

Supporting Information

Structure-Guided Discovery of Potent and Selective Inhibitors of ERK1/2 from a Modestly Active and Promiscuous Chemical Start Point

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Table S1 – Kinase Selectivity of **35**

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S2

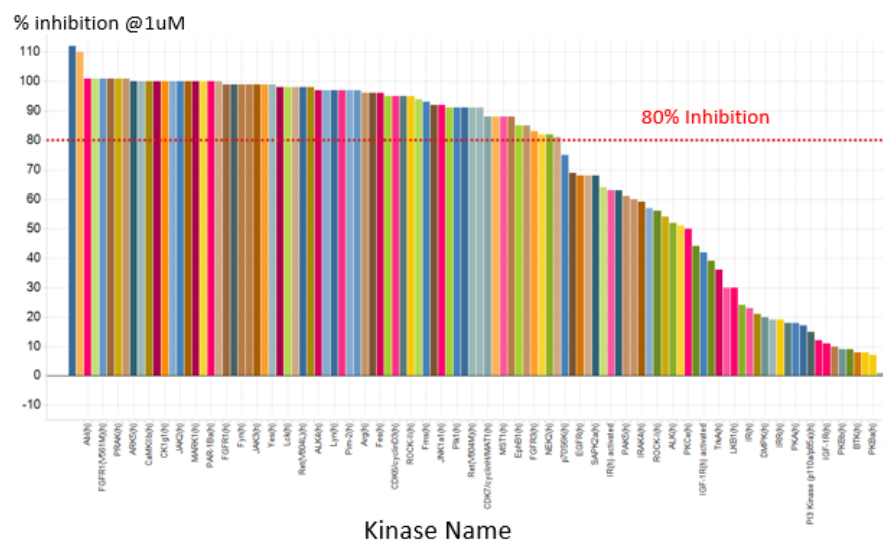


Figure S2 – Overlay of compound **14** (blue) and **23** (PDB Code 5NHV, brown) in ERK2 crystal structure.

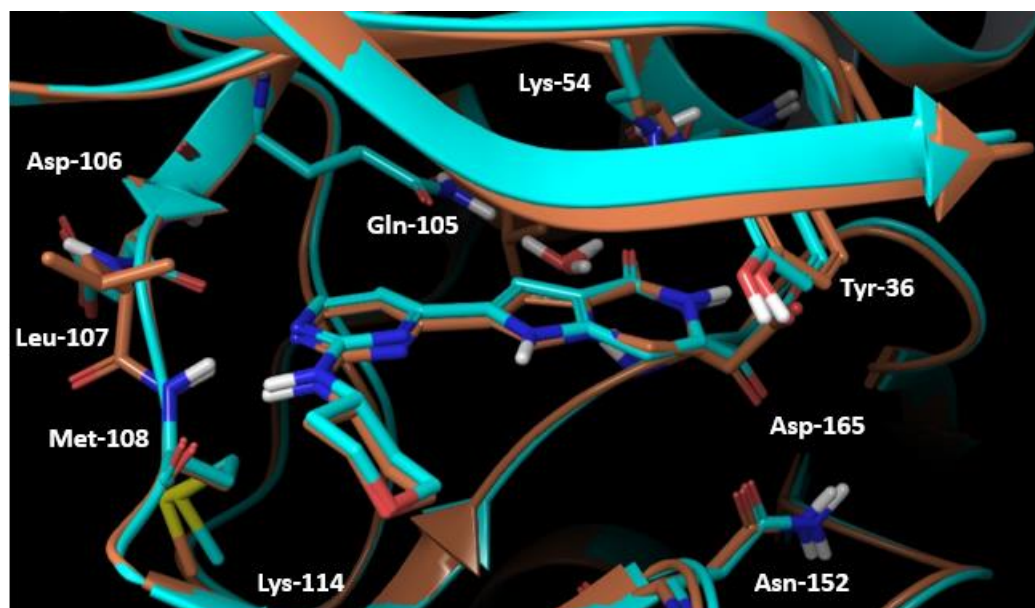
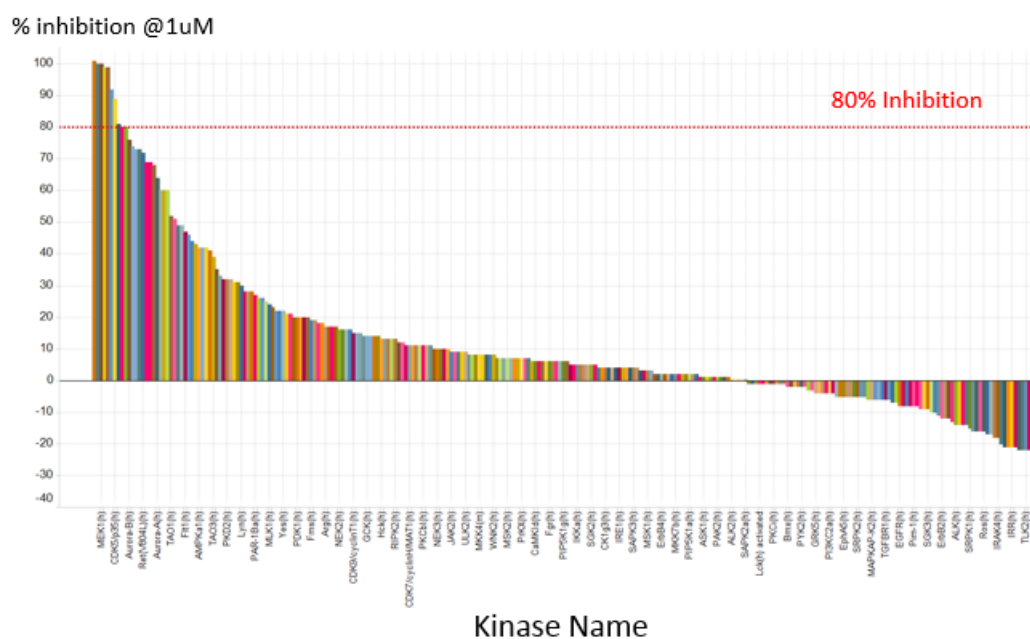


Table S1 – Kinase selectivity of **35** – Actives >80% @ 1uM. Note the Eurofins assays for RAF and MEK1 (red) are coupled assays, thereby compounds active in ERK1/2 may also appear active against RAF and MEK1.

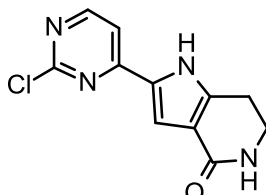
Kinase Name	Inhibition (%)
MAPK2	101
MAPK1	100
MEK1	100
BRAF	99
CRAF	99
MEK1	98
CDK5/p25	92
CDK5/p35	89
ARK5	81
Aurora-C	80
CDK2/cyclinA	80



Experimental S1 – Full compound synthesis and characterisation.

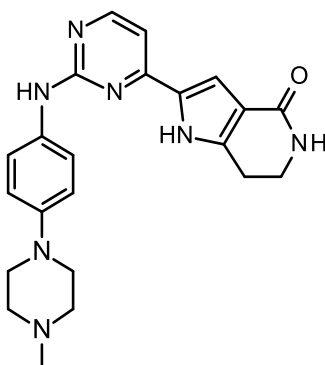
Synthesis of Compound 4

2-(2-Chloropyrimidin-4-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (**37**)



Piperidine-2,4-dione (280 mg, 2.6 mmol) was added in one portion to 2-bromo-1-(2-chloropyrimidin-4-yl)ethanone (600 mg, 2.6 mmol) and ammonium acetate (790 mg, 10 mmol) in ethanol (5 mL). The resulting mixture was stirred for 1 hour and then concentrated to dryness. The crude residue was triturated with water to give a solid which was collected by filtration and dried under vacuum. This was dried and then triturated with TBME to give a solid which was collected by filtration and dried under vacuum to afford **37** (370 mg, 58.7 %) as an orange solid. ^1H NMR (400 MHz, DMSO) δ 2.86 (t, J = 6.8 Hz, 2H), 3.40 (td, J = 2.4, 6.8 Hz, 2H), 7.16 (s, 1H), 7.35 (s, 1H), 7.78 – 7.82 (m, 1H), 8.54 (d, J = 5.4 Hz, 1H), 12.19 (s, 1H); Purity 100% by LC-MS, m/z : $\text{ES}^+ [\text{M}+\text{H}]^+ = 249$.

2-(2-(4-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (**4**)

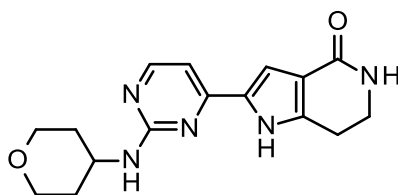


37 (150 mg, 0.60 mmol), 4-(4-methylpiperazin-1-yl)aniline (150 mg, 0.78 mmol) and tosic acid (230 mg, 1.2 mmol) was suspended in 4-methyl-2-pentanol (5 mL) and sealed into a microwave tube. The reaction was heated to 140 °C for 1 hour in the microwave reactor and cooled to RT. The reaction was dissolved in

methanol/water and purified by ion exchange chromatography, using an SCX-2 column (10 g). The desired product was eluted from the column using 7M NH₃/MeOH and evaporated to dryness. The crude product (290mg) was dissolved in 6 mL DMSO, filtered and purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5μ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% NH₃) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford **4** (84 mg, 35 %) as a yellow solid. ¹H NMR (400 MHz, DMSO) δ 2.23 (s, 3H), 2.44 – 2.49 (m, 4H), 2.88 (t, *J* = 6.8 Hz, 2H), 3.04 – 3.13 (m, 4H), 3.42 (dt, *J* = 3.4, 6.7 Hz, 2H), 6.91 (d, *J* = 9.0 Hz, 2H), 7.06 (d, *J* = 5.2 Hz, 1H), 7.10 (s, 2H), 7.65 (dd, *J* = 2.4, 9.1 Hz, 2H), 8.33 (d, *J* = 5.2 Hz, 1H), 9.07 (s, 1H), 11.74 (s, 1H); Purity 99.9% by LC-MS, *m/z*: ES⁺ [M+H]⁺ 405.

Synthesis of Compound 6

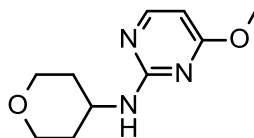
2-(2-((Tetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-6,7-dihydro-1*H*-pyrrolo[3,2-*c*]pyridin-4(5*H*)-one (6)



Triethylamine (0.2 mL, 1.5 mmol) was added to **37** (120 mg, 0.48 mmol), and tetrahydro-2*H*-pyran-4-amine (98 mg, 0.97 mmol) in DMF (2 mL) at 25°C under air. The resulting solution was stirred at 90 °C for 8 hours. The solvent was removed under reduced pressure. The crude product was purified by preparative HPLC (Phenomenex Gemini-NX axia Prep C18 OBD column, 5μ silica, 50 mm diameter, 150 mm length), using decreasingly polar mixtures of water (containing 0.1% NH₃) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford **6** (20 mg, 13.2 %) as a white solid. ¹H NMR (300 MHz, DMSO, 30°C) δ 1.53 – 1.57 (m, 2H), 1.82 – 1.86 (m, 2H), 2.86 (t, *J* = 6.6 Hz, 2H), 3.42 – 3.58 (m, 4H), 3.87 (m, 2H), 4.13 (s, 1H), 6.85 – 7.08 (m, 4H), 8.17 (d, *J* = 5.1 Hz, 1H), 11.65 (s, 1H); Purity 95.0% by LC-MS, *m/z*: ES⁺ [M+H]⁺ 314.

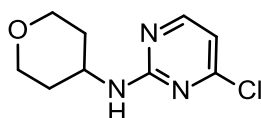
Synthesis of Compound 7

4-Methoxy-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrimidin-2-amine (**38**)



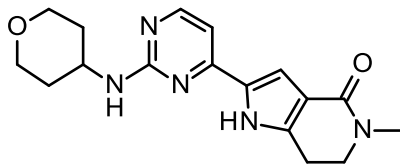
DIPEA (26.1 mL, 149.42 mmol) was added to 2-chloro-4-methoxypyrimidine (18 g, 120 mmol) and tetrahydro-2*H*-pyran-4-amine (19 g, 190 mmol) in 2-propanol (80 mL). The resulting mixture was stirred at 130 °C for overnight. The reaction mixture was poured into water (300 mL), the precipitate was collected by filtration, washed with water (100 mL) and dried under vacuum to afford **38** (16 g, 61 %) as a white solid. ¹H NMR (400 MHz, CD₃OD, 22°C) δ 1.55 – 1.65 (m, 2H), 1.96 – 2.00 (m, 2H), 3.51 – 3.58 (m, 2H), 3.90 (s, 3H), 3.96 – 4.03 (m, 3H), 6.03 (d, *J* = 6 Hz, 1H), 7.94 (d, *J* = 6 Hz, 1H); Purity 100% by LC-MS, *m/z*: ES⁺ [M+H]⁺ 210.

4-Chloro-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrimidin-2-amine (**39**)



38 (16 g, 76 mmol) in hydrogen chloride (50 mL) at 90°C. The resulting solution was stirred at 90 °C for 3 hours. The resulting mixture was evaporated to dryness and the residue was azeotroped with toluene to afford crude 2-((tetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-ol (15 g) as a white solid. A solution of 2-((tetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-ol (15 g, 76 mmol) in POCl₃ (50 mL) was heated at 100 °C for 8 hours. The solvent was removed under reduced pressure. The reaction mixture was quenched with saturated NaHCO₃ (300 mL), extracted with DCM (3 x 200 mL), the organic layer was dried over Na₂SO₄, filtered and evaporated to afford the desired product **39** (14 g, 85 %) as a pale yellow solid. ¹H NMR (400 MHz, CDCl₃, 22°C) δ 1.49 – 1.59 (m, 2H), 2.01 – 2.11 (m, 2H), 3.51 – 3.57 (m, 2H), 3.96 – 4.09 (m, 3H), 5.15 – 5.17 (m, 1H), 6.57 (d, *J* = 5.2 Hz, 1H), 8.13 (d, *J* = 5.2 Hz, 1H); *m/z* (ES⁺) [M+H]⁺ = 214.

5-Methyl-2-(2-((tetrahydro-2H-pyran-4-yl)amino)pyrimidin-4-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (7)



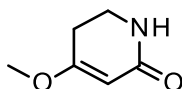
Bis(triphenylphosphine)palladium(II) chloride (0.8 g, 1.2 mmol) was added to **39** (5 g, 23 mmol), and tributyl(1-ethoxyvinyl)stannane (13 g, 35 mmol) in DMF (50 mL) at 25°C under nitrogen. The resulting mixture was stirred at 100 °C for 12 hours. The reaction mixture was diluted with EtOAc and 4 g of KF was added to the solution, the resulting mixture was stirred at room temperature for 2 hours. The mixture was filtered through a Celite pad. The filtrate was washed with water (2 x 50 mL), dried and concentrated. The crude product was purified by flash silica chromatography, elution gradient 5 to 40% EtOAc in petroleum ether. Pure fractions were evaporated to dryness to afford 4-(1-ethoxyvinyl)-N-(tetrahydro-2H-pyran-4-yl)pyrimidin-2-amine (5.8 g, 99%) as a white solid.

NBS (360 mg, 2.01 mmol) was added to 4-(1-ethoxyvinyl)-N-(tetrahydro-2H-pyran-4-yl)pyrimidin-2-amine (500 mg, 2.01 mmol) in THF (10 mL) and water (0.5 mL) at 25°C under air. The resulting solution was stirred at 25 °C for 2 hours. The reaction mixture was poured onto water (25 mL), extracted with DCM (3 x 25 mL), the organic layer was washed with brine and dried over Na₂SO₄, filtered and evaporated to afford 2-bromo-1-(2-((tetrahydro-2H-pyran-4-yl)amino)pyrimidin-4-yl)ethanone (560 mg, 94 %) as brown solid. The residue was dissolved in ethanol (15 mL), then ammonium acetate (720 mg, 9.4 mmol) and 1-methylpiperidine-2,4-dione (240 mg, 1.9 mmol), 2-bromo-1-(2-((tetrahydro-2H-pyran-4-yl)amino)pyrimidin-4-yl)ethanone (560 mg, 1.9 mmol) were added. The mixture was stirred at ambient temperature for 18 hours. The solvent was removed under reduced pressure to give the crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 30% EtOAc in petroleum ether. Pure fractions were evaporated to dryness to afford the crude product. The crude product was purified by preparative HPLC (XBridge Shield RP18 OBD column, 5μ silica, 19 mm diameter, 150 mm length), using decreasingly polar mixtures of water (containing 0.1% NH₃) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford **7** (100 mg, 16.3 %) as a yellow solid. ¹H NMR(400 MHz, DMSO, 20 °C) δ 1.46 – 1.56 (m, 2H), 1.82 – 1.85 (m, 2H), 2.91 (s, 3H), 2.92 – 2.97 (m, 2H), 3.35 – 3.55 (m, 4H), 3.86 – 3.89 (m, 2H), 4.12 (s,

1H), 6.88 – 6.89 (m, 2H), 7.04 (d, $J = 1.8$ Hz, 1H), 8.16 (d, $J = 3.9$ Hz, 1H), 11.62 (1H, s); Purity 99.6% by LC-MS, m/z : ES^+ $[M+H]^+$ 328.

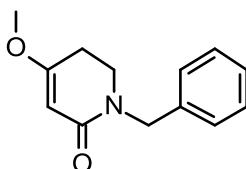
Synthesis of Compound 8

4-Methoxy-5,6-dihydropyridin-2(1H)-one (40)



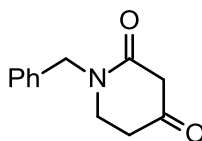
Trimethoxymethane (3.9 mL, 35 mmol) was added in one portion to piperidine-2,4-dione (2 g, 18 mmol) and 4-methylbenzenesulfonic acid (0.12 g, 0.7 mmol) in methanol (50 mL) at 20°C under air. The resulting solution was stirred at 70 °C for 17 hours. The reaction mixture was evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 2% MeOH in DCM. Pure fractions were evaporated to dryness to afford **40** (2.1 g, 93 %) as a white solid. 1H NMR (400 MHz, Chloroform- d , 22°C) δ 2.44 (t, $J = 10.5$ Hz, 2H), 3.42 (t, $J = 10.5$ Hz, 2H), 3.69 (s, 3H), 5.06 (s, 1H), 6.32 (s, 1H).

1-Benzyl-4-methoxy-5,6-dihydropyridin-2(1H)-one (41)



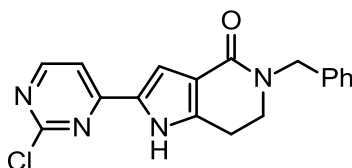
Sodium hydride (0.63 g, 15 mmol) was added slowly to **40** (1g, 7.8 mmol) in DMF (10 mL) at 0°C over a period of 2 minutes under nitrogen. The resulting mixture was stirred at 25 °C for 1 hour. The reaction mixture was poured into ice water and extracted with EtOAc (3 x 50 mL), and washed with saturated brine. The organic layer was dried over Na_2SO_4 , filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 50% EtOAc in petroleum ether. Pure fractions were evaporated to dryness to afford **41** (1.300 g, 76 %) as a pale yellow oil. 1H NMR (400 MHz, Chloroform- d) δ 2.44 (t, $J = 10.5$ Hz, 2H), 3.31 (t, $J = 10.5$ Hz, 2H), 3.71 (s, 3H), 4.64 (s, 2H), 5.24 (s, 1H), 7.24 - 7.39 (m, 5H); m/z : ES^+ $[M+H]^+$ 218.

1-Benzylpiperidine-2,4-dione (42)



Hydrochloric acid (6.0M in water, 400 mL, 2300 mmol) was added to **41** (40 g, 184 mmol) in tetrahydrofuran (500 mL) at 0°C under air. The resulting solution was stirred at 25 °C for 3 hours. The reaction mixture was evaporated to dryness and redissolved in EtOAc (150 mL), and washed sequentially with water (50 mL x 2), saturated NaHCO₃ (50 mL), and saturated brine (75 mL). The organic layer was dried over Na₂SO₄, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 50% EtOAc in petroleum ether. Pure fractions were evaporated to dryness to afford **42** (30 g, 80 %) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 2.49 - 2.53 (m, 2H), 3.43 (s, 2H), 3.51 (m, 2H), 4.61 (s, 2H), 7.28 - 7.36 (m, 5H); *m/z*: ES⁺ [M+H]⁺ 204.

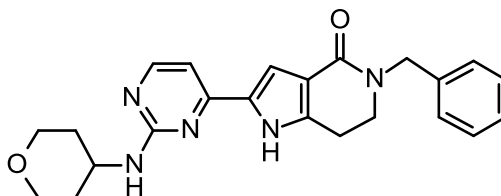
5-Benzyl-2-(2-chloropyrimidin-4-yl)-6,7-dihydro-1*H*-pyrrolo[3,2-*c*]pyridin-4(5*H*)-one (43)



N-Bromosuccinimide (2.89 g, 16.25 mmol) was added to 2-chloro-4-(1-ethoxyvinyl)pyrimidine (3 g, 16.25 mmol) in THF (90 mL) and water (10mL) at 25°C over a period of 1 minute under air. The resulting solution was stirred at rt for 10 minutes. The solvent was removed under reduced pressure. The reaction mixture was diluted with EtOAc (50 mL), and washed sequentially with water (25 mL) and saturated brine (25 mL). The organic layer was dried over Na₂SO₄, filtered and evaporated to afford crude 2-bromo-1-(2-chloropyrimidin-4-yl)ethanone (2.4 g, 67 %). 2-Bromo-1-(2-chloropyrimidin-4-yl)ethanone (174 mg, 0.74 mmol) was dissolved in EtOH (3 mL), then ammonium acetate (56.9 mg, 0.74 mmol) and **42** (150 mg, 0.74 mmol) were added at 25°C under argon. The resulting solution was stirred at ambient temperature for 3 hours. The solvent was removed under reduced pressure. The reaction mixture was diluted with EtOAc (10 mL), and washed sequentially with water (10 mL), and saturated brine (10 mL). The organic layer was dried over Na₂SO₄, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 10 to 80% EtOAc in petroleum ether. Pure fractions were evaporated to dryness to afford **43** (85 mg, 34.0 %) as a brown solid. ¹H NMR (300 MHz, DMSO, 30°C) δ 2.90 – 2.95 (m, 2H), 3.47 – 3.52 (m, 2H), 3.87 (d, *J* = 10.5

Hz, 2H), 4.63 (s, 2H), 7.20 – 7.37 (m, 5H), 7.44 (d, $J = 2.4$ Hz, 1H), 7.85 (d, $J = 5.4$ Hz, 1H), 8.56 (d, $J = 5.4$ Hz, 1H), 12.25 (s, 1H). m/z : ES^+ $[M+H]^+$ 339.

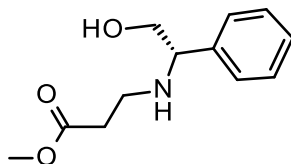
5-Benzyl-2-(2-((tetrahydro-2H-pyran-4-yl)amino)pyrimidin-4-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (8)



Triethylamine (0.074 mL, 0.53 mmol) was added to **43** (60 mg, 0.18 mmol) and tetrahydro-2H-pyran-4-amine (22 mg, 0.21 mmol) in DMF (2 mL) under air. The resulting solution was stirred at 90 °C for 6 hours. The solvent was removed under reduced pressure. The crude product was purified by preparative HPLC (XSelect CSH Prep C18 OBD column, 5 μ silica, 19 mm diameter, 150 mm length), using decreasingly polar mixtures of water (containing % NH_3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford **8** (10 mg, 14 %) as a pale yellow solid. 1H NMR (300 MHz, DMSO, 30°C) δ 1.41 – 1.53 (m, 2H), 1.81 – 1.93 (m, 2H), 2.92 – 2.95 (m, 2H), 3.42 – 3.54 (m, 4H), 3.87 (d, $J = 10.5$ Hz, 2H), 3.89(s, 1H), 4.62 (s, 2H), 6.90 (d, $J = 5.1$ Hz, 1H), 7.10 (d, $J = 2.4$ Hz, 1H), 7.26 – 7.34 (m, 6H), 8.20 (s, 1H), 11.65 (s, 1H). Purity 100% by LC-MS, m/z : ES^+ $[M+H]^+$ 404.

Synthesis of Compound 9

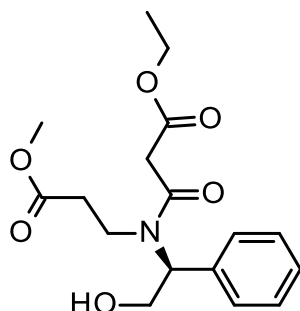
(S)-Methyl 3-((2-hydroxy-1-phenylethyl)amino)propanoate (44)



Methyl acrylate (600 mg, 6.9 mmol) was added to (S)-2-amino-2-phenylethanol (1040 mg, 7.6 mmol) in MeOH (17 mL) at 25°C under nitrogen. The resulting mixture was stirred at 50 °C for 18 hours. The reaction mixture was evaporated to dryness to afford crude product. The crude product was purified by flash silica (80g) chromatography, elution gradient 10 to 100% EtOAc in heptane. Pure fractions were evaporated to dryness to

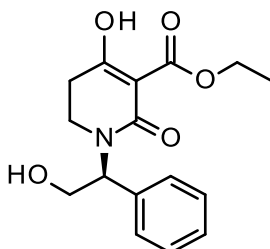
afford **44** (1220 mg, 79 %) as a colourless oil. ^1H NMR (400 MHz, DMSO) δ 2.28 (s, 1H), 2.39 – 2.44 (m, 2H), 2.58 (td, J = 5.7, 11.9 Hz, 2H), 3.23 – 3.29 (m, 1H), 3.41 (dt, J = 4.7, 9.6 Hz, 1H), 3.57 (s, 3H), 3.64 (dd, J = 4.4, 8.5 Hz, 1H), 4.84 (t, J = 5.5 Hz, 1H), 7.19 – 7.34 (m, 5H); m/z : ES^+ $[\text{M}+\text{H}]^+$ 224.

(S)-Ethyl 3-((2-hydroxy-1-phenylethyl)(3-methoxy-3-oxopropyl)amino)-3-oxopropanoate (45)



Ethyl 3-chloro-3-oxopropanoate (0.701 mL, 5.48 mmol) was added dropwise to **44** (1.2 g, 5.5 mmol) and *N*-ethyl-*N*-isopropylpropan-2-amine (0.95 mL, 5.5 mmol) in DCM (11 mL) at $<5^\circ\text{C}$ over a period of 20 minutes under nitrogen. The resulting mixture was stirred at 0°C for 15 minutes. The reaction mixture was quenched with water and then partitioned between DCM and water, organic layer separated and aqueous layer extracted with DCM. Combined organic layers were washed sequentially with saturated NaHCO_3 , saturated brine, dried over MgSO_4 , filtered and evaporated to dryness to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 5 to 70% EtOAc in heptane. Pure fractions were evaporated to dryness to afford **45** (1.3 g, 68 %) as a colourless oil. ^1H NMR (400 MHz, DMSO) δ 1.19 (t, J = 7.1 Hz, 3H), 2 – 2.08 (m, 1H), 2.31 – 2.69 (m, 2H), 3.23 – 4.04 (m, 8H), 4.10 (qd, J = 2.4, 7.1 Hz, 2H), 4.89 – 4.97 (m, 1H), 5.1 – 5.45 (m, 1H), 7.24 – 7.42 (m, 5H); m/z : ES^+ $[\text{M}+\text{H}]^+$ 338.

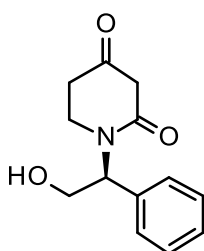
(S)-Ethyl-4-hydroxy-1-(2-hydroxy-1-phenylethyl)-2-oxo-1,2,5,6-tetrahydropyridine-3-carboxylate (46)



Sodium hydride (0.15 g, 3.8 mmol) was added portionwise to EtOH (17 mL) at $<5^\circ\text{C}$ over a period of 2 minutes under nitrogen. The resulting solution was stirred at 0°C for 10 minutes. A solution of **45** (1.2 g, 3.4 mmol) in

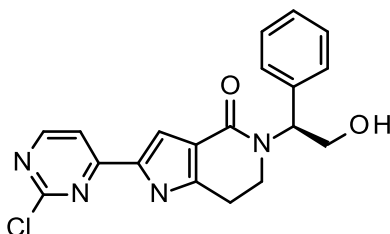
EtOH (4.3 mL) was added dropwise to the stirred reaction mixture at <5°C, over a period of 15 minutes under nitrogen. The resulting mixture was stirred at 0 °C and allowed to warm to ambient temperature and stir overnight. The precipitate was collected by filtration, washed with EtOH then Et₂O and dried under vacuum to afford sodium salt of **46** (1 g, 99 %) as a white solid, which was used without further purification. ¹H NMR (400 MHz, DMSO) δ 1.13 (t, *J* = 7.1 Hz, 3H), 1.86 – 2.06 (m, 2H), 2.83 (ddd, *J* = 5.0, 7.2, 12.2 Hz, 1H), 3.10 (ddd, *J* = 4.7, 8.9, 13.2 Hz, 1H), 3.7 – 3.9 (m, 2H), 3.93 (q, *J* = 7.1 Hz, 2H), 4.74 – 4.81 (m, 1H), 5.66 (t, *J* = 6.9 Hz, 1H), 7.17 – 7.32 (m, 5H); *m/z*: ES⁻ [M-H]⁻ 304.

(S)-1-(2-hydroxy-1-phenylethyl)piperidine-2,4-dione (47)



46 (930 mg, 3.06 mmol) in a mixture of water (27.8 mL) and acetic acid (2.78 mL) was heated at 90°C for 2 hours and evaporated to dryness. The crude product was purified by flash silica chromatography, elution gradient 0 to 7% MeOH in DCM. Pure fractions were evaporated to dryness to afford **47** (300 mg, 42.0 %) as a white solid. ¹H NMR (400 MHz, DMSO) δ 2.27 – 2.38 (m, 1H), 2.50 (p, *J* = 1.8 Hz, 1H), 3.28 – 3.61 (m, 4H), 3.76 – 3.94 (m, 2H), 4.96 (t, *J* = 5.5 Hz, 1H), 5.61 (t, *J* = 7.0 Hz, 1H), 7.21 – 7.38 (m, 5H); *m/z*: ES⁺ [M+H]⁺ 234.

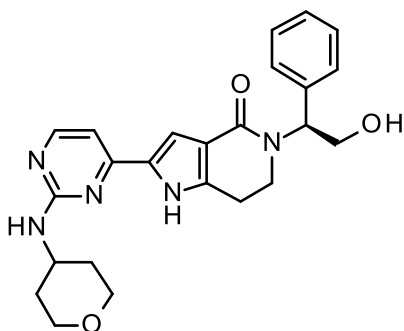
(S)-2-(2-Chloropyrimidin-4-yl)-5-(2-hydroxy-1-phenylethyl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (48)



Ammonium acetate (460 mg, 6 mmol) was added to 2-bromo-1-(2-chloropyrimidin-4-yl)ethanone (280 mg, 1.2 mmol) and **47** (280 mg, 1.2 mmol) in ethanol (9.7 mL). The resulting suspension was stirred at 20 °C for 20 hours. The solvent was removed *in vacuo* and partitioned between EtOAc and water, organic layer was

separated and the aqueous layer was extracted with EtOAc, combined organic layers were washed with saturated brine, dried over MgSO₄, filtered and evaporated to dryness to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 4% MeOH in DCM. Pure fractions were evaporated to dryness to afford **48** (290 mg, 66 %) as a yellow solid. ¹H NMR (400 MHz, DMSO) δ 2.76 – 2.96 (m, 2H), 3.24 (dt, *J* = 6.5, 12.7 Hz, 1H), 3.55 (ddd, *J* = 5.6, 8.4, 13.6 Hz, 1H), 3.84 – 4.01 (m, 2H), 4.92 (t, *J* = 5.5 Hz, 1H), 5.73 – 5.81 (m, 1H), 7.26 (dt, *J* = 4.1, 8.5 Hz, 1H), 7.34 (d, *J* = 4.5 Hz, 4H), 7.42 (d, *J* = 2.3 Hz, 1H), 7.83 (d, *J* = 5.4 Hz, 1H), 8.55 (d, *J* = 5.4 Hz, 1H), 12.19 (s, 1H); *m/z*: ES⁺ [M+H]⁺ 369.

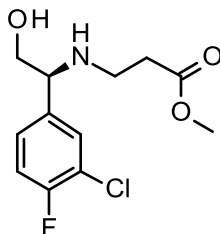
(*S*)-5-(2-hydroxy-1-phenylethyl)-2-(2-(((tetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-6,7-dihydro-1*H*-pyrrolo[3,2-*c*]pyridin-4(5*H*)-one (9)



N,N'-Diisopropylethylamine (170 µl, 1 mmol), **48** (75 mg, 0.2 mmol) and tetrahydro-2*H*-pyran-4-amine (61 mg, 0.61 mmol) were suspended in NMP (1100 µl) and sealed into a microwave tube. The reaction was heated to 200 °C for 70 minutes in the microwave reactor and cooled to RT. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5µ silica, 30 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% NH₃) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford **9** (51.3 mg, 58.6 %) as a yellow solid. ¹H NMR (400 MHz, DMSO) δ 1.51 (q, *J* = 11.2 Hz, 2H), 1.83 (d, *J* = 10.7 Hz, 2H), 2.76 – 2.96 (m, 2H), 3.22 (dt, *J* = 6.5, 12.8 Hz, 1H), 3.39 – 3.48 (m, 2H), 3.54 (ddd, *J* = 5.7, 8.4, 13.6 Hz, 1H), 3.82 – 3.9 (m, 3H), 3.96 (dt, *J* = 6.0, 11.7 Hz, 1H), 4.09 (s, 1H), 4.90 (t, *J* = 5.4 Hz, 1H), 5.73 – 5.8 (m, 1H), 6.79 (s, 1H), 6.88 (d, *J* = 5.2 Hz, 1H), 7.08 (d, *J* = 2.2 Hz, 1H), 7.22 – 7.38 (m, 5H), 8.16 (d, *J* = 5.2 Hz, 1H), 11.60 (s, 1H); Purity 97.9% by LC-MS, *m/z*: ES[−] [M-H][−] 432.

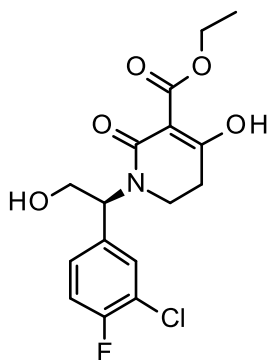
Synthesis of Compound 10

(*S*)-Methyl 3-((1-(3-chloro-4-fluorophenyl)-2-hydroxyethyl)amino)propanoate (**49**)



Methyl acrylate (0.40 mL, 4.4 mmol) was added dropwise to (*S*)-2-amino-2-(3-chloro-4-fluorophenyl)ethanol, HCl (1.0 g, 4.4 mmol) and *N*-ethyl-*N*-isopropylpropan-2-amine (0.77 mL, 4.4 mmol) in MeOH (15 mL). The resulting solution was stirred at 50 °C for 18 hours. The solvent was removed *in vacuo* and the residue taken up in EtOAc (100 mL) and washed sequentially with saturated NaHCO₃ (20 mL) and saturated brine (20 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford **49** (1.2 g, 97 %) as a white solid. ¹H NMR (400 MHz, DMSO) δ 2.38 – 2.46 (m, 2H), 2.53 – 2.62 (m, 3H), 3.24 – 3.29 (m, 1H), 3.40 (dt, *J* = 5.1, 10.3 Hz, 1H), 3.58 (s, 3H), 3.65 (dd, *J* = 4.9, 7.7 Hz, 1H), 4.87 (t, *J* = 5.5 Hz, 1H), 7.28 – 7.38 (m, 2H), 7.51 (dd, *J* = 1.7, 7.5 Hz, 1H); *m/z*: ES⁺ [M+H]⁺ 276.

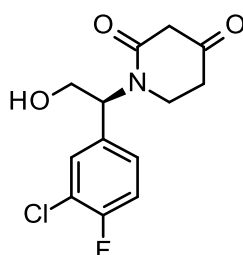
(*S*)-Ethyl 1-(1-(3-chloro-4-fluorophenyl)-2-hydroxyethyl)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carboxylate (**50**)



Ethyl malonyl monochloride (0.54 mL, 4.3 mmol) was added to **49** (1.2 g, 4.3 mmol) and *N,N*-diisopropylethylamine (0.74 mL, 4.3 mmol) in DCM (60 mL) at 0 °C over a period of 5 minutes under nitrogen. The resulting solution was stirred and allowed to warm to room temperature over 18 hours. It was diluted with DCM (100 mL) and washed with brine (50 mL), dried (sodium sulfate), concentrated *in vacuo* and adsorbed onto silica. The crude product was purified by flash silica chromatography, elution gradient 50 to 100% EtOAc

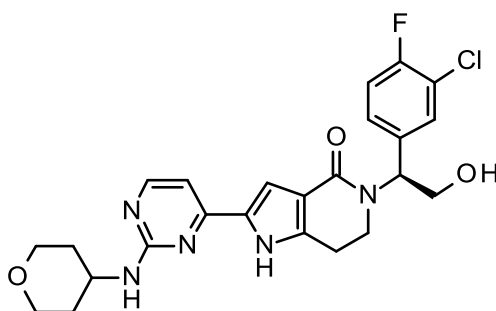
in heptane. Pure fractions were evaporated to dryness then dissolved in ethanol (20 mL). Sodium hydride (60% dispersion) (85 mg, 2.1 mmol) was added portionwise at 0 °C, and the resulting solution was allowed to warm to ambient temperature and stirred for 3 days. The solvent was removed *in vacuo* and the residue dried under vacuum to leave **50** (760 mg, 99 %) as a white solid. ¹H NMR (400 MHz, DMSO) δ 1.12 (t, *J* = 7.1 Hz, 3H), 1.84 – 2.05 (m, 2H), 2.83 (ddd, *J* = 4.9, 7.6, 12.2 Hz, 1H), 3.10 (ddd, *J* = 4.7, 8.7, 12.4 Hz, 1H), 3.29 (s, 1H), 3.72 (dd, *J* = 6.1, 10.9 Hz, 1H), 3.8 – 3.88 (m, 1H), 3.93 (q, *J* = 7.1 Hz, 2H), 4.92 (s, 1H), 5.59 (t, *J* = 6.8 Hz, 1H), 7.22 – 7.38 (m, 2H), 7.45 (dd, *J* = 1.7, 7.3 Hz, 1H); *m/z*: ES⁺ [M+H]⁺ 358.

(S)-1-(1-(3-Chloro-4-fluorophenyl)-2-hydroxyethyl)piperidine-2,4-dione (51)



Acetic acid (0.18 mL, 3.2 mmol) was added to **50** (755 mg, 2.11 mmol) in water (25 mL). The resulting solution was stirred at 80 °C for 2 hours. It was cooled to room temperature and neutralised with sodium bicarbonate (270 mg, 3.2 mmol). The product was extracted from the aqueous mixture with ethyl acetate (2 x 100 mL) and the combined organics were dried (sodium sulfate) and concentrated *in vacuo* to give **51** (610 mg, 100 %) as a white solid. ¹H NMR (400 MHz, DMSO) δ 2.30 – 2.48 (m, 2H), 3.04 (s, 1H), 3.35 – 3.55 (m, 3H), 3.80 – 3.91 (m, 2H), 4.91 – 5.12 (m, 1H), 5.53 (dt, *J* = 6.2, 12.5 Hz, 1H), 7.25 – 7.44 (m, 2H), 7.44 – 7.62 (m, 1H); *m/z*: ES⁺ [M+H]⁺ 286.

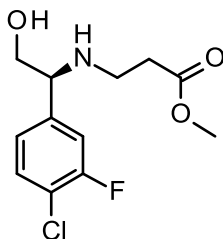
(S)-5-(1-(3-Chloro-4-fluorophenyl)-2-hydroxyethyl)-2-(2-((tetrahydro-2H-pyran-4-yl)amino)pyrimidin-4-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (10)



Ammonium acetate (809 mg, 10.5 mmol) was added to 2-bromo-1-(2-chloropyrimidin-4-yl)ethanone (495 mg, 2.10 mmol) and **51** (600 mg, 2.10 mmol) in ethanol (30 mL). The resulting suspension was stirred at 20 °C for 18 hours. The solvent was removed *in vacuo* then the residue was triturated with water (10 mL). The resulting solid was azeotroped with toluene and dried under vacuum to yield crude (*S*)-5-(1-(3-chloro-4-fluorophenyl)-2-hydroxyethyl)-2-(2-chloropyrimidin-4-yl)-6,7-dihydro-1*H*-pyrrolo[3,2-*c*]pyridin-4(5*H*)-one (889 mg) as a brown solid. A 200 mg portion of this solid was dissolved in NMP (3 mL), then *N,N'*-diisopropylethylamine (0.411 mL, 2.37 mmol), and tetrahydro-pyran-4-ylamine (144 mg, 1.42 mmol) were added. The mixture was heated to 200 °C for 70 minutes in the microwave reactor and cooled to RT. It was diluted with NMP (2 mL) and filtered. The crude product was purified by preparative HPLC (Waters SunFire column, 5 μ silica, 30 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 0.1% formic acid) and MeCN as eluents, followed by HPLC (Waters XBridge Prep C18 OBD column, 5 μ silica, 30 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% NH₃) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford **10** (18 mg, 7.8 %) as an off white solid. ¹H NMR (500 MHz, DMSO, 30°C) δ 1.48 – 1.55 (m, 2H), 1.83 – 1.87 (m, 2H), 2.56 – 2.59 (m, 1H), 2.81 – 2.87 (m, 1H), 2.89 – 2.95 (m, 1H), 3.21 – 3.28 (m, 1H), 3.45 (t, *J* = 11.7 Hz, 2H), 3.53 – 3.60 (m, 1H), 3.84 – 3.94 (m, 3H), 3.96 – 4.00 (m, 1H), 5.01 (t, *J* = 5.7 Hz, 1H), 5.71 (t, *J* = 6.9 Hz, 1H), 6.90 (d, *J* = 5.0 Hz, 2H), 7.09 (d, *J* = 2.2 Hz, 1H), 7.36 – 7.41 (m, 2H), 7.53 – 7.56 (m, 1H), 8.18 (d, *J* = 5.0 Hz, 1H), 11.63 (1H, s). Purity 100% by LC-MS, *m/z*: ES⁺ [M+H]⁺ 486.

Synthesis of Compound 11

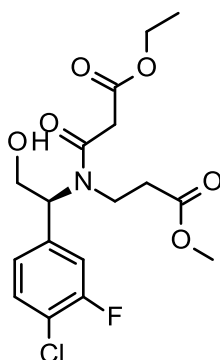
(*S*)-Methyl 3-((1-(4-chloro-3-fluorophenyl)-2-hydroxyethyl)amino)propanoate (52**)**



Methyl acrylate (0.37 mL, 4.1 mmol) was added dropwise to (*S*)-2-amino-2-(4-chloro-3-fluorophenyl)ethanol, HCl (920 mg, 4.1 mmol) and *N*-ethyl-*N*-isopropylpropan-2-amine (0.71 mL, 4.1 mmol) in MeOH (10 mL). The resulting solution was stirred at 50 °C for 3 hours. The reaction mixture was evaporated to dryness and

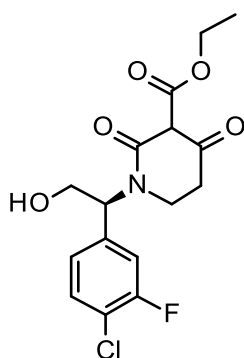
redissolved in EtOAc (50 mL), and washed sequentially with saturated NaHCO₃ (50 mL) and saturated brine (50 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford **52** (1070 mg, 95 %) as a colourless oil. ¹H NMR (400 MHz, CDCl₃) δ 2.46 – 2.55 (m, 2H), 2.73 (ddd, *J* = 5.5, 6.4, 12.0 Hz, 1H), 2.78 – 2.86 (m, 1H), 3.47 (dd, *J* = 8.3, 10.7 Hz, 1H), 3.69 (m, 4H), 3.76 (dd, *J* = 4.3, 8.2 Hz, 1H), 7.05 (d, *J* = 8.2 Hz, 1H), 7.15 (dd, *J* = 1.9, 10.0 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 1H); *m/z*: ES⁺ [M+H]⁺ 276.

(S)-Ethyl 3-((1-(4-chloro-3-fluorophenyl)-2-hydroxyethyl)(3-methoxy-3-oxopropyl)amino)-3-oxopropanoate (53)



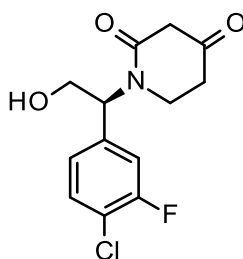
Ethyl 3-chloro-3-oxopropanoate (0.41 g, 2.7 mmol) was added dropwise to **52** (0.76 g, 2.7 mmol) and ethyl 3-chloro-3-oxopropanoate (0.41 g, 2.7 mmol) in DCM (15 mL) cooled to 0°C over a period of 10 minutes. The resulting solution was stirred at 0 °C for 20 minutes. The reaction mixture was diluted with DCM (25 mL), and washed saturated NaHCO₃ (25 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 50% EtOAc in heptane. Pure fractions were evaporated to dryness to afford **53** (0.49 g, 46.0 %) as a colourless oil. ¹H NMR (400 MHz, CDCl₃) δ 1.28 (dt, *J* = 7.1, 9.9 Hz, 3H), 2.35 – 2.47 (m, 1H), 2.52 (q, *J* = 7.3, 8.5 Hz, 1H), 3.41 (d, *J* = 5.9 Hz, 2H), 3.53 – 3.6 (m, 2H), 3.66 (s, 3H), 4.14 – 4.22 (m, 2H), 4.64 – 4.83 (m, 2H), 5.16 – 5.3 (m, 1H), 5.43 (t, *J* = 6.8 Hz, 1H), 7.09 (d, *J* = 8.3 Hz, 1H), 7.18 (d, *J* = 10.1 Hz, 1H), 7.35 – 7.49 (m, 1H).

Ethyl 1-((S)-1-(4-chloro-3-fluorophenyl)-2-hydroxyethyl)-2,4-dioxopiperidine-3-carboxylate (54**)**



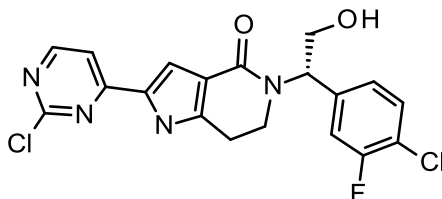
Sodium hydride (35 mg, 0.86 mmol) was added in one portion to **53** (310 mg, 0.79 mmol) in EtOH (8 mL) cooled to 0 °C under nitrogen. The resulting solution was stirred at 0 °C for 1 hour. The reaction was quenched with acetic acid (0.049 mL, 0.86 mmol) and evaporated to dryness to give **54** (280 mg, 100 %) as a white solid. ¹H NMR (500 MHz, DMSO) δ 1.19 (t, *J* = 7.1 Hz, 3H), 1.92 – 2.07 (m, 2H), 2.82 – 2.9 (m, 1H), 3.11 (dd, *J* = 4.3, 7.9 Hz, 1H), 3.44 (q, *J* = 7.0 Hz, 1H), 3.88 (dd, *J* = 7.1, 11.1 Hz, 1H), 3.94 (q, *J* = 7.0 Hz, 2H), 4.11 (q, *J* = 7.1 Hz, 2H), 5.62 (t, *J* = 6.8 Hz, 1H), 7.17 (dd, *J* = 1.9, 8.4 Hz, 1H), 7.31 (dd, *J* = 1.5, 10.9 Hz, 1H), 7.53 (t, *J* = 8.1 Hz, 1H). *m/z*: ES⁺ [M+H]⁺ 358.

(S)-1-(1-(4-Chloro-3-fluorophenyl)-2-hydroxyethyl)piperidine-2,4-dione (55**)**



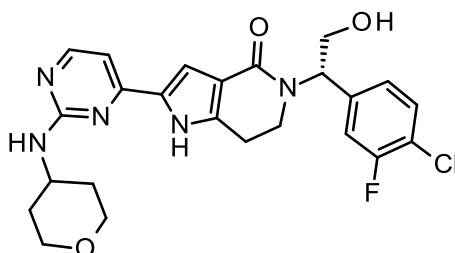
54 (280 mg, 0.79 mmol) was added to acetic acid (0.7 mL) and water (7 mL). The resulting solution was stirred at 80 °C for 2 hours. The reaction mixture was quenched with 2M NaOH (6.2 mL), extracted with EtOAc (2 x 25 mL), the organic layer was dried over MgSO₄, filtered and evaporated to afford **55** (160 mg, 72 %) as colourless gum. ¹H NMR (400 MHz, CDCl₃) δ 1.27 (dt, *J* = 7.1, 10.3 Hz, 3H), 2.34 – 2.5 (m, 1H), 2.53 – 2.68 (m, 1H), 3.27 – 3.40 (m, 1H), 3.55 (dd, *J* = 4.8, 8.1 Hz, 1H), 4.02 – 4.16 (m, 1H), 4.16 – 4.26 (m, 1H), 5.78 (dd, *J* = 5.1, 8.1 Hz, 1H), 7 – 7.1 (m, 1H), 7.14 (dd, *J* = 1.8, 9.9 Hz, 1H), 7.41 (t, *J* = 7.9 Hz, 1H); *m/z*: ES⁺ [M+H]⁺ 286.

(S)-5-(1-(4-Chloro-3-fluorophenyl)-2-hydroxyethyl)-2-(2-chloropyrimidin-4-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (56)



Ammonium acetate (220 mg, 2.8 mmol) was added in one portion to **55** (160 mg, 0.57 mmol) and 2-bromo-1-(2-chloropyrimidin-4-yl)ethanone (130 mg, 0.57 mmol) in ethanol (5 mL). The resulting solution was stirred at 20 °C for 18 hours. The reaction mixture was concentrated and diluted with EtOAc (25 mL), and washed sequentially with water (25 mL) and saturated brine (25 mL). The organic layer was dried over MgSO₄, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford **56** (28 mg, 12 %) as a yellow solid. *m/z*: ES⁺ [M+H]⁺ 421; ¹H NMR (400 MHz, DMSO) δ 2.71 (dd, *J* = 6.1, 12.8 Hz, 1H), 3.10 (d, *J* = 7.0 Hz, 1H), 3.33 – 3.44 (m, 1H), 3.71 (dd, *J* = 5.1, 11.6 Hz, 1H), 3.75 – 3.84 (m, 1H), 3.83 (s, 1H), 4.86 (d, *J* = 5.3 Hz, 1H), 5.49 – 5.64 (m, 1H), 7.04 (d, *J* = 8.4 Hz, 1H), 7.17 – 7.28 (m, 2H), 7.37 (t, *J* = 8.1 Hz, 1H), 7.66 (d, *J* = 5.4 Hz, 1H), 8.38 (d, *J* = 5.4 Hz, 1H), 12.05 (s, 1H). *m/z*: ES⁺ [M+H]⁺ 421.

(S)-5-(1-(4-Chloro-3-fluorophenyl)-2-hydroxyethyl)-2-(((tetrahydro-2H-pyran-4-yl)amino)pyrimidin-4-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (11)

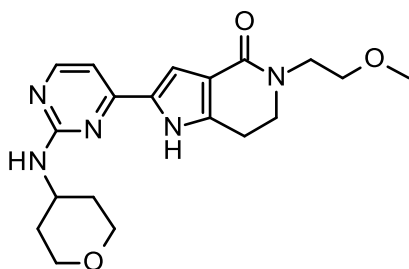


Tetrahydro-2H-pyran-4-amine (19 mg, 0.19 mmol), **56** (27 mg, 0.06 mmol) and N-ethyl-N-isopropylpropan-2-amine (0.056 mL, 0.32 mmol) were suspended in NMP (1 mL) and sealed into a microwave tube. The reaction was heated to 200 °C for 70 minutes in the microwave reactor and cooled to RT. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5μ silica, 50 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% NH₃) and MeCN as eluents. Fractions

containing the desired compound were evaporated to dryness to afford **11** (5.0 mg, 18 %) as a gum. ^1H NMR (400 MHz, CDCl_3) δ 1.56 (d, J = 8.7 Hz, 2H), 2.04 (d, J = 5.6 Hz, 2H), 2.87 (t, J = 6.7 Hz, 2H), 3.32 (dt, J = 6.1, 12.3 Hz, 1H), 3.47 – 3.65 (m, 4H), 3.95 – 4.03 (m, 2H), 4.06 – 4.15 (m, 2H), 4.21 (dd, J = 5.2, 11.5 Hz, 1H), 4.99 (d, J = 7.7 Hz, 1H), 5.81 (dd, J = 5.2, 8.1 Hz, 1H), 6.77 (d, J = 5.3 Hz, 1H), 7.10 (d, J = 8.3 Hz, 1H), 7.17 (d, J = 12.8 Hz, 2H), 7.37 (t, J = 7.9 Hz, 1H), 8.22 (d, J = 5.2 Hz, 1H), 9.48 (s, 1H); Purity 100% by HPLC, m/z : ES^+ $[\text{M}+\text{H}]^+$ 486.

Synthesis of Compound 12

5-(2-methoxyethyl)-2-(2-(((tetrahydro-2H-pyran-4-yl)amino)pyrimidin-4-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (12)



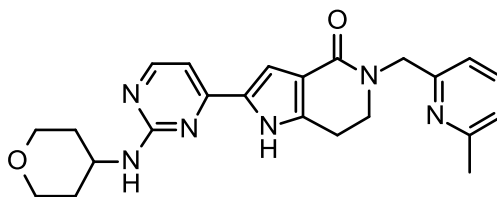
Bis(triphenylphosphine)palladium(II) chloride (0.8 g, 1.2 mmol) was added to **37** (5 g, 23 mmol), and tributyl(1-ethoxyvinyl)stannane (13 g, 35 mmol) in DMF (50 mL) at 25°C under nitrogen. The resulting mixture was stirred at 100 °C for 12 hours. The reaction mixture was diluted with EtOAc and 4 g of KF was added to the solution, the resulting mixture was stirred at room temperature for 2 hours. The mixture was filtered through a Celite pad. The filtrate was washed with water (2 x 50 mL), dried and concentrated. The crude product was purified by flash silica chromatography, elution gradient 5 to 40% EtOAc in PE. Pure fractions were evaporated to dryness to afford 4-(1-ethoxyvinyl)-N-(tetrahydro-2H-pyran-4-yl)pyrimidin-2-amine (5.80 g, 99%) as a white solid.

NBS (1.1 g, 6 mmol) was added to 4-(1-ethoxyvinyl)-N-(tetrahydro-2H-pyran-4-yl)pyrimidin-2-amine (1.5 g, 6 mmol) in THF (20 mL) and water (2 mL) at 25°C under air. The resulting solution was stirred at 25 °C for 30 minutes. The solvent was removed under reduced pressure. The reaction mixture was diluted with EtOAc (200 mL), and washed sequentially with water (50 mL), saturated brine (50 mL). The organic layer was dried over Na_2SO_4 , filtered and evaporated to afford crude product **12** (1.8 g, 100 %) as a brown solid. The product was

dissolved in ethanol (20 mL), then 1-(2-methoxyethyl)piperidine-2,4-dione (1.2 g, 7.2 mmol) and ammonium acetate (2.3 g, 30 mmol) were added. The resulting mixture was stirred at 25 °C for 12 hours. The solvent was removed under reduced pressure. The crude product was purified by flash silica chromatography, elution gradient 0 to 4% MeOH in DCM. Pure fractions were evaporated to dryness to afford a yellow solid. This was purified by preparative HPLC (XSelect CSH Prep C18 OBD column, 5 μ silica, 19 mm diameter, 150 mm length), using decreasingly polar mixtures of water (containing 0.03% NH₃) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford **12** (1.20 g, 53.9 %) as a white solid. ¹H NMR (400 MHz, DMSO, 20°C) δ 1.50 – 1.55 (m, 2H), 1.81 – 1.84 (m, 2H), 2.91 – 2.93 (m, 2H), 3.26 (s, 3H), 3.41 – 3.66 (m, 8H), 3.87 – 3.89 (m, 2H), 4.11 (s, 1H), 6.88 (d, J = 5.2 Hz, 2H), 7.04 (d, J = 2 Hz, 1H), 8.16 (d, J = 5.2 Hz, 1H); Purity 99.6% by LC-MS, m/z : ES⁺ [M+H]⁺ 372.

Synthesis of Compound 13

5-((6-Methylpyridin-2-yl)methyl)-2-((2-(((tetrahydro-2H-pyran-4-yl)amino)pyrimidin-4-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (13)



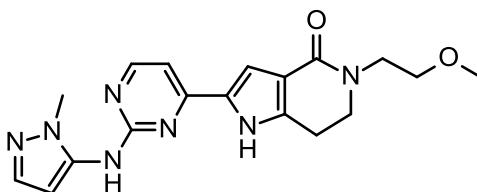
Bis(triphenylphosphine)palladium(II) chloride (0.82 g, 1.1 mmol) was added to **37** (5 g, 23 mmol), and tributyl(1-ethoxyvinyl)stannane (13 g, 35 mmol) in DMF (50 mL) at 25°C under nitrogen. The resulting mixture was stirred at 100 °C for 12 hours. The reaction mixture was diluted with EtOAc and 4 g of KF was added to the solution, the resulting mixture was stirred at room temperature for 2 hours. The mixture was filtered through a Celite pad. The filtrate was washed with water (2 x 50 mL), dried and concentrated. The crude product was purified by flash silica chromatography, elution gradient 5 to 40% EtOAc in PE. Pure fractions were evaporated to dryness to afford 4-(1-ethoxyvinyl)-N-(tetrahydro-2H-pyran-4-yl)pyrimidin-2-amine (5.8 g, 99%) as a white solid.

NBS (1 g, 6 mmol) was added to 4-(1-ethoxyvinyl)-N-(tetrahydro-2H-pyran-4-yl)pyrimidin-2-amine (1.5 g, 6 mmol) in THF (20 mL) and water (2 mL) at 25°C under air. The resulting solution was stirred at 25 °C for 30

minutes. The solvent was removed under reduced pressure. The reaction mixture was diluted with EtOAc (200 mL), and washed sequentially with water (50 mL), saturated brine (50 mL). The organic layer was dried over Na₂SO₄, filtered and evaporated to afford crude product **13** (1.8 g, 100 %) as a brown solid. The product was dissolved in ethanol (20 mL), then ammonium acetate (380 mg, 5 mmol) and 1-((6-methylpyridin-2-yl)methyl)piperidine-2,4-dione (260 mg, 1.2 mmol) were added. The resulting solution was stirred at room temperature for 16 hours. The solvent was removed under reduced pressure. The crude product was purified by flash silica chromatography, elution gradient 0 to 6% MeOH in DCM. Pure fractions were evaporated to dryness to afford crude product. This was purified by preparative HPLC (XBridge Prep C18 OBD column, 5 μ silica, 19 mm diameter, 150 mm length), using decreasingly polar mixtures of water (containing 0.1% NH₃) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford **13** (60 mg, 14 %) as a white solid. ¹H NMR (400 MHz, Methanol-d₄) δ 1.62 – 1.66 (m, 2H), 2.00 – 2.03 (m, 2H), 2.55 (s, 3H), 3.06 (t, *J* = 7.2 Hz, 2H), 3.60 – 3.62 (m, 2H), 3.74 t, *J* = 7.2 Hz, 2H), 3.99 – 4.02 (m, 2H), 4.18 (bs, 1H), 4.81 (s, 1H), 4.88 (s, 2H), 6.88 (d, *J* = 5.2 Hz, 1H), 7.16 – 7.24 (m, 3H), 7.71 (t, *J* = 8 Hz, 1H), 8.14 (d, *J* = 5.2 Hz, 1H); Purity 99.3% by LC-MS, *m/z*: ES⁺ [M+H]⁺ 419.

Synthesis of Compound 14

5-(2-methoxyethyl)-2-(2-((1-methyl-1*H*-pyrazol-5-yl)amino)pyrimidin-4-yl)-6,7-dihydro-1*H*-pyrrolo[3,2-*c*]pyridin-4(5*H*)-one (14)

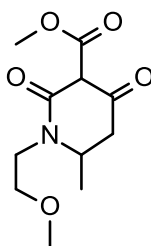


2-(2-Chloropyrimidin-4-yl)-5-(2-methoxyethyl)-6,7-dihydro-1*H*-pyrrolo[3,2-*c*]pyridin-4(5*H*)-one (150 mg, 0.49 mmol), 1-methyl-1*H*-pyrazol-5-amine (140 mg, 1.47 mmol), Cs₂CO₃ (320 mg, 0.98 mmol) and 2nd Generation RuPhos precatalyst (38 mg, 0.05 mmol) were mixture in 1,4-dioxane (10 mL) and sealed into a microwave tube. The mixture was degassed with nitrogen for 10 minutes and the tube sealed. The reaction was stirred at 110 °C for 3 hours. The reaction was incomplete so the temperature was increased to 130°C and the reaction mixture was stirred for a further 16 hours. The solvent was removed under reduced pressure. The crude product was purified by flash silica chromatography, elution gradient 0 to 8% MeOH in DCM. Pure fractions were

evaporated to dryness to afford crude product. The crude product was purified by preparative HPLC (XBridge Prep C18 OBD column, 5 μ silica, 19 mm diameter, 150 mm length), using decreasingly polar mixtures of water (containing 0.1% NH₃) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford **14** (25 mg, 14%) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 2.92 (t, J = 6.8 Hz, 2H), 3.26 (s, 3H), 3.45 – 3.48 (m, 2H), 3.53 – 3.56 (m, 2H), 3.62 (t, J = 6.8 Hz, 2H), 3.68 (s, 3H), 6.29 (d, J = 1.6 Hz, 1H), 7.09 (s, 1H), 7.16 (d, J = 5.2 Hz, 1H), 7.35 (d, J = 1.6 Hz, 1H), 8.35 (d, J = 5.2 Hz, 1H), 9.15 (s, 1H), 11.76 (s, 1H); Purity 99.2% by LC-MS, m/z : ES⁺ [M+H]⁺ 368.

Synthesis of Compounds 15 and 16

Methyl 1-(2-methoxyethyl)-6-methyl-2,4-dioxopiperidine-3-carboxylate (57)

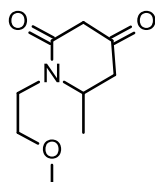


(*E*)-Methyl but-2-enoate (15 g, 150 mmol) was added dropwise to 2-methoxyethanamine (11 g, 150 mmol) in MeOH (200 mL) at 0°C under nitrogen. DBU (2.2 mL, 15 mmol) was added and the resulting mixture was stirred at 0 °C for 4 hours. The solvent was removed under reduced pressure to afford the crude product methyl 3-((2-methoxyethyl)amino)butanoate (22 g, 85 %) as a yellow liquid. Methyl 3-chloro-3-oxopropanoate (14 mL, 139 mmol) was added dropwise to methyl 3-((2-methoxyethyl)amino)butanoate (22 g, 127 mmol) and TEA (18 mL, 127 mmol) in DCM (50 mL) at 0°C under nitrogen. The resulting mixture was stirred at 0 °C for 16 hours. The reaction mixture was quenched with water (250 mL), extracted with DCM (3 x 250 mL), the organic layer was washed with brine and dried over Na₂SO₄, filtered and evaporated to afford crude methyl 3-(3-methoxy-N-(2-methoxyethyl)-3-oxopropanamido)butanoate (37 g) as a brown liquid.

Potassium carbonate (37 g, 265 mmol) was added to methyl 3-(3-methoxy-N-(2-methoxyethyl)-3-oxopropanamido)butanoate (37 g, 132 mmol) in DMF (30 mL) under nitrogen. The resulting mixture was stirred at 120 °C for 4 hours. The precipitate was collected by filtration, washed with EtOAc (50 mL). The solid was dissolved with water(300 mL). The solution was adjusted to pH 5 with 2M HCl, then extracted with DCM (4 x 300 mL), the organic layer was washed with brine and dried over Na₂SO₄, filtered and evaporated to

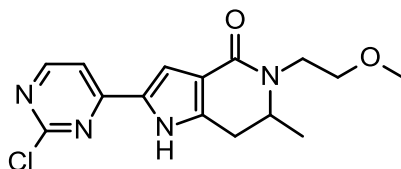
afford **57**. ^1H NMR(400 MHz, Chloroform- d) δ 1.22 (d, J = 9.2 Hz, 3H), 2.33 (dd, J = 15.2, 2 Hz, 1H), 2.98 - 3.14 (m, 2H), 3.34 (s, 3H), 3.51 - 3.61 (m, 2H), 3.74 - 3.80 (m, 1H), 3.91 (s, 3H), 4.01 - 4.06 (m, 1H); m/z : ES^+ $[\text{M}+\text{H}]^+$ 244.

1-(2-Methoxyethyl)-6-methylpiperidine-2,4-dione (58)



57 (11 g, 47 mmol) in water (20 mL) and acetonitrile (10 mL). The resulting mixture was stirred at 100 °C for 4 hours. The resulting mixture was evaporated to dryness and the residue was azeotroped with toluene to afford **58** (8.3 g, 95%) as a yellow liquid. ^1H (400 MHz, Chloroform- d) δ 1.25 (d, J = 9.2 Hz, 3H), 2.51 - 2.53 (m, 1H), 2.85 (dd, J = 10, 6 Hz, 1H), 3.22 - 3.33 (m, 3H), 3.35 (s, 3H), 3.51 - 3.66 (m, 2H), 3.99 - 4.05 (m, 2H); m/z : ES^+ $[\text{M}+\text{H}]^+$ 186.

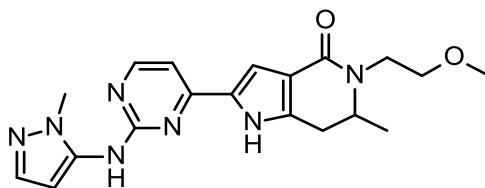
2-(2-Chloropyrimidin-4-yl)-5-(2-methoxyethyl)-6-methyl-6,7-dihydro-1H-pyrrolo[3,2-*c*]pyridin-4(5H)-one (59)



Bis(triphenylphosphine)palladium(II) chloride (3.5 g, 5 mmol) was added to 2,4-dichloropyrimidine (15 g, 100 mmol), and tributyl(1-ethoxyvinyl)stannane (44 g, 120 mmol) in DMF (50 mL) at 25°C under nitrogen. The resulting mixture was stirred at 80 °C for 2 hours. The reaction mixture was diluted with EtOAc and 12 g of KF was added to the solution, the resulting mixture was stirred at room temperature for 2 hours. The mixture was filtered through a Celite pad. The filtrate was washed with water (2 x 100 mL), dried and concentrated. The crude product was purified by flash silica chromatography, elution gradient 5 to 15% EtOAc in PE. Pure fractions were evaporated to dryness to afford 2-chloro-4-(1-ethoxyvinyl)pyrimidine (18 g, 97 %) as a white solid.

NBS (1.446 g, 8.12 mmol) was added to 2-chloro-4-(1-ethoxyvinyl)pyrimidine (1.5 g, 8.1 mmol) in THF (20 mL), water (1 mL) at 25°C under air. The resulting solution was stirred at 25 °C for 30 minutes. The solvent was removed by distillation under vacuum. The reaction mixture was diluted with EtOAc (100 mL), washed with water (20 mL), brine (20 mL) and dried under vacuum to afford 2-bromo-1-(2-chloropyrimidin-4-yl)ethanone (1.9 g) as a yellow oil. 2-Bromo-1-(2-chloropyrimidin-4-yl)ethanone (1.5 g, 6.37 mmol) was added to **58** (1.4 g, 7.6 mmol) and ammonium acetate (2.5 g, 32 mmol) in ethanol (20 mL) at 25°C under air. The resulting mixture was stirred at r.t. for 16 hours. The solvent was removed under reduced pressure. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% MeOH in DCM. Pure fractions were evaporated to dryness to afford **59** (1 g, 50 %) as a yellow solid. ¹H NMR (300 MHz, DMSO) δ 1.23 (d, *J* = 6.5 Hz, 3H), 2.66 – 2.71 (m, 1H), 3.03 – 3.12 (m, 1H), 3.31 – 3.35 (m, 1H), 3.36 (s, 3H), 3.55 – 3.60 (m, 2H), 4.01 – 4.10 (m, 1H), 4.21 – 4.28 (m, 1H), 7.28 (s, 1H), 7.34 (d, *J* = 5.4 Hz, 1H), 8.45 (d, *J* = 5.4 Hz, 1H), 9.74 (s, 1H); *m/z*: ES⁺ [M+H]⁺ 321.

5-(2-methoxyethyl)-6-methyl-2-(2-((1-methyl-1*H*-pyrazol-5-yl)amino)pyrimidin-4-yl)-6,7-dihydro-1*H*-pyrrolo[3,2-*c*]pyridin-4(5*H*)-one (15 and 16)



59 (340 mg, 1.1 mmol), 1-methyl-1*H*-pyrazol-5-amine (310 mg, 3.1 mmol), cesium carbonate (1020 mg, 3.2 mmol) and 3rd Generation BrettPhos precatalyst (95 mg, 0.11 mmol) were mixture in 1,4-dioxane (3 mL) and sealed into a microwave tube. The mixture was degassed with nitrogen for 10 minutes and the tube sealed. The reaction was heated to 100 °C for 2 hours in the microwave reactor and cooled to RT.

The solvent was removed under reduced pressure. The crude product was purified by flash silica chromatography, elution gradient 0 to 8% MeOH in DCM. Pure fractions were evaporated to dryness to afford crude product (300 mg). The crude product was purified by preparative HPLC (XBridge Prep C18 OBD column, 5μ silica, 19 mm diameter, 150 mm length), using decreasingly polar mixtures of water (containing 0.1% NH₃) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the racemic mixture (190 mg, 49 %) as a white solid. ¹H NMR (400 MHz, DMSO) δ 1.13 (d, *J* = 6.5 Hz,

3H), 2.74 (d, $J = 15.0$ Hz, 1H), 3.03 (dt, $J = 6.2, 12.5$ Hz, 1H), 3.15 (dd, $J = 6.4, 16.5$ Hz, 1H), 3.26 (s, 3H), 3.4 - 3.52 (m, 2H), 3.68 (s, 3H), 3.86 - 3.94 (m, 1H), 3.99 (dt, $J = 5.6, 13.9$ Hz, 1H), 6.29 (d, $J = 1.9$ Hz, 1H), 7.08 (s, 1H), 7.14 (d, $J = 5.3$ Hz, 1H), 7.34 (d, $J = 1.9$ Hz, 1H), 8.33 (d, $J = 5.3$ Hz, 1H), 9.08 (s, 1H), 11.69 (s, 1H). Purity 99.9% by LC-MS, m/z : $ES^+ [M+H]^+ 382$.

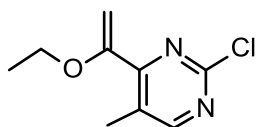
The racemate was purified by preparative HPLC (Chiral Technologies IC column, 20 μ m silica, 50 mm diameter, 250 mm length), MeCN/EtOH, 200 mL/min. EtOH increased after first eluted to reduce run time. Fractions containing the desired compounds were evaporated to dryness to afford **15** (84 mg, 0.2 mmol, 49 %) as a white solid and **16** (78 mg, 0.2 mmol, 45 %) as a white solid.

15: 1H NMR (400 MHz, DMSO) δ 1.13 (d, $J = 6.5$ Hz, 3H), 2.74 (d, $J = 15.0$ Hz, 1H), 3.03 (dt, $J = 6.2, 12.5$ Hz, 1H), 3.15 (dd, $J = 6.4, 16.5$ Hz, 1H), 3.26 (s, 3H), 3.4 - 3.52 (m, 2H), 3.68 (s, 3H), 3.86 - 3.94 (m, 1H), 3.99 (dt, $J = 5.6, 13.9$ Hz, 1H), 6.29 (d, $J = 1.9$ Hz, 1H), 7.08 (s, 1H), 7.14 (d, $J = 5.3$ Hz, 1H), 7.34 (d, $J = 1.9$ Hz, 1H), 8.33 (d, $J = 5.3$ Hz, 1H), 9.08 (s, 1H), 11.69 (s, 1H). Purity 100% by LC-MS, m/z : $ES^+ [M+H]^+ 382$. Chiral purity 100% by HPLC.

16: 1H NMR (400 MHz, DMSO) δ 1.13 (d, $J = 6.5$ Hz, 3H), 2.74 (d, $J = 15.0$ Hz, 1H), 3.03 (dt, $J = 6.2, 12.5$ Hz, 1H), 3.15 (dd, $J = 6.4, 16.5$ Hz, 1H), 3.26 (s, 3H), 3.4 - 3.52 (m, 2H), 3.68 (s, 3H), 3.86 - 3.94 (m, 1H), 3.99 (dt, $J = 5.6, 13.9$ Hz, 1H), 6.29 (d, $J = 1.9$ Hz, 1H), 7.08 (s, 1H), 7.14 (d, $J = 5.3$ Hz, 1H), 7.34 (d, $J = 1.9$ Hz, 1H), 8.33 (d, $J = 5.3$ Hz, 1H), 9.08 (s, 1H), 11.69 (s, 1H). Purity 100% by LC-MS, m/z : $ES^+ [M+H]^+ 382$. Chiral purity 100% by HPLC.

Synthesis of Compounds 17 and 18

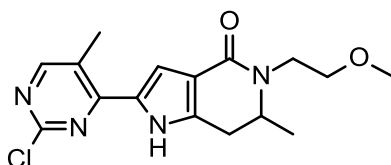
2-Chloro-4-(1-ethoxyvinyl)-5-methylpyrimidine (**60**)



$Pd(PPh_3)_2Cl_2$ (1.1 g, 1.5 mmol) was added to 2,4-dichloro-5-methylpyrimidine (5.0 g, 31 mmol) and tributyl(1-ethoxyvinyl)stannane (12 g, 34 mmol) in DMF (50 mL) at 25°C under nitrogen. The resulting solution was stirred at 80 °C for 3 hours. The solvent was removed by distillation under vacuum. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% EtOAc in petroleum ether. Pure fractions

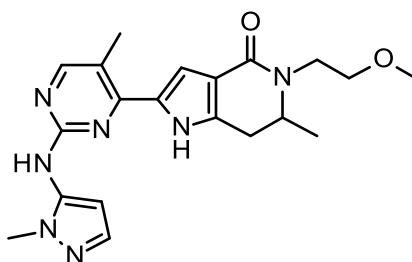
were evaporated to dryness to afford **60** (6 g, 98 %) as a colourless oil. ^1H NMR (500 MHz, CDCl_3 , 25 °C) δ 1.40 (t, J = 6.9 Hz, 3H), 3.93 (q, J = 6.9 Hz, 2H), 2.37 (s, 3H), 4.54 (d, J = 2.5 Hz, 1H), 4.54 (d, J = 2.5 Hz, 1H), 8.39 (s, 1H), 5.00 (d, J = 2.8 Hz, 1H); m/z : ES^+ $[\text{M}+\text{H}]^+$ 199.

2-(2-Chloro-5-methylpyrimidin-4-yl)-5-(2-methoxyethyl)-6-methyl-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (61)



1-Bromopyrrolidine-2,5-dione (0.90 g, 5.0 mmol) was added to **60** (1 g, 5 mmol) in THF (10 mL) and water (1 mL) at 25 °C under air. The resulting solution was stirred at 25 °C for 12 hours. The reaction mixture was diluted with DCM (50 mL), and washed sequentially with water (2 x 25 mL), saturated brine (20 mL), the organic layer was dried over Na_2SO_4 , filtered and evaporated to afford 2-bromo-1-(2-chloro-5-methylpyrimidin-4-yl)ethanone (1.3 g, 100%) product as a white solid. The product was dissolved in ethanol (30 mL), then ammonium acetate (2.0 g, 25 mmol) and 1-(2-methoxyethyl)-6-methylpiperidine-2,4-dione (0.94 g, 5.1 mmol) were added at ambient temperature. The resulting solution was stirred at 25 °C for 12 hours. The solvent was removed by distillation under vacuum. The crude product was purified by flash silica chromatography, elution gradient 0 to 8% MeOH in DCM. Pure fractions were evaporated to dryness to afford **61** (1.3 g, 77 %) as a yellow oil. ^1H NMR (300 MHz, DMSO, 25 °C) δ 1.14 (d, J = 6.0 Hz, 3H), 2.74 (dd, J = 16.8, 1.2, 1H), 3.01 – 3.08 (m, 1H), 3.11 – 3.17 (m, 1H), 3.27 (s, 3H), 3.32 (s, 3H), 3.42 – 3.50 (m, 2H), 3.91 – 4.03 (m, 2H), 7.38 (d, J = 2.4 Hz, 1H), 7.81 (d, J = 5.2 Hz, 1H), 8.53 (d, J = 5.2 Hz, 1H); m/z : ES^+ $[\text{M}+\text{H}]^+$ 335.

5-(2-methoxyethyl)-6-methyl-2-(5-methyl-2-((1-methyl-1H-pyrazol-5-yl)amino)pyrimidin-4-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one and 5-(2-methoxyethyl)-6-methyl-2-(5-methyl-2-((1-methyl-1H-pyrazol-5-yl)amino)pyrimidin-4-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (17 and 18)



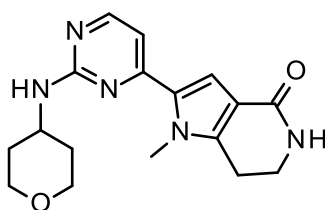
61 (700 mg, 2.1 mmol), 1-methyl-*1H*-pyrazol-5-amine (610 mg, 6.3 mmol), Cs₂CO₃ (1300 mg, 4.2 mmol) and 3rd Generation BrettPhos precatalyst (95 mg, 0.1 mmol) in 1,4-dioxane (5 mL) was stirred under an atmosphere of nitrogen at 130 °C for 12 hours. The solvent was removed by distillation under vacuum. The crude product was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford a yellow solid (403 mg). This was purified by preparative HPLC (XSelect CSH Prep C18 OBD column, 5μ silica, 19 mm diameter, 150 mm length), using decreasingly polar mixtures of water (containing 0.05% NH₄HCO₃) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford racemic 5-(2-methoxyethyl)-6-methyl-2-(5-methyl-2-((1-methyl-*1H*-pyrazol-5-yl)amino)pyrimidin-4-yl)-6,7-dihydro-*1H*-pyrrolo[3,2-*c*]pyridin-4(*5H*)-one (290 mg, 35.1 %) as a white solid. The racemate was purified by preparative chiral-HPLC on a AS column, eluting isocratically with 30% EtOH in Hex (modified with 0.2% IPA) as eluent. The fractions containing the desired compound were evaporated to dryness to afford **17** (113 mg, 39 %) as a white solid and **18** (115 mg, 40 %) also as a white solid.

17: ¹H NMR (300 MHz, CDCl₃, 25 °C) δ 1.23 (d, *J* = 6.6 Hz, 3H), 2.38 (s, 3H), 2.67 (dd, *J* = 16.2, 1.2, 1H), 3.03 – 3.12 (m, 1H), 3.28 – 3.32 (m, 1H), 3.37 (s, 3H), 3.56 – 3.62 (m, 2H), 3.79 (s, 3H), 3.98 – 4.03 (m, 1H), 4.20 – 4.28 (m, 1H), 6.25 (d, *J* = 1.8 Hz, 1H), 6.85 (s, 1H), 7.21 (d, *J* = 2.1 Hz, 1H), 7.51 (d, *J* = 2.1 Hz, 1H), 8.15 (s, 1H), 9.64 (s, 1H); Purity 100% by LC-MS, *m/z*: ES⁺ [M+H]⁺ 396. Chiral purity: 99.7% by HPLC.

18: ¹H NMR (300 MHz, CDCl₃, 25 °C) δ 1.23 (d, *J* = 6.6 Hz, 3H), 2.38 (s, 3H), 2.67 (dd, *J* = 16.2, 1.2, 1H), 3.03 – 3.12 (m, 1H), 3.28 – 3.32 (m, 1H), 3.37 (s, 3H), 3.56 – 3.62 (m, 2H), 3.79 (s, 3H), 3.98 – 4.03 (m, 1H), 4.20 – 4.28 (m, 1H), 6.25 (d, *J* = 1.8 Hz, 1H), 6.85 (s, 1H), 7.21 (d, *J* = 2.1 Hz, 1H), 7.51 (d, *J* = 2.1 Hz, 1H), 8.15 (s, 1H), 9.64 (s, 1H); Purity 99.9% by LC-MS, *m/z*: ES⁺ [M+H]⁺ 396. Chiral purity: 100% by HPLC.

Synthesis of Compound 19

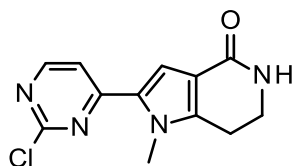
1-Methyl-2-(2-((tetrahydro-2*H*-pyran-4-yl)amino)pyrimidin-4-yl)-6,7-dihydro-*1H*-pyrrolo[3,2-*c*]pyridin-4(*5H*)-one (19)



Methyl iodide (0.15 mL, 2.4 mmol) was added to **6** (150 mg, 0.48 mmol), NaOH (190 mg, 4.8 mmol) and TBAB (77 mg, 0.2 mmol) in DCM (10 mL) and water (8 mL) at 25 °C. The resulting mixture was stirred at 25 °C for 12 hours. The solvent (DCM) was removed under vacuum. The precipitate was collected by filtration, washed with water (20 mL) and dried under vacuum. The crude product was purified by preparative HPLC (XSelect CSH Prep C18 OBD column, 5 μ silica, 19 mm diameter, 150 mm length), using decreasingly polar mixtures of water (containing 0.1% NH_4HCO_3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford **19** (30 mg, 19%) as a white solid. ^1H NMR (300 MHz, DMSO, 23.1 °C) δ 1.49 – 1.57 (m, 2H) 1.83 – 1.87 (m, 2H), 2.83 – 2.88 (m, 2H), 3.37 – 3.44 (m, 4H), 3.86 – 3.90 (m, 3H), 3.95 (s, 3H), 6.88 (d, J = 5.1 Hz, 1H), 7.02 – 7.11 (m, 3H), 8.16 (d, J = 5.1 Hz, 1H); Purity 99.3% by LC-MS, m/z : ES^+ $[\text{M}+\text{H}]^+$ 328.

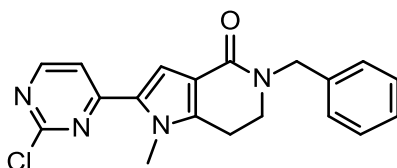
Synthesis of Compound 20

2-(2-Chloropyrimidin-4-yl)-1-methyl-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (62**)**



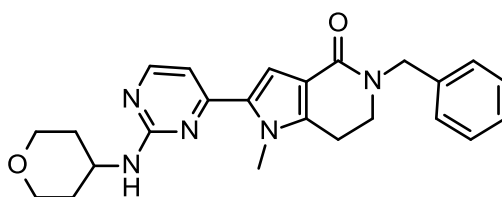
Sodium hydride (60% dispersion) (24 mg, 0.60 mmol) was added to 2-(2-chloropyrimidin-4-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (150 mg, 0.60 mmol) in DMF (12 mL) under nitrogen. The resulting suspension was stirred at 20 °C for 30 minutes. Iodomethane (0.038 mL, 0.60 mmol) was added and the resulting solution was stirred at 20 °C for 18 hours. It was diluted with ethyl acetate (75 mL) and washed with 50 % brine (20 mL), dried (magnesium sulfate), concentrated *in vacuo* and adsorbed onto silica. The crude product was purified by flash silica chromatography, elution gradient 0 to 7.5% MeOH in DCM. Pure fractions were evaporated to dryness to afford **62** (130 mg, 82 %) as a brown solid. ^1H NMR (400 MHz, DMSO, 27 °C) δ 2.88 (t, J = 7.0 Hz, 2H), 3.43 (t, J = 7.0 Hz, 2H), 3.91 (s, 3H), 7.21 (s, 1H), 7.37 (s, 1H), 7.84 (d, J = 5.3 Hz, 1H), 8.54 (d, J = 5.3 Hz, 1H); m/z : ES^+ $[\text{M}+\text{H}]^+$ 263.

5-Benzyl-2-(2-chloropyrimidin-4-yl)-1-methyl-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (63)



Sodium hydride (60% dispersion) (21 mg, 0.5 mmol) was added to **62** (120 mg, 0.48 mmol) in THF (15 mL) under nitrogen. The resulting suspension was stirred at 20 °C for 30 minutes. Benzyl bromide (0.062 mL, 0.52 mmol) was added followed by tetrabutylammonium iodide (2.64 mg, 7.14 μ mol) and the resulting solution stirred at 20 °C for 3 days. It was diluted with ethyl acetate (50 mL) and washed with brine (10 mL), dried (magnesium sulfate) and concentrated *in vacuo* to give **63** (150 mg, 89 %) as a yellow solid. ^1H NMR (400 MHz, DMSO, 27°C) δ 2.97 (t, J = 7.0 Hz, 2H), 3.54 (t, J = 7.0 Hz, 2H), 3.93 (s, 3H), 4.64 (s, 2H), 7.29 - 7.36 (m, 5H), 7.47 (s, 1H), 7.91 (d, J = 5.3 Hz, 1H), 8.58 (d, J = 5.3 Hz, 1H); m/z : ES^+ $[\text{M}+\text{H}]^+$ 353.

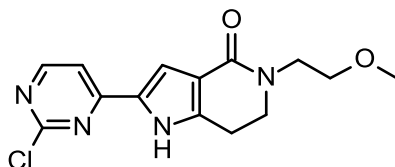
5-Benzyl-1-methyl-2-((tetrahydro-2H-pyran-4-yl)amino)pyrimidin-4-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (20)



N,N'-Diisopropylethylamine (0.36 mL, 2.1 mmol), **61** (140 mg, 0.4 mmol) and tetrahydro-pyran-4-ylamine (125 mg, 1.2 mmol) were suspended in NMP (3.5 mL) and sealed into a microwave tube. The reaction was heated to 200 °C for 70 minutes in the microwave reactor and cooled to RT. The mixture was diluted with NMP (1.5 mL) and filtered. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5 μ silica, 30 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% NH_3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford **20** (81 mg, 47 %) as a white solid. ^1H NMR (500 MHz, DMSO) δ 1.53 (qd, J = 4.4, 12.1, 12.8 Hz, 2H), 1.86 (dd, J = 2.2, 12.5 Hz, 2H), 2.95 (q, J = 6.7 Hz, 2H), 3.38 (td, J = 2.0, 11.6 Hz, 2H), 3.52 (t, J = 7.0 Hz, 2H), 3.83 – 3.93 (m, 3H), 3.94 (s, 3H), 4.63 (s, 2H), 6.92 (d, J = 5.3 Hz, 1H), 7.09 (s, 1H), 7.21 – 7.39 (m, 6H), 8.18 (d, J = 5.3 Hz, 1H); Purity 100% by LC-MS, m/z : ES^+ $[\text{M}+\text{H}]^+$ 418.

Synthesis of Compound 21

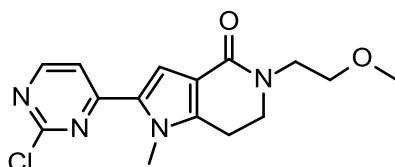
2-(2-Chloropyrimidin-4-yl)-5-(2-methoxyethyl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (**64**)



1-bromopyrrolidine-2,5-dione (4.82 g, 27.08 mmol) was added portionwise to 2-chloro-4-(1-ethoxyvinyl)pyrimidine (5.0 g, 27.08 mmol) in THF (50 mL) and water at 25°C over a period of 5 minutes under air. The resulting solution was stirred at 25 °C for 30 minutes. The reaction mixture was diluted with DCM (100 mL), and washed sequentially with water (50 mL X3). The organic layer was dried over Na₂SO₄, filtered and evaporated to afford crude 2-bromo-1-(2-chloropyrimidin-4-yl)ethanone (6.8 g) as a yellow oil.

2-Bromo-1-(2-chloropyrimidin-4-yl)ethanone (1.3 g, 5.4 mmol) was added to 1-(2-methoxyethyl)piperidine-2,4-dione (0.93 g, 5.44 mmol) and ammonium acetate (2.1 g, 27 mmol) in EtOH (50 mL) at 25°C under air. The resulting solution was stirred at RT for 12 hours. The solvent was removed under reduced pressure. The crude product was purified by flash silica chromatography, elution gradient 0 to 70% EtOAc in petroleum ether. Pure fractions were evaporated to dryness to afford **64** (0.52 g, 31 %) as a yellow solid. ¹H NMR (400 MHz, DMSO, 20.0 °C) δ 3.00 (t, *J* = 6.8 Hz, 2H), 3.41 (s, 3H), 3.57 – 3.61 (m, 2H), 3.68 – 3.72 (m, 2H), 3.77 (d, *J* = 6.8 Hz, 2H), 7.33 (s, 1H), 7.63 (d, *J* = 5.2 Hz, 1H), 8.47 (d, *J* = 5.2 Hz, 1H); *m/z*: ES⁺ [M+H]⁺ 307.

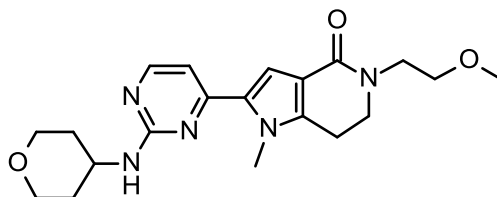
2-(2-Chloropyrimidin-4-yl)-5-(2-methoxyethyl)-1-methyl-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (**65**)



Iodomethane (340 mg, 2.4 mmol) was added to **64** (480 mg, 1.6 mmol), tetrabutylammonium bromide (51 mg, 0.16 mmol) and NaOH (630 mg, 16 mmol) in DCM (5mL) and water (3 mL). The resulting solution was stirred at 25 °C for 10 hours. The reaction mixture was poured into water (20 mL), extracted with DCM (3 x 20 mL), the organic layer was dried over Na₂SO₄, filtered and evaporated to afford **65** (250 mg, 49.3 %) as yellow oil.

^1H NMR (300 MHz, DMSO, 20.0 °C) δ 2.95 (t, J = 6.8 Hz, 2H), 3.23 (s, 3H), 3.46 – 3.49 (m, 2H), 3.54 – 3.59 (m, 2H), 3.66 (d, J = 6.8 Hz, 2H), 3.92 (s, 3H), 7.40 (s, 1H), 7.86 (d, J = 5.6 Hz, 1H), 8.55 (d, J = 5.6 Hz, 1H); m/z : ES^+ $[\text{M}+\text{H}]^+$ 321.

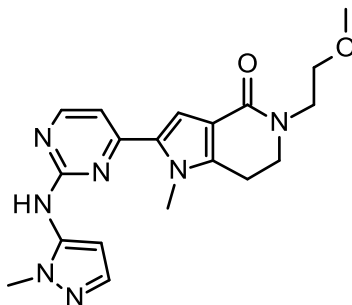
5-(2-Methoxyethyl)-1-methyl-2-(2-(((tetrahydro-2H-pyran-4-yl)amino)pyrimidin-4-yl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (21)



Methyl iodide (0.067 mL, 1.1 mmol) was added to **65** (200 mg, 0.54 mmol), NaOH (32 mg, 0.8 mmol) and TBAB (17 mg, 0.05 mmol) in DCM (10 mL) and water (6 mL) at 25°C. The resulting mixture was stirred at 25 °C for 12 hours. The reaction mixture was diluted with DCM (50 mL), and washed sequentially with water (25 mL), saturated brine (2 x 25 mL). The organic layer was dried over Na_2SO_4 , filtered and evaporated to afford crude product. The crude product was purified by preparative HPLC (XSelect CSH Prep C18 OBD column, 5 μ silica, 19 mm diameter, 150 mm length), using decreasingly polar mixtures of water (containing 0.03% NH_3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford **21** (100 mg, 48 %) as a yellow solid. ^1H NMR (400 MHz, DMSO, 19°C) δ 1.52 – 1.55 (m, 2H), 1.82 – 1.86 (m, 2H), 2.91 (t, J = 6.8 Hz, 2H), 3.26 (s, 3H), 3.34 – 3.37 (m, 2H), 3.45 – 3.48 (m, 2H), 3.52 – 3.55 (m, 2H), 3.61 – 3.65 (m, 2H), 3.86 – 3.90 (m, 3H), 3.94 (s, 3H), 6.90 (d, J = 5.2 Hz, 1H), 7.04 (s, 1H), 7.10 (s, 1H), 8.16 (d, J = 5.2 Hz, 1H); Purity 99.8%, by LC-MS, m/z : ES^+ $[\text{M}+\text{H}]^+$ 386.

Synthesis of Compound 22

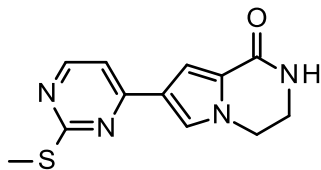
5-(2-Methoxyethyl)-1-methyl-2-(2-((1-methyl-1*H*-pyrazol-5-yl)amino)pyrimidin-4-yl)-6,7-dihydro-1*H*-pyrrolo[3,2-*c*]pyridin-4(5*H*)-one (22)



65 (250mg, 0.78 mmol), 1-methyl-1*H*-pyrazol-5-amine (150 mg, 1.6 mmol) and p-Toluenesulfonic acid (130 mg, 0.78 mmol) were dissolved in 1,4-dioxane (3 mL) and sealed into a microwave tube. The reaction was heated to 130 °C for 1 hour in the microwave reactor and cooled to RT. The reaction mixture was evaporated to dryness and redissolved in DCM (10 mL), and washed sequentially with water (2 x 20 mL), saturated brine (2 x 20 mL). The organic layer was dried over MgSO₄, filtered and evaporated. The crude product was purified by preparative HPLC (XBridge Prep C18 OBD column, 5μ silica, 19 mm diameter, 150 mm length), using decreasingly polar mixtures of water (containing 0.03% NH₃) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford **22** (9 mg, 3%) as a yellow solid. ¹H NMR (300 MHz, DMSO, 20.0 °C) δ 2.86 – 2.91 (m, 2H), 3.25 (s, 3H), 3.43 – 3.44 (m, 2H), 3.46 – 3.48 (m, 2H), 3.52 – 3.64 (m, 5H), 3.70 (s, 3H), 5.98 (s, 1H), 6.16 (d, *J* = 2.1 Hz, 1H), 7.14 (s, 1H), 7.18 (d, *J* = 5.4 Hz, 1H), 7.36 (d, *J* = 2.1 Hz, 1H), 8.30 (d, *J* = 5.4 Hz, 1H); Purity 99.2% by LC-MS, *m/z*: ES⁺ [M+H]⁺ 382.

Synthesis of Compound 23

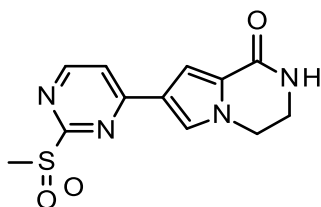
7-(2-(Methylthio)pyrimidin-4-yl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (66)



2-(Methylthio)-4-(tributylstannyl)pyrimidine (540 mg, 1.3 mmol), 7-bromo-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (310 mg, 1.4 mmol) and Pd-118 (85 mg, 0.13 mmol) were suspended in de-gassed DMF (5 mL) and

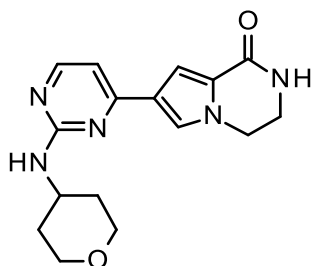
sealed into a microwave tube. The reaction was heated to 150 °C for 45 minutes in the microwave reactor and cooled to room temperature. Further Pd-118 (42 mg) was added and the mixture heated at 150 °C for a further 20 minutes. The mixture was heated at 150 °C for a further 1 hour, then cooled to room temperature. The mixture was filtered, concentrated, then purified by flash silica chromatography, elution gradient 0.3 to 4% MeOH in DCM. Pure fractions were evaporated then re-columned through a pad of 10% KF/silica (eluent 10% MeOH/DCM) and evaporated to dryness to afford **66** (26 mg, 7.6 %) as a white solid. ¹H NMR (400 MHz, CDCl₃, 27°C) δ 2.89 (s, 3H), 3.64 - 3.74 (m, 2H), 4.17 - 4.25 (m, 2H), 7.10 (d, *J* = 5.23 Hz, 1H), 7.35 - 7.42 (m, 2H), 7.62 (d, *J* = 1.55 Hz, 1H), 8.40 (d, *J* = 5.24 Hz, 1H); *m/z*: ES⁺ [M+H]⁺ 261.

7-(2-(Methylsulfonyl)pyrimidin-4-yl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one (67)



3-Chlorobenzoperoxoic acid (59 mg, 0.24 mmol) was added to **66** (25 mg, 0.1 mmol) in DCM (3 mL) at 22 °C under nitrogen. The resulting solution was stirred at 22 °C for 4 hours. LCMS indicated mainly product. The reaction mixture was diluted with DCM (50 mL), and washed with 2M sodium carbonate (50 mL). The organic layer was evaporated onto silica then purified by flash silica chromatography, elution gradient 0.5 to 10% MeOH in DCM. Pure fractions were evaporated to dryness to afford **67** (34 mg, 98 %) as a yellow solid. ¹H NMR (400 MHz, CDCl₃, 27°C) δ 2.96 (s, 3H), 3.72 - 3.80 (m, 2H), 4.18 - 4.28 (m, 2H), 6.51 (s, 1H), 7.40 - 7.47 (m, 2H), 7.77 (s, 1H), 8.73 (d, *J* = 5.24 Hz, 1H); *m/z*: ES⁺ [M+H]⁺ 293.

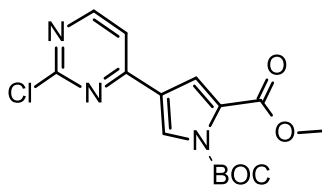
7-(2-((Tetrahydro-2H-pyran-4-yl)amino)pyrimidin-4-yl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one (23)



67 (34 mg, 0.09 mmol), tetrahydro-2*H*-pyran-4-amine (19 mg, 0.19 mmol) and *N*-ethyl-*N*-isopropylpropan-2-amine (0.041 mL, 0.23 mmol) were dissolved in NMP (3 mL) and sealed into a microwave tube. The reaction was heated to 150 °C for 4 hours in the microwave reactor and cooled to RT. The reaction mixture was diluted with EtOAc (25 mL), and washed with water (25 mL). The aqueous layer was extracted with further EtOAc (25 mL) then combined organics were evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 2.5 to 10% MeOH in DCM. Pure fractions were evaporated to dryness to afford **23** (7 mg, 24 %) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 1.58 (ddd, *J* = 4.3, 11.1, 23.9 Hz, 2H), 1.98 – 2.12 (m, 2H), 3.57 (td, *J* = 2.1, 11.6, 11.6 Hz, 2H), 3.70 – 3.78 (m, 2H), 4.00 (dd, *J* = 3.4, 11.8 Hz, 2H), 4.05 – 4.17 (m, 1H), 4.17 – 4.25 (m, 2H), 5.22 (s, 1H), 5.92 (s, 1H), 6.72 (d, *J* = 5.3 Hz, 1H), 7.41 (d, *J* = 1.5 Hz, 1H), 7.48 (s, 1H), 8.22 (d, *J* = 5.2 Hz, 1H); Purity 100% by LC-MS, *m/z*: ES⁺ [M+H]⁺ 314.

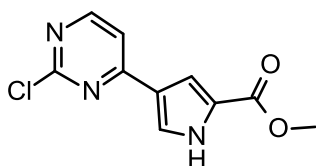
Synthesis of Compounds 24 and 25

1-*tert*-butyl 2-methyl 4-(2-chloropyrimidin-4-yl)-1*H*-pyrrole-1,2-dicarboxylate (68)



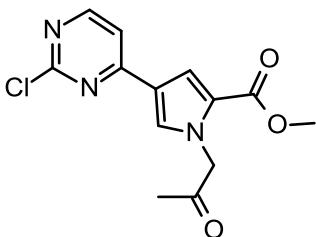
Pd(PPh₃)₄ (0.82 g, 0.71 mmol) was added to a de-gassed solution of 2,4-dichloropyrimidine (2.1 g, 14 mmol), 1-*tert*-butyl 2-methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrrole-1,2-dicarboxylate (5 g, 14 mmol) and potassium phosphate (9.1 g, 43 mmol) in dioxane (60 mL) and water (15 mL) at 22°C under nitrogen. The resulting solution was stirred at 70 °C for 5 hours. The reaction mixture was concentrated and diluted with DCM (125 mL), and water (25 mL). The layers were partitioned, then the aqueous extracted with further DCM (25 mL). The organic layer was evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 5 to 50% EtOAc in heptane. Pure fractions were evaporated to dryness to afford **68** (4.4 g, 91 %) as a colourless oil. ¹H NMR (400 MHz, DMSO) δ 1.56 (s, 9H), 3.82 (s, 3H), 7.51 (d, *J* = 1.8 Hz, 1H), 7.99 (d, *J* = 5.3 Hz, 1H), 8.31 (d, *J* = 1.8 Hz, 1H), 8.72 (d, *J* = 5.3 Hz, 1H); *m/z*: ES⁺ [M+H]⁺ 338.

Methyl 4-(2-chloropyrimidin-4-yl)-1H-pyrrole-2-carboxylate (69)



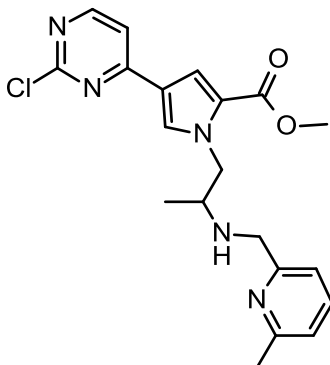
2,2,2-trifluoroacetic acid (15 mL, 195 mmol) was added to **68** (4.4 g, 13 mmol) in DCM (20 mL) at 22 °C. The resulting solution was stirred at 22 °C for 2 hours. 2M aqueous sodium carbonate solution (100 mL) was added, resulting in the precipitation of a white solid. DCM (50 mL) was added, but little dissolution occurred. The white solid was collected by filtration then dried in a vacuum oven to yield **69** (2.6 g, 85 %) as a white solid. ¹H NMR (400 MHz, DMSO) δ 3.80 (s, 3H), 7.45 (d, *J* = 1.7 Hz, 1H), 7.83 (d, *J* = 5.3 Hz, 1H), 7.90 (d, *J* = 1.7 Hz, 1H), 8.58 (d, *J* = 5.3 Hz, 1H), 12.60 (s, 1H); *m/z*: ES⁺ [M+H]⁺ 238.

Methyl 4-(2-chloropyrimidin-4-yl)-1-(2-oxopropyl)-1H-pyrrole-2-carboxylate (70)



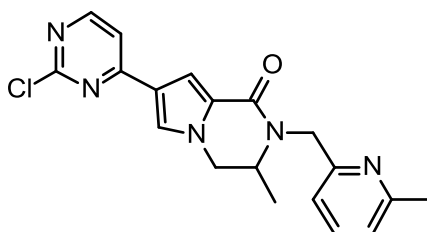
1-Chloropropan-2-one (0.23 mL, 2.8 mmol) was added to **69** (640 mg, 2.7 mmol), potassium carbonate (450 mg, 3.2 mmol) and 1,4,7,10,13,16-hexaoxacyclooctadecane (36 mg, 0.13 mmol) in 1,4-dioxane (10 mL) at 22 °C under nitrogen. The resulting mixture was stirred at 101 °C for 3 hours. Water (20 mL) was added, and the mixture was allowed to cool to RT. The resulting white solid was collected by filtration, washed with water (10 mL) and dried in a vacuum oven to yield methyl **70** (650 mg, 82 %) as white solid. ¹H NMR (400 MHz, DMSO) δ 2.18 (s, 3H), 3.74 (s, 3H), 5.27 (s, 2H), 7.59 (d, *J* = 1.9 Hz, 1H), 7.81 (d, *J* = 5.3 Hz, 1H), 7.97 (d, *J* = 1.9 Hz, 1H), 8.62 (d, *J* = 5.3 Hz, 1H); *m/z*: ES⁺ [M+H]⁺ 294.

Methyl 4-(2-chloropyrimidin-4-yl)-1-(2-(((6-methylpyridin-2-yl)methyl)amino)propyl)-1H-pyrrole-2-carboxylate (71)



N-ethyl-N-isopropylpropan-2-amine (0.27 mL, 1.5 mmol) was added to (6-methylpyridin-2-yl)methanamine hydrochloride (120 mg, 0.73 mmol), **70** (210 mg, 0.73 mmol) and magnesium sulfate (8.8 mg, 0.07 mmol) in THF (10 mL) at 22°C under nitrogen. The resulting mixture was stirred at 22 °C for 10 minutes. Sodium triacetoxyborohydride (230 mg, 1.1 mmol) was added, then the mixture was stirred for a further 3 hours. The reaction mixture was diluted with EtOAc (25 mL), and washed with saturated NaHCO₃ (25 mL). The aqueous layer was extracted with further EtOAc (25 mL) then combined organics were evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0.5 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford **71** (130 mg, 47 %) as a colourless gum. ¹H NMR (400 MHz, CDCl₃, 30°C) δ 1.13 (d, *J* = 6.5 Hz, 3H), 2.04 (s, 3H), 3.11 (m, 1H), 3.74 (d, *J* = 15.9 Hz, 1H), 3.82 (s, 3H), 3.89 (d, *J* = 15.9 Hz, 1H), 4.32 - 4.36 (m, 2H), 6.95 – 6.95 (m, 2H), 7.25 - 7.31 (m, 1H), 7.43 - 7.49 (m, 2H), 7.74 (d, *J* = 1.7 Hz, 1H), 8.45 (d, *J* = 5.2Hz, 1H); *m/z*: ES⁺ [M+H]⁺ 400.

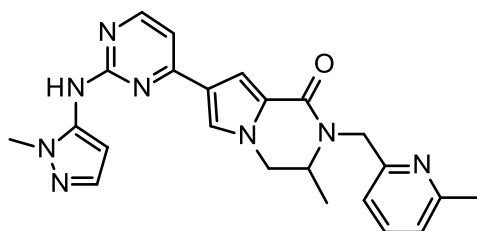
7-(2-Chloropyrimidin-4-yl)-3-methyl-2-((6-methylpyridin-2-yl)methyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one (72)



Trimethylaluminum, 2M in hexanes (0.51 mL, 1.01 mmol) was added dropwise to **71** (130 mg, 0.34 mmol) in THF (2 mL) and toluene (2 mL) at 22°C in a microwave tube under nitrogen. The resulting solution was stirred at 22 °C, then transferred to a microwave and heated at 120 °C for 1 hour. LCMS indicated incomplete

reaction. The mixture was heated at 150 °C for 1 hour. Saturated Rochelle's salt (7 mL) was then added cautiously (care - gas evolved!) and water (10 mL) was added then the mixture was extracted with DCM (2 x 40 mL). The organics were dried (Na₂SO₄) and concentrated to yield **72** (110 mg, 86 %) as a white solid. ¹H NMR (400 MHz, DMSO, 30°C) δ 1.15 (d, *J* = 6.6 Hz, 3H), 2.46 (s, 3H), 3.95 – 3.99 (m, 1H), 4.19 (dd, *J* = 2.4, 13.1 Hz, 1H), 4.30 (d, *J* = 16.0 Hz, 1H), 4.37 (dd, *J* = 4.2, 13.0 Hz, 1H), 5.13 (d, *J* = 16.0 Hz, 1H), 7.15 (m, 2H), 7.40 (d, *J* = 1.8 Hz, 1H), 7.65 (m, 1H), 7.81 (d, *J* = 1.7 Hz, 1H), 7.93 (d, *J* = 5.2 Hz, 1H), 8.59 (d, *J* = 5.2 Hz, 1H); *m/z*: ES⁺ [M+H]⁺ 368.

3-Methyl-7-(2-((1-methyl-1*H*-pyrazol-5-yl)amino)pyrimidin-4-yl)-2-((6-methylpyridin-2-yl)methyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (24 and 25)



72 (103 mg, 0.28 mmol), 1-methyl-1*H*-pyrazol-5-amine (30 mg, 0.31 mmol) and sodium 2-methylpropan-2-olate (54 mg, 0.56 mmol) were suspended in *tert*-butanol (2 mL) in a microwave, and de-gassed for 10 minutes, then BrettPhos 3rd generation pre-catalyst (12.69 mg, 0.01 mmol) was added, and the microwave tube was sealed. The reaction was heated to 80 °C for 1 hour in the microwave reactor and cooled to RT. The reaction mixture was diluted with EtOAc (20 mL), and washed with water (15 mL). The aqueous layer was extracted with further EtOAc (20 mL) and DCM (20 mL) then combined organics were evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0.5 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford the racemic mixture (56 mg, 47 %) as a white solid. ¹H NMR (400 MHz, DMSO) δ 1.14 (d, *J* = 6.6 Hz, 3H), 2.45 (s, 3H), 3.69 (s, 3H), 3.91 - 3.99 (m, 1H), 4.17 (dd, *J* = 2.4, 13.1 Hz, 1H), 4.28 (d, *J* = 16.0 Hz, 1H), 4.34 (dd, *J* = 4.2, 13.0 Hz, 1H), 5.12 (d, *J* = 16.0 Hz, 1H), 6.27 (d, *J* = 1.9 Hz, 1H), 7.12 - 7.18 (m, 3H), 7.26 (d, *J* = 1.7 Hz, 1H), 7.33 (d, *J* = 1.9 Hz, 1H), 7.64 (t, *J* = 7.7 Hz, 1H), 7.70 (d, *J* = 1.7 Hz, 1H), 8.33 (d, *J* = 5.2 Hz, 1H), 9.20 (s, 1H); Purity 98.3% by LC-MS, *m/z*: ES⁺ [M+H]⁺ 429.

Racemic 3-methyl-7-(2-((1-methyl-1*H*-pyrazol-5-yl)amino)pyrimidin-4-yl)-2-((6-methylpyridin-2-yl)methyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (52 mg), was purified by preparative HPLC (Chiral Technologies IA

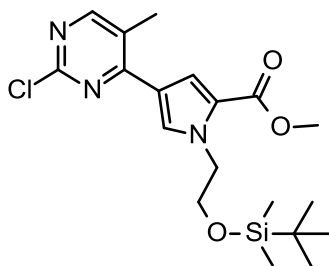
column, 20 μ m silica, 50 mm diameter, 250 mm length), Heptane/EtOH 50/50 at 150 mL/min. Fractions containing the desired compounds were evaporated to dryness to afford **24** (19 mg, 0.044 mmol, 44.2 %) as a white solid and **25** (20 mg, 0.047 mmol, 46.5 %) as a white solid. The product was analysed by analytical HPLC (Chiral Technologies IA column, 3 μ m silica, 4.6 mm diameter, 50 mm length), using a 50/50 mixture of Heptane/EtOH as eluents at 2mL/min.

24: ^1H NMR (400 MHz, DMSO) δ 1.14 (d, J = 6.6 Hz, 3H), 2.45 (s, 3H), 3.69 (s, 3H), 3.91 - 3.99 (m, 1H), 4.17 (dd, J = 2.4, 13.1 Hz, 1H), 4.28 (d, J = 16.0 Hz, 1H), 4.34 (dd, J = 4.2, 13.0 Hz, 1H), 5.12 (d, J = 16.0 Hz, 1H), 6.27 (d, J = 1.9 Hz, 1H), 7.12 - 7.18 (m, 3H), 7.26 (d, J = 1.7 Hz, 1H), 7.33 (d, J = 1.9 Hz, 1H), 7.64 (t, J = 7.7 Hz, 1H), 7.70 (d, J = 1.7 Hz, 1H), 8.33 (d, J = 5.2 Hz, 1H), 9.20 (s, 1H); Purity 100% by LC-MS, m/z : ES^+ $[\text{M}+\text{H}]^+$ 429. Enantiomeric purity 99.9% by HPLC.

25: ^1H NMR (400 MHz, DMSO) δ 1.14 (d, J = 6.6 Hz, 3H), 2.45 (s, 3H), 3.69 (s, 3H), 3.91 - 3.99 (m, 1H), 4.17 (dd, J = 2.4, 13.1 Hz, 1H), 4.28 (d, J = 16.0 Hz, 1H), 4.34 (dd, J = 4.2, 13.0 Hz, 1H), 5.12 (d, J = 16.0 Hz, 1H), 6.27 (d, J = 1.9 Hz, 1H), 7.12 - 7.18 (m, 3H), 7.26 (d, J = 1.7 Hz, 1H), 7.33 (d, J = 1.9 Hz, 1H), 7.64 (t, J = 7.7 Hz, 1H), 7.70 (d, J = 1.7 Hz, 1H), 8.33 (d, J = 5.2 Hz, 1H), 9.20 (s, 1H); Purity 100% by LC-MS, m/z : ES^+ $[\text{M}+\text{H}]^+$ 429. Enantiomeric purity 99.9% by HPLC.

Synthesis of Compound 26

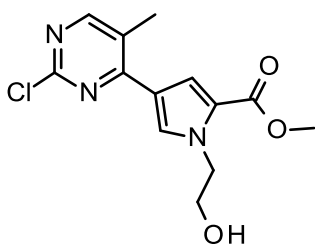
Methyl 1-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-4-(2-chloro-5-methylpyrimidin-4-yl)-1*H*-pyrrole-2-carboxylate (73)



Sodium hydride (60% dispersion in mineral oil) (0.34 g, 8.4 mmol) was added to methyl 4-(2-chloro-5-methylpyrimidin-4-yl)-1*H*-pyrrole-2-carboxylate (1.7 g, 6.8 mmol) in DMF (30 mL) at 22° under nitrogen. The resulting mixture was stirred at 22 °C for 15 minutes then (2-bromoethoxy)(*tert*-butyl)dimethylsilane (1.6 mL, 7.4 mmol) was added. The resulting mixture was stirred at 60 °C for 4 hours (during this time a further 0.2 mL of bromide SM was added). The reaction mixture was with ethyl acetate and washed with water (x 5), brine,

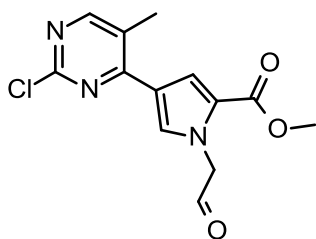
dried (MgSO₄) and concentrated. The residue was purified by flash silica chromatography, elution gradient 5 to 30% EtOAc in heptane. Pure fractions were evaporated to dryness to afford **73** (1.9 g, 70 %) as a white solid. ¹H NMR (400 MHz, DMSO) δ 0.12 (s, 6H), 0.78 (s, 9H), 2.4 - 2.43 (m, 3H), 3.79 (s, 3H), 3.86 (t, *J* = 5.2 Hz, 2H), 4.52 (t, *J* = 5.2 Hz, 2H), 7.48 (d, *J* = 2.0 Hz, 1H), 7.91 (d, *J* = 2.0 Hz, 1H), 8.51 (d, *J* = 0.7 Hz, 1H); *m/z*: ES⁺ [M+H]⁺ 410.

Methyl 4-(2-chloro-5-methylpyrimidin-4-yl)-1-(2-hydroxyethyl)-1H-pyrrole-2-carboxylate (74)



Triethylamine trihydrofluoride (3.9 mL, 23 mmol) was added to **73** (1.9 g, 4.7 mmol) in THF (30 mL) at 22°C under nitrogen. The resulting solution was stirred at 22 °C for 3.5 hours. The reaction mixture was diluted with NaHCO₃ solution (100 mL), and extracted with EtOAc (2 x 200 mL). The organic layer was dried (MgSO₄) and concentrated to afford crude product. The crude product was triturated with EtOAc, collected by filtration, and dried under vacuum to give **74** (1.2 g, 87 %) as a white solid. ¹H NMR (400 MHz, DMSO) δ 2.41 - 2.44 (m, 3H), 3.69 (q, *J* = 5.5 Hz, 2H), 3.79 (s, 3H), 4.46 (t, *J* = 5.5 Hz, 2H), 4.87 (t, *J* = 5.4 Hz, 1H), 7.47 (d, *J* = 2.0 Hz, 1H), 7.91 (d, *J* = 2.0 Hz, 1H), 8.51 (d, *J* = 0.7 Hz, 1H); *m/z*: ES⁺ [M+H]⁺ 296.

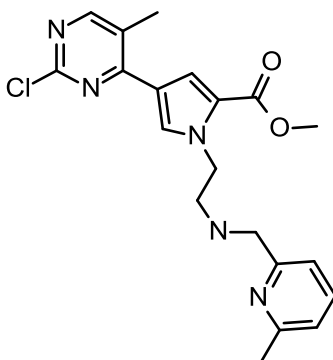
Methyl 4-(2-chloro-5-methylpyrimidin-4-yl)-1-(2-oxoethyl)-1H-pyrrole-2-carboxylate (75)



Dess-Martin Periodinane (1.9 g, 4.5 mmol) was added portionwise to **74** (1.2 g, 4.1 mmol) in DCM (40 mL) at 20°C. The resulting solution was stirred at RT for 3 hours. The reaction mixture was poured into saturated NaHCO₃ (100 mL) and water (30 mL) containing sodium thiosulfate (4.5 g, 28 mmol). The resulting suspension was stirred vigorously for 10 minutes, before separating the layers. The aqueous layer was extracted with further DCM (3 x 200 mL), then organics were dried (MgSO₄) and evaporated to afford **75** (1.2 g, 100 %)

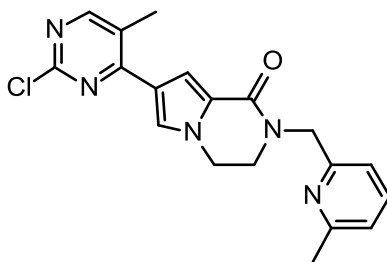
as a white solid. ^1H NMR (400 MHz, DMSO) δ 2.42 - 2.44 (m, 3H), 3.76 (s, 3H), 5.34 (s, 2H), 7.51 (d, J = 2.0 Hz, 1H), 7.97 (d, J = 2.0 Hz, 1H), 8.54 (d, J = 0.7 Hz, 1H), 9.65 (s, 1H); m/z : ES^+ $[\text{M}+\text{H}]^+$ 294.

Methyl 4-(2-chloro-5-methylpyrimidin-4-yl)-1-(2-(((6-methylpyridin-2-yl)methyl)amino)ethyl)-1H-pyrrole-2-carboxylate (76)



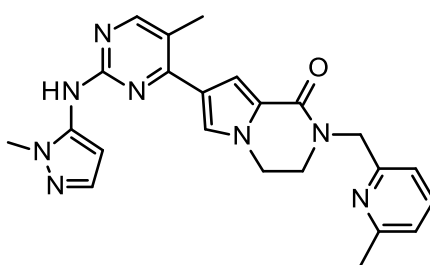
N-Ethyl-*N*-isopropylpropan-2-amine (0.11 mL, 0.61 mmol) was added to (6-methylpyridin-2-yl)methanamine (69 mg, 0.56 mmol), **75** (150 mg, 0.5 mmol) and magnesium sulfate (6.2 mg, 0.05 mmol) in THF (2 mL) and DMA (0.5 mL) at 22°C. The resulting mixture was stirred at 22 °C for 10 minutes. Sodium triacetoxyborohydride (150 mg, 0.72 mmol) was added, then the mixture was stirred for a further 20 hours. The reaction mixture was diluted with EtOAc (100 mL), and washed with saturated NaHCO_3 (50 mL). The aqueous layer was extracted with EtOAc (100 mL) and the combined organic layers were dried (MgSO_4) and concentrated. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% MeOH in EtOAc. Pure fractions were evaporated to dryness to afford **76** (120 mg, 59 %) as a colourless gum. ^1H NMR (400 MHz, DMSO) δ 2.40 (s, 3H), 2.41 (s, 3H), 2.89 (t, J = 6.1 Hz, 2H), 3.73 (s, 2H), 3.77 (s, 3H), 4.49 (t, J = 6.0 Hz, 2H), 7.06 (d, J = 7.6 Hz, 1H), 7.09 (d, J = 7.6 Hz, 1H), 7.47 (d, J = 2.0 Hz, 1H), 7.56 (t, J = 7.7 Hz, 1H), 7.98 (d, J = 2.0 Hz, 1H), 8.51 (s, 1H); m/z : ES^+ $[\text{M}+\text{H}]^+$ 400.

7-(2-Chloro-5-methylpyrimidin-4-yl)-2-((6-methylpyridin-2-yl)methyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one (77)



Trimethylaluminum (2M in toluene) (0.42 mL, 0.83 mmol) was added dropwise to **76** (110 mg, 0.28 mmol) in THF (1.2 mL) and toluene (1.2 mL) at 22 °C in a microwave tube under nitrogen. The resulting solution was stirred at 22 °C, then transferred to a microwave and heated at 150 °C for 30 minutes. Saturated Rochelle's salt (5 mL) was then added cautiously (care - gas evolved!) and water (20 mL) was added then the mixture was extracted with DCM (3 x 50 mL). The organics were concentrated then purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford **77** (88 mg, 86 %) as a white solid. ¹H NMR (400 MHz, DMSO) δ 2.42 - 2.44 (m, 3H), 2.45 (s, 3H), 3.76 - 3.81 (m, 2H), 4.33 (dd, *J* = 5.1, 6.6 Hz, 2H), 4.73 (s, 2H), 7.1 - 7.17 (m, 2H), 7.29 (d, *J* = 1.8 Hz, 1H), 7.65 (t, *J* = 7.7 Hz, 1H), 7.85 (d, *J* = 1.8 Hz, 1H), 8.51 (d, *J* = 0.7 Hz, 1H); *m/z*: ES⁺ [M+H]⁺ 368.

7-(5-Methyl-2-((1-methyl-1*H*-pyrazol-5-yl)amino)pyrimidin-4-yl)-2-((6-methylpyridin-2-yl)methyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one (26)

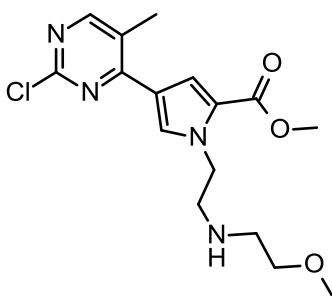


77 (78 mg, 0.21 mmol), 1-methyl-1*H*-pyrazol-5-amine (41 mg, 0.42 mmol), BrettPhos 3rd generation pre-catalyst (9.6 mg, 11 μmol) and cesium carbonate (103 mg, 0.53 mmol) were suspended in degassed *tert*-butanol (2 mL) under nitrogen in a microwave vial. The reaction was heated to 100 °C for 1 hour under microwave irradiation. The reaction mixture was diluted with EtOAc (100 mL), and washed with brine (50 mL). The aqueous layer was extracted with DCM (2x) and the combined organics were evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in

DCM. Pure fractions were evaporated to dryness to afford **26** (71 mg, 78 %) as a yellow foam. ^1H NMR (400 MHz, DMSO) δ 2.33 (s, 3H), 2.45 (s, 3H), 3.68 (s, 3H), 3.75 - 3.8 (m, 2H), 4.29 - 4.34 (m, 2H), 4.72 (s, 2H), 6.26 (d, J = 1.9 Hz, 1H), 7.12 (d, J = 7.8 Hz, 1H), 7.14 (d, J = 7.7 Hz, 1H), 7.25 (d, J = 1.7 Hz, 1H), 7.33 (d, J = 1.9 Hz, 1H), 7.6 - 7.68 (m, 2H), 8.24 (s, 1H), 9.07 (s, 1H); Purity 100% by LC-MS, m/z : ES^+ $[\text{M}+\text{H}]^+$ 429.

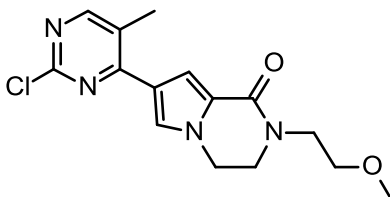
Synthesis of Compound 27

Methyl 4-(2-chloro-5-methylpyrimidin-4-yl)-1-(2-((2-methoxyethyl)amino)ethyl)-1H-pyrrole-2-carboxylate (78)



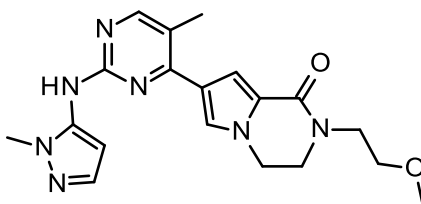
N-Ethyl-*N*-isopropylpropan-2-amine (0.069 mL, 0.40 mmol) was added to 2-methoxyethanamine (27 mg, 0.36 mmol), methyl 4-(2-chloro-5-methylpyrimidin-4-yl)-1-(2-oxoethyl)-1H-pyrrole-2-carboxylate (97 mg, 0.33 mmol) and magnesium sulfate (4 mg, 0.03 mmol) in THF (1.3 mL) at 22°C. The resulting mixture was stirred at 22 °C for 10 minutes. Sodium triacetoxyborohydride (98 mg, 0.46 mmol) was added, then the mixture was stirred for a further 20 hours. The reaction mixture was diluted with EtOAc (100 mL), and washed with saturated NaHCO_3 (50 mL). The aqueous layer was extracted with EtOAc (100 mL) and the combined organic layers were dried (MgSO_4) and concentrated. The crude product was purified by flash silica chromatography, elution gradient 0 to 6% MeOH in EtOAc. Pure fractions were evaporated to dryness to afford **78** (56 mg, 48.1 %) as a colourless gum. ^1H NMR (400 MHz, CDCl_3) δ 2.45 (s, 3H), 2.76 - 2.82 (m, 2H), 3.04 (t, J = 6.3 Hz, 2H), 3.34 (s, 3H), 3.43 - 3.49 (m, 2H), 3.85 (s, 3H), 4.50 (t, J = 6.3 Hz, 2H), 7.54 (d, J = 2.0 Hz, 1H), 7.72 (d, J = 2.0 Hz, 1H), 8.31 (s, 1H); m/z : ES^+ $[\text{M}+\text{H}]^+$ 353.

7-(2-Chloro-5-methylpyrimidin-4-yl)-2-(2-methoxyethyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one (79)



Trimethylaluminum (2M in toluene) (0.24 mL, 0.48 mmol) was added dropwise to **78** (56 mg, 0.16 mmol) in THF (0.6 mL) and toluene (0.6 mL) at 22 °C in a microwave tube under nitrogen. The resulting solution was stirred at 22 °C, then transferred to a microwave and heated at 150 °C for 30 minutes. Saturated Rochelle's salt (5 mL) was then added cautiously (care - gas evolved!) and water (20 mL) was added then the mixture was extracted with DCM (3 x 50 mL). The organics were concentrated then purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford **79** (41 mg, 81 %) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 2.47 (s, 3H), 3.36 (s, 3H), 3.63 (t, *J* = 4.9 Hz, 2H), 3.74 (t, *J* = 4.9 Hz, 2H), 3.85 (dd, *J* = 5.0, 6.8 Hz, 2H), 4.20 (dd, *J* = 5.0, 6.7 Hz, 2H), 7.40 (d, *J* = 1.7 Hz, 1H), 7.63 (d, *J* = 1.7 Hz, 1H), 8.32 (s, 1H); *m/z*: ES⁺ [M+H]⁺ 321.

2-(2-Methoxyethyl)-7-(5-methyl-2-((1-methyl-1*H*-pyrazol-5-yl)amino)pyrimidin-4-yl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one (27)

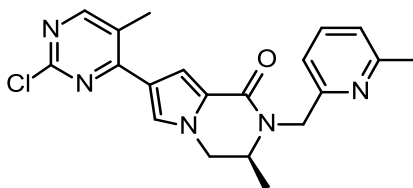


79 (41 mg, 0.13 mmol), 1-methyl-1*H*-pyrazol-5-amine (19 mg, 0.19 mmol), BrettPhos 3rd generation pre-catalyst (5.8 mg, 6.4 μmol) and cesium carbonate (104 mg, 0.32 mmol) were suspended in degassed *tert*-butanol (1.1 mL) under nitrogen in a microwave vial. The reaction was heated to 100 °C for 1 hour under microwave irradiation. The reaction mixture was diluted with EtOAc (100 mL), and washed with water (5 x 25 mL), brine (25 mL), dried (MgSO₄) and concentrated. The crude product was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford **27** (9 mg, 19 %) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 2.39 (s, 3H), 3.36 (s, 3H), 3.62 (t, *J* = 4.9 Hz, 2H), 3.73 (t, *J* =

4.9 Hz, 2H), 3.78 (s, 3H), 3.83 (dd, $J = 5.0, 6.7$ Hz, 2H), 4.15 - 4.2 (m, 2H), 6.30 (d, $J = 1.9$ Hz, 1H), 6.74 (s, 1H), 7.37 - 7.42 (m, 2H), 7.46 (d, $J = 1.9$ Hz, 1H), 8.16 (s, 1H); Purity 100% by LC-MS, m/z : $ES^+ [M+H]^+$ 382.

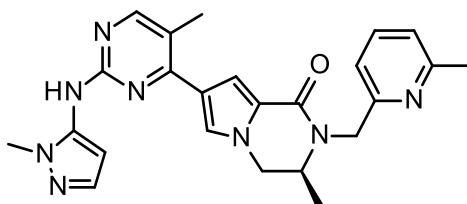
Synthesis of Compound 28

(*S*)-7-(2-Chloro-5-methylpyrimidin-4-yl)-3-methyl-2-((6-methylpyridin-2-yl)methyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2*H*)-one (80)



Sodium hydride (13 mg, 0.31 mmol) was added to (*S*)-7-(2-chloro-5-methylpyrimidin-4-yl)-3-methyl-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2*H*)-one (79 mg, 0.29 mmol) in DMF (3 mL) at 22 °C under nitrogen. The resulting suspension was stirred at RT for 30 minutes, then 2-(chloromethyl)-6-methylpyridine (0.038 mL, 0.31 mmol) was added. The resulting solution was stirred at 22 °C for 3 hours. LCMS indicated 91% product. The reaction mixture was quenched with saturated NH_4Cl (20 mL) and then the mixture extracted with DCM (2 x 20 mL) and evaporated to dryness to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0.5 to 3% MeOH in DCM. Pure fractions were evaporated to dryness to afford **80** (91 mg, 83 %) as a white solid. 1H NMR (400 MHz, DMSO) δ 1.15 (d, $J = 6.6$ Hz, 3H), 2.43 (s, 3H), 2.46 (s, 3H), 3.96 - 4.00 (m, 1H), 4.23 (dd, $J = 2.1, 13.1$ Hz, 1H), 4.30 (d, $J = 16.0$ Hz, 1H), 4.38 (dd, $J = 4.2, 13.1$ Hz, 1H), 5.13 (d, $J = 16.0$ Hz, 1H), 7.12 - 7.18 (m, 2H), 7.28 (d, $J = 1.7$ Hz, 1H), 7.65 (t, $J = 7.7$ Hz, 1H), 7.86 (d, $J = 1.6$ Hz, 1H), 8.50 (s, 1H); m/z : $ES^+ [M+H]^+$ 382.

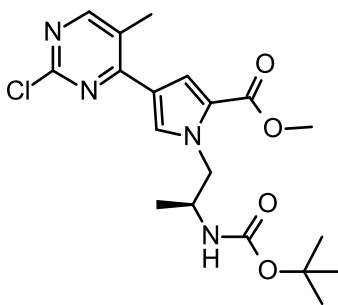
(*S*)-3-Methyl-7-(5-methyl-2-((1-methyl-1*H*-pyrazol-5-yl)amino)pyrimidin-4-yl)-2-((6-methylpyridin-2-yl)methyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2*H*)-one (28)



80 (89 mg, 0.21 mmol), 1-methyl-1*H*-pyrazol-5-amine (23 mg, 0.25 mmol) and cesium carbonate (150 mg, 0.45 mmol) were suspended in *tert*-butanol (3 mL) and de-gassed for 5 minutes, then BrettPhos 3rd generation pre-catalyst (9.3 mg, 10 μ mol) was added. The reaction was sealed in a microwave tube and heated to 100 °C in the microwave for 1 hour. LCMS indicated complete reaction. The reaction mixture was diluted with DCM (30 mL), and washed with brine (30 mL). The aqueous layer was extracted with DCM (2 x 30 mL) then combined organics were evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0.5 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford **28** (76 mg, 84 %) as a white solid. ¹H NMR (400 MHz, DMSO) δ 1.15 (d, *J* = 6.6 Hz, 3H), 2.32 (s, 3H), 2.46 (s, 3H), 3.68 (s, 3H), 3.94 - 3.98 (m, 1H), 4.20 (dd, *J* = 2.2, 13.0 Hz, 1H), 4.29 (d, *J* = 15.9 Hz, 1H), 4.36 (dd, *J* = 4.2, 13.0 Hz, 1H), 5.13 (d, *J* = 16.0 Hz, 1H), 6.26 (d, *J* = 1.8 Hz, 1H), 7.15 (dd, *J* = 4.6, 7.6 Hz, 2H), 7.25 (d, *J* = 1.6 Hz, 1H), 7.32 (d, *J* = 1.8 Hz, 1H), 7.61 - 7.67 (m, 2H), 8.23 (s, 1H), 9.06 (s, 1H); Purity 96.3% by LC-MS, *m/z*: ES⁺ [M+H]⁺ 443.

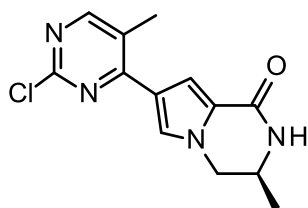
Synthesis of Compound 29

(S)-Methyl 1-(2-((*tert*-butoxycarbonyl)amino)propyl)-4-(2-chloro-5-methylpyrimidin-4-yl)-1*H*-pyrrole-2-carboxylate (81)



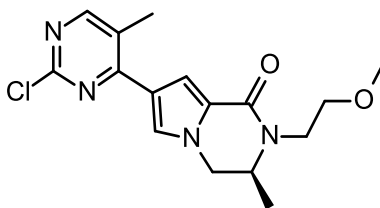
(*S*)-*tert*-Butyl 4-methyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (0.5 g, 2.1 mmol) was added to methyl 4-(2-chloro-5-methylpyrimidin-4-yl)-1*H*-pyrrole-2-carboxylate (0.43 g, 1.62 mmol), potassium carbonate (2.019 g, 14.61 mmol) and 1,4,7,10,13,16-hexaoxacyclooctadecane (0.107 g, 0.41 mmol) in 1,4-dioxane (20 mL) at 22°C under nitrogen. The resulting suspension was stirred at 50 °C for 20 hours. The mixture was diluted with water (50 mL) and the product extracted with EtOAc (3 x 70 mL). Organics were dried (Na₂SO₄) and concentrated to yield **81** (0.65 g, 98 %) as a white solid. ¹H NMR (400 MHz, DMSO) δ 1.08 (d, *J* = 6.6 Hz, 3H), 1.16 (s, 9H), 2.42 (s, 3H), 3.80 (s, 3H), 3.84 - 4.01 (m, 2H), 4.60 (dd, *J* = 1.0, 10.0 Hz, 1H), 6.77 (d, *J* = 8.8 Hz, 1H), 7.43 (s, 1H), 7.81 (s, 1H), 8.51 (s, 1H); *m/z*: ES⁺ [M+H]⁺ 409.

(S)-7-(2-Chloro-5-methylpyrimidin-4-yl)-3-methyl-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one (82)



Hydrogen chloride, 4.0M in dioxane (7.88 mL, 31.50 mmol) was added to **81** (0.644 g, 1.58 mmol) in methanol (5 mL) at 22 °C. The resulting mixture was stirred at 22 °C for 2 hours, then concentrated *in vacuo*. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 1M NH₃/MeOH. The solution was concentrated, then re-dissolved in DCM (4 mL), and ammonia, 7.0M in methanol (22.5 mL, 160 mmol) was added. The resulting mixture was stirred at 22 °C for 5 hours. The resulting suspension was filtered, and the solid was dried under vacuum to yield **82** (160 mg, 0.58 mmol, 37 %) as a yellow solid. The filtrate was concentrated to yield **82** (180 mg, 0.66 mmol, 42 %) as a yellow solid. ¹H NMR (400 MHz, DMSO) δ 1.20 (d, *J* = 6.0 Hz, 3H), 2.4 - 2.45 (m, 3H), 3.84 - 3.92 (m, 2H), 4.25 - 4.34 (m, 1H), 7.23 (d, *J* = 1.8 Hz, 1H), 7.81 (d, *J* = 1.8 Hz, 1H), 7.92 (s, 1H), 8.49 (d, *J* = 0.7 Hz, 1H); *m/z*: ES⁺ [M+H]⁺ 277.

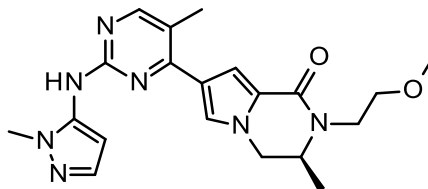
(S)-7-(2-Chloro-5-methylpyrimidin-4-yl)-2-(2-methoxyethyl)-3-methyl-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one (83)



Sodium hydride (13 mg, 0.31 mmol) was added to **82** (79 mg, 0.29 mmol) in DMF (3 mL) at 22 °C under nitrogen. The resulting suspension was stirred at RT for 30 minutes then 1-bromo-2-methoxyethane (0.03 mL, 0.31 mmol) was added. The resulting solution was stirred at 22 °C for 3 hours. LCMS indicated 68% product. The reaction mixture was quenched with saturated NH₄Cl (20 mL) and then the mixture extracted with DCM (2 x 20 mL) and evaporated to dryness to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0.5 to 3% MeOH in DCM. Pure fractions were evaporated to dryness to afford **83** (71 mg, 74 %) as a white solid. ¹H NMR (400 MHz, DMSO) δ 1.13 (d, *J* = 6.6 Hz, 3H), 2.42 (s, 3H), 3.17 - 3.25 (m, 1H), 3.28 (s, 3H), 3.44 - 3.56 (m, 2H), 3.92 - 4.04 (m, 2H), 4.20 (dd, *J* = 2.1, 13.1 Hz, 1H), 4.26

(dd, $J = 4.1, 13.2$ Hz, 1H), 7.23 (d, $J = 1.8$ Hz, 1H), 7.81 (d, $J = 1.8$ Hz, 1H), 8.49 (d, $J = 0.7$ Hz, 1H); m/z : ES^+ $[M+H]^+$ 335.

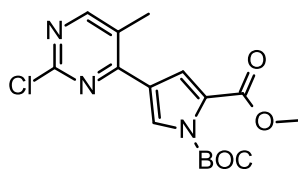
(S)-2-(2-Methoxyethyl)-3-methyl-7-(5-methyl-2-((1-methyl-1H-pyrazol-5-yl)amino)pyrimidin-4-yl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one (29)



83 (71 mg, 0.21 mmol), 1-methyl-1H-pyrazol-5-amine (25 mg, 0.25 mmol) and cesium carbonate (150 mg, 0.47 mmol) were suspended in *tert*-butanol (3 mL) and de-gassed for 5 minutes, then BrettPhos 3rd generation pre-catalyst (9.6 mg, 11 μ mol) was added. The reaction was sealed in a microwave tube and heated to 100 °C in the microwave for 1 hour. LCMS indicated complete reaction. The reaction mixture was diluted with DCM (30 mL), and washed with brine (30 mL). The aqueous layer was extracted with DCM (2 x 30 mL) then combined organics were evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0.5 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford **29** (56 mg, 67 %) as a white solid. ¹H NMR (400 MHz, DMSO) δ 1.13 (d, $J = 6.6$ Hz, 3H), 2.31 (s, 3H), 3.15 - 3.26 (m, 1H), 3.28 (s, 3H), 3.44 - 3.56 (m, 2H), 3.68 (s, 3H), 3.92 - 3.98 (m, 2H), 4.18 (dd, $J = 1.8, 12.9$ Hz, 1H), 4.24 (dd, $J = 4.1, 12.9$ Hz, 1H), 6.25 (d, $J = 1.8$ Hz, 1H), 7.19 (d, $J = 1.6$ Hz, 1H), 7.32 (d, $J = 1.8$ Hz, 1H), 7.60 (d, $J = 1.6$ Hz, 1H), 8.22 (s, 1H), 9.05 (s, 1H); Purity 100% by LC-MS, m/z : ES^+ $[M+H]^+$ 396.

Synthesis of Compound 35

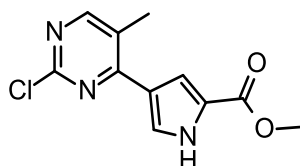
1-*tert*-Butyl 2-methyl 4-(2-chloro-5-methylpyrimidin-4-yl)-1H-pyrrole-1,2-dicarboxylate (30)



Tetrakis(triphenylphosphine)palladium(0) (0.98 g, 0.85 mmol) was added to a de-gassed solution of 2,4-dichloro-5-methylpyrimidine (4.6 g, 28 mmol), 1-*tert*-butyl 2-methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrole-1,2-dicarboxylate (10 g, 28 mmol) and potassium phosphate (18 g, 85 mmol) in dioxane (120

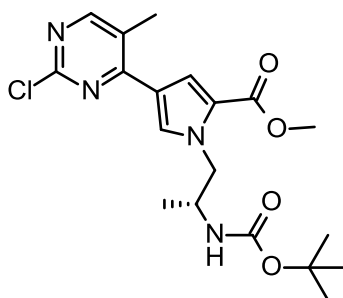
ml) and water (30 ml) at 22°C under nitrogen. The resulting solution was stirred at 80 °C for 4 h. The reaction mixture was concentrated and diluted with EtOAc (150 mL) and brine (100 mL). The layers were partitioned, then the aqueous extracted with further EtOAc (2 x 150 mL). Combined organics were evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution solvent 5-50% EtOAc in heptane. Pure fractions were evaporated to dryness to afford **30** (6.4 g, 64 %) as a white solid. ¹H NMR (400 MHz, DMSO) δ 1.56 (s, 9H), 2.41 – 2.47 (m, 3H), 3.83 (s, 3H), 7.39 (d, *J* = 1.9 Hz, 1H), 8.01 (d, *J* = 1.9 Hz, 1H), 8.61 (d, *J* = 0.7 Hz, 1H); *m/z*: ES⁺ [M-BOC+H]⁺ 252.

Methyl 4-(2-chloro-5-methylpyrimidin-4-yl)-1H-pyrrole-2-carboxylate (31)



Hydrogen chloride, 4.0M in dioxane (45 mL, 180 mmol) was added to **30** (6.4 g, 18 mmol) in methanol (40 mL) at 22°C. The resulting mixture was stirred at 22 °C for 18 h. The white solid was collected by filtration and washed with diethyl ether. The solid was added to water (150 mL) and EtOH (20 mL) and the suspension was stirred for 30 minutes, then 2M sodium carbonate (40 mL) was added. The product was extracted with DCM (3 x 200 mL). Combined organics were concentrated to yield **31** (4.6 g, 100 %) as a white solid. ¹H NMR (400 MHz, DMSO) δ 2.38 – 2.45 (m, 3H), 3.81 (s, 3H), 7.39 (d, *J* = 1.7 Hz, 1H), 7.72 (d, *J* = 1.7 Hz, 1H), 8.50 (s, 1H), 12.64 (s, 1H); *m/z*: ES⁺ [M+H]⁺ 252.

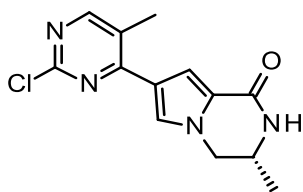
(R)-Methyl 1-(2-((*tert*-butoxycarbonyl)amino)propyl)-4-(2-chloro-5-methylpyrimidin-4-yl)-1H-pyrrole-2-carboxylate (32)



Potassium carbonate (40 g, 287 mmol) was added to (*R*)-*tert*-butyl 4-methyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (9.8 g, 42 mmol), **31** (8 g, 32 mmol) and 18-Crown-6 (2.1 g, 8 mmol) in 1,4-dioxane (100 mL) at

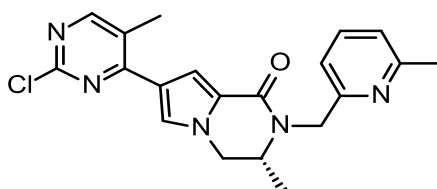
22°C under nitrogen. The resulting mixture was stirred at 100 °C for 16 h. The mixture was diluted with ethyl acetate (600 mL) and washed with water (3 x 300 mL), saturated brine (200 mL), dried (MgSO₄) and concentrated. The crude product was purified by flash silica chromatography, elution gradient 0 to 60% EtOAc in heptane. Pure fractions were evaporated to dryness to afford **32** (12 g, 93 %) as a white solid. ¹H NMR (400 MHz, DMSO) δ 1.08 (d, *J* = 6.6 Hz, 3H), 1.16 (s, 9H), 2.42 (s, 3H), 3.80 (s, 3H), 3.83 – 4.02 (m, 2H), 4.60 (dd, *J* = 3.2, 12.9 Hz, 1H), 6.77 (d, *J* = 9.0 Hz, 1H), 7.43 (s, 1H), 7.81 (s, 1H), 8.51 (s, 1H); *m/z*: ES⁺ [M+H]⁺ 409.

(*R*)-7-(2-Chloro-5-methylpyrimidin-4-yl)-3-methyl-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (33)



Trifluoroacetic acid (30 mL) was added to **32** (7.6 g, 19 mmol) in DCM (53 mL) at 22°C. The resulting mixture was stirred at 22 °C for 2 h. The resulting solution was concentrated then purified by ion exchange chromatography. The desired product was eluted from the column using 1M ammonia/methanol solution then evaporated to dryness to afford (*R*)-methyl 1-(2-aminopropyl)-4-(2-chloro-5-methylpyrimidin-4-yl)-1*H*-pyrrole-2-carboxylate as an off white solid. This material was dissolved in DCM (50 mL) then 7M ammonia/methanol solution (100 mL) was added and the solution was stirred at ambient temperature for a further 18 h. The reaction was concentrated and the residue was triturated with ether to yield **33** (4.90 g, 95 %) as a white solid. ¹H NMR (400 MHz, DMSO) δ 1.20 (d, *J* = 5.9 Hz, 3H), 2.42 (s, 3H), 3.83 – 3.93 (m, 2H), 4.25 – 4.35 (m, 1H), 7.23 (d, *J* = 1.7 Hz, 1H), 7.81 (d, *J* = 1.7 Hz, 1H), 7.92 (s, 1H), 8.49 (s, 1H); *m/z*: ES⁺ [M+H]⁺ 277.

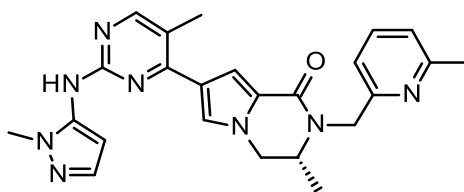
(*R*)-7-(2-Chloro-5-methylpyrimidin-4-yl)-3-methyl-2-((6-methylpyridin-2-yl)methyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (34)



Sodium hydride (60% dispersion in mineral oil) (1.1 g, 27 mmol) was added to **33** (7 g, 25 mmol) in DMF (150 mL) at 22 °C under nitrogen. The resulting suspension was stirred at RT for 30 minutes. 2-(Chloromethyl)-6-methylpyridine (3.7 g, 26 mmol) in DMF (10 mL) was added and the resulting solution was stirred at 22 °C for

18 h. The reaction mixture was diluted with ethyl acetate (400 mL) and quenched with saturated NH_4Cl (400 mL). The organic layer was washed with brine (400 mL) water (400 mL) and concentrated. A small amount of solid was observed in the final aqueous layer, which was isolated by filtration (confirmed to be pure product) then added to the crude product. The crude product was stirred in diethyl ether (150 mL) for 1 hour, then collected by filtration and dried under vacuum to yield **34** (7.9 g, 83 %) as a white solid. ^1H NMR (400 MHz, DMSO) δ 1.15 (d, J = 6.6 Hz, 3H), 2.43 (s, 3H), 2.46 (s, 3H), 3.98 (ddd, J = 2.4, 4.2, 6.6 Hz, 1H), 4.23 (dd, J = 2.3, 13.1 Hz, 1H), 4.30 (d, J = 16.0 Hz, 1H), 4.38 (dd, J = 4.3, 13.1 Hz, 1H), 5.13 (d, J = 16.0 Hz, 1H), 7.15 (t, J = 6.9 Hz, 2H), 7.28 (d, J = 1.7 Hz, 1H), 7.64 (t, J = 7.7 Hz, 1H), 7.85 (d, J = 1.7 Hz, 1H), 8.50 (s, 1H); m/z : ES^+ $[\text{M}+\text{H}]^+$ 382.

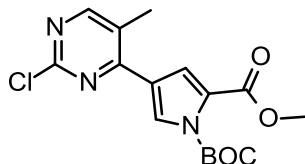
(R)-3-Methyl-7-(5-methyl-2-((1-methyl-1H-pyrazol-5-yl)amino)pyrimidin-4-yl)-2-((6-methylpyridin-2-yl)methyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one (35)



34 (130 mg, 0.35 mmol), 1-methyl-1H-pyrazol-5-amine (37 mg, 0.38 mmol) and caesium carbonate (250 mg, 0.77 mmol) were suspended in *tert*-butanol (3 mL) and de-gassed for 5 minutes, then BrettPhos 3rd generation pre-catalyst (16 mg, 0.02 mmol) was added. The reaction was heated to 83 °C for 2 h. LCMS indicated complete reaction. The reaction mixture was diluted with EtOAc (30 mL), and washed with brine (30 mL). The aqueous layer was extracted with DCM (2 x 30 mL) then combined organics were evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0.5 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford **35** (120 mg, 77 %) as a yellow solid. ^1H NMR (400 MHz, DMSO- d_6) δ 1.15 (d, J = 6.6 Hz, 3H), 2.32 (s, 3H), 2.46 (s, 3H), 3.68 (s, 3H), 3.96 (dt, J = 3.4, 6.7 Hz, 1H), 4.20 (dd, J = 2.3, 13.0 Hz, 1H), 4.29 (d, J = 15.9 Hz, 1H), 4.36 (dd, J = 4.2, 13.0 Hz, 1H), 5.13 (d, J = 16.0 Hz, 1H), 6.26 (d, J = 1.8 Hz, 1H), 7.15 (dd, J = 4.6, 7.6 Hz, 2H), 7.25 (d, J = 1.7 Hz, 1H), 7.32 (d, J = 1.9 Hz, 1H), 7.61 – 7.68 (m, 2H), 8.23 (s, 1H), 9.06 (s, 1H); ^{13}C NMR (176 MHz, DMSO- d_6) 16.8, 16.9, 23.9, 35.3, 48.7, 48.8, 51.5, 97.8, 112.3, 116.6, 118.2, 121.5, 122.8, 124.2, 126.0, 137.0, 137.1, 138.7, 156.9, 157.3, 157.5, 158.5, 158.6, 159.7; Purity 99.7% by LC-MS, m/z : ES^+ $[\text{M}+\text{H}]^+$ 443; HRMS (ES^+) for $\text{C}_{24}\text{H}_{27}\text{N}_8\text{O}$ (MH^+): calcd 443.23023; found 443.23032.

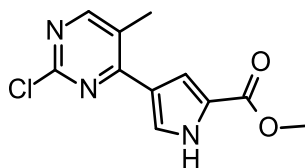
Synthesis of Compound 36

1-*tert*-Butyl 2-methyl 4-(2-chloro-5-methylpyrimidin-4-yl)-1*H*-pyrrole-1,2-dicarboxylate (**84**)



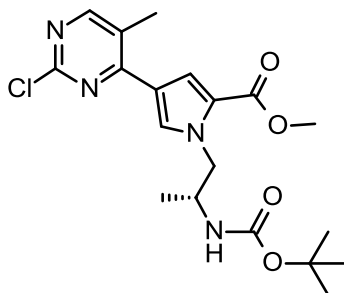
$\text{Pd}(\text{PPh}_3)_4$ (0.98 g, 0.85 mmol) was added to a de-gassed solution of 2,4-dichloro-5-methylpyrimidine (4.6 g, 28 mmol), 1-*tert*-butyl 2-methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrrole-1,2-dicarboxylate (10 g, 28 mmol) and potassium phosphate (18 g, 85 mmol) in Dioxane (120 mL) and water (30 mL) at 22 °C under nitrogen. The resulting solution was stirred at 80 °C for 4 hours. The reaction mixture was concentrated and diluted with EtOAc (150 mL), and brine (100 mL). The layers were partitioned, then the aqueous extracted with further EtOAc (2 x 150 mL). Combined organics were evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution solvent 5-50% EtOAc in heptane. Pure fractions were evaporated to dryness to afford **84** (6.4 g, 64 %) as a white solid. ^1H NMR (400 MHz, DMSO) δ 1.56 (s, 9H), 2.41 - 2.47 (m, 3H), 3.83 (s, 3H), 7.39 (d, J = 1.9 Hz, 1H), 8.01 (d, J = 1.9 Hz, 1H), 8.61 (d, J = 0.7 Hz, 1H). m/z : ES^+ [M-BOC+H] $^+$ 252.

Methyl 4-(2-chloro-5-methylpyrimidin-4-yl)-1*H*-pyrrole-2-carboxylate (**85**)



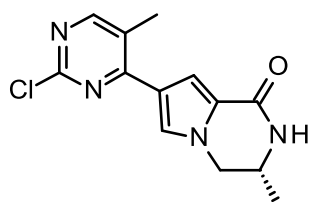
Hydrogen chloride, 4.0M in dioxane (45.1 mL, 180.51 mmol) was added to **84** (6.4 g, 18 mmol) in methanol (40 mL) at 22 °C. The resulting mixture was stirred at 22 °C for 18 hours. The white solid was collected by filtration and washed with diethyl ether. The solid was added to water (150 mL) and EtOH (20 mL) and the suspension was stirred for 30 minutes, then 2M sodium carbonate (40 mL) was added. The product was extracted with DCM (3 x 200 mL). Combined organics were concentrated to yield **85** (4.6 g, 99 %) as a white solid. ^1H NMR (400 MHz, DMSO) δ 2.41 (s, 3H), 3.80 (s, 3H), 7.39 (d, J = 1.7 Hz, 1H), 7.72 (d, J = 1.7 Hz, 1H), 8.50 (s, 1H), 12.64 (s, 1H); m/z : ES^+ [M+H] $^+$ 252.

(R)-Methyl 1-(2-((*tert*-butoxycarbonyl)amino)propyl)-4-(2-chloro-5-methylpyrimidin-4-yl)-1*H*-pyrrole-2-carboxylate (86**)**



Potassium carbonate (3.9 g, 29 mmol) was added to (*R*)-*tert*-butyl 4-methyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (0.978 g, 4.12 mmol), **85** (0.80 g, 3.2 mmol) and 1,4,7,10,13,16-hexaoxacyclooctadecane (0.21 g, 0.79 mmol) in 1,4-dioxane (10 mL) at 22°C under nitrogen. The resulting mixture was stirred at 100 °C for 16 hours. The mixture was cooled to ambient temperature; 1M citric acid (50 mL) was added and the product was extracted with EtOAc (2 x 50 mL); the combined extracts were washed with saturated brine (100 mL), dried over MgSO₄ and evaporated to dryness to afford a yellow gum. The crude product was purified by flash silica chromatography, elution gradient 0 to 40% EtOAc in heptane. Pure fractions were evaporated to dryness to afford **86** (0.92 g, 72%) as a white gum. ¹H NMR (400 MHz, DMSO) δ 0.89 (d, *J* = 6.6 Hz, 3H), 0.97 (s, 9H), 2.23 (s, 3H), 3.61 (s, 3H), 3.67 – 3.82 (m, 2H), 4.41 (dd, *J* = 3.0, 12.9 Hz, 1H), 6.58 (d, *J* = 9.0 Hz, 1H), 7.24 (s, 1H), 7.62 (s, 1H), 8.32 (s, 1H); *m/z*: ES⁺ [M+H]⁺ 409.

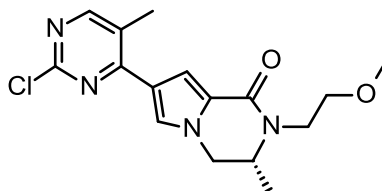
(R)-7-(2-Chloro-5-methylpyrimidin-4-yl)-3-methyl-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (87**)**



TFA (2 mL) was added to **86** (0.93 g, 2.3 mmol) in DCM (5 mL) at 22°C. The resulting mixture was stirred at 22 °C for 2 hours. The resulting suspension was concentrated then purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 1M NH₃/MeOH and pure fractions were evaporated to dryness to afford (*R*)-methyl 1-(2-aminopropyl)-4-(2-chloro-5-methylpyrimidin-4-yl)-1*H*-pyrrole-2-carboxylate as an off white solid. This material was dissolved in DCM (5 mL) and added 1M ammonia/methanol solution (5 mL) and stirred at ambient temperature for a further 16 hours. The solvents were removed *in vacuo* to give **87** (0.63 g, 100%) as an off white solid. ¹H NMR (400 MHz, DMSO) δ 1.20 (d, *J* =

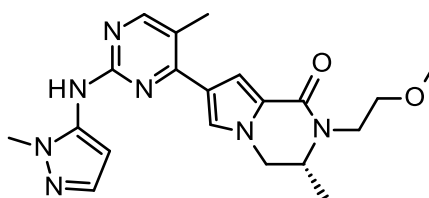
5.8 Hz, 3H), 2.42 (s, 3H), 3.83 – 3.92 (m, 2H), 4.25 - 4.34 (m, 1H), 7.23 (d, $J = 1.8$ Hz, 1H), 7.81 (d, $J = 1.7$ Hz, 1H), 7.92 (s, 1H), 8.49 (s, 1H); m/z : ES^+ $[M+H]^+$ 277.

(*R*)-7-(2-Chloro-5-methylpyrimidin-4-yl)-2-(2-methoxyethyl)-3-methyl-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (88)



Sodium hydride (0.04 g, 0.99 mmol) was added to **87** (0.25 g, 0.90 mmol) in DMF (4.1 mL) at $<5^{\circ}C$ under nitrogen. The resulting suspension was stirred at RT for 30 minutes. 1-bromo-2-methoxyethane (0.093 mL, 0.99 mmol) was added and the resulting solution stirred at RT for 18 hours. The reaction mixture was quenched with saturated NH_4Cl and then the mixture extracted twice with DCM, combined organic layers were washed with saturated brine, passed through a phase separating cartridge and evaporated to dryness to afford crude product. The crude product was purified by flash silica (12g, grace) chromatography, elution gradient 10 to 100% EtOAc in heptane. Pure fractions were evaporated to dryness to afford **88** (0.22 g, 73.1 %) as a white solid. 1H NMR (400 MHz, DMSO) δ 1.13 (d, $J = 6.6$ Hz, 3H), 2.43 (s, 3H), 3.16 - 3.27 (m, 1H), 3.28 (s, 3H), 3.42 - 3.63 (m, 2H), 3.86 - 4.12 (m, 2H), 4.14 - 4.35 (m, 2H), 7.23 (d, $J = 1.8$ Hz, 1H), 7.82 (d, $J = 1.8$ Hz, 1H), 8.50 (d, $J = 0.7$ Hz, 1H); m/z : ES^+ $[M+H]^+$ 335.

(*R*)-2-(2-Methoxyethyl)-3-methyl-7-(5-methyl-2-((1-methyl-1*H*-pyrazol-5-yl)amino)pyrimidin-4-yl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (36)

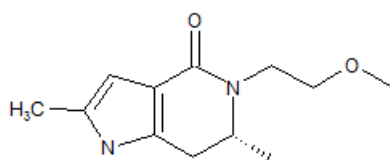


88 (81 mg, 0.24 mmol), 1-methyl-1*H*-pyrazol-5-amine (25.8 mg, 0.27 mmol) and sodium 2-methylpropan-2-olate (46.5 mg, 0.48 mmol) were suspended in *tert*-butanol (2 mL) in a microwave, and de-gassed for 10 minutes, then BrettPhos 3rd generation pre-catalyst (10.97 mg, 0.01 mmol) was added, and the microwave tube was sealed. The reaction was heated to $80^{\circ}C$ for 1 hour in the microwave reactor and cooled to RT. LCMS

indicated complete reaction with some evidence of Chloro hydrolysis. The reaction mixture was diluted with DCM (20 mL), and washed with water (10 mL) and saturated NaHCO₃ (10 mL). The aqueous layer was extracted with DCM (2 x 20 mL) then combined organics were passed through a phase separating cartridge and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0-7% MeOH in DCM. Pure fractions were evaporated to dryness to afford **36** (45 mg, 47 %) as a pale yellow solid. ¹H NMR (400 MHz, DMSO) δ 1.13 (d, J = 6.6 Hz, 3H), 2.32 (s, 3H), 3.13 - 3.25 (m, 1H), 3.28 (s, 3H), 3.4 - 3.61 (m, 2H), 3.68 (s, 3H), 3.87 - 4.06 (m, 2H), 4.12 - 4.35 (m, 2H), 6.26 (d, J = 1.7 Hz, 1H), 7.20 (s, 1H), 7.33 (d, J = 1.7 Hz, 1H), 7.61 (s, 1H), 8.23 (s, 1H), 9.06 (s, 1H); Purity 97.3% by LC-MS, m/z : ES⁺ [M+H]⁺ 396.

Experimental S2 – VCD Analysis of compound **16**

The experimental VCD spectrum of enantiomer **16** was compared to the DFT calculated spectra for both enantiomers. The experimental spectrum obtained on **16** fits satisfactorily with the calculated spectrum for the (R) enantiomer indicating this stereochemistry.

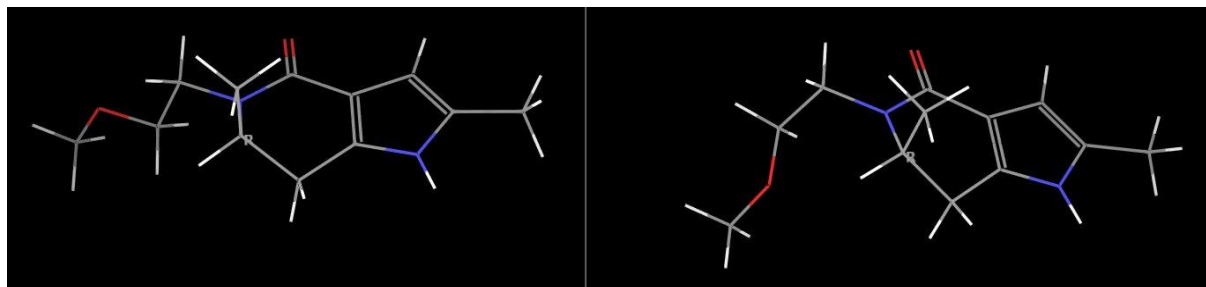


Truncated version used in calculations

The solid sample was easily dissolved in a small volume of CDCl_3 (8 mg in 100 μl). The solution was transferred to a 0.100 mm BaF_2 cell and a VCD spectrum acquired for six hours in a Bruker PMA50 instrument. The resolution was 4 cm^{-1} . Before comparison to the calculated spectra, a blank spectrum of CDCl_3 in the same cell was subtracted.

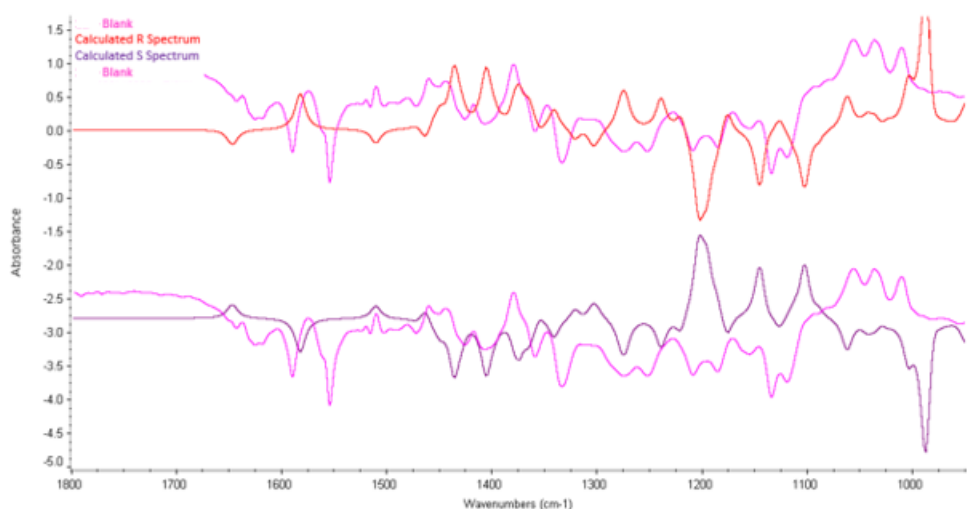
Computational Spectral Simulations: A Monte Carlo molecular mechanics search for low energy geometries was conducted for a truncated version of the *R* enantiomer. *MacroModel* within the *Maestro* graphical interface (Schrödinger Inc.) was used to generate 30 starting coordinates for conformers. All conformers within 5 kcal/mole of the lowest energy conformer were used as starting point for density functional theory (DFT) minimizations within *Gaussian09* (1). Optimized structures, harmonic vibrational frequencies/intensities, VCD rotational strengths, and free energies at STP (including zero-point energies) were determined at B3LYP/6-311++G** level of theory. Two unique conformations were found which differed only in the orientation of the ether side chain. An average spectrum was computed from these individual VCD spectra according to their Boltzmann distribution. In these simulations, an in-house program was used to fit Lorentzian line shapes (12 cm^{-1} line width) to the computed spectra thereby allowing direct comparisons between simulated and experimental spectra. The corresponding simulated spectrum of the (*S*) enantiomer was obtained by inversion of the (*R*) spectrum.

Two conformations contributing to the calculated VCD spectrum in the proportions 0.75 (left) to 0.25 (right)



Fit between calculated and experimental spectra: The fit between simulated spectra and experimental spectrum is shown in Figure 3. As there is only a single experimental spectrum, this was compared to both simulated spectra. There is a fair match between the calculated (*R*) spectrum and **16**. In particular, the positive peaks between 950 and 1050 cm^{-1} , the negative peaks between 1100 and 1200 cm^{-1} and the positive peaks between 1380 and 1450 cm^{-1} all fit better with (*R*) enantiomer.

Comparison of simulated spectra for the *R* enantiomer (red) and the *S* enantiomer (purple) and the single experimental spectrum of **16 (pink)**



Reference

1. Gaussian 09, Revision D.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2013.)