Supporting Information

INCB050465 (Parsaclisib), a Novel Next-Generation Inhibitor of Phosphoinositide 3-Kinase Delta (PI3Kδ)

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Biological Assays

In vitro Biology.

PI3Kδ SPA Assay. The PI3K assays were carried out at room temperature in 20 mM 4-morpholinepropanesulfonic acid, pH 6.7, 10 mM $MgCl_2$, 5 mM DTT, and 0.03% 3-[(3-cholamidopropyl)-dimethylammonio]-1-propanesulfonic acid in a 384-well plate with a final volume of 15 µL. Reactions were initiated by the addition of ATP, the final reaction mixture consisted of 20 µM D-myo-phosphatidylinositol 4,5-bisphosphate (Echelon Biosciences, Salt Lake City, UT), 20 µM ATP, 0.2 µCi [γ-^{33}P] ATP (Perkin–Elmer, Waltham, MA), 1.3 nM PI3Kδ (Millipore, Bedford, MA) and varying concentration of inhibitors. After 120 min incubation, the reactions were terminated by the addition of 40 µL wheat germ agglutinin YSi SPA scintillation beads (1.0 mg/mL) suspended in quench buffer: 150 mM potassium phosphate pH 8.0, 20% glycerol, 25 mM EDTA. The radioactivity of the product was determined by scintillation counting on Topcount (Perkin-Elmer). IC_{50} determination was performed by curve fitting using the GraphPad Prism 3.0 software.

PI3K Filter Binding Assay. The kinase reaction was conducted at room temperature in 20 mM 4-morpholinepropanesulfonic acid, pH 6.7, 10 mM $MgCl_2$, 5 mM dithiothreitol and 0.03% 3-[(3-cholamidopropyl)-dimethylammonio]-1-propanesulfonic acid in a 96-well plate with a final volume of 25 µL. The reaction mixture contained 50 µM D-myophosphatidylinositol 4,5-bisphosphate (Echelon Biosciences, SaltLake City, UT), the kinase and varying concentration of inhibitors. The final concentration of PI3K isoforms α, β, δ and γ (Millipore, Bedford, MA) in the assay were 1.3, 9.4, 0.3 and 3 nM respectively. Reactions were initiated by the addition of ATP to a final concentration of 1000 µM containing 2.2 µCi [γ-^{33}P] ATP (Perkin-Elmer, Boston, MA) and terminated by the addition of 100 µL quench buffer (1 M potassium phosphate, pH 8.0, 30 mM EDTA) after incubation for 120 min. The reaction solution was then filtered with 96-well MultiScreen IP 0.45 mm polyvinylidene difluoride filter plates (Millipore, Billerica, MA). The filter plate was washed with 7 X 200 µL wash buffer containing 1 M potassium phosphate (pH 8.0) and 1 mM ATP. The plate was air dried at 37 °C for 2 h before the

addition of 120 μL Microscint 20 scintillation cocktail (Perkin-Elmer, Boston, MA) in each well. The radioactivity of the product was determined by scintillation counting on Topcount (Perkin-Elmer). IC_{50} determination was performed by curve fitting using the GraphPad Prism 3.0 software.

SU-DHL-6 Cell Viability Assay. SU-DHL-6 cells (ATCC, Human B cell chronic lymphocytic leukemia/lymphoma) were cultured in 96 well plates (Perkin Elmer View Plate-96 FTC Black 96 well, sterile, w/lid; Product # 6005225) at 1 x 10^5/well in 100 μL of RPMI1640, 10% FBS in the presence of different amounts of test compounds also in 100 μL bringing the total volume of cells and compound to 200 μL and incubated 4 d at 37 °C in 5% CO_2. On the fourth day, 100 μL of the CellTiter-GLO Luminescent (Promega, Madison, WI; cat # 3582) agent was added to each well and allowed to incubate at rt for 10 min to stabilize luminescent signal, to determine the number of viable cells in culture based on quantitation of the ATP present, which signals the presence of metabolically active cells. The plates recorded luminescence by measuring the luminescence with TopCount (Packard Bioscience). IC_{50} determination was performed by fitting the curve of percent inhibition activity versus the log of the inhibitor concentration using GraphPad Prism 3.0 software.

Pfeiffer Cell Proliferation Assay. Pfeiffer cells (CRL-2632, ATCC Human non-Hodgkin's B cell lymphoma) were cultured in 96 well plates (Costar cat # 3474 Ultra Low Cluster Plate, Flat Bottom, Ultra Low Attachment) at 1.5 x 10^3/well in 100 μL of RPMI1640 10% FBS, in the presence of different amount of test compounds also in 100 μL bringing the total volume of cells and compound to 200 μL, incubated for 4 d at 37 °C in 5% CO_2. On the fourth day, [^{3}H]-thymidine (1 μCi/well) (PerkinElmer, Boston, MA) in RPMI1640, 10% FBS was then added to the Pfeiffer cell cultures for an additional 24 h before the incorporated radioactivity was separated by filtration with water through GF/B filters (Packard Bioscience, Meriden, CT) and measured by liquid scintillation counting with a TopCount (Packard Bioscience). IC_{50} determination was performed by fitting the curve of percent inhibition activity versus the log of the inhibitor concentration using GraphPad Prism 3.0 software. To estimate the clinical plasma concentration (total drug) needed to achieve IC_{50}, the IC_{50} value from the Pfeiffer cell assay was corrected

for the fraction unbound in media to approximate IC_{50}, and then corrected for the fraction unbound in human plasma.

RAMOS pAKT FACS Assay. RAMOS (ATCC, Human B cell lymphocyte, Burkett's lymphoma) cells were plated in standard 96 well deep well polypropylene plates at 1 x 10^6/well in 100 μL of serum free RPMI1640, in the presence of different amount of test compounds in 14 μL and 245 μL of serum free RPMI1640. Plates were incubated 2 h at 37 °C in 5% CO_2. 10 μL/well (4 μg/mL) of anti-IgM/anti IgG, was added and incubated for 15 min in 37 °C water bath. 120 μL of Lyse/Fix solution was then added and incubated for 10 min in 37 °C water bath. Spin plate at 1600 rpm for 5 min and decant supernatant. 200 μL/well of permeabilization buffer was added and left on ice for 30 min. Can store in -80 °C overnight if needed. 800 μL/well of staining buffer was added and plates spun at 1600 rpm for 5 min and supernatant decanted. 25 μL/well of 1 μg/mL anti-p-AKT (Ser473) Alexa Fluor 488 antibody was added and incubated in the dark at rt for 1 h. 500 μL/well of standard staining buffer was added and spun for 5 min at 1600 rpm. The supernatant was decanted and resuspended in 400 μL of staining buffer. Lastly, add 200 μL to standard 96 well U bottom polypropylene plate and read on Flow Cytometer. IC_{50} determination was performed by fitting the curve of percent inhibition activity versus the log of the inhibitor concentration using GraphPad Prism 3.0 software.

Whole Blood Assay. The effect of PI3Kd inhibition on anti-IgE antibody-induced CD63 expression on basophils in human whole blood was evaluated using the Flow Cast kit (ALPCO) according to the manufacturer's instructions. IC_{50} determination was performed by fitting the curve of percent inhibition activity versus the log of the inhibitor concentration using GraphPad Prism 3.0 software.

HEK 293 Cell Viability Assay. Human Embryonic Kidney 293 cells (HEK293), DMEM with high glucose and Fetal bovine serum (FBS) were purchased from Thermo Fisher Scientific (Waltham, MA.). CellTiter-Glo® Luminescent Cell Viability Assay kit was purchased from Promega (Madison, WI). HEK 293 Cell were cultured in DMEM with high glucose with 10% FBS at 37 °C, 5% CO_2. Following cells plating in 96-well white clear bottom assay plate (CELLCOAT® Tissue Culture Plates,

Greiner Bio-One) at 2000 cells per well, the cells were treated with compounds in the final assay at 20 μM. 72 h after incubation at 37 °C, 5% CO_2, CellTiter-Glo™ reagent were added and luminescence signal was read with Pherastar microplate reader (BMG Labtech). Test compound cell viability were calculated and reported as percentage of inhibition relative to wells with DMSO only (0% inhibition) and wells with no cells but assay medium only (100% inhibition).

hERG Filter Binding Assay. hERG filter binding assays were performed using hERG K^+ Channel membrane (Perkin Elmer) in 96-well polystyrene plate (Fisher scientific). Test compound and control compound Dofetilide were incubated at 4 °C for 24 h in 200 μL of hERG membrane in binding buffer (10 mM HEPES, 130 mM NaCl, 5 mM KCl, 0.8 mM $MgCl_2$, EGTA 1mM, 10 mM glucose at pH 7.4) containing [^{3}H] Dofetilide (0.06 μCi/well, Sequoia Research Product). The final membrane protein concentration is 14 μg/well. Each compound was tested at final concentration of 30 μM. Following aspiration onto GF/C filter plates by Harvester (Perkin Elmer), the plates were washed 6 times with 240 μL wash buffer (25 mM Tris–HCl, 130 mM NaCl, 5.5 mM KCl, 0.8 mM $MgCl_2$, 0.05 mM $CaCl_2$, 5 mM Glucose, BSA 0.01% at pH 7.4, 4 °C) and dried at 37 °C for 30 min. The radioactivity was counted in a Packard Topcount Scintillation Counter after addition of 50 μL of scintillant (Packard Microscint-20). Test compound inhibitory effects were calculated and reported as percentage of inhibition relative to wells with 1.25 μM Dofedtilide (100% inhibition) and wells with DMSO only (0% inhibition).

hERG Patch Clamp Assay. The in vitro effects of **20** on ionic currents in voltage-clamped human embryonic kidney cells (HEK293) that stably express the human ether-à-go-go-related gene (hERG) were determined. **20** was evaluated at 10, 30, 100 or 300 μM. All experiments were performed under physiological temperature conditions (35 ± 2 ºC). The IC50 for the inhibitory effect of **20** on hERG potassium current was 188.0 μM (Hill coefficient = 1.0). Under identical conditions, the positive control (60 nM terfenadine) inhibited hERG potassium current confirming the sensitivity of the test system to hERG inhibition.

PXR-mediated human/rat CYP3A induction assay. HepG2 cells from American Type Culture Collection (Manassas, VA) were transiently transfected with pRL-TK vector expressing Renilla luciferase

reporter (Promega, Madison, WI), CMV vector expressing CYP3A-Luc reporter and CMV vector expressing human PXR or rat PXR. The transfected cells were dispensed at 3 x 10^4 cells/100 μL/well in 96-well plates and cultured for 24 h at 37 °C in humidified incubator supplied with 5% CO_2. Transfected cells were then subjected to compound treatment for 24 h with 0.6% DMSO in the final assay at 10 μM. Rifampicin (3, 10, and 30 μM) and prenenolone 16α-carbonitrile (3, 10, and 30 μM) were used as positive controls for the human PXR and rat PXR assays, respectively. After the addition of Dual-Glo® luciferase reagent (Promega, Madison, WI) and incubation at rt for 10 min, the firefly luminescence was read on TopCount (Perkin Elmer, Boston, MA). After the first reading, the Dual-Glo® Stop & Glo® reagent (Promega, Madison, WI) were added and kept at rt for 10 min before Renilla luminescence was read on TopCount. The percentage of induction was reported based on the ratio of firefly/Renilla luminescence normalized to the control compound wells within each assay plate.

In vivo Biology.

Pfeiffer (CRL-2632, ATCC, Rockville, MD) tumor fragments (1 cm × 1 cm) were implanted subcutaneously on the flanks of Female SCID mice (5-9 weeks of age; Charles River Laboratories, Wilmington, MA). The treatment of tumor bearing mice was started 21 days after tumor implantation for efficacy studies and 29 days after tumor implantation for pharmacodynamic studies. For efficacy studies, animals were sorted to obtain roughly equivalent mean tumor volumes in each group. Starting mean tumor volume in the efficacy study was 233 mm^3, and groups consisted of 7 animals. Mean tumor volume in the pharmacodynamic study ranged from 614 to 692 mm^3, and groups consisted of 3 animals. Experimental therapeutic agents were administered to mice orally (using 5% DMAC in 0.5% methylcellulose as the vehicle) twice daily for 15 days for the efficacy study and once for the pharmacodynamic (PD) study, with tumors harvested 4 h post dose. Blood collection was performed by cardiac puncture after euthanasia.

The endpoints in these xenograft models for efficacy determinations were the evaluation of tumor growth and overt tolerability. The size of subcutaneous tumors was measured 2 to 3 times weekly using

a digital caliper. The tumor volume was calculated by measuring the tumor in 2 dimensions and utilizing the equation: Volume = [Length × (Width2)]/2; where the larger number was length and the smaller number was width. Effects on tumor growth were reported as percent tumor growth inhibition (%TGI, see below). %TGI was calculated with the equation: (1- (Tx vol. / control vol.))*100, where control volume was the vehicle or untreated tumor volume on a given day, and Tx volume was any treatment group tumor volume on that same day. Statistical differences between treatment and vehicle controls were assessed using ANOVA: Single Factor test.

The endpoints for PD assessments were phospho-AKT determined from tumor lysates. Tumors were harvested, rapidly flash frozen in liquid nitrogen and maintained at -80°C until processed for analysis. The tumor fragments were thawed and homogenized in a cell lysis buffer containing protease and phosphatase inhibitors. Protein concentrations were determined for all samples using standard methods and equivalent amounts of protein were analyzed for pAkt (Ser473, Cell Signaling #4060), Akt (Cell Signaling, #9272) and/or beta-actin (Cell Signaling, #4970) by western blot.

In validating the Pfeiffer model, the standard of care agent bendamustine and the PI3Kδ inhibitor idelalisib were each evaluated three times. Bendamustine administered at 6 mg/kg provided 46%, 60%, and 71% TGI. Idelalisib administered at 100 mg/kg provided 53%, 61%, and 63% TGI.

ADME Assays

Cyp Inhibition. The potential for **20** to inhibit selective substrates for human liver microsomal CYP1A2 (7--ethoxyresorufin), CYP2B6 (bupropion), CYP2C8 (amodiaquine), CYP2C9 (diclofenac), CYP2C19 (S-mephenytoin), CYP2D6 (bufuralol), and CYP3A4 (midazolam and testosterone) was determined using human liver microsomes, and a NADPH regenerating system (0.4 unit/mL G6PDH, 1.3 mM NADP, 3.35 mM G6P final). The final concentrations of **20** were 0.0, 0.1, 0.25, 1.0, 2.5, 10, and 25 μM. In addition, the known selective inhibitors α-naphthoflavone (CYP1A2), ticlopidine (CYP2B6), quercetin (CYP2C8), sulfaphenazole (CYP2C9), tranylcypromine (CYP2C19), quinidine (CYP2D6), and ketoconazole (CYP3A4) were included as positive controls. The final volume of acetonitrile and/or methanol was less than 1% for all incubations. These assays were conducted at 37°C using a 96-well format with substrates at their respective K_m concentrations. Incubations were stopped by the addition of 1 volume of methanol containing 0.2 μM dextrorphan as internal standard. Samples were vortexed and centrifuged, and the resulting supernatants were used for analysis by LC/MS.

Protein Binding. The in vitro protein binding was determined using plasma from humans as well as the media used in the Pfeiffer cell proliferation assay. The Multi-Equilibrium Dialyzer System™ and diachema membranes from Harvard Apparatus (Holliston, MA) were used for the experiment. Equilibrium dialysis was carried out in teflon cells separated by a dialysis membrane with a molecular weight cut-off of 10,000 daltons. A plasma sample (1 mL) or media containing compound was added to one side of the membrane, while 1 mL of 0.133 M phosphate buffer (pH 7.4) was added to the other side. The cells were rotated at a speed of 12 rpm in a 37 °C water bath for 2 h. Buffer and matrix samples were drained separately into empty pre-weighed tubes. The tubes were reweighed and the exact volume of sample recovered from each side of the dialysis cell was calculated. The same volume of either buffer or matrix was then added to the samples to ensure a final 1:1 buffer/matrix mixture was obtained for all the samples. An equal aliquot from each sample was protein precipitated with acetonitrile. The resulting supernatants were collected after centrifugation for analysis by LC/MS/MS.

Caco-2. Caco-2 cells were grown at 37 ^{o}C in an atmosphere of 5% CO_2 in DMEM growth medium supplemented with 10% (v/v) fetal bovine serum, 1% (v/v) non-essential amino acids, penicillin (100 unit/mL), and streptomycin (100 mg/mL). Confluent cell monolayers were subcultured every seven days by treatment with 0.25% trypsin containing 1 mM EDTA. Caco-2 cells were seeded at a density of 4,000 cells/well in 24-well plates on transwell PET (Polyethylene Terephthalate) membrane filters. The cells were grown until fully differentiated after 21 days and all experiments were conducted between 21 and 26 days. Cells of passage numbers 21 to 45 were used in these studies.

Cell culture media was removed and replaced with Hank's balanced salt solution. Cell membrane confluence was confirmed by measuring transepithelial electrical resistance (TEER) using a Millicell-ERS Voltohmmeter. Caco-2 cell monolayers with TEER values ≥ 300 $\Omega \cdot cm^2$ were used for transport experiments. For permeability studies in the absorptive direction (A-B), solutions of compounds (50 μM) in 1% (v/v) DMSO/HBSS were added to the donor compartment (apical side). HBSS solution with 4% BSA was added in the receiver compartment (basolateral side). The apical volume was 0.2 mL and the basolateral volume was 0.6 mL. Studies were of 120 min incubation, and 0.1 mL of sample was removed from the receiver side at the end of the 120 min incubation and the same volume of acetonitrile was added for protein precipitation. The supernatants were collected after centrifugation for analysis by LC/MS.

Human Intrinsic Clearance. Compounds (1.0 μM) were incubated with pooled human liver microsomes at a final protein concentration of 0.5 mg/mL. Compounds were added in acetonitrile and the final volume of organic was 0.02%. Incubations were carried out in duplicate in 100 mM KH_2PO_4 (pH 7.4) at a temperature of 37^{o}C. Incubations were commenced with the addition of cofactor (1 mM NADPH). Control incubations (without cofactor) were also included. At 0, 10, 20 and 30 min, aliquots were removed and added to a termination solution (100% methanol) containing dextrorphan as an internal standard. Terminated incubation mixtures were vortexed and centrifuged, and the resulting supernatants were used for analysis by LC/MS. The scaling method used for the calculation of apparent intrinsic clearance was described by Obach (*Drug Metab. Dispos.* **1999**, *27*, 1350-1359).

Pharmacokinetic Studies. Male rats were given either a 4 mg/kg intravenous or 4 mg/kg oral dose. The vehicle for IV dosing was 5% dimethylacetamide (DMAC) and 10% propylene glycol (PG) in saline. The vehicle for oral dosing was a 0.5% methylcellulose (MC) aqueous solution. Male beagle dogs were given either a 2 mg/kg intravenous or 4 mg/kg oral dose. The vehicle for IV dosing was 5% DMAC and 10% PG in saline. The vehicle for oral dosing was 5% DMAC in 0.5% MC aqueous solution. Male cynomolgus monkeys were given either a 2 mg/kg intravenous or 4 mg/kg oral dose. The vehicle for IV dosing was 5% DMAC and 10% PG in saline. The vehicle for oral dosing was 0.5% MC aqueous solution.

Blood samples from each study were collected using EDTA as the anticoagulant at pre-dose until 24 hrs post-dose and centrifuged to obtain plasma. An analytical method for the quantification of **20** in plasma was developed and utilized for non-GLP studies. The method uses a protein-precipitation extraction of samples using 10% methanol in acetonitrile followed by LC/MS/MS analysis. The assay demonstrated a linear assay range from 2 to 2500 nM, utilizing 0.1 mL of plasma. The plasma concentration-time data was used to determine the pharmacokinetic parameters by standard non-compartmental methods.

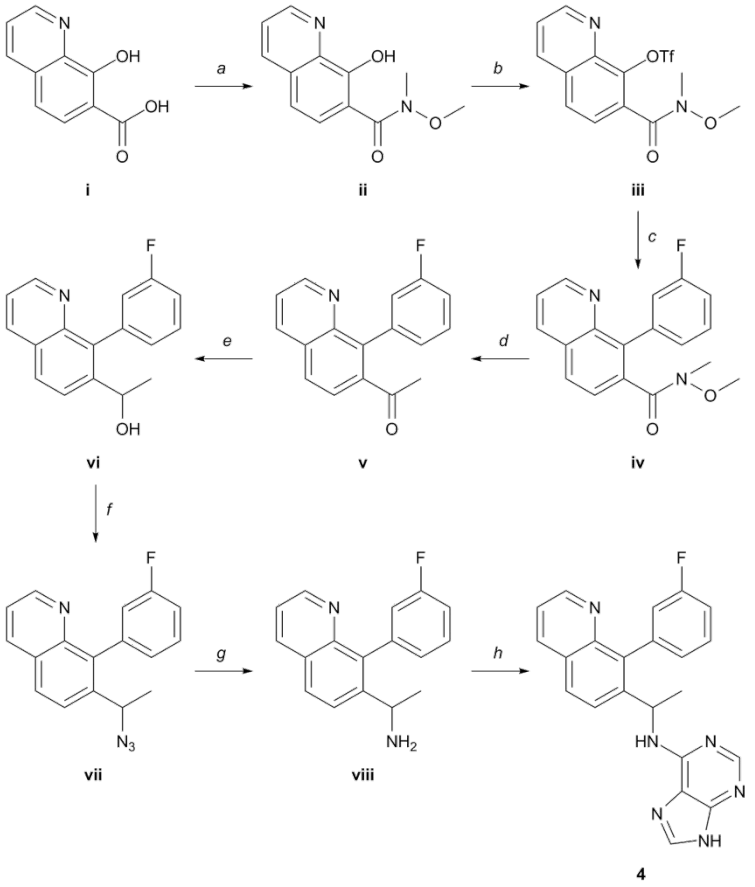
General Experimental Procedures and Analytical Characterization Methods

All reactions were run under an atmosphere of dry nitrogen. Unless otherwise noted, all reactions were performed at ambient temperature which averaged 20 °C. All solvents were used without further purification as acquired from commercial sources. NMR spectra were obtained using either a Varian Mercury-300, Mercury-400, or Inova-500 spectrometer. Chemical shifts are reported in parts per million relative to tetramethylsilane (TMS) as internal standard. All final products were characterized by ^{1}H NMR, HRMS or LCMS, and HPLC methods.

Purifications by flash chromatography were performed on RediSep columns using an Isco CombiFlash SG100c. Preparative LC purifications were performed on a Waters FractionLynx system using UV-triggered or mass directed fractionation and compound-specific method optimization (K. Blom, B. Glass, R. Sparks, A. Combs, "Preparative LC-MS Purification: Improved Compound Specific Method Optimization", *J. Combi. Chem.* (**2004**), *6*, 874-883).

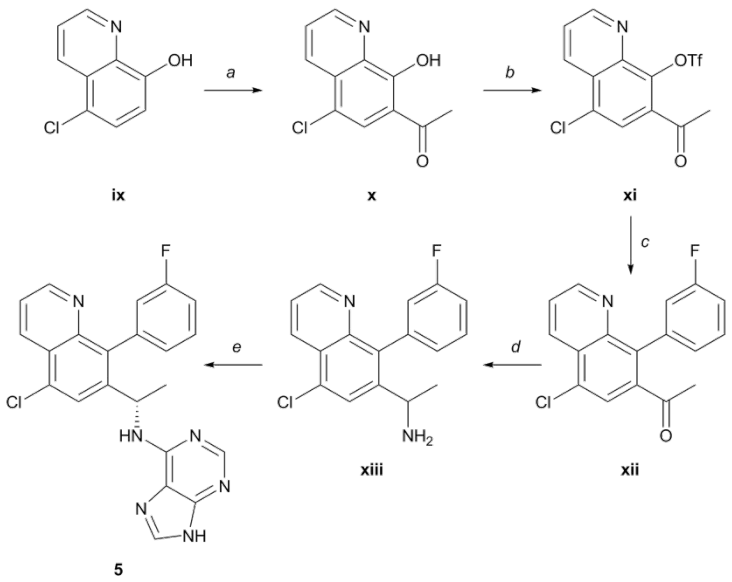
Synthetic Schemes

Scheme S1. Synthesis of **4**.[a]



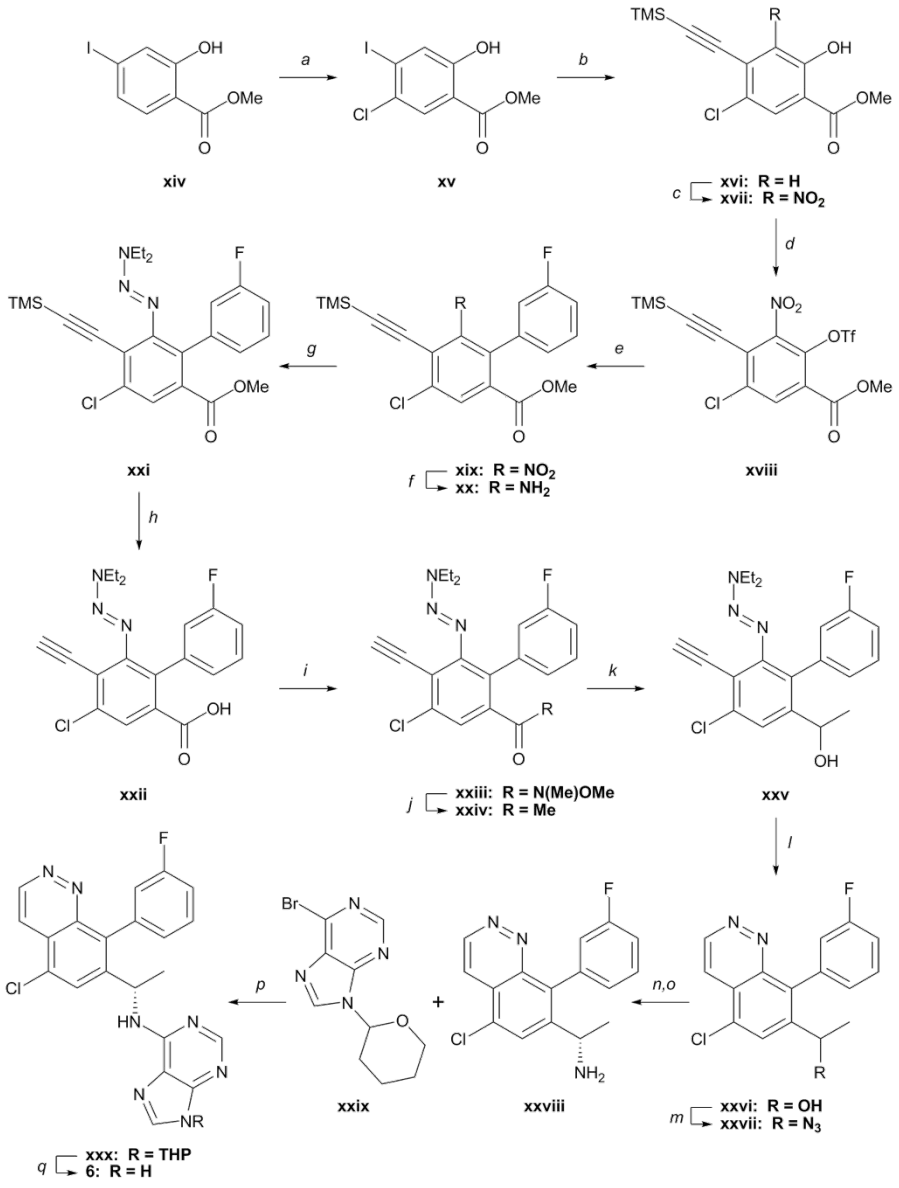
[a]Reagents: (a) MeNH(OMe) · HCl, PyBroP, *i*-Pr_2EtN, CH_2Cl_2, rt, o/n, 52.5%; (b) $(CF_3SO_2)_2O$, Et_3N, CH_2Cl_2, -78 °C, 1 h, 30.8%; (c) (3-fluorophenyl)boronic acid, $Pd(PPh_3)_4$, Na_2CO_3 (10 % aq. soln.), 1,4-dioxane, 100 °C, 3 h, quantitative; (d) MeMgBr (3.0 M in ether), THF, rt, o/n, 97.6%; (e) $NaBH_4$, MeOH, rt, 30 min, 95.8%; (f) MsCl, Et_3N, CH_2Cl_2, rt, 30 min; then NaN_3, DMF, rt, o/n; (g) Me_3P (1.0 M in THF), THF, H_2O, rt, 1 h; (h) 6-bromo-9*H*-purine, *i*-Pr_2EtN, EtOH, reflux, o/n.

Scheme S2. Synthesis of **5**.[a]



[a]Reagents: (a) $AlCl_3$, AcCl, 0 °C, 4 h; then 130 °C, 12 h, 68.0%; (b) $(CF_3SO_2)_2O$, Et_3N, CH_2Cl_2, -78 °C, 1 h, 52.9%; (c) (3-fluorophenyl)(iodo)zinc (0.5 M in THF), $Pd(PPh_3)_4$, THF, 60 °C, o/n, 52.9%; (d) NH_4OAc, MeOH, MeCN, 65 °C, 30 min; then $NaBH_3CN$, 65 °C, 4 h, 97.0%; (e) 6-bromo-9*H*-purine, *i*-Pr_2EtN, EtOH, 100 °C, o/n, 10.2%; then chiral separation.

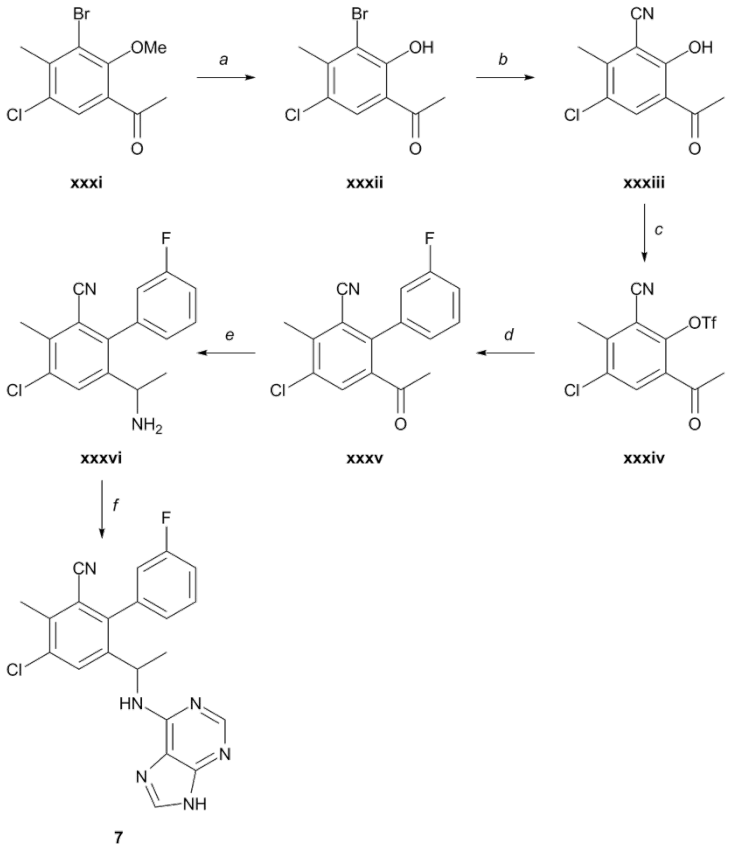
Scheme S3. Synthesis of **6**.[a]



[a]Reagents: (a) NCS, AcOH, 110 °C, 1.5 h, 97.3%; (b) trimethylsilylacetylene, $PdCl_2(PPh_3)_2$, CuI, Et_3N, 75 °C, 3.5 h, 92.7%; (c) HNO_3, AcOH, 55 °C, 2 h, 67.3%; (d) $(CF_3SO_2)_2O$, Et_3N, CH_2Cl_2, -10 °C, 30 min, 85.2%; (e) (3-fluorophenyl)boronic acid, $Pd(PPh_3)_4$, $NaHCO_3$, toluene, H_2O, 80 °C, 6 h, 87.9%; (f) Fe, NH_4Cl (5.0 M in H_2O), 6 M HCl, 60 °C, 3 h, quantitative; (g) 12 M HCl, THF, MeCN, H_2O, $NaNO_2$, -5 °C, 30 min; then Et_2NH, K_2CO_3, 0 °C, 30 min, 71.8%; (h) 1 M NaOH, THF, MeOH, 60 °C, 1.5 h, quantitative; (i) MeNH(OMe) · HCl, HBTU, *i*-Pr_2EtN, DMF, rt, 1 h, 87.2%; (j) MeMgCl (3.0 M in THF), THF, 0 °C to rt, 1 h, 97.7%; (k) $NaBH_4$, MeOH, 0 °C, 30 min, quantitative; (l) 1,2-dichlorobenzene, 200 °C, 15 min in microwave, 73.2%; (m) MsCl, *i*-Pr_2EtN, CH_2Cl_2, -5 °C, 30 min; then

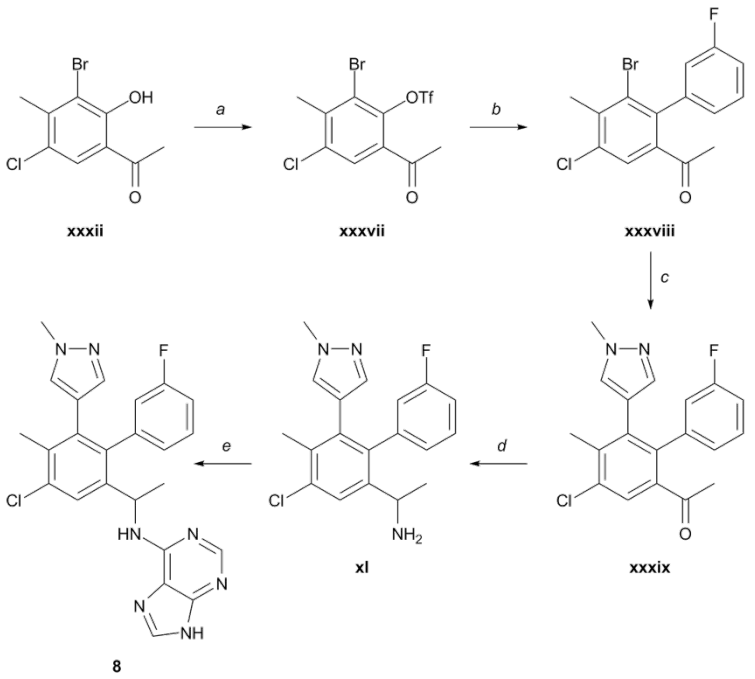
NaN_3, DMF, 60 °C, 30 min, 77.6%; (n) chiral separation; (o) Me_3P (1.0 M in THF), THF, H_2O, rt, 1 h; (p) *i*-Pr_2EtN, EtOH, 90 °C, 18 h; (q) 1 N HCl, EtOH, rt, 1 h, 62.9%.

Scheme S4. Synthesis of **7**.[a]



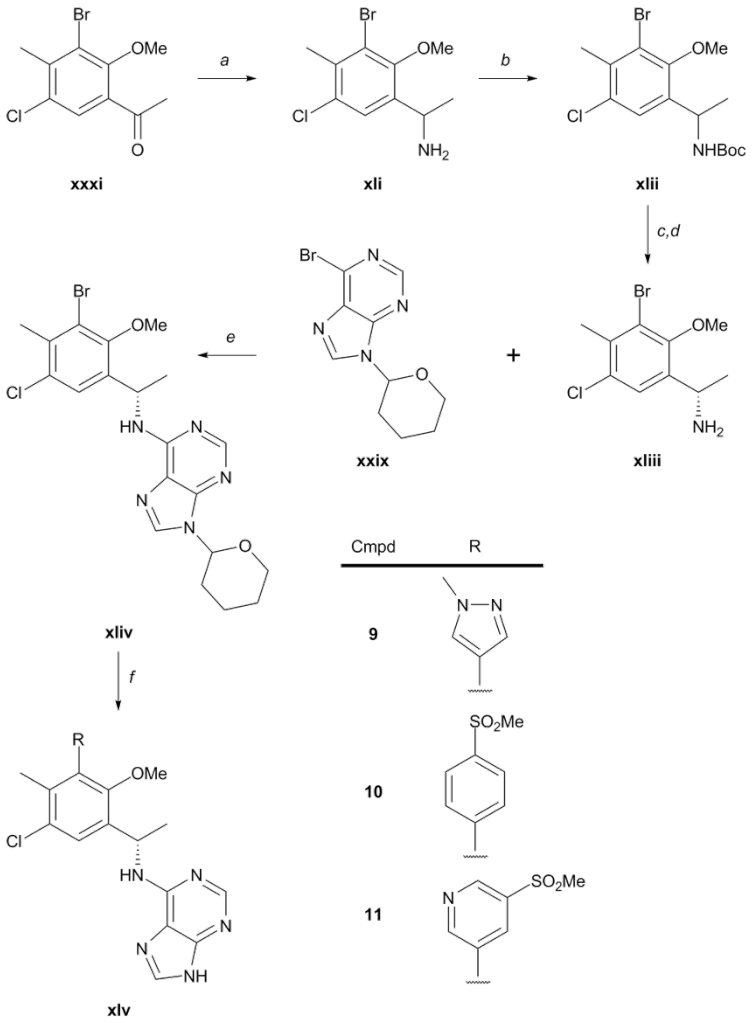
[a]Reagents: (a) BBr_3, CH_2Cl_2, -78 °C (10 min) to 0 °C, 96.0%; (b) CuCN, NMP, 200 °C, 1 h, 95.9%; (c) $(CF_3SO_2)_2O$, Et_3N, CH_2Cl_2, -78 °C to 0 °C, 30 min, 42.1%; (d) (3-fluorophenyl)boronic acid, $Pd(PPh_3)_4$, $NaHCO_3$, toluene, water, 80 °C, 2 h, 98.5%; (e) NH_4OAc, $NaBH_3CN$, MeOH, MeCN, 60 °C (sealed tube), 4.5 h; (f) 6-bromo-9*H*-purine, *i*-Pr_2EtN, *i*-PrOH, 90 °C, o/n.

Scheme S5. Synthesis of **8**.[a]



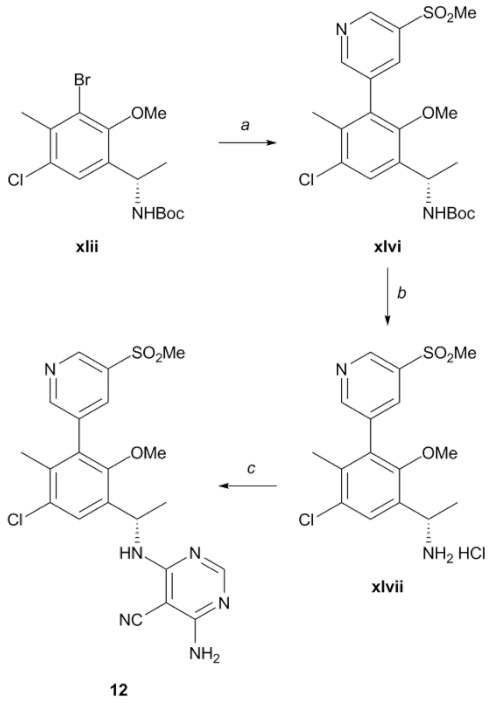
[a]Reagents: (a) $(CF_3SO_2)_2O$, Et_3N, CH_2Cl_2, -78 °C (10 min) to 0 °C, 70.8%; (b) (3-fluorophenyl)boronic acid, $Pd(PPh_3)_4$, $NaHCO_3$, toluene, water, 80 °C, o/n, 93.0%; (c) 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole, $Pd(PPh_3)_4$, $NaHCO_3$, toluene, water, 80 °C, o/n, 17.0%; (d) NH_4OAc, $NaBH_3CN$, MeOH, MeCN, 65 °C, o/n; (e) 6-bromo-9*H*-purine, *i*-Pr_2EtN, EtOH, 100 °C, o/n.

Scheme S6. Synthesis of **9**-**11**.[a]



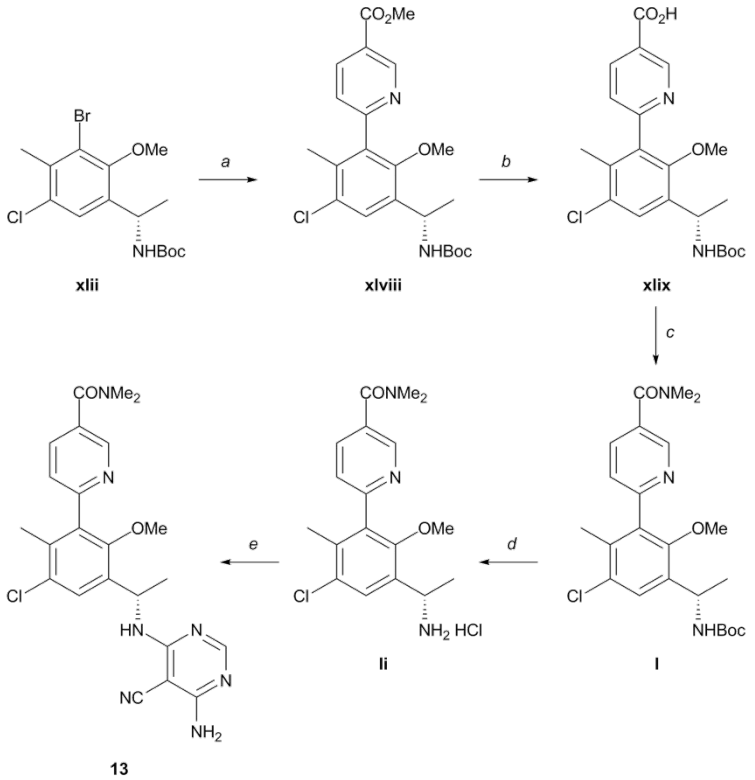
[a]Reagents: (a) Ti(O*i*-Pr)$_4$, 2 M NH_3 in EtOH, 0 °C to 60 °C, o/n; then $NaBH_4$, 0 °C to rt, 1 h, 73.9%; (b) $(Boc)_2O$, *i*-Pr_2EtN, 1,4-dioxane, rt, o/n, 66.9%; (c) chiral separation; (d) TFA, CH_2Cl_2, rt, 30 min, 95.7%; (e) *i*-Pr_2EtN, EtOH, 120 °C, o/n; (f) 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (to give **9**) or [4-(methylsulfonyl)phenyl]boronic acid (to give **10**) or [5-(methylsulfonyl)pyridin-3-yl]boronic acid (to give **11**), $Pd(PPh_3)_4$, 1 M Na_2CO_3, 1,4-dioxane, 90 °C, o/n; then 6 N HCl, rt, 30 min.

Scheme S7. Synthesis of **12**.[a]



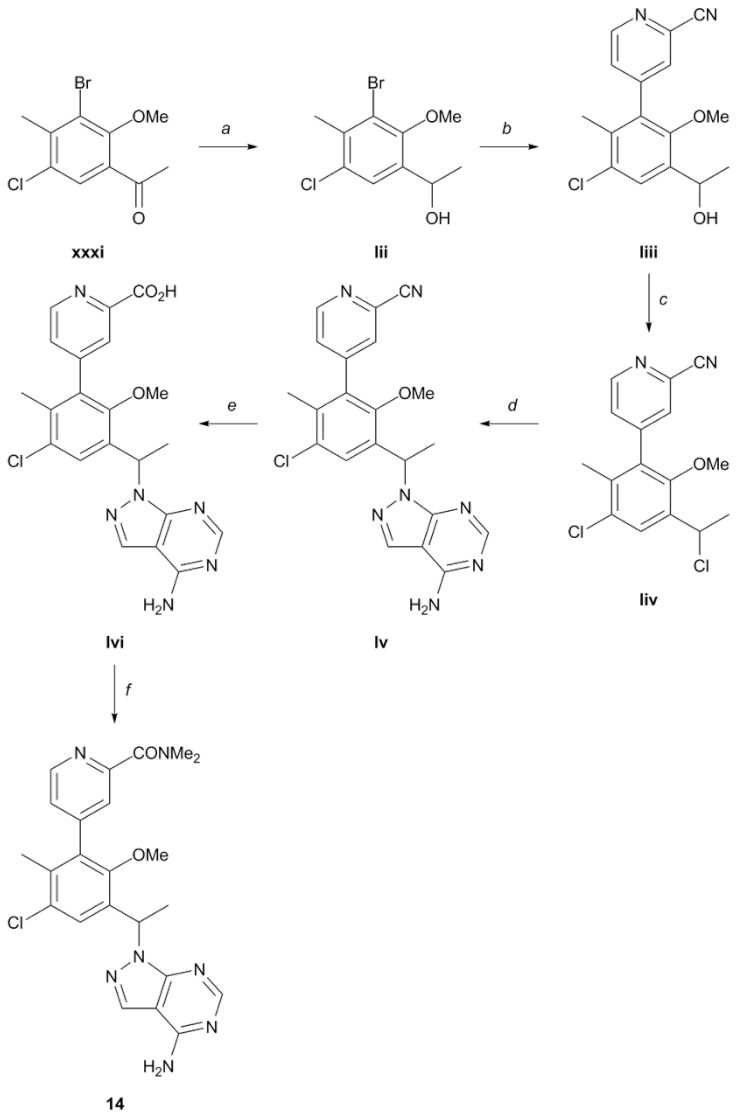
[a]Reagents: (a) [5-(Methylsulfonyl)pyridin-3-yl]boronic acid, $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, Na_2CO_3, MeCN, H_2O, 95 °C, 2 h, 85.7%; (b) 4 M HCl in 1,4-dioxane, CH_2Cl_2, rt, 30 min, 96.8%; (c) 4-amino-6-chloropyrimidine-5-carbonitrile, *i*-Pr_2EtN, *n*-BuOH, 120 °C, 3 h.

Scheme S8. Synthesis of **13**.[a]



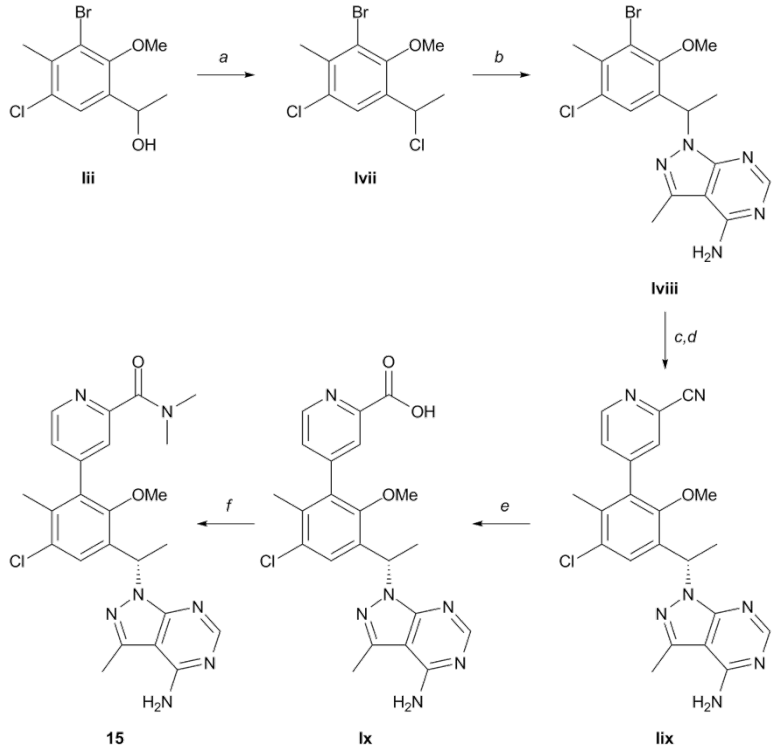
[a]Reagents: (a) Methyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate, $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, $Pd(OAc)_2$, CuCl, Cs_2CO_3, DMF, 100 °C, o/n, 66.7%; (b) 1 N NaOH, MeOH, rt, 45 min, 54.5%; (c) Me_2NH (2.0 M in THF), BOP, Et_3N, DMF, 0 °C to rt, 1 h, 70.8%; (d) 4 M HCl in 1,4-dioxane, rt, 30 min; (e) 4-amino-6-chloropyrimidine-5-carbonitrile, *i*-Pr_2EtN, *n*-BuOH, 120 °C, 3 h, 7.17%.

Scheme S9. Synthesis of **14**.[a]



[a]Reagents: (a) $NaBH_4$, MeOH, 0 °C to rt, 2.5 h, 97.0%; (b) 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-2-carbonitrile, $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, Na_2CO_3, MeCN, H_2O; (c) cyanuric chloride, CH_2Cl_2, DMF, rt, o/n, 89.3%; (d) 4-aminopyrazolo[3,4-*d*]pyrimidine, NaH, DMF, 30 °C, o/n; (e) 1.0 N NaOH, EtOH, 95 °C, 6 h; (f) Me_2NH (2.0 M in THF), BOP, Et_3N, DMF rt, 1 h.

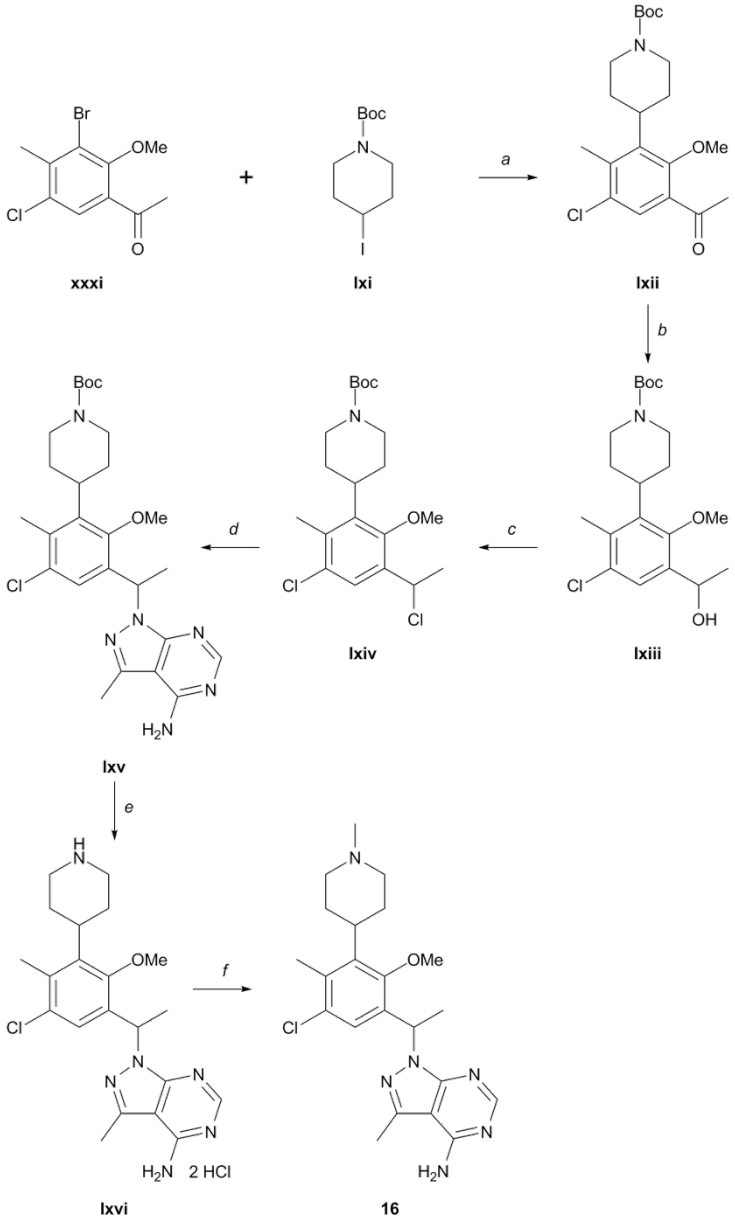
Scheme S10. Synthesis of **15**.[a]



liii lvii lviii lix lx 15

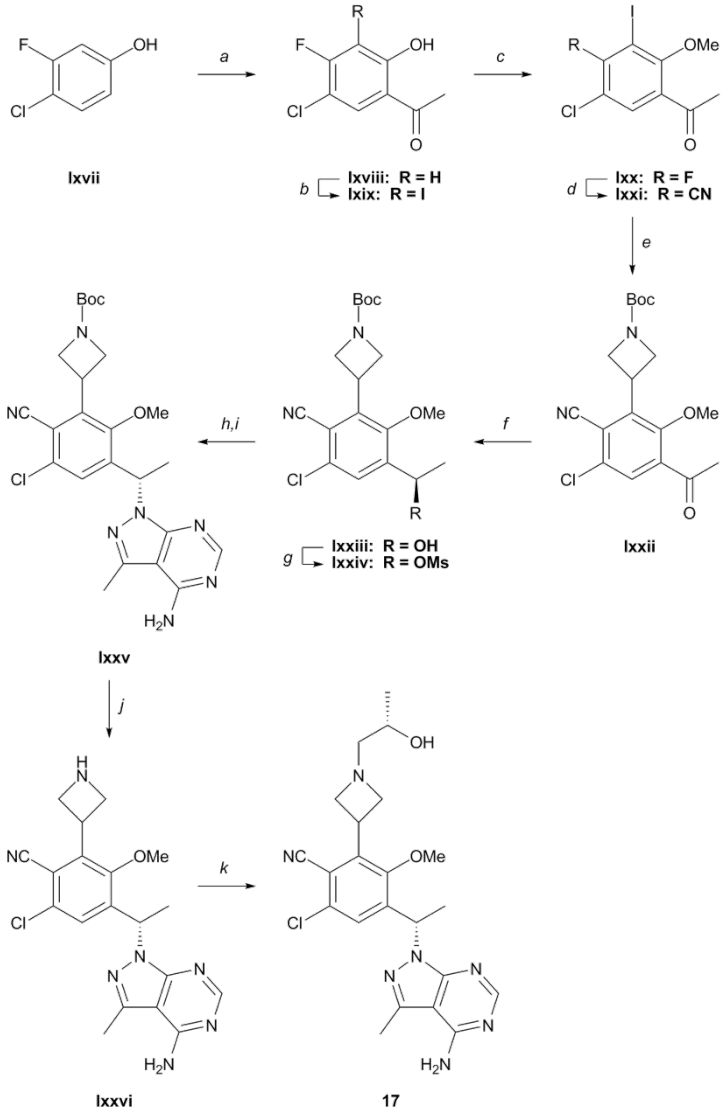
[a]Reagents: (a) Cyanuric chloride, CH_2Cl_2, DMF, rt, o/n, 80.3%; (b) 3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine, NaH, DMF, 30 °C, o/n, 50.0%; (c) chiral separation; (d) 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-2-carbonitrile, $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, Na_2CO_3, MeCN, H_2O, 95 °C, 2 h, 94.7%; (e) 1 N NaOH, EtOH, 95 °C, 6 h; (f) Me_2NH (2.0 M in THF), BOP, Et_3N, THF, DMF, rt, 1 h.

Scheme S11. Synthesis of **16**.[a]



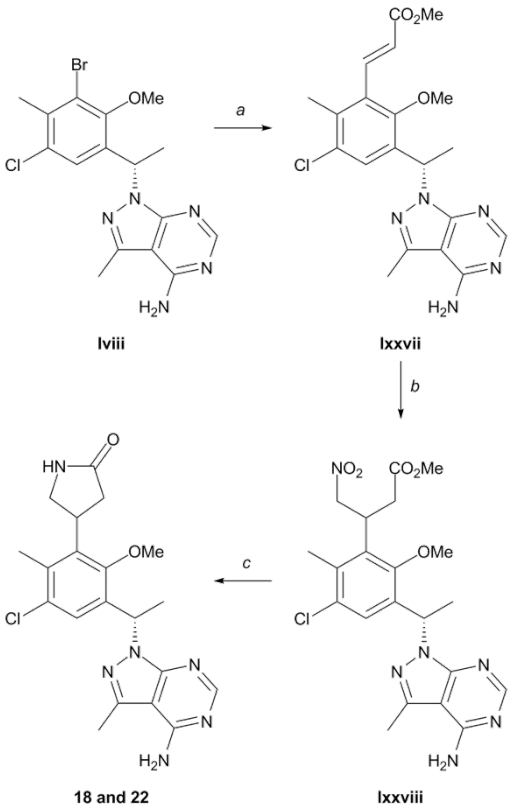
[a]Reagents: (a) LiCl, Zn, 140 °C, 10 min; then $BrCH_2CH_2Br$, THF, 60 °C, 10 min; then TMSCl, I_2, THF, 60 °C, 10 min; then *tert*-butyl 4-iodopiperidine-1-carboxylate (**lxi**), THF, 50 °C, o/n; then 1-(3-bromo-5-chloro-2-methoxy-4-methylphenyl)ethanone (**xxxi**), $Pd(OAc)_2$, CPhos, toluene, 0 °C to 60 °C, 34.1%; (b) $NaBH_4$, MeOH, 0 °C, 1 h, 46.4%; (c) cyanuric chloride, CH_2Cl_2, DMF, rt, o/n, 73.7%; (d) 3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine, Cs_2CO_3, KI, DMF, 140 °C, 1 h, 44.0%; (e) 4 M HCl in 1,4-dioxane, CH_2Cl_2, rt, 6 h, quantitative; (f) $NaBH(OAc)_3$ resin, 12 M formaldehyde in H_2O, *i*-Pr_2EtN, CH_2Cl_2, 0 °C, 1 h.

Scheme S12. Synthesis of **17**.[a]



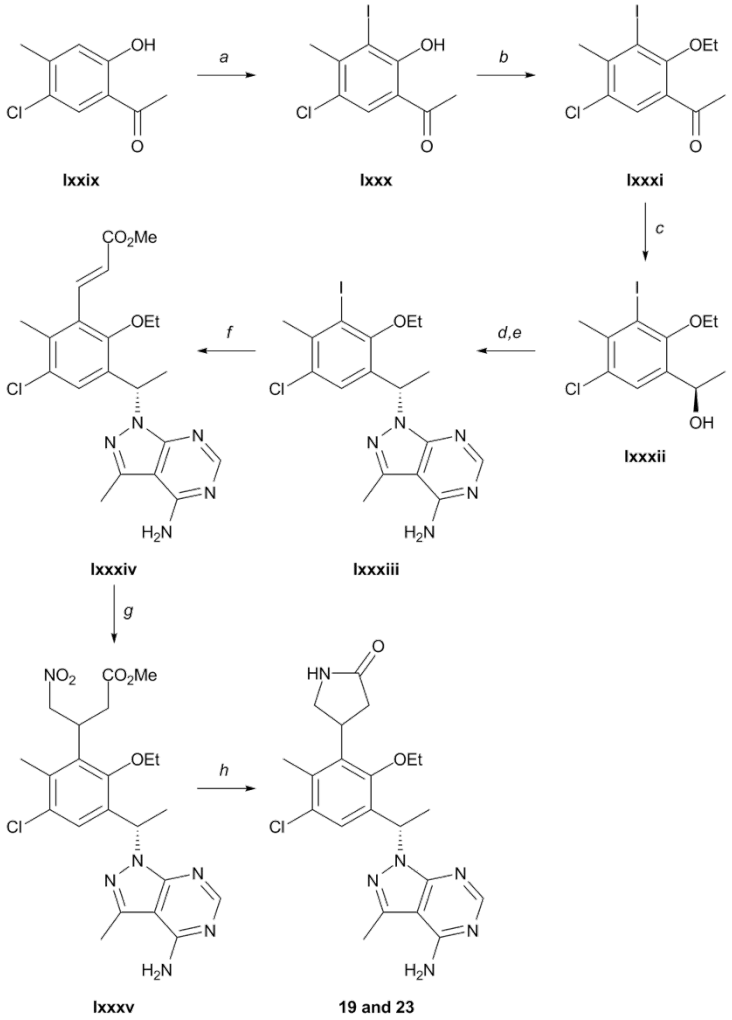
[a]Reagents: (a) AcCl, 60 °C, 2 h; then $AlCl_3$, 20 °C to 180 °C, 30 min, quantitative; (b) NIS, AcOH, 90 °C, 17 h, 90.2%; (c) MeI, K_2CO_3, DMF, 100 °C, 15 min, 84.4%; (d) KCN, DMF, 45 °C, 5 h, 67.7%; (e) Zn, Celite®; then DMA, $BrCH_2CH_2Br$, 70 °C, 15 min; then TMSCl, rt, 1 h; then *tert*-butyl 3-iodoazetidine-1-carboxylate, DMA, 40 °C, 2 h; then $Pd_2(dba)_3$, tri-(2-furyl)phosphine; then 4-acetyl-6-chloro-2-iodo-3-methoxybenzonitrile (**lxxi**), 70 °C, 2 h, 85.2%; (f) (3a*S*)-1-methyl-3,3-diphenyltetrahydro-3*H*-pyrrolo[1,2-*c*][1,3,2]oxazaborole, $BH_3 \cdot$ THF (1.0 M in THF), THF, -30 °C to -5 °C, 30 min, 96.6%; (g) Ms_2O, Et_3N, CH_2Cl_2, 0 °C, 30 min; (h) 3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine, NaH, DMF, 0 °C, 30 min; then **lxxiv**, 0 °C, 30 min; then 50 °C, 1 h, 76.7%; (i) chiral separation; (j) TFA, CH_2Cl_2, rt, 30 min, 99.3%; (k) (*S*)-(-)-methyloxirane, EtOH, 125 °C, 15 min in microwave, 57.3%.

Scheme S13. Synthesis of **18** and **22**.[a]



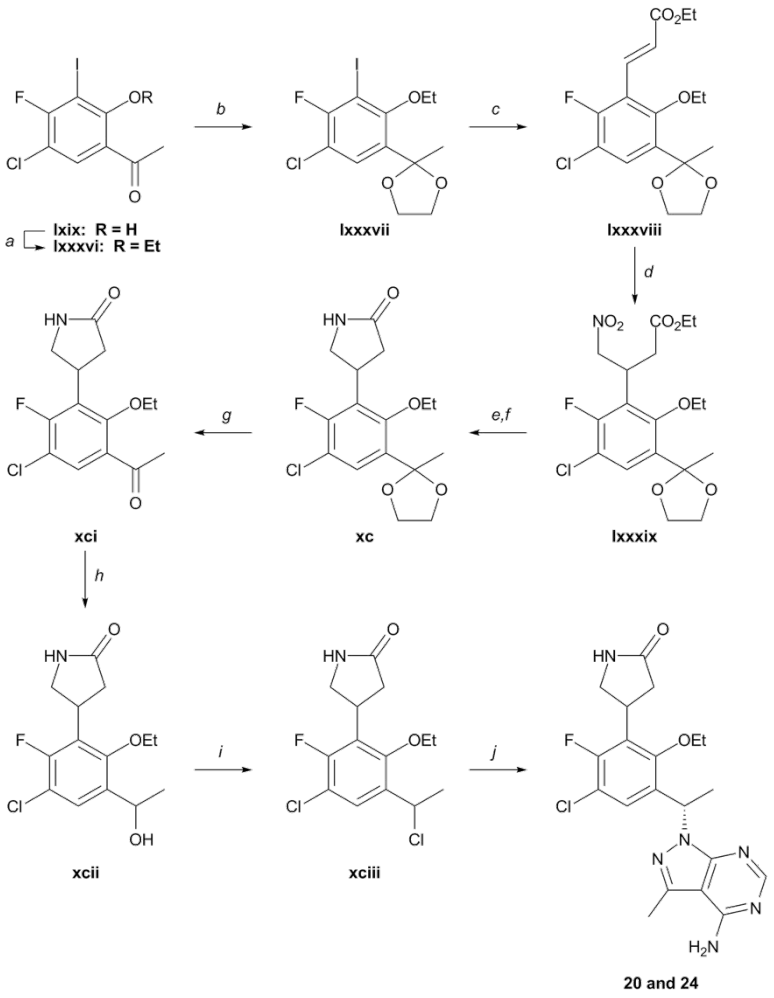
[a]Reagents: (a) Methyl acrylate, Ph_3P, $Pd(OAc)_2$, Et_3N, DMF, 130 °C, 20 h, 45.0%; (b) $MeNO_2$, DBU, 60 °C, 23 h; then 90 °C, 13 h, 25.8%; (c) $NiCl_2 \cdot 6H_2O$, $NaBH_4$, MeOH, 0 °C, 30 min; then 60 °C, 3 h, 9.13% (for **18**) and 8.69% (for **22**).

Scheme S14. Synthesis of **19** and **23**.[a]



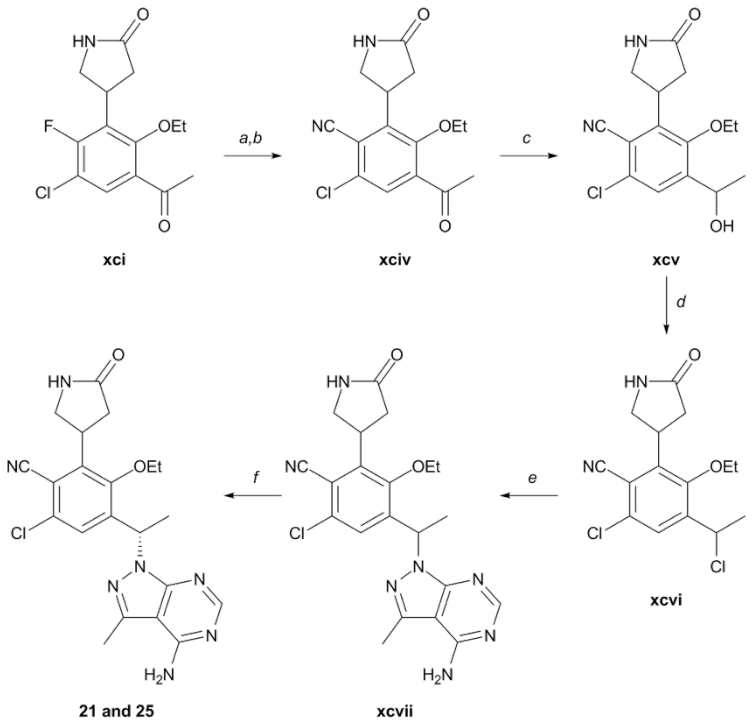
[a]Reagents: (a) NIS, AcOH, rt, 2 d, 99.7%; (b) EtI, K_2CO_3, DMF, 60 °C, 1 h, 91.7%; (c) (3a*S*)-1-methyl-3,3-diphenyltetrahydro-3*H*-pyrrolo[1,2-*c*][1,3,2]oxazaborole, $BH_3 \cdot THF$ (1.0 M in THF), THF, -30 °C to 0 °C, 94.1% (92%ee); (d) Ms_2O, Et_3N, CH_2Cl_2, 0 °C, 30 min; then 3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine, Cs_2CO_3, DMF, 60 °C, 2 h, 32.0%; (e) chiral separation; (f) methyl acrylate, Ph_3P, $Pd(OAc)_2$, Et_3N, MeCN, 100 °C, 16 h, 72.4%; (g) $MeNO_2$, DBU, 90 °C, 22 h, 47.6%; (h) $NiCl_2 \cdot 6H_2O$, $NaBH_4$, MeOH, 0 °C to rt, 30 min; then 60 °C, 1.5 h, 19.0% (**19**) and 22.6% (**23**).

Scheme S15. Synthesis of **20** and **24**.[a]



[a]Reagents: (a) EtI, K_2CO_3, DMF, 60 °C, 1 h, 90.6%; (b) $HOCH_2CH_2OH$, TsOH · H_2O, toluene, reflux, 3 h, 99.2%; (c) ethyl (2*E*)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)acrylate, Pd(dppf)Cl_2 · CH_2Cl_2, K_2CO_3, 1,4-dioxane, H_2O, 80 °C, 2 h, 95.8%; (d) $MeNO_2$, DBU, 60 °C, 15 h, 88.9%; (e) Raney Ni, H_2, EtOH, H_2O, rt, 3 h; then toluene, 110 °C, 12 h, 74.8%; (f) chiral separation; (g) 6 N HCl, MeOH, H_2O, rt, 30 min, 98.7% (peak 1), 98.0% (peak 2); (h) $NaBH_4$, MeOH, 0 °C, 30 min, 99.3% (peak 1), 97.8% (peak 2); (i) $SOCl_2$, CH_2Cl_2, DMF, rt, 30 min, 87.4% (peak 1), 88.8% (peak 2); (j) 3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine, Cs_2CO_3, KI, DMF, 100 °C, 4.5 h; then separation of diastereoisomers, 30.4% (**20**, from peak 2) and 25.4% (**24**, from peak 1).

Scheme S16. Synthesis of **21** and **25**.[a]



[a]Reagents: (a) NaCN, DMSO, 80 °C, 3 h, 70.7%; (b) chiral separation; (c) $NaBH_4$, MeOH, 0 °C, 30 min, quantitative (peak 1), quantitative (peak 2); (d) $SOCl_2$, CH_2Cl_2, DMF, 20 °C, 2 h, 96.9% (peak 1), 97.5% (peak 2); (e) 3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine, Cs_2CO_3, KI, DMF, 90 °C, 3 h, 43.2% (peak 1) and 43.8% (peak 2); (f) chiral separation.

Experimental Procedures and Analytical Data for Compounds 4-25

The synthesis of **4** is illustrated in **Scheme S1**.

***N*-{1-[8-(3-Fluorophenyl)quinolin-7-yl]ethyl}-9*H*-purin-6-amine (4).**

Step a. 8-Hydroxy-*N*-methoxy-*N*-methylquinoline-7-carboxamide (**ii**). A mixture of 8-hydroxyquinoline-7-carboxylic acid (5.00 g, 0.0264 mmol), bromotris(pyrrolidino)phophonium hexafluorophosphate (14.8 g, 0.0317 mmol), and *N*,*N*-diisopropylethylamine (18.4 mL, 0.106 mmol) in dichloromethane (100 mL) was stirred at rt for 30 min. The reaction mixture was treated with *N*,*O*-dimethylhydroxylamine hydrochloride (3.09 g, 0.0317 mmol) slowly and the resulting suspension was stirred at rt overnight. The reaction mixture was washed with 1.0 N sodium hydroxide in water. The aqueous phase was separated, acidified with 12 N hydrogen chloride in water slowly, extracted with ethyl acetate, dried over magnesium sulfate, filtered, and concentrated to a crude residue. Purification by flash column chromatography using methanol in dichloromethane (0% to 10%) gave the desired product **ii** (3.20 g, 52.5%). LCMS calculated for $C_{12}H_{13}N_2O_3$ $(M+H)^+$: m/z = 233.1; Found: 233.0.

Step b. 7-{[Methoxy(methyl)amino]carbonyl}quinolin-8-yl trifluoromethanesulfonate (**iii**). A solution of 8-hydroxy-*N*-methoxy-*N*-methylquinoline-7-carboxamide (3.20 g, 0.0138 mmol) and triethylamine (5.76 mL, 0.0413 mmol) in dichloromethane at -78 °C was treated with trifluoromethanesulfonic anhydride (2.78 mL, 0.0165 mmol) dropwise and stirred at -78 °C for 1 h. The reaction was diluted with water. The organic layer was separated, washed with brine, dried over magnesium sulfate, filtered, and concentrated to a crude residue. Purification by flash column chromatography using ethyl acetate in hexanes (0% to 80%) gave the desired product **iii** (1.54 g, 30.8%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 – 8.93 (m, 1H), 8.28 – 8.10 (m, 1H), 7.84 (dd, *J* = 8.4, 3.0 Hz, 1H), 7.67 – 7.44 (m, 2H), 3.42 (s, 3H), 3.39 (s, 3H). LCMS calculated for $C_{13}H_{12}F_3N_2O_5S$ $(M+H)^+$: m/z = 365.0; Found: 365.0.

Step c. 8-(3-Fluorophenyl)-*N*-methoxy-*N*-methylquinoline-7-carboxamide (**iv**). A mixture of 7-{[methoxy(methyl)amino]carbonyl}quinolin-8-yl trifluoromethanesulfonate (0.240 g, 0.660 mmol) and (3-fluorophenyl)boronic acid (0.111 g, 0.791 mmol) in 1,4-dioxane was treated with a solution of sodium

carbonate (0.105 g, 0.988 mmol) in water (1.00 mL) followed by tetrakis(triphenylphosphine)palladium(0) (0.0381 g, 0.0329 mmol) and stirred at 100 °C for 3 h. The reaction mixture was cooled, diluted with ethyl acetate, washed with water, dried over magnesium sulfate, filtered, and concentrated to a crude residue. Purification by flash column chromatography using ethyl acetate in hexanes (0% to 60%) gave the desired product **iv** (0.200 g, quantitative). LCMS calculated for $C_{18}H_{16}FN_2O_2$ $(M+H)^+$: m/z = 311.1; Found: 311.0.

Step d. 1-[8-(3-Fluorophenyl)quinolin-7-yl]ethanone (**v**). A mixture of 8-(3-fluorophenyl)-*N*-methoxy-*N*-methylquinoline-7-carboxamide (0.200 g, 0.644 mmol) in tetrahydrofuran was treated with 3.0 M methylmagnesium bromide in ether (0.430 mL, 1.29 mmol) and stirred at rt for 2 h. The reaction mixture was treated with additional 3.0 M methylmagnesium bromide in ether (1.00 mL, 3.00 mmol) and stirred at rt overnight. The reaction mixture was quenched with saturated aqueous ammonium chloride solution and extracted with ethyl acetate. The organic layer was separated and washed with saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, filtered, and concentrated to give the desired product **v** (0.166 g, 97.6%) that was used without further purification. LCMS calculated for $C_{17}H_{13}FNO$ $(M+H)^+$: m/z = 266.1; Found: 266.0.

Step e. 1-[8-(3-Fluorophenyl)quinolin-7-yl]ethanol (**vi**). A mixture of 1-[8-(3-fluorophenyl)quinolin-7-yl]ethanone (0.166 g, 0.626 mmol) in methanol was treated with sodium tetrahydroborate (0.0237 g, 0.626 mmol) and stirred at rt for 30 min. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was separated and washed with brine, dried over magnesium sulfate, filtered, and concentrated to give the desired product **vi** (0.160 g, 95.8%) that was used without further purification. LCMS calculated for $C_{17}H_{15}FNO$ $(M+H)^+$: m/z = 268.1; Found: 268.1.

Step f. 7-(1-Azidoethyl)-8-(3-fluorophenyl)quinoline (**vii**). A mixture of 1-[8-(3-fluorophenyl)quinolin-7-yl]ethanol (0.160 g, 0.598 mmol) in dichloromethane (4.00 mL) was treated with triethylamine (0.125 mL, 0.898 mmol) followed by methanesulfonyl chloride (0.0579 mL, 0.748 mmol) and stirred at rt for 30 min. The reaction mixture was diluted with dichloromethane, washed with saturated

aqueous sodium bicarbonate solution and brine, dried over magnesium sulfate, filtered, and concentrated to give the intermediate mesylate that was used immediately without further purification.

The crude mesylate was dissolved in *N*,*N*-dimethylformamide (2.00 mL), treated with sodium azide (0.194 g, 2.99 mmol), and stirred at rt overnight. The reaction mixture was diluted with ethyl acetate, washed with water and brine, dried over magnesium sulfate, filtered, and concentrated to give the desired product **vii** that was used without further purification. LCMS calculated for $C_{17}H_{14}FN_4$ $(M+H)^+$: m/z = 293.1; Found: 293.0.

Step g. 1-[8-(3-Fluorophenyl)quinolin-7-yl]ethanamine (**viii**). A solution of 7-(1-azidoethyl)-8-(3-fluorophenyl)quinoline (0.146 g, 0.500 mmol) in tetrahydrofuran (1.00 mL) and water (0.360 mL) was treated with 1.0 M trimethylphosphine in tetrahydrofuran (0.600 mL, 0.600 mmol) and stirred at rt for 1 h. The reaction mixture was diluted with ethyl acetate and extracted with 1.0 N hydrogen chloride in water (2x). The combined aqueous layers were neutralized with solid sodium bicarbonate and extracted with dichloromethane (2x). The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered, and concentrated to give the desired product **viii** that was used without further purification. LCMS calculated for $C_{17}H_{16}FN_2$ $(M+H)^+$: m/z = 267.1; Found: 267.0.

Step h. *N*-{1-[8-(3-Fluorophenyl)quinolin-7-yl]ethyl}-9*H*-purin-6-amine (**4**). A mixture of 1-[8-(3-fluorophenyl)quinolin-7-yl]ethanamine (0.0720 g, 0.270 mmol), 6-bromo-9*H*-purine (0.108 g, 0. 541 mmol), and *N*,*N*-diisopropylethylamine (0.0565 mL, 0.324 mmol) in ethanol (0.9 mL) was stirred at reflux overnight. The reaction mixture was concentrated and the resultant residue was purified by preparative LCMS (XBridge C18 Column, eluting with a gradient of acetonitrile in water with 0.1% trifluoroacetic acid, at flow rate of 60 mL/min) to give the desired product **4** as a TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.50 (br s, 1H), 8.82 (dd, J = 4.3, 1.8 Hz, 1H), 8.59 – 8.40 (m, 3H), 8.10 (d, J = 8.7 Hz, 1H), 7.92 – 7.84 (m, 1H), 7.60 – 7.48 (m, 2H), 7.42 (M, 1H), 7.33 – 7.13 (m, 3H), 5.36 (d, J = 11.0 Hz, 1H), 1.55 (d, J = 7.0 Hz, 3H). LCMS for $C_{22}H_{18}FN_6$ $(M+H)^+$: m/z = 385.2; Found: 385.1.

The synthesis of **5** is illustrated in **Scheme S2**.

(*S*)-*N*-(1-(5-Chloro-8-(3-fluorophenyl)quinolin-7-yl)ethyl)-9*H*-purin-6-amine (5).

Step a. 1-(5-Chloro-8-hydroxyquinolin-7-yl)ethanone (**x**). A mixture of 5-chloro-8-quinolinol, (6.67 g, 37.1 mmol), aluminum trichloride (20.0 g, 150 mmol), and acetyl chloride (12.1 mL, 170 mmol) was stirred at 0 °C for 4 h and then heated at 130 °C for 12 h. The reaction mixture was quenched slowly and carefully with water (39 mL) and 12 N hydrogen chloride in water (39 mL). The resultant solid was filtered and dried under reduced pressure. The solid was dissolved in water (50 mL), diluted with dichloromethane (100 mL), cooled with an ice bath, and treated with 20% aqueous sodium hydroxide to pH~4. The solid was filtered, washed with water, and air dried to give desired product (~2 g). The aqueous layer from the filtrate was separated and extracted with dichloromethane (2x). The combined organic extracts were washed with water, brine, and dried over magnesium sulfate, filtered, and concentrated to give additional desired product **x** (5.60 g total, 68.0% combined yield). LCMS for $C_{11}H_9ClNO_2$ $(M+H)^+$: m/z = 222.0; Found: 222.0.

Step b. 7-Acetyl-5-chloroquinolin-8-yl trifluoromethanesulfonate (**xi**). The desired product **xi** was prepared in a manner similar to the procedure of **iii** using 1-(5-chloro-8-hydroxyquinolin-7-yl)ethanone as the starting material. LCMS calculated for $C_{12}H_8ClF_3NO_4S$ $(M+H)^+$: m/z = 354.0; Found: 353.9.

Step c. 1-[5-Chloro-8-(3-fluorophenyl)quinolin-7-yl]ethanone (**xii**). A mixture of 7-acetyl-5-chloroquinolin-8-yl trifluoromethanesulfonate (1.42 g, 4.00 mmol) and a solution of 0.5 M (3-fluorophenyl)(iodo)zinc in tetrahydrofuran (16.0 mL, 8.01 mmol) in tetrahydrofuran (40 mL) was treated with tetrakis(triphenylphosphine)palladium(0) (463 mg, 0.400 mmol) and stirred at 60 °C overnight. The reaction mixture was cooled, quenched with saturated sodium bicarbonate solution, and filtered over a pad of Celite. The filtrate was extracted with ethyl acetate (2x). The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered, and concentrated to a crude residue. Purification by flash column chromatography using ethyl acetate in hexanes (0% to 50%) gave the desired product **xii** (3.21 g, 52.9%). LCMS calculated for $C_{17}H_{12}ClFNO$ $(M+H)^+$: m/z = 300.1; Found: 300.0.

Step d. 1-[5-Chloro-8-(3-fluorophenyl)quinolin-7-yl]ethanamine (**xiii**). A mixture of 1-[5-chloro-8-(3-fluorophenyl)quinolin-7-yl]ethanone (600 mg, 2.00 mmol) and ammonium acetate (1.54 g, 20.0

mmol) in methanol (11 mL) and acetonitrile (11 mL) in a sealed tube was stirred at 65 °C for 30 min. The reaction mixture was cooled, treated with sodium cyanoborohydride (252 mg, 4.00 mmol), and stirred at 65 °C for 4 h. The reaction mixture was cooled to rt, quenched with saturated sodium bicarbonate solution, and extracted with dichloromethane (2x). The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated to give the desired product **xiii** (0.582 g, 97.0%) that was used without further purification. LCMS calculated for $C_{17}H_{15}ClFN_2$ $(M+H)^+$: m/z = 301.1; Found: 301.0.

Step e. (*S*)-*N*-(1-(5-Chloro-8-(3-fluorophenyl)quinolin-7-yl)ethyl)-9*H*-purin-6-amine (**5**). A mixture of 1-[5-chloro-8-(3-fluorophenyl)quinolin-7-yl]ethanamine (0.382 g, 1.27 mmol), 6-bromo-9*H*-purine (0.506 g, 2.54 mmol), and *N*,*N*-diisopropylethylamine (0.442 mL, 2.54 mmol) in ethanol (4.40 mL) was stirred at reflux overnight. The reaction mixture was concentrated and the resultant residue was purified by preparative LCMS (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.1% ammonium hydroxide, at flow rate of 60 mL/min) to give the desired product (54.0 mg, 10.2%) as a mixture of enantiomers. The mixture of enantiomers was purified by chiral HPLC (Chiral Technologies ChiralPak IA column, 20 x 250 mm, 5 micron particle size, eluting with 15% ethanol in hexanes at 12 mL/min) to give desired product **5** as the first eluting peak and its enantiomer as the second eluting peak (retention times = 9.24 min and 12.5 min). LCMS for $C_{22}H_{17}ClFN_6$ $(M+H)^+$: m/z = 419.1; Found: 419.0.

The synthesis of **6** is illustrated in **Scheme S3**.

(*S*)-*N*-(1-(5-chloro-8-(3-fluorophenyl)cinnolin-7-yl)ethyl)-7*H*-purin-6-amine (6).

Step a. Methyl 5-chloro-2-hydroxy-4-iodobenzoate (**xv**). A solution of methyl 2-hydroxy-4-iodobenzoate (100 g, 360 mmol) in acetic acid (400 mL) was treated with *N*-chlorosuccinimide (52.8 g, 395 mmol) and stirred at 110 °C for 1 h. The reaction mixture was treated with additional *N*-chlorosuccinimide (4.80 g, 36.0 mmol) and heated at 110 °C for 30 min. The reaction mixture was cooled to 20 °C and the resultant solid was filtered. The solid was washed with acetic acid (250 mL) and water (1 L) and dried under reduced pressure over the weekend to give the desired product **xv** (109 g, 97.3%)

as an orange solid that was used without further purification. LCMS calculated for $C_8H_7ClIO_3$ $(M+H)^+$: m/z = 312.9; Found: 312.9.

Step b. Methyl 5-chloro-2-hydroxy-4-[(trimethylsilyl)ethynyl]benzoate (**xvi**). A mixture of copper(I) iodide (3.98 g, 20.9 mmol) in degassed triethylamine (116 mL) was treated with trimethylsilylacetylene (16.4 mL, 116 mmol), degassed with nitrogen, and stirred at rt for 10 min. The reaction mixture was treated with bis(triphenylphosphine)palladium(II) chloride (2.04 g, 2.90 mmol), degassed with nitrogen, and stirred at rt for 30 min. The reaction mixture was treated with methyl 5-chloro-2-hydroxy-4-iodobenzoate (18.1 g, 58.1 mmol), degassed with nitrogen, and stirred at 75 °C for 1.5 h. The reaction mixture was treated with additional trimethylsilylacetylene (16.4 mL, 116 mmol) and stirred at 75 °C for 2 h. The reaction mixture was filtered over a pad of Celite and washed with ethyl acetate. The filtrate was concentrated to give a crude tan solid. Purification by flash column chromatography using ethyl acetate in hexanes (0% to 10%) gave the desired product **xvi** (15.2 g, 92.7%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.58 (s, 1H), 7.84 (s, 1H), 7.12 (s, 1H), 3.96 (s, 3H), 0.28 (s, 9H). LCMS calculated for $C_{13}H_{16}ClO_3Si$ $(M+H)^+$: m/z = 283.1; Found: 282.9.

Step c. Methyl 5-chloro-2-hydroxy-3-nitro-4-[(trimethylsilyl)ethynyl]benzoate (**xvii**). A solution of methyl 5-chloro-2-hydroxy-4-[(trimethylsilyl)ethynyl]benzoate (15.0 g, 53.2 mmol) in acetic acid (2.23 mL, 39.2 mmol) at 55 °C was treated with a solution of nitric acid (7.80 mL, 186 mmol) in acetic acid (2.23 mL, 39.2 mmol) dropwise and stirred at 55 °C for 30 min. The reaction mixture was treated with additional nitric acid (7.80 mL, 186 mmol) in acetic acid (2.23 mL, 39.2 mmol) and stirred at 55 °C for another 1.5 h. The reaction mixture was cooled with an ice bath and ice was added to the reaction mixture followed by cold water which was stirred until the ice melted. The resultant solid was filtered and washed with cold water to give the desired product **xvii** (11.7 g, 67.3%) that was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.19 (s, 1H), 7.98 (s, 1H), 4.01 (s, 3H), 0.27 (s, 9H). LCMS calculated for $C_{13}H_{15}ClNO_5Si$ $(M+H)^+$: m/z = 328.0; Found: 327.8.

Step d. Methyl 5-chloro-3-nitro-2-{[(trifluoromethyl)sulfonyl]oxy}-4-[(trimethylsilyl)ethynyl]benzoate (**xviii**). A suspension of methyl 5-chloro-2-hydroxy-3-nitro-4-

[(trimethylsilyl)ethynyl]benzoate (8.00 g, 24.4 mmol) in dichloromethane at -10 °C was treated with triethylamine (8.50 mL, 61.0 mmol) followed by trifluoromethanesulfonic anhydride (8.21 mL, 48.8 mmol) dropwise and stirred at -10 °C for 30 min. The reaction mixture was diluted with water, warmed to rt, and extracted with dichloromethane (200 mL). The organic layer was separated and washed with water and brine, dried over sodium sulfate, filtered, and concentrated to a crude residue. Purification by flash column chromatography using ethyl acetate in hexanes (0% to 10%) gave the desired product **xviii** (9.54 g, 85.2%). LCMS calculated for $C_{14}H_{14}ClF_3NO_7SSi$ $(M+H)^+$: m/z = 460.0; Found: 459.7.

Step e. Methyl 4-chloro-3'-fluoro-6-nitro-5-[(trimethylsilyl)ethynyl]biphenyl-2-carboxylate (**xix**). A biphasic solution of methyl 5-chloro-3-nitro-2-{[(trifluoromethyl)sulfonyl]oxy}-4-[(trimethylsilyl)ethynyl]benzoate (9.50 g, 20.6 mmol) and (3-fluorophenyl)boronic acid (4.34 g, 31.0 mmol) in toluene (207 mL) and saturated sodium bicarbonate solution (207 mL) was degassed with nitrogen. The reaction mixture was treated with tetrakis(triphenylphosphine)palladium(0) (1.19 g, 1.03 mmol), degassed with nitrogen, and stirred at 80 °C for 6 h. The reaction mixture was cooled to rt and diluted with ethyl acetate (100 mL). The organic layer was separated, washed with saturated sodium bicarbonate solution (100 mL) and brine, dried over sodium sulfate, filtered, and concentrated to a crude residue. Purification by flash column chromatography using ethyl acetate in hexanes (0% to 10%) gave the desired product **xix** (7.37 g, 87.9%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.36 (ddd, *J* = 8.5, 7.7, 5.8 Hz, 1H), 7.12 (tdd, *J* = 8.5, 2.6, 1.0 Hz, 1H), 6.97 (ddd, *J* = 7.6, 1.6, 1.0 Hz, 1H), 6.95 – 6.90 (m, 1H), 3.64 (s, 3H), 0.26 (s, 9H). LCMS calculated for $C_{19}H_{18}ClFNO_4Si$ $(M+H)^+$: m/z = 406.1; Found: 406.0.

Step f. Methyl 6-amino-4-chloro-3'-fluoro-5-[(trimethylsilyl)ethynyl]biphenyl-2-carboxylate (**xx**). A suspension of iron (5.82 g, 104 mmol) (<10 micron) in ethanol was treated with 6.0 N hydrogen chloride in water (1.45 mL, 8.68 mmol) and stirred at 60 °C for 2 h. The reaction mixture was treated with 5.0 M ammonium chloride in water (14.9 mL, 74.6 mmol), followed by methyl 4-chloro-3'-fluoro-6-nitro-5-[(trimethylsilyl)ethynyl]biphenyl-2-carboxylate (7.045 g, 17.36 mmol) and stirred at 60 °C for 3 h. The reaction mixture was filtered over a pad of Celite and washed with methanol. The filtrate was

concentrated to a crude solid that was diluted with ethyl acetate (200 mL) and saturated sodium bicarbonate solution (100 mL). The organic layer was separated and washed with brine, dried over sodium sulfate, filtered, and concentrated to give the desired product **xx** (6.57 g, quantitative) that was used without further purification. LCMS calculated for $C_{19}H_{20}ClFNO_2Si$ $(M+H)^+$: m/z = 376.1; Found: 375.8.

Step g. Methyl 4-chloro-6-[(1*E*)-3,3-diethyltriaz-1-en-1-yl]-3'-fluoro-5-[(trimethylsilyl)ethynyl]biphenyl-2-carboxylate (**xxi**). A suspension of methyl 6-amino-4-chloro-3'-fluoro-5-[(trimethylsilyl)ethynyl]biphenyl-2-carboxylate (11.4 g, 30.4 mmol) in tetrahydrofuran (29.1 mL), acetonitrile (29.1 mL), and water (33.6 mL) at -5 °C was treated with 12.0 N hydrogen chloride in water (20.2 mL, 243 mmol) followed by a solution of sodium nitrite (4.19 g, 60.7 mmol) in acetonitrile (7.58 mL) and water (22.8 mL) dropwise and stirred at -5 °C for 30 min. The yellow suspension was then transferred slowly via syringe in 5 mL portions (to keep cold) and added dropwise to a stirred solution of diethylamine (31.4 mL, 304 mmol) and potassium carbonate (25.2 g, 182 mmol) in acetonitrile (91.2 mL) and water (273 mL) that had been cooled at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. The reaction mixture was diluted with saturated sodium bicarbonate solution (200 mL) and extracted with ethyl acetate (2 x 200 mL). The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated to a crude residue. Purification by flash column chromatography using dichloromethane in hexanes (0% to 50%) gave the desired product **xxi** (10.0 g, 71.8%). LCMS calculated for $C_{23}H_{28}ClFN_3O_2Si$ $(M+H)^+$: m/z = 460.2; Found: 459.8.

Step h. 4-Chloro-6-[(1E)-3,3-diethyltriaz-1-en-1-yl]-5-ethynyl-3'-fluorobiphenyl-2-carboxylic acid (**xxii**). A suspension of methyl 4-chloro-6-[(1*E*)-3,3-diethyltriaz-1-en-1-yl]-3'-fluoro-5-[(trimethylsilyl)ethynyl]biphenyl-2-carboxylate (10.0 g, 21.8 mmol) in methanol (32.6 mL) and tetrahydrofuran (32.6 mL) was treated with 1.0 N sodium hydroxide in water (87.1 mL, 87.1 mmol) dropwise and stirred at 60 °C for 1.5 h. The reaction mixture was cooled at 0 °C and quenched with 3.0 N hydrogen chloride in water (36.3 mL, 109 mmol) dropwise. The reaction mixture was concentrated to remove most of the methanol and tetrahydrofuran and poured into 1.0 N hydrogen chloride in water (100 mL) and extracted with ethyl acetate (2 x 200 mL). The combined organic extracts were washed with

brine (100 mL), dried over sodium sulfate, filtered, and concentrated to give the desired product **xxii** (8.18 g, quantitative) that was used without further purification. LCMS calculated for $C_{19}H_{18}ClFN_3O_2$ $(M+H)^+$: m/z = 374.1; Found: 373.8.

Step i. 4-Chloro-6-[(1E)-3,3-diethyltriaz-1-en-1-yl]-5-ethynyl-3'-fluoro-*N*-methoxy-*N*-methylbiphenyl-2-carboxamide (**xxiii**). A solution of 4-chloro-6-[(1*E*)-3,3-diethyltriaz-1-en-1-yl]-5-ethynyl-3'-fluorobiphenyl-2-carboxylic acid (8.14 g, 21.8 mmol) in *N*,*N*-dimethylformamide was treated with *N*,*N*-diisopropylethylamine (13.3 mL, 76.2 mmol) followed by *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (10.7 g, 28.3 mmol) and stirred at rt for 5 min. The reaction mixture was treated with *N*,*O*-dimethylhydroxylamine hydrochloride (2.76 g, 28.3 mmol) and stirred at rt for 1 h. The reaction mixture was poured into 0.5 N hydrogen chloride in water (200 mL) and extracted with ethyl acetate into (2 x 200 mL). The combined organic extracts were washed with saturated sodium bicarbonate solution (150 mL) and brine (100 mL), dried over sodium sulfate, filtered, and concentrated to give a crude product. Purification by flash column chromatography using ethyl acetate in hexanes (0% to 10%) gave the desired product **xxiii** (7.92 g, 87.2%). LCMS calculated for $C_{21}H_{23}ClFN_4O_2$ $(M+H)^+$: m/z = 417.1; Found: 416.9.

Step j. 1-{4-Chloro-6-[(1*E*)-3,3-diethyltriaz-1-en-1-yl]-5-ethynyl-3'-fluorobiphenyl-2-yl}ethanone (**xxiv**). A solution of 4-chloro-6-[(1*E*)-3,3-diethyltriaz-1-en-1-yl]-5-ethynyl-3'-fluoro-*N*-methoxy-*N*-methylbiphenyl-2-carboxamide (6.29 g, 15.1 mmol) in tetrahydrofuran at 0 °C was treated with a solution of 3.0 M methylmagnesium chloride in tetrahydrofuran (20.1 mL, 60.4 mmol) dropwise and stirred at rt for 1 h. The reaction mixture was cooled to 0 °C, quenched with 1.0 N hydrogen chloride in water (60.4 mL, 60.4 mmol), poured into 0.2 N hydrogen chloride in water (200 mL) and extracted with ethyl acetate (2 x 200 mL). The organic and aqueous layers were removed and the insoluble white solids that remained in the bottom of the separatory funnel was diluted with 6.0 N hydrogen chloride in water (10 mL) and ethyl acetate (100 mL). The combined organic extracts were washed with saturated sodium bicarbonate solution and brine, dried over sodium sulfate, filtered, and concentrated to a crude residue.

Purification by flash column chromatography using ethyl acetate in hexanes (0% to 20%) gave the desired product **xxiv** (5.48 g, 97.7%). LCMS calculated for $C_{20}H_{20}ClFN_3O$ $(M+H)^+$: m/z = 372.1; Found: 371.9.

Step k. 1-{4-Chloro-6-[(1*E*)-3,3-diethyltriaz-1-en-1-yl]-5-ethynyl-3'-fluorobiphenyl-2-yl}ethanol (**xxv**). The desired product **xxv** was prepared in a manner similar to the procedure of **vi** using 1-{4-chloro-6-[(1*E*)-3,3-diethyltriaz-1-en-1-yl]-5-ethynyl-3'-fluorobiphenyl-2-yl}ethanone as the starting material. LCMS calculated for $C_{20}H_{22}ClFN_3O$ $(M+H)^+$: m/z = 374.1; Found: 374.1.

Step l. 1-[5-Chloro-8-(3-fluorophenyl)cinnolin-7-yl]ethanol (**xxvi**). A solution of 1-{4-chloro-6-[(1*E*)-3,3-diethyltriaz-1-en-1-yl]-5-ethynyl-3'-fluorobiphenyl-2-yl}ethanol (4.96 g, 13.3 mmol) in 1,2-dichlorobenzene was heated in the microwave at 200 °C for 15 min. The reaction mixture was concentrated to give a crude residue. Purification by flash column chromatography using acetonitrile in dichloromethane (0% to 20%) gave the desired product **xxvi** (2.94 g, 73.2%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.42 (d, *J* = 6.0 Hz, 1H), 8.28 – 8.17 (m, 2H), 7.57 – 7.40 (m, 1H), 7.24 – 7.14 (m, 2H), 7.14 – 7.01 (m, 2H), 5.16 – 4.97 (m, 1H), 1.46 (dd, *J* = 6.4, 2.1 Hz, 3H). LCMS calculated for $C_{16}H_{13}ClFN_2O$ $(M+H)^+$: m/z = 303.1; Found: 302.8.

Step m. 7-(1-Azidoethyl)-5-chloro-8-(3-fluorophenyl)cinnoline (**xxvii**). The desired product **xxvii** was prepared in a manner similar to the procedure of **vii** using 1-[5-chloro-8-(3-fluorophenyl)cinnolin-7-yl]ethanol as the starting material. LCMS calculated for $C_{16}H_{12}ClFN_5$ $(M+H)^+$: m/z = 328.1; Found: 327.9.

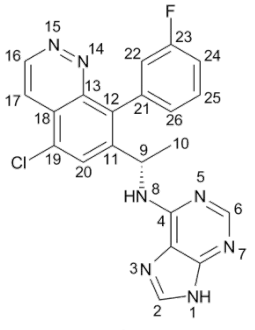
Step n. Chiral purification of 7-(1-azidoethyl)-5-chloro-8-(3-fluorophenyl)cinnoline (**xxvii**). The material from Step m was purified by chiral HPLC (Chiral Technologies ChiralCel OD-H column, 30 x 250 mm, 5 micron particle size, eluting with 10% ethanol in hexanes at 20 mL/min) to give the individual enantiomers of **xxvii** as peak 1 and peak 2 (retention times = 1.59 min and 3.94 min).

Step o (derived from Step n, peak 1). 1-[5-Chloro-8-(3-fluorophenyl)cinnolin-7-yl]ethanamine (**xxviii**). The desired product **xxviii** was prepared in a manner similar to the procedure of **viii** using 7-(1-azidoethyl)-5-chloro-8-(3-fluorophenyl)cinnoline as the starting material. LCMS calculated for $C_{16}H_{14}ClFN_3$ $(M+H)^+$: m/z = 302.1; Found: 301.9.

Step p (derived from Step n, peak 1). *N*-{1-[5-Chloro-8-(3-fluorophenyl)cinnolin-7-yl]ethyl}-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purin-6-amine (**xxx**). A solution of 1-[5-chloro-8-(3-fluorophenyl)cinnolin-7-yl]ethanamine (1.20 g, 3.98 mmol), 6-bromo-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine (1.69 g, 5.96 mmol), and *N*,*N*-diisopropylethylamine (2.08 mL, 11.9 mmol) in ethanol (20.4 mL) was stirred at 90 °C for 18 h. The reaction mixture was concentrated to give the desired product **xxx** that was used immediately without further purification.

Step q (derived from Step n, peak 1). (*S*)-*N*-(1-(5-chloro-8-(3-fluorophenyl)cinnolin-7-yl)ethyl)-7*H*-purin-6-amine (**6**). A mixture of *N*-{1-[5-Chloro-8-(3-fluorophenyl)cinnolin-7-yl]ethyl}-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purin-6-amine (2.00 g, 3.98 mmol) and 1.0 N hydrogen chloride in water (34.8 mL, 34.8 mmol) in ethanol (20.4 mL) was stirred at rt for 1 h. The reaction mixture was concentrated and the residue was diluted with methanol and re-concentrated several times to give a crude residue that was purified by preparative LCMS (XBridge C18 Column, eluting with a gradient of acetonitrile in water with 0.1% trifluoroacetic acid, at flow rate of 60 mL/min). The LCMS fractions were treated with ammonium hydroxide, concentrated to remove acetonitrile, and extracted with ethyl acetate (2 x 200 mL). The combined organic extracts were combined, dried with sodium sulfate, filtered, and concentrated to give the desired product **6** (1.05 g, 62.9%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.95 (br s, 1H), 9.49 (d, J = 6.0 Hz, 1H), 8.54 – 8.34 (m, 2H), 8.28 (d, J = 6.0 Hz, 1H), 8.15 (s, 1H), 8.07 (d, J = 11.0 Hz, 1H), 7.71 – 7.52 (m, 2H), 7.43 – 7.20 (m, 2H), 5.38 (br s, 1H), 1.50 (d, J = 7.0 Hz, 3H). LCMS for $C_{21}H_{16}ClFN_7$ $(M+H)^+$: m/z = 420.1; Found: 419.8.

Figure S1. NMR numbering scheme for **6**.



6

Table S1. ^{1}H and ^{13}C NMR spectral assignments for **6** performed in DMSO-d_6.

Position	^{1}H Chemical Shift (δ ppm)	Multiplicity	Coupling Constant (*J* Hz)	Relative Intensity	^{13}C Chemical Shift (δ ppm)
2	8.14	s	--	1H	139.6
3	12.95	s	--	1H	--
3a	--	--	--	--	127.6
4	--	--	--	--	150.4
6	8.10, 8.07	s	--	1H	152.5, 152.3
7a	--	--	--	--	153.5
8	8.38	m	--	1H	--
9	5.42	m	--	1H	47.4
10	1.50	d	6.1	3H	22.2
11	--	--	--	--	147.2
12	--	--	--	--	136.4
13	--	--	--	--	149.8
16	9.44	d	5.0	1H	146.2
17	8.19	d	4.6	1H	119.2
18	--	--	--	--	123.4
19	--	--	--	--	130.0
20	8.45	m	--	1H	129.5
21	--	--	--	--	138.5 ($^{3}J_{CF}$=6.7 Hz)
22	7.65, 7.29	m, m	-- --	1H	118.3 ($^{2}J_{CF}$=22.1 Hz)
23	--	--	--	--	162.2 ($^{1}J_{CF}$=243.6 Hz)
24	7.24	m	--	1H	114.9 ($^{2}J_{CF}$=20.8 Hz)
25	7.57	m	--	1H	130.0
26	7.67, 7.34	m, m	-- --	1H	127.4

The synthesis of **7** is illustrated in **Scheme S4**.

4-Chloro-3'-fluoro-3-methyl-6-[1-(9*H*-purin-6-ylamino)ethyl]biphenyl-2-carbonitrile (7).

Step a. 1-(3-Bromo-5-chloro-2-hydroxy-4-methylphenyl)ethanone (**xxxii**). A mixture of 1-(3-bromo-5-chloro-2-methoxy-4-methylphenyl)ethanone (1.00 g, 3.60 mmol) in dichloromethane at -78 °C

was treated with 1.0 M boron tribromide in dichloromethane (3.78 mL, 3.78 mmol) and stirred at -78 °C for 10 min. The reaction mixture was warmed to 0 °C, quenched with water, and extracted with dichloromethane (2x). The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated to give the desired product **xxxii** (0.912 g, 96.0%) that was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.95 (d, *J* = 1.0 Hz, 1H), 7.72 (s, 1H), 2.64 (d, *J* = 0.7 Hz, 3H), 2.59 (d, *J* = 0.7 Hz, 3H).

Step b. 3-Acetyl-5-chloro-2-hydroxy-6-methylbenzonitrile (**xxxiii**). A mixture of 1-(3-bromo-5-chloro-2-hydroxy-4-methylphenyl)ethanone (4.85 g, 18.4 mmol) and copper cyanide (2.47 g, 27.6 mmol) in *N*-methylpyrrolidinone was stirred at 200 °C for 1 h. The reaction mixture was cooled to rt and diluted with ethyl acetate and 1.0 N hydrogen chloride in water. The aqueous layer was separated and extracted with ethyl acetate. The combined organic extracts were washed with water and brine, dried over magnesium sulfate, filtered, and concentrated to give the desired product **xxxiii** (3.70 g, 95.9%) that was used without further purification. LCMS calculated for $C_{10}H_9ClNO_2$ $(M+H)^+$: m/z = 210.0; Found: 210.1.

Step c. 6-Acetyl-4-chloro-2-cyano-3-methylphenyl trifluoromethanesulfonate (**xxxiv**). The desired product **xxxiv** was prepared in a manner similar to the procedure of **iii** using 3-acetyl-5-chloro-2-hydroxy-6-methylbenzonitrile as the starting material. LCMS calculated for $C_{11}H_8ClF_3NO_4S$ $(M+H)^+$: m/z = 342.0; Found: 342.1.

Step d. 6-Acetyl-4-chloro-3'-fluoro-3-methylbiphenyl-2-carbonitrile (**xxxv**). The desired product **xxxv** was prepared in a manner similar to the procedure of **xix** using 6-acetyl-4-chloro-2-cyano-3-methylphenyl trifluoromethanesulfonate as the starting material. LCMS calculated for $C_{16}H_{12}ClFNO$ $(M+H)^+$: m/z = 288.1; Found: 288.1.

Step e. 6-(1-Aminoethyl)-4-chloro-3'-fluoro-3-methylbiphenyl-2-carbonitrile (**xxxvi**). The desired product **xxxvi** was prepared in a manner similar to the procedure of **xiii** using 6-acetyl-4-chloro-3'-fluoro-3-methylbiphenyl-2-carbonitrile as the starting material. LCMS calculated for $C_{16}H_{15}ClFN_2$ $(M+H)^+$: m/z = 289.1; Found: 289.1.

Step f. 4-Chloro-3'-fluoro-3-methyl-6-[1-(9*H*-purin-6-ylamino)ethyl]biphenyl-2-carbonitrile (**7**). The desired product **7** was prepared in a manner similar to the procedure of **4** using 6-(1-aminoethyl)-4-chloro-3'-fluoro-3-methylbiphenyl-2-carbonitrile as the starting material. LCMS for $C_{21}H_{17}ClFN_6$ $(M+H)^+$: m/z = 407.1; Found: 407.1.

The synthesis of **8** is illustrated in **Scheme S5**.

***N*-{1-[4-Chloro-3'-fluoro-5-methyl-6-(1-methyl-1*H*-pyrazol-4-yl)biphenyl-2-yl]ethyl}-9*H*-purin-6-amine (8).**

Step a. 6-Acetyl-2-bromo-4-chloro-3-methylphenyl trifluoromethanesulfonate (**xxxvii**). The desired product **xxxvii** was prepared in a manner similar to the procedure of **iii** using 1-(3-bromo-5-chloro-2-hydroxy-4-methylphenyl)ethanone as the starting material. LCMS calculated for $C_{10}H_8BrClF_3O_4S$ $(M+H)^+$: m/z = 394.9, 396.9; Found: 394.9, 396.7.

Step b. 1-(6-Bromo-4-chloro-3'-fluoro-5-methylbiphenyl-2-yl)ethanone (**xxxviii**). The desired product **xxxviii** was prepared in a manner similar to the procedure of **xix** using 6-acetyl-2-bromo-4-chloro-3-methylphenyl trifluoromethanesulfonate as the starting material. LCMS calculated for $C_{15}H_{12}BrClFO$ $(M+H)^+$: m/z = 341.0, 343.0; Found: 340.9, 343.1.

Step c. 1-[4-Chloro-3'-fluoro-5-methyl-6-(1-methyl-1*H*-pyrazol-4-yl)biphenyl-2-yl]ethanone (**xxxix**). A solution of 1-(6-bromo-4-chloro-3'-fluoro-5-methylbiphenyl-2-yl)ethanone (0.100 g, 0.293 mmol) in toluene was treated with a solution of sodium hydrogencarbonate (0.0492 g, 0.585 mmol) in water (1 mL) followed by 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (0.0731 g, 0.351 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.0173 g, 14.9 μmol). The reaction mixture was degassed with nitrogen for 5 min and stirred at 80 °C overnight. The reaction mixture was concentrated to a crude residue. Purification by flash column chromatography using ethyl acetate in hexanes (0% to 35%) gave the desired product **xxxix** (17.0 mg, 17.0%). LCMS calculated for $C_{19}H_{17}ClFN_2O$ $(M+H)^+$: m/z = 343.1; Found: 343.1.

Step d. 1-[4-Chloro-3'-fluoro-5-methyl-6-(1-methyl-1*H*-pyrazol-4-yl)biphenyl-2-yl]ethanamine (**xl**). The desired product **xl** was prepared in a manner similar to the procedure of **xiii** using 1-[4-chloro-

3'-fluoro-5-methyl-6-(1-methyl-1*H*-pyrazol-4-yl)biphenyl-2-yl]ethanone as the starting material. LCMS calculated for $C_{19}H_{20}ClFN_3$ $(M+H)^+$: m/z = 344.1; Found: 344.1.

Step e. *N*-{1-[4-chloro-3'-fluoro-5-methyl-6-(1-methyl-1*H*-pyrazol-4-yl)biphenyl-2-yl]ethyl}-9*H*-purin-6-amine (**8**). The desired product **8** was prepared in a manner similar to the procedure of **4** using 1-[4-chloro-3'-fluoro-5-methyl-6-(1-methyl-1*H*-pyrazol-4-yl)biphenyl-2-yl]ethanamine as the starting material. LCMS for $C_{24}H_{22}ClFN_7$ $(M+H)^+$: m/z = 462.2; Found: 462.0.

The syntheses of **9**-**11** are illustrated in **Scheme S6**.

***N*-{(1*S*)-1-[5-Chloro-2-methoxy-4-methyl-3-(1-methyl-1*H*-pyrazol-4-yl)phenyl]ethyl}-9*H*-purin-6-amine (9).**

Step a. 1-(3-Bromo-5-chloro-2-methoxy-4-methylphenyl)ethanamine (**xli**). A mixture of 1-(3-bromo-5-chloro-2-methoxy-4-methylphenyl)ethanone (2.30 g, 8.29 mmol) and 2.0 M ammonia in ethanol (20.7 mL, 41.4 mmol) at 0 °C was treated with titanium tetraisopropoxide (4.89 mL, 16.6 mmol) and stirred at 60 °C overnight. The reaction mixture was cooled to 0 °C and treated with sodium tetrahydroborate (0.470 g, 12.4 mmol) and stirred at rt for another 1 h. The reaction mixture was quenched with 2.0 M ammonium chloride in water. The resultant solid was filtered and washed with acetonitrile. The filtrate was concentrated to remove most of the organic solvents and extracted with dichloromethane. The organic extract was washed with saturated sodium bicarbonate solution, water, and brine, dried over sodium sulfate, filtered, and concentrated to a crude residue. Purification by flash column chromatography using methanol in dichloromethane (0% to 10%) gave the desired product **xli** (1.70 g, 73.9%). LCMS calculated for $C_{10}H_{11}BrClO$ $(M-NH_2)^+$: m/z = 261.0, 263.0; Found: 260.9, 262.9.

Step b. *tert*-Butyl [1-(3-bromo-5-chloro-2-methoxy-4-methylphenyl)ethyl]carbamate (**xlii**). A solution of 1-(3-bromo-5-chloro-2-methoxy-4-methylphenyl)ethanamine (20.0 g, 71.8 mmol) in 1,4-dioxane (279 mL) and *N*,*N*-diisopropylethylamine (25.0 mL, 144 mmol) at rt was treated with di-*tert*-butyldicarbonate (19.6 g, 89.7 mmol) portionwise and stirred at rt overnight. The reaction mixture was diluted with ethyl acetate, washed with water, 1.0 N hydrogen chloride in water, and brine, dried over

magnesium sulfate, filtered, and concentrated to give the crude product. Recrystallization from hexanes gave desired product **xlii** (18.2 g, 66.9%) as a mixture of enantiomers.

Step c. Chiral purification of *tert*-butyl [1-(3-bromo-5-chloro-2-methoxy-4-methylphenyl)ethyl]carbamate (**xlii**). The material from Step b was purified by chiral HPLC (Chiral Technologies ChiralPak AD-H column, 20 x 250 mm, 5 micron particle size, eluting with 3% ethanol in hexanes at 18 mL/min) to give the individual enantiomers of **xlii** as peak 1 and peak 2 (retention times = 0.522 min and 1.54 min).

Step d. (1*S*)-1-(3-Bromo-5-chloro-2-methoxy-4-methylphenyl)ethanamine (**xliii**). A solution of *tert*-butyl [(1*S*)-1-(3-bromo-5-chloro-2-methoxy-4-methylphenyl)ethyl]carbamate (0.206 g, 0.544 mmol) (peak 2 from step c) in dichloromethane (2.00 mL) was treated with trifluoroacetic acid (2.00 mL) dropwise and stirred at rt for 30 min. The reaction mixture was concentrated and the resultant residue was diluted with dichloromethane. This solution was added dropwise to an ice cooled saturated potassium carbonate solution (25 mL). The mixture was diluted with more dichloromethane. The organic extract was separated, dried over sodium sulfate, filtered, and concentrated to give the desired product **xliii** (0.145 g, 95.7%) that was used without further purification. LCMS calculated for $C_{10}H_{14}BrClNO$ $(M+H)^+$: m/z = 278.0, 280.0; Found: 277.9, 279.9.

Step e. *N*-[(1*S*)-1-(3-Bromo-5-chloro-2-methoxy-4-methylphenyl)ethyl]-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purin-6-amine (**xliv**). The desired product **xliv** was prepared in a manner similar to the procedure of **xxx** using (1*S*)-1-(3-bromo-5-chloro-2-methoxy-4-methylphenyl)ethanamine as the starting material. LCMS calculated for $C_{20}H_{24}BrClN_5O_2$ $(M+H)^+$: m/z = 480.1, 482.1; Found: 480.1, 482.0.

Step f. *N*-{(1*S*)-1-[5-Chloro-2-methoxy-4-methyl-3-(1-methyl-1*H*-pyrazol-4-yl)phenyl]ethyl}-9*H*-purin-6-amine (**9**). A mixture of *N*-[(1*S*)-1-(3-bromo-5-chloro-2-methoxy-4-methylphenyl)ethyl]-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purin-6-amine (0.030 g, 0.062 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (15.6 mg, 0.0749 mmol), 1.0 M sodium carbonate in water (0.156 mL, 0.156 mmol) and tetrakis(triphenylphosphine)palladium(0) (4.32 mg, 3.74 μmol) in 1,4-dioxane (0.5 mL) was degassed with nitrogen for 5 min and stirred at 90 °C overnight. The reaction mixture was

treated with 6.0 N hydrogen chloride in water (0.104 mL, 0.6 mmol) and stirred at rt for 30 min. The reaction mixture was diluted with methanol, filtered and purified by preparative LCMS (XBridge C18 Column, eluting with a gradient of acetonitrile in water with 0.1% trifluoroacetic acid, at flow rate of 60 mL/min) to give the desired product **9** as a TFA salt. LCMS for $C_{19}H_{21}ClN_7O$ $(M+H)^+$: m/z = 398.1; Found: 398.1.

(*S*)-*N*-(1-(5-Chloro-2-methoxy-6-methyl-4'-(methylsulfonyl)biphenyl-3-yl)ethyl)-9*H*-purin-6-amine (10). The desired product **10** was prepared in a manner similar to the procedure of **9** using [4-(methylsulfonyl)phenyl]boronic acid as the starting material. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.32 – 8.20 (m, 1H), 8.20 – 8.11 (m, 2H), 8.06 – 7.98 (m, 2H), 7.73 – 7.61 (m, 2H), 7.57 (d, *J* = 7.9 Hz, 1H), 5.88 – 5.58 (m, 1H), 3.42 (s, 3H), 3.31 (s, 3H), 1.99 (s, 3H), 1.51 (d, *J* = 6.9 Hz, 3H). LCMS for $C_{22}H_{23}ClN_5O_3S$ $(M+H)^+$: m/z = 472.1; Found: 472.0.

(*S*)-*N*-(1-(5-Chloro-2-methoxy-4-methyl-3-(5-(methylsulfonyl)pyridin-3-yl)phenyl)ethyl)-9*H*-purin-6-amine (11). The desired product **11** was prepared in a manner similar to the procedure of **9** using [5-(methylsulfonyl)pyridin-3-yl]boronic acid as the starting material. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.84 (br s, 1H), 9.12 (d, *J* = 2.2 Hz, 1H), 8.89 (d, *J* = 28.4 Hz, 1H), 8.33 (d, *J* = 34.3 Hz, 1H), 8.25 – 8.02 (m, 3H), 7.74 (s, 1H), 5.77 (br s, 1H), 3.44 (s, 3H), 3.40 (s, 3H), 2.04 (s, 3H), 1.52 (d, *J* = 6.8 Hz, 3H). LCMS for $C_{21}H_{22}ClN_6O_3S$ $(M+H)^+$: m/z = 473.1; Found: 473.0.

The synthesis of **12** is illustrated in **Scheme S7**.

4-Amino-6-[((1*S*)-1-{5-chloro-2-methoxy-4-methyl-3-[5-(methylsulfonyl)pyridin-3-yl]phenyl}ethyl)amino]pyrimidine-5-carbonitrile (12).

Step a. *tert*-Butyl ((1*S*)-1-{5-chloro-2-methoxy-4-methyl-3-[5-(methylsulfonyl)pyridin-3-yl]phenyl}ethyl)carbamate (**xlvi**). A mixture of *tert*-butyl [(1*S*)-1-(3-bromo-5-chloro-2-methoxy-4-methylphenyl)ethyl]carbamate (0.110 g, 0.290 mmol), [5-(methylsulfonyl)pyridin-3-yl]boronic acid (0.0642 g, 0.320 mmol), sodium carbonate (61.6 mg, 0.581 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (1:1) (28.5 mg, 0.0349 mmol) in acetonitrile (2.00 mL) and water (0.600 mL) was degassed with nitrogen and stirred

at 95 °C for 2 h. The reaction mixture was diluted with ethyl acetate, washed with saturated sodium bicarbonate solution, water, and brine, dried over sodium sulfate, filtered, and concentrated to a crude residue. Purification by flash column chromatography using ethyl acetate in hexanes (0% to 20%) gave the desired product **xlvi** (0.120 g, 85.7%). LCMS calculated for $C_{21}H_{28}ClN_2O_5S$ $(M+H)^+$: m/z = 455.1; Found: 455.1.

Step b. (*S*)-1-(5-Chloro-2-methoxy-4-methyl-3-(5-(methylsulfonyl)pyridin-3-yl)phenyl)ethanamine hydrochloride (**xlvii**). A solution of *tert*-butyl ((1*S*)-1-{5-chloro-2-methoxy-4-methyl-3-[5-(methylsulfonyl)pyridin-3-yl]phenyl}ethyl)carbamate (0.120 g, 0.317 mmol) in dichloromethane (1.00 mL) was treated with 4.0 N hydrogen chloride in 1,4-dioxane (1.00 mL, 4.00 mmol) and stirred at rt for 30 min. The reaction mixture was concentrated to give the desired product **xlvii** (0.120 g, 96.8%) that was used immediately without further purification.

Step c. 4-Amino-6-[((1*S*)-1-{5-chloro-2-methoxy-4-methyl-3-[5-(methylsulfonyl)pyridin-3-yl]phenyl}ethyl)amino]pyrimidine-5-carbonitrile (**12**). A mixture of (*S*)-1-(5-chloro-2-methoxy-4-methyl-3-(5-(methylsulfonyl)pyridin-3-yl)phenyl)ethanamine hydrochloride (0.120 g, 0.308 mmol), 4-amino-6-chloropyrimidine-5-carbonitrile (49.9 mg, 0.323 mmol), and *N*,*N*-diisopropylethylamine (0.295 mL, 1.54 mmol) in 1-butanol (3.00 mL) was stirred at 120 °C for 3 h. The reaction mixture was concentrated and the resultant residue was purified by preparative LCMS (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.1% ammonium hydroxide, at flow rate of 60 mL/min) to give the desired product **12**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.19 (d, *J* = 2.3 Hz, 1H), 8.84 (d, *J* = 2.1 Hz, 1H), 8.22 (dd, *J* = 2.1, 2.1 Hz, 1H), 8.13 (s, 1H), 7.38 (s, 1H), 5.69 (d, *J* = 7.3 Hz, 1H), 5.64 – 5.53 (m, 1H), 5.45 (s, 2H), 3.36 (s, 3H), 3.18 (s, 3H), 2.14 (s, 3H), 1.57 (d, *J* = 7.0 Hz, 3H). LCMS calculated for $C_{21}H_{22}ClN_6O_3S$ $(M+H)^+$: m/z = 473.1; Found: 473.0.

The synthesis of **13** is illustrated in **Scheme S8**.

6-(3-{(1*S*)-1-[(6-Amino-5-cyanopyrimidin-4-yl)amino]ethyl}-5-chloro-2-methoxy-6-methylphenyl)-*N*,*N*-dimethylnicotinamide (13).

Step a. Methyl 6-(3-{(1*S*)-1-[(*tert*-butoxycarbonyl)amino]ethyl}-5-chloro-2-methoxy-6-methylphenyl)nicotinate (**xlviii**). A mixture of *tert*-butyl [(1*S*)-1-(3-bromo-5-chloro-2-methoxy-4-methylphenyl)ethyl]carbamate (2.00 g, 5.28 mmol), methyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate (3.47 g, 13.2 mmol), [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (1:1) (431 mg, 0.528 mmol), palladium acetate (59.3 mg, 0.264 mmol), cuprous monochloride (520 mg, 5.28 mmol), and cesium carbonate (3.44 g, 10.6 mmol) in *N*,*N*-dimethylformamide (140 mL) was degassed with nitrogen for 5 min and stirred at 100 °C overnight. The reaction mixture was poured into water (300 mL) and extracted with ethyl acetate. The organic extract was washed with brine, dried over sodium sulfate, filtered and concentrated to a crude residue. Purification by flash column chromatography using ethyl acetate in hexanes (0% to 50%) gave the desired product **xlviii** (1.40 g, 66.7%). LCMS calculated for $C_{22}H_{28}ClN_2O_5$ $(M+H)^+$: m/z = 435.2; Found: 435.1.

Step b. 6-(3-{(1*S*)-1-[(*tert*-Butoxycarbonyl)amino]ethyl}-5-chloro-2-methoxy-6-methylphenyl)nicotinic acid (**xlix**). A solution of methyl 6-(3-{(1*S*)-1-[(*tert*-butoxycarbonyl)amino]ethyl}-5-chloro-2-methoxy-6-methylphenyl)nicotinate (340 mg, 0.782 mmol) in methanol (12.0 mL) was treated with 1.0 N sodium hydroxide in water (3.12 mL, 3.12 mmol) and stirred at rt for 45 min. The reaction mixture was quenched with acetic acid until pH ~ 4 and the reaction mixture was concentrated to a residue that was diluted with ethyl acetate. The organic solution was dried with sodium sulfate, filtered, and concentrated to a crude residue. The crude material was stirred with dichloromethane, filtered, and the filtrate was concentrated to a crude residue. Purification by flash column chromatography using ethyl acetate in hexanes (0% to 50%) gave the desired product **xlix** (0.180 g, 54.5%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.41 (dd, *J* = 2.2, 0.9 Hz, 1H), 8.44 (dd, *J* = 8.1, 2.2 Hz, 1H), 7.51 (d, *J* = 8.1 Hz, 1H), 7.36 (s, 1H), 5.17 – 4.85 (m, 1H), 3.37 (s, 3H), 2.09 (s, 3H), 1.49 – 1.37 (m, 12H). LCMS calculated for $C_{21}H_{26}ClN_2O_5$ $(M+H)^+$: m/z = 421.2; Found: 421.1.

Step c. *tert*-butyl [(1*S*)-1-(5-Chloro-3-{5-[(dimethylamino)carbonyl]pyridin-2-yl}-2-methoxy-4-methylphenyl)ethyl]carbamate (**l**). A solution of 6-(3-{(1*S*)-1-[(*tert*-butoxycarbonyl)amino]ethyl}-5-

chloro-2-methoxy-6-methylphenyl)nicotinic acid (110 mg, 0.261 mmol) and benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (173 mg, 0.392 mmol) in *N*,*N*-dimethylformamide at 0 °C was treated with 2.0 M dimethylamine in tetrahydrofuran (2.61mL, 5.23 μmol) followed by adding triethylamine (0.109 mL, 0.784 mmol) and was stirred at rt for 1 h. The reaction mixture was poured into ethyl acetate and washed with saturated sodium bicarbonate solution and brine, dried over sodium sulfate, filtered, and concentrated to a crude residue. Purification by flash column chromatography using ethyl acetate in hexanes (0% to 80%) gave the desired product **l** (0.0850 g, 70.8%).

Step d. 6-{3-[(1*S*)-1-Aminoethyl]-5-chloro-2-methoxy-6-methylphenyl}-*N*,*N*-dimethylnicotinamide hydrochloride (**li**). A mixture of *tert*-butyl [(1*S*)-1-(5-chloro-3-{5-[(dimethylamino)carbonyl]pyridin-2-yl}-2-methoxy-4-methylphenyl)ethyl]carbamate (17.1 mg, 0.0382 mmol) was treated with 4.0 M hydrogen chloride in 1,4-dioxane (1.00 mL, 4.00 mmol) and stirred at rt for 30 min. The reaction mixture was concentrated to give the desired product **li** that was used immediately without further purification.

Step e. 6-(3-{(1*S*)-1-[(6-Amino-5-cyanopyrimidin-4-yl)amino]ethyl}-5-chloro-2-methoxy-6-methylphenyl)-*N*,*N*-dimethylnicotinamide (**13**). A solution of 6-{3-[(1*S*)-1-Aminoethyl]-5-chloro-2-methoxy-6-methylphenyl}-*N*,*N*-dimethylnicotinamide hydrochloride (0.0147 g, 0.0382 mmol) in 1-butanol (1.00 mL) was treated with *N*,*N*-diisopropylethylamine (33.2 μL, 0.191 mmol) and 4-amino-6-chloropyrimidine-5-carbonitrile (7.08 mg, 0.0458 mmol) and stirred at 120 °C for 3 h. The reaction mixture was concentrated to a crude residue. Purification by preparative LCMS (XBridge C18 Column, eluting with a gradient of acetonitrile in water with 0.1% trifluoroacetic acid, at flow rate of 60 mL/min) to give the desired product **13** (1.90 mg, 7.17%) as a TFA salt. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.91 – 8.74 (m, 1H), 8.11 (s, 1H), 7.88 (dd, *J* = 8.0, 2.2 Hz, 1H), 7.50 – 7.40 (m, 1H), 7.33 (s, 1H), 5.79 (d, *J* = 7.4 Hz, 1H), 5.67 – 5.51 (m, 1H), 5.42 (s, 2H), 3.40 (s, 3H), 3.18 (s, 3H), 3.10 (s, 3H), 2.09 (s, 3H), 1.55 (d, *J* = 6.9 Hz, 3H). LCMS for $C_{23}H_{25}ClN_7O_2$ $(M+H)^+$: m/z = 466.2; Found: 466.1.

The synthesis of **14** is illustrated in **Scheme S9**.

4-{3-[1-(4-Amino-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl]-5-chloro-2-methoxy-6-methylphenyl}-*N*,*N*-dimethylpyridine-2-carboxamide (14).

Step a. 1-(3-Bromo-5-chloro-2-methoxy-4-methylphenyl)ethanol (**lii**). The desired product **lii** was prepared in a manner similar to the procedure of **vi** using 1-(3-bromo-5-chloro-2-methoxy-4-methylphenyl)ethanone as the starting material. LCMS calculated for $C_{10}H_{11}BrClO$ $(M\text{-}OH)^+$: m/z = 261.0, 263.0; Found: 261.0, 263.0.

Step b. 4-[3-Chloro-5-(1-hydroxyethyl)-6-methoxy-2-methylphenyl]pyridine-2-carbonitrile (**liii**). The desired product **liii** was prepared in a manner similar to the procedure of **xlvi** using 1-(3-bromo-5-chloro-2-methoxy-4-methylphenyl)ethanol and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-2-carbonitrile as the starting materials. LCMS calculated for $C_{16}H_{16}ClN_2O_2$ $(M+H)^+$: m/z = 303.1; Found: 303.0.

Step c. 4-[3-Chloro-5-(1-chloroethyl)-6-methoxy-2-methylphenyl]pyridine-2-carbonitrile (**liv**). A mixture of cyanuric chloride (170 mg, 0.941 mmol) and *N*,*N*-dimethylformamide (72.9 μL, 0.941 mmol) was stirred at rt for 10 min, treated with a solution of 4-[3-chloro-5-(1-hydroxyethyl)-6-methoxy-2-methylphenyl]pyridine-2-carbonitrile (190 mg, 0.628 mmol) in dichloromethane (4.00 mL), and stirred at rt overnight. The reaction mixture was diluted with dichloromethane, washed with saturated sodium bicarbonate solution, water, and brine, dried over sodium sulfate, filtered, and concentrated to give the desired product **liv** (0.180 g, 89.3%) that was used without further purification. LCMS calculated for $C_{16}H_{15}Cl_2N_2O$ $(M+H)^+$: m/z = 321.1; Found: 321.0.

Step d. 4-{3-[1-(4-Amino-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl]-5-chloro-2-methoxy-6-methylphenyl}pyridine-2-carbonitrile (**lv**). A solution of 4-[3-chloro-5-(1-chloroethyl)-6-methoxy-2-methylphenyl]pyridine-2-carbonitrile (90.0 mg, 0.280 mmol) and 4-aminopyrazolo[3,4-*d*]pyrimidine (56.8 mg, 0.420 mmol) in *N*,*N*-dimethylformamide (4.00 mL) was treated with sodium hydride (20.2 mg, 0.504 mmol) and stirred at 30 °C overnight. The reaction mixture was concentrated to give the desired product **lv** (along with the regioisomer 4-{3-[1-(7-amino-2*H*-pyrazolo[4,3-*d*]pyrimidin-2-yl)ethyl]-5-

chloro-2-methoxy-6-methylphenyl}pyridine-2-carbonitrile) that were used without further purification. LCMS calculated for $C_{21}H_{19}ClN_7O$ $(M+H)^+$: m/z = 420.1; Found: 420.1.

Step e. 4-{3-[1-(4-Amino-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl]-5-chloro-2-methoxy-6-methylphenyl}pyridine-2-carboxylic acid (**lvi**). A mixture of 4-{3-[1-(4-amino-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl]-5-chloro-2-methoxy-6-methylphenyl}pyridine-2-carbonitrile (30.0 mg, 0.0714 mmol) (which also contained 4-{3-[1-(7-amino-2*H*-pyrazolo[4,3-*d*]pyrimidin-2-yl)ethyl]-5-chloro-2-methoxy-6-methylphenyl}pyridine-2-carbonitrile) in ethanol (0.300 mL) was treated with 1.0 N sodium hydroxide in water (0.285 mL, 0.285 mmol) and stirred at 95 °C for 6 h. The reaction mixture was cooled to rt and adjusted to pH ~ 3 with 12 M hydrogen chloride in water. The reaction mixture was concentrated to give the desired product **lvi** (along with the regioisomer 4-{3-[1-(7-amino-2*H*-pyrazolo[4,3-*d*]pyrimidin-2-yl)ethyl]-5-chloro-2-methoxy-6-methylphenyl}pyridine-2-carboxylic acid) that was used without further purification. LCMS calculated for $C_{21}H_{20}ClN_6O_3$ $(M+H)^+$: m/z = 439.1; Found: 439.2.

Step f. 4-{3-[1-(4-Amino-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl]-5-chloro-2-methoxy-6-methylphenyl}-*N*,*N*-dimethylpyridine-2-carboxamide (**14**). A solution of 4-{3-[1-(4-amino-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl]-5-chloro-2-methoxy-6-methylphenyl}pyridine-2-carboxylic acid (9.29 mg, 0.0212 mmol) (which also contained 4-{3-[1-(7-amino-2*H*-pyrazolo[4,3-*d*]pyrimidin-2-yl)ethyl]-5-chloro-2-methoxy-6-methylphenyl}pyridine-2-carboxylic acid) and benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (9.36 mg, 0.0212 mmol) in *N*,*N*-dimethylformamide was treated with a solution of 2.0 M dimethylamine in tetrahydrofuran (0.138 mL, 0.275 mmol) followed by triethylamine (8.85 μL, 0.0635 mmol) and stirred at rt for 1 h. The reaction mixture was diluted with methanol and purified by preparative LCMS (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.1% ammonium hydroxide, at flow rate of 60 mL/min) to give desired product **14**. LCMS for $C_{23}H_{25}ClN_7O_2$ $(M+H)^+$: m/z = 466.2; Found: 466.2.

The synthesis of **15** is illustrated in **Scheme S10**.

4-{3-[(1*S*)-1-(4-Amino-3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl]-5-chloro-2-methoxy-6-methylphenyl}-*N*,*N*-dimethylpyridine-2-carboxamide (15).

Step a. 3-Bromo-1-chloro-5-(1-chloroethyl)-4-methoxy-2-methylbenzene (**lvii**). The desired product **lvii** was prepared in a manner similar to the procedure of **liv** using 1-(3-bromo-5-chloro-2-methoxy-4-methylphenyl)ethanol as the starting material.

Step b. 1-[1-(3-Bromo-5-chloro-2-methoxy-4-methylphenyl)ethyl]-3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (**lviii**). A solution of 3-bromo-1-chloro-5-(1-chloroethyl)-4-methoxy-2-methylbenzene (0.150 g, 0.503 mmol) and 3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.113 g, 0.755 mmol) in *N*,*N*-dimethylformamide (8.00 mL) was treated with sodium hydride (36 mg, 0.91 mmol) and stirred at 30 °C overnight. The reaction mixture was diluted with dichloromethane, washed with saturated sodium bicarbonate solution, water, and brine, dried over sodium sulfate, filtered, and concentrated to a crude residue. Purification by flash column chromatography using dichloromethane in ethyl acetate (0% to 70%) gave the desired product **lviii** (0.0950 g, 50.0%). LCMS calculated for $C_{16}H_{18}BrClN_5O$ $(M+H)^+$: m/z = 410.0, 412.0; Found: 410.0, 412.1.

Step c. Chiral purification of 1-[1-(3-Bromo-5-chloro-2-methoxy-4-methylphenyl)ethyl]-3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (**lviii**). The material from Step b was purified by chiral HPLC (Phenomenex Lux Cellulose C-2, 21.1 x 250 mm, 5 micron particle size, eluting with 5% ethanol in hexanes at 22 mL/min) to give the individual enantiomers of **lviii** as peak 1 and peak 2 (retention times = 12.4 min and 14.9 min).

Step d. 4-{3-[(1*S*)-1-(4-Amino-3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl]-5-chloro-2-methoxy-6-methylphenyl}pyridine-2-carbonitrile (**lix**). The desired product **lix** was prepared in a manner similar to the procedure of **xlvi** using 1-[(1*S*)-1-(3-bromo-5-chloro-2-methoxy-4-methylphenyl)ethyl]-3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (peak 1 from step c) and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-2-carbonitrile as the starting materials. LCMS calculated for $C_{22}H_{21}ClN_7O$ $(M+H)^+$: m/z = 434.1; Found: 434.1.

Step e. 4-{3-[(1*S*)-1-(4-Amino-3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl]-5-chloro-2-methoxy-6-methylphenyl}pyridine-2-carboxylic acid (**lx**). The desired product **lx** was prepared in a manner similar to the procedure of **lvi** using 4-{3-[(1*S*)-1-(4-amino-3-methyl-1*H*-pyrazolo[3,4-

d]pyrimidin-1-yl)ethyl]-5-chloro-2-methoxy-6-methylphenyl}pyridine-2-carbonitrile as the starting material. LCMS calculated for $C_{22}H_{22}ClN_6O_3$ $(M+H)^+$: m/z = 453.1; Found: 453.2.

Step f. 4-{3-[(1*S*)-1-(4-amino-3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl]-5-chloro-2-methoxy-6-methylphenyl}-*N*,*N*-dimethylpyridine-2-carboxamide (**15**). The desired product **15** was prepared in a manner similar to the procedure of **14** using 4-{3-[(1*S*)-1-(4-amino-3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl]-5-chloro-2-methoxy-6-methylphenyl}pyridine-2-carboxylic acid as the starting material. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.68 (d, *J* = 4.9 Hz, 1H), 8.38 (s, 1H), 7.60 (s, 1H), 7.50 – 7.35 (m, 2H), 6.33 (q, *J* = 7.0 Hz, 1H), 3.22 (s, 3H), 3.01 (s, 3H), 2.95 (s, 3H), 2.63 (s, 3H), 2.04 (s, 3H), 1.81 (d, *J* = 7.0 Hz, 3H). LCMS for $C_{24}H_{27}ClN_7O_2$ $(M+H)^+$: m/z = 480.2; Found: 480.2. The synthesis of **16** is illustrated in **Scheme S11**.

1-{1-[5-Chloro-2-methoxy-4-methyl-3-(1-methylpiperidin-4-yl)phenyl]ethyl}-3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (16).

Step a. *tert*-Butyl 4-(3-acetyl-5-chloro-2-methoxy-6-methylphenyl)piperidine-1-carboxylate (**lxii**). A microwave vial equipped with a magnetic stir bar and a rubber septum was charged with lithium chloride (0.324 g, 7.66 mmol). The vial was heated at 140 °C for 10 min under high vacuum and backfilled with nitrogen after cooling to rt. Zinc (0.501 g, 7.66 mmol) was added and the vial was heated at 140 °C for 10 min under high vacuum and backfilled with nitrogen after cooling to rt. Tetrahydrofuran (4.00 mL) and 1,2-dibromoethane (24.2 μL, 0.281 mmol) were added via syringe and the mixture was heated at 60 °C for 10 min and cooled to rt. The reaction mixture was treated with a mixture of chlorotrimethylsilane (38.4 μL, 0.303 mmol) and iodine (71.3 mg, 0.281 mmol) in tetrahydrofuran (4.00 mL), stirred at 60° for 10 min, and cooled to rt. The reaction mixture was treated with *tert*-butyl 4-iodopiperidine-1-carboxylate (1.19 g, 3.83 mmol) in tetrahydrofuran and stirred at 50 °C overnight. In a separate microwave vial a mixture of 1-(3-bromo-5-chloro-2-methoxy-4-methylphenyl)ethanone (0.600 g, 2.16 mmol), palladium acetate (58.2 mg, 0.259 mmol), 2'-(dicyclohexylphosphino)-*N*,*N*,*N*′,*N*′-tetramethylbiphenyl-2,6-diamine (230 mg, 0.519 mmol) in toluene (66 mmol) was evacuated under high vacuum, backfilled with nitrogen, cooled to 0 °C, and treated with the zinc reagent slowly via syringe.

The reaction mixture was heated at 60 °C overnight, cooled, and diluted with ethyl acetate and saturated ammonium chloride solution. The aqueous layer was separated and extracted with ethyl acetate (2x). The combined organic extracts were washed with water and brine, dried over magnesium sulfate, filtered, and concentrated to a crude residue. Purification by flash column chromatography using ethyl acetate in hexanes (0% to 20%) gave the desired product **lxii** (0.280 g, 34.1%). LCMS calculated for $C_{20}H_{28}ClNNaO_4$ $(M+Na)^+$: m/z = 404.2; Found: 404.1.

Step b. *tert*-Butyl 4-[3-chloro-5-(1-hydroxyethyl)-6-methoxy-2-methylphenyl]piperidine-1-carboxylate (**lxiii**). The desired product **lxiii** was prepared in a manner similar to the procedure of **vi** using *tert*-butyl 4-(3-acetyl-5-chloro-2-methoxy-6-methylphenyl)piperidine-1-carboxylate as the starting material. LCMS calculated for $C_{20}H_{30}ClNNaO_4$ $(M+Na)^+$: m/z = 406.2; Found: 406.1.

Step c. *tert*-Butyl 4-[3-chloro-5-(1-chloroethyl)-6-methoxy-2-methylphenyl]piperidine-1-carboxylate (**lxiv**). The desired product **lxiv** was prepared in a manner similar to the procedure of **liv** using *tert*-butyl 4-[3-chloro-5-(1-hydroxyethyl)-6-methoxy-2-methylphenyl]piperidine-1-carboxylate as the starting material. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 1H), 5.43 (q, J = 6.8 Hz, 1H), 3.76 (s, 3H), 2.90 – 2.66 (m, 2H), 2.40 (s, 3H), 2.25 – 2.04 (m, 4H), 1.81 – 1.74 (m, 4H), 1.65 – 1.55 (m, 2H), 1.48 (s, 9H). LCMS calculated for $C_{16}H_{21}ClNO_3$ (M-Cl-(*t*-Bu)+H)$^+$: m/z = 310.1; Found: 310.0.

Step d. *tert*-Butyl 4-{3-[1-(4-amino-3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl]-5-chloro-2-methoxy-6-methylphenyl}piperidine-1-carboxylate (**lxv**). A mixture of 3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (34.7 mg, 0.233 mmol), cesium carbonate (103 mg, 0.317 mmol), and potassium iodide (3.51 mg, 0.0212 mmol) in *N*,*N*-dimethylformamide (3.0 mL) was treated with *tert*-butyl 4-[3-chloro-5-(1-chloroethyl)-6-methoxy-2-methylphenyl]piperidine-1-carboxylate (85.1 mg, 0.212 mmol) and stirred at 140 °C for 1 h. The reaction mixture was diluted with methanol and purified by preparative LCMS (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.1% ammonium hydroxide, at flow rate of 60 mL/min) to give the desired product **lxv** (48.0 mg, 44.0%). LCMS for $C_{26}H_{36}ClN_6O_3$ $(M+H)^+$: m/z = 515.3; Found: 515.2.

Step e. 1-[1-(5-Chloro-2-methoxy-4-methyl-3-piperidin-4-ylphenyl)ethyl]-3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine dihydrochloride (**lxvi**). A solution of *tert*-butyl 4-{3-[1-(4-amino-3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl]-5-chloro-2-methoxy-6-methylphenyl}piperidine-1-carboxylate (48.0 mg, 0.0932 mmol) in dichloromethane was treated with 4.0 M hydrogen chloride in 1,4-dioxane (0.186 mL, 0.746 mmol) and stirred at rt for 6 h. The reaction mixture was concentrated to give the desired product **lxvi** (45.0 mg, quantitative) that was used without further purification.

Step f. 1-{1-[5-Chloro-2-methoxy-4-methyl-3-(1-methylpiperidin-4-yl)phenyl]ethyl}-3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (**16**). A mixture of 1-[1-(5-chloro-2-methoxy-4-methyl-3-piperidin-4-ylphenyl)ethyl]-3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine dihydrochloride (19.5 mg, 0.0400 mmol) and *N*,*N*-diisopropylethylamine (27.8 μL, 0.160 mmol) in dichloromethane at 0 °C was treated with a solution of 12.0 M formaldehyde in water (33.3 μL, 0.400 mmol) and stirred for 10 min. The reaction mixture was treated with sodium triacetoxyborohydride on resin (25.7 mg, 0.0600 mmol) and stirred at 0 °C for 1 h. The reaction mixture was diluted with methanol and purified by preparative LCMS (XBridge C18 Column, eluting with a gradient of acetonitrile in water with 0.1% trifluoroacetic acid, at flow rate of 60 mL/min) to give the desired product **16**. LCMS for $C_{22}H_{30}ClN_6O$ $(M+H)^+$: m/z = 429.2; Found: 429.1.

The synthesis of **17** is illustrated in **Scheme S12**.

4-[(1*S*)-1-(4-Amino-3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl]-6-chloro-2-{1-[(2*S*)-2-hydroxypropyl]azetidin-3-yl}-3-methoxybenzonitrile (17).

Step a. 1-(5-Chloro-4-fluoro-2-hydroxyphenyl)ethanone (**lxviii**). A solution of 4-chloro-3-fluorophenol (24.5 g, 167 mmol) in acetyl chloride (17.4 mL, 245 mmol) was stirred at 60 °C for 2 h. The reaction mixture was cooled to 20 °C, treated with aluminum trichloride (33.4 g, 251 mmol) portionwise, and heated at 180 °C for 30 min. The reaction mixture was cooled to 20 °C and the solution hardened into a solid block that was not easy to break apart. This material was cooled to 0 °C and quenched slowly with 1.0 N hydrogen chloride in water in portions. The solid block of material slowly broke apart with enough HCl and this heterogenous mixture was stirred at 20 °C overnight to ensure uniformity. The solid

was filtered, washed with copious amounts of water, and dried under vacuum to give desired product **lxviii** (31.5 g, quantitative) that was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.44 (dd, *J* = 1.5, 0.7 Hz, 1H), 7.78 (dd, *J* = 8.1, 0.7 Hz, 1H), 6.77 (dd, *J* = 10.2, 0.7 Hz, 1H), 2.61 (d, *J* = 0.7 Hz, 3H).

Step b. 1-(5-Chloro-4-fluoro-2-hydroxy-3-iodophenyl)ethanone (**lxix**). A solution of 1-(5-chloro-4-fluoro-2-hydroxyphenyl)ethanone (25.0 g, 133 mmol) in acetic acid (200 mL) was treated with *N*-iodosuccinimide (35.8 g, 159 mmol) and stirred at 90 °C for 17 h. The reaction mixture was concentrated, diluted with ethyl acetate, and quenched with saturated sodium bicarbonate solution until the bubbling stopped. The aqueous layer was separated and re-extracted with ethyl acetate. The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated to a crude residue. This material was recrystallized from methanol (cooled in freezer overnight) to give 29.2 g of the desired product. The mother liquor was concentrated and the residue was purified by flash column chromatography using dichloromethane in hexanes (20% to 50%) to give an additional 8.36 g of the desired product **lxix** (37.6 g, 90.2% combined yield).

Step c. 1-(5-Chloro-4-fluoro-3-iodo-2-methoxyphenyl)ethanone (**lxx**). A mixture of 1-(5-chloro-4-fluoro-2-hydroxy-3-iodophenyl)ethanone (20.0 g, 63.6 mmol) and potassium carbonate (22.8 g, 165 mmol) in *N*,*N*-dimethylformamide was treated with methyl iodide (8.71 mL, 140 mmol) and stirred at 100 °C for 15 min. The reaction mixture was diluted with water and extracted with ethyl acetate (2x). The combined organic extracts were dried with magnesium sulfate, filtered, and concentrated to give a crude solid. Purification by flash column chromatography using ethyl acetate in hexanes (5% to 20%) gave the desired product **lxx** (17.6 g, 84.4%). LCMS calculated for $C_9H_8ClFIO_2$ $(M+H)^+$: m/z = 328.9; Found: 328.9.

Step d. 4-Acetyl-6-chloro-2-iodo-3-methoxybenzonitrile (**lxxi**). A solution of 1-(5-chloro-4-fluoro-3-iodo-2-methoxyphenyl)ethanone (17.1 g, 52.0 mmol) in *N*,*N*-dimethylformamide (200 mL) was treated with potassium cyanide (5.08 g, 78.1 mmol) and stirred at 45 °C for 5 h. The reaction mixture was poured into saturated sodium bicarbonate solution (~700 mL) and extracted with ethyl acetate (3 x

200mL). The combined organic extracts were washed with water (3 x 400mL) and brine, dried over magnesium sulfate, filtered, and concentrated to a crude residue. Purification by flash column chromatography using ethyl acetate in hexanes (5% to 20%) gave the desired product **lxxi** (11.8 g, 67.7%). LCMS calculated for $C_{10}H_8ClINO_2$ $(M+H)^+$: m/z = 335.9; Found: 335.8.

Step e. *tert*-Butyl 3-(3-acetyl-5-chloro-6-cyano-2-methoxyphenyl)azetidine-1-carboxylate (**lxxii**). Zinc (5.03 g, 76.9 mmol) and oven-dried Celite (520 mg) were added to a round bottom flask and the flask was heated with a heat gun while under reduced pressure for 5 min and then back-filled with nitrogen. *N*,*N*-Dimethylacetamide (52.7 mL) was added followed by 1,2-dibromoethane (0.398 mL, 4.61 mmol) and the mixture was heated at 70 °C for 15 min and then cooled to rt. Chlorotrimethylsilane (0.586 mL, 4.61 mmol) was added dropwise and stirring was continued at rt for 1 h. A solution of *tert*-butyl 3-iodoazetidine-1-carboxylate (16.3 g, 57.7 mmol) in *N*,*N*-dimethylacetamide (26.3 mL) was then added slowly (maintained internal temp below 40 °C with water bath cooling) and the resulting mixture was heated at 40 °C for 2 h. The zinc reagent was filtered through a plastic filter cartridge (adapted with septa-seal) directly into a clean, dry flask (flushed with nitrogen) (care was taken to minimize exposure to the atmosphere by transferring the slurry with a cannula needle onto the sealed filter setup, with everything under positive nitrogen pressure). The zinc reagent was treated with tris(dibenzylideneacetone)dipalladium(0) (670 mg, 0.732 mmol) and tri-(2-furyl)phosphine (340 mg, 1.46 mmol) and bubbled with nitrogen for a 5 min. A solution of 4-acetyl-6-chloro-2-iodo-3-methoxybenzonitrile (12.9 g, 38. 5 mmol) in *N*,*N*-dimethylacetamide (118 mL) was degassed by bubbling nitrogen (in the addition funnel) and was then added quickly to the zinc reagent and the resulting mixture was stirred at 70 °C for 2 h. The reaction mixture was poured into saturated ammonium chloride solution (200 mL) and extracted into ethyl acetate (4 x 200 mL). The combined organic extracts were washed with water (4 x 200 mL) and brine (150 mL), dried over magnesium sulfate, filtered, and concentrated to a crude residue. Purification by flash column chromatography using ethyl acetate in hexanes (5% to 40%) gave the desired product **lxxii** (12.0 g, 85.2%). LCMS calculated for $C_{18}H_{21}ClN_2NaO_4$ $(M+Na)^+$: m/z = 387.1; Found: 387.0.

Step f. *tert*-Butyl 3-{3-chloro-2-cyano-5-[(1*R*)-1-hydroxyethyl]-6-methoxyphenyl}azetidine-1-carboxylate (**lxxiii**). A solution of (3a*S*)-1-methyl-3,3-diphenyltetrahydro-3*H*-pyrrolo[1,2-*c*][1,3,2]oxazaborole (4.29 g, 15.5 mmol) in tetrahydrofuran (46.1 mL) was treated with 1.0 M borane-THF complex in tetrahyrofuran (18.6 mL, 18.6 mmol) and stirred at 20 °C for 15 min. The reaction mixture was cooled to -30 °C and treated with a solution of *tert*-butyl 3-(3-acetyl-5-chloro-6-cyano-2-methoxyphenyl)azetidine-1-carboxylate (5.65 g, 15.5 mmol) in tetrahydrofuran (48.5 mL) slowly. The temperature of the reaction was -20 °C after the addition was complete. The reaction mixture was warmed to -5 °C over a period of 30 min. The reaction mixture was quenched with water at 0 °C, poured into saturated sodium bicarbonate solution, and extracted with ethyl acetate. The aqueous layer was separated and extracted with ethyl acetate. The combined organic extracts were washed with water and brine, dried with magnesium sulfate, filtered, and concentrated to a crude oil. Purification by flash column chromatography using ethyl acetate in hexanes (0% to 100%) gave the desired product **lxxiii** (5.49 g, 96.6%) as a 95:5 mixture of enantiomers. LCMS calculated for $C_{14}H_{16}ClN_2O_4$ (M-[*t*-Bu+H]+H)+: m/z = 311.1; Found: 311.1.

Step g. *tert*-Butyl 3-(3-Chloro-2-cyano-6-methoxy-5-{(1*R*)-1-[(methylsulfonyl)oxy]ethyl}phenyl)azetidine-1-carboxylate (**lxxiv**). A solution of *tert*-butyl 3-{3-chloro-2-cyano-5-[(1*R*)-1-hydroxyethyl]-6-methoxyphenyl}azetidine-1-carboxylate (8.60 g, 23.4 mmol) in dichloromethane was treated with triethylamine (8.17 mL, 58.6 mmol). The reaction mixture was cooled at 0 °C, treated with methanesulphonic anhydride (6.13 g, 35.2 mmol), and stirred at 0 °C for 30 min. The reaction mixture was diluted with dichloromethane (125 mL) and washed with water and brine, dried over magnesium sulfate, filtered, and concentrated to a crude mesylate intermediate as a 95:5 mixture of enantiomers that was used without further purification. LCMS calculated for $C_{19}H_{25}ClN_2NaO_6S$ $(M+Na)^+$: m/z = 467.1; Found: 467.1.

Step h. *tert*-Butyl 3-{3-[(1*S*)-1-(4-amino-3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl]-5-chloro-6-cyano-2-methoxyphenyl}azetidine-1-carboxylate (**lxxv**). A solution of 3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (4.09 g, 27.4 mmol) in *N*,*N*-dimethylformamide (82.4 mL) at 0 °C was

treated with sodium hydride (1.19 g, 29.8 mmol) (60% in mineral oil) and stirred for 30 min at 0 °C. The reaction mixture was treated with a solution of *tert*-butyl 3-(3-chloro-2-cyano-6-methoxy-5-{(1*R*)-1-[(methylsulfonyl)oxy]ethyl}phenyl)azetidine-1-carboxylate (10.6 g, 23.8 mmol) in *N*,*N*-dimethylformamide (165 mL) dropwise over 10 min and stirred at 0 °C for 30 min and at 50 °C for 1 h. The reaction mixture was diluted with saturated sodium bicarbonate solution and extracted with ethyl acetate (3 x 200 mL). The organic layer was separated and washed with water (4 x 150 mL) and brine, dried over magnesium sulfate, filtered, and concentrated to a crude residue. Purification by flash column chromatography using methanol in dichloromethane (2% to 7%, dichloromethane contained 0.5% triethylamine) gave the desired product **lxxv** (9.10 g, 76.7%) as a 95:5 mixture of enantiomers. LCMS calculated for $C_{20}H_{21}ClN_7O_3$ (M-[*t*-Bu+H]+H)+: m/z = 442.1; Found: 442.1.

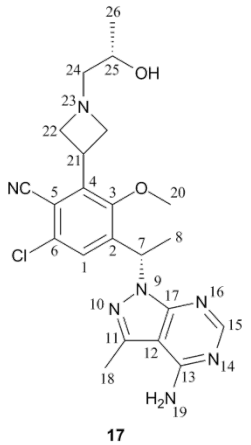
Step i. Chiral purification of *tert*-butyl 3-{3-[(1*S*)-1-(4-amino-3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl]-5-chloro-6-cyano-2-methoxyphenyl}azetidine-1-carboxylate (**lxxv**). The material from Step h was purified by chiral HPLC (Chiral Technologies ChiralPak AD-H column, 20 x 250 mm, 5 micron particle size, eluting with 10% ethanol in hexanes at 17 mL/min) to give the individual enantiomers of **lxxv** as peak 1 and peak 2 (retention times = 1.94 min and 4.73 min). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (s, 1H), 7.53 (s, 1H), 7.34 (br s, 2H), 6.26 (q, *J* = 7.0 Hz, 1H), 4.49 – 4.33 (m, 1H), 4.30 – 4.14 (m, 4H), 3.71 (s, 3H), 2.56 (s, 3H), 1.74 (d, *J* = 7.0 Hz, 3H), 1.38 (s, 9H).

Step j. 4-[(1*S*)-1-(4-Amino-3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl]-2-azetidin-3-yl-6-chloro-3-methoxybenzonitrile (**lxxvi**). A solution of *tert*-butyl 3-{3-[(1*S*)-1-(4-amino-3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl]-5-chloro-6-cyano-2-methoxyphenyl}azetidine-1-carboxylate (6.68 g, 13.4 mmol) (peak 1 from step i) in dichloromethane (34.3 mL) was treated with trifluoroacetic acid (34.3 mL) dropwise and stirred at rt for 30 min. The reaction mixture was concentrated to an oil and reconcentrated from ethanol (2x) to a residue. The residue was dissolved in a minimum amount of methanol added dropwise to ice cooled saturated sodium bicarbonate solution (200 mL) and extracted several times with 3:1 dichloromethane/isopropanol to give the desired product (5.30 g, 99.3%) that was

used without further purification. LCMS calculated for $C_{19}H_{21}ClN_7O$ $(M+H)^+$: m/z = 398.1; Found: 398.0.

Step k. 4-[(1*S*)-1-(4-Amino-3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl]-6-chloro-2-{1-[(2*S*)-2-hydroxypropyl]azetidin-3-yl}-3-methoxybenzonitrile (**17**). A solution of 4-[(1*S*)-1-(4-amino-3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl]-2-azetidin-3-yl-6-chloro-3-methoxybenzonitrile (4.83 g, 12.1 mmol) in ethanol (242 mL) was treated with (*S*)-(-)-methyloxirane (2.13 mL, 30.3 mmol) and heated at 125 °C for 15 min in the microwave (this was performed in multiple batches). The reaction mixture was concentrated to a crude residue. Purification by flash column chromatography using methanol in dichloromethane (0% to 15%, dichloromethane contained 0.5% triethylamine) gave the desired product **17** (3.17 g, 57.3%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (s, 1H), 7.47 (s, 1H), 7.42 (br s, 2H), 6.24 (q, *J* = 7.0 Hz, 1H), 4.37 (d, *J* = 4.3 Hz, 1H), 4.19 – 4.01 (m, 1H), 4.00 – 3.87 (m, 2H), 3.64 (s, 3H), 3.61 – 3.49 (m, 1H), 3.13 – 2.97 (m, 2H), 2.56 (s, 3H), 2.29 (d, *J* = 5.7 Hz, 2H), 1.73 (d, *J* = 7.0 Hz, 3H), 1.01 (d, *J* = 6.2 Hz, 3H). LCMS for $C_{22}H_{27}ClN_7O_2$ $(M+H)^+$: m/z = 456.2; Found: 456.1.

Figure S2. NMR numbering scheme for **17**.



17

Table S2. ^{1}H and ^{13}C NMR spectral assignments for **17** performed in DMSO-d_6.

Position	^{1}H Chemical Shift (δ ppm)	Multiplicity	Coupling Constant (*J* Hz)	Relative Intensity	^{13}C Chemical Shift (δ ppm)
1	7.46	s	--	1H	127.1
2	--	--	--	--	143.2
3	--	--	--	--	154.4
4	--	--	--	--	143.2

5	--	--	--	--	111.3
6	--	--	--	--	132.1
7	6.24	q	7.4	1H	48.7
8	1.72	d	7.0	3H	21.1
11	--	--	--	--	141.8
12	--	--	--	--	99.5
13	--	--	--	--	158.9
15	8.11	s	--	1H	156.4
17	--	--	--	--	154.3
18	2.56	s	--	3H	15.0
19	7.31	br s	--	2H	--
20	3.64	s	--	3H	61.8
21	4.07	m	--	1H	32.4
22	3.94, 3.07	dd, m	5.9, 12.8, --	4H	61.5, 61.2
24	2.28	d	5.9	2H	67.1
25	3.57	m	--	1H	65.3
26	1.00	d	6.2	3H	22.1
27	--	--	--	--	115.3
29	4.32	d	4.6	1H	--

The syntheses of **18** and **22** are illustrated in **Scheme S13**.

Diastereoisomers of 4-{3-[(1*S*)-1-(4-Amino-3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl]-5-chloro-2-methoxy-6-methylphenyl}pyrrolidin-2-one (18 and 22).

Step a. Methyl (2*E*)-3-{3-[(1*S*)-1-(4-amino-3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl]-5-chloro-2-methoxy-6-methylphenyl}acrylate (**lxxvii**). A solution of 1-[(1*S*)-1-(3-bromo-5-chloro-2-methoxy-4-methylphenyl)ethyl]-3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.293 g, 0.713 mmol) in *N*,*N*-dimethylformamide was degassed with nitrogen for 5 min, treated with methyl acrylate (0.514 mL, 5.71 mmol), triphenylphosphine (0.0262 g, 0.0999 mmol), and palladium acetate (0.0160 g, 0.0713 mmol) followed by triethylamine (0.298 mL, 2.14 mmol) and heated at 130 °C for 20 h. The reaction mixture was filtered and purified by preparative LCMS (XBridge C18 Column, eluting with a gradient of acetonitrile in water with 0.1% trifluoroacetic acid, at flow rate of 60 mL/min) to give the desired product **lxxvii** (0.170 g, 45.0%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.08 (br s, 1H), 8.17 (s, 1H),

7.77 (d, *J* = 16.3 Hz, 1H), 7.52 (s, 1H), 6.73 (br s, 1H), 6.48 – 6.35 (m, 2H), 3.82 (s, 3H), 3.68 (s, 3H), 2.68 (s, 3H), 2.37 (s, 3H), 1.87 (d, *J* = 7.0 Hz, 3H). LCMS calculated for $C_{20}H_{23}ClN_5O_3$ $(M+H)^+$: m/z = 416.1; Found: 416.1.

Step b. Methyl 3-{3-[(1*S*)-1-(4-amino-3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl]-5-chloro-2-methoxy-6-methylphenyl}-4-nitrobutanoate (**lxxviii**). A solution of methyl (2*E*)-3-{3-[(1*S*)-1-(4-amino-3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl]-5-chloro-2-methoxy-6-methylphenyl}acrylate (0.0880 g, 0.212 mmol) in nitromethane (0.571 mL) was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (0.0316 mL, 0.212 mmol) and stirred at 60 °C for 20 h. The reaction mixture was treated with additional 1,8-diazabicyclo[5.4.0]undec-7-ene (0.0316 mL, 0.212 mmol) and stirred at 60 °C for 3 h. The reaction mixture was treated with another portion of 1,8-diazabicyclo[5.4.0]undec-7-ene (0.0316 mL, 0.212 mmol) and heated at 90 °C for 13 h. The reaction mixture was diluted with methanol and purified by preparative LCMS (XBridge C18 Column, eluting with a gradient of acetonitrile in water with 0.1% trifluoroacetic acid, at flow rate of 60 mL/min) to give the desired product **lxxviii** (31.0 mg, 25.8%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.31 (br s, 1H), 8.19 (d, *J* = 2.3 Hz, 1H), 7.51 (d, *J* = 6.3 Hz, 1H), 6.43 – 6.21 (m, 2H), 4.91 – 4.70 (m, 2H), 4.50 (br s, 1H), 3.96 (d, *J* = 6.8 Hz, 3H), 3.65 (d, *J* = 6.3 Hz, 3H), 2.91 – 2.74 (m, 1H), 2.68 (d, *J* = 7.8 Hz, 3H), 2.45 (s, 3H), 1.87 (dd, *J* = 16.1, 7.0 Hz, 3H). LCMS calculated for $C_{21}H_{26}ClN_6O_5$ $(M+H)^+$: m/z = 477.2; Found: 477.1.

Step c. 4-{3-[(1*S*)-1-(4-Amino-3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl]-5-chloro-2-methoxy-6-methylphenyl}pyrrolidin-2-one (**18** and **22**). A solution of methyl 3-{3-[(1*S*)-1-(4-amino-3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl]-5-chloro-2-methoxy-6-methylphenyl}-4-nitrobutanoate trifluoroacetate (0.0310 g, 0.0525 mmol) in methanol (0.373 mL) was treated with nickel chloride hexahydrate (0.0251 g, 0.105 mmol) and stirred at 20 °C for 5 min. The reaction mixture was cooled to 0 °C, treated with sodium tetrahydroborate (0.02126 g, 0.5618 mmol), and stirred at 0 °C for 30 min and at 60 °C for 3 h. The reaction mixture was treated with saturated sodium bicarbonate solution (2 mL) and ethyl acetate and filtered over Celite. The Celite was washed with EA and the filtrate was concentrated to a residue. Purification by preparative LCMS (XBridge C18 column, eluting with a

gradient of acetonitrile/water containing 0.1% ammonium hydroxide, at flow rate of 60 mL/min) gave the desired products **18** and **22** as a mixture of diastereoisomers (4.10 mg, 18.6%). The mixture of diastereoisomers was purified by chiral HPLC (Phenomenex Lux Cellulose C-1, 21.1 x 250 mm, 5 micron particle size, eluting with 20% ethanol in hexanes at 18 mL/min) to give **18** (2.10 mg, 9.13%) as the first eluting peak and **22** (2.00 mg, 8.69%) as the second eluting peak (retention times = 15.3 min and 22.5 min). **18**: LCMS for $C_{20}H_{24}ClN_6O_2$ $(M+H)^+$: m/z = 415.2; Found: 415.1. **22**: LCMS for $C_{20}H_{24}ClN_6O_2$ $(M+H)^+$: m/z = 415.2; Found: 415.1.

The syntheses of **19** and **23** are illustrated in **Scheme S14**.

Diastereoisomers of 4-{3-[(1*S*)-1-(4-amino-3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl]-5-chloro-2-ethoxy-6-methylphenyl}pyrrolidin-2-one (19 and 23).

Step a. 1-(5-Chloro-2-hydroxy-3-iodo-4-methylphenyl)ethanone (**lxxx**). A solution of 1-(5-chloro-2-hydroxy-4-methylphenyl)ethanone (20.0 g, 108 mmol) in acetic acid (200 mL) was treated with *N*-iodosuccinimide (29.2 g, 130 mmol) and stirred at rt for 2 d. The reaction mixture was concentrated to remove most of the acetic acid, quenched with saturated sodium bicarbonate, and diluted with ethyl acetate. An insoluble solid was filtered and the organic layer of the filtrate was separated, washed with water and brine, dried over magnesium sulfate, filtered, and concentrated to give the desired product **lxxx** (33.5 g, 99.7%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.21 (s, 1H), 7.71 (s, 1H), 2.65 (s, 3H), 2.63 (s, 3H). LCMS calculated for $C_9H_9ClIO_2$ $(M+H)^+$: m/z = 310.9; Found: 311.0.

Step b. 1-(5-Chloro-2-ethoxy-3-iodo-4-methylphenyl)ethanone (**lxxxi**). A solution of 1-(5-chloro-2-hydroxy-3-iodo-4-methylphenyl)ethanone (18.9 g, 60.9 mmol) in *N,N*-dimethylformamide (60.8 mL) was treated with iodoethane (7.30 mL, 91.3 mmol) followed by potassium carbonate (16.8 g, 122 mmol) and stirred at 60 °C for 1 h. The mixture was cooled to rt, diluted with ethyl ether, washed with water, dried over magnesium sulfate, filtered, and concentrated to give the crude product. Purification by flash column chromatography using ethyl acetate in hexanes (0% to 10%) gave the desired product **lxxxi** (18.9 g, 91.7%). LCMS calculated for $C_{11}H_{13}ClIO_2$ $(M+H)^+$: m/z = 339.0; Found: 339.0.

Step c. (1*R*)-1-(5-Chloro-2-ethoxy-3-iodo-4-methylphenyl)ethanol (**lxxxii**). A solution of (3a*S*)-1-methyl-3,3-diphenyltetrahydro-3*H*-pyrrolo[1,2-*c*][1,3,2]oxazaborole (0.819 g, 2.95 mmol) in tetrahydrofuran (8.79 mL) was treated with 1.0 M borane-THF complex in tetrahyrofuran (3.54 mL, 3.54 mmol) and stirred at 20 °C for 15 min. The reaction mixture was cooled to -30 °C and treated with a solution of 1-(5-chloro-2-ethoxy-3-iodo-4-methylphenyl)ethanone (1.00 g, 2.95 mmol) in tetrahydrofuran (9.25 mL) dropwise. The reaction mixture was warmed slowly to 0 °C. The reaction mixture was quenched with water at 0 °C and warmed to rt. The reaction mixture was concentrated to remove most of the tetrahydrofuran, poured into 10% potassium carbonate solution, and extracted with ethyl acetate. The organic layer was dried with magnesium sulfate, filtered, and concentrated to give a crude oil. Purification by flash column chromatography using ethyl acetate in hexanes (0% to 30%) gave the desired product **lxxxii** (0.941 g, 94.1%) as a 96:4 mixture of enantiomers (retention times = 3.56 min and 4.28 min; Chiral Technologies ChiralPak AD-H column, 20 x 250 mm, 5 micron particle size, eluting with 5% ethanol in hexanes at 1 mL/min). LCMS for $C_{11}H_{13}ClIO$ $(M-(OH))^+$: m/z = 323.0; Found: 322.9.

Step d. 1-[(1*S*)-1-(5-Chloro-2-ethoxy-3-iodo-4-methylphenyl)ethyl]-3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (**lxxxiii**). A solution of (1*R*)-1-(5-chloro-2-ethoxy-3-iodo-4-methylphenyl)ethanol (0.936 g, 2.75 mmol) in dichloromethane (13.8 mL) was treated with triethylamine (1.15 mL, 8.24 mmol), cooled to 0 °C, treated with methanesulfonic anhydride (0.718 g, 4.12 mmol), and stirred at 0 °C for 30 min. The reaction mixture was diluted with dichloromethane, washed with water, dried over sodium sulfate, filtered, and concentrated to give the intermediate mesylate that was used immediately without further purification.

The crude mesylate was dissolved in *N*,*N*-dimethylformamide (11.0 mL), treated with cesium carbonate (1.34 g, 4.12 mmol) followed by 3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.471 g, 3.16 mmol) and stirred at 60 °C for 2 h. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was separated and concentrated to give the crude product. This material was diluted with dichloromethane and the resultant solid was filtered. The filtrate was concentrated to give the crude product. Purification by flash column chromatography using acetonitrile (containing 3%

methanol) in dichloromethane (0% to 100%) gave the desired product **lxxxiii** (0.416 g, 32.0%). LCMS for $C_{17}H_{20}ClIN_5O$ $(M+H)^+$: m/z = 472.0; Found: 472.0.

Step e. Chiral purification of 1-[(1*S*)-1-(5-chloro-2-ethoxy-3-iodo-4-methylphenyl)ethyl]-3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (**lxxxiii**). The material from Step d was purified by chiral HPLC (Chiral Technologies ChiralPak IA column, 20 x 250 mm, 5 micron particle size, eluting with 3% ethanol in hexanes at 18 mL/min) to give the desired product **lxxxiii** (0.351 g, 27.0%) as a single enantiomer (retention time = 13.5 min).

Step f. Methyl (2*E*)-3-{3-[(1*S*)-1-(4-amino-3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl]-5-chloro-2-ethoxy-6-methylphenyl}acrylate (**lxxxiv**). A suspension of 1-[(1*S*)-1-(5-chloro-2-ethoxy-3-iodo-4-methylphenyl)ethyl]-3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.611 g, 1.30 mmol) in acetonitrile (7.44 mL) in a sealed tube was degassed with nitrogen and treated with triphenylphosphine (47.6 mg, 0.181 mmol), methyl acrylate (0.408 mL, 4.53 mmol), and palladium acetate (0.029 g, 0.130 mmol) followed by triethylamine (0.542 mL, 3.88 mmol) and heated at 100 °C for 16 h. The reaction mixture was cooled to room temperature, filtered, and the solids washed with acetonitrile. The filtrate was concentrated to a residue. Purification by flash column chromatography using ethyl acetate (containing 3% methanol) in hexanes (0% to 100%) gave the desired product **lxxxiv** (0.403 g, 72.4%). LCMS for $C_{21}H_{25}ClN_5O_3$ $(M+H)^+$: m/z = 430.2; Found: 430.2.

Step g. Diastereoisomers of methyl 3-{3-[(1*S*)-1-(4-amino-3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl]-5-chloro-2-ethoxy-6-methylphenyl}-4-nitrobutanoate (**lxxxv**). A solution of methyl (2*E*)-3-{3-[(1*S*)-1-(4-amino-3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl]-5-chloro-2-ethoxy-6-methylphenyl}acrylate (0.401 g, 0.933 mmol) in nitromethane (6.26 mL) was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (0.139 mL, 0.933 mmol) and stirred at 90 °C for 22 h. The reaction mixture was concentrated, diluted with methanol, and purified by preparative LCMS (XBridge C18 Column, eluting with a gradient of acetonitrile in water with 0.1% trifluoroacetic acid, at flow rate of 60 mL/min). The LCMS fractions were concentrated to remove acetonitrile, treated with solid sodium bicarbonate, and extracted with ethyl acetate. The organic extract was dried with sodium sulfate, filtered,

and concentrated to give the desired product **lxxxv** (0.218 g, 47.6%) as a mixture of diastereoisomers. LCMS for $C_{22}H_{28}ClN_6O_5$ $(M+H)^+$: m/z = 491.2; Found: 491.2.

Step h. Diastereoisomers of 4-{3-[(1*S*)-1-(4-amino-3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl]-5-chloro-2-ethoxy-6-methylphenyl}pyrrolidin-2-one (**19** and **23**). A solution of methyl 3-{3-[(1*S*)-1-(4-amino-3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl]-5-chloro-2-ethoxy-6-methylphenyl}-4-nitrobutanoate (0.089 g, 0.180 mmol) in methanol (1.29 mL) was treated with nickel chloride hexahydrate (86.9 mg, 0.362 mmol) and stirred for 5 min. The reaction mixture was cooled to 0 °C, treated with sodium tetrahydroborate (73.5 mg, 1.94 mmol) in four portions, and stirred at rt for 30 min. The reaction mixture was heated at 60 °C for 1.5 h, cooled to rt, diluted with saturated sodium bicarbonate solution (10 mL) and dichloromethane (25 mL), and filtered through Celite®. The Celite® was washed with dichloromethane and the organic layer from the filtrate was separated, washed with brine, dried over sodium sulfate, filtered, and concentrated to a residue. The crude residue was diluted with methanol and purified by preparative LCMS (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.1% ammonium hydroxide, at flow rate of 60 mL/min) to give the desired diastereoisomer **19** (16 mg, 19.0%) and diastereoisomer **23** (19 mg, 22.6%). **19**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.10 (s, 1H), 7.89 (s, 1H), 7.34 (s, 1H), 6.21 (q, J = 7.1 Hz, 1H), 4.38 – 4.22 (m, 1H), 3.93 – 3.80 (m, 1H), 3.79 – 3.67 (m, 1H), 3.65 – 3.55 (m, 1H), 3.28 – 3.20 (m, 1H), 2.54 (s, 3H), 2.29 (dd, J = 17.5, 8.3 Hz, 1H), 2.21 (s, 3H), 1.70 (d, J = 7.0 Hz, 3H), 1.40 (t, J = 6.9 Hz, 3H). LCMS for $C_{21}H_{26}ClN_6O_2$ $(M+H)^+$: m/z = 429.2; Found: 429.2. **23**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.11 (s, 1H), 7.89 (s, 1H), 7.33 (s, 1H), 6.20 (q, J = 7.1 Hz, 1H), 4.38 – 4.22 (m, 1H), 3.90 – 3.68 (m, 2H), 3.65 – 3.56 (m, 1H), 3.28 – 3.17 (m, 1H), 2.54 (s, 3H), 2.32 (dd, J = 17.3, 8.5 Hz, 1H), 2.21 (s, 3H), 1.69 (d, J = 7.0 Hz, 3H), 1.39 (t, J = 6.9 Hz, 3H). LCMS for $C_{21}H_{26}ClN_6O_2$ $(M+H)^+$: m/z = 429.2; Found: 429.2.

The syntheses of **20** and **24** are illustrated in **Scheme S15**.

4-(3-((*S*)-1-(4-Amino-3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl)-5-chloro-2-ethoxy-6-fluorophenyl)pyrrolidin-2-one (20 and 24).

Step a. 1-(5-Chloro-2-ethoxy-4-fluoro-3-iodophenyl)ethanone (**lxxxvi**). A solution of 1-(5-chloro-4-fluoro-2-hydroxy-3-iodophenyl)ethanone (22.0 g, 70.0 mmol) and potassium carbonate (25.1 g, 182 mmol) in *N,N*-dimethylformamide (60.0 mL) was treated with iodoethane (12.3 mL, 154 mmol) and stirred at 60 °C for 1 h. The mixture was cooled to rt and diluted with ethyl acetate and water. The aqueous layer was separated and extracted with ethyl acetate. The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated to give the crude product. Purification by flash column chromatography using ethyl acetate in hexanes (0% to 20%) gave the desired product **lxxxvi** (21.7 g, 90.6%). LCMS calculated for $C_{10}H_{10}ClFIO_2$ $(M+H)^+$: m/z = 342.9, 344.9; Found: 342.9, 344.8.

Step b. 2-(5-Chloro-2-ethoxy-4-fluoro-3-iodophenyl)-2-methyl-1,3-dioxolane (**lxxxvii**). A solution of 1-(5-chloro-2-ethoxy-4-fluoro-3-iodophenyl)ethanone (20.0 g, 58.4 mmol) and 1,2-ethanediol (6.51 mL, 117 mmol) in toluene (188 mL) was treated with *p*-toluenesulfonic acid monohydrate (1.11 g, 5.84 mmol). The flask was fitted with a Dean-Stark trap that was filled with sieves, and refluxed for 3 h. The reaction mixture was cooled to rt, added to a saturated sodium bicarbonate solution (250 mL) that was cooled to 0 °C, and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, filtrered, and concentrated to a crude oil. Purification by flash column chromatography using ethyl acetate in hexanes (0% to 20%) gave the desired product **lxxxvii** (22.4 g, 99.2%). LCMS for $C_{12}H_{14}ClFIO_3$ $(M+H)^+$: m/z = 387.0; Found: 386.9.

Step c. Ethyl (2*E*)-3-[3-chloro-6-ethoxy-2-fluoro-5-(2-methyl-1,3-dioxolan-2-yl)phenyl]acrylate (**lxxxviii**). A mixture of 2-(5-chloro-2-ethoxy-4-fluoro-3-iodophenyl)-2-methyl-1,3-dioxolane (22.4 g, 58.0 mmol), ethyl (2*E*)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)acrylate (15.6 mL, 69.6 mmol), and potassium carbonate (24.0 g, 174 mmol) in 1,4-dioxane (227 mL) and water (114 mL) was degassed with nitrogen for 10 min. The reaction mixture was treated with [1,1'-bis (diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (1:1) (2.37 g, 2.90 mmol), degassed with nitrogen for another 10 min, and heated at 80 °C for 2 h. The reaction mixture was filtered through Celite® and washed with ethyl acetate (300 mL). The filtrate was poured into water (400 mL). The aqueous layer was separated and extracted with additional ethyl acetate (300 mL). The

combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated to a crude solid. Purification by flash column chromatography using ethyl acetate in hexanes (0% to 30%) gave the desired product **lxxxviii** (19.9 g, 95.8%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 16.5 Hz, 1H), 7.56 (d, *J* = 8.6 Hz, 1H), 6.70 (dd, *J* = 16.5, 0.9 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 4.10 – 3.99 (m, 2H), 3.91 (q, *J* = 7.0 Hz, 2H), 3.87 – 3.76 (m, 2H), 1.73 (s, 3H), 1.44 (t, *J* = 7.0 Hz, 3H), 1.33 (t, *J* = 7.1 Hz, 3H). LCMS for $C_{17}H_{21}ClFO_5$ $(M+H)^+$: m/z = 359.1; Found: 359.1.

Step d. Ethyl 3-[3-chloro-6-ethoxy-2-fluoro-5-(2-methyl-1,3-dioxolan-2-yl)phenyl]-4-nitrobutanoate (**lxxxix**). A solution of ethyl (2*E*)-3-[3-chloro-6-ethoxy-2-fluoro-5-(2-methyl-1,3-dioxolan-2-yl)phenyl]acrylate (10.0 g, 27.9 mmol) in nitromethane (100 mL) was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (4.58 mL, 30.6 mmol) and stirred at 60 °C for 15 h. The reaction mixture was poured into water (400 mL) and extracted with ethyl acetate (2 x 300 mL). The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated to a crude oil. Purification by flash column chromatography using ethyl acetate in hexanes (0% to 30%) gave the desired product **lxxxix** (10.4 g, 88.9%) as a mixture of enantiomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 9.1 Hz, 1H), 4.82 (ddd, *J* = 12.5, 7.6, 1.4 Hz, 1H), 4.68 (dd, *J* = 12.5, 7.2 Hz, 1H), 4.54 – 4.40 (m, 1H), 4.15 – 3.90 (m, 6H), 3.89 – 3.75 (m, 2H), 2.85 (ddd, *J* = 16.0, 8.6, 1.4 Hz, 1H), 2.73 (dd, *J* = 16.1, 6.2 Hz, 1H), 1.70 (s, 3H), 1.47 (t, *J* = 7.0 Hz, 3H), 1.21 (t, *J* = 7.1 Hz, 3H). LCMS for $C_{18}H_{24}ClFNO_7$ $(M+H)^+$: m/z = 420.1; Found: 420.1.

Step e. 4-[3-Chloro-6-ethoxy-2-fluoro-5-(2-methyl-1,3-dioxolan-2-yl)phenyl]pyrrolidin-2-one (**xc**). A suspension of ethyl 3-[3-chloro-6-ethoxy-2-fluoro-5-(2-methyl-1,3-dioxolan-2-yl)phenyl]-4-nitrobutanoate (1.00 g, 2.38 mmol) in ethanol (15.8 mL) was warmed to dissolve the solid. The solution was cooled back to ambient temperature, degassed with nitrogen, and treated with a slurry of 2800 Raney nickel in water (1.50 mL). The reaction mixture was degassed again with nitrogen and hydrogenated with a balloon of hydrogen for 3 h. The reaction mixture was filtered through Celite® and concentrated to give the intermediate amino ester (0.927 g, 99.9%) that was used without further purification.

The intermediate amino ester was dissolved in toluene (12.0 mL) and heated at 110 °C for 12 h. The reaction mixture was cooled to ambient temperature, at which point a solid precipitated from solution. This mixture was cooled to 0 °C, stirred for 30 min, filtered, washed with cold toluene, and dried to give the desired product **xc** (0.613 g, 74.8%) as a mixture of enantiomers. LCMS for $C_{16}H_{20}ClFNO_4$ $(M+H)^+$: m/z = 344.1; Found: 344.1.

Step f. Chiral purification of 4-[3-chloro-6-ethoxy-2-fluoro-5-(2-methyl-1,3-dioxolan-2-yl)phenyl]pyrrolidin-2-one (**xc**). The material from Step e was purified by chiral HPLC (Phenomenex Lux Cellulose C-1, 21.2 x 250 mm, 5 micron particle size, eluting with 20% ethanol in hexanes at 18 mL/min) to give the individual enantiomers of **xc** as peak 1 and peak 2 (retention times = 5.39 min and 7.01 min).

Step g (derived from Step f, peak 1). Single enantiomer of 4-(3-acetyl-5-chloro-2-ethoxy-6-fluorophenyl)pyrrolidin-2-one (**xci**). A solution of 4-[3-chloro-6-ethoxy-2-fluoro-5-(2-methyl-1,3-dioxolan-2-yl)phenyl]pyrrolidin-2-one (1.71 g, 4.97 mmol) (from Step f, peak 1) in methanol (17.1 mL) was treated with 6.0 N hydrogen chloride in water (11.4 mL, 68.6 mmol) dropwise and stirred at 20 °C for 30 min. The reaction mixture was added dropwise to ice cooled saturated sodium bicarbonate solution (75 mL) and extracted with ethyl acetate (2 x 100 mL). The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated to give the desired product **xci** (1.47 g, 98.7%) that was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84 (s, 1H), 7.70 (d, J = 8.6 Hz, 1H), 4.16 – 3.99 (m, 1H), 3.83 (q, J = 7.0 Hz, 2H), 3.65 – 3.54 (m, 1H), 3.30 – 3.23 (m, 1H), 2.55 (s, 3H), 2.33 (dd, J = 16.8, 8.4 Hz, 1H), 1.30 (t, J = 7.0 Hz, 3H). LCMS for $C_{14}H_{16}ClFNO_3$ $(M+H)^+$: m/z = 300.1; Found: 300.0.

Step g (derived from Step f, peak 2). Single enantiomer of 4-(3-acetyl-5-chloro-2-ethoxy-6-fluorophenyl)pyrrolidin-2-one (**xci**). A solution of 4-[3-chloro-6-ethoxy-2-fluoro-5-(2-methyl-1,3-dioxolan-2-yl)phenyl]pyrrolidin-2-one (1.71 g, 4.97 mmol) (from Step f, peak 2) in methanol (17.1 mL) was treated with 6.0 N hydrogen chloride in water (11.4 mL, 68.6 mmol) dropwise and stirred 20 °C for 30 min. The reaction mixture was added dropwise to ice cooled saturated sodium bicarbonate solution

(75 mL) and extracted with ethyl acetate (2 x 100 mL). The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated to give the desired product **xci** (1.46 g, 98.0%) that was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84 (s, 1H), 7.70 (d, J = 8.6 Hz, 1H), 4.13 – 4.00 (m, 1H), 3.87 – 3.77 (m, 2H), 3.65 – 3.55 (m, 1H), 3.31 – 3.23 (m, 1H), 2.55 (s, 3H), 2.32 (ddd, J = 16.9, 8.4, 1.6 Hz, 1H), 1.30 (t, J = 7.0 Hz, 3H). LCMS for $C_{14}H_{16}ClFNO_3$ $(M+H)^+$: m/z = 300.1; Found: 300.1.

Step h (derived from Step f, peak 1). 4-[3-Chloro-6-ethoxy-2-fluoro-5-(1-hydroxyethyl)phenyl]pyrrolidin-2-one (**xcii**). A solution of 4-(3-acetyl-5-chloro-2-ethoxy-6-fluorophenyl)pyrrolidin-2-one (0.402 g, 1.34 mmol) in anhydrous methanol (6.72 mL) at 0 °C was treated with sodium tetrahydroborate (0.101 g, 2.68 mmol) and stirred at 0° C for 30 min. The reaction mixture was quenched with water at 0 °C and poured into a mixture of water (50 mL) and ethyl acetate (100 mL) while stirring. The mixture was warmed to ambient temperature and the aqueous layer was separated and extracted with additional ethyl acetate (50 mL). The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated to give crude residues. Purification by flash column chromatography using acetonitrile (containing 7% methanol) in dichloromethane (0% to 100%) gave the desired product **xcii** (0.402 g, 99.3%) as a mixture of diastereoisomers that was used without further purification. LCMS for $C_{14}H_{18}ClFNO_3$ $(M+H)^+$: m/z = 302.1; Found: 302.0.

Step h (derived from Step f, peak 2). 4-[3-Chloro-6-ethoxy-2-fluoro-5-(1-hydroxyethyl)phenyl]pyrrolidin-2-one (**xcii**). A solution of 4-(3-acetyl-5-chloro-2-ethoxy-6-fluorophenyl)pyrrolidin-2-one (0.402 g, 1.34 mmol) in anhydrous methanol (6.72 mL) at 0 °C was treated with sodium tetrahydroborate (0.101 g, 2.68 mmol) and stirred at 0° C for 30 min. The reaction mixture was quenched with water at 0 °C and poured into a mixture of water (50 mL) and ethyl acetate (100 mL) while stirring. The mixture was warmed to ambient temperature and the aqueous layer was separated and extracted with additional ethyl acetate (50 mL). The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated to give crude residues. Purification by flash column chromatography using acetonitrile (containing 7% methanol) in dichloromethane (0% to 100%) gave the

desired product **xcii** (0.396 g, 97.8%) as a mixture of diastereoisomers that was used without further purification. LCMS for $C_{14}H_{18}ClFNO_3$ $(M+H)^+$: m/z = 302.1; Found: 302.1.

Step i (derived from Step f, peak 1). 4-[3-Chloro-5-(1-chloroethyl)-6-ethoxy-2-fluorophenyl]pyrrolidin-2-one (**xciii**). A solution of 4-[3-chloro-6-ethoxy-2-fluoro-5-(1-hydroxyethyl)phenyl]pyrrolidin-2-one (0.412 g, 1.36 mmol) in dichloromethane (11.8 mL) was treated with *N*,*N*-dimethylformamide (10.6 μL, 0.136 mmol) followed by thionyl chloride (0.209 mL, 2.87 mmol) dropwise and stirred at 20 °C for 30 min. The reaction mixture was added dropwise to ice cooled saturated sodium bicarbonate solution and extracted with dichloromethane. The organic layer was separated and washed with brine, dried over sodium sulfate, filtered, and concentrated to give the desired product **xciii** (0.382 g, 87.4%) as a mixture of diastereoisomers along with the styrene by-product that formed from chloride elimination. The ratio of the desired product to the styrene by-product was about 83:17. The mixture was used without further purification. LCMS for $C_{14}H_{17}Cl_2FNO_2$ $(M+H)^+$: m/z = 320.1; Found: 320.0.

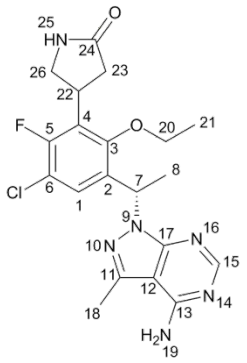
Step i (derived from Step f, peak 2). 4-[3-Chloro-5-(1-chloroethyl)-6-ethoxy-2-fluorophenyl]pyrrolidin-2-one (**xciii**). A solution of 4-[3-chloro-6-ethoxy-2-fluoro-5-(1-hydroxyethyl)phenyl]pyrrolidin-2-one (0.412 g, 1.36 mmol) in dichloromethane (11.8 mL) was treated with *N*,*N*-dimethylformamide (10.6 μL, 0.136 mmol) followed by thionyl chloride (0.209 mL, 2.87 mmol) dropwise and stirred at 20 °C for 30 min. The reaction mixture was added dropwise to ice cooled saturated sodium bicarbonate solution and extracted with dichloromethane. The organic layer was separated and washed with brine, dried over sodium sulfate, filtered, and concentrated to give the desired product **xciii** (0.388 g, 88.8%) as a mixture of diastereoisomers along with the styrene by-product that formed from chloride elimination. The ratio of the desired product to the styrene by-product was about 82:18. The mixture was used without further purification. LCMS for $C_{14}H_{17}Cl_2FNO_2$ $(M+H)^+$: m/z = 320.1; Found: 320.0.

Step j (derived from Step f, peak 1). 4-(3-((*S*)-1-(4-Amino-3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl)-5-chloro-2-ethoxy-6-fluorophenyl)pyrrolidin-2-one (**24**). A mixture of 4-[3-

chloro-5-(1-chloroethyl)-6-ethoxy-2-fluorophenyl]pyrrolidin-2-one (0.355 g, 1.11 mmol) (from Step i containing the styrene by-product), 3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.190 g, 1.28 mmol), cesium carbonate (0.542 g, 1.66 mmol), and potassium iodide (18.4 mg, 0.111 mmol) in *N*,*N*-dimethylformamide (7.40 mL) was heated at 100 °C for 4.5 h. The reaction mixture was poured into water (30 mL) and extracted with ethyl acetate (3 x 50 mL) to give the desired product as a mixture of diastereoisomers. Purification by preparative LCMS (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.1% ammonium hydroxide, at flow rate of 60 mL/min) gave the undesired diastereoisomer as the first eluting peak (0.131 g, 27.3%) and the desired product **24** as the second eluting peak (0.122 g, 25.4%). **24**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.12 (s, 1H), 7.82 (s, 1H), 7.52 (d, J = 8.5 Hz, 1H), 7.30 (br s, 1H), 6.23 (q, J = 7.0 Hz, 1H), 4.05 – 3.90 (m, 1H), 3.88 – 3.78 (m, 2H), 3.63 – 3.53 (m, 1H), 3.29 – 3.20 (m, 1H), 2.54 (s, 3H), 2.38 – 2.21 (m, 1H), 1.70 (d, J = 7.1 Hz, 3H), 1.39 (t, J = 6.9 Hz, 3H). LCMS for $C_{20}H_{23}ClFN_6O_2$ $(M+H)^+$: m/z = 433.2; Found: 433.1.

Step j (derived from Step f, peak 2). 4-(3-((*S*)-1-(4-Amino-3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl)-5-chloro-2-ethoxy-6-fluorophenyl)pyrrolidin-2-one (**20**). A mixture of 4-[3-chloro-5-(1-chloroethyl)-6-ethoxy-2-fluorophenyl]pyrrolidin-2-one (0.355 g, 1.11 mmol) (from Step i containing the styrene by-product), 3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.190 g, 1.28 mmol), cesium carbonate (0.542 g, 1.66 mmol), and potassium iodide (18.4 mg, 0.111 mmol) in *N*,*N*-dimethylformamide (7.40 mL) was heated at 100 °C for 4.5 h. The reaction mixture was poured into water (30 mL) and extracted with ethyl acetate (3 x 50 mL) to give the desired product as a mixture of diastereoisomers. Purification by preparative LCMS (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.1% ammonium hydroxide, at flow rate of 60 mL/min) gave the desired product **20** as the first eluting peak (0.146 g, 30.4%) and the undesired diastereoisomer as the second eluting peak (0.140 g, 29.2%). **20**: LCMS for $C_{20}H_{23}ClFN_6O_2$ $(M+H)^+$: m/z = 433.2; Found: 433.1.

Figure S3. NMR numbering scheme for **20**.



20

Table S3. ^{1}H and ^{13}C NMR spectral assignments for **20** performed in DMSO-d_6.

Position	^{1}H Chemical Shift (δ ppm)	Multiplicity	Coupling Constant (*J* Hz)	Relative Intensity	^{13}C Chemical Shift (δ ppm)
1	7.56	d	8.4	1H	127.1
2	--	--	--	--	132.8 ($^{4}J_{CF}$=2.9 Hz)
3	--	--	--	--	153.5 ($^{3}J_{CF}$=7.0 Hz)
4	--	--	--	--	126.2 ($^{2}J_{CF}$=12.2 Hz)
5	--	--	--	--	156.0 ($^{1}J_{CF}$=249.5 Hz)
6	--	--	--	--	115.8 ($^{2}J_{CF}$=18.2 Hz)
7	6.24	q	7.2	1H	48.1
8	1.70	d	7.1	3H	21.4
11	--	--	--	--	140.9
12	--	--	--	--	98.9
13	--	--	--	--	158.4
15	8.12	s	--	1H	155.8
17	--	--	--	--	153.6
18	2.54	s	--	3H	14.5
19	7.28	br s	--	1.2H	--
20	3.88, 3.80	m, m	--, --	2H	71.9
21	1.40	t	6.9	3H	15.3
22	3.98	m	--	1H	29.4
23	2.55, 2.30	m, dd	--, 17.1, 8.7	2H	35.9
24	--	--	--	--	175.3
25	7.79	s	--	1H	--
26	3.57, 3.25	dd, dd	9.8, 9.6; 9.2, 8.6	2H	46.6

Table S4. ^{19}F NMR spectral assignments for **20** performed in DMSO-d_6.

Position	^{19}F Chemical Shift (δ ppm)	Multiplicity	Coupling Constants (*J* Hz)	Relative Intensity
5	-113.2	d	7.9	1F

Figure S4. ^{1}H NMR spectrum for **20** performed in DMSO-d_6.

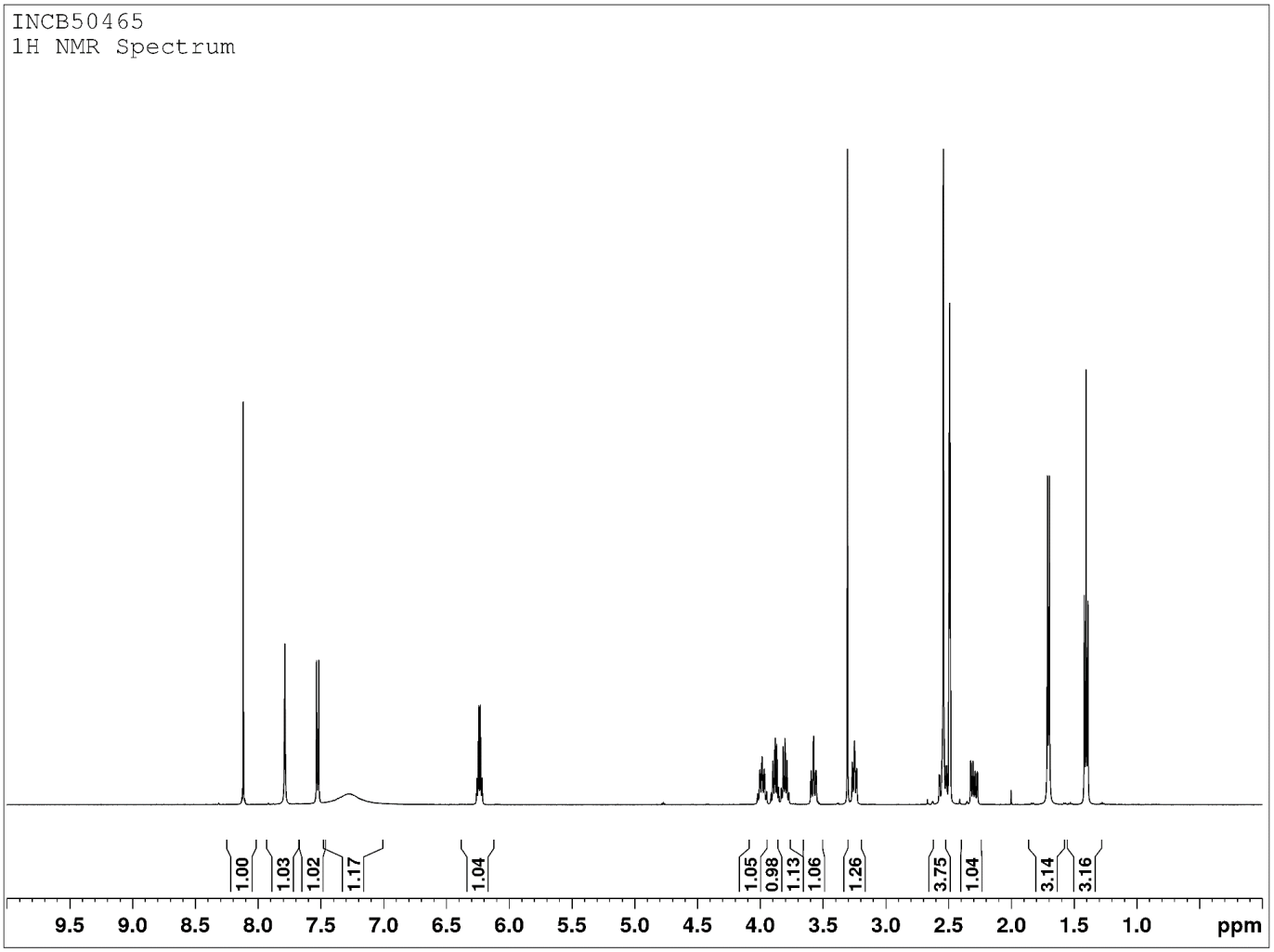


Figure S5. ^{13}C NMR spectrum for **20** performed in DMSO-d_6.

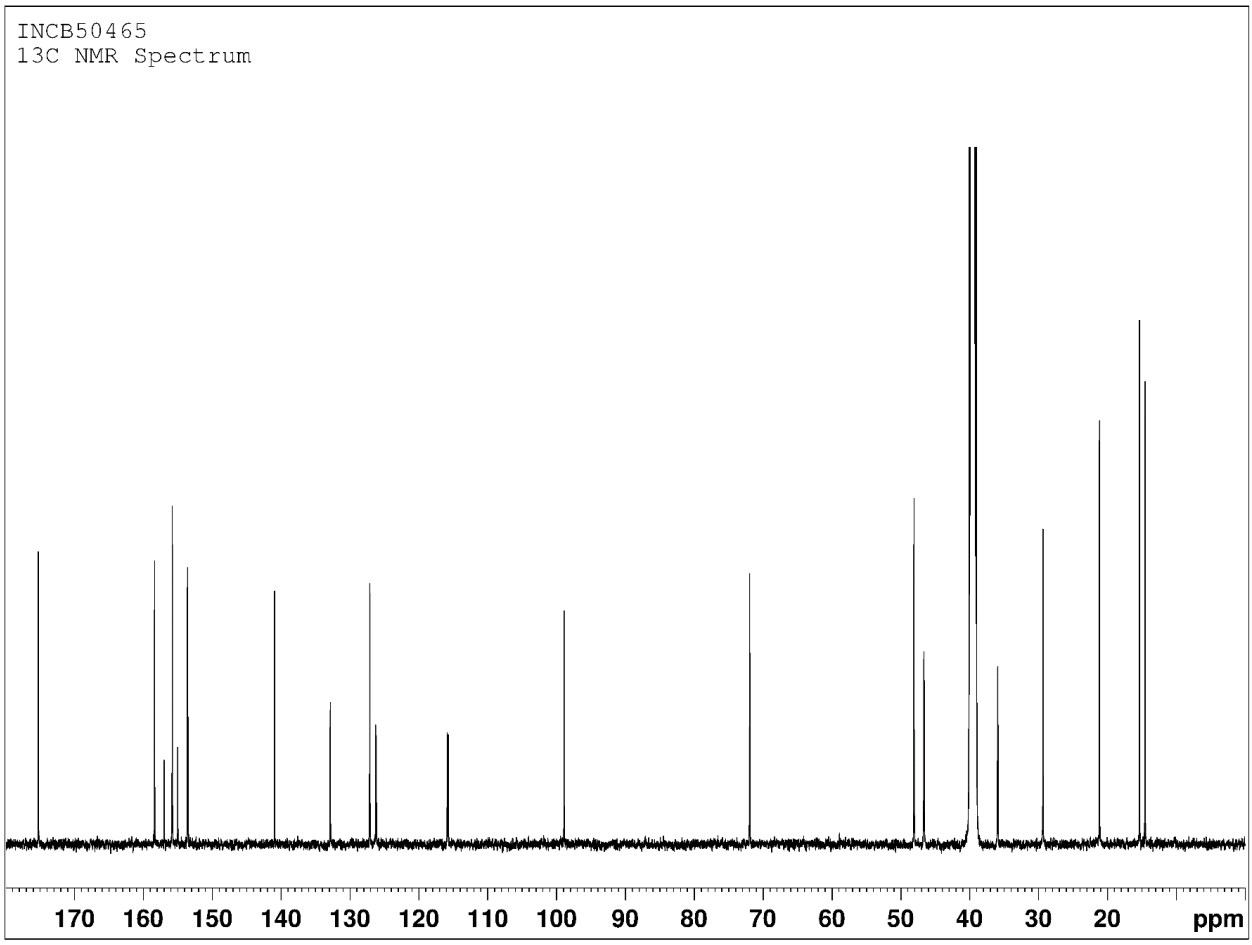
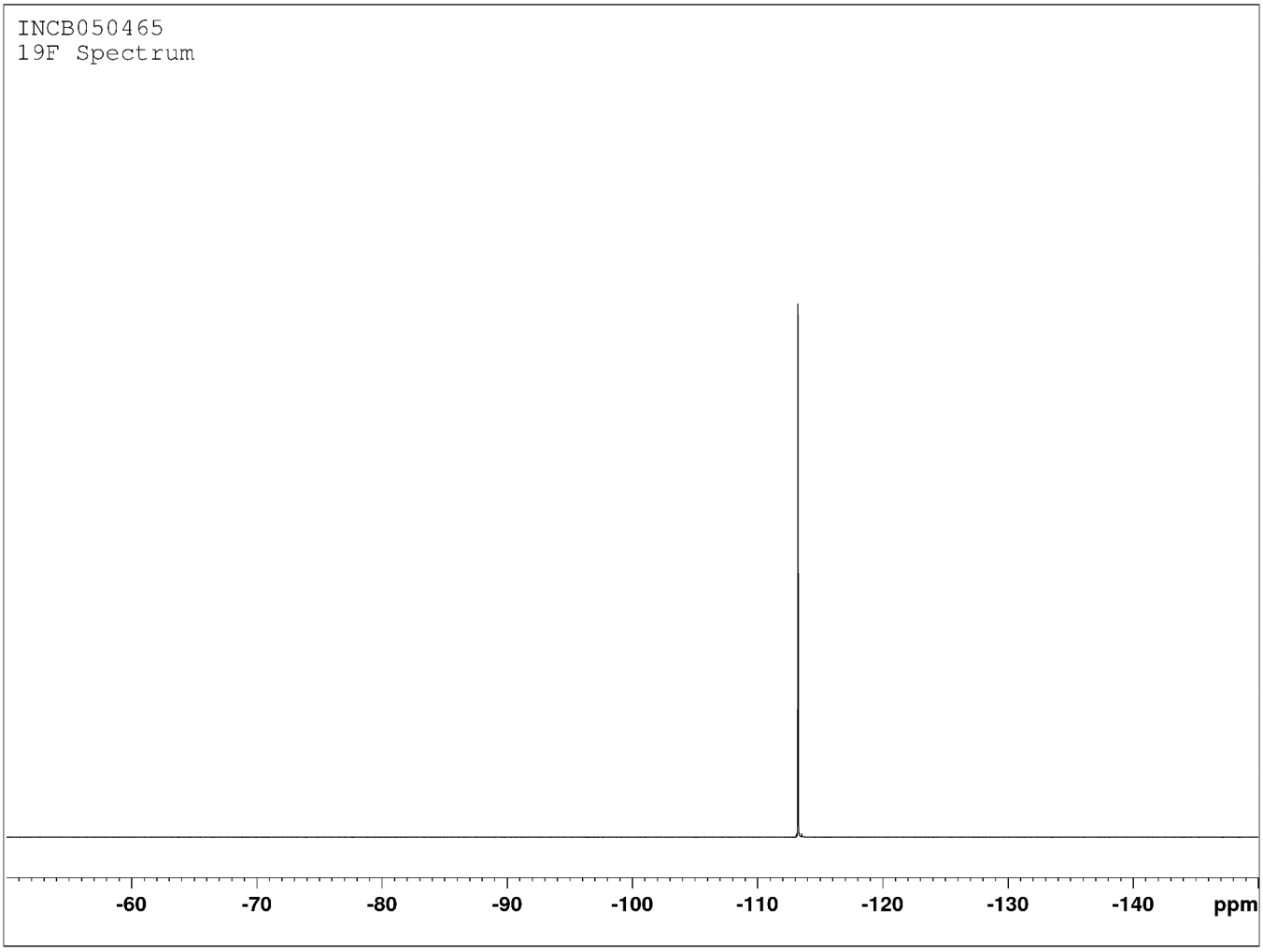


Figure S6. ^{19}F NMR spectrum for **20** performed in DMSO-d_6.



Structure Proof for 20 using 2D NMR

Complete structure assignment and proof of bond connectivity was performed using multiple 2D NMR experiments.

Figure S7. COSY NMR spectrum for **20** performed in DMSO-d_6.

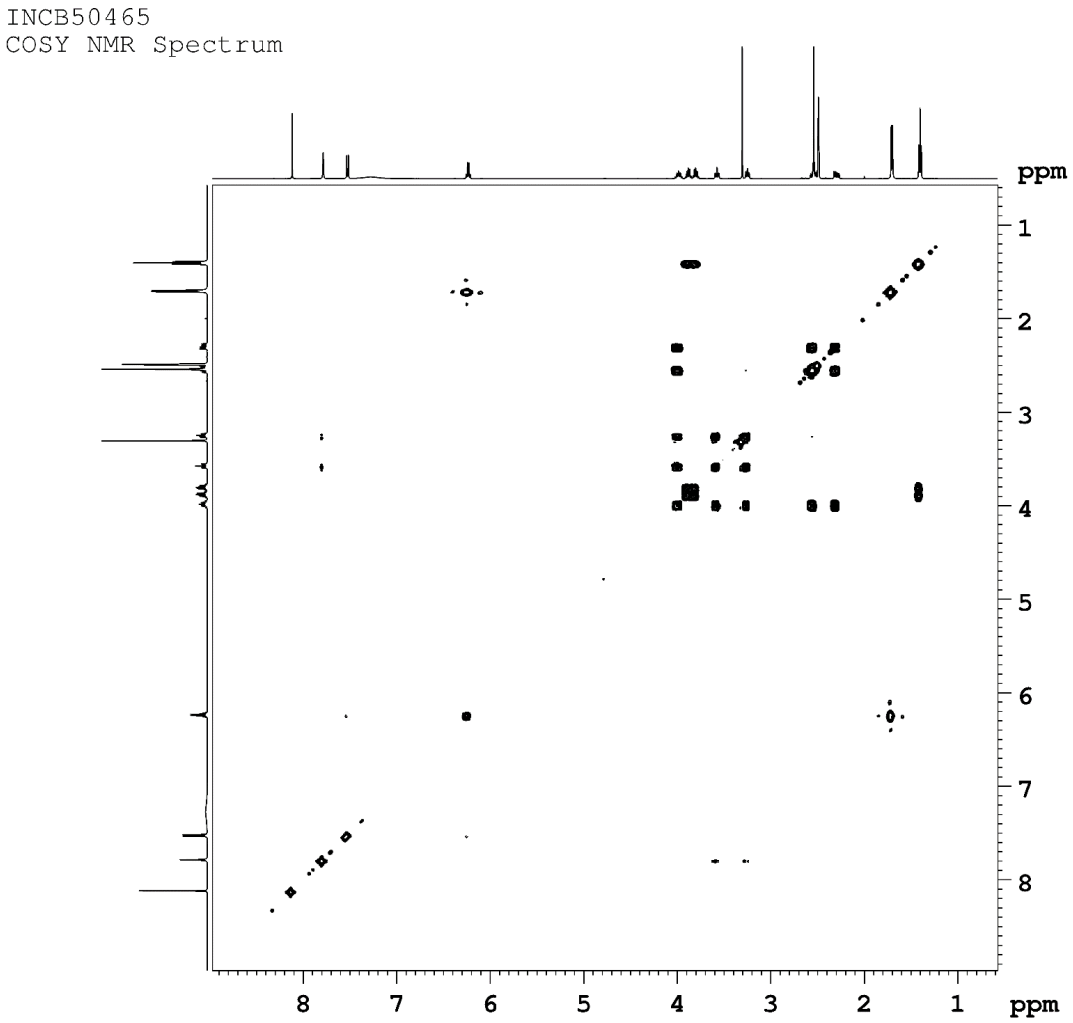


Figure S8. HSQC NMR spectrum for **20** performed in DMSO-d_6.

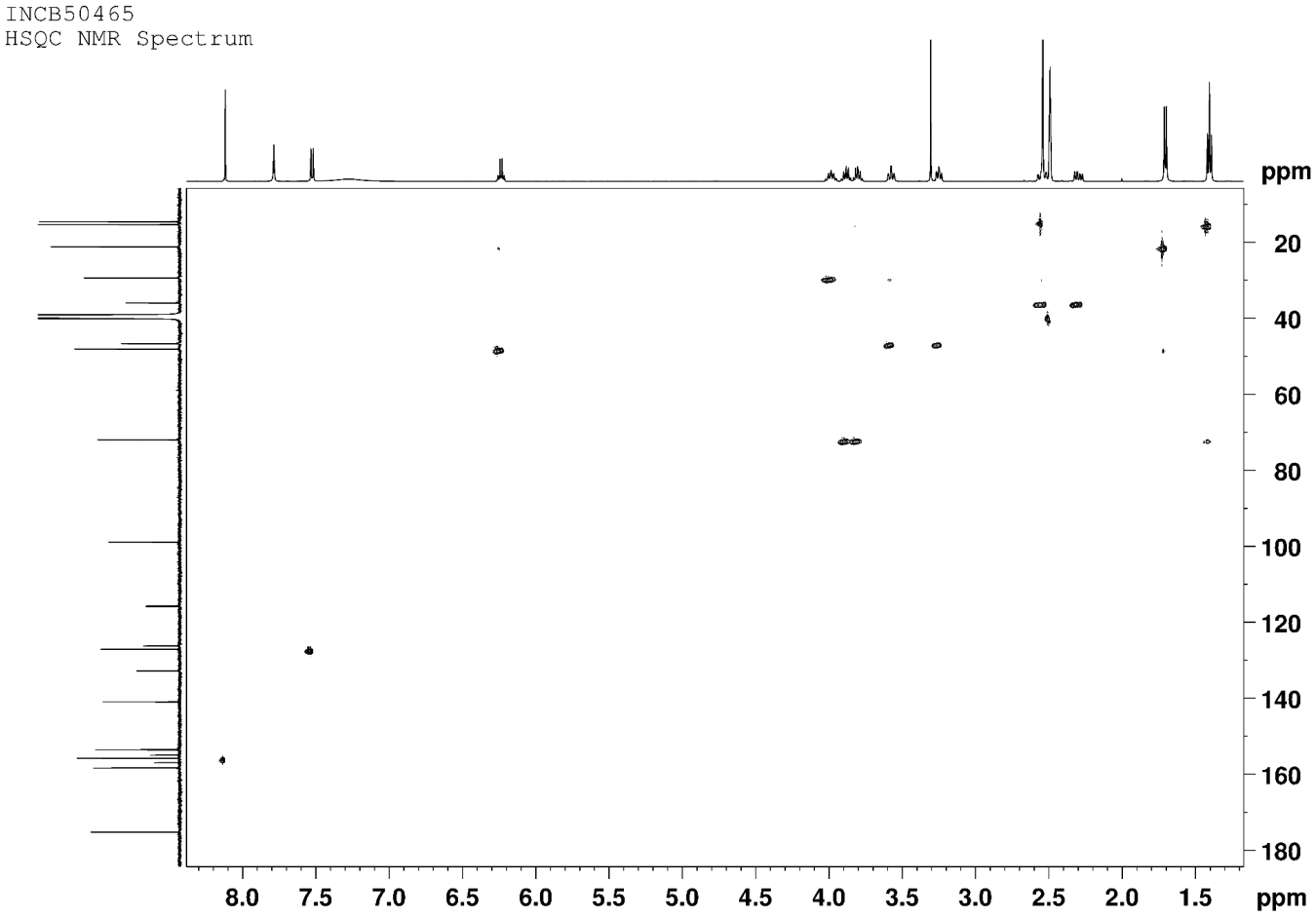


Figure S9. HMBC NMR spectrum for **20** performed in DMSO-d_6.

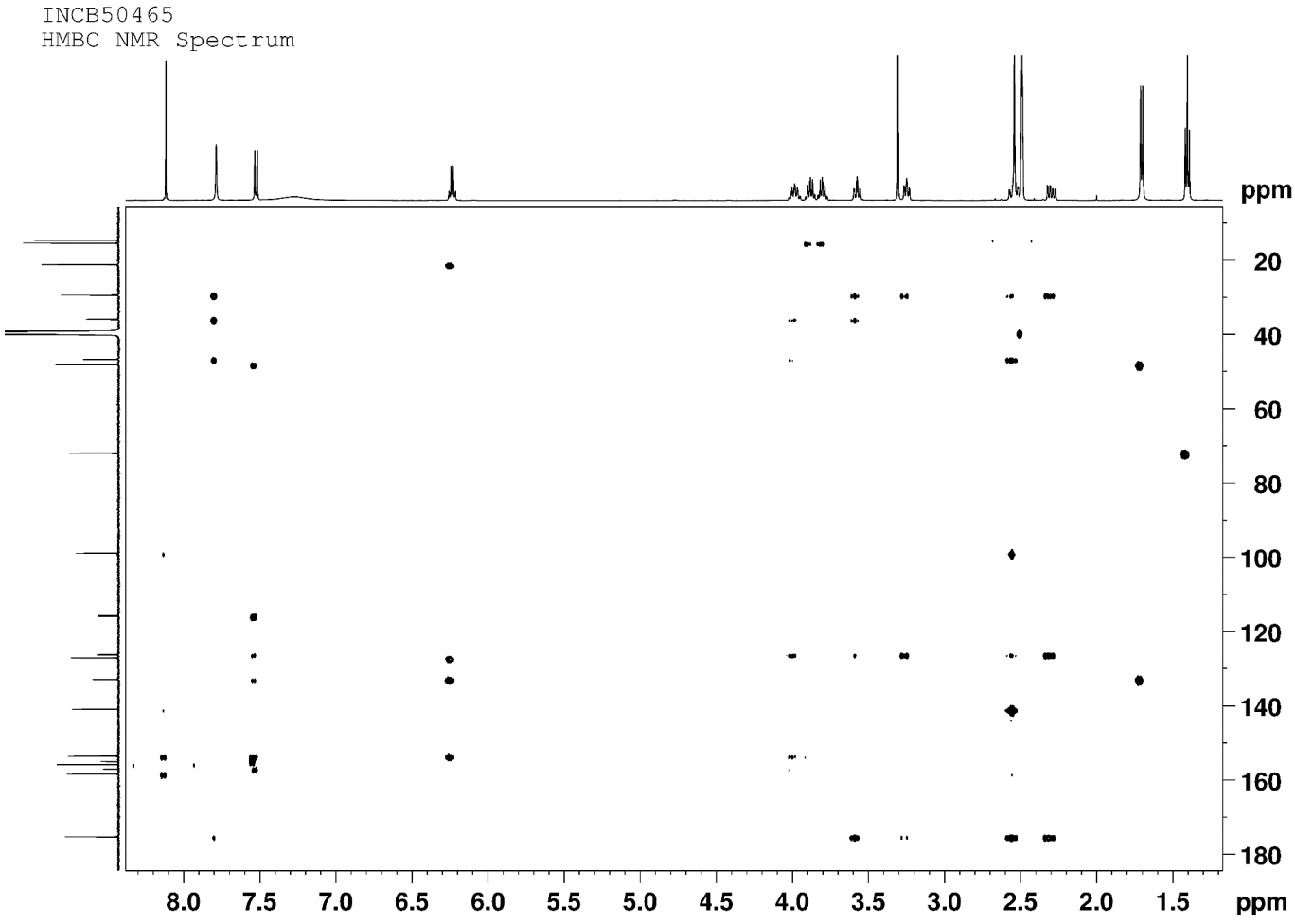
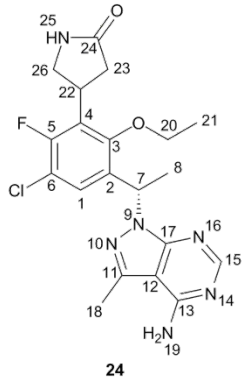


Figure S10. NMR numbering scheme for **24**.



24

Table S5. ^{1}H and ^{13}C NMR spectral assignments for **24** performed in DMSO-d_6.

Position	^{1}H Chemical Shift (δ ppm)	Multiplicity	Coupling Constant (*J* Hz)	Relative Intensity	^{13}C Chemical Shift (δ ppm)
1	7.52	d	8.4	1H	127.8
2	--	--	--	--	133.5 ($^{4}J_{CF=}$3.6 Hz)

3	--	--	--	--	154.2
4	--	--	--	--	126.9 ($^2J_{CF}$=12.4Hz)
5	--	--	--	--	156.8 ($^1J_{CF}$=250.0 Hz)
6	--	--	--	--	116.5 ($^2J_{CF}$=18.3 Hz)
7	6.23	q	7.1	1H	48.8
8	1.70	d	7.0	3H	21.8
11	--	--	--	--	141.7
12	--	--	--	--	99.6
13	--	--	--	--	159.1
15	8.12	s	--	1H	156.5
17	--	--	--	--	154.3
18	2.54	s	--	3H	15.2
19	7.29	br s	--	2H	--
20	3.84	m	--	2H	72.6
21	1.40	d	7.0	3H	16.1
22	3.98	m	--	1H	30.1
23	2.55, 2.30	m, dd	--, 16.7, 9.1	2H	36.6
24	--	--	--	--	176.0
25	7.84	s	--	1H	--
26	3.59, 3.26	dd, dd	9.3, 8.9 9.1, 8.9	2H	47.4

The syntheses of **21** and **25** are illustrated in **Scheme S16**.

4-((*S*)-1-(4-Amino-3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl)-6-chloro-3-ethoxy-2-(5-oxopyrrolidin-3-yl)benzonitrile (21 and 25).

Step a. Enantiomers of 4-acetyl-6-chloro-3-ethoxy-2-(5-oxopyrrolidin-3-yl)benzonitrile (**xciv**). A racemic mixture of 4-(3-acetyl-5-chloro-2-ethoxy-6-fluorophenyl)pyrrolidin-2-one (0.200 g, 0.667 mmol) and sodium cyanide (0.0572 g, 1.17 mmol) in dimethyl sulfoxide (1.50 mL) was stirred at 80 °C for 3 h. The reaction mixture was poured into water (35 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated to give a crude residue. Purification by flash column chromatography using ethyl ether

(containing 10% methanol) in hexanes (0% to 100%) gave the desired product **xciv** (0.145 g, 70.7%) as a mixture of enantiomers. LCMS for $C_{15}H_{16}ClN_2O_3$ $(M+H)^+$: m/z = 307.1; Found: 307.0.

Step b. Chiral purification of 4-acetyl-6-chloro-3-ethoxy-2-(5-oxopyrrolidin-3-yl)benzonitrile (**xciv**). The material from Step a was purified by chiral HPLC (Phenomenex Lux Cellulose C-2, 21.2 x 250 mm, 5 micron particle size, eluting with 60% ethanol in hexanes at 18 mL/min) to give the individual enantiomers of **xciv** as peak 1 and peak 2 (retention times = 18.5 min and 23.1 min).

Step c (derived from Step b, peak 1). 6-Chloro-3-ethoxy-4-(1-hydroxyethyl)-2-(5-oxopyrrolidin-3-yl)benzonitrile (**xcv**). A solution of 4-acetyl-6-chloro-3-ethoxy-2-(5-oxopyrrolidin-3-yl)benzonitrile (0.825 g, 2.69 mmol) (from Step b, peak 1) in anhydrous methanol (13.5 mL) at 0 °C was treated with sodium tetrahydroborate (0.204 g, 5.38 mmol) and stirred at 0° C for 30 min. The reaction mixture was quenched with water at 0 °C and poured into a mixture of water (50 mL) and ethyl acetate (100 mL) while stirring. The mixture was warmed to ambient temperature and the aqueous layer was separated and extracted with additional ethyl acetate (50 mL). The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated to give the desired product **xcv** (0.842 g, quantitative) as a mixture of diastereoisomers that was used without further purification. LCMS for $C_{15}H_{18}ClN_2O_3$ $(M+H)^+$: m/z = 309.1; Found: 309.1.

Step c (derived from Step b, peak 2). 6-Chloro-3-ethoxy-4-(1-hydroxyethyl)-2-(5-oxopyrrolidin-3-yl)benzonitrile (**xcv**). A solution of 4-acetyl-6-chloro-3-ethoxy-2-(5-oxopyrrolidin-3-yl)benzonitrile (0.864 g, 2.82 mmol) (from Step b, peak 2) in anhydrous methanol (14.1 mL) at 0 °C was treated with sodium tetrahydroborate (0.213 g, 5.63 mmol) and stirred at 0° C for 30 min. The reaction mixture was quenched with water at 0 °C and poured into a mixture of water (50 mL) and ethyl acetate (100 mL) while stirring. The mixture was warmed to ambient temperature and the aqueous layer was separated and extracted with additional ethyl acetate (50 mL). The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated to give the desired product **xcv** (0.902 g, quantitative) as a mixture of diastereoisomers that was used without further purification. LCMS for $C_{15}H_{18}ClN_2O_3$ $(M+H)^+$: m/z = 309.1; Found: 309.1.

Step d (derived from Step b, peak 1). 6-Chloro-4-(1-chloroethyl)-3-ethoxy-2-(5-oxopyrrolidin-3-yl)benzonitrile (**xcvi**). A solution of 6-chloro-3-ethoxy-4-(1-hydroxyethyl)-2-(5-oxopyrrolidin-3-yl)benzonitrile (0.830 g, 2.69 mmol) in dichloromethane (23.2 mL) was treated with *N*,*N*-dimethylformamide (0.0208 mL, 0.269 mmol) followed by thionyl chloride (0.490 mL, 6.72 mmol) dropwise and stirred at 20 °C for 2 h. The reaction mixture was added dropwise to ice cooled saturated sodium bicarbonate solution and extracted with dichloromethane. The organic layer was separated and washed with brine, dried over sodium sulfate, filtered, and concentrated to give the desired product **xcvi** (0.853 g, 96.9%) as a mixture of diastereoisomers that was used without further purification. LCMS for $C_{15}H_{17}Cl_2N_2O_2$ $(M+H)^+$: m/z = 327.1; Found: 327.1.

Step d (derived from Step b, peak 2). 6-Chloro-4-(1-chloroethyl)-3-ethoxy-2-(5-oxopyrrolidin-3-yl)benzonitrile (**xcvi**). A solution of 6-chloro-3-ethoxy-4-(1-hydroxyethyl)-2-(5-oxopyrrolidin-3-yl)benzonitrile (0.870 g, 2.82 mmol) in dichloromethane (24.3 mL) was treated with *N*,*N*-dimethylformamide (0.0218 mL, 0.282 mmol) followed by thionyl chloride (0.514 mL, 7.04 mmol) dropwise and stirred at 20 °C for 2 h. The reaction mixture was added dropwise to ice cooled saturated sodium bicarbonate solution and extracted with dichloromethane. The organic layer was separated and washed with brine, dried over sodium sulfate, filtered, and concentrated to give the desired product **xcvi** (0.899 g, 97.5%) as a mixture of diastereoisomers that was used without further purification. LCMS for $C_{15}H_{17}Cl_2N_2O_2$ $(M+H)^+$: m/z = 327.1; Found: 327.1.

Step e (derived from Step b, peak 1). 4-[1-(4-Amino-3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl]-6-chloro-3-ethoxy-2-(5-oxopyrrolidin-3-yl)benzonitrile (**xcvii**). A mixture of 6-chloro-4-(1-chloroethyl)-3-ethoxy-2-(5-oxopyrrolidin-3-yl)benzonitrile (0.846 g, 2.58 mmol), 3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.463 g, 3.10 mmol), cesium carbonate (1.26 g, 3.88 mmol), and potassium iodide (0.0429 mg, 0.258 mmol) in *N*,*N*-dimethylformamide (17.2 mL) was heated at 90 °C for 3 h. The reaction mixture was poured into a mixture of water (100 mL) and ethyl acetate (100 mL) and filtered through Celite® to remove black solids. The aqueous layer was separated and extracted with ethyl acetate (2 x 100 mL). The combined organic extracts were washed with brine, dried over sodium

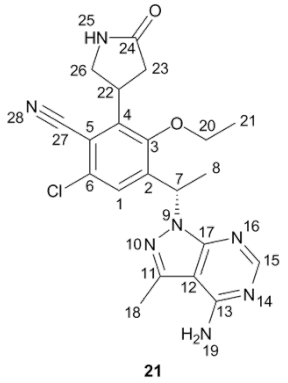
sulfate, filtered, and concentrated to a crude residue. Purification by flash column chromatography using methanol in dichloromethane (0% to 20%) gave the desired product **xcvii** (0.492 g, 43.2%) as a mixture of diastereoisomers. Analytical chiral HPLC analysis of the diastereoisomers revealed a mixture of four isomers instead of the desired two isomers due to epimerization.

Step e (derived from Step b, peak 2). 4-[1-(4-Amino-3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl]-6-chloro-3-ethoxy-2-(5-oxopyrrolidin-3-yl)benzonitrile (**xcvii**). A mixture of 6-chloro-4-(1-chloroethyl)-3-ethoxy-2-(5-oxopyrrolidin-3-yl)benzonitrile (0.894 g, 2.73 mmol), 3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.489 g, 3.28 mmol), cesium carbonate (1.34 g, 4.10 mmol), and potassium iodide (0.0454 mg, 0.273 mmol) in *N*,*N*-dimethylformamide (18.2 mL) was heated at 90 °C for 3 h. The reaction mixture was poured into a mixture of water (100 mL) and ethyl acetate (100 mL) and filtered through Celite® to remove black solids. The aqueous layer was separated and extracted with ethyl acetate (2 x 100 mL). The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated to a crude residue. Purification by flash column chromatography using methanol in dichloromethane (0% to 20%) gave the desired product **xcvii** (0.525 g, 43.8%) as a mixture of diastereoisomers. Analytical chiral HPLC analysis of the diastereoisomers revealed a mixture of four isomers instead of the desired two isomers due to epimerization.

Step f. Chiral purification of 4-((*S*)-1-(4-amino-3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl)-6-chloro-3-ethoxy-2-(5-oxopyrrolidin-3-yl)benzonitrile (**21** and **25**). The material from both Steps e were combined and purified by chiral HPLC (Phenomenex Lux Cellulose C-2, 21.2 x 250 mm, 5 micron particle size, eluting with 60% ethanol in hexanes at 18 mL/min) to give an undesired diastereoisomer as the first eluting peak, desired product **21** as the second eluting peak, desired product **25** as the third eluting peak, and an undesired diastereoisomer as the fourth eluting peak (retention times = 11.7 min, 14.9 min, 17.8 min, and 26.3 min). **21**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.12 (s, 1H), 7.88 (s, 1H), 7.58 (s, 1H), 7.30 (br s, 2H), 6.26 (q, J = 7.0 Hz, 1H), 4.32 – 4.20 (m, 1H), 4.00 – 3.91 (m, 1H), 3.90 – 3.81 (m, 1H), 3.65 – 3.59 (m, 1H), 3.49 – 3.42 (m, 1H), 2.55 (s, 3H), 1.74 (d, J = 7.0 Hz, 3H), 1.43 (t, J = 6.9 Hz, 3H). LCMS for $C_{21}H_{23}ClN_7O_2$ $(M+H)^+$: m/z = 440.2; Found: 440.2. **25**: ^{1}H NMR (500

MHz, DMSO-d_6) δ 8.12 (s, 1H), 7.88 (s, 1H), 7.56 (s, 1H), 7.30 (br s, 2H), 6.26 (q, J = 7.0 Hz, 1H), 4.32 – 4.19 (m, 1H), 3.97 – 3.82 (m, 2H), 3.67 – 3.59 (m, 1H), 3.49 – 3.40 (m, 1H), 2.59 – 2.52 (m, 3H), 1.73 (d, J = 7.0 Hz, 3H), 1.42 (t, J = 6.9 Hz, 3H). LCMS for $C_{21}H_{23}ClN_7O_2$ $(M+H)^+$: m/z = 440.2; Found: 440.2.

Figure S11. NMR numbering scheme for **21**.



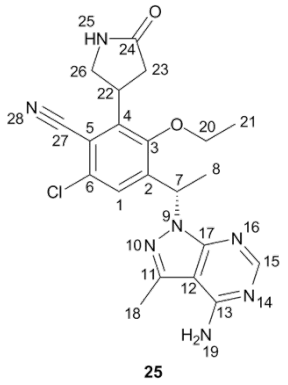
21

Table S6. ^{1}H and ^{13}C NMR spectral assignments for **21** performed in DMSO-d_6.

Position	^{1}H Chemical Shift (δ ppm)	Multiplicity	Coupling Constant (J Hz)	Relative Intensity	^{13}C Chemical Shift (δ ppm)
1	7.58	s	--	1H	128.0
2	--	--	--	--	143.2
3	--	--	--	--	153.8
4	--	--	--	--	143.1
5	--	--	--	--	111.7
6	--	--	--	--	133.0
7	6.26	q	7.1	1H	49.1
8	1.74	d	7.1	3H	21.1
11	--	--	--	--	141.8
12	--	--	--	--	99.5
13	--	--	--	--	158.9
15	8.12	s	--	1H	156.4
17	--	--	--	--	154.3
18	2.55	s	--	3H	15.0
19	7.30	br s	--	2H	--
20	3.95, 3.86	m, m	--, --	2H	72.7
21	1.43	t	6.9	3H	15.8
22	4.26	m	--	1H	31.4

23	2.59, 2.54	m, m	--, --	2H	36.9
24	--	--	--	--	175.1
25	7.88	s	--	1H	--
26	3.62, 3.46	dd, dd	9.8, 9.8, 9.1, 9.4	2H	47.5
27	--	--	--	--	114.6

Figure S12. NMR numbering scheme for **25**.



25

Table S7. ^{1}H and ^{13}C NMR spectral assignments for **25** performed in DMSO-d_6.

Position	**^{1}H Chemical Shift (δ ppm)**	**Multiplicity**	**Coupling Constant (*J* Hz)**	**Relative Intensity**	**^{13}C Chemical Shift (δ ppm)**
1	7.57	s	--	1H	127.9
2	--	--	--	--	143.1
3	--	--	--	--	153.7
4	--	--	--	--	143.0
5	--	--	--	--	111.7
6	--	--	--	--	132.9
7	6.26	q	7.1	1H	48.8
8	1.74	d	7.2	3H	20.9
11	--	--	--	--	141.7
12	--	--	--	--	99.3
13	--	--	--	--	158.8
15	8.12	s	--	1H	156.5
17	--	--	--	--	154.2
18	2.56	s	--	3H	14.5
19	7.30	br s	--	2H	--
20	3.93, 3.87	m, m	--, --	2H	72.4

21	1.43	t	7.2	3H	15.7
22	4.26	m	--	1H	31.1
23	2.59, 2.54	m, m	--, --	2H	36.5
24	--	--	--	--	175.1
25	7.89	s	--	1H	--
26	3.63, 3.44	dd, dd	10.1, 9.8, 9.1, 9.6	2H	47.3
27	--	--	--	--	114.3

X-ray Crystal Structure of 20

CRYSTAL DATA: C20 H32 Cl2 F N6 O6.50, from H_2O, colorless, flat needle, ~0.550 x 0.100 x 0.050mm, monoclinic, C2, a = 36.80(8) Å, b = 5.506(12) Å, c = 13.08(3) Å, beta = 102.76(2) °, Vol = 2585(9) $Å^3$, Z = 4, T = -100.°C, Formula weight = 550.41, Density = 1.414g/cm^3, μ(Mo) = 0.31mm^{-1}

DATA COLLECTION: Bruker SMART APEX-II CCD system, MoKalpha radiation, standard focus tube, anode power = 50kV x 30mA, crystal to plate distance = 5.0cm, 512 x 512 pixels/frame, beam center = (259.19,253.13), total frames = 1209, oscillation/frame = 0.50°, exposure/frame = 180.1 sec/frame, SAINT integration, hkl min/max = (-45 , 45 , -6 , 6 , -16 , 15), data input to shelx = 10004, unique data = 5165, two-theta range = 3.19 to 52.52°, completeness to two-theta 52.52 = 99.80%, R(int-xl) = 0.0848, SADABS correction applied.

SOLUTION AND REFINEMENT: Structure solved using XS(Shelxtl), refined using shelxtl software package, refinement by full-matrix least squares on F^2, scattering factors from Int. Tab. Vol C Tables 4.2.6.8 and 6.1.1.4, number of data = 5165, number of restraints = 1, number of parameters = 353, data/parameter ratio = 14.63, goodness-of-fit on F^2 = 1.01, R indices[I>4sigma(I)] R1 = 0.0702, wR2 = 0.1448, R indices (all data) R1 = 0.1281, wR2 = 0.1695, max difference peak and hole = 0.513 and -0.357 e/$Å^3$, refined flack parameter = -0.02(8). All of the hydrogen atoms except NH hydrogens were idealized using a riding model. The NH hydrogens were found from a difference map and fully refined. The water hydrogens were assigned using the OLEX2 program and the positions are not entirely clear. The water at O4 sits on a crystallographic 2-fold axis and it has hydrogens disordered because of this. This could lead to disorder in neighboring waters.

RESULTS: This study determines the structure of **20**. The asymmetric unit contains one molecule, one chloride, and five water molecules as shown in Figure S13 with thermal ellipsoids drawn to the 50% probability level. The predicted structure is confirmed. The water molecules form in channels along the a-axis as shown in the packing diagram (Figure S14). The chloride is found close to N1-H1. Nitrogen N4

is protonated from the HCl forming a salt. The flack parameter refines to 0.03(8) indicating the correct enantiomeric setting. The absolute configuration is determined to be R at C7 and S at C13

Table S8. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for 20. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
Cl(1)	2122(1)	29847(4)	1353(2)	38(1)
F(1)	2774(1)	31295(9)	564(3)	39(1)
O(1)	3888(2)	31192(10)	-1066(4)	34(1)
N(1)	3801(2)	33035(12)	421(5)	29(2)
C(1)	3226(2)	29076(13)	1718(6)	24(2)
Cl(2)	4478(1)	26975(4)	1084(2)	46(1)
O(2)	3667(1)	26730(9)	2999(4)	27(1)
N(2)	3300(2)	25587(11)	4878(4)	24(2)
C(2)	2861(2)	29733(15)	1377(5)	28(2)
N(3)	3143(2)	27532(10)	5282(4)	23(1)
C(3)	2578(2)	28844(15)	1816(6)	28(2)
O(4)	5000	29963(18)	0	48(2)
N(4)	4176(2)	23751(12)	7044(5)	27(2)
C(4)	2658(2)	27209(14)	2622(5)	27(2)
O(5)	4497(3)	31972(15)	2411(5)	72(2)
N(5)	3814(2)	22812(11)	5367(5)	26(2)
C(5)	3019(2)	26463(14)	3023(5)	25(2)
N(6)	4084(2)	26833(14)	8139(5)	30(2)
O(6)	4922(3)	33189(18)	5971(7)	77(2)
C(6)	3302(2)	27486(13)	2596(5)	24(2)
O(7)	4767(2)	27964(15)	6762(6)	69(2)
C(7)	3538(2)	29930(14)	1219(6)	27(2)
O(8)	4762(2)	23830(12)	8702(5)	45(2)
C(8)	3613(3)	32646(14)	1290(6)	33(2)
C(9)	3748(2)	31276(13)	-277(6)	28(2)
C(10)	3493(2)	29432(14)	35(6)	29(2)
C(11)	3896(2)	28417(15)	3695(6)	33(2)
C(12)	4278(2)	27405(18)	4013(6)	42(2)
C(13)	3115(2)	24512(14)	3866(5)	26(2)
C(14)	2775(2)	23056(15)	4031(6)	35(2)
C(15)	3364(2)	27959(13)	6232(5)	22(2)
C(16)	3663(2)	26250(13)	6428(6)	22(2)
C(17)	3970(2)	25698(12)	7263(6)	22(2)
C(18)	4093(2)	22430(14)	6147(6)	29(2)
C(19)	3607(2)	24790(14)	5548(5)	23(2)
C(20)	3270(2)	29992(14)	6871(6)	28(2)

Table S9. Bond lengths [A] and angles [deg] for 20.

Cl(1)-C(3)	1.740(8)

F(1)-C(2)	1.350(9)
O(1)-C(9)	1.253(9)
N(1)-C(9)	1.315(10)
N(1)-C(8)	1.472(10)
N(1)-H(1)	0.89(9)
C(1)-C(2)	1.367(11)
C(1)-C(6)	1.422(10)
C(1)-C(7)	1.517(11)
O(2)-C(6)	1.395(9)
O(2)-C(11)	1.436(9)
N(2)-C(19)	1.340(9)
N(2)-N(3)	1.377(8)
N(2)-C(13)	1.473(9)
C(2)-C(3)	1.386(11)
N(3)-C(15)	1.347(9)
C(3)-C(4)	1.369(11)
O(4)-HA	0.8497
O(4)-HB	0.8499
N(4)-C(18)	1.358(10)
N(4)-C(17)	1.379(10)
N(4)-H(4)	0.94(7)
C(4)-C(5)	1.380(11)
C(4)-HD	0.9300
O(5)-HE	0.8502
O(5)-HF	0.8501
N(5)-C(18)	1.294(9)
N(5)-C(19)	1.380(10)
C(5)-C(6)	1.403(11)
C(5)-C(13)	1.525(10)
N(6)-C(17)	1.292(10)
N(6)-H(6')	0.96(8)
N(6)-H(6)	0.84(8)
O(6)-HI	0.8498
O(6)-HJ	0.8501
O(7)-HK	0.8500
O(7)-HL	0.8499
C(7)-C(8)	1.519(11)
C(7)-C(10)	1.545(10)
C(7)-HM	0.9800
O(8)-HN	0.8497
O(8)-HO	0.8497
C(8)-HP	0.9700
C(8)-HQ	0.9700
C(9)-C(10)	1.498(11)
C(10)-HR	0.9700
C(10)-HS	0.9700
C(11)-C(12)	1.484(11)
C(11)-HT	0.9700
C(11)-HU	0.9700
C(12)-HV	0.9600
C(12)-HW	0.9600
C(12)-HX	0.9600
C(13)-C(14)	1.540(11)
C(13)-HY	0.9800
C(14)-HZ	0.9600
C(14)-H(0AA)	0.9600
C(14)-H(1AA)	0.9600
C(15)-C(16)	1.426(10)
C(15)-C(20)	1.484(10)
C(16)-C(19)	1.382(10)
C(16)-C(17)	1.422(10)
C(18)-H(2AA)	0.9300

C(20)-H(3AA)	0.9600
C(20)-H(4AA)	0.9600
C(20)-H(5AA)	0.9600

C(9)-N(1)-C(8)	114.0(7)
C(9)-N(1)-H(1)	122(5)
C(8)-N(1)-H(1)	120(5)
C(2)-C(1)-C(6)	115.5(7)
C(2)-C(1)-C(7)	124.1(7)
C(6)-C(1)-C(7)	120.4(7)
C(6)-O(2)-C(11)	115.3(6)
C(19)-N(2)-N(3)	111.5(6)
C(19)-N(2)-C(13)	127.8(6)
N(3)-N(2)-C(13)	120.5(6)
F(1)-C(2)-C(1)	118.2(7)
F(1)-C(2)-C(3)	118.8(7)
C(1)-C(2)-C(3)	123.1(7)
C(15)-N(3)-N(2)	105.7(6)
C(4)-C(3)-C(2)	119.9(8)
C(4)-C(3)-Cl(1)	120.2(7)
C(2)-C(3)-Cl(1)	119.9(6)
HA-O(4)-HB	109.5
C(18)-N(4)-C(17)	124.4(7)
C(18)-N(4)-H(4)	126(5)
C(17)-N(4)-H(4)	109(5)
C(3)-C(4)-C(5)	120.9(8)
C(3)-C(4)-HD	119.6
C(5)-C(4)-HD	119.6
HE-O(5)-HF	109.5
C(18)-N(5)-C(19)	111.4(6)
C(4)-C(5)-C(6)	117.8(7)
C(4)-C(5)-C(13)	122.3(7)
C(6)-C(5)-C(13)	119.8(7)
C(17)-N(6)-H(6')	119(5)
C(17)-N(6)-H(6)	121(5)
H(6')-N(6)-H(6)	120(7)
HI-O(6)-HJ	109.5
O(2)-C(6)-C(5)	117.9(7)
O(2)-C(6)-C(1)	119.4(7)
C(5)-C(6)-C(1)	122.5(7)
HK-O(7)-HL	109.5
C(1)-C(7)-C(8)	114.9(7)
C(1)-C(7)-C(10)	116.9(6)
C(8)-C(7)-C(10)	102.4(6)
C(1)-C(7)-HM	107.4
C(8)-C(7)-HM	107.4
C(10)-C(7)-HM	107.4
HN-O(8)-HO	109.5
N(1)-C(8)-C(7)	101.8(6)
N(1)-C(8)-HP	111.4
C(7)-C(8)-HP	111.4
N(1)-C(8)-HQ	111.4
C(7)-C(8)-HQ	111.4
HP-C(8)-HQ	109.3
O(1)-C(9)-N(1)	125.0(8)
O(1)-C(9)-C(10)	126.6(7)
N(1)-C(9)-C(10)	108.4(7)
C(9)-C(10)-C(7)	102.5(6)
C(9)-C(10)-HR	111.3
C(7)-C(10)-HR	111.3
C(9)-C(10)-HS	111.3
C(7)-C(10)-HS	111.3

HR-C(10)-HS	109.2
O(2)-C(11)-C(12)	108.7(7)
O(2)-C(11)-HT	109.9
C(12)-C(11)-HT	109.9
O(2)-C(11)-HU	109.9
C(12)-C(11)-HU	109.9
HT-C(11)-HU	108.3
C(11)-C(12)-HV	109.5
C(11)-C(12)-HW	109.5
HV-C(12)-HW	109.5
C(11)-C(12)-HX	109.5
HV-C(12)-HX	109.5
HW-C(12)-HX	109.5
N(2)-C(13)-C(5)	110.8(6)
N(2)-C(13)-C(14)	108.2(6)
C(5)-C(13)-C(14)	113.8(7)
N(2)-C(13)-HY	108.0
C(5)-C(13)-HY	108.0
C(14)-C(13)-HY	108.0
C(13)-C(14)-HZ	109.5
C(13)-C(14)-H(0AA)	109.5
HZ-C(14)-H(0AA)	109.5
C(13)-C(14)-H(1AA)	109.5
HZ-C(14)-H(1AA)	109.5
H(0AA)-C(14)-H(1AA)	109.5
N(3)-C(15)-C(16)	109.6(6)
N(3)-C(15)-C(20)	118.9(6)
C(16)-C(15)-C(20)	131.6(7)
C(19)-C(16)-C(17)	117.5(7)
C(19)-C(16)-C(15)	105.5(6)
C(17)-C(16)-C(15)	136.9(7)
N(6)-C(17)-N(4)	118.4(7)
N(6)-C(17)-C(16)	128.7(7)
N(4)-C(17)-C(16)	112.8(6)
N(5)-C(18)-N(4)	125.7(7)
N(5)-C(18)-H(2AA)	117.1
N(4)-C(18)-H(2AA)	117.1
N(2)-C(19)-N(5)	124.3(6)
N(2)-C(19)-C(16)	107.7(6)
N(5)-C(19)-C(16)	128.0(7)
C(15)-C(20)-H(3AA)	109.5
C(15)-C(20)-H(4AA)	109.5
H(3AA)-C(20)-H(4AA)	109.5
C(15)-C(20)-H(5AA)	109.5
H(3AA)-C(20)-H(5AA)	109.5
H(4AA)-C(20)-H(5AA)	109.5

Symmetry transformations used to generate equivalent atoms:

Table S10. Anisotropic displacement parameters (A^2 x 10^3) for 20. The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

U11	U22	U33	U23	U13	U12

Cl(1)	34(1)	42(1)	37(1)	6(1)	3(1)	12(1)
F(1)	43(3)	43(3)	31(3)	18(2)	5(2)	14(2)
O(1)	52(4)	25(3)	28(3)	-1(2)	14(3)	-4(3)
N(1)	44(5)	20(3)	26(4)	-5(3)	13(3)	-8(3)
C(1)	35(5)	20(4)	17(4)	-8(3)	4(3)	3(3)
Cl(2)	45(1)	31(1)	67(2)	-2(1)	22(1)	-5(1)
O(2)	27(3)	28(3)	25(3)	-7(2)	3(2)	1(3)
N(2)	34(4)	19(3)	17(3)	-2(2)	2(3)	3(3)
C(2)	36(5)	26(4)	19(4)	0(4)	2(3)	6(4)
N(3)	36(4)	18(3)	15(3)	-5(3)	7(3)	3(3)
C(3)	30(5)	34(4)	19(4)	3(3)	5(3)	11(4)
O(4)	62(7)	42(5)	45(6)	0	21(5)	0
N(4)	33(4)	24(3)	22(4)	-3(3)	-1(3)	9(3)
C(4)	34(5)	25(4)	21(4)	-6(3)	4(3)	-2(4)
O(5)	106(6)	50(4)	54(4)	-2(4)	5(4)	-17(5)
N(5)	36(4)	16(3)	24(3)	-1(3)	4(3)	6(3)
C(5)	38(5)	21(4)	16(4)	-8(3)	6(3)	1(4)
N(6)	38(4)	27(4)	22(4)	-2(3)	-4(3)	7(4)
O(6)	55(5)	110(7)	65(5)	-17(5)	8(4)	-15(5)
C(6)	29(4)	24(4)	17(4)	-11(3)	3(3)	1(3)
O(7)	67(6)	77(6)	62(5)	5(4)	11(4)	13(5)
C(7)	33(5)	20(4)	30(4)	-3(4)	10(3)	-3(4)
O(8)	44(4)	50(4)	36(3)	1(3)	-2(3)	1(3)
C(8)	50(6)	22(4)	32(4)	-5(4)	18(4)	-4(4)
C(9)	42(5)	19(4)	24(4)	2(3)	10(4)	4(4)
C(10)	33(5)	22(4)	31(4)	-12(3)	6(3)	-4(4)
C(11)	39(5)	30(5)	29(5)	-9(4)	2(4)	-4(4)
C(12)	35(5)	61(7)	28(4)	-3(4)	5(4)	0(5)
C(13)	40(5)	17(4)	18(4)	-7(3)	3(3)	1(4)
C(14)	46(6)	25(4)	30(4)	4(4)	0(4)	3(4)
C(15)	32(5)	18(4)	18(4)	-3(3)	9(3)	4(3)
C(16)	29(5)	14(4)	22(4)	3(3)	5(3)	2(3)
C(17)	30(5)	13(4)	22(4)	-1(3)	0(3)	3(3)
C(18)	34(5)	17(4)	36(5)	-4(3)	7(4)	5(4)
C(19)	29(4)	17(4)	24(4)	3(3)	9(3)	-3(4)
C(20)	40(5)	21(4)	25(4)	-5(4)	7(3)	3(4)

Table S11. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for 20.

	x	y	z	U(eq)
H(1)	4000(20)	34030(160)	500(60)	40(30)
HA	5150	29230	-305	72
HB	5035	29479	631	72
H(4)	4380(20)	23520(140)	7610(60)	30(20)
HD	2466	26592	2904	33
HE	4474	30810	1973	108
HF	4475	33318	2085	108
H(6')	4280(20)	26140(160)	8660(60)	40(20)
H(6)	3970(20)	28070(150)	8290(60)	20(20)
HI	5035	33057	6609	116
HJ	4864	34668	5834	116
HK	4938	28097	7316	104
HL	4758	29257	6403	104

HM	3767	29113	1584	33
HN	4861	22643	8450	68
HO	4813	23732	9367	68
HP	3382	33564	1189	40
HQ	3772	33084	1958	40
HR	3569	27792	-90	35
HS	3237	29676	-342	35
HT	3794	28680	4309	40
HU	3902	29964	3345	40
HV	4434	28519	4479	62
HW	4269	25880	4363	62
HX	4378	27160	3402	62
HY	3289	23372	3655	31
HZ	2650	22340	3379	52
H(0AA)	2856	21799	4538	52
H(1AA)	2607	24122	4279	52
H(2AA)	4249	21137	6087	35
H(3AA)	3063	30887	6467	43
H(4AA)	3481	31048	7070	43
H(5AA)	3203	29355	7488	43

Figure S13. X-ray crystal structure of **20**.

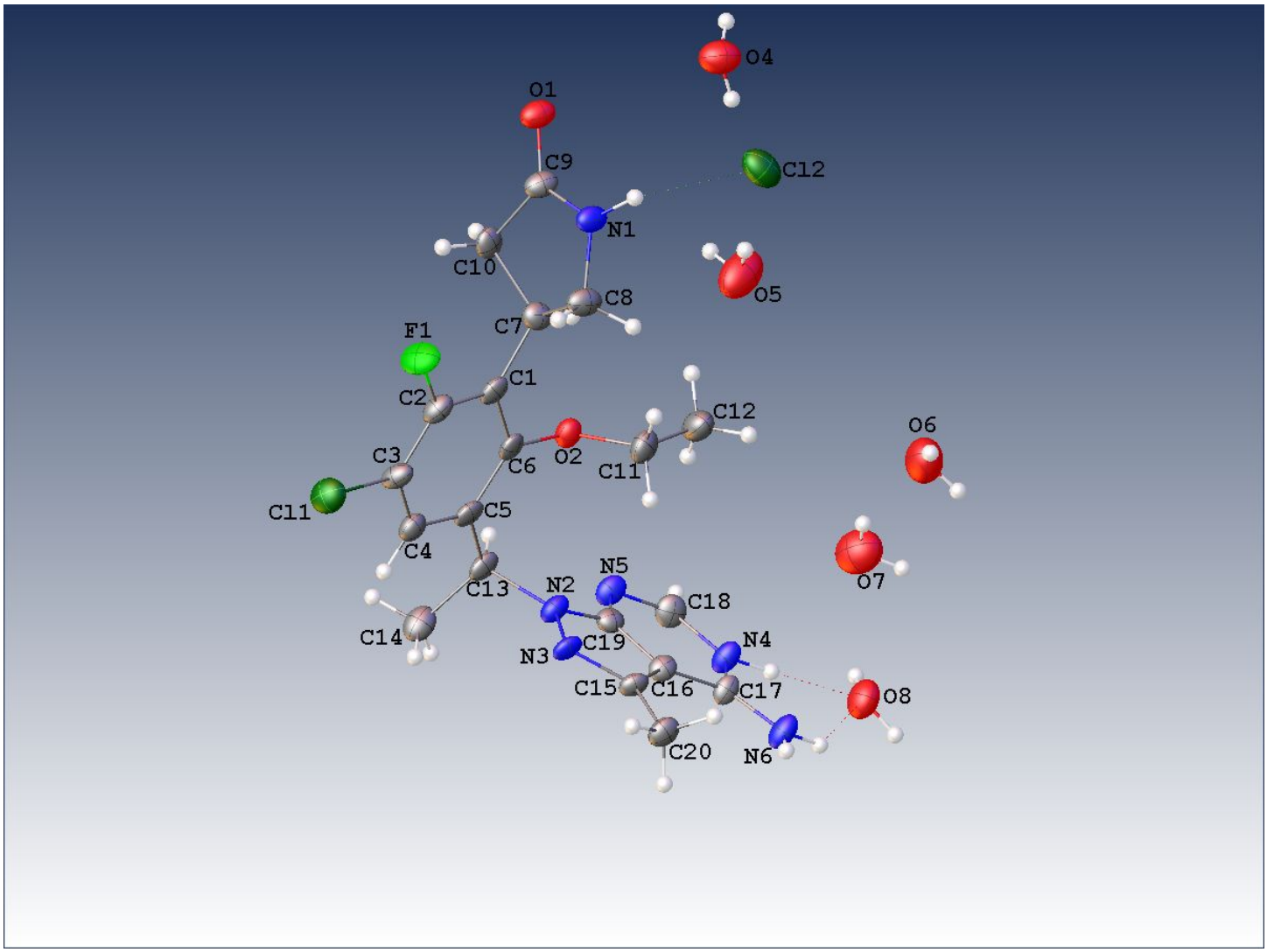
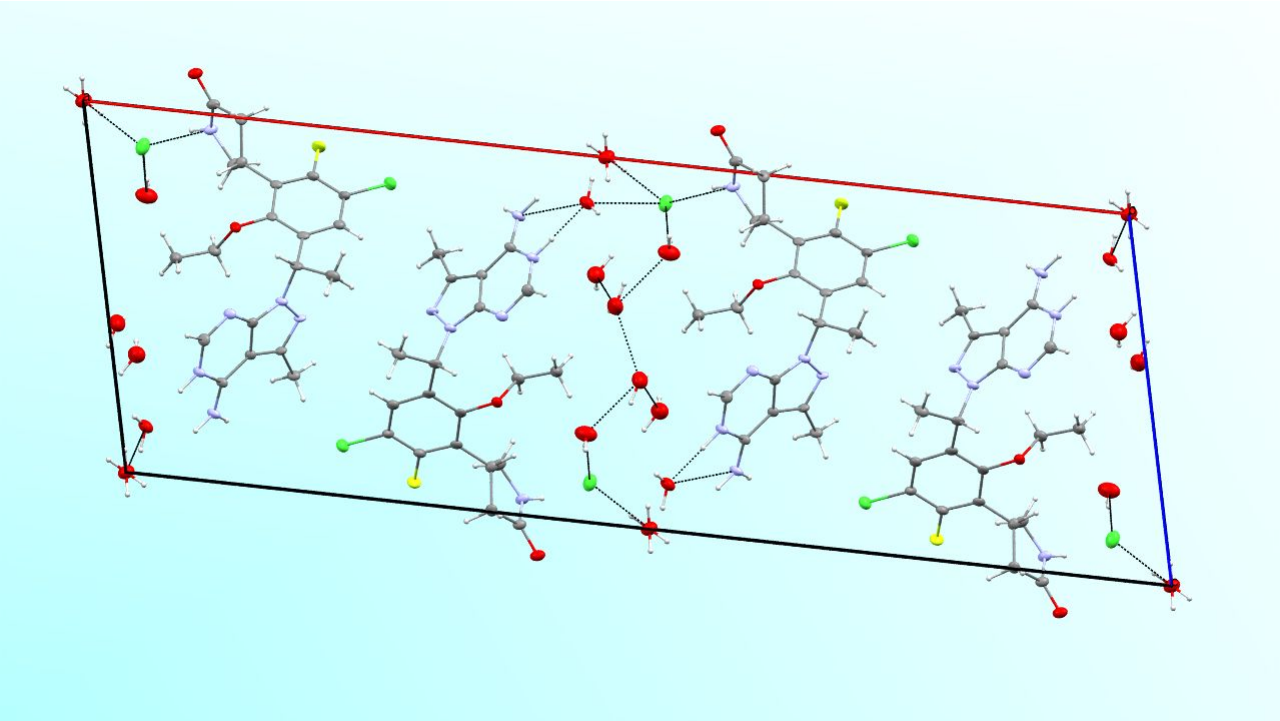


Figure S14. Packing diagram of **20**.



HPLC Purity Analysis

HPLC purity was determined using a Waters Acquity UPLC BEH C18 column (2.1 x 100 mm, 1.7 μM particle size), with a water/0.05% TFA and acetonitrile/0.05% TFA gradient at a flow rate of 0.75 mL/min over a total run time of 5 min.

Table S12. HPLC purity and retention times of compounds **4**-**25**.

Compound	HPLC Retention Time t_R (min)	Purity (%)
4	1.61	85.2
5	2.53	97.4
6	2.30	99.4
7	2.93	97.2
8	2.66 and 2.72 (atropisomers)	96.6
9	2.33	98.9
10	2.59	97.0
11	2.28	99.8
12	2.69	99.6
13	2.47	99.9
14	2.46	99.7
15	2.60	91.6
16	1.99	95.2
17	1.69	98.8
18	2.21	98.4
19	2.30	99.6
20	2.16	97.4
21	2.07	99.1
22	2.21	97.4
23	2.32	99.1
24	2.21	97.8
25	2.11	98.9

In Vitro Profile and Physiochemical Properties of 20

The calculated properties (cLogP, PSA, MW) were generated from ChemDraw 10.

Table S13. In vitro profile and physiochemical properties of **20**.

In Vitro Assays	Result	N
PI3Kδ SPA IC_{50} (nM)	<1.0	7
PI3Kδ FB IC_{50} (nM)	1.1 ± 0.50	11
PI3Kα FB IC_{50} (nM)	>20,000	4
PI3Kβ FB IC_{50} (nM)	>20,000	4
PI3Kγ FB IC_{50} (nM)	>10,000	5
SU-DHL-6 IC_{50} (nM)	1.6 ± 0.90	22
Pfeiffer IC_{50} (nM)	2.5 ± 0.65	8
RAMOS IC_{50} (nM)	1.1 ± 0.85	11
WB IC_{50} (nM)	2.0 ± 1.2	5
hERG patch IC_{50} (nM)	188,000	1
Cyp Inh. (1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4) IC_{50} (nM)	>25,000	2
PXR %Induction (%)	1	2
In Vitro ADME		
% fraction unbound in human plasma	5.8	1
Human Intrinsic Clearance (L/h/kg)	0.65 ± 0.07	2
Caco-2 P_{app} ($x10^{-6}$) (cm/s)	1.0 ± 0.08	3
Physiochemical and Calculated Properties		
MW	432.2	
cLogP	1.0	
HBD	3	
HBA (Total N + O)	8	
PSA ($Å^2$)	105	
LE (RAMOS)	0.42	
LLE (RAMOS)	8.0	
Solubility at pH 7.4 (μg/mL)	210 ± 72	3

In Vitro Assays of compounds **3-25**

Table S14. In vitro profile of compounds **3-25**.

Cmpd	PI3Kδ IC_{50} (nM)	N	SU-DHL-6 Viability IC_{50} (nM)	N	Pfeiffer Proliferation IC_{50} (nM)	N	HEK293 (% inhibition @ 20 μM)	N	hERG binding (% inhibition @ 30 μM)	N
3	3.4 ± 2.4	144	18 ± 8.7	16	14 ± 6.7	44	32 ± 8.7	26	3.8 ± 9.2	4
4	430 ± 140	7	1800 ± 600	3	490 ± 170	5	0.29 ± 6.4	7	18 ± 4.6	6
5	8.4 ± 2.7	7	140 ± 68	5	50 ± 18	4	52 ± 14	13	38 ± 7.2	8
6	13 ± 4.4	24	73 ± 25	16	26 ± 11	29	-2.7 ± 15	13	20 ± 8.8	3
7	99 ± 29	4	1300 ± 240	5	660 ± 150	3	7.7 ± 7.7	7	37 ± 6.6	6
8	5.3 ± 1.2	3	60 ± 9.6	3	8.7 ± 3.9	6	8.6 ± 2.1	7	71 ± 4.4	6
9	2.8 ± 0.12	3	100 ± 32	4	120 ± 86	5	-1.3 ± 2.5	7	32 ± 7.2	7
10	3.6 ± 0.92	8	170 ± 65	5	130 ± 81	5	19 ± 2.8	7	47 ± 7.2	6
11	1.7 ± 0.47	3	14 ± 3.1	4	9.5 ± 3.2	5	55 ± 2.7	4	28 ± 7.5	7
12	0.99 ± 0.50	6	3.1 ± 0.45	6	3.4 ± 1.9	6	79 ± 4.3	15	36 ± 15	7
13	1.8 ± 0.60	10	21 ± 4.4	14	17 ± 4.3	7	27 ± 11	11	-2.5 ± 14	4
14	120 ± 37	7	840 ± 250	5	610 ± 22	3	0.43 ± 2.7	7	14 ± 9.7	7
15	0.93 ± 0.18	3	7.4 ± 1.2	4	8.6 ± 5.8	10	7.5 ± 1.8	3	16 ± 11	8
16	11 ± 1.2	5	44 ± 9.9	4	11 ± 3.9	3	12 ± 9.5	8	44 ± 10	7
17	1.9 ± 0.61	9	2.4 ± 0.97	32	1.5 ± 0.79	8	32 ± 14	15	6.1 ± 5.5	7
18	2.4 ± 0.61	5	13 ± 1.1	4	51 ± 12	3	-0.57 ± 1.8	7	9.5 ± 9.1	7
19	1.4 ± 0.45	3	2.1 ± 0.80	8	4.8 ± 2.1	7	2.5 ± 3.0	8	13 ± 6.7	7
20	<1.0	7	1.6 ± 0.90	22	2.5 ± 0.65	8	-0.4 ± 6.6	10	12 ± 5.4	4
21	<1.0	3	0.47 ± 0.12	8	1.7 ± 0.45	5	6.7 ± 2.8	7	20 ± 6.4	7
22	3.5 ± 1.3	5	46 ± 22	4	62 ± 10	3	1.3 ± 1.4	7	7.1 ± 9.3	7
23	1.6 ± 0.50	4	5.1 ± 1.0	5	4.9 ± 1.8	4	-1.7 ± 2.5	7	14 ± 8.4	7
24	<1.0	3	4.3 ± 1.6	6	3.3 ± 0.67	4	2.1 ± 1.8	8	3.4 ± 6.2	7
25	<1.0	3	1.3 ± 0.59	6	2.3 ± 0.63	4	4.9 ± 6.5	7	22 ± 5.3	7

In Vitro ADME of compounds **3-25**

Table S15. In vitro ADME profile of compounds **3-25**.

Cmpd	% f_u in human plasma	N	% f_u in media	N	Human Intrinsic Clearance (L/h/kg)	N	Caco-2 P_{app} ($x10^{-6}$) (cm/s)	N
3	17 ± 2.3	2	80	1	0.7	1	6.5 ± 0.95	2
4	10	1	66	1	0.7	1	5.0	1
5	1.4	1	28	1	0.7	1	7.0	1
6	5.9 ± 0.22	3	63	1	0.8 ± 0	2	10	1
7	0.64	1	ND		1.1	1	5.2	1
8	ND		ND		1.0	1	22	1
9	2.9	1	23	1	1.1	1	22	1
10	1.3	1	31	1	0.9 ± 0.07	2	2.2	1
11	12	1	49	1	0.8 ± 0.01	2	0.5	1
12	14	1	69	1	0.6	1	7.9	1
13	22	1	78	1	0.8 ± 0.14	2	8.1	1
14	9.2	1	67	1	1.0 ± 0	2	6.8	1
15	8.9	1	62	1	0.9	1	14	1
16	19	1	92	1	0.8	1	12	1
17	42	1	100	1	0.6	1	7.9 ± 0.61	3
18	10	1	93	1	0.7	1	2.8 ± 0.2	2
19	6.5	1	63	1	0.7	1	1.9	1
20	5.8	1	9.8	1	0.65 ± 0.07	2	1.0 ± 0.08	3
21	23	1	57	1	0.7	1	0.3	1
22	9.0	1	75	1	0.6	1	4.7	1
23	8.8	1	86	1	0.9	1	3.0	1
24	15	1	63	1	0.7	1	2.7	1
25	25	1	85	1	0.7	1	0.8	1

f_u = fraction unbound; ND = not determined.

Pharmacokinetic Parameters of **3**, **5**, **6**, **10-13**, **17**, **19-21**, **23**, and **24**

Table S16. Pharmacokinetic parameters of **3**, **5**, and **6**, after a single dose in Sprague-Dawley rats and cynomolgus monkeys.

		3[b]	**3**[b]	**5**[a]	**6**[a]
Route	PK Parameters	Rat	Monkey	Rat	Rat
IV	Dose (mg/kg)	5	0.5	ND	ND
	Hepatic ER (%)	43	42		
	Vd_{ss} (L/kg)	1.52 ± 0.16	1.30		
	$t_{1/2}$ (h)	5.3 ± 0.3	1.3		
Oral	Dose (mg/kg)	10	10	5	5
	C_{max} (nM)	4.82 ± 1.5	1.61 ± 1.5	625 ± 547	2039 ± 1023
	T_{max} (h)	0.5 ± 0.0	2.7 ± 1.5	1.2 ± 0.8	3.0 ± 1.7
	$AUC_{0-\infty}$ (nM·h)	8840 ± 1500	4910 ± 1600	1575 ± 731	13490 ± 7501
	$t_{1/2}$ (h)	1.9 ± 1	3.8 ± 0.6	1.1 ± 0.4	2.1 ± 0.3
	F (%)	54 ± 13	21 ± 7	-	-

[a]Dosed in a cassette; [b]dosed discretely; ND = not determined.

Table S17. Pharmacokinetic parameters of **11**, **12**, and **13**, after a single dose in Sprague-Dawley rats and cynomolgus monkeys.

		11[a]	**12**[a]	**13**[a]	**13**[a]
Route	PK Parameters	Rat	Rat	Rat	Monkey
IV	Dose (mg/kg)	2.5	ND	ND	1
	Hepatic ER (%)	81			75
	Vd_{ss} (L/kg)	2.64 ± 0.4			0.4
	$t_{1/2}$ (h)	1.1 ± 0.2			0.2
Oral	Dose (mg/kg)	5	4	4	2
	C_{max} (nM)	933 ± 709	1730 ± 46	2170 ± 950	35 ± 20
	T_{max} (h)	1.8 ± 1.5	1.3 ± 1.0	1.9 ± 1.5	2.8 ± 2.0
	$AUC_{0-\infty}$ (nM·h)	3016 ± 1669	10379 ± 2659	7760 ± 1340	198 ± 55
	$t_{1/2}$ (h)	1.1 ± 0.2	2.0 ± 0.5	1.4 ± 0.2	4.9 ± 0.8
	F (%)	48 ± 27	-	-	5.8 ± 1.6

[a]Dosed in a cassette; ND = not determined.

Table S18. Pharmacokinetic parameters of **17**, **19**, and **20**, after a single dose in Sprague-Dawley rats and cynomolgus monkeys.

		17[b]	**17**[b]	**19**[a]	**20**[a]
Route	PK Parameters	Rat	Monkey	Rat	Rat
IV	Dose (mg/kg)	2.5	1	2	2
	Hepatic ER (%)	58	15	29	19
	Vd_{ss} (L/kg)	5.7 ± 0.6	2.26	1.61 ± 0.2	1.43 ± 0.2
	$t_{1/2}$ (h)	2.2 ± 0.5	5.88	4.0 ± 2.0	4.5 ± 0.8
Oral	Dose (mg/kg)	5	1	4	4
	C_{max} (nM)	1360 ± 135	511	4535 ± 2458	4167 ± 1654
	T_{max} (h)	0.5 ± 0.1	2.5	0.3 ± 0.1	0.5 ± 0.0
	$AUC_{0-\infty}$ (nM·h)	6785 ± 1388	4060	10691 ± 6190	17459 ± 8787
	$t_{1/2}$ (h)	2.9 ± 0.4	6.43	2.7 ± 1.1	3.5 ± 0.3
	F (%)	>100	63	>100	99 ± 57

[a]Dosed in a cassette; [b]dosed discretely.

Table S19. Pharmacokinetic parameters of **21**, **23**, and **24**, after a single dose in Sprague-Dawley rats and cynomolgus monkeys.

		21[b]	**21**[b]	**23**[a]	**24**[b]
Route	PK Parameters	Rat	Monkey	Rat	Rat
IV	Dose (mg/kg)	2	1	2	2
	Hepatic ER (%)	53 ± 17	19	80	37
	Vd_{ss} (L/kg)	1.5 ± 0.4	1.3	1.92 ± 0.4	1.76 ± 0.1
	$t_{1/2}$ (h)	1.2 ± 0.4	7.0	0.95 ± 0.1	2.1 ± 1.5
Oral	Dose (mg/kg)	4	2	4	4
	C_{max} (nM)	1251 ± 811	470	1595 ± 1072	5365 ± 2566
	T_{max} (h)	0.3 ± 0.0	1.1	0.3 ± 0.1	0.3 ± 0.1
	$AUC_{0-\infty}$ (nM·h)	2333 ± 1311	2076	3229 ± 2314	10003 ± 1099
	$t_{1/2}$ (h)	1.8 ± 2.2	7.5	1.6 ± 0.3	3.2 ± 1.4
	F (%)	-	21	86 ± 62	97 ± 11

[a]Dosed in a cassette; [b]dosed discretely.

Table S20. Summary of pharmacokinetic parameters of **20**[b] after a single dose in Sprague-Dawley rats, beagle dogs, and cynomolgus monkeys.

		Species		
Route	PK Parameters	Rat	Dog	Monkey
IV	Dose (mg/kg)	4	2	2
	Hepatic ER (%)	26	2	5.2
	Vd_{ss} (L/kg)	1.54 ± 0.22	0.32	0.72
	$t_{1/2}$ (h)	4.0 ± 1.6	5.6	7.3
Oral	Dose (mg/kg)	4	4	4
	C_{max} (μM)	4.5 ± 1.6	30	6.3
	T_{max} (h)	0.3 ± 0.13	0.4	2.5
	$AUC_{0-\infty}$ (μM·h)	8.3 ± 1.7	251	54
	$t_{1/2}$ (h)	3.6 ± 1.4	6.1	9.4
	F (%)	74 ± 15	> 100	79

[b]Dosed discretely.