Supporting information

Discovery of 8-amino-imidazo[1,5-a]pyrazines as reversible BTK inhibitors for the treatment of rheumatoid arthritis

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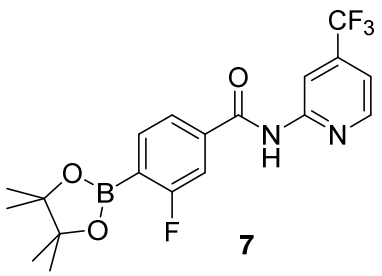
Normal phase column chromatography was carried out in the indicated solvent system (in the percentage of volume) using pre-packed silica gel cartridges for use on the Isco CombiFlashR or Biotage. LC-MS analysis was done using Agilent 1100 series LC-MSD VL on a YMC-Pack ODS-AQ column ((120 Å, 5 um particle size, 2.0 mm x 50 mm). The flowing phase was MeCN and H_2O which add 0.05% (v/v) TFA. The flow rate was 2 mL / min. The effluent was monitored with a wavelength detector at 220. Nuclear Magnetic Resonance spectra were recorded on Varian spectrometers. Spectra were taken in the indicated solvent at ambient temperature, and the chemical shifts are reported in parts per million (ppm (δ)) relative to the lock of the solvent used. Resonance patterns are recorded with the following notations: br (broad), s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). High resolution mass spectra (HRMS) were acquired by use of Waters Xevo G2 Qtof Mass Spectrometer with Acquity UPLC BEH C18 1.7um column.



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3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-N-(4-(trifluoromethyl)-pyridin-2-yl)benzamide

(a) 4-bromo-3-fluorobenzoyl chloride

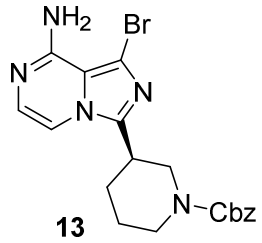
To a stirred mixture 4-bromo-3-fluorobenzoic acid (**4**, 10.0 g, 45.7 mmol) in DCM (100 ml) at 0 °C was added oxalyl chloride (4.80 ml, 54.8 mmol) and several drops of DMF. The mixture was then stirred at room temperature overnight. The mixture was then concentrated by rotary evaporation and coevaporated with toluene to provide 4-bromo-3-fluorobenzoyl chloride (10.5 g) as a yellow solid, which was taken to the next step.

(b) 4-bromo-3-fluoro-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide

4-bromo-3-fluorobenzoyl chloride (3.60 g, 14.40 mmol) was added to a stirred solution of DIEA (3.02 ml, 17.28 mmol), DMAP (0.176 g, 1.440 mmol) and 4-(trifluoromethyl)pyridin-2-amine (**5**, 2.45 g, 15.11 mmol) in THF (36 ml) and then the mixture was stirred at 50 °C for 12 h. The mixture was diluted with EtOAc, extracted twice with 0.1 N HCl, twice with 0.1 M KOH, washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated to afford 4-bromo-3-fluoro-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide (**6**) as a tan solid (4.59 g).

(c) 3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide

A premixed and degassed solution of $Pd(OAc)_2$ (15.46 mg, 0.069 mmol) and X-Phos (65.6 mg, 0.138 mmol) in 1 mL of dioxane that had been stirred for 20 minutes was added to a stirred, degassed mixture of bis(pinicolato)diboron (699 mg, 2.75 mmol), potassium acetate (405 mg, 4.13 mmol) and 4-bromo-3-fluoro-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide (500 mg, 1.377 mmol) in dioxane (10 ml). The mixture was stirred at 90 °C for 6h. The reaction mixture was filtered and concentrated in vacuo. The residue was purified by MPLC (10 to 30% ethyl acetate in hexanes) to afford 3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide (**7**) as a white solid (424 mg). LC-MS: $C_{19}H_{19}BF_4N_2O_3$, found $[M+1]^+$: 393.2, ^{1}HNMR ($CDCl_3$, 500 MHz) δ: 9.15 (1H, d, J = 12.0 Hz), 8.69 (1H, s), 8.52 (1H, d, J= 5.5 Hz), 7.86 (1H, t, J = 9.0 Hz), 7.65 (1H, m), 7.34 (1H, d, J = 5.0 Hz), 1.40 (12H, s) ppm.



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(*R*)-benzyl 3-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)piperidine-1-carboxylate

(a) (*R*)-benzyl 3-((3-chloropyrazin-2-yl)methylcarbamoyl)piperidine-1-carboxylate (10)

To a solution of (3-chloropyrazin-2-yl)methanamine.hydrochloride (**8**, 1.85 g, 10.28 mmol), (*R*)-piperidine-1,3-dicarboxylic acid 1-benzylester (**9**, 2.71 g, 10.28 mmol) and HATU (4.1 g, 10.79 mmol) in dichloromethane (75 mL) was added triethylamine (5.73 mL, 41.1 mmol) and the reaction mixture was stirred at 0°C for 4 hr. and after warming up to room temperature over night. The mixture was washed with 0.1 M HCl-solution, 5% $NaHCO_3$, water and brine, dried over sodium sulfate and concentrated *in vacuo* to give crude (*R*)-benzyl 3-((3-chloropyrazin-2-yl)methylcarbamoyl)piperidine-1-carboxylate (**10)** which was used directly in the next step without further purification.

(b) (*R*)-benzyl 3-(8-chloroimidazo[1,5-a]pyrazin-3-yl)piperidine-1-carboxylate (**11**)

(*R*)-benzyl 3-((3-chloropyrazin-2-yl)methylcarbamoyl)piperidine-1-carboxylate (**10**, 5.03 g, 10.28 mmol theor.) was dissolved in acetonitrile (40 ml), phosphorus oxychloride (4.82 ml, 51.7 mmol) was added and the mixture was stirred for 5 h at 80°C. The mixture was added dropwise to 25% aq. ammonia (81 mL) in 250 mL crushed ice keeping the temperature below 0°C. The resulting suspension was stirred another 15 min after which it was extracted with ethyl acetate (3x). The combined organic layers were washed with water, brine, dried over sodium sulfate and concentrated *in vacuo*. The product was purified using silica gel chromatography (heptane/ethyl acetate = 100/0 to 50/50 v/v%)) to give 2.77 g of (*R*)-benzyl 3-(8-chloroimidazo[1,5-a]pyrazin-3-yl)piperidine-1-carboxylate (**11**, 57.7%). LC-MS: $C_{19}H_{19}ClN_4O_2$, found $[M+1]^+$ 371.2.

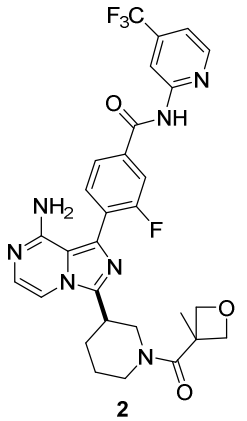
(c) (*R*)-benzyl 3-(1-bromo-8-chloroimidazo[1,5-a]pyrazin-3-yl)piperidine-1-carboxylate (**12**)

N-Bromosuccinimide (1.329 g, 7.47 mmol) was added to a stirred solution of (*R*)-benzyl 3-(8-chloroimidazo[1,5-a]pyrazin-3-yl)piperidine-1-carboxylate (7.47 mmol, 2.77 g) in DMF (40

mL). The reaction was stirred 1h at room temperature. The reaction was quenched with 50 mL sat. $Na_2S_2O_3$ (aq) and ethyl acetate (50 mL).Brine (50 mL) was added and the mixture was then separated. The aqeous layer was extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried over sodium sulfate, filtered and evaporated. The residue was purified by column chromatography on silica gel , eluting with (DCM/MeOH 50/1) to give to give 3.18 g of (*R*)-benzyl 3-(1-bromo-8-chloroimidazo[1,5-a]pyrazin-3-yl)piperidine-1-carboxylate (**12**, 95%). LC-MS: $C_{19}H_{18}BrClN_4O_2$, found $[M+1]^+$ 448.7, 450.7.

(d) (*R*)-benzyl 3-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)piperidine-1-carboxylate (**13**)

(*R*)-benzyl 3-(1-bromo-8-chloroimidazo[1,5-a]pyrazin-3-yl)piperidine-1-carboxylate (**12**, 1.5 g, 3.34 mmol) was heated in ammonia/i-PrOH (2M, 50 mL0 in a sealed vessel at 120 ^oC for 18 hrs overnight.The mixture was concentrated. The residue was purified by column chromatography on silica gel , eluting with CH_2Cl_2/MeOH (20/1) to give to give 1.39 g of (*R*)-benzyl 3-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)piperidine-1-carboxylate (**13**, 97%). LC-MS: $C_{19}H_{20}BrN_5O_2$, found $[M+1]^+$ 430.2, 432.2. ^{1}HNMR (CD_3OD, 400 MHz): d 7.53 (1H, br), 7.33 (5H, br), 6.90 (1H, br), 5.12 (2H, m), 5.09 (2H, m), 3.71 (1H, m), 3.20 (1H, m), 3.03 (1H, m), 2.10 (1H, m), 1.86 (2H, m), 1.65 (1H, m).



2

(R)-4-(8-amino-3-(1-(3-methyloxetane-3-carbonyl)piperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-3-fluoro-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide

(a) (R)-benzyl 3-(8-amino-1-(2-fluoro-4-((4-(trifluoromethyl)pyridin-2-yl)carbamoyl) phenyl)imidazo[1,5-a]pyrazin-3-yl)piperidine-1-carboxylate (**14**)

The $PdCl_2$(dppf)-CH_2Cl_2 adduct (0.170 g, 0.232 mmol) was added to a stirred, cooled room temperature mixture of 3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-N-(4-

(trifluoromethyl)pyridin-2-yl)benzamide (23.41 g, 45.7 mmol) and (*R*)-benzyl 3-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)piperidine-1-carboxylate (2.0 g, 4.65 mmol) and potassium carbonate aqueous solution (2M, 13.94 mmol) in dioxane (10 mL). Tthe mixture was degassed and put under nitrogen atomosphere, then was stirred at 60 °C overnight. After cooled to room temperature, the mixture was partitioned between ethyl acetate and water. The organic layer was seperated and the aqueous layer was extracted. The combined organic phases was washed with water and brine, then dried and concentrated. The crude product was purified by MPLC (120 g silica gel, 0-5% MeOH in methylene chloride) to afford (R)-benzyl 3-(8-amino-1-(2-fluoro-4-((4-(trifluoromethyl)pyridin-2-yl)carbamoyl) phenyl)imidazo[1,5-a]pyrazin-3-yl)piperidine-1-carboxylate (2.4 g, 80%). LC-MS: $C_{32}H_{27}F_4N_7O_3$, found $[M+1]^+$ 634.2.

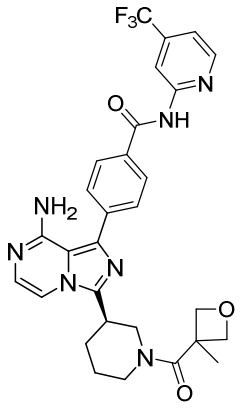
(b) (R)-4-(8-amino-3-(piperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-3-fluoro-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide (**15**)

A solution of (R)-benzyl 3-(8-amino-1-(2-fluoro-4-((4-(trifluoromethyl)pyridin-2-yl)carbamoyl) phenyl)imidazo[1,5-a]pyrazin-3-yl)piperidine-1-carboxylate (450 mg, 0.710 mmol) in methylenechloride (1.5 ml) was treated with iodomethylsilane (142 mg, 0.710 mmol) at 5 ^{0}C for 1 hr. The reaction mixture was quenched with HCl (1M, 0.710 mmol). The organic layer was separated and the aqueous layer was extracted with methylenechloride (2x, 1ml). The aqueous layer was then basified by NaOH (1 M) to pH 9 and extracted with three times CH_2Cl_2:MeOH (9:1), dried over magensium sulfate, filtered and concentrated afford (R)-4-(8-amino-3-(piperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-3-fluoro-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide (**15**, 355 mg, 99%). LC-MS: $C_{24}H_{21}F_4N_7O$, found $[M+1]^+$ 500.2

(c) (R)-4-(8-amino-3-(1-(3-methyloxetane-3-carbonyl)piperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-3-fluoro-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide (**2**)

To a solution of (R)-4-(8-amino-3-(piperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-3-fluoro-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide (350 mg, 0.701 mmol) in methylenechloride (1.5 mL) along with triethylamine (71 mg, 0.701 mml) and 3-methyloxetane-3-carboxylic acid (81 mg, 0.701 mmol), was added 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide (223 mg, 0.701 mmol). The reaction mixture was stirred at room temperature for 1 hour. The reaction was quenched with water and extracted with methylenechloride. The crude was purified my MPLC (40 g silica gel, 0 to 10% MeOH/1%NH_3H_2O in methylenechloride) to afford (R)-4-(8-amino-3-(1-(3-methyloxetane-3-carbonyl)piperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-3-fluoro-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide (300 mg, 71.6%) as white solid. ^{1}HNMR (DMSO-D6, 500 Mhz) δ 11.45 (1H, s), 8.70 (1H, d, J = 5.5 Hz), 8.55 (1H, s), 8.01 (1H, d, J = 10.0 Hz), 8.00 (1H, d, J = 9.0 Hz), 7.72 (1H, dd, J = 32, 5.0 Hz), 7.64 (1H, t, 7.5 hz), 7.57

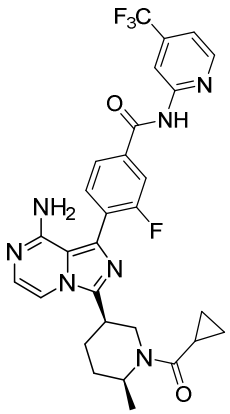
(1H, d, J = 4.5 Hz), 7.11 (1H, d, J = 4.0 Hz), 6.07 (2H, s), 4.80 (2H, m), 4.41 (1H, dd, J = 16, 13 Hz), 4.29 (1H, t, J = 7.0 Hz), 4.20 (1H, dd, J = 20, 6.0 Hz), 3.44 (1H, m), 3.05 (3H, m), 2.09 (1H, m), 1.83 (2H, m), 1.61 (1H, m), 1.56 (3H, s) ppm; ^{13}CNMR (DMSO-D_6, 150 Mhz) δ 172.7, 165.1, 153.1, 151.6, 150.0, 141.7, 138.3, 135.2, 132.6, 128.3, 126.5, 126.2, 124.3, 116.0, 115.8, 115.5, 115.4, 110.0, 106.2, 78.7, 78.5, 59.8, 48.5, 45.4, 44.6, 44.1, 43.9, 41.5, 33.2, 32.9, 29.5, 28.5, 24.8, 24.0, 23.0, 20.8, 14.1 ppm; HRMS: $C_{29}H_{27}F_4N_7O_3$, found $[M+H]^+$ 598.2192.



1

(R)-4-(8-amino-3-(1-(3-methyloxetane-3-carbonyl)piperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide

^{1}HNMR (DMSO-D_6, 500 Mhz) δ 11.3 (1H, s), 8.68 (1H, d, J = 5 Hz), 8.57 (1H, s), 8.16 (2H, d, J= 8.5 Hz), 7.77 (2H, d, J = 8.0Hz), 7.68 (1H, d, J = 5.0hz), 7.54 (1H, d, J = 5.0 Hz), 7.12 (1H, t, J = 4.5 Hz), 6.17 (2H, s), 4.80 (2H, m), 4.42 (1H, t, J = 13.5 Hz), 4.29 (1H, t, J = 6.5 Hz), 4.20 (1H, dd, J = 15, 5.0 hz), 4.44 (1H, m), 3.09 (3H, m), 2.08 (1H, m), 1.84 (2H, m), 1.61 (1H, m), 1.57 (3H, s) ppm; ^{13}CNMR (DMSO-D_6,150 MHz) δ 172.3, 166.4, 153.3, 151.7, 149.9 141.7, 138.4, 133.0, 132.1, 129.1, 128.5, 128.2, 115.1, 114.1, 109.8, 106.3, 78.5, 48.6, 45.4, 44.6, 44.1, 41.5, 33.2, 32.8, 29.5, 28.5, 24.7, 24.0, 23.0 ppm; HRMS: $C_{29}H_{28}F_3N_7O_3$, found $[M+H]^+$ 580.2289.



3

4-(8-amino-3-((3R,6S)-1-(cyclopropanecarbonyl)-6-methylpiperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-3-fluoro-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide

^{1}HNMR (DMSO-D6, 500 Mhz) δ 11.5 (1H, s), 8.70 (1H, d, J = 5.0 Hz), 8.55 (1H, s), 8.02 (1H, d, J = 11 Hz), 8.00 (1H, d, J = 8.0 Hz), 7.71 (1H, dd, J = 43, 5.0 Hz), 7.64 (1H, d, J = 4.0 hz), 7.57 (1H, d, J = 4.6 Hz), 7.09 (1H, s, J = 5.0 Hz), 6.06 (2H, s), 4.75 (1/2H, m), 4.69 (1/2H, m), 4.51 (1/2H, d, J = 14.5 Hz), 4.32 (1/2H, d, J = 14.5 Hz), 3.53 (1/2H, t, J = 13.0 Hz), 3.37 (1/2H, m), 3.17 (1/2H, t, J = 11.0 Hz), 2.95 (1/2H, t, J = 13.0 Hz), 2.00 (2H, m), 1.92 (1.5H, m), 1.76 (1H, m), 1.61 (1/2H, d, J = 13.0 Hz), 1.29 (1.5H, d, J = 6.0 Hz), 1.12 (1.5 H, d, J = 7.5 Hz), 0.73 (4H, m) ppm; ^{13}CNMR (DMSO-D_6, 150 Mhz) δ 171.5, 171.0, 160.0, 158.3, 153.1, 151.6, 150.0, 142.2, 142.0, 138.5, 138.3, 138.1, 135.2, 132.6, 128.2, 126.5, 126.2, 124.3, 116.0, 115.8, 115.5, 109.9, 106.4, 106.1, 47.0, 43.0, 42.8, 34.0, 33.4, 29.8, 28.6, 25.5, 24.3, 23.7, 16.7, 15.3, 11.1, 10.7, 6.9, 6.6 ppm. Two different rotomers exist in DMSO solution; HRMS: $C_{29}H_{27}F_4N_7O_2$, found $[M+H]^+$ 582.2253.

(R)-4-(8-amino-3-(1-(3-methyloxetane-3-carbonyl)piperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-3-fluoro-N-(4-methylpyridin-2-yl)benzamide (**16**): **^{1}H-NMR** (400MHz, MeOD) δ ppm 8.31 (s, 1H), 8.07-8.00 (m, 2H), 7.89-7.78 (m, 3H), 7.43 (s, 1H), 7.05-7.03 (m, 1H), 4.51-4.34 (m, 2H), 3.57-3.39 (m, 2H), 3.18 (s, 4H), 2.58 (s, 4H), 2.19-1.90 (m, 3H), 1.70-1.62(m, 4H). **MS-ESI** (m/z): 544 $(M+1)^+$.

(R)-4-(8-amino-3-(1-(3-methyloxetane-3-carbonyl)piperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(difluoromethyl)pyridin-2-yl)-3-fluorobenzamide (**17**): **^{1}H-NMR** (400MHz, MeOD) δ ppm 8.51-8.46 (m, 2H), 8.00-7.77 (m, 4H), 7.33-7.32 (m, 1H), 7.03-7.01 (m, 1H), 6.87-6.73 (m, 1H), 4.56-4.27 (m, 3H), 3.60-3.39 (m, 2H), 3.18-2.64 (m, 2H), 2.20-1.90 (m, 3H), 1.71-1.62 (m, 4H). **MS-ESI** (m/z): 580 $(M+1)^+$.

(R)-4-(8-amino-3-(1-(3-methyloxetane-3-carbonyl)piperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-cyclopropylpyridin-2-yl)-3-fluorobenzamide (**18**): **^{1}H-NMR** (400MHz, MeOD) δ ppm 8.51-8.46 (m, 2H), 8.00-7.77 (m, 4H), 7.33-7.32 (m, 1H), 7.03-7.01 (m, 1H), 6.87-6.73 (m, 1H), 4.56-4.27 (m, 3H), 3.60-3.39 (m, 2H), 3.18-2.64 (m, 2H), 2.20-1.90 (m, 3H), 1.71-1.62 (m, 4H). **MS-ESI** (m/z): 570 $(M+1)^+$.

(R)-4-(8-amino-3-(1-(3-methyloxetane-3-carbonyl)piperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-cyanopyridin-2-yl)-3-fluorobenzamide (**19**): **^{1}H-NMR** (400MHz, MeOD) δ ppm 8.59-8.57 (m, 2H), 8.00-7.87 (m, 3H), 7.80-7.76 (m, 1H), 7.46-7.45 (m, 1H), 7.03-7.02 (m, 1H), 4.54-4.27 (m, 3H), 3.45-3.38 (m, 2H), 3.19-2.76 (m, 2H), 2.20-1.90 (m, 3H), 1.72-1.62 (m, 4H). **MS-ESI** (m/z): 554 $(M+1)^+$.

(R)-4-(8-amino-3-(1-(3-methyloxetane-3-carbonyl)piperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-ethoxypyridin-2-yl)-3-fluorobenzamide (**20**): **^{1}H-NMR** (400MHz, MeOD) δ ppm 8.06-7.99 (m, 2H), 7.94-7.83 (m, 3H), 7.06-7.04 (m, 1H), 6.91-6.86 (m, 1H), 6.76-6.74 (m, 1H), 4.54-4.27 (m, 3H), 3.45-3.38 (m, 2H), 3.19-2.76 (m, 2H), 2.20-1.90 (m, 3H), 1.72-1.62 (m, 4H). **MS-ESI** (m/z): 575 $(M+1)^+$.

(R)-4-(8-amino-3-(1-(3-methyloxetane-3-carbonyl)piperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-cyclopropoxypyridin-2-yl)-3-fluorobenzamide (**21**): **^{1}H-NMR** (400MHz, MeOD) δ ppm 8.28-8.27 (m, 1H), 8.07-8.00 (m, 2H), 7.89-7.83 (m, 2H), 7.61 (s, 1H), 7.23-7.21 (m, 1H), 7.05-7.03 (m, 1H), 4.54-4.27 (m, 3H), 4.15 (s, 1H), 3.45-3.38 (m, 2H), 3.19-2.76 (m, 2H), 2.19-1.91 (m, 3H), 1.72-1.62 (m, 4H), 099-0.90 (m, 4H). **MS-ESI** (m/z): 586 $(M+1)^+$.

(R)-N-(4-(1H-pyrazol-1-yl)pyridin-2-yl)-4-(8-amino-3-(1-(3-methyloxetane-3-carbonyl)piperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-3-fluorobenzamide (**22**): **^{1}H-NMR** (400MHz, MeOD) δ ppm 8.60-8.48 (s, 1H), 8.46-8.42 (m, 2H), 8.02-7.95 (m, 2H), 7.88-7.80 (m, 3H), 7.78-7.71 (m, 1H), 7.04-7.02 (d, *J* = 8.6Hz, 1H), 6.64-6.63 (m, 1H), 4.37-4.4.34 (m, 3H), 3.61-3.39 (m, 2H), 3.20-2.82 (m, 2H), 2.38-1.82 (m, 3H), 1.74-1.63 (m, 4H). **MS-ESI** (m/z): 596.6 $(M+1)^+$.

(R)-4-(8-amino-3-(1-(3-methyloxetane-3-carbonyl)piperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(chlorodifluoromethoxy)pyridin-2-yl)-3-fluorobenzamide (**23**): **^{1}H-NMR** (400MHz, MeOD) δ

ppm 8.45-8.44 (d, *J* = 4.7Hz, 1H), 8.30 (s, 1H), 7.99-7.81 (m, 3H), 7.79-7.77 (m, 1H), 7.12-7.11 (m, 1H), 7.03-7.02 (m, 1H), 4.52-4.25 (m, 3H), 3.61-3.39 (m, 2H), 3.18-2.65 (m, 2H), 1.98-1.84 (m, 3H), 1.75-1.59(m, 4H). **MS-ESI** (m/z): 630 $(M+1)^+$.

(R)-4-(8-amino-3-(1-(3-methyloxetane-3-carbonyl)piperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-3-fluoro-N-(3-methylpyridin-2-yl)benzamide (24): **^{1}H-NMR** (400MHz, MeOD) δ ppm 8.44-8.43 (d, *J* = 4.7Hz, 1H), 8.27-8.24 (m, 1H), 8.18-7.98 (m, 2H), 7.89-7.82 (m, 2H), 761-7.58 (m, 1H), 7.05-7.03 (m, 1H), 4.52-4.25 (m, 3H), 3.61-3.39 (m, 2H), 3.18-2.65 (m, 2H), 2.52 (m, 3H), 1.98-1.84 (m, 3H), 1.75-1.59(m, 4H). **MS-ESI** (m/z): 544.6 $(M+1)^+$.

(R)-4-(8-amino-3-(1-(3-methyloxetane-3-carbonyl)piperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-3-fluoro-N-(pyridazin-3-yl)benzamide (**25**): **^{1}H-NMR H14546-061-1** (400MHz, MeOD) δ ppm 9.00-8.99 (d, *J* = 4.7Hz, 1H), 8.62-8.62 (d, *J* = 8.6Hz, 1H), 8.03-7.91 (m, 2H), 7.89-7.88 (m, 1H), 7.83-7.79 (m, 2H), 7.04-7.02 (m, 1H), 4.52-4.25 (m, 3H), 3.61-3.39 (m, 2H), 3.18-2.65 (m, 2H), 1.98-1.84 (m, 3H), 1.75-1.59(m, 4H). **MS-ESI** (m/z): 531 $(M+1)^+$.

(R)-4-(8-amino-3-(1-(3-methyloxetane-3-carbonyl)piperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(6-ethylpyrimidin-4-yl)-3-fluorobenzamide (**26**): **^{1}H-NMR** (400MHz, MeOD) δ ppm 8.95 (s, 1H), 8.44 (s, 1H), 8.01-7.94 (m, 2H), 7.89-7.87 (m, 1H), 7.83-7.81 (m, 1H), 7.04-7.03 (d, *J* = 4.7Hz, 1H), 4.52-4.25 (m, 3H), 3.61-3.39 (m, 2H), 3.18-2.65 (m, 4H), 2.20-1.90 (m, 3H), 1.75-1.59 (m, 3H), 1.39-1.35-1.59(m, 3H). **MS-ESI** (m/z): 559 $(M+1)^+$.

(R)-4-(8-amino-3-(1-(3-methyloxetane-3-carbonyl)piperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-3-fluoro-N-(4-methylpyrimidin-2-yl)benzamide (**27**): **^{1}H-NMR** (400 MHz, MeOD) δ ppm 8.57 (d, *J*= 5.2 Hz, 1H), 7.78~8.06 (m, 4H), 7.28 (d, *J*= 5.2 Hz, 1H), 7.04 (d, *J*= 5.6 Hz, 1H), 4.95~5.05 (m, 2H), 4.27~4.55 (m, 3H), 3.38~3.55 (m, 2H), 3.16~3.22 (m, 2H), 2.64 (s, 3H), 1.89~2.25 (m, 3H), 1.60~1.78 (m, 4H). **MS-ESI** (m/z): 545 $(M+1)^+$.

(R)-4-(8-amino-3-(1-(3-methyloxetane-3-carbonyl)piperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-3-fluoro-N-(5-methylpyrazin-2-yl)benzamide (**28**): **^{1}H-NMR** (400 MHz, MeOD) δ ppm 9.36 (s, 1H), 8.35 (s, 1H), 7.75~8.05 (m, 4H), 7.03 (d, *J*= 5.6 Hz, 1H), 4.95~5.01 (m, 2H), 4.27~4.52 (m, 3H),

3.36~3.57 (m, 2H), 3.16~3.21 (m, 2H), 2.53 (s, 3H), 1.90~2.25 (m, 3H), 1.58~1.77 (m, 4H). **MS-ESI** (m/z): 545 $(M+1)^+$.

(R)-4-(8-amino-3-(1-(3-methyloxetane-3-carbonyl)piperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-3-fluoro-N-(thiazol-2-yl)benzamide (29): **^{1}H-NMR** (400 MHz, MeOD) δ ppm 7.78~8.08 (m, 4H), 7.53 (d, *J*= 2.8 Hz, 1H), 7.20 (d, *J*= 3.2 Hz, 1H), 7.03 (d, *J*= 6.0 Hz, 1H), 4.95~5.02 (m, 2H), 4.25~4.55 (m, 3H), 3.39~3.60 (m, 2H), 3.15~3.22 (m, 2H), 1.91~2.25 (m, 3H), 1.58~1.78 (m, 4H). **MS-ESI** (m/z): 536 $(M+1)^+$.

(R)-4-(8-amino-3-(1-(3-methyloxetane-3-carbonyl)piperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(5-cyanothiazol-2-yl)-3-fluorobenzamide (**30**): **^{1}H-NMR** (400MHz, MeOD) δ ppm 8.20 (s, 1H), 8.07-8.00 (m, 2H), 7.89-7.81 (m, 2H), 7.04-7.03 (d, *J* = 4.7Hz, 1H), 4.52-4.25 (m, 3H), 3.61-3.39 (m, 2H), 3.18-2.65 (m, 2H), 2.52 (m, 3H), 1.98-1.84 (m, 3H), 1.75-1.59(m, 4H). **MS-ESI** (m/z): 561 $(M+1)^+$.

(R)-4-(8-amino-3-(1-(3-methyloxetane-3-carbonyl)piperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-2-fluoro-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide (**31**): **^{1}H-NMR** (400 MHz, CDCl3) δ ppm 9.24 (d, *J*= 14.6 Hz, 1H), 8.65 (s, 1H), 8.45 (d, *J*= 5.2 Hz, 1H), 8.22 (t, *J*= 8.0 Hz, 1H), 7.53~7.61 (m, 2H), 7.36 (d, *J*= 4.8 Hz, 1H), 7.26 (d, *J*= 4.8 Hz, 1H), 7.10~7.15 (m, 1H), 5.11~5.15 (m, 2H), 4.93~4.98 (m, 2H), 4.64~4.78 (m, 1H), 4.24~4.35 (m, 2H), 2.80~3.12 (m, 4H), 1.90~2.20 (m, 3H), 1.60~1.65 (m, 4H). **MS-ESI** (m/z): 598 $(M+1)^+$.

(R)-4-(8-amino-3-(1-(3-methyloxetane-3-carbonyl)piperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-2-chloro-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide (**32**): **^{1}H-NMR**(400 MHz, MeOD) δ ppm 8.59-8.58 (m, 2H), 7.88-7.84 (m, 4H), 7.89-7.88 (d, *J* = 6.26 Hz, 1H), 7.67-7.62 (m, 2H),7.46-7.45(d, *J* =4.70 Hz, 1H), 7.05-7.04(d, *J* =6.26 Hz, 1H), 4.59-4.3 (m, 3H),3.46-3.44(m, 2H),3.20-3.12(m,2H),2.19-2.18(m,1H), 2.14-1.92 (m,2H), 1.71-1.63(m,4H). **MS-ESI** (m/z): 614 $(M+1)^+$.

(R)-4-(8-amino-3-(1-(3-methyloxetane-3-carbonyl)piperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-3-methoxy-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide (**33**): **^{1}HNMR** (MeOD 400 MHz): δ 8.62 (d, *J* = 7.6 Hz, 2H), 7.75-7.86 (m, 3H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.44 (d, *J* = 4.8 Hz, 1H), 6.99 (d, *J* = 6.0

Hz, 1H), 4.92-5.00 (m, 2H), 4.28-4.54 (m, 3H), 3.94 (s, 3H), 3.18-3.59 (m, 4H), 1.90-2.20 (m, 3H), 1.62-1.70 (m, 4H). **MS-ESI** (m/z): 610 $(M+1)^+$.

(R)-4-(8-amino-3-(1-(3-methyloxetane-3-carbonyl)piperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-3-(trifluoromethoxy)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide (**34**): **^{1}H-NMR** (400 MHz, MeOD) δ ppm 8.61 (s, 2H), 8.17-8.12 (m, 2H), 7.91-7.84 (q, *J* = 8 Hz, 2H), 7.45-7.44 (d, *J* = 5.2 Hz, 1H), 7.04-7.03 (d, *J* = 5.6 Hz, 1H), 4.97-4.95 (m, 2H), 4.36-4.26 (m, 3H), 3.19 (s, 3H), 2.22-2.19 (m, 1H), 2.6-2.02 (m, 2H), 1.71-1.62 (m, 4H). **MS-ESI** (m/z): 664 $(M+1)^+$.

(R)-4-(8-amino-3-(1-(3-methyloxetane-3-carbonyl)piperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-2-methoxy-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide (**35**): **^{1}H NMR** (400 MHz, MeOD) δ ppm 8.57 (s, 2H), 8.17**~**8.18 (d, *J* = 7.6 Hz, 1H), 7.86**~**7.87 (d, *J* = 5.6 Hz, 1H), 7.46 (s, 1H), 7.40 (s, 2H), 7.04**~**7.05 (d, *J* = 4.8 Hz, 1H), 4.92 (m, 3H), 4.27**~**4.41 (m, 3H), 4.14 (s, 3H), 3.17**~**3.29 (m, 3H), 2.14**~**2.21 (m, 1H), 1.89**~**2.03 (m, 2H), 1.64**~**1.70 (m, 4H). **MS-ESI** (m/z): 610 $(M+1)^+$.

(R)-4-(8-amino-3-(1-(3-methyloxetane-3-carbonyl)piperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-2,3-difluoro-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide (**36**): **^{1}H NMR** (500 MHz, DMSO-D_6) δ ppm 11.54 (1H, s), 8.83 (1H, d, J = 5.5 Hz), 8.51 (1H, s), 7.98 (1H, dd, J = 17.0, 5.5 Hz), 7.64 (1H, t, J = 6.5 Hz), 7.58 (1H, d, J = 5.0 Hz), 7.47 (1H, t, 7.0 Hz), 7.19 (1H, d, J = 5.5 Hz), 4.80 (2H, m), 4.38 (1H, m), 4.29 (1H, m), 4.18 (1H, m), 3.37-3.59 (2H, m), 3.13 (2H, m), 2.98 (1H, m), 1.74-1.88 (2H, m), 1.50-1.63 (4H, m). **MS-ESI** (m/z): 616.3 $(M+1)^+$.

4-(8-amino-3-((3R,6S)-6-methyl-1-(3-methyloxetane-3-carbonyl)piperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-3-fluoro-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide (**37**): **^{1}HNMR** (MeOD, 400MHz) δ: 8.60 (s, 2H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.98 (d, *J* = 10.4 Hz, 1H), 7.86-7.90 (m, 1H), 7.80 (t, *J* = 7.6 Hz, 1H), 7.44 (d, *J* = 4.4 Hz, 1H), 7.04 (d, *J* = 5.6 Hz, 1H), 4.82-5.00 (m, 2H), 4.27-4.40 (m, 2H), 2.98-3.45 (m, 2H), 1.81-2.29 (m, 4H), 1.72 (s, 2H), 1.61 (s, 1H), 1.42 (d, *J* = 6.8 Hz, 2H), 1.25 (d, *J* = 6.8 Hz, 1H). **MS-ESI** (m/z): 612 $(M+1)^+$.

4-(8-amino-3-((3R,6R)-6-(difluoromethyl)-1-(3-methyloxetane-3-carbonyl)piperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide (**38**): **^{1}HNMR** (400 MHz, MeOD) δ= 8.65 (t, *J* = 5.2 Hz, 2H), 8.21 (d, *J* = 8.4 Hz, 2H), 7.89~7.95 (m, 3H), 7.60 (d, *J* = 12

Hz, 1H), 7.09 (d, *J* = 6 Hz, 1H), 6.10~6.51 (m, 1H), 5.01~5.05 (m, 2H), 4.35~4.41 (m, 2H), 3.80~3.87 (m, 1H), 3.53~3.58 (m, 1H), 3.20~3.24 (m, 1H), 1.96~2.24 (m, 5H), 1.69~1.79 (m, 3H); **MS-ESI**: M/Z (M+1): 630.1.

4-(8-amino-3-((3R,6R)-6-(methoxymethyl)-1-(3-methyloxetane-3-carbonyl)piperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide (**39**): **^{1}HNMR** (400MHz, CD_3OD): δ= 8.62 ~ 8.63 (m, 2 H), 8.23 (d, *J* = 8.4 Hz, 2 H), 7.88 ~ 7.91 (m, 3 H), 7.45 (d, *J* = 6.0 Hz, 1 H), 7.07 (d, *J* = 6.0 Hz, 1 H), 4.96 ~ 5.02 (m, 2 H), 4.31 ~ 4.39 (m, 2 H), 3.63 ~ 3.90 (m, 3 H), 3.42 (d, *J* = 6.0 Hz, 3 H), 3.07 ~ 3.22 (m, 2 H), 2.22 ~ 2.27 (m, 1 H), 1.90 ~ 2.09 (m, 4 H), 1.67 ~ 1.78 (m, 3 H). **MS (ESI)**: M/Z (M+1): 624.3.

4-(8-amino-3-((3R,6R)-1-(3-methyloxetane-3-carbonyl)-6-(trifluoromethyl)piperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-3-fluoro-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide (**40**): **^{1}H-NMR** (400 MHz, MeOD) δ ppm 8.60 (s, 2H), 8.01-7.80 (m, 4H), 7.44-7.43 (d, *J* = 4.7 Hz, 1H), 7.06-7.04 (d, *J* = 8.6 Hz, 1H), 5.36-5.35 (m, 1H), 4.99-4.98 (m, 2H), 4.36-4.31 (m, 2H), 3.95-3.19 (m, 4H), 2.26-2.06 (m, 4H), 1.65 (s, 3H). **MS-ESI** (m/z): 666 $(M+1)^+$.

4-(3-((3R,6S)-1-acetyl-6-methylpiperidin-3-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-3-fluoro-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide (**41**): **^{1}H NMR** (400MHz, METHANOL-d_4) δ ppm 8.62 - 8.55 (m, 2H), 8.03 - 7.76 (m, 4H), 7.43 (d, *J*=4.7 Hz, 1H), 7.03 (dd, *J*=2.7, 5.9 Hz, 1H), 4.71 - 4.59 (m, 1H), 4.40 - 4.30 (m, 1H), 4.03 - 3.93 (m, 1H), 3.71 (s, 1H), 3.49 - 3.38 (m, 1H), 3.13 (s, 1H), 2.15 (d, *J*=20.0 Hz, 3H), 2.02 - 1.97 (m, 1H), 1.83 - 1.70 (m, 1H), 1.37 (d, *J*=6.7 Hz, 2H), 1.24 (d, *J*=6.7 Hz, 1H). **MS-ESI** (m/z):556$(M+1)^+$.

4-(8-amino-3-((3R,6S)-6-methyl-1-propionylpiperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-3-fluoro-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide(**42**): **^{1}HNMR** (MeOD, 400MHz) δ: 8.61 (s, 2H), 8.03 (d, *J* = 8.0 Hz, 1H), 7.86-7.98 (m, 2H), 7.81 (t, *J* = 7.6 Hz, 1H), 7.45 (d, *J* = 5.2 Hz, 1H), 7.02 (d, *J* = 6.0 Hz, 1H), 3.10-4.98 (m, 4H), 1.78-2.56 (m, 6H), 1.38 (d, *J* = 6.8 Hz, 2H), 1.26 (d, *J* = 6.8 Hz, 1H), 1.15 (t, *J* = 6.8 Hz, 2H), 1.10 (t, *J* = 6.8 Hz, 1H). **MS-ESI** (m/z): 570 $(M+1)^+$.

4-(8-amino-3-((3R,6S)-1-(3-methoxypropanoyl)-6-methylpiperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-3-fluoro-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide (**43**): **^{1}HNMR** (H13280-0720-A7,

MeOD, 400MHz) δ: 8.61 (s, 2H), 7.87-8.03 (m, 3H), 7.81 (t, *J* = 7.6 Hz, 1H), 7.45 (d, *J* = 5.2 Hz, 1H), 7.01-7.05 (m, 1H), 3.16-4.99 (m, 5H), 3.11 (s, 3H), 2.58-2.82 (m, 2H), 1.80-2.21 (m, 4H), 1.38 (d, *J* = 6.8 Hz, 2H), 1.27 (d, *J* = 6.8 Hz, 1H). **MS-ESI** (m/z): 600 $(M+1)^+$.

4-(8-amino-3-((3R,6S)-6-methyl-1-(5-methylisoxazole-4-carbonyl)piperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-3-fluoro-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide (**44**): **^{1}HNMR** (H13280-0722-A9, MeOD, 400MHz) δ: 8.62 (s, 2H), 8.48 (s, 1H), 8.03 (d, *J* = 7.6 Hz, 1H), 7.98 (d, *J* = 10.4 Hz, 1H), 7.90-7.92 (m, 1H), 7.83 (t, *J* = 6.8 Hz, 1H), 7.45 (d, *J* = 5.2 Hz, 1H), 7.05 (d, *J* = 5.6 Hz, 1H), 3.33-4.68 (m, 4H), 2.54 (s, 3H), 1.80-2.24 (m, 4H), 1.42 (d, *J* = 6.0 Hz, 3H). **MS-ESI** (m/z): 623 $(M+1)^+$.

4-(8-amino-3-((3R,6S)-1-((R)-2-hydroxypropanoyl)-6-methylpiperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-3-fluoro-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide (45): **^{1}H NMR** (400MHz, METHANOL-d_4) δ ppm 8.61 (br. s., 2H), 8.04 - 7.78 (m, 4H), 7.47 - 7.41 (m, 1H), 7.07 - 7.00 (m, 1H), 4.69 - 4.47 (m, 3H), 4.27 - 4.16 (m, 1H), 3.69 - 3.56 (m, 1H), 3.47 - 3.37 (m, 1H), 3.19 (d, *J*=11.7 Hz, 1H), 2.25 (br. s., 1H), 2.06 - 1.91 (m, 2H), 1.81 (d, *J*=12.1 Hz, 1H), 1.43 - 1.24 (m, 5H). **MS-ESI** (m/z):586$(M+1)^+$.

4-(8-amino-3-((3R,6S)-1-((S)-2-hydroxypropanoyl)-6-methylpiperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-3-fluoro-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide (**46**): **^{1}H NMR** (400MHz, MeOD) δ ppm 8.69 - 8.56 (m, 2H), 8.06 - 7.79 (m, 4H), 7.49 - 7.41 (m, 1H), 7.08 - 7.02 (m, 1H), 4.77 - 4.34 (m, 3H), 4.24 - 4.02 (m, 1H), 3.67 - 3.40 (m, 2H), 3.28 - 3.20 (m, 1H), 2.29 - 1.75 (m, 5H), 1.41 (br. s., 6H). **MS-ESI** (m/z): 586.1$(M+1)^+$.

4-(8-amino-3-((3R,6S)-1-(3-hydroxy-2,2-dimethylpropanoyl)-6-methylpiperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-3-fluoro-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide (**47**): **^{1}H NMR** (400MHz, MeOD) δ ppm 8.71 - 8.55 (m, 2H), 8.08 - 7.79 (m, 4H), 7.50 - 7.42 (m, 1H), 7.09 - 7.01 (m, 1H), 5.16 - 5.02 (m, 1H), 4.78 - 4.66 (m, 1H), 4.55 - 4.49 (m, 1H), 4.24 - 4.18 (m, 1H), 3.70 - 3.38 (m, 2H), 3.23 - 3.07 (m, 1H), 2.79 - 2.68 (m, 1H), 2.58 - 2.44 (m, 1H), 2.30 - 1.74 (m, 5H), 1.42 - 1.24 (m, 7H). **MS-ESI** (m/z): 614.1 $(M+1)^+$.

4-(8-amino-3-((3R,6S)-1-(2-hydroxy-2-methylpropanoyl)-6-methylpiperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-3-fluoro-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide (**48**): **^{1}H NMR** (400MHz, MeOD) δ ppm 8.73 - 8.55 (m, 2H), 8.11 - 7.94 (m, 2H), 7.93 - 7.75 (m, 2H), 7.51 - 7.41 (m, 1H), 7.10 - 7.00 (m, 1H), 5.47 - 5.24 (m, 1H), 5.14 - 5.01 (m, 1H), 4.69 - 4.48 (m, 1H), 3.41 (br. s., 1H), 3.26 - 3.08 (m, 1H), 2.39 - 2.25 (m, 1H), 2.08 - 1.76 (m, 3H), 1.56 - 1.22 (m, 8H). **MS-ESI** (m/z): 600.1$(M+1)^+$.

4-(8-amino-3-((3R,6S)-1-(1-hydroxycyclobutane-1-carbonyl)-6-methylpiperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-3-fluoro-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide (**49**): **^{1}H NMR** (400MHz, MeOD) δ ppm 8.62 (br. s., 2H), 8.05 - 7.80 (m, 4H), 7.50 - 7.42 (m, 1H), 7.09 - 7.02 (m, 1H), 4.66 - 4.54 (m, 1H), 4.32 - 4.13 (m, 1H), 3.50 - 3.36 (m, 1H), 3.27 - 3.18 (m, 1H), 2.94 - 2.64 (m, 2H), 2.47 - 1.56 (m, 10H), 1.42 - 1.26 (m, 3H). **MS-ESI** (m/z): 612.1 $(M+1)^+$.

4-(8-amino-3-((3R,6S)-6-methyl-1-(tetrahydrofuran-2-carbonyl)piperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-3-fluoro-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide (**50**): **^{1}H NMR** (400MHz, MeOD) δ ppm 8.65 - 8.60 (m, 2H), 8.06 - 7.95 (m, 3H), 7.92 - 7.78 (m, 2H), 7.48 - 7.43 (m, 1H), 7.09 - 7.03 (m, 1H), 4.82 - 4.61 (m, 3H), 4.48 - 4.41 (m, 1H), 4.23 - 4.16 (m, 1H), 4.02 - 3.86 (m, 3H), 3.57 - 3.41 (m, 2H), 3.26 - 3.17 (m, 1H), 2.37 - 1.75 (m, 11H), 1.44 - 1.39 (m, 2H), 1.32 - 1.26 (m, 2H). **MS-ESI** (m/z): 612.1$(M+1)^+$.

The protocol for biology assays:

BTK enzymatic binding assay: BTK enzymatic activity was determined with the LANCE (Lanthanide Chelate Excite) TR-FRET (Time-resolved fluorescence resonance energy transfer) assay. In this assay, the potency (IC_{50}) of each compound was determined from an eleven point (1:3 serial dilution; final compound concentration range in assay from 1000 nM to 0.017 nM) titration curve using the following outlined procedure. To each well of a black non-binding surface Corning 384-well microplate (Corning Catalog #3820), 5 nL of compound (2000 fold dilution in final assay volume of 10 μL) was dispensed, followed by the addition of 7.5 μL of 1x kinase buffer (50 mM Hepes 7.5, 10 mM $MgCl_2$, 0.01% Brij-35, 1 mM EGTA, 0.05% BSA, 1 mM DTT) containing 26.67 pg/μL (266.7 pM) of 25P BTK enzyme (recombinant protein from baculovirus-transfected *Sf9* cells: full-length BTK; MW = 79378 Da). Following a 60 minute

compound and enzyme incubation, each reaction was initiated by the addition of 2.5 µL 1x kinase buffer containing 8 μM biotinylated "A5" peptide (Biotin-EQEDEPEGDYFEWLE-NH2), and 100 µM ATP. The final reaction in each well of 10 μL consisted of 200 pM 25P BTK, 2 μM biotin-A5-peptide, and 25 μM ATP. Phosphorylation reactions were allowed to proceed for 120 minutes. Reactions were immediately quenched by the addition of 20 uL of 1x quench buffer (15 mM EDTA, 25 mM Hepes 7.3, 0.1% Triton X-100) containing detection reagents (0.626 nM of LANCE-Eu-W1024-anti-phosphoTyrosine antibody, PerkinElmer and 86.8 nM of streptavidin-conjugated Dylight 650, Dyomics/ThermoFisher Scientific). After 60 minutes incubation with detection reagents, reaction plates were read on a PerkinElmer EnVision plate reader using a standard TR-FRET protocol. Briefly, excitation of donor molecules (Eu-chelate:anti-phospho-antibody) with a laser light source at 337 nm produces energy that can be transferred to Dylight-650 acceptor molecules if this donor:acceptor pair is within close proximity. Fluorescence intensity at both 665 nm (acceptor) and 615 nm (donor) were measured and a TR-FRET ratio calculated for each well (acceptor intensity/donor intensity). IC_{50} values were determined by 4 parameter fit of TR-FRET ratio values vs. (Log_{10}) compound concentrations.

BTK human PBMC functional assay: Frozen human PBMCs were thawed and allowed to recover overnight in RPMI 1640 (ThermoFisher, Waltham, MA, USA) supplemented with 10% heat-inactivated fetal bovine serum (Sigma-Aldrich, St Louis, MO, USA). The following day the PBMCs were transferred to RPMI with 5% FBS and incubated with compound for 1 h at 37 °C and 5% CO_2 in a humidified atmosphere. After this time samples were stimulated with 40 ng/mL Goat anti-human IgM F(ab')2 (Jackson ImmunoResearch, West Grove, PA, USA) for 18 h at 37 °C and 5% CO_2 in a humidified atmosphere. Reactions were terminated with prewarmed Cytofix (BD Biosciences Pharmingen, San Diego, CA, USA). Cell surface staining was achieved using a cocktail of antibodies: anti-CD45-V450, anti-CD3-APC, and anti-CD20-PerCP-Cy5.5 and anti-CD69-PE (all from BD Biosciences Pharmingen, San Diego, CA, USA) in stain buffer BSA (BD Biosciences Pharmingen, San Diego, CA, USA) for 30 min at at 4 °C. $CD20^+$ cells were gated and analyzed for CD69 expression.

Kinase Panel selectivity assays: Compounds were tested at three concentrations (1, 0.1 and 0.01 uM) against a commercially available panel of 265 human kinases.Ten point compound

concentration response curves were generated (at half-log intervals from 1 uM) for 19 kinases that demonstratedactivity in the initial test. The plot of percent effect versus the log of compound concentration was fit with a 4-parameter concentration response equation to calculate IC_{50} values. For kinases showing < 100-fold selectivity of the BTK IC_{50} a second replicate was generated.

BTK human whole blood assays: Human whole blood obtained from donors with consent was incubated with BTK inhibitors for 1 h at 37 °C and 5% CO_2 in a humidified atmosphere. After this time samples were stimulated with 40 ng/mL anti-CD79b (BD Biosciences Pharmingen, San Diego, CA, USA) for 3 h at 37 °C and 5% CO_2 in a humidified atmosphere. The reaction was halted by placing assay plates on ice for 5 min. Cell surface staining was achieved using a cocktail of antibodies: anti-CD45-V450, anti-CD3-APC, and anti-CD20-PerCP-Cy5.5 and anti-CD69-PE (all from BD Biosciences Pharmingen, San Diego, CA, USA) in stain buffer containing BSA (BD Biosciences Pharmingen, San Diego, CA, USA) for 30 min at at 4 °C. Lysis and fixation of whole blood was performed using FACS Lysis/Fix buffer (BD Biosciences Pharmingen, San Diego, CA, USA). Cells were washed and resuspended in FACS Reading Buffer (FACS buffer with 0.5% pluronic acid) $CD20^+$ cells were gated and analyzed for CD69 expression.

The rat model of collagen-induced arthritis (CIA): Rat collagen-induced arthritis model and compound treatment: Female Lewis rats (125-175g) received i.d. injections at the base of the tail with an emulsion of type II collagen (Elastin Products Company, Inc.) and Incomplete Freund's adjuvant (Sigma) on day 1 and 7 (0.9 mg collagen/150 ul emulsion/spot x 2 spots). Hind paw thickness measurements by a caliper and clinical scores were performed throughout the study. Compound **3** was dosed daily starting from the first day of the study at 5 ml/kg QD. All animal studies were reviewed and approved by the Merck IACUC. The Guide for the Care and Use of Laboratory Animals was followed in the conduct of all animal studies. Veterinary care was given to any animals requiring medical attention.