SUPPORTING INFORMATION

Discovery of CNS-Penetrant Apoptosis Signal-Regulating Kinase 1 (ASK1) Inhibitors

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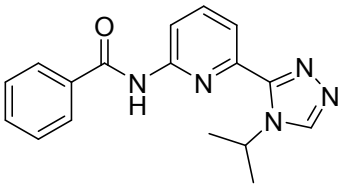
EXPERIMENTAL SECTION

All solvents and chemicals used were reagent grade. Anhydrous solvents were purchased from Sigma-Aldrich and used as received. Analytical thin layer chromatography (TLC) and silica gel column chromatography were performed on Merck silica gel 60 (230-400 mesh). Removal of solvents was conducted by using a rotary evaporator and residual solvents were removed from non-volatile compounds using a vacuum manifold maintained at approximately 1 Torr. NMR spectra were recorded on a Bruker Avance 400 MHz, 500 MHz and 600 MHz NMR spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) relative to residual undeuterated solvent as internal reference and coupling constants (*J*) are reported in hertz (Hz). Splitting patterns are indicated as follows: s = singlet; d = doublet; t = triplet; q = quartet; qn = quintet; dd = doublet of doublets; dt = doublet of triplets; tt = triplet of triplets; m = multiplet; br = broad peak. All yields reported are isolated yields. All final compounds were purified to ≥95% purity as determined by LC/MS analysis (using a lineal gradient of elution: 90% water in trifluoroacetic acid (containing 0.1% v/v)/10% CH_3CN in trifluoroacetic acid (containing 0.1% v/v) to 10% water in trifluoroacetic acid (containing 0.1% v/v) and 90% CH_3CN in trifluoroacetic acid (0.1% v/v) for 2 minutes and

then holding at 10% water in trifluoroacetic acid (0.1% v/v) and 90% CH_3CN in trifluoroacetic acid (0.1% v/v) up to 3 minutes at a flowrate of 3 mL/min (injection volume 5µL and using a Waters Sunfire C18 3.5 uM 4.6x20mm IS column)). MS mode: MS:ESI+ scan range 100-1000 daltons. PDA detection 210-400 nm. Final compounds were analyzed using UPLC (Water's Acquity (Waters Milford, MA)) coupled with an AB Sciex 6600 Triple-TOF mass spectrometer (AB Sciex Framingham, MA). A Water's Acquity HSS T3 (1.7um beads, 2.1x50mm) column was used for separation. Mobile phase A was water with 0.1% formic acid and mobile phase B was acetonitrile with 0.1% formic acid. The flow rate was 0.45 ml/min and the following gradient was used from 0-0.2 minutes 5% B and increased linearly to 65% B at 5 minutes and 90% at 6.1 min and remained there for 0.4 minutes, dropped back to 5% B over 0.1 minutes and remained there for 0.4 minutes. The mass spectrometer was operated in positive ion mode. An electrospray ionization source was used with the following parameters: Ionspray voltage floating 4500 V, ion source gas 1 50 (arbitrary units), ion source gas 2 50 (arbitrary units), curtain gas 30 (arbitrary units), and temperature 500 °C.

(i) Experimental procedures for all the compounds described in this manuscript

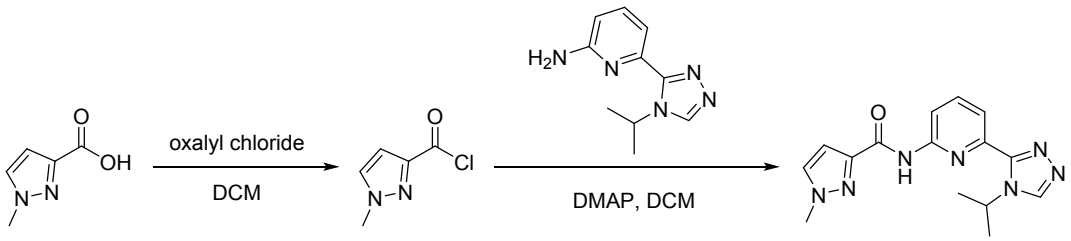
Compound 5: *N*-(6-(4-isopropyl-4*H*-1,2,4-triazol-3-yl)pyridin-2-yl)benzamide



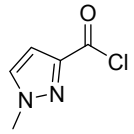
To a solution of DMAP (29 mg, 0.24 mmol) in dichloromethane (1.00 mL) was added benzoyl chloride (31 mg, 0.22 mmol, 26 µL) at room temperature. After 5 min 6-(4-isopropyl-1,2,4-triazol-3-yl)pyridin-2-amine (41 mg, 0.20 mmol) was added to the above mixture. The reaction mixture was stirred at room temperature for 24 hours and was partitioned between EtOAc and water. Upon addition of 1N HCl a precipitate formed and the title compound (20 mg, 32%) was collected by filtration as an off white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.74 (s, 1H), 8.86 (s, 1H), 8.19 (dd, *J*=8.28, 1.00 Hz, 1H), 8.02 (dd, *J*=8.28, 7.53 Hz, 1H), 7.99 - 7.94 (m, 2H), 7.87 (dd,

J=7.53, 1.00 Hz, 1H), 7.65 - 7.61 (m, 1H), 7.59 - 7.53 (m, 2H), 5.78 - 5.66 (m, 1H), 1.44 (d, *J*=6.53 Hz, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 167.1, 152.0, 150.4, 146.7, 146.6, 139.9, 135.0, 132.5, 128.9, 128.6, 119.6, 115.5, 48.3, 23.7. HRMS (*m/z*): $[M + H]^+$ calcd. for $C_{17}H_{18}N_5O$ 308.1506; found: 308.1506. HPLC (CH_3CN in 0.1% TFA): t_R = 1.50 min (100% purity).

Compound 6: *N*-(6-(4-Isopropyl-4*H*-1,2,4-triazol-3-yl)pyridin-2-yl)-1-methyl-1*H*-pyrazole-3-carboxamide

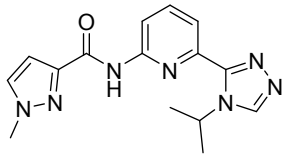


Step A: 1-Methyl-1*H*-pyrazole-3-carbonyl chloride



To a stirred solution of 1-methylpyrazole-3-carboxylic acid (28 mg, 0.22 mmol) in DCM (1 mL) was added oxalyl chloride (24 µL, 0.29 mmol), followed by a catalytic amount of DMF (1 drop). The reaction was stirred at rt for 2 h. The reaction mixture was evaporated *in vacuo* and the product was used without further purification in the next step.

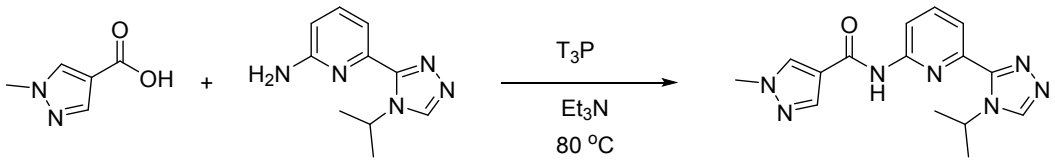
Step B: *N*-(6-(4-Isopropyl-4*H*-1,2,4-triazol-3-yl)pyridin-2-yl)-1-methyl-1*H*-pyrazole-3-carboxamide



To a stirred solution of 1-methylpyrazole-3-carbonyl chloride (32 mg, 0.22 mmol) in dichloromethane (1 mL) was added DMAP (29 mg, 0.24 mmol) and the mixture was stirred at rt for 5 minutes. After this time 6-(4-isopropyl-1,2,4-triazol-3-yl)pyridin-2-amine (41 mg, 0.2 mmol) was added. The mixture was stirred at rt overnight. The reaction was quenched with MeOH,

purified by prep-HPLC (using a Sunfire Prep C18 OBD 5 μm; 30x50mm column; and using water (containing 0.1% TFA)-MeCN (0.1%TFA) as mobile phase; from 10-90%) to give the title compound (20 mg, 24%) as a white powder after lyophilization. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.34 - 9.24 (m, 1H), 8.40 (dd, *J*=0.88, 8.41 Hz, 1H), 8.05 (dd, *J*=7.65, 8.41 Hz, 1H), 7.87 (dd, *J*=0.75, 7.53 Hz, 1H), 7.72 (d, *J*=2.76 Hz, 1H), 6.88 (d, *J*=2.51 Hz, 1H), 5.75 (spt, *J*=6.73 Hz, 1H), 4.02 (s, 3H), 1.62 (d, *J*=6.78 Hz, 6H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.99 (s, 1H), 9.01 (s, 1H), 8.21 (dd, *J*=0.75, 8.28 Hz, 1H), 8.03 (t, *J*=7.91 Hz, 1H), 7.91 (d, *J*=2.26 Hz, 1H), 7.85 (dd, *J*=0.88, 7.65 Hz, 1H), 6.85 (d, *J*=2.26 Hz, 1H), 5.62 (spt, *J*=6.65 Hz, 1H), 3.98 (s, 3H), 1.48 (d, *J*=6.53 Hz, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 160.0, 150.8, 149.9, 145.8, 145.3, 143.2, 139.7, 133.5, 119.3, 114.6, 107.0, 48.2, 39.2, 23.1. HRMS (*m/z*): $[M + H]^+$ calcd. for $C_{15}H_{18}N_7O$ 312.1567; found: 312.1571. HPLC (CH_3CN in 0.1% TFA): t_R = 1.21 min (100% purity).

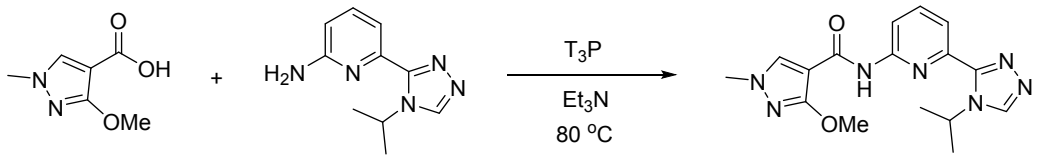
Compound 7: *N*-(6-(4-Isopropyl-4*H*-1,2,4-triazol-3-yl)pyridin-2-yl)-1-methyl-1*H*-pyrazole-4-carboxamide



To a mixture of 6-(4-isopropyl-1,2,4-triazol-3-yl)pyridin-2-amine (61 mg, 0.30 mmol) and 1-methyl-1*H*-pyrazole-4-carboxylic acid (45 mg, 0.36 mmol) in a reaction vial was added triethylamine (0.5 mL, 3.6 mmol) and propylphosphonic anhydride (≥50 wt% in EtOAc, 0.5 mL). The mixture was heated at 80 °C for 4 h. After this time the mixture was quenched with a small amount of MeOH (~ 2 mL) and then it was partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by normal phase column eluted with EtOAc/EtOH (3/1) to give the title compound (34 mg, 36%). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.82 (s, 1H), 8.32 - 8.20 (m, 2H), 8.08 (s, 1H), 7.98 (t, *J*=8.03 Hz, 1H), 7.81 (d, *J*=7.53 Hz, 1H), 5.75 (quin, *J*=6.71 Hz, 1H), 3.97 (s, 3H), 1.54 (d, *J*=6.78 Hz, 6H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.31 (s, 1H), 8.87 (s, 1H), 8.44 (s, 1H), 8.17 (dd, *J*=0.88, 8.41 Hz, 1H), 8.09 (s, 1H), 8.01 – 7.95 (m, 1H), 7.77 (dd, *J*=0.88, 7.66 Hz, 1H), 5.58 (spt, *J*=6.65 Hz, 1H), 3.91 (s, 3H), 1.44 (d, *J*=6.78 Hz, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 161.5, 152.1, 150.6, 146.6, 143.5,

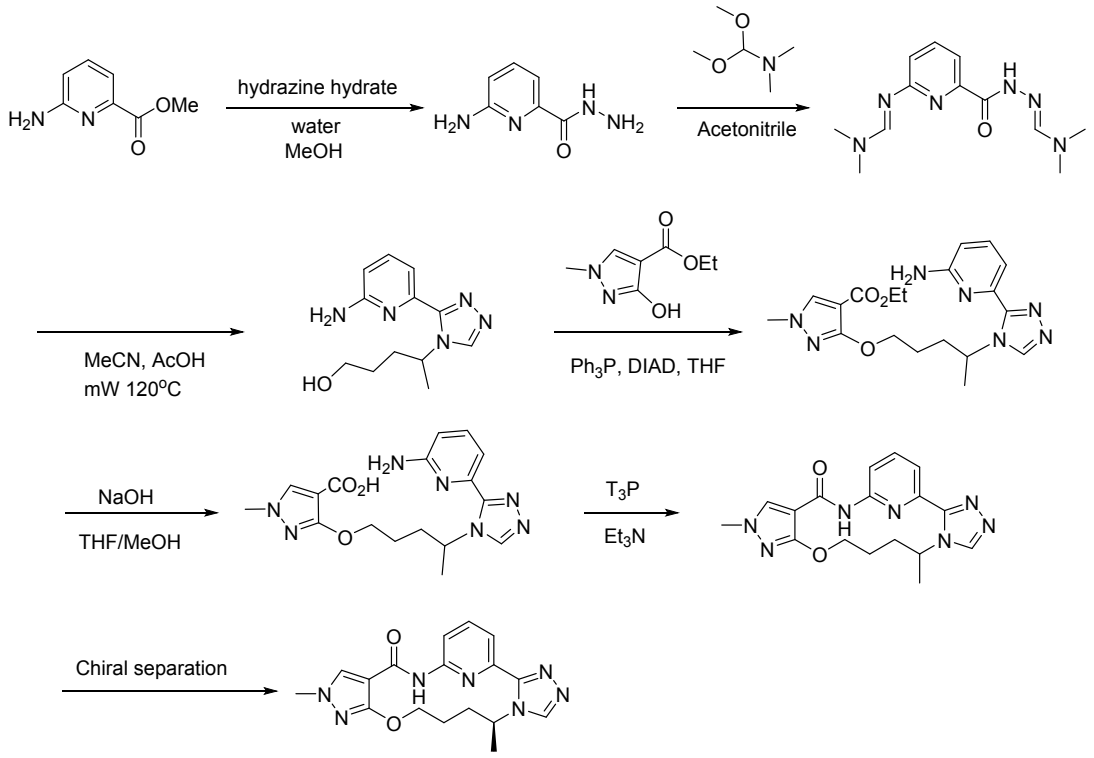
140.0, 139.8, 133.7, 119.5, 118.2, 115.5, 48.3, 39.4, 23.6. HRMS (*m/z*): $[M + H]^+$ calcd. for $C_{15}H_{18}N_7O$ 312.1567; found: 312.1571. HPLC (CH_3CN in 0.1% TFA): t_R = 1.05 min (100% purity).

Compound 8: *N*-(6-(4-Isopropyl-4*H*-1,2,4-triazol-3-yl)pyridin-2-yl)-3-methoxy-1-methyl-1*H*-pyrazole-4-carboxamide

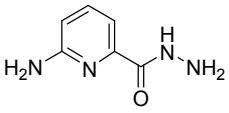


To a mixture of 6-(4-isopropyl-1,2,4-triazol-3-yl)pyridin-2-amine (72 mg, 0.35 mmol) and 3-methoxy-1-methyl-pyrazole-4-carboxylic acid (55 mg, 0.35 mmol) in a reaction vial was added triethylamine (0.73 mL, 5.3 mmol) and propylphosphonic anhydride (≥50 wt% in EtOAc, 0.63 mL). The mixture was heated at 80 °C for 4 h. After this time the mixture was quenched with a small amount of MeOH (~ 2 mL) and then it was partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was triturated with MeCN (~ 2 mL) and dried under vacuum to give the title compound (22 mg, 18%) as a yellow solid. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 8.85 (s, 1H), 8.34 (d, *J*=7.94 Hz, 1H), 8.10 – 7.93 (m, 2H), 7.81 (d, *J*=7.94 Hz, 1H), 5.62 - 5.29 (m, 1H), 4.10 (s, 3H), 3.81 (s, 3H), 1.64 (d, *J*=6.71 Hz, 6H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.28 (s, 1H), 8.90 (s, 1H), 8.25 - 8.19 (m, 2H), 8.00 (t, *J*=8.03 Hz, 1H), 7.81 (dd, *J*=0.88, 7.66 Hz, 1H), 5.33 (spt, *J*=6.73 Hz, 1H), 4.01 (s, 3H), 3.77 (s, 3H), 1.54 (d, *J*=6.78 Hz, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 160.0, 159.8, 151.3, 150.4, 146.5, 143.8, 140.4, 136.3, 119.2, 113.7, 101.6, 57.6, 48.9, 39.1, 23.6. HRMS (*m/z*): $[M + H]^+$ calcd. for $C_{16}H_{20}N_7O_2$ 342.1673; found: 342.1679. HPLC (CH_3CN in 0.1% TFA): t_R = 1.26 min (100% purity).

Compound 9: (*S*)-5^1,10-Dimethyl-1^4*H*,5^1*H*-6-oxa-3-aza-2(2,6)-pyridina-1(3,4)-triazola-5(4,3)-pyrazolacyclodecaphan-4-one

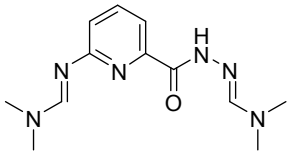


Step A: 6-Aminopicolinohydrazide



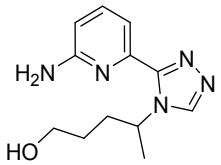
A solution of methyl 6-aminopicolinate (1.0 g, 6.6 mmol), hydrazine hydrate (2.3 g, 23 mmol, 2.2 mL, 50% purity) in water (3 mL) and MeOH (3 mL) was heated at 100 °C for 2 h. After this time, the volatiles were removed under reduced pressure to afford a white product which was co-evaporated with toluene (40 mL) to give the title compound (980 mg, 98%). MS (ESI): 153.0 $[M + H]^+$.

Step B: (*E*)-*N'*-(6-(2-((*E*)-(Dimethylamino)methylene)hydrazine-1-carbonyl)pyridin-2-yl)-*N,N*-dimethylformimidamide



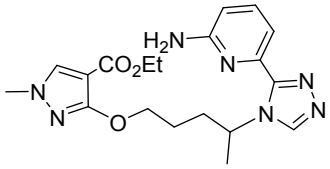
1,1-Dimethoxy-*N*,*N*-dimethyl-methanamine (2.6 mL, 19.7 mmol) was added to a mixture of 6-aminopicolinohydrazide (1.0 g, 6.6 mmol) in MeCN (10 mL) at rt and the reaction was heated at 75 °C for 4 h. The reaction was cooled to rt and filtered to give the title compound (1.5 g, 87%). MS (ESI): $[M + H]^+$ calcd. for $C_{12}H_{19}N_6O$ 263.3; found 263.0.

Step C: 4-(3-(6-Aminopyridin-2-yl)-4*H*-1,2,4-triazol-4-yl)pentan-1-ol



To a mixture of (*E*)-*N*'-(6-(2-((*E*)-(dimethylamino)methylene)hydrazine-1-carbonyl)pyridin-2-yl)-*N*,*N*-dimethylformimidamide (1.31g, 5mmol) and 4-aminopentan-1-ol (567 mg, 5.5 mmol) in MeCN (12 mL) was added AcOH (4 mL). The mixture was heated with mW irradiation at 120 °C for 2 h (x2). Concentrated and co-evaporated with MeCN (x3), the residue was treated with 1N NaOH to make it pH~9-10. The resulting mixture was concentrated and purified by normal phase column eluted with EtOAc/EtOH 3/1 to get the title compound as an oil (340 mg, 28%). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.80 - 8.72 (m, 1H), 7.56 (dd, *J*=7.40, 8.41 Hz, 1H), 7.20 (dd, *J*=0.75, 7.28 Hz, 1H), 6.64 (dd, *J*=0.75, 8.28 Hz, 1H), 6.71 - 6.60 (m, 1H), 5.54 - 5.38 (m, 1H), 3.49 (t, *J*=6.40 Hz, 2H), 2.00 – 1.74 (m, 3H), 1.54 (d, *J*=6.78 Hz, 3H), 1.46 - 1.27 (m, 2H). MS (ESI): $[M + H]^+$ calcd. for $C_{12}H_{18}N_5O$ 248.3; found 248.0.

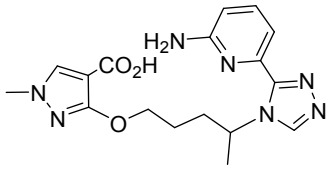
Step D: Ethyl 3-((4-(3-(6-aminopyridin-2-yl)-4*H*-1,2,4-triazol-4-yl)pentyl)oxy)-1-methyl-1*H*-pyrazole-4-carboxylate



To a mixture of ethyl 3-hydroxy-1-methyl-pyrazole-4-carboxylate (131 mg, 0.77 mmol), 4-[3-(6-amino-2-pyridyl)-1,2,4-triazol-4-yl]pentan-1-ol (190 mg, 0.77 mmol), triphenylphosphine (262 mg, 1 mmol) in THF (2.5 mL) was added DIAD (211 μL, 1.1 mmol). The resulting mixture was stirred at rt overnight. The mixture was loaded onto a normal phase column and eluted with EtOAc/EtOH (3/1) to get the title compound (125 mg, 41%). ^{1}H NMR

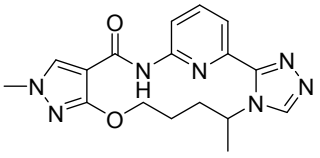
(500 MHz, CD_3OD) δ ppm 8.79 (s, 1H), 7.86 (s, 1H), 7.54 (dd, *J*=7.33, 8.55 Hz, 1H), 7.19 (d, *J*=7.32 Hz, 1H), 6.52-6.75 (m, 1H), 5.64 - 5.45 (m, 1H), 4.09-4.29 (m, 4H), 3.71 (s, 3H), 2.15 – 1.95 (m, 2H), 1.78 - 1.65 (m, 2H), 1.54 (d, *J*=6.71 Hz, 3H), 1.30 - 1.23 (m, 3H). MS (ESI): $[M + H]^+$ calcd. for $C_{19}H_{26}N_7O_3$ 400.5; found 400.2.

Step E: 3-((4-(3-(6-Aminopyridin-2-yl)-4*H*-1,2,4-triazol-4-yl)pentyl)oxy)-1-methyl-1*H*-pyrazole-4-carboxylic acid



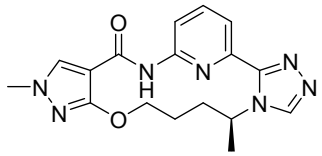
To a solution of ethyl 3-((4-(3-(6-aminopyridin-2-yl)-4*H*-1,2,4-triazol-4-yl)pentyl)oxy)-1-methyl-1*H*-pyrazole-4-carboxylate (500 mg, 1.25 mmol) in THF (3 mL) and MeOH (2 mL) was added 1N NaOH (3 mL, 3 mmol). The mixture was heated at 65 °C for 1 h. It was neutralized by adding 1N HCl (3mL), concentrated and lyophilized to give the title compound as a white powder. MS (ESI): $[M + H]^+$ calcd. for $C_{17}H_{22}N_7O_3$ 372.4; found 372.0.

Step F: 5^1,10-Dimethyl-1^4*H*,5^1*H*-6-oxa-3-aza-2(2,6)-pyridina-1(3,4)-triazola-5(4,3)-pyrazolacyclodecaphan-4-one



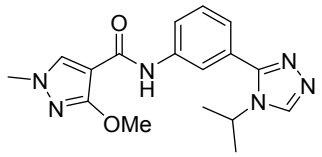
To a mixture of 3-[4-[3-(6-amino-2-pyridyl)-1,2,4-triazol-4-yl]pentoxy]-1-methyl-pyrazole-4-carboxylic acid (394 mg, 1.1 mmol) in triethylamine (3 mL) was added propylphosphonic anhydride (≥50 wt% in EtOAc, 3 mL). The mixture was heated with 80 °C for 4 h. The reaction was taken in EtOAc and satd.$NaHCO_3$. The aqueous layer was re-extracted with EtOAc (x3). The combined organic phases were concentrated to give 227 mg crude product. The product was then triturated with a small amount of EtOAc/EtOH (3/1) and dried under vacuum to give the title compound as an off-white solid (86 mg, 23%). MS (ESI): $[M + H]^+$ calcd. for $C_{17}H_{20}N_7O_2$ 354.4; found 354.2.

Step G: (*S*)-5^1,10-Dimethyl-1^4*H*,5^1*H*-6-oxa-3-aza-2(2,6)-pyridina-1(3,4)-triazola-5(4,3)-pyrazolacyclodecaphan-4-one



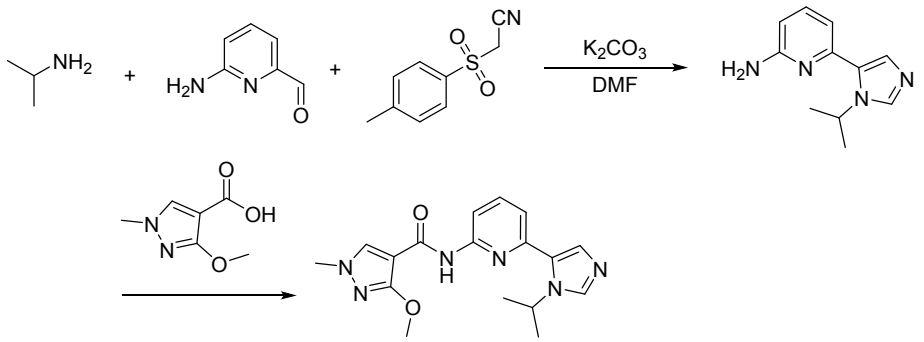
5^1,10-dimethyl-1^4*H*,5^{1}H-6-oxa-3-aza-2(2,6)-pyridina-1(3,4)-triazola-5(4,3)-pyrazolacyclodecaphan-4-one (85 mg, 0.24 mmol) was isolated by SFC (using a Chiralpak AD-H 5µm, 30x250mm column and using 30% MeOH in 0.1% Et_2NH in CO_2 as the mobile phase at a flow rate of 100 mL/min) to give the title compound as an off-white solid (27 mg, 32%, first eluted isomer, stereochemistry arbitrarily assigned). ^{1}H NMR (500 MHz, CD_3OD) δ ppm 8.82 (s, 1H), 8.03 – 7.90 (m, 2H), 7.80 (ddd, *J*=0.75, 4.14, 7.91 Hz, 2H), 4.93 - 4.76 (m, 1H), 4.70 - 4.59 (m, 1H), 4.30 - 4.18 (m, 1H), 3.79 (s, 3H), 3.23 - 3.10 (m, 1H), 2.23 - 2.10 (m, 1H), 1.92 - 1.73 (m, 2H), 1.62 (d, *J*=7.03 Hz, 2H), 1.68 - 1.53 (m, 1H). HRMS (*m/z*): $[M + H]^+$ calcd. for $C_{17}H_{20}N_7O_2$ 354.1673; found: 354.1679. HPLC (CH_3CN in 0.1% TFA): t_R = 1.24 min (100% purity).

Compound 10: *N*-(3-(4-Isopropyl-4*H*-1,2,4-triazol-3-yl)phenyl)-3-methoxy-1-methyl-1*H*-pyrazole-4-carboxamide

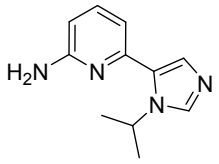


The title compound was synthesized according to the general procedure described in Compound 8 and using 3-(4-isopropyl-4*H*-1,2,4-triazol-3-yl)aniline to give the title compound (7.8 mg, 11%) as a pale-yellow oil. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.91 - 8.75 (m, 1H), 8.03 (t, *J*=2.01 Hz, 1H), 7.95 (s, 1H), 7.73 (ddd, *J*=1.00, 2.26, 8.28 Hz, 1H), 7.55 (t, *J*=7.91 Hz, 1H), 7.40 - 7.29 (m, 1H), 4.70 - 4.51 (m, 1H), 4.16 - 4.02 (m, 3H), 3.79 (s, 3H), 1.52 (d, *J*=6.78 Hz, 6H). MS (ESI): $[M + H]^+$ calcd. for $C_{17}H_{21}N_6O_2$ 341.4; found 341.0.

Compound 11: *N*-(6-(1-Isopropyl-1*H*-imidazol-5-yl)pyridin-2-yl)-3-methoxy-1-methyl-1*H*-pyrazole-4-carboxamide

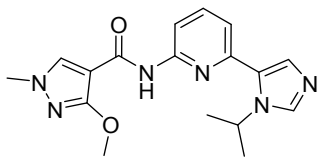


Step A: 6-(1-Isopropyl-1*H*-imidazol-5-yl)pyridin-2-amine



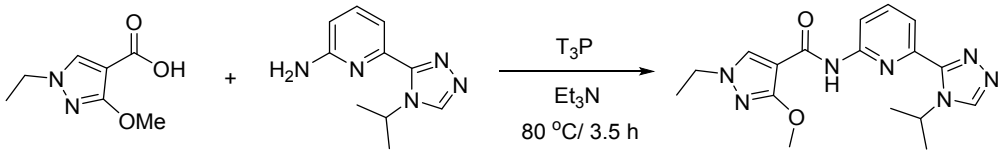
A mixture of propan-2-amine (1.4 mL, 16 mmol), 6-aminopyridine-2-carbaldehyde (997 mg, 8.16 mmol) in DMF (8 mL) was heated to 100 °C for 30 min, resulting in a dark solution. The mixture was brought to rt, and K_2CO_3 (2.26 g, 16.3 mmol) and TosMIC (1.59 g, 8.16 mmol) was added. The resulting mixture was stirred at 100 °C overnight. The reaction mixture was partitioned between EtOAc and satd.$NaHCO_3$. The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by normal phase column eluted with EtOAc/EtOH (3/1) to give a dark brown solid, which is further purified by trituration with MeCN (5 mL) to get the title compound (402 mg, 24%) as a grey crystalline solid. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.89 (s, 1H), 7.50 (dd, *J*=8.16, 7.66 Hz, 1H), 7.19 (d, *J*=1.00 Hz, 1H), 6.83 (d, *J*=7.28 Hz, 1H), 6.52 (d, *J*=8.28 Hz, 1H), 5.32 (dt, *J*=13.36, 6.75 Hz, 1H), 1.49 (d, *J*=6.78 Hz, 6H). MS (ESI): $[M + H]^+$ calcd. for $C_{11}H_{15}N_4$ 203.3; found 203.0.

Step B: *N*-(6-(1-Isopropyl-1*H*-imidazol-5-yl)pyridin-2-yl)-3-methoxy-1-methyl-1*H*-pyrazole-4-carboxamide



The title compound was synthesized according to the general procedure described in Compound 8 and using 6-(1-isopropyl-1*H*-imidazol-5-yl)pyridin-2-amine to give the title compound (80 mg, 29%) as an off-white solid. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.13 (d, *J*=8.28 Hz, 1H), 8.06 - 7.95 (m, 2H), 7.84 (t, *J*=8.03 Hz, 1H), 7.54 - 7.35 (m, 2H), 5.49 - 5.31 (m, 1H), 4.12 (s, 3H), 3.83 (s, 3H), 1.62 (d, *J*=6.78 Hz, 6H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.18 (s, 1H), 8.21 (s, 1H), 8.04 – 7.98 (m, 2H), 7.84 (t, *J*=7.91 Hz, 1H), 7.45 - 7.40 (m, 2H), 5.29 (quin, *J*=6.71 Hz, 1H), 4.01 (s, 3H), 3.76 (s, 3H), 1.52 (d, *J*=6.78 Hz, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 159.4, 159.2, 150.6, 148.6, 139.4, 137.4, 135.7, 130.3, 129.6, 117.2, 110.4, 101.2, 57.1, 47.7, 39.1, 23.5. HRMS (*m/z*): $[M + H]^+$ calcd. for $C_{17}H_{21}N_6O_2$ 341.1721; found: 341.1731. HPLC (CH_3CN in 0.1% TFA): t_R = 1.19 min (100% purity).

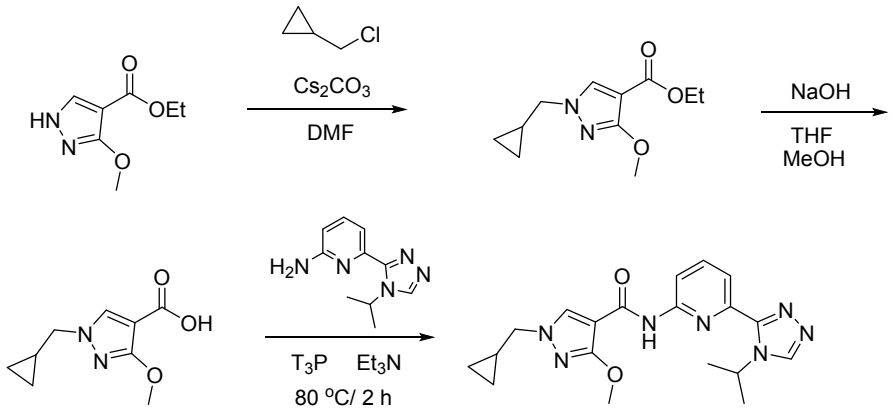
Compound 12: 1-Ethyl-*N*-(6-(4-isopropyl-4*H*-1,2,4-triazol-3-yl)pyridin-2-yl)-3-methoxy-1*H*-pyrazole-4-carboxamide



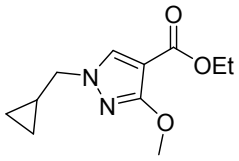
To a mixture of 6-(4-isopropyl-1,2,4-triazol-3-yl)pyridin-2-amine (102 mg, 0.5 mmol) and 1-ethyl-3-methoxy-pyrazole-4-carboxylic acid (85 mg, 0.5 mmol) in a reaction vial was added triethylamine (1 mL, 7.21 mmol) and propylphosphonic anhydride (≥50 wt% in EtOAc, 1 mL). The mixture was heated at 80 °C for 3.5 h. After this time the mixture was quenched with a small amount of MeOH (~ 2 mL) and then it was partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was triturated with MeCN (~ 2 mL) to give the title compound (13 mg, 7%) as a pale brown solid. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.85 (s, 1H), 8.34 (d, *J*=8.28 Hz, 1H), 8.06 (s, 1H), 7.98 (t, *J*=8.03 Hz, 1H), 7.81 (d, *J*=7.28 Hz, 1H), 5.44 (quin, *J*=6.78 Hz, 1H), 4.17 – 3.95 (m, 5H), 1.64 (d, *J*=6.78 Hz, 6H), 1.46 (t, *J*=7.28 Hz, 3H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.30 (s, 1H), 8.90 (s, 1H), 8.27 (s, 1H), 8.22 (dd, *J*=0.88, 8.41 Hz, 1H), 8.00 (t, *J*=7.91 Hz, 1H), 7.80 (dd, *J*=0.88, 7.66 Hz, 1H), 5.33 (spt, *J*=6.73 Hz, 1H), 4.10 - 3.97 (m, 5H), 1.54 (d, *J*=6.78 Hz, 6H), 1.37 (t, *J*=7.15 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 159.6, 159.2, 150.8, 149.9, 146.0, 143.3, 139.9, 134.3, 118.7, 113.2, 101.0, 57.0, 48.4,

46.8, 23.0, 14.8. HRMS (*m/z*): $[M + H]^+$ calcd. for $C_{17}H_{22}N_7O_2$ 356.1829; found: 356.1829. HPLC (CH_3CN in 0.1% TFA): t_R = 1.44 min (100% purity).

Compound 13: 1-(Cyclopropylmethyl)-*N*-(6-(4-isopropyl-4*H*-1,2,4-triazol-3-yl)pyridin-2-yl)-3-methoxy-1*H*-pyrazole-4-carboxamide

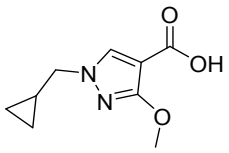


Step A: Ethyl 1-(cyclopropylmethyl)-3-methoxy-1*H*-pyrazole-4-carboxylate



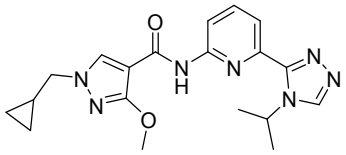
A mixture of ethyl 3-methoxy-1*H*-pyrazole-4-carboxylate (190 mg, 1.0 mmol), (chloromethyl)cyclopropane (136 mg, 1.5 mmol) and Cs_2CO_3 (326 mg, 1.0 mmol) in DMF (2 mL) was heated in a reaction vial at 80 °C for 1 h. The mixture was partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc. The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The residue was purified by normal phase column eluted with 30-40% EtOAc in heptane to give the title intermediate (180 mg, 80%) as a white solid. MS (ESI): $[M + H]^+$ calcd. for $C_{11}H_{17}N_2O_3$ 225.3; found 225.1.

Step B: 1-(Cyclopropylmethyl)-3-methoxy-1*H*-pyrazole-4-carboxylic acid



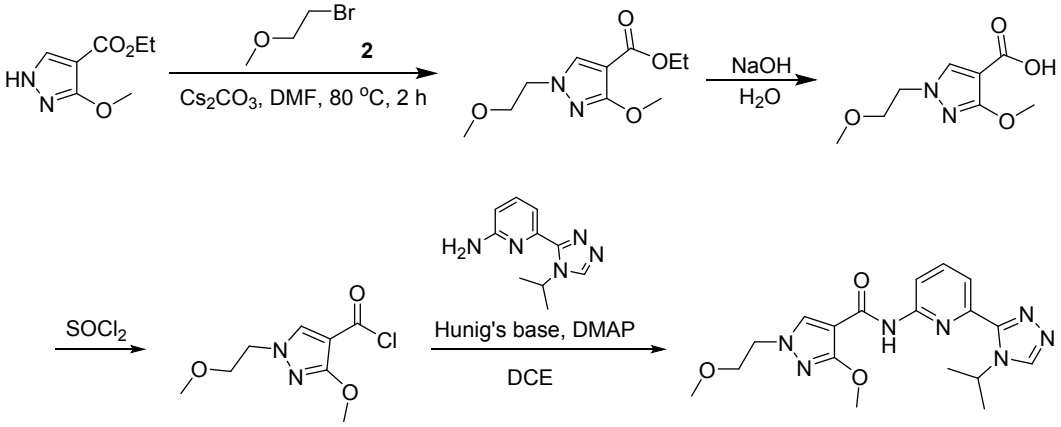
To a solution of ethyl 1-(cyclopropylmethyl)-3-methoxy-1*H*-pyrazole-4-carboxylate (178 mg, 0.79 mmol) in THF (1.5 mL) and MeOH (1.5 mL) was added 1N NaOH (1.5 mL). The mixture was heated at 60°C for 2 h. The mixture was acidified with 1N HCl (2 mL) and then it was partitioned between EtOAc and water. The organic phase was separated, dried over $MgSO_4$, filtered and concentrated to give the title intermediate as a white solid (146 mg, 94%). MS (ESI): $[M + H]^+$ calcd. for $C_9H_{13}N_2O_3$ 197.2; found 197.1.

Step C: 1-(Cyclopropylmethyl)-*N*-(6-(4-isopropyl-4*H*-1,2,4-triazol-3-yl)pyridin-2-yl)-3-methoxy-1*H*-pyrazole-4-carboxamide

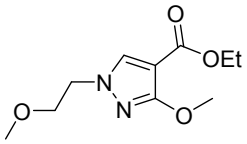


To a mixture of 6-(4-isopropyl-1,2,4-triazol-3-yl)pyridin-2-amine (61 mg, 0.3 mmol) and 1-(cyclopropylmethyl)-3-methoxy-pyrazole-4-carboxylic acid (59 mg, 0.3 mmol) in a reaction vial was added triethylamine (1.1 mL, 7.91 mmol) and propylphosphonic anhydride (≥50 wt% in EtOAc, 0.8 mL). The mixture was heated at 80 °C for 2 h. After this time the mixture was quenched with a small amount of MeOH (~ 0.5 mL) and partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by normal phase column (eluted with 100% EtOAc to EtOAc/EtOH 3/1) to give the title compound as a pale yellow solid (24 mg, 21%). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.85 (s, 1H), 8.34 (d, *J*=8.03 Hz, 1H), 8.11 (s, 1H), 7.97 (t, *J*=7.91 Hz, 1H), 7.81 (d, *J*=7.28 Hz, 1H), 5.44 (dt, *J*=13.36, 6.75 Hz, 1H), 4.11 (s, 3H), 3.98 - 3.86 (m, 2H), 1.69 - 1.60 (m, 6H), 1.41 - 1.19 (m, 1H), 0.81 - 0.51 (m, 2H), 0.50 - 0.19 (m, 2H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.31 (s, 1H), 8.90 (s, 1H), 8.28 (s, 1H), 8.23 (dd, *J*=0.75, 8.28 Hz, 1H), 8.00 (t, *J*=7.91 Hz, 1H), 7.81 (dd, *J*=0.75, 7.53 Hz, 1H), 5.34 (quin, *J*=6.71 Hz, 1H), 4.03 (s, 3H), 3.88 (d, *J*=7.28 Hz, 2H), 1.54 (d, *J*=6.53 Hz, 6H), 1.33 - 1.20 (m, 1H), 0.59 - 0.48 (m, 2H), 0.43 - 0.31 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 159.6, 159.2, 150.8, 149.9, 143.3, 146.0, 139.9, 134.5, 118.7, 113.2, 101.1, 57.1, 56.1, 48.4, 23.0, 10.1, 3.5. HRMS (*m/z*): $[M + H]^+$ calcd. for $C_{19}H_{24}N_7O_2$ 382.1986; found: 382.1983. HPLC (CH_3CN in 0.1% TFA): t_R = 1.64 min (100% purity).

Compound 14: *N*-(6-(4-Isopropyl-4*H*-1,2,4-triazol-3-yl)pyridin-2-yl)-3-methoxy-1-(2-methoxyethyl)-1*H*-pyrazole-4-carboxamide

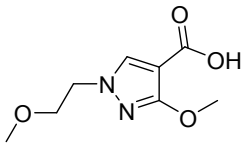


Step A: Ethyl 3-methoxy-1-(2-methoxyethyl)-1*H*-pyrazole-4-carboxylate



To a solution of ethyl 3-methoxy-1*H*-pyrazole-4-carboxylate (30 g, 176 mmol) in DMF (350 mL) was added 1-bromo-2-methoxyethane (31.8 g, 229 mmol) and Cs_2CO_3 (57.4 g, 176 mmol). The mixture was stirred at 80 °C for 2 h. The mixture was concentrated in *vacuo*. The residue was taken into EtOAc (300 ml x 3) and brine. The combined organic phases were washed with sat. NaCl (500 ml x 2),dried over Na_2SO_4, filtered and concentrated *in vacu*o to give a residue which was purified by column chromatography on silica gel (PE:EA = 4:1 to 1:1) to give the title compound (28 g, 70%) as yellow oil. ^{1}HNMR (400 MHz, CD_3OD) δ ppm 7.90 (s, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 4.15 - 4.11 (m, 2H), 3.91 (s, 3H), 3.70 (t, *J* = 4.8 Hz, 2H), 3.31 (s, 3H), 1.29 (t, *J* = 6.8 Hz, 3H).

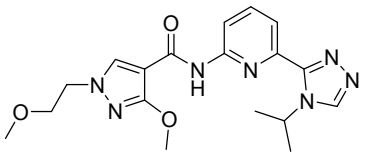
Step B: 3-Methoxy-1-(2-methoxyethyl)-1*H*-pyrazole-4-carboxylic acid



A solution of NaOH (9.8 g, 245.3 mmol) in H_2O (300 mL) was added to ethyl 3-methoxy-1-

(2-methoxyethyl)-1*H*-pyrazole-4-carboxylate (28 g, 122.6 mmol) and heated at 100 °C for 2 h. The mixture was acidified with 2N HCl (30 ml) and extracted with DCM/MeOH (500 ml/50 ml x 3). The organic phases were dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to give the title compound (15 g, 61%) as a white solid. ^{1}HNMR (400 MHz, DMSO-d_6) δ ppm 11.94 (s, 1H), 8.00 (s, 1H), 4.12 (t, *J* = 5.2 Hz, 2H), 3.82 (s, 3H), 3.65 (t, *J* = 5.2 Hz, 2H), 3.24 (s, 3H). MS (ESI): $[M + H]^+$ calcd. for $C_8H_{13}N_2O_4$ 201.2; found 201.0.

Step C: *N*-(6-(4-Isopropyl-4*H*-1,2,4-triazol-3-yl)pyridin-2-yl)-3-methoxy-1-(2-methoxyethyl)-1*H*-pyrazole-4-carboxamide

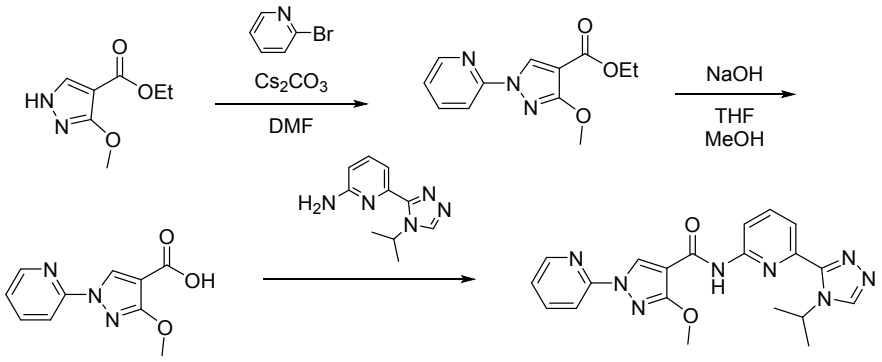


The mixture of 3-methoxy-1-(2-methoxyethyl)pyrazole-4-carboxylic acid (81.00 mg, 0.40 mmol) in thionyl chloride (0.5 mL, 6.85 mmol) was heated at 80 °C for 5 min. The mixture was concentrated and co-evaporated with MeCN to get the crude intermediate (85 mg, 98%).

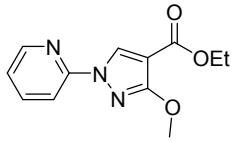
To a mixture of the above acid chloride (85 mg, 0.39 mmol), 6-(4-isopropyl-4*H*-1,2,4-triazol-3-yl)pyridin-2-amine (80 mg, 0.39 mmol) and DMAP (48 mg, 0.39 mmol) in DCE (1.00 mL) was added Hunig's base (340 μL, 1.94 mmol). The mixture was stirred at rt overnight and partitioned between EtOAc/sat. $NaHCO_3$. The aqueous layer was extracted with EtOAc (x3). The combined organic phases were dried over $MgSO_4$, filtered and evaporated *in vacuo*. The residue was purified by column chromatography using EtOAc/EtOH (3/1) as eluent to give the title compound (35 mg, 23%) as a white powder after lyophilization. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.85 (s, 1H), 8.42 - 8.28 (m, 1H), 8.06 (s, 1H), 8.04 - 7.92 (m, 1H), 7.81 (d, *J*=7.28 Hz, 1H), 5.64 - 5.25 (m, 1H), 4.20 (t, *J*=5.02 Hz, 2H), 4.11 (s, 3H), 3.74 (t, *J*=5.02 Hz, 2H), 3.34 (s, 3H), 1.64 (d, *J*=6.78 Hz, 6H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.30 (s, 1H), 8.90 (s, 1H), 8.25 - 8.19 (m, 2H), 8.00 (t, *J*=7.91 Hz, 1H), 7.81 (dd, *J*=0.88, 7.66 Hz, 1H), 5.34 (spt, *J*=6.65 Hz, 1H), 4.19 (t, *J*=5.27 Hz, 2H), 4.05 – 3.98 (m, 3H), 3.68 (t, *J*=5.27 Hz, 2H), 3.25 (s, 3H), 1.54 (d, *J*=6.53 Hz, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 160.1, 159.8, 151.2, 150.4, 146.5, 143.8, 140.4, 136.2, 119.3, 113.7, 101.7, 70.0, 58.4, 57.6, 52.1, 48.9, 23.6; HRMS (*m/z*): $[M + H]^+$ calcd. for

$C_{18}H_{24}N_7O_3$ 386.1935; found: 386.1943. HPLC (CH_3CN in 0.1% TFA): t_R = 1.37 min (95% purity).

Compound 15: *N*-(6-(4-Isopropyl-4*H*-1,2,4-triazol-3-yl)pyridin-2-yl)-3-methoxy-1-(pyridin-2-yl)-1*H*-pyrazole-4-carboxamide

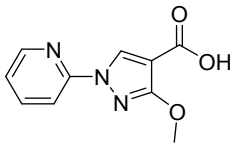


Step A: Ethyl 3-methoxy-1-(pyridin-2-yl)-1*H*-pyrazole-4-carboxylate



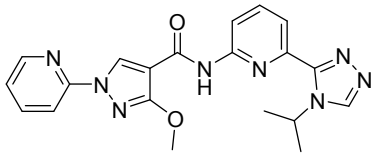
A mixture ethyl 3-methoxy-1*H*-pyrazole-4-carboxylate (170 mg, 1.0 mmol), 2-bromopyridine (174 mg, 1.1 mmol) and Cs_2CO_3 (326 mg, 1.0 mmol) in DMF (1 mL) was heated in a sealed tube at 120 °C overnight. The mixture was partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc. The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography eluting with 10-20% EtOAc in heptane to give the title intermediate (36 mg, 15%) as a white solid. MS (ESI): $[M + H]^+$ calcd. for $C_{12}H_{14}N_3O_3$ 248.3; found 248.1.

Step B: 3-Methoxy-1-(pyridin-2-yl)-1*H*-pyrazole-4-carboxylic acid



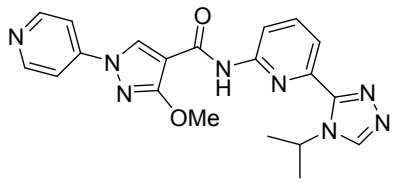
To ethyl 3-methoxy-1-(2-pyridyl)pyrazole-4-carboxylate (35.8 mg, 0.145 mmol) in THF (0.5 mL) and MeOH (0.5 mL) was added 1*N* sodium hydroxide (0.3 mL, 0.3 mmol) in a reaction vial. The reaction mixture was heated at 60 °C for 1.5 h. The mixture was acidified by 1N HCl, concentrated to give a solid which was used without further purification in the next step.

Step C: *N*-(6-(4-Isopropyl-4*H*-1,2,4-triazol-3-yl)pyridin-2-yl)-3-methoxy-1-(pyridin-2-yl)-1*H*-pyrazole-4-carboxamide



To a mixture of 6-(4-isopropyl-1,2,4-triazol-3-yl)pyridin-2-amine (30 mg, 0.15 mmol) and 3-methoxy-1-(2-pyridyl)pyrazole-4-carboxylic acid (32 mg, 0.15 mmol) in a reaction vial was added triethylamine (0.5 mL, 3.61 mmol) and propylphosphonic anhydride (≥50 wt% in EtOAc, 0.5 mL). The mixture was heated at 80 °C for 1.5 h and quenched with MeOH and water. The suspension was filtered and washed with water, EtOAc, and MeOH to give the title compound (9 mg, 15%) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 10.47 (s, 1H), 9.87 (s, 1H), 9.72 (s, 1H), 9.34 (d, *J*=3.76 Hz, 1H), 9.06 (d, *J*=8.03 Hz, 1H), 8.97 - 8.77 (m, 2H), 8.67 (t, *J*=8.78 Hz, 2H), 8.23 (dd, *J*=6.78, 5.02 Hz, 1H), 6.46 - 5.94 (m, 1H), 4.96 (s, 3H), 2.35 (d, *J*=6.53 Hz, 6H). HRMS (*m/z*): $[M + H]^+$ calcd. for $C_{20}H_{21}N_8O_2$ 405.1782; found: 405.1783. HPLC (CH_3CN in 0.1% TFA): t_R = 1.78 min (95% purity).

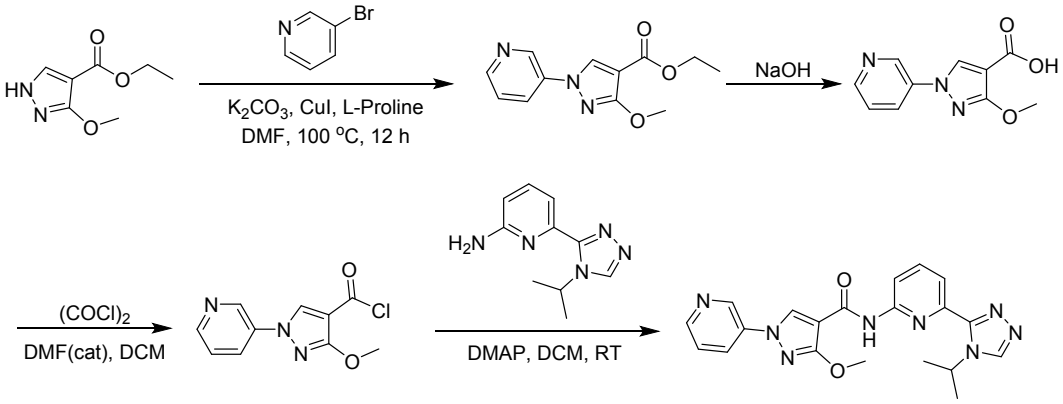
Compound 16: *N*-(6-(4-Isopropyl-4*H*-1,2,4-triazol-3-yl)pyridin-2-yl)-3-methoxy-1-(pyridin-4-yl)-1*H*-pyrazole-4-carboxamide



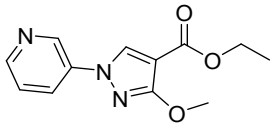
The title compound was synthesized according to the general procedure described in Compound 15 and using 4-chloropyridine (236 mg). The final product was purified by trituration

with MeOH (20 ml) to give the title compound (120 mg, 65% for the last two steps) as a gray solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 9.57 (s, 1H), 9.35 (s, 1H), 8.87 (s, 1H), 8.69 - 8.63 (m, 2H), 8.24 (d, *J*=8.25 Hz, 1H), 8.04 (t, *J*=7.98 Hz, 1H), 7.93 - 7.88 (m, 2H), 7.85 (dd, *J*=0.73, 7.52 Hz, 1H), 5.43 (dt, *J*=6.69, 13.39 Hz, 1H), 4.16 (s, 3H), 1.54 (d, *J*=6.79 Hz, 6H). ^{13}C NMR (151 MHz, DMSO-d_6) δ ppm 161.0, 158.8, 151.0, 150.5, 149.8, 146.1, 144.6, 143.1, 139.8, 133.4, 119.0, 113.5, 111.7, 106.3, 57.3, 48.2, 23.0. HRMS (*m/z*): $[M + H]^+$ calcd. for $C_{20}H_{21}N_8O_2$ 405.1782; found: 405.1780. HPLC (CH_3CN in 0.1% TFA): t_R = 1.10 min (100% purity).

Compound 17: *N*-(6-(4-Isopropyl-4*H*-1,2,4-triazol-3-yl)pyridin-2-yl)-3-methoxy-1-pyridin-3-yl)-1*H*-pyrazole-4-carboxamide



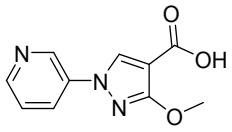
Step A: Ethyl 3-methoxy-1-(pyridin-3-yl)-1*H*-pyrazole-4-carboxylate



A solution of ethyl 3-methoxy-1*H*-pyrazole-4-carboxylate (2 g, 11.8 mmol), 3-bromopyridine (2.79 g, 17.6 mmol), *L*-proline (270 mg, 2.36 mmol), CuI (224 mg, 1.18 mmol) and K_2CO_3 (4.06 g, 29.4 mmol) in DMF (30 mL) was stirred at 100 °C under N_2 for 17 h. After this time the mixture was diluted with H_2O (100 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a crude residue which was purified by HPLC (using a Phenomenex Synergi C18 4μm, 150x30mm column and using water (containing 0.05%HCl) and MeCN from 16 to 36% as the mobile phase

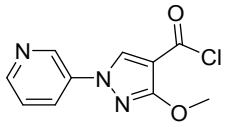
at a flow rate of 25 mL/min) to give the title compound (600 mg, 21%) as a white solid. MS (ESI): $[M + H]^+$ calcd. for $C_{12}H_{14}N_3O_3$ 248.3; found 248.0.

Step B: 3-Methoxy-1-(pyridin-3-yl)-1*H*-pyrazole-4-carboxylic acid



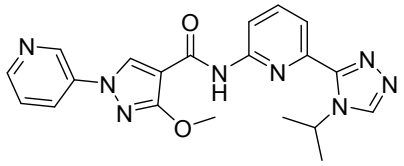
A mixture of ethyl 3-methoxy-1-(pyridin-3-yl)-1*H*-pyrazole-4-carboxylate (500 mg, 2.0 mmol) and NaOH (243 mg, 6.1 mmol) in MeOH/H_2O (6 mL, 5/1) was heated at 50 °C for 3 h. After this time, the mixture was concentrated *in vacuo* and diluted with water (10 mL). The pH of the mixture was adjusted to 3-4 by addition of aqueous HCl (3M) and then it was extracted with EtOAc (300 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to give the title compound (300 mg, 68%) as a white solid.

Step C: 3-Methoxy-1-(pyridin-3-yl)-1*H*-pyrazole-4-carbonyl chloride



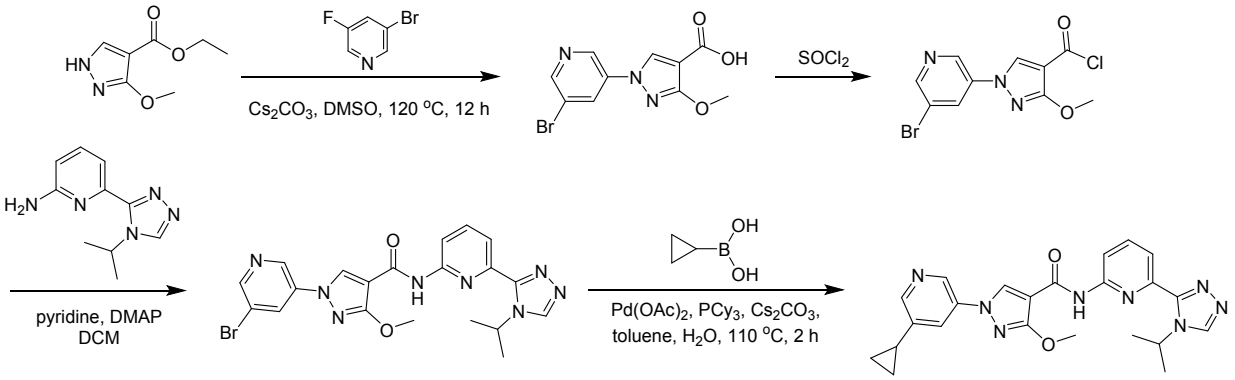
To a solution of 3-methoxy-1-(pyridin-3-yl)-1*H*-pyrazole-4-carboxylic acid (150 mg, 0.68 mmol) in DCM (10 mL) under N_2 was added $(COCl)_2$ (174 mg, 1.37 mmol) followed by DMF (5 drops) and the mixture was stirred at 25 °C for 2 h. After this time the mixture was concentrated under reduced pressure to give the title compound (162 mg, crude) which was used without further purification in the next step.

Step D: *N*-(6-(4-Isopropyl-4*H*-1,2,4-triazol-3-yl)pyridin-2-yl)-3-methoxy-1-(pyridin-3-yl)-1*H*-pyrazole-4-carboxamide

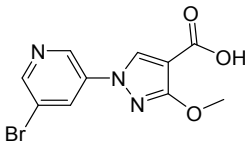


To a solution of 3-methoxy-1-(pyridin-3-yl)-1*H*-pyrazole-4-carbonyl chloride (162 mg, 0.68 mmol) and 6-(4-isopropyl-4*H*-1,2,4-triazol-3-yl)pyridin-2-amine (277 mg, 1.36 mmol) in DCM (10 mL) under a N_2 atmosphere was added DMAP (166 mg, 1.36 mmol) and the mixture was stirred at 25 ^oC for 17 h. After this time the mixture was concentrated *in vacuo* and purified by prep-HPLC (using a Waters Xbridge Prep OBD C18 5µm, 150x30mm column and using water (containing 0.05% $NH_3.H_2O$) and MeCN, from 20 to 50% as the mobile phase at a flow rate of 25 mL/min) to give the title compound (29 mg, 5%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.46 (s, 1H), 9.19 - 9.16 (m, 1H), 9.13 (d, *J*=2.2 Hz, 1H), 8.90 (s, 1H), 8.53 (d, *J*=3.9 Hz, 1H), 8.30 - 8.20 (m, 2H), 8.02 (t, *J*=7.9 Hz, 1H), 7.83 (d, *J*=7.5 Hz, 1H), 7.55 (dd, *J*=4.6, 8.1 Hz, 1H), 5.45 - 5.25 (m, 1H), 4.14 (s, 3H), 1.53 (d, *J*=6.6 Hz, 6H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.47 (s, 1H), 9.18 (s, 1H), 9.15 (d, *J*=2.76 Hz, 1H), 8.91 (s, 1H), 8.54 (dd, *J*=1.38, 4.64 Hz, 1H), 8.30 - 8.23 (m, 2H), 8.04 (t, *J*=8.03 Hz, 1H), 7.84 (dd, *J*=0.88, 7.65 Hz, 1H), 7.59 - 7.54 (m, 1H), 5.38 (spt, *J*=6.69 Hz, 1H), 4.16 (s, 3H), 1.55 (d, *J*=6.78 Hz, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 161.3, 159.6, 151.1, 150.4, 148.0, 146.6, 143.8, 140.5, 140.2, 135.7, 133.7, 126.0, 124.7, 119.6, 113.9, 105.8, 58.0, 48.9, 23.6. HRMS (*m/z*): $[M + H]^+$ calcd. for $C_{20}H_{21}N_8O_2$ 405.1782; found: 405.1782. HPLC (CH_3CN in 0.1% TFA): t_R = 1.25 min (98% purity).

Compound 18: 1-(5-Cyclopropylpyridin-3-yl)-*N*-(6-(4-isopropyl-4*H*-1,2,4-triazol-3-yl)pyridin-2-yl)-3-methoxy-1*H*-pyrazole-4-carboxamide

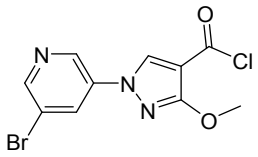


Step A: 1-(5-Bromopyridin-3-yl)-3-methoxy-1*H*-pyrazole-4-carboxylic acid



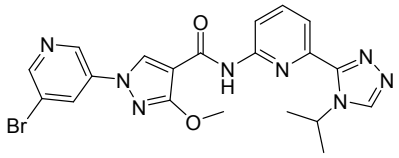
To a solution of ethyl 3-methoxy-1*H*-pyrazole-4-carboxylate (10 g, 59 mmol) in DMSO (100 mL) was added Cs_2CO_3 (58.6 g, 0.18 mol) and 3-bromo-5-fluoropyridine (10.3 g, 59 mmol). The mixture was stirred at 120 °C for 18 h. The mixture was poured into water (500 mL) and adjusted to pH~3 with 2N HCl. The resulting solids were filtered off and lyophilized to give the title compound (10 g, 57%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.53 (br s, 1H), 9.11 (s, 1H), 9.04 (s, 1H), 8.64 (s, 1H), 8.54 (d, J = 1.6 Hz, 1H), 3.98 (s, 3H).

Step B: 1-(5-Bromopyridin-3-yl)-3-methoxy-1*H*-pyrazole-4-carbonyl chloride



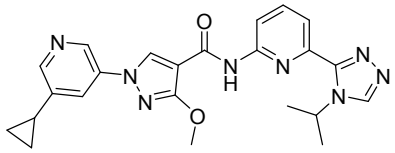
A mixture of 1-(5-bromopyridin-3-yl)-3-methoxy-1*H*-pyrazole-4-carboxylic acid (9.5 g, 3.1 mmol) in $SOCl_2$ (90 mL) was heated at 60 °C for 2 h, and concentrated under vacuum to give the crude title compound (10g, crude) as an off-white solid. HPLC samples were prepared in methanol giving the mass of the corresponding methyl ester.

Step C: 1-(5-Bromopyridin-3-yl)-*N*-(6-(4-isopropyl-4*H*-1,2,4-triazol-3-yl)pyridin-2-yl)-3-methoxy-1*H*-pyrazole-4-carboxamide



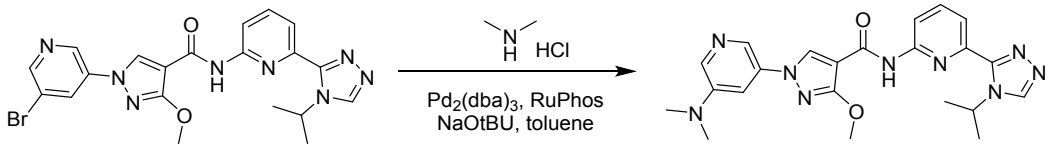
To a solution of 1-(5-bromopyridin-3-yl)-3-methoxy-1*H*-pyrazole-4-carbonyl chloride (10 g, crude, 3.1 mmol) in DCM (120 mL) was added 6-(4-isopropyl-4*H*-1,2,4-triazol-3-yl)pyridin-2-amine (6.3 g, 3.1 mmol). Pyridine (10 mL) was added to adjust to pH~8. DMAP (7.6 g, 6.2 mmol) was addedand the resulting mixture was stirred at 29 °C for 0.5 h. A precipitate formed which was filtered off and washed several times with water and MeOH. After lyophilization the title compound (12 g, 80%, two steps) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.20 (s, 1H), 8.89 (d, J = 2.0 Hz, 1H), 8.62 (d, J = 2.0 Hz, 1H), 8.49 (s, 1H), 8.39 - 8.36 (m, 2H), 8.22 (t, J = 2.0 Hz, 1H), 8.01 (d, J = 7.6 Hz, 1H), 7.92 - 7.89 (m, 1H), 5.51 - 5.47 (m, 1H), 4.22 (s, 3H), 1.63 (d, J = 6.8 Hz, 6H).

Step D: 1-(5-Cyclopropylpyridin-3-yl)-*N*-(6-(4-isopropyl-4*H*-1,2,4-triazol-3-yl)pyridin-2-yl)-3-methoxy-1*H*-pyrazole-4-carboxamide



To a solution of 1-(5-bromopyridin-3-yl)-*N*-(6-(4-isopropyl-4*H*-1,2,4-triazol-3-yl)pyridin-2-yl)-3-methoxy-1*H*-pyrazole-4-carboxamide (100 mg, 0.2 mmol) in toluene/water (10 mL, 10:1) was added cyclopropylboronic acid (106.6 mg, 1.24 mmol), PCy_3 (58 mg, 0.2 mmol), Cs_2CO_3 (404.4 mg, 1.24 mmol). $Pd(OAc)_2$ (23.2 mg, 0.1 mmol) was added under N_2 and the resulting mixture was heated at 110 ^oC for 2 h. The mixture was concentrated and purified by HPLC (using a Waters Xbridge Prep OBD C18 150 x 30mm x 5μm column, and using water (0.05% ammonia hydroxide v/v)-MeCN as mobile phase, from 30-60% at a flow rate of 25 mL/min) to give the title compound (46.3 mg, 50%). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.42 (s, 1H), 9.18 (s, 1H), 8.94 - 8.84 (m, 2H), 8.37 (s, 1H), 8.24 (d, J = 8.4 Hz, 1H), 8.02 (t, J = 8 Hz, 1H), 7.88 - 7.80 (m, 2H), 5.36 (m, 1H), 4.14 (s, 3H), 2.10 - 1.97 (m, 1H), 1.55 (d, J = 6.6 Hz, 6H), 1.12 - 0.97 (m, 2H), 0.89 (d, J = 3.6 Hz, 2H). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.44 (s, 1H), 9.20 (s, 1H), 8.91 (s, 1H), 8.89 (d, J=2.51 Hz, 1H), 8.39 (d, J=1.76 Hz, 1H), 8.25 (dd, J=1.00, 8.28 Hz, 1H), 8.03 (t, J=8.03 Hz, 1H), 7.88 - 7.82 (m, 2H), 5.37 (quin, J=6.65 Hz, 1H), 4.15 (s, 3H), 2.05 (tt, J=5.02, 8.41 Hz, 1H), 1.55 (d, J=6.53 Hz, 6H), 1.11 - 1.02 (m, 2H), 0.94 - 0.85 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 161.1, 159.6, 151.0, 150.4, 146.6, 146.3, 141.0, 140.5, 137.2, 135.6, 133.9, 121.6, 119.6, 113.9, 105.6, 100.2, 58.0, 48.9, 23.6, 13.1, 10.2. HRMS (*m/z*): $[M + H]^+$ calcd. for $C_{23}H_{25}N_8O_2$ 445.2095; found: 445.2090. HPLC (CH_3CN in 0.1% TFA): t_R = 1.44 min (100% purity).

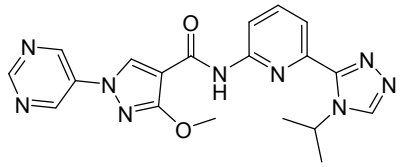
Compound 19: 1-(5-(Dimethylamino)pyridin-3-yl)-*N*-(6-(4-isopropyl-4*H*-1,2,4-triazol-3-yl)pyridin-2-yl)-3-methoxy-1*H*-pyrazole-4-carboxamide



To a solution of 1-(5-bromopyridin-3-yl)-*N*-(6-(4-isopropyl-4*H*-1,2,4-triazol-3-yl)pyridin-

2-yl)-3-methoxy-1*H*-pyrazole-4-carboxamide (100 mg, 0.21 mmol), dimethylamine hydrochloride (20.2 mg, 0.25 mmol), RuPhos (19.3 mg, 0.041 mmol), NaO*t*Bu (79.5 mg, 0.83 mmol) and $Pd_2(dba)_3$ (19 mg, 0.021 mmol) in toluene (8 mL) was heated at 100 °C for 12 h. The mixture was concentrated and purified by prep-HPLC (using a Waters Xbridge Prep OBD C18 150 x 30 mm x 5 μm column; and using water (containing 0.04%NH_3H_2O+10mM NH_4HCO_3)-MeCN as mobile phase; from 29-43%, at a 25 mL/min flow rate) to give the title compound (15 mg, 16.%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.47 (s, 1H), 9.21 (s, 1H), 8.92 (s, 1H), 8.42 (d, J = 2.0 Hz, 1H), 8.27 (d, J = 8.4 Hz, 1H), 8.10 - 8.01 (m, 2H), 7.85 (d, J = 7.6 Hz, 1H), 7.48 (t, J = 2.4 Hz, 1H), 5.38 (quin, J = 6.4 Hz, 1H), 4.16 (s, 3H), 3.03 (s, 6H), 1.56 (d, J = 6.8 Hz, 6H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.45 (s, 1H), 9.19 (s, 1H), 8.91 (s, 1H), 8.40 (d, J=2.01 Hz, 1H), 8.26 (dd, J=0.88, 8.41 Hz, 1H), 8.08 - 8.00 (m, 2H), 7.84 (dd, J=0.88, 7.66 Hz, 1H), 7.46 (t, J=2.38 Hz, 1H), 5.37 (spt, J=6.65 Hz, 1H), 4.15 (s, 3H), 3.02 (s, 6H), 1.55 (d, J=6.78 Hz, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 161.0, 159.7, 151.1, 150.4, 146.8, 146.6, 140.5, 135.9, 133.8, 133.5, 133.3, 127.4, 119.5, 113.9, 107.6, 105.3, 57.9, 48.9, 40.2, 23.6. HRMS (*m/z*): $[M + H]^+$ calcd. for $C_{22}H_{26}N_9O_2$ 448.2204; found: 448.2193. HPLC (CH_3CN in 0.1% TFA): t_R = 1.27 min (97% purity).

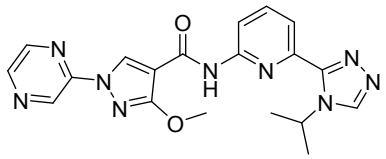
Compound 20: *N*-(6-(4-Isopropyl-4*H*-1,2,4-triazol-3-yl)pyridin-2-yl)-3-methoxy-1-(pyrimidin-5-yl)-1*H*-pyrazole-4-carboxamide



The title compound was synthesized according to the general procedure described in Compound 17 and using 5-bromopyrimidine. The final product was purified by prep-HPLC (Xtimate C18 150 x 25mm x 5 μm, water (10mM NH_4HCO_3)-MeCN as mobile phase, from 23 - 53%, flow rate (ml/min): 25) to give the title compound (34 mg, yield 9.2% for the last two steps) as a white solid. ^{1}HNMR (400 MHz, DMSO-d_6) δ ppm 9.49 (s, 1H), 9.36 (s, 2H), 9.27 (s, 1H), 9.17 (s, 1H), 8.92 (s, 1H), 8.26 (d, J = 8.0 Hz, 1H), 8.05 (t, J = 8.0 Hz, 1H), 7.86 (d, J = 7.2 Hz, 1H), 5.48 – 5.31 (m, 1H), 4.18 (s, 3H), 1.56 (d, J = 6.8 Hz, 6H). ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 9.46 (s, 1H), 9.34 (s, 2H), 9.22 (s, 1H), 9.15 (s, 1H), 8.87 (s, 1H), 8.27 - 8.23 (m, 1H), 8.04

(t, *J*=7.98 Hz, 1H), 7.86 (dd, *J*= 0.73, 7.70 Hz, 1H), 5.39 (quin, *J*=6.74 Hz, 1H), 4.18 (s, 3H), 1.56 (d, *J*=6.79 Hz, 6H). ^{13}C NMR (151 MHz, DMSO-d_6) δ ppm 161.1, 158.7, 155.7, 150.4, 149.8, 146.5, 146.1, 143.1, 139.8, 133.8, 133.6, 119.0, 113.4, 105.9, 57.5, 48.2, 22.9. HRMS (*m/z*): [M + H]$^+$ calcd. for $C_{19}H_{20}N_9O_2$ 406.1734; found: 406.1742. HPLC (CH_3CN in 0.1% TFA): t_R = 1.39 min (100% purity).

Compound 21: *N*-(6-(4-Isopropyl-4*H*-1,2,4-triazol-3-yl)pyridin-2-yl)-3-methoxy-1-(pyrazin-2-yl)-1*H*-pyrazole-4-carboxamide



The title compound was synthesized according to the general procedure described in Compound 17 and using 2-chloropyrazine. The final product was purified by prep-HPLC (using a Waters Xbridge Prep OBD C18 150 x 30mm x 5 μm column, and using water (containing 0.05% ammonia hydroxide v/v)-MeCN as mobile phase, from 24-54%, at a 25 mL/min flow rate) to give the title compound (22 mg, 8% for the last two steps) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.74 (s, 1H), 9.17 (d, *J*=1.6 Hz, 1H), 9.10 (s, 1H), 8.91 (s, 1H), 8.67 (d, *J*=2.4 Hz, 1H), 8.61 (m, 1H), 8.23 (dd, J=3.6Hz, 0.8Hz, 1H), 8.04 (t, *J*=8.0 Hz, 1H), 7.85 (dd, *J*=7.6, 0.8 Hz, 1H), 5.49 - 5.39 (m, 1H), 4.17 (s, 3H), 1.53 (d, *J*=6.8 Hz, 6H). ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 9.65 (br s, 1H), 9.17 (s, 1H), 9.05 (s, 1H), 8.86 (s, 1H), 8.66 (d, *J*=2.38 Hz, 1H), 8.59 (d, *J*=1.28 Hz, 1H), 8.23 (d, *J*=8.25 Hz, 1H), 8.03 (t, *J*=7.98 Hz, 1H), 7.85 (d, *J*=7.70 Hz, 1H), 5.44 (quin, *J*=6.69 Hz, 1H), 4.18 (s, 3H), 1.54 (d, *J*=6.79 Hz, 6H). ^{13}C NMR (151 MHz, DMSO-d_6) δ ppm 161.6, 158.7, 150.5, 149.8, 146.1, 145.8, 143.0, 142.7, 142.5, 139.7, 134.3, 131.7, 119.0, 113.7, 106.3, 57.3, 48.1, 23.0. HRMS (*m/z*): [M + H]$^+$ calcd. for $C_{19}H_{20}N_9O_2$ 406.1734; found: 406.1727. HPLC (CH_3CN in 0.1% TFA): t_R = 1.58 min (100% purity).

(ii) Experimental conditions for crystallization, collection and refinement statistics for compound 21

Crystallization was performed using an E.coli expressed human ASK1 construct encoding residues 659-951 encoding a T838E mutation at 7 mg/mL with compound Compound **21** added to 0.5 mM. Crystals grew in 0.1M BisTRIS pH 5.5, 0.2 M ammonium acetate, 3% sorbitol and 12% PEG3350 and X-ray diffraction data was collected at the Swiss Light Source facility (PSI, Xo6DA (PXIII)).

(iii) Kinase selectivity profile for compound 21

Compound	DiscoveRx Gene Symbol	Entrez Gene Symbol	Percent Control	Compound concentration (nM)
21	AAK1	AAK1	37	100
21	ABL1(E255K)-phosphorylated	ABL1	81	100
21	ABL1(F317I)-nonphosphorylated	ABL1	89	100
21	ABL1(F317I)-phosphorylated	ABL1	78	100
21	ABL1(F317L)-nonphosphorylated	ABL1	71	100
21	ABL1(F317L)-phosphorylated	ABL1	68	100
21	ABL1(H396P)-nonphosphorylated	ABL1	34	100
21	ABL1(H396P)-phosphorylated	ABL1	79	100
21	ABL1(M351T)-phosphorylated	ABL1	66	100
21	ABL1(Q252H)-nonphosphorylated	ABL1	11	100
21	ABL1(Q252H)-phosphorylated	ABL1	22	100
21	ABL1(T315I)-nonphosphorylated	ABL1	12	100
21	ABL1(T315I)-phosphorylated	ABL1	6.2	100
21	ABL1(Y253F)-phosphorylated	ABL1	96	100
21	ABL1-nonphosphorylated	ABL1	57	100
21	ABL1-phosphorylated	ABL1	75	100
21	ABL2	ABL2	95	100
21	ACVR1	ACVR1	97	100
21	ACVR1B	ACVR1B	86	100
21	ACVR2A	ACVR2A	66	100
21	ACVR2B	ACVR2B	100	100
21	ACVRL1	ACVRL1	100	100
21	ADCK3	CABC1	93	100

21	ADCK4	ADCK4	93	100
21	AKT1	AKT1	100	100
21	AKT2	AKT2	96	100
21	AKT3	AKT3	83	100
21	ALK	ALK	80	100
21	ALK(C1156Y)	ALK	83	100
21	ALK(L1196M)	ALK	90	100
21	AMPK-alpha1	PRKAA1	81	100
21	AMPK-alpha2	PRKAA2	100	100
21	ANKK1	ANKK1	40	100
21	ARK5	NUAK1	16	100
21	ASK1	MAP3K5	2	100
21	ASK2	MAP3K6	76	100
21	AURKA	AURKA	100	100
21	AURKB	AURKB	97	100
21	AURKC	AURKC	67	100
21	AXL	AXL	49	100
21	BIKE	BMP2K	21	100
21	BLK	BLK	100	100
21	BMPR1A	BMPR1A	81	100
21	BMPR1B	BMPR1B	92	100
21	BMPR2	BMPR2	0.85	100
21	BMX	BMX	97	100
21	BRAF	BRAF	82	100
21	BRAF(V600E)	BRAF	94	100
21	BRK	PTK6	100	100
21	BRSK1	BRSK1	99	100
21	BRSK2	BRSK2	92	100
21	BTK	BTK	97	100
21	BUB1	BUB1	84	100
21	CAMK1	CAMK1	69	100
21	CAMK1B	PNCK	65	100
21	CAMK1D	CAMK1D	76	100
21	CAMK1G	CAMK1G	88	100
21	CAMK2A	CAMK2A	60	100
21	CAMK2B	CAMK2B	60	100
21	CAMK2D	CAMK2D	85	100
21	CAMK2G	CAMK2G	88	100
21	CAMK4	CAMK4	100	100
21	CAMKK1	CAMKK1	81	100
21	CAMKK2	CAMKK2	55	100

21	CASK	CASK	86	100
21	CDC2L1	CDK11B	100	100
21	CDC2L2	CDC2L2	96	100
21	CDC2L5	CDK13	85	100
21	CDK11	CDK19	91	100
21	CDK2	CDK2	100	100
21	CDK3	CDK3	100	100
21	CDK4	CDK4	90	100
21	CDK4-cyclinD1	CDK4	100	100
21	CDK4-cyclinD3	CDK4	92	100
21	CDK5	CDK5	93	100
21	CDK7	CDK7	36	100
21	CDK8	CDK8	96	100
21	CDK9	CDK9	98	100
21	CDKL1	CDKL1	75	100
21	CDKL2	CDKL2	93	100
21	CDKL3	CDKL3	94	100
21	CDKL5	CDKL5	62	100
21	CHEK1	CHEK1	93	100
21	CHEK2	CHEK2	72	100
21	CIT	CIT	0.2	100
21	CLK1	CLK1	2.5	100
21	CLK2	CLK2	12	100
21	CLK3	CLK3	61	100
21	CLK4	CLK4	4.9	100
21	CSF1R	CSF1R	86	100
21	CSF1R-autoinhibited	CSF1R	98	100
21	CSK	CSK	82	100
21	CSNK1A1	CSNK1A1	77	100
21	CSNK1A1L	CSNK1A1L	84	100
21	CSNK1D	CSNK1D	100	100
21	CSNK1E	CSNK1E	93	100
21	CSNK1G1	CSNK1G1	69	100
21	CSNK1G2	CSNK1G2	95	100
21	CSNK1G3	CSNK1G3	79	100
21	CSNK2A1	CSNK2A1	100	100
21	CSNK2A2	CSNK2A2	100	100
21	CTK	MATK	75	100
21	DAPK1	DAPK1	99	100
21	DAPK2	DAPK2	95	100
21	DAPK3	DAPK3	100	100

21	DCAMKL1	DCLK1	68	100
21	DCAMKL2	DCLK2	93	100
21	DCAMKL3	DCLK3	1	100
21	DDR1	DDR1	100	100
21	DDR2	DDR2	91	100
21	DLK	MAP3K12	91	100
21	DMPK	DMPK	25	100
21	DMPK2	CDC42BPG	92	100
21	DRAK1	STK17A	6.7	100
21	DRAK2	STK17B	3.4	100
21	DYRK1A	DYRK1A	0.7	100
21	DYRK1B	DYRK1B	11	100
21	DYRK2	DYRK2	87	100
21	EGFR	EGFR	89	100
21	EGFR(E746-A750del)	EGFR	100	100
21	EGFR(G719C)	EGFR	95	100
21	EGFR(G719S)	EGFR	79	100
21	EGFR(L747-E749del, A750P)	EGFR	94	100
21	EGFR(L747-S752del, P753S)	EGFR	100	100
21	EGFR(L747-T751del,Sins)	EGFR	100	100
21	EGFR(L858R)	EGFR	97	100
21	EGFR(L858R,T790M)	EGFR	84	100
21	EGFR(L861Q)	EGFR	100	100
21	EGFR(S752-I759del)	EGFR	86	100
21	EGFR(T790M)	EGFR	92	100
21	EIF2AK1	EIF2AK1	78	100
21	EPHA1	EPHA1	71	100
21	EPHA2	EPHA2	98	100
21	EPHA3	EPHA3	88	100
21	EPHA4	EPHA4	95	100
21	EPHA5	EPHA5	100	100
21	EPHA6	EPHA6	97	100
21	EPHA7	EPHA7	93	100
21	EPHA8	EPHA8	92	100
21	EPHB1	EPHB1	92	100
21	EPHB2	EPHB2	100	100
21	EPHB3	EPHB3	98	100
21	EPHB4	EPHB4	100	100
21	EPHB6	EPHB6	92	100
21	ERBB2	ERBB2	96	100
21	ERBB3	ERBB3	83	100

21	ERBB4	ERBB4	89	100
21	ERK1	MAPK3	100	100
21	ERK2	MAPK1	99	100
21	ERK3	MAPK6	90	100
21	ERK4	MAPK4	100	100
21	ERK5	MAPK7	100	100
21	ERK8	MAPK15	79	100
21	ERN1	ERN1	62	100
21	FAK	PTK2	100	100
21	FER	FER	70	100
21	FES	FES	99	100
21	FGFR1	FGFR1	85	100
21	FGFR2	FGFR2	51	100
21	FGFR3	FGFR3	100	100
21	FGFR3(G697C)	FGFR3	82	100
21	FGFR4	FGFR4	99	100
21	FGR	FGR	92	100
21	FLT1	FLT1	98	100
21	FLT3	FLT3	16	100
21	FLT3(D835H)	FLT3	30	100
21	FLT3(D835V)	FLT3	9.6	100
21	FLT3(D835Y)	FLT3	14	100
21	FLT3(ITD)	FLT3	5.3	100
21	FLT3(ITD,D835V)	FLT3	0.45	100
21	FLT3(ITD,F691L)	FLT3	0	100
21	FLT3(K663Q)	FLT3	50	100
21	FLT3(N841I)	FLT3	6.3	100
21	FLT3(R834Q)	FLT3	24	100
21	FLT3-autoinhibited	FLT3	64	100
21	FLT4	FLT4	94	100
21	FRK	FRK	100	100
21	FYN	FYN	79	100
21	GAK	GAK	20	100
21	GCN2(Kin.Dom.2,S808G)	EIF2AK4	70	100
21	GRK1	GRK1	60	100
21	GRK2	ADRBK1	100	100
21	GRK3	ADRBK2	90	100
21	GRK4	GRK4	29	100
21	GRK7	GRK7	64	100
21	GSK3A	GSK3A	87	100
21	GSK3B	GSK3B	73	100

21	HASPIN	GSG2	96	100
21	HCK	HCK	95	100
21	HIPK1	HIPK1	83	100
21	HIPK2	HIPK2	86	100
21	HIPK3	HIPK3	77	100
21	HIPK4	HIPK4	100	100
21	HPK1	MAP4K1	58	100
21	HUNK	HUNK	100	100
21	ICK	ICK	87	100
21	IGF1R	IGF1R	100	100
21	IKK-alpha	CHUK	84	100
21	IKK-beta	IKBKB	84	100
21	IKK-epsilon	IKBKE	36	100
21	INSR	INSR	100	100
21	INSRR	INSRR	89	100
21	IRAK1	IRAK1	23	100
21	IRAK3	IRAK3	99	100
21	IRAK4	IRAK4	37	100
21	ITK	ITK	93	100
21	JAK1(JH1domain-catalytic)	JAK1	88	100
21	JAK1(JH2domain-pseudokinase)	JAK1	100	100
21	JAK2(JH1domain-catalytic)	JAK2	25	100
21	JAK3(JH1domain-catalytic)	JAK3	7.7	100
21	JNK1	MAPK8	61	100
21	JNK2	MAPK9	92	100
21	JNK3	MAPK10	77	100
21	KIT	KIT	94	100
21	KIT(A829P)	KIT	19	100
21	KIT(D816H)	KIT	12	100
21	KIT(D816V)	KIT	5.2	100
21	KIT(L576P)	KIT	63	100
21	KIT(V559D)	KIT	83	100
21	KIT(V559D,T670I)	KIT	80	100
21	KIT(V559D,V654A)	KIT	68	100
21	KIT-autoinhibited	KIT	100	100
21	LATS1	LATS1	100	100
21	LATS2	LATS2	67	100
21	LCK	LCK	89	100
21	LIMK1	LIMK1	93	100
21	LIMK2	LIMK2	96	100
21	LKB1	STK11	73	100

21	LOK	STK10	24	100
21	LRRK2	LRRK2	0	100
21	LRRK2(G2019S)	LRRK2	2	100
21	LTK	LTK	98	100
21	LYN	LYN	100	100
21	LZK	MAP3K13	76	100
21	MAK	MAK	99	100
21	MAP3K1	MAP3K1	83	100
21	MAP3K15	MAP3K15	6.1	100
21	MAP3K2	MAP3K2	65	100
21	MAP3K3	MAP3K3	78	100
21	MAP3K4	MAP3K4	92	100
21	MAP4K2	MAP4K2	3.6	100
21	MAP4K3	MAP4K3	11	100
21	MAP4K4	MAP4K4	7.2	100
21	MAP4K5	MAP4K5	42	100
21	MAPKAPK2	MAPKAPK2	67	100
21	MAPKAPK5	MAPKAPK5	49	100
21	MARK1	MARK1	96	100
21	MARK2	MARK2	78	100
21	MARK3	MARK3	100	100
21	MARK4	MARK4	91	100
21	MAST1	MAST1	90	100
21	MEK1	MAP2K1	78	100
21	MEK2	MAP2K2	90	100
21	MEK3	MAP2K3	72	100
21	MEK4	MAP2K4	87	100
21	MEK5	MAP2K5	2.9	100
21	MEK6	MAP2K6	98	100
21	MELK	MELK	75	100
21	MERTK	MERTK	96	100
21	MET	MET	96	100
21	MET(M1250T)	MET	100	100
21	MET(Y1235D)	MET	86	100
21	MINK	MINK1	13	100
21	MKK7	MAP2K7	100	100
21	MKNK1	MKNK1	87	100
21	MKNK2	MKNK2	75	100
21	MLCK	MYLK3	100	100
21	MLK1	MAP3K9	93	100
21	MLK2	MAP3K10	78	100

21	MLK3	MAP3K11	16	100
21	MRCKA	CDC42BPA	78	100
21	MRCKB	CDC42BPB	47	100
21	MST1	STK4	92	100
21	MST1R	MST1R	100	100
21	MST2	STK3	32	100
21	MST3	STK24	98	100
21	MST4	MST4	50	100
21	MTOR	MTOR	49	100
21	MUSK	MUSK	84	100
21	MYLK	MYLK	85	100
21	MYLK2	MYLK2	100	100
21	MYLK4	MYLK4	94	100
21	MYO3A	MYO3A	75	100
21	MYO3B	MYO3B	100	100
21	NDR1	STK38	82	100
21	NDR2	STK38L	85	100
21	NEK1	NEK1	100	100
21	NEK10	NEK10	79	100
21	NEK11	NEK11	87	100
21	NEK2	NEK2	97	100
21	NEK3	NEK3	84	100
21	NEK4	NEK4	96	100
21	NEK5	NEK5	90	100
21	NEK6	NEK6	88	100
21	NEK7	NEK7	93	100
21	NEK9	NEK9	93	100
21	NIK	MAP3K14	22	100
21	NIM1	MGC42105	75	100
21	NLK	NLK	69	100
21	OSR1	OXSR1	62	100
21	p38-alpha	MAPK14	90	100
21	p38-beta	MAPK11	92	100
21	p38-delta	MAPK13	85	100
21	p38-gamma	MAPK12	88	100
21	PAK1	PAK1	96	100
21	PAK2	PAK2	85	100
21	PAK3	PAK3	71	100
21	PAK4	PAK4	92	100
21	PAK6	PAK6	95	100
21	PAK7	PAK7	84	100

21	PCTK1	CDK16	83	100
21	PCTK2	CDK17	98	100
21	PCTK3	CDK18	93	100
21	PDGFRA	PDGFRA	23	100
21	PDGFRB	PDGFRB	24	100
21	PDPK1	PDPK1	97	100
21	PFCDPK1(P.falciparum)	CDPK1	100	100
21	PFPK5(P.falciparum)	MAL13P1.279	89	100
21	PFTAIRE2	CDK15	89	100
21	PFTK1	CDK14	100	100
21	PHKG1	PHKG1	100	100
21	PHKG2	PHKG2	100	100
21	PIK3C2B	PIK3C2B	90	100
21	PIK3C2G	PIK3C2G	73	100
21	PIK3CA	PIK3CA	99	100
21	PIK3CA(C420R)	PIK3CA	84	100
21	PIK3CA(E542K)	PIK3CA	74	100
21	PIK3CA(E545A)	PIK3CA	89	100
21	PIK3CA(E545K)	PIK3CA	98	100
21	PIK3CA(H1047L)	PIK3CA	100	100
21	PIK3CA(H1047Y)	PIK3CA	98	100
21	PIK3CA(I800L)	PIK3CA	66	100
21	PIK3CA(M1043I)	PIK3CA	95	100
21	PIK3CA(Q546K)	PIK3CA	100	100
21	PIK3CB	PIK3CB	100	100
21	PIK3CD	PIK3CD	51	100
21	PIK3CG	PIK3CG	95	100
21	PIK4CB	PI4KB	31	100
21	PIKFYVE	PIKFYVE	83	100
21	PIM1	PIM1	97	100
21	PIM2	PIM2	100	100
21	PIM3	PIM3	94	100
21	PIP5K1A	PIP5K1A	17	100
21	PIP5K1C	PIP5K1C	82	100
21	PIP5K2B	PIP4K2B	40	100
21	PIP5K2C	PIP4K2C	87	100
21	PKAC-alpha	PRKACA	99	100
21	PKAC-beta	PRKACB	82	100
21	PKMYT1	PKMYT1	77	100
21	PKN1	PKN1	68	100
21	PKN2	PKN2	41	100

21	PKNB(M.tuberculosis)	pknB	93	100
21	PLK1	PLK1	87	100
21	PLK2	PLK2	54	100
21	PLK3	PLK3	78	100
21	PLK4	PLK4	95	100
21	PRKCD	PRKCD	40	100
21	PRKCE	PRKCE	66	100
21	PRKCH	PRKCH	56	100
21	PRKCI	PRKCI	100	100
21	PRKCQ	PRKCQ	71	100
21	PRKD1	PRKD1	26	100
21	PRKD2	PRKD2	5.2	100
21	PRKD3	PRKD3	6.5	100
21	PRKG1	PRKG1	90	100
21	PRKG2	PRKG2	96	100
21	PRKR	EIF2AK2	97	100
21	PRKX	PRKX	100	100
21	PRP4	PRPF4B	96	100
21	PYK2	PTK2B	99	100
21	QSK	KIAA0999	94	100
21	RAF1	RAF1	100	100
21	RET	RET	65	100
21	RET(M918T)	RET	53	100
21	RET(V804L)	RET	24	100
21	RET(V804M)	RET	45	100
21	RIOK1	RIOK1	28	100
21	RIOK2	RIOK2	73	100
21	RIOK3	RIOK3	19	100
21	RIPK1	RIPK1	90	100
21	RIPK2	RIPK2	100	100
21	RIPK4	RIPK4	81	100
21	RIPK5	DSTYK	67	100
21	ROCK1	ROCK1	4.2	100
21	ROCK2	ROCK2	3.6	100
21	ROS1	ROS1	17	100
21	RPS6KA4(Kin.Dom.1-N-terminal)	RPS6KA4	94	100
21	RPS6KA4(Kin.Dom.2-C-terminal)	RPS6KA4	72	100
21	RPS6KA5(Kin.Dom.1-N-terminal)	RPS6KA5	100	100
21	RPS6KA5(Kin.Dom.2-C-terminal)	RPS6KA5	88	100
21	RSK1(Kin.Dom.1-N-terminal)	RPS6KA1	73	100
21	RSK1(Kin.Dom.2-C-terminal)	RPS6KA1	96	100

21	RSK2(Kin.Dom.1-N-terminal)	RPS6KA3	3.7	100
21	RSK2(Kin.Dom.2-C-terminal)	RPS6KA3	78	100
21	RSK3(Kin.Dom.1-N-terminal)	RPS6KA2	7.4	100
21	RSK3(Kin.Dom.2-C-terminal)	RPS6KA2	100	100
21	RSK4(Kin.Dom.1-N-terminal)	RPS6KA6	0.5	100
21	RSK4(Kin.Dom.2-C-terminal)	RPS6KA6	100	100
21	S6K1	RPS6KB1	63	100
21	SBK1	SBK1	48	100
21	SGK	SGK1	67	100
21	SgK110	SgK110	100	100
21	SGK2	SGK2	82	100
21	SGK3	SGK3	100	100
21	SIK	SIK1	97	100
21	SIK2	SIK2	67	100
21	SLK	SLK	28	100
21	SNARK	NUAK2	3.2	100
21	SNRK	SNRK	79	100
21	SRC	SRC	99	100
21	SRMS	SRMS	97	100
21	SRPK1	SRPK1	31	100
21	SRPK2	SRPK2	95	100
21	SRPK3	SRPK3	26	100
21	STK16	STK16	87	100
21	STK33	STK33	38	100
21	STK35	STK35	59	100
21	STK36	STK36	94	100
21	STK39	STK39	80	100
21	SYK	SYK	86	100
21	TAK1	MAP3K7	3.6	100
21	TAOK1	TAOK1	77	100
21	TAOK2	TAOK2	95	100
21	TAOK3	TAOK3	88	100
21	TBK1	TBK1	51	100
21	TEC	TEC	83	100
21	TESK1	TESK1	65	100
21	TGFBR1	TGFBR1	95	100
21	TGFBR2	TGFBR2	93	100
21	TIE1	TIE1	87	100
21	TIE2	TEK	78	100
21	TLK1	TLK1	90	100
21	TLK2	TLK2	100	100

21	TNIK	TNIK	9.4	100
21	TNK1	TNK1	57	100
21	TNK2	TNK2	100	100
21	TNNI3K	TNNI3K	100	100
21	TRKA	NTRK1	100	100
21	TRKB	NTRK2	100	100
21	TRKC	NTRK3	100	100
21	TRPM6	TRPM6	92	100
21	TSSK1B	TSSK1B	100	100
21	TSSK3	TSSK3	77	100
21	TTK	TTK	70	100
21	TXK	TXK	85	100
21	TYK2(JH1domain-catalytic)	TYK2	20	100
21	TYK2(JH2domain-pseudokinase)	TYK2	90	100
21	TYRO3	TYRO3	99	100
21	ULK1	ULK1	6.8	100
21	ULK2	ULK2	0.6	100
21	ULK3	ULK3	87	100
21	VEGFR2	KDR	100	100
21	VPS34	PIK3C3	36	100
21	VRK2	VRK2	64	100
21	WEE1	WEE1	100	100
21	WEE2	WEE2	100	100
21	WNK1	WNK1	70	100
21	WNK2	WNK2	86	100
21	WNK3	WNK3	84	100
21	WNK4	WNK4	80	100
21	YANK1	STK32A	91	100
21	YANK2	STK32B	100	100
21	YANK3	STK32C	100	100
21	YES	YES1	97	100
21	YSK1	STK25	87	100
21	YSK4	MAP3K19	4.5	100
21	ZAK	ZAK	84	100
21	ZAP70	ZAP70	73	100