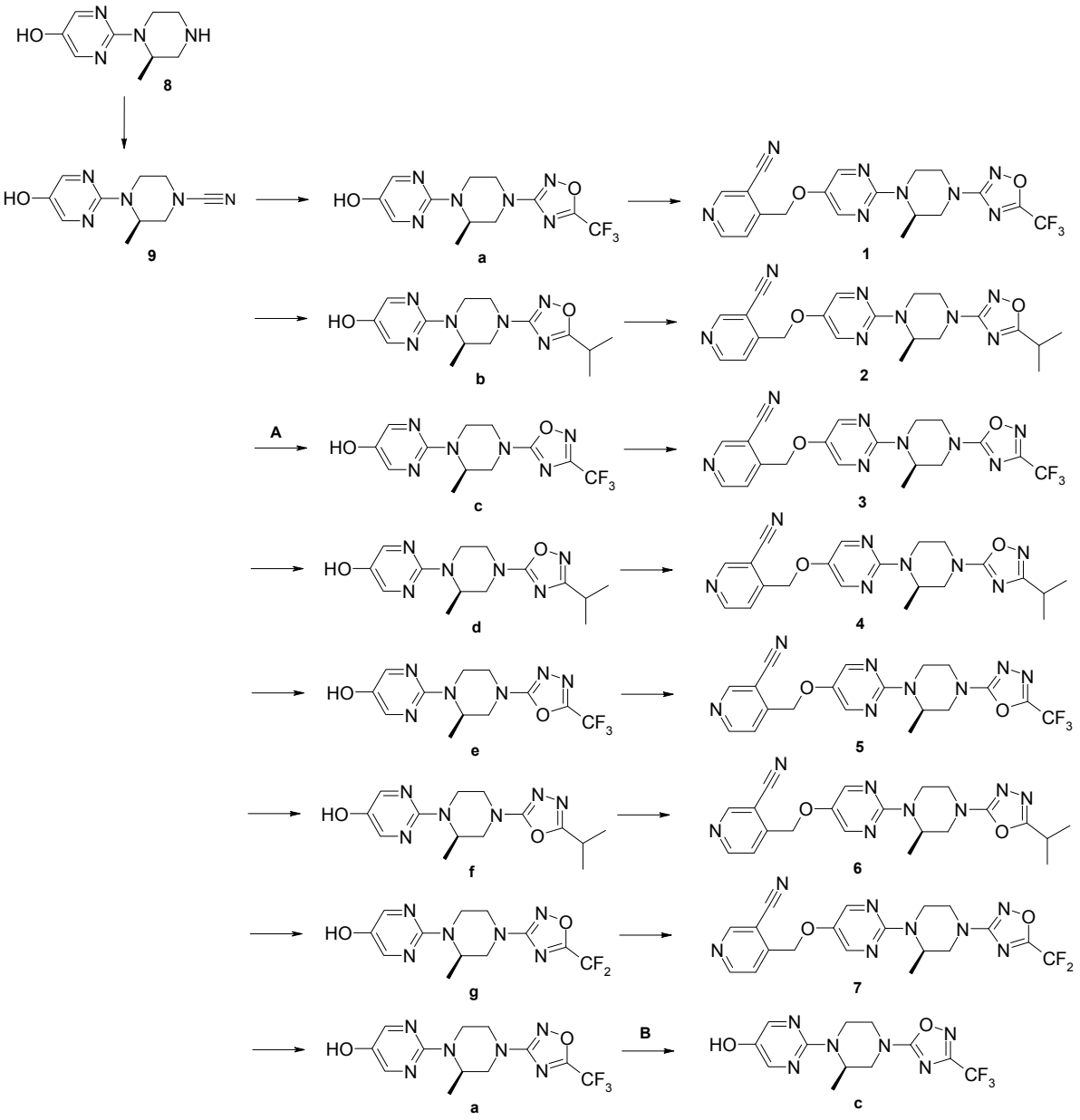
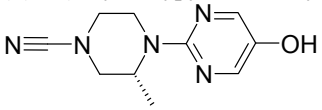
Supporting Information.

Experimental Section: Summary scheme



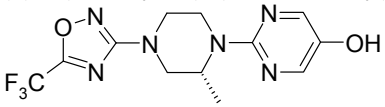
General experimental details: All solvents and chemicals used were reagent grade. Flash column chromatography was carried out using prepacked silica cartridges (from 4 g up to 330 g) from Redisep, Biotage, or Crawford and eluted using an Isco Companion system. Purity and characterization of compounds 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.

(*R*)-4-(5-hydroxypyrimidin-2-yl)-3-methylpiperazine-1-carbonitrile (9).



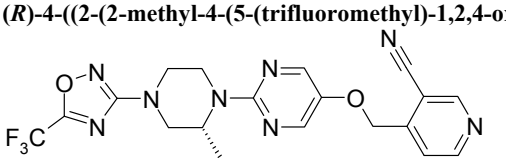
A slurry of sodium bicarbonate (4.39 g, 52.25 mmol) in water (20 mL) was added to (*R*)-2-(2-methylpiperazin-1-yl)pyrimidin-5-ol dihydrochloride (3.49 g, 13.06 mmol) in CH_2Cl_2 (70 mL) at 0 °C. A solution of cyanogen bromide (1.66 g, 15.68 mmol) in CH_2Cl_2 (10 mL) was added and the resulting suspension 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 Na_2SO_4, filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in CH_2Cl_2. Pure fractions were evaporated to dryness to afford (*R*)-4-(5-hydroxypyrimidin-2-yl)-3-methylpiperazine-1-carbonitrile (1.70 g, 59%) as a white solid.
m.p. 121 – 122 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.08 (s, 2H), 4.92 – 4.85 (m, 1H), 4.85 (s, 1H), 4.46 – 4.39 (m, 1H), 3.48 – 3.40 (m, 1H), 3.38 – 3.28 (m, 1H), 3.27 – 3.12 (m, 3H), 1.30 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.4, 145.9, 143.5, 118.2, 53.2, 48.8, 46.1, 37.6, 13.5; **IR** (Nujol) ν_{max} 3264, 2215, 1473, 1473, 1441, 1388, 1290, 1230, 1168, 1042, 837; **LRMS** (ES+) m/z $(M+H)^+$ = 220.

(*R*)-2-(2-methyl-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)piperazin-1-yl)pyrimidin-5-ol (a).



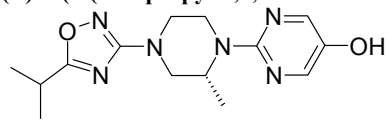
Hydroxylamine hydrochloride (3.48 g, 50.1 mmol) was added to (*R*)-4-(5-hydroxypyrimidin-2-yl)-3-methylpiperazine-1-carbonitrile (5.49 g, 25.04 mmol) and sodium carbonate (3.11 g, 25.0 mmol) in DMF (80 mL) at 20 °C. The resulting suspension was stirred at 80 °C for 30 minutes. The reaction was cooled to 25 °C and toluene (120 mL) was added, followed by pyridine (8.10 mL, 100.2 mmol) and trifluoroacetic anhydride (14.00 mL, 100.2 mmol) with water bath cooling. The reaction was stirred at 45 °C for 40 minutes then cooled, and the toluene evaporated. Ethyl acetate was added and washed with water, brine, dried over Na_2SO_4, filtered and evaporated to give crude product that was purified by flash silica chromatography, elution gradient 10 to 40% EtOAc in CH_2Cl_2. Pure fractions were evaporated to dryness to afford (*R*)-2-(2-methyl-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)piperazin-1-yl)pyrimidin-5-ol (3.14 g, 38%) as a pale yellow oil.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 2H), 5.55 (s, 1H), 4.95 – 4.79 (m, 1H), 4.47 – 4.40 (m, 1H), 4.10 – 4.04 (m, 1H), 3.92 (dt, *J* = 13.0, 1.7 Hz, 1H), 3.46 – 3.32 (m, 2H), 3.20 (td, *J* = 12.4, 3.8 Hz, 1H), 1.29 (d, *J* = 6.7 Hz, 3H); **LRMS** (ES+) m/z $(M+H)^+$ = 331.

(*R*)-4-((2-(2-methyl-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)piperazin-1-yl)pyrimidin-5-yloxy)methyl)nicotinonitrile (1).



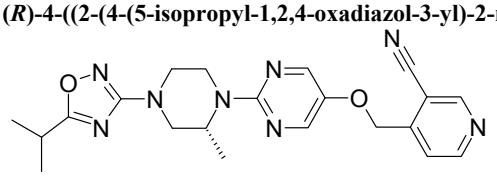
Cesium carbonate (5.49 g, 16.86 mmol) was added to 4-(chloromethyl)nicotinonitrile (2.14 g, 14.05 mmol) and (*R*)-2-(2-methyl-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)piperazin-1-yl)pyrimidin-5-ol (4.64 g, 14.05 mmol) in DMF (60 mL). The resulting mixture was stirred at 20 °C for 70 hours. The reaction mixture was quenched with water (15 mL), extracted with EtOAc (2 x 20 mL), the organic layer was dried over $MgSO_4$, filtered and evaporated to afford a beige solid that was purified by flash silica chromatography, elution gradient 10 to 30% EtOAc in CH_2Cl_2. The oil was triturated with isohexane/Et_2O to give a solid which was collected by filtration and dried under vacuum to give (*R*)-4-((2-(2-methyl-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)piperazin-1-yl)pyrimidin-5-yloxy)methyl)nicotinonitrile (3.43 g, 55%) as a white solid.
m.p. 83 – 84 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.91 (s, 1H), 8.85 (d, *J* = 5.2 Hz, 1H), 8.20 (s, 2H), 7.66 (dd, *J* = 5.1, 0.7 Hz, 1H), 5.22 (s, 2H), 5.02 – 4.91 (m, 1H), 4.52 (ddd, *J* = 13.4, 3.2, 2.3 Hz, 1H), 4.10 – 3.98 (m, 1H), 3.88 (dt, *J* = 12.8, 1.7 Hz, 1H), 3.39 – 3.26 (m, 2H), 3.15 (td, *J* = 12.3, 3.7 Hz, 1H), 1.25 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.4, 164.5 (q, *J* = 43.8 Hz), 157.8, 153.4, 152.9, 148.8, 146.5 (2C), 144.8, 121.8, 115.4 (q, *J* = 274.8 Hz), 114.7, 108.1, 68.8, 50.2, 46.5, 45.7, 37.8, 14.2; **IR** (Nujol) ν_{max} 2234, 1615, 1583, 1274, 1163, 1088, 1061, 1035, 991, 909, 837, 791 cm^{-1}; **HRMS** (ESI) calc. for $C_{19}H_{18}O_2N_8F_3(M+H)^+$ 447.1499 found 447.1497.

(*R*)-2-(4-(5-isopropyl-1,2,4-oxadiazol-3-yl)-2-methylpiperazin-1-yl)pyrimidin-5-ol (b)



Hydroxylamine hydrochloride (0.146 g, 2.10 mmol) was added to (*R*)-4-(5-hydroxypyrimidin-2-yl)-3-methylpiperazine-1-carbonitrile (0.23 g, 1.05 mmol) and sodium carbonate (0.130 g, 1.05 mmol) in DMF (4 mL) under nitrogen. The resulting solution was stirred at 80 °C for 2 hours. The reaction mixture was cooled to room temperature dissolved in DMF (4 mL) and *N*-ethyldiisopropylamine (0.200 ml, 1.16 mmol), isobutyric acid (0.107 mL, 1.16 mmol) and 1-hydroxybenzotriazole (0.177 g, 1.16 mmol) were added. The resulting solution was stirred at 20 °C for 10 minutes. 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.244 g, 1.27 mmol) was added and the resulting solution was stirred at 20 °C for 18 hours. The reaction 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 (0.120 g, 38%) as a white solid.
m.p. 147 – 148 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09 (s, 2H), 7.22 (s, 1H), 4.89 – 4.77 (m, 1H), 4.41 – 4.30 (m, 1H), 4.02 – 3.92 (m, 1H), 3.81 (dt, *J* = 12.6, 1.6 Hz, 1H), 3.35 – 3.19 (m, 2H), 3.15 – 2.97 (m, 2H), 1.36 (d, *J* = 7.0 Hz, 6H), 1.21 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** (175 MHz, $CDCl_3$) δ 183.1, 170.5, 157.0, 146.1, 143.0, 50.3, 46.8, 45.8, 38.3, 27.7, 20.0 (2C), 14.1; **IR** (Nujol) ν_{max} 2232, 1582, 1556, 1465, 1443, 1408, 1226, 1169, 1043, 917 cm^{-1}; **HRMS** (ESI) calc. for $C_{14}H_{21}O_2N_6(M+H)^+$ 305.1720 found 305.1719.

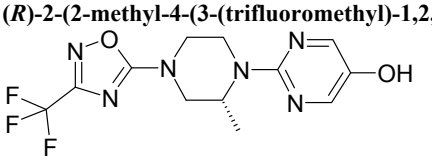
(*R*)-4-((2-(4-(5-isopropyl-1,2,4-oxadiazol-3-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yloxy)methyl)nicotinonitrile (2)



Potassium carbonate (0.084 mL, 1.48 mmol) was added to (*R*)-2-(4-(5-isopropyl-1,2,4-oxadiazol-3-yl)-2-methylpiperazin-1-yl)pyrimidin-5-ol (0.15 g, 0.49 mmol) and 4-(bromomethyl)nicotinonitrile (0.194 g, 0.99 mmol) in ethyl acetate (20 mL) under nitrogen. The resulting solution was stirred at 40 °C for 16 hours. The reaction mixture was diluted with EtOAc (20 mL), and washed sequentially with water (15 mL), saturated brine (15 mL). The organic layer was dried over $MgSO_4$, 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 (*R*)-4-((2-(4-(5-isopropyl-1,2,4-oxadiazol-3-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yloxy)methyl)nicotinonitrile (0.045 g, 22%) as a white solid.

m.p. 170 – 172 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.91 (s, 1H), 8.85 (d, *J* = 5.2 Hz, 1H), 8.20 (s, 2H), 7.66 (dd, *J* = 5.2, 0.6 Hz, 1H), 5.22 (s, 2H), 4.96 – 4.86 (m, 1H), 4.47 (ddd, *J* = 13.4, 3.3, 2.2 Hz, 1H), 4.01(ddt, *J* = 12.4, 3.5, 1.8 Hz, 1H), 3.85 (dt, *J* = 12.6, 1.7 Hz, 1H), 3.31 (ddd, *J* = 13.4, 12.3, 3.7 Hz, 1H), 3.22 (dd, *J* = 12.7, 4.0 Hz, 1H), 3.14 – 2.99 (m, 2H), 1.36 (d, *J* = 7.0 Hz, 6H), 1.25 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) 183.0, 170.8, 158.0, 153.4, 153.0, 148.9, 146.6, 144.7, 121.8, 114.8, 108.1, 68.8, 50.3, 46.6, 45.9, 38.2, 27.7, 20.1 (2C), 14.3; **IR** (Nujol) ν_{max} 2234, 1586, 1548, 1461, 1376, 1287, 1269, 1223, 1176, 1036, 927, 834 cm^{-1}; **HRMS** (ESI) calc. for $C_{21}H_{25}O_2N_8$ $(M+H)^+$ 421.2095 found 421.2092.

(*R*)-2-(2-methyl-4-(3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)piperazin-1-yl)pyrimidin-5-ol (c).

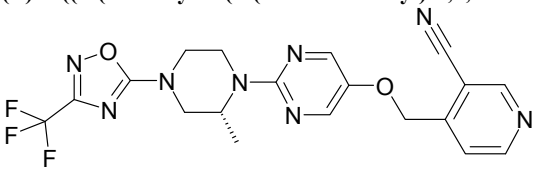


Method A: Zinc chloride (1M in Et_2O, 22.48 mL, 22.48 mmol) was added to 2,2,2-trifluoro-*N*-hydroxyacetimidamide (1.766 g, 13.79 mmol) and (*R*)-4-(5-hydroxypyrimidin-2-yl)-3-methylpiperazine-1-carbonitrile (2.24 g, 10.22 mmol) in THF (45 mL) and ethyl acetate (50 mL) over a period of 10 minutes under nitrogen. The resulting solution was stirred at 20 °C for 24 hours. All volatiles were removed under reduced pressure and the solid was triturated with Et_2O (50 mL) and collected by filtration, washed with Et_2O (2 x 10 mL) and dried under vacuum. 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 azeotroped with toluene (50 mL). The crude product was purified by flash silica chromatography by pre-absorbing the material onto celite using mixtures of MeOH and CH_2Cl_2 and columned using eluent of CH_2Cl_2 to 100% EtOAc in 10% jumps then MeOH:EtOAc (1:9). All product containing fractions were combined and evaporated to dryness to afford (*R*)-2-(2-methyl-4-(3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)piperazin-1-yl)pyrimidin-5-ol (2.63 g, 58%) as a dark gum.

Method B: Potassium tert-butoxide (127 mg, 1.14 mmol) was added to (*R*)-2-(2-methyl-4-(5-(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 suspension was stirred for 16 hours. The reaction mixture was diluted with EtOAc (20 mL), and washed sequentially with water (3 x 10 mL) and saturated brine (10 mL). The organic layer was evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 50% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford (*R*)-2-(2-methyl-4-(3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)piperazin-1-yl)pyrimidin-5-ol (25 mg, 20%) as a colourless gum.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 2H), 5.03 – 4.81 (m, 2H), 4.48 – 4.39 (m, 1H), 4.16 – 4.08 (m, 1H), 3.93 (dt, *J* = 13.1, 1.7 Hz, 1H), 3.44 (dd, *J* = 13.0, 3.9 Hz, 1H), 3.31 – 3.17 (m, 2H), 1.15 (d, *J* = 6.5 Hz, 3H); **LRMS** (ES+) m/z $(M+H)^+$ = 331.

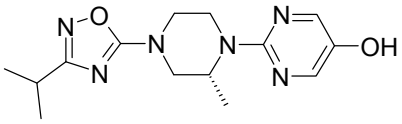
(*R*)-4-((2-(2-methyl-4-(3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)piperazin-1-yl)pyrimidin-5-yloxy)methyl)nicotinonitrile (3).



Potassium carbonate (31.4 mg, 0.23 mmol) was added to (*R*)-2-(2-methyl-4-(3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)piperazin-1-yl)pyrimidin-5-ol (25 mg, 0.08 mmol) and 4-(chloromethyl)nicotinonitrile (23.1 mg, 0.15 mmol) in acetonitrile (1 mL) at 20 °C. The resulting suspension was stirred at 60 °C for 90 minutes. The reaction mixture was diluted with CH_2Cl_2 (10 mL), and washed with water (5 mL). The organic layer was purified by flash silica chromatography, elution gradient 0 to 60% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford (*R*)-4-((2-(2-methyl-4-(3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)piperazin-1-yl)pyrimidin-5-yloxy)methyl)-nicotinonitrile (17 mg, 50%) as a colourless solid.

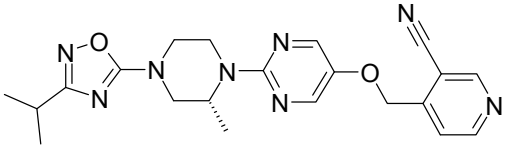
m.p. 150 – 151 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.92 (s, 1H), 8.86 (d, *J* = 5.2 Hz, 1H), 8.22 (s, 2H), 7.66 (d, *J* = 5.1 Hz, 1H), 5.23 (s, 2H), 5.07 – 4.96 (m, 1H), 4.65 – 4.51 (m, 1H), 4.26 – 4.12 (m, 1H), 4.01 (d, *J* = 13.1 Hz, 1H), 3.51 (dd, *J* = 13.1, 4.0 Hz, 1H), 3.41 – 3.25 (m, 2H), 1.24 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) 172.3, 161.9 (q, *J* = 39.0 Hz), 157.5, 153.4, 153.0, 148.6, 146.4, 145.1, 121.8, 118.1 (q, *J* = 272.1 Hz), 114.7, 108.1, 68.7, 50.3, 46.3, 45.9, 37.7, 14.0; **IR** (Nujol) ν_{max} 2227, 1648, 1590, 1546, 1465, 1401, 1345, 1293, 1234, 1155, 1089, 1058, 908, 837 cm^{-1}; **HRMS** (ESI) calc. for $C_{19}H_{18}O_2N_8F_3(M+H)^+$ 447.1499 found 447.1499.

(*R*)-2-(4-(3-isopropyl-1,2,4-oxadiazol-5-yl)-2-methylpiperazin-1-yl)pyrimidin-5-ol (d).



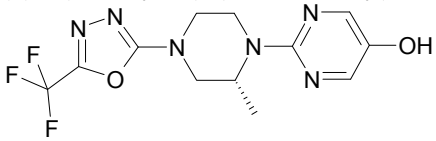
Zinc chloride (1M in Et_2O; 5.07 mL, 5.07 mmol) was added to (*R*)-4-(5-hydroxypyrimidin-2-yl)-3-methylpiperazine-1-carbonitrile (505 mg, 2.30 mmol) and *N*-hydroxyisobutyramidine (318 mg, 3.11 mmol) in THF (7.0 mL) and ethyl acetate (9.0 mL) over a period of 10 minutes under nitrogen. The resulting 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 CH_2Cl_2. 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 (477 mg, 68%) as a light brown gum.
^{1}H NMR (400 MHz, DMSO) δ 9.24 (s, 1H), 8.05 (s, 2H), 4.84 – 4.72 (m, 1H), 4.31 (dd, *J* = 12.7, 3.1 Hz, 1H), 3.97 (d, *J* = 10.8 Hz, 1H), 3.81 (d, *J* = 12.9 Hz, 1H), 3.37 (dd, *J* = 13.0, 3.9 Hz, 1H), 3.26 – 3.08 (m, 2H), 2.82 (hept, *J* = 6.9 Hz, 1H), 1.19 (d, *J* = 6.9 Hz, 6H), 1.06 (d, *J* = 6.7 Hz, 3H); **LRMS** (ES+) m/z $(M+H)^+$ = 305.

(*R*)-4-((2-(4-(3-isopropyl-1,2,4-oxadiazol-5-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yloxy)methyl)nicotinonitril (4).



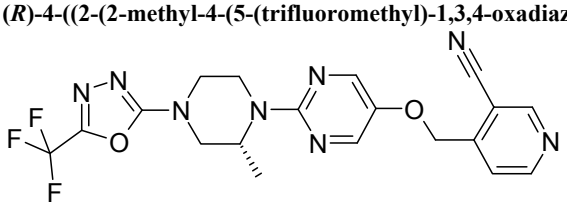
Cesium carbonate (4.75 g, 14.59 mmol) was added to (*R*)-2-(4-(3-isopropyl-1,2,4-oxadiazol-5-yl)-2-methylpiperazin-1-yl)pyrimidin-5-ol (1.11 g, 3.65 mmol) and 4-(chloromethyl)nicotinonitrile (4.80 g, 31.46 mmol) in acetonitrile (80 mL). The resulting suspension was stirred at 20 °C for 18 hours. It was 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 (1.051 g, 68%) as a white solid.
m.p. 115 – 116 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.91 (s, 1H), 8.85 (d, *J* = 5.2 Hz, 1H), 8.20 (s, 2H), 7.68 – 7.63 (m, 1H), 5.22 (s, 2H), 4.99 – 4.89 (m, 1H), 4.56 – 4.44 (m, 1H), 4.20 – 4.08 (m, 1H), 3.96 (dd, *J* = 14.7, 1.6 Hz, 1H), 3.41 (dd, *J* = 13.0, 4.0 Hz, 1H), 3.35-3.20 (m, 2H), 2.91 (hept, *J* = 7.0 Hz, 1H), 1.30 (d, *J* = 7.0 Hz, 6H), 1.23 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.8, 171.4, 157.7, 153.4, 152.9, 148.7, 146.5, 144.9, 121.8, 114.7, 108.1, 68.7, 50.1, 46.5, 45.7, 37.9, 27.0, 20.4 (2C), 14.1; **IR** (Nujol) ν_{max} 2230, 1621, 1592, 1552, 1460, 1408, 1347, 1281, 1265, 1222, 1180, 1034, 1017, 839 cm^{-1}; **HRMS** (ESI) calc. for $C_{21}H_{25}O_2N_8$ $(M+H)^+$ 421.2095 found 421.2091.

(*R*)-2-(2-methyl-4-(5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl)piperazin-1-yl)pyrimidin-5-ol (e).



Sodium azide (0.096 mL, 2.74 mmol) was added to triethylamine hydrochloride (0.377 g, 2.74 mmol) and (*R*)-4-(5-hydroxypyrimidin-2-yl)-3-methylpiperazine-1-carbonitrile (0.20 g, 0.91 mmol) in toluene (10 mL) under nitrogen. The resulting suspension was stirred at 80 °C for 18 hours. Methanol and ethyl acetate were added then the mixture was partitioned between EtOAc (50 mL) and water (10 mL). The organic layer was removed and the aqueous layer was acidified to pH 4 with 2M HCl, and further extracted with CH_2Cl_2 (4 x 20 mL). The combined organics were evaporated to a yellow gum and then azeotroped with toluene (10 mL). Trifluoroacetic anhydride (0.257 mL, 1.82 mmol) was added dropwise with *N,N*-di-isopropylethylamine (0.476 mL, 2.73 mmol) in dry CH_2Cl_2 (28 mL) at 0 °C over a period of 2 minutes under nitrogen. The resulting solution was stirred at room temperature for 2 days. A second portion of trifluoroacetic anhydride (0.257 mL, 1.82 mmol) was added and the solution was stirred at room temperature for a further 2 days. The reaction mixture was washed sequentially with water (10 mL) and saturated $NaHCO_3$ (10 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product which was purified by flash silica chromatography, elution gradient 0 to 70% EtOAc in CH_2Cl_2. Pure fractions were evaporated to dryness to afford (*R*)-2-(2-methyl-4-(5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl)piperazin-1-yl)pyrimidin-5-ol (56 mg, 19%) as a yellow oil.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 2H), 4.90 (ddd, *J* = 10.7, 5.2, 3.1 Hz, 1H), 4.86 (s, 1H), 4.50 – 4.39 (m, 1H), 4.00 (dt, *J* = 14.8, 3.9 Hz, 1H), 3.82 (d, *J* = 12.9 Hz, 1H), 3.40 (dd, *J* = 12.9, 4.0 Hz, 1H), 3.30 – 3.16 (m, 2H), 1.16 (d, *J* = 6.8 Hz, 3H); **LRMS** (ES+) m/z $(M+H)^+$ = 331.

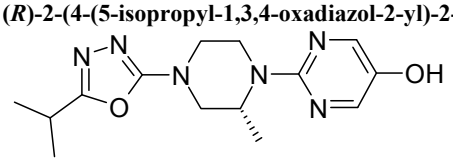
(*R*)-4-((2-(2-methyl-4-(5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl)piperazin-1-yl)pyrimidin-5-yloxy)methyl)nicotinonitrile (5).



Potassium carbonate (28.1 mg, 0.20 mmol) was added in one portion to (*R*)-2-(2-methyl-4-(5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl)piperazin-1-yl)pyrimidin-5-ol (56 mg, 0.17 mmol) and 4-(chloromethyl)nicotinonitrile (25.9 mg, 0.17 mmol) in butyronitrile (2 mL) at 20 °C under nitrogen. The resulting suspension was stirred at room temperature for 18 hours. The reaction was incomplete and further 4-(chloromethyl)nicotinonitrile (25.9 mg, 0.17 mmol) and potassium carbonate (28.1 mg, 0.20 mmol) was added and the suspension was stirred at room temperature for a further 18 hours. The reaction mixture was diluted with EtOAc (50 mL), and washed with 2M K_2CO_3 aq. (20 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product that was purified by flash silica

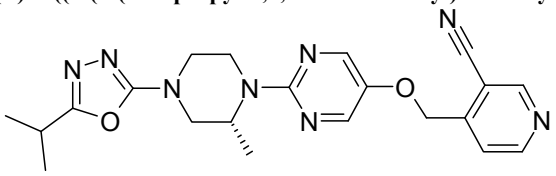
chromatography, elution gradient 0 to 50% EtOAc in CH_2Cl_2. Pure fractions were evaporated to dryness to afford (*R*)-4-((2-(2-methyl-4-(5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl)piperazin-1-yl)pyrimidin-5-yloxy)methyl)nicotinonitrile (54.0 mg, 71%) as a yellow solid.
m.p. 88 – 90 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.92 (s, 1H), 8.86 (d, *J* = 5.2 Hz, 1H), 8.21 (s, 2H), 7.66 (dd, *J* = 5.1, 0.5 Hz, 1H), 5.23 (s, 2H), 5.06 – 4.95 (m, 1H), 4.64 – 4.51 (m, 1H), 4.14 – 4.04 (d, *J* = 10.1 Hz, 1H), 3.90 (dt, *J* = 12.9, 1.6 Hz, 1H), 3.47 (dd, *J* = 12.9, 4.0 Hz, 1H), 3.40 – 3.23 (m, 2H), 1.26 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) 165.2, 157.6, 153.4, 153.0, 148.9 (q, *J* = 45.4 Hz), 148.7, 146.4, 145.0, 121.8, 116.2 (q, *J* = 270.2 Hz), 114.7, 108.1, 68.7, 50.3, 46.2, 45.9, 37.6, 14.1; **IR** (Nujol) ν_{max} 2228, 1638, 1591, 1551, 1443, 1400, 1330, 1275, 1230, 1152, 1066, 990, 910, 834 cm^{-1}; **HRMS** (ESI) calc. for $C_{19}H_{18}O_2N_8F_3$ $(M+H)^+$ 447.1499 found 447.1497.

(*R*)-2-(4-(5-isopropyl-1,3,4-oxadiazol-2-yl)-2-methylpiperazin-1-yl)pyrimidin-5-ol (f).



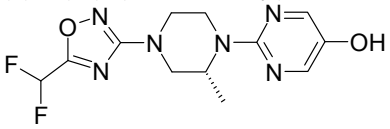
Sodium azide (0.192 mL, 5.47 mmol) was added to triethylamine hydrochloride (0.753 g, 5.47 mmol) and (*R*)-4-(5-hydroxypyrimidin-2-yl)-3-methylpiperazine-1-carbonitrile (0.4 g, 1.82 mmol) in toluene (20 mL) under nitrogen. The resulting suspension was stirred at 80 °C for 18 hours. The suspension was cooled to room temperature and methanol and ethyl acetate were added to dissolve the solid. The reaction was partitioned between EtOAc (50 mL) and water (10 mL). The organic layer was removed and the aqueous layer was acidified to pH 4 with 2M HCl, and further extracted with CH_2Cl_2 (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 CH_2Cl_2 (3 x 100 mL). A white solid precipitated and this was filtered off and combined with the organics. The combined organics were dried (Na_2SO_4), filtered and evaporated to a yellow gum and then azeotroped with toluene (10 mL). The product was dissolved in chlorobenzene (10 mL) and cooled to 0 °C then *N,N*-di-isopropylethylamine (0.413 mL, 2.37 mmol) was added followed by isobutyric anhydride (0.262 mL, 1.58 mmol) added dropwise over a period of 2 minutes under nitrogen. The reaction mixture was stirred at 130 °C for 18 hours and cooled to room temperature. The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed sequentially with water (10 mL) and saturated $NaHCO_3$ (10 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. LC-MS analysis indicated that the isobutyric ester of the phenol had formed during the reaction. This was cleaved by addition of tetrabutylammonium hydroxide in MeOH (1.00 mL, 1.00 mmol) to a solution in THF (15 mL). The resulting solution was stirred at ambient temperature for 40 minutes. HCl (0.603 mL, 1.21 mmol) was added and the reaction was diluted with EtOAc (15 mL), and washed sequentially with water (10 mL) and saturated brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford (*R*)-2-(4-(5-isopropyl-1,3,4-oxadiazol-2-yl)-2-methylpiperazin-1-yl)pyrimidin-5-ol (300 mg, 29%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 2H), 7.31 (s, 1H), 4.94 – 4.84 (m, 1H), 4.48 – 4.38 (m, 1H), 4.01 – 3.91 (m, 1H), 3.77 (dt, *J* = 12.6, 1.6 Hz, 1H), 3.38 – 3.22 (m, 3H), 3.15 (td, *J* = 12.2, 3.5 Hz, 1H), 1.35 (d, *J* = 7.0 Hz, 6H), 1.21 (d, *J* = 6.7 Hz, 3H); **LRMS** (ES+) m/z $(M+H)^+$ = 305.

(*R*)-4-((2-(4-(5-isopropyl-1,3,4-oxadiazol-2-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yloxy)methyl)nicotinonitrile (6).



Potassium carbonate (0.106 g, 0.77 mmol) was added to (3-cyanopyridin-4-yl)methyl methanesulfonate (0.163 g, 0.77 mmol) and (*R*)-2-(4-(5-isopropyl-1,3,4-oxadiazol-2-yl)-2-methylpiperazin-1-yl)pyrimidin-5-ol (0.212 g, 0.70 mmol) in butyronitrile (6 mL) at 25 °C under nitrogen. The resulting solution was stirred at 55 °C for 6 hours. The reaction mixture was diluted with EtOAc (75 mL), and washed sequentially with water (20 mL) and saturated brine (20 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to afford crude product that was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5µ silica, 50 mm diameter, 150 mm length), using decreasingly polar mixtures of water (containing 0.5% NH_3) and MeCN as eluents. The fractions were combined and the pH adjusted to ~7 with 2M HCl aq and 1M $NaHCO_3$ aq. The bulk of the organic solvent was removed under reduced pressure to give a white suspension. The suspension was extracted with CH_2Cl_2 (2 x 50 mL) and the combined organics dried over Na_2SO_4, filtered and evaporated to afford (*R*)-4-((2-(4-(5-isopropyl-1,3,4-oxadiazol-2-yl)-2-methylpiperazin-1-yl)pyrimidin-5-yloxy)methyl)nicotinonitrile as a yellow gum that was dissolved in a few drops of ether and dried under high vacuum to form a white solid (191 mg, 65%).
^{1}H NMR (400 MHz, CDCl3) δ 8.89 (s, 1H), 8.83 (d, *J* = 5.2 Hz, 1H), 8.18 (s, 2H), 7.65 (d, *J* = 5.2 Hz, 1H), 5.21 (s, 2H), 4.98 – 4.87 (m, 1H), 4.52 – 4.46 (m, 1H), 4.02 – 3.92 (m, 1H), 3.78 (dt, *J* = 12.7, 1.6 Hz, 1H), 3.30 (ddd, *J* = 13.0, 8.2, 3.5 Hz, 2H), 3.12 (td, *J* = 12.3, 3.6 Hz, 1H), 3.04 (sept, *J* = 7.0 Hz, 1H), 1.33 (d, *J* = 7.0 Hz, 6H), 1.23 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.4, 163.8, 156.8, 152.5, 151.9, 147.8, 145.5, 143.8, 120.8, 113.8, 107.1, 67.8, 49.5, 45.3, 45.0, 36.8, 25.4, 18.9, 13.2; **IR** (Nujol) ν_{max} 2227, 1621, 1591, 1571, 1550, 1066, 1446, 1281, 1229, 1206, 1175, 911, 863 cm^{-1}; **HRMS** (ESI) calc. for $C_{21}H_{25}O_2N_8$ $(M+H)^+$ 421.2095 found 421.2093.

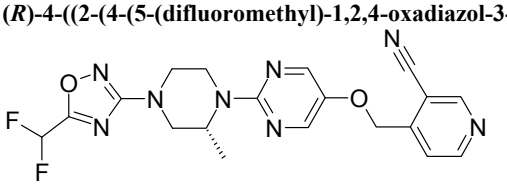
(*R*)-2-(4-(5-(difluoromethyl)-1,2,4-oxadiazol-3-yl)-2-methylpiperazin-1-yl)pyrimidin-5-ol (g).



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 (12 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 water and brine, dried over Na_2SO_4, filtered and evaporated to give crude product which was purified by flash silica

chromatography, elution gradient 10 to 30% EtOAc in CH_2Cl_2. 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. **^{1}H NMR** (400 MHz, $CDCl_3$) 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 (dt, *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 $MgSO_4$, 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% NH_3) and MeCN as eluents. Fractions containing the desired compound were neutralised with 1M HCl, the acetonitrile was evaporated and the residue extracted into CH_2Cl_2, 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; **^{1}H NMR** (400 MHz, $CDCl_3$) 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); **^{13}C NMR** (101 MHz, $CDCl_3$) 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) ν_{max} 2231, 1609, 1583, 1289, 1270, 1228, 1179, 1115, 1081, 1063, 1041, 910, 833, 822 cm^{-1}; **HRMS** (ESI) calc. for $C_{19}H_{18}O_2N_8F_2$ $(M+H)^+$ 429.1594 found 429.1590.