Supporting Information.

Experimental Section: Summary scheme

General experimental details: All solvents and chemicals used were reagent grade. Flash column chromatography was carried out using prepacked silica cartridges (from 4 g up to 330 g) from RediSep, Biotage, or Crawford and eluted using an Isco Companion system. Purity and characterization of compounds were established by a combination of liquid chromatography-mass spectroscopy (LC-MS) and NMR analytical techniques and was >95% for all compounds. $^1$H NMR were recorded on a Bruker Avance DPX400 (400 MHz) and were determined in CDCl$_3$ or DMSO-d$_6$. $^{13}$C NMR spectra were recorded at 101 or 175 MHz. Chemical shifts are reported in ppm relative to tetramethylsilane (TMS) (0.00 ppm) or solvent peaks as the internal reference and coupling constant (J) values are reported in Hertz (Hz). Splitting patterns are indicated as follows: s, singlet; d, doublet; t, triplet; m, multiplet. Merck precoated thin layer chromatography (TLC) plates (silica gel 60 F$_{254}$, 0.25 mm, art. 5715) were used for TLC analysis. Solutions were dried over anhydrous magnesium sulfate, and solvent was removed by rotary evaporation under reduced pressure. Optical rotations were measured on a polarimeter at a wavelength of 589 nM corresponding to the sodium D-line in solutions of methanol.
A slurry of sodium bicarbonate (4.39 g, 52.25 mmol) in water (20 mL) was added to (R)-2-(2-methylpiperazin-1-yl)pyrimidin-5-ol dihydrochloride (3.49 g, 13.06 mmol) in CH2Cl2 (70 mL) at 0 °C. A solution of cyanogen bromide (1.66 g, 15.68 mmol) in CH2Cl2 (10 mL) was added and the resulting suspension was stirred at 0 °C for 30 minutes and then at room temperature for 30 minutes. The mixture was washed with saturated aqueous sodium bicarbonate (50 mL) and the aqueous layer acidified and extracted into EtOAc and the combined organics then dried over Na2SO4, filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in CH2Cl2. Pure fractions were evaporated to dryness to afford (R)-4-(5-hydroxy-2-methylpiperazin-1-yl)pyrimidin-5-ol (5.70 g, 59%) as a white solid.

**HRMS (ESI) calc. for C19H18O2N8F3(M+H)+ 447.1499 found 447.1497. [a]D 22 -46.8.**

(R)-4-(5-hydroxy-2-methylpiperazin-1-yl)pyrimidin-5-ol (b).

Cesium carbonate (5.49 g, 16.86 mmol) was added to (R)-4-(5-hydroxy-2-methylpiperazin-1-yl)pyrimidin-5-ol (3.14 g, 58%) in DMF (60 mL). The reaction mixture was stirred at 80 °C for 70 hours. The reaction mixture was quenched with water (15 mL), extracted with EtOAc (2 x 20 mL), the organic layer was dried over MgSO4, filtered and evaporated to afford a beige solid that was purified by flash silica chromatography, elution gradient 10 to 30% EtOAc in CH2Cl2. The oil was triturated with isohexane/Et2O to give a solid which was collected by filtration and dried under vacuum in vacuo. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% EtOAc in CH2Cl2. The resulting solution was diluted with ethyl acetate (20 mL) and washed with water (25 mL) then brine (2 x 50 mL) and concentrated in vacuo. The crude product was purified by flash silica chromatography, elution gradient 0 to 30% EtOAc in heptane. Pure fractions were evaporated to dryness to afford (R)-2-(4-(5-isopropyl-1,2,4-oxadiazol-3-yl)-2-methylpiperazin-1-yl)pyrimidin-5-ol (0.12 g, 38%) as a white solid.

**HRMS (ESI) calc. for C19H21O2N6(M+H)+ 305.1720 found 305.1719.**
(R)-4-((2-(4-(5-isopropyl-1,2,4-oxadiazol-3-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)methyl)nicotinonitrile (2) was assessed to have a chiral purity $>99\%$ based on HPLC analysis with comparison to the racemate (Column: $5\mu$m Chiralpak AD-H (250mm x 4.6mm); Eluent: iso-Hexane/IPA/TEA 80/20/0.1; Flowrate: 1 ml/min; Runtime 30 minutes).

Method A: Zinc chloride (1M in Et$_2$O, 22.48 mL, 22.48 mmol) was added to 2,2,2-trifluoro-N-hydroxyacetimidamide (1.766 g, 13.79 mmol) and (R)-4-(5-hydroxypyrinidin-2-yl)-3-methylpiperazine-1-carbonitrile (2.24 g, 10.22 mmol) in THF (45 mL) and ethyl acetate (50 mL) over a period of 10 minutes under nitrogen. The resulting solution was stirred at 20 °C for 24 hours. All volatiles were removed under reduced pressure and the residue azeotroped with toluene (50 mL). The material was dissolved in ethanol (100 mL) then concentrated hydrochloric acid (10 mL) was added and the resulting solution was stirred at 110 °C for 18 hours. All volatiles were removed under reduced pressure and the residue centrifuged with toluene (50 mL). 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 (R)-4-((2-(4-(5-isopropyl-1,2,4-oxadiazol-3-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)methyl)nicotinonitrile (0.045 g, 22%) as a white solid.

HRMS (ESI) calc. for C$_{21}$H$_{25}$O$_2$N$_8$F$_3$ (M+H)$^+$ 447.1499; [a]$^\circ$D = 7.0 Hz, 6H), 1.25 (d, $J$ = 6.5 Hz, 3H); LRMS (ES+) m/z (M+H)$^+$ = 331.

Method B: Potassium tert-butoxide (127 mg, 1.14 mmol) was added to (R)-(2)-(2-methyl-4-(3-trifluoromethyl)-1,2,4-oxadiazol-3-yl)piperazin-1-yl)pyrimidin-5-ol (125 mg, 0.38 mmol) and hydroxylamine hydrochloride (79 mg, 1.14 mmol) in DMF (3 mL) under nitrogen. The resulting solution was stirred at 110 °C for 18 hours. All volatiles were removed under reduced pressure and the residue azeotroped with toluene (50 mL). 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 (R)-4-((2-(2-methyl-4-(3-trifluoromethyl)-1,2,4-oxadiazol-3-yl)piperazin-1-yl)pyrimidin-5-yl)oxy)methyl)nicotinonitrile (25 mg, 20%) as a colourless gum.

HRMS (ESI) calc. for C$_{21}$H$_{23}$O$_2$N$_8$F$_3$ (M+H)$^+$ 421.2092. [a]$^\circ$D = 18 -67.6.

(R)-2-(2-methyl-1,2,4-oxadiazol-5-yl)piperazin-1-yl)pyrimidin-5-ol (d).
Zinc chloride (1 M in Et2O; 5.07 mL, 5.07 mmol) was added to (R)-4-(5-hydroxyprazinimid-2-yl)-3-methylpiperazine-1-carbinitrile (505 mg, 2.30 mmol) and N-hydroxyisobutryramide (318 mg, 3.11 mmol) in THF (7.0 mL) and ethyl acetate (9.0 mL) over a period of 10 minutes under nitrogen. The resulting solution was stirred at 20 °C for 3 hours. Solvent was removed in vacuo and the residue was dried under vacuum to give a pale yellow foam. This was dissolved in ethanol (20 mL) and concentrated hydrochloric acid (2.5 mL) was added. The resulting solution was stirred at 100 °C for 18 hours. It was cooled, concentrated in vacuo, azeotroped with toluene and adsorbed onto silica. The crude product was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in CH2Cl2. Pure fractions were evaporated to dryness to afford (R)-2-(4-(3-isopropyl-1,2,4-oxadiazol-5-yl)-2-methylpiperazin-1-yl)pyrimidin-5-ol (56 mg, 19%) as a yellow oil.

Cesium carbonate (4.75 g, 14.59 mmol) was added to (R)-2(4-(3-isopropyl-1,2,4-oxadiazol-5-yl)-2-methylpiperazin-1-yl)pyrimidin-5-ol (1.11 g, 3.65 mmol) and 4-(chloromethyl)nicotinonitrile (4.80 g, 31.46 mmol) in acetonitrile (80 mL). The resulting suspension was stirred at 20 °C for 18 hours. It was then concentrated in vacuo and adsorbed onto silica. The crude product was purified by flash silica chromatography, elution gradient 0 to 100% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford the final product as a colourless gum (1.16 g). This was triturated overnight with diethyl ether (15 mL) to give (R)-4-(2-(4-(3-isopropyl-1,2,4-oxadiazol-5-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yloxy)methyl)nicotinonitrile (4).
Sodium azide (0.192 mL, 5.47 mmol) was added to triethylamine hydrochloride (0.753 g, 5.47 mmol) and (R)-4-(5-hydroxypyrimidin-2-yl)-3-methylpiperazine-1-carbonitrile (0.4 g, 1.82 mmol) in toluene (20 mL) under nitrogen. The resulting suspension was stirred at 130 °C for 18 hours and cooled to room temperature. The reaction mixture was diluted with CH2Cl2 (50 mL), washed sequentially with water (10 mL) and saturated NaHCO3 (10 mL). The organic layer was dried over MgSO4, filtered and evaporated to leave a white suspension. The suspension was extracted with CH2Cl2 (2 x 50 mL) and the combined organics dried over Na2SO4, filtered and evaporated to afford crude product (300 mg, 29%).


Hydroxylamine hydrochloride (0.919 g, 13.23 mmol) was added to (R)-4-(5-hydroxypyrimidin-2-yl)-3-methylpiperazine-1-carbonitrile (1.45 g, 6.61 mmol) and sodium carbonate (0.820 g, 6.61 mmol) in DMF (20 mL) at 20 °C. The resulting suspension was stirred at 80 °C for 30 minutes. Toluene (18 mL) was added, followed by pyridine (2.14 mL, 26.4 mmol) and difluoroacetic anhydride (3.29 mL, 26.4 mmol). The reaction was stirred at 80 °C for 1 hour. The reaction was cooled and the toluene evaporated. Ethyl acetate was added and the mixture was washed with 2M HCl, and further extracted with CH2Cl2 (2 x 30 mL). A solid precipitated into the organic layer and a few drops of methanol were added to re-dissolve it. The aqueous layer was extracted again with CH2Cl2 (3 x 100 mL). A white solid precipitated and this was filtered off and washed sequentially with water (10 mL) and saturated brine (10 mL). The organic layer was dried over MgSO4, filtered and evaporated to afford (R)-2-(4-(5-isopropyl-1,3,4-oxadiazol-2-yl)-2-methylpiperazin-1-yl)pyrimidin-5-ol (54.0 mg, 71%) as a yellow solid.

washed with water and brine, dried over Na₂SO₄, filtered and evaporated to give crude product which was purified by flash silica chromatography, elution gradient 10 to 30% EtOAc in CH₂Cl₂. Pure fractions were evaporated to dryness to afford (R)-2-(4-(5-(difluoromethyl)-1,2,4-oxadiazol-3-yl)-2-methylpiperazin-1-yl)pyrimidin-5-ol (1.80 g, 87%) as a pale yellow oil which solidified on standing.

**1H NMR** (400 MHz, CDCl₃) δ 8.13 (s, 2H), 6.65 (t, J = 52.4 Hz, 1H), 6.01 (s, 1H), 4.94 – 4.81 (m, 1H), 4.46 – 4.34 (m, 1H), 4.07 – 3.97 (m, 1H), 3.87 (dd, J = 12.8, 1.7 Hz, 1H), 3.39 – 3.26 (m, 2H), 3.14 (td, J = 12.3, 3.7 Hz, 1H), 1.23 (d, J = 6.7 Hz, 3H); **LRMS (ES+) m/z (M+H)+** = 313.

(R)-4-((2-(4-(5-(difluoromethyl)-1,2,4-oxadiazol-3-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yloxy)methyl)nicotinonitrile (7).

Cesium carbonate (1.377 g, 4.23 mmol) was added to 4-(chloromethyl)nicotinonitrile (1.280 g, 3.52 mmol) and (R)-2-(4-(5-(difluoromethyl)-1,2,4-oxadiazol-3-yl)-2-methylpiperazin-1-yl)pyrimidin-5-ol (1.10 g, 3.52 mmol) in DMF (20 mL). The resulting mixture was stirred at 20 °C for 20 hours. The reaction mixture was quenched with water (15 mL), extracted with EtOAc (2 x 20 mL) and the organic layer was dried over MgSO₄, filtered and evaporated to afford a beige solid. Purified by preparative HPLC (Phenomenex Gemini C18 110A (axia) column, 5μ silica, 30 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 0.5% NH₃) and MeCN as eluents. Fractions containing the desired compound were neutralised with 1M HCl, the acetonitrile was evaporated and the residue extracted into CH₂Cl₂, dried and evaporated to dryness to afford the product as a yellow gum which was purified by flash alumina chromatography, elution gradient 10 to 50% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford (R)-4-((2-(4-(5-(difluoromethyl)-1,2,4-oxadiazol-3-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yloxy)methyl)nicotinonitrile (0.510 g, 34%) as a white solid.

**m.p.** 126 – 127 °C; **1H NMR** (400 MHz, CDCl₃) δ 8.91 (s, 1H), 8.85 (d, J = 5.2 Hz, 1H), 8.20 (s, 2H), 7.66 (dd, J = 5.2, 0.8 Hz, 1H), 6.65 (t, J = 52.4 Hz, 1H), 5.22 (s, 2H), 4.87 – 4.85 (m, 1H), 4.56 – 4.47 (m, 1H), 4.07 – 3.98 (m, 1H), 3.88 (dt, J = 12.8, 1.7 Hz, 1H), 3.38 – 3.28 (m, 2H), 3.13 (td, J = 12.3, 3.7 Hz, 1H), 1.25 (d, J = 6.7 Hz, 3H); **13C NMR** (101 MHz, CDCl₃) δ = 170.6, 167.4 (t, J = 29.5 Hz), 157.9, 153.5, 153.0, 148.8, 146.5 (2C), 144.8, 121.8, 114.8, 108.1, 105.6 (t, J = 244.4 Hz), 68.8, 50.3, 46.6, 45.8, 37.9, 14.3; **IR (Nujol)** νmax 2231, 1609, 1583, 1289, 1270, 1228, 1179, 1115, 1081, 1063, 1041, 910, 832, 822 cm⁻¹; **HRMS (ESI)** calc. for C₁₉H₁₈O₂N₈F₂ (M+H)+ 429.1594 found 429.1590. [a]D -60.9.