Supporting Information

Potent and Selective Amidopyrazole Inhibitors of IRAK4 that are Efficacious in a Rodent Model of Inflammation

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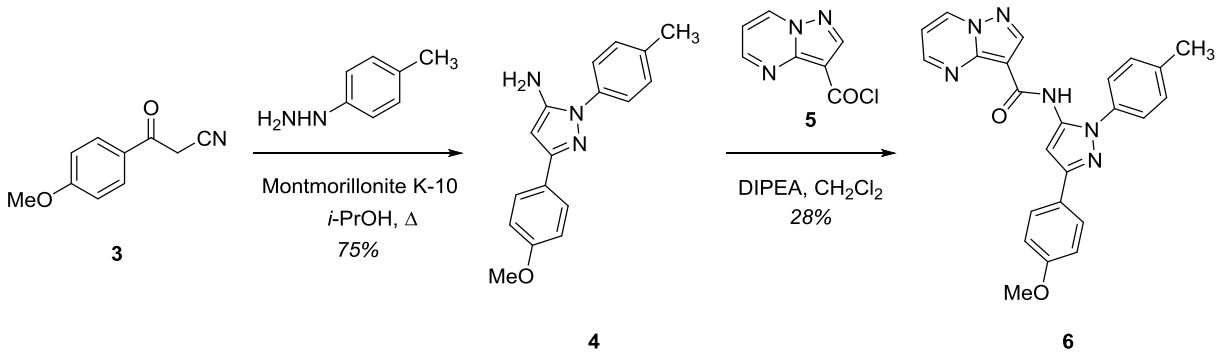
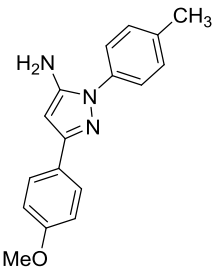
1. Synthesis and characterization for compounds 4-12, 14-33

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, or an Analogix Intelliflash™ 280 instrument. ^{1}H NMR spectrum were recorded on a Varian 400 MHz VNMRS or Bruker DRX500. 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 Phenomenex Gemini C18 column, 4.6 x 100 mm, 5 µm, 110A using a 5 minute gradient of 10 to 95% acetonitrile w/ 0.05% TFA and a flow rate of 1.0 mL/min. The total run time is 10 minutes. 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 compounds were determined to be >95% pure by LC-MS .

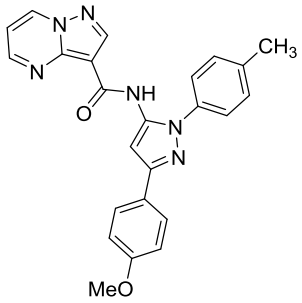
Compounds **6**-**12**, and **14** were prepared using the methods outlined below, with **6** as an example.





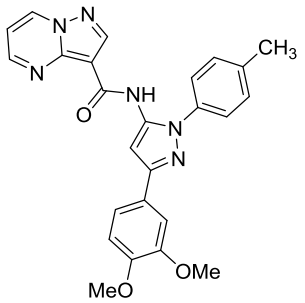
3-(4-methoxyphenyl)-1-(*p*-tolyl)-1*H*-pyrazol-5-amine (4)

A mixture of 3-(4-methoxyphenyl)-3-oxopropanenitrile **3** (690 mg, 3.94 mmol), p-tolylhydrazine (636 mg, 0.400 mmol), montmorillonite K-10 clay (1.0 g), and *i*-PrOH (30 mL) was heated at reflux for 2 d. The mixture was filtered. The filtrate was concentrated *in vacuo*. EtOAc (200 mL) was added and the mixture was washed with 1M NaOH (2 x 200 mL) and brine (200 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to give 828 mg (75%) of pyrazole **4**, that was used without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.72 (m, 2H), 7.47 (m, 2H), 7.27 (m, 2H), 6.90 (m, 2H), 5.88 (s, 1H), 3.81 (s, 3H), 3.79 (br s, 2H), 2.39 (s, 3H).



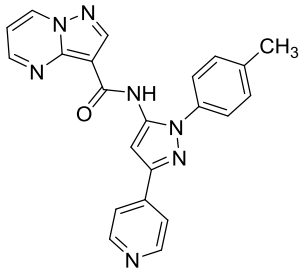
***N*-(3-(4-methoxyphenyl)-1-(*p*-tolyl)-1H-pyrazol-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (6)**

A mixture of pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (51 mg, 0.31 mmol) and thionyl chloride (3 mL) was heated at 80 ˚C for 1.5 h. The mixture was concentrated *in vacuo*. Aminopyrazole **4** (92 mg, 0.33 mmol) and DCM (5 mL) were added. DIPEA (60 µL, 0.34 mmol) was added and the mixture was stirred at rt for 2 h. The mixture was concentrated *in vacuo*, and the residue was purified by silica gel chromatography, eluting with a solvent gradient of 0 to 100% EtOAc in hexanes to give 37 mg (28%) of **6** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.33 (br s, 1H), 8.78 (dd, *J* = 7.2, 2.0 Hz, 1H), 8.74 (s, 1H), 8.71 (dd, *J* = 4.0, 2.0 Hz, 1H), 7.85 (m, 2H), 7.54 (m, 2H), 7.35 (m, 2H), 7.19 (s, 1H), 6.99 (dd, *J* = 7.2, 4.0 Hz, 1H), 6.94 (m, 2H), 3.83 (s, 3H), 2.47 (s, 3H). LCMS rt = 5.32 min, *m/z* = 425.



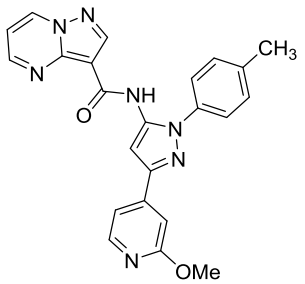
***N*-(3-(3,4-dimethoxyphenyl)-1-(*p*-tolyl)-1H-pyrazol-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (7)**

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.35 (br s, 1H), 8.79 (dd, *J* = 7.0, 1.6 Hz, 1H), 8.73 (s, 1H), 8.31 (dd, *J* = 4.0, 1.6 Hz, 1H), 7.55 (m, 2H), 7.47 (d, *J* = 2.0 Hz, 1H), 7.45 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.36 (m, 2H), 7.21 (s, 1H), 7.00 (dd, *J* = 7.0, 4.0 Hz, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 3.95 (s, 3H), 3.91 (s, 3H), 2.48 (s, 3H). LCMS rt = 4.03 min, *m/z* = 455.



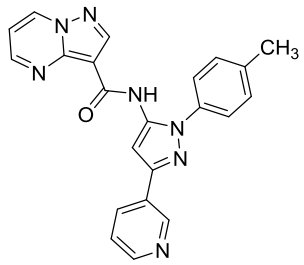
***N*-(3-(pyridin-4-yl)-1-(*p*-tolyl)-1*H*-pyrazol-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (8)**

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (dd, *J* = 4.4, 1.6 Hz, 2H), 8.58 (dd, *J* = 7.0, 2.0 Hz, 1H), 8.46 (dd, *J* = 4.2, 2.0 Hz, 1H), 7.71 (s, 1H), 7.64 (dd, *J* = 4.4, 1.6 Hz, 2H), 7.28 (m, 2H), 7.10 (m, 2H), 6.85 (dd, *J* = 7.0, 4.2 Hz, 1H), 6.62 (s, 1H), 3.36 (s, 3H), 2.30 (s, 3H). LCMS rt = 3.45 min, *m/z*= 396.



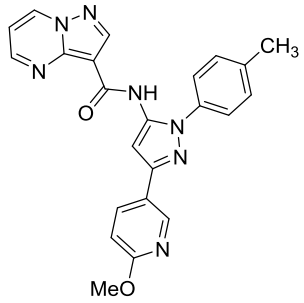
***N*-(3-(2-methoxypyridin-4-yl)-1-(*p*-tolyl)-1*H*-pyrazol-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (9)**

^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.37 (br s, 1H), 8.78 (dd, *J* = 6.8, 1.6 Hz, 1H), 8.74 (s, 1H), 8.30 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.18 (dd, *J* = 5.2, 0.8 Hz, 1H), 7.53 (m, 2H), 7.41 (dd, *J* = 5.6, 1.6 Hz, 1H), 7.37 (m, 2H), 7.29 (s, 1H), 7.23 (dd, *J* = 1.6, 0.8 Hz, 1H), 7.00 (dd, *J* = 6.8, 4.0 Hz, 1H). LCMS rt = 3.90 min, *m/z* = 426.



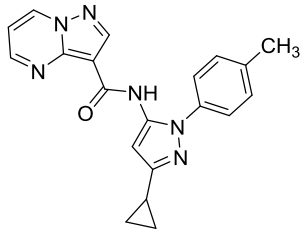
***N*-(3-(pyridin-3-yl)-1-(*p*-tolyl)-1*H*-pyrazol-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (10)**

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.38 (br s, 1H), 9.14 (dd, *J* = 2.2, 0.8 Hz, 1H), 8.78 (dd, *J* = 7.0, 2.0 Hz, 1H), 8.74 (s, 1H), 8.55 (dd, *J* = 4.8, 1.8 Hz, 1H), 8.31 (dd, *J* = 4.4, 2.0 Hz, 1H), 8.19 (ddd, *J* = 8.0, 2.2, 1.8 Hz, 1H), 7.54 (m, 2H), 7.36 (m, 2H), 7.33 (ddd, *J* = 8.0, 4.8, 0.8 Hz), 7.29, (s, 1H), 7.01 (dd, *J* = 7.0, 4.4 Hz, 1H), 2.49 (s, 3H). LCMS rt = 2.98 min, *m/z* = 396.



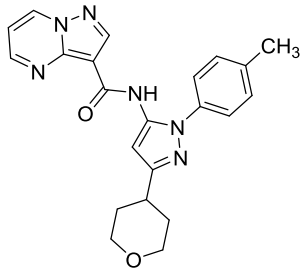
***N*-(3-(6-methoxypyridin-3-yl)-1-(*p*-tolyl)-1*H*-pyrazol-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (11)**

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.35 (br s, 1H), 8.78 (dd, *J* = 7.2, 1.8 Hz, 1H), 8.73 (s, 1H), 8.65 (dd, *J* = 2.4, 0.6 Hz, 1H), 8.31 (dd, *J* = 4.0, 1.8 Hz, 1H), 8.12 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.53 (m, 2H), 7.35 (m, 2H), 7.19 (s, 1H), 7.00 (dd, *J* = 7.2, 4.0 Hz, 1H), 6.78 (dd, *J* = 8.6, 0.6 Hz, 1H), 3.97 (s, 3H), 2.47 (s, 3H). LCMS rt = 4.73 min, *m/z* = 426.



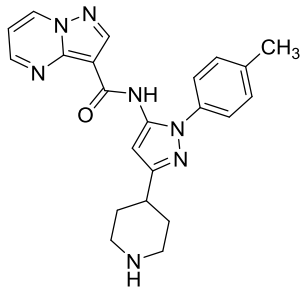
***N*-(3-cyclopropyl-1-(*p*-tolyl)-1H-pyrazol-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (12)**

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.24 (br s, 1H), 8.76 (dd, *J* = 7.2, 1.6 Hz, 1H), 8.69 (s, 3H), 8.29 (dd, *J* = 4.2, 1.6 Hz, 1H), 7.45 (m, 2H), 7.30 (m, 2H), 6.97 (dd, *J* = 6.8, 4.2 Hz, 1H), 6.54 (s, 3H), 2.44 (s, 3H), 1.99 (m, 1H), 0.93 (m 2H), 0.83 (m, 2H). LCMS rt = 3.87 min, *m/z* = 359.



_N_-(3-(tetrahydro-2_H_-pyran-4-yl)-1-(_p_-tolyl)-1_H_-pyrazol-5-yl)pyrazolo[1,5-_a_]pyrimidine-3-carboxamide (14)

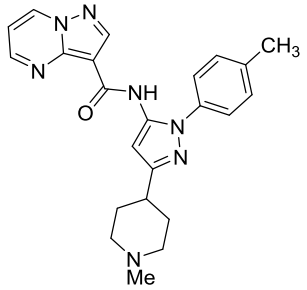
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.28 (br s, 1H), 8.77 (dd, *J* = 7.0, 1.6 Hz, 1H), 8.71 (s, 1H), 8.30 (dd, *J* = 4.2, 1.6 Hz, 1H), 7.46 (m, 2H), 7.31 (m, 2H), 6.98 (dd, *J* = 7.0, 4.2 Hz, 1H), 6.76 (s, 1H), 4.06 (m, 2H), 3.54 (dt, *J* = 2.8, 10.8 Hz, 2H), 2.53 (m, 1H), 2.45 (s, 3H), 1.97-1.84 (m, 4H). LCMS rt = 3.58 min, *m/z* = 403.



_N_-(3-(piperidin-4-yl)-1-(_p_-tolyl)-1_H_-pyrazol-5-yl)pyrazolo[1,5-_a_]pyrimidine-3-carboxamide (15)

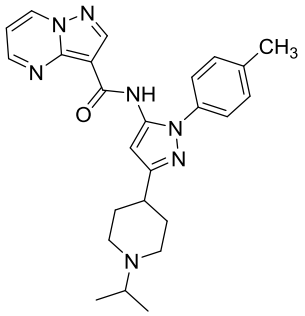
A solution of tert-butyl 4-(5-(pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1-(*p*-tolyl)-1*H*-pyrazol-3-yl)piperidine-1-carboxylate (5.80 g, 11.6 mmol), prepared according to the general method outlined for compound **6**, TFA (20 mL), and CH_2Cl_2 (200 mL) was stirred at rt for 1h. The solution was concentrated *in vacuo* and the residue so obtained was triturated with hexanes/EtOH to give 5.55 g (93%) of the TFA salt of **15** as a white solid. ^{1}H NMR (CD_3OD, 400 MHz) δ 9.09 (dd, *J* = 7.2, 1.6 Hz, 1H), 8.62 (s, 1H), 8.41 (dd, *J* = 4.0, 1.6 Hz, 1H), 7.45 (app s, 4H), 7.19 (dd, *J* = 7.2, 4.0 Hz, 1H), 6.74 (s, 1H), 3.46 (m, 2H), 3.15 (m, 2H), 3.06 (tt, *J* = 11.6, 4.4 Hz, 1H), 2.49 (s, 3H), 2.25 (m, 2H), 1.98 (m, 2H). LCMS rt = 3.20, *m/z* = 402.

Compounds **16-17**, and **30** were prepared using the general method below, using **16** as an example.



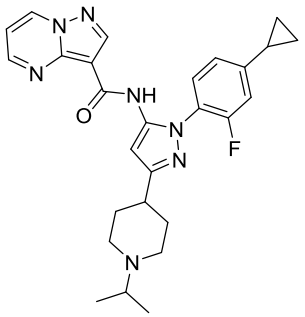
_N_-(3-(1-methylpiperidin-4-yl)-1-(_p_-tolyl)-1_H_-pyrazol-5-yl)pyrazolo[1,5-_a_]pyrimidine-3-carboxamide (16)

Formaldehyde (50 µL, 37% soln in water, 0.67 mmol) and DIPEA (120 µL, 0.687 mmol) were added to a mixture of **15** (120 mg , 0.233 mmol) and CH_2Cl_2 (5 mL). The resulting mixture was stirred at rt for 15 min. $NaBH(OAc)_3$ (151, 0.712 mmol) was added and the mixture was stirred at RT for 20 h. Sat $NaHCO_3$ (30 mL) was added and the mixture was extracted with DCM (3 x 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. A small amount of hexanes and CH_2Cl_2 was added and the solution was concentrated *in vacuo* to give **16** as a foamy white solid that was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.25 (br s, 1H), 8.76 (dd, *J* = 6.8, 1.6 Hz, 1H), 8.71 (s, 1H), 8.30 (dd, *J* = 4.0, 1.6 Hz, 1H), 7.46 (m, 2H), 7.30 (m, 2H), 6.80 (dd, *J* = 6.8, 4.0 Hz, 1H), 6.75 (s, 1H), 2.95 (m, 2H), 2.68 (m, 2H), 2.44 (s, 3H), 2.30 (s, 3H), 2.09-2.02 (m, 3H), 1.86 (m, 2H). LCMS rt = 2.36 min, *m/z* = 416.



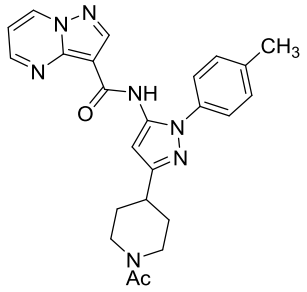
_N_-(3-(1-isopropylpiperidin-4-yl)-1-(_p_-tolyl)-1_H_-pyrazol-5-yl)pyrazolo[1,5-_a_]pyrimidine-3-carboxamide (17)

^{1}H NMR (400 MHz, CD_3OD) δ 9.10 (dd, *J* = 7.2, 1.6 Hz, 1H), 8.64 (s, 1H), 8.42 (dd, *J* = 4.4, 1.6 Hz, 1H), 7.47 (app s, 4H), 7.20 (dd, *J* = 7.2, 4.4 Hz, 1H), 6.76 (s, 1H), 3.63-3.48 (m, 3H), 3.22 (m, 2H), 3.07 (m, 1H), 2.51 (s, 3H), 2.33 (m, 2H), 2.04 (m, 2H), 1.40 (d, *J* = 6.8 Hz, 6H). LCMS rt = 2.51 min, *m/z* = 444.



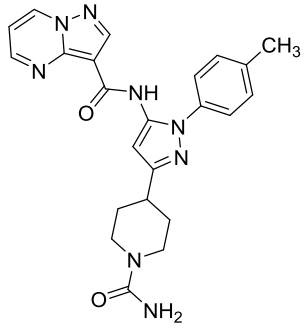
_N_-(1-(4-cyclopropyl-2-fluorophenyl)-3-(1-isopropylpiperidin-4-yl)-1_H_-pyrazol-5-yl)pyrazolo[1,5-_a_]pyrimidine-3-carboxamide (30)

^{1}H NMR (400 MHz, CD_3OD) δ 9.10 (dd, *J* = 6.8, 1.8 Hz, 1H), 8.63 (s, 1H), 8.54 (br s, 1H), 8.35 (dd, *J* = 4.0, 1.8 Hz, 1H), 7.45 (t, *J* = 8.0 Hz, 1H), 7.22-7.17 (m, 3H), 6.71 (s, 1H), 3.23 (app br s, 1H), 2.90-2.81 (m, 4H), 2.19 (m, 2H), 2.10 (m, 1H), 1.97 (m, 2H), 1.27 (d, *J* = 6.8 Hz, 1H), 1.15 (m, 2H), 0.85 (m, 2H). LCMS rt = 2.88 min, *m/z* = 488.



***N*-(3-(1-acetylpiperidin-4-yl)-1-(*p*-tolyl)-1*H*-pyrazol-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (18)**

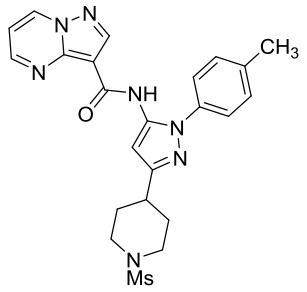
AcCl (20 µL, 0.28 mmol) and TEA (40 µL, 0.29 mmol) were added to a mixture of **15** (104 mg, 0.259 mmol) and CH_2Cl_2 (15 mL). The resulting mixture was stirred at rt for 24 h. CH_2Cl_2 (50 mL) was added. The mixture was washed with water (50 mL), 1 M HCl (50 mL), and brine (50 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by silica gel chromatography, eluting with a solvent gradient of 0 to 10% MeOH in CH_2Cl_2 to give **18** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.28 (br s, 1H), 8.76 (dd, *J* = 7.0, 2.0 Hz, 1H), 8.70 (s, 1H), 8.29 (dd, *J* = 4.2, 2.0 Hz, 1H), 7.44 (m, 2H), 7.31 (m, 2H), 6.98 (dd, *J* = 7.0, 4.2 Hz, 1H), 6.73 (s, 1H), 4.63 (m, 1H), 3.89 (m, 1H), 3.18 (dt, *J* = 2.6, 11.8 Hz, 1H), 2.94 (tt, *J* = 11.8, 4.4 Hz, 1H), 2.75 (dt, *J* = 2.6, 12.8 Hz, 1H), 2.45 (s, 3H), 2.11-2.03 (m, 5H), 1.83-1.66 (m, 2H). LCMS rt = 3.23 min, *m/z* = 444.



***N*-(3-(1-carbamoylpiperidin-4-yl)-1-(*p*-tolyl)-1*H*-pyrazol-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (19)**

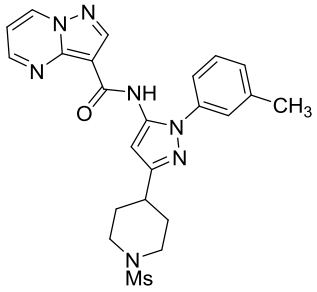
Trimethylsilyl isocyanate (70 µL, 0.52 mmol) was added to a mixture of **15** (70 mg, 0.14 mmol), TEA, (40 µL, 0.29 mmol), and THF (5 mL). The mixture was stirred at rt for 22 h. Sat NH_4Cl (30 mL) was added and the mixture was extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was triturated with hexanes/EtOH to give **19** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.08 (dd, *J* = 7.2, 1.6 Hz, 1H), 8.62 (s, 1H), 8.42 (dd, *J* = 4.2, 1.6 Hz, 1H), 7.48-7.43 (m, 4H), 7.19 (dd, *J* = 7.2, 4.2 Hz, 1H), 6.69 (s, 1H), 4.22-4.019 (m, 2H), 3.07-2.86 (m, 3H), 2.50 (s, 3H), 2.06-2.00 (m, 2H), 1.76-1.66 (m, 2H). LCMS rt = 3.15 min, *m/z* = 445.

Compounds **20-26** were prepared using the general method below, with **20** as an example.



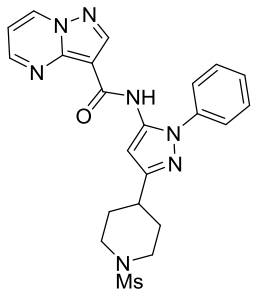
***N*-(3-(1-(methylsulfonyl)piperidin-4-yl)-1-(*p*-tolyl)-1*H*-pyrazol-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (20)**

A mixture of piperidine **15** (1.24 g, 2.41 mmol), MsCl (230 µL, 2.95 mmol), DIPEA (510 µL, 2.92 mmol), and DCM (30 mL) was stirred at rt for 2 d. Sat $NaHCO_3$ (100 mL) was added and the mixture was extracted with DCM (3 x 100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by silica gel chromatography, eluting with a solvent gradient of 0 to 100% EtOAc in hexanes to give 530 mg (46%) of **20** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.29 (br s, 1H), 8.77 (dd, *J* = 6.8, 1.6 Hz, 1H), 8.71 (s, 3H), 8.30 (dd, *J* = 4.0, 1.6 Hz, 1H), 7.45 (m, 2H), 7.32 (m, 2H), 6.99 (dd, *J* = 6.8, 4.0 Hz, 1H), 6.75 (s, 1H), 3.85 (m, 2H), 2.88-2.81 (m, 3H), 2.80 (s, 3H), 2.45 (s, 3H), 2.15 (m, 2H), 1.93 (m 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 156.3, 151.1, 147.7, 146.1, 138.6, 137.6, 137.0, 136.0, 130.3, 125.9, 109.6, 105.8, 94.8, 46.4, 35.8, 35.4, 31.6, 21.6. LCMS rt **=** 4.05 min, *m/z* = 480. HRMS for $C_{23}H_{26}O_3N_7S$ calc 480.1812, found 480.1816.



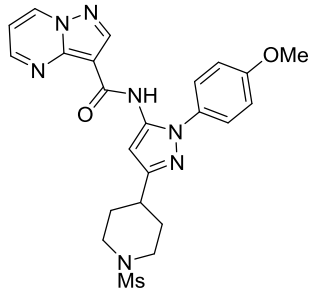
***N*-(3-(1-(methylsulfonyl)piperidin-4-yl)-1-(*m*-tolyl)-1*H*-pyrazol-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (21)**

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.32 (br s, 1H), 8.79 (dd, *J* = 6.8, 1.6 Hz,, 1H), 8.71 (s, 1H), 8.31 (dd, *J* = 4.4, 1.6 Hz, 1H), 7.38 (m, 3H), 7.27 (m, 1H), 6.99 (m, 1H), 6.77 (s, 1H), 3.86 (m, 2H), 2.84 (m, 6H), 2.42 (s, 3H), 2.17 (m, 2H), 1.95 (m, 2H). LCMS rt = 0.90 min, *m/z* = 480.



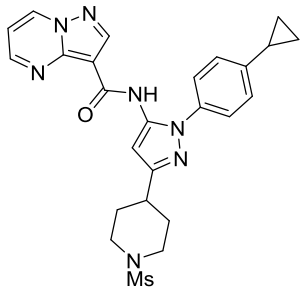
_N_-(3-(1-(methylsulfonyl)piperidin-4-yl)-1-phenyl-1_H_-pyrazol-5-yl)pyrazolo[1,5-_a_]pyrimidine-3-carboxamide (22)

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.35 (br s, 1H), 8.78 (dd, *J* = 6.8, 2.0 Hz,, 1H), 8.72 (s, 1H), 8.31 (dd, *J* = 4.0, 1.6 Hz, 1H), 7.61-7.45 (m, 5H), 6.99 (m, 1H), 6.79 (s, 1H), 3.86 (m, 2H), 2.90-2.80 (m, 6H), 2.18 (m, 2H), 2.00-1.93 (m, 2H). LCMS rt = 1.98 min, *m/z* = 488.



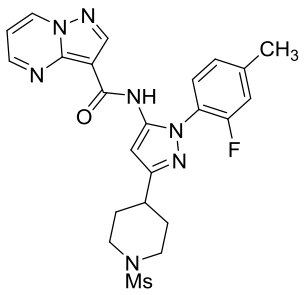
_N_-(1-(4-methoxyphenyl)-3-(1-(methylsulfonyl)piperidin-4-yl)-1_H_-pyrazol-5-yl)pyrazolo[1,5-_a_]pyrimidine-3-carboxamide (23)

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.23 (br s, 1H), 8.76 (dd, *J* = 7.0, 1.6 Hz, 1H), 8.71 (s, 1H), 8.30 (dd, *J* = 4.2, 1.6 Hz, 1H), 7.48 (m, 2H), 7.03 (m 2H), 6.97 (dd, *J* = 7.0, 4.2 Hz, 1H), 6.73 (s, 1H), 3.88 (s, 3H), 3.84 (m, 1H), 2.88-2.83 (m, 2H), 2.82 (s, 3H), 2.17-2.13 (m, 2H), 1.98-1.88 (m, 2H). LCMS rt = 3.84 min, *m/z* = 496.



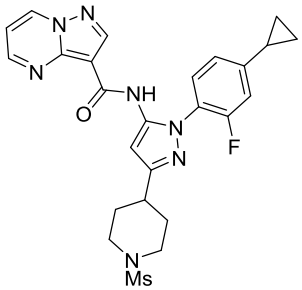
_N_-(1-(4-cyclopropylphenyl)-3-(1-(methylsulfonyl)piperidin-4-yl)-1_H_-pyrazol-5-yl)pyrazolo[1,5-_a_]pyrimidine-3-carboxamide (24)

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.26 (br s, 1H), 8.76 (dd, *J* = 6.8, 1.6 Hz, 1H), 8.71 (s, 1H), 8.30 (dd, *J* = 4.0, 1.6 Hz, 1H), 7.44 (m, 2H), 7.19 (m, 2H), 6.99 (dd, *J* = 6.8, 4.0 Hz, 1H), 6.74 (s, 1H), 3.84 (m, 2H), 2.88-2.79 (m, 6H), 2.15 (m, 2H), 2.02-1.88 (m, 3H), 1.06 (m, 2H), 0.73 (m, 2H). LCMS rt = 4.52 min, *m/z* = 506.



***N*-(1-(2-fluoro-4-methylphenyl)-3-(1-(methylsulfonyl)piperidin-4-yl)-1*H*-pyrazol-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (25)**

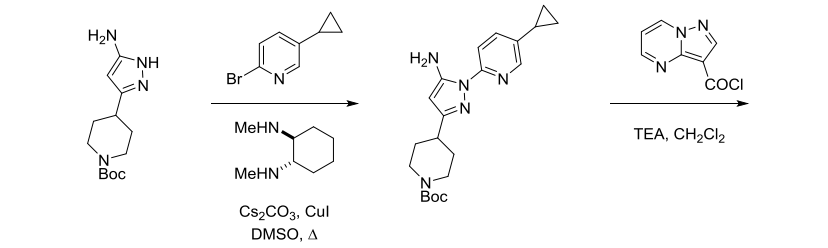
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.11 (br s, 1H), 8.77 (dd, *J* = 7.2, 1.6 Hz, 1H), 8.69 (s, 1H), 8.26 (dd, *J* = 4.0, 1.6 Hz, 1H), 7.42 (t, *J* = 8.0 Hz, 1H), 7.12-7.09 (m, 2H), 6.98 (dd, *J* = 7.2, 4.0 Hz, 1H), 6.71 (s, 1H), 3.84 (m, 2H), 2.88-2.79 (m, 6H), 2.47 (s, 3H), 2.15 (m, 2H), 1.95 (m, 2H). LCMS rt = 4.27 min, *m/z* = 498.

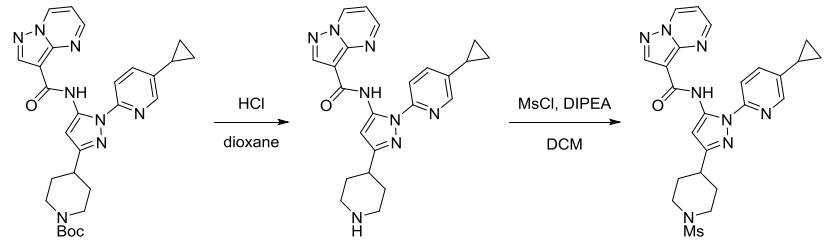


***N*-(1-(4-cyclopropyl-2-fluorophenyl)-3-(1-(methylsulfonyl)piperidin-4-yl)-1*H*-pyrazol-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (26)**

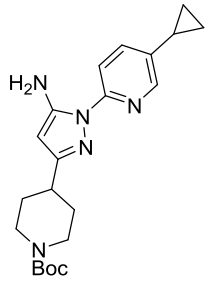
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.10 (br s, 1H), 8.77 (dd, *J* = 7.2, 2.0 Hz, 1H), 8.69 (s, 1H), 8.25 (dd, *J* = 4.0, 2.0 Hz, 1H), 7.40 (t, *J* = 8.0 Hz, 1H), 7.02-6.93 (m, 3H), 6.71 (s, 1H), 3.84 (m, 2H), 2.89-2.79 (m, 6H), 2.17 (m, 2H), 2.01-1.88 (m, 3H), 1.11 (m, 2H), 0.75 (m, 2H). LCMS rt = 3.87 min, *m/z* = 524.

Compounds **27**-**29** were prepared using the general methods below, with **28** as an example.



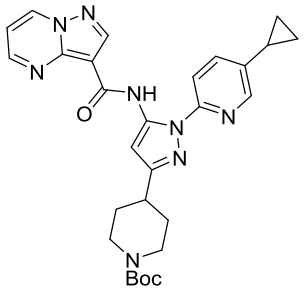


28



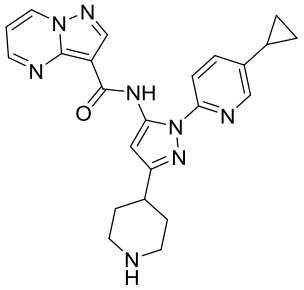
***tert*-butyl 4-(5-amino-1-(5-cyclopropylpyridin-2-yl)-1*H*-pyrazol-3-yl)piperidine-1-carboxylate**

A mixture of *tert*-butyl 4-(5-amino-1*H*-pyrazol-3-yl)piperidine-1-carboxylate (300 mg, 1.13 mmol), prepared according to the general method outlined for compound **6**, 2-bromo-5-cyclopropylpyridine (234 mg, 1.18 mmol), copper(I) iodide (22 mg, 0.12 mmol), (1S,2S)-N^1,N^2-dimethylcyclohexane-1,2-diamine (16 mg, 0.11 mmol), Cs_2CO_3 (734 mg, 2.25 mmol), and DMSO (3 mL) was purged with N_2 for 30 min. The mixture was heated to 130 ˚C in a sealed tube for 15 h. The mixture was cooled to rt and water (30 mL) was added. The mixture was extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by silica gel chromatography, eluting with a solvent gradient of 0 to 40 % EtOAc in hexanes to give the expected product as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (m, 1H), 7.74 (m, 1H), 7.32 (m, 1H), 5.88 (br s, 2H), 5.26 (s, 1H), 4.10 (m, 2H), 2.79 (m, 2H), 2.67 (m, 1H), 1.88-1.79 (m, 3H), 1.61-1.54 (m, 2H), 1.42 (s, 9H), 1.20 (t, *J* = 7.2 Hz, 1H), 0.94 (m, 2H), 0.63 (m, 2H).



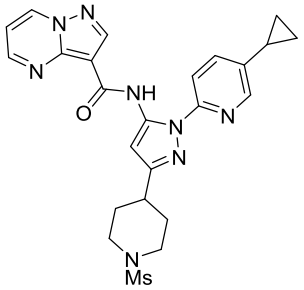
tert-butyl 4-(1-(5-cyclopropylpyridin-2-yl)-5-(pyrazolo[1,5-a]pyrimidine-3-carboxamido)-1H-pyrazol-3-yl)piperidine-1-carboxylate

This compound was prepared according to the general method outlined for compound **6**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (m, 3H), 8.14 (m, 1H), 7.75 (m, 1H), 7.35 (m, 1H), 6.93 (m, 2H), 4.27-4.02 (br s, 2H), 2.94-2.77(m, 3H), 1.90 (m, 2H), 1.87 (m, 1H), 1.71 (m, 2H), 1.44 (s, 9H), 1.00 (m, 2H), 0.67 (m, 2H).



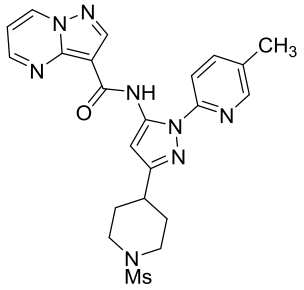
***N*-(1-(5-cyclopropylpyridin-2-yl)-3-(piperidin-4-yl)-1*H*-pyrazol-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide**

tert-Butyl 4-(1-(5-cyclopropyridin-2-yl)-5-(pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-3-yl)piperidine-1-carboxylate (219 mg, 0.414 mmol), hydrogen chloride solution (1.0 mL, 4M in dioxane, 4.0 mmol), DCM (10 mL), MeOH (3 mL) were combined and the mixture was stirred at room temperature overnight. The mixture was concentrated to give the desired product as a white solid, that was used without further purification.



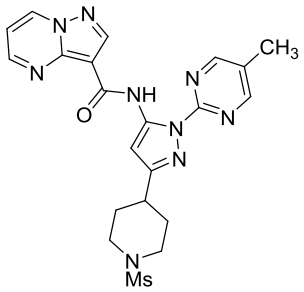
***N*-(1-(5-cyclopropylpyridin-2-yl)-3-(1-(methylsulfonyl)piperidin-4-yl)-1*H*-pyrazol-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (28)**

This compound was prepared according to the general method outlined for compound **20**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (m, 2H), 8.74 (m, 1H), 8.27 (m, 1H), 7.83 (m, 1H), 7.44 (m, 1H), 7.08 (m, 1H), 6.97 (s, 1H), 3.84 (m, 2H), 2.99 (m, 2H), 2.82 (m, 1H), 2.28 (m, 1H), 2.13 (m, 2H), 1.95 (m, 3H), 1.16 (m, 2H), 1.05 (m, 2H), 1.03 (m, 2H), 0.73 (m, 2H). LCMS rt = 1.07, *m/z* = 533.



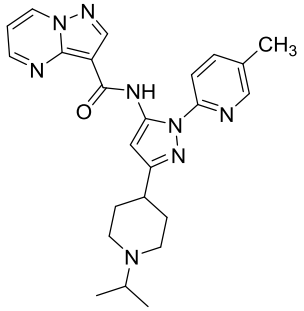
***N*-(1-(5-methylpyridin-2-yl)-3-(1-(methylsulfonyl)piperidin-4-yl)-1*H*-pyrazol-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (27)**

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (s, 1H), 8.79 (dd, *J* = 2.8, 1.6 Hz, 1H), 8.77 (s, 1H), 8.30 (dd, *J* = 1.6, 0.8 Hz, 1H), 7.91 (m, 1H), 7.66 (m, 1H), 7.09 (m, 1H), 7.03 (s, 1H), 3.86-3.82 (m, 2H), 2.93-2.81 (m, 3H), 2.81 (s, 3H), 2.40 (s, 3H), 2.22-2.11 (m, 2H), 2.02-1.95 (m, 2H). LCMS rt = 1.97 min, *m/z* = 480.



***N*-(3-(1-isopropylpiperidin-4-yl)-1-(5-methylpyridin-2-yl)-1*H*-pyrazol-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (29)**

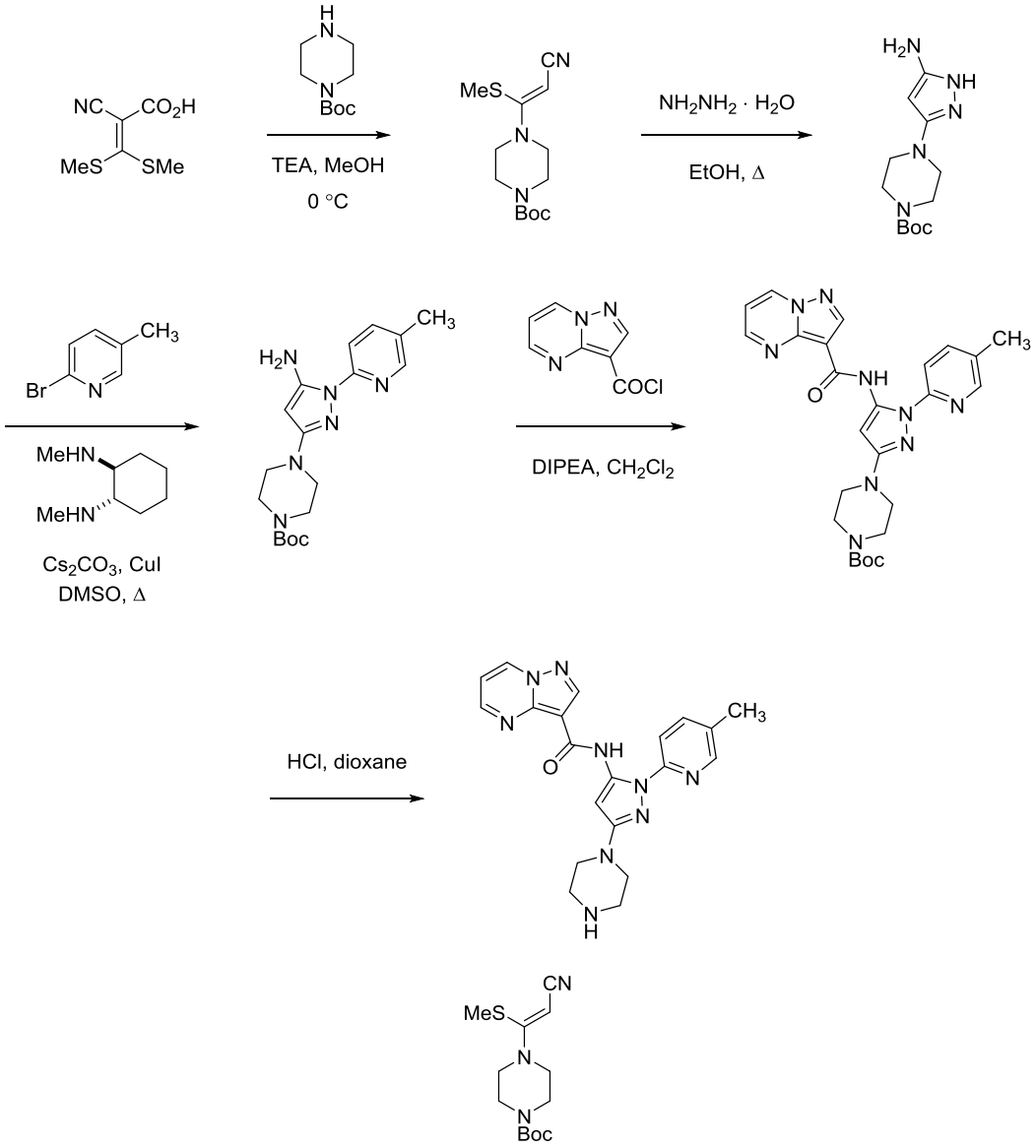
This compound was prepared according to the general method outlined for compound **20**. LCMS rt = 0.82 min, *m/z* = 482.



***N*-(1-(5-methylpyrimidin-2-yl)-3-(1-(methylsulfonyl)piperidin-4-yl)-1*H*-pyrazol-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (31)**

A mixture of *N*-(1-(5-methylpyridin-2-yl)-3-(piperidin-4-yl)-1H-pyrazol-5-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (0.045 mmol), acetone (0.090 mmol), and MP-cyanoborohydride (2.35 mmol/g, Biotage, 100 mg) in 1 mL of MeOH/HOAc (10:1) was shaken at room temperature. After the amine was consumed, the solid was filtered off. The solutions were concentrated in GeneVac. The residues were purified by HPLC to afford the desired products. LCMS rt = 1.10 min, *m/z* = 445.

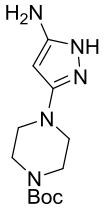
Compounds **32** and **33** were prepared using the general methods below, using **32** as an example.



***tert*-butyl (*Z*)-4-(2-cyano-1-(methylthio)vinyl)piperazine-1-carboxylate**

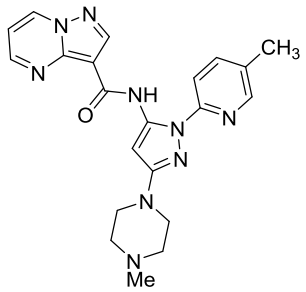
Triethylamine (3.78 g, 37.3 mmol) and *tert*-butyl piperazine-1-carboxylate (Gradl, S.; Rudolph, J.; Ren, L., WO 2011025951, 13.9 g, 74.7 mmol) were added dropwise to a solution of 2-cyano-3,3-bis(methylthio)acrylic acid (7.06 g, 37.3 mmol) in MeOH (60 mL), that had been precooled to 0 ˚C. The

mixture was concentrated *in vacuo* (water bath temperature about 20 ˚C), to give the expected product that was used without further purification.



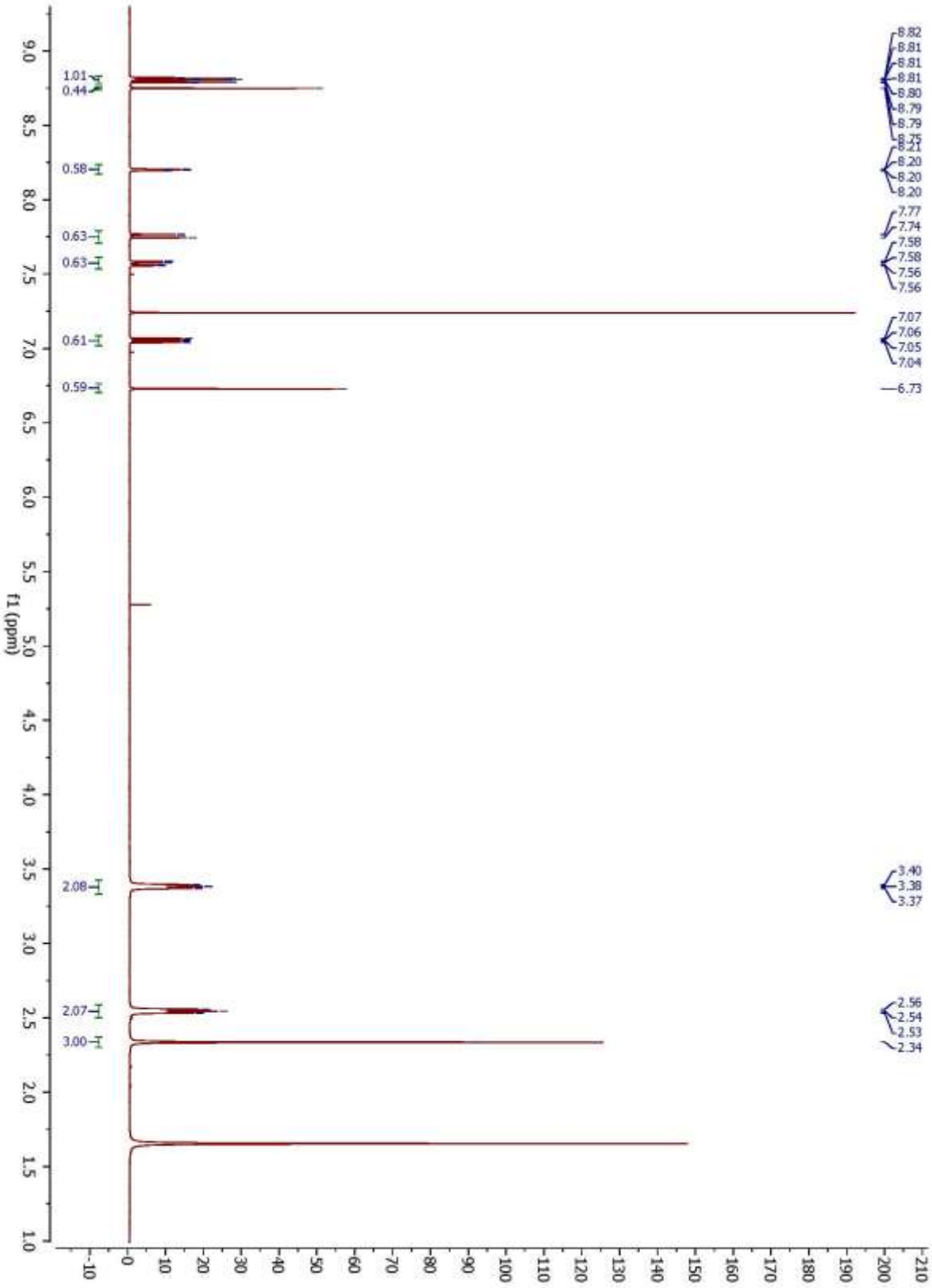
***tert*-butyl 4-(5-amino-1*H*-pyrazol-3-yl)piperazine-1-carboxylate**

A mixture of (*Z*)-*tert*-butyl 4-(2-cyano-1-(methylthio)vinyl)piperazine-1-carboxylate (5.94 g, 20.9 mmol) and hydrazine monohydrate (4.5 mL) in EtOH (50 mL) was heated to reflux for 14 hours. After cooling to room temperature, the reaction mixture was concentrated *in vacuo*. The residue was purified by silica gel chromatography, eluting with a solvent gradient of 0 to 10% MeOH in CH_2Cl_2 to give the expected product.



***N*-(3-(4-methylpiperazin-1-yl)-1-(5-methylpyridin-2-yl)-1*H*-pyrazol-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (32)**

This compound was prepared following the general method outlined for compound **16**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82-8.79 (m, 3H), 8.75 (s, 1H), 8.20 (m, 1H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.58-7.56 (m, 1H), 7.07-7.04 (m, 1H), 6.73 (s, 1H), 3.30-3.37 (m, 4H), 2.56-2.53 (m, 4H), 2.34 (app s, 6H). HRMS for $C_{21}H_{23}N_9O_1$ calc 418.2098, found 418.2093.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0.63
0.63
0.61
0.59
2.08
2.07
3.00
8.82
8.81
8.81
8.81
8.80
8.79
8.79
8.75
8.21
8.20
8.20
8.20
7.77
7.74
7.58
7.58
7.56
7.56
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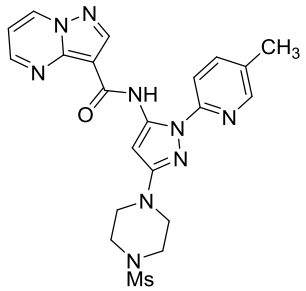

***N*-(1-(5-methylpyridin-2-yl)-3-(4-(methylsulfonyl)piperazin-1-yl)-1*H*-pyrazol-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (33)**

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (m, 3H), 8.75 (s, 1H), 8.22 (m, 1H), 7.75 (m, 1H), 7.60 (m, 1H), 7.07 (m, 1H), 6.75 (s, 1H), 3.50 (t, *J* = 5.6 Hz, 4H), 3.36 (t, *J* = 5.6 Hz, 4H), 2.81 (s, 3H), 2.36 (s, 3H). LCMS rt = 2.10 min, *m/z* = 482.

2. 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. Analogues were tested in duplicate, with the average value given. The coefficient of variation was <30%.

3. Solubility determination

The chromatographic system consists of an Agilent 1200 HPLC/DAD system and ChemStation software, both from Agilent Technologies, USA. The separations are carried out on a Supelco Ascentis Express C18, 30 mm x 3.0 mm I.D., 2.7 µm HPLC column. The mobile phase consists of phosphate buffered saline at pH 7 (mobile phase A) and acetonitrile (mobile phase B). The column oven temperature is set to 30°C and the HPLC analysis consists of a gradient. The injection volume is 5 µL and the spectrophotometric detection is set to 215, 238 and 254 nm.

A 10 mM stock solution of the compound in DMSO is supplied for analysis. Dilute 2.5 µL of stock solution (10 mM) into 247.5 µL of organic co-solvents (10% MeCN/80% MeOH/10% DMSO) to create a standard solution of 100 µM. To create the solubility solutions, dilute 5 µL of 10 mM DMSO stock solution into 245 µL of phosphate buffered saline (PBS) (pH 7) solution. Seal each solubility solution and shake for 24 hours at 25°C. Filter the equilibrated solubility solutions by centrifugation using a filter (0.45 µ, polypropylene). Into a 384 well plate, place 50 µL each of the 100 µM standard solution and the filtered equilibrated pH 7 solution. Heat seal the plate.

Each standard and solubility solution is anaylyzed by HPLC/DAD. The solubility value is calculated by the following equation:

Solubility = (Peak area of sample/ Peak area of standard) (Standard concentration)

HPLC:

LogD Values for HPLC Standards

Caffeine	-0.1
Warfarin	0.85
Ketoconazole	3.48
Diphenyl Ether	4.21
Captopril	-0.81
Hydrocortisone	1.52
Carbamazepine	1.65
Imipramine	2.31
Terafenadine	4.05

Column: Agilent Poroshell 120 EC-C18 (2.7 µM, 3.0 x 30 mm)

Mobile phase: A = MeCN
B = PBS (pH 7)

Gradient:	Time	%A	%B	Flow [ml/min]
	0	5	95	1.5
	0.2	5	95	1.5
	1.0	98	2	1.5
	1.4	98	2	2.0
	1.5	5	95	1.5

V_{inj}: 5 µl

T: 30°C

λ: 215, 254, 238 nm

4. Measurement of *in vivo* cytokine levels in rat peritonitis model

Compounds were freshly resuspended in either 0.4% methylcellulose or 10% Tween 80 in water and reduced to fine particles by sonication to obtain an even suspension prior to administration. Lewis female rats (Charles River; 125g, 9 animals/group) were dosed with compound by oral gavage.

One hour later, animals were injected intraperitoneally (IP) with TLR2 agonist (PAM2CSK4, 4 mg/kg) freshly prepared in saline. Animals were lightly anesthetized with isoflurane vapors to achieve accurate IP injection. Three hours later, animals were terminated and blood was collected and processed to obtain serum. Aliquots were frozen at -20˚C and compound concentrations and cytokine levels subsequently determined. A custom Mesoscale rat cytokine kit (Meso Scale Diagnostics) was used to measure TNFα, IL-6, CINC (IL-8), γ-IFN and IL-1β. The approximate lower limits of detection as reported by the manufacturer were 5-30 pg/mL. Statistical significance was determined using the Mann-Whitney U test.

5. 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^{o}C for 1 hour. Human TNFα (3 ng/ml, R&D Systems) or LPS-EK (30 ng/ml, InvivoGen) was subsequently added and allowed to incubate for 4 or 5 hours, respectively. To quantitate SEAP activity, supernatants were harvested and mixed with Quanti-Blue (InvivoGen) detection reagent. Plates were incubated at 25^{o}C for 30 minutes and OD630 was measured using a spectrophotometer.

6. Mouse antibody induced arthritis model

Female BALB/c mice (8-12 weeks, 20-30g) were immunized on day 0 with an arthogenic monoclonal antibody (CIA-MAB-50, 2.5 mg, IV). On day 3, mice were boosted with LPS (E. coli 055:B5) prepared in saline (25 µg, IP) and were dosed with compounds (100 mg/kg) or dexamethasone (2 mg/kg) q.d. by oral gavage on days 3 through 10. Compounds were formulated 10 mg/mL in 0.4% methylcellulose. Paw size was assessed on days 0, 3, 6, 8 and 10. Statistical significance was determined using the Mann-Whitney U test.

7. Kinase counterscreen

Kinase counterscreening was performed at Invitrogen. Kinases in the panel of 108 were chosen based on structural homology to IRAK4. The following compounds gave greater than 80% inhibition of kinases at the concentrations indicated:

Compound **6**:

IRAK4: 91% inhib @ 10 µM

MINK1: 86% inhib @ 10 μM

Compound **8**:

FLT3: 83% inhib @ 10 μM

IRAK4: 92% inhib @ 10 μM

MINK1: 97% inhib @ 10 μM

TRKB: 98% inhib @ 10 μM

IRAK1: 88% inhib @ 10 μM

LRRK2: 83% inhib @ 10 μM

Compound **20**:

IRAK4: 106% inhib @ 10 μM

TRKB: 84% inhib @ 10 μM

Compound **27**:

IRAK4: 93% inhib @ 10 μM

Compound **32**:

FLT3: 89% inhib @ 10 μM

IRAK4: 101% inhib @ 10 μM, 99% inhib @ 1 μM

LRRK2: 91% inhib @ 10 LRRK2: 91% inhib @ 10 μM

MERTK: 85% inhib @ 10 μM

TRKB: 96% inhib @ 10 μM

8. Plasma protein binding

Plasma protein binding was assessed as described in, Curran, R. E.; Claxton, C. R. J.; Hutchison, L.; Harradine, P. J.; Martin I. J.; Littlewood, P. Control and Measurement of Plasma pH in Equilibrium Dialysis: Influence on Drug Plasma Protein Binding. *Drug Metab. Dispos.* **2011**, *39*, 551-557.