.2, 2.0 Hz, 2H), 7.71 (d, J = 1.4 Hz, 1H), 4.55 (s, 2H), 4.34 (p, J = 6.9 Hz, 1H), 3.90 (s, 3H), 3.68 – 3.55 (m, 1H), 1.34 – 1.26 (m, 9H), 1.14 (ddt, J = 13.2, 8.4, 4.5 Hz, 1H), 0.63 – 0.53 (m, 1H), 0.41 (qd, J = 9.1, 4.8 Hz, 2H), 0.25 (p, J = 5.0, 4.5 Hz, 1H). ESI MS $[M+H]^+$ for $C_{27}H_{30}N_5O$; calcd. 440.2, found 440.2.

2-[(*1S*)-1-Cyclopropylethyl]-7-methoxy-5-[3-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl]-2,3-dihydro-1*H*-isoindol-1-one (**49**)



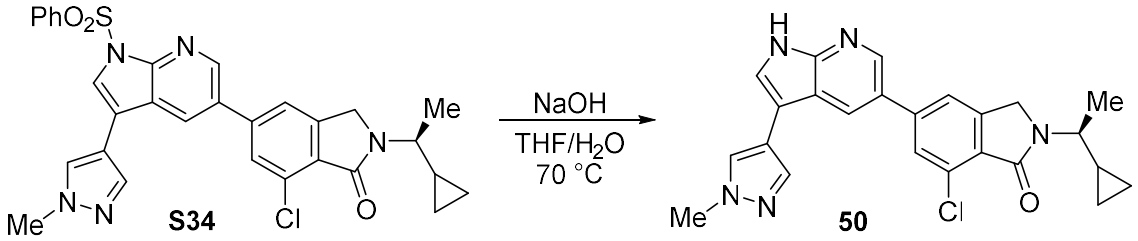
S37 was prepared in a similar manner to **S6** using methyl 4-bromo-2-fluoro-6-methylbenzoate.

A mixture of **S37** (400 mg, 1.34 mmol, 1.0 equiv) and K_2CO_3 (556 mg, 4.02 mmol, 3.0 equiv) in MeOH (2.0 mL) was stirred at 60 °C for 4 h. After cooling, the reaction mixture was diluted with EtOAc and washed with H_2O (2x). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. The crude material was purified by column chromatography (0 to 50% gradient of EtOAc and hexanes) to afford **S38**.

A mixture of **S38** (40 mg, 0.13 mmol, 1.0 equiv), **S33** (60 mg, 0.13 mmol, 1.0 equiv), (dppf)$PdCl_2$ (9.5 mg, 0.013 mmol, 10 mol %), 2 M aqueous Na_2CO_3 (0.13 mL, 0.26 mmol, 2.0 equiv), and dioxane (1.3 mL) was stirred at 100 °C under a nitrogen atmosphere for 2 h. After cooling the reaction mixture, 6 N aqueous NaOH (0.26 mL, 1.6 mmol, 12 equiv) was added and the resulting mixture was stirred at 80 °C for 1 h. Upon complete conversion, as judged by LCMS analysis, the reaction mixture was cooled to 25 °C and diluted with EtOAc. The organic phase was separated, washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude material was purified by reversed-phase HPLC (10-90% gradient of ACN/H_2O with 0.1% TFA) to afford **49** as a white solid (12 mg, 17%, TFA salt). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.66 – 8.60 (m, 2H),

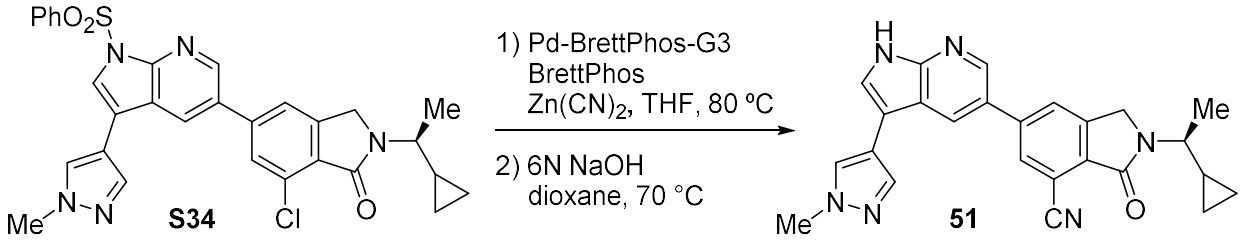
8.11 (s, 1H), 7.90 (s, 1H), 7.72 (s, 1H), 7.45 (s, 1H), 7.31 (s, 1H), 4.70 – 4.47 (m, 2H), 4.02 (s, 3H), 3.98 (s, 3H), 3.65 (dq, *J* = 9.5, 6.8 Hz, 1H), 1.37 (d, *J* = 6.9 Hz, 3H), 1.20 – 1.06 (m, 1H), 0.72 – 0.60 (m, 1H), 0.54 – 0.45 (m, 1H), 0.44 – 0.37 (m, 1H), 0.37 – 0.28 (m, 1H). ESI MS $[M+H]^+$ for $C_{25}H_{26}N_5O_2$, calcd. 428.2, found 428.2.

7-Chloro-2-[(1*S*)-1-cyclopropylethyl]-5-[3-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl]-2,3-dihydro-1*H*-isoindol-1-one (**50**)



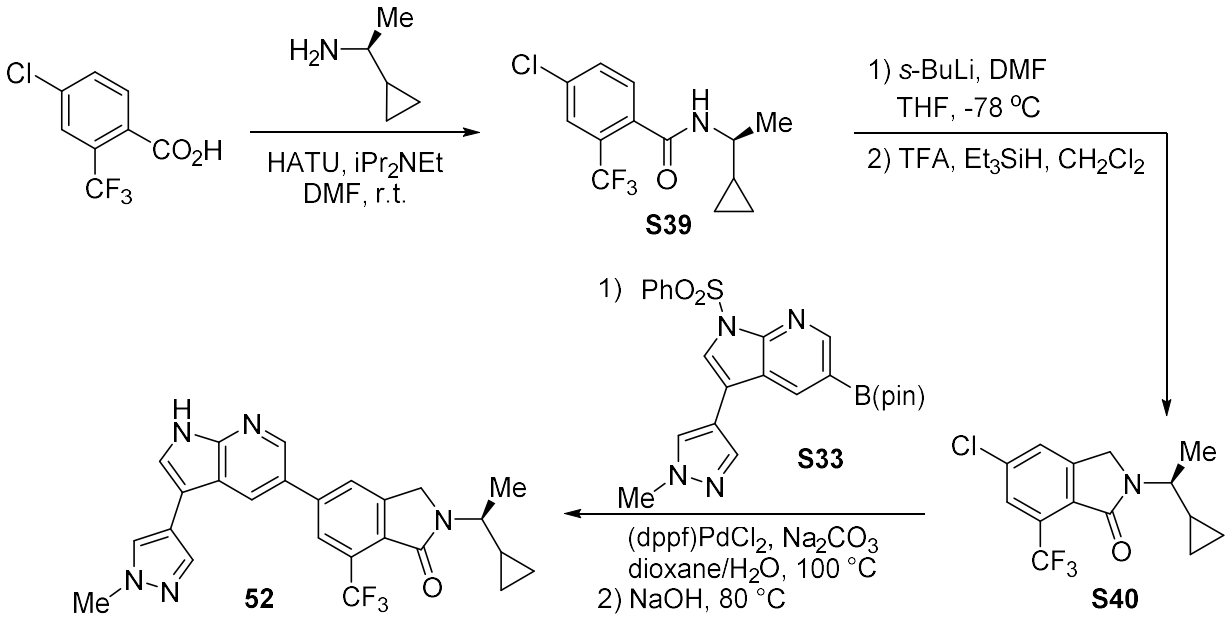
To a suspension of **S34** (90 mg, 0.16 mmol) in THF (0.8 mL) was added a 6.0 M aqueous solution of NaOH (31.5 μL). The reaction mixture was stirred at 70 ˚C for 1.5 h and neutralized with 1.0 M aqueous HCl. The crude material was purified by reversed-phase HPLC (H_2O/ACN+0.1% TFA), 5-95% gradient (45 min) to afford **50** as a white solid (50 mg, 57%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.87 (s, 1H), 8.62 (d, *J* = 2.1 Hz, 1H), 8.51 – 8.43 (m, 1H), 8.28 – 8.22 (m, 1H), 8.01 – 7.96 (m, 1H), 7.95 – 7.88 (m, 2H), 7.76 (d, *J* = 2.5 Hz, 1H), 4.59 (s, 2H), 3.89 (s, 3H), 3.64 – 3.51 (m, 1H), 1.29 (d, *J* = 6.8 Hz, 3H), 1.14 (tt, *J* = 8.0, 3.6 Hz, 1H), 0.64 – 0.50 (m, 1H), 0.46 – 0.32 (m, 2H), 0.29 – 0.16 (m, 1H). ESI MS $[M+H]^+$ for $C_{24}H_{23}ClN_5O$, calcd. 432.1, found 432.1.

2-[(1*S*)-1-Cyclopropylethyl]-6-[3-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl]-3-oxo-2,3-dihydro-1*H*-isoindole-4-carbonitrile (**51**)



A vial charged with **S34** (95 mg, 0.17 mmol), zinc cyanide (44 mg, 0.25 mmol), Pd-BrettPhos-G3 (15 mg, 0.017 mmol), and BrettPhos (9 mg, 0.02 mmol) was evacuated and backfilled with nitrogen (2x) then degassed THF (1.7 mL) was added. The sealed via was heated to 80 °C overnight. After cooling to room temperature, the reaction was diluted with EtOAc and washed with water and brine. The organics were dried over $MgSO_4$ and concentrated under reduced pressure to provide crude protected **51** (75 mg, 0.13 mmol). Dioxane (1.5 ml) and 6M NaOH (0.5 mL) were added and the mixture was heated to 70 °C for 1 hour. After cooling to room temperature, the reaction was diluted with EtOAc and washed with water and brine. The organics were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography (C18, MeCN/H_2O with 0.1% TFA) and subsequent lyophilization afforded **51** as a white solid (23 mg, 42%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.88 (s, 1H), 8.66 (d, J = 2.2 Hz, 1H), 8.53 (d, J = 2.2 Hz, 1H), 8.45 (d, J = 1.5 Hz, 1H), 8.37 (s, 1H), 8.25 (s, 1H), 7.94 (s, 1H), 7.77 (d, J = 2.5 Hz, 1H), 4.67 (s, 2H), 3.60 (dq, J = 9.3, 6.9 Hz, 1H), 1.32 (d, J = 6.8 Hz, 3H), 1.22 – 1.07 (m, 1H), 0.68 – 0.52 (m, 1H), 0.49 – 0.34 (m, 2H), 0.32 – 0.17 (m, 1H). ESI MS $[M+H]^+$ for $C_{25}H_{23}N_6O$, calcd. 423.2, found 423.1.

2-[(1*S*)-1-Cyclopropylethyl]-5-[3-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl]-7-(trifluoromethyl)-2,3-dihydro-1*H*-isoindol-1-one (**52**)

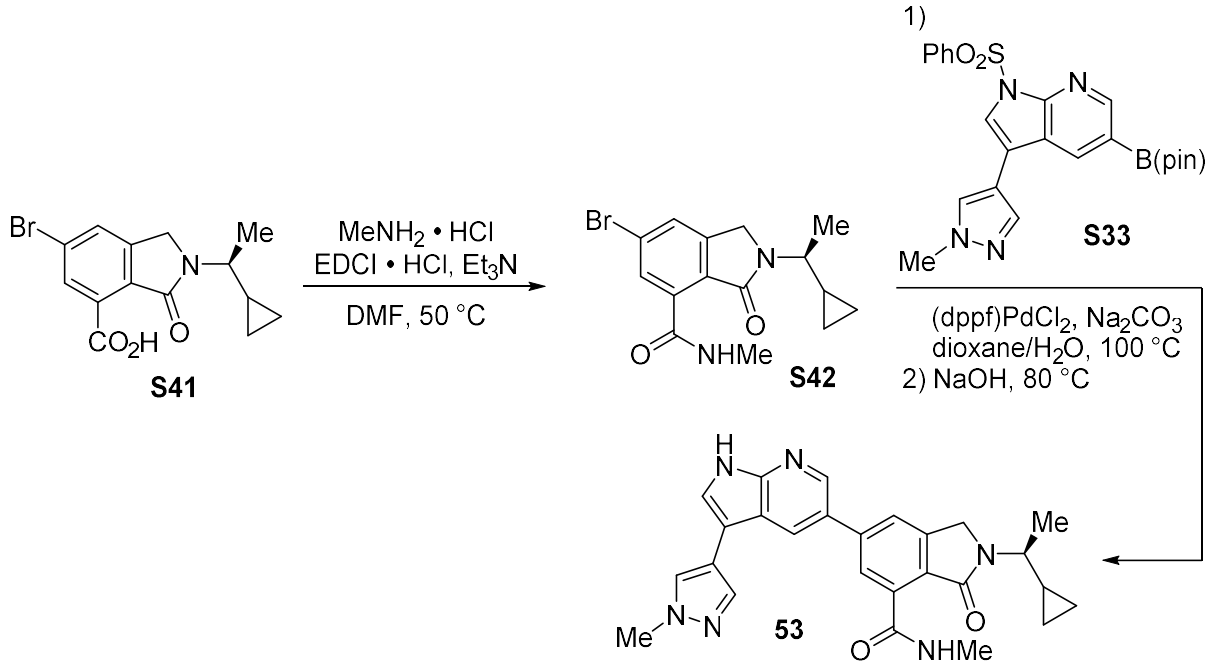


A mixture of 4-chloro-2-(trifluoromethyl)benzoic acid (20 g, 89 mmol), (*S*)-1-cyclopropylethan-1-amine (9.32 g, 107 mmol, 1.2 equiv.), HATU (40.7 g, 107 mmol, 1.2 equiv.), and diisopropylethylamine (48 mL, 270 mmol, 3 equiv.) in anhydrous DMF (297 mL) was stirred at r.t. for 2 h. The reaction mixture was quenched with saturated aqueous NH_4Cl, extracted with EtOAc, evaporated and the crude product was purified by column chromatography (0 to 40% gradient of EtOAc in Hexanes) to give **S39** as a white solid (25.5 g, 98%).

S39 (8.2 g, 28 mmol) was dissolved in THF (140 mL) and cooled to -78 °C, then *sec*-Butyllithium (1.4 M in cyclohexane, 50 mL, 70 mmol, 2.5 equiv.) was added dropwise. After 20 min at -78 °C, DMF (10.8 mL, 140 mmol, 5.0 equiv) was added dropwise. The reaction mixture was stirred at -78 °C for 1 h, then was carefully quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The crude product was then dissolved in CH_2Cl_2 (90 mL) and cooled to 0 °C. Et_3SiH (4.5 mL) and TFA (45 mL) were added and the reaction mixture was stirred at r.t. for 20 min. The reaction mixture was concentrated, quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The crude mixture was purified by column chromatography (0 to 30% gradient of EtOAc in Hexanes) to give **S40** as a white solid (7.15 g, 84%).

A mixture of **S40** (43 mg, 0.14 mmol, 1.0 equiv), **S33** (100 mg, 0.21 mmol, 1.5 equiv), (dppf)$PdCl_2$ (10 mg, 0.014 mmol, 10 mol %), 1 M aqueous Na_2CO_3 (0.57 mL, 0.57 mmol, 4 equiv), and dioxane (1.4 mL) was stirred at 100 °C under a nitrogen atmosphere for 20 min. After cooling the reaction mixture, 6 N aqueous NaOH (0.16 mL, 0.98 mmol, 7 equiv) was added and the resulting mixture was stirred at 80 °C for 0.5 h. Upon complete conversion, as judged by LCMS analysis, the reaction mixture was cooled to r.t., and diluted with EtOAc. The organic phase was separated, washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude material was purified by flash column chromatography (silica, MeOH/CH_2Cl_2 gradient) to afford **52** as a white solid (29 mg, 45%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.89 (d, J = 2.6 Hz, 1H), 8.64 (d, J = 2.2 Hz, 1H), 8.51 (d, J = 2.2 Hz, 1H), 8.31 (s, 1H), 8.24 (s, 1H), 8.13 (s, 1H), 7.92 (s, 1H), 7.77 (d, J = 2.6 Hz, 1H), 4.68 (s, 2H), 3.89 (s, 3H), 3.60 (m, 1H), 1.30 (d, J = 6.8 Hz, 3H), 1.16 (m, 1H), 0.58 (m, 1H), 0.45 – 0.36 (m, 2H), 0.26 (m, 1H). ESI MS $[M+H]^+$ for $C_{25}H_{23}F_3N_5O$, calcd. 466.2, found 466.2.

2-[(*1S*)-1-Cyclopropylethyl]-*N*-methyl-6-[3-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl]-3-oxo-2,3-dihydro-1*H*-isoindole-4-carboxamide (**53**)

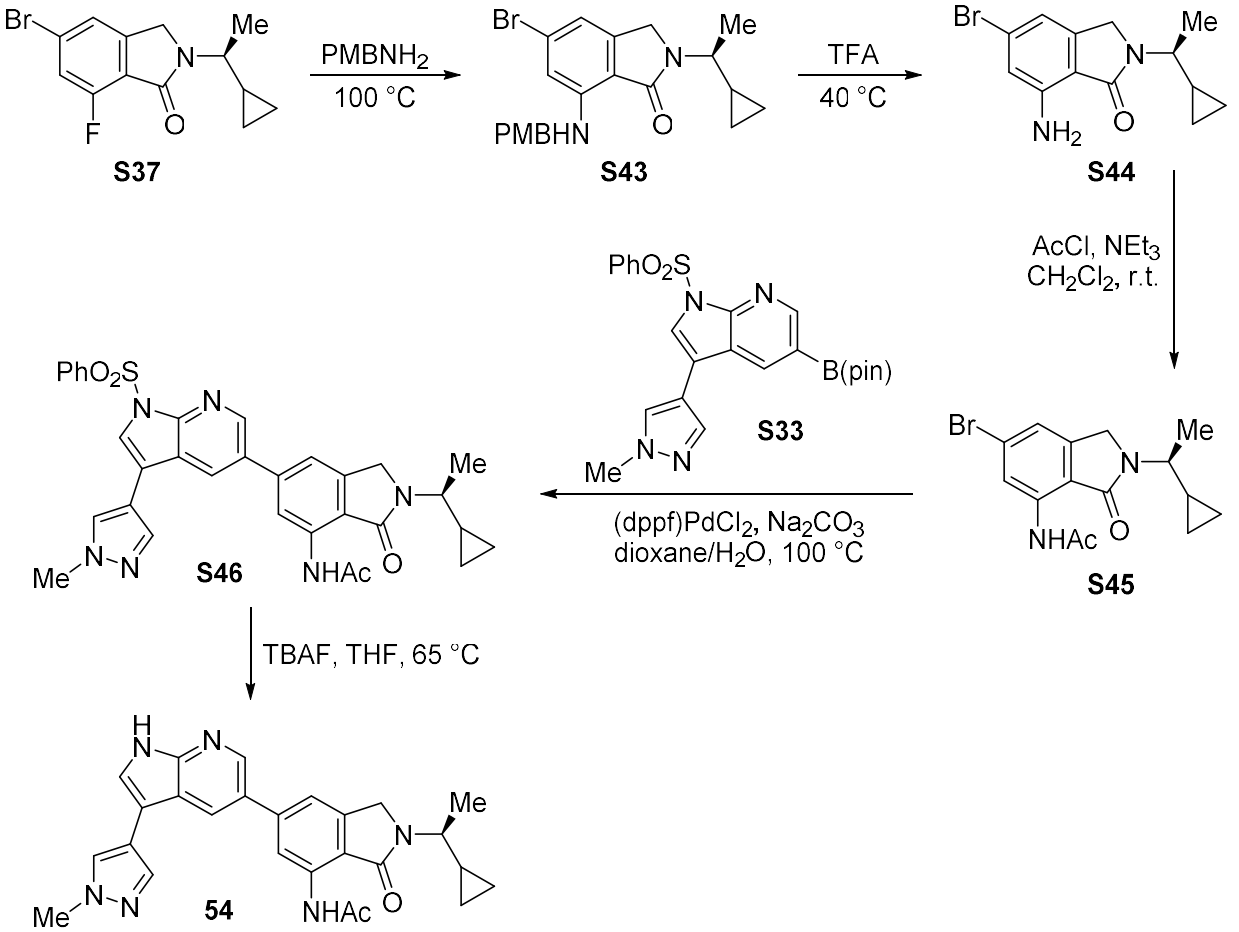


A mixture of **S41**[4] (250 mg, 0.771 mmol, 1.0 equiv), methylamine hydrochloride (52.1 mg, 0.771 mmol, 1.0 equiv), Et_3N (0.22 mL, 1.5 mmol, 2.0 equiv), and EDCI·HCl (163 mg, 0.848 mmol, 1.1 equiv.) in anhydrous DMF (1.54 mL) was stirred at 50 °C for 3 h. The reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification by flash column chromatography (silica, hexanes/EtOAc gradient) afforded **S42** (24 mg, 9% yield).

A mixture of **S42** (24 mg, 0.072 mmol, 1.0 equiv), **S33** (34 mg, 0.072 mmol, 1.0 equiv), (dppf)$PdCl_2$ (5.1 mg, 0.0070 mmol, 10 mol %), 2 M aqueous Na_2CO_3 (0.070 mL, 0.14 mmol, 2.0 equiv), and dioxane (0.72 mL) was stirred at 100 °C under a nitrogen atmosphere for 2 h. After cooling the reaction mixture, 6 N aqueous NaOH (0.14 mL, 0.84 mmol, 12 equiv) was added and the resulting mixture was stirred at 80 °C for 1 h. Upon complete conversion, as judged by LCMS analysis, the reaction mixture was cooled to 25 °C and diluted with EtOAc. The organic phase was separated, washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude material was purified by reversed-phase HPLC (10-90% gradient of ACN/H_2O with 0.1% TFA) to afford **53** as a white solid (10 mg, 24%, TFA salt). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.70 – 8.62 (m, 3H), 8.15 (d, J = 1.7 Hz, 1H), 8.13 (d, J = 0.8 Hz, 1H), 7.91 (d, J = 0.8 Hz, 1H), 7.71 (s,

1H), 4.83 – 4.69 (m, 2H), 3.99 (s, 3H), 3.78 – 3.68 (m, 1H), 3.04 (s, 3H), 1.44 (d, *J* = 6.8 Hz, 3H), 1.26 – 1.16 (m, 1H), 0.76 – 0.68 (m, 1H), 0.58 – 0.50 (m, 1H), 0.50 – 0.42 (m, 1H), 0.41 – 0.33 (m, 1H). ESI MS $[M+H]^+$ for $C_{26}H_{27}N_6O_2$, calcd. 455.2, found 455.2.

N-{2-[(1*S*)-1-cyclopropylethyl]-6-[3-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl]-3-oxo-2,3-dihydro-1*H*-isoindol-4-yl}acetamide (**54**)



S37 (3.00 g, 10.0 mmol, 1.0 equiv.) was combined with neat $PMBNH_2$ (4 mL) and stirred at 100 °C for 14 h. The reaction mixture was cooled and partitioned between 10% aq. citric acid solution and EtOAc. The aq. layer was separated and back extracted with additional EtOAc. The organic layers were combined and washed with additional 10% aq. citric acid solution, brine, and dried over $MgSO_4$. Concentration under reduced pressure furnished **S43** that was used crude in the next step.

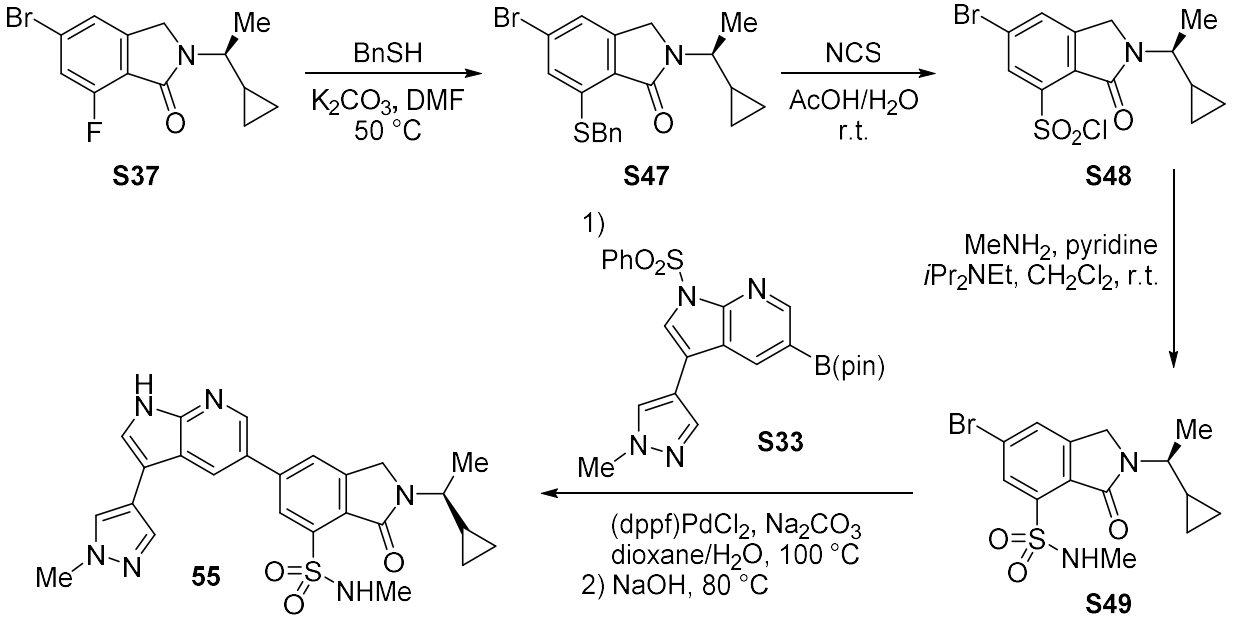
S43 was combined with TFA (15 mL) and stirred at 40 °C for 3 h. The reaction mixture was concentrated under reduced pressure and quenched with sat. aq. $NaHCO_3$ solution and diluted with EtOAc. The organic layers were combined, washed with brine and dried over $MgSO_4$. Concentration under reduced pressure and purification by column chromatography (SiO_2, hexanes to 50% EtOAc gradient) furnished **S44** as a white solid (2.89 g, ~98%, minor impurity co-eluted that was taken forward in the next step).

To a mixture of **S44** (250 mg, 0.850 mmol), NEt_3 (236 µL, 1.70 mmol), and CH_2Cl_2 (6.0 mL) at r.t. was added acetyl chloride (71 µL, 1.0 mmol). The reaction mixture was stirred at r.t. for 17 h and quenched with H_2O. The organic phase was dried over Na_2SO_4 and concentrated. The crude material was purified by column chromatography (hexanes/EtOAc), 0-50% gradient to afford **S45** (89 mg, 31%).

A mixture of **S45** (89.2 mg, 0.265 mmol), **S33** (147 mg, 0.317 mmol), (dppf)$PdCl_2$ (19 mg, 0.027 mmol), 2 M aqueous Na_2CO_3 (0.40 mL, 0.80 mmol), and dioxane (2.7 mL) was stirred at 100 °C under a nitrogen atmosphere for 6 h. The mixture was cooled, filtered through celite, and concentrated. The crude material was purified by column chromatography (hexanes/EtOAc), 20-100% gradient to afford **S46** (159 mg, 100%).

To a mixture of **S46** (159 mg, 0.265 mmol) and THF (10.6 mL) at r.t. was added TBAF (265 µL, 0.265 mmol, 1 M in THF). The reaction mixture was stirred at 65 °C for 2.5 h, cooled, and concentrated. The crude material was purified twice by reversed-phase HPLC (5-95% gradient of ACN/H_2O with 0.1% TFA) to afford **54** (15 mg, 10%, TFA salt). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.87 (d, J = 2.5 Hz, 1H), 10.36 (s, 1H), 8.62 (d, J = 1.2 Hz, 1H), 8.49 (d, J = 2.1 Hz, 1H), 8.35 (d, J = 2.1 Hz, 1H), 8.20 (d, J = 0.8 Hz, 1H), 7.87 (d, J = 0.8 Hz, 1H), 7.77 (d, J = 2.5 Hz, 1H), 7.67 (d, J = 1.3 Hz, 1H), 4.64 (s, 2H), 3.90 (s, 3H), 3.62 – 3.50 (m, 1H), 2.18 (s, 3H), 1.33 (d, J = 6.8 Hz, 3H), 1.18 (ddt, J = 12.8, 7.9, 4.2 Hz, 1H), 0.60 (dq, J = 12.2, 4.6, 3.6 Hz, 1H), 0.50 – 0.35 (m, 2H), 0.31 – 0.21 (m, 1H). ESI MS $[M+H]^+$ for $C_{26}H_{27}N_6O_2$; calcd 455.2, found 455.2.

2-[(1*S*)-1-Cyclopropylethyl]-*N*-methyl-6-[3-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl]-3-oxo-2,3-dihydro-1*H*-isoindole-4-sulfonamide (**55**)



To a solution of **S37** (2.50 g, 8.4 mmol) and benzyl mercaptan (1.18 mL, 10.1 mmol) in DMF (28 mL) was added potassium carbonate (3.47 g, 25.2 mmol). The mixture was heated to 50 °C overnight. After cooling to room temperature, the reaction was partitioned between EtOAc and water. The organics were washed with water (3x) and brine then dried over $MgSO_4$ and the solvent removed under reduced pressure. Purification by column chromatography (SiO_2, 10 → 50% EtOAc/hexanes) afforded **S47** (1.88 g, 56% yield). ESI MS $[M+H]^+$ for $C_{20}H_{20}BrNOS$, calcd. 402.0, found 402.0.

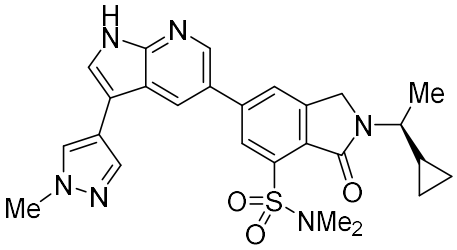
To a solution of **S47** (1.88 g, 4.68 mmol) in acetic acid (28 mL) and H_2O (3 mL) was added N-chlorosuccinimide (1.87 g, 14.0 mmol). The reaction was stirred at room temperature for two hours then diluted with EtOAc and washed with water (2x) and brine. The organics were dried over $MgSO_4$ and concentrated under reduced pressure to provide crude **S48** which is used without further purification.

To a solution of crude **S48** (758 mg, 2.0 mmol) in CH_2Cl_2 (16 mL) was added methylamine hydrochloride (270 g, 4.0 mmol) followed by pyridine (2.7 mL) and *i*Pr_2NEt (697 µL, 4.0 mmol). After two hours the reaction was diluted with EtOAc and washed sequentially with 0.2 M HCl, water, and brine. The organics were dried over $MgSO_4$ and concentrated under reduced pressure.

Purification by column chromatography (SiO_2, 20 → 70% EtOAc/hexanes) afforded **S49** as an off-white solid (500 mg, 67%). ESI MS $[M+H]^+$ for $C_{14}H_{17}BrN_2O_3S$, calcd. 373.0, found 373.0.

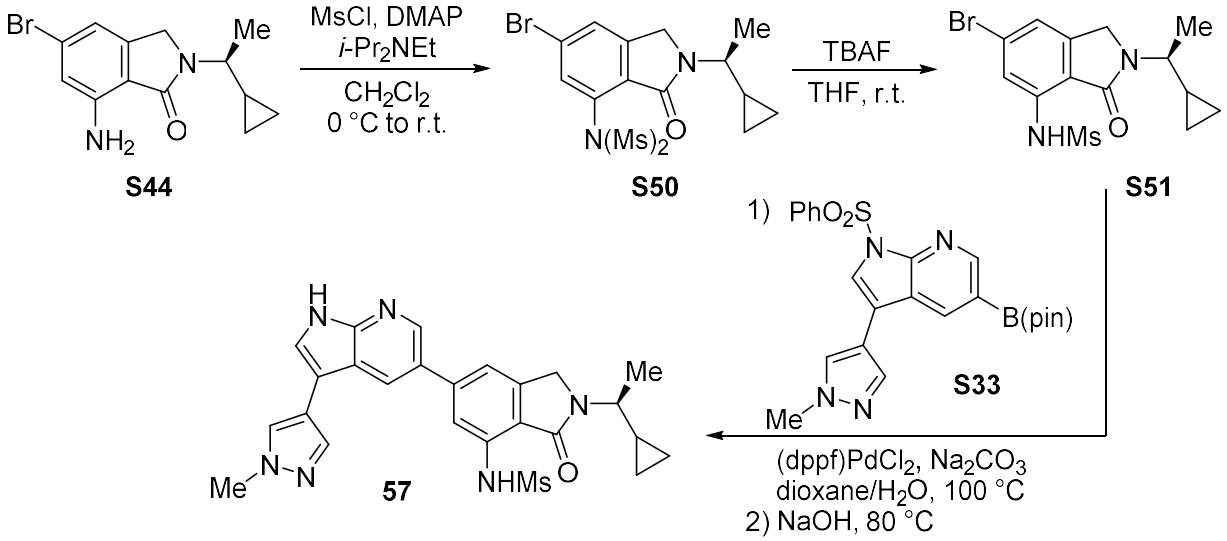
The final step was carried out using **S49** in a similar fashion to that described for **49** to afford **55**. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.94 (d, *J* = 2.5 Hz, 1H), 8.63 (d, *J* = 2.1 Hz, 1H), 8.53 – 8.49 (m, 1H), 8.36 (d, *J* = 1.6 Hz, 1H), 8.26 – 8.23 (m, 1H), 8.17 (d, *J* = 1.6 Hz, 1H), 7.93 (d, *J* = 0.8 Hz, 1H), 7.80 (d, *J* = 2.5 Hz, 1H), 7.66 (q, *J* = 5.1 Hz, 1H), 4.79 (s, 2H), 3.91 (s, 3H), 3.76 – 3.61 (m, 1H), 2.52 (d, *J* = 5.2 Hz, 3H), 1.35 (d, *J* = 6.8 Hz, 3H), 1.29 – 1.14 (m, 1H), 0.69 – 0.56 (m, 1H), 0.52 – 0.40 (m, 2H), 0.38 – 0.25 (m, 1H). ESI MS $[M+H]^+$ for $C_{25}H_{27}N_6O_3S$, calcd. 491.2, found 491.2.

2-[(1*S*)-1-Cyclopropylethyl]-*N*,*N*-dimethyl-6-[3-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl]-3-oxo-2,3-dihydro-1*H*-isoindole-4-sulfonamide (**56**)



56 was prepared in a similar manner to **55** using dimethylamine. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.92 (d, *J* = 2.5 Hz, 1H), 8.60 (d, *J* = 2.1 Hz, 1H), 8.47 (d, *J* = 2.1 Hz, 1H), 8.31 (d, *J* = 1.5 Hz, 1H), 8.20 (s, 1H), 8.12 (d, *J* = 1.5 Hz, 1H), 7.90 (d, *J* = 0.8 Hz, 1H), 7.78 (d, *J* = 2.5 Hz, 1H), 4.66 (s, 2H), 3.89 (s, 3H), 3.62 (m, 1H), 2.83 (s, 6H), 1.29 (d, *J* = 6.8 Hz, 3H), 1.14 (m, 1H), 0.58 (m, 1H), 0.45 – 0.35 (m, 2H), 0.24 (m, 1H). ESI MS $[M+H]^+$ for $C_{26}H_{29}N_6O_3S$, calcd. 505.2, found 505.2.

N-{2-[(1*S*)-1-Cyclopropylethyl]-6-[3-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl]-3-oxo-2,3-dihydro-1*H*-isoindol-4-yl}methanesulfonamide (**57**)



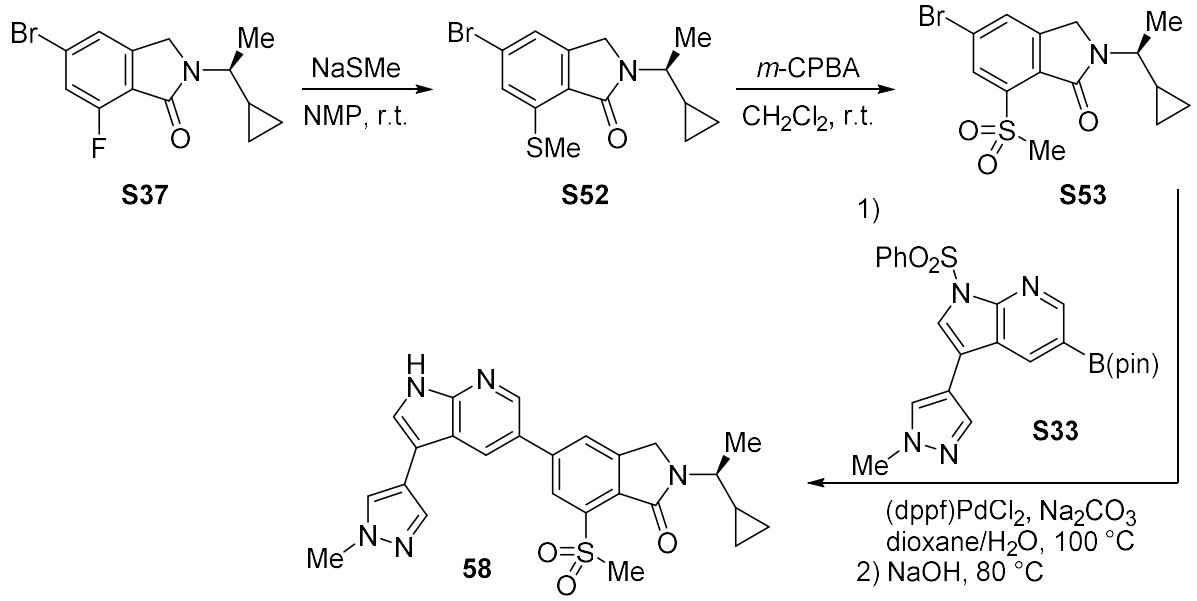
S44 (1.00 g, 3.38 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (10 mL) and the mixture was cooled to 0 °C. To this solution was added DMAP (40 mg, 0.34 mmol, 10 mol%), *i*-Pr_2NEt (1.6 mL, 10.1 mmol, 3.0 equiv.) and MsCl (0.7 mL, 8.5 mmol, 2.5 equiv.). The reaction mixture was warmed to r.t. and stirred for 1 h. The reaction was quenched with 1 M aq. HCl solution and diluted with EtOAc. The aq. layer was separated and back extracted with additional EtOAc. The organic layers were combined, washed with brine and dried over $MgSO_4$. Concentration under reduced pressure furnished **S50** that was taken crude into the next step.

S50 was dissolved in THF (5 mL) and TBAF (1.0 M in THF, 5.4 mL, 5.4 mmol, 1.6 equiv.) was added. An additional portion of TBAF (1.0 M in THF, 3.0 mL, 0.9 equiv.) was added after 15 min, followed by a final portion of TBAF (1.0 M in THF, 3.0 mL, 0.9 equiv.) after 2 h. The reaction mixture was stirred for an additional 1 h, then quenched with 1 M aq. HCl solution and diluted with EtOAc. The aq. layer was separated and back extracted with additional EtOAc. The organic layers were combined, washed with brine and dried over $MgSO_4$. Concentration under reduced pressure and purification by flash column chromatography (SiO_2, hexanes to 50% EtOAc gradient) furnished **S51** as a yellow solid (0.766 g, 2.1 mmol, 60% over 2 steps).

The final step was carried out using **S51** in a similar fashion to that described for **49** to afford **57**. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.89 (d, *J* = 2.6 Hz, 1H), 9.60 (s, 1H), 8.56 (d, *J* = 2.1 Hz, 1H), 8.43 – 8.38 (m, 1H), 8.21 (d, *J* = 0.8 Hz, 1H), 7.89 (d, *J* = 0.8 Hz, 1H), 7.77 (d, *J* = 2.5 Hz, 1H),

7.73 – 7.70 (m, 1H), 7.66 – 7.64 (m, 1H), 4.67 (s, 2H), 3.90 (s, 3H), 3.62 – 3.51 (m, 1H), 3.33 (s, 3H), 1.33 (d, J = 6.8 Hz, 3H), 1.24 – 1.12 (m, 1H), 0.65 – 0.54 (m, 1H), 0.52 – 0.38 (m, 2H), 0.32 – 0.22 (m, 1H). ESI MS $[M+H]^+$ for $C_{25}H_{27}N_6O_3S$, calcd. 491.2, found 491.2.

2-[(*1S*)-1-Cyclopropylethyl]-7-methanesulfonyl-5-[3-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl]-2,3-dihydro-1*H*-isoindol-1-one (**58**)



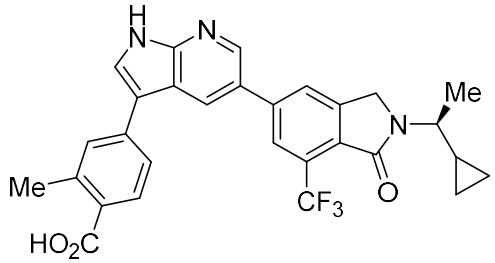
To a solution of **S37** (1.5 g, 5.1 mmol) in dry NMP (25 mL) under nitrogen at r.t. was added sodium methanethiolate (393 mg, 5.61 mmol) portionwise. The reaction mixture was stirred at r.t. for 30 min, diluted with EtOAc (50 mL), and subsequently washed with brine (2 x 20 mL). The organic layer was then dried over Na_2SO_4, and concentrated. The crude material was triturated with hexanes (50 mL) to afford **S52** as an off-white solid (1.2 g, 72%).

A solution of **S52** (1.2 g, 3.7 mmol) in dry CH_2Cl_2 (17 mL) was cooled to 0 ˚C and *m*-CPBA (2.1 g, 9.2 mmol) was added portionwise. After complete addition, the reaction was stirred at r.t. for 1 h. The reaction was diluted with CH_2Cl_2 (50 mL) and aqueous $NaHCO_3$ (20 mL). The organic layer was separated, dried over Na_2SO_4, concentrated, and purified by column chromatography (hexanes/EtOAc), 0-50% gradient (30 min) to afford **S53** as an off-white solid (1.2 g, 91%).

A mixture of **S53** (152 mg, 0.327 mmol, 1.0 equiv), **S33** (142 mg, 0.396 mmol, 1.1 equiv), $(dppf)PdCl_2$ (24 mg, 0.033 mmol, 10 mol %), 2 M aqueous Na_2CO_3 (0.33 mL, 0.65 mmol, 2.0

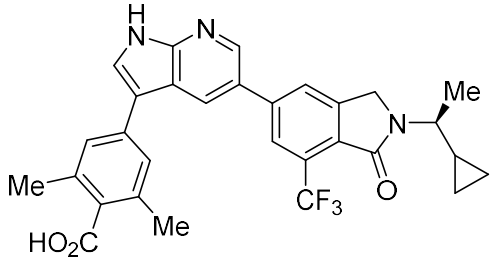
equiv), and dioxane (3.3 mL) was stirred at 100 °C under a nitrogen atmosphere for 2 h. After cooling the reaction mixture, 6 N aqueous NaOH (0.40 mL, 2.40 mmol, 7.3 equiv) was added and the resulting mixture was stirred at 80 °C for 0.5 h. Upon complete conversion, as judged by LCMS analysis, the reaction mixture was cooled to 25 °C and diluted with EtOAc. The organic phase was separated, washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude material was purified by flash column chromatography (silica, MeOH/CH_2Cl_2 gradient) to afford **58** as a white solid (17 mg, 11%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.88 (s, 1H), 8.65 – 8.58 (m, 1H), 8.47 (d, *J* = 1.5 Hz, 1H), 8.25 (dd, *J* = 2.2, 0.7 Hz, 1H), 7.96 (d, *J* = 1.5 Hz, 1H), 7.77 (d, *J* = 0.8 Hz, 1H), 7.69 – 7.66 (m, 1H), 7.47 (d, *J* = 2.5 Hz, 1H), 4.80 – 4.47 (m, 2H), 4.03 (s, 3H), 3.89 – 3.77 (m, 1H), 3.68 (s, 3H), 1.40 (d, *J* = 6.8 Hz, 3H), 1.12 – 1.01 (m, 1H), 0.74 – 0.62 (m, 1H), 0.54 – 0.37 (m, 3H). ESI MS $[M+H]^+$ for $C_{25}H_{26}N_5O_3S$, calcd. 476.2, found 476.2.

4-(5-{2-[(1*S*)-1-cyclopropylethyl]-1-oxo-7-(trifluoromethyl)-2,3-dihydro-1*H*-isoindol-5-yl}-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2-methylbenzoic acid (**59**)



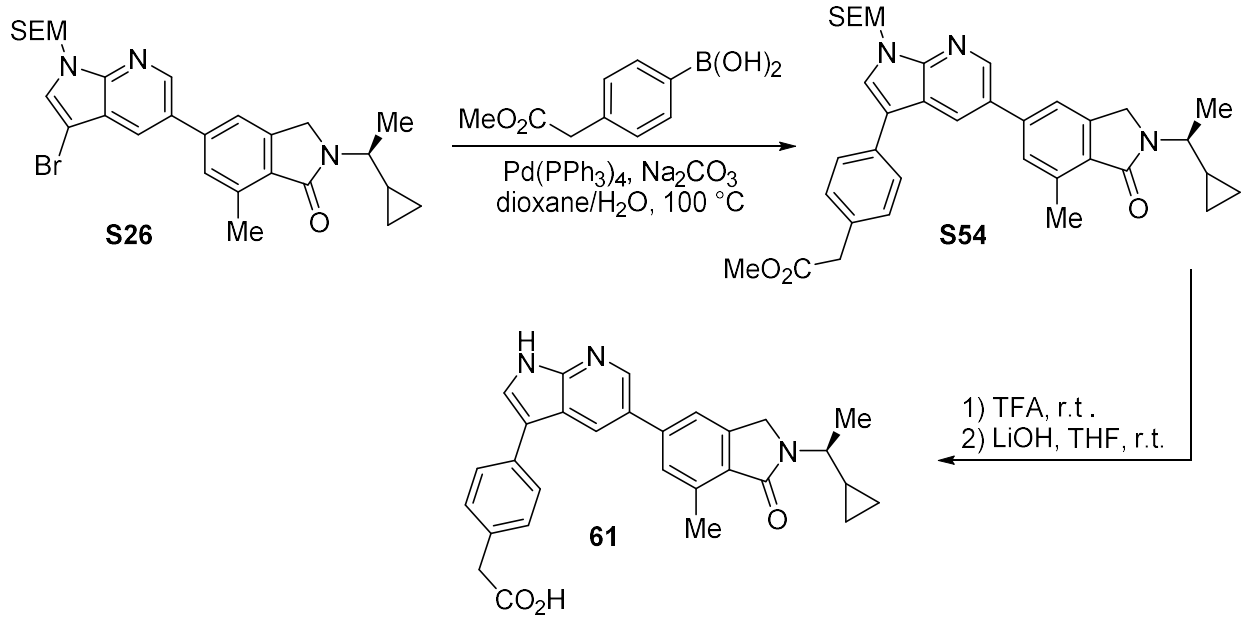
59 was prepared in a similar manner to **26** using **S40**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.28 (d, *J* = 2.8 Hz, 1H), 8.69 (d, *J* = 2.1 Hz, 1H), 8.64 (d, *J* = 2.1 Hz, 1H), 8.32 (s, 1H), 8.13 (s, 1H), 8.10 (d, *J* = 2.7 Hz, 1H), 7.93 (d, *J* = 8.1 Hz, 1H), 7.76 (m, 1H), 7.73 (s, 1H), 4.68 (s, 2H), 3.60 (m, 1H), 2.61 (s, 3H), 1.30 (d, *J* = 6.8 Hz, 3H), 1.14 (m, 1H), 0.58 (m, 1H), 0.46 – 0.34 (m, 2H), 0.26 (m, 1H). ESI MS $[M+H]^+$ for $C_{29}H_{25}F_3N_3O_3$, calcd. 520.2, found 520.2.

4-(5-{2-[(1*S*)-1-cyclopropylethyl]-1-oxo-7-(trifluoromethyl)-2,3-dihydro-1*H*-isoindol-5-yl}-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2,6-dimethylbenzoic acid (**60**)



60 was prepared in a similar manner to **29** using **S40**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.19 (d, J = 2.7 Hz, 1H), 8.68 (d, J = 2.1 Hz, 1H), 8.59 (d, J = 2.2 Hz, 1H), 8.31 (d, J = 1.4 Hz, 1H), 8.13 (d, J = 1.4 Hz, 1H), 7.98 (d, J = 2.7 Hz, 1H), 7.51 (t, J = 0.7 Hz, 2H), 4.70 (s, 2H), 3.68 – 3.54 (m, 1H), 2.37 (s, 6H), 1.31 (d, J = 6.8 Hz, 3H), 1.23 – 1.12 (m, 1H), 0.59 (dq, J = 8.9, 4.5, 3.4 Hz, 1H), 0.42 (ddt, J = 14.5, 9.3, 5.2 Hz, 2H), 0.31 – 0.21 (m, 1H). ESI MS $[M+H]^+$ for $C_{30}H_{27}F_3N_3O_3$; calcd 534.2, found 534.1.

2-[4-(5-{2-[(1*S*)-1-Cyclopropylethyl]-7-methyl-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl}-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)phenyl]acetic acid (**61**)

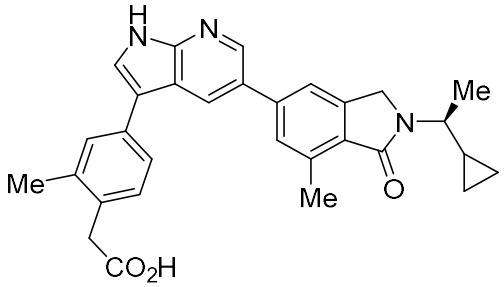


To a mixture of **S26** (216 mg, 0.400 mmol), 4-(methoxycarbonylmethyl)phenylboronic acid (85 mg, 0.44 mmol), $Pd(PPh_3)_4$ (46 mg, 0.040 mmol), and Na_2CO_3 (93 mg, 0.88 mmol) under nitrogen

was added degassed dioxane (2.0 mL) and degassed H_2O (0.5 mL). The reaction mixture was stirred at reflux for 14 h, cooled, and diluted with brine (10 mL). The solids were collected by filtration, washed with water, dried, and purified by column chromatography (hexanes/EtOAc), 0-100% gradient (30 min) to afford **S54** as an off-white solid (95 mg, 40%). ESI MS $[M+H]^+$ for $C_{36}H_{44}N_3O_4Si$, calcd. 610.3, found 610.2.

S54 (95 mg, 0.16 mmol) was dissolved in TFA (1.0 mL) and stirred at r.t. for 3h. Subsequently, TFA was removed and the crude material was redissolved in THF. To this mixture was added a 0.5 M aqueous solution of LiOH (0.5 mL) and stirred at r.t. for 14 h. The reaction was neutralized with 1.0 M aqueous HCl and purified by reversed phase HPLC (H_2O/ACN+0.1%TFA), 5-95% gradient (45 min) to afford **61** as a white solid (30 mg, 32%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.05 (s, 1H), 8.60 (d, J = 2.1 Hz, 1H), 8.47 (d, J = 2.0 Hz, 1H), 7.90 (d, J = 2.6 Hz, 1H), 7.82 – 7.59 (m, 4H), 7.33 (d, J = 8.3 Hz, 2H), 4.53 (s, 2H), 3.66 – 3.48 (m, 3H), 2.67 (d, J = 0.6 Hz, 3H), 1.27 (d, J = 6.8 Hz, 3H), 1.12 (dtd, J = 13.0, 8.4, 4.9 Hz, 1H), 0.56 (ddd, J = 9.6, 8.0, 4.2 Hz, 1H), 0.43 – 0.30 (m, 2H), 0.27 – 0.17 (m, 1H) [exchangeable carboxylic acid proton not observed]. ESI MS $[M+H]^+$ for $C_{29}H_{28}N_3O_3$, calcd. 466.2, found 466.2.

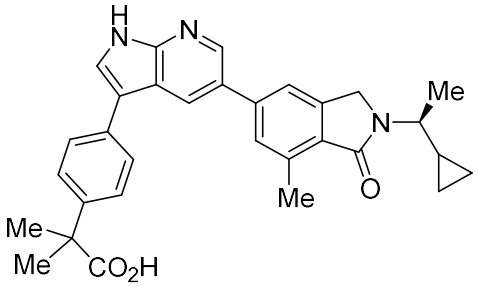
2-[4-(5-{2-[(1*S*)-1-Cyclopropylethyl]-7-methyl-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl}-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2-methylphenyl]acetic acid (**62**)



62 was prepared in a similar manner to **61** using methyl 2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-phenylacetate. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.61 (d, J = 2.1 Hz, 1H), 8.47 (d, J = 2.1 Hz, 1H), 7.89 (d, J = 2.6 Hz, 1H), 7.79 (s, 1H), 7.64 (s, 1H), 7.56 (d, J = 6.8 Hz, 2H), 7.27 (d, J = 8.4 Hz, 1H), 4.55 (s, 2H), 3.59 (m, 3H), 2.69 (s, 3H), 2.32 (s, 3H), 1.29 (d, J = 6.8 Hz, 3H), 1.19 – 1.08 (m, 1H), 0.63 – 0.53 (m, 1H), 0.47 – 0.33 (m, 2H), 0.24 (p, J = 4.7 Hz, 1H)

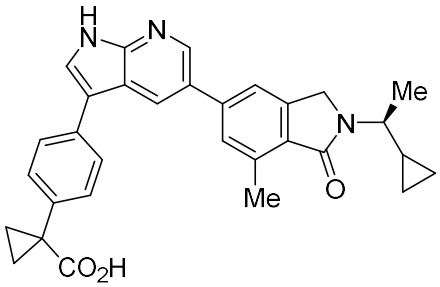
[exchangeable carboxylic acid and azaindole NH protons not observed]. ESI MS $[M+H]^+$ for $C_{30}H_{30}N_3O_3$, calcd. 480.2, found 480.1.

2-[4-(5-{2-[(1*S*)-1-Cyclopropylethyl]-7-methyl-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl}-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)phenyl]-2-methylpropanoic acid (**63**)



63 was prepared in a similar manner to **61** using 2-(4-boronophenyl)-2-methylpropanoic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.04 (d, J = 2.6 Hz, 1H), 8.61 (d, J = 2.1 Hz, 1H), 8.50 – 8.45 (m, 1H), 7.89 (d, J = 2.6 Hz, 1H), 7.78 (s, 1H), 7.76 – 7.71 (m, 2H), 7.64 (d, J = 1.3 Hz, 1H), 7.45 – 7.38 (m, 2H), 4.53 (s, 2H), 3.63 – 3.51 (m, 1H), 2.68 (s, 3H), 1.50 (s, 6H), 1.27 (d, J = 6.8 Hz, 3H), 1.11 (ddt, J = 4.5, 8.2, 13.0 Hz, 1H), 0.56 (ddd, J = 4.3, 8.1, 9.4 Hz, 1H), 0.46 – 0.31 (m, 2H), 0.27 – 0.17 (m, 1H) [exchangeable carboxylic acid and azaindole NH protons not observed]. ESI MS $[M+H]^+$ for $C_{31}H_{32}N_3O_3$, calcd. 494.2, found 494.1.

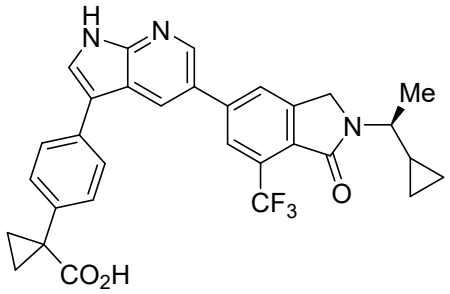
1-[4-(5-{2-[(1*S*)-1-Cyclopropylethyl]-7-methyl-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl}-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)phenyl]cyclopropane-1-carboxylic acid (**64**)



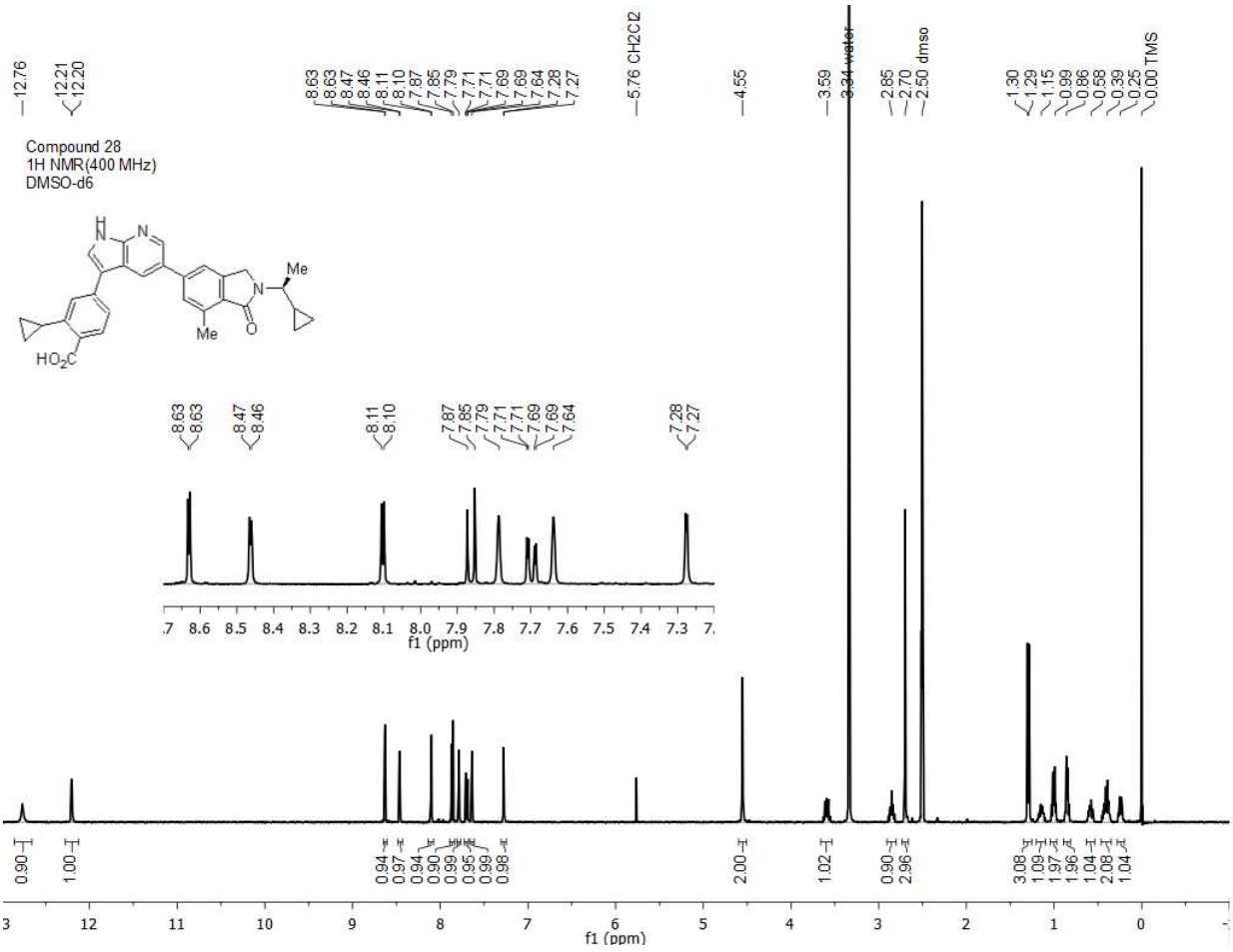
64 was prepared in a similar manner to **61** using [4-(1′-carboxycyclopropyl)phenyl]boronic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.05 (d, J = 2.7 Hz, 1H), 8.60 (d, J = 2.1 Hz, 1H), 8.48 – 8.44 (m, 1H), 7.89 (d, J = 2.6 Hz, 1H), 7.77 (dd, J = 1.6, 0.8 Hz, 1H), 7.72 – 7.66 (m, 2H), 7.63 (dd, J

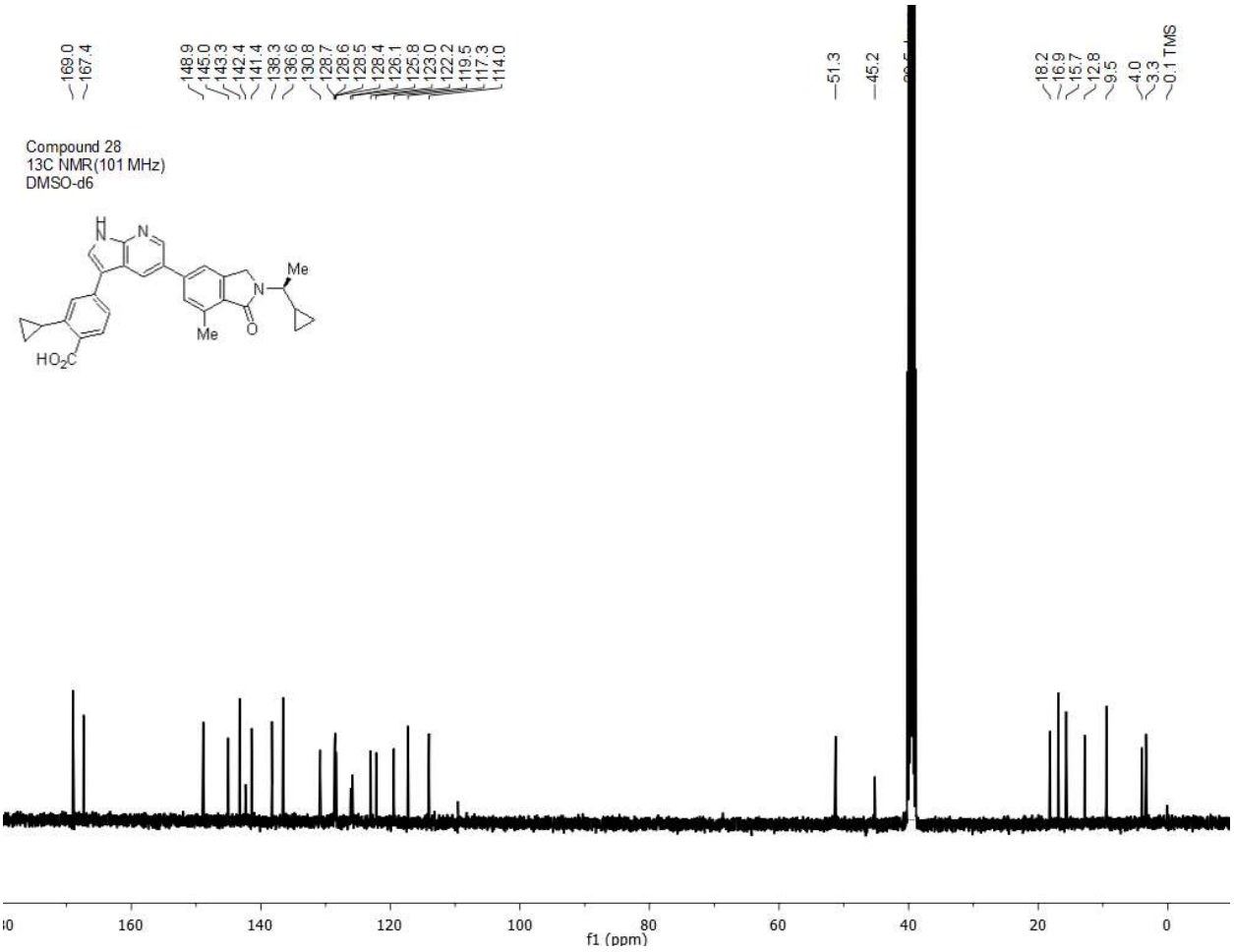
= 1.6, 0.8 Hz, 1H), 7.41 – 7.36 (m, 2H), 4.53 (s, 2H), 3.63 – 3.49 (m, 1H), 2.68 (d, *J* = 0.7 Hz, 3H), 1.46 (q, *J* = 3.8 Hz, 2H), 1.27 (d, *J* = 6.9 Hz, 3H), 1.19 – 1.03 (m, 3H), 0.62 – 0.49 (m, 1H), 0.46 – 0.31 (m, 2H), 0.29 – 0.16 (m, 1H) [exchangeable carboxylic acid proton signal not observed]. ^{13}C NMR (101 MHz, DMSO-d_6) δ 175.5, 167.4, 148.6, 143.3, 142.0, 141.4, 137.6, 136.6, 133.3, 130.9, 128.6, 128.4, 128.3, 126.1, 126.0, 124.8, 119.5, 117.5, 117.0, 114.8, 109.6, 51.3, 45.2, 28.3, 18.2, 16.9, 15.8, 15.7, 4.0, 3.3. ESI MS $[M+H]^+$ for $C_{31}H_{30}N_3O_3$, calcd. 492.2, found 492.2.

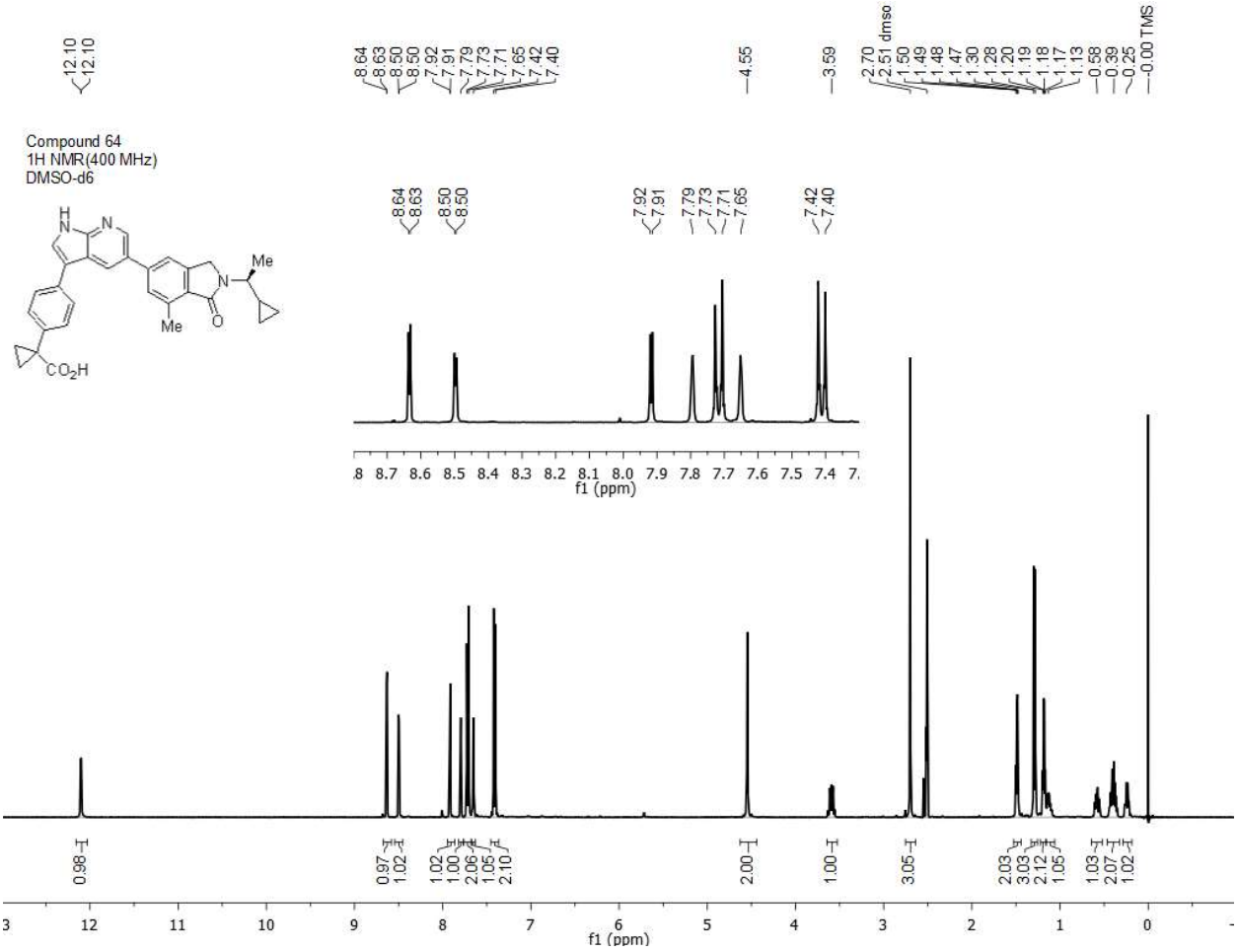
1-[4-(5-{2-[(1*S*)-1-cyclopropylethyl]-1-oxo-7-(trifluoromethyl)-2,3-dihydro-1*H*-isoindol-5-yl}-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)phenyl]cyclopropane-1-carboxylic acid (**65**)

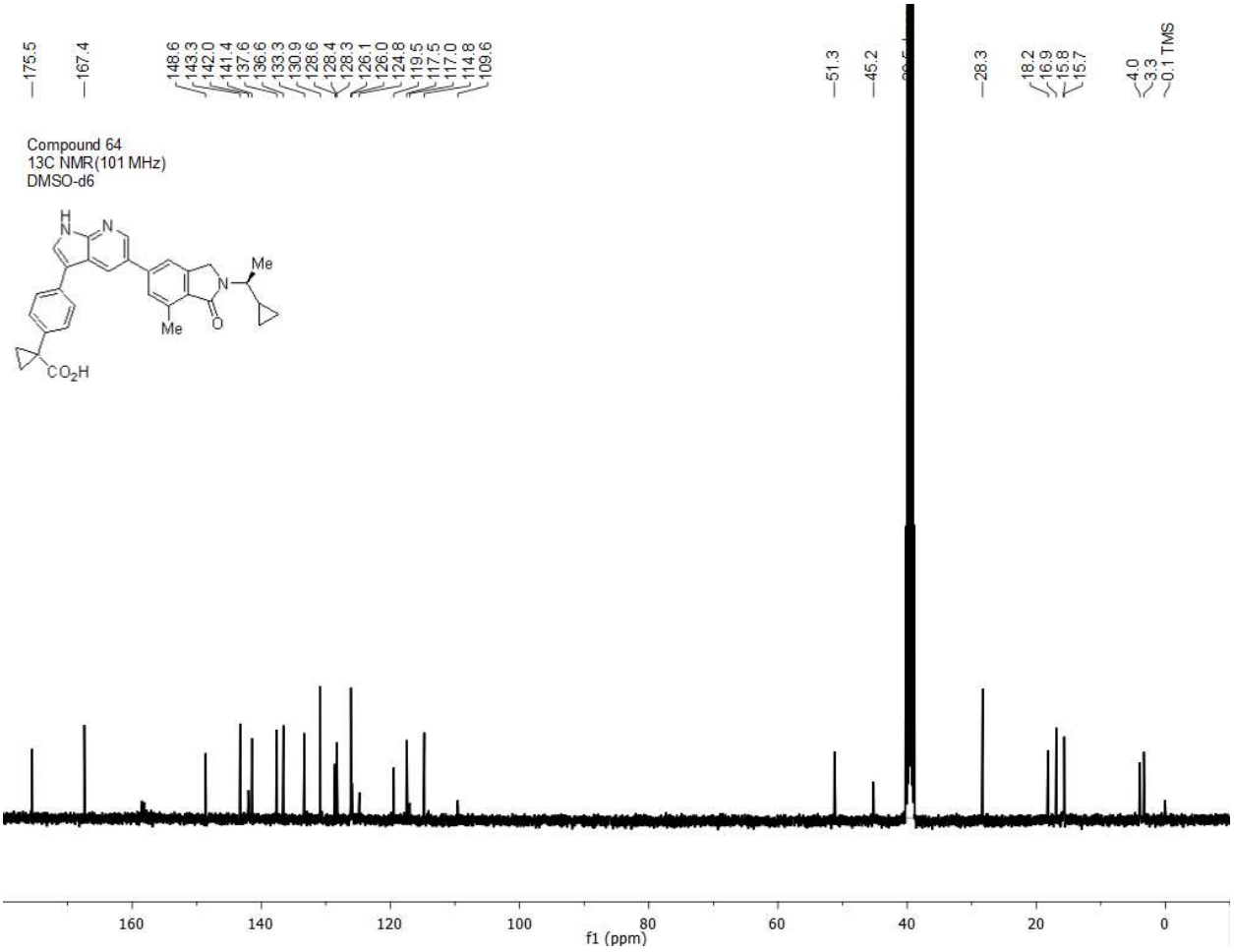


65 was prepared in a similar manner to **64** using **S40**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.14 (d, *J* = 2.6 Hz, 1H), 8.68 (d, *J* = 2.1 Hz, 1H), 8.57 (d, *J* = 2.1 Hz, 1H), 8.31 (s, 1H), 8.13 (s, 1H), 7.92 (d, *J* = 2.6 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 4.67 (s, 2H), 3.59 (m, 1H), 1.46 (q, *J* = 3.8 Hz, 2H), 1.29 (d, *J* = 6.8 Hz, 3H), 1.19 – 1.09 (m, 3H), 0.57 (m, 1H), 0.45 – 0.35 (m, 2H), 0.25 (m, 1H). ESI MS $[M+H]^+$ for $C_{31}H_{27}F_3N_3O_3$, calcd. 546.2, found 546.2.


Compound 28
1H NMR(400 MHz)
DMSO-d6
12.76
12.21
12.20
8.63
8.63
8.47
8.46
8.11
8.10
7.87
7.85
7.79
7.71
7.71
7.69
7.69
7.64
7.28
7.27
5.76 CH2Cl2
4.55
3.59
3.34 water
2.85
2.70
2.50 dmso
1.30
1.29
1.15
0.99
0.86
0.58
0.39
0.25
0.00 TMS
Me
Me
O
N
HO2C
f1 (ppm)
0.90
1.00
0.94
0.97
0.94
0.90
0.99
0.95
0.99
0.98
2.00
1.02
0.90
2.96
3.08
1.09
1.97
1.96
1.04
2.08
1.04

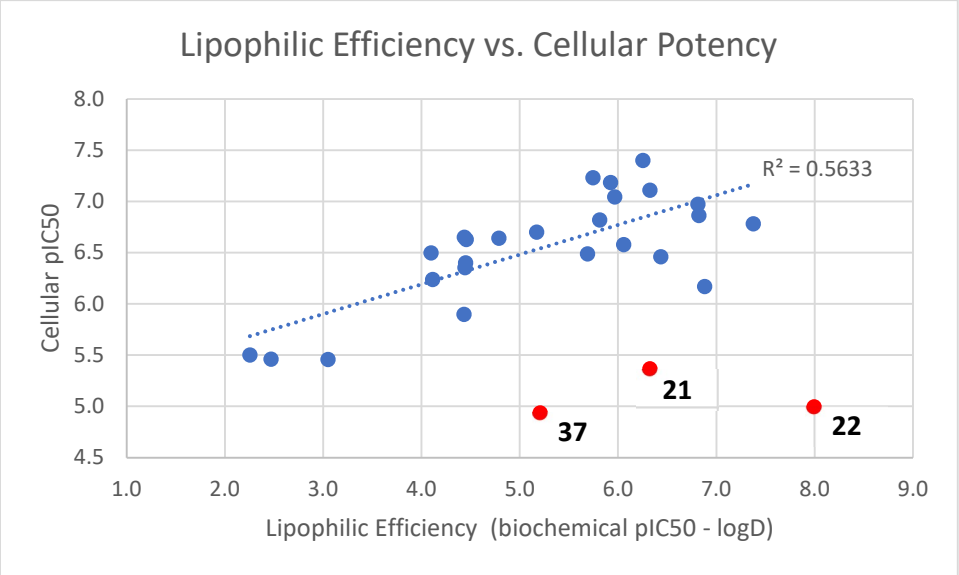

169.0
167.4
148.9
145.0
143.3
142.4
141.4
138.3
136.6
130.8
128.7
128.6
128.5
128.4
126.1
125.8
123.0
122.2
119.5
117.3
114.0
51.3
45.2
18.2
16.9
15.7
12.8
9.5
4.0
3.3
0.1 TMS
Compound 28
13C NMR(101 MHz)
DMSO-d6
H
N
N
Me
N
O
Me
HO2C
160
140
120
100
80
60
40
20
0
f1 (ppm)


Compound 64
1H NMR(400 MHz)
DMSO-d6
f1 (ppm)


175.5
167.4
148.6
143.3
142.0
141.4
137.6
136.6
133.3
130.9
128.6
128.4
128.3
126.1
126.0
124.8
119.5
117.5
117.0
114.8
109.6
51.3
45.2
28.3
18.2
16.9
15.8
15.7
4.0
3.3
0.1 TMS
Compound 64
13C NMR(101 MHz)
DMSO-d6
Me
Me
CO2H
160
140
120
100
80
60
40
20
0
f1 (ppm)

Lipophilic efficiency versus cellular potency

If compounds with a particularly unique geometry (**21**, **22**, and **37**) are excluded, a modest correlation is observed between cellular potency plotted against biochemical assay-derived lipophilic efficiency values.



Compound	LE	Cellular pIC50
12	4.4	6.7
13	4.1	6.5
14	3.0	5.5
15	4.1	6.2
16	2.3	5.5
17	4.4	6.4
18	2.5	5.5
19	5.2	6.7
20	4.8	6.6
21	6.3	5.4
22	8.0	5.0
23	4.4	5.9
24	5.7	6.5
25	6.8	6.9
26	6.3	7.1
27	5.7	7.2
28	6.3	7.4
29	6.0	7.0

30	5.9	7.2
31	6.9	6.2
32	6.4	6.5
33	7.4	6.8
34	5.8	6.8
35	6.8	7.0
36	6.1	6.6
37	5.2	4.9
38	4.5	6.6
39	4.4	6.4

[1] Noriyasu, H.; Masanori, I.; Hironori M.; Masami, O.; Hironao, S.; Yoshihiro, S.; Tomoyuki, T. Imidazopyridin-2-on Derivative. *WIPO* **2010**, WO 2010/016490 A1.
[2] Prepared according to literature protocols: Hong, S.; Kim, J.; Seo, J. H.; Jung, K. H.; Hong, S.-S.; Hong, S. *J. Med. Chem.* **2012**, *55*, 11, 5337-5349.
[3] Mogemark, M.; Pemberton, N.; Petersen, J.; Perry, M.; Karabelas, K.; Zlatoidsky, P.; Cox, R.; Tyrchan, C. Novel Inhibitors of Phosphatidylinositol 3-Kinase Gamma. *WIPO* **2017**, WO 2017/ 153527 A1.
[4] Cox, R.; Karabelas, K.; Mogemark, M.; Pemberton, N.; Perry, M.; Petersen, J.; Tyrchan, C.; Zlatoidsky, P. Novel Inhibitors of Phosphatidylinositol 3-Kinase Gamma. *WIPO* **2017**, 2017/153527 A1.