

## Identification and optimisation of 7-azaindole PAK1 inhibitors with improved potency and kinase selectivity

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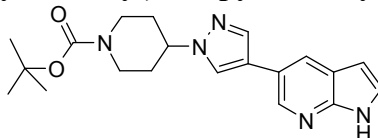
## Procedures for synthesis and characterisation of compounds

### General

All solvents and chemicals used were reagent grade. Anhydrous solvents tetrahydrofuran (THF), methanol (MeOH), dichloromethane (DCM), dimethoxyethane (DME) were purchased from Aldrich. Flash column chromatography was carried out using prepacked silica cartridges (from 4 g to 300 g) from Biotage or Crawford and eluted using an Isco Companion system. Preparative HPLC was carried out on a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 19 mm diameter, 100 mm length, gradient 5 to 95% MeCN/1% NH<sub>3</sub> in H<sub>2</sub>O. Purity and characterization of compounds were established by a combination of liquid chromatography–mass spectroscopy (LC-MS) and NMR analytical techniques. <sup>1</sup>H NMR spectra were recorded on a Bruker Avance or Avance II spectrometer at a proton frequency of 300, 400 or 500 MHz and were determined in CDCl<sub>3</sub>, DMSO-*d*<sub>6</sub> or MeOD. Chemical shifts are reported in ppm relative to tetramethylsilane (TMS) (0.00 ppm) or solvent signal. Splitting patterns are indicated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad peak. Merck precoated thin layer chromatography (TLC) plates (silica gel 60 F<sub>254</sub>, 0.25 mm) were used for TLC analysis.

### 3-(2-Chlorobenzyl)-5-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine (1)

#### *tert*-Butyl 4-(4-(1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (42)

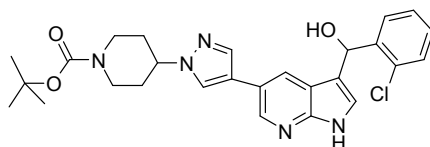


To a degassed mixture of *tert*-butyl 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (**41**) (1.00 g, 2.12 mmol), 5-bromo-1H-pyrrolo[2,3-b]pyridine (0.348 g, 1.77 mmol), DME (20 mL), and water (2 mL) were added sequentially K<sub>2</sub>CO<sub>3</sub> (0.733 g, 5.30 mmol) and 1,1'-bis(diphenylphosphino)ferrocene-palladium dichloride (0.145 g, 0.18 mmol). The resulting red mixture was warmed to 100 °C. After 2 h, the mixture was cooled to rt and diluted with EtOAc (100 mL). The mixture was washed with brine (75 mL) and dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated under reduced pressure. The resulting residue was purified by flash silica chromatography, elution gradient 50 to 100% EtOAc in hexanes for 15 min followed by isocratic 10% methanol in EtOAc for 8 min to afford the title compound as a beige foam solid (0.598 g, 92%).

*m/z* (ES<sup>+</sup>) [M+H]<sup>+</sup> = 368;

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  1.43 (s, 9H), 1.82 (dd, 2H), 2.06 (d, 2H), 2.94 (br s, 2H), 3.96 - 4.15 (m, 2H), 4.37 (s, 1H), 6.42 (dd, 1H), 7.44 (t, 1H), 7.91 (s, 1H), 8.10 (d, 1H), 8.28 (s, 1H), 8.48 (d, 1H), 11.56 (br s, 1H).

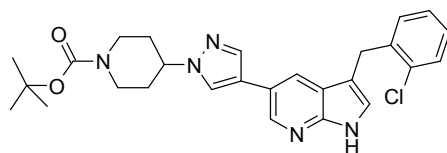
#### *tert*-Butyl 4-(4-(3-((2-chlorophenyl)(hydroxy)methyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate



To a solution of **42** (0.27 mL, 2.39 mmol) in MeOH (21 mL) cooled to 0 °C was added KOH (0.855 g, 15.2 mmol). The ice bath was removed, and the reaction was stirred for 18 h. The red solution was diluted with EtOAc (100 mL) and washed with brine (75 mL). The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated under reduced pressure. The resulting residue was purified by flash silica chromatography, elution gradient 100% EtOAc for 50 min to afford the title compound (0.473 g, 43%).

$m/z$  ( $ES^+$ )  $[M+H]^+ = 508$ .

***tert*-Butyl 4-(4-(3-(2-chlorobenzyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate**

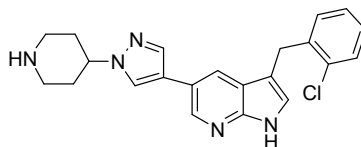


To a solution of *tert*-butyl 4-(4-(3-(2-chlorophenyl)(hydroxy)methyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (0.2 g, 0.39 mmol) in DCM (1.9 mL) was added sequentially triethylsilane (1.51 mL, 9.45 mmol) and TFA (0.485 mL, 6.30 mmol). After stirring at rt for 1 h, the yellow solution was concentrated under reduced pressure to minimal volume and the resulting solution was diluted with EtOAc (50 mL) and basified with saturated aqueous  $NaHCO_3$ . The layers were separated and the organic layer was washed with brine (20 mL), dried over  $Na_2SO_4$ , filtered, and concentrated under reduced pressure. The resulting residue was purified by flash silica chromatography, eluting with 100% EtOAc in hexanes to afford the title compound as a light yellow solid (0.124 g, 64%).

$m/z$  ( $ES^+$ )  $[M+H]^+ = 492$ ;

$^1H$  NMR (300 MHz,  $DMSO-d_6$ )  $\delta$  1.43 (s, 9H), 1.82 (dd, 2H), 2.05 (d, 2H), 2.94 (br s, 2H), 4.06 (d, 2H), 4.16 (s, 2H), 4.37 (br s, 1H), 5.76 (s, 1H), 7.14 - 7.25 (m, 2H), 7.29 - 7.39 (m, 1H), 7.41 - 7.50 (m, 1H), 7.88 (s, 1H), 8.05 (d, 1H), 8.20 - 8.33 (m, 1H), 8.47 (d, 1H), 11.41 (br s, 1H).

**3-(2-Chlorobenzyl)-5-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine (1)**



To a mixture of *tert*-butyl 4-(4-(3-(2-chlorobenzyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (0.120 g, 0.24 mmol) and 4 M HCl in dioxane (5 mL, 20 mmol) was added MeOH (2 mL). After stirring at rt for 5 min, all solids dissolved. The light yellow solution was stirred at rt for an additional 6 min and was then concentrated under reduced pressure to afford crude product (160 mg) which was purified by preparative HPLC, XBridge Prep C18 OBD, 5  $\mu m$  silica, 19 x 100 mm, gradient 30 to 50% MeCN/0.2%  $NH_4OH$  in  $H_2O$  to afford the title compound as a white solid (33 mg, 35%).

$m/z$  ( $ES^+$ )  $[M+H]^+ = 392$

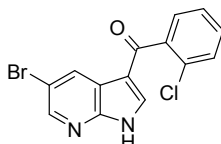
HRMS calculated for  $C_{22}H_{22}ClN_5$   $[M+H]^+ 392.1642$ , found 392.1664;

$^1H$  NMR (300 MHz,  $DMSO-d_6$ )  $\delta$  1.62 - 1.84 (m, 2H), 1.91 (d, 2H), 2.48 - 2.60 (m, 2H), 2.98 (d, 2H), 3.93 - 4.24 (m, 3H), 7.07 - 7.14 (m, 1H), 7.14 - 7.23 (m, 2H), 7.23 - 7.33 (m, 1H), 7.33 - 7.45 (m, 1H), 7.79 (s, 1H), 7.98 (d, 1H), 8.14 (s, 1H), 8.40 (d, 1H), 11.32 (br s, 1H) NH not observed.

**(2-Chlorophenyl)-[5-[1-(4-piperidyl)pyrazol-4-yl]-1H-pyrrolo[2,3-b]pyridin-3-yl]methanone (2)**

**(5-Bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)-(2-chlorophenyl)methanone**

**General procedure A: Friedel-Crafts acylation**



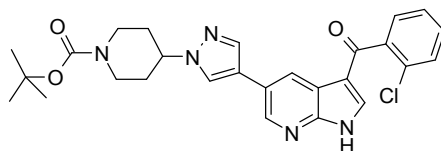
To a suspension of 5-bromo-1H-pyrrolo[2,3-b]pyridine (9 g, 45.7 mmol) in DCM (190 mL) was added over 5 min powdered aluminum chloride (12.2 g, 91.4 mmol). There was a exotherm of around 5  $^{\circ}C$  and

the faint yellow suspension darkened and went into solution. After 45 min, a solution of 2-chlorobenzoyl chloride (8.97 mL, 70.8 mmol) in DCM (20 mL) was added (slight exotherm of around 5 °C). The reaction mixture (now a pale yellow suspension) was stirred at rt for 18 h then cooled to 0 °C and quenched with MeOH (40 mL) and diluted with EtOAc (100 mL). The mixture was evaporated to dryness and the resulting cream solid was suspended in EtOAc (400 mL). This was then cautiously basified with saturated aqueous NaHCO<sub>3</sub> and the solid material removed by filtration. The layers were separated and the organic layer was washed with brine (100 mL), dried (MgSO<sub>4</sub>), filtered, and concentrated under reduced pressure. The resulting solid was triturated with Et<sub>2</sub>O to afford the title compound as a pale green solid (7.92 g, 52%).

m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 335;

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 7.50 (m, 1H), 7.54 - 7.63 (m, 3H), 7.93 (d, 1H), 8.49 (d, 1H), 8.54 (d, 1H), 12.95 (s, 1H).

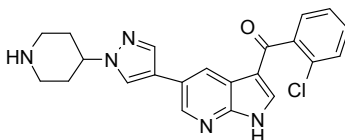
**tert-Butyl 4-[4-[3-(2-chlorobenzoyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyrazol-1-yl]piperidine-1-carboxylate**



(5-Bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)(2-chlorophenyl)methanone and *tert*-butyl 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (450 mg, 1.19 mmol) were weighed out into an round-bottomed flask followed by the addition of toluene (3 mL), EtOH (6 mL), H<sub>2</sub>O (3 mL). To this was added K<sub>3</sub>PO<sub>4</sub> (886 mg, 4.17 mmol) and the reaction mixture degassed with nitrogen several times. Pd(*t*Bu<sub>3</sub>P)<sub>2</sub> (30 mg, 0.05 mmol) was then added and the reaction degassed 2 times and then heated to 60 °C under nitrogen. After 30 mins further Pd(*t*Bu<sub>3</sub>P)<sub>2</sub> was added and the reaction heated at 80 °C for 18 h. Solvent was removed and the residue taken up in EtOAc (50 mL) and H<sub>2</sub>O (30 mL), shaken, EtOAc layer collected and aqueous layer re-extracted with EtOAc (50 mL). The combined organics were then washed with brine, dried (MgSO<sub>4</sub>), filtered and concentrated to dryness. EtOAc (20 mL) was added to crude product and the resulting solid filtered. The filtrate was concentrated and purified by flash silica chromatography elution gradient 10 to 80% EtOAc in isohexane to afford the title compound a yellow solid (112 mg, 18%).

**(2-Chlorophenyl)-[5-[1-(4-piperidyl)pyrazol-4-yl]-1H-pyrrolo[2,3-b]pyridin-3-yl]methanone (2)**

**General procedure B: TFA removal of Boc group**



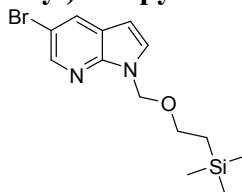
*tert*-Butyl 4-[4-[3-(2-chlorobenzoyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]pyrazol-1-yl]piperidine-1-carboxylate (112 mg, 0.22 mmol) was stirred in DCM (1.5 mL) and TFA (0.5 mL) added. The reaction was stirred at rt for 1 h and then evaporated to dryness. The crude material was purified by preparative HPLC to afford the title compound (44 mg, 10%).

m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 406;

HRMS calculated for C<sub>22</sub>H<sub>20</sub>ClN<sub>5</sub>O [M+H]<sup>+</sup> 406.1435, found 406.1452;

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 1.85 (qd, 3H), 2.02 (d, 2H), 2.57 - 2.68 (m, 1H), 3.07 (d, 2H), 4.07 (br s, 1H), 4.23 (tt, 1H), 7.47 - 7.52 (m, 3H), 7.54 - 7.63 (m, 4H), 7.78 (s, 1H), 7.94 (d, 1H), 8.35 (s, 1H), 8.54 (d, 1H), 8.67 (d, 1H).

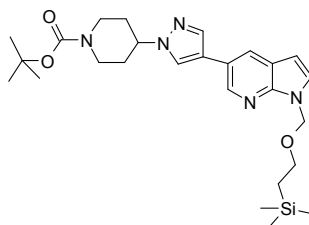
**3-(2-Chlorophenyl)-5-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine (3)**

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

Sodium hydride (0.406 g, 10.2 mmol) was added to 5-bromo-1H-pyrrolo[2,3-b]pyridine (1 g, 5.08 mmol) in THF (25 mL) under nitrogen at 0 °C. The resulting solution was stirred at 0 °C for 30 min. (2-(Chloromethoxy)ethyl)trimethylsilane (1.35 mL, 7.61 mmol) was then added and the resulting bright yellow reaction mixture was stirred for 2 h at rt. The reaction mixture was diluted with water (150 mL), extracted twice with EtOAc (75 mL). The organic layer was dried (MgSO<sub>4</sub>), filtered and evaporated to afford a brown oil which was purified by flash silica chromatography, elution gradient 2 to 10% MeOH in DCM to afford the title compound as a colourless oil (1.31 g, 79%).

m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 327;

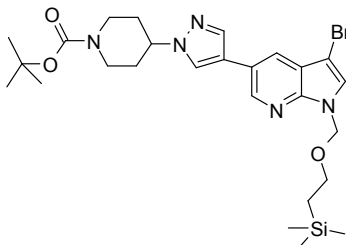
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ -0.00 (s, 9H), 0.96 (dd, 2H), 3.60 (dd, 2H), 5.69 (s, 2H), 6.50 (d, 1H), 7.40 (d, 1H), 8.05 (d, 1H), 8.41 (d, 1H).

***tert*-Butyl 4-(4-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate**

*tert*-Butyl 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (749 mg, 1.99 mmol), 5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (500 mg, 1.53 mmol) and K<sub>2</sub>CO<sub>3</sub> (633 mg, 4.58 mmol) were added to DME (20 mL) and water (6.7 mL) and degassed with nitrogen for 5 min. Tetrakis(triphenylphosphine)palladium(0) (88 mg, 0.08 mmol) was added and the reaction heated at 80 °C for 30 min. The reaction mixture was poured into 50 mL citric acid (50 mL), extracted with EtOAc (3 x 50 mL), and the organic layers washed with water (100 mL) then brine (100 mL), dried (MgSO<sub>4</sub>), filtered and the solvent evaporated to yield crude product as a brown oil (1.14 g). The crude product was purified by flash silica chromatography, elution gradient 1 to 10% MeOH in DCM to afford the title compound as a pale yellow oil (480 mg, 63%).

m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 498;

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ -0.07 (s, 9H), 0.90 (m, 2H), 1.49 (s, 9H), 1.99 (m, 2H), 2.18 (m, 2H), 2.92 (t, 2H), 3.56 (m, 2H), 4.30 (m, 3H), 5.67 (s, 2H), 6.50 (d, 1H), 7.34 (d, 1H), 7.68 (s, 1H), 7.80 (m, 1H), 7.96 (d, 1H), 8.47 (d, 1H).

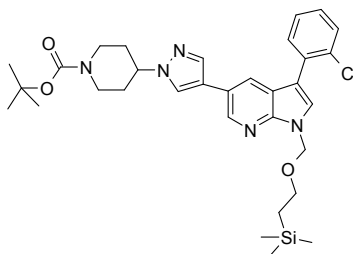
***tert*-Butyl 4-(4-(3-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate**

*tert*-Butyl 4-(4-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (220 mg, 0.44 mmol) in DCM (5 mL) was cooled to 0 °C. Bromine (0.023 mL, 0.44 mmol) in DCM (2 mL) was then added dropwise and the yellow reaction mixture stirred at 0 °C for 10 min. The reaction mixture was poured into sodium metabisulfite solution (25 mL), then extracted with DCM (2 x 20 mL). The organic extracts were washed with water (20 mL) then brine (20 mL), dried (MgSO<sub>4</sub>), filtered and the solvent evaporated to afford the title compound as a white gum (255 mg, 100%).

*m/z* (ES<sup>+</sup>) [M+H]<sup>+</sup> = 576;

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ -0.06 (s, 9H), 0.91 (m, 2H), 1.49 (s, 9H), 1.97 (m, 2H), 2.19 (d, 2H), 2.93 (t, 2H), 3.56 (m, 2H), 4.31 (m, 3H), 5.64 (s, 2H), 7.38 (s, 1H), 7.72 (s, 1H), 7.83 (s, 1H), 7.88 (d, 1H), 8.50 (d, 1H).

***tert*-Butyl 4-(4-(3-(2-chlorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate**

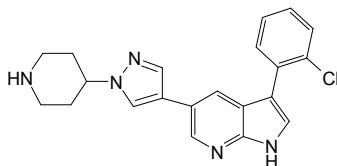


*tert*-Butyl 4-(4-(3-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (500 mg, 0.87 mmol), (2-chlorophenyl)boronic acid (176 mg, 1.13 mmol) and K<sub>2</sub>CO<sub>3</sub> (360 mg, 2.60 mmol) were added to DME (10 mL) and water (3.33 mL) and degassed thoroughly under nitrogen for 5 min. Tetrakis(triphenylphosphine)palladium(0) (50.1 mg, 0.04 mmol) was then added and the reaction heated at 75 °C for 4 h. The reaction mixture was poured into water (100 mL), extracted with EtOAc (2 x 20 mL), the organic layer washed with water (50 mL) and then brine (50 mL), dried (MgSO<sub>4</sub>), filtered and evaporated to afford crude product as a brown oil. The crude product was purified by flash silica chromatography, elution gradient 10 to 100% EtOAc in heptane. Pure fractions were evaporated to dryness to afford the title compound as a pale yellow oil (360 mg, 68%).

*m/z* (ES<sup>+</sup>) [M+H]<sup>+</sup> = 608;

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ -0.05 (s, 9H), 1.26 (t, 2H), 1.48 (s, 9H), 1.97 (qd, 2H), 2.18 (m, 2H), 2.91 (t, 2H), 3.63 (m, 2H), 4.30 (ddt, 3H), 5.74 (s, 2H), 7.30 (td, 1H), 7.35 (m, 1H), 7.53 (m, 2H), 7.57 (s, 1H), 7.67 (s, 1H), 7.78 (s, 1H), 7.94 (d, 1H), 8.52 (d, 1H).

**3-(2-Chlorophenyl)-5-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine (3)**



6N HCl in IPA (5 mL, 30.0 mmol) was added to *tert*-butyl 4-(4-(3-(2-chlorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (360 mg, 0.59 mmol) and the mixture stirred for 40 min at 60 °C. The reaction mixture was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH<sub>3</sub>/MeOH and pure fractions were evaporated to dryness to afford crude product as a colourless gum. The crude product was purified by flash silica chromatography, elution gradient 1 to 10% MeOH/NH<sub>3</sub> in DCM to afford the title compound as a white crystalline solid (64.5 mg, 29%).

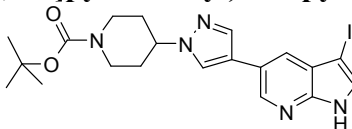
*m/z* (ES<sup>+</sup>) [M+H]<sup>+</sup> = 378;

HRMS calculated for C<sub>21</sub>H<sub>20</sub>ClN<sub>5</sub> [M+H]<sup>+</sup> 378.1485, found 378.1497;

$^1\text{H}$  NMR (400 MHz, MeOD)  $\delta$  2.32 (dtd, 4H), 3.20 (m, 2H), 3.37 (s, 1H), 3.55 (dt, 2H), 4.56 (dd, 1H), 7.38 (m, 2H), 7.57 (ddd, 2H), 7.60 (s, 1H) 7.91 (m, 1H), 8.06 (d, 1H), 8.11 (d, 1H), 8.49 (d, 1H), NH not observed.

### **3-(2-Chlorophenyl)sulfonyl-5-[1-(4-piperidyl)pyrazol-4-yl]-1H-pyrrolo[2,3-b]pyridine (4)**

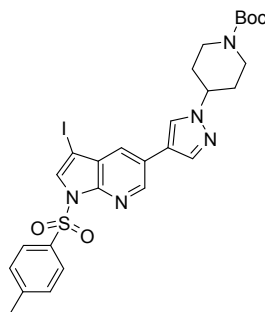
***tert*-Butyl 4-(4-(3-iodo-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine- 1-carboxylate**



KOH (5.0 g, 88 mmol) was added to a solution of *tert*-butyl 4-(4-(1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine- 1-carboxylate (8.0 g, 22 mmol) in DMF (200 mL). The mixture was stirred for 20 min and cooled to 0 °C. Iodine (5.6 g, 22 mmol) was added in portions and the reaction mixture was stirred for 30 min. Water (800 mL) was added and the resulting mixture was extracted with EtOAc (3 x 500 mL). The combined organic phases were washed with 5% KHSO<sub>4</sub> solution (3 x 500 mL), saturated NaHCO<sub>3</sub> solution (3 x 500 mL) and brine (500 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to dryness. The residue was purified by flash column chromatography, eluting with 3% MeOH in DCM to afford the title compound (8.1 g, 75%).

$^1\text{H}$  NMR (300 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  1.45 (s, 9H), 1.85 (m, 2H), 2.10 (m, 2H), 2.90 (m, 2H), 4.10 (m, 2H), 7.38 (m, 1H), 7.75 (s, 1H), 7.82 (s, 1H), 8.00 (s, 1H), 8.42 (s, 1H), 8.54 (s, 1H), 12.07 (br s, 1H).

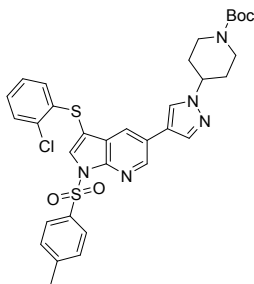
***tert*-Butyl 4-(4-(3-iodo-1-tosyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl) piperidine-1-carboxylate**



NaH (60% dispersion in mineral oil, 530 mg, 13.2 mmol) was added to a solution of *tert*-butyl 4-(4-(1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine- 1-carboxylate (5.0 g, 10.3 mmol) in DMF (100 mL) at 0 °C. The mixture was stirred for 30 min and tosyl chloride (2.3 g, 12.1 mmol) was added. The reaction mixture was stirred at rt for 3 h and then quenched with ice-water (500 mL). The precipitate was collected by filtration, washed with water and dried under vacuum to afford the title compound (5.8 g, 88%).

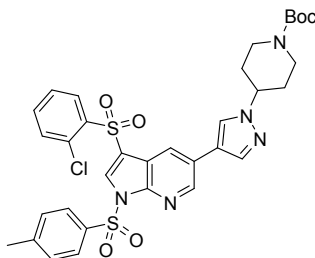
$^1\text{H}$  NMR (300 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  1.43 (s, 9H), 1.80 (m, 2H), 2.05 (m, 2H), 2.35 (s, 3H), 2.95 (m, 2H), 4.08 (m, 2H), 4.37 (m, 1H), 7.44 (d, 2H), 7.91 (d, 1H), 8.03 (d, 2H), 8.07 (s, 1H), 8.13 (s, 1H), 8.51 (s, 1H), 8.69 (d, 1H).

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



CuI (1.6 g, 8.6 mmol) and K<sub>2</sub>CO<sub>3</sub> (1.3 g, 9.2 mmol) were added to a solution of *tert*-butyl 4-(4-(3-iodo-1-tosyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl) piperidine-1-carboxylate (3.0 g, 6.1 mmol) and 2-chlorobenzenethiol (1.1 g, 7.3 mmol) in DMF (120 mL). The reaction mixture was heated at 70 °C for 5 h under nitrogen. After cooling, the reaction was quenched with 10% aqueous ammonia solution (300 mL) and the resulting mixture was extracted with EtOAc (3 x 300 mL). The combined organic phases were washed with saturated NaHCO<sub>3</sub> solution (3 x 300 mL) and brine (300 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to dryness. The residue was purified by flash column chromatography, eluting with 5% MeOH in DCM to the title compound (2.2 g, 71%) which was used directly in the next step.

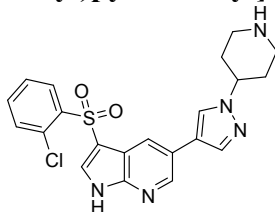
***tert*-Butyl 4-(4-(3-(2-chlorophenylsulfonyl)-1-tosyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate**



*m*-CPBA (0.84 g, 3.9 mmol) was added to a solution of *tert*-butyl 4-(4-(3-(2-chlorophenylthio)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl) piperidine-1-carboxylate (2.58 g, 3.9 mmol) in DCM (50 mL) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C and the solvent was removed under vacuum. The residue was purified by flash column chromatography, eluting with 5% MeOH in DCM to afford the title compound (580 mg, 21%).

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 1.43 (s, 9H), 1.80 (m, 2H), 2.05 (m, 2H), 2.36 (s, 3H), 2.95 (m, 2H), 4.08 (m, 2H), 4.37 (m, 1H), 7.45 (d, 2H), 7.50 (m, 1H), 7.55 (m, 1H), 7.75 (m, 1H), 7.90 (s, 1H), 7.95 (s, 1H), 8.05 (d, 2H), 8.38 (s, 1H), 8.44 (d, 1H), 8.65 (s, 1H), 8.70 (d, 1H)

**3-(2-Chlorophenyl)sulfonyl-5-[1-(4-piperidyl)pyrazol-4-yl]-1H-pyrrolo[2,3-b]pyridine (4)**



K<sub>2</sub>CO<sub>3</sub> (207 mg, 1.5 mmol) was added to a solution of *tert*-butyl 4-(4-(3-(2-chlorophenylsulfonyl)-1-tosyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (350 mg, 0.5 mmol) in MeOH (25 mL). The reaction mixture was stirred at rt for 2 h under nitrogen and the solvent was removed under vacuum. The residue was purified by flash column chromatography, eluting with 5% MeOH in DCM to afford *tert*-butyl 4-[4-[3-(2-chlorophenyl)sulfonyl-1H-pyrrolo[2,3-b]pyridin-5-yl]pyrazol-1-yl]piperidine-1-carboxylate which was dissolved in dioxane (5 mL). 4M HCl in dioxane solution (10 mL) was added at 0 °C with stirring and the resulting solution was stirred at rt for 5 h. The mixture was concentrated in vacuum and the residue was treated with MeOH to remove the residual acid to afford the title compound (160 mg, 72%) as its HCl salt.



m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 442;

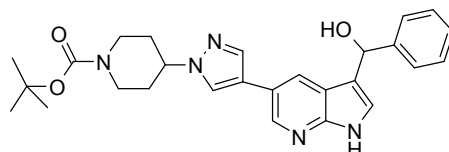
HRMS calculated for C<sub>21</sub>H<sub>20</sub>ClN<sub>5</sub>O<sub>2</sub>S.ClH [M+H]<sup>+</sup> 442.1104, found 442.1115;

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 2.20 (m, 4H), 3.10 (m, 2H), 3.65 (m, 2H), 4.53 (m, 1H), 7.55 - 7.68 (m, 3H), 8.03 (s, 1H), 8.10 (s, 1H), 8.46 (d, 1H), 8.50 - 8.60 (m, 2H), 8.68 (d, 1H), 8.96 (m, 1H), 9.22 (m, 1H), 13.05 (s, 1H).

### **Phenyl(5-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone (5)**

***tert*-Butyl 4-(4-(3-(hydroxy(phenyl)methyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (43)**

**General procedure C: Benzyl alcohol formation using KOH**

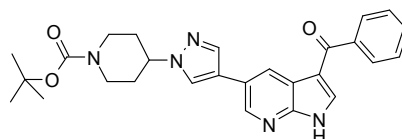


To a solution of *tert*-butyl 4-(4-(1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (**42**) (0.2 g, 0.54 mmol) and benzaldehyde (0.072 mL, 0.71 mmol) in MeOH (1.8 mL) at rt was added KOH (0.214 g, 3.81 mmol) in one portion. After 18 h the reaction was poured into EtOAc and washed with 50% brine. The organic layer was then dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography, elution gradient 50 to 100% EtOAc to afford the title compound as a white foam (231 mg, 45%).

m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 474.

***tert*-Butyl 4-(4-(3-benzoyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate**

**General procedure D: MnO<sub>2</sub> oxidation**

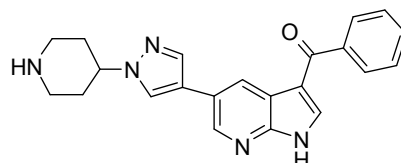


A mixture of **43** (0.231 g, 0.49 mmol), manganese dioxide (0.509 g, 5.85 mmol), and DCM (49 mL) was stirred at rt for 20 h. The mixture was then filtered, washed with DCM (20 mL), and the filtrate was concentrated under reduced pressure to afford the title compound as a light yellow foam solid (0.201 g, 87%).

m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 472.

### **Phenyl(5-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone (5)**

**General procedure E: HCl removal of protecting group**



A solution of *tert*-butyl 4-(4-(3-benzoyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (0.201 g, 0.43 mmol), MeOH (0.5 mL), and 4 M HCl in dioxane (3 mL, 12.00 mmol) was stirred at rt for 15 min then concentrated under reduced pressure to afford crude product which was

purified by preparative HPLC, XBridge Prep C18 OBD, 5  $\mu$ m silica, 19 x 100mm, gradient 25 to 45% MeCN/0.2% NH<sub>4</sub>OH in H<sub>2</sub>O to afford the title compound as a white solid (30 mg, 19%).

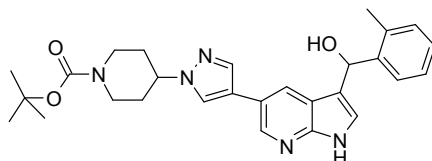
m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 372;

HRMS calculated for C<sub>22</sub>H<sub>21</sub>N<sub>5</sub>O [M+H]<sup>+</sup> 372.1824, found 372.1823;

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  1.62 - 1.86 (m, 2H), 1.86 - 2.04 (m, 2H), 2.47 - 2.64 (m, 2H), 2.99 (d, 2H), 3.96 - 4.34 (m, 1H), 7.33 - 7.63 (m, 3H), 7.67 - 7.81 (m, 2H), 7.87 (s, 1H), 7.98 (s, 1H), 8.27 (s, 1H), 8.58 (s, 2H) 2 x NH not observed.

**(5-(1-(Piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)(o-tolyl)methanone (6)**

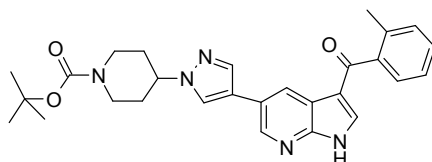
***tert*-Butyl 4-(4-(3-(methoxy(o-tolyl)methyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate**



**General procedure C** was used to afford the title compound as a white foam (180 mg, 26%).

m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 488.

***tert*-Butyl 4-(4-(3-(2-methylbenzoyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate**

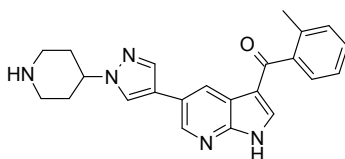


**General procedure D** was used to afford the title compound as a white foam (94 mg, 88%).

m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 486;

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  1.39 - 1.50 (m, 9H), 1.86 (dd, 2H), 1.99 - 2.13 (m, 2H), 2.30 (s, 3H), 2.95 (br s, 2H), 3.95 - 4.20 (m, 2H), 4.40 (br s, 1H), 7.30 - 7.49 (m, 4H), 7.71 (s, 1H), 7.95 (s, 1H), 8.41 (s, 1H), 8.62 (dd, 2H), 12.57 (s, 1H).

**(5-(1-(Piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)(o-tolyl)methanone (6)**



**General procedure E** was used to afford the title compound as a pale yellow solid (22 mg, 29%).

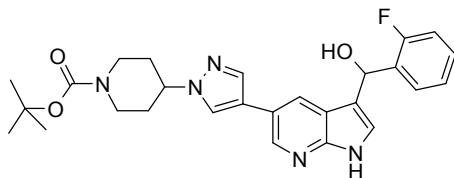
m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 386;

HRMS calculated for C<sub>23</sub>H<sub>23</sub>N<sub>5</sub>O [M+H]<sup>+</sup> 386.1981, found 386.1976;

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  1.77 (dq, 2H), 1.87 - 2.00 (m, 2H), 2.23 (s, 3H), 2.48 - 2.62 (m, 2H), 2.99 (d, 2H), 4.04 - 4.30 (m, 1H), 7.19 - 7.31 (m, 2H), 7.31 - 7.41 (m, 2H), 7.60 - 7.69 (m, 1H), 7.85 (s, 1H), 8.27 (s, 1H), 8.50 (d, 1H), 8.58 (d, 1H), 2 x NH not observed.

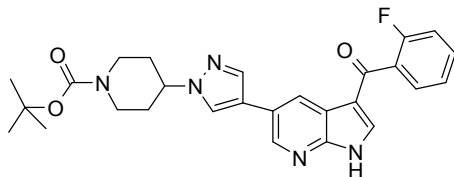
**(2-Fluorophenyl)(5-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone (7)**

***tert*-Butyl 4-(4-(3-((2-fluorophenyl)(hydroxy)methyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate**



**General procedure C** was used to afford the title compound as a white foam (240 mg, 42%).  
 $m/z$  ( $ES^+$ )  $[M+H]^+ = 492$ .

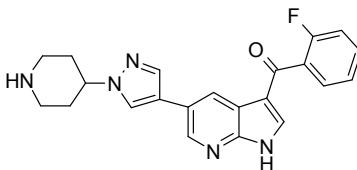
**tert-Butyl 4-(4-(3-(2-fluorobenzoyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate**



**General procedure D** was used to afford the title compound as a cream solid (198 mg, 85%).  
 $m/z$  ( $ES^+$ )  $[M+H]^+ = 490$ ;

$^1H$  NMR (300 MHz,  $DMSO-d_6$ )  $\delta$  1.44 (s, 9H), 1.86 (dd, 2H), 2.08 (d, 2H), 2.95 (br s, 2H), 4.07 (d, 2H), 4.41 (br s, 1H), 7.31 - 7.45 (m, 2H), 7.56 - 7.68 (m, 2H), 7.89 - 7.99 (m, 2H), 8.42 (s, 1H), 8.65 (dd, 2H), 12.68 (s, 1H).

**(2-Fluorophenyl)(5-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone (7)**



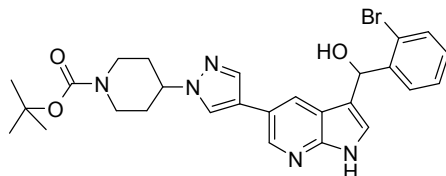
**General procedure E** was used to afford the title compound as a white solid (45 mg, 30%).  
 $m/z$  ( $ES^+$ )  $[M+H]^+ = 390$ ;

HRMS calculated for  $C_{22}H_{20}FN_5O$   $[M+H]^+ 390.1730$ , found 390.1744;

$^1H$  NMR (300 MHz,  $DMSO-d_6$ )  $\delta$  1.62 - 1.87 (m, 2H), 1.87 - 2.03 (m, 2H), 2.48 - 2.62 (m, 2H), 3.00 (d, 2H), 4.16 (tt, 1H), 7.19 - 7.39 (m, 2H), 7.46 - 7.64 (m, 2H), 7.77 - 7.98 (m, 2H), 8.28 (s, 1H), 8.53 (d, 1H), 8.59 (d, 1H), 2 x NH not observed.

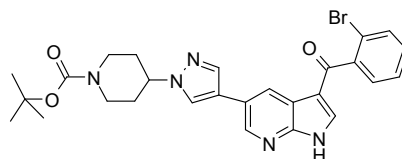
**2-([5-[1-(Piperidin-4-yl)-1H-pyrazol-4-yl]-1H-pyrrolo[2,3-b]pyridin-3-yl]carbonyl)benzonitrile (8)**

**tert-Butyl 4-(4-[3-[(2-bromophenyl)(hydroxy)methyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]-1H-pyrazol-1-yl)piperidine-1-carboxylate**



**General procedure C** was used to afford the title compound as a yellow solid (8.5 g, 95%).  
 $m/z$  ( $ES^+$ )  $[M+H]^+ = 552$ .

**tert-Butyl 4-(4-[3-[(2-bromophenyl)carbonyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]-1H-pyrazol-1-yl)piperidine-1-carboxylate**

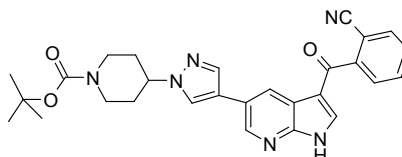


Into a 250-mL 3-necked round-bottom flask, was placed a solution of *tert*-butyl 4-(4-[3-[(2-bromophenyl)(hydroxy)methyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]-1H-pyrazol-1-yl)piperidine-1-carboxylate (8.5 g, 15.4 mmol) in THF (100 mL), Dess-Martin periodinane (7.2 g, 17.0 mmol). The resulting solution was stirred for 1 h at rt then diluted with EtOAc (100 mL) and saturated NaHCO<sub>3</sub> (100 mL). The solids were filtered. The resulting solution was extracted with EtOAc (100 mL) and the organic layers combined, washed with brine (100 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under vacuum. The resulting mixture was washed with EtOAc (100 mL) to afford the title compound as a off-white solid (4.8 g, 57%).

m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 550;

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 1.43 (s, 9H), 1.82 - 1.92 (m, 2H), 2.05 - 2.09 (d, 2H), 2.95 (br, 2H), 4.04 (d, 2H), 4.36 - 4.41 (m, 1H), 7.44 - 7.54 (m, 3H), 7.74 - 7.76 (m, 2H), 7.97 (s, 1H), 8.44 (s, 1H), 8.56 (d, 1H), 8.67 (d, 1H), 12.70 (s, 1H).

***tert*-Butyl 4-(4-[3-[(2-cyanophenyl)carbonyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]-1H-pyrazol-1-yl)piperidine-1-carboxylate**

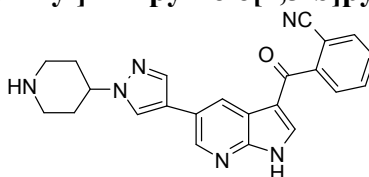


Into a 250-mL 3-necked round-bottom flask, was placed a solution of *tert*-butyl 4-(4-[3-[(2-bromophenyl)carbonyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]-1H-pyrazol-1-yl)piperidine-1-carboxylate (4.5 g, 8.18 mmol) in DMF (90 mL), Zn(CN)<sub>2</sub> (1.5 g, 12.82 mmol), Pd(dppf)Cl<sub>2</sub>CH<sub>2</sub>Cl<sub>2</sub> (1.35 g, 1.65 mmol), dppf (750 mg, 4.03 mmol). The resulting solution was stirred for 4 h at 140 °C. The reaction mixture was cooled. The reaction was then quenched by the addition of 400 mL of water. The solids were collected by filtration and washed with H<sub>2</sub>O (2 x 50 mL). The residue was purified by flash silica chromatography eluting with 100% EtOAc to afford the title compound as a yellow solid (2.5 g, 62%).

m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 497;

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 1.43 (s, 9H), 1.83 - 1.92 (m, 2H), 2.05 - 2.09 (d, 2H), 2.95 (br, 2H), 4.01 - 4.09 (m, 2H), 4.40 - 4.44 (m, 1H), 7.75 - 7.92 (m, 3H), 8.01 - 8.05 (m, 3H), 8.47 (s, 1H), 8.68 (d, 2H), 12.83 (s, 1H).

**2-([5-[1-(Piperidin-4-yl)-1H-pyrazol-4-yl]-1H-pyrrolo[2,3-b]pyridin-3-yl]carbonyl)benzonitrile (8)**



Into a 100-mL 3-necked round-bottom flask, was placed *tert*-butyl 4-(4-[3-[(2-cyanophenyl)carbonyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]-1H-pyrazol-1-yl)piperidine-1-carboxylate (1 g, 2.01 mmol) and 2 M HCl in ether (30 mL). The resulting solution was stirred for 1 h at rt. The resulting mixture was concentrated under vacuum. The resulting mixture was diluted with saturated K<sub>2</sub>CO<sub>3</sub> (20 mL) solution. The solids were collected by filtration and dried. This resulted in the title compound as a brown solid (600 mg, 75%).

m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 397;

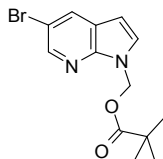
HRMS calculated for C<sub>23</sub>H<sub>20</sub>N<sub>6</sub>O [M+H]<sup>+</sup> 397.1777, found 397.1768;

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 1.79 - 1.90 (m, 2H), 2.03 - 2.05 (m, 2H), 2.58 - 2.66 (m, 2H), 3.05 (d, 2H), 4.19 - 4.28 (m, 1H), 7.74 - 7.79 (m, 1H), 7.82 - 7.90 (m, 2H), 7.98 - 8.05 (m, 3H), 8.40 (s, 1H), 8.65 - 8.69 (dd, 2H), 2 x NH not observed.

**(2-Methoxyphenyl)(5-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone (9)**

**(5-Bromo-1H-pyrrolo[2,3-b]pyridin-1-yl)methyl pivalate**

**General procedure F: Pivoylation**

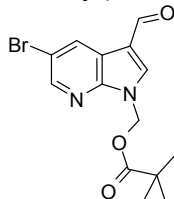


To a degassed solution of **38** (5.32 g, 27.00 mmol) in DMF (50 mL) at 0 °C with vigorous stirring was added 60 wt% sodium hydride in mineral oil (1.35 g, 33.8 mmol). After 15 min, chloromethyl pivalate (3.89 mL, 27.00 mmol) was added dropwise, and stirring was continued for 30 min. The reaction was then quenched with the addition of MeOH (5 mL), [CARE: gas evolution]. The mixture was poured into water (500 mL) and EtOAc (400 mL). The layers were separated and the organic layer was washed with water (500 mL) and brine (200 mL) before being dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated under reduced pressure. The resulting yellow oil was purified by flash silica chromatography eluting with 10% EtOAc in hexanes to afford the title compound as a clear colourless oil (4.91 g, 58%).

m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 311;

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 1.07 (s, 9H), 6.22 (s, 2H), 6.56 (d, 1H), 7.70 (d, 1H), 8.27 (d, 1H), 8.38 (d, 1H).

**(5-Bromo-3-formyl-1H-pyrrolo[2,3-b]pyridin-1-yl)methyl pivalate (44)**

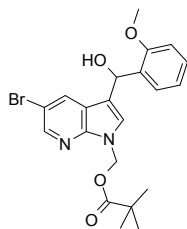


To a solution of (5-bromo-1H-pyrrolo[2,3-b]pyridin-1-yl)methyl pivalate (5.9 g, 19.0 mmol) in DMF (5.8 mL) at 0 °C was added slowly phosphorousoxychloride (1.91 mL, 20.5 mmol), resulting in a yellow-orange solution. Once addition was complete, the reaction was warmed to 50 °C and maintained under these conditions for 2 h. Approximately half way through this time period, another 5.8 mL of DMF was added to ensure adequate mixing of resultant yellow-orange mixture. The reaction was poured into a rapidly stirring mixture of EtOAc (200 mL) and saturated aqueous sodium bicarbonate (200 mL) at 0 °C. After basification was complete, the organic layer was washed with water (200 mL) and brine (200 mL) before being dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated under reduced pressure. The resulting light yellow oil was purified by flash silica chromatography, elution gradient 10 to 35% EtOAc in hexanes to afford the title compound as a white solid (4.52 g, 70%).

m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 341;

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 1.09 (s, 9H), 6.30 (s, 2H), 8.58 (s, 2H), 8.68 (s, 1H), 9.99 (s, 1H).

**(5-bromo-3-(hydroxy(2-methoxyphenyl)methyl)-1H-pyrrolo[2,3-b]pyridin-1-yl)methyl pivalate**

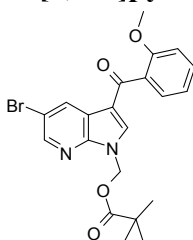


To a solution of **44** (0.406 g, 1.20 mmol) in THF (10 mL) at 0 °C was added dropwise 1 M (2-methoxyphenyl)magnesium bromide in THF (1.74 mL, 1.74 mmol), resulting in a yellow solution. After 5 min, the reaction was quenched with saturated aqueous ammonium chloride. The mixture was extracted with EtOAc (100 mL), and the organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated under reduced pressure. The resulting residue was purified by flash silica chromatography, elution gradient 10 to 75% EtOAc in hexanes to afford the title compound as a white semi-crystalline solid (0.518 g, 97%).

$m/z$  (ES<sup>+</sup>) [M+H]<sup>+</sup> = 449;

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  1.06 (s, 9H), 3.75 (s, 3H), 5.65 - 5.80 (m, 1H), 6.15 (s, 2H), 6.19 (d, 1H), 6.88 - 7.04 (m, 2H), 7.17 - 7.32 (m, 2H), 7.57 (dd, 1H), 8.12 (d, 1H), 8.34 (d, 1H).

**(5-Bromo-3-(2-methoxybenzoyl)-1H-pyrrolo[2,3-b]pyridin-1-yl)methyl pivalate (45)**



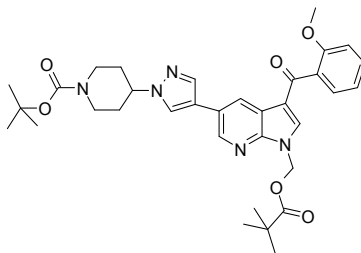
**General procedure D** was used to afford the title compound as a clear colourless gum (0.262 g, 88%).

$m/z$  (ES<sup>+</sup>) [M+H]<sup>+</sup> = 449;

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  1.07 (s, 9H), 3.74 (s, 3H), 6.24 (s, 2H), 7.03 - 7.15 (m, 1H), 7.23 (d, 1H), 7.38 (dd, 1H), 7.55 (s, 1H), 8.11 (s, 1H), 8.52 - 8.61 (m, 2H)

***tert*-Butyl 4-(4-(3-(2-methoxybenzoyl)-1-(pivaloyloxymethyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate**

**General procedure G: Suzuki-Miyaura reaction with dppf in DME/H<sub>2</sub>O**



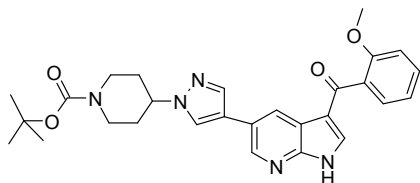
To a degassed mixture of *tert*-butyl 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (0.355 g, 0.94 mmol), **45** (0.262 g, 0.59 mmol), DME (5.4 mL), and water (0.54 mL) were added sequentially K<sub>2</sub>CO<sub>3</sub> (0.244 g, 1.77 mmol) and 1,1'-bis(diphenylphosphino)ferrocene-palladium dichloride (0.048 g, 0.06 mmol). The mixture was warmed to 100 °C. After 1.5 h, the red-black mixture was cooled and diluted with EtOAc (50 mL) and water (50 mL). The organic layer was washed with brine (30 mL) and dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated under reduced pressure. The resulting residue was purified by flash silica chromatography, elution gradient 20 to 80% EtOAc in hexanes to afford the title compound as a light reddish-orange foam solid (0.310 g, 86%).

m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 618;

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 1.08 (s, 9H), 1.44 (s, 9H), 1.86 (dd, 2H), 2.08 (d, 2H), 2.95 (br s, 2H), 3.74 (s, 3H), 4.07 (d, 2H), 4.41 (br s, 1H), 6.24 (s, 2H), 7.01 - 7.14 (m, 1H), 7.22 (d, 1H), 7.30 - 7.44 (m, 1H), 7.46 - 7.59 (m, 1H), 7.98 (s, 2H), 8.44 (s, 1H), 8.60 (d, 1H), 8.71 (d, 1H)

***tert*-Butyl 4-(4-(3-(2-methoxybenzoyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate**

**General procedure H: Removal of pivaloyl group**

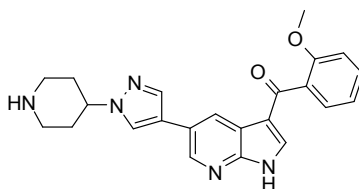


To a reddish-brown solution of *tert*-butyl 4-(4-(3-(2-methoxybenzoyl)-1-(pivaloyloxymethyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (0.310 g, 0.50 mmol) in MeOH (2 mL) and THF (2 mL) was added NaOH (0.1 g, 2.50 mmol). After stirring at rt for 10 mins the reaction was diluted with EtOAc (50 mL) and washed with brine (30 mL). The organic layer was separated, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated under reduced pressure. The resulting residue was purified by flash silica chromatography, elution gradient 80 to 100% EtOAc in hexanes to afford the title compound as a white foam solid (0.250 g, 99%).

m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 502;

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 1.44 (s, 9H), 1.86 (dd, 2H), 2.08 (d, 2H), 2.95 (br s, 2H), 3.74 (s, 3H), 4.02 - 4.15 (m, 2H), 4.41 (br s, 1H), 6.98 - 7.11 (m, 1H), 7.18 (d, 1H), 7.27 - 7.39 (m, 1H), 7.45 - 7.55 (m, 1H), 7.72 (s, 1H), 7.94 (s, 1H), 8.39 (s, 1H), 8.54 (d, 1H), 8.63 (d, 1H), 12.49 (s, 1H).

**(2-Methoxyphenyl)(5-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone (9)**



**General procedure E** was used to afford the title compound as a white solid (70 mg, 35%).

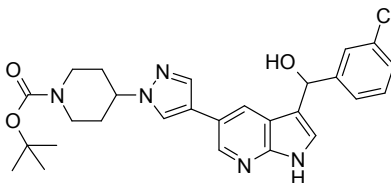
m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 402;

HRMS calculated for C<sub>23</sub>H<sub>23</sub>N<sub>5</sub>O<sub>2</sub> [M-H] 400.1773, found 400.1760;

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 1.64 - 1.85 (m, 2H), 1.87 - 1.99 (m, 2H), 2.53 (t, 2H), 2.99 (d, 2H), 3.66 (s, 3H), 4.06 - 4.30 (m, 1H), 6.93 - 7.05 (m, 1H), 7.11 (d, 1H), 7.27 (dd, 1H), 7.35 - 7.48 (m, 1H), 7.64 (s, 1H), 7.83 (s, 1H), 8.24 (s, 1H), 8.44 (d, 1H), 8.54 (d, *J* = 1.88 Hz, 1H), 2 x NH not observed.

**(3-Chlorophenyl)(5-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone (10)**

***tert*-Butyl 4-(4-(3-((3-chlorophenyl)(hydroxy)methyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate**

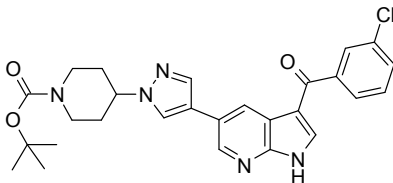


**General procedure C** was used to afford the title compound as a white foam (183 mg, 33%).

m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 508;

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 1.43 (s, 9H), 1.83 (dd, 2H), 2.05 (d, 2H), 2.94 (br s, 2H), 4.06 (d, 2H), 4.38 (br s, 1H), 5.84 (d, 1H), 5.98 (d, 1H), 7.17 - 7.31 (m, 2H), 7.35 (t, 1H), 7.41 - 7.49 (m, 1H), 7.54 (s, 1H), 7.83 (s, 1H), 8.02 (d, 1H), 8.23 (s, 1H), 8.45 (d, 1H), 11.43 (br s, 1H).

**tert-Butyl 4-(4-(3-(3-chlorobenzoyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate**

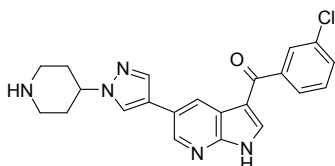


**General procedure D** was used to afford the title compound as a white solid (45 mg, 50%).

m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 506;

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 1.44 (s, 9H), 1.86 (dd, 2H), 2.08 (d, 2H), 2.95 (br s, 2H), 3.91 - 4.16 (m, 2H), 4.41 (br s, 1H), 7.61 (d, 1H), 7.70 (d, 1H), 7.74 - 7.84 (m, 2H), 7.97 (s, 1H), 8.12 (s, 1H), 8.42 (s, 1H), 8.67 (s, 2H), 12.68 (br s, 1H),

**(3-Chlorophenyl)(5-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone (10)**



**General procedure E** was used to afford the title compound as a white solid (23 mg, 96%).

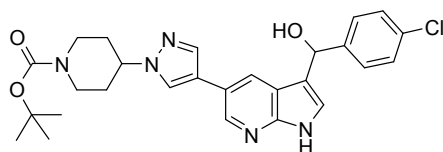
m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 406;

HRMS calculated for C<sub>22</sub>H<sub>20</sub>ClN<sub>5</sub>O [M+H]<sup>+</sup> 406.1435, found 406.1411;

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 1.65 - 1.86 (m, 2H), 1.87 - 2.00 (m, 2H), 2.48 - 2.61 (m, 2H), 2.99 (d, 2H), 3.97 - 4.27 (m, 1H), 7.48 - 7.57 (m, 1H), 7.58 - 7.67 (m, 1H), 7.68 - 7.76 (m, 2H), 7.87 (s, 1H), 8.04 (s, 1H), 8.27 (s, 1H), 8.58 (q, 2H), 2 x NH not observed.

**(4-Chlorophenyl)(5-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone (11)**

**tert-Butyl 4-(4-(3-((4-chlorophenyl)(hydroxy)methyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate**

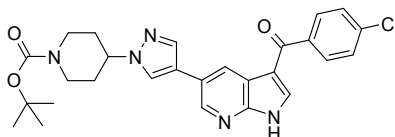


**General procedure C** was used to afford the title compound as a light beige foam (0.169 g, 61%).

m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 508.

**tert-Butyl 4-(4-(3-(4-chlorobenzoyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate**



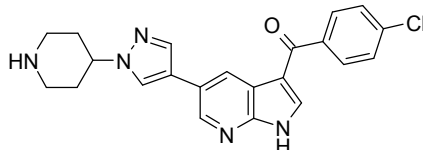


**General procedure D** was used to afford the title compound as a white solid (50 mg, 72%).

$m/z$  ( $ES^+$ )  $[M+H]^+ = 506$ ;

$^1H$  NMR (300 MHz,  $DMSO-d_6$ )  $\delta$  1.44 (s, 9H), 1.86 (dd, 2H), 2.08 (d, 2H), 2.78 - 3.11 (m, 2H), 3.95 - 4.15 (m, 2H), 4.32 - 4.54 (m, 1H), 7.62 (d, 2H), 7.86 (d, 2H), 7.97 (s, 1H), 8.11 (s, 1H), 8.41 (s, 1H), 8.66 (s, 2H), 12.66 (s, 1H).

**(4-chlorophenyl)(5-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone (11)**



**General procedure E** was used to afford the title compound as a white solid (14 mg, 49%).

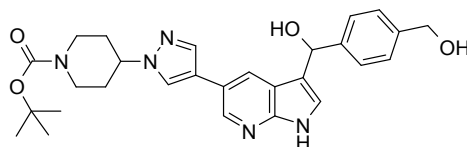
$m/z$  ( $ES^+$ )  $[M+H]^+ = 406$ ;

HRMS calculated for  $C_{22}H_{20}ClN_5O$   $[M+H]^+ 406.1435$ , found 406.1411;

$^1H$  NMR (300 MHz,  $DMSO-d_6$ )  $\delta$  1.66 - 1.94 (m, 2H), 1.96 - 2.12 (m, 2H), 2.62 (t, 2H), 3.07 (d, 2H), 4.24 (t, 1H), 7.62 (d, 2H), 7.86 (d, 2H), 7.95 (s, 1H), 8.11 (s, 1H), 8.35 (s, 1H), 8.66 (s, 2H) 2 x NH not observed.

**(4-(Hydroxymethyl)phenyl)(5-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone (12)**

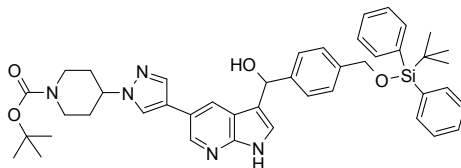
***tert*-Butyl 4-(4-(3-((4-(hydroxymethyl)phenyl)(methoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate**



**General procedure C** was used to afford the title compound as yellow foam (164 mg, 15%).

$m/z$  ( $ES^+$ )  $[M+H]^+ = 518$ .

***tert*-Butyl 4-(4-(3-((4-((tert-butyldiphenylsilyloxy)methyl)phenyl)(hydroxy)methyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate**

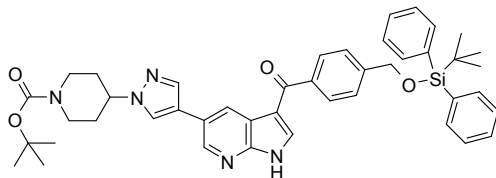


To a solution of *tert*-butyl 4-(4-(3-(hydroxy(4-(hydroxymethyl)phenyl)methyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (0.11 g, 0.21 mmol) in DCM (10 mL) was added imidazole (0.021 g, 0.32 mmol) then *tert*-butyldiphenylchlorosilane (0.054 mL, 0.21 mmol) was added. After 35 min, the mixture was diluted with EtOAc (50 mL) and washed with saturated aqueous sodium bicarbonate (25 mL) and brine (25 mL). The organic layer was dried ( $Na_2SO_4$ ), filtered, and concentrated under reduced pressure. The resulting residue was purified by flash silica chromatography, elution gradient 20 to 100% EtOAc in hexanes to afford the title compound as a light yellow foam solid (0.109 g, 70%).

m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 742;

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 1.01 (s, 9H), 1.42 (s, 9H), 1.82 (dd, 2H), 2.03 (d, 2H), 2.92 (br s, 2H), 4.05 (d, 2H), 4.36 (br s, 1H), 4.74 (s, 2H), 5.66 (d, 1H), 5.96 (d, 1H), 7.19 (d, 1H), 7.29 (d, 2H), 7.34 - 7.50 (m, 8H), 7.56 - 7.68 (m, 4H), 7.82 (s, 1H), 8.00 (d, 1H), 8.22 (s, 1H), 8.44 (d, 1H), 11.38 (d, 1H).

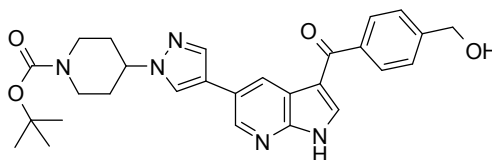
***tert*-Butyl 4-(4-(3-(4-((*tert*-butyldiphenylsilyloxy)methyl)benzoyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate**



**General procedure D** was used to afford the title compound as an off white solid (34 mg, 33%).

m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 742.

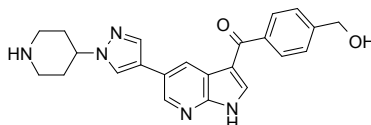
***tert*-Butyl 4-(4-(3-(4-(hydroxymethyl)benzoyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate**



To a solution of *tert*-butyl 4-(4-(3-(4-((*tert*-butyldiphenylsilyloxy)methyl)benzoyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (33.7 mg, 0.05 mmol) in THF (0.4 mL) at 0 °C was added 1 M TBAF in THF (0.055 mL, 0.05 mmol) dropwise. After 30 min, the light yellow solution was diluted with EtOAc (20 mL) and washed with brine (15 mL). The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated under reduced pressure to afford the title compound (25 mg, 100%) which was used without further purification.

m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 502.

**(4-(Hydroxymethyl)phenyl)(5-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone (12)**



To *tert*-butyl 4-(4-(3-(4-(hydroxymethyl)benzoyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (0.025 g, 0.05 mmol) in DCM (0.500 mL) was added TFA (5.7 mg, 0.05 mmol). After stirring at rt for 10 min, the clear colourless solution was concentrated under reduced pressure to afford crude product which was purified by preparative HPLC, XBridge Prep C18 OBD, 5 μm silica, 19 x 100mm, gradient 10 to 40% MeCN/0.2% NH<sub>4</sub>OH in H<sub>2</sub>O to afford the title compound as a white solid (10 mg, 50%).

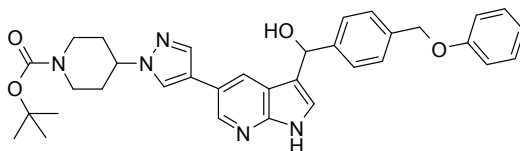
m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 402;

HRMS calculated for C<sub>22</sub>H<sub>20</sub>ClN<sub>5</sub>O [M+H]<sup>+</sup> 402.1930, found 402.1943;

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 1.65 - 1.86 (m, 2H), 1.88 - 1.99 (m, 2H), 2.54 (t, 2H), 3.00 (d, 2H), 4.05 - 4.25 (m, 1H), 4.55 (d, 2H), 5.28 (t, 1H), 7.43 (d, 2H), 7.74 (d, 2H), 7.87 (s, 1H), 7.98 (s, 1H), 8.27 (s, 1H), 8.58 (s, 2H), 2 x NH not observed.

**(4-(Phenoxymethyl)phenyl)(5-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone (13)**

***tert*-Butyl 4-(4-(3-(hydroxy(4-(phenoxyethyl)phenyl)methyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate**

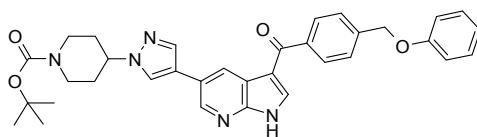


**General procedure C** was used to afford the title compound as a beige foam solid (294 mg, 37%).

$m/z$  ( $ES^+$ )  $[M+H]^+ = 580$ ;

$^1H$  NMR (300 MHz,  $DMSO-d_6$ )  $\delta$  1.43 (s, 9H), 1.83 (dd, 2H), 2.05 (d, 2H), 2.74 - 3.10 (m, 2H), 4.06 (d, 2H), 4.27 - 4.46 (m, 1H), 5.06 (s, 2H), 5.70 (d, 1H), 5.98 (d, 1H), 6.87 - 6.95 (m, 1H), 6.99 (d, 2H), 7.20 (d, 1H), 7.23 - 7.31 (m, 2H), 7.34 - 7.45 (m, 2H), 7.47 - 7.58 (m, 2H), 7.82 (s, 1H), 7.90 - 8.09 (m, 1H), 8.22 (s, 1H), 8.43 (d, 1H), 11.38 (d, 1H).

***tert*-Butyl 4-(4-(3-(4-(phenoxyethyl)benzoyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate**

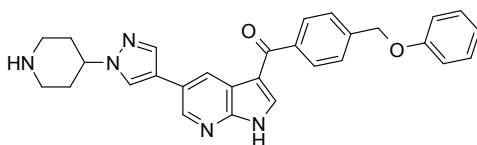


**General procedure D** was used to afford the title compound as a white solid (80 mg, 77%).

$m/z$  ( $ES^+$ )  $[M+H]^+ = 578$ ;

$^1H$  NMR (300 MHz,  $DMSO-d_6$ )  $\delta$  1.44 (s, 9H), 1.86 (dd, 2H), 2.08 (d, 2H), 2.95 (br s, 2H), 4.01 - 4.15 (m, 2H), 4.41 (br s, 1H), 5.24 (s, 2H), 6.87 - 7.02 (m, 1H), 7.06 (d, 2H), 7.25 - 7.41 (m, 2H), 7.64 (d, 2H), 7.87 (d, 2H), 7.97 (s, 1H), 8.09 (s, 1H), 8.41 (s, 1H), 8.67 (d, 2H), 12.61 (s, 1H).

**(4-(Phenoxyethyl)phenyl)(5-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone (13)**



**General procedure E** was used to afford the title compound as a white solid (46 mg, 93%).

$m/z$  ( $ES^+$ )  $[M+H]^+ = 478$ ;

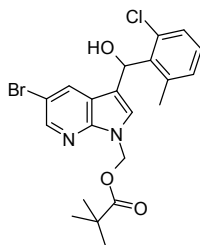
HRMS calculated for  $C_{29}H_{27}N_5O_2$   $[M+H]^+ 478.2243$ , found 478.2236;

$^1H$  NMR (300 MHz,  $DMSO-d_6$ )  $\delta$  1.66 - 1.87 (m, 2H), 1.86 - 1.97 (m, 2H), 2.47 - 2.61 (m, 2H), 2.99 (d, 2H), 3.94 - 4.31 (m, 1H), 5.17 (s, 2H), 6.81 - 6.95 (m, 1H), 6.99 (d, 2H), 7.26 (t, 2H), 7.56 (d, 2H), 7.80 (d, 2H), 7.87 (s, 1H), 8.01 (s, 1H), 8.27 (s, 1H), 8.58 (d, 2H), 2 x NH not observed.

**(2-Chloro-6-methylphenyl)(5-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone (14)**

**(5-Bromo-3-((2-chloro-6-methylphenyl)(hydroxy)methyl)-1H-pyrrolo[2,3-b]pyridin-1-yl)methyl pivalate**

**General procedure I: Benzyl alcohol formation using BuLi**

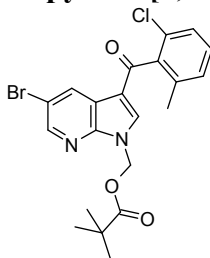


To a solution of 2-bromo-1-chloro-3-methylbenzene (0.089 mL, 0.68 mmol) in THF (3.00 mL) at -107 °C was added dropwise 1.8 M n-butyllithium in hexanes (0.360 mL, 0.65 mmol), maintaining an internal reaction temperature of < -99 °C. After addition was complete, the clear colourless solution was stirred at -100 °C for 3 min. Then a solution of (5-bromo-3-formyl-1H-pyrrolo[2,3-b]pyridin-1-yl)methyl pivalate (0.2 g, 0.59 mmol) in THF (0.6 mL) was added. The internal reaction temperature rose to -66 °C and was maintained at this temperature. After 12 min, the yellow solution was poured into brine (30 mL), extracted with EtOAc (30 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure. The resulting light yellow oil was purified by column chromatography, elution gradient 0-60% EtOAc in hexanes to afford the title compound as a clear colourless glass (0.227 g, 83%).

m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 465;

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 1.04 (s, 9H), 2.25 (s, 3H), 5.99 - 6.31 (m, 3H), 6.63 (d, 1H), 7.04 - 7.31 (m, 3H), 7.31 - 7.42 (m, 1H), 7.84 (d, 1H), 8.37 (d, 1H).

**(5-Bromo-3-(2-chloro-6-methylbenzoyl)-1H-pyrrolo[2,3-b]pyridin-1-yl)methyl pivalate**

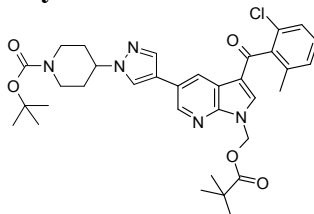


**General procedure D** was used to afford the title compound as a clear colourless glass (200 mg, 93%).

m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 463;

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 1.04 (s, 9H), 2.18 (s, 3H), 6.24 (s, 2H), 7.26 - 7.55 (m, 3H), 8.10 (br s, 1H), 8.61 (d, 2H).

**tert-Butyl 4-(4-(3-(2-chloro-6-methylbenzoyl)-1-((pivaloyloxy)methyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate**

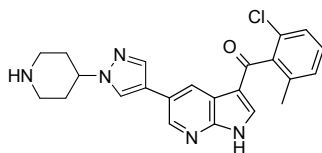


**General procedure G** was used to afford the title compound as as an orange foam (205 mg, 75%).

m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 634;

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 1.05 (s, 9H), 1.44 (s, 9H), 1.86 (dd, 2H), 2.08 (d, 2H), 2.19 (s, 3H), 2.79 - 3.12 (m, 2H), 3.99 - 4.19 (m, 2H), 4.28 - 4.52 (m, 1H), 6.25 (s, 2H), 7.25 - 7.52 (m, 3H), 7.98 (d, 2H), 8.48 (s, 1.4H), 8.76 (d, 1H).

**(2-Chloro-6-methylphenyl)(5-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone (14)**



**General procedure E** was used to afford the title compound as a white solid (80 mg, 60%).

$m/z$  ( $ES^+$ )  $[M+H]^+ = 420$ ;

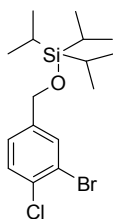
HRMS calculated for  $C_{23}H_{22}ClN_5O$   $[M+H]^+ 420.1591$ , found 420.1590;

$^1H$  NMR (300 MHz,  $DMSO-d_6$ )  $\delta$  1.65 - 1.85 (m, 2H), 1.94 (d, 2H), 2.12 (s, 3H), 2.48 - 2.63 (m, 2H), 2.99 (d, 2H), 3.97 - 4.31 (m, 1H), 7.13 - 7.43 (m, 3H), 7.68 (br s, 1H), 7.84 (br s, 1H), 8.27 (br s, 1H), 8.58 (d, 1H), 2 x NH not observed

**(2-Chloro-5-(hydroxymethyl)phenyl)(5-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone (15)**

**(3-Bromo-4-chlorophenyl)triisopropylsilane**

**General procedure J: TIPS silylation**

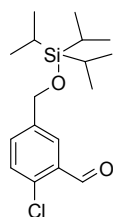


To a solution of (3-bromo-4-chlorophenyl)methanol (2.71 g, 12.2 mmol) and imidazole (1.67 g, 24.5 mmol) in DCM (58 mL) was added chlorotriisopropylsilane (2.9 mL, 13.5 mmol) in one portion. After stirring at rt for 2 h the white mixture was diluted with EtOAc (150 mL) and washed with saturated aqueous sodium bicarbonate (100 mL) and brine (100 mL). The organic layer was dried ( $Na_2SO_4$ ), filtered, and concentrated under reduced pressure. The resulting residue was purified by flash silica chromatography, eluting with 100% hexanes to afford the title compound as a clear colourless oil (4.34 g, 94%).

$^1H$  NMR (300 MHz,  $DMSO-d_6$ )  $\delta$  0.97 - 1.09 (m, 18H), 1.10 - 1.23 (m, 3H), 4.81 (s, 2H), 7.37 (d, 1H), 7.61 (d, 1H), 7.71 (s, 1H).

**2-Chloro-5-((triisopropylsilyloxy)methyl)benzaldehyde**

**General procedure K: Br to aldehyde**

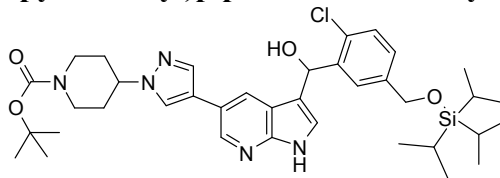


To a solution of (3-bromo-4-chlorobenzoyloxy)triisopropylsilane (2.3 g, 6.09 mmol) in THF (56 mL) at -106 °C was added dropwise 1.8 M n-butyllithium in hexanes (3.72 mL, 6.70 mmol), maintaining an internal reaction temperature below -101 °C. After addition was complete, clear colourless solution was warmed to -95 °C, and DMF (1.41 mL, 18.3 mmol) was added rapidly dropwise, resulting in an internal reaction temperature of -75 °C after addition was complete. The reaction was warmed to -65 °C and quenched with brine (50 mL). The mixture was warmed to rt and then diluted with EtOAc (100 mL). The organic layer was separated, dried ( $Na_2SO_4$ ), filtered and concentrated under reduced pressure. The resulting residue was purified by flash silica chromatography, eluting with 5% EtOAc in hexanes to afford the title compound as a colourless oil (2.00 g, 100%).

$m/z$  ( $ES^+$ )  $[M+H]^+ = 326$ ;

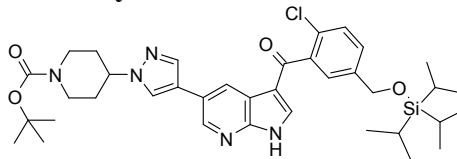
<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 1.01 - 1.09 (m, 18H), 1.10 - 1.24 (m, 3H), 4.87 (s, 2H), 7.54 - 7.69 (m, 2H), 7.89 (s, 1H), 10.35 (s, 1H).

**tert-Butyl 4-(4-(3-((2-chloro-5-((triisopropylsilyloxy)methyl)phenyl)(hydroxy)methyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate**



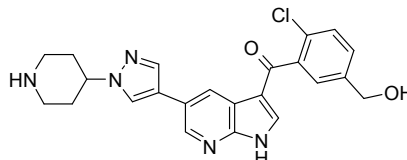
**General procedure C** was used to afford the title compound as a light yellow foam solid (0.607 g, 71%).  
m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 694.

**tert-Butyl 4-(4-(3-(2-chloro-5-((triisopropylsilyloxy)methyl)benzoyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate**



**General procedure D** was used to afford the title compound as a light yellow solid (117 mg, 39%).  
m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 692.

**(2-chloro-5-(hydroxymethyl)phenyl)(5-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone (15)**



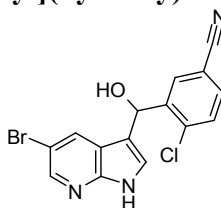
**General procedure E** was used to afford the title compound as a white solid (48 mg, 65%).  
m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 436;

HRMS calculated for C<sub>23</sub>H<sub>22</sub>ClN<sub>5</sub>O<sub>2</sub> [M+H]<sup>+</sup> 436.1540, found 436.1530;

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 1.56 - 1.87 (m, 2H), 1.87 - 2.04 (m, 2H), 2.54 (t, 2H), 2.99 (d, 2H), 4.00 - 4.32 (m, 1H), 4.49 (s, 3H), 5.28 (br s, 1H), 7.20 - 7.58 (m, 3H), 7.70 (s, 1H), 7.87 (s, 1H), 8.28 (s, 1H), 8.47 (d, 1H), 8.59 (d, 1H), NH not observed.

**4-Chloro-3-([5-[1-(piperidin-4-yl)-1H-pyrazol-4-yl]-1H-pyrrolo[2,3-b]pyridin-3-yl]carbonyl)benzonitrile (16)**

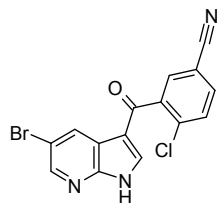
**3-([5-Bromo-1H-pyrrolo[2,3-b]pyridin-3-yl](hydroxy)methyl)-4-chlorobenzonitrile**



**General procedure C** was used to afford the title compound as a yellow solid (16.5 g, 82%).  
m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 362.

### 3-([5-Bromo-1H-pyrrolo[2,3-b]pyridin-3-yl]carbonyl)-4-chlorobenzonitrile

#### General procedure O: Dess-Martin periodinane oxidation

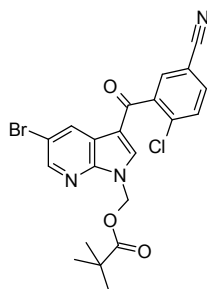


Into a 500-mL 3-necked round-bottom flask, was placed a solution of 3-([5-bromo-1H-pyrrolo[2,3-b]pyridin-3-yl](hydroxymethyl)-4-chlorobenzonitrile (16.5 g, 45.5 mmol) in tetrahydrofuran (170 mL), Dess-Martin periodinane (22 g, 51.9 mmol). The resulting solution was stirred for 1 h at rt. The resulting solution was diluted with EtOAc (4000 mL) and saturated NaHCO<sub>3</sub> (400 mL), then filtered. The filtrate was extracted with EtOAc (2 x 200 mL) and the organic layers combined, washed with brine (150 mL) dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated under vacuum to afford the title compound as a off white solid (10 g, 61%).

m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 360;

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 7.86 (d, 1H), 8.03 - 8.20 (m, 3H), 8.50 (d, 1H), 8.62 (d, 1H), 12.93 (br s, 1H).

### [5-Bromo-3-[(2-chloro-5-cyanophenyl)carbonyl]-1H-pyrrolo[2,3-b]pyridin-1-yl]methyl 2,2-dimethylpropanoate



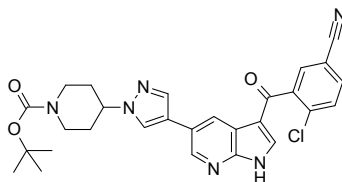
**General procedure F** was used to afford the title compound as a yellow solid (6.5g, 49%).

m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 474;

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 1.07 (s, 9H), 6.23 (s, 2H), 7.87 (d, 1H), 8.07 - 8.11 (dd, 1H), 8.17 (d, 1H), 8.31 (s, 1H), 8.62 (d, 1H), 8.66 (d, 1H).

### *tert*-Butyl 4-[4-[3-[(2-chloro-5-cyanophenyl)carbonyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]-1H-pyrazol-1-yl]piperidine-1-carboxylate

#### General procedure L: Suzuki-Miyaura reaction with dppf in dioxane/H<sub>2</sub>O



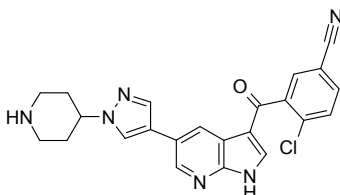
Into a 100-mL sealed tube, was placed a solution of [5-bromo-3-[(2-chloro-5-cyanophenyl)carbonyl]-1H-pyrrolo[2,3-b]pyridin-1-yl]methyl 2,2-dimethylpropanoate (4.5 g, 9.48 mmol) in 1,4-dioxane (45 mL)/H<sub>2</sub>O (4.5 mL), *tert*-butyl 4-[4-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl]piperidine-1-carboxylate (3.6 g, 9.54 mmol), Pd(dppf)Cl<sub>2</sub> CH<sub>2</sub>Cl<sub>2</sub> (900 mg, 1.10 mmol), K<sub>3</sub>PO<sub>4</sub> (6.3 g, 29.7 mmol). The reaction mixture was irradiated with microwave radiation for 45 min at 100 °C. The reaction mixture was cooled to rt, NaOH (1.9 g, 47.5 mmol) added and stirred for an additional 1 h. The resulting solution was diluted with EtOAc (200 mL), dried over (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under

vacuum. The residue was purified by flash silica chromatography, eluting with EtOAc to afford the title compound as a yellow solid (1.5 g, 30%).

$m/z$  ( $ES^+$ )  $[M+H]^+ = 531$ ;

$^1H$  NMR (300 MHz,  $DMSO-d_6$ )  $\delta$  1.43 (s, 9H), 1.80 - 1.92 (m, 2H), 2.05 - 2.09 (d, 2H), 2.94 (br s, 2H), 4.05 - 4.09 (m, 2H), 4.44 (m, 1H), 7.85 (d, 1H), 8.05 - 8.12 (m, 3H), 8.13 (d, 1H), 8.47 (s, 1H), 8.64 (d, 1H), 8.69 (d, 1H). NH not observed.

**4-Chloro-3-([5-[1-(piperidin-4-yl)-1H-pyrazol-4-yl]-1H-pyrrolo[2,3-b]pyridin-3-yl]carbonyl)benzonitrile (16)**



**General procedure E** was used to afford the title compound as a yellow solid (700 mg, 86%).

$m/z$  ( $ES^+$ )  $[M+H]^+ = 431$ ;

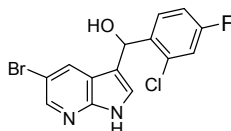
HRMS calculated for  $C_{23}H_{19}ClN_6O$   $[M+H]^+ 431.1387$ , found 431.1397;

$^1H$  NMR (300 MHz,  $DMSO-d_6$ )  $\delta$  1.83 - 1.96 (m, 2H), 2.03 - 2.06 (m, 2H), 2.59 - 2.72 (m, 2H), 3.01 - 3.13 (m, 2H), 4.27 - 4.31 (m, 1H), 7.81 - 7.84 (m, 1H), 7.97 - 8.04 (m, 3H), 8.12 (d, 1H), 8.39 (s, 1H), 8.62 (d, 1H), 8.68 (d, 1H). 2 x NH not observed.

**(2-Chloro-4-fluorophenyl)(5-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone (17)**

**(5-Bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)(2-chloro-4-fluorophenyl)methanol**

**General procedure M: Benzyl alcohol formation using tetramethylguanidine**



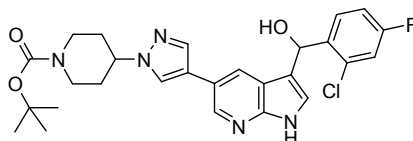
**38** (611 mg, 3.10 mmol), 2-chloro-4-fluorobenzaldehyde (492 mg, 3.10 mmol) and 1,1,3,3-tetramethylguanidine (143 mg, 1.24 mmol) were added to water (20 mL) and THF (6.7 mL) and heated at 60 °C for 3 d. The reaction mixture was quenched with water (50 mL), extracted with EtOAc (2 x 50 mL), the organic layer dried ( $MgSO_4$ ), filtered and evaporated to afford white solid. The crude solid was triturated with DCM to give a solid which was collected by filtration and dried under vacuum to afford the title compound as a yellow solid (530 mg, 48%).

$m/z$  ( $ES^+$ )  $[M+H]^+ = 357$ ;

$^1H$  NMR (400 MHz,  $DMSO-d_6$ )  $\delta$  5.97 (d, 1H), 6.18 (d, 1H), 7.14 (d, 1H), 7.29 (td, 1H), 7.38 (dd, 1H), 7.83 (dd, 1H), 8.08 (d, 1H), 8.25 (d, 1H), 11.74 (d, 1H).

***tert*-Butyl 4-(4-(3-((2-chloro-4-fluorophenyl)(hydroxy)methyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate**

**General procedure N: Suzuki-Miyaura reaction with  $Pd(PPh_3)_4$**



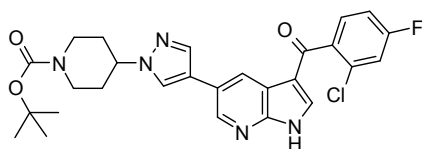


*tert*-Butyl 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (552 mg, 1.46 mmol), (5-bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)(2-chloro-4-fluorophenyl)methanol (400 mg, 1.12 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (65.0 mg, 0.06 mmol) and K<sub>2</sub>CO<sub>3</sub> (466 mg, 3.37 mmol) were dissolved in DME (50 mL) and water (10 mL) and heated at 85 °C for 2 h. The reaction mixture was quenched with water (50 mL), extracted with EtOAc (3 x 50 mL), and the organic layer dried (MgSO<sub>4</sub>), filtered and evaporated to afford a yellow gum. The crude product was purified by flash silica chromatography, elution gradient 90 to 100% EtOAc in heptane to afford a pale yellow solid, which was triturated with Et<sub>2</sub>O to give a solid which was collected by filtration and dried under vacuum to afford the title compound as a white solid (340 mg, 57%).

m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 526;

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.49 (s, 9H), 1.96 (dd, 2H), 2.17 (d, 2H), 2.76 (s, 1H), 2.91 (t, 2H), 4.29 (m, 3H), 6.47 (s, 1H), 6.99 - 7.09 (m, 2H), 7.14 (dd, 1H), 7.65 (s, 1H), 7.72 (dd, 1H), 7.75 (d, 1H), 8.01 (d, 1H), 8.43 (d, 1H), 9.44 (s, 1H).

***tert*-Butyl 4-(4-(3-(2-chloro-4-fluorobenzoyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate**

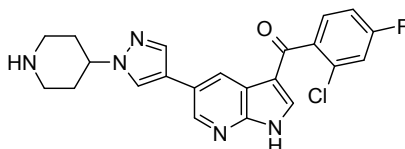


**General procedure D** was used to afford the title compound as a white solid (0.210 g, 62%).

m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 524;

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.50 (s, 9H), 2.01 (td, 2H), 2.14 - 2.26 (m, 2H), 2.94 (t, 2H), 4.32 (m, 3H), 7.11 (td, 1H), 7.22 - 7.3 (m, 1H), 7.50 (dd, 1H), 7.60 (s, 1H), 7.81 (s, 1H), 7.88 (d, 1H), 8.59 (d, 1H), 8.79 (d, 1H), 11.02 (s, 1H).

**(2-Chloro-4-fluorophenyl)(5-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone (17)**



**General procedure E** was used to afford the title compound as a pale yellow solid (65.0 mg, 38%).

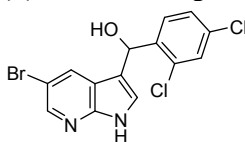
m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 424;

HRMS calculated for C<sub>22</sub>H<sub>19</sub>ClFN<sub>5</sub>O [M+H]<sup>+</sup> 424.1340, found 424.1337;

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 1.86 (m, 2H), 1.96 - 2.1 (m, 2H), 2.57 - 2.69 (m, 2H), 3.08 (d, 2H), 4.24 (tt, 1H), 7.36 (td, 1H), 7.60 (dd, 1H), 7.64 (dd, 1H), 7.84 (s, 1H), 7.94 - 7.96 (m, 1H), 8.36 (s, 1H), 8.58 (d, 1H), 8.67 (d, 1H), 2 x NH not observed.

**(2,4-Dichlorophenyl)(5-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone (18)**

**(5-Bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)(2,4-dichlorophenyl)methanol**

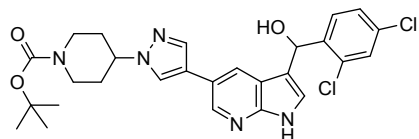


**General procedure M** was used to afford the title compound as a white solid (1.64 g, 87%).

m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 373;

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 6.01 (d, 1H), 6.17 (d, 1H), 7.16 (s, 1H), 7.51 (dd, 1H), 7.54 (d, 1H), 7.83 (d, 1H), 8.10 (d, 1H), 8.26 (d, 1H), 11.75 (s, 1H).

***tert*-Butyl 4-(4-(3-((2,4-dichlorophenyl)(hydroxy)methyl)-1H-pyrrolo[2,3-*b*]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate**

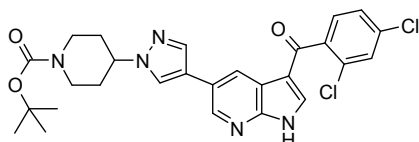


**General procedure N** was used to afford the title compound as a yellow foam (500 mg, 69%).

*m/z* (ES<sup>+</sup>) [M+H]<sup>+</sup> = 542;

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.49 (s, 9H), 1.96 (qd, 2H), 2.17 (d, 2H), 2.81 - 3.03 (m, 3H), 4.29 (ddt, 3H), 6.45 (d, 1H), 7.00 (d, 1H), 7.31 (dd, 1H), 7.39 (d, 1H), 7.68 (d, 1H), 7.71 (d, 1H), 7.75 (s, 1H), 8.01 (d, 1H), 8.43 (d, 1H), 9.52 (s, 1H).

***tert*-Butyl 4-(4-(3-(2,4-dichlorobenzoyl)-1H-pyrrolo[2,3-*b*]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate**

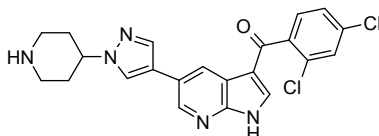


**General procedure D** was used to afford the title compound as a white solid (200 mg, 40%).

*m/z* (ES<sup>+</sup>) [M+H]<sup>+</sup> = 540;

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.50 (s, 9H), 1.99 (qd, 2H), 2.21 (d, 2H), 2.94 (t, 2H), 4.34 (ddt, 3H), 7.38 (dd, 1H), 7.43 (d, 1H), 7.53 (d, 1H), 7.59 (s, 1H), 7.80 (s, 1H), 7.88 (d, 1H), 8.59 (d, 1H), 8.78 (d, 1H), 10.80 (s, 1H).

**(2,4-Dichlorophenyl)(5-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-*b*]pyridin-3-yl)methanone (18)**



**General procedure E** was used to afford the title compound as a white solid (98 mg, 60%).

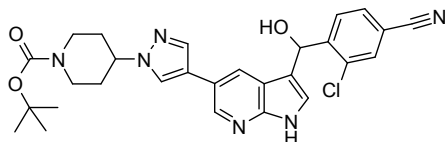
*m/z* (ES<sup>+</sup>) [M+H]<sup>+</sup> = 440;

HRMS calculated for C<sub>22</sub>H<sub>19</sub>Cl<sub>2</sub>N<sub>5</sub>O [M+H]<sup>+</sup> 440.1045, found 440.1036;

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 1.85 (qd, 2H), 2.02 (d, 2H), 2.57 - 2.66 (m, 2H), 3.07 (d, 2H), 4.23 (tt, 1H), 7.57 (dd, 1H), 7.60 (d, 1H), 7.77 (d, 1H), 7.87 (s, 1H), 7.9 - 7.98 (m, 1H), 8.35 (s, 1H), 8.57 (d, 1H), 8.66 (d, 1H), 2 x NH not observed.

**3-Chloro-4-([5-[1-(piperidin-4-yl)-1H-pyrazol-4-yl]-1H-pyrrolo[2,3-*b*]pyridin-3-yl]carbonyl)benzonitrile (19)**

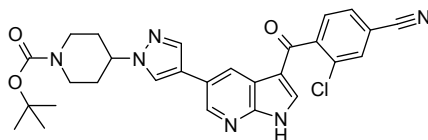
***tert*-Butyl 4-(4-[3-[(2-chloro-4-cyanophenyl)(hydroxy)methyl]-1H-pyrrolo[2,3-*b*]pyridin-5-yl]-1H-pyrazol-1-yl)piperidine-1-carboxylate**



**General procedure C** was used to afford the title compound as a brown oil (7.68 g, 100%) which was used crude in the following step without purification.

$m/z$  ( $ES^+$ )  $[M+H]^+ = 533$ .

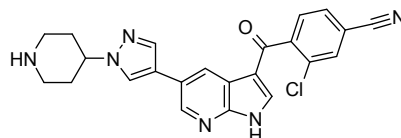
**tert-Butyl 4-(4-[3-[(2-chloro-4-cyanophenyl)carbonyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]-1H-pyrazol-1-yl)piperidine-1-carboxylate**



**General procedure O** was used to afford the title compound as a yellow solid (3.71 g, 48%).

$m/z$  ( $ES^+$ )  $[M+H]^+ = 531$ .

**3-Chloro-4-([5-[1-(piperidin-4-yl)-1H-pyrazol-4-yl]-1H-pyrrolo[2,3-b]pyridin-3-yl]carbonyl)benzonitrile (19)**



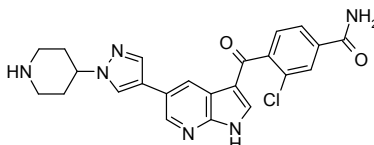
**General procedure E** was used to afford the title compound as a light yellow solid (89 mg, 24%).

$m/z$  ( $ES^+$ )  $[M+H]^+ = 431$ ;

HRMS calculated for  $C_{23}H_{19}ClN_6O$   $[M+H]^+ 431.1387$ , found 431.1397;

$^1H$  NMR (300 MHz,  $DMSO-d_6$ )  $\delta$  1.85 - 1.98 (m, 2H), 2.05 - 2.08 (m, 2H), 2.68 - 2.75 (m, 2H), 3.12 - 3.16 (m, 2H), 4.20 - 4.33 (m, 1H), 7.76 (d, 1H), 7.92 (s, 1H), 7.97 - 7.99 (m, 2H), 8.24 (d, 1H), 8.40 (s, 1H), 8.61 (s, 1H), 8.70 (s, 1H), 2 x NH not observed.

**3-Chloro-4-([5-[1-(piperidin-4-yl)-1H-pyrazol-4-yl]-1H-pyrrolo[2,3-b]pyridin-3-yl]carbonyl)benzamide (20)**



Into a 50-mL round-bottom flask, was placed **19** (350 mg, 0.81 mmol), ethanol (8 mL), water (4 mL), and hydrido(dimethylphosphinous acid-kP)[hydrogen bis(dimethylphosphinito-kP)]platinum(II) (Ghafter-Parkins catalyst) (5 mg, 0.01 mmol) and stirred at 80 °C for 16 h. The resulting mixture was concentrated under vacuum then purified by preparative HPLC, XBridge Prep C18 OBD, 5  $\mu$ m silica, 19 x 150mm, gradient 5% to 95% MeCN/0.03%  $NH_3$  in  $H_2O$ . This resulted in the title compound as a light yellow solid (80 mg, 22%).

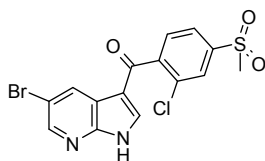
$m/z$  ( $ES^+$ )  $[M+H]^+ = 449$ ;

HRMS calculated for  $C_{23}H_{21}ClN_6O_2$   $[M+H]^+ 449.1493$ , found 431.1511;

$^1H$  NMR (300 MHz,  $DMSO-d_6$ )  $\delta$  1.80 - 1.93 (m, 2H), 2.01 - 2.09 (m, 2H), 2.61 - 2.73 (m, 2H), 3.07 - 3.15 (m, 2H), 4.21 - 4.29 (m, 1H), 7.64 - 7.66 (m, 2H), 7.86 (s, 1H), 7.95 - 7.98 (m, 2H), 8.07 (d, 1H), 8.21 (s, 1H), 8.37 (s, 1H), 8.57 (d, 1H), 8.68 (d, 1H), 2 x NH not observed.

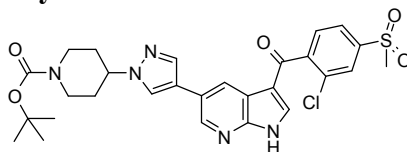
**4-(4-[3-[(2-Chloro-4-methanesulfonylphenyl)carbonyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]-1H-pyrazol-1-yl)piperidine (21)**

**5-Bromo-3-[(2-chloro-4-methanesulfonylphenyl)carbonyl]-1H-pyrrolo[2,3-b]pyridine**



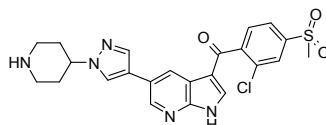
**General procedure A** was used to afford the title compound as a white solid (1.15 g, 53%).  
 $m/z$  ( $ES^+$ )  $[M+H]^+ = 415$ .

**tert-Butyl 4-(4-[3-[(2-chloro-4-methanesulfonylphenyl)carbonyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]-1H-pyrazol-1-yl)piperidine-1-carboxylate**



**General procedure L** was used to afford the title compound as a yellow solid (245 mg, 35%).  
 $m/z$  ( $ES^+$ )  $[M+H]^+ = 584$ .

**4-(4-[3-[(2-Chloro-4-methanesulfonylphenyl)carbonyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]-1H-pyrazol-1-yl)piperidine formate**



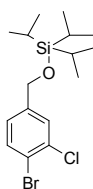
**General procedure B** was used to afford the title compound as a white solid (79 mg, 29%).  
 $m/z$  ( $ES^+$ )  $[M+H]^+ = 484$ ;

HRMS calculated for  $C_{23}H_{22}ClN_5O_3S$   $[M+H]^+ 484.1210$ , found 484.1196;

$^1H$  NMR (400 MHz,  $DMSO-d_6$ )  $\delta$  1.94 - 2.02 (m, 2H), 2.11 (d, 2H), 2.72 - 2.80 (m, 2H), 2.84 (s, 3H), 3.18 - 3.24 (t, 2H), 4.32 - 4.40 (m, 1H), 7.82 - 7.88 (m, 2H), 7.94 (s, 1H), 8.00 (s, 1H), 8.32 (s, 1H), 8.39 (d, 1H), 8.62 (s, 1H), 8.70 (d, 1H), 2 x NH not observed.

**(2-chloro-4-(hydroxymethyl)phenyl)(5-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone (22)**

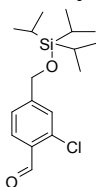
**(4-Bromo-3-chlorobenzoyloxy)triisopropylsilane**



**General procedure J** was used to afford the title compound as a clear colourless oil (1.31 g, 81%).

$^1H$  NMR (300 MHz,  $DMSO-d_6$ )  $\delta$  0.98 - 1.09 (m, 18H), 1.09 - 1.23 (m, 3H), 4.79 (s, 2H), 7.26 (d, 1H), 7.56 (s, 1H), 7.75 (d, 1H).

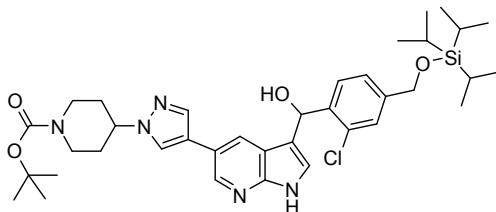
**2-chloro-4-((triisopropylsilyloxy)methyl)benzaldehyde**



**General procedure K** was used to afford the title compound as a clear colourless oil (0.95 g, 84%).  
 $m/z$  ( $ES^+$ )  $[M+H]^+ = 326$ ;

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 0.96 - 1.11 (m, 18H), 1.11 - 1.25 (m, 3H), 4.91 (s, 2H), 7.50 (d, 1H), 7.56 (s, 1H), 7.88 (d, 1H), 10.31 (s, 1H).

**tert-Butyl 4-(4-(3-((2-chloro-4-((triisopropylsilyloxy)methyl)phenyl)(hydroxy)methyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate**

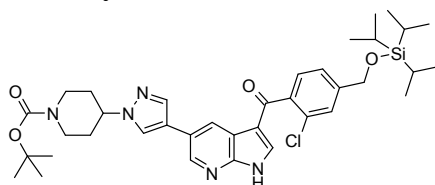


**General procedure C** was used to afford the title compound as a yellow foam solid (748 mg, 88%).

m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 694;

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 0.95 - 1.07 (m, 18H), 1.07 - 1.23 (m, 3H), 1.43 (s, 9H), 1.84 (dd, 2H), 2.06 (d, 2H), 2.94 (br s, 2H), 4.07 (d, 2H), 4.38 (br s, 1H), 4.81 (s, 2H), 5.81 (d, 1H), 6.22 (d, 1H), 7.01 (d, 1H), 7.30 - 7.42 (m, 2H), 7.79 - 7.89 (m, 2H), 8.06 (d, 1H), 8.25 (s, 1H), 8.45 (d, 1H), 11.40 (d, 1H).

**tert-Butyl 4-(4-(3-(2-chloro-4-((triisopropylsilyloxy)methyl)benzoyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate**

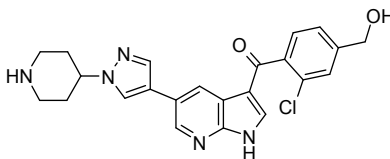


**General procedure D** was used to afford the title compound as a yellow solid (298 mg, 76%).

m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 692;

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 1.05 - 1.13 (m, 18H), 1.13 - 1.26 (m, 3H), 1.44 (s, 9H), 1.86 (dd, 2H), 2.08 (d, 2H), 2.95 (br s, 2H), 3.96 - 4.15 (m, 2H), 4.28 - 4.48 (m, 1H), 4.92 (s, 2H), 7.41 - 7.49 (m, 1H), 7.49 - 7.59 (m, 2H), 7.78 (s, 1H), 7.96 (s, 1H), 8.43 (s, 1H), 8.58 (d, 1H), 8.67 (d, 1H), 12.66 (s, 1H).

**(2-Chloro-4-(hydroxymethyl)phenyl)(5-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone (22)**



**General procedure E** was used to afford the title compound as a white solid (62 mg, 33%).

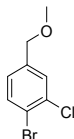
m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 436;

HRMS calculated for C<sub>23</sub>H<sub>22</sub>ClN<sub>5</sub>O<sub>2</sub> [M+H]<sup>+</sup> 436.1540, found 436.1530;

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 1.72 - 1.94 (m, 2H), 1.94 - 2.08 (m, 2H), 2.55 - 2.70 (m, 2H), 3.06 (d, 2H), 4.01 - 4.37 (m, 1H), 4.61 (s, 2H), 5.45 (br s, 1H), 7.19 - 7.45 (m, 1H), 7.51 (d, 2H), 7.77 (s, 1H), 7.93 (s, 1H), 8.34 (s, 1H), 8.53 (d, 1H), 8.65 (d, 1H), 2 x NH not observed.

**(2-Chloro-4-(methoxymethyl)phenyl)(5-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone (23)**

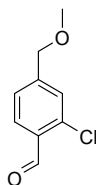
**1-Bromo-2-chloro-4-(methoxymethyl)benzene**



To a solution of (4-bromo-3-chlorophenyl)methanol (9.5 g, 42.9 mmol) in DMF (80 mL) was added sequentially NaH 60% dispersion in mineral oil (2.47 g, 51.5 mmol) and methyl iodide (5.42 mL, 85.8 mmol). The reaction was stirred at 20 °C for 30 min. The reaction mixture was quenched by carefully adding water (50 mL), extracted with Et<sub>2</sub>O (3 x 100 mL), the organic layer was separated, dried (MgSO<sub>4</sub>), filtered and evaporated to afford a yellow liquid which was purified by distillation at 1.0 mBar, collecting fractions that distilled at 80 °C to afford the title compound as a colourless liquid (9.50 g, 94%).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.39 (s, 3H), 4.39 (s, 2H), 7.08 (dd, 1H), 7.44 (d, 1H), 7.57 (d, 1H).

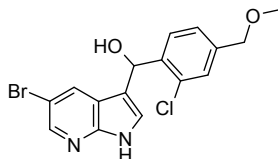
### 2-Chloro-4-(methoxymethyl)benzaldehyde



**General procedure K** was used to afford the title compound as a pale yellow liquid (2.60 g, 66%).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.44 (s, 3H), 4.49 (s, 2H), 7.32 (ddd, 1H), 7.41 - 7.48 (m, 1H), 7.90 (d, 1H), 10.46 (d, 1H).

### (5-Bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)(2-chloro-4-(methoxymethyl)phenyl)methanol

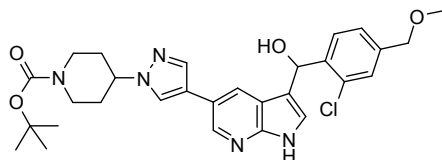


**General procedure C** was used to afford the title compound as a white solid (740 mg, 82%).

m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 383;

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 3.29 (s, 3H), 4.41 (s, 2H), 5.96 (d, 1H), 6.18 (d, 1H), 7.16 (d, 1H), 7.3 - 7.39 (m, 2H), 7.80 (d, 1H), 8.06 (d, 1H), 8.25 (d, 1H), 11.76 (s, 1H)

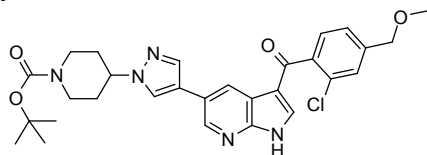
### *tert*-Butyl 4-(4-(3-((2-chloro-4-(methoxymethyl)phenyl)(hydroxymethyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate



**General procedure L** was used to afford the title compound as a white solid (210 mg, 15%).

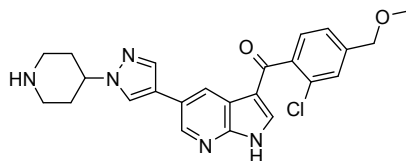
m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 552;

### *tert*-Butyl 4-(4-(3-(2-chloro-4-(methoxymethyl)benzoyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate



**General procedure O** was used to afford the title compound as a yellow foam (190 mg, 91%).  
 $m/z$  ( $ES^+$ )  $[M+H]^+ = 550$ ;

**(2-Chloro-4-(methoxymethyl)phenyl)(5-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone (23)**



**General procedure E** was used to afford the title compound as a beige solid (78 mg, 50%).

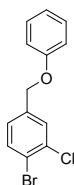
$m/z$  ( $ES^+$ )  $[M+H]^+ = 450$ ;

HRMS calculated for  $C_{24}H_{24}ClN_5O_2$   $[M+H]^+ 450.1697$ , found 450.1712;

$^1H$  NMR (400 MHz,  $DMSO-d_6$ )  $\delta$  1.86 (qd, 2H), 2.02 (d, 2H), 2.64 (td, 2H), 3.08 (d, 2H), 3.37 (s, 3H), 4.18 - 4.3 (m, 1H), 4.52 (s, 2H), 7.4 - 7.45 (m, 1H), 7.51 - 7.58 (m, 2H), 7.81 (s, 1H), 7.96 (s, 1H), 8.37 (s, 1H), 8.56 (d, 1H), 8.67 (d, 1H), 2 x NH not observed.

**(2-Chloro-4-(phenoxyethyl)phenyl)(5-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone (24)**

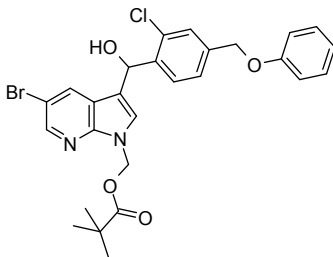
**1-Bromo-2-chloro-4-(phenoxyethyl)benzene**



To a solution of tributylphosphine (0.694 mL, 2.78 mmol), phenol (0.261 g, 2.78 mmol), and (4-bromo-3-chlorophenyl)methanol (0.535 g, 2.42 mmol) in THF (15 mL) at 0 °C was added a solution of 1,1'-(azodicarbonyl)dipiperidine (0.701 g, 2.78 mmol) and THF (10 mL) dropwise over 5 min. The resulting orange mixture was maintained under these conditions for 2 h then filtered and washed with  $Et_2O$  (50 mL). The filtrate was concentrated under reduced pressure and then diluted with  $Et_2O$ . The resulting mixture was stirred vigorously for 5 min and then filtered. The filtrate was concentrated under reduced pressure, and the resulting light orange-yellow oil was purified by flash silica chromatography, elution gradient 0-20%  $EtOAc$  in hexanes to afford the title compound as a white solid (540 mg, 71%).

$^1H$  NMR (300 MHz,  $DMSO-d_6$ )  $\delta$  5.11 (s, 2H), 6.79 - 7.16 (m, 3H), 7.20 - 7.48 (m, 3H), 7.71 (d, 1H), 7.79 (d, 1H).

**(5-Bromo-3-((2-chloro-4-(phenoxyethyl)phenyl)(hydroxy)methyl)-1H-pyrrolo[2,3-b]pyridin-1-yl)methyl pivalate**

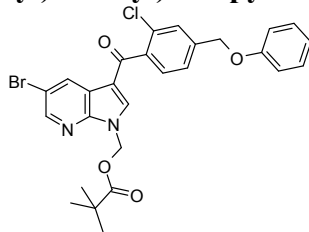


**General procedure I** was used to afford the title compound as a white foam solid (0.431 g, 51%).

$m/z$  ( $ES^+$ )  $[M+H]^+ = 557$ ;

$^1H$  NMR (300 MHz,  $DMSO-d_6$ )  $\delta$  1.05 (s, 9H), 5.12 (s, 2H), 6.05 - 6.27 (m, 4H), 6.85 - 6.98 (m, 1H), 7.02 (d, 2H), 7.25 - 7.39 (m, 3H), 7.44 - 7.53 (m, 2H), 7.81 (d, 1H), 8.17 (d, 1H), 8.38 (d, 1H).

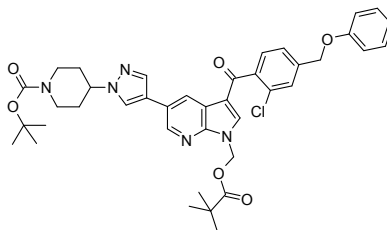
**(5-bromo-3-(2-chloro-4-(phenoxy)methyl)benzoyl)-1H-pyrrolo[2,3-b]pyridin-1-yl)methyl pivalate**



**General procedure D** was used to afford the title compound as a clear colourless glass (374 mg, 87%).  
 $m/z$  ( $ES^+$ )  $[M+H]^+ = 555$ ;

$^1H$  NMR (300 MHz,  $DMSO-d_6$ )  $\delta$  1.00 - 1.11 (m, 9H), 5.24 (s, 2H), 6.25 (s, 2H), 6.92 - 7.03 (m, 1H), 7.07 (d, 2H), 7.26 - 7.41 (m, 2H), 7.61 (d, 2H), 7.72 (s, 1H), 8.19 (s, 1H), 8.53 - 8.68 (m, 2H).

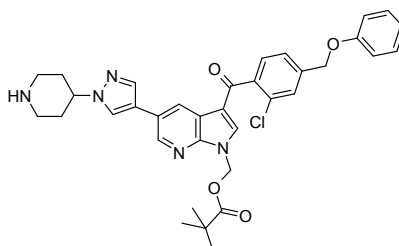
**tert-Butyl 4-(4-(3-(2-chloro-4-(phenoxy)methyl)benzoyl)-1-((pivaloyloxy)methyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate**



**General procedure G** was used to afford the title compound as a light brown gum (111 mg, 85%).  
 $m/z$  ( $ES^+$ )  $[M+H]^+ = 726$ ;

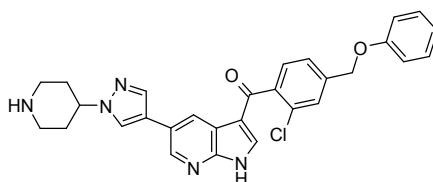
$^1H$  NMR (300 MHz,  $DMSO-d_6$ )  $\delta$  1.08 (s, 18H), 1.74 - 1.95 (m, 2H), 2.02 - 2.16 (m, 2H), 2.83 - 3.09 (m, 2H), 4.05 - 4.13 (m, 2H), 4.31 - 4.50 (m, 1H), 5.24 (s, 2H), 6.26 (s, 2H), 6.99 (s, 1H), 7.08 (d, 2H), 7.33 (d, 2H), 7.61 (d, 2H), 7.72 (s, 1H), 8.02 (s, 1H), 8.07 (s, 1H), 8.48 (s, 1H), 8.63 (d, 1H), 8.76 (d, 1H).

**(3-(2-Chloro-4-(phenoxy)methyl)benzoyl)-5-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-1-yl)methyl pivalate**



**General procedure E** was used to afford the title compound as a orange foam (90 mg, 100%) which was used without further purification.

**(2-Chloro-4-(phenoxy)methyl)phenyl(5-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone (24)**

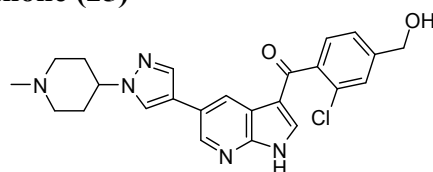


**General procedure H** was used to afford the title compound as a white solid (30.0 mg, 42%).  
 $m/z$  ( $ES^+$ )  $[M+H]^+ = 512$ ;  
HRMS calculated for  $C_{29}H_{26}ClN_5O_2$   $[M+H]^+ 512.1853$ , found 512.1843;



<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 1.60 - 1.86 (m, 2H), 1.94 (d, 2H), 2.53 (t, 2H), 2.99 (d, 2H), 3.96 - 4.25 (m, 1H), 5.15 (s, 2H), 6.91 (t, 1H), 7.00 (d, 2H), 7.17 - 7.33 (m, 2H), 7.43 - 7.54 (m, 2H), 7.60 (s, 1H), 7.73 (s, 1H), 7.86 (s, 1H), 8.26 (s, 1H), 8.45 (br s, 1H), 8.56 (s, 1H), 2 x NH not observed.

**(2-Chloro-4-(hydroxymethyl)phenyl)(5-(1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone (25)**



To a solution of **22** (0.117 g, 0.23 mmol) in THF (2 mL) and MeOH (0.5 mL) was added sequentially 37 wt% aqueous formaldehyde (0.2 mL, 2.69 mmol) and MP-(OAc)<sub>3</sub>BH (200 mg, 2.3 mmol/g). After 5 min the mixture was filtered, and the filtrate was quenched with concentrated aqueous NH<sub>4</sub>OH (3 mL). The mixture was concentrated under reduced pressure, and the resulting residue was purified by reverse phase HPLC, XBridge Prep C18 OBD, 5 μm silica, 4.6 x 50 mm, gradient 10 to 40% MeCN/0.2% NH<sub>4</sub>OH in H<sub>2</sub>O to afford the title compound as a white solid (58 mg, 56%).

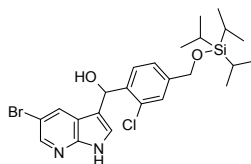
m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 450;

HRMS calculated for C<sub>24</sub>H<sub>24</sub>ClN<sub>5</sub>O<sub>2</sub> [M+H]<sup>+</sup> 450.1697, found 450.1712;

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 1.78 - 2.06 (m, 6H), 2.15 (s, 3H), 2.81 (d, 2H), 3.83 - 4.23 (m, 1H), 4.53 (s, 2H), 5.37 (br s, 1H), 7.22 - 7.38 (m, 1H), 7.38 - 7.51 (m, 2H), 7.70 (s, 1H), 7.88 (s, 1H), 8.30 (s, 1H), 8.48 (d, 1H), 8.59 (d, 1H), 12.36 - 12.71 (m, 1H).

**1-(4-(4-(3-(2-Chloro-4-(hydroxymethyl)benzoyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidin-1-yl)ethanone (26)**

**(5-Bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)(2-chloro-4-(((triisopropylsilyl)oxy)methyl)phenyl)methanol**

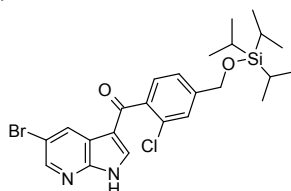


**General procedure C** was used to afford the title compound as a white solid (2.47 g, 52%).

m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 525;

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 1.05 (d, 18H), 1.1 - 1.21 (m, 3H), 4.81 (s, 2H), 5.89 (d, 1H), 6.18 (d, 1H), 7.14 (d, 1H), 7.36 (d, 2H), 7.77 (d, 1H), 8.04 (d, 1H), 8.24 (d, 1H), 11.71 (s, 1H).

**(5-Bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)(2-chloro-4-(((triisopropylsilyl)oxy)methyl)phenyl)methanone**

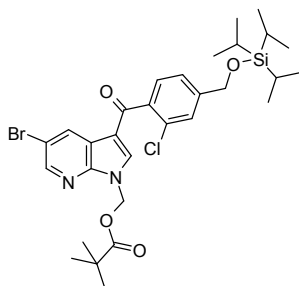


**General procedure D** was used to afford the title compound as a cream solid (4.47 g, 52%).

m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 523;

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 1.09 (d, 18H), 1.16 - 1.25 (m, 3H), 4.92 (s, 2H), 7.45 (d, 1H), 7.55 (d, 2H), 7.94 (s, 1H), 8.48 (d, 1H), 8.53 (d, 1H), 12.92 (s, 1H).

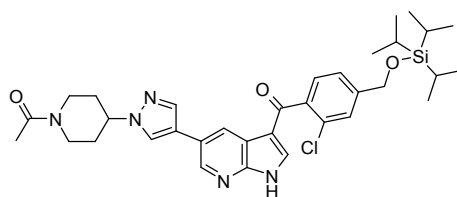
**(5-Bromo-3-(2-chloro-4-(((triisopropylsilyl)oxy)methyl)benzoyl)-1H-pyrrolo[2,3-b]pyridin-1-yl)methyl pivalate**



**General procedure F** was used to afford the title compound as a colourless gum (4.98 g, 95%).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.13 (d, 27H), 1.17 - 1.25 (m, 3H), 4.90 (s, 2H), 6.20 (s, 2H), 7.33 - 7.38 (m, 1H), 7.40 (d, 1H), 7.47 - 7.52 (m, 1H), 7.68 (s, 1H), 8.49 (d, 1H), 8.81 (d, 1H).

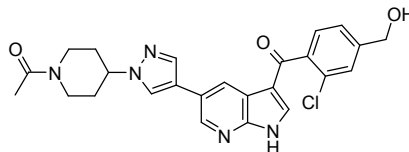
**1-(4-(4-(3-(2-Chloro-4-(((triisopropylsilyl)oxy)methyl)benzoyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidin-1-yl)ethanone**



**General procedure L** was used to afford the title compound as a colourless gum (197 mg, 64%).

$m/z$  ( $\text{ES}^+$ )  $[\text{M}+\text{H}]^+ = 634$ ;

**1-(4-(4-(3-(2-Chloro-4-(hydroxymethyl)benzoyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidin-1-yl)ethanone (26)**



6 N HCl in IPA (15 mL, 90.00 mmol) was added to 1-(4-(4-(3-(2-chloro-4-(((triisopropylsilyl)oxy)methyl)benzoyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidin-1-yl)ethanone (193 mg, 0.30 mmol), at 25 °C. The resulting solution was stirred at rt for 2 h. The reaction mixture was quenched with saturated  $\text{NaHCO}_3$  (50 mL) and extracted with DCM (3 x 15 mL). The combined organics were washed with brine (20 mL), dried ( $\text{MgSO}_4$ ), filtered and evaporated to afford crude product. The crude solid was triturated with  $\text{Et}_2\text{O}$  to give a solid which was collected by filtration and dried under vacuum to afford the title compound as a white solid (130 mg, 89%).

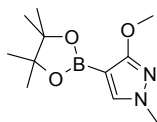
$m/z$  ( $\text{ES}^+$ )  $[\text{M}+\text{H}]^+ = 478$ ;

HRMS calculated for  $\text{C}_{25}\text{H}_{24}\text{ClN}_5\text{O}_3$   $[\text{M}+\text{H}]^+ 478.1646$ , found 478.1654;

$^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  1.81 (qd, 1H), 1.96 (qd, 1H), 2.06 (s, 3H), 2.08 - 2.16 (m, 2H), 2.75 (t, 1H), 3.19 - 3.28 (m, 1H), 3.95 (d, 1H), 4.43 - 4.52 (m, 2H), 4.60 (d, 2H), 5.47 (t, 1H), 7.39 - 7.43 (m, 1H), 7.51 - 7.54 (m, 2H), 7.79 (s, 1H), 7.98 (d, 1H), 8.42 (s, 1H), 8.57 (d, 1H), 8.67 (d, 1H), 12.68 (s, 1H).

**2-Chloro-4-(hydroxymethyl)phenyl(5-(3-methoxy-1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone (27)**

**3-Methoxy-1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole**

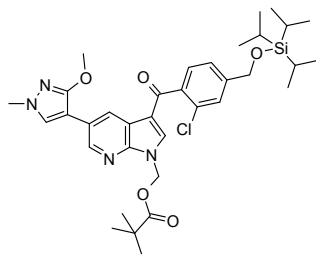


Butyllithium 1.6M in hexanes (12.3 mL, 19.6 mmol) was added dropwise to 4-bromo-3-methoxy-1-methyl-1H-pyrazole (3.0 g, 15.7 mmol) in THF (60 mL) at -78 °C over a period of 5 min under nitrogen. The resulting cream suspension was stirred at -78 °C for 20 min. 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.81 mL, 23.56 mmol) was added dropwise to the reaction at at -78 °C over a period of 5 min and the resulting pale yellow solution was allowed to warm to rt and stirred at 20 °C for 1 h. The reaction mixture was quenched with water (50 mL) and brine (50 mL) and neutralised with 2M HCl solution. The aqueous was extracted with EtOAc (2 x 50 mL), the organics combined, dried (MgSO<sub>4</sub>), filtered and evaporated to afford crude product which was purified by flash silica chromatography, elution gradient 40 to 80% EtOAc in heptanes to afford the title compound as a white solid (2.71 g, 72%).

m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 239;

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.30 (s, 12H), 3.72 (s, 3H), 3.93 (s, 3H), 7.43 (s, 1H).

**(3-(2-Chloro-4-((triisopropylsilyloxy)methyl)benzoyl)-5-(3-methoxy-1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-1-yl)methyl pivalate**

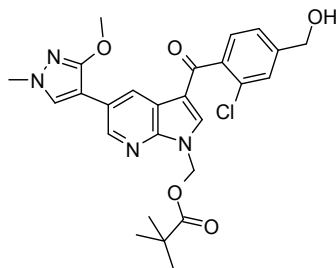


**General procedure G** was used to afford the title compound as an amber gum (151 mg, 72%).

m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 667;

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 1.01 - 1.13 (m, 27H), 1.13 - 1.30 (m, 3H), 3.76 (s, 3H), 3.91 (s, 1H), 3.95 (s, 3H), 4.94 (s, 2H), 6.25 (s, 2H), 7.41 - 7.51 (m, 1H), 7.52 - 7.64 (m, 2H), 8.02 (s, 1H), 8.16 (s, 1H), 8.67 (dd, 1H).

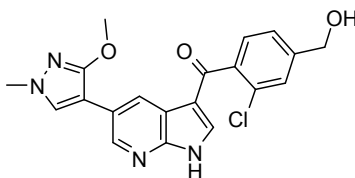
**(3-(2-Chloro-4-(hydroxymethyl)benzoyl)-5-(3-methoxy-1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-1-yl)methyl pivalate**



**General procedure E** was used to afford the title compound as an orange solid which was carried through to the next step without purification (112 mg, 97%).

m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 511.

**(2-Chloro-4-(hydroxymethyl)phenyl)(5-(3-methoxy-1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone (27)**



**General procedure H** was used to afford the title compound as an off white solid (64.0 mg, 73%).

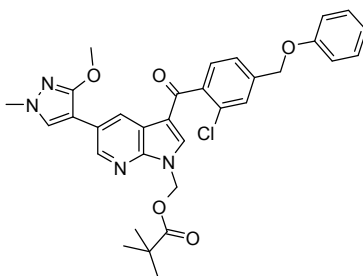
$m/z$  ( $ES^+$ )  $[M+H]^+ = 397$ ;

HRMS calculated for  $C_{20}H_{17}ClN_4O_3$   $[M+H]^+ 397.1067$ , found 397.1034;

$^1H$  NMR (300 MHz,  $DMSO-d_6$ )  $\delta$  3.67 (s, 3H), 3.85 (s, 3H), 4.52 (s, 2H), 7.26 - 7.33 (m, 1H), 7.33 - 7.39 (m, 1H), 7.41 (s, 1H), 7.61 (s, 1H), 7.93 (s, 1H), 8.41 (br s, 2H), 2 x NH not observed.

**(2-Chloro-4-(phenoxymethyl)phenyl)(5-(3-methoxy-1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone (28)**

**(3-(2-Chloro-4-(phenoxymethyl)benzoyl)-5-(3-methoxy-1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-1-yl)methyl pivalate**

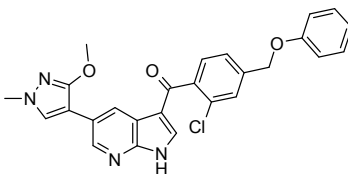


**General procedure G** was used to afford the title compound as a light brown gum (0.078 g, 82%).

$m/z$  ( $ES^+$ )  $[M+H]^+ = 587$ ;

$^1H$  NMR (300 MHz,  $DMSO-d_6$ )  $\delta$  1.01 - 1.10 (m, 9H), 3.76 (s, 3H), 3.95 (s, 3H), 5.24 (s, 2H), 6.25 (s, 2H), 6.99 (s, 1H), 7.08 (d, 2H), 7.33 (d, 2H), 7.60 (s, 2H), 7.72 (s, 1H), 8.06 (s, 1H), 8.16 (s, 1H), 8.68 (dd, 2H).

**(2-Chloro-4-(phenoxymethyl)phenyl)(5-(3-methoxy-1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone (28)**



**General procedure H** was used to afford the title compound as a white solid (42 mg, 67%).

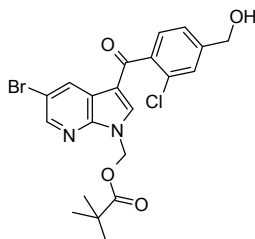
$m/z$  ( $ES^+$ )  $[M+H]^+ = 473$ ;

HRMS calculated for  $C_{26}H_{21}ClN_4O_3$   $[M+H]^+ 473.1380$ , found 473.1382;

$^1H$  NMR (300 MHz,  $DMSO-d_6$ )  $\delta$  3.68 (s, 3H), 3.87 (s, 3H), 5.15 (s, 2H), 6.91 (t, 1H), 7.00 (d, 2H), 7.18 - 7.35 (m, 2H), 7.39 - 7.55 (m, 2H), 7.60 (s, 1H), 7.73 (s, 1H), 8.03 (s, 1H), 8.52 (s, 2H), NH not observed.

**(2-Chloro-4-((2-fluorophenoxy)methyl)phenyl)(5-(3-methoxy-1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone (29)**

**(5-Bromo-3-(2-chloro-4-(hydroxymethyl)benzoyl)-1H-pyrrolo[2,3-b]pyridin-1-yl)methyl pivalate**

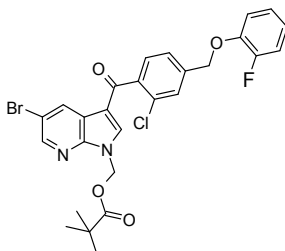


6N HCl in IPA (15 mL, 90.00 mmol) was added to (5-bromo-3-(2-chloro-4-(((triisopropylsilyl)oxy)methyl)benzoyl)-1H-pyrrolo[2,3-b]pyridin-1-yl)methyl pivalate (1g, 1.57 mmol), at 25 °C. The resulting solution was stirred at rt for 2 h. The reaction mixture was quenched with saturated NaHCO<sub>3</sub> (50 mL) and extracted with DCM (3 x 15 mL). The organics were washed with brine (20 mL) and the organic layer was dried (MgSO<sub>4</sub>), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 10 to 40% EtOAc in heptane. Pure fractions were evaporated to dryness to afford the title compound as a white solid (0.737 g, 98%).

m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 481;

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.14 (s, 9H), 1.92 (t, 1H), 4.80 (d, 2H), 6.19 (s, 2H), 7.35 - 7.4 (m, 1H), 7.43 (d, 1H), 7.51 - 7.53 (m, 1H), 7.68 (s, 1H), 8.50 (d, 1H), 8.84 (d, 1H)

**(5-Bromo-3-(2-chloro-4-((2-fluorophenoxy)methyl)benzoyl)-1H-pyrrolo[2,3-b]pyridin-1-yl)methyl pivalate**

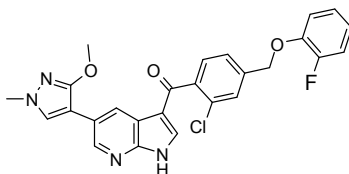


Diisopropylazodicarboxylate (166 μL, 0.84 mmol) was added dropwise to (5-bromo-3-(2-chloro-4-(hydroxymethyl)benzoyl)-1H-pyrrolo[2,3-b]pyridin-1-yl)methyl pivalate (368 mg, 0.77 mmol), 2-fluorophenol (82 μL, 0.92 mmol) and triphenylphosphine (221 mg, 0.84 mmol) in DCM (3.6 mL) at 0 °C under nitrogen. The resulting mixture was allowed to warm up to rt and stirred for 18 h. The reaction mixture was purified by flash silica chromatography, elution gradient 10 to 100% EtOAc in heptane. Pure fractions were evaporated to dryness to afford the title compound as a colourless gum (338 mg, 77%).

m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 575;

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 1.07 (s, 9H), 5.31 (s, 2H), 6.25 (s, 2H), 6.96 - 7.04 (m, 1H), 7.17 (t, 1H), 7.22 - 7.33 (m, 2H), 7.58 - 7.67 (m, 2H), 7.73 (s, 1H), 8.19 (s, 1H), 8.59 - 8.65 (m, 2H)

**(2-Chloro-4-((2-fluorophenoxy)methyl)phenyl)(5-(3-methoxy-1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone (29)**



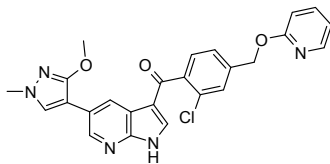
**General procedure L** was used to afford the title compound as a white solid (140 mg, 49%).

m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 491;

HRMS calculated for C<sub>26</sub>H<sub>20</sub>ClFN<sub>4</sub>O<sub>3</sub> [M+H]<sup>+</sup> 491.1286, found 491.1263;

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 3.76 (s, 3H), 3.94 (s, 3H), 5.30 (s, 2H), 6.97 - 7.04 (m, 1H), 7.16 (d, 1H), 7.23 - 7.33 (m, 2H), 7.59 (t, 2H), 7.69 (s, 1H), 7.82 (s, 1H), 8.10 (s, 1H), 8.62 (s, 2H), 12.64 (s, 1H)

**(2-Chloro-4-((pyridin-2-yloxy)methyl)phenyl)(5-(3-methoxy-1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone (30)**



1M *t*BuOK in THF (0.431 mL, 0.43 mmol) was added to (3-(2-chloro-4-(hydroxymethyl)benzoyl)-5-(3-methoxy-1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-1-yl)methyl pivalate (200 mg, 0.39 mmol) and 2-chloropyridine (0.041 mL, 0.43 mmol) in dioxane (2 mL) at 20 °C under nitrogen. The resulting mixture was heated to 60 °C and stirred for 2 h. POM appeared to have been removed but only a small amount of product had formed. Most of the material was out of solution so added DMF (2 mL). The resulting mixture was heated to 75 °C and stirred for 18 h. The reaction was quenched with water (50 mL) and neutralised with 2M HCl. The mixture was extracted with EtOAc (3 x 40 mL). The organics were combined, washed with brine (30 mL), dried (MgSO<sub>4</sub>), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 50 to 100% EtOAc in heptane. Pure fractions were evaporated to dryness then triturated with MeOH and filtered and vacuum oven dried at 50 °C overnight to afford the title compound as a white solid (115 mg, 62%)

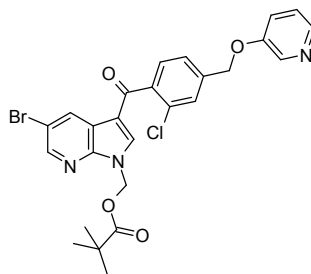
*m/z* (ES<sup>+</sup>) [M+H]<sup>+</sup> = 474;

HRMS calculated for C<sub>25</sub>H<sub>20</sub>ClN<sub>5</sub>O<sub>3</sub> [M+H]<sup>+</sup> 474.1333, found 474.1317

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 3.76 (s, 3H), 3.94 (s, 3H), 5.47 (s, 2H), 6.96 (d, 1H), 7.04 (dd, 1H), 7.55 (s, 2H), 7.67 (s, 1H), 7.74 - 7.84 (m, 2H), 8.10 (s, 1H), 8.21 (dd, 1H), 8.61 (t, 2H), 12.63 (s, 1H).

**(2-Chloro-4-((pyridin-3-yloxy)methyl)phenyl)(5-(3-methoxy-1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone (31)**

**(5-Bromo-3-(2-chloro-4-((pyridin-3-yloxy)methyl)benzoyl)-1H-pyrrolo[2,3-b]pyridin-1-yl)methyl pivalate**

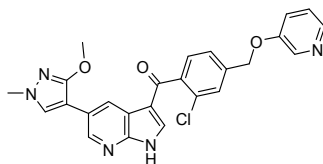


Diisopropylazodicarboxylate (118 μL, 0.60 mmol) was added dropwise to (5-bromo-3-(2-chloro-4-(hydroxymethyl)benzoyl)-1H-pyrrolo[2,3-b]pyridin-1-yl)methyl pivalate (261 mg, 0.54 mmol), pyridin-3-ol (62.1 mg, 0.65 mmol) and triphenylphosphine (157 mg, 0.60 mmol) in DCM (2.6 mL) at 0 °C under nitrogen. The resulting mixture was allowed to warm up to rt and stirred for 18 h. The reaction mixture was purified by flash silica chromatography, elution gradient 10 to 100% EtOAc in heptanes to afford the title compound as a colourless gum (117 mg, 39%).

*m/z* (ES<sup>+</sup>) [M+H]<sup>+</sup> = 556;

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 1.07 (s, 9H), 5.32 (s, 2H), 6.25 (s, 2H), 7.38 (dd, 1H), 7.51 - 7.55 (m, 1H), 7.59 - 7.66 (m, 2H), 7.75 (s, 1H), 8.18 (s, 1H), 8.23 (dd, 1H), 8.43 (d, 1H), 8.59 - 8.64 (m, 2H)

**(2-Chloro-4-((pyridin-3-yloxy)methyl)phenyl)(5-(3-methoxy-1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone (31)**



**General procedure L** was used to afford the title compound as a white solid (11.7 mg, 12%).

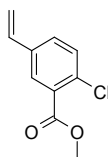
$m/z$  ( $ES^+$ )  $[M+H]^+ = 474$ ;

HRMS calculated for  $C_{25}H_{20}ClN_5O_3$   $[M+H]^+ 474.1333$ , found 474.1317

$^1H$  NMR (400 MHz,  $DMSO-d_6$ )  $\delta$  3.81 (s, 3H), 4.00 (s, 3H), 5.36 (s, 2H), 7.44 (ddd, 1H), 7.58 (ddd, 1H), 7.61 - 7.66 (m, 2H), 7.76 (d, 1H), 7.87 (s, 1H), 8.17 (s, 1H), 8.28 (dd, 1H), 8.48 (d, 1H), 8.67 (d, 2H), 12.71 (s, 1H).

**2-(4-Chloro-3-[[5-(3-methoxy-1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl]carbonyl]phenyl)ethan-1-ol (32)**

**Methyl 2-chloro-5-ethenylbenzoate**



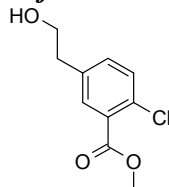
Into a 500-mL round-bottom flask, was placed a solution of methyl 5-bromo-2-chlorobenzoate (2.2 g, 8.82 mmol) in n-BuOH (150 mL), potassium trifluoro(vinyl)borate (1.3 g, 9.71 mmol),  $Pd(PPh_3)_2Cl_2$  (1.2 g, 1.71 mmol),  $NEt_3$  (33 mL, 237 mmol). The resulting solution was stirred for 4 h at 100 °C, the solids were removed by filtration and the filtrate was concentrated under vacuum. Water (30 mL) was added and the resulting solution was extracted with of EtOAc (3 x 50 mL), organic layers combined washed with brine (50 mL), dried ( $Na_2SO_4$ ), and concentrated. The residue was purified by flash silica chromatography, eluting with 2.5% EtOAc in petroleum ether to afford the title compound as yellow oil (1.16 g, 67%).

$m/z$  ( $ES^+$ )  $[M+H]^+ = 197$ ;

$^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  3.94 (s, 3H), 5.34(d, 1H), 5.78 (d, 1H), 6.64-6.71 (m, 1H), 7.39-7.47 (m, 2H), 7.82 (s, 1H).

**Methyl 2-chloro-5-(2-hydroxyethyl)benzoate**

**General procedure P: hydroborylation/alcohol formation**

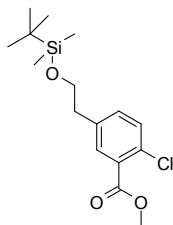


Into a 100-mL round-bottom flask, was placed methyl 2-chloro-5-ethenylbenzoate (1.0 g, 5.1 mmol), a solution of 9-borabicyclo[3.3.1]nonane in THF (7.6 mL, 7.6 mmol) was stirred at 25 °C overnight, then  $H_2O_2$  (30%) (1.7 mL, 15 mmol) and 3N NaOH (2.7 mL) were added to the solution at -30 °C. The resulting solution was stirred for 3 h at 0 - 10 °C. After concentration under vacuum, the resulting solution was extracted with EtOAc (3 x 30 mL), organic layers combined, washed with brine (50 mL), dried ( $Na_2SO_4$ ), and concentrated. The residue was purified by flash silica chromatography, elution gradient 10 to 50% EtOAc in petroleum ether to afford the title compound as light yellow oil (733 mg, 67%).

$^1H$  NMR (300 MHz,  $DMSO-d_6$ )  $\delta$  2.73-2.77 (m, 2H), 3.60-3.64 (m, 2H), 3.85 (s, 3H), 4.64-4.68 (m, 1H), 7.41-7.52 (m, 2H), 7.66 (s, 1H).

## Methyl 5-[2-[(*tert*-butyldimethylsilyl)oxy]ethyl]-2-chlorobenzoate

### General procedure Q: silylation

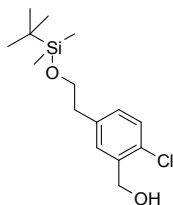


Into a 25-mL round-bottom flask, was placed a solution of methyl 2-chloro-5-(2-hydroxyethyl)benzoate (733 mg, 3.41 mmol) in DMF (5 mL) was stirred at 0 °C, then *tert*-butyl(chloro)dimethylsilane (421 mg, 2.79 mmol) and 4H-imidazole (189 mg, 2.78 mmol) were added. The resulting solution was stirred for 1 h at rt. Water (10 mL) and EtOAc (30 mL) were added. The resulting solution was extracted with EtOAc (3 x 50 mL), organic layers combined, washed with brine (50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated. The residue was purified by flash silica chromatography, eluting with 0 to 3% EtOAc in petroleum ether to afford the title compound as light yellow oil (700 mg, 62%).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.03 (s, 6H), 0.89 (s, 9H), 2.82-2.85 (m, 2H), 3.81-3.84 (m, 2H), 3.96 (s, 3H), 7.29-7.31 (m, 1H), 7.39 (d, 1H), 7.73 (s, 1H).

## (5-[2-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-2-chlorophenyl)methanol

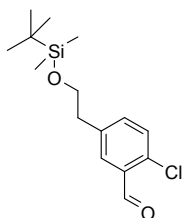
### General procedure R: LiAlH<sub>4</sub> reduction



Into a 25-mL round-bottom flask, was placed a solution of methyl 5-[2-[(*tert*-butyldimethylsilyl)oxy]ethyl]-2-chlorobenzoate (700 mg, 2.13 mmol) in THF (5 mL), LiAlH<sub>4</sub> (121 mg, 3.19 mmol) was then added. The resulting solution was stirred for 30 min at -35 °C. The reaction was then quenched by the addition of water (3 mL). The resulting solution was extracted with EtOAc (3 x 30 mL) and the organic layers combined, washed with brine (30 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under vacuum to give the title compound as light yellow oil (764 mg, 119%) which was used without further purification.

## 5-[2-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-2-chlorobenzaldehyde

### General procedure S: IBX oxidation to aldehyde



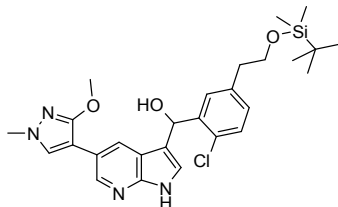
Into a 25-mL round-bottom flask, was placed a solution of (5-[2-[(*tert*-butyldimethylsilyl)oxy]ethyl]-2-chlorophenyl)methanol (764 mg, 2.54 mmol) in DMSO (5 mL) and IBX (1.07 g, 3.82 mmol) was then added. The resulting solution was stirred for 16 h at rt, solids were filtered off, and water (10 mL) was added. The resulting solution was extracted with EtOAc (3 x 30 mL), organic layers combined, washed with brine (30 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated. The residue was purified by flash silica



chromatography, eluting with 5% EtOAc in petroleum ether to afford the title compound as an off-white oil (677 mg, 89%).

$^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  0.01 (s, 6H), 0.87 (s, 9H), 2.88-2.91(m, 2H), 3.85-3.88 (m, 2H), 7.61-7.64 (m, 2H), 7.82 (s, 1H), 10.41(s, 1H).

**(5-[2-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-2-chlorophenyl)[5-(3-methoxy-1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl]methanol**

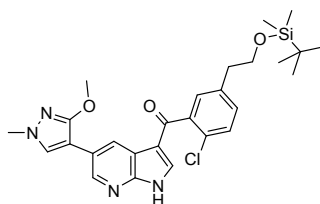


**General procedure C** was used to afford the title compound as a off-white solid (230 mg, 100%) which was used without further purification.

$m/z$  ( $\text{ES}^+$ )  $[\text{M}+\text{H}]^+ = 527$ .

**4-[3-[(5-[2-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-2-chlorophenyl)carbonyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]-3-methoxy-1-methyl-1H-pyrazole**

**General procedure T: IBX oxidation to ketone**



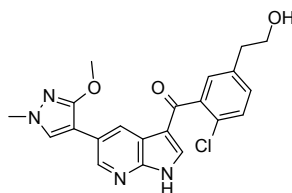
Into a 25-mL round-bottom flask, was placed a solution of (5-[2-[(*tert*-butyldimethylsilyl)oxy]ethyl]-2-chlorophenyl)[5-(3-methoxy-1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl]methanol (200 mg, 0.38 mmol) in DMSO (10 mL) and IBX (160 mg, 0.57 mmol) was added. The resulting solution was stirred for 16 h at rt, water (10 mL) added then extracted with EtOAc (3 x 30 mL). The organic layers were combined, washed with saturated  $\text{NaHSO}_3$  (30 mL) and brine (30 mL), dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated under vacuum. The residue was purified by flash silica chromatography, eluting with 2.5% MeOH in DCM to afford the title compound as a yellow solid (145 mg, 73%).

$m/z$  ( $\text{ES}^+$ )  $[\text{M}+\text{H}]^+ = 525$ ;

$^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  0.01 (s, 6H), 0.85 (s, 9H), 2.85-2.89 (m, 2H), 3.78-3.88 (m, 6H), 3.99 (s, 3H), 7.45-7.47 (m, 2H), 7.54-7.56 (m, 1H), 7.76-7.78 (m, 1H), 8.17 (s, 1H), 8.63-8.67 (m, 2H).

**2-(4-Chloro-3-[[5-(3-methoxy-1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl]carbonyl]phenyl)ethan-1-ol (32)**

**General procedure U: Desilylation with AcOH**



Into a 50-mL round-bottom flask, was placed a solution of 4-[3-[(5-[2-[(*tert*-butyldimethylsilyl)oxy]ethyl]-2-chlorophenyl)carbonyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]-3-methoxy-1-methyl-1H-pyrazole (135 mg, 0.26 mmol) in AcOH/THF/ $\text{H}_2\text{O}$  (1.7/3.5/3.5 mL). After stirring for 16 h at rt, saturated  $\text{Na}_2\text{CO}_3$  (10 mL) was added and the resulting solution extracted with EtOAc (3 x 40

mL). The organic layers were combined, washed with saturated Na<sub>2</sub>CO<sub>3</sub> (40 mL) and brine (40 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under vacuum. The crude product was purified by preparative HPLC, XBridge Prep C18 OBD, 5 µm silica, 19 x 150 mm, gradient 20% to 95% MeCN/0.1% NH<sub>4</sub>HCO<sub>3</sub> in H<sub>2</sub>O to afford the title compound as a off-white solid (24.8 mg, 23%).

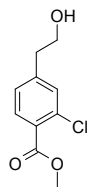
m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 411;

HRMS calculated for C<sub>21</sub>H<sub>19</sub>ClN<sub>4</sub>O<sub>3</sub> [M+H]<sup>+</sup> 411.1224, found 411.1234;

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 2.75-2.80 (m, 2H), 3.61-3.67 (m, 2H), 3.75 (s, 3H), 3.93 (s, 3H), 4.64-4.67 (m, 1H), 7.38-7.41 (m, 2H), 7.47-7.50 (m, 1H), 7.79 (s, 1H), 8.11 (s, 1H), 8.58-8.61 (m, 2H), 12.64 (s, 1H).

### **2-(3-Chloro-4-[[5-(3-methoxy-1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl]carbonyl]phenyl)ethan-1-ol (33)**

#### **Methyl 2-chloro-4-(2-hydroxyethyl)benzoate**

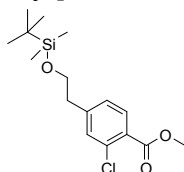


**General procedure P** was used to afford the title compound as a light yellow oil (2.42 g, 65%).

m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 215;

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 2.75-2.79 (m, 2H), 3.63-3.67 (m, 2H), 3.84 (s, 3H), 4.53-4.72 (m, 1H), 7.29-7.34 (m, 1H), 7.45 (s, 1H), 7.74 (d, 1H).

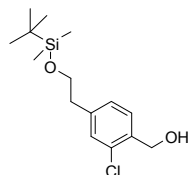
#### **Methyl 4-[2-[(*tert*-butyldimethylsilyl)oxy]ethyl]-2-chlorobenzoate**



**General procedure Q** was used to afford the title compound as a light yellow oil (2.63 g, 71%).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.02 (s, 6H), 0.89 (s, 9H), 2.83-2.86 (m, 2H), 3.83-3.86 (m, 2H), 3.94 (s, 3H), 7.17-7.20 (m, 1H), 7.36 (s, 1H), 7.81 (d, 1H).

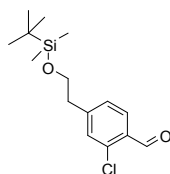
#### **(4-[2-[(*tert*-butyldimethylsilyl)oxy]ethyl]-2-chlorophenyl)methanol**



**General procedure R** was used to afford the title compound as a light yellow oil (710 mg, 78%).

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 0.02 (s, 6H), 0.88 (s, 9H), 2.77-2.80 (m, 2H), 3.80-3.83 (m, 2H), 4.57 (d, 2H), 5.35-5.38 (m, 1H), 7.24 (d, 1H), 7.32 (s, 1H), 7.48 (d, 1H).

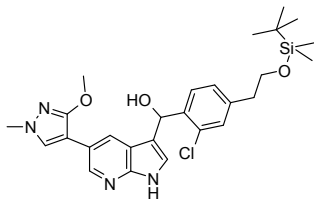
#### **4-[2-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-2-chlorobenzaldehyde**



**General procedure S** was used to afford the title compound as a light yellow oil (588 mg, 85%).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.01 (s, 6H), 0.89 (s, 9H), 2.86-2.89 (m, 2H), 3.85-3.88 (m, 2H), 7.26-7.30 (m, 1H), 7.37 (s, 1H), 7.88 (d, 1H), 10.48 (s, 1H).

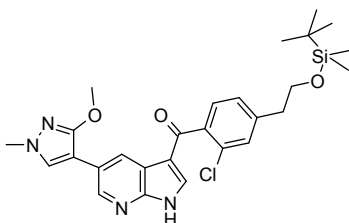
**(4-[2-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-2-chlorophenyl)[5-(3-methoxy-1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl]methanol**



**General procedure C** was used to afford the title compound as a off-white solid (250 mg, 108%) which was used directly in the next step without purification.

$m/z$  ( $\text{ES}^+$ )  $[\text{M}+\text{H}]^+ = 527$ .

**4-[3-[(4-[2-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-2-chlorophenyl)carbonyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]-3-methoxy-1-methyl-1H-pyrazole**

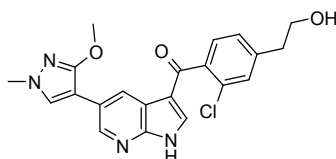


**General procedure T** was used to afford the title compound as a yellow solid (180 mg, 75%).

$m/z$  ( $\text{ES}^+$ )  $[\text{M}+\text{H}]^+ = 525$ ;

$^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ )  $\delta$  0.02 (s, 6H), 0.88 (s, 9H), 2.85-2.89 (m, 2H), 3.75(s, 3H), 3.85-3.89 (m, 2H), 3.96 (s, 3H), 7.34-7.36 (m, 1H), 7.47-7.49 (m, 2H), 7.72-7.74 (m, 1H), 8.02 (s, 1H), 8.13-8.64 (m, 2H), NH not observed.

**2-(3-Chloro-4-[[5-(3-methoxy-1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl]carbonyl]phenyl)ethan-1-ol**



**General procedure U** was used to afford the title compound as a off-white solid (50.7 mg, 40%).

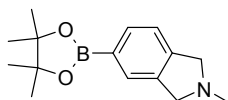
$m/z$  ( $\text{ES}^+$ )  $[\text{M}+\text{H}]^+ = 411$ ;

HRMS calculated for  $\text{C}_{21}\text{H}_{19}\text{ClN}_4\text{O}_3$   $[\text{M}+\text{H}]^+ 411.1224$ , found 411.1234;

$^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ )  $\delta$  2.79-2.84 (m, 2H), 3.66-3.72 (m, 2H), 3.75 (s, 3H), 3.93 (s, 3H), 4.70-4.73 (m, 1H), 7.31-7.34 (m, 1H), 7.45 (s, 2H), 7.77 (s, 1H), 8.10 (s, 1H), 8.57-8.61 (m, 2H), 12.63 (s, 1H).

**(2-Chlorophenyl)-[5-(2-methylisoindolin-5-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl]methanone (34)**

**2-Methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoindoline**



To a degassed yellow solution of 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (102 g, 0.41 mol), 5-bromo-2-methyl-isoindoline (80 g, 0.38 mol) and KOAc (110 g, 1.1mol) in DMF (1.2 L) was

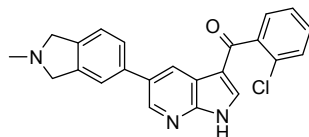
added Pd(dppf)<sub>2</sub>Cl<sub>2</sub> (8g, 10 mmol). The reaction was heated at 100 °C under nitrogen for 15 h. The cooled reaction mixture was concentrated and partitioned between EtOAc (500 mL) and water (500 mL). The mixture was filtered and the EtOAc layer was separated, evaporated to dryness and the crude product was purified by flash silica chromatography, eluting with 5% EtOAc in heptanes to afford the title compound as a brown solid (55 g, 56%).

m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 260;

<sup>1</sup>H NMR (300 MHz, MeOD) δ 1.32 (s, 12H), 3.11 (s, 3H), 4.48 - 4.54 (m, 2H), 4.90 - 4.91 (m, 1H), 7.39 - 7.41 (m, 1H), 7.73 - 7.76 (m, 2H).

### **(2-Chlorophenyl)-[5-(2-methylisoindolin-5-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl]methanone (34)**

**General procedure V: Suzuki-Miyaura reaction with shaking**



To a mixture of (5-bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)(2-chlorophenyl)methanone (77 mg, 0.20 mmol) in dioxane/EtOH/H<sub>2</sub>O (5/2/1 mL) was added 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoindoline

(62 mg, 0.24 mmol), followed by K<sub>2</sub>CO<sub>3</sub> (69 mg, 0.50 mmol) and Pd(dppf)Cl<sub>2</sub> (10 mg, 0.015 mmol) under nitrogen atmosphere. Then the reaction mixture was shaken at 120 °C for 16 h. The crude product was purified by preparative HPLC to afford the title compound (2 mg, 3%).

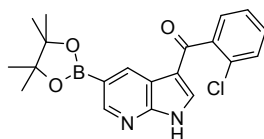
m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 388;

HRMS calculated for C<sub>23</sub>H<sub>18</sub>ClN<sub>3</sub>O [M+H]<sup>+</sup> 388.1217, found 388.1189;

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 2.53 (s, 3H), 3.87 (s, 2H), 3.91 (s, 2H), 7.37 (d, 1H), 7.48-7.65 (m, 6H), 7.88 (s, 1H), 8.57 (s, 1H), 8.66 (d, 1H), 12.81 (s, 1H)

### **7-[3-[(2-Chlorophenyl)carbonyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]-2-methyl-1,2,3,4-tetrahydroisoquinoline (35)**

**(2-Chlorophenyl)(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone**

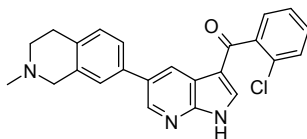


To a degassed yellow solution of 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (499 mg, 1.97 mmol) and (5-bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)(2-chlorophenyl)methanone (300 mg, 0.89 mmol) in DMF (4.06 mL) was added Pd(dppf)<sub>2</sub>Cl<sub>2</sub> (52.3 mg, 0.07 mmol) and potassium acetate (180 mg, 1.83 mmol). The reaction was heated at 100 °C under nitrogen for 18 h. The cooled reaction mixture was filtered through celite® and washed with MeCN (20 mL). The filtrate was evaporated to dryness and the crude product was purified by flash silica chromatography, elution gradient 40 to 100% EtOAc in heptane then trituration with diethyl ether to afford the title compound as a yellow solid (148 mg, 43%).

m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 383;

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 1.36 (s, 12H), 7.46-7.52 (m, 1H), 7.53-7.62 (m, 3H), 7.83 (s, 1H), 8.60 (d, 1H), 8.82 (d, 1H), 12.76 (s, 1H).

### **7-[3-[(2-Chlorophenyl)carbonyl]-1H-pyrrolo[2,3-b]pyridin-5-yl]-2-methyl-1,2,3,4-tetrahydroisoquinoline (35)**



Into a 10-mL round-bottom flask, was placed a solution of 7-bromo-2-methyl-1,2,3,4-tetrahydroisoquinoline (235 mg, 1.04 mmol, 2.00 equiv) in DME/H<sub>2</sub>O (6/2 mL), 3-[(2-chlorophenyl)carbonyl]-5-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine (200 mg, 0.52 mmol), Na<sub>2</sub>CO<sub>3</sub> (386 mg, 3.61 mmol), Pd(dppf)<sub>2</sub>Cl<sub>2</sub> (76 mg, 0.10 mmol). The final reaction mixture was irradiated with microwave radiation for 10 min at 120 °C. The resulting solution was filtered through celite®. The filtrate was extracted with EtOAc (3 x 20 mL) and the organic layers combined, washed with brine (20 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under vacuum. The crude product was purified by preparative HPLC, XBridge Shield RP18 OBD, 5 µm silica, 19 x 150mm, gradient 10% to 65% MeCN/0.1% NH<sub>4</sub>HCO<sub>3</sub> in H<sub>2</sub>O to afford the title compound as a off-white solid (27.8 mg, 13%).

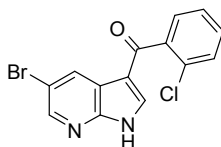
m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 402;

HRMS calculated for C<sub>24</sub>H<sub>20</sub>ClN<sub>3</sub>O [M+H]<sup>+</sup> 402.1373, found 402.1369;

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 2.17 (s, 3H), 2.59 (s, 2H), 2.73-2.74 (m, 2H), 2.86-2.99 (m, 2H), 7.26 (s, 1H), 7.41-7.76 (m, 6H), 7.87 (s, 1H), 8.54 (s, 1H), 8.65 (s, 1H), 12.76 (s, 1H).

**(2-Chlorophenyl)(5-(2-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone (36)**

**(5-Bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)-(2-chlorophenyl)methanone**

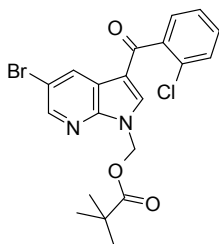


To a suspension of **38** (9 g, 45.7 mmol) in DCM (190 mL) was added over 5 min powdered aluminum chloride (12.2 g, 91.4 mmol). There was a exotherm of around 5 °C and the faint yellow suspension darkened and went into solution. After 45 min, a solution of 2-chlorobenzoyl chloride (8.97 mL, 70.8 mmol) in DCM (20 mL) was added (slight exotherm of around 5 °C). The reaction mixture (now a pale yellow suspension) was stirred at rt for 18 h then cooled to 0 °C and quenched with MeOH (40 mL) and diluted with EtOAc (100 mL). The mixture was evaporated to dryness and the resulting cream solid was suspended in EtOAc (400 mL). This was then cautiously basified with saturated aqueous NaHCO<sub>3</sub> and the solid material removed by filtration. The layers were separated and the organic layer was washed with brine (100 mL), dried (MgSO<sub>4</sub>), filtered, and concentrated under reduced pressure. The resulting solid was triturated with Et<sub>2</sub>O to afford the title compound as a pale green solid (7.92 g, 52%).

m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 335;

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 7.50 (m, 1H), 7.54-7.63 (m, 3H), 7.93 (d, 1H), 8.49 (d, 1H), 8.54 (d, 1H), 12.95 (s, 1H).

**[5-Bromo-3-(2-chlorobenzoyl)pyrrolo[2,3-b]pyridin-1-yl]methyl 2,2-dimethylpropanoate (39)**

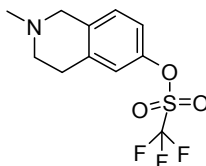


To a solution of (5-bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)(2-chlorophenyl)methanone (7.92g, 23.60 mmol) in DMF (99 ml) was added sequentially chloromethyl pivalate (4.08 ml, 28.3 mmol) and 60 wt% sodium hydride in mineral oil (1.32 g, 33.0 mmol). The reaction was stirred at 20 °C for 30 min. The reaction mixture was quenched by adding water (400 mL) and diluted with EtOAc (300 mL). The organics were separated, washed with water (2 x 200 mL) and saturated brine (100 mL), dried (MgSO<sub>4</sub>), filtered and evaporated to afford an orange oil which was triturated with heptane to afford the title compound as a off-white solid (9.26 g, 87%).

m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 451;

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 1.07 (s, 9H), 6.25 (s, 2H), 7.5 - 7.67 (m, 4H), 8.15 (s, 1H), 8.60 (s, 2H).

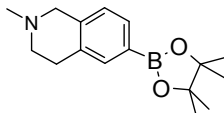
### (2-Methyl-3,4-dihydro-1H-isoquinolin-6-yl) trifluoromethanesulfonate



To a solution of 2-methyl-3,4-dihydro-1H-isoquinolin-6-ol (37 g, 227 mmol) and triethylamine (45 g, 453 mmol) in DCM (1.5 L) was added trifluoromethanesulfonic anhydride (96 g, 340 mmol) at -15 °C. The mixture was stirred at 0 °C for 1 h. The reaction was quenched with saturated NaHCO<sub>3</sub> solution (1 L). The aqueous was extracted with EtOAc (3 x 1.5 L). The organics were combined, dried (MgSO<sub>4</sub>), filtered and concentrated under reduce pressure to afford the title compound as a black oil which was used in the next step without purification (75 g, >100%).

m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 296.

### 2-Methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydroisoquinoline (40)

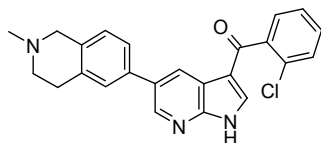


To a stirred solution of (2-methyl-3,4-dihydro-1H-isoquinolin-6-yl) trifluoromethanesulfonate (75 g, 254 mmol) in DMF (1.5 L) under nitrogen was added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (77.4 g, 304 mmol), KOAc (74.8 g, 762 mmol) and Pd(dppf)Cl<sub>2</sub> (10 g, 14 mmol). The mixture was stirred at 90 °C for 18 h. The solution was cooled to room temperature and diluted with water (2 L). The mixture was extracted with EtOAc (5 x 1 L), and the combined organic layers were washed with brine (1 L), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure to give crude product which was purified by silica gel flash chromatography eluting with 10% EtOAc in petroleum ether to afford the title compound as a brown oil (29.1 g, 42 %).

m/z (ES<sup>+</sup>) [M+H]<sup>+</sup> = 274.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.33 (s, 12H), 2.58 (s, 3H), 3.10-2.87 (m, 4H), 3.87 (s, 2H), 7.04-7.02 (d, 1H), 7.58-7.56 (m, 2H).

### (2-Chlorophenyl)(5-(2-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone (36)



To a stirred degassed solution of **39** (300 mg, 0.67 mmol), **40** (237 mg, 0.87 mmol) and  $K_2CO_3$  (277 mg, 2.00 mmol) in DME (6 mL) and water (2 mL) was added  $Pd(PPh_3)_4$  (77 mg, 0.07 mmol) and the reaction heated at 75 °C for 2 h. 2M NaOH (2 mL) was then added and the reaction was stirred for 10 min at rt. The reaction mixture was poured into water (50 mL), extracted with EtOAc (2 x 50 mL). The organics were combined, washed with water (50 mL) then brine (50 mL), dried ( $MgSO_4$ ), filtered and evaporated to afford a brown oil. This was purified by flash silica chromatography, elution gradient 0.5 to 10% MeOH in DCM and trituration with  $Et_2O$  to afford the title compound as a pale yellow solid (66.2 mg, 25%).

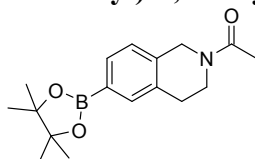
$m/z$  ( $ES^+$ )  $[M+H]^+ = 402$ ;

HRMS calculated for  $C_{24}H_{20}ClN_3O$   $[M+H]^+ 402.1373$ , found 402.1369;

$^1H$  NMR (300 MHz,  $DMSO-d_6$ )  $\delta$  2.33 (s, 1H), 2.39 (s, 2H), 2.67 (s, 3H), 2.95 (s, 2H), 3.56 (s, 2H), 7.20 (s, 1H), 7.46 (s, 2H), 7.58 (d, 3H), 7.87 (s, 1H), 8.55 (s, 1H), 8.66 (s, 1H), 12.76 (s, 1H).

**1-[6-[3-(2-Chlorobenzoyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-3,4-dihydro-1H-isoquinolin-2-yl]ethanone (37)**

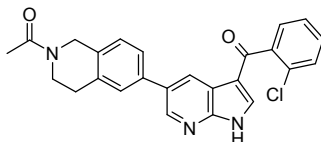
**1-(6-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydroisoquinolin-2(1H)-yl)ethanone**



4,4,4',4',5,5,5',5'-Octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.04 g, 4.11 mmol), 1-(6-bromo-3,4-dihydroisoquinolin-2(1H)-yl)ethanone (870 mg, 3.42 mmol), KOAc (1.0 g, 10.2 mmol) and  $Pd(dppf)Cl_2$  (125 mg, 0.17 mmol) in 1,4-dioxane (20 mL) was stirred under an atmosphere of nitrogen at 90 °C for 2 h. The reaction mixture was cooled to rt. The crude product was purified by flash silica chromatography, elution gradient 2 to 4% MeOH in DCM to afford the title compound as a yellow oil which was used without further purification (1.2 g).

$m/z$  ( $ES^+$ )  $[M+H]^+ = 302$ .

**1-[6-[3-(2-Chlorobenzoyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-3,4-dihydro-1H-isoquinolin-2-yl]ethanone (37)**



**General procedure V** was used to afford the title compound (6.5 mg, 6.5%).

$m/z$  ( $ES^+$ )  $[M+H]^+ = 430$ ;

HRMS calculated for  $C_{25}H_{20}ClN_3O_2$   $[M+H]^+ 430.1322$ , found 430.1329;

$^1H$  NMR (500 MHz,  $DMSO-d_6$ )  $\delta$  2.11 (s, 3H), 2.96 (br s, 2H), 3.73 (t, 2H), 4.67 (s, 2H), 7.31 (d, 1H), 7.46-7.59 (m, 6H), 7.76 (s, 1H), 8.50 (d, 1H), 8.63 (d, 1H), 12.40 (s, 1H).

## Kinase selectivity data for compounds 1, 2, 30 and 36

Table 1. %inhibition data for compound **1** tested at 10  $\mu$ M concentration

AKT1	45	JNK3	32	P70S6K	91
AKT2	64	LCK	96	PAK4	92
AMPK	94	MAP2K1	87	PAK5	77
AurKB	57	MAPK1	2	PAK6	80
AuroraC	96	MAPK12	21	PBK	83
BRK2	97	MAPK13	37	PDPK1	28
CAMK	88	MAPK15	81	PIM1	63
CAMKKalpha	82	MAPK3	31	PIM2	13
CAMKKbeta	76	MAPK9	48	PIM3	68
CDK2:CA	96	MAPKAPK1A	80	PKA	80
CHK1	76	MAPKAPK1B	82	PKCa	39
CHK2	71	MAPKAPK2	24	PKCz	28
CK1	50	MAPKAP-K3	27	PKD1	90
CK2	4	MAPKAPK5	72	PLK1	32
CSK	89	MARK3	96	PRK2	97
DYRK1A	66	MELK	90	ROCK2	90
DYRK2	29	MNK1	30	smMLCK	68
DYRK3	-30	MNK2	9	Src	98
GSK3b	35	MSK1	44	SRPK1	23
HIPK2	73	MST2	96		
HIPK3	42	NEK2a	98		
Hu EF2K	16	NEK6	17		
Hu SGK	49	NEK7	8		
IKKb	38	p38a	75		
JNK1	42	p38b	67		

Table 2. %inhibition data for compound **2** tested at 1  $\mu$ M concentration

AKT2	24	JAK2	91	P70S6K	30
AurKB	18	JNK1	12	PAK4	29
BTK	84	LCK	94	PBK	18
CAMK1d	10	MAP2K1	77	PDPK1	11
CAMKKbeta	30	MAP3K1	13	PIM3	10
CDK2:CA	49	MAP3K11	77	PKA	31
CHK2	24	MAP3K7	72	PKCa	12
CSK	80	MAP4K2	79	PRK2	36
CSNK1d	29	MAPK1	63	PKCz	1
CSNK2A1	7	MAPK13	17	PKD1	43
DYRK1A	10	MAPK9	1	PLK1	8
DYRK3	1	MAPKAPK1B	16	RIPK2	92
Hu EF2K	19	MAPKAPK2	0	ROCK2	31
EPHB3	95	MAPKAPK5	-4	Hu SGK	10



EPHRA2	67	MARK2	20	smMLCK	33
FGFR1	80	MARK3	63	src	90
FLT1	32	MARK4	24	SRPK1	0
GSK3b	59	MELK	78	MST2	68
HIPK2	10	MNK1	2	STK11	-2
IGF1R	12	MSK1	26	SYK	73
IKKb	16	NEK2a	58	TBK1	11
IKKe	36	NEK6	-1	TTK	27
INSR	56	p38a	42	YES	87
IRAK4	19	p38b	46		

Table 3. %inhibition data for compound **30** tested at 1  $\mu$ M concentration

ABL2	93	FGFR4	3	PDPK1	17
				PIK3CA	
ABL1	101	FLT1	96	p85a	11
				PIK3CB	
ACVR1B	28	FLT3	67	p85a	4
				PIK3CD	
AKT1	-11	MTOR	3	p85a	8
AKT2	23	FYN	101	PIK3C2G	38
				PIK3CG	
ALK	43	GSK3A	103	p120	36
NUAK1	85	GSK3B	98	PIM2	9
AURKB	101	IGF1R	34	PIP5K1A	5
AURKC	89	IGF1R	95	PIP5K1C	30
AXL	96	IKBKB	14	PIP4K2A	4
BLK	101	INSR	79	PRKACA	19
BMX	101	INSR	100	PRKCA	17
BTK	107	INSRR	97	PRKCE	3
CaMK1	70	IRAK4	66	PRKCQ	65
CAMK2B	6	JAK2	65	PRKG1	11
CDK1/CCNB1	63	JAK3	89	PLK1	-3
CDK2/CCNA2	57	MAPK8	31	PRKAA2	42
CDK6/CCND3	33	KDR	94	PTK2	66
CDK7/CCNH/MNAT1	77	LCK	101	PTK6	97
CDK9/CCNT1	67	LCKactivated	102	RET	85
CHEK1	43	LYN	99	RET V804M	80
KIT	94	MAP2K1	92	RET V804L	94
RAF1	104	MAP2K7	54	ROCK1	67
CSF1R	100	MAP3K7	56	ROCK2	79
CSNK1G1	11	MAP3K9	85	ROS1	6
CSNK2A2	-7	RPS6KA1	57	SGK1	-16
DDR2	93	MAPKAPK2	-13	MYLK	24
DMPK	-4	PRAK	8	SRC 1-530	101
DYRK2	9	MARK1	38	SRC	101

EEF2K	-14	MARK2	38	SRPK1	-1
EGFR	48	MET	99	STK10	88
EGFR T790M L858R	87	MINK1	93	STK11	5
EPHA5	51	MKNK2	57	STK17A	12
EPHB1	32	RPS6KA5	37	STK4	101
EPHB4	13	MST1R	63	TBK1	37
ERBB4	55	NEK2	100	TGFBR1	9
FER	78	MAPK14	10	NTRK1	102
FES	70	RPS6KB1	84	TYRO3	84
FGFR1	80	PAK2	100	ULK2	13
FGFR1 V561M	54	PAK4	80	YES1	100
FGFR2	77	PAK7	49		
FGFR3	53	PDGFRB	55		

Table 4. %inhibition data for compound **36** tested at 0.1  $\mu$ M concentration

ABL2	94	FGFR4	2	PDGFRB	68
ABL1	96	FLT1	53	PDPK1	-6
				PIK3CA	
ACVR1B	92	FLT3	52	p85a	-3
				PIK3CB	
AKT1	-1	MTOR	-14	p85a	2
				PIK3CD	
AKT2	-1	FYN	97	p85a	16
ALK	-1	GSK3A	21	PIK3C2G	4
				PIK3CG	
NUAK1	82	GSK3B	10	p120	0
AURKB	64	IGF1R	16	PIM2	5
AURKC	18	IGF1R	18	PIP5K1A	2
AXL	35	IKBKB	4	PIP5K1C	18
BLK	86	INSR	8	PIP4K2A	2
BMX	91	INSR	8	PRKACA	4
BTK	71	INSRR	-4	PRKCA	8
CaMK1	3	IRAK4	-5	PRKCE	-3
CAMK2B	8	JAK2	6	PRKCQ	5
CDK1/CCNB1	9	JAK3	16	PRKG1	-31
CDK2/CCNA2	-6	MAPK8	6	PLK1	-3
CDK6/CCND3	24	KDR	58	PRKAA2	7
CDK7/CCNH/MNAT1	27	LCK	100	PTK2	16
CDK9/CCNT1	31	LCKactivated	98	PTK6	100
CHEK1	11	LYN	100	RET	99
				RET	
KIT	26	MAP2K1	19	V804M	40
RAF1	38	MAP2K7	-2	RET V804L	49
CSF1R	85	MAP3K7	-6	ROCK1	4
CSNK1G1	-2	MAP3K9	20	ROCK2	34
CSNK2A2	-11	RPS6KA1	15	ROS1	10
DDR2	57	MAPKAPK2	3	SGK1	13

DMPK	0	PRAK	-3	MYLK	20
DYRK2	-1	MARK1	15	SRC 1-530	99
EEF2K	-10	MARK2	18	SRC	98
EGFR	20	MET	8	SRPK1	-1
EGFR T790M L858R	10	MINK1	92	STK10	-8
EPHA5	69	MKNK2	0	STK11	11
EPHB1	78	RPS6KA5	9	STK17A	5
EPHB4	87	MST1R	12	STK4	43
ERBB4	19	NEK2	1	TBK1	-5
FER	-17	MAPK14	15	TGFBR1	76
FES	18	RPS6KB1	13	NTRK1	59
FGFR1	60	PAK1	100	TYRO3	28
FGFR1 V561M	29	PAK2	90	ULK2	52
FGFR2	50	PAK4	13	YES1	100
FGFR3	53	PAK7	28		

## Protein expression, purification, crystallisation and structure determination for 15 in PAK1

The kinase domain of human PAK1 (residues 249-545 containing two point mutations D389N and T423E) was expressed with an TEV cleavable N-terminal 6xHis-tag in *E. coli*, and purified according as described previously<sup>1,2</sup>. Initial protein crystals were grown using the hanging drop method using a low potency (~1  $\mu$ M) ATP-competitive tool compound. The reservoir solution contained 14-16% PEG 3350, 0.2 M ammonium sulfate and 100 mM HEPES (pH 7.6). Drops were set up with 2  $\mu$ L protein solution and 2  $\mu$ L reservoir solution. Trays were incubated at 20 °C, and crystals appeared after 1 week and reached the final size after 2 weeks. Crystals were soaked in reservoir solution containing 5 mM of compound **15** for 24 h. Crystals were transferred to a soaking solution containing 20% glycerol, and were vitrified in liquid nitrogen. X-ray diffraction data was collected at cryogenic temperature using synchrotron radiation at the Diamond Light Source. Diffraction data was processed with XDS<sup>3</sup> and scaled using SCALA<sup>4</sup>, as implemented in the autoPROC routines from Global Phasing<sup>5</sup>. The structure was solved by molecular replacement using MOLREP<sup>6</sup> and the coordinates of Protein Data Bank accession code 1YHV. Protein and inhibitor were modeled into the electron density using Coot<sup>7</sup>, and the model was refined using BUSTER<sup>8</sup>. Crystallographic statistics for the human PAK1 in complex with compound **15** are as follows: space group  $P2_1$ , unit cell dimensions  $a=62.39$  Å,  $b=83.36$  Å,  $c=66.01$  Å,  $\alpha=90^\circ$ ,  $\beta=105^\circ$ ,  $\gamma=90^\circ$ ; resolution range 83-2.49 Å (2.63-2.49 Å); 64,319 total reflections with 22,335 unique reflections; overall redundancy of 2.9 (2.7); overall completeness of 97.6% (96.7%);  $R_{\text{merge}}$  of 4.1% (56.9%); and mean  $I/\sigma(I)$  of 14.1 (1.4). The final refined model has a  $R_{\text{work}}$  of 20.8% and  $R_{\text{free}}$  of 22.8%. Atomic coordinates and structure factors have been deposited in the Protein Data Bank under accession code (4P90).

## References.

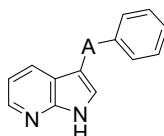
1. Lei, M.; Robinson, M.A.; Harrison, S.C. *Structure* **2005** *13*, 769.
2. Lei, M.; Lu, W.; Meng, W.; Parrini, M.C.; Eck, M.J.; Mayer, B.J.; Harrison, S.C. *Cell* **2000** *102*, 387.
3. Kabsch, W. *Acta Crystallogr. D Biol. Crystallogr.* **2010** *66*, 125.
4. Bailey, S. *Acta Crystallogr. D Biol. Crystallogr.* **1994** *50*, 760.
5. Vonnrhein, C.; Flensburg, C.; Keller, P.; Sharff, A.; Smart, O.; Paciorek, W.; Womack, T.; Bricogne, G. *Acta Crystallogr. D Biol. Crystallogr.* **2011** *67*, 293.
6. Vagin, A.; Teplyakov, A. *Acta Crystallogr. D Biol. Crystallogr.* **2010** *66*, 22.
7. Emsley, P.; Lohkamp, B.; Scott, W.G.; Cowtan, K. *Acta Crystallogr. D Biol. Crystallogr.* **2010** *66*, 486.
8. Smart, O.S.; Womack, T.O.; Flensburg, C.; Keller, P.; Paciorek, W.; Sharff, A.; Vonnrhein, C.; Bricogne, G. *Acta Crystallogr. D Biol. Crystallogr.* **2012** *68*, 368.

## logD<sub>7.4</sub> measurement:

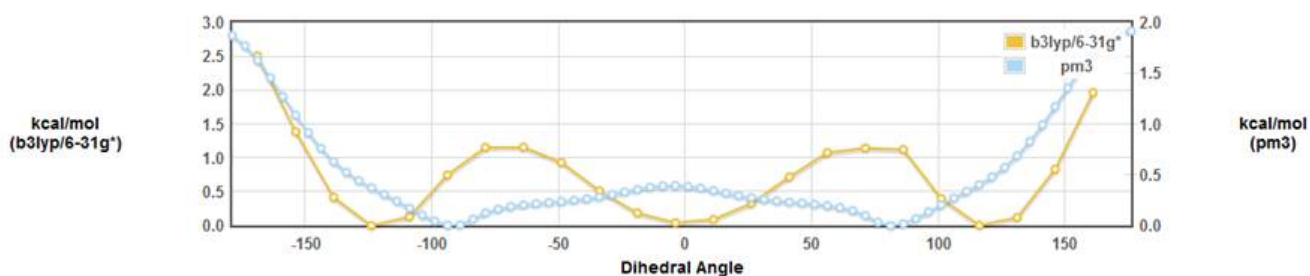
LogD<sub>7.4</sub> measurements were made using a shake-flask method where the extent of partitioning between pH 7.4 buffer and octanol was measured. Compounds were dissolved in a known volume buffer, and following the addition of a known amount of octanol, the solutions were shaken for 30 min. Following centrifugation, analysis of the aqueous layer was performed by LC–UV to quantify the amount of compound in solution and then compared to analysis of the compound in solution before the addition of octanol to calculate the partitioning coefficient, D<sub>7.4</sub>.

## Torsion scans for carbon, carbonyl and sulfone linker :

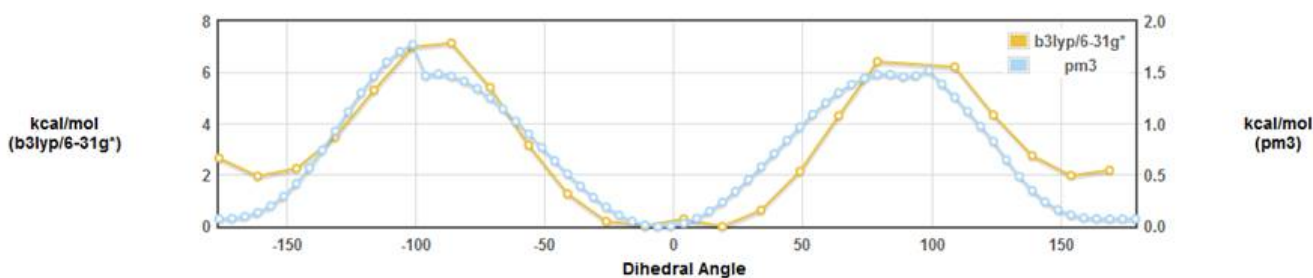
Torsional profiles were calculated using Gaussian 09 (Revision C.01). This specified torsion was initially driven at 5 degree intervals and the molecule fully optimised using semi-empirical PM3 level theory. For the final profile structures were taken at 15 degree intervals and optimised by density functional theory (DFT), using B3LYP/6-31G\*. The ortho-Cl group was removed to avoid smaller deviations. Proposed binding mode is 0 degrees. Orange line is using B3LYP/6-31G\*. Blue line is the initial geometry optimisation at a lower level of theory (PM3). Sulfone linker is at a maxima at the required binding mode geometry.



### Carbon linker:



### Carbonyl linker:



### Sulfone linker:

