Supporting Information

Development of inhibitors of SAICAR synthetase (PurC) from *Mycobacterium abscessus* using a fragment-based approach.

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Synthetic Chemistry

General Procedures

Air and moisture-sensitive reactions were carried out in oven-dried glassware, sealed with rubber septa, under a positive pressure of dry nitrogen. Air and moisture-sensitive liquids and reagents were transferred via syringe. Reactions were stirred using Teflon-coated magnetic stir bars. The solvents such as dichloromethane (DCM), ethyl acetate, methanol and petroleum ether (PE) were distilled prior to use. Acetonitrile (ACN), dimethylsulphoxide (DMSO), 1,4-dioxane and tetrahydrofuran (THF) was purchased as anhydrous from commercial suppliers. All commercial reagents were used without further purifications.

Flash column chromatography was performed using automated Biotage Isolera purification systems with appropriately sized Biotage SNAP cartridges, containing KP 50 μm silica. Microwave heating was performed using a Biotage Initiator+ system with sealed Biotage microwave reaction vials. Analytical thin layer chromatography (TLC) was performed using Merck glass-backed silica plates visualised with 254 or 365 nm ultraviolet light. High resolution mass spectrometry (HRMS) was performed using Waters Vion IMS QTof systems and the accuracy were within 5 ppm of calculated mass.

Nuclear magnetic resonance (NMR) spectra were recorded on 400 MHz Avance III HD or 500 MHz DCH Cryoprobe Bruker spectrometers. ^{1}H NMR data are presented in the following order: chemical shift (in ppm on a δ scale relative to the residual solvent resonance peak), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (J, in Hz), and integration. ^{13}C and ^{19}F NMR spectra were proton-decoupled, with chemical shifts recorded, and further description are provided for certain peaks. ^{11}B NMR spectra were also reported for boron containing compounds. All spectra were reported as observed, in some cases in the ^{13}C NMR there is overlap with some peaks due to the splitting from the fluorine atom(s) on the phenyl ring.

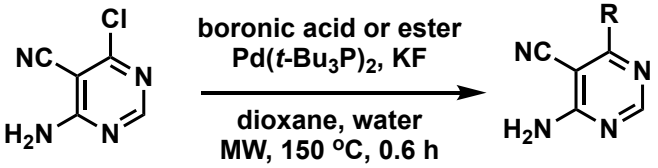
A combination of TLC and LCMS analysis was used to monitor reaction progress.

All screened compounds possessed a purity of at least 95% as determined by LCMS analysis. The LCMS was carried out using a Waters Aquity UPLC system. The mobile phase was water (+1% formic acid) and acetonitrile. The samples were run over four minutes and a gradient elution was used as in the table below. Data collection started after 1 minute so the solvent peak is not observed. Peaks corresponding to the desired product are described, including the retention time (rt) and % purity by integration.

Time (min/sec)	Flow rate (mL/min)	Ratio Water: Acetonitrile
0	0.8	95:5
0.30	0.8	95:5
2.30	0.8	5:95
3.20	0.8	95:5
3.50	0.8	95:5

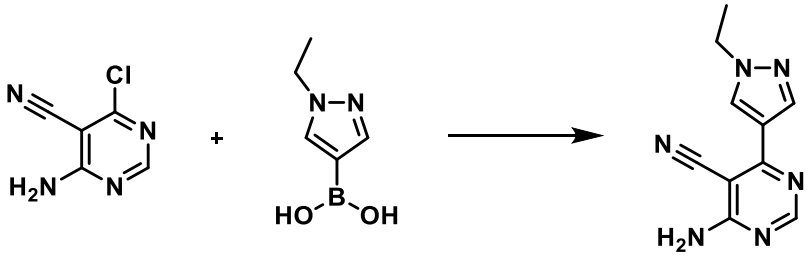
The column was maintained at a temperature of 40^{o}C and the UV detection was at a wavelength of 254 nm. The column used was a C18+ Cortecs® UPLC column (1.6 μm, 2.1 x 50 mm).

General procedure A: Suzuki coupling reaction[1]



4-Amino-6-chloropyrimidine-5-carbonitrile (0.6 mmol, 1 eq), boronic acid or boronate pinacol ester (0.66 mmol, 1.1 eq), KF (1.8 mmol, 3 eq), and bis(tri-tert-butylphosphine)palladium(0) (0.012 mmol, 0.02 eq) were suspended in 1,4-dioxane (6 mL) and water (1 mL). The mixture was degassed and flushed with nitrogen for 10 min. The reaction mixture was then heated at 150 °C for 40 min in a sealed vial under microwave irradiation. After cooling to room temperature, the mixture was diluted with ethyl acetate and washed with water and brine. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was subjected to silica gel flash column chromatography (Biotage Isolera, 12 g silica column, using a mixture of EtOAc/PE or MeOH/EtOAc or MeOH/DCM) to afford the desired product.

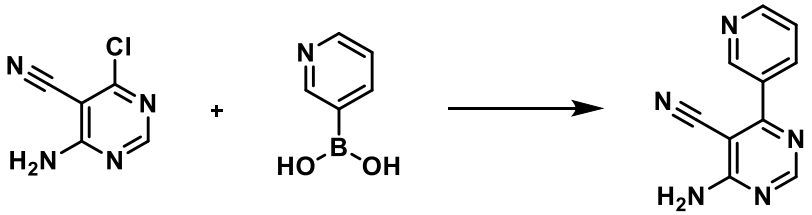
4-Amino-6-(1-ethyl-1*H*-pyrazol-4-yl)pyrimidine-5-carbonitrile (9)



4-Amino-6-chloropyrimidine-5-carbonitrile 3 (93 mg) and ethyl pyrazole-4-boronic acid **32** (92 mg) were reacted following the General Procedure A to obtain compound **9** as a white solid (40-100% EtOAc/PE gradient) (89 mg, 69%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 (s, 1H), 8.47 (s, 1H), 8.20 (s, 1H), 7.80 (s, 2H), 4.25 (q, J = 7.2 Hz, 2H), 1.41 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.5, 160.6, 160.4, 139.3, 131.7, 119.3, 116.9, 82.8, 47.2, 15.8. LCMS (ESI$^+$): *m/z* 215.2 [M+H]$^+$, (ESI$^-$): *m/z* 213.1 [M-H]$^-$, rt 1.28 minutes, >99%. HRMS (ESI): *m/z* calculated for $C_{10}H_{11}N_6$ [M+H]$^+$ requires 215.1039, found 215.1042. R_f: 0.29 (100% EtOAc).

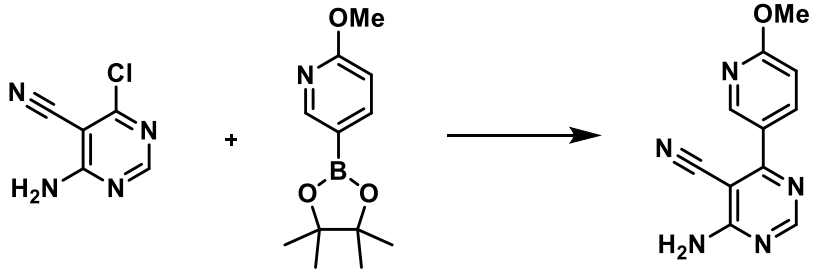
4-Amino-6-(pyridin-3-yl)pyrimidine-5-carbonitrile (10)



4-Amino-6-chloropyrimidine-5-carbonitrile (93 mg) and pyridine-3-boronic acid **33** (82 mg) were reacted following the General Procedure A to obtain compound **10** as a yellow solid (40-100% EtOAc/PE gradient)(30 mg, 25%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.02 (d, J = 1.5 Hz, 1H), 8.76 (d, J = 3.7 Hz, 1H), 8.65 (s, 1H), 8.25 (d, J = 7.8 Hz, 1H), 8.22 – 7.72 (br m, 2H), 7.60 (dd, J = 7.8, 4.9 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.9, 164.3, 160.4, 151.9, 149.4, 136.6, 132.6, 123.9, 115.9, 87.3. LCMS (ESI$^+$): *m/z* 198.2 [M+H]$^+$, (ESI$^-$): *m/z* 196.2 [M-H]$^-$, rt 1.16 minutes, >99%. HRMS (ESI): m/z calculated for $C_{10}H_8N_5$ [M+H]$^+$ requires 198.0774, found 198.0779. R_f: 0.27 (100% EtOAc)

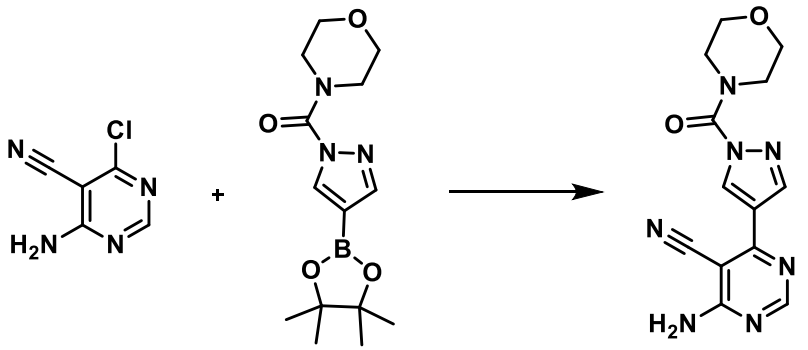
4-Amino-6-(6-methoxypyridin-3-yl)pyrimidine-5-carbonitrile (11)



4-Amino-6-chloropyrimidine-5-carbonitrile (93 mg) and 2-methoxypyridine-5-boronic acid pinacol ester **34** (155 mg) were reacted following the General Procedure A to obtain compound **11** as a white solid (40-70% EtOAc/PE gradient)(37 mg, 27%).

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.73 (d, *J* = 2.4 Hz, 1H), 8.60 (s, 1H), 8.20 (dd, *J* = 8.7, 2.4 Hz, 1H), 8.17 – 7.59 (br m, 2H), 7.00 (d, *J* = 8.7 Hz, 1H), 3.95 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d$_6$) δ 165.5, 164.5, 160.3, 147.9, 139.7, 126.2, 116.3, 110.9, 86.3, 54.2. LCMS (ESI$^+$): *m/z* 228.2 [M+H]$^+$, (ESI$^-$): *m/z* 226.1 [M-H]$^-$, rt 1.34 minutes, >99%. HRMS (ESI): *m/z* calculated for $C_{11}H_{10}N_5O$ [M+H]$^+$ requires 228.0880, found 228.0881. R$_f$: 0.24 (50% EtOAc/hexanes).

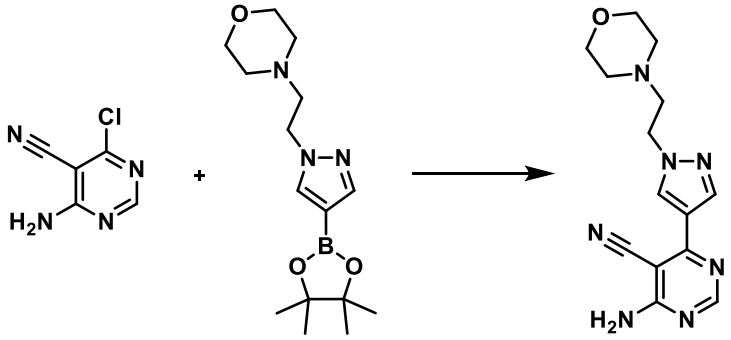
4-Amino-6-(1-(morpholine-4-carbonyl)-1*H*-pyrazol-4-yl)pyrimidine-5-carbonitrile (12)



4-Amino-6-chloropyrimidine-5-carbonitrile **3** (31 mg, 0.2 mmol) and **37** (61 mg, 0.22 mmol) were reacted following the General Procedure A to obtain compound **12** as a white solid (50-100% EtOAc/PE gradient) (22 mg, 37%).

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.90 (s, 1H), 8.55 (s, 1H), 8.40 (s, 1H), 7.96 (br s, 2H), 3.79 – 3.63 (m, 8H). ^{13}C NMR (101 MHz, DMSO-d$_6$) δ 164.3, 160.6, 159.5, 150.2, 141.6, 133.4, 120.8, 116.5, 84.2, 66.3, 46.9. LCMS (ESI$^+$): *m/z* 300.3 [M+H]$^+$, (ESI$^-$): *m/z* 298.1 [M-H]$^-$, rt 1.36 minutes, >99%. HRMS (ESI): *m/z* calculated for $C_{13}H_{14}N_7O_2$ [M+H]$^+$ requires 300.1204, found 300.1208. R$_f$: 0.32 (100% EtOAc).

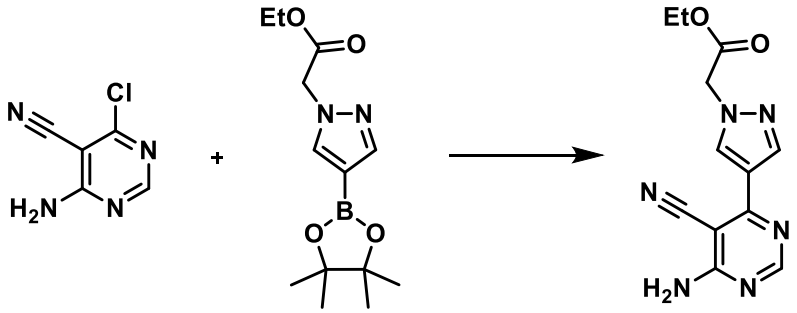
4-Amino-6-(1-(2-morpholinoethyl)-1*H*-pyrazol-4-yl)pyrimidine-5-carbonitrile (13)



4-Amino-6-chloropyrimidine-5-carbonitrile **3** (93 mg) and 1-(2-morpholinoethyl)-1H-pyrazole-4-boronic acid pinacol ester **38a** (0.203 g) were reacted following the General Procedure A to obtain compound **13** as a white solid (2-10% MeOH/DCM gradient) (58 mg, 32%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.62 (s, 1H), 8.47 (s, 1H), 8.18 (s, 1H), 7.79 (br s, 2H), 4.34 (t, *J* = 6.2 Hz, 2H), 3.56 (t, *J* = 4.3, 4H), 2.73 (t, *J* = 6.2 Hz, 2H), 2.43 (s, 4H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.5, 160.6, 160.4, 139.3, 132.8, 119.2, 116.8, 82.8, 66.6, 57.8, 53.5, 49.3. LCMS (ESI$^+$): m/z 300.3 [M+H]$^+$, (ESI$^-$): *m/z* 298.2 [M-H]$^-$, rt 0.56 minutes, >99%. HRMS (ESI): *m/z* calculated for $C_{14}H_{18}N_7O$ [M+H]$^+$ requires 300.1568, found 300.1566. R_f: 0.32 (10% MeOH/DCM).

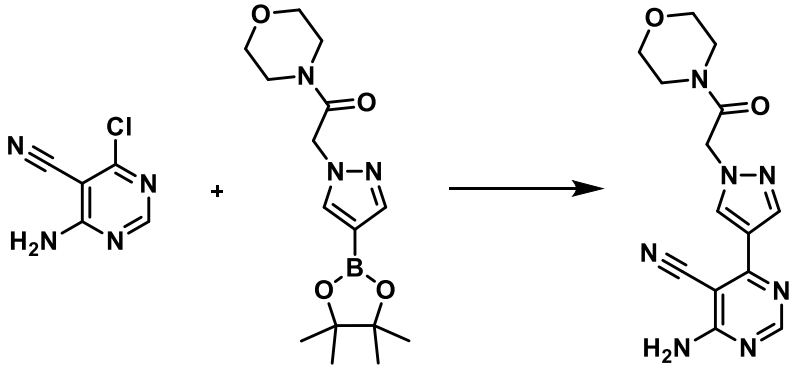
Ethyl 2-(4-(6-amino-5-cyanopyrimidin-4-yl)-1*H*-pyrazol-1-yl)acetate (14)



4-Amino-6-chloropyrimidine-5-carbonitrile **3** (93 mg) and 1-(ethoxycarbonyl)methyl-1H-pyrazole-4-boronic acid pinacol ester **38b** (185 mg) were reacted following the General Procedure A to obtain compound **14** as a white solid (50-100% EtOAc/PE gradient) (62 mg, 38%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.61 (s, 1H), 8.49 (s, 1H), 8.23 (s, 1H), 7.84 (br s, 2H), 5.22 (s, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 1.23 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.3, 164.5, 160.5, 160.4, 139.9, 133.9, 119.9, 116.7, 83.1, 79.6, 61.7, 53.3, 14.5. LCMS (ESI$^+$): *m/z* 295.2 [M+Na]$^+$, (ESI$^-$): *m/z* 271.2 [M-H]$^-$, rt 0.54 minutes, >99%. HRMS (ESI): *m/z* calculated for $C_{12}H_{13}N_6O_2$ [M+H]$^+$ requires 273.1095, found 273.1097. R_f: 0.47 (100% EtOAc).

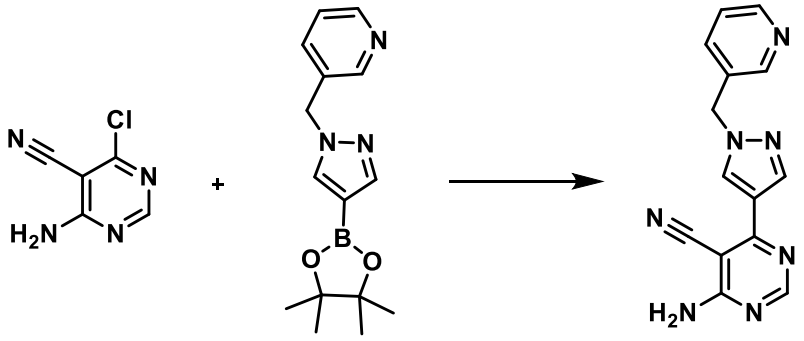
4-Amino-6-(1-(2-morpholino-2-oxoethyl)-1*H*-pyrazol-4-yl)pyrimidine-5-carbonitrile (15)



4-Amino-6-chloropyrimidine-5-carbonitrile **3** (93 mg) and **38c** (330 mg) were reacted following the General Procedure A to obtain compound **15** as a white solid (0-10 % MeOH/EtOAc gradient) (39 mg, 19%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (s, 1H), 8.49 (s, 1H), 8.19 (s, 1H), 7.82 (br s, 2H), 5.31 (s, 2H), 3.68 – 3.56 (m, 4H), 3.55 – 3.42 (m, 4H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.6, 164.5, 160.5, 160.5, 139.4, 134.0, 119.6, 116.8, 82.8, 66.4, 66.3, 53.5, 45.2, 42.4. LCMS (ESI+): *m/z* 336.2 [M+Na]$^+$, (ESI-): *m/z* 312.2 [M-H]$^-$, rt 0.53 minutes, >99%. HRMS (ESI): *m/z* calculated for $C_{14}H_{15}N_7O_2Na$ [M+Na]$^+$ requires 336.1179, found 336.1170. R_f: 0.10 (100% EtOAc).

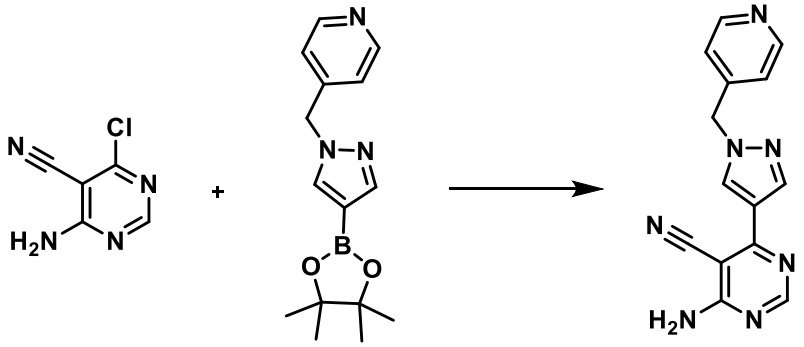
4-Amino-6-(1-(pyridin-3-ylmethyl)-1*H*-pyrazol-4-yl)pyrimidine-5-carbonitrile (16)



4-Amino-6-chloropyrimidine-5-carbonitrile **3** (93 mg) and 1-(3-pyridylmethyl)-1H-pyrazole-4-boronic acid pinacol ester **51** (188 mg) were reacted following the General Procedure A to obtain compound **16** as a white solid (0-10 % MeOH/EtOAc gradient) (115 mg, 69%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.73 (s, 1H), 8.59 (d, *J* = 1.2 Hz, 1H), 8.56 – 8.51 (m, 1H), 8.48 (s, 1H), 8.23 (s, 1H), 7.82 (br s, 2H), 7.73 (d, *J* = 7.7 Hz, 1H), 7.40 (dd, *J* = 7.7, 4.8 Hz, 1H), 5.52 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.5, 160.4, 160.4, 149.6, 149.6, 140.1, 136.2, 132.8, 132.7, 124.2, 119.8, 116.7, 83.1, 53.0. LCMS (ESI+): *m/z* 278.2 $[M+H]^+$, rt 1.04 minutes, 96%. HRMS (ESI): *m/z* calculated for $C_{14}H_{12}N_7$ $[M+H]^+$ requires 278.1148, found 278.1153. R_f: 0.28 (10% MeOH/DCM).

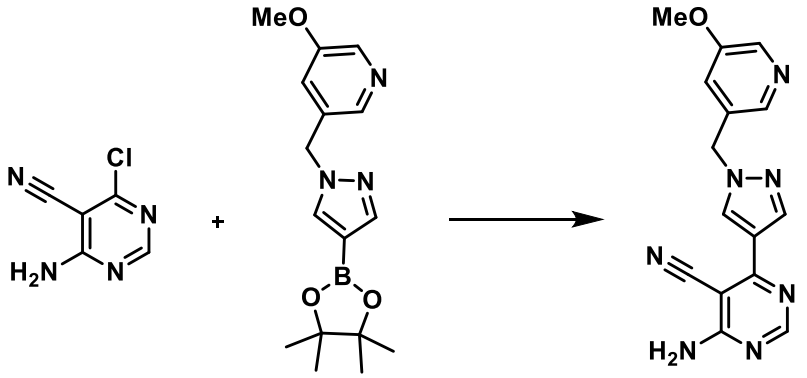
4-Amino-6-(1-(pyridin-4-ylmethyl)-1*H*-pyrazol-4-yl)pyrimidine-5-carbonitrile (17)



4-Amino-6-chloropyrimidine-5-carbonitrile **3** (93 mg) and **52** (188 mg) were reacted following the General Procedure A to obtain compound **17** as an off-white solid (0-10 % MeOH/EtOAc gradient) (121 mg, 73%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.75 (s, 1H), 8.55 (d, *J* = 5.9 Hz, 2H), 8.49 (s, 1H), 8.27 (s, 1H), 7.83 (br s, 2H), 7.20 (d, *J* = 5.9 Hz, 2H), 5.55 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.5, 160.5, 160.3, 150.4, 146.2, 140.3, 133.3, 122.7, 119.9, 116.8, 83.1, 54.3. LCMS (ESI^+): *m/z* 278.2 $[M+H]^+$, (ESI^-): *m/z* 276.1 $[M-H]^-$, rt 0.67 minutes, 97%. HRMS (ESI): *m/z* calculated for $C_{14}H_{12}N_7$ $[M+H]^+$ requires 278.1148, found 278.1149. R_f: 0.30 (10% MeOH/EtOAc).

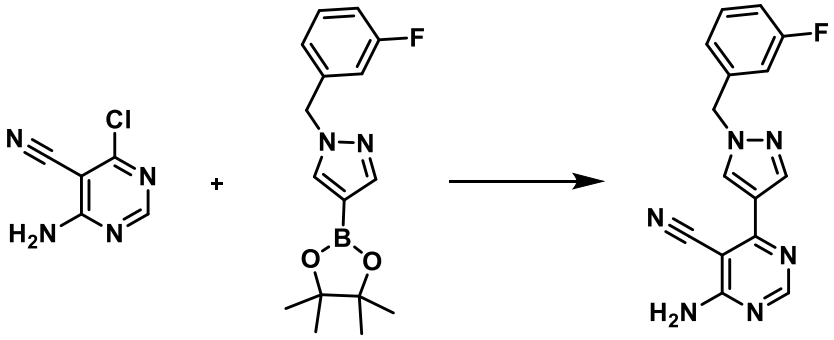
4-Amino-6-(1-((5-methoxypyridin-3-yl)methyl)-1*H*-pyrazol-4-yl)pyrimidine-5-carbonitrile (18)



4-Amino-6-chloropyrimidine-5-carbonitrile **3** (63 mg, 0.4 mmol) and **53** (142 mg, 0.44 mmol) were reacted following the General Procedure A to obtain the product as an off-white solid (0-10 % MeOH/EtOAc gradient) (46 mg, 37%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.73 (s, 1H), 8.48 (s, 1H), 8.26 (d, *J* = 2.7 Hz, 1H), 8.23 (s, 1H), 8.17 (d, *J* = 1.2 Hz, 1H), 7.82 (br s, 2H), 7.39 – 7.34 (m, 1H), 5.50 (s, 2H), 3.82 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.5, 160.4, 155.7, 141.7, 140.1, 137.4, 133.5, 132.7, 120.6, 119.8, 116.8, 83.1, 56.1, 52.9. LCMS (ESI+): *m/z* 308.2 $[M+H]^+$, (ESI^-): *m/z* 306.1 $[M-H]^-$, rt 1.25 minutes, >99%. HRMS (ESI): *m/z* calculated for $C_{15}H_{14}N_7O$ $[M+H]^+$ requires 308.1254, found 308.1251. R_f: 0.29 (100% EtOAc).

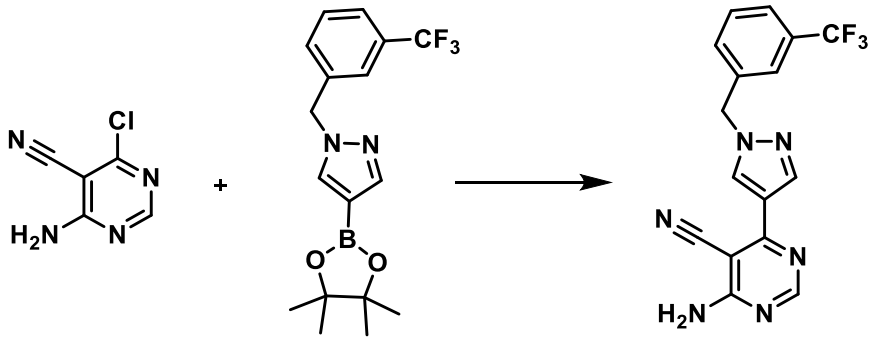
4-Amino-6-(1-(3-fluorobenzyl)-1*H*-pyrazol-4-yl)pyrimidine-5-carbonitrile (19)



4-Amino-6-chloropyrimidine-5-carbonitrile **3** (93 mg) and **54** (199 mg) were reacted following the General Procedure A to obtain compound **19** as a white solid (40-100 % EtOAc/PE gradient) (71 mg, 40%).

^{1}H NMR (400 MHz, MeOD) δ 8.58 (s, 1H), 8.46 (s, 1H), 8.35 (d, *J* = 0.6 Hz, 1H), 7.41 (td, *J* = 7.9, 6.0 Hz, 1H), 7.17 – 7.12 (m, 1H), 7.11 – 7.03 (m, 2H), 5.47 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.5, 162.5 (d, *J* = 244 Hz), 160.4, 140.1, 139.9 (d, *J* = 7.5 Hz), 132.8, 131.1 (d, *J* = 8.3 Hz), 124.3 (d, *J* = 2.7 Hz), 119.8, 116.8, 115.2 (d, *J* = 21.0Hz), 115.1 (d, *J* = 21.8 Hz), 83.1, 54.9. ^{19}F NMR (376 MHz, MeOD) δ -114.5. LCMS (ESI+): *m/z* 295.2 $[M+H]^+$, (ESI^-): *m/z* 293.1 $[M-H]^-$, rt 1.66 minutes, >99%. HRMS (ESI): *m/z* calculated for $C_{15}H_{12}FN_6$ $[M+H]^+$ requires 295.1102, found 295.1101. R_f: 0.62 (100% EtOAc).

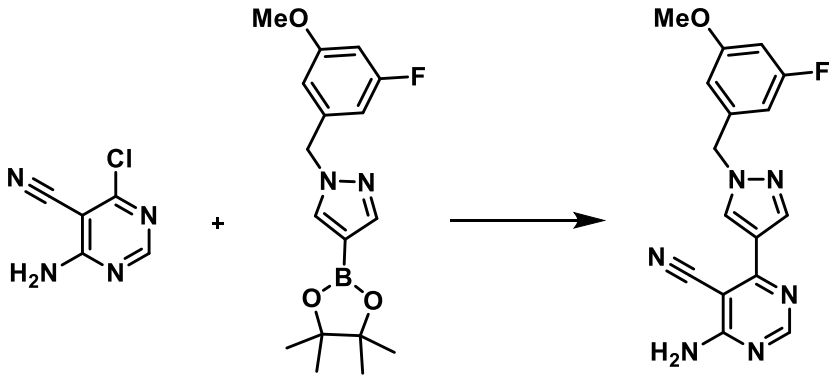
4-Amino-6-(1-(3-(trifluoromethyl)benzyl)-1*H*-pyrazol-4-yl)pyrimidine-5-carbonitrile (20)



4-Amino-6-chloropyrimidine-5-carbonitrile **3** (93 mg) and **55** (0.232 g) were reacted following the General Procedure A to obtain the product **20** as an off-white solid (50-100 % EtOAc/PE gradient) (0.168 g, 81%).

^{1}H NMR (400 MHz, MeOD) δ 8.62 (s, 1H), 8.46 (s, 1H), 8.37 (s, 1H), 7.71 – 7.62 (m, 2H), 7.61 – 7.55 (m, 2H), 5.56 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.0, 160.0, 159.9, 139.7, 138.2, 132.5, 132.0, 129.8, 128.7-128.1 (m), 124.6 (dq, *J* = 15.5, 4.0 Hz), 124.1 (q, *J* = 273 Hz), 119.4, 116.3, 82.6, 54.3. ^{19}F NMR (376 MHz, MeOD) δ -64.2. LCMS (ESI$^+$): *m/z* 345.2 $[M+H]^+$, (ESI$^-$): *m/z* 343.1 $[M-H]^-$, rt 1.84 minutes, >99%. HRMS (ESI): *m/z* calculated for $C_{16}H_{12}F_3N_6$ $[M+H]^+$ requires 345.1070, found 345.1058. R_f: 0.59 (100% EtOAc).

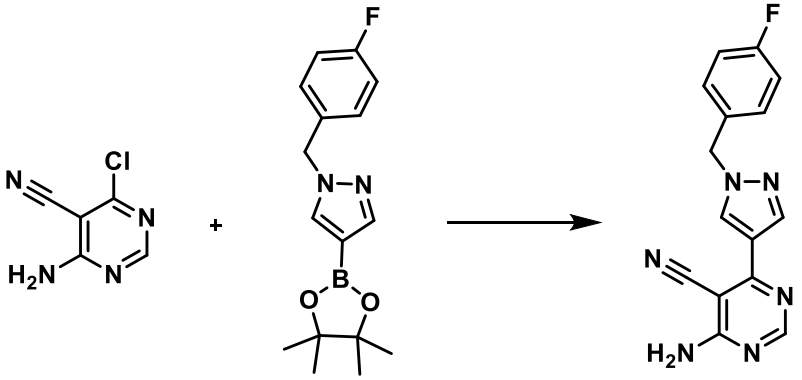
4-Amino-6-(1-(3-fluoro-5-methoxybenzyl)-1*H*-pyrazol-4-yl)pyrimidine-5-carbonitrile (21)



4-Amino-6-chloropyrimidine-5-carbonitrile **3** (93 mg) and **56** (0.219 g) were reacted following the General Procedure A to obtain the product **21** as an off-white solid (50-100 % EtOAc/PE gradient) (0.133 g, 68%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.69 (s, 1H), 8.48 (s, 1H), 8.23 (s, 1H), 7.83 (s, 2H), 6.79 (dt, *J* = 11.0, 2.3 Hz, 1H), 6.74 (s, 1H), 6.69 (dd, *J* = 9.2, 1.4 Hz, 1H), 5.43 (s, 2H), 3.75 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.5, 163.4 (d, *J* = 243 Hz), 161.3 (d, *J* = 11.6 Hz), 160.4, 140.4 (d, *J* = 9.7 Hz), 140.0, 132.8, 119.8, 116.8, 110.6 (d, *J* = 2.6 Hz), 106.9 (d, *J* = 22.5 Hz), 101.2 (d, *J* = 25.1 Hz), 83.1, 56.1, 54.9. ^{19}F NMR (376 MHz, DMSO) δ -111.3. LCMS (ESI+): m/z 325.2 $[M+H]^+$, (ESI-): *m/z* 323.1 $[M-H]^-$, rt 1.71 minutes, >99%. HRMS (ESI): *m/z* calculated for $C_{16}H_{14}FON_6$ $[M+H]^+$ requires 325.1208, found 325.1204. R_f: 0.54 (100% EtOAc).

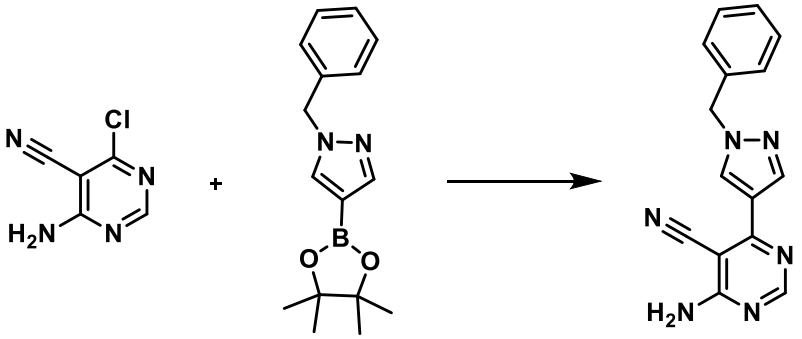
4-Amino-6-(1-(4-fluorobenzyl)-1*H*-pyrazol-4-yl)pyrimidine-5-carbonitrile (22)



4-Amino-6-chloropyrimidine-5-carbonitrile **3** (93 mg) and **57** (0.199 g) were reacted following the General Procedure A to obtain the product **22** as an off-white solid (50-100 % EtOAc/PE gradient) (70 mg, 40%).

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.67 (s, 1H), 8.47 (s, 1H), 8.22 (s, 1H), 7.82 (br s, 2H), 7.43 – 7.34 (m, 2H), 7.20 (app t, J = 8.8 Hz, 2H), 5.45 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 164.5, 162.2 (d, *J* = 243 Hz), 160.4, 139.9, 133.4 (d, *J* = 3.0 Hz), 132.5, 130.6 (d, *J* = 8.3 Hz), 119.7, 118.7, 116.8, 115.9 (d, *J* = 21.5 Hz), 83.0, 54.7. ^{19}F NMR (376 MHz, DMSO-d$_6$) δ -114.5. LCMS (ESI+): *m/z* 295.2 $[M+H]^+$, (ESI$^-$): *m/z* 293.1 $[M-H]^-$, rt 1.65 minutes, >99%. HRMS (ESI): *m/z* calculated for $C_{15}H_{12}FN_6$ $[M+H]^+$ requires 295.1102, found 295.1105. R_f: 0.56 (100% EtOAc).

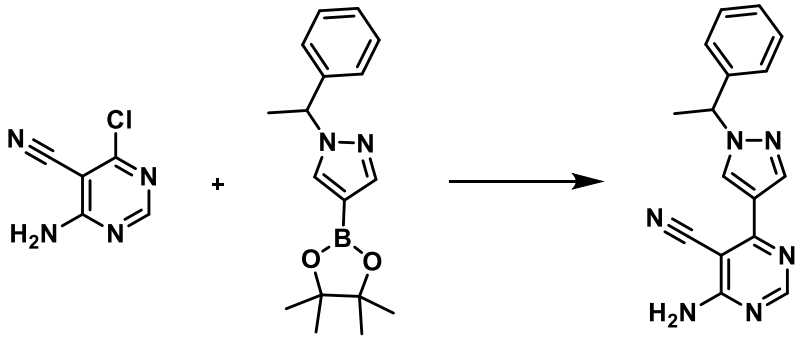
4-Amino-6-(1-benzyl-1*H*-pyrazol-4-yl)pyrimidine-5-carbonitrile (23)



4-Amino-6-chloropyrimidine-5-carbonitrile **3** (93 mg) and **58** (0.188 g) were reacted following the General Procedure A to obtain the product **23** as a white solid (50-90 % EtOAc/PE gradient) (47 mg, 28%).

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.66 (s, 1H), 8.47 (s, 1H), 8.23 (s, 1H), 7.81 (br s, 2H), 7.43 – 7.25 (m, 5H), 5.46 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 164.5, 160.5, 160.4, 139.9, 137.2, 132.6, 129.1, 128.3, 128.3, 119.7, 118.6, 116.8, 82.9, 55.6. LCMS (ESI$^+$): *m/z* 277.2 $[M+H]^+$, (ESI$^-$): *m/z* 275.1 $[M-H]^-$, rt 1.62 minutes, >99%. HRMS (ESI): *m/z* calculated for $C_{15}H_{13}N_6$ $[M+H]^+$ requires 277.1196, found 277.1193. R_f: 0.55 (100% EtOAc).

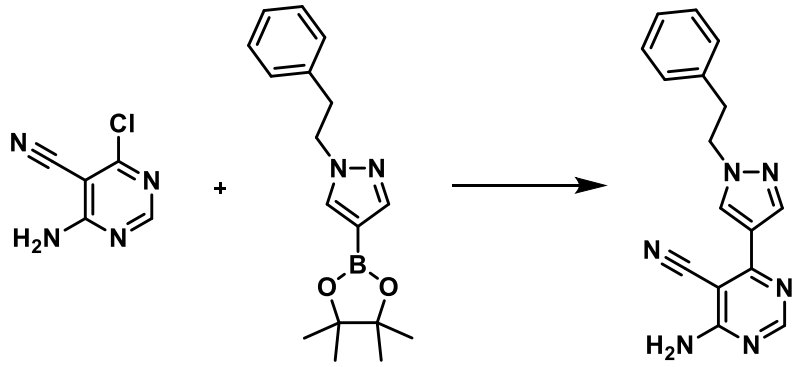
4-Amino-6-(1-(1-phenylethyl)-1*H*-pyrazol-4-yl)pyrimidine-5-carbonitrile (24)



4-Amino-6-chloropyrimidine-5-carbonitrile **3** (47 mg, 0.3 mmol) and **59** (98 mg, 0.33 mmol) were reacted following the General Procedure A to obtain the product **24** as a white solid (50-100 % EtOAc/PE gradient) (28 mg, 33%).

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.61 (s, 1H), 8.47 (s, 1H), 8.24 (s, 1H), 7.80 (br s, 2H), 7.40 – 7.25 (m, 5H), 5.78 (q, *J* = 7.0 Hz, 1H), 1.85 (d, *J* = 7.0 Hz, 3H).^{13}C NMR (101 MHz, DMSO-d$_6$) δ 164.5, 160.5, 160.4, 142.0, 139.4, 131.2, 129.0, 128.2, 126.9, 119.4, 116.8, 82.9, 60.9, 21.3. LCMS (ESI$^+$): *m/z* 291.2 [M+H]$^+$, (ESI$^-$): *m/z* 289.1 [M-H]$^-$, rt 1.71 minutes, >99%. HRMS (ESI): *m/z* calculated for $C_{16}H_{15}N_6$ [M+H]$^+$ requires 291.1353, found 291.1349. R_f: 0.52 (100% EtOAc).

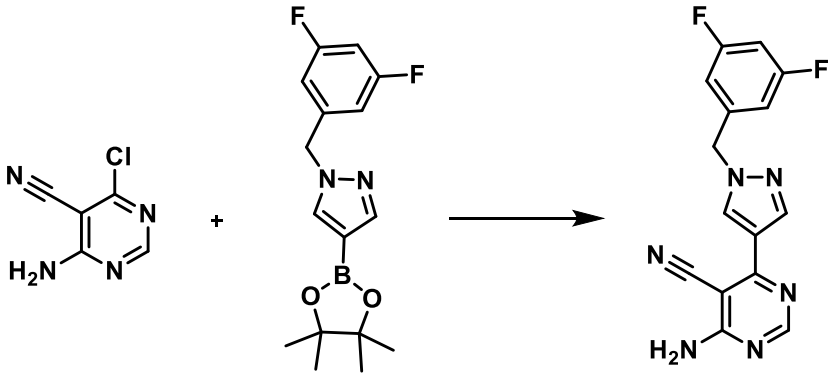
4-Amino-6-(1-phenethyl-1*H*-pyrazol-4-yl)pyrimidine-5-carbonitrile (25)



4-Amino-6-chloropyrimidine-5-carbonitrile **3** (47 mg, 0.3 mmol) and **60** (98 mg, 0.33 mmol) were reacted following the General Procedure A to obtain the product **25** as a white solid (50-100% EtOAc/PE gradient) (32 mg, 37%).

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.45 (s, 1H), 8.43 (s, 1H), 8.22 (s, 1H), 7.79 (br s, 2H), 7.33 – 7.24 (m, 2H), 7.24 – 7.16 (m, 3H), 4.47 (t, *J* = 7.3 Hz, 2H), 3.15 (t, *J* = 7.3 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 164.5, 160.5, 160.4, 139.5, 138.4, 132.4, 129.1, 128.8, 126.9, 119.1, 116.8, 82.8, 53.2, 36.2. LCMS (ESI+): *m/z* 291.2 [M+H]$^+$, (ESI$^-$): *m/z* 289.2 [M-H]$^-$, rt 1.71 minutes, >99%. HRMS (ESI): *m/z* calculated for $C_{16}H_{15}N_6$ [M+H]$^+$ requires 291.1353, found 291.1350. R_f: 0.53 (100% EtOAc).

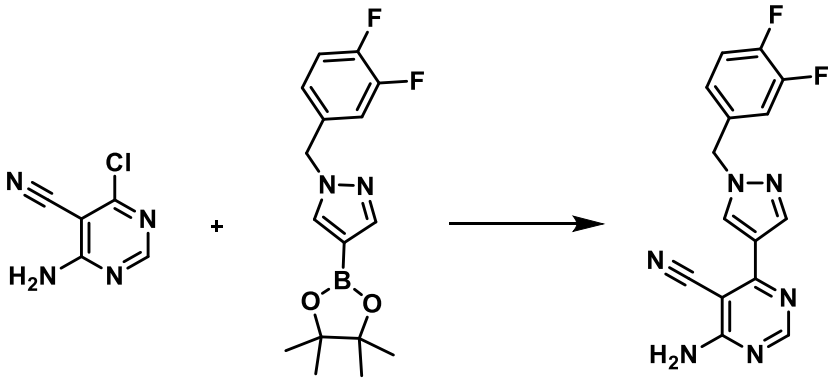
4-Amino-6-(1-(3,5-difluorobenzyl)-1*H*-pyrazol-4-yl)pyrimidine-5-carbonitrile (26)



4-Amino-6-chloropyrimidine-5-carbonitrile **3** (93 mg) and **61** (0.211 g) were reacted following the General Procedure A to obtain the product **26** as an off-white solid (50-90 % EtOAc/PE gradient) (75 mg, 40%).

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.73 (s, 1H), 8.49 (s, 1H), 8.25 (s, 1H), 7.84 (br s, 2H), 7.21 (tt, *J* = 9.4, 2.2 Hz, 1H), 7.03 (d, *J* = 6.4 Hz, 2H), 5.50 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 164.5, 162.8 (d, *J* = 247 Hz), 162.7 (d, *J* = 247 Hz) 160.5, 160.4, 141.6 (t, *J* = 9.3 Hz), 140.3, 133.0, 119.9, 116.7, 111.4 (m), 103.9 (app t, J = 25.6 Hz), 83.2, 54.5. ^{19}F NMR (376 MHz, DMSO-d$_6$) δ -109.4. LCMS (ESI+): *m/z* 313.2 $[M+H]^+$, (ESI-): *m/z* 311.0 $[M-H]^-$, rt 1.73 minutes, >99%. HRMS (ESI): m/z calculated for $C_{15}H_{11}N_6F_2$ $[M+H]^+$ requires 313.1008, found 313.1003. R_f: 0.34 (100% EtOAc).

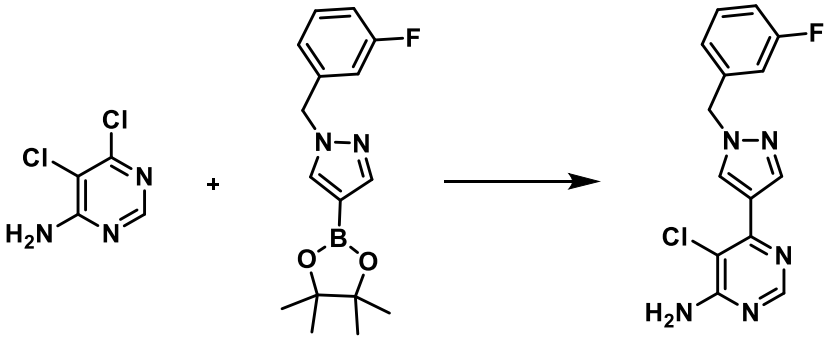
4-Amino-6-(1-(3,4-difluorobenzyl)-1*H*-pyrazol-4-yl)pyrimidine-5-carbonitrile (27)



4-Amino-6-chloropyrimidine-5-carbonitrile **3** (93 mg) and **62** (0.211 g) were reacted following the General Procedure A to obtain the product **27** as an off-white solid (50-90 % EtOAc/PE gradient) (93 mg, 50%).

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.70 (s, 1H), 8.48 (s, 1H), 8.23 (s, 1H), 7.84 (br s, 2H), 7.50 – 7.38 (m, 2H), 7.21 – 7.14 (m, 1H), 5.46 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 164.1, 160.1, 160.0, 149.3, dd, J = 246, 12.9 Hz), 149.2 (dd, J = 245, 12.1 Hz),139.8, 134.5 (dd, *J* = 5.9, 3.8 Hz), 132.4, 125.1 (dd, *J* = 6.8, 3.4 Hz), 119.4, 118.2 (d, *J* = 17.3 Hz), 117.6 (d, *J* = 17.5 Hz), 116.4, 82.7, 53.9. ^{19}F NMR (376 MHz, DMSO-d$_6$) δ -138.3 (d, *J* = 22.3 Hz), -139.8 (d, *J* = 22.3 Hz). LCMS (ESI+): m/z 313.2 $[M+H]^+$, (ESI-): m/z 311.1 $[M-H]^-$, rt 1.70 minutes, >99%. HRMS (ESI): m/z calculated for $C_{15}H_{11}F_2N_6$ $[M+H]^+$ requires 313.1008, found 313.1004. R_f: 0.34 (100% EtOAc).

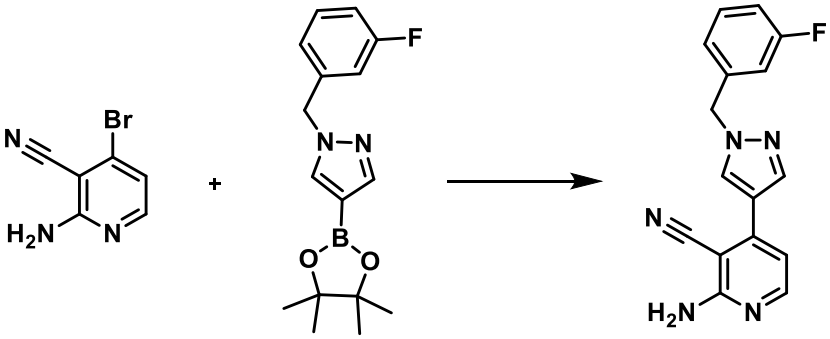
5-Chloro-6-(1-(3-fluorobenzyl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (28)



5,6-Dichloropyrimidin-4-amine **6** (98 mg) and **54** (0.199 g) were reacted following the General Procedure A to obtain the product **28** as a white solid (20-80 % EtOAc/PE gradient) (39 mg, 22 %).

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.71 (d, J = 0.7 Hz, 1H), 8.25 (s, 1H), 8.20 (d, J = 0.7 Hz, 1H), 7.41 (m, 1H), 7.28 (br s, 2H), 7.13 (m, 3H), 5.44 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.2 (d, J = 244 Hz), 160.6, 155.5, 152.4, 140.4, 139.9 (d, J = 7.4 Hz), 132.7, 130.7 (d, J = 8.3 Hz), 123.9 (d, J = 2.8 Hz), 119.2, 114.7 (d, J = 21.0 Hz), 114.6 (d, J = 21.8 Hz), 107.1, 54.4. ^{19}F NMR (376 MHz, DMSO-d_6) δ -113.0. LCMS: *m/z* $[M+H]^+$ 304.1, rt 1.54 min, >99 %. HRMS: (ESI) *m/z* calculated for $C_{14}H_{12}N_5FCl$ $[M+H]^+$ requires 304.0760, found 304.0758. R_f: 0.43 (80% EtOAc/hexanes).

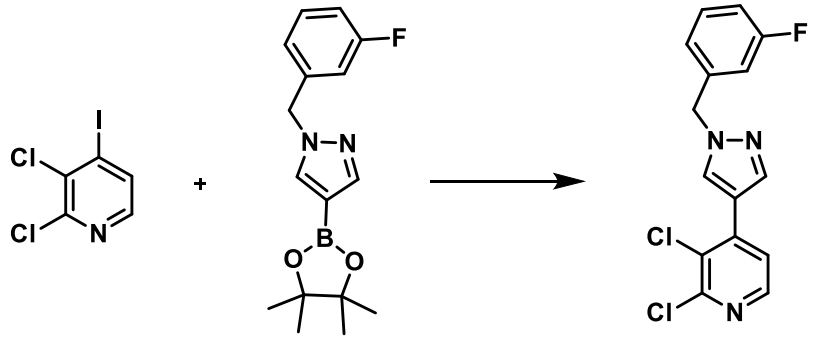
2-Amino-4-(1-(3-fluorobenzyl)-1*H*-pyrazol-4-yl)nicotinonitrile (29)



2-Amino-4-bromonicotinonitrile **7** (59 mg, 0.3 mmol) and **54** (100 mg, 0.33 mmol) were reacted following the General Procedure A to obtain the product **29** as a white solid (60-100 % EtOAc/PE gradient) (54 mg, 61 %).

^{1}H NMR (500 MHz, DMSO-d_6): δ 8.55 (s, 1H), 8.10 (m, 2H), 7.40 (m, 1H), 7.12 (m, 3H), 6.84 (d, J = 5.3 Hz, 1H), 6.81 (br s, 2H), 5.44 (s, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 162.2 (d, J = 243 Hz), 161.4, 152.7, 144.5, 139.8 (d, J = 7.3 Hz), 138.7, 130.7 (d, J = 8.2 Hz), 130.5, 123.8 (d, J = 2.7 Hz), 117.7, 114.7 (d, J = 20.7 Hz), 114.6 (d, J = 21.9 Hz), 110.3, 85.1, 54.5. ^{19}F NMR (376 MHz, DMSO-d_6) δ -113.0. LCMS: *m/z* $[M+H]^+$ 294.2, rt 1.59 mins, >99 %. HRMS (ESI): m/z calculated for $C_{16}H_{13}N_5F$ $[M+H]^+$ requires 294.1150, found 294.1153. R_f: 0.60 (100% EtOAc).

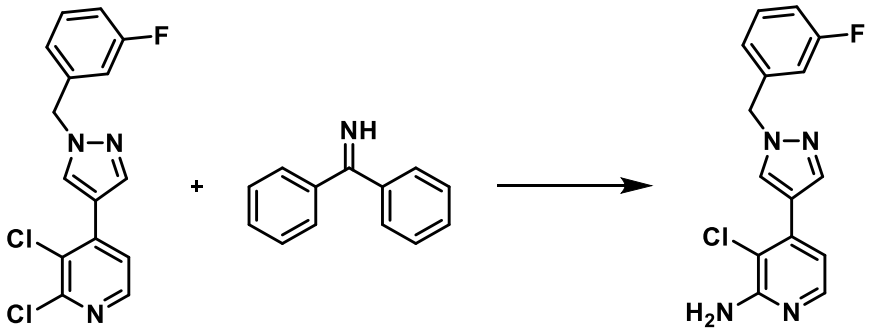
2,3-Dichloro-4-(1-(3-fluorobenzyl)-1*H*-pyrazol-4-yl)pyridine (66)



2,3-Dichloro-4-iodopyridine **65** (0.292 g, 1.06 mmol) and **54** (0.355 g, 1.18 mmol) were reacted following the General Procedure A to obtain the product **66** as a white solid (20-80 % EtOAc/PE gradient) (0.191 g, 56 %).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.73 (d, *J* = 0.8 Hz, 1H), 8.32 (d, *J* = 5.2 Hz, 1H), 8.19 (d, *J* = 0.8 Hz, 1H), 7.75 (d, *J* = 5.2 Hz, 1H), 7.42 (m, 1H), 7.14 (m, 3H), 5.46 (s, 2H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -113.0. LCMS: *m/z* $[M+H]^+$ 322.1, rt 2.15 min (>99%). HRMS: (ESI) *m/z* calculated $[M+H]^+$ $C_{15}H_{11}N_3Cl_2F$ = 322.0309, observed 322.0313; R_f: 0.70 (70% EtOAc/hexanes)

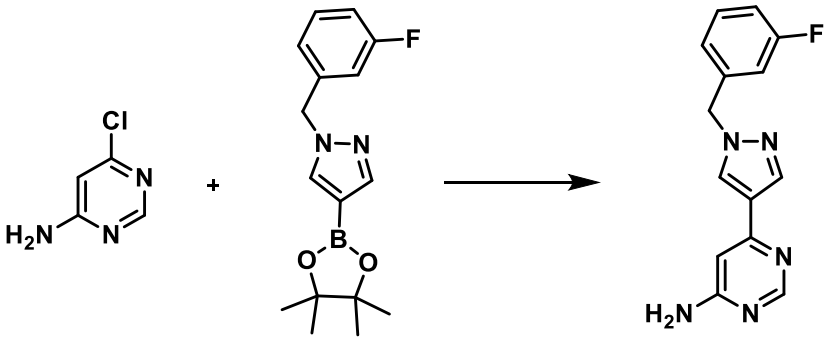
5-Chloro-6-(1-(3-fluorobenzyl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (30)



To a stirred solution of **66** (81 mg, 0.25 mmol) in toluene (2 mL) was added sodium *t*-butoxide (34.1 mg, 0.36 mmol), bis(di(phenylphosphino)binaphthyl) (25 mg, 0.04 mmol), tris(dibenzylideneacetone)dipalladium(0) (15 mg, 0.016 mmol) and benzophenone imine (52 µL, 0.31 mmol) and the mixture was degassed for 5 min. The reaction mixture was then heated to 80 °C and stirred overnight in a sealed tube. The mixture was cooled and a solution of 1M HCl (4 mL) and THF (4 mL) added. The reaction was stirred at RT for 5 h. The resulting aqueous mixture was washed with EtOAc. The aqueous layer was basified with $NaHCO_3$ (aqueous sat. solution) and extracted with EtOAc. The organic layer was dried ($MgSO_4$) and evaporated *in vacuo*. The crude product was purified by column chromatography (20-90 % EtOAc/PE gradient) to yield a white solid (48 mg, 0.158 mmol, 63 %).

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.52 (d, *J* = 0.8 Hz, 1H), 8.01 (d, *J* = 0.8 Hz, 1H), 7.82 (d, *J* = 5.2 Hz, 1H), 7.39 (td, *J* = 8.0, 6.1, 1H), 7.11 (m, 3H), 6.79 (d, *J* = 5.2 Hz, 1H), 6.25 (s, 2H), 5.41 (s, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 162.2 (d, *J* = 244 Hz), 156.7, 145.8, 140.1 (d, *J* = 7.4 Hz), 139.4, 138.4, 131.1, 130.7 (d, *J* = 8.3 Hz), 123.8 (d, *J* = 2.8 Hz), 117.6, 114.6 (d, *J* = 20.9 Hz), 114.5 (d, *J* = 21.9 Hz), 112.2, 109.7, 54.3 (d, *J* = 1.9 Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ -113.0. LCMS: *m/z* $[M + H]^+$ 303.1, retention time 1.37 mins, (>99%). HRMS: (ESI) *m/z* calculated for $C_{15}H_{13}N_4FCl$ $[M+H]^+$ requires 303.0807, observed 303.0813. R_f: 0.17 (50% EtOAc/hexane).

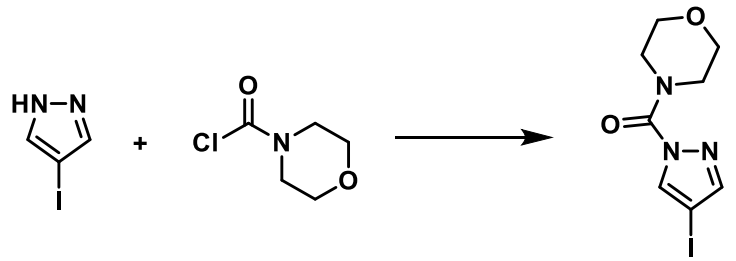
6-(1-(3-Fluorobenzyl)-1*H*-pyrazol-4-yl)pyrimidin-4-amine (31)



4-Amino-6-chloropyrimidine **8** (78 mg) and **54** (199 mg) were reacted following the General Procedure A to obtain the product as a yellow solid (0-5 % MeOH/EtOAc gradient) (56 mg, 35 %).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 (s, 1H), 8.30 (s, 1H), 7.96 (s, 1H), 7.46 – 7.35 (m, 1H), 7.19 – 7.07 (m, 3H), 6.75 (s, 2H), 6.57 (s, 1H), 5.40 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.4, 162.6 (d, *J* = 244 Hz), 159.0, 156.5, 140.4 (d, *J* = 7.3 Hz), 138.3, 131.1 (d, *J* = 8.4 Hz), 130.4, 124.2 (d, *J* = 2.8 Hz), 122.2, 115.0 (d, *J* = 20.9 Hz) ,114.9 (d, *J* = 21.7 Hz), 98.6, 54.8. ^{19}F NMR (376 MHz, DMSO-d_6) δ -113.1. R_f: 0.09 (100% EtOAc).

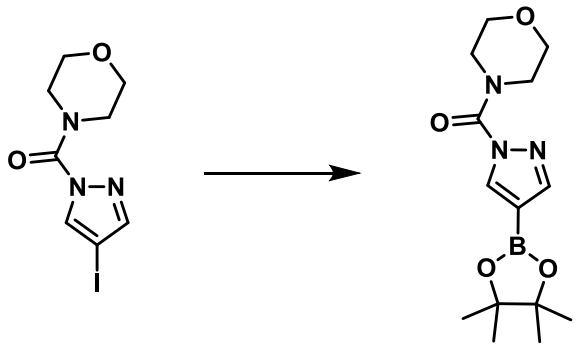
(4-Iodo-1H-pyrazol-1-yl)(morpholino)methanone (36)[2]



To a solution of 4-iodopyrazole **35** (582 mg, 3 mmol, 1 eq) and triethylamine (0.46 mL, 3.3 mmol, 1.1 eq) in DCM (15 mL) was added 4-morpholinecarbonyl chloride (0.38 mL, 3.3 mmol, 1.1 eq). The reaction was left to stir overnight at rt. The reaction was then diluted with brine and the mixture was extracted with EtOAc. The combined organic layer was washed with saturated aq. $NaHCO_3$, brine and dried over $MgSO_4$ and evaporated. The crude product was purified by column chromatography (10-40 % EtOAc/PE) to yield a white solid (0.623 g, 63 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.63 (s, 1H), 3.98 – 3.71 (m, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.8, 146.6, 136.4, 66.7, 59.9. LCMS (ESI+): m/z 114.2 $[M+H]^+$, (ESI-): m/z 117.0 $[M-H]^-$, rt 1.61 minutes, 100%. HRMS (ESI): m/z calculated for $C_8H_{10}IN_3O_2Na$ $[M+Na]^+$ requires 329.9710, found 329.9715. R_f: 0.38 (33% EtOAc/hexanes).

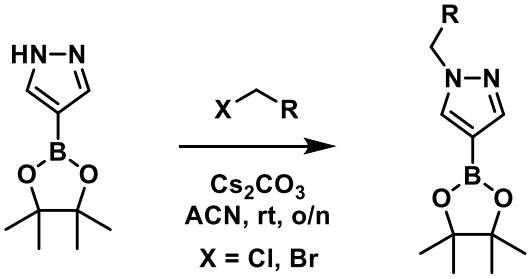
Morpholino(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl)methanone (37)[3]



A sealed tube was charged with **36** (200 mg, 0.65 mmol, 1 mmol), bis(pinacolato)diboron (231 mg, 0.91 mmol, 1.4 mmol), KOAc (255 mg, 2.6 mmol, 4 mmol), Pd(dppf)Cl_2.DCM (27 mg, 0.03 mmol, 5 mol%) and DMSO (3 mL). The mixture was degassed and purged with N_2 for 10 min then it was heated at 80 ^oC for 3 h. The reaction was cooled to rt, diluted with EtOAc and filtered through a pad of celite. The filtrate was washed with brine, dried over Na_2SO_4 and evaporated. The crude product was purified by column chromatography (40-100 % EtOAc/PE) to yield a white solid (105 mg, 53 %).

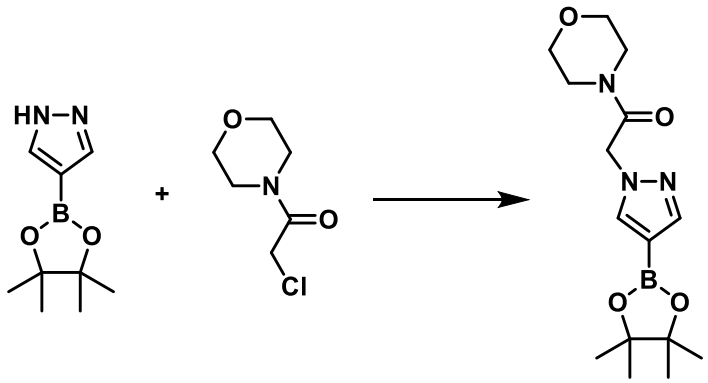
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.87 (s, 1H), 4.02 – 3.72 (m, 8H), 1.35 (s, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.9, 146.9, 139.2, 83.8, 77.2, 66.7, 24.8. LCMS (ESI+): m/z 308.2 $[M+H]^+$, (ESI-): m/z 324.0 $[M+H_2O-H]^-$, rt 1.77 minutes, 86%. HRMS (ESI): m/z calculated for $C_{14}H_{22}BN_3O_4Na$ $[M+Na]^+$ requires 330.1596, found 330.1600. R_f: 0.27 (70% EtOAc/hexanes).

General procedure B: Synthesis of pyrazole-4-boronic acid pinacol ester derivatives[4]



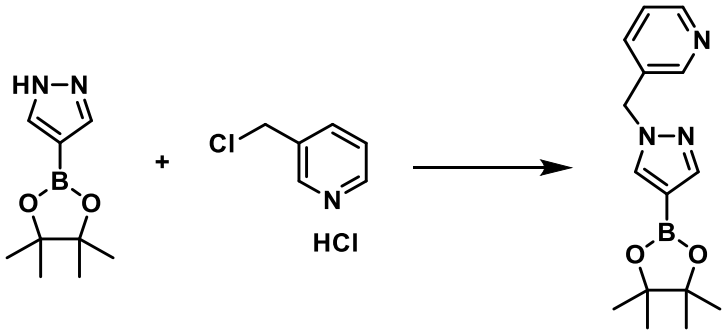
To a solution of pyrazole-4-boronic acid pinacol ester (3 mmol, 1 eq) in acetonitrile (to make up a 0.6 M solution) was added Cs_2CO_3 (9 mmol, 3 eq) and corresponding alkyl halide (6 mmol, 2 eq). The mixture was stirred at rt for 16 h. The insoluble material was removed by filtration and the filtrate was concentrated *in vacuo* to afford a crude product. The residue was purified by silica gel flash column chromatography (Biotage Isolera system, 12 g silica column, using a mixture of EtOAc/PE) to afford the desired product.

1-Morpholino-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl)ethan-1-one (38c)



To a solution of pyrazole-4-boronic acid pinacol ester (250 mg, 1.3 mmol, 1 eq) in acetonitrile (2 mL) was added K_2CO_3 (534 mg, 3.9 mmol, 3 eq) and 4-(chloroacetyl)morphiline (421 mg, 2.6 mmol, 2 eq). The mixture was heated at 70 °C for 16 h. The reaction was allowed to cool to rt. The mixture was diluted with ethyl acetate and washed with water. The organic layer separated and dried with $MgSO_4$ and concentrated *in vacuo* to afford a crude yellow oil (400 mg) which was used without further purification.

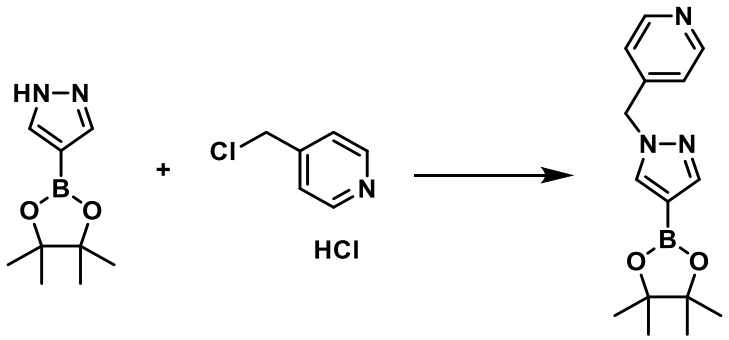
3-((4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl)methyl)pyridine (51)



Pyrazole-4-boronic acid pinacol ester (0.582 g) and 3-(chloromethyl)pyridine.HCl **39** (0.984 g) were reacted following the General Procedure B to obtain the product as a white solid (20-100 % EtOAc/PE gradient) (332 mg, 39%).

^{1}H NMR (400 MHz, acetone-d_6): δ 8.60 (d, J = 2.4 Hz, 1H), 8.52 (dd, J = 4.8, 1.7 Hz, 1H), 7.98 (s, 1H), 7.69 (dt, J = 7.7, 1.9 Hz, 1H), 7.65 (s, 1H), 7.35 (m, 1H), 5.46 (s, 2H), 1.29 (s, 12H). ^{13}C NMR (100 MHz, acetone-d_6) δ 149.3, 149.1, 145.3, 136.6, 135.3, 132.9, 123.4, 82.9, 52.5, 24.2. ^{11}B NMR (128 MHz, acetone-d_6): δ 29.7. LCMS: *m/z* $[M+H]^+$ 286.3, rt 1.49 min >99%. HRMS: (ESI) *m/z* calculated for $C_{15}H_{21}BO_2N_3$ $[M+H]^+$ 286.1721, observed 286.1726. R_f: 0.14 (70% EtOAc/hexanes)

4-((4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl)methyl)pyridine (52)

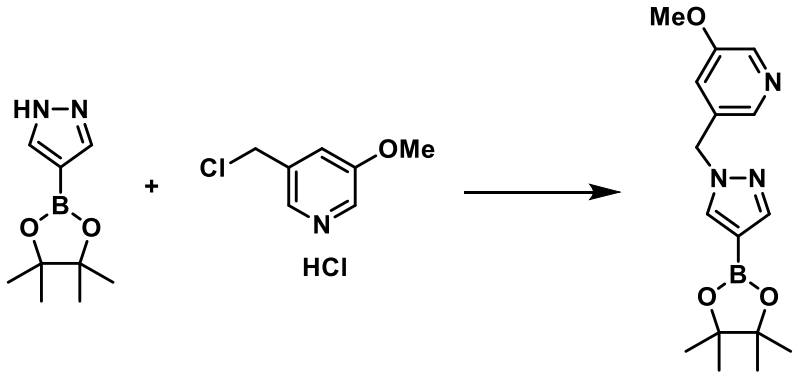


Pyrazole-4-boronic acid pinacol ester (582 mg) and 4-(chloromethyl)pyridine.HCl **40** (984 mg) were reacted following the General Procedure B to obtain the product as a colourless oil (40-100 % EtOAc/PE gradient) (326 mg, 38%) which turns orange after a few days at ambient temperature storage.

^{1}H NMR (400 MHz, Acetone-d_6) δ 8.54 (dd, *J* = 4.5, 1.5 Hz, 2H), 8.00 (s, 1H), 7.68 (s, 1H), 7.16 (d, *J* = 5.8 Hz, 2H), 5.47 (s, 2H), 1.30 (s, 12H). ^{13}C NMR (100 MHz, Acetone-d_6) δ 149.9, 146.3, 145.4, 137.1, 122.1, 82.9, 53.7, 24.2. ^{11}B NMR (128 MHz, Acetone-d_6) δ 29.6. LCMS (ESI+): m/z 286.3 $[M+H]^+$, (ESI

): m/z 302.0 $[M+H_2O-H]^-$, rt 1.29 min, >99%. HRMS (ESI): m/z calculated for $C_{15}H_{21}BN_3O_2$ $[M+H]^+$ requires 286.1721, found 286.1722. R_f: 0.27 (70% EtOAc/hexanes).

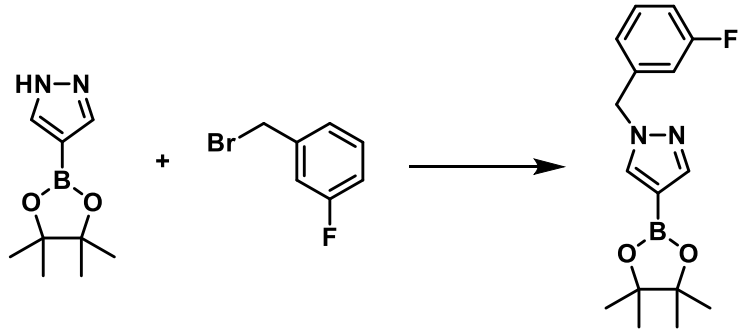
3-Methoxy-5-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl)methyl)pyridine (53)



Pyrazole-4-boronic acid pinacol ester (330 mg, 1.7 mmol) and 3-(chloromethyl)-5-methoxypyridine.HCl **41** (495 mg, 3.4 mmol) were reacted following the General Procedure B to obtain the product as a clear colourless oil (40-100 % EtOAc/PE gradient) (167 mg, 31%).

^{1}H NMR (400 MHz, Acetone-d_6) δ 8.23 (d, *J* = 2.7 Hz, 1H), 8.18 (d, *J* = 1.2 Hz, 1H), 7.96 (s, 1H), 7.64 (s, 1H), 7.31 – 7.27 (m, 1H), 5.43 (s, 2H), 3.87 (s, 3H), 1.29 (s, 12H). ^{13}C NMR (100 MHz, Acetone-d_6) δ 155.7, 145.2, 141.3, 136.9, 136.6, 133.5, 119.7, 82.9, 55.1, 52.4, 24.2. R_f: 0.25 (100% EtOAc).

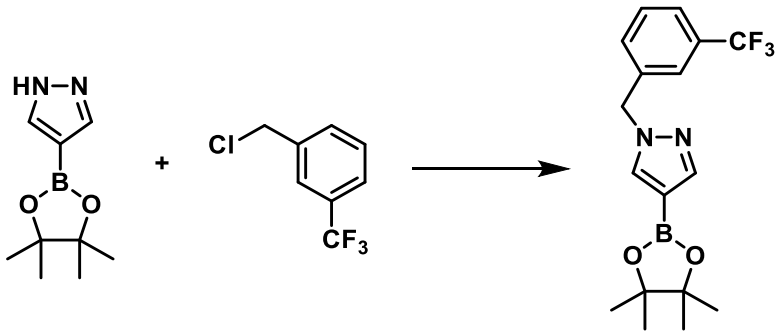
1-(3-Fluorobenzyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (54)



Pyrazole-4-boronic acid pinacol ester (582 mg) and 3-fluorobenzyl bromide **42** (0.74 mL, 1.13 g) were reacted following the General Procedure B to obtain the product as a clear colourless oil (0-50 % EtOAc/PE gradient) (673 mg, 74%).

^{1}H NMR (400 MHz, acetone-d_6): δ 7.95 (s, 1H), 7.65 (s, 1H), 7.40 (m, 1H), 7.09 (m, 3H), 5.43 (s 2H), 1.29 (s, 12H). ^{13}C NMR (100 MHz, acetone-d_6) δ 162.8 (d, *J* = 244.4 Hz), 145.2, 140.4 (d, *J* = 7.4 Hz), 136.7, 130.4 (d, *J* = 8.3 Hz), 123.6 (d, *J* = 2.9 Hz), 114.4 (d, *J* = 22.4 Hz), 114.3 (d, *J* = 21.6 Hz), 82.9, 54.4, 24.2. ^{19}F NMR (376 MHz, acetone-d_6) δ -114.6; ^{11}B NMR (128 MHz, Acetone-d_6) δ 29.9; LCMS: *m/z* $[M+H]^+$ 303.2, rt 2.15 min, (86%); HRMS: (ESI) *m/z* calculated for $C_{16}H_{21}N_2O_2BF$ $[M+H]^+$ 303.1674, observed 303.1681; R_f: 0.48 (30% EtOAc/hexanes).

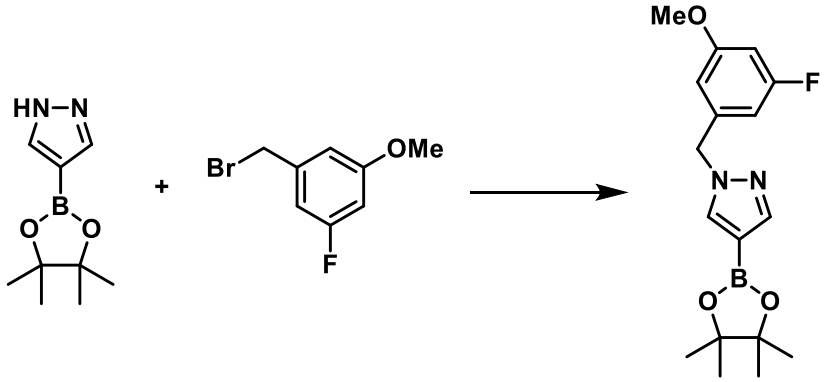
4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(3-(trifluoromethyl)benzyl)-1*H*-pyrazole (55)



Pyrazole-4-boronic acid pinacol ester (0.582 g) and 3-(trifluoromethyl)benzyl chloride **43** (0.93 mL, 1.17 g) were reacted following the General Procedure B to obtain the product as a clear colourless oil (0-40 % EtOAc/PE gradient) (1.15 g, 99%).

^{1}H NMR (400 MHz, Acetone-d_6) δ 8.00 (s, 1H), 7.69 – 7.65 (m, 3H), 7.62 – 7.58 (m, 2H), 5.53 (s, 2H), 1.29 (s, 12H). ^{13}C NMR (100 MHz, Acetone-d_6) δ 140.2, 146.6, 138.0, 132.9 (app d, *J* = 1.2 Hz), 131.4 (q, *J* = 31.9 Hz), 130.7, 125.5 (q, *J* = 271 Hz), 84.1, 55.6, 25.4. ^{19}F NMR (376 MHz, Acetone-d_6) δ -63.1. ^{11}B NMR (128 MHz, Acetone-d_6) δ 29.4. LCMS (ESI+): m/z 353.2 $[M+H]^+$, rt 2.22 min, 93%; HRMS: (ESI) *m/z* calculated for $C_{17}H_{21}N_2O_2BF_3$ $[M+H]^+$ 353.1643, observed 353.1642; R_f: 0.51 (20% EtOAc/hexanes).

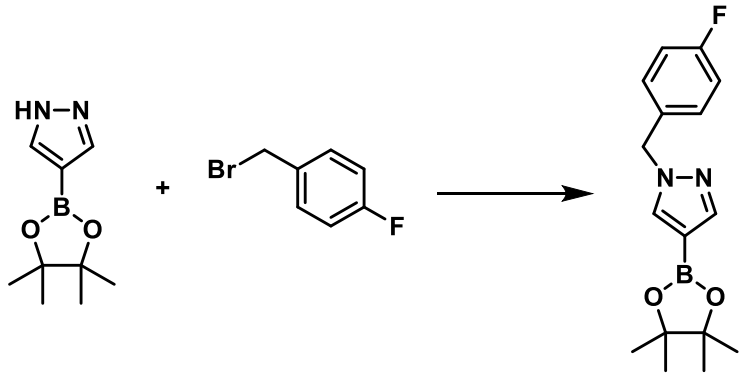
1-(3-Fluoro-5-methoxybenzyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (56)



Pyrazole-4-boronic acid pinacol ester (0.388 g, 2 mmol) and 3-fluoro-5-methoxybenzyl bromide **44** (0.876 g, 4 mmol) were reacted following the General Procedure B to obtain the product as a white solid (0-50 % EtOAc/PE gradient) (0.540 g, 81%).

^{1}H NMR (400 MHz, Acetone-d_6) δ 7.94 (s, 1H), 7.65 (s, 1H), 6.75 – 6.70 (m, 1H), 6.67 (dt, *J* = 10.9, 2.3 Hz, 1H), 6.64 – 6.59 (m, 1H), 5.38 (s, 2H), 3.81 (s, 3H), 1.29 (s, 12H). ^{13}C NMR (100 MHz, Acetone-d_6) δ 163.5 (d, *J* = 243 Hz), 161.4 (d, *J* = 11.5 Hz), 145.1, 140.8 (d, *J* = 9.6 Hz), 136.7, 109.8 (d, *J* = 2.7 Hz), 106.3 (d, *J* = 22.7 Hz), 100.3 (d, *J* = 25.4 Hz), 82.9, 55.1, 54.5, 24.2. ^{19}F NMR (376 MHz, Acetone-d_6) δ -113.1. ^{11}B NMR (128 MHz, Acetone-d_6) δ 29.5. LCMS (ESI+): m/z 333.2 $[M+H]^+$, rt 2.11 min, 92%. HRMS: (ESI) *m/z* calculated for $C_{17}H_{23}N_2O_3BF$ $[M+H]^+$ 333.1781, observed 333.1781; R_f: 0.51 (20% EtOAc/hexanes).

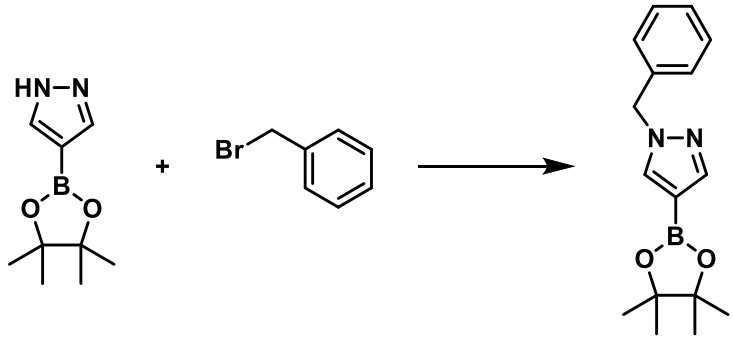
1-(4-Fluorobenzyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (57)



Pyrazole-4-boronic acid pinacol ester (0.388 g, 2 mmol) and 4-fluorobenzyl bromide **45** (0.756 g, 4 mmol) were reacted following the General Procedure B to obtain the product as a clear colourless oil (0-50 % EtOAc/PE gradient) (0.460 g, 76%).

^{1}H NMR (400 MHz, Acetone-d_6) δ 7.90 (s, 1H), 7.63 (s, 1H), 7.38 (dd, *J* = 8.5, 5.5 Hz, 2H), 7.13 (t, *J* = 8.8 Hz, 2H), 5.39 (s, 2H), 1.29 (s, 12H). ^{13}C NMR (100 MHz, Acetone-d_6) δ 162.3 (d, *J* = 244 Hz), 145.0, 136.3, 133.6 (d, *J* = 3.2 Hz), 129.9 (d, *J* = 8.3 Hz), 115.2 (d, *J* = 21.7 Hz), 82.9, 54.2, 24.2. ^{19}F NMR (376 MHz, Acetone-d_6) δ -116.4. ^{11}B NMR (128 MHz, Acetone-d_6) δ 29.6. LCMS: *m/z* $[M+H]^+$ 303.2, rt 2.06 min, 86%; HRMS: (ESI) *m/z* calculated for $C_{16}H_{21}N_2O_2BF$ $[M+H]^+$ 303.1674, observed 303.1675; R_f: 0.27 (20% EtOAc/hexanes).

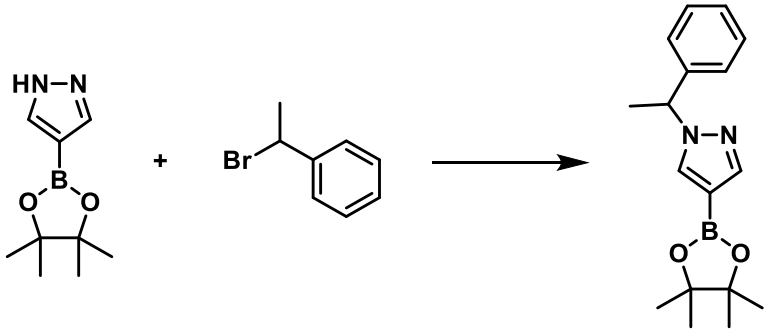
1-Benzyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (58)



Pyrazole-4-boronic acid pinacol ester (0.582 g) and benzyl bromide **46** (0.7 mL, 1.02 g) were reacted following the General Procedure B to obtain the product as a clear colourless oil (0-50 % EtOAc/PE gradient) (0.645 g, 76%).

^{1}H NMR (400 MHz, Acetone-d_6) δ 7.88 (s, 1H), 7.63 (s, 1H), 7.40 – 7.28 (m, 5H), 5.39 (s, 2H), 1.29 (s, 12H). ^{13}C NMR (100 MHz, Acetone-d_6) δ 144.9, 137.5, 136.3, 128.5, 127.8, 127.7, 82.9, 55.1, 24.2. ^{11}B NMR (128 MHz, Acetone-d_6) δ 29.5. LCMS: *m/z* $[M+H]^+$ 285.2, rt 2.05 min, 88%; HRMS: (ESI) *m/z* calculated for $C_{16}H_{22}N_2O_2B$ $[M+H]^+$ 285.1769, observed 285.1767; R_f: 0.49 (20% EtOAc/hexanes).

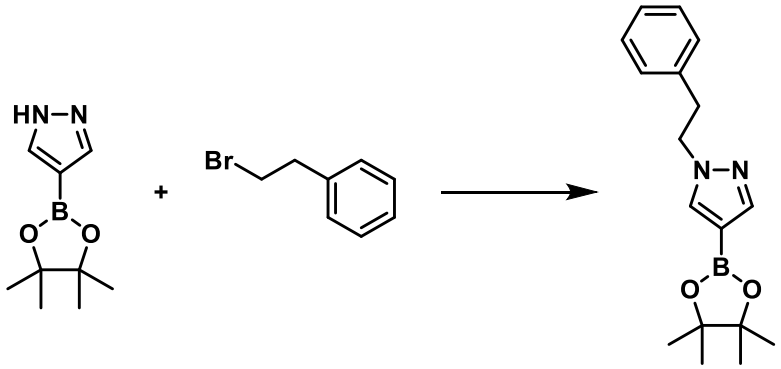
1-(1-Phenylethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (59)



Pyrazole-4-boronic acid pinacol ester (0.388 g, 2 mmol) and (1-bromoethyl)benzene **47** (0.55 mL, 740 mg, 4 mmol) were reacted following the General Procedure B to obtain the product as a clear colourless oil (0-30 % EtOAc/PE gradient) (0.290 g, 45%).

^{1}H NMR (400 MHz, Acetone-d_6) δ 7.87 (s, 1H), 7.64 (s, 1H), 7.41 – 7.26 (m, 5H), 5.66 (q, J = 7.1 Hz, 1H), 1.90 (d, J = 7.1 Hz, 3H), 1.29 (s, 12H). ^{13}C NMR (100 MHz, Acetone-d_6) δ 144.5, 142.5, 134.9, 128.4, 127.5, 126.4, 82.8, 60.7, 24.2, 20.8. ^{11}B NMR (128 MHz, Acetone-d_6) δ 29.6. LCMS: *m/z* $[M+H]^+$ 299.2, rt 2.14 min, 81%; HRMS: (ESI) *m/z* calculated for $C_{17}H_{23}N_2O_2BNa$ $[M+Na]^+$ 321.1745, observed 321.1743; R_f: 0.40 (20% EtOAc/hexanes)

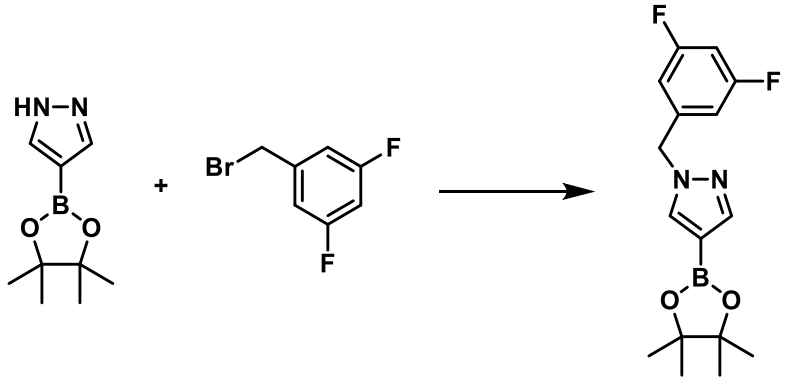
1-Phenethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (60)



Pyrazole-4-boronic acid pinacol ester (388 mg, 2 mmol) and (2-bromoethyl)benzene **48** (0.54 mL, 740 mg, 4 mmol) were reacted following the General Procedure B to obtain the product as a clear colourless oil (0-30 % EtOAc/PE gradient) (206 mg, 35%).

^{1}H NMR (400 MHz, Acetone-d_6) δ 7.69 (s, 1H), 7.62 (s, 1H), 7.32 – 7.17 (m, 5H), 4.41 (t, *J* = 7.4 Hz, 2H), 3.19 (t, *J* = 7.4 Hz, 2H), 1.28 (s, 12H). ^{13}C NMR (100 MHz, Acetone-d_6) δ 144.7, 138.5, 136.4, 128.7, 128.4, 126.4, 82.8, 52.7, 36.4, 24.2. ^{11}B NMR (128 MHz, Acetone-d_6) δ 29.5. LCMS: *m/z* $[M+H]^+$ 299.2, rt 2.12 min, 89%; HRMS: (ESI) *m/z* calculated for $C_{17}H_{24}N_2O_2B$ $[M+H]^+$ 299.1925, observed 299.1926; R_f: 0.55 (20% EtOAc/hexanes).

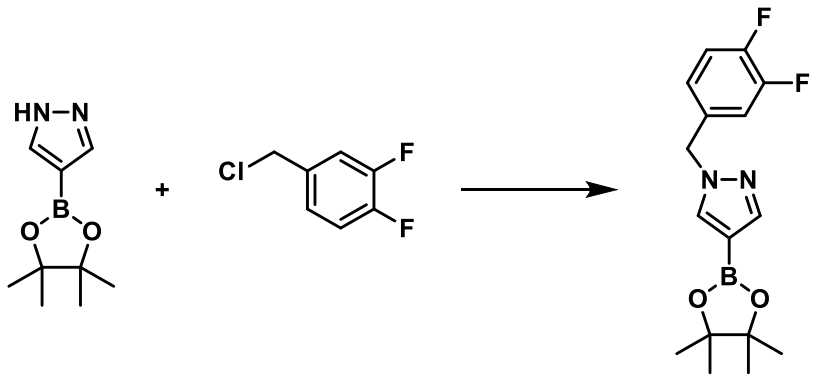
1-(3,5-Difluorobenzyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (61)



Pyrazole-4-boronic acid pinacol ester (388 mg, 2 mmol) and 3,5-difluorobenzyl bromide **49** (828 mg, 4 mmol) were reacted following the General Procedure B to obtain the product as a pale yellow solid (0-30 % EtOAc/PE gradient) (452 mg, 71%).

^{1}H NMR (400 MHz, Acetone-d_6) δ 7.99 (s, 1H), 7.67 (s, 1H), 7.08 – 6.89 (m, 3H), 5.46 (s, 2H), 1.30 (s, 12H).^{13}C NMR (100 MHz, Acetone-d_6) δ 163.1 (d, *J* = 239.0 Hz) 162.9 (d, *J* = 247 Hz), 145.4, 142.1 (app t, *J* = 9.1 Hz), 136.9, 111.1 – 110.0 (m), 102.8 (app t, *J* = 25.8 Hz), 82.9, 53.9, 24.2. ^{19}F NMR (376 MHz, acetone-d_6) δ -111.1. ^{11}B NMR (128 MHz, Acetone-d_6) δ 28.6. LCMS: *m/z* $[M+H]^+$ 321.2, rt 2.13 min, (74%). HRMS: (ESI) *m/z* calculated for $C_{16}H_{20}N_2O_2BF_2$ $[M+H]^+$ 321.1580, observed 321.1587. R_f: 0.43 (20% EtOAc/hexanes).

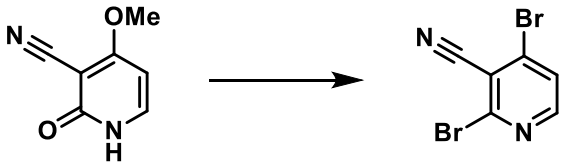
1-(3,4-Difluorobenzyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (62)



Pyrazole-4-boronic acid pinacol ester (388 mg, 2 mmol) and 3,5-difluorobenzyl chloride **50** (650 mg, 4 mmol) were reacted following the General Procedure B to obtain the product as a clear colourless oil (0-30 % EtOAc/PE gradient) (367 mg, 57%).

^{1}H NMR (400 MHz, Acetone-d_6) δ 7.96 (s, 1H), 7.65 (s, 1H), 7.37 – 7.25 (m, 2H), 7.20 – 7.14 (m, 1H), 5.41 (s, 2H), 1.29 (s, 12H). ^{13}C NMR (100 MHz, Acetone-d_6) δ 149.9 (dd, *J* = 246.5, 13.0 Hz), 149.6 (dd, *J* = 245.9, 12.4 Hz), 145.2, 136.6, 135.1 (dd, *J* = 5.6, 3.8 Hz), 124.5 (dd, *J* = 6.6, 3.7 Hz), 117.4 (d, *J* = 17.4 Hz), 116.9 (d, *J* = 17.8 Hz), 82.9, 53.8, 24.2. ^{19}F NMR (376 MHz, DMSO-d_6) δ -139.4 (d, *J* = 20.8 Hz), -141.2 (d, *J* = 20.8 Hz). ^{11}B NMR (128 MHz, Acetone-d_6) δ 29.7. LCMS: *m/z* $[M+H]^+$ 321.2, rt 2.11 min, 84%. HRMS: (ESI) *m/z* calculated for $C_{16}H_{20}N_2O_2BF_2$ $[M+H]^+$ 321.1580, observed 321.1586. R_f: 0.29 (20% EtOAc/hexanes).

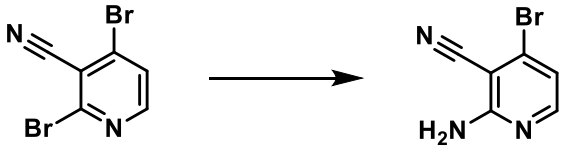
2,4-Dibromonicotinonitrile (64)[5]



3-Cyano-4-methoxy-2-pyridone **63** (5.0 g, 33.3 mmol) was dissolved in acetonitrile (134 mL) and $POBr_3$ (17.9 g, 62.5 mmol) was added. The reaction mixture was stirred for 16 h at 80 °C. Water (100 mL) and brine (100 mL) were added and the solution extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with $NaHCO_3$ sat. solution (100 mL), the organic layer separated, and the aqueous layer extracted with EtOAc (2 × 100 mL). The organic extracts were combined, dried (Na_2SO_4), filtered and evaporated until dryness. The solid residue was treated with diisopropyl ether, the resulting solid filtered, dried *in vacuo* and purified by column chromatography (multiple columns, 50-100 % EtOAc in PE) to yield the product as a white solid (4.36 g, 16.6 mmol, 50 %).

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.52 (d, *J* = 5.4 Hz, 1H), 8.05 (d, *J* = 5.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.9, 144.5, 138.5, 127.9, 116.6, 115.9; LCMS: *m/z* $[M + H]^+$ 279.4, rt 1.78 min, >99%. R_f: 0.90 (100% EtOAc).

2-Amino-4-bromonicotinonitrile (7)[5]



2,4-Dibromonicotinonitrile **64** (1.0 g, 3.82 mmol) was dissolved in THF (8 mL) and aqueous ammonia (30 %, 8 mL) was added. The reaction mix was heated at 100 °C for 1 h in a sealed tube (Caution – done behind a blast shield). The reaction was cooled, washed with water (16 mL), and extracted with EtOAc (3 × 16 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated until dryness. Crude product was dissolved in DCM (approx. 10 mL) and the resulting solid (unwanted regioisomer) filtered off. The filtrate was collected and dried. The solid recovered was purified again using column chromatography (0-20 % EtOAc in DCM). This gave a white solid as the final product (92 mg, 0.467 mmol, 12 %).

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.06 (d, J = 5.3 Hz, 1H), 7.24 (br s, 2H), 6.97 (d, J = 5.3 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.7, 154.0, 137.0, 116.2, 116.0, 92.4. LCMS: *m/z* $[M + H]^+$ 200.0, rt 1.45 min, >99 %. HRMS: (ESI) *m/z* (calculated $[M+H]^+$ $C_6H_5N_3Br$ = 197.9661, observed 197.9667. R_f: 0.33 (20% EtOAc in DCM)

Isothermal Titration Calorimetry (ITC)

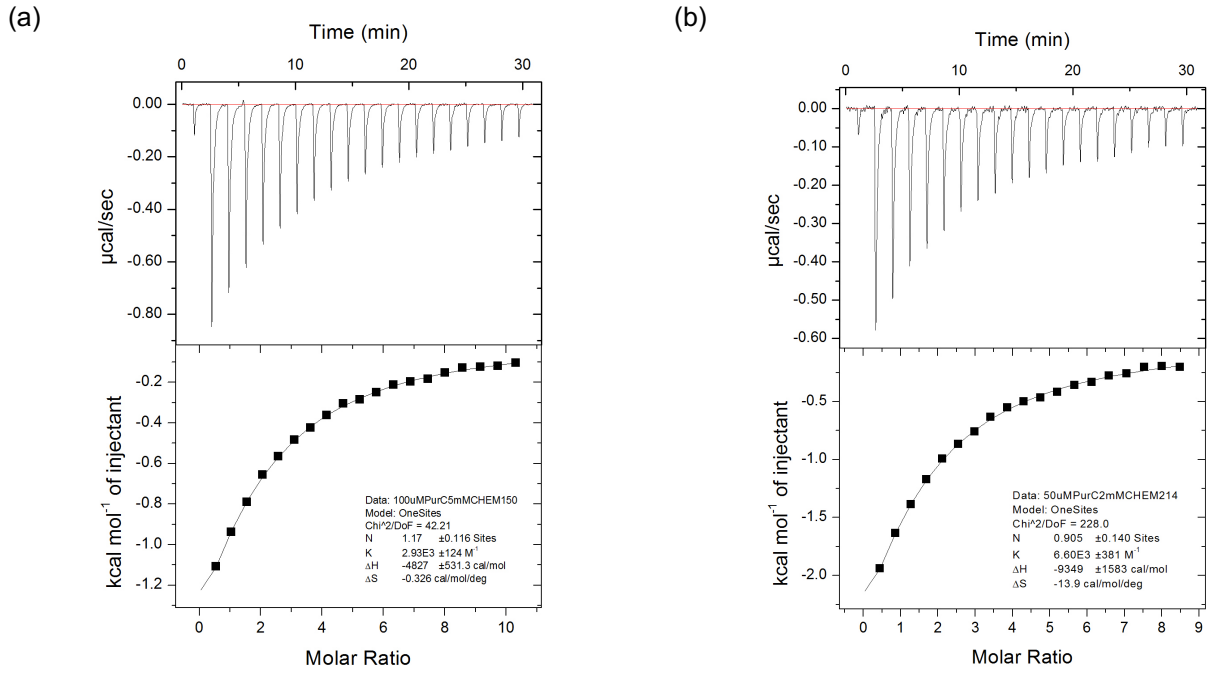


Figure S1: ITC traces between (a) 100 μM *Mab*PurC and 5 mM Fragment **1** (b) 50 μM *Mab*PurC and 2 mM compound **3**.

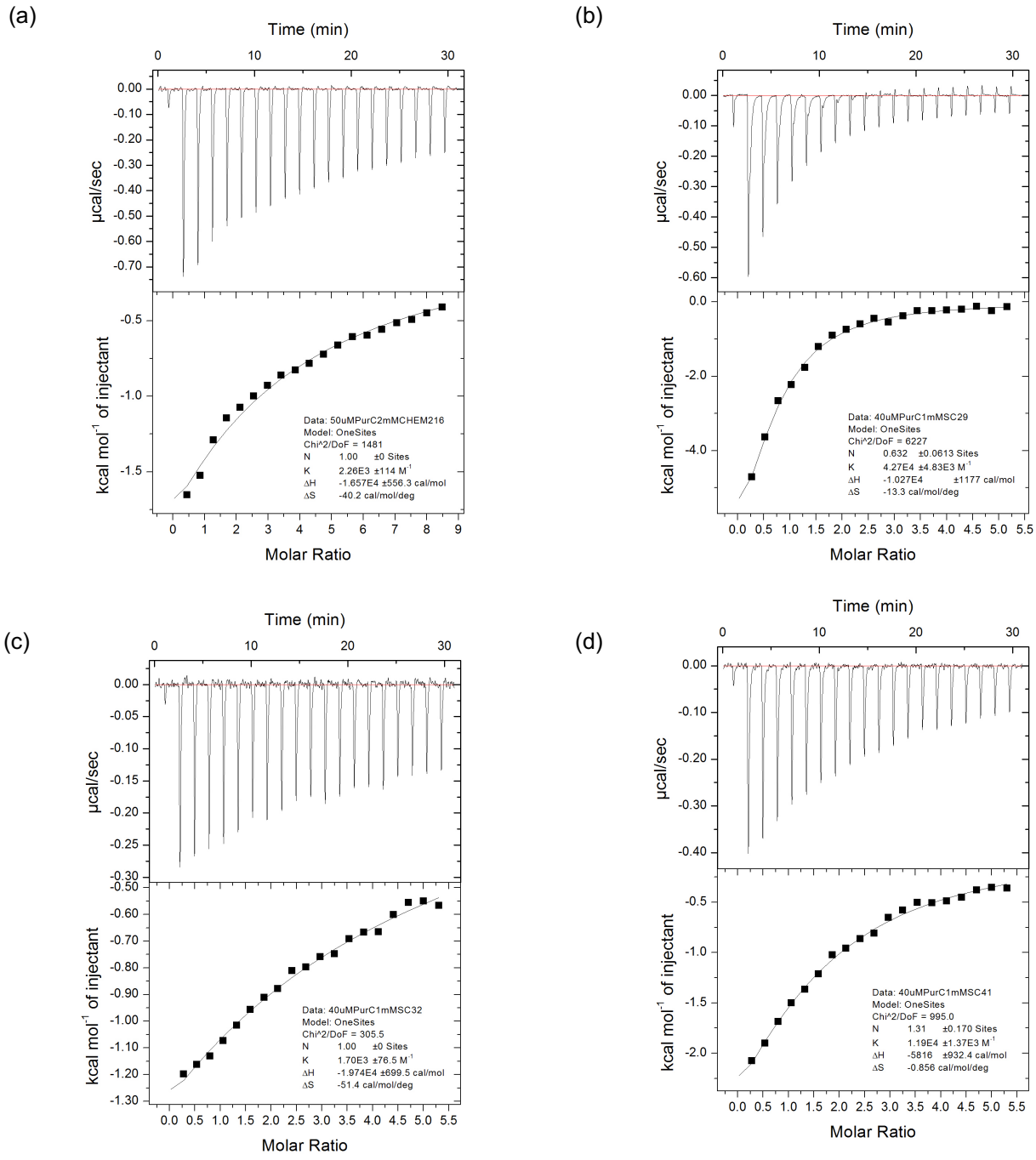


Figure S2: ITC traces between (a) 50 μM *Mab*PurC and 2 mM compound **6** (b) 40 μM *Mab*PurC and 1 mM compound **9** (c) 40 μM *Mab*PurC and 1 mM compound **10** and (d) 40 μM *Mab*PurC and 1 mM compound **11**.

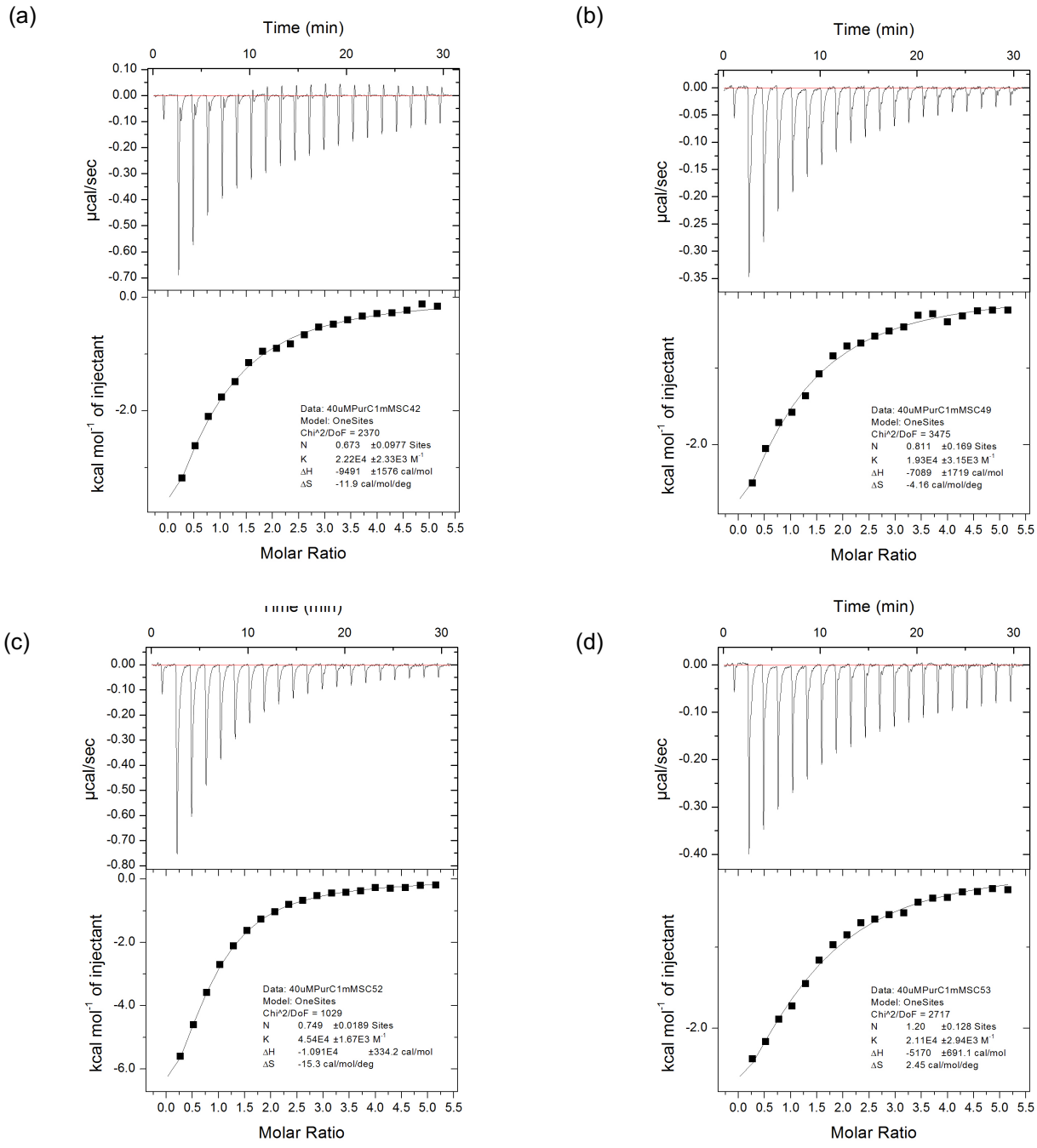


Figure S3: ITC traces between 40 µM *Mab*PurC and (a) 1 mM compound **12** (b) 1 mM compound **13** (c) 1 mM compound **14** and (d) 1 mM compound **15**

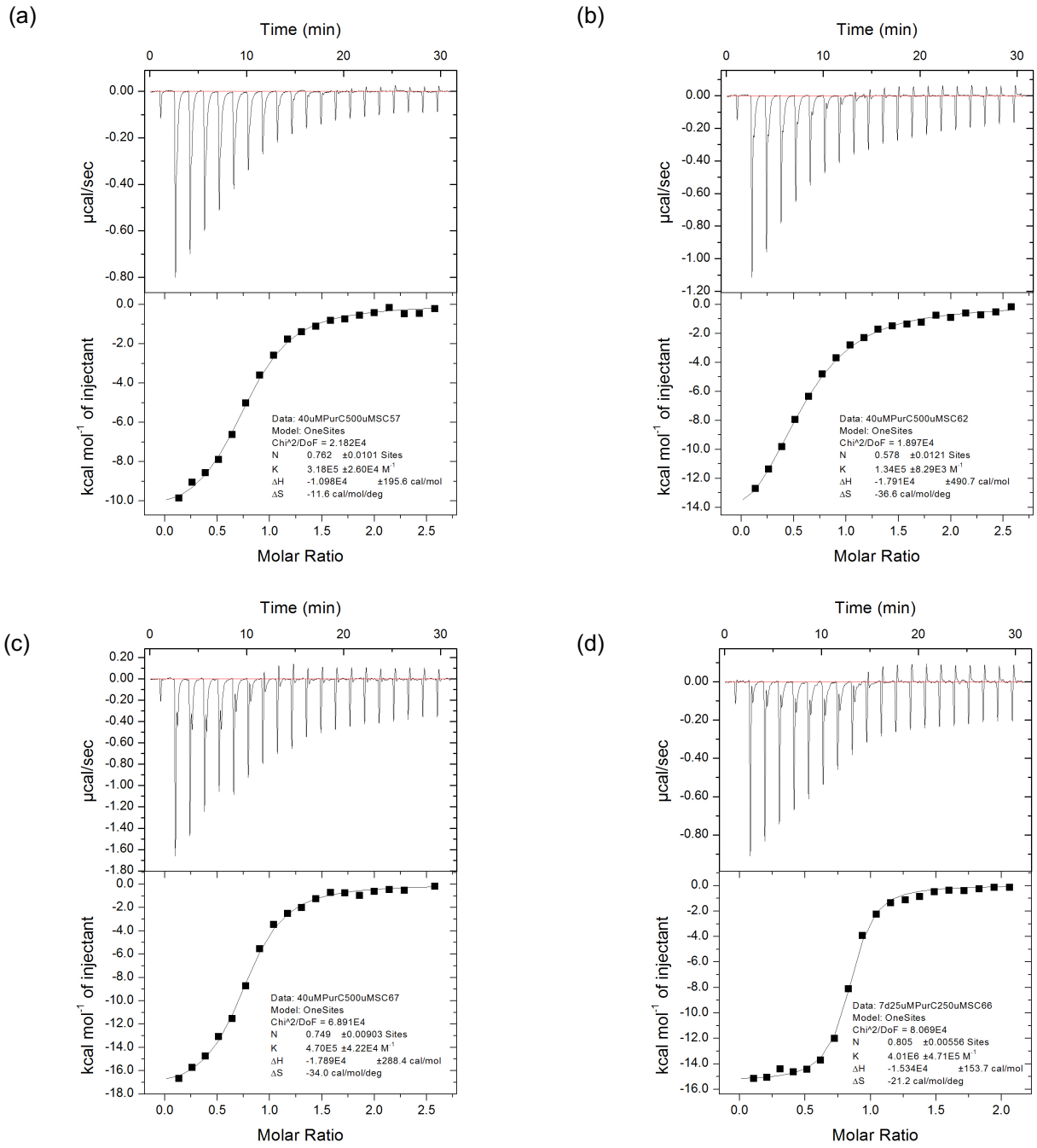


Figure S4: ITC traces between 40 μM *Mab*PurC and (a) 500 μM compound **16** (b) 500 μM compound **17** and (c) 500 μM compound **18** and (d) ITC trace between 25 μM *Mab*PurC and 250 μM compound **19** in the presence of 7% v/v DMSO

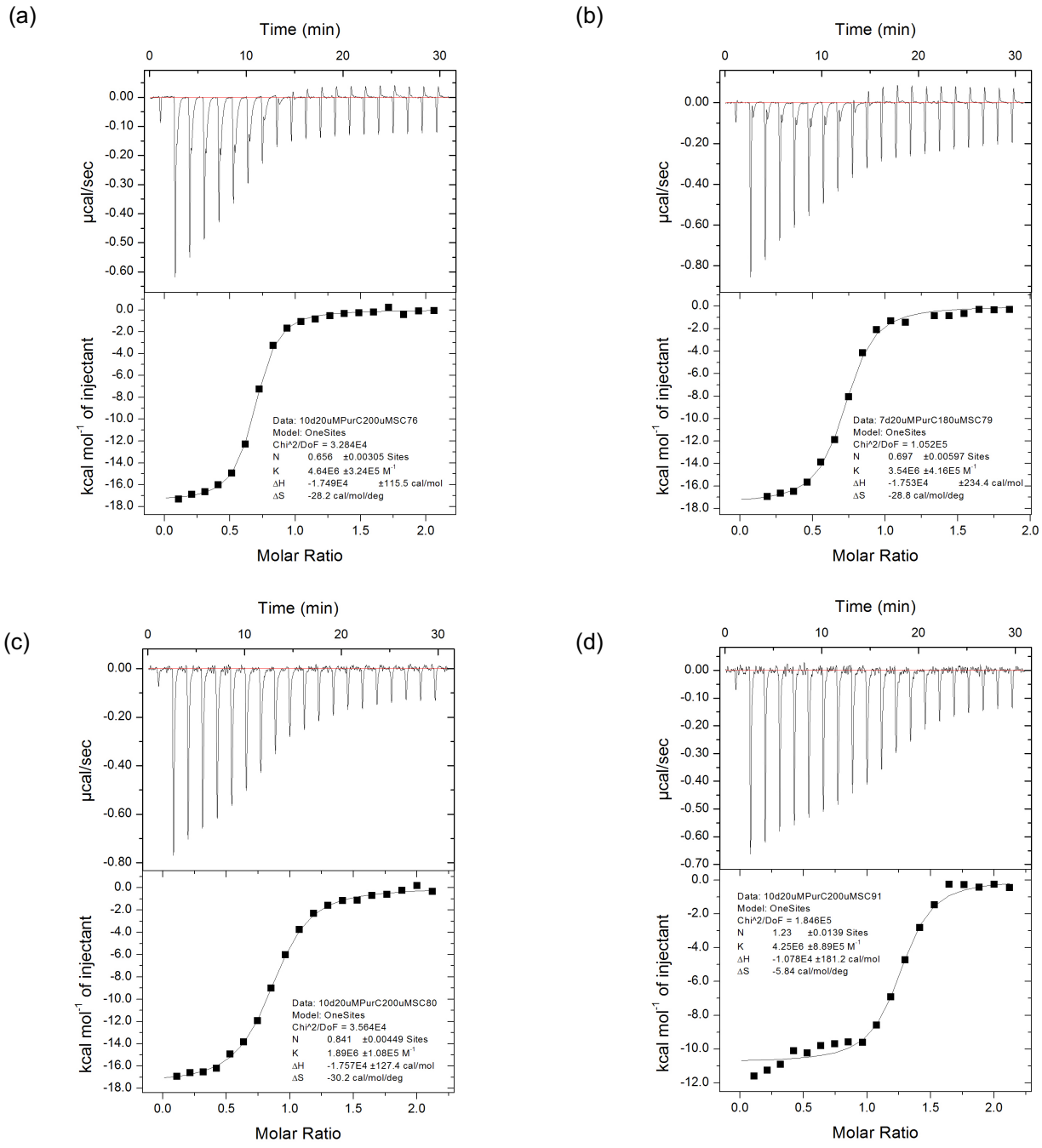
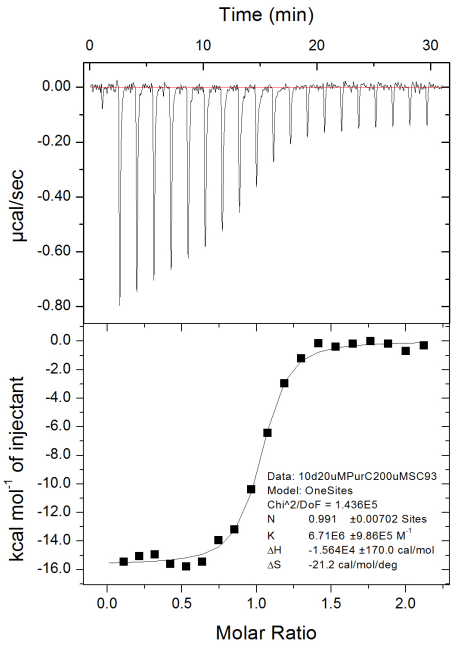
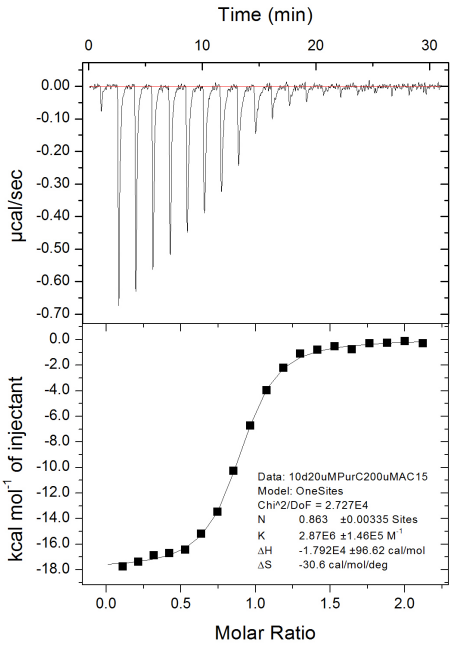


Figure S5: ITC traces between 20 μM *Mab*PurC and (a) 200 μM compound **22** in the presence of 10% v/v DMSO (b) 180 μM compound **23** in the presence of 7% v/v DMSO (c) 200 μM compound **24** in the presence of 10% v/v DMSO and (d) 200 μM compound **26** in the presence of 10% v/v DMSO

(a)



(b)



(c)

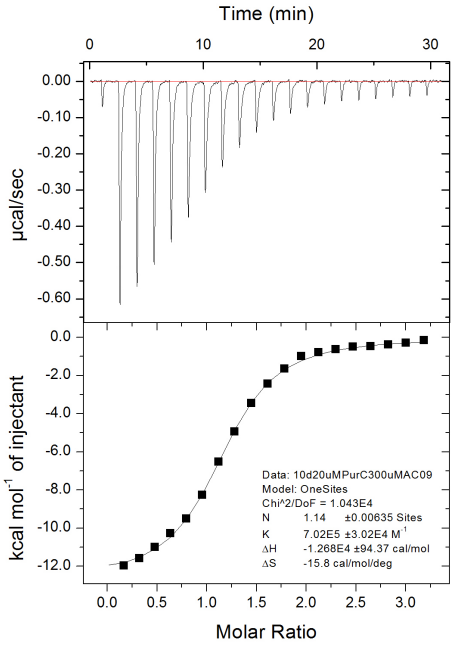


Figure S6: ITC traces in the presence of 10% v/v DMSO between 20 μM *Mab*PurC and (a) 200 μM compound **27** (b) 200 μM compound **28** and (c) 300 μM compound **29**

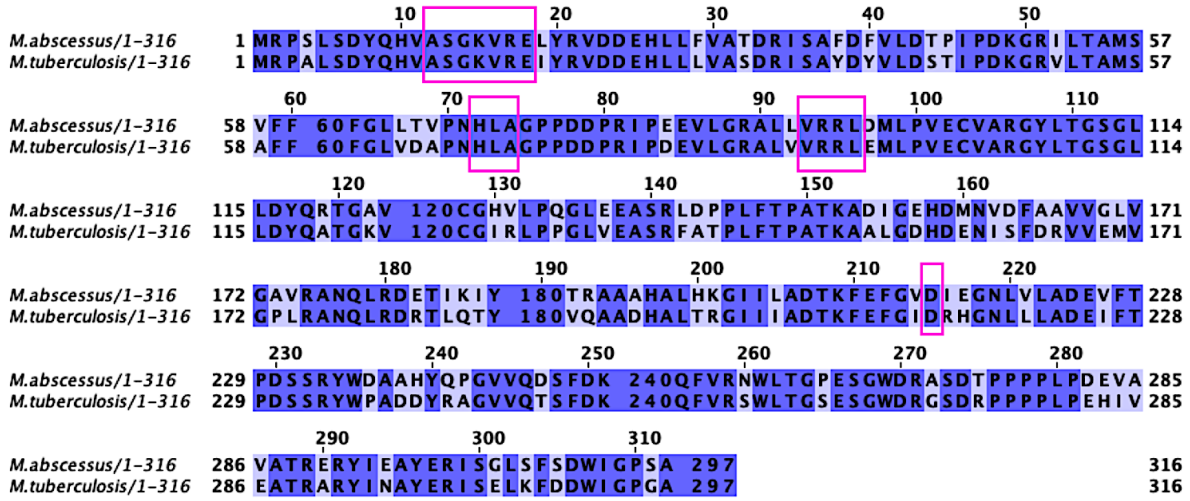


Figure S7: Multiple sequence alignment of *M. abscessus* and *M. tuberculosis* PurC orthologs coloured from white to dark purple indicating increasing percentage conservation of amino acid residues. The overall percentage identity between the two sequences is 75 %. The important catalytic residues and those involved in interactions with the lead compounds in this study are highlighted in pink box.

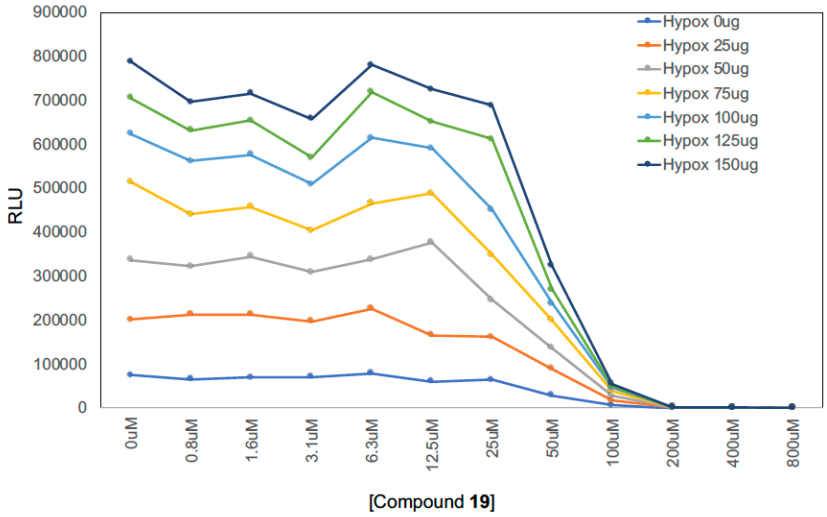


Figure S8: Hypoxanthine rescue experiment with Compound **19** in *Mab*. Hypoxanthine was added in at different concentations to see whether this would show a rescue of PurC in Mab in the presence of compound **19**. The readings were carried out after 48 hours

Table S1: Diffraction data and model refinement statistics

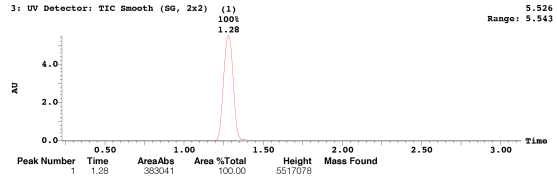
Ligand	PurC free enzyme	PurC + ATP	PurC + Fragment 1
PDB Codes	**6YVQ**	**6YX3**	**6Z0R**
Resolution range (Å)	45.02 - 1.479 (1.532 - 1.479)	37.16 - 1.22 (1.263 - 1.22)	45.07 - 1.308 (1.355 - 1.308)
Space group	P 1 21 1	P 1 21 1	P 1 21 1
Unit cell	48.078 64.287 48.02 90 110.55 90	47.758 64.114 49.013 90 111.48 90	47.493 64.729 48.238 90 110.88 90
Total reflections	78975 (4271)	122763 (1647)	117608 (6927)
Unique reflections	41008 (2349)	62427 (994)	60940 (3997)
Multiplicity	1.9 (1.8)	2.0 (1.7)	1.9 (1.7)
Completeness (%)	89.54 (51.77)	76.39 (12.22)	92.54 (60.97)
Mean I/sigma(I)	10.90 (2.09)	23.35 (2.61)	15.77 (2.13)
Wilson B-factor	16.52	9.46	15.5
R-merge	0.03556 (0.229)	0.02062 (0.3439)	0.02211 (0.304)
R-meas	0.05029	0.02916	0.03127
CC1/2	0.996 (0.848)	0.999 (0.658)	0.999 (0.803)
CC*	0.999 (0.958)	1 (0.891)	1 (0.944)
R-work	0.1620 (0.2295)	0.1614 (0.2948)	0.1798 (0.2575)
R-free	0.1968 (0.2740)	0.1792 (0.3362)	0.2022 (0.2930)
Number of non-hydrogen atoms	2572	2746	2609
macromolecules	2270	2293	2281
ligands	22	47	22
water	280	406	306
Protein residues	295	297	295
RMS(bonds)	0.006	0.006	0.006
RMS(angles)	1	1.1	1.04
Ramachandran favored (%)	98	98	99
Ramachandran outliers (%)	0.34	0.33	0
Clashscore	1.56	1.31	1.11
Average B-factor	22.7	16.9	21.3
macromolecules	21.3	14.6	20.1
ligands	28.8	30	21.4
solvent	33	28.2	30

Protein/ Ligand	PurC + Fragment 2	PurC + Compound 9	PurC + Compound 13
PDB Code	**6Z0Q**	**6YY6**	**6YY8**
Resolution range (Å)	45.88 - 1.535 (1.59 - 1.535)	39.37 - 1.499 (1.553 - 1.499)	37.05 - 1.3 (1.346 - 1.3)
Space group	P 1 21 1	P 1 21 1	P 1 21 1
Unit cell	48.247 65.201 49.051 90 110.73 90	47.582 64.368 48.037 90 110.85 90	47.787 64.771 48.311 90 110.8 90
Total reflections	78438 (7777)	83504 (8585)	134072 (12981)
Unique reflections	41356 (4073)	41921 (4308)	67485 (6620)
Multiplicity	1.9 (1.9)	2.0 (2.0)	2.0 (2.0)
Completeness (%)	97.34 (96.36)	96.47 (99.93)	99.76 (98.50)
Mean I/sigma(I)	13.86 (2.11)	18.59 (4.26)	21.17 (3.56)
Wilson B-factor	18.56	15.62	13.63
R-merge	0.03273 (0.3815)	0.01857 (0.1375)	0.01674 (0.1699)
R-meas	0.04628	0.02627	0.02367
CC1/2	0.998 (0.769)	0.999 (0.963)	0.999 (0.94)
CC*	0.999 (0.932)	1 (0.99)	1 (0.984)
R-work	0.1869 (0.2461)	0.1768 (0.2268)	0.1530 (0.1979)
R-free	0.2310 (0.2660)	0.2034 (0.2462)	0.1802 (0.2191)
Number of non-hydrogen atoms	2592	2618	2661
macromolecules	2272	2275	2283
ligands	21	30	40
water	299	313	338
Protein residues	295	295	295
RMS(bonds)	0.008	0.006	0.006
RMS(angles)	1.02	1.02	1.04
Ramachandran favored (%)	99	99	99
Ramachandran outliers (%)	0	0	0
Clashscore	1.34	2	0.88
Average B-factor	23	20.8	18.6
macromolecules	21.8	19.4	16.7
ligands	35.4	27.1	31
solvent	31.4	30.8	30.4

Protein/ Ligand	PurC + Compound 14	PurC + Compound 16	PurC + Compound 19
PDB Code	6YY7	6YY9	6YYA
Resolution range (Å)	44.92 - 1.347 (1.395 - 1.347)	44.73 - 1.413 (1.463 - 1.413)	39.54 - 1.409 (1.459 - 1.409)
Space group	P 1 21 1	P 1 21 1	P 1 21 1
Unit cell	47.682 64.753 48.013 90 110.68 90	47.792 64.761 48.069 90 110.64 90	47.801 64.956 48.277 90 110.81 90
Total reflections	120492 (12020)	104026 (9742)	104979 (9597)
Unique reflections	60403 (6036)	52437 (5139)	53031 (5035)
Multiplicity	2.0 (2.0)	2.0 (1.9)	2.0 (1.9)
Completeness (%)	99.94 (99.95)	99.82 (98.52)	99.38 (94.77)
Mean I/sigma(I)	16.07 (2.33)	24.11 (7.35)	17.64 (5.35)
Wilson B-factor	15.25	14.92	16.09
R-merge	0.02152 (0.2639)	0.01616 (0.1131)	0.02298 (0.1348)
R-meas	0.03044	0.02286	0.03249
CC1/2	0.999 (0.878)	0.997 (0.919)	0.998 (0.959)
CC*	1 (0.967)	0.999 (0.979)	1 (0.99)
R-work	0.1580 (0.2293)	0.1680 (0.2021)	0.1864 (0.2355)
R-free	0.1856 (0.2728)	0.1900 (0.2529)	0.2152 (0.2508)
Number of non-hydrogen atoms	2647	2603	2566
macromolecules	2292	2278	2272
ligands	38	35	44
water	317	290	250
Protein residues	295	295	294
RMS(bonds)	0.006	0.006	0.007
RMS(angles)	1.01	1.03	1.09
Ramachandran favored (%)	98	99	98
Ramachandran outliers (%)	0	0	0
Clashscore	2.19	1.99	1.1
Average B-factor	20.9	19.9	21.6
macromolecules	19.3	18.6	20.7
ligands	27.4	24.7	22.3
solvent	31.4	29.4	30.3

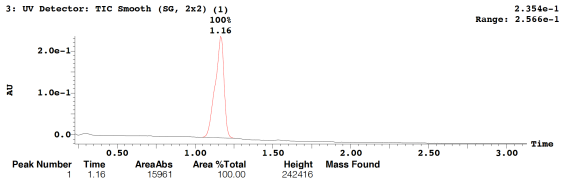
Protein/ Ligand	PurC + Compound 24	PurC + Compound 27	PurC + Compound 28
PDB Code	6YYB	6YYD	6YYC
Resolution range (Å)	44.94 - 1.508 (1.562 - 1.508)	45.21 - 1.387 (1.437 - 1.387)	44.48 - 1.274 (1.319 - 1.274)
Space group	P 1 21 1	P 1 21 1	P 1 21 1
Unit cell	47.68 64.087 47.972 90 110.49 90	47.708 64.471 48.372 90 110.82 90	47.596 64.174 48.262 90 110.85 90
Total reflections	83357 (8055)	107031 (10496)	133393 (10681)
Unique reflections	41939 (4050)	53901 (5303)	67061 (5381)
Multiplicity	2.0 (2.0)	2.0 (2.0)	2.0 (2.0)
Completeness (%)	98.31 (95.56)	97.31 (96.28)	94.67 (76.23)
Mean I/sigma(I)	9.17 (2.12)	7.30 (0.87)	5.55 (0.68)
Wilson B-factor	13.38	15.87	14.25
R-merge	0.0544 (0.3673)	0.04541 (0.8003)	0.05419 (0.7874)
R-meas	0.07694	0.06422	0.07664
CC1/2	0.99 (0.793)	0.998 (0.458)	0.997 (0.692)
CC*	0.997 (0.94)	0.999 (0.793)	0.999 (0.904)
R-work	0.2193 (0.2673)	0.1988 (0.3347)	0.2222 (0.4070)
R-free	0.2492 (0.3075)	0.2228 (0.3559)	0.2556 (0.3966)
Number of non-hydrogen atoms	2524	2609	2608
macromolecules	2266	2276	2288
ligands	27	32	30
water	231	301	290
Protein residues	294	295	295
RMS(bonds)	0.006	0.006	0.006
RMS(angles)	1	1	1.03
Ramachandran favored (%)	99	98	99
Ramachandran outliers (%)	0.34	0	0
Clashscore	2	1.55	1.1
Average B-factor	17.2	20.4	19.3
macromolecules	16.5	19.2	18.3
ligands	15.8	20.6	19.1
solvent	24.8	29.3	27

Compound **9**



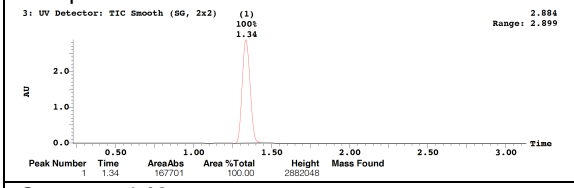
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.28	389041	100.00	5517078	

Compound **10**



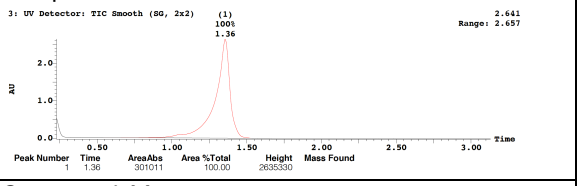
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.16	15961	100.00	242416	

Compound **11**



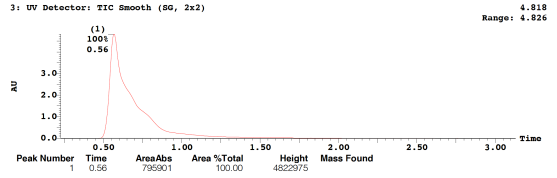
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.34	167701	100.00	2882048	

Compound **12**



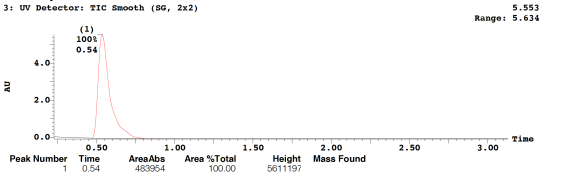
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.36	301011	100.00	2635330	

Compound **13**



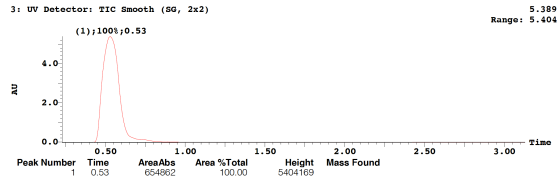
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	0.56	795901	100.00	4822975	

Compound **14**



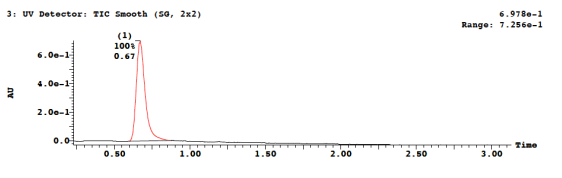
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	0.54	483954	100.00	5611197	

Compound **15**

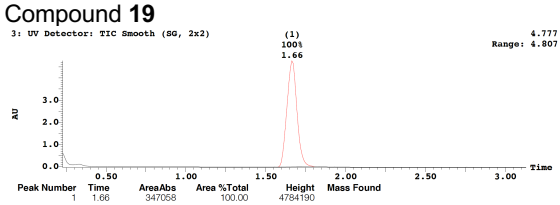


Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	0.53	654862	100.00	5404169	

Compound **17**

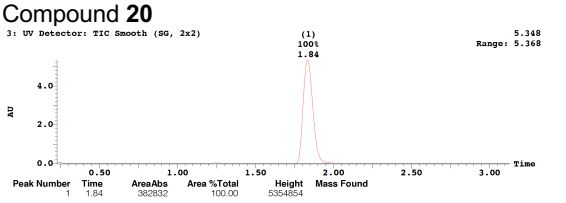


Compound **19**



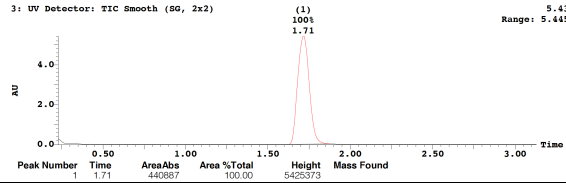
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.66	347058	100.00	4764190	

Compound **20**



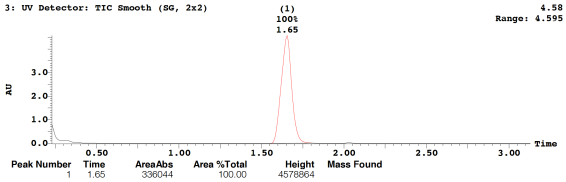
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.84	382832	100.00	5354854	

Compound **21**



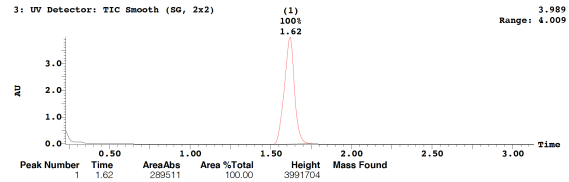
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.71	440887	100.00	5425373	

Compound **22**



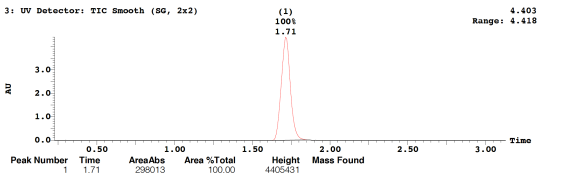
Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.65	336044	100.00	4578864	

Compound **23**



Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.62	289511	100.00	3991704	

Compound **24**



Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
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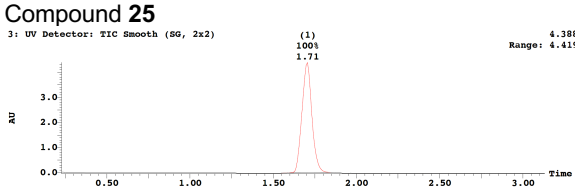
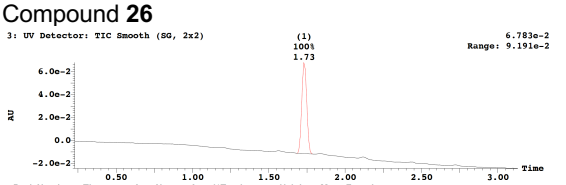
Compound **25**



Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.71	303925	100.00	4391098	

Compound **26**



Peak Number	Time	AreaAbs	Area %Total	Height	Mass Found
1	1.73	3007	100.00	79215	

Compound **27**

Compound **28**

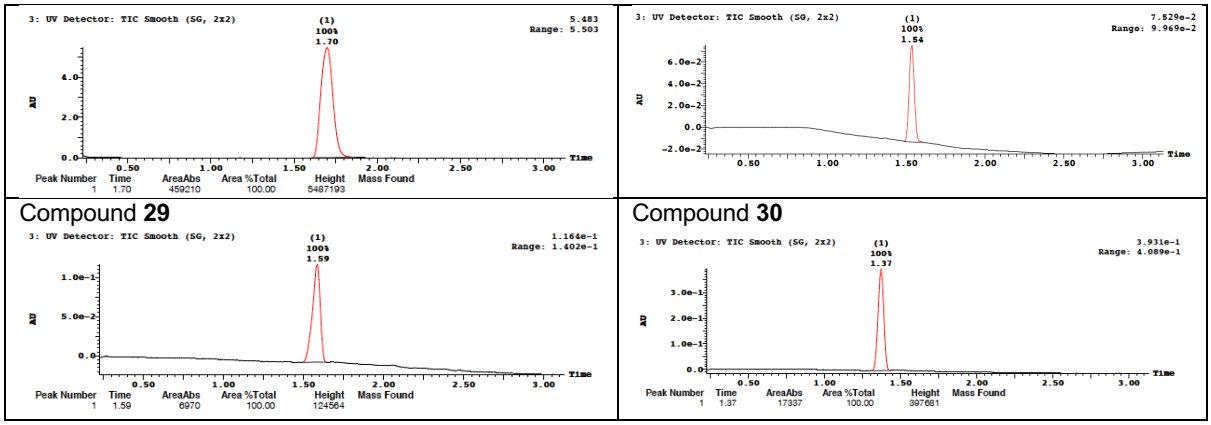


Figure S9: Selected LMCS chromatograms of screened compounds

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