Supporting Information

Discovery and Structure Enabled Synthesis of 2,6-Diaminopyrimidin-4-one IRAK4 Inhibitors

W. Michael Seganish[†], Thierry O. Fischmann[‡], Brad Sherborne[€], Julius Matasi[†], Brian Lavey[†], William T. McElroy[†], Deen Tulshian[†], James Tata[†], Christopher Sondey[ℓ], Charles G. Garlisi[ℓ], Kristine Devito[ℓ], James Fossetta[§], Daniel Lundell[§], Xiaoda Niu[ℓ]

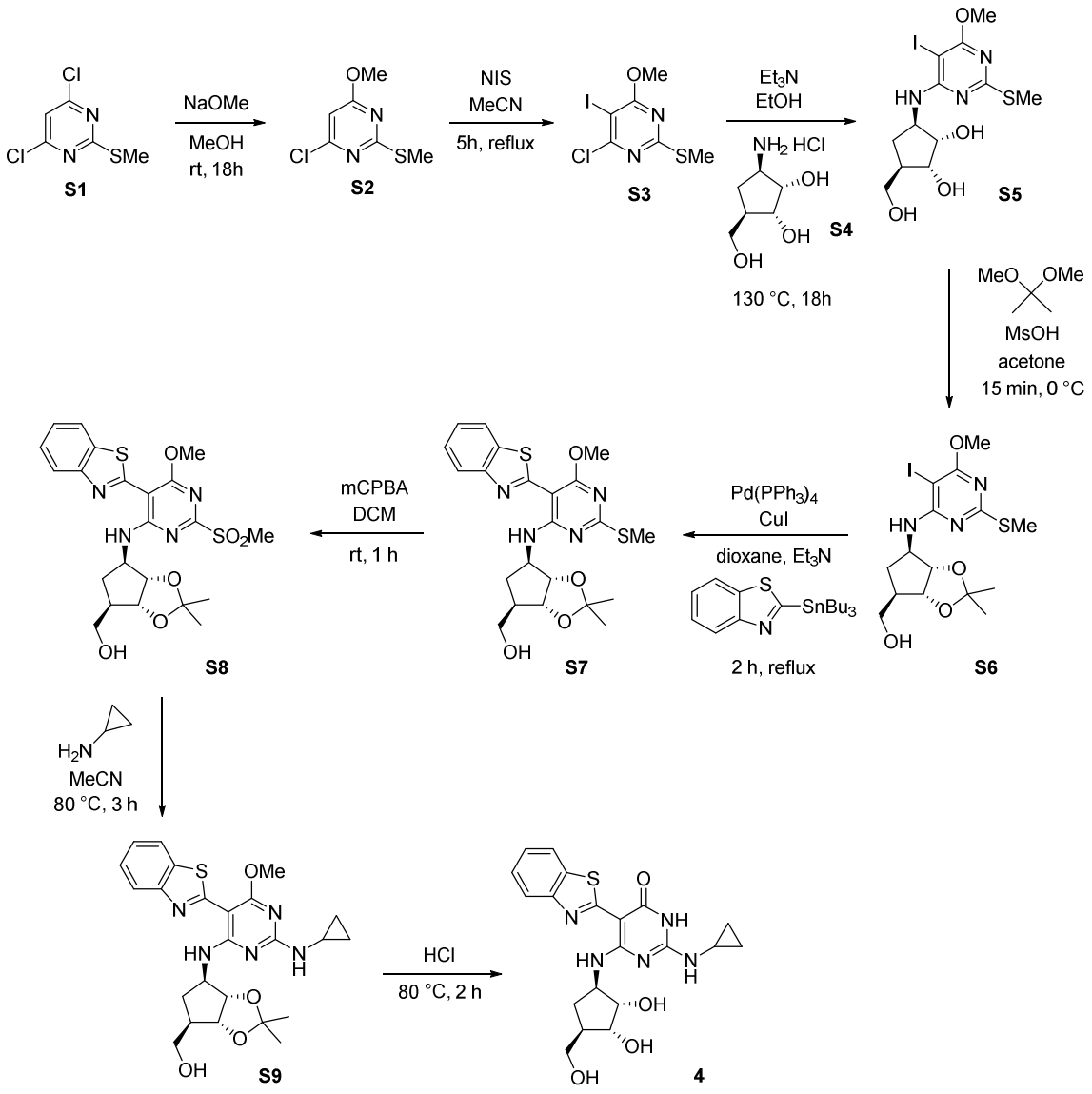
[†]*Discovery Chemistry,* [‡]*Structural Sciences,* [€]*Computational Chemistry,* [ℓ]*In Vitro Pharmacology,*
[§]*Respiratory and Immunology*
Merck Research Laboratories, 2015 Galloping Hill Rd., Kenilworth, New Jersey 07033, United States

Table of Contents

1. Synthesis and characterization for compounds 4 and 19

General Methods. All reactions were performed under an atmosphere of N_2. Solvents and reagents were purchased from commercial sources and used without purification. Flash chromatography was performed using RediSep®R_f disposable columns manufactured by Teledyne Isco, and an Analogix Intelliflash™ 280 instrument. ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Varian 400 VNMRS. Chemical shifts are reported in parts per million (ppm). Coupling constants (J) are given in Hertz (Hz). Spin multiplicities are indicated by standard notation. LC-MS analyses were performed using Zorbox SB-C18 column (3.0 x 50 mm) with a 3.5 min run time (1 mL/min flow) and a gradient of 90:10 to 10:90 water:MeCN with 0.1% TFA added. MS analyses were performed with an AB-SCIEX API-150EX MS system with ESI(+) detection, and a Shimadzu LC-10ADvp and Shimadzu SPD-10Avp detector. All final compounds tested in biological assays were >95% pure as judged by LCMS and ^{1}H NMR analysis.

Compounds **4-18** were prepared using the methods outlined below, with **4** as an example.



Step 1: 4-chloro-6-methoxy-2-(methylthio)pyrimidine (S2)

4,6-Dichloro-2-(methylthio)pyrimidine (40 g, 205 mmol) was dissolved in methanol (1025 mL) and cooled to 0 °C. Sodium methoxide (55.4 g, 1025 mmol) was added slowly and the mixture was stirred at room temperature for 18 h. 300 mL of 3 M HCl was added and the methanol was evaporated. Additional water (500 mL) was added and the mixture was filtered, washed with water and dried to give the title

compound (36.0 g, 92%) as a white solid. **^{1}H NMR** ($CDCl_3$) δ 6.41 (s, 1H), 3.97 (s, 3H), 2.55 (s, 3H); **^{13}C NMR** ($CDCl_3$) δ 172.8, 169.7, 160.2, 102.3, 54.4, 14.2; **LCMS** (ESI) 2.40 min, 191 (M+H).

Step 2: 4-chloro-5-iodo-6-methoxy-2-(methylthio)pyrimidine (S3)

Compound **2** (10 g, 52.5 mmol) was dissolved in MeCN (150 mL) and NIS (14.2 g, 62.9 mmol was added. The solution was heated to reflux for 5 h and cooled to room temperature. The solvent was evaporated and the residue was dissolved in EtOAc. The organics were washed with sat. $NaHCO_3$ and sat. NaS_2O_3, dried ($MgSO_4$), filtered and concentrated to give the title compound as a white solid (15.8 g 95**%). ^{1}H NMR** ($CDCl_3$) δ 4.04 (s, 3H), 2.54 (s, 3H); **LCMS** (ESI) 2.64 min, 317 (M+H).

Step 3: (1S,2R,3R,5R)-3-(hydroxymethyl)-5-(5-iodo-6-methoxy-2-(methylthio)pyrimidin-4-ylamino)cyclopentane-1,2-diol (S5)

Compound **3** (5.00 g, 15.7 mmol) and (1R,2S,3R,5R)-3-amino-5-(hydroxymethyl)cyclopentane-1,2-diol hydrochloride (**S4**) (5.80 g, 31.6 mmol) were dissolved in EtOH (50 mL). Triethylamine (6.60 mL, 47.4 mmol) was added, the reaction was sealed, and heated to 130 ºC for 18 h. The reaction mixture was cooled to room temperature and concentrated. The residue was purified via column chromatography on silica gel (EtOAc/hexanes) to give the title compound as a colorless oil (4.70 g, 70%). **LCMS** (ESI) 1.23 min, 428 (M+H).

Step 4: ((3aR,4R,6R,6aS)-6-(5-iodo-6-methoxy-2-(methylthio)pyrimidin-4-ylamino)-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-yl)methanol (S6)

Compound **S5** (4.00 g, 9.36 mmol) was dissolved in acetone (10 mL) and 2,2-dimethoxypropane (5.75 mL, 46.8 mmol) was added. The solution was cooled to 0 ºC and methanesulfonic acid (2 drops) was added. The solution was stirred for 15 min and Et_3N (1 mL) was added. The acetone was evaporated and the residue was dissolved in EtOAc, washed with water and brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified via column chromatography on silica gel (EtOAc/hexanes) to give the title compound as a white solid (4.29 g, 98%). **^{1}H NMR** ($CDCl_3$) δ 6.21 (d, J = 8 Hz, 1H), 4.65-4.59 (m, 2H), 4.45-4.44 (m, 1H), 3.94 (s, 3H), 3.89-3.85 (m, 1H), 3.76-3.73 (m, 1H), 2.61-2.55 (m, 1H), 2.52 (s, 3H), 2.40-2.34 (m, 1H), 1.85 (br s, 1H), 1.65-1.57 (m, 2H), 1.49 (s, 3H), 1.28 (s, 3H); **^{13}C NMR** ($CDCl_3$) δ 170.4, 166.7, 161.0, 110.9, 87.1, 83.6, 64.4, 57.6, 54.8, 47.1, 33.4, 27.1, 24.7, 14.4; **LCMS** (ESI) 2.54 min, 468 (M+H); **HRMS** (ESI, M+H) calculated for $C_{15}H_{23}IN_3O_4S$: 468.0454 found 468.0431.

Step 5: ((3aR,4R,6R,6aS)-6-(5-(benzo[d]thiazol-2-yl)-6-methoxy-2-(methylthio)pyrimidin-4-ylamino)-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-yl)methanol (S7)

2-Tributylstannylbenzothiazole (1.18 g, 2.78 mmol), compound **S6** (1.00 g, 2.14 mmol), Tetrakis(triphenylphosphine)palladium (0.495 g, 0.428 mmol), and CuI (0.082 g, 0.428 mmol) were combined. Dioxane (45 ml) was added followed by Et_3N (1.19 ml, 8.56 mmol) and the mixture was degassed and heated to reflux for 2 h. The solution was cooled to room temperature and an aqueous 10% KF solution was added and the mixture was stirred for 30 min. The mixture was diluted with EtOAc and washed with water, brine, dried ($MgSO_4$), filtered and evaporated to dryness. The residue was purified by column chromatography on silica gel, eluting with EtOAc/hexane to give the title compound (600 mg, 59% yield) as a yellow foam. **^{1}H NMR** ($CDCl_3$) δ 7.94 (d, *J* = 8 Hz, 1H), 7.87 (d, *J* = 8 Hz, 1H), 7.45 (t, *J* = 5 Hz, 1H), 7.33 (t, *J* = 5 Hz, 1H), 4.70-4.59 (m, 3H), 4.15 (s, 3H), 3.86-3.83 (m, 2H), 2.61 (s, 3H), 2.59-2.52 (m, 1H), 2.45-2.42 (m, 2H). 1.83-1.78 (m, 1H), 1.67-1.66 (m, 1H), 1.53 (s, 3H), 1.31 (s, 3H); **^{13}C NMR** ($CDCl_3$) δ 170.9, 166.1, 161.5, 157.7, 152.1, 133.3, 125.0, 122.6, 121.5, 121.4 112.7, 111.4, 88.3, 83.1, 64.1, 58.2, 55.2, 33.4, 27.4, 24.3, 14.6; **LCMS** (ESI) 2.77 min, 475 (M+H); **HRMS** (ESI, M+H) calculated for $C_{22}H_{27}N_4O_4S_2$: 475.1474 found 475.1481.

Step 6: ((3aR,4R,6R,6aS)-6-(5-(benzo[d]thiazol-2-yl)-6-methoxy-2-(methylsulfonyl)pyrimidin-4-ylamino)-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-yl)methanol (S8)

Compound **S7** (600 mg. 1.27 mmol) was dissolved in DCM (25 mL). mCPBA (711 mg, 3.18 mmol, 77% wt/wt) was added in one portion and the solution was stirred at room temperature for 1 h. A saturated aqueous solution of $NaHCO_3$ was added and the mixture was stirred for 10 min. The layers were separated and the organics were dried ($MgSO_4$), filtered and concentrated to give 640 mg (99%) of the title compound as a yellow solid. **MS** (ESI): 507 (M+H).

Step 7: ((3aR,4R,6R,6aS)-6-((5-(benzo[d]thiazol-2-yl)-2-(cyclopropylamino)-6-methoxypyrimidin-4-yl)amino)-2,2-dimethyltetrahydro-4H-cyclopenta[d][1,3]dioxol-4-yl)methanol (S9)

Compound **S8** (100 mg, 0.197 mmol) was dissolved in MeCN (2 mL) and cyclopropylamine (168 µL, 1.97 mmol) was added. The reaction was heated to 80 °C for 1 h. The solvent was evaporated and the residue was purified by column chromatography on silica gel, eluting with EtOAc/hexane to give the title compound (86.3 mg 88%) as a yellow solid. **MS** (ESI): 498 (M+H).

5-(Benzo[d]thiazol-2-yl)-2-(cyclopropylamino)-6-((1R,2S,3R,4R)-2,3-dihydroxy-4-(hydroxymethyl)cyclopentylamino)pyrimidin-4(3H)-one (4)

Compound **S9** (50 mg, 0.104 mmol) was suspended in concentrated HCl (2 mL) and heated to 100 °C for 4 h. The residue was cooled to room temperature and partitioned between 1 M K_2CO_3 and DCM. The

organic layer was separated and evaporated to dryness to give the title compound (38 mg, 86 %) as a white solid.

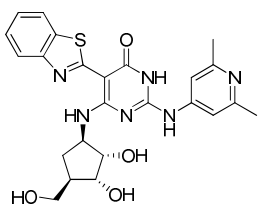
^{1}H NMR (DMSO) δ 7.90 (d, *J* = 8 Hz, 1H), 7.74 (d, *J* = 8 Hz, 1H), 7.37 (t, *J* = 5 Hz, 1H), 7.21 (t, *J* = 5 Hz, 1H), 4.76 (s, 1H), 4.65 (m, 1H), 4.49, (s, 1H), 4.39-4.36 (m, 1H), 3.80-3.76 (m, 2H), 3.49-3.32 (m, 2H), 2.74-2.71 (m, 1H), 2.39-2.31 (m, 2H), 1.97 (m, 1H), 1.24-1.21 (m, 2H), 0.76 (d, *J* = 5.2, 2H), 0.55 (d, *J* = 5.2, 2H); **^{13}C NMR** (DMSO) δ 175.4, 161.2, 159.8, 155.4, 152.9, 136.5, 127.1, 125.0, 124.6, 122.2, 106.4, 88.6, 77.2, 65.2, 49.8, 35.5, 25.4, 23.7, 8.6 (2C); **LCMS** (ESI) 1.96 min, 430 (M+H); **HRMS** (ESI, M+H) calculated for $C_{20}H_{24}N_5O_4S_2$: 430.1549 found 430.1555.

Kinase Selectivity Data for Compound **4** (kinases with <100 fold selectivity versus Merck generated IRAK4 IC_{50}, see below for details):

Kinase	**IC_{50} (nM)**
IRAK4 Merck generated (Invitrogen generated)	25 (58)
FLT3	138
CSF1R	499
CLK2	944
KIT	1639
MINK1	1913
DYRK3	2094

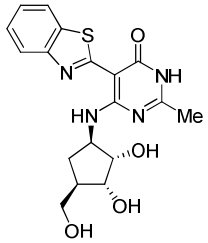
The following compounds were prepared using a similar synthetic sequence to compound **4**:

5-(Benzo[d]thiazol-2-yl)-6-(((1R,2S,3R,4R)-2,3-dihydroxy-4-(hydroxymethyl)cyclopentyl)amino)-2-((2,6-dimethylpyridin-4-yl)amino)pyrimidin-4(3H)-one (5)



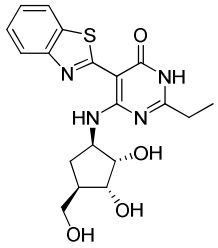
^{1}H NMR (DMSO) δ 11.40 (m, 1H), 11.15 (d, *J* = 6.8 Hz, 1H), 11.00 (s, 1H), 7.98 (d, *J* = 7.6 Hz, 1H), 7.89-7.50 (m, 3H), 7.42 (t, *J* = 8 Hz, 1H), 7.30 (t, *J* = 8 Hz, 1H), 5.00-4.60 (m, 3H), 4.44 (m, 1H), 3.90-3.70 (m, 2H), 3.60-3.40 (m, 2H), 2.62 (S, 6H), 2.40 (m, 1H), 2.05 (m, 1H), 1.44 (m, 1H); **LCMS**: 1.91 min, 495 (M+H)

5-(Benzo[d]thiazol-2-yl)-6-((1R,2S,3R,4R)-2,3-dihydroxy-4-(hydroxymethyl)cyclopentylamino)-2-methylpyrimidin-4(3H)-one (6)



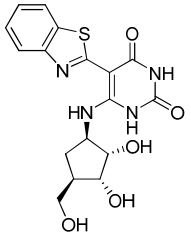
^{1}H NMR (DMSO) δ 12.21 (br s, 1H), 11.03 (d, *J* = 7.6 Hz, 1H), 7.97 (d, *J* = 8 Hz, 1H), 7.87 (d, *J* = 8 Hz, 1H), 7.43 (t, *J* = 5 Hz, 1H), 7.30 (t, *J* = 5 Hz, 1H), 4.50-4.48 (m, 1H), 3.80-3.77 (m, 2H), 3.49-3.46 (m, 2H), 2.31-2.29 (m, 1H), 2.30 (s, 3H), 2.00-1.98 (m, 1H), 1.25-1.20 (m 1H); **LCMS** 1.53 min, 389 (M+H)

5-(Benzo[d]thiazol-2-yl)-6-((1R,2S,3R,4R)-2,3-dihydroxy-4-(hydroxymethyl)cyclopentylamino)-2-ethylpyrimidin-4(3H)-one (7)



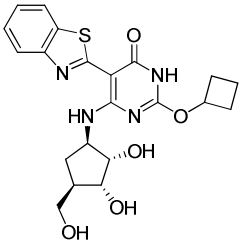
^{1}H NMR (DMSO) δ 12.19 (s, 1H), 11.01 (d, *J* = 7.2 Hz, 1H), 7.98 (d, *J* = 8 Hz, 1H), 7.87 (d, *J* = 8 Hz, 1H), 7.44 (t, *J* = 5 Hz, 1H), 7.30 (t, *J* = 5 Hz, 1H), 3.84-3.79 (m, 2H), 3.48-3.43 (m, 2H), 2.59-2.53 (m, 2H), 2.38-2.30 (m, 1H), 1.99 (br s, 1H), 1.31-1.20 (m, 4H); **LCMS** 1.59 min, 403 (M+H)

5-(Benzo[d]thiazol-2-yl)-6-((1R,2S,3R,4R)-2,3-dihydroxy-4-(hydroxymethyl)cyclopentylamino)pyrimidine-2,4(1H,3H)-dione (8)



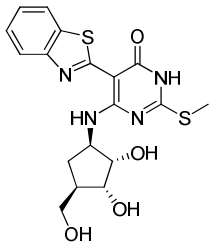
^{1}H NMR (DMSO) δ 7.94 (d, *J* = 8 Hz, 1H), 7.77 (d, *J* = 8 Hz, 1H), 7.40 (t, *J* = 5 Hz, 1H), 7.26 (t, *J* = 5 Hz, 1H), 4.17-4.13 (m, 1H), 3.49-3.42 (m, 3H), 2.36-2.89 (m, 1H), 2.01-2.00 (m, 1H), 1.41- 1.36 (m, 1H); **LCMS** 1.87 min, 391 (M+H)

5-(Benzo[d]thiazol-2-yl)-2-cyclobutoxy-6-((1R,2S,3R,4R)-2,3-dihydroxy-4-(hydroxymethyl)cyclopentylamino)pyrimidin-4(3H)-one (9)



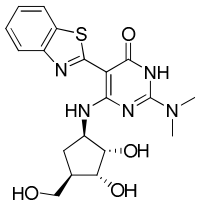
^{1}H NMR (DMSO) δ 11.07 (s, 1H), 10.96 (s, 1H), 7.96-7.84 (m, 1H); 7.82-7.76 (m, 1H), 7.41-7.38 (m, 1H), 7.26-7.24 (m, 1H), 4.35-4.33 (m, 1H), 4.15-4.13 (m, 2H), 3.82-3.77 (m, 2H), 3.51-3.45 (m, 2H), 3.29-3.26 (m, 2H), 2.39-2.31 (m, 1H), 2.17-2.13 (m, 2H), 1.86-1.68 (m, 2H); **LCMS** 2.00 min, 445 (M+H)

5-(Benzo[d]thiazol-2-yl)-6-((1R,2S,3R,4R)-2,3-dihydroxy-4-(hydroxymethyl)cyclopentylamino)-2-(methylthio)pyrimidin-4(3H)-one (10)



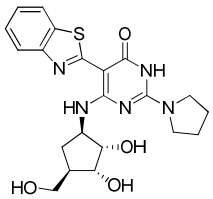
^{1}H NMR (DMSO) δ 11.05 (d, *J* = 6.4, 1H), 7.99 (d, *J* = 8 Hz, 1H), 7.86 (d, *J* = 8 Hz, 1H), 7.43 (t, *J* = 5 Hz, 1H), 7.29 (t, *J* = 5 Hz, 1H), 4.48-4.42 (m, 1H), 3.83-3.78 (m, 2H), 2.57 (s, 3H), 2.47-2.31 (m, 1H), 2.01-2.00 (m, 1H), 1.35-1.21 (m, 2H); **LCMS** 1.62 min, 421 (M+H)

5-(Benzo[d]thiazol-2-yl)-6-(((1R,2S,3R,4R)-2,3-dihydroxy-4-(hydroxymethyl)cyclopentyl)amino)-2-(dimethylamino)pyrimidin-4(3H)-one (11)



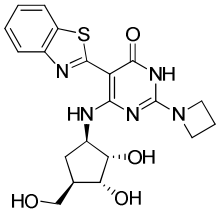
^{1}H NMR (DMSO) δ 10.78 (m, 2H), 7.90 (d, *J* = 8 Hz, 1H), 7.74 (d, *J* = 7.6 Hz, 1H), 7.36 (t, *J* = 8.2 Hz, 1H), 7.20 (t, *J* = 8.2 Hz, 1H), 4.25 (m, 1H), 3.84-3.73 (m, 2H), 3.55-3.40 (m, 2H), 3.16 (s, 6H), 2.34 (m, 1H), 1.99 (m, 1H), 1.27 (m, 1H); **LCMS**: 1.61 min, 418 (M+H)

5-(Benzo[d]thiazol-2-yl)-6-(((1R,2S,3R,4R)-2,3-dihydroxy-4-(hydroxymethyl)cyclopentyl)amino)-2-(pyrrolidin-1-yl)pyrimidin-4(3H)-one (12)



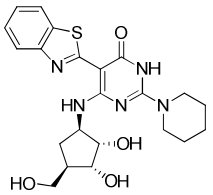
^{1}H NMR (DMSO) δ 10.99 (s, 1H), 10.81 (d, *J* = 6.4 Hz, 1H), 7.91 (d, *J* = 8 Hz, 1H), 7.76 (d, *J* = 8 Hz, 1H), 7.37 (dd, *J* = 8, 7.2 Hz, 1H), 7.23 (dd, *J* = 8, 7.2 Hz, 1H), 4.30 (m, 1H), 3.85-3.20 (m, 12H), 2.34 (m, 1H), 1.99 (m, 1H), 1.30 (m, 1H); **LCMS**: 2.05 min., 444 (M+H)

2-(Azetidin-1-yl)-5-(benzo[d]thiazol-2-yl)-6-(((1R,2S,3R,4R)-2,3-dihydroxy-4-(hydroxymethyl)cyclopentyl)amino)pyrimidin-4(3H)-one (13)



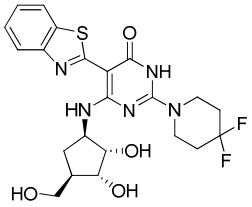
^{1}H NMR (DMSO) δ 11.08 (s, 1H), 10.88 (d, *J* = 7.2 Hz, 1H), 7.89 (d, *J* = 7.6 Hz, 1H), 7.74 (d, *J* = 8 Hz, 1H), 7.36 (t, *J* = 8.4 Hz, 1H), 7.21 (t, *J* = 8 Hz, 1H), 4.30 (m, 1H), 4.11 (t, *J* = 7.6 Hz, 4H), 3.81-3.75 (m, 2H), 3.51-3.40 (m, 2H), 2.40-2.24 (m, 2H), 2.06-180 (m, 2H), 1.25 (m, 1H); **LCMS**: 2.01 min, 430 (M+H)

5-(Benzo[d]thiazol-2-yl)-6-(((1R,2S,3R,4R)-2,3-dihydroxy-4-(hydroxymethyl)cyclopentyl)amino)-2-(piperidin-1-yl)pyrimidin-4(3H)-one· (14)



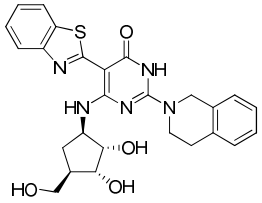
^{1}H NMR (DMSO) δ 10.6 (s, 1H), 10.76 (d, *J* = 7.2 Hz, 1H), 7.90 (d, *J* = 8 Hz, 1H), 7.74 (d, *J* = 7.6 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.21 (t, *J* = 8 Hz, 1H), 4.29 (m, 1H), 3.82-3.75 (m, 2H), 3.69-3.68 (m, 4H), 3.53-3.42 (m, 2H), 2.33 (m, 1H), 1.99 (m, 1H), 1.63-1.45 (m, 5H), 1.26 (m, 1H); **LCMS**: 1.77 min, 458 (M+H)

5-(Benzo[d]thiazol-2-yl)-2-(4,4-difluoropiperidin-1-yl)-6-(((1R,2S,3R,4R)-2,3-dihydroxy-4-(hydroxymethyl)cyclopentyl)amino)pyrimidin-4(3H)-one (15)



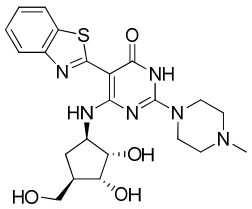
^{1}H NMR (DMSO) δ 11.15 (s, 1H), 10.81 (d, *J* = 6.8 Hz, 1H), 7.91 (d, *J* = 7.6 Hz, 1H), 7.76 (d, *J* = 7.6 Hz, 1H), 7.38 (t, *J* = 8 Hz, 1H), 7.23 (t, *J* = 8 Hz, 1H), 4.30 (m, 1H), 3.95-3.20 (m, 7H), 2.34 (m, 1H), 2.15-1.88 (m, 5H), 1.30 (m, 1H); **LCMS**: 1.92 min, 493 (M+H)

5-(Benzo[d]thiazol-2-yl)-2-(3,4-dihydroisoquinolin-2(1H)-yl)-6-(((1R,2S,3R,4R)-2,3-dihydroxy-4-(hydroxymethyl)cyclopentyl)amino)pyrimidin-4(3H)-one (16)



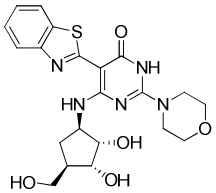
^{1}H NMR (DMSO) δ 11.03 (s, 1H), 10.81 (d, *J* = 6.8 Hz, 1H), 7.91 (d, *J* = 7.2 Hz, 1H), 7.76 (d, *J* = 8 Hz, 1H), 7.37 (dd, *J* = 8, 7.2 Hz, 1H), 7.25-7.15 (m, 5H), 4.87 (s, 2H), 4.36 (m, 1H), 3.95-3.40 (m, 6H), 2.92 (t, *J* = 6.2 Hz, 2H), 2.38 (m, 1H), 2.03 (m, 1H), 1.32 (m, 1H); **LCMS**: 2.10 min., 505 (M+H)

5-(Benzo[d]thiazol-2-yl)-6-(((1R,2S,3R,4R)-2,3-dihydroxy-4-(hydroxymethyl)cyclopentyl)amino)-2-(4-methylpiperazin-1-yl)pyrimidin-4(3H)-one (17)



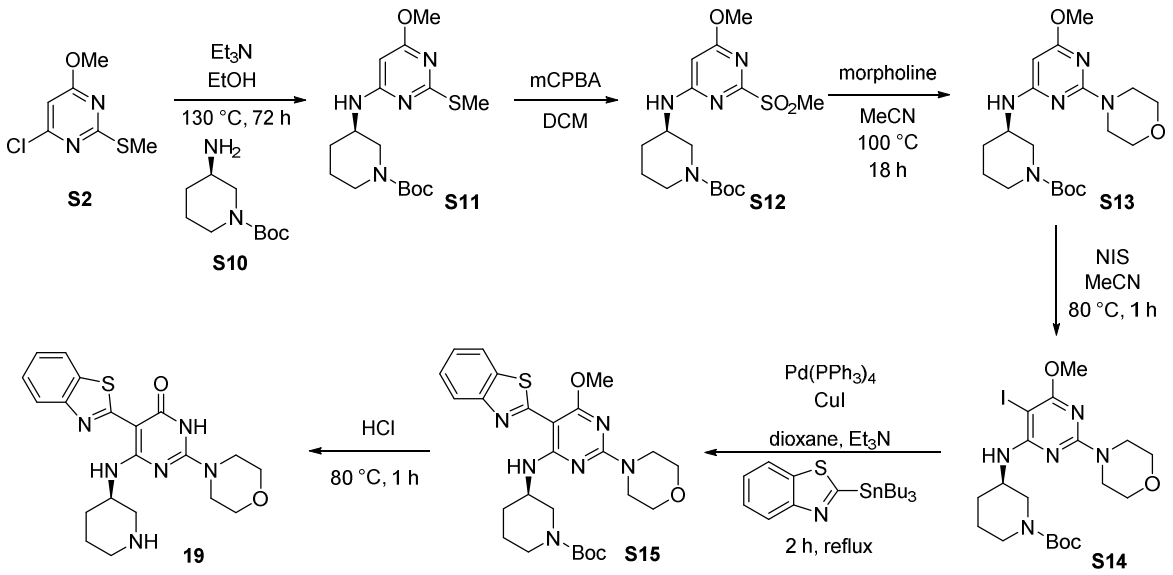
^{1}H NMR (DMSO) δ 11.23 (s, 1H), 10.85 (d, *J* = 7.2 Hz, 1H), 10.60 (m, 1H), 7.92 (d, *J* = 8 Hz, 1H), 7.78 (d, *J* = 8 Hz, 1H), 7.37 (t, *J* = 8.3 Hz, 1H), 7.24 (t, *J* = 8.3 Hz, 1H), 4.57 (m, 1H) 4.30 (m, 1H), 3.80 (m, 2H), 3.60-3.20 (m, 8H), 3.10 (m, 1H), 2.78 (s, 3H), 2.33 (m, 1H), 2.02 (m, 1H), 1.32 (m, 1H); **LCMS**: 1.81 min, 473 (M+H)

5-(Benzo[d]thiazol-2-yl)-6-(((1R,2S,3R,4R)-2,3-dihydroxy-4-(hydroxymethyl)cyclopentyl)amino)-2-morpholinopyrimidin-4(3H)-one (18)



^{1}H NMR (DMSO) δ 10.99 (s, 1H), 10.81 (d, *J* = 6.8 Hz, 1H), 7.91 (d, *J* = 8 Hz, 1H), 7.76 (d, *J* = 7.6 Hz, 1H), 7.37 (t, *J* = 8 Hz, 1H), 7.22 (t, *J* = 7.6 Hz, 1H), 4.30 (m, 1H), 3.80 (m, 2H), 3.75-3.40 (m, 10H), 2.32 (m, 1H), 1.99 (m, 1H), 1.26 (m, 1H); **LCMS**: 1.98 min, 460 (M+H)

Compounds **19-31** were prepared using the methods outlined below, with **19** as an example.



Step 1: (R)-Tert-butyl 3-(6-methoxy-2-(methylthio)pyrimidin-4-ylamino)piperidine-1-carboxylate (S11)

Compound **S2** (3.6 g, 18.9 mmol) and (R)-1-Boc-3-aminopiperidine (S10) (9.45 g, 47.2 mmol) were dissolved in ethanol (50 mL) and TEA (10.5 mL, 76 mmol) was added. The reaction was sealed and heated to 130 °C for 72 h. The orange solution was concentrated and the residue was purified by column chromatography on silica gel, eluting with EtOAc/hexane to give the title compound as a white foam (3.08 g, 48%). **^{1}H NMR** ($CDCl_3$) δ 5.40 (s, 1H), 4.78 (br s, 1H), 3.88 (s, 3H), 3.84-3.81 (m, 1H), 3.58-3.56 (m, 2H), 3.17-3.05 (m, 2H), 2.49 (s, 3H), 2.04-1.91 (m, 1H), 1.75-1.67 (m, 1H), 1.57-1.51 (m, 2H), 1.44 (s, 9H); **^{13}C NMR** ($CDCl_3$) δ 170.7, 169.8, 162.9, 154.8, 80.9, 79.7, 60.3, 53.4, 48.4, 47.1, 30.0, 28.3, 22.9, 13.8; **LCMS** (ESI) 2.30 min, 355 (M+H).

Step 2: (R)-Tert-butyl 3-(6-methoxy-2-(methylsulfonyl)pyrimidin-4-ylamino)piperidine-1-carboxylate (S12)

Compound **S11** (526 mg, 1.48 mmol) was dissolved in DCM (20 mL) and cooled to 0 °C. mCPBA (640 mg, 3.71 mmol) was added in one portion and the reaction mixture was stirred at room temperature for 1

h. Sat. $NaHCO_3$ was added and the mixture stirred for 10 min. The layers were separated, the organic was dried ($MgSO_4$), filtered, and concentrated to give the title compound (544 mg, 99%) as a yellow foam that was used without further purification. **LCMS** (ESI) 2.42 min, 387 (M+H).

Step 3: (R)-Tert-butyl 3-(6-methoxy-2-morpholinopyrimidin-4-ylamino)piperidine-1-carboxylate (S13)

Compound **S12** (150 mg, 0.405 mmol) was dissolved in acetonitrile (2 mL) and morpholine (0.282 mL, 3.24 mmol) was added, The solution was sealed and heated to 100 °C for 18 h. The solution was concentrated and the residue was purified by column chromatography on silica gel, eluting with EtOAc/hexane to give the title compound (113 mg, 70%) as a colorless oil. **^{1}H NMR** ($CDCl_3$) δ 5.13 (s, 1H), 4.52-4.51 (m, 1H), 3.82 (s, 3H), 3.72 (s, 8H), 3.62-3.59 (m, 2H), 3.14-3.10 (m, 2H), 1.94 (m, 1H), 1.72-1.70 (m, 1H), 1.55-1.53 (m, 2H), 1.43 (s, 9H); **^{13}C NMR** ($CDCl_3$) δ 171.1, 163.9, 161.4, 154.9, 79.8, 75.5, 66.8, 53.0, 52.6, 48.8, 47.1, 44.3, 30.3, 28.4, 23.0; **LCMS** (ESI) 2.02 min, 394 (M+H).

Step 4: (R)-Tert-butyl 3-(5-iodo-6-methoxy-2-morpholinopyrimidin-4-ylamino)piperidine-1-carboxylate (S14)

Compound **S13** (113 mg, 0.287 mmol) was dissolved in acetonitrile (3 mL) and NIS (129 mg, 0.574 mmol) was added. The solution was heated to reflux for 1 h. The solvent was evaporated and the residue dissolved in EtOAc, washed with sat. $NaHCO_3$, NaS_2O_3, water, and brine. The organics were dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography on silica gel, eluting with EtOAc/hexane to give the title compound (96 mg, 64%) as a colorless foam. **^{1}H NMR** ($CDCl_3$) δ 5.07 (d, J = 6.8 Hz, 1H), 3.99 (br s, 1H), 3.88 (s, 3H), 3.86-3.73 (m, 8H), 3.43 (br s, 3H), 1.90-1.86 (m, 1H), 1.70-1.63 (m, 2H), 1.56-1.55 (m, 1H), 1.42 (s, 9H); **^{13}C NMR** ($CDCl_3$) δ 167.4, 161.2, 160.8, 154.8, 79.6, 66.8, 54.0, 48.6, 47.3, 44.4, 29.9, 28.4, 28.5, 28.4, 22.6; **LCMS** (ESI) 2.95 min, 520 (M+H).

Step 5: (R)-Tert-butyl 3-(5-(benzo[d]thiazol-2-yl)-6-methoxy-2-morpholinopyrimidin-4-ylamino)piperidine-1-carboxylate (S15)

2-Tributylstannylbenzothiazole (221 mg, 0.520 mmol), compound **S14** (150 mg, 0.289 mmol), Tetrakis(triphenylphosphine)palladium (67 mg, 0.0578 mmol), and CuI (11 mg, 0.0578 mmol) were combined. Dioxane (4 mL) was added followed by Et_3N (161 μL, 1.16 mmol) and the mixture was degassed and heated to reflux for 2 h. The solution was cooled to room temperature and an aqueous 10% KF solution was added and the mixture was stirred for 30 min. The mixture was diluted with EtOAc and washed with water, brine, dried ($MgSO_4$), filtered and evaporated to dryness. The residue was purified by column chromatography on silica gel, eluting with EtOAc/hexane to give the title compound (213 mg, 78%) as a yellow solid. **^{1}H NMR** ($CDCl_3$) δ 10.74 (br s, 1H), 7.86-7.82 (m, 2H), 7.41 (t, *J* = 7.2 Hz, 1H), 7.27 (t, *J* = 7.2 Hz, 1H), 4.25 (br s, 1H), 4.09 (s, 3H), 3.87 (br s, 4H), 3.78-3.76 (m, 4H), 3.52 (br s, 4H), 2.03 (br s, 1H), 1.90 (br s, 1H), 1.76-1.73 (m, 1H), 1.66-1.64 (m, 1H), 1.33 (s, 9H); **^{13}C NMR** ($CDCl_3$) δ 167.6, 160.8, 159.3, 154.9, 151.3, 144.4, 133.4, 125.4, 123.4, 121.0, 120.5, 105.9, 100.2. 86.7, 79.3, 76.6, 67.0, 53.3, 46.5, 44.2, 30.2, 28.3; **LCMS** (ESI) 3.28 min, 527 (M+H).

Step 6: (R)-5-(Benzo[d]thiazol-2-yl)-2-morpholino-6-(piperidin-3-ylamino)pyrimidin-4(3H)-one (19)

Compound **S15** (260 mg, 0.494 mmol) was dissolved in concentrated HCl (7 ml) and heated to 80 °C for 1 h. The solution was evaporated to approximately 1 mL. The residue was basified with 1M NaOH and diluted with water, filtered and the solid washed with water. The white solid was dried to give the title compound (199 mg, 98%) as a white solid. **^{1}H NMR** (DMSO) δ 10.86 (d, *J* = 7.2 Hz, 1H), 7.92 (d, *J* = 8 Hz, 1H), 7.72 (d, *J* = 8 Hz, 1H), 7.38 (t, *J* = 8.4 Hz, 1H), 7.22 (t, *J* = 8.4 Hz, 1H), 4.18-4.16 (m, 1H), 3.67 (m, 8H), 3.15-3.12 (m, 1H), 2.87-2.83 (m, 1H), 2.74-2.64 (m, 2H), 1.95 (m, 1H), 1.75-1.45 (m, 4H); **^{13}C NMR** (DMSO) δ 174.3, 168.5, 159.9, 159.7, 155.8, 139.2, 144.6, 125.9, 124.1, 122.6, 121.7, 72.0, 59.4, 55.7, 52.1, 47.4, 35.7, 29.8; **LCMS** (ESI) 1.49 min, 413 (M+H); **HRMS** (ESI, M+H) calculated for $C_{20}H_{25}N_6O_2S$: 413.1760 found 413.1765.

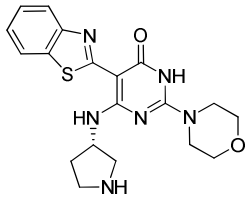
Kinase Selectivity Data for Compound **19** (kinases with <100 fold selectivity versus Merck generated IRAK4 IC_{50}, see below for details):

Kinase	IC_{50} (nM)
IRAK4 Merck generated (Invitrogen generated)	19 (30)
FLT3	28
KIT	70
CSF1R	189

PDGFRA	193
MERTK	553
CLK2	612
NTRK3 (TRKC)	808
AXL	847
BLK	885
NTRK2 (TRKB)	1222
NTRK1 (TRKA)	1858

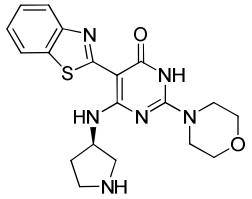
The following compounds were prepared using a similar synthetic sequence to compound **19**:

(S)-5-(Benzo[d]thiazol-2-yl)-2-morpholino-6-(pyrrolidin-3-ylamino)pyrimidin-4(3H)-one (20)



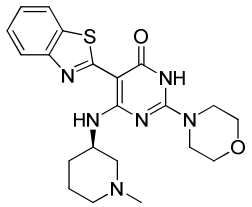
^{1}H NMR (DMSO) δ 10.77 (d, *J* = 6.4 Hz, 1H), 7.73 (d, *J* = 8 Hz, 1H), 7.53 (d, *J* = 8 Hz, 1H), 7.23 (t, *J* = 8.4 Hz, 1H), 7.05 (t, *J* = 8.4 Hz, 1H), 4.49 (m, 1H), 3.60-3.42 (m, 8 H), 3.42-3.06 (m, 5H), 2.13-2.10 (m, 1H), 1.77-1.74 (m, 1H); **LCMS** 1.72 min, 399 (M+H)

(R)-5-(Benzo[d]thiazol-2-yl)-2-morpholino-6-(pyrrolidin-3-ylamino)pyrimidin-4(3H)-one (21)



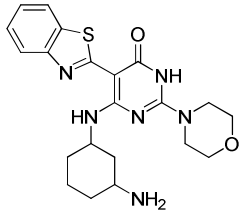
^{1}H NMR (DMSO) δ 10.78 (d, *J* = 6.4 Hz, 1H), 7.73 (d, *J* = 8 Hz, 1H), 7.53 (d, *J* = 8 Hz, 1H), 7.26 (t, *J* = 8.4 Hz, 1H), 7.04 (t, *J* = 8.4 Hz, 1H), 4.52 (m, 1H), 3.60-3.42 (m, 8 H), 3.42-3.06 (m, 5H), 2.13-2.11 (m, 1H), 1.77-1.72 (m, 1H); **LCMS** 1.76 min, 399 (M+H)

(R)-5-(Benzo[d]thiazol-2-yl)-6-(1-methylpiperidin-3-ylamino)-2-morpholinopyrimidin-4(3H)-one (22)



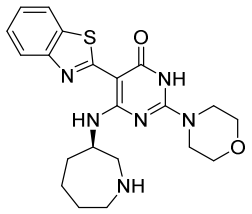
^{1}H NMR (DMSO) δ 11.28 (br s, 1H), 11.12 (s, 1H), 10.66 (d, *J* = 7.2 Hz, 1H), 7.95-7.93 (m, 1H), 7.77-7.73 (m, 1H), 7.43-7.34 (m, 1H), 7.28-7.21 (m, 1H), 4.61-4.59 (m, 1H), 3.77-3.66 (m, 8H), 3.49-3.37 (m, 2H), 3.06 (m, 1H), 2.88-2.80 (m, 2H), 2.75 (s, 3H), 2.13-2.10 (m, 1H), 1.95 (br s, 1H), 1.71-1.64 (m, 1H); **LCMS** 1.86 min, 427 (M+H)

6-(3-Aminocyclohexylamino)-5-(benzo[d]thiazol-2-yl)-2-morpholinopyrimidin-4(3H)-one (23)



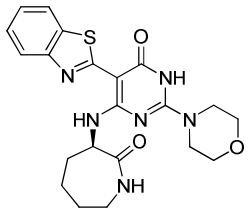
^{1}H NMR (major) (DMSO) δ 11.06 (br s, 1H), 10.70 (d, *J* = 7.2 Hz, 1H), 8.23 (br s, 2H), 7.94 (d, *J* = 8 Hz, 1H), 7.76 (d, *J* = 8 Hz, 1H), 7.38 (t, *J* = 8.4 Hz, 1H), 7.23 (t, *J* = 8.4 Hz, 1H), 5.96 (br s, 2H), 4.08-4.04, (m, 1H), 3.68 (m, 8H), 3.20-3.15 (m, 1H), 2.06-1.74 (m, 3H), 1.49-1.30 (m, 3H); **LCMS** 1.87 min, 427 (M+H)

(R)-6-(azepan-3-ylamino)-5-(benzo[d]thiazol-2-yl)-2-morpholinopyrimidin-4(3H)-one (24)



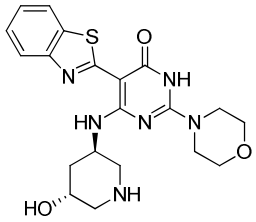
^{1}H NMR (DMSO) δ 11.14 (br s, 1H), 10.70 (d, *J* = 6.8 Hz, 1H), 9.39 (br s, 1H), 9.13 (br s, 1H), 7.95 (d, *J* = 8 Hz, 1H), 7.75 (d, *J* = 8 Hz, 1H), 7.40 (t, *J* = 8.4 Hz, 1H), 7.26 (t, *J* = 8.4 Hz, 1H), 4.99 (br s, 3H), 4.58, (m, 1H), 3.76-3.65 (m, 8H), 3.41-3.29 (m, 2H), 3.15 (m, 2H), 2.12-1.95 (m, 1H), 1.95-1.89 (m, 3H), 1.80-1.76 (m, 1H); **LCMS** 1.89 min, 427 (M+H)

(R)-3-(5-(Benzo[d]thiazol-2-yl)-2-morpholino-6-oxo-1,6-dihydropyrimidin-4-ylamino)azepan-2-one (25)



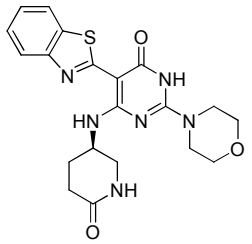
^{1}H NMR (DMSO) δ 11.10 (br s, 1H), 10.71 (d, *J* = 6.8 Hz, 1H), 9.40 (br s, 1H), 9.02 (br s, 1H), 7.90 (d, *J* = 8 Hz, 1H), 7.71 (d, *J* = 8 Hz, 1H), 7.31 (t, *J* = 8.4 Hz, 1H), 7.25 (t, *J* = 8.4 Hz, 1H), 5.12 (br s, 1H), 4.49, (m, 1H), 3.70-3.61 (m, 8H), 3.40-3.21 (m, 2H), 3.01 (m, 2H), 2.01-1.85 (m, 1H), 1.90-1.83 (m, 3H), 1.78-1.71 (m, 1H); **LCMS** 2.12 min, 441 (M+H)

5-(benzo[d]thiazol-2-yl)-6-(((3R,5R)-5-hydroxypiperidin-3-yl)amino)-2-morpholinopyrimidin-4(3H)-one (26)



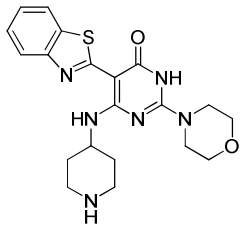
^{1}H NMR (DMSO) δ 11.11 (s, 1H), 10.72 (d, *J* = 7.6 Hz, 1H), 9.36-9.34 (m, 1H), 9.01 (m, 1H), 7.93 (d, *J* = 7.6 Hz, 1H), 7.76 (d, *J* = 7.6 Hz, 1H), 7.40 (t, *J* = 7.2 Hz, 1H), 7.24 (t, *J* = 7.2 Hz, 1H), 4.64-4.62 (m, 1H), 4.31 (s, 1H), 3.74-3.68 (m, 8H), 3.45-3.38 (m, 1H), 3.06 (s, 2H), 2.93-2.85 (m, 1H), 2.14-2.11 (m, 1H), 1.99-1.93 (m, 1H), 1.21 (s, 1H); **LCMS** 1.69 min, 429 (M+H)

(R)-5-(Benzo[d]thiazol-2-yl)-2-morpholino-6-(6-oxopiperidin-3-ylamino)pyrimidin-4(3H)-one (27)



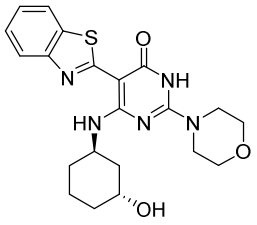
^{1}H NMR (DMSO) δ 11.15 (d, *J* = 7.6 Hz, 1H), 7.93 (d, *J* = 8 Hz, 1H), 7.70 (d, *J* = 8 Hz, 1H), 7.58 (s, 1H), 7.38 (t, *J* = 8.4 Hz, 1H), 7.23 (t, *J* = 8.4 Hz, 1H), 4.54-4.51, (m, 1H), 3.68 (m, 8H), 3.52-3.49 (m, 1H), 3.32-3.20 (m, 1H), 2.49-2.48 (m, 2H), 2.47-2.36 (m, 2H), 2.09-1.97 (m, 2H); **LCMS** 1.94 min, 427 (M+H)

5-(Benzo[d]thiazol-2-yl)-2-morpholino-6-(piperidin-4-ylamino)pyrimidin-4(3H)-one (28)



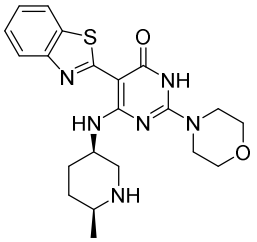
^{1}H NMR (DMSO) δ 10.82 (d, *J* = 7.2 Hz, 1H), 7.91 (d, *J* = 8 Hz, 1H), 7.72 (d, *J* = 8 Hz, 1H), 7.36 (t, *J* = 8.4 Hz, 1H), 7.25 (t, *J* = 8.4 Hz, 1H), 4.21 (m, 1H), 3.66 (m, 8H), 3.30 (s, 3H), 3.07-3.03 (m, 2H), 2.80-2.65 (m, 2H), 2.01-1.99 (m, 2H), 1.61-1.53 (m, 2H); **LCMS** 1.74 min, 413 (M+H)

5-(benzo[d]thiazol-2-yl)-6-(((1R,3R)-3-hydroxycyclohexyl)amino)-2-morpholinopyrimidin-4(3H)-one (29)



^{1}H NMR (DMSO) δ 10.98 (s, 1H), 10.75 (d, *J* = 7.2 Hz, 1H), 7.92 (d, *J* = 7.2 Hz, 1H), 7.74 (d, *J* = 7.2 Hz, 1H), 7.34 (t, *J* = 8.4 Hz, 1H), 7.20 (t, *J* = 8.4 Hz, 1H), 4.71 (br s, 2H), 4.06-4.02 (m, 1H), 3.66 (m, 8H), 3.57-3.51 (m, 1H), 2.20-2.10 (m, 1H), 1.97-1.95 (m, 1H), 1.81-1.68 (M, 2H), 1.58-1.55 (m, 1H), 1.38-1.1.14 (m, 3H); **LCMS** 2.04 min, 428 (M+H)

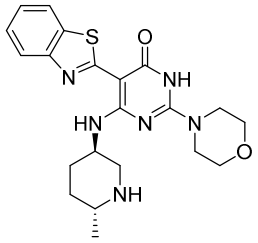
5-(benzo[d]thiazol-2-yl)-6-(((3R,6S)-6-methylpiperidin-3-yl)amino)-2-morpholinopyrimidin-4(3H)-one (30)



^{1}H NMR (DMSO) δ 11.11 (br s, 1H), 11.00 (d, *J* = 6.4 Hz, 1H), 9.73 (m, 1H), 8.32 (m, 1H), 7.94 (d, *J* = 6.4 Hz, 1H), 7.74 (d, *J* = 6.4 Hz, 1H), 7.42 (t, *J* = 7.2 Hz, 1H), 7.27 (t, *J* = 7.2 Hz, 1H), 4.42 (s, 1H), 3.71-3.66 (m,

8H), 3.32 (m, 2H), 3.18-3.14 (m, 1H), 2.05-1.98 (m, 3H), 1.83-1.80 (m, 1H), 1.28 (d, *J* = 6.4 Hz, 3H); **LCMS** 1.81 min, 427 (M+H)

5-(benzo[d]thiazol-2-yl)-6-(((3R,6R)-6-methylpiperidin-3-yl)amino)-2-morpholinopyrimidin-4(3H)-one (31)



^{1}H NMR (DMSO) δ 11.10 (br s, 1H), 10.65 (d, *J* = 6.4 Hz, 1H), 9.42 (m, 1H), 9.14 (m, 1H), 7.94 (d, *J* = 6.4 Hz, 1H), 7.75 (d, *J* = 6.4 Hz, 1H), 7.40 (t, *J* = 7.2 Hz, 1H), 7.25 (t, *J* = 7.2 Hz, 1H), 4.45 (s, 1H), 3.75-3.65 (m, 8H), 3.53-3.51 (m, 1H), 3.20 (m, 1H), 2.84-2.81 (m, 1H), 2.13-2.10 (m, 1H), 1.97-1.94 (m, 1H), 1.83-1.80 (m, 1H), 1.68-1.65 (m, 1H), 1.28 (d, *J* = 6.4 Hz, 3H); **LCMS** 1.80 min, 427 (M+H)

2. *In vitro* and *in vivo* pharmacokinetic data for compounds 19 and 31 in male Wistar Han rats. For *in vivo* PK, IV dosed at 2 mg/kg as a solution of 1 mg/mL in 20% HPBCD. PO dosed at 10 mg/kg as a suspension of 2 mg/mL in 0.4% methylcellulose.

	19	**31**
Plasma protein binding (rat, % unbound)	36	3.9
Rat hepatocyte Cl (μL/min*10^6 cells)	27	29
AUC (IV, μM*h)	1.82	2.56
AUC (PO, μM*h)	1.10	5.37
%F	13	42
Cl (mL/min/kg)	45	51
Vd (L/kg)	4.16	3.13
$T_{1/2}$ (h)	1.6	3.6
MRT (h)	1.5	3.4
C_{max} (μM)	0.469	1.27
T_{max} (h)	1.5	2.7

3. IRAK4 kinase assay

The kinase activity of IRAK4 is measured by its ability to phosphorylate a fluorescently labeled synthetic peptide in the presence of ATP. The assay format is based on the Immobilized Metal Ion Affinity-Based Fluorescence Polarization (IMAP) platform developed by Molecular Devices. Briefly, reaction mixture (20 μL) contains the assay buffer (20 mM Tris.Cl, pH 7.2, 1 mM $MgCl_2$, 1 mM DTT, and 0.02% Tween 20), 0.5 nM GST tagged IRAK4 (SignalChem), 100 nM peptide substrate and 100 μM ATP. The amino acid sequence of the peptide substrate is 5FAM-RKRQGSVRRRVH-COOH (Cat#: RP7030, Molecular Devices). The reaction is initiated by adding substrates ATP and RP7030, and terminated by adding Stop solution (60 μL) after 30 minutes of incubation at 25 ^{o}C. The Stop solution is prepared with IMAP Progressive Reagent A/B and Binding reagent according to vender's instruction. The extent of phosphorylation of the peptide is measured by changes in Fluorescence Polarization (FP) resulting from binding of phosphate group on the peptide with immobilized metal coordination complexes on the nanoparticles included in the Stop solution. Errors in the calculated IRAK4 IC_{50} values range from 4-12% from duplicate experiments.

4. THP-1 Cellular Assay

THP1-XBlue cells containing an NF-kB-inducible secreted embryonic alkaline phosphatase (SEAP) reporter gene (InvivoGen) were pre-adhered to 96-well assay plates with RPMI 1640 culture media containing 10% fetal calf serum. Compounds in DMSO were added and assay plates were incubated at 37°C for 1 hour. LPS-EK (30 ng/ml, InvivoGen) was subsequently added and allowed to incubate 5 hours. To quantitate SEAP activity, supernatants were harvested and mixed with Quanti-Blue (InvivoGen) detection reagent. Plates were incubated at 25°C for 30 minutes and OD630 was measured using a spectrophotometer.

5. hPBMC Assay

Frozen human PBMCs were thawed and incubated in culture medium with 0.5% FBS (RPMI+GlutMax +amino acid+NaPyruvate) overnight. 36 μL of PBMC cells (20K) were plated into 384-well with compounds and incubated at 37 °C for 0.5 hour. 4 μL of R848 (final concentration 1.5 μg/ml; R&D #4536) was added into each well and incubated at 37 °C for 5 hours. Additional 50 μL of medium were added and the plate was spin at 1000 x g for 5 min. 15 μL of supernatant was transferred to human TNFα assay plate (Meso Scale Discovery #K211BHB) and TNFα was measured according to MSD manufacture's protocol.

6. Kinase Selectivity Data

Selected compounds were screened at Invitrogen to assess kinase selectivity. Compounds were routinely screened against a selected panel of 111 kinases at 3 concentrations (100 nM, 1 μM and 10 μM). This screen included IRAK4 to provide a reference data point to compare to our internally generated IRAK4 IC_{50} data (total 112 kinases screened including IRAK4). Kinases were selected for inclusion based on historical data indicating that they may be potential off target hits for this series of compounds and/or because they are proposed to play a role in inflammation. Compounds that appeared active (>50% activity @ 1 μM) were screened in a 10 point dose response to assess fold selectivity versus IRAK4. A complete listing of all of the kinases that were routinely screened is listed below:

ABL1	GSK3A (GSK3 alpha)	PDK1 Direct
ACVR1B (ALK4)	GSK3B (GSK3 beta)	PIM1
ADRBK1 (GRK2)	HCK	PKN1 (PRK1)
AKT1 (PKB alpha)	HIPK2	PLK1
AMPK A1/B1/G1	IGF1R	PRKACA (PKA)
AMPK A2/B1/G1	IKBKB (IKK beta)	PRKCI (PKC iota)
AURKA (Aurora A)	IKBKE (IKK epsilon)	PRKCQ (PKC theta)
AXL	INSR	PRKCZ (PKC zeta)
BLK	IRAK4	PRKG2 (PKG2)
BMX	ITK	PTK6 (Brk)
BRAF	JAK2	RAF1 (cRAF) Y340D Y341D
BRSK1 (SAD1)	KDR (VEGFR2)	RET
BTK	KIT	ROCK1
CAMK4 (CaMKIV)	LCK	ROS1
CDC42 BPA (MRCKA)	MAP2K1 (MEK1)	RPS6KA3 (RSK2)
CDK1/cyclin B	MAP2K6 (MKK6)	RPS6KB1 (p70S6K)
CDK2/cyclin A	MAP3K8 (COT)	SGK (SGK1)
CDK5/p25	MAPK1 (ERK2)	SRC
CDK5/p35	MAPK13 (p38 delta)	SRMS (Srm)
CHEK1 (CHK1)	MAPK14 (p38 alpha)	SRPK1
CLK2	Direct	STK22D (TSSK1)
CSF1R (FMS)	MAPK8 (JNK1)	SYK
CSNK1D (CK1 delta)	MAPK9 (JNK2)	TAOK2 (TAO1)
CSNK1E (CK1 epsilon)	MAPKAPK2	TBK1

CSNK1G1 (CK1 gamma 1)	MAPKAPK5 (PRAK)	TEK (Tie2)
CSNK2A1 (CK2 alpha 1)	MARK2	TXK
DAPK3 (ZIPK)	MELK	TYRO3 (RSE)
DCAMKL2 (DCK2)	MERTK (cMER)	ZAP70
DYRK1A	MET (cMet)	IRAK1
DYRK3	MINK1	LRRK2
EGFR (ErbB1)	MKNK1 (MNK1)	NUAK1 (ARK5)
EPHA2	MST4	PIK3CA/PIK3R1 (p110
ERBB4 (HER4)	NEK2	alpha/p85 alpha)
FGFR2	NTRK1 (TRKA)	SPHK1
FGR	NTRK2 (TRKB)	DDR2
FLT3	NTRK3 (TRKC)	MAP3K3 (MEKK3)
FRK (PTK5)	PAK2 (PAK65)	MAP3K7/MAP3K7IP1
GRK4	PASK	(TAK1-TAB1)
	PDGFRA (PDGFR alpha)	