Discovery of spiro-azaindoline inhibitors of hematopoietic progenitor kinase 1 (HPK1)

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Supporting Information

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Kinase selectivity data for compound 25

Source: ThermoFisher SelectScreen

Kinase	% inhibition at 0.1 μM	Kinase	% inhibition at 0.1 μM
MAP4K4	103.5	ITK	5.5
Mink1	98.5	ROCK1	5.5
KHS1	96.5	Aurora_A	5
Flt3	88.5	DYRK1A	4.5
HPK1	81.5	MLK1	4.5
GLK	78.5	PKC_theta	4.5
TrkA	67	JAK3	4
GCK	66	TYK2	4
LRRK2	43	Yes	4
MST2	39	Kit	3.5
MARK1	37	MRCK_alpha	3.5
Abl	33.5	FGFR1	3
Aurora_B	24	GSK3_beta	3
PKD1	21	CLK1	2.5
MST4	11.5	Blk	1
Fgr	9	JAK1	1
DMPK	7.5	PDGFR_alpha	1
Lyn	7.5	PDK1	1
MuSK	7.5	Syk	0
Src	7.5	TGFBR1	0
SLK	7	PAK4	-0.5
CLK2	6.5	CLK4	-1
KDR	6	IRAK1	-1.5
CDK5/p25	5.5	Fyn	-2

Kinase	IC_{50} (nM)
GCK (MAP4K2)	117
GLK (MAP4K3)	16.0
MAP4K4	13.9
KHS1 (MAP4K5)	12.5
Mink1 (MAP4K6)	18.2

General Methods

All chemicals were purchased from commercial suppliers and used as received. Flash chromatography was carried out with pre–packed SiO_2 cartridges from either Teledyne ISCO or SiliCycle on an Teledyne ISCO Rf200 chromatography system using gradient elution, or with pre-packed silica gel cartridges from Biotage using a Biotage SP4 or an Isolara 4 MPLC system using gradient elution. NMR spectra were recorded on a Bruker Avance 400, Bruker DPX 400M, Bruker Avance III 400, Bruker AV III 400 or 500 NMR spectrometer, and referenced to tetramethylsilane. The following abbreviations are used: br = broad signal, s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet.

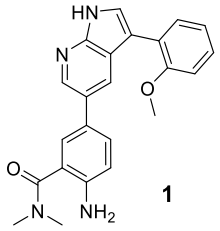
Preparative HPLC was performed on a Polaris C_{18} 5 µM column (50 × 21 mm), a Waters Sunfire OBD Phenomenex Luna Phenyl Hexyl column (150 × 19 mm) or a Waters Xbridge Phenyl column (150 × 19 mm), eluting with mixtures of water–acetonitrile or water–methanol, optionally containing a modifier (0.1% V/V formic acid or 10 mM ammonium bicarbonate).

Low-resolution mass spectra were recorded on a Sciex 15 mass spectrometer in ES+ mode, a Micromass ZQ single quadrapole LC-MS in ES+, ES- mode, or a Quattro Micro LC-MS-MS in ES+, ES- mode.

All final compounds were purified to > 95% chemical purity as assayed by either: a) HPLC (Waters Acquity UPLC column 21 x 50 mm, 1.7 µM) with gradient of 0–90% acetonitrile (containing 0.038% TFA) in 0.1% aqueous TFA, with UV detection at λ= 254 and 210 as well as CAD detection with an ESA Corona detector; b) HPLC (Phenomenex Luna C_{18} (2) column 4.6 x 100 mm, 5 µM) with gradient of 5–95% acetonitrile in water (with 0.1% formic acid in each mobile phase), with UV DAD detection between λ = 210 and 400 nm; c) HPLC (Waters Xterra MS C_{18} column 4.6 x 100 mm, 5 µM) with gradient of 5–95% acetonitrile in water (with 10 mM ammonium bicarbonate in the aqueous mobile phase), with UV DAD detection between λ = 210 and 400 nm; d) HPLC (Supelco, Ascentis® Express C_{18} or Hichrom Halo C_{18} column 4.6 x 150 mm, 2.7 µM) with gradient of 4–100% acetonitrile in water (with 0.1% formic acid in each mobile phase), with UV DAD detection between λ = 210 and 400 nm; e) HPLC (Phenomenex, Gemini NX C_{18} column 4.6 x 150 mm, 3 µM) with gradient of 4.5–100% acetonitrile in water (with 10 mM ammonium bicarbonate in the aqueous mobile phase), with UV DAD detection between λ = 210 and 400 nm.

Synthetic Procedures

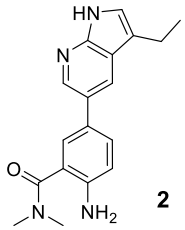
Compound 1: 2-Amino-5-(3-(2-methoxyphenyl)-1H-pyrrolo[2,3-*b*]pyridin-5-yl)-*N,N*-dimethylbenzamide



1

The title compound was prepared following the procedure as described in US patent No. 20070043068.

Compound 2: 2-Amino-5-(3-ethyl-1H-pyrrolo[2,3-*b*]pyridin-5-yl)-*N,N*-dimethylbenzamide



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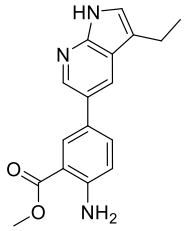
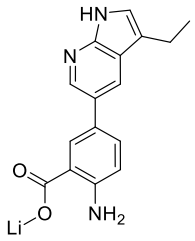
Step 1: Methyl 2-amino-5-(3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)benzoate



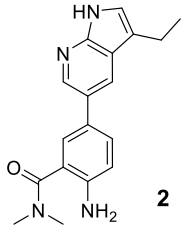
A mixture of 3-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine (112 mg, 0.41 mmol), methyl 2-amino-5-bromobenzoate (94 mg, 0.41 mmol), XPhosPdG2 (19 mg, 0.025 mmol), XPhos (12 mg, 0.025 mmol), K_3PO_4 (174 mg, 0.82 mmol) in dioxane (1.7 mL) and water (0.3 mL) were placed in a tube and degassed under argon with sonication. The reaction mixture was sealed and heated under microwave irradiation at 100 °C for 24h. The cooled mixture was diluted with methanol, loaded onto an SCX-2 cartridge (5 g). The cartridge was washed with methanol and the product eluted with 2M NH_3 in methanol. The product fractions were pooled and concentrated *in vacuo*. The product was further purified by chromatography on silica (using 2M NH_3 in methanol/dichloromethane 2-10% as eluant) to give the product as a white solid (86 mg, 71%).

Step 2: Lithium 2-amino-5-(3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)benzoate



A mixture of methyl 2-amino-5-(3-ethyl-1H-pyrrolo[2,3-*b*]pyridin-5-yl)benzoate (86 mg, 0.29 mmol), lithium hydroxide (24 mg, 0.58 mmol) in methanol (6 mL) and water (2 mL) was stirred at 50 °C overnight. The mixture was concentrated in vacuo and used without further purification in the following step.

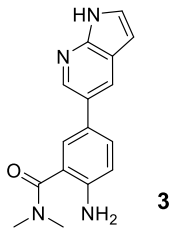
Step 3: 2-Amino-5-(3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-*N,N*-dimethylbenzamide



2

To a mixture of lithium 2-amino-5-(3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)benzoate (0.29 mmol), dimethylamine hydrochloride (95 mg, 1.2 mmol), DIPEA (0.3 mL, 1.7 mmol) in DMF (6 mL) was added HATU (220 mg, 0.58 mmol) portionwise over 5 min. The mixture was stirred for 30 min then the mixture was diluted with methanol, loaded onto an SCX-2 cartridge (10 g) and the cartridge was washed with methanol and the product eluted with 2M NH_3 in methanol. The product fractions were pooled and concentrated *in vacuo*. The product was further purified by reverse phase chromatography (C_{18}) to give the product as a white solid (60 mg, 67%). LCMS (ESI) *m/z* calcd for $C_{18}H_{20}N_4O$ $[M+H]^+$: 309.4. Found 309.1. ^{1}H NMR (400 MHz, $CDCl_3$) δ11.21 (s, 1H), 8.35 (d, J=2.0 Hz, 1H), 8.00 (d, *J* = 2.2 Hz, 1H), 7.44 (dd, *J* = 2.3, 8.4 Hz, 1H), 7.31 (d, *J* = 2.2 Hz, 1H), 7.18 (s, 1H), 6.80 - 6.77 (m, 1H), 5.20 (s, 2H), 2.95 (s, 6H), 2.71 (q, *J* = 7.5 Hz, 2H), 1.24 (t, *J* = 7.5 Hz, 4H).

Compound 3: 2-amino-*N,N*-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-5-yl)benzamide

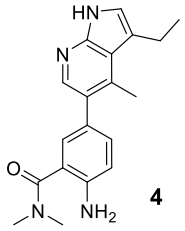


3

A mixture of 5-bromo-1H-pyrrolo[2,3-b]pyridine (0.10 g, 0.51 mmol), tert-butyl *N*-[2-(dimethylcarbamoyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate (0.23 g, 0.60 mmol), potassium carbonate (0.14 g, 1.0 mmol) and $Pd(dppf)_2Cl_2$ (36 mg, 0.05 mmol) in dioxane (5 mL) and water (1 mL) was heated to 90 ^{o}C under a nitrogen atmosphere for 2 h. The mixture was cooled to RT, filtered and concentrated in vacuo to give a crude residue.

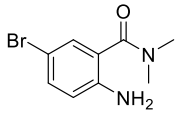
The crude residue was dissolved in MeOH (10 mL). 4M HCl in 1.4-dioxane (20 mmol, 5 mL) was added. The resulting mixture was stirred at RT for 6 h and concentrated. The crude product was purified by reverse-phase HPLC to give the title compound (24 mg, 17%). LCMS (ESI) *m/z* calcd for $C_{16}H_{16}N_4O$ $[M+H]^+$: 281.1. Found 281.2. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.58 (s, 1H), 8.41 (d, *J*=2.2 Hz, 1H), 8.15 – 7.98 (m, 1H), 7.56 – 7.40 (m, 2H), 7.32 (d, *J*=2.3 Hz, 1H), 6.82 (d, *J*=8.4 Hz, 1H), 6.49 –6.39 (m, 1H), 5.25 (s, 2H), 2.98 (s, 6H).

Compound 4: 2-Amino-5-(4-methyl-3-ethyl-1H-pyrrolo[2,3-*b*]pyridin-5-yl)-*N,N*-dimethylbenzamide



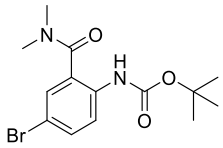
4

Step 1: 2-amino-5-bromo-*N,N*-dimethylbenzamide



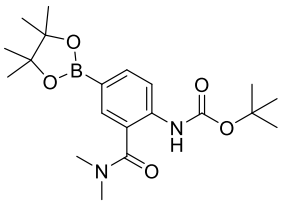
A mixture of 2-amino-5-bromobenzoic acid (35 g, 162 mmol), dimethylamine (2M in THF, 162 mL, 324 mmol), EDCI (44 g, 324 mmol) and DIPEA (42 g, 324 mmol) in DMF (500 mL) was stirred at room temperature for 16 h. Water (1.5 L) was added to the reaction mixture which was extracted with ethyl acetate (4 x 500 mL). The combined organic layers were washed with water (500 mL), brine (300 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound as a pale-yellow solid (35 g, 87%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.21-7.23 (m, 2H), 6.60-6.62 (d, 1H), 4.36 (s, 2H), 3.06 (s, 6H).

Step 2: tert-butyl 4-bromo-2-(dimethylcarbamoyl)phenylcarbamate



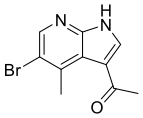
A mixture of di-tert-butyldicarbonate (61 g, 280 mmol) and 2-amino-5-bromo-*N,N*-dimethylbenzamide (34 g, 140 mmol) in 2-methyl-2-propanol (300 mL) was stirred at 90 ^{o}C. The mixture was cooled to room temperature and the solid was filtered to give the title compound as a white solid (39 g, 81%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.84 (s, 1H), 7.51-7.53 (m, 2H), 7.42-7.43 (m, 1H), 2.85-2.92 (d, 6H), 1.43 (s, 9H).

Step 3: tert-butyl 2-(dimethylcarbamoyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate



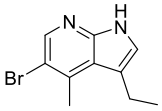
A mixture of tert-butyl *N*-[4-bromo-2-(dimethylcarbamoyl)phenyl]carbamate (20 g, 58 mmol), bis(pinacolato)diboron (22 g, 87 mmol), potassium acetate (12 g, 117 mmol) and $Pd(dppf)_2Cl_2$ (4.76 g, 6 mmol) in 1,4-dioxane (200 mL) was stirred at 100 °C for 2 h. The mixture was cooled to RT and filtered through Celite. The filtrate was diluted with water (200 mL) and the resulting solution was extracted with ethyl acetate (200 mL x 3). The combined organic layers were dried (Na_2SO_4), concentrated under reduced pressure to give a crude residue. The residue was purified by chromatography on silica gel eluting with 0-10% ethyl acetate in cyclohexane to give the title compound (19 g, 83.7%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.87 (s, 1H), 7.69 (m, 1H), 7.64-7.64 (m, 1H), 7.48 (s, 1H), 2.86-2.94 (d, 6H), 1.44 (s, 9H), 1.28 (s, 12H).

Step 4: 1-(5-bromo-4-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)ethan-1-one



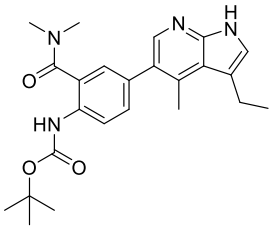
A mixture of 5-bromo-4-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (5 g, 24 mmol) and $AlCl_3$ (32 g, 240 mmol) in dichloromethane (100 mL) was stirred at 0°C for 10 min. Acetyl chloride (2.3 mL, 36 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 16 h. The mixture was poured onto 300 mL ice water, neutralized with 20% NaOH to pH 9 and extracted with ethyl acetate (150 mL x 3). The organic layers were combined, dried (Na_2SO_4) and concentrated *in vacuo* to afford the title compound (4 g, 67%) as a brown solid, which was carried onto the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.19 (s, 1H), 8.47 (s, 1H), 8.05 (s, 1H), 3.03 (s, 3H), 2.06 (s, 3H).

Step 5: 5-bromo-3-ethyl-4-methyl-1H-pyrrolo[2,3-*b*]pyridine



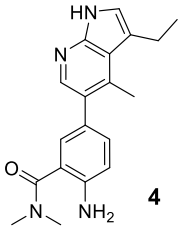
5-bromo-3-ethyl-4-methyl-1H-pyrrolo[2,3-*b*]pyridine (9.2 g, 36 mmol) was stirred in trifluoroacetic acid (75 mL) at 50 °C, followed by the addition of triethylsilane (32 mL, 218 mmol). The resulting mixture was stirred at 70 °C for 16 h. Additional triethylsilane (16 mL, 109 mmol) was added dropwise, and the mixture was stirred at 70 °C for another 16 h. The mixture was cooled to RT, concentrated *in vacuo* and neutralized with aqueous 2 M sodium hydroxide. The precipitate formed was isolated by filtration, dissolved in a minimum amount of dichloromethane and purified by silica gel chromatography eluting with 0-30% ethyl acetate in cyclohexane to give the title compound (5.0 g, 57%) as a white solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.48 (s, 1H), 8.19 (s, 1H), 7.21 (s, 1H), 2.80-2.86 (m, 2H), 2.66 (s, 3H), 1.22-1.25 (m, 3H).

Step 6: tert-butyl 2-(dimethylcarbamoyl)-4-(3-ethyl-4-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)phenylcarbamate



A mixture of 5-bromo-3-ethyl-4-methyl-1H-pyrrolo[2,3-*b*]pyridine (6.7 g, 28 mmol), tert-butyl *N*-[2-(dimethylcarbamoyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate (13 g, 34 mmol), potassium carbonate (7.7 g, 56 mmol) and $Pd(dppf)_2Cl_2$ (2.3 g, 2.8 mmol) in dioxane (200 mL) and water (10 mL) was heated to 90 °C under a nitrogen atmosphere for 2 h. The mixture was cooled to RT and concentrated in vacuo to give a crude residue. The residue was purified by silica gel chromatography eluting with 0-50% ethyl acetate in cyclohexane to give the title compound (8.8 g, 75%) as a light-yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.31 (s, 1H), 8.80 (s, 1H), 7.97 (s, 1H), 7.69-7.71 (d, 1H), 7.37-7.378 (m, 1H), 2.96 (s, 6H), 2.88-2.90 (m, 2H), 2.55 (s, 3H), 1.47 (s, 9H), 1.25-1.29 (m, 3H).

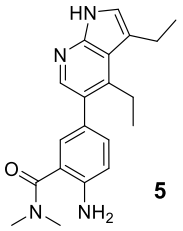
Step 7: 2-amino-5-(4-methyl-3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-*N,N*-dimethylbenzamide



4

To a solution of tert-butyl 2-(dimethylcarbamoyl)-4-(3-ethyl-4-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)phenylcarbamate (5 g, 20.9 mmol) in methanol (20 mL) was added HCl in dioxane (4N, 20 mL, 80 mmol). The mixture was stirred at room temperature for 6 h and concentrated *in vacuo.* To the resulting residue was added NH_3 (7N in methanol, 4 mL). The resultant mixture was then concentrated *in vacuo* and the residue was purified by chromatography on silica eluting with dichloromethane/methanol (20:1 to 10:1) to give the title product as a grey-white solid (3.7 g, 97.3%). LCMS (ESI) *m/z* calcd for $C_{19}H_{22}N_4O$ $[M+H]^+$: 323.2. Found 323.2. ^{1}H NMR (400 MHz, CD_3OD) δ 7.92 (s, 1H), 7.15-7.17 (dd, 1H), 7.13 (s, 1H), 7.05-7.06 (d, 1H), 6.89-6.91 (d, 1H), 3.10 (s, 6H), 2.95-2.97 (m, 2H), 2.61 (s, 3H), 1.32-1.36 (m, 3H).

Compound 5: 2-Amino-5-(4-ethyl-3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-*N,N*-dimethylbenzamide

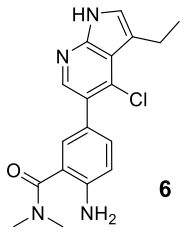


5

The title compound was prepared in a fashion analogous to compound **4**. LCMS (ESI) *m/z* calcd for $C_{20}H_{24}N_4O$ $[M+H]^+$: 337.2. Found 337.2. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.44 (s, 1H), 8.01 (s,

1H), 7.07-7.26 (m, 3H), 6.78-6.80 (d, 1H), 3.09 (s, 6H), 2.89-2.96 (m, 4H), 1.36 (t, 3H), 1.08 (t, 3H).

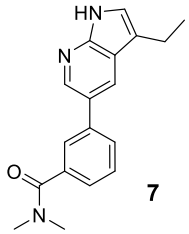
Compound 6: 2-Amino-5-(4-chloro-3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-*N,N*-dimethylbenzamide



6

The title compound was prepared in a fashion analogous to Compound **4**. LCMS (ESI) *m/z* calcd for $C_{18}H_{19}ClN_4O$ $[M+H]^+$: 343.1/345.1 Found 343.1/345.1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (s, 1H), 8.15 (s, 1H), 7.25-7.29 (m, 2H), 7.13 (s, 1H), 6.82 (d, 1H), 4.53 (s, 2H), 3.12 (s, 6H), 2.98-3.04 (m, 2H),1.33 (t, 3H).

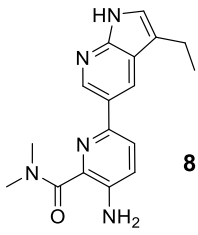
Compound 7: 3-(3-Ethyl-1*H*-pyrrolo[2,3-b]pyridin-5-yl)-*N,N*-dimethylbenzamide



7

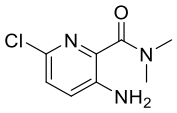
A mixture of 3-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine (100 mg, 0.37 mmol), 3-bromo-*N,N*-dimethylbenzamide (84 mg, 0.37 mmol), XPhosPd G2 (17 mg, 0.02 mmol), XPhos (10.5 mg, 0.02 mmol), K_3PO_4 (156 mg, 0.74 mmol) in dioxane (1.7 mL) were placed in a tube and degassed under argon with sonication. The reaction mixture was sealed and heated at 100 °C overnight. The reaction mixture was cooled and diluted with methanol. The methanolic extract was loaded onto an SCX-2 cartridge (5g) and the product eluted with 2M NH_3 in methanol. The product fractions were concentrated and purified further by reverse-phase chromatography (C_{18}) using an acetonitrile/water gradient buffered with ammonia to give the product as a white solid (61 mg, 56%). LCMS (ESI) *m/z* calcd for $C_{18}H_{19}N_3O$ $[M+H]^+$: 294.1. Found 294.2. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.37 (s, 1H), 8.48 (d, *J* = 2.1 Hz, 1H), 8.19 (d, *J* = 2.2 Hz, 1H), 7.78 - 7.75 (m, 1H), 7.69 (t, *J* = 1.5 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 1H), 7.34 - 7.31 (m, 1H), 7.25 (s, 1H), 3.00 (3H, s), 2.95 (3H, s), 2.73 (dq, *J* = 0.8, 7.5 Hz, 2H), 1.26 (t, *J* = 7.5 Hz, 3H).

Compound 8: 3-Amino-6-(3-ethyl-1H-pyrrolo[2,3-*b*]pyridin-5-yl)-*N,N*-dimethylpicolinamide



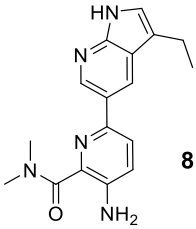
8

Step 1: 3-amino-6-chloro-*N,N*-dimethylpicolinamide



To a suspension of 3-amino-6-chloro-2-pyridinecarboxylic acid (344 mg, 2 mmol) in dichloromethane (6 mL) was added DIPEA (1 mL, 6 mmol), followed by HATU (912 mg, 2.5 mmol) and the resulting mixture stirred for 10 min; dimethylamine hydrochloride (244 mg, 3 mmol) was added and the mixture was stirred for 4 h. The mixture was diluted with dichloromethane and the organic extract was washed with sodium hydroxide (1N, 10 mL), brine, dried (Na_2SO_4) and evaporated. The crude residue was purified by chromatography on silica using 1-4% methanol in dichloromethane to give the product as a pale-yellow solid (240 mg, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 - 7.09 (m, 1H), 7.03 - 7.00 (m, 1H), 4.89 (s, 2H), 3.18 - 3.16 (m, 3H), 3.10 (s, 3H), 2.80 (s, 3H).

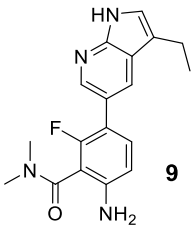
Step 2: 3-amino-6-(3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-*N,N*-dimethylpicolinamide



8

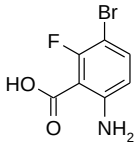
A mixture of 3-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (136 mg, 0.5 mmol), 3-amino-6-chloro-*N,N*-dimethylpicolinamide (100 mg, 0.5 mmol), XPhosPdG2 (24 mg, 0.03 mmol), XPhos (14 mg, 0.03 mmol), K_3PO_4 (212 mg, 1.0 mmol) in dioxane (2 mL) and water (0.3 mL) were placed in a tube and degassed under nitrogen with sonication. The reaction mixture was sealed and heated under microwave irradiation at 150 °C for 1h. The reaction mixture was cooled and diluted with dichloromethane; the dichloromethane phase was dried and evaporated. The residue was purified on C18 silica using a gradient of water: acetonitrile (0.1% formic acid modifier) as eluant. The combined product fractions were evaporated, and the residue was dissolved in methanol and passed through an SCX-2 cartridge; the product was eluted using 2M NH_3 in methanol as eluant to give a white solid (46 mg, 30%). LCMS (ESI) *m/z* calcd for $C_{17}H_{19}N_5O$ $[M+H]^+$: 310.2. Found 310.2. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.29 (s, 1H), 8.74 (d, *J* = 2.1 Hz, 1H), 8.34 (d, *J* = 1.9 Hz, 1H), 7.79 - 7.76 (m, 1H), 7.21 - 7.19 (m, 2H), 5.57 (s, 2H), 3.06 (s, 3H), 3.03 (s, 3H), 2.72 (dq, *J* = 0.8, 7.5 Hz, 2H), 1.26 (t, *J* = 7.5 Hz, 3H).

Compound 9: 6-Amino-3-(3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-fluoro-*N,N*-dimethylbenzamide



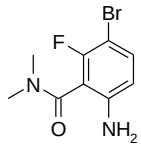
9

Step 1: 6-Amino-3-bromo-2-fluorobenzoic acid



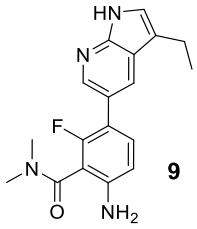
A suspension of 2-amino-6-fluorobenzoic acid (6 g, 38.7 mmol) in chloroform (80 mL) was cooled in ice. Bromine (2.19 mL, 42.6 mmol) was added dropwise and the mixture was stirred at 0 °C for 0.5 h, then at room temperature for 16 h. The solid was filtered, washed with dichloromethane and dried in vacuo at 40 °C to give the title compound (12.3 g). Analysis by LCMS showed the desired product. The material was used without further purification. LCMS (ESI) *m/z* calcd for $C_7H_5BrFNO_2$ $[M-H_2O]^+$: 216/218. Found 216/218.

Step 2: 6-Amino-3-bromo-2-fluoro-*N,N*-dimethylbenzamide



DIPEA (16.4 mL, 96 mmol) was added to a suspension of crude product from step 1 (10.28 g) in dry dichloromethane (100 mL) to give a solution. HATU (18.2 g, 48 mmol) was added and the mixture was stirred for 5 min before addition of dimethylamine (2M in tetrahydrofuran, 24.0 mL, 48 mmol) with cooling in a cold water-bath. The mixture was stirred at room temperature for 3 h, and then washed with 1M sodium hydroxide and brine. The aqueous phases were re-extracted twice with dichloromethane. The combined organic phases were dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica eluting with 0-50% ethyl acetate/cyclohexane to give a mixture of the title compound (4.79 g) containing some unbrominated analogue. This material was further purified by chromatography (eluting with 0-50% ethyl acetate/cyclohexane) to give a 1.5:1 mixture of title compound and unbrominated analogue (3.55 g). . LCMS (ESI) *m/z* calcd for $C_9H_{10}BrFN_2O$ $[M+H]^+$: 261.0, Found 261.0

Step 3: 6-amino-3-(3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-fluoro-*N,N*-dimethylbenzamide

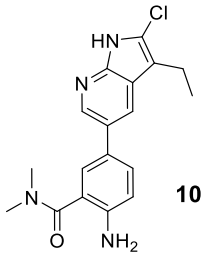


9

A mixture of 3-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine (680 mg, 2.5 mmol), 6-amino-3-bromo-2-fluoro-*N,N*-dimethylbenzamide (780 mg, 3 mmol), XPhosPdG2 (120 mg, 0.15 mmol), XPhos (70 mg, 0.15 mmol), K_3PO_4 (1.06 g, 5 mmol) in dioxane (9 mL) and water (1.5 mL) was placed in a tube and degassed under nitrogen with sonication. The reaction mixture was sealed and heated under microwave irradiation at 125 °C for 1h. The reaction mixture was cooled and diluted with ethyl acetate. The ethyl acetate layer was washed with water, brine, dried (Na_2SO_4) and evaporated. The residue was purified on silica using a gradient of 0-3% methanol in dichloromethane as eluant. The combined product fractions were evaporated to give a pale-yellow solid (412 mg, 51%). LCMS (ESI) *m/z* calcd for $C_{18}H_{19}FN_4O$ $[M+H]^+$: 327.2. Found 327.3. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.30 (s, 1H), 8.26 -

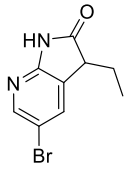
8.21 (m, 1H), 7.95 - 7.92 (m, 1H), 7.33 - 7.22 (m, 2H), 6.64 (d, *J* = 8.7 Hz, 1H), 5.37 (s, 2H), 3.02 (s, 3H), 2.92 (s, 3H), 2.71 (q, *J* = 7.5 Hz, 2H), 1.26 (t, *J* = 7.5 Hz, 3H).

Compound 10: 2-Amino-5-(2-chloro-3-ethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-*N,N*-dimethylbenzamide



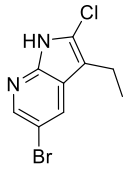
10

Step 1: 5-bromo-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-2(3*H*)-one



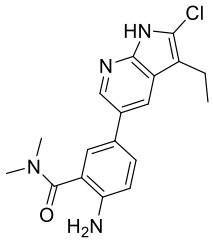
To a solution of 5-bromo-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridine (500 mg, 2.22 mmol) in acetonitrile (25 mL) was added NCS (325 mg, 2.44 mmol). The mixture was stirred at 40 ^{o}C for 6 h. After 6 h, the reaction mixture was washed with water (30 mL) and extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was then purified by chromatography on silica gel (0-50% ethyl acetate in petroleum ether) to provide 5-bromo-3-ethyl-1*H*-pyrrolo[2,3-b]pyridin-2(3*H*)-one (350 mg,1.21 mmol, 54% yield) as a white solid. LCMS (ESI) *m/z* calcd for $C_9H_9BrN_2O$ $[M+H]^+$: 241.0. Found 241.1.

Step 2: 5-bromo-2-chloro-3-ethyl-1*H*-pyrrolo[2,3-b]pyridine



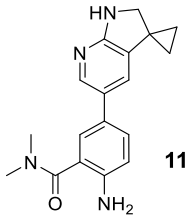
A solution of 5-bromo-3-ethyl-1*H*-pyrrolo[2,3-b]pyridin-2(3*H*)-one (200 mg, 0.83 mmol) in phosphorus oxychloride (4.0 mL, 43.57 mmol) was stirred at 100 ^{o}C for 16 h. The reaction mixture was slowly poured into 200 mL of water, and then neutralized to pH 8.0 with saturated Na_2CO_3 aqueous solution. The resultant mixture was extracted with dichloromethane (3 x 100 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was then purified via flash chromatography on silica gel (0-30% ethyl acetate in petroleum ether) to provide 5-bromo-2-chloro-3-ethyl-1*H*-pyrrolo[2,3-b]pyridine (200 mg,0.74 mmol, 89% yield) as a white solid. . LCMS (ESI) *m/z* calcd for $C_9H_8BrClN_2$ $[M+H]^+$: 259.0. Found 259.0. ^{1}H NMR (400 MHz, CD_3OD) δ 8.21 (d, *J* = 2.0 Hz, 1H), 8.09 (d, *J* = 2.0 Hz, 1H), 2.74 (q, *J* = 7.2 Hz, 2H), 1.24 (t, *J* = 7.2 Hz, 3H).

Step 3: 2-Amino-5-(2-chloro-3-ethyl-1H-pyrrolo[2,3-*b*]pyridin-5-yl)-*N,N*-dimethylbenzamide



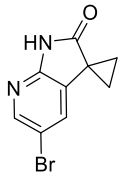
A mixture of 5-bromo-2-chloro-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridine (13 mg, 0.05 mmol), 2-amino-*N,N*-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (15 mg, 0.05 mmol), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride.dichloromethane complex (4 mg, 0.01 mmol), cesium carbonate (49 mg, 0.15 mmol), 1,4-dioxane (1.5 mL) and water (0.5 mL) was stirred at 100 °C for 1.5 h. The reaction was then diluted with water (10 mL), extracted with ethyl acetate (3 x 10 mL), dried over Na_2SO_4, filtered and concentrated. The crude product was purified by preparative reverse phase HPLC (C_{18}, eluting with acetonitrile/water + 0.05% formic acid) to give 2-amino-5-(2-chloro-3-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-*N,N*-dimethylbenzamide (4 mg, 23%) as an off white solid. . LCMS (ESI) *m/z* calcd for $C_{18}H_{19}ClN_4O$ $[M+H]^+$: 343.1. Found 343.1. ^{1}H NMR (400 MHz, CD_3OD) δ 8.35 (s, 1H), 8.04 (s, 1H), 7.50 (dd, *J* = 2.0, 8.0 Hz, 1H), 7.39 (d, *J* = 2.0 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 3.12 (br, 6H), 2.80 (q, *J* = 8.0 Hz, 2H), 1.28 (t, *J* = 7.6 Hz, 3H).

Compound 11: 2-Amino-5-(1',2'-dihydrospiro[cyclopropane-1,3'-pyrrolo[2,3-*b*]pyridin]-5'-yl)-*N,N*-dimethylbenzamide



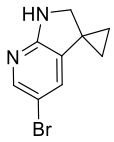
11

Step 1: 5'-Bromospiro[cyclopropane-1,3'-pyrrolo[2,3-*b*]pyridin]-2'(1'*H*)-one



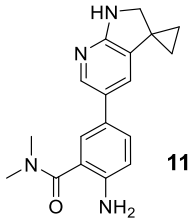
To a solution of 5-bromo-1,3-dihydro-2*H*-pyrrolo[2,3-*b*]pyridin-2-one (10 g, 50 mmol) and di-isopropylamine (14.2 mL, 100 mmol) in THF (200 mL) at -30 °C was added dropwise *n*-BuLi (2.5N, 80 mL, 200 mmol) over 35 min. The reaction mixture was stirred at -30 °C for 10 min, then allowed to warm to 0 °C, and treated with 1,2-dibromoethane (12.8 mL, 150 mmol). The reaction mixture was allowed to warm to RT, then stirred for 16h. The mixture was diluted with ethyl acetate and water. The organic extract was washed with brine, dried (Na_2SO_4) and concentrated. The residue was triturated with Et_2O, filtered and dried *in vacuo*, to afford the title compound (4.54 g, 36%) as a light brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.31 (s, 1H), 8.15 (d, *J* = 2.3 Hz, 1H), 7.66 (d, *J* = 2.3 Hz, 1H), 1.76 - 1.70 (m, 2H), 1.58 - 1.52 (m, 2H).

Step 2: 5'-Bromo-1',2'-dihydrospiro[cyclopropane-1,3'-pyrrolo[2,3-*b*]pyridine]



To a suspension of 5'-bromospiro[cyclopropane-1,3'-pyrrolo[2,3-*b*]pyridin]-2'(1'*H*)-one (4.34 g, 18.1 mmol) in dichloromethane (90 mL) at 0 °C was added DIBAL (1M in dichloromethane, 90 mL, 90 mmol) dropwise over 45 min. The reaction mixture was allowed to warm to RT, stirred for 16h, then cooled to 0 °C. Water (30 mL) was added dropwise to the mixture, followed by ethyl acetate and solid sodium bicarbonate. The mixture was filtered and concentrated. The residue was purified by chromatography on silica (eluting with 1-4% methanol in dichloromethane) to afford the title compound (2.94 g, 72%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.66 (d, *J* = 2.2 Hz, 1H), 6.99 (d, *J* = 2.0 Hz, 1H), 6.77 (s, 1H), 3.51 (d, *J* = 1.2 Hz, 2H), 1.06 - 1.02 (m, 2H), 0.97 - 0.93 (m, 2H).

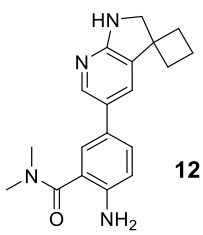
Step 3: 2-Amino-5-(1',2'-dihydrospiro[cyclopropane-1,3'-pyrrolo[2,3-*b*]pyridin]-5'-yl)-*N,N*-dimethylbenzamide



11

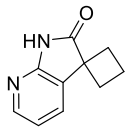
A mixture of 5'-bromo-1',2'-dihydrospiro[cyclopropane-1,3'-pyrrolo[2,3-b]pyridine] (83 mg, 0.37 mmol), 2-amino-*N,N*-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (107 mg, 0.37 mmol), XPhosPdG2 (17 mg, 0.02 mmol), XPhos (11 mg, 0.02 mmol), K_3PO_4 (152 mg, 0.74 mmol) in dioxane (1.7 mL) and water (0.3 mL) was degassed and purged with argon under sonication. The mixture was heated at 100 °C for 12 h. The cooled mixture was diluted with methanol and loaded onto an SCX-2 cartridge. The cartridge was washed with methanol and the product was eluted with 2M NH_3 in methanol. The product fractions were concentrated *in vacuo* and were further purified by reverse phase chromatography to give the product as an off-white solid (51 mg, 45%). LCMS (ESI) *m/z* calcd for $C_{18}H_{20}N_4O$ $[M+H]^+$: 309.2. Found 309.2. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84 (d, *J* = 2.0 Hz, 1H), 7.28 (dd, *J* = 2.2, 8.6 Hz, 1H), 7.15 (d, *J* = 2.0 Hz, 1H), 7.05 (d, *J* = 2.0 Hz, 1H), 6.72 (d, *J* = 8.8 Hz, 1H), 6.46 (bs, 1H), 5.13 (bs, 2H), 3.50 (d, *J* = 1.0 Hz, 2H), 2.94 (s, 6H), 1.10 - 1.06 (m, 2H), 0.96 - 0.91 (m, 2H)

Compound 12: 2-Amino-5-(1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[2,3-*b*]pyridin]-5'-yl)-*N,N*-dimethylbenzamide



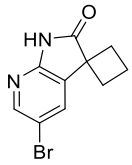
12

Step 1: Spiro[cyclobutane-1,3'-pyrrolo[2,3-*b*]pyridin]-2'(1'*H*)-one



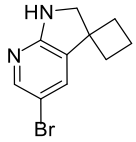
n-BuLi (1.6N in hexanes, 9.3 mL, 14.9 mmol) was added dropwise to a solution of 1,3-dihydro-2*H*-pyrrolo[2,3-*b*]pyridin-2-one (1 g, 7.50 mmol) in dry THF (50 mL) at -78 °C. TMEDA (2.2 mL, 15 mmol) was then added and the mixture stirred for 1h at -78 °C. 1,3-Dibromopropane (0.76 mL, 7.5 mmol) was added in one portion and the mixture allowed to warm up to RT overnight. The mixture was quenched with saturated aqueous ammonium chloride (100 mL) then extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4) and evaporated. The residue was purified by chromatography on silica (eluting with 30-100% ethyl acetate in cyclohexane) to afford the title compound (255 mg, 20%). LCMS (ESI) *m/z* calcd for $C_{10}H_{10}N_2O$ $[M+H]^+$: 175.1. Found 175.1.

Step 2: 5'-Bromospiro[cyclobutane-1,3'-pyrrolo[2,3-*b*]pyridin]-2'(1'*H*)-one



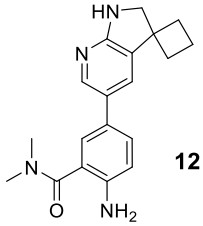
NBS (338 mg, 1.90 mmol) was added portionwise to a solution of spiro[cyclobutane-1,3'-pyrrolo[2,3-*b*]pyridin]-2'(1'*H*)-one (304 mg, 1.90 mmol) in dry DMF (3 mL). The reaction mixture was stirred for 18h at RT. Further NBS (85 mg, 0.475 mmol) was added and the mixture stirred for 4h. The mixture was partitioned between ethyl acetate and water (30 mL). The aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. The residue was suspended in 2-propanol (10 mL) and heated under microwave irradiation at 150 °C for 5 min. The slurry was cooled to RT and filtered to give the title compound (296 mg, 65%) as a pale pink solid. LCMS (ESI) *m/z* calcd for $C_{10}H_9BrN_2O$ $[M+H]^+$: 253.0/255.0. Found 253.0/255.0.

Step 3: 5'-Bromo-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[2,3-*b*]pyridine]



Borane-THF complex (1.0M in THF, 5 mL, 5.0 mmol) was added to a suspension of 5'-bromospiro[cyclobutane-1,3'-pyrrolo[2,3-*b*]pyridin]-2'(1'*H*)-one (271 mg, 1.07 mmol) in THF (5 mL). The reaction mixture was stirred at RT overnight and was quenched with methanol (1 mL) and HCl (1.25N aq., 2 mL). The mixture was heated under reflux for 2h and concentrated *in vacuo*. The residue was purified by chromatography on silica (eluting with 0-5% 2M NH_3-methanol in dichloromethane) to afford the title compound (158 mg, 58%). LCMS (ESI) *m/z* calcd for $C_{10}H_{11}BrN_4$ $[M+H]^+$: 239.0/241.0. Found 239.0/241.0.

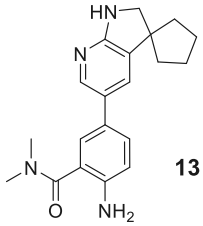
Step 4: 2-Amino-5-(1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[2,3-*b*]pyridin]-5'-yl)-*N,N*-dimethylbenzamide



12

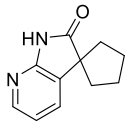
A mixture of 5'-bromo-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[2,3-b]pyridine] (79 mg, 0.33 mmol), 2-amino-*N,N*-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (96 mg, 0.33 mmol), XPhosPdG2 (16 mg, 0.02 mmol), XPhos (9 mg, 0.02 mmol), K_3PO_4 (140 mg, 0.66 mmol) in dioxane (1.7 mL) and water (0.3 mL) was degassed and purged with argon under sonication. The mixture was heated at 100 °C for 12 h. The cooled mixture was diluted with methanol and loaded onto an SCX-2 cartridge. The cartridge was washed with methanol and the product was eluted with 2M NH_3 in methanol. The product fractions were concentrated *in vacuo* and were further purified by reverse phase chromatography to give the product as an off-white solid (70 mg, 66%). LCMS (ESI) *m/z* calcd for $C_{19}H_{20}N_4O$ $[M+H]^+$: 323.2. Found 323.2. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (d, *J* = 2.0 Hz, 1H), 7.70 (d, *J* = 2.0 Hz, 1H), 7.35 (dd, *J* = 2.2, 8.6 Hz, 1H), 7.23 (d, *J* = 2.4 Hz, 1H), 6.76 (d, *J* = 8.3 Hz, 1H), 6.31 (bs, 1H), 5.15 (bs, 2H), 3.55 (d, *J* = 1.0 Hz, 2H), 2.96 (s, 6H), 2.38 - 2.28 (m, 2H), 2.18 - 2.09 (m, 2H), 2.07 - 1.89 (m, 2H)

Compound 13: 2-Amino-5-(1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridin]-5'-yl)-*N,N*-dimethylbenzamide



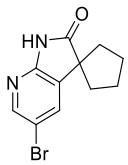
13

Step 1: Spiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridin]-2'(1'H)-one



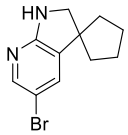
To a slurry of 7-azaoxindole (507 mg, 3.8 mmol) in THF (25 mL) at -78 °C, was added dropwise *n*-BuLi (2.5N hexanes, 3.0 mL, 7.86 mmol) and TMEDA (1.1 mL, 7.6 mmol). The reaction mixture was stirred at -78 °C for 1h, then was treated with 1,4-diiodobutane (0.5 mL, 3.8 mmol). The reaction mixture was allowed to warm to RT and stirred at RT for 18 h. The reaction was quenched with saturated aqueous ammonium chloride and the product extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on silica (eluting 30-100% ethyl acetate in cyclohexane), to afford the title compound (137 mg, 19%) as a colourless solid. LCMS (ESI) *m/z* calcd for $C_{11}H_{12}N_2O$ $[M+H]^+$: 189.1. Found 189.1.

Step 2: 5'-Bromospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridin]-2'(1'*H*)-one



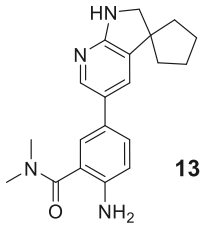
A solution of spiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridin]-2'(1'*H*)-one (137 mg, 0.73 mmol) and NBS (130 mg, 0.73 mmol) in DMF (1.5 mL) was stirred at RT for 16h. The reaction mixture was diluted with water and the product extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on silica (eluting with 20-100% ethyl acetate in cyclohexane), to afford the title compound (149 mg, 76%) as a colourless solid. LCMS (ESI) *m/z* calcd for $C_{11}H_{11}BrN_2O$ $[M+H]^+$: 267.0/269.0. Found 267.0/269.1.

Step 3: 5'-Bromo-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]



To a solution of 5'-bromospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridin]-2'(1'*H*)-one (149 mg, 0.56 mmol) in THF (1 mL) was added borane (1N in THF, 2 mL, 2 mmol). The reaction mixture was stirred at RT for 16h. A further portion of borane (1N in THF, 2 mL, 2 mmol) was added, and the reaction mixture was stirred at RT for 16h. The reaction was quenched with methanol and concentrated. The residue was diluted in HCl (1.25 N, 20 mL) and refluxed for 2h. The mixture was then stirred at RT for 2 days. The mixture was concentrated, and the residue was purified by chromatography on silica (eluting with 1-10% 2M NH_3-methanol in dichloromethane), to afford the title compound (59 mg, 42%) as a white solid. LCMS (ESI) *m/z* calcd for $C_{11}H_{13}BrN_2$ $[M+H]^+$: 253.0/255.0. Found 253.1/255.1.

Step 4: 2-Amino-5-(1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridin]-5'-yl)-*N,N*-dimethylbenzamide

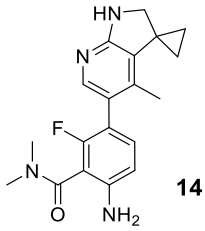


13

A degassed mixture of 5'-bromo-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine] (59 mg, 0.23 mmol), 2-amino-*N,N*-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (68 mg, 0.23 mmol), XPhos (7 mg, 0.014 mmol), XPhosPdG2 (11 mg, 0.014 mmol) and K_3PO_4 (99 mg, 0.47 mmol) in 1,4-dioxane (1.7 mL) and water (0.3 mL) was heated in a sealed tube at 100 ^oC for 16h. The cooled mixture was concentrated and then passed through a SCX-2 cartridge. The cartridge was first washed with methanol followed by 2M NH_3-methanol to elute the product. The resulting brown gum was purified by reverse phase chromatography (C18) to afford the title compound (35 mg, 45%) as a colourless solid. LCMS (ESI) *m/z* calcd for

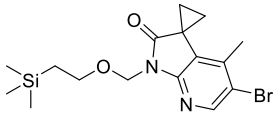
$C_{20}H_{24}N_4O$ $[M+H]^+$: 337.0. Found 337.2. ^1H NMR (400 MHz, DMSO-d_6) δ 7.84 (d, *J* = 2.0 Hz, 1H), 7.44 (d, *J* = 2.0 Hz, 1H), 7.31(dd, *J* = 2.2, 8.6 Hz, 1H), 7.18, (d, *J* = 2.0 Hz, 1H), 6.74 (d, *J* = 8.8 Hz, 1H), 6.30 (bs, 1H), 5.10 (bs, 2H), 3.28 (d, *J* = 1.0 Hz, 2H), 2.95 (s, 6H), 1.87- 1.66 (m, 8H)

Compound 14: 6-Amino-2-fluoro-*N,N*-dimethyl-3-(4'-methyl-1',2'-dihydrospiro[cyclopropane-1,3'-pyrrolo[2,3-b]pyridin]-5'-yl)benzamide



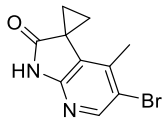
14

Step 1: 5'-bromo-4'-methyl-1'-((2-(trimethylsilyl)ethoxy)methyl)spiro[cyclopropane-1,3'-pyrrolo[2,3-b]pyridin]-2'(1'H)-one



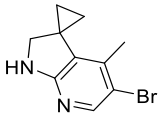
To a mixture of 5-bromo-4-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1,3-dihydro-2*H*-pyrrolo[2,3-*b*]pyridin-2-one (1.07 g, 3 mmol) and Cs_2CO_3 (2.4 g, 7.5 mmol) in DMF (15 mL) was added 1-chloro-2-iodoethane (691 mg, 3.6 mmol) and the mixture was stirred for 24 h. The mixture was diluted with water (150 mL) and extracted with ethyl acetate (2 x 30 mL). The combined extracts were washed with brine, dried (Na_2SO_4) and evaporated. The crude product was purified on silica using 10-20% ethyl acetate in cyclohexane as eluant to afford the product 5'-bromo-4'-methyl-1'-((2-(trimethylsilyl)ethoxy)methyl)spiro[cyclopropane-1,3'-pyrrolo[2,3-b]pyridin]-2'(1'H)-one as a pink solid (878 mg, 76%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.29 (1H, s), 5.30 - 5.30 (2H, m), 3.71 - 3.66 (2H, m), 2.21 (3H, s), 1.95 - 1.90 (2H, m), 1.80 - 1.75 (2H, m), 1.01 - 0.96 (2H, m), 0.00 (9H, s)

Step 2: 5'-bromo-4'-methylspiro[cyclopropane-1,3'-pyrrolo[2,3-b]pyridin]-2'(1'H)-one



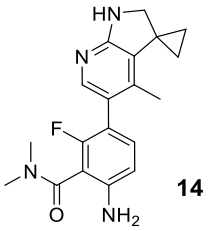
5'-bromo-4'-methyl-1'-((2-(trimethylsilyl)ethoxy)methyl)spiro[cyclopropane-1,3'-pyrrolo[2,3-*b*]pyridin]-2'(1'*H*)-one (878 mg, 2.28 mmol) was dissolved in dichloromethane (20 mL), TFA was added and the solution was stirred for 2h and the solvent was removed *in vacuo*. The residue was dissolved in dichloromethane and washed with $NaHCO_3$ (satd. aq. soln), brine, dried and evaporated. The residue was dissolved in 2N methanolic ammonia (50 mL) and the solution stirred at RT overnight. The solvent was removed *in vacuo* and the residue was purified by chromatography on silica using 1-5% methanol in dichloromethane as eluant to give the product as a beige solid (567 mg, 98%). LCMS (ESI) *m/z* calcd for $C_{10}H_9BrN_2O$ $[M+H]^+$: 253.0/255.0. Found 253.1/255.1. ^1H NMR (400 MHz, DMSO) δ 10.48 (s, 1H), 8.17 (s, 1H), 2.13 (s, 3H), 1.99 (ddd, *J*=4.0, 4.0, 4.0 Hz, 2H), 1.45 (ddd, *J*=3.9, 3.9, 3.9 Hz, 2H).

Step 3: 5'-bromo-4'-methyl-1',2'-dihydrospiro[cyclopropane-1,3'-pyrrolo[2,3-b]pyridine]



5'-bromo-4'-methylspiro[cyclopropane-1,3'-pyrrolo[2,3-b]pyridin]-2'(1'H)-one (313 mg, 1.24 mmol) was dissolved in dichloromethane (7 mL) and the solution was cooled in ice-water. DIBAL (6.2 mL, 6.2 mmol, 1M dichloromethane) was added dropwise and the solution was stirred for 30 min at 0 °C then warmed to RT. The mixture was quenched by addition of Rochelle's salt and the mixture was stirred for 1 h. The mixture was diluted with dichloromethane and the product extracted with additional dichloromethane. The combined dichloromethane extracts were washed with brine, dried (Na_2SO_4) and evaporated. The crude residue was purified on silica eluting with 0-3% methanol in dichloromethane to give the product as a white solid (183 mg, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) 7.85 (1H, s), 4.46 (1H, s), 3.53 (2H, d, *J*=1.6 Hz), 2.05 (3H, s), 1.47 - 1.43 (2H, m), 0.89 - 0.84 (2H, m).

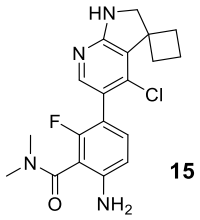
Step 4: 6-Amino-2-fluoro-*N,N*-dimethyl-3-(4'-methyl-1',2'-dihydrospiro[cyclopropane-1,3'-pyrrolo[2,3-*b*]pyridin]-5'-yl)benzamide



14

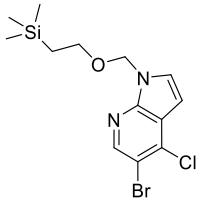
A mixture of 5'-bromo-4'-methyl-1',2'-dihydrospiro[cyclopropane-1,3'-pyrrolo[2,3-*b*]pyridine] (120 mg, 0.5 mmol), 6-amino-2-fluoro-*N,N*-dimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (185 mg, 0.6 mmol), XPhosPdG2 (24 mg, 0.03 mmol), XPhos (14 mg, 0.03 mmol), K_3PO_4 (212 mg, 1.0 mmol) in dioxane (1.8 mL) and water (0.3 mL) were placed in a tube and degassed under nitrogen with sonication. The reaction mixture was sealed and heated under microwave irradiation at 100 °C for 1 h. The reaction mixture was cooled and diluted with ethyl acetate. The ethyl acetate layer was washed with water, brine, dried (Na_2SO_4) and evaporated. The residue was purified on C_{18} silica using a gradient of water:acetonitrile (0.1% NH_3 modifier) as eluant. The combined product fractions were concentrated to give the product (78 mg) which was further purified on silica using 0-3% methanol in dichloromethane as eluant to afford the product as a white solid (54 mg, 32%). LCMS (ESI) *m/z* calcd for $C_{19}H_{21}FN_4O$ $[M+H]^+$: 341.2. Found 341.2. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.39 (s, 1H), 6.89 (t, *J* = 8.5 Hz, 1H), 6.54 (d, *J* = 8.2 Hz, 1H), 6.42 (s, 1H), 5.31 (s, 2H), 3.40 (s, 2H), 2.98 (s, 3H), 2.87 (s, 3H), 1.75 (s, 3H), 1.45-1.37 (m, 2H), 0.85-0.77 (m, 2H).

Compound 15: 6-Amino-3-(4'-chloro-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[2,3-b]pyridin]-5'-yl)-2-fluoro-*N,N*-dimethylbenzamide



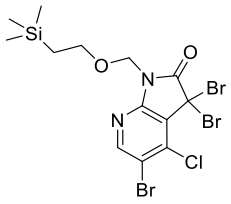
15

Step 1: 5-Bromo-4-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridine



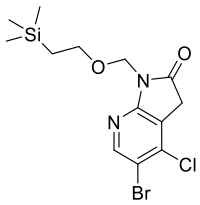
To a solution of 5-bromo-4-chloro-1*H*-pyrrolo[2,3-*b*]pyridine (50 g, 216 mmol) in dry DMF (500 mL) at 0 °C, was added sodium hydride (60% in oil, 17.3 g, 432 mmol). The reaction mixture was stirred at RT for 45 min, then cooled to -78 °C. 2-(Trimethylsilyl)ethoxymethyl chloride (54 g, 324 mmol) was added, and the mixture was stirred at RT for 16h. The reaction mixture was poured into ice water (200 mL), and then extracted with ethyl acetate (3 x 300 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on silica (eluting with 0-10% ethyl acetate in petroleum ether) to afford the title compound (70 g, 90%) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.44 (d, *J* = 3.6 Hz, 1H), 6.66 (d, *J* = 3.6 Hz, 1H), 5.69 (s, 2H), 3.60-3.56 (m, 2H), 0.98-0.94 (m, 2H), 0.00 (s, 9H).

Step 2: 3,3,5-Tribromo-4-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1,3-dihydro-2*H*-pyrrolo[2,3-*b*]pyridin-2-one



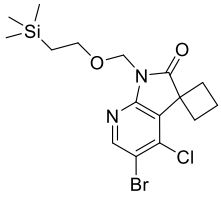
A mixture of 5-bromo-4-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridine (70.0 g, 193.5 mmol) and NBS (103.3g, 580 mmol) in *tert*-butyl alcohol (1.5 L) was stirred at RT for 3 h. The reaction mixture was concentrated *in vacuo* to give the title compound (67g, 65%) as a yellow oil. LCMS (ESI) *m/z* calcd for $C_{13}H_{16}Br_3ClN_2O_2Si$ $[M+H]^+$: 534.8. Found 533.0.

Step 3: 5-Bromo-4-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1,3-dihydro-2*H*-pyrrolo[2,3-*b*]pyridin-2-one



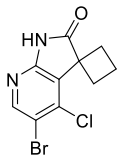
A mixture of 3,3,5-tribromo-4-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1,3-dihydro-2*H*-pyrrolo[2,3-*b*]pyridin-2-one (55 g, 102.7 mmol) and zinc powder (137.5 g, 2.1 mol) in THF (1 L) and sat. ammonium chloride (1 L) was stirred at RT for 20 min. The reaction mixture was filtered, and the filtrate was poured into water (500 mL) and extracted with ethyl acetate (3x1 L). The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on silica (eluting with 0-5% ethyl acetate in petroleum ether) to afford the title compound (30 g, 77%) as a brown solid. ^{1}H NMR ($CDCl_3$) δ 8.39 (s, 1H), 5.22 (s, 2H), 3.70 - 3.65 (m, 4H), 1.00 - 0.95 (m, 2H), 0.00 (s, 9H).

Step 4: 5'-Bromo-4'-chloro-1'-((2-(trimethylsilyl)ethoxy)methyl)spiro[cyclobutane-1,3'-pyrrolo[2,3-*b*]pyridin]-2'(1'*H*)-one



To a solution of 5-bromo-4-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1,3-dihydro-2*H*-pyrrolo[2,3-*b*]pyridin-2-one (250 mg, 0.66 mmol) in DMF (5 mL) was added lithium hydride (20 mg, 2.47 mmol). The mixture was stirred at RT for 15 mins, then cooled to 0 °C. 1,3-diiodopropane (0.15 mL, 1.32 mmol) was added and the mixture stirred at RT for 16h. The mixture was quenched cautiously with water, then the solvent removed *in vacuo*. The residue was partitioned between ethyl acetate and saturated aqueous ammonium chloride and the aqueous layer was further extracted with ethyl acetate twice. The combined organic extracts were dried (sodium sulfate), filtered and the solvent removed *in vacuo*. The residue was purified by chromatography on silica (solvent gradient 0-10% ethyl acetate in cyclohexane) to afford the title compound (66 mg, 24%) as colourless oil.

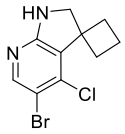
Step 5: 5'-bromo-4'-chlorospiro[cyclobutane-1,3'-pyrrolo[2,3-*b*]pyridin]-2'(1'*H*)-one



To a solution of 5'-bromo-4'-chloro-1'-((2-(trimethylsilyl)ethoxy)methyl)spiro[cyclobutane-1,3'-pyrrolo[2,3-*b*]pyridin]-2'(1'*H*)-one (752 mg, 1.8 mmol) in dichloromethane (8 mL) was added TFA (2 mL) and the mixture stirred at RT for 2 h. The solvent was removed *in vacuo* and the residue was basified with saturated aqueous sodium bicarbonate. The mixture was extracted with dichloromethane five times. The combined organic extracts were dried (sodium sulfate), filtered and the solvent removed *in vacuo*. The residue was dissolved in 2M ammonia in methanol (16 mL) stirred at RT for 16 h. The solvent was removed *in vacuo* and the residue was partitioned

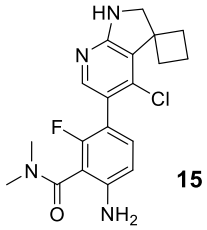
between ethyl acetate and water and the aqueous layer was further extracted with ethyl acetate twice. methanol was added to the combined organic extracts to dissolve the suspended material then the mixture was filtered, and the solvent removed *in vacuo*. The residue was purified by chromatography on silica (solvent gradient 0-3% methanol in dichloromethane) to afford the title compound (449 mg, 87%) as a cream solid. LCMS (ESI) *m/z* calcd for $C_{10}H_8BrClN_2O$ $[M+H]^+$: 287/289. Found 287/289.

Step 6: 5'-bromo-4'-chloro-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[2,3-*b*]pyridine]



To a solution of 5'-bromo-4'-chlorospiro[cyclobutane-1,3'-pyrrolo[2,3-*b*]pyridin]-2'(1'*H*)-one (449 mg, 1.56 mmol) in dichloromethane (10 mL) at 0 °C under nitrogen was added DIBAL(1M in dichloromethane, 7.74 mL, 7.74 mmol) dropwise. The mixture was stirred at 0 °C for 15 min, then allowed to RT and stirred for 5 h. The mixture was cooled to -78 °C and quenched by dropwise addition of water (1.2 mL), then allowed to RT and ethyl acetate (3.5 mL) added followed by saturated aqueous sodium bicarbonate. The mixture was stirred vigorously for 15 min. The mixture was filtered, dried (sodium sulfate) and the solvent removed *in vacuo*. The residue was purified by silica gel chromatography (0-3% methanol in dichloromethane) to afford the title compound (285 mg, 67%) as an off-white solid. LCMS (ESI) *m/z* calcd for $C_{10}H_{10}BrClN_2$ $[M+H]^+$: 273/275. Found 273/275.

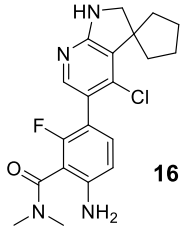
Step 7: 6-Amino-3-(4'-chloro-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[2,3-*b*]pyridin]-5'-yl)-2-fluoro-*N,N*-dimethylbenzamide



15

A mixture of 5'-bromo-4'-chloro-1',2'-dihydrospiro[cyclobutane-1,3'-pyrrolo[2,3-b]pyridine] (140 mg, 0.51 mmol), 6-amino-2-fluoro-*N,N*-dimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (188 mg, 0.61 mmol),), XPhosPdG2 (39 mg, 0.05 mmol), XPhos (27 mg, 0.056 mmol), K_3PO_4 (216 mg, 1.02 mmol) in dioxane (4 mL) and water (1 mL) were placed in a tube and degassed under argon. The reaction mixture was sealed and heated at 100 °C for 16 h. The reaction mixture was cooled and diluted with water then extracted with ethyl acetate. The combined organics were dried (Na_2SO_4) and evaporated. The residue was purified by silica gel chromatography using 0-5% methanol in ethyl acetate as eluant to afford the title compound (86 mg, 45%) as a white solid. LCMS (ESI) *m/z* calcd for $C_{19}H_{20}ClFN4O$ $[M+H]^+$: 375.1. Found 375.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.60 (s, 1H), 6.98 (t, *J* = 8.5 Hz, 1H), 6.85 (s, 1H), 6.56 (d, *J* = 8.4 Hz, 1H), 5.39 (s, 2H), 3.70 (s, 2H), 2.99 (s, 3H), 2.90 (s, 3H), 2.89-2.75 (m, 2H), 2.09-1.92 (m, 4H).

Compound 16: Synthesis of 6-amino-3-(4'-chloro-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridin]-5'-yl)-2-fluoro-*N,N*-dimethylbenzamide

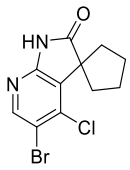


16

Step 1: 5'-bromo-4'-chloro-1'-((2-(trimethylsilyl)ethoxy)methyl)spiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridin]-2'(1'*H*)-one

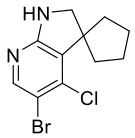
To a mixture of 5-bromo-4-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1,3-dihydro-2*H*-pyrrolo[2,3-*b*]pyridin-2-one (500 mg, 1.3 mmol) and Cs_2CO_3 (1.27 g, 3.9 mmol) in DMF (5 mL) was added 1,4-diiodobutane (410 mg, 1.3 mmol) and the mixture was stirred for 2 h. The mixture was diluted with water (150 mL) and extracted with ethyl acetate (2 x 30 mL). The combined extracts were washed with brine, dried (Na_2SO_4) and evaporated. The crude product was purified by silica gel chromatography using 0-20% ethyl acetate in cyclohexane as eluant to afford the title compound as a colourless oil (530 mg, 94%).

Step 2: 5'-Bromo-4'-chlorospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridin]-2'(1'*H*)-one



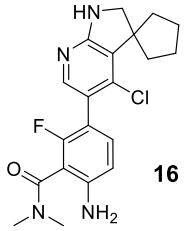
To a solution of 5'-bromo-4'-chloro-1'-((2-(trimethylsilyl)ethoxy)methyl)spiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridin]-2'(1'*H*)-one (530 mg, 1.2 mmol) in dichloromethane (1 mL) was added TFA (0.5 mL) and the mixture stirred at RT for 2 h. The solvent was removed *in vacuo* and the residue was basified with saturated aqueous sodium bicarbonate. The mixture was extracted with dichloromethane. The combined organic extracts were dried (sodium sulfate), filtered and the solvent removed *in vacuo*. The residue was dissolved in 2M ammonia in methanol (6 mL) stirred at RT for 68 h. The solvent was removed *in vacuo* and the residue was purified by chromatography by silica gel chromatography (0-5% methanol in dichloromethane) to afford the title compound (250 mg, 70%) as a white solid. LCMS (ESI) *m/z* calcd for $C_{11}H_{10}BrClN_2O$ $[M+H]^+$: 301/303. Found 301/303.

Step 3: 5'-Bromo-4'-chloro-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]



To a solution 5'-bromo-4'-chlorospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridin]-2'(1'*H*)-one (247 mg, 0.82 mmol) in dichloromethane (3 mL) at 0 °C under nitrogen was added DIBAL (1M in dichloromethane, 4 mL, 4 mmol) dropwise. The mixture was stirred at 0 °C for 15 mins, then allowed to warm to RT and stirred for 18 h. The mixture was quenched by addition of sat. aq. Rochelle's salt and stirred for 1 hour. The mixture was extracted with dichloromethane and the combined organic extracts were dried (sodium sulfate) and the solvent removed *in vacuo*. The residue was purified by chromatography by silica gel chromatography (0-5% methanol in dichloromethane) to afford the title compound (120 mg, 5%) as a white solid. LCMS (ESI) *m/z* calcd for $C_{11}H_{12}BrClN_2$ $[M+H]^+$: 287/289. Found 287/289.

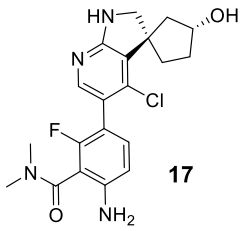
Step 4: 6-Amino-3-(4'-chloro-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridin]-5'-yl)-2-fluoro-*N,N*-dimethylbenzamide (G03054309)



16

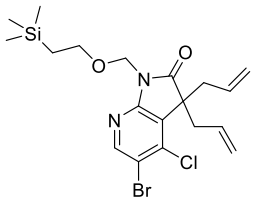
A mixture of 5'-bromo-4'-chloro-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine] (110 mg, 0.38 mmol), 6-amino-2-fluoro-*N,N*-dimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (170 mg, 0.50 mmol), XPhosPdG2 (16 mg, 0.023 mmol), XPhos (11 mg, 0.023 mmol), K_3PO_4 (81 mg, 0.38 mmol) in dioxane (3 mL) and water (0.6 mL) were placed in a tube and degassed under argon. The reaction mixture was sealed and heated at 90°C for 16 h. The reaction mixture was cooled, filtered and the filtrate was evaporated. The residue was purified by silica gel chromatography (0-10% methanol in dichloromethane) to afford the title compound (40 mg, 27%) as a white solid. LCMS (ESI) *m/z* calcd for $C_{20}H_{22}ClFN_4O$ $[M+H]^+$: 389.2. Found 389.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.60 (s, 1H), 6.97 (t, *J* = 8.5 Hz, 1H), 6.83 (brs, 1H), 6.55 (d, *J* = 8.4 Hz, 1H), 5.37 (s, 2H), 2.99 (s, 3H), 2.88 (s, 3H), 2.21-2.10 (m, 2H), 1.81-1.63 (m, 6H).

Compound 17: (±)-6-Amino-3-((1S*,3R*)-4'-chloro-3-hydroxy-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-b]pyridin]-5'-yl)-2-fluoro-*N,N*-dimethylbenzamide



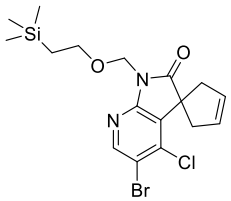
17

Step 1: 3,3-Diallyl-5-bromo-4-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1,3-dihydro-2*H*-pyrrolo[2,3-*b*]pyridin-2-one



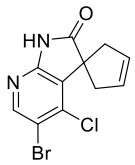
Allyl bromide (1.90 mL, 22.0 mmol) was added dropwise to a stirred mixture of 5-bromo-4-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1,3-dihydro-2*H*-pyrrolo[2,3-*b*]pyridin-2-one (3.78 g, 10.0 mmol) and cesium carbonate (8.15 g, 25.0 mmol) in DMF (30 mL). The reaction mixture was stirred at RT for 3h, then partitioned between ethyl acetate and water. The organic extract was washed with water (x 2), brine, dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on silica (eluting with 0-50% ethyl acetate in cyclohexane) to give the title compound (3.95 g, 86%) as a pale orange oil. LCMS (ESI) *m/z* calcd for $C_{19}H_{26}BrClN_2O_2Si$ $[M+H-CH_2CH_2OCH_2]^+$: 399.2. Found 399.0.

Step 2: 5'-Bromo-4'-chloro-1'-((2-(trimethylsilyl)ethoxy)methyl)spiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridin]-3-en-2'(1'*H*)-one



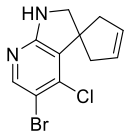
A solution of 3,3-diallyl-5-bromo-4-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1,3-dihydro-2*H*-pyrrolo[2,3-*b*]pyridin-2-one (3.95 g, 8.63 mmol) and Grubbs II catalyst (100 mg) in dichloromethane was stirred at RT for 18h. The mixture was concentrated. The residue was purified by chromatography by silica gel chromatography (0-20% ethyl acetate in cyclohexane) to give the title compound (3.78 g, quant) as a pale-yellow oil. LCMS (ESI) *m/z* calcd for $C_{17}H_{22}BrClN_2O_2Si$ $[M+H-CH_2CH_2OCH_2]^+$: 371.0. Found 371.1.

Step 3: 5'-Bromo-4'-chlorospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridin]-3-en-2'(1'*H*)-one



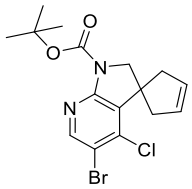
A solution of 5'-bromo-4'-chloro-1'-((2-(trimethylsilyl)ethoxy)methyl)spiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridin]-3-en-2'(1'*H*)-one (8.63 mmol) in TFA (12 mL) and dichloromethane (36 mL) was stirred at RT for 1 h. The reaction mixture was partitioned between dichloromethane and saturated aqueous sodium bicarbonate. The organic extract was concentrated and dissolved in 2M NH_3 in methanol. The mixture was stirred at RT for 18h and concentrated to afford the title compound (2.73 g, quant) as an off-white solid. LCMS (ESI) *m/z* calcd for $C_{11}H_8BrClN_2O$ $[M+H]^+$: 299.0. Found 299.1.

Step 4: 5'-Bromo-4'-chloro-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridin]-3-ene



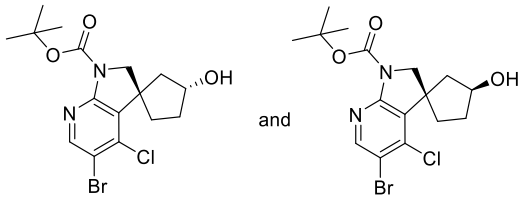
To a stirred suspension of 5'-bromo-4'-chlorospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridin]-3-en-2'(1'*H*)-one (1.35 g, 4.51 mmol) in dichloromethane (33 mL) at 0°C, was added DIBAL (1M in dichloromethane, 21.0 mL, 21.0 mmol) dropwise. The reaction mixture was stirred at 0 °C for 5 min, then allowed to warm up to RT, and stirred for 18h. The reaction was cooled to 0 °C, water (7 mL) was added carefully with vigorous stirring and the resulting gelatinous mixture was allowed to warm to RT. Ethyl acetate (~30 mL) and sodium bicarbonate (~7 g) were added. The resulting suspension was filtered through Celite and washed with dichloromethane/ethyl acetate. The residue was purified by chromatography by silica gel chromatography (0-100% ethyl acetate in cyclohexane) to give the title compound (0.91 g, 71%) as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 7.98 (s, 1H), 5.75 (s, 2H), 4.59 (br s, NH), 3.58 (s, 2H), 3.14 (m, 2H), 2.49 (m, 2H).

Step 5: tert-Butyl 5'-bromo-4'-chlorospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridin]-3-ene-1'(2'*H*)-carboxylate



Sodium hydride (60% in oil, 1.68 g, 42 mmol) was added portionwise to an ice-cooled solution of 5'-bromo-4'-chloro-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridin]-3-ene (10.0 g, 35 mmol) in THF (60 mL). After 10 min a solution of di-*tert*-butyl dicarbonate (11.46 g, 52.53 mmol) in THF (40 mL) was added and the mixture was stirred at RT for 6h. After cooling in an ice bath, aq. sat. ammonium chloride was added, and the mixture extracted twice with ethyl acetate. A 10% aq. citric acid solution was added, followed by further extraction with ethyl acetate. The organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. The residue was purified by chromatography by silica gel chromatography (0-12% ethyl acetate in cyclohexane) to afford the title compound (12.06 g, 89%) as a pale-yellow solid. LCMS (ESI) *m/z* calcd for $C_{16}H_{18}BrClN_2O_2$ $[M\text{-}^tBu+2H]^+$: 329/331/333. Found 329/331/333.

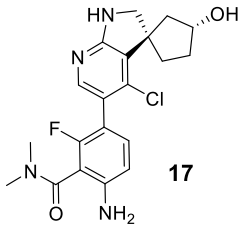
Step 6: (±)-tert-Butyl (1*R**,3*R**)-5'-bromo-4'-chloro-3-hydroxyspiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]-1'(2'H)-carboxylate and (±)-tert-butyl *(1R*,3S**)-5'-bromo-4'-chloro-3-hydroxyspiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]-1'(2'*H*)-carboxylate



Borane dimethylsulfide complex (1 mL, 10.53 mmol) was added over 5 min to an ice-cooled solution of *tert*-butyl 5'-bromo-4'-chlorospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridin]-3-ene-1'(2'*H*)-carboxylate (2.8 g, 7.26 mmol) in THF (30 mL). The mixture was stirred at RT for 1h,

then re-cooled in an ice bath. A further portion of borane dimethylsulfide complex (0.15 mL, 1.58 mmol) was added. The mixture was stirred at RT for 20 min, then re-cooled in an ice bath. An aqueous solution of sodium hydroxide (1N, 10.7 mL, 10.7 mmol) was slowly added. A hydrogen peroxide (30%, 2.14 mL, 20.93 mmol) was added. The mixture stirred at RT for 18 h. Ethyl acetate and aq. sat. ammonium chloride were added. The aqueous phase was extracted with ethyl acetate and the combined organic extracts were washed with 10% aq. sodium metabisulfite, then brine, dried ($MgSO_4$) and evaporated. The residue was purified by chromatography on silica gel (0-20% ethyl acetate in cyclohexane) to afford (±)-*tert*-butyl (1*R*,*3*S**)-5'-bromo-4'-chloro-3-hydroxyspiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]-1'(2'*H*)-carboxylate (1.71g, 58%) and (±)-*tert*-butyl (1*R*,3R**)-5'-bromo-4'-chloro-3-hydroxyspiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]-1'(2'*H*)-carboxylate (0.52g, 18%). LCMS (ESI) *m/z* calcd for $C_{16}H_{20}BrClN_2O_3$ $[M-{}^{t}Bu+2H]^+$: 347/349/351. Found 347/349/351.

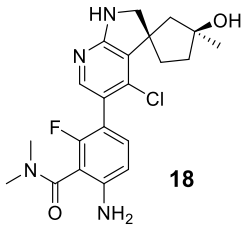
Step 7: (±)-6-Amino-3-((*1R*,3S**)-4'-chloro-3-hydroxy-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridin]-5'-yl)-2-fluoro-*N,N*-dimethylbenzamide



17

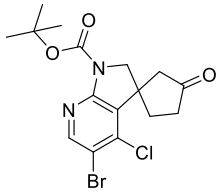
A mixture of (±)-tert-butyl (1R*,3S*)-5-bromo-4-chloro-3'-hydroxy-spiro[2H-pyrrolo[2,3-b]pyridine-3,1'-cyclopentane]-1-carboxylate (222 mg, 0.550 mmol), 6-amino-2-fluoro-N,N-dimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (271 mg, 0.880 mmol), XPhos (26 mg, 0.050 mmol) XPhosPd G2 (43 mg, 0.050 mmol) and potassium phosphate tribasic (236 mg, 1.1 mmol) in 1,4-dioxane (3 mL) was added to a microwave tube. The reaction tube was evacuated and purged with argon. The sealed tube was heated at 80 °C for 2h. The mixture was passed through a SCX cartridge and the products eluted with 2N NH_3 in MeOH. The mixture was then concentrated. The residue was treated with TFA (0.74 mL, 9.61 mmol) for 12h. The mixture was then loaded onto a SCX cartridge (10g). The cartridge was washed with MeOH. The product then eluted with 2N NH_3 in MeOH and concentrated. The crude product was further purified by silica gel chromatography using 0-10% 2N NH_3 in MeOH in DCM as eluant. The product fractions were concentrated, re-dissolved in EtOAc and allowed to crystallize. The white solid was removed by filtration and dried in vacuo (40 mg, 18%). LCMS (ESI) *m/z* calcd for C20H22ClFN4O2 $[M+H]^+$: 405.1. Found 405.2. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.59 (s, 1H), 6.96 (t, *J* = 8.5 Hz, 1H), 6.79 (s, 1H), 6.54 (d, *J* = 8.4 Hz, 1H), 5.38 (s, 2H), 4.64 (d, *J* = 3.2 Hz, 1H), 3.59 (d, *J* = 9.5 Hz, 1H), 3.42 (d, *J* = 9.4 Hz, 1H), 3.17 (d, *J* = 5.2 Hz, 1H), 2.99 (s, 3H), 2.88 (s, 3H), 2.29 (td, *J* = 13.0, 5.7 Hz, 1H), 2.19-2.06 (m, 1H), 2.05-1.94 (m, 1H), 1.90-1.79 (m, 1H), 1.71 (d, *J* = 14.6 Hz, 1H), 1.70-1.59 (m, 1H).

Compound 18: (±)-6-Amino-3-((1*R,3*S**)-4'-chloro-3-hydroxy-3-methyl-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridin]-5'-yl)-2-fluoro-*N,N*-dimethylbenzamide**



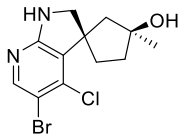
18

Step 1: tert-Butyl 5'-bromo-4'-chloro-3-oxospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]-1'(2'*H*)-carboxylate



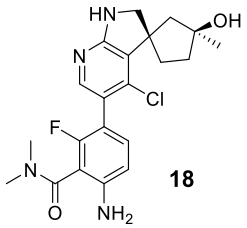
Dess-Martin periodinane (832 mg, 1.96 mmol) was added to a solution of (±)-*tert*-butyl (1*R*,*3*R**)-5'-bromo-4'-chloro-3-hydroxyspiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]-1'(2'*H*)-carboxylate and (±)-*tert*-butyl (1*R*,*3*S**)-5'-bromo-4'-chloro-3-hydroxyspiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]-1'(2'*H*)-carboxylate (660 mg, 1.63 mmol) in dichloromethane (9 mL). The mixture was stirred at RT for 18h, and then diluted with dichloromethane and washed with water. The aqueous phase was extracted with dichloromethane and the combined organic extracts were dried ($MgSO_4$) and evaporated to afford the title compound (0.7g, 100%) as a white solid. LCMS (ESI) *m/z* calcd for $C_{16}H_{18}BrClN_2O_3$ $[M+Na]^+$: 423/425. Found 423/425.

Step 2: 5'-Bromo-4'-chloro-3-methyl-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridin]-3-ol



To a solution of *tert*-butyl 5'-bromo-4'-chloro-3-oxospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]-1'(2'*H*)-carboxylate (274 mg, 0.68 mmol) in THF (3 mL) at -50 °C was added methylmagnesium bromide (3M in Et_2O, 0.23 mL, 0.69 mmol). The reaction mixture was stirred at RT for 30 min., then was quenched by addition of saturated aqueous ammonium chloride (5 mL). The mixture was extracted with ethyl acetate. The organic extracts were dried (Na_2SO_4) and evaporated. The residue was purified by chromatography on silica gel (eluting with 0-30% ethyl acetate in cyclohexane). The resulting residue was dissolved in dichloromethane, and TFA (0.46 mL) was added. The resulting solution was stirred at RT for 30 min, then was passed through an SCX-2 cartridge (washing with methanol) then the product was eluted with 2M NH_3 in methanol. Product fractions were pooled and concentrated *in vacuo*. The resulting residue was purified by chromatography on silica (eluting with 0-50% ethyl acetate in cyclohexane) to give the title compound (65 mg, 30%) as a solid. LCMS (ESI) *m/z* calcd for $C_{12}H_{14}BrClN_2O$ $[M+H]^+$: 317/319/321. Found 317/319/321.

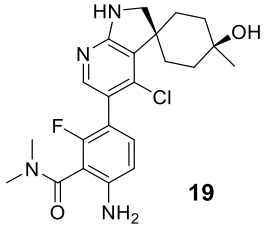
Step 3: (±)-6-Amino-3-((1*R**,3*S**)-4'-chloro-3-hydroxy-3-methyl-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridin]-5'-yl)-2-fluoro-*N,N*-dimethylbenzamide



18

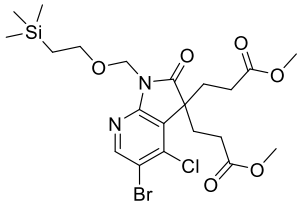
To a mixture of 5'-bromo-4'-chloro-3-methyl-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridin]-3-ol (60 mg, 0.188 mmol), XPhosPdG2 (9 mg, 0.011 mmol), XPhos (5 mg, 0.011 mmol) and 6-amino-2-fluoro-*N,N*-dimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (116, 0.378 mmol) in 1,4-dioxane (2 mL) was added 1M potassium phosphate (0.38 mL, 0.38 mmol). The mixture was degassed and heated in a sealed vial at 100 °C for 3 h. The cooled reaction mixture was loaded onto an SCX-2 cartridge. The cartridge was washed with methanol and the product eluted with 2M ammonia in methanol. Product fractions were pooled and concentrated *in vacuo.* The product was purified by silica chromatography (0-10% methanol/dichloromethane) and then further purified using reverse phase HPLC (0.5% ammonia in water/MeCN) to give the title compound (27 mg, 34% yield) as a colourless solid. LCMS (ESI) *m/z* calcd for $C_{21}H_{24}ClFN_4O_2$ $[M+H]^+$: 419.2. Found 419.2. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.58 (s, 1H), 6.96 (t, *J* = 8.5 Hz, 1H), 6.76 (s, 1H), 6.55 (d, *J*=8.3 Hz, 1H), 5.39 - 5.36 (m, 2H), 4.38 (s, 1H), 3.72 (d, *J* = 9.6 Hz, 1H), 3.42 (d, *J* = 9.6 Hz, 1H), 2.99 (s, 3H), 2.88 (s, 3H), 2.41 - 2.29 (m, 1H), 2.06 - 1.74 (m, 6H), 1.28 (d, *J* = 4.1 Hz, 3H).

Compound 19: 6-amino-3-((1s,4s)-4'-chloro-4-hydroxy-4-methyl-1',2'-dihydrospiro[cyclohexane-1,3'-pyrrolo[2,3-b]pyridin]-5'-yl)-2-fluoro-*N,N*-dimethylbenzamide



19

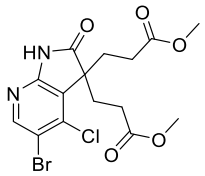
Step 1: Dimethyl 3,3'-(5-bromo-4-chloro-2-oxo-1-((2-(trimethylsilyl)ethoxy)methyl)-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridine-3,3-diyl)dipropionate



Potassium *tert*-butoxide (39 mg, 0.35 mmol) was added to a suspension of 5-bromo-4-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1,3-dihydro-2*H*-pyrrolo[2,3-*b*]pyridine-2-one (2.0 g, 5.29 mmol) in DMSO (8 mL). After stirring at RT for 10 min the mixture was heated to 45°C and methyl acrylate (1.48 mL, 16.4 mmol) was added dropwise over 10 min. The reaction mixture was stirred at 45°C for 1h then was partitioned between ethyl acetate and water. The aqueous phase was extracted with ethyl acetate. The combined organic extracts were washed with water, brine, dried (Na_2SO_4) and evaporated. The residue was purified by chromatography on silica (eluting

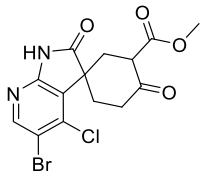
with 10-30% ethyl acetate in cyclohexane) to afford the title compound (2.56 g, 88%) as a pink gum. LCMS (ESI) *m/z* calcd for $C_{21}H_{30}BrClN_2O_6Si$ $[M+Na]^+$: 571/573/575. Found 571/573/575.

Step 2: Dimethyl 3,3'-(5-bromo-4-chloro-2-oxo-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridine-3,3-diyl)dipropionate



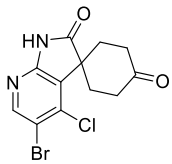
To an ice-cooled solution of dimethyl 3,3'-(5-bromo-4-chloro-2-oxo-1-((2-(trimethylsilyl)ethoxy)methyl)-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridine-3,3-diyl)dipropionate (2.56 g, 4.66 mmol) in dichloromethane (40 mL) was added TFA (12 mL). The mixture was stirred at RT for 1h then toluene was added and evaporated (2x). The residue was dissolved in methanol (10 mL), cooled in an ice bath and methanol.NH_3 (30 mL) was added. The mixture was stirred at RT for 1h, then concentrated aq. NH_3 (5 mL) was added. Stirring was continued for 1 h. The mixture was concentrated under reduced pressure and then partitioned between ethyl acetate and water. The aqueous phase was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. The residue was purified by chromatography on silica (eluting with 30-70% ethyl acetate in cyclohexane) to afford the title compound (1.5 g, 77%) as a colourless gum. LCMS (ESI) *m/z* calcd for $C_{15}H_{16}BrClN_2O_5$ $[M+Na]^+$: 441/443/445. Found 441/443/445.

Step 3: Methyl 5'-bromo-4'-chloro-2',4-dioxo-1',2'-dihydrospiro[cyclohexane-1,3'-pyrrolo[2,3-*b*]pyridine]-3-carboxylate



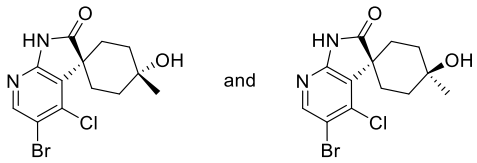
Sodium *tert*-butoxide (2M in THF, 4.45 mL, 8.9 mmol) was added over 20 min to a solution of dimethyl 3,3'-(5-bromo-4-chloro-2-oxo-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridine-3,3-diyl)dipropionate (1.21 g, 2.87 mmol) in DMSO (12 mL). The mixture was stirred at RT for 10 min. then was partitioned between ethyl acetate and aq. sat. ammonium chloride. The aqueous phase was extracted with ethyl acetate. The combined organic extracts were washed with water, brine, dried (Na_2SO_4) and evaporated. The residue was purified by chromatography on silica (eluting with 1-5% methanol in dichloromethane) to afford the title compound (0.943 g, 77%) as a light brown foam. LCMS (ESI) *m/z* calcd for $C_{14}H_{12}BrClN_2O_4$ $[M+H]^+$: 387.0/389.0/391.0. Found 387/389/391.

Step 4: 5'-Bromo-4'-chlorospiro[cyclohexane-1,3'-pyrrolo[2,3-*b*]pyridine]-2',4(1'*H*)-dione



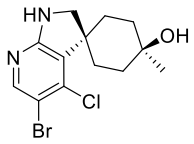
A mixture of methyl 5'-bromo-4'-chloro-2',4-dioxo-1',2'-dihydrospiro[cyclohexane-1,3'-pyrrolo[2,3-*b*]pyridine]-3-carboxylate (1.01 g, 2.61 mmol), HCl (3N aq., 50 mL), methanol (5 mL) and 1,4-dioxane (10 mL) was stirred at 100°C for 1h. After cooling to RT and concentration under reduced pressure, ethyl acetate was added. The mixture was neutralised by addition of sat. aq. sodium bicarbonate. The aqueous phase was extracted with ethyl acetate and the combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by chromatography on silica gel (eluting with 1-5% methanol in dichloromethane) to afford the title compound (0.655 g, 76%) as an off-white solid. LCMS (ESI) *m/z* calcd for $C_{12}H_{10}BrClN_2O_2$ $[M+H]^+$: 329/331/333. Found 329/331/333.

Step 5: (1*r*,4*r*)-5'-Bromo-4'-chloro-4-hydroxy-4-methylspiro[cyclohexane-1,3'-pyrrolo[2,3-*b*]pyridine]-2'(1'*H*)-one and (1*s*,4*s*)-5'-bromo-4'-chloro-4-hydroxy-4-methylspiro[cyclohexane-1,3'-pyrrolo[2,3-*b*]pyridine]-2'(1'*H*)-one



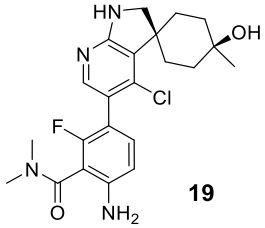
To an ice-cooled solution of 5'-bromo-4'-chlorospiro[cyclohexane-1,3'-pyrrolo[2,3-*b*]pyridine]-2',4(1'*H*)-dione (0.115 g, 0.35 mmol) in THF (3 mL) was added methylmagnesium chloride (3M in THF, 0.5 mL, 1.5 mmol) over 5 min. The mixture was stirred at 0 °C for 30 min then was quenched with aq. sat. ammonium chloride and extracted with ethyl acetate (2x). The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. The residue was purified by chromatography on silica gel (eluting with 2-10% methanol in dichloromethane) to afford (1*r*,4*r*)-5'-bromo-4'-chloro-4-hydroxy-4-methylspiro[cyclohexane-1,3'-pyrrolo[2,3-*b*]pyridine]-2'(1'*H*)-one (0.0319 g, 26%). LCMS (ESI) *m/z* calcd for $C_{13}H_{14}BrClN_2O_2$ $[M+H]^+$: 345/347/349. Found 345/347/349. Later fractions gave (1*s*,4*s*)-5'-bromo-4'-chloro-4-hydroxy-4-methylspiro[cyclohexane-1,3'-pyrrolo[2,3-*b*]pyridine]-2'(1'*H*)-one (0.054 g, 45%). LCMS (ESI) *m/z* calcd for $C_{13}H_{14}BrClN_2O_2$ $[M+H]^+$: 345/347/349. Found 345/347/349.

Step 6: (1s,4s)-5'-bromo-4'-chloro-4-methyl-1',2'-dihydrospiro[cyclohexane-1,3'-pyrrolo[2,3-b]pyridin]-4-ol



To an ice-cooled suspension of (1*r*,4*r*)-5'-bromo-4'-chloro-4-hydroxy-4-methylspiro[cyclohexane-1,3'-pyrrolo[2,3-*b*]pyridine]-2'(1'*H*)-one (0.0319 g, 0.092 mmol) in dichloromethane (2 mL) was added DIBAL (1.0 M in dichloromethane 0.65 mL, 0.65 mmol) over 5 min. The mixture was stirred in the ice bath for 10 min, then at RT for 16h. More DIBAL (1M in dichloromethane, 0.65 mL, 0.65 mmol) was added. The reaction mixture was stirred at RT for a further 3 h, then was cooled in an ice bath. Water (0.052 mL) was added cautiously, then 15% aqueous NaOH (0.05 mL) and water (0.13 mL) were added. The mixture was stirred at RT for 1h. Celite and Na_2SO_4 were added and the mixture was stirred for an additional 30 min. The mixture was then filtered and concentrated. The residue was purified by chromatography on silica gel (eluting with 2-6% methanol in dichloromethane) to afford the title compound (0.0157 g, 51%) as a colourless gum. LCMS (ESI) *m/z* calcd for $C_{13}H_{16}BrClN_2O$ $[M+H]^+$: 331/333/335. Found 331/333/335.

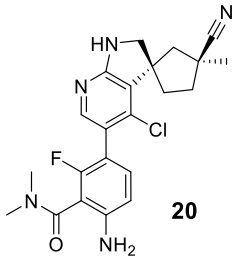
Step 7: 6-Amino-3-((1s,4s)-4'-chloro-4-hydroxy-4-methyl-1',2'-dihydrospiro[cyclohexane-1,3'-pyrrolo[2,3-*b*]pyridin]-5'-yl)-2-fluoro-*N,N*-dimethylbenzamide



19

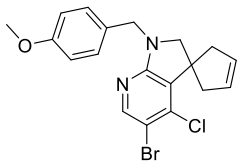
To a mixture of 5-bromo-4-chloro-1'-methyl-spiro[1,2-dihydropyrrolo[2,3-b]pyridine-3,4'-cyclohexane]-1'-ol (16 mg, 0.050 mmol), 6-amino-2-fluoro-*N,N*-dimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (22.3 mg,0.0700 mmol), XPhos Pd G2 (3.8 mg, 0 mmol) and XPhos (2.3 mg, 0 mmol) in 1,4-dioxane (0.5 mL) was added 1M potassium phosphate (0.1 mL, 0.1 mmol) . The mixture was degassed and heated in a sealed vial at 100 °C for 1 h. The cooled reaction mixture was diluted with dichloromethane (15 mL) and loaded on to a 10 g silica gel cartridge. The cartridge was washed with dichloromethane and the product was eluted with dichloromethane containing 10% 2M NH_3 in methanol. The product was further purified by reverse phase HPLC (0.5% TFA in water/ACN) to give 6-amino-3-(4-chloro-1'-hydroxy-1'-methyl-spiro[1,2-dihydropyrrolo[2,3-b]pyridine-3,4'-cyclohexane]-5-yl)-2-fluoro-*N,N*-dimethylbenzamide (10.4 mg, 0.0240 mmol, 49.8%). LCMS (ESI) *m/z* calcd for $C_{22}H_{26}ClFN_4O_2$ $[M+H]^+$: 433.2. Found 433.2. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.58 (s, 1H), 6.95 (t, *J* = 8.5 Hz, 1H), 6.90 (s, 1H), 6.54 (d, *J* = 8.4 Hz, 1H), 5.37 (brs, 2H), 4.40 (s, 1H), 3.43 (s, 2H), 2.99 (s, 3H), 2.88 (s, 3H), 2.32-2.20 (m, 2H), 1.59-1.48 (m, 6H), 1.21 (s, 3H).

Compound 20: (±)-**6-Amino-3-((1*R**,3*S**)-4'-chloro-3-cyano-3-methyl-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-b]pyridin]-5'-yl)-2-fluoro-*N,N*-dimethylbenzamide**



20

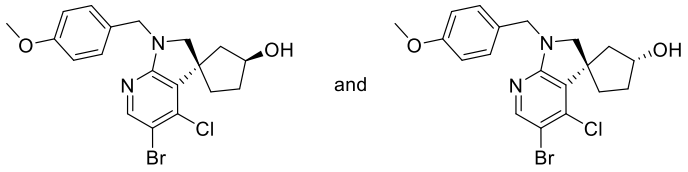
Step 1: 5'-Bromo-4'-chloro-1'-(4-methoxybenzyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridin]-3-ene



Sodium hydride (60% in mineral oil, 0.84 g, 21 mmol) was added portionwise to an ice-cooled solution of 5'-bromo-4'-chloro-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridin]-3-ene (5.0 g, 17.51 mmol) in THF (90 mL). After 10 min 1-(bromomethyl)-4-methoxybenzene (3.09 mL, 22.76 mmol) and 15-crown-5 (100 mg, 0.45 mmol) were added and the mixture was stirred

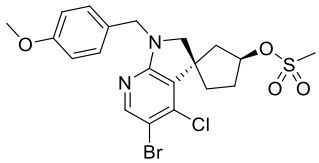
at RT for 3h. After cooling in an ice bath, aq. sat. ammonium chloride was added, and the mixture extracted twice with ethyl acetate. The organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. The residue was purified by chromatography on silica gel (eluting with 0-20% ethyl acetate in cyclohexane) to afford the title compound (5.06 g, 71%) as a colourless oil. LCMS (ESI) *m/z* calcd for $C_{19}H_{18}BrClN_2O$ $[M+H]^+$: 405.0/407.0/409.0. Found 405/407/409.

Step 2: (±)-(1*R**,3*S**)-5'-Bromo-4'-chloro-1'-(4-methoxybenzyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridin]-3-ol and (±)-(1*R**,3*R**)-5'-Bromo-4'-chloro-1'-(4-methoxybenzyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridin]-3-ol



Borane dimethylsulfide complex (1.6 mL,16.9 mmol) was added over 5 min to an ice-cooled solution of 5'-bromo-4'-chloro-1'-(4-methoxybenzyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridin]-3-ene (4.57 g, 11.26 mmol) in THF (60 mL). The mixture was stirred at RT for 45 min, then re-cooled in an ice bath. NaOH (1N aq., 16.9 mL, 16.9 mmol) was added, very cautiously at first, then hydrogen peroxide (30%, 3.34 mL, 29.5 mmol) was added, and the mixture stirred at RT for 16 h. Ethyl acetate and saturated aqueous ammonium chloride were added. The aqueous phase was extracted with more ethyl acetate and the combined organic extracts were washed with 10% aq. sodium metabisulfite, then brine, dried (Na_2SO_4) and evaporated. The residue was purified by chromatography on silica gel (eluting with 20-50% ethyl acetate in cyclohexane) to afford (±)-(1R*,3S*)-5'-bromo-4'-chloro-1'-(4-methoxybenzyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-b]pyridin]-3-ol (1.76 g, 37%). Later fractions gave a mixture of (±)-(1R*,3S*)-5'-bromo-4'-chloro-1'-(4-methoxybenzyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridin]-3-ol and (1*RS*,3*RS*)-5'-bromo-4'-chloro-1'-(4-methoxybenzyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridin]-3-ol (2.38 g, 50% yield). LCMS (ESI) *m/z* calcd for $C_{19}H_{20}BrClN_2O_2$ $[M+H]^+$: 423.0/425.0/427.0. Found 423/425/427.

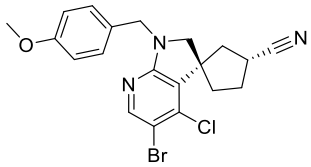
Step 3: (±)- (1R*,3S*)-5'-Bromo-4'-chloro-1'-(4-methoxybenzyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridin]-3-yl methanesulfonate



Methanesulfonyl chloride (0.53 mL, 6.89 mmol) was added over 5 min to a solution of (1*RS*,3*SR*)-5'-bromo-4'-chloro-1'-(4-methoxybenzyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridin]-3-ol (1.945 g, 4.59 mmol) and triethylamine (1.28 mL, 9.18 mmol) in dichloromethane (30 mL). The mixture was stirred at RT for 30 min then was diluted with dichloromethane and washed with aq. sodium bicarbonate. The aqueous phase was extracted with dichloromethane and the combined organic extracts were dried (Na_2SO_4) and evaporated. The residue was purified by chromatography on silica gel (eluting with 20-50% ethyl acetate in

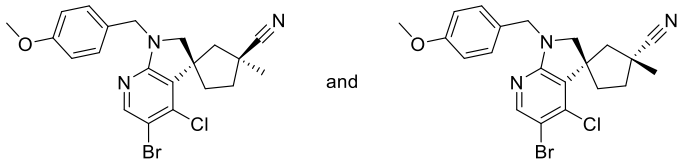
cyclohexane) to afford the title compound (2.192 g, 95%) as a colourless gum. LCMS (ESI) *m/z* calcd for $C_{20}H_{22}BrClN_2O_4S$ $[M+H]^+$: 501.0/503.0/505.0. Found 501/503/505.

Step 4: (±)-(1*R**,3*R**)-5'-Bromo-4'-chloro-1'-(4-methoxybenzyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]-3-carbonitrile



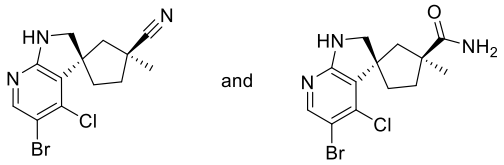
Sodium cyanide (1.07 g, 6.97 mmol) was added to solution of (±)-(1R*,3S*)-5'-bromo-4'-chloro-1'-(4-methoxybenzyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridin]-3-yl methanesulfonate (2.19 g, 4.37 mmol) and 15-crown-5 (0.26 mL, 1.31 mmol) in DMSO (35 mL). The mixture was stirred at 60°C for 1h, then at 80°C for 1 h. The cooled reaction mixture was partitioned between ethyl acetate and water. The aqueous phase was extracted with ethyl acetate. The combined organic extracts were washed with water, brine, dried (Na_2SO_4) and evaporated. The residue was purified by chromatography on silica gel (eluting with 10-40% ethyl acetate in cyclohexane) to afford the title compound as a colourless solid (1.425 g, 75%). LCMS (ESI) *m/z* calcd for $C_{20}H_{19}BrClN_3O$ $[M+H]^+$: 432.0/434.0/435.0. Found 432/434/436.

Step 5: (±)-(1*R**,3*S**)-5'-Bromo-4'-chloro-1'-(4-methoxybenzyl)-3-methyl-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]-3-carbonitrile and (±)-(1*R**,3*R**)-5'-bromo-4'-chloro-1'-(4-methoxybenzyl)-3-methyl-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]-3-carbonitrile



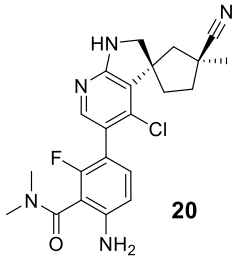
A solution of (±)-(1*R**,3*R**)-5'-bromo-4'-chloro-1'-(4-methoxybenzyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]-3-carbonitrile (0.40 g, 0.92 mmol) and iodomethane (0.075 mL, 1.2 mmol) in THF (5 mL) was cooled to -78 °C and lithium bis(trimethylsilyl)amide solution (1M in THF, 1.02 mL, 1.02 mmol) added over 5 min. The mixture was stirred at -78 °C for 30 min, then quenched with saturated aqueous ammonium chloride and allowed to warm to RT and extracted with ethyl acetate (2x). The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. The residue was purified by chromatography on silica gel (eluting with 10-25% ethyl acetate in cyclohexane) to afford (±)-(1R*,3S*)-5'-bromo-4'-chloro-1'-(4-methoxybenzyl)-3-methyl-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]-3-carbonitrile (0.338 g, 80%) as a colourless gum. LCMS (ESI) $[M+H]^+$ 446/448/450. Later fractions gave (±)-(1R*,3R*)-5'-bromo-4'-chloro-1'-(4-methoxybenzyl)-3-methyl-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]-3-carbonitrile (0.0846 g, 20%) as a colourless gum. LCMS (ESI) *m/z* calcd for $C_{21}H_{21}BrClN_3O$ $[M+H]^+$: 446.1/447.1/450.1. Found 446/448/450.

Step 6: (±)-(1*R**,3*S**)-5'-Bromo-4'-chloro-3-methyl-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]-3-carbonitrile and (±)-(1*R**,3*S**)-5'-bromo-4'-chloro-3-methyl-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]-3-carboxamide



A mixture of (±)-(1*R**,3*S**)-5'-bromo-4'-chloro-1'-(4-methoxybenzyl)-3-methyl-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]-3-carbonitrile (0.337 g, 0.75 mmol), anisole (0.5 mL) and TFA (5 mL) was stirred at 80 °C for 22h. The cooled reaction mixture was concentrated. Toluene was added and reaction mixture concentrated *in vacuo* to remove excess TFA. The residue was purified on SCX-2 cartridge (eluting with methanol then 1N NH_3 in methanol then a 1:1 mixture of 2N NH_3 in methanol and dichloromethane). The residue was purified by chromatography on silica gel (eluting with 2-10% methanol.NH_3 in dichloromethane) to afford (±)-(1*R**,3*S**)-5'-bromo-4'-chloro-3-methyl-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]-3-carbonitrile (0.132 g, 54%) as a colourless gum. LCMS (ESI) *m/z* calcd for $C_{13}H_{13}BrClN_3$ $[M+H]^+$: 326.0/328.0/330.0. Found 326/328/330. Later fractions gave (±)-(1*R**,3*S**)-5'-bromo-4'-chloro-3-methyl-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]-3-carboxamide (0.0886 g, 34%) as a white solid. LCMS (ESI) *m/z* calcd for $C_{13}H_{15}BrClN_3O$ $[M+H]^+$: 343.0/346.0/348.0. Found 344/346/348.

Step 7: (±)-6-Amino-3-((1*R**,3*S**)-4'-chloro-3-cyano-3-methyl-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridin]-5'-yl)-2-fluoro-*N,N*-dimethylbenzamide



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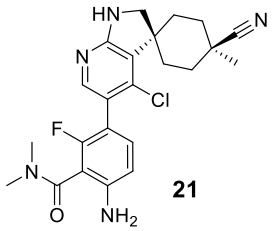
To a mixture of (±)-(1*R**,3*S**)-5'-Bromo-4'-chloro-3-methyl-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]-3-carbonitrile (24.5 mg, 0.08 mmol), XPhosPdG2 (5.9 mg, 0.010 mmol), XPhos (3.58 mg, 0.010 mmol) and 6-amino-2-fluoro-*N,N*-dimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (37 mg, 0.12 mmol) in 1,4-dioxane (0.5 mL) was added 1M potassium phosphate (0.15 mL, 0.15 mmol). The mixture was degassed and heated in a sealed vial at 100 °C for 1 h. The cooled reaction mixture was diluted with dichloromethane (20 mL) and loaded on to a 10 g silica cartridge. The cartridge was washed with dichloromethane containing 2% of 2M ammonia in methanol. The product was then eluted with dichloromethane containing 6% of 2M ammonia in methanol and evaporated. The product was then further purified using reverse phase HPLC (0.5% TFA in water/MeCN). The product was then loaded onto an SCX cartridge. The cartridge was washed with methanol and then eluted with a 1M ammonia in methanol solution to give the title compound (13.3 mg, 41.4%) as a colourless solid. LCMS (ESI) *m/z* calcd for $C_{22}H_{23}ClFN_5O$ $[M+H]^+$: 428.2. Found 428.0. ^1H NMR (400 MHz, DMSO-d_6, 80°C): δ 7.64 (s, 1H), 6.95 (t, *J* = 8.5 Hz, 1H), 6.67 (s, 1H), 6.57 (d, *J* = 8.4 Hz, 1H), 5.17 (brs, 2H), 3.66 (d, *J* = 9.6 Hz, 1H), 3.52 (d, *J* = 9.7 Hz, 1H), 2.99 (s, 3H), 2.88 (s, 3H), 2.56-2.50 (m, 1H), 2.37 (d, *J* = 13.8 Hz, 1H), 2.28-2.17 (m, 2H), 2.05-1.91 (m, 2H), 1.48 (s, 3H).

Compound 21: 6-amino-3-((1s,4s)-4'-chloro-4-cyano-4-methyl-1',2'-dihydrospiro[cyclohexane-1,3'-pyrrolo[2,3-b]pyridin]-5'-yl)-2-fluoro-*N,N*-dimethylbenzamide



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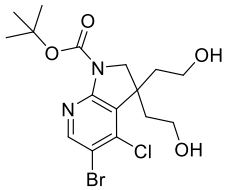
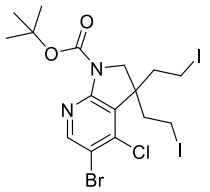
Step 1: *tert*-Butyl 5-bromo-4-chloro-3,3-bis(2-hydroxyethyl)-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate



Ozone was passed into a solution of *tert*-butyl 5'-bromo-4'-chlorospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]-3-ene-1'(2'*H*)-carboxylate (3.0 g, 7.78 mmol) in dichloromethane (20 mL) and methanol (65 mL) at -78°C for 1.5h. Air, then nitrogen, was passed through the solution. Sodium borohydride (1.47 g, 38.9 mmol) was then added portionwise over 10 min at -78°C. The reaction mixture was allowed to warm to -15°C when more sodium borohydride (0.3 g, 7.9 mmol) was added. Warming was continued to RT when more sodium borohydride (0.3 g, 7.9 mmol) was added. Stirring was continued for a further 30 min at RT. The reaction mixture was cooled in an ice bath and sat.aq. sodium carbonate (50 g in 55 mL water) was added. The mixture was stirred at RT for 10 min, then concentrated. The residual suspension was extracted with ethyl acetate (2x). The combined extracts were washed with water, brine, dried (Na_2SO_4) and evaporated. The residue was purified by chromatography on silica gel (eluting with 50-100% ethyl acetate in dichloromethane, then 100% methyl acetate) to afford the title compound (2.754g, 84%) as white solid. LCMS (ESI) *m/z* calcd for $C_{16}H_{22}BrClN_2O_4$ $[M+H-{}^tBu]^+$: 365/367/369. Found 365/367/369.

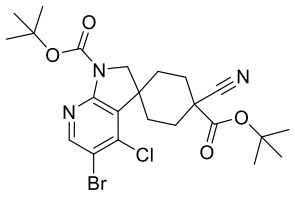
Step 2: *tert*-Butyl 5-bromo-4-chloro-3,3-bis(2-iodoethyl)-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate



Methanesulfonyl chloride (1.11 mL, 14.36 mmol) was added over 15 min to an ice-cooled mixture of *tert*-butyl 5-bromo-4-chloro-3,3-bis(2-hydroxyethyl)-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate (2.75 g, 6.53 mmol) and triethylamine (2.18 mL, 15.67 mmol) in dichloromethane (50 mL). The mixture was stirred at RT for 1.5 h then diluted with dichloromethane, washed successively with 1M HCl, water and aq. sodium bicarbonate, dried (Na_2SO_4), and concentrated to give crude *tert*-butyl 5-bromo-4-chloro-3,3-bis(2-methylsulfonyloxyethyl)-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate (4.02 g, quantitative) as a colourless foam. LCMS (ESI) $[M+Na]^+$ 599/601/603. The residue was dissolved in acetone (65 mL) and sodium iodide (4.89 g, 32.6 mmol) was added. The mixture

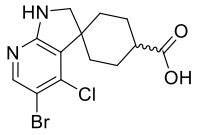
was heated under reflux for 3h. The cooled reaction mixture was filtered, the solid was washed with acetone and the filtrate concentrated. The residue was taken up in dichloromethane, washed successively with water, aq. sodium thiosulfate, water, dried (Na_2SO_4) and evaporated to give the title compound (4.16 g, 99%) as a colourless solid. LCMS (ESI) *m/z* calcd for $C_{16}H_{20}BrClI_2N_2O_2$ $[M+Na]^+$: 663/665/667. Found 663/665/667.

Step 3: Di-*tert*-butyl 5'-bromo-4'-chloro-4-cyanospiro[cyclohexane-1,3'-pyrrolo[2,3-*b*]pyridine]-1',4(2'*H*)-dicarboxylate



To a suspension of *tert*-butyl 5-bromo-4-chloro-3,3-bis(2-iodoethyl)-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate (1.544 g, 2.41 mmol) in DMF (15 mL) was added *tert*-butyl cyanoacetate (0.407 g, 2.89 mmol). Sodium hydride (60% in oil, 0.211 g, 5.3 mmol) was added portionwise over 15 min. The mixture was stirred at RT for 1 h then poured into ethyl acetate and aq. ammonium chloride. The aqueous phase was extracted with ethyl acetate. The combined extracts were washed with water, brine, dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on silica gel (eluting with 5-25% ethyl acetate in cyclohexane) to afford the title compound (1.054 g, 83%) as a colourless solid. LCMS (ESI) *m/z* calcd for $C_{23}H_{29}BrClN_3O_4$ $[M+Na]^+$: 548/550/552. Found 548/550/552.

Step 4: 5'-Bromo-4'-chloro-1',2'-dihydrospiro[cyclohexane-1,3'-pyrrolo[2,3-*b*]pyridine]-4-carboxylic acid

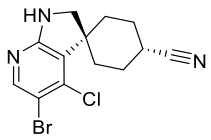


A mixture of di-*tert*-butyl 5'-bromo-4'-chloro-4-cyanospiro[cyclohexane-1,3'-pyrrolo[2,3-*b*]pyridine]-1',4(2'*H*)-dicarboxylate (0.974. g, 1.85 mmol), dioxane (4 mL) and HCl (6M aq., 14 mL) was stirred on a hotplate at 100°C for 20 min, then heated at 150°C under microwave irradiation for 1 h. The cooled reaction mixture was evaporated and the residue on SCX-2 cartridge (eluting sequentially with aq. MeCN, MeCN, 5% NH_3 in MeCN, 1M methanol.NH_3) to afford the title compound as a mixture of isomers (0.639 g, quantitative). LCMS (ESI) *m/z* calcd for $C_{13}H_{14}BrClN_2O_2$ $[M+Na]^+$: 345/347/349. Found 345/347/349.

Step 5: (1*r*,4*r*)-5'-Bromo-4'-chloro-1',2'-dihydrospiro[cyclohexane-1,3'-pyrrolo[2,3-*b*]pyridine]-4-carboxamide and (1*s*,4*s*)-5'-bromo-4'-chloro-1',2'-dihydrospiro[cyclohexane-1,3'-pyrrolo[2,3-*b*]pyridine]-4-carboxamide

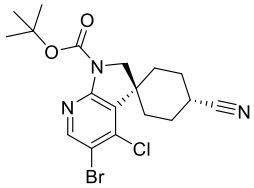
To a solution of 5'-bromo-4'-chloro-1',2'-dihydrospiro[cyclohexane-1,3'-pyrrolo[2,3-*b*]pyridine]-4-carboxylic acid (0.291 g, 0.84 mmol) in DMF (3 mL) was added ammonium chloride (0.09 g, 1.68 mmol) and DIPEA (0.73 mL, 4.21 mmol). HATU (0.48 g, 1.26 mmol) was added portionwise over 5 min. The mixture was stirred at RT for 20 min, then partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The aqueous phase was extracted with ethyl acetate. The combined organic extracts were washed with water, then brine, and concentrated. The residue was purified by chromatography on silica gel (eluting with 2-20% methanol.NH_3 in dichloromethane) to afford (1*r*,4*r*)-5'-bromo-4'-chloro-1',2'-dihydrospiro[cyclohexane-1,3'-pyrrolo[2,3-*b*]pyridine]-4-carboxamide (0.10 g, 34%) as a colourless solid. LCMS (ESI) *m/z* calcd for $C_{13}H_{15}BrClN_3O$ $[M+H]^+$: 344/346/348. Found 344/346/348. Later fractions gave (1*s*,4*s*)-5'-bromo-4'-chloro-1',2'-dihydrospiro[cyclohexane-1,3'-pyrrolo[2,3-*b*]pyridine]-4-carboxamide (0.17 g, 59%) as a colourless solid. LCMS (ESI) *m/z* calcd for $C_{13}H_{15}BrClN_3O$ $[M+H]^+$: 344/346/348. Found 344/346/348.

Step 6: (1*r*,4*r*)-5'-Bromo-4'-chloro-1',2'-dihydrospiro[cyclohexane-1,3'-pyrrolo[2,3-*b*]pyridine]-4-carbonitrile



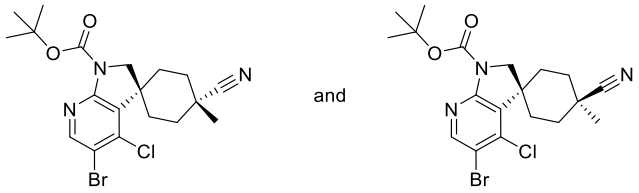
To a suspension of (1*r*,4*r*)-5'-bromo-4'-chloro-1',2'-dihydrospiro[cyclohexane-1,3'-pyrrolo[2,3-*b*]pyridine]-4-carboxamide (0.10 g, 0.29 mmol) in dichloromethane (7 mL) was added triethylamine (0.2 mL, 1.45 mmol). The mixture was cooled to -20 °C and trifluoroacetic anhydride (0.1 mL, 0.72 mmol) was added over 5 min. The resulting solution was allowed to warm to 5 °C over 30 min, then diluted with dichloromethane, washed with water, dried (Na_2SO_4) and concentrated. The residue was dissolved in methanol (5 mL). Ammonia in methanol (4M, 5 mL) was added and the mixture stirred for 10 min, then concentrated to dryness. The residue was purified by chromatography on silica gel (eluting with 1-4% 4M ammonia in methanol in dichloromethane) to afford the title compound (0.086 g, 91%) as a colourless solid. LCMS (ESI) *m/z* calcd for $C_{13}H_{13}BrClN_3$ $[M+H]^+$: 326/328/330. Found 326/328/330.

Step 7: *tert*-Butyl (1*r*,4*r*)-5'-Bromo-4'-chloro-4-cyanospiro[cyclohexane-1,3'-pyrrolo[2,3-*b*]pyridine]-1'(2'*H*)-carboxylate



Sodium hydride (60% in oil, 13.2 mg, 0.33 mmol) was added to a solution of (1*r*,4*r*)-5'-bromo-4'-chloro-1',2'-dihydrospiro[cyclohexane-1,3'-pyrrolo[2,3-*b*]pyridine]-4-carbonitrile (90 mg, 0.27 mmol) and di-*tert*-butyl dicarbonate (78 mg, 0.36 mmol) in THF (2 mL). The mixture was stirred at RT for 2 days, and then partitioned between ethyl acetate and 10% aq. citric acid. The organic phase was washed with water, brine, dried (Na_2SO_4) and evaporated. The residue was purified by chromatography on silica gel (eluting with 20-50% ethyl acetate in cyclohexane) to afford the title compound (0.117 g, quantitative) as a white solid. LCMS (ESI) *m/z* calcd for $C_{18}H_{21}BrClN_3O_2$ $[M+Na]^+$: 448/450/452. Found 448/450/452.

Step 8: *tert*-Butyl (1*r*,4*r*)-5'-bromo-4'-chloro-4-cyano-4-methylspiro[cyclohexane-1,3'-pyrrolo[2,3-*b*]pyridine]-1'(2'*H*)-carboxylate and *tert*-butyl (1*s*,4*s*)-5'-bromo-4'-chloro-4-cyano-4-methylspiro[cyclohexane-1,3'-pyrrolo[2,3-*b*]pyridine]-1'(2'*H*)-carboxylate

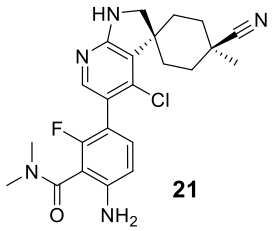


A solution of *tert*-butyl (1*r*,4*r*)-5'-bromo-4'-chloro-4-cyanospiro[cyclohexane-1,3'-pyrrolo[2,3-*b*]pyridine]-1'(2'*H*)-carboxylate (0.0805 g, 0.567 mmol) and iodomethane (0.035 mL, 0.57 mmol) in THF (2 mL) was cooled to -78°C and lithium bis(trimethylsilyl)amide solution (1M in THF, 0.34 mL, 0.34 mmol) added. The mixture was stirred at -78°C for 20 min, then quenched with saturated aqueous ammonium chloride and allowed to warm to RT. The resulting mixture was extracted with ethyl acetate (2x). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on silica gel (eluting with 10-30% ethyl acetate in cyclohexane) to afford a mixture of the title compounds (0.058 g, 48%) as a white solid. . LCMS (ESI) *m/z* calcd for $C_{19}H_{23}BrClN_3O_2$ $[M+Na]^+$: 462/464/466. Found 462/464/466.

Step 9: (1*r*,4*r*)-5'-Bromo-4'-chloro-4-methyl-1',2'-dihydrospiro[cyclohexane-1,3'-pyrrolo[2,3-*b*]pyridine]-4-carbonitrile and (1*s*,4*s*)-5'-bromo-4'-chloro-4-methyl-1',2'-dihydrospiro[cyclohexane-1,3'-pyrrolo[2,3-*b*]pyridine]-4-carbonitrile

TFA (1 mL) was added to a solution of *tert*-butyl (1*r*,4*r*)-5'-bromo-4'-chloro-4-cyano-4-methylspiro[cyclohexane-1,3'-pyrrolo[2,3-*b*]pyridine]-1'(2'*H*)-carboxylate and *tert*-butyl (1*s*,4*s*)-5'-bromo-4'-chloro-4-cyano-4-methylspiro[cyclohexane-1,3'-pyrrolo[2,3-*b*]pyridine]-1'(2'*H*)-carboxylate (0.058 g, 0.13 mmol) in dichloromethane (2 mL). The mixture was stirred at RT for 1h, then more TFA (1 mL) was added. Stirring was continued for a further 1.5h. Toluene was added and the mixture evaporated (2x). The residue was dissolved in methanol and purified on SCX-2 cartridge (eluting with methanol then 1N methanol.NH_3). The residue was purified by chromatography on silica gel (eluting with 30-100% ethyl acetate in cyclohexane) to afford (1*r*,4*r*)-5'-bromo-4'-chloro-4-methyl-1',2'-dihydrospiro[cyclohexane-1,3'-pyrrolo[2,3-*b*]pyridine]-4-carbonitrile (0.0228 g, 51%) as a colourless solid. LCMS (ESI) *m/z* calcd for $C_{14}H_{15}BrClN_3$ $[M+H]^+$: 340/342/344. Found 340/342/344. Later fractions gave (1*s*,4*s*)-5'-bromo-4'-chloro-4-methyl-1',2'-dihydrospiro[cyclohexane-1,3'-pyrrolo[2,3-*b*]pyridine]-4-carbonitrile (0.0124 g, 28%) as a colourless solid. . LCMS (ESI) *m/z* calcd for $C_{14}H_{15}BrClN_3$ $[M+H]^+$: 340/342/344. Found 340/342/344.

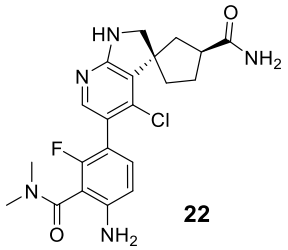
Step 10: 6-Amino-3-((1*s*,4*s*)-4'-chloro-4-cyano-4-methyl-1',2'-dihydrospiro[cyclohexane-1,3'-pyrrolo[2,3-*b*]pyridin]-5'-yl)-2-fluoro-*N,N*-dimethylbenzamide



21

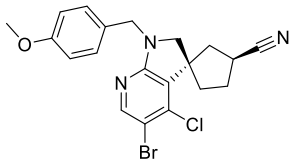
To a mixture of (1s,4s)-5'-bromo-4'-chloro-4-methyl-1',2'-dihydrospiro[cyclohexane-1,3'-pyrrolo[2,3-b]pyridine]-4-carbonitrile (19.9 mg, 0.0600 mmol), 6-amino-2-fluoro-*N,N*-dimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (28.8 mg, 0.0900 mmol), XPhosPdG2 (4.6 mg, 0.010 mmol) and XPhos (2.78 mg, 0.0100 mmol) in 1,4-dioxane (0.75 mL) was added 1M potassium phosphate (0.12 mL, 0.12 mmol) . The mixture was degassed and heated in a sealed vial at 90 °C for 1 h. The cooled reaction mixture was diluted with dichloromethane (20 mL) and loaded on to a 10 g silica cartridge. The cartridge was washed with dichloromethane. The desired product was eluted with dichloromethane containing 5% 2N NH_3 in methanol and concentrated. The product was further purified by reverse phase HPLC (0.5% TFA in water/MeCN) to give the title compound (15.8 mg, 61.2%) as a colourless solid. LCMS (ESI) *m/z* calcd for $C_{23}H_{25}ClFN_5O$ $[M+H]^+$: 442.2. Found 442.4. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.60 (s, 1H), 6.98 (s, 1H), 6.96 (t, *J* = 8.5 Hz, 1H), 6.54 (d, *J* = 8.4 Hz, 1H), 5.38 (brs, 2H), 3.48 (s, 2H), 2.99 (s, 3H), 2.88 (s, 3H), 2.35-2.24 (m, 2H), 1.97-1.89 (m, 2H), 1.83-1.77 (m, 2H), 1.59-1.51 (m, 2H), 1.44 (s, 3H).

Compound 22: (±)-(1*R,3*S**)-5'-(4-Amino-3-(dimethylcarbamoyl)-2-fluorophenyl)-4'-chloro-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-b]pyridine]-3-carboxamide**



22

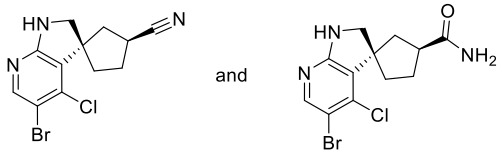
Step 1: (±)-(1*R**,3*S**)-5'-Bromo-4'-chloro-1'-(4-methoxybenzyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]-3-carbonitrile



Sodium cyanide (0.342 g, 6.97 mmol) was added to solution of (±)-(1*R**,3*R**)-5'-bromo-4'-chloro-1'-(4-methoxybenzyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridin]-3-yl methanesulfonate (0.70 g, 1.39 mmol) and 15-crown-5 (0.083 mL, 0.42 mmol) in DMSO (10 mL). The mixture was stirred at 80°C for 1.5h. The cooled reaction mixture was partitioned between ethyl acetate and water. The aqueous phase was extracted with more ethyl acetate and the combined organic extracts were washed with water, then brine, dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on silica gel (eluting with 10-30%

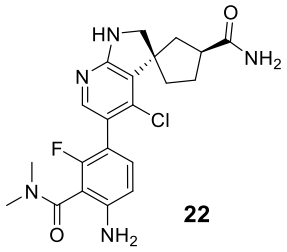
ethyl acetate in cyclohexane) to afford the title compound as a colourless gum (0.489 g, 81%). LCMS (ESI) *m/z* calcd for $C_{20}H_{19}BrClN_3O$ $[M+H]^+$: 432/434/436. Found 432/434/436.

Step 2: (±)-(1*R**,3*S**)-5'-Bromo-4'-chloro-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-b]pyridine]-3-carbonitrile and (±)-(1*R**,3*S**)-5'-bromo-4'-chloro-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-b]pyridine]-3-carboxamide



A mixture of (±)-(1*R**,3*S**)-5'-bromo-4'-chloro-1'-(4-methoxybenzyl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]-3-carbonitrile (0.408 g, 0.944 mmol), anisole (1 mL) and TFA (10 mL) was stirred at 80°C for 20h. The cooled reaction mixture was concentrated. Toluene was added and concentrated. The residue was dissolved in methanol/H_2O (9:1) and passed through a SCX-2 cartridge (eluting with methanol then with 4M NH_3 in methanol) The residue was purified by chromatography on silica gek (eluting with 2-10% 4M NH_3 in methanol in dichloromethane) to afford (±)-(1*R**,3*S**)-5'-bromo-4'-chloro-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]-3-carbonitrile as a colourless gum (0.08 g, 27%). LCMS (ESI) *m/z* calcd for $C_{12}H_{11}BrClN_3$ $[M+H]^+$: 312/314/316. Found 312/314/316. Later fractions gave (±)-(1*R**,3*S**)-5'-bromo-4'-chloro-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]-3-carboxamide as a white solid (0.192 g, 62%). LCMS (ESI) *m/z* calcd for $C_{12}H_{13}BrClN_3O$ $[M+H]^+$: 330/332/334. Found 330/332/334.

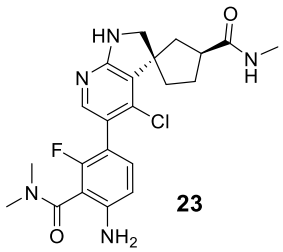
Step 3: (±)-(1*R**,3*S**)-5'-(4-amino-3-(dimethylcarbamoyl)-2-fluorophenyl)-4'-chloro-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]-3-carboxamide



22

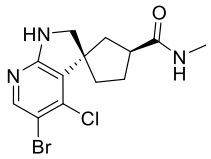
To a mixture of (±)-(1*R**,3*S**)-5'-bromo-4'-chloro-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]-3-carboxamide (18.6 mg, 0.056 mmol), XPhos Pd G2 (4.4 mg, 0.0056 mmol), XPhos (2.7 mg, 0.0056 mmol) and 6-amino-2-fluoro-*N,N*-dimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (34.8 mg, 0.12 mmol) in 1,4-dioxane (0.5 mL) was added 1M potassium phosphate (0.12 mL, 0.12 mmol) . The mixture was degassed and heated in a sealed vial at 100 °C for 2 h. The cooled reaction mixture was diluted with dichloromethane (10 mL) and loaded on to a 2 g silica cartridge. The product was eluted with dichloromethane containing 2-14% 2M NH_3 in methanol and concentrated to give the product as a white solid (15.7 mg, 65%). LCMS (ESI) *m/z* calcd for $C_{21}H_{23}ClFN_5O_2$ $[M+H]^+$: 432.2. Found 432.2. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.61 (s, 1H), 7.34 (brs, 1H), 6.97 (t, *J* = 8.5 Hz, 1H), 6.83 (s, 1H), 6.79 (brs, 1H), 6.55 (d, *J* = 8.2 Hz, 1H), 5.39 (brs, 2H), 3.46-3.34 (m, 2H), 2.99 (s, 3H), 2.95-2.89 (m, 1H), 2.89 (s, 3H), 2.08-1.92 (m, 2H), 1.87-1.81 (m, 1H), 1.77-1.67 (m, 1H)

Compound 23: (±)-(1*R,3*S**)-5'-(4-amino-3-(dimethylcarbamoyl)-2-fluorophenyl)-4'-chloro-N-methyl-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-b]pyridine]-3-carboxamide**



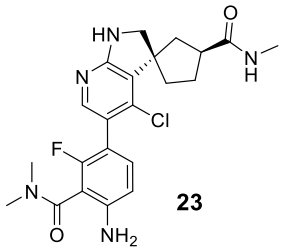
23

Step 1: (±)-(1*R**,3*S**)-5'-Bromo-4'-chloro-*N*-methyl-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]-3-carboxamide



A mixture of (±)-(1*R**,3*S**)-5'-bromo-4'-chloro-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]-3-carbonitrile (80 mg, 0.256 mmol) and HCl (6M aq., 6 mL) was heated in a sealed tube at 90 °C for 1.25 h. The cooled mixture was evaporated to dryness. Toluene was added and evaporated (2x) to give (±)-(1*R**,3*S**)-5'-bromo-4'-chloro-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]-3-carboxylic acid as the HCl salt. To this salt was added methylamine hydrochloride (26 mg, 0.384 mmol), DMF (1 mL) and DIPEA (0.266 mL, 1.54 mmol). HATU (0.195 g, 0.512 mmol) was added portionwise over 5 min. The mixture was stirred at RT for 30 min, then partitioned between ethyl acetate and aq. sodium bicarbonate. The aqueous phase was extracted with more ethyl acetate and the combined organic extracts were washed with water, then brine, and evaporated. The residue was purified by chromatography on silica gel (eluting with 2-20% 4M ammonia in methanol in dichloromethane) to afford the title compound (75 mg, 85%) as a colourless solid. LCMS (ESI) *m/z* calcd for $C_{13}H_{15}BrClN_3O$ $[M+H]^+$: 344/346/348. Found 344/346/348.

Step 2: (±)-(1*R**,3*S**)-5'-(4-Amino-3-(dimethylcarbamoyl)-2-fluorophenyl)-4'-chloro-N-methyl-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]-3-carboxamide

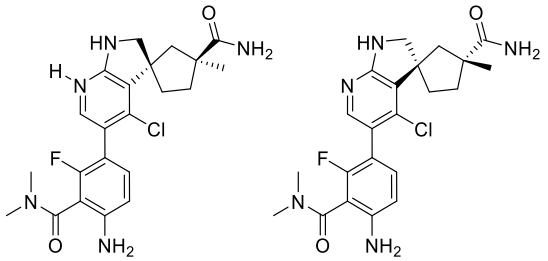


23

To a mixture of (±)-(1*R**,3*S**)-5'-Bromo-4'-chloro-*N*-methyl-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]-3-carboxamide (99 mg, 0.288 mmol), XPhosPdG2 (22.7 mg, 0.029 mmol), XPhos (13.8mg, 0.029 mmol) and 6-amino-2-fluoro-*N,N*-dimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (178 mg, 0.58 mmol) in 1,4-dioxane (2 mL) was added 1M

potassium phosphate (0.58 mL, 0.58 mmol). The mixture was degassed and heated in a sealed vial at 100 °C for 1 h. The cooled reaction mixture was partitioned between ethyl acetate and water. The aqueous phase was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried (sodium sulfate) and concentrated. The residue was purified by chromatography on silica gel (2-10% 2M NH_3 in methanol/dichloromethane) give the title compound (60 mg, 47%) as a colourless solid. LCMS (ESI) *m/z* calcd for $C_{22}H_{25}ClFN_5O_2$ $[M+H]^+$: 446.2. Found 446.2. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.82 (q, *J* = 4.6 Hz, 1H), 7.61 (s, 1H), 6.97 (t, *J* = 8.5 Hz, 1H), 6.84 (brs, 1H), 6.55 (d, *J* = 8.5 Hz, 1H), 5.39 (brs, 2H), 3.47 (d, *J* = 9.5 Hz, 1H), 3.36 (d, *J* = 9.4 Hz, 1H), 2.99 (s, 3H), 2.94-2.88 (m, 1H), 2.88 (s, 3H), 2.58 (d, *J* = 4.5 Hz, 3H), 2.06-1.89 (m, 2H), 1.86-1.67 (m, 3H).

Compounds 24, 25 and 26: 5'-(4-Amino-3-(dimethylcarbamoyl)-2-fluorophenyl)-4'-chloro-3-methyl-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-b]pyridine]-3-carboxamide



25 **26**

To a mixture of (±)-(1*R**,3*S**)-5-bromo-4-chloro-1'-methyl-spiro[1,2-dihydropyrrolo[2,3-b]pyridine-3,3'-cyclopentane]-1'-carboxamide (88.6 mg, 0.260 mmol), XPhosPd G2 (20.2 mg, 0.0300 mmol), XPhos (12.2 mg, 0.0300 mmol) and 6-amino-2-fluoro-*N,N*-dimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (127 mg, 0.410 mmol) in 1,4-dioxane (2 mL) was added 1M potassium phosphate (0.51 mL, 0.51 mmol) . The mixture was degassed and heated in a sealed vial at 100 °C for 1 h. The cooled reaction mixture was diluted with dichloromethane (25 mL) and loaded on to a 20 g silica cartridge. The cartridge was washed with dichloromethane. The product was eluted with dichloromethane containing 12-14% 2N NH_3 in methanol and concentrated to give the product as a racemic mixture (compound **24**, 96.8 mg).

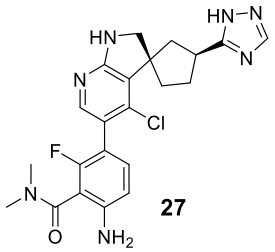
The enantiomers were separated using chiral SFC to give the two single enantiomers:

Compound **25**: (1*R*,3*S*)-5-[4-amino-3-(dimethylcarbamoyl)-2-fluoro-phenyl]-4-chloro-1'-methyl-spiro[1,2-dihydropyrrolo[2,3-b]pyridine-3,3'-cyclopentane]-1'-carboxamide (40.9 mg, 0.0917 mmol, 35.7% yield)) as white solids. LCMS (ESI) *m/z* calcd for $C_{22}H_{25}ClFN_5O_2$ $[M+H]^+$: 446.2. Found 446.0. HRMS *m/z* calcd for $C_{22}H_{25}ClFN_5O_2$ $[M+H]^+$: 446.1759. Found 446.1747. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.59 (s, 1H), 7.23 (brs, 1H), 6.97 (t, *J* = 8.5 Hz, 1H), 6.88 (brs, 1H), 6.80 (s, 1H), 6.55 (d, *J* = 8.3 Hz, 1H), 5.38 (brs, 2H), 3.45 (d, *J* = 9.3 Hz, 1H), 3.24 (d, *J* = 9.3 Hz, 1H), 2.99 (s, 3H), 2.89 (s, 3H), 2.47-2.39 (m, 2H), 2.23-2.15 (m, 1H), 1.94-1.85 (m, 1H), 1.73-1.61 (m, 2H), 1.30 (d, *J* = 3.9 Hz, 3H). ^{13}C NMR (101 MHz, methanol-d_4) δ 182.3, 166.8, 164.0, 156.6 (d, *J* = 243.2 Hz), 147.1 (d, *J* = 6.6 Hz), 147.0, 139.1, 132.9 (d, *J* = 5.1 Hz), 124.7 (d, *J* = 2.6 Hz), 120.9, 111.5 (d, *J* = 17 Hz), 111.0 (d, *J* = 2.9 Hz), 108.8 (d, *J* = 23 Hz), 59.1, 52.8, 49.9, 37.1 (d, *J* = 2.3 Hz), 36.4 (d, *J* = 2.9 Hz), 36.3, 33.7, 26.2.

Compound **26**: (1*S*,3*R*)-5-[4-amino-3-(dimethylcarbamoyl)-2-fluoro-phenyl]-4-chloro-1'-methyl-spiro[1,2-dihydropyrrolo[2,3-b]pyridine-3,3'-cyclopentane]-1'-carboxamide (42.8 mg, 0.0960

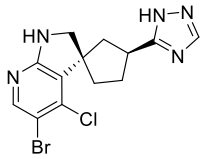
mmol, 37.3% yield). LCMS (ESI) *m/z* calcd for $C_{22}H_{25}ClFN_5O_2$ $[M+H]^+$: 446.2. Found 446.0. ^1H NMR (400 MHz, DMSO-d_6) δ 7.59 (s, 1H), 7.23 (brs, 1H), 6.97 (t, *J* = 8.5 Hz, 1H), 6.88 (brs, 1H), 6.80 (s, 1H), 6.55 (d, *J* = 8.4 Hz, 1H), 5.38 (brs, 2H), 3.45 (d, *J* = 9.4 Hz, 1H), 3.24 (d, *J* = 9.4 Hz, 1H), 2.99 (s, 3H), 2.88 (s, 3H), 2.48-2.39 (m, 2H), 2.23-2.15 (m, 1H), 1.94-1.85 (m, 1H), 1.72-1.62 (m, 2H), 1.30 (d, *J* = 3.8 Hz, 3H)

Compound 27: (±)-(1*R,3*S**)-6-Amino-3-(4'-chloro-3-(1H-1,2,4-triazol-5-yl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-b]pyridin]-5'-yl)-2-fluoro-*N,N*-dimethylbenzamide**



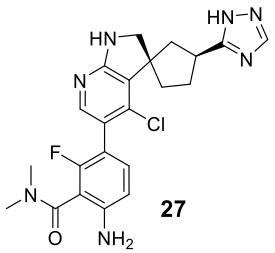
27

Step 1: (±)-(1*R**,3*S**)-5'-Bromo-4'-chloro-3-(1*H*-1,2,4-triazol-5-yl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]



A mixture of (±)-(1*R**,3*S**)-5'-bromo-4'-chloro-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]-3-carboxamide (75 mg, 0.227 mmol) and *N,N*-dimethylformamide dimethyl acetal (1.25 mL) was stirred at 60 °C for 1h. Toluene was added and evaporated (2x). To the residue was added acetic acid (2 mL) and hydrazine hydrate (0.5 mL). The mixture was stirred at 90 °C for 2h and then evaporated. The residue was partitioned between ethyl acetate and aq. sodium bicarbonate. The aqueous phase was extracted with ethyl acetate. The combined organic extracts were washed with water, then brine, and concentrated. The residue was purified by chromatography on silica gel (eluting with 2-12% 2M NH_3-methanol in dichloromethane) to afford the title compound (80 mg, 100%) as a colourless solid. LCMS (ESI) *m/z* calcd for $C_{13}H_{13}BrClN_5$ $[M+H]^+$: 354/356/358. Found 354/356/358.

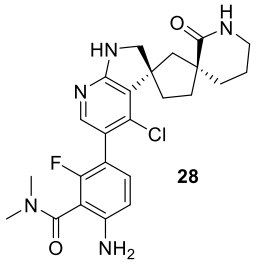
Step 2: (±)-6-Amino-3-((1*R**,3*S**)-4'-chloro-3-(1*H*-1,2,4-triazol-5-yl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridin]-5'-yl)-2-fluoro-*N,N*-dimethylbenzamide



27

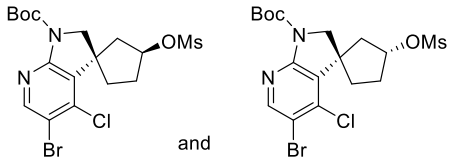
To a mixture of (±)-(1*R**,3*S**)-5'-bromo-4'-chloro-3-(1*H*-1,2,4-triazol-5-yl)-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine] (107 mg, 0.30 mmol), XPhosPd G2 (23.8 mg, 0.030 mmol), XPhos (14.5 mg, 0.030 mmol) and 6-amino-2-fluoro-*N,N*-dimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (186 mg, 0.60 mmol) in 1,4-dioxane (2 mL) was added 1M potassium phosphate (0.60 mL, 0.60 mmol). The mixture was degassed and heated in a sealed vial at 100 °C for 1 h. The cooled reaction mixture was partitioned between ethyl acetate and water. The aqueous phase was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried (sodium sulfate) and concentrated. The residue was purified by chromatography on silica gel(2-14% 2M NH_3 in methanol/dichloromethane). The product was further purified by reverse phase HPLC (C_{18}, 0.5% TFA in water/MeCN) to give the title compound (23 mg, 17%) as a colourless solid. LCMS (ESI) *m/z* calcd for $C_{22}H_{23}ClFN_7O$ $[M+H]^+$: 456.2. Found 456.2. ^1H NMR (400 MHz, DMSO-d_6) δ 13.67 (brs, 1H), 7.84 (brs, 1H), 7.63 (s, 1H), 6.99 (t, *J* = 8.5 Hz, 1H), 6.85 (brs, 1H), 6.56 (d, *J* = 8.3 Hz, 1H), 5.40 (brs, 2H), 3.60-3.50 (m, 1H), 3.42 (brs, 1H), 2.99 (s, 3H), 2.89 (s, 3H), 2.84-2.72 (m, 1H), 2.22-2.03 (m, 3H), 1.98-1.89 (m, 3H).

Compound 28: 6-amino-3-((3*R*,3'*R*)-4''-chloro-2-oxo-1'',2''-dihydrodispiro[piperidine-3,1'-cyclopentane-3',3''-pyrrolo[2,3-*b*]pyridin]-5''-yl)-2-fluoro-*N*,*N*-dimethylbenzamide



28

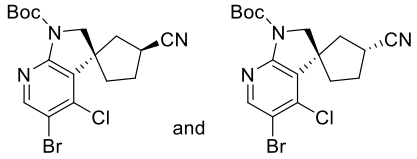
Step 1: (±)-*tert*-butyl (1*R**,3*S**)-5'-bromo-4'-chloro-3-((methylsulfonyl)oxy)spiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]-1'(2'*H*)-carboxylate and (±)-*tert*-butyl (1*R**,3*R**)-5'-bromo-4'-chloro-3-((methylsulfonyl)oxy)spiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]-1'(2'*H*)-carboxylate



Under an atmosphere of N_2, an oven-dried 250-mL round-bottom flask with magnetic stirbar was charged with a mixture of (±)-*tert*-butyl (1*R**,3*S**)-5'-bromo-4'-chloro-3-((methylsulfonyl)oxy)spiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]-1'(2'*H*)-carboxylate and (±)-*tert*-butyl (1*R**,3*R**)-5'-bromo-4'-chloro-3-((methylsulfonyl)oxy)spiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]-1'(2'*H*)-carboxylate (3140 mg, 7.77 mmol), dichloromethane (52 mL), and triethylamine (2.17 mL, 15.5 mmol). Methanesulfonyl chloride (0.9 mL, 11.7 mmol) was added dropwise to the reaction mixture over the course of 5 minutes, and the reaction mixture was stirred at room temperature for an additional 45 minutes. The reaction was diluted with saturated aqueous sodium bicarbonate (50 mL), and the organic layer was collected. The aqueous layer was extracted with dichloromethane (2 x 25 mL). The combined organic layers were washed sequentially with 0.5 M aqueous HCl (1 x 50 mL) and saturated aqueous sodium chloride (1 x 50 mL). The combined organic layers were then dried over anhydrous sodium sulfate and filtered through a polyethylene filter frit, and the filtrate was concentrated via rotary evaporation. The residue was purified by chromatography on silica gel (eluting with 10-70%

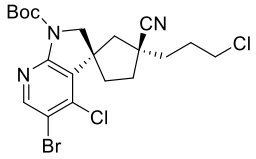
isopropyl acetate in heptane) to afford a mixture of the title compounds (3.7 g, 99%) as a colorless oil that was used without further separation. LCMS (ESI) *m/z* calcd for $C_{17}H_{22}BrClN_2O_5S$ [M+H]$^+$: 481/483/485. Found 481/483/485.

Step 2: (±)-*tert*-butyl (1*R**,3*S**)-5'-bromo-4'-chloro-3-cyanospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]-1'(2'*H*)-carboxylate and (±)-*tert*-butyl (1*R**,3*R**)-5'-bromo-4'-chloro-3cyanospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]-1'(2'*H*)-carboxylate



Under an atmosphere of N_2, an oven-dried 250-mL round-bottom flask with magnetic stirbar was charged with a mixture of (±)-*tert*-butyl (1*R**,3*S**)-5'-bromo-4'-chloro-3-hydroxyspiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]-1'(2'*H*)-carboxylate and (±)-*tert*-butyl (1*R**,3*R**)-5'-bromo-4'-chloro-3-hydroxyspiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]-1'(2'*H*)-carboxylate (3700 mg, 7.70 mmol), sodium cyanide (1600 mg, 32.6 mmol), dimethylsulfoxide (51 mL), and 15-crown-5 (0.46 mL, 2.3 mmol). The reaction mixture was heated to 60 °C and stirred for 16 hours. The reaction was partitioned between 0.2 M aqueous sodium hydroxide (150 mL) and isopropyl acetate (100 mL), and the organic layer was collected. The aqueous layer was extracted with isopropyl acetate (2x100 mL). The combined organic layers were washed sequentially with water (3x100 mL) and saturated aqueous sodium chloride (2x100 mL). The combined organic layers were then dried over anhydrous sodium sulfate and filtered through a polyethylene filter frit, and the filtrate was concentrated via rotary evaporation. The residue was purified by chromatography on silica gel (eluting with 15-70% isopropyl acetate in heptane) to afford a mixture of the title compounds (1.95 g, 62%) as a white solid that was used without further separation. LCMS (ESI) *m/z* calcd for $C_{17}H_{19}BrClN_3O_2$ [M+H]$^+$: 412/414/416. Found 412/414/416.

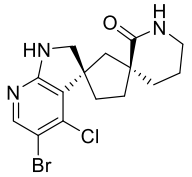
Step 3: (±)-*tert*-butyl (1*R**,3*R**)-5'-bromo-4'-chloro-3-(3-chloropropyl)-3-cyanospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]-1'(2'*H*)-carboxylate



Under an atmosphere of N_2, an oven-dried 40-mL septum-capped vial with magnetic stirbar was charged with a mixture of (±)-*tert*-butyl (1*R**,3*S**)-5'-bromo-4'-chloro-3-cyanospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]-1'(2'*H*)-carboxylate and (±)-*tert*-butyl (1*R**,3*R**)-5'-bromo-4'-chloro-3cyanospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]-1'(2'*H*)-carboxylate (1000 mg, 2.42 mmol) and tetrahydrofuran (16 mL). The reaction mixture was cooled to –78 °C in a dry ice/acetone bath. A 1.0 M solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran (3.15 mL, 3.15 mmol) was added dropwise to the reaction mixture and stirred for 30 minutes at –78 °C. 1-chloro-3-iodopropane (0.78 mL, 7.3 mmol) was added dropwise, and the reaction mixture was stirred for 3 hours at –78 °C. The reaction was quenched by addition of 30 mL saturated aqueous ammonium chloride, warmed to room temperature, and extracted with isopropyl acetate (3x40 mL). The combined organic layers were washed with saturated aqueous sodium chloride (1x100 mL), dried over anhydrous sodium sulfate, and filtered through a polyethylene filter frit. The filtrate was concentrated via rotary evaporation. The residue was purified by chromatography on silica gel (eluting with 0-40% isopropyl acetate in heptane) to afford the title

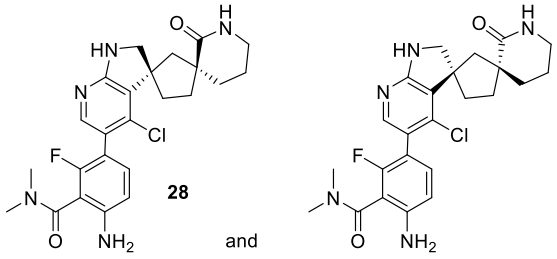
compound (365 mg, 31%) as a white solid. LCMS (ESI) *m/z* calcd for $C_{20}H_{24}BrCl_2N_3O_2$ $[M+H]^+$: 488/490/492. Found 488/490/492.

Step 4: (±)-(3*R**,3'*R**)-5''-bromo-4''-chloro-1'',2''-dihydrodispiro[piperidine-3,1'-cyclopentane-3',3''-pyrrolo[2,3-*b*]pyridin]-2-one



A 25-mL microwave reaction vessel was charged with (±)-*tert*-butyl (1*R**,3*R**)-5'-bromo-4'-chloro-3-(3-chloropropyl)-3-cyanospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]-1'(2'*H*)-carboxylate (365 mg, 0.746 mmol), sodium iodide (224 mg, 1.49 mmol), and 7 M ammonia in methanol (10.7 mL, 74.6 mmol). The reaction mixture was sealed and heated at 120 °C in a Biotage microwave reactor for 7 hours. The solvent was removed by rotary evaporation, and the residue was re-suspended in 2.5 M HCl in 1,4-dioxane (8 mL). The reaction mixture was heated at 100 °C in a Biotage microwave reactor for 1 hour. The solvent was removed by rotary evaporation, and the residue was partitioned between saturated aqueous sodium bicarbonate (30 mL) and isopropyl acetate (30 mL). The organic layer was collected, and the aqueous layer was extracted with isopropyl acetate (2x20 mL). The combined organic layers were washed with saturated aqueous sodium chloride (1x100 mL), dried over anhydrous sodium sulfate, and filtered through a polyethylene filter frit. The filtrate was concentrated via rotary evaporation. The residue was purified by chromatography on silica gel (eluting with 0-5% methanol in dichloromethane) to afford the title compound (132 mg, 48%) as a yellow solid. LCMS (ESI) *m/z* calcd for $C_{15}H_{17}BrClN_3O$ $[M+H]^+$: 370/372/374. Found 370/372/374.

Step 5; 6-amino-3-((3*R*,3'*R*)-4''-chloro-2-oxo-1'',2''-dihydrodispiro[piperidine-3,1'-cyclopentane-3',3''-pyrrolo[2,3-*b*]pyridin]-5''-yl)-2-fluoro-*N*,*N*-dimethylbenzamide (Compound **28**) and 6-amino-3-((3*S*,3'*S*)-4''-chloro-2-oxo-1'',2''-dihydrodispiro[piperidine-3,1'-cyclopentane-3',3''-pyrrolo[2,3-*b*]pyridin]-5''-yl)-2-fluoro-*N*,*N*-dimethylbenzamide



28 and

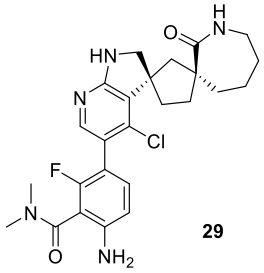
A 5-mL microwave reaction vessel was charged with (±)-(3*R**,3'*R**)-5''-bromo-4''-chloro-1'',2''-dihydrodispiro[piperidine-3,1'-cyclopentane-3',3''-pyrrolo[2,3-*b*]pyridin]-2-one (132 mg, 0.356 mmol), XPhosPd G2 (22.9 mg, 0.028 mmol), XPhos (13.7 mg, 0.028 mmol) and 6-amino-2-fluoro-*N,N*-dimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (121 mg, 0.39 mmol). Degassed 1,4-dioxane (3 mL) and 1.4 M aqueous potassium phosphate (0.53 mL, 0.75 mmol) were added, and the reaction mixture was heated in Biotage microwave reactor at 100 °C for 10 h. The cooled reaction mixture was partitioned between isopropyl acetate (15 mL) and saturated aqueous sodium chloride (15 mL). The aqueous layer was extracted with isopropyl acetate (1x10 mL). The combined organic layers were dried over anhydrous sodium sulfate and filtered through a polyethylene filter frit. The filtrate was concentrated via rotary evaporation. The residue was purified by reverse phase HPLC (C_{18}, 0.1% ammonium

hydroxide in water/MeCN), followed by chiral SFC to give the separated enantiomers as white solids:

Compound **28**: 6-amino-3-((3*R*,3'*R*)-4''-chloro-2-oxo-1'',2''-dihydrodispiro[piperidine-3,1'-cyclopentane-3',3''-pyrrolo[2,3-*b*]pyridin]-5''-yl)-2-fluoro-*N*,*N*-dimethylbenzamide (36.1 mg, 0.077 mmol, 22% yield). LCMS (ESI) *m/z* calcd for $C_{24}H_{27}ClFN_5O_2$ $[M+H]^+$: 472.2. Found 472.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.59 (s, 1H), 7.39 (s, 1H), 6.96 (t, *J* = 8.5 Hz, 1H), 6.83 (s, 1H), 6.55 (d, *J* = 8.4 Hz, 1H), 5.37 (s, 2H), 3.81 (dd, *J* = 9.6, 6.1 Hz, 1H), 3.14 (br s, 2H), 2.99 (s, 3H), 2.88 (s, 3H), 2.20 (d, *J* = 13.4 Hz, 1H), 2.14 – 1.96 (m, 2H), 1.86 – 1.60 (m, 6H).

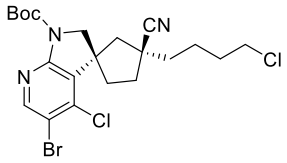
6-amino-3-((3*S*,3'*S*)-4''-chloro-2-oxo-1'',2''-dihydrodispiro[piperidine-3,1'-cyclopentane-3',3''-pyrrolo[2,3-*b*]pyridin]-5''-yl)-2-fluoro-*N*,*N*-dimethylbenzamide (33.4 mg, 0.071 mmol, 20% yield). LCMS (ESI) *m/z* calcd for $C_{24}H_{27}ClFN_5O_2$ $[M+H]^+$: 472.2. Found 472.1.^{1}H NMR (400 MHz, DMSO-d_6) δ 7.59 (s, 1H), 7.39 (s, 1H), 6.96 (t, *J* = 8.5 Hz, 1H), 6.83 (s, 1H), 6.55 (d, *J* = 8.4 Hz, 1H), 5.37 (s, 2H), 3.81 (dd, *J* = 9.7, 6.1 Hz, 1H), 3.14 (br s, 2H), 2.99 (s, 3H), 2.88 (s, 3H), 2.20 (d, *J* = 13.4 Hz, 1H), 2.14 – 1.95 (m, 2H), 1.86 – 1.60 (m, 6H).

Compound 29: 6-amino-3-((3*S*,3'*R*)-4''-chloro-2-oxo-1'',2''-dihydrodispiro[azepane-3,1'-cyclopentane-3',3''-pyrrolo[2,3-*b*]pyridin]-5''-yl)-2-fluoro-*N*,*N*-dimethylbenzamide



29

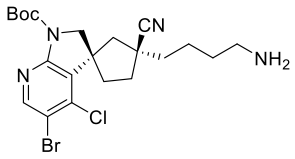
Step 1: (±)-*tert*-butyl (1*R**,3*S**)-5'-bromo-4'-chloro-3-(4-chlorobutyl)-3-cyanospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]-1'(2'*H*)-carboxylate



Under an atmosphere of N_2, an oven-dried 40-mL septum-capped vial with magnetic stirbar was charged with a mixture of (±)-*tert*-butyl (1*R**,3*S**)-5'-bromo-4'-chloro-3-cyanospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]-1'(2'*H*)-carboxylate and (±)-*tert*-butyl (1R*,3R*)-5'-bromo-4'-chloro-3cyanospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]-1'(2'*H*)-carboxylate (500 mg, 1.21 mmol) and tetrahydrofuran (8 mL). The reaction mixture was cooled to –78 °C in a dry ice/acetone bath. A 1.0 M solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran (1.58 mL, 1.58 mmol) was added dropwise to the reaction mixture and stirred for 30 minutes at –78 °C. 1-chloro-4-iodobutane (0.44 mL, 3.64 mmol) was added dropwise, and the reaction mixture was stirred for 2 hours at –78 °C. The reaction was quenched by addition of 10 mL saturated aqueous ammonium chloride, warmed to room temperature, and extracted with isopropyl acetate (3x20 mL). The combined organic layers were washed with saturated aqueous sodium chloride (1x50 mL), dried over anhydrous sodium sulfate, and filtered through a polyethylene filter frit. The filtrate was concentrated via rotary evaporation. The residue was purified by chromatography on silica gel (eluting with 0-40% isopropyl acetate in heptane) to afford the title compound (135

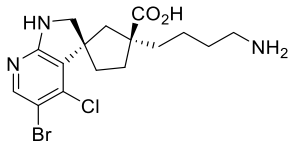
mg, 22%) as a pale yellow oil. LCMS (ESI) *m/z* calcd for $C_{21}H_{26}BrCl_2N_3O_2$ $[M+H]^+$: 502/504/506. Found 502/504/506.

Step 2: (±)-*tert*-butyl (1*R**,3*S**)-3-(4-aminobutyl)-5'-bromo-4'-chloro-3-cyanospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]-1'(2'*H*)-carboxylate



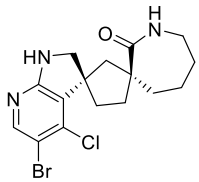
A 5-mL microwave reaction vessel was charged with (±)-*tert*-butyl (1*R**,3*S**)-5'-bromo-4'-chloro-3-(4-chlorobutyl)-3-cyanospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]-1'(2'*H*)-carboxylate (100 mg, 0.199 mmol), sodium iodide (59.6 mg, 0.397 mmol), and 7 M ammonia in methanol (2.84 mL, 19.9 mmol). The reaction mixture was sealed and heated at 120 °C in a Biotage microwave reactor for 7 hours. The solvent was removed by rotary evaporation. The residue was purified by reverse-phase chromatography on C18-silica gel (eluting with 5-50% acetonitrile in water containing 0.1% formic acid) to afford the title compound (80 mg, 80%) as a colorless solid. LCMS (ESI) *m/z* calcd for $C_{21}H_{28}BrClN_4O_2$ $[M+H]^+$: 483/485. Found 483/485.

Step 3: (±)-(1*R**,3*S**)-3-(4-aminobutyl)-5'-bromo-4'-chloro-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]-3-carboxylic acid



A 5-mL microwave reaction vessel was charged with (±)-*tert*-butyl (1*R**,3*S**)-3-(4-aminobutyl)-5'-bromo-4'-chloro-3-cyanospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]-1'(2'*H*)-carboxylate (80 mg, 0.165 mmol) and 12 M hydrochloric acid in water (3.31 mL, 40.3 mmol). The reaction mixture was sealed and heated at 120 °C in a Biotage microwave reactor for 3 hours. The solvent was removed by rotary evaporation. The residue was re-suspended in methanol and the solvent was removed by rotary evaporation. This afforded the title compound (bis-HCl salt; 65 mg, 82%) as a tan solid that was used without further purification. LCMS (ESI) *m/z* calcd for $C_{16}H_{21}BrClN_3O_2$ $[M+H]^+$: 402/404. Found 402/404.

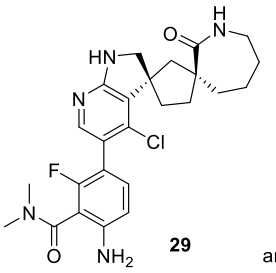
Step 4: (±)-(3*S**,3'*R**)-5''-bromo-4''-chloro-1'',2''-dihydrodispiro[azepane-3,1'-cyclopentane-3',3''-pyrrolo[2,3-*b*]pyridin]-2-one



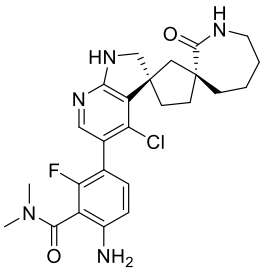
Under an atmosphere of N_2, an oven-dried 40-mL septum-capped vial with magnetic stirbar was charged with (±)-(1*R**,3*S**)-3-(4-aminobutyl)-5'-bromo-4'-chloro-1',2'-dihydrospiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridine]-3-carboxylic acid bis-HCl salt (58 mg, 0.12 mmol), 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate (71 mg, 0.18 mmol), dimethylformamide (12.2 mL), and triethylamine (0.077 mL, 0.55 mmol).

The reaction mixture was stirred under N_2 at room temperature for 5 hours. The reaction was diluted with 30 mL saturated aqueous sodium bicarbonate and extracted with isopropyl acetate (3x30 mL). The combined organic layers were washed with water (1x100 mL), saturated aqueous sodium chloride (1x100 mL), dried over anhydrous sodium sulfate, and filtered through a polyethylene filter frit. The filtrate was concentrated via rotary evaporation to afford the title compound (44 mg, 94%) as an orange solid that was used without further purification. LCMS (ESI) *m/z* calcd for $C_{16}H_{19}BrClN_3O$ $[M+H]^+$: 384/386. Found 384/386.

Step 5: 6-amino-3-((3*S*,3'*R*)-4''-chloro-2-oxo-1'',2''-dihydrodispiro[azepane-3,1'-cyclopentane-3',3''-pyrrolo[2,3-*b*]pyridin]-5''-yl)-2-fluoro-*N*,*N*-dimethylbenzamide (Compound **29**) and 6-amino-3-((3*R*,3'*S*)-4''-chloro-2-oxo-1'',2''-dihydrodispiro[azepane-3,1'-cyclopentane-3',3''-pyrrolo[2,3-*b*]pyridin]-5''-yl)-2-fluoro-*N*,*N*-dimethylbenzamide



29 and



A 5-mL microwave reaction vessel was charged with (±)-(3*S**,3'*R**)-5''-bromo-4''-chloro-1'',2''-dihydrodispiro[azepane-3,1'-cyclopentane-3',3''-pyrrolo[2,3-*b*]pyridin]-2-one (45 mg, 0.12 mmol), XPhosPd G2 (7.5 mg, 0.009 mmol), XPhos (4.5 mg, 0.009 mmol) and 6-amino-2-fluoro-*N,N*-dimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (40 mg, 0.13 mmol). Degassed 1,4-dioxane (1 mL) and 1.4 M aqueous potassium phosphate (0.18 mL, 0.25 mmol) were added, and the reaction mixture was heated in Biotage microwave reactor at 100 °C for 10 h. The cooled reaction mixture was partitioned between isopropyl acetate (15 mL) and saturated aqueous sodium chloride (15 mL). The aqueous layer was extracted with isopropyl acetate (1x10 mL). The combined organic layers were dried over anhydrous sodium sulfate and filtered through a polyethylene filter frit. The filtrate was concentrated via rotary evaporation. The residue was purified by reverse phase HPLC (C_{18}, 0.1% ammonium hydroxide in water/MeCN), followed by chiral SFC to give the separated enantiomers as white solids:

Compound **29**: 6-amino-3-((3*S*,3'*R*)-4''-chloro-2-oxo-1'',2''-dihydrodispiro[azepane-3,1'-cyclopentane-3',3''-pyrrolo[2,3-*b*]pyridin]-5''-yl)-2-fluoro-*N*,*N*-dimethylbenzamide (12.1 mg, 0.011 mmol, 21% yield). LCMS (ESI) *m/z* calcd for $C_{25}H_{29}ClFN_5O_2$ $[M+H]^+$: 486.2. Found 486.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.60 (s, 1H), 7.46 (t, *J* = 6.1 Hz, 1H), 6.97 (t, *J* = 8.5 Hz, 1H), 6.81 (s, 1H), 6.55 (d, *J* = 8.4 Hz, 1H), 5.38 (s, 2H), 3.35 (d, *J* = 8.9 Hz, 1H), 3.26 (d, *J* = 9.8 Hz, 1H), 3.14 – 3.01 (m, 2H), 2.99 (s, 3H), 2.88 (s, 3H), 2.48 – 2.25 (m, 3H), 2.20 (t, *J* = 14.1 Hz, 1H), 1.80 – 1.55 (m, 7H), 1.38 – 1.28 (m, 1H).

6-amino-3-((3*R*,3'*S*)-4''-chloro-2-oxo-1'',2''-dihydrodispiro[azepane-3,1'-cyclopentane-3',3''-pyrrolo[2,3-*b*]pyridin]-5''-yl)-2-fluoro-*N*,*N*-dimethylbenzamide (13.8 mg, 0.013 mmol, 24% yield). LCMS (ESI) *m/z* calcd for $C_{25}H_{29}ClFN_5O_2$ $[M+H]^+$: 486.2. Found 486.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.60 (s, 1H), 7.46 (t, *J* = 6.1 Hz, 1H), 6.97 (t, *J* = 8.5 Hz, 1H), 6.81 (s, 1H), 6.55 (d, *J* = 8.4 Hz, 1H), 5.38 (s, 2H), 3.35 (d, *J* = 8.9 Hz, 1H), 3.26 (d, *J* = 9.8 Hz, 1H), 3.13 – 3.01 (m,

2H), 2.99 (s, 3H), 2.88 (s, 3H), 2.46 – 2.26 (m, 3H), 2.20 (t, *J* = 14.1 Hz, 1H), 1.81 – 1.54 (m, 7H), 1.38 – 1.28 (m, 1H).

Biochemical and cellular assay protocols

HPK1 Lantha Binding Biochemical Assay

Materials:

Reagent	**Vender-Cat#**
white ProxiPlate 384 F(assay plate)	PerkinElmer-6008289
384-well Microplate(compound plate)	Labcyte-LP-0200
HPK1 enzyme	Signalchem-M23-11G
Tracer-222	Invitrogen-PV6121
Eu-Anti-GST Ab	Invitrogen-PV5594
Assay Buffer	2mM DTT(Sigma-43815), 0.01% BRIJ-35(Sigma-B4184), 10mM $MgCl_2$, 50mM HEPES(Invitrogen-15630130)

Procedure:

I. Compound Dilution:

The compounds to be tested were diluted by preparing 12.5 µL/well of 5 mM compound (100X) in columns 2 and 13 and 10 µL/well of DMSO in columns 3-12, 14-23, and wells A1-H1 and I24-P24 of the compound plate using a Bravo liquid handling platform. For the reference compound, the top concentration was 1 mM. To the plate was added 10 µL 2 mM staurosporine in wells J1-P1 and A24-H24. A 11 point 5-fold compound serial dilution was performed using the Bravo liquid handling platform. From the plate were transferred 2.5 µL of the solutions from column 2 and column 13 to the 10 µL of DMSO in columns 3 and 14 & so on. The compound plate was centrifuged at 2500 rpm for 1 min. From the compound plate was transferred 80 nL of the compounds into an assay plate using the Echo liquid handler system. One compound plate makes two assay plates. Each assay plate is sealed and stored in an N_2 cabinet.

II. Assay Condition:

The following assay concentrations and times were used: 2 nM HPK1, 2 nM Eu-Anti-GST Ab, and 15 nM Tracer222, with 60 min incubation time.

III. HPK1 Lantha Binding Assay:

For the binding assay, 4 µL 2X HPK1 and Eu-anti-GST antibody were added to each well of the assay plate using a Multidrop reagent dispenser. The solutions were incubated in a 23C incubator for 1h. To each well of the assay plate was added 4 µL 2X Tracer-222 using a Multidrop reagent dispenser. The solutions were again incubated in a 23 °C incubator for 1h. The results of the assay were read using an Envision plate reader with the following parameters:TR_FRET, 340ex/615 and 665em; 100 µsec Delay; and 200 µsec integration.

IV. Analysis:

Compound K_i was analyzed using Morrison ki fit model in XL-fit

a. fit = (1-((((E+x)+(Ki*(1+(S/Kd))))-(((((E+x)+(Ki*(1+(S/Kd))))^2) - ((4*E)*x))^0.5))/(2*E)))
   res = (y-fit)
b. Parameters:
   E = enzyme concentration
   S= Tracer222 concentration, K_d = Tracer222 Kd
   All measurements are reported using the same units (nM).

HPK1 HTRF Enzymatic Assay

I. Assay Principle:

HPK-FL enzyme phosphorylates Biotin-SLP-76 substrate in the presence of ATP at 1mM and varying concentrations of test compound. Product is detected by FRET using Eu-anti-pSLP76 Ab and SA-XL665. Also see www.cisbio.com/HTRF for additional HTRF technology information.

II. Instrumentation:

Echo555 compound dispenser
Agilent Bravo
Perkin Elmer Envision

III. Final Assay Conditions:

HPK1 full length, T165E-S171E:	0.125 nM
Biotin-SLP76:	100 nM
ATP:	1 mM (ATP Km = 20 µM)
Eu-anti-pSLP76:	2 nM
SA-XL665:	8.3 nM
Preincubation time:	30 min
Kinase reaction time:	60 min
Temperature:	ambient
Total volume:	12 µl
ATP_{app} K_m:	17.7 µM

IV. Materials:

Assay plate: White ProxiPlate 384 (PerkinElmer cat# 6008289)
Kinase: HPK1 full length double mutant (T165E, S171E)
Substrate: Biotin-SLP76

ATP: 100 mM ATP
BSG: 2% BSG
DMSO: DMSO (Sigma cat # 34869-100ML**)**
Reaction Buffer: H_2O/50 mM HEPES, pH 7.5/10 mM $MgCl_2$/2 mM TCEP/0.01% Brij-35/0.01% BSG
Detection mix: Eu-anti-pSLP76/SA-XL665 (Cisbio, #610SAXAC)

V. HTRF Enzymatic Assay Procedure K_i determination Procedure:

To a 384 well Proxiplate with 80 nL compound or DMSO spotted on was added 4 µl/well kinase mix. The mixture was preincubated for 30 minutes and then 4 µl/well substrate mix was added. The solution was incubated for 60 min and then 4 µl/well detection mix was added. The solution was incubated for another 60 min. The plates were then loaded onto a Perkin Elmer Envision and the TR-FRET signal was measured at 615 and 665 nm. A ratio of 665/620 was used to calculate the % activity at each concentration of compound.

LCK Zlyte Enzyme assay

In a polypropylene plate, 10 nM LCK, and test compound, dispensed acoustically via Echo, are incubated together in a kinase reaction buffer for 30 minutes. Then, the addition of substrate mix: peptide substrate labeled with both coumarin (donor fluorphore), fluorescein (acceptor fluorphore), and 90 µM ATP (at Km), begins the reaction and incubated at room temp for 90 minutes at 10 µL total volume. The reaction is quenched with 5 µL (1:2) with development reagent (protease) and allowed to incubate at room temp for one hour. The plate is analyzed on a Perkin Elmer Envision by FRET mode. The high ratio of coumarin / fluorescein represents 0% phosphorylation rate while low ratio of coumarin / fluorescein represents 100% phosphorylation rate. See Perkin Elmer website on Z-Lyte assay technology for any further details.

Jurkat pSLP76 Cellular Assay

Cell Culture

Jurkat cells, clone E6-1, was obtained from ATCC (Manassas, VA) and maintained in complete growth medium: RPMI supplemented with 10% heat inactivated fetal bovine serum and 1X GlutaMAX™ (Invitrogen; Carlsbad, CA). Frozen primary human pan T cells (#70024, Stemcell Technologies) was thawed and maintained in complete medium during assay: RPMI supplemented with 10% heat inactivated fetal bovine serum, 1X GlutaMAX™ , sodium pyruvate and non-essential amino acids, 55µM beta-mercaptoethanol (Invitrogen) and 10mM Hepes.

Jurkat pSLP76 ELISA

Cells were seeded in 96-well plates and treated with varying concentrations of test compounds for 30 minutes in a humidified incubator at 37°C and 5% CO_2. Cells were then stimulated with anti-CD3 DynaBeads (#111.51D, Invitrogen) at a 4:1 bead:cell ratio in a humidified incubator at 37°C and 5% CO_2 for 10 minutes. Cold RIPA buffer was added to lyse the cells on a shaker at 4°C for 30 minutes. Cell lysates was transferred to a pre-blocked ELISA plate coated with anti-pSLP76(S376) capture antibody (Genentech) and incubated at room temperature shaking for 2 hours. ELISA plate was washed and incubated with biotinylated anti-SLP76 detection antibody (Thermo; Waltham, MA) at room temperature shaking for 1 hour. Plate was washed and incubated with streptavidin-Horseradish Peroxidase (#RPN4401V, GE) at room temperature

shaking for 20 minutes. After another wash, plate was incubated with TMB substrate solution (#7004, Cell Signaling) at room temperature in the dark shaking for 20 minutes. STOP solution (#7002, Cell Signaling) was added and plate was read on SoftMax Pro (Molecular Devices; San Jose, CA) for absorbance at 450 nm.

Human T-cell IL2 Induction Assay

Primary human pan T cells were thawed from frozen vials and seeded in 96-well plates in assay medium (RPMI, 10% heat-inactivated fetal bovine serum, GlutaMAX, sodium pyruvate, non-essential amino acid, 10mM HEPES, 55μM beta-mercaptoethanol). Cells were treated with varying concentrations of test compounds for 30 minutes in a humidified incubator at 37°C and 5% CO_2. Cells were then transferred to a plate pre-coated with a fixed concentration (determined separately for each donor lot) of anti-human CD3 (#16-0037-81, eBioscience). Soluble anti-human CD28 (#555725, BD Bioscience) was added and cells were stimulated in a humidified incubator at 37°C and 5% CO_2 for 4 hours. Supernatant from cell culture was transferred to a MSD single spot plate pre-coated with an anti-human IL-2 antibody (#K151AHB-4, Meso Scale Discovery). Measurements were made according to manufacturer's instructions. Briefly, MSD plate was incubated with supernatant overnight at 4°C with gentle shaking. After washing, MSD plate was incubated with SULFO-tagged anti-human IL-2 detection antibody at room temperature shaking for 2 hours. Plate was washed again before addition of MSD read buffer and read on a MSD SECTOR S 600 instrument. Data was normalized to stimulated/untreated controls to calculate % activity at each concentration of compound.

DMPK Experimental Protocols

Liver Microsomes Metabolic Stability Assay Protocol

Experiments were carried out as previously described (*Drug Metab. Lett.* **2014**, *1*, 67-72). Values shown are for predicted hepatic clearance using intrinsic clearance and a conversion factor for liver blood flow to predict hepatic clearance(*J. Pharmacol. Exp. Ther.* **1997**, *283*, 46-58). $Cl_{hep}= (Q.Cl_{int})/(Q+Cl_{int})$ where Cl_{hep}= predicted hepatic clearance, Q= liver blood flow and Cl_{int}= intrinsic clearance. Liver blood flow values in mL/min/kg: rat= 55.2, dog= 30.9, human= 20.7, mouse= 90.

Hepatocyte Stability Assay

Metabolic stability of compounds are assessed using a hepatocyte stability assay. Cryopreserved human hepatocytes from a 10 donor pool are quickly thawed at 37 °C, suspended in prewarmed In VitroGRO™ HT Medium, and then centrifuged at 100×g at room temperature for 10 min. The supernatants are discarded, and cells are resuspended in 5 mL Dulbecco's Modified Eagle Medium (DMEM) medium. Cell viability in suspension is counted on a Hepatometer ® Vision (Lonza, NC), and viable cells are then adjusted to 1.0×10^6 cells/mL in DMEM. Compounds are first diluted to 2 μM with DMEM medium, and then aliquots of 125 μL of drug-containing medium are transferred to 96-well non-coated plates. Incubation is initiated by the addition of 125 μL of hepatocyte suspension to yield a total incubation volume of 250 μL.

Final concentration of each compound is 1 μM, and final cell density is 0.5×10^6 cells/mL. Incubations are conducted in a humidified incubator at 37 °C. Aliquots of 50 μL incubation medium are taken out at different time intervals (0, 60, 120 and 180 min), and immediately mixed with 100 μL of ice-cold acetonitrile containing 50 nM propranolol (internal standard). Samples are then centrifuged at 3000 x g for 5min, and 80 μL of supernatant is taken out and diluted with 160 μL of water prior to LC/MS-MS analysis.

MDCK Permeability Assay Protocol

The MDCKI (Madin-Darby canine kidney) cell line used in the permeability assay was acquired from American Type Culture Collection (Manassas, VA). The cells were seeded on 24-well Millicell plates (Millipore, Billerca, MA) 4 days prior to use (polyethylene terephtalate membrane, 1 mm pore size) at a seeding density of 2.5×10^5 cells/mL at 37 °C with 5% CO_2 and 95% humidity. Compound was tested at 10 μM (MDCKI) in the apical-to-basolateral (A-B) and basolateral-to-apical (B-A) directions. The compound was dissolved in transport buffer consisting of Hank's balanced salt solution and 10 mM HEPES (Invitrogen Corporation, Grand Island, NY). Transepithelial electrical resistance (TEER) and lucifer yellow (LY) permeability were used to monitor monolayer integrity at the beginning and the end of the experiments, respectively. Compound was analyzed by LC-MS/MS. The apparent permeability (P_{app}), in the A-B and B-A directions, was calculated as:

$P_{app} = (dQ/dt)\bullet(1/AC_0)$

Where: dQ/dt = rate of compound appearance in the receiver compartment; A = Surface area of the insert; C_0= Initial substrate concentration at T0.

The efflux ratio (ER) was calculated as ($P_{app,\ B\text{-}A}/P_{app,\ A\text{-}B}$).

Time-dependent inhibition (TDI) assay

Time-dependent CYP inhibition experiments were carried out as described in:

(a) Mukadam, S.; Tay, S.; Tran, D.; Wang, L.; Delarosa, E. M.; Khojasteh, S. C.; Halladay, J.; Kenny, J. R. Evaluation of time-dependent cytochrome P450 inhibition in a high-throughput, automated assay: Introducing a novel area under the curve shift approach. *Drug Metab. Lett*. **2012**, *6*, 45–53.

(b) Obach, R. S.; Walsky, R. L.; Venkatakrishnan, K. Mechanism-based inactivation of human cytochrome P450 enzymes and the prediction of drug-drug interactions. *Drug Metab. Dispos.* **2007**, *35*, 246–255.

PK Studies

The pharmacokinetics of compound **25** was evaluated following a single intravenous bolus (IV) dose of 1 mg/kg as a solution in 35% PEG400 in water, and oral dose (PO) of 25 mg/kg as a suspension in 0.5% methylcellulose, 0.2% Tween in water (MCT). Six female C57BL/6 mice (6-9 weeks old) ranging from 15 to 25 g were obtained from Lingchang/Vital River Laboratory Animal Co. (Beijing, China). The IV and PO groups consisted of 3 animals each.

Animals were not fasted before dosing. Serial blood samples (10μL per mouse per time point) were collected via tail nick at 0.033 (IV), 0.25, 0.5 (PO), 1, 2, 4, 6, 8, and 24 hours post dose,

and were immediately placed into tubes containing 40 µL of 1.7mg/ml Potassium (K2) EDTA in water. Diluted blood samples were mixed and then stored at -70 °C or lower until bioanalysis. The concentration of test compound in each blood sample was determined by a non-validated LC-MS/MS assay at Wuxi AppTech, Inc. Pharmacokinetic analysis was performed at Genentech using non-compartmental analysis (NCA) with Phoenix® WinNonlin™ version 6.4.

Pharmacokinetic study of 25 following a single intravenous or oral administration to female C57BL/6 mice:

PK Parameter	**Mean**	**SD**
IV CL (mL/min/Kg)	56.6	1.61
IV V_{ss} (L/Kg)	1.92	0.466
IV MRT (h)	0.564	0.120
PO F (%)	13.1	3.8
PO MRT (h)	1.8	0.330

X-ray Crystallography Protocols

METHODS

Protein purification

HPK1 S171A (HPK1_SA) and HPK1 T165E/S171E (HPK1_TSEE) proteins were expressed and purified following a previously published protocol (Wu, 2019).

Crystallization, data collection and structure determination

HPK1_S171A and HPK1_TSEE were crystallized and soaked with compounds following a previously published protocol (Wu, 2019).

X-ray diffraction data were collected under cryogenic temperature using rotation method at various synchrotrons as described below. Each data set was collected from a single crystal.

The direction data of HPK1_SA + **3** were collected at the Advanced Light Source (ALS) beam line 5.0.5 using an ADSC Q315 CCD detector. The raw images were integrated using program iMOSFLM (Battye, 2011) and scaled using program AIMLESS (Evans, 2013). The diffraction pattern was severely anisotropic and resulted in relatively low completeness. We performed anisotropic scaling with program STARANISO (Tickle, 2018).

The diffraction data of HPK1_TSEE + **GNE1858** were collected at the Advanced Photon Source (APS) beamline 21-IDF with a Rayonix M225 CCD detector. Data reduction was done using XDS (Kabsch, 2010) and the CCP4 program suite (Winn, 2011).

The diffraction data of HPK1_TSEE + **14** were collected at Stanford Synchrotron Radiation Light-source (SSRL) beamline 12-2 with a PILATUS 6M detector. Data reduction was done using XDS (Kabsch, 2010) and the CCP4 program suite (Winn, 2011).

The diffraction data of HPK1_TSEE + **17** were collected at SSRL beamline 12-2 with a PILATUS 6M detector. Data reduction was done using HPK2000 (Otwinowski, 1997).

The apo HPK1_SA + **3** structure was phased by molecular replacement (MR) using program Phaser (McCoy, 2007). The HPK1_SA apo structure (PDB:6CQE) was used as the MR search model. For HPK1_TSEE + **GNE1858,** HPK1_TSEE + **14,** and HPK1_TSEE + **17**, the HPK1_TSEE apo structure (PDB:6CQD) was used as the MR search model. For all cases, initial difference electron density indicated ligand presence in the ATP binding site. Manual rebuilding was performed with graphics program COOT (Emsley, 2004). The structure was further refined iteratively using program REFMAC5 (Murshudov, 1997) and PHENIX (Adams, 2010) using maximum likelihood target functions, anisotropic individual B-factor refinement and TLS refinement. The data reduction and structure refinement statistics are shown in Table S1.

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Table S1 Crystallography statistics

	HPK1_SA **+ 2**	HPK1_TSEE + **GNE1858**	HPK1_TSEE **+ 14**	HPK1_TSEE **+ 17**
PDB code	7R9L	7R9N	7R9P	7R9T
Space group	$C222_1$	P1	P1	P1
Unit cell	*a*=90.9Å, *b*=96.8Å, *c*=76.3Å, α=β=γ=90°	*a*=52.0Å, *b*=58.0Å, *c*=61.6Å, α=70.4°, β=66.4°, γ=68.6°	*a*=53.3Å, *b*=57.1Å, *c*=61.6Å, α=85.8, β=85.4°, γ=67.6°	*a*=52.3Å, *b*=58.3Å, *c*=61.7Å, α=70.0, β=66.2°, γ=68.2°
Resolution	2.33 Å	1.50 Å	2.27 Å	2.00 Å
Total measured reflections	40331 (2751) [1]	195029 (28924)[1]	106277 (15298) [1]	35176 (3131) [1]
Completeness (%)	81.2 (53.0) (ellipsoidal) 58.3 (14.3) (Spherical)	93.9 (94.1)	88.8 (87.3)	87.1 (77.9)
Redundancy	4.7 (6.4)	2.2 (2.2)	3.9 (3.9)	2.2 (2.1)
I/σ	7.1 (1.0)	11.7 (3.2)	14.3 (2.5)	8.9 (2.5)
Rsym	0.134 (1.664)	0.050 (0.241)	0.050 (0.417)	0.116 (0.312)
$CC_{1/2}$ in highest resolution shell	0.558	0.883	0.852	0.765
Resolution range	50-2.33 Å	50 - 1.50 Å	50-2.27 Å	50-2.00 Å
Rcryst / Rfree2	0.227/0.284	0.166/0.191	0.210/0.232	0.198/0.229
Non-hydrogen atoms	2249	5588	4795	5263
Water molecules	6	881	174	654
Average B	62.4 $Å^2$	20.1 $Å^2$	51.5 $Å^2$	24.5 $Å^2$
r.m.s.d. bond lengths	0.003 Å	0.006 Å	0.004 Å	0.004 Å
r.m.s.d. angles	0.635°	0.941°	0.639°	0.665°
Ramachandran	0.897/0.099/0.004/0	0.928/0.072/0/0	0.911/0.087/0.002/0	0.916/0.082/0.002/0

[1]Values in parentheses are of the highest resolution shell

[2]Value of Rfree is calculated for 5% randomly chosen reflections not included in the refinement.