Supporting Information for:

**Alkylation of nitrogen-containing heterocycles via *in situ* sulfonyl transfer**

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I. General Information

All reagents and solvents were obtained from commercial suppliers and used without further purification, unless otherwise noted. Silica gel chromatography was performed using medium pressure ISCO systems employing columns pre-packaged by commercial vendors. $^1$H and $^{13}$C NMR characterization data were collected at 300 K on either a Varian Unity 600 spectrometer operating at 600 and 151 MHz (respectively) or a Bruker Avance III 400 spectrometer operating at 400 and 100 MHz (respectively). Chemical shifts reported in parts per million relative to CHCl$_3$ ($^1$H NMR; 7.26 ppm, $^{13}$C NMR; 77.23 ppm). $^1$H NMR data are reported as follows: chemical shift (multiplicity, coupling constant (Hz), number of hydrogens). IR spectra were recorded on a Nicolet Avatar 360 FT-IR spectrometer and only partial data are provided. High resolution mass spectroscopy (HRMS) was performed on an Agilent (6220) LC-MS TOF using a Xbridge C18 2.5 μm 3.0 X 5.0 mm at 60 °C; ammonium formate: water as mobile phase A1 and 50:50 methanol:acetonitrile as mobile Phase B1. Optical Rotation was recorded on a Perkin Elmer 343 polarimeter and samples were inserted into a quartz cell with a path length of 1 dm.

II. Synthesis and Characterization Data for Substrates

**General Procedure 1:** Synthesis of mesylated azoles.

The heterocycle (5 mmol) was weighed into a round bottom flask, which was then fitted with a stirring bar and capped with a septum. Dichloromethane (DCM, 0.3M) was added to the flask and the mixture was left to stir until dissolution occurred. Triethylamine (1.3 equiv) was added to the mixture and the solution was cooled to 0 °C in an ice bath. Methanesulfonylchloride (1.1 equiv) was added to the mixture dropwise via syringe. The mixture was allowed to stir at 0 °C for 10 minutes, then warmed to rt, and left to stir for an additional 30 minutes. The reaction progress could be monitored by TLC (heptanes/EtOAc). Upon completion, the mixture was quenched with aqueous NH$_4$Cl, diluted with DCM. The phases were separated and the aqueous phase was extracted with DCM (2x). The organic phases were combined and washed with brine, then dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The crude was obtained as a colorless solid or oil and was often used directly. If purity was not sufficient, the material could be purified through column chromatography.

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1-(Methylsulfonyl)-1H-pyrazole-4-carbonitrile, 4a

The titled compound was prepared using Procedure 1, using cyanopyrazole (1g, 10.74 mmol), CH₂Cl₂ (36 ml, 0.3M), NEt₃ (0.95 ml, 1.1 equiv), and MsCl (2 ml, 1.3 equiv). The crude was obtained as a crystalline colorless solid (1.71g, 93%) and was used without further purification. ¹H NMR (CDCl₃, 400 MHz) δ ppm 8.49 (s, 1 H), 8.06 (s, 1 H), 3.46 (s, 3 H); ¹³C NMR (CDCl₃, 101MHz): δ (ppm) 145.6, 135.8, 111.2, 96.0, 41.4; IR (neat): 3121, 2956, 2921, 2851, 2240, 1544, 1461, 1372, 1326, 1184, 1167, 1067, 942 cm⁻¹; MS(ES⁺): 170.2 (M-H⁺); M. p. = 142–144 °C (decomp).

1-(Methylsulfonyl)-1H-pyrazole, 4b

The titled compound was prepared using Procedure 1, using pyrazole (0.5 g, 7.39 mmol), CH₂Cl₂ (24.6 ml, 0.3M), NEt₃ (1.55 ml, 1.3 equiv), and MsCl (0.69 ml, 1.1 equiv). The crude was obtained as a colorless oil (1.07g, >95%) and was used without further purification. The characterization data was consistent with literature.¹ ¹H NMR (CDCl₃, 400MHz): δ (ppm) 8.06 (d, J =2.7 Hz, 1H), 7.84 (d, J =1.2 Hz, 1H), 6.47 (dd, J =2.7, 1.6 Hz, 1H), 3.34 (s, 3H).

1-(Methylsulfonyl)-4-(trifluoromethyl)-1H-pyrazole, 4c

The titled compound was prepared using Procedure 1, using 4-trifluoromethylpyrazole (1.36 g, 10 mmol), CH₂Cl₂ (20 ml, 0.5 M), NEt₃ (1.54 ml, 1.1 equiv), and MsCl (0.82 ml, 1.05 equiv). The crude was obtained as an off-white solid (2.1 g, 98%) and was used without further purification. ¹H NMR (CDCl₃, 400MHz): δ (ppm) 8.36 (q, J =0.8 Hz, 1H), 8.00 (s, 1H), 3.42 (s, 3H); ¹⁹F NMR (CDCl₃, 376MHz): δ (ppm) -57.59 (s, 3F); ¹³C NMR (CDCl₃, 101MHz): δ (ppm) 141.5 (q, J =2.2 Hz), 130.3 (q, J =4.2 Hz), 121.3 (q, J=266.3 Hz), 116.3 (q, J=38.9 Hz), 41.4; IR (neat): 3144, 3122, 3025, 3006, 2925, 1588, 1398, 1371, 1354, 1262, 1179, 1125, 1060, 961, 950 cm⁻¹; MS(ES⁺): 196.5 (M-F+H⁺); M. p. = 125-127 °C.

4-Iodo-1-(methylsulfonyl)-1H-pyrazole, 4d

The titled compound was prepared using Procedure 1, using 4-iodopyrazole (1.94 g, 10 mmol), CH₂Cl₂ (20 ml, 0.5 M), NEt₃ (1.54 ml, 1.1 equiv), and MsCl (0.82 ml, 1.05 equiv). The crude was obtained as a yellow solid (2.72 g, quantitative) and was used without further purification. ¹H NMR (CDCl₃, 400MHz): δ (ppm) 8.11 (d, J =0.8 Hz, 1H), 7.82 (s, 1H), 3.35 (s, 3H); ¹³C NMR (CDCl₃, 101MHz): δ (ppm) 149.7, 134.6, 61.0, 41.3; IR (neat): 3136, 3015, 2928, 2853, 1365, 1335, 1299, 1198, 1172, 1142, 1057, 976, 940 cm⁻¹; HRMS (ESI): [M+H+] Calcd for C₄H₆IN₂O₂S: 272.9189; Found: 272.9188; M. p. = 73–76 °C.

1-Tosyl-1H-pyrazole-4-carbonitrile, 4e

Cyanopyrazole (250 mg, 2.7 mmol) was weighed into a 25 ml round bottom flask. Pyridine (2.5 ml) was added and the solution was cooled to 0 °C in an ice bath. TsCl (627 mg, 1.2 equiv) in pyridine (2.5 ml) was added to the reaction dropwise, observe formation of a yellow color. The mixture was allowed to warm to room temperature and was stirred overnight. In morning the reaction mixture was quenched with NH₄Cl (aq, sat), diluted with EtOAc, extracted into ethyl acetate, washed with NH₄Cl (aq), then CuSO₄ (aq) solution. The organic phases were combined washed with NaHCO₃ then brine. After drying over MgSO₄, filtering, and concentrating under reduced pressure, the crude was obtained as a crystalline colorless solid. The crude was columned to remove residual pyridine (12 g cartridge, 20-40% EtOAc in heptane). Product was obtained as a colorless solid (330 mg, 50%). ¹H NMR (CDCl₃, 400 MHz) δ ppm 8.52 (s, 1 H) 7.95 (d, J =8.59 Hz, 2 H) 7.92 (s, 1 H) 7.40 (dd, J =8.59, 0.78 Hz, 2 H) 2.47 (s, 3 H); ¹³C NMR (CDCl₃, 101MHz): δ (ppm) 147.4, 145.4, 135.8, 132.3, 130.4, 128.8, 111.4, 95.7, 21.8; IR (neat): 3135, 2923, 2851, 2243, 1594, 1549, 1389, 1333, 1195, 1177, 10901, 1065 cm⁻¹; HRMS (ESI): [M+H⁺] Calcd for C₁₁H₁₀N₃O₂S: 272.9189; Found: 272.9188; M. p. = 73–76 °C.

1-((Trifluoromethyl)sulfonyl)-1H-pyrazole-4-carbonitrile, 4f

Cyanopyrazole (250 mg, 2.7 mmol) was weighed into a 25 ml round bottom flask. CH₂Cl₂ (9 ml, 0.3M) was added, followed by pyridine (0.5 ml, 2 equiv). The solution was cooled to 0 °C in an ice bath. Tf₂O (0.5 ml, 1.1 equiv) was added to the reaction dropwise. Observe smoking upon Tf₂O addition. The mixture was stirred at 0 °C for 30 minutes, then was quenched with water and NH₄Cl(aq). The mixture was diluted with EtOAc, extracted into ethyl acetate, washed with NH₄Cl(aq), NaHCO₃ (aq), and brine. After drying over MgSO₄, filtering, and concentrating, the crude was obtained as a pale yellow oily solid. The crude is purified by chromatography (12g cartridge, 0-50% EtOAc in heptanes, notably product is not very UV active). Isolate the
desired product as a colorless crystalline solid (305 mg, 51%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ (ppm) 8.56 (s, 1 H) 8.21 (s, 1 H); $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ (ppm) -73.30 (s, 3 F); $^{13}$C NMR (CDCl$_3$, 101MHz): $\delta$ (ppm) 147.6, 139.0, 118.8 (q, $J$=320 Hz), 109.9, 99.4; IR (neat): 3128, 2965, 2922, 2252, 1564, 1435, 1315, 1221, 1132, 1058, 1001, 974 cm$^{-1}$; MS(ESI): 224.1 (M-H$^+$); M. p. = 55–56 oC.

5-Methyl-1-(methylsulfonyl)-1H-pyrazole and 3-methyl-1-(methylsulfonyl)-1H-pyrazole, 4g

The titled compounds were prepared using Procedure 1, using 3-methylpyrazole (300 mg, 3.22 mmol), CH$_2$Cl$_2$ (10.7 ml, 0.3 M), NEt$_3$ (0.68 ml, 1.5 equiv), and MsCl (0.3 ml, 1.2 equiv). The mixture was allowed to stir at room temperature for 2 hours before quenching. The crude was obtained as a pale yellow oil, which solidified over time (0.71 g, quantitative). The crude consisted of an inseparable mixture of 2 regioisomers in a ratio of 1:1.1. Minor $^1$H NMR (CDCl$_3$, 600MHz): $\delta$ (ppm) 8.07 (d, $J$=2.9 Hz, 1H), 7.88 (d, $J$=8.2 Hz, 2H), 7.38-7.47 (m, 3H), 6.75 (d, $J$=2.9 Hz, 1H), 3.36 (s, 3H); $^{13}$C NMR (CDCl$_3$, 151MHz): $\delta$ (ppm) 156.8, 132.1, 131.1, 129.2, 128.6, 126.3, 106.1, 41.1; IR (neat): 3145, 3024, 2932, 1533, 1501, 1454, 1365, 1322, 1304, 1177, 1150, 1069, 1033, 981, 944 cm$^{-1}$; HRMS (ESI): [M+H$^+$] Calcd for C$_{10}$H$_{11}$N$_2$O$_2$S: 223.0536; Found: 223.0534; M. p. = 110–112 oC.

Major isomer (4h-1): $^1$H NMR (CDCl$_3$, 600MHz): $\delta$ (ppm) 8.07 (d, $J$=2.9 Hz, 1H), 7.88 (d, $J$=8.2 Hz, 2H), 7.38-7.47 (m, 3H), 6.75 (d, $J$=2.9 Hz, 1H), 3.36 (s, 3H); $^{13}$C NMR (CDCl$_3$, 151MHz): $\delta$ (ppm) 156.8, 132.1, 131.1, 129.2, 128.6, 126.3, 106.1, 41.1; IR (neat): 3145, 3024, 2932, 1533, 1501, 1454, 1365, 1322, 1304, 1177, 1150, 1069, 1033, 981, 944 cm$^{-1}$; HRMS (ESI): [M+H$^+$] Calcd for C$_{10}$H$_{11}$N$_2$O$_2$S: 223.0536; Found: 223.0534; M. p. = 110–112 oC.

Minor isomer (4h-2): $^1$H NMR (CDCl$_3$, 600MHz): $\delta$ (ppm) 7.80 (d, $J$=1.2 Hz, 1H), 7.40-7.51 (m, 5H), 6.41 (d, $J$=1.2 Hz, 1H), 3.22 (s, 3H); $^{13}$C NMR (CDCl$_3$, 151MHz): $\delta$ (ppm) 147.4, 143.3, 129.7, 129.4, 128.9, 127.8, 110.9, 42.0; IR (neat): 3135, 3017, 2931, 1446, 1409, 1368, 1325, 1292, 1236, 1178, 1136, 1104, 1035, 978, 951 cm$^{-1}$; HRMS (ESI): [M+H$^+$] Calcd for C$_{10}$H$_{11}$N$_2$O$_2$S: 223.0536; Found: 223.0531; M. p. = 71–72 oC.

3-Phenyl-1-tosyl-1H-pyrazole, 4i

3-Phenylpyrazole (581 mg, 4.03 mmol) was weighed into a 25 ml round bottom flask. Pyridine (6.5 ml, 20 equiv) was added, reaction was cooled to 0 oC. A solution of TsCl (920 mg, 1.2 equiv) was added to the mixture and the reaction was allowed to warm to 50°C. The yellow solution was allowed to stir at room temperature over the weekend. The reaction mixture was then diluted with NH$_4$Cl (aq) and EtOAc, extracted into EtOAc, then washed with 1N NaOH (2x), 1N HCl (5x), water, brine. The solution was dried over MgSO$_4$ and concentrated to give the crude as a colorless solid (1.03 g, 86% yield). The crude material consists of a single regioisomer. $^1$H NMR (CDCl$_3$, 400MHz): $\delta$ (ppm) 8.13 (d, $J$=2.7 Hz, 1H), 7.95 (d, $J$=8.6 Hz, 2H), 7.35-7.43 (m, 3H), 7.33 (d, $J$=7.8 Hz, 2H), 6.70 (d, $J$=2.7 Hz, 1H), 2.42 (s, 3H); $^{13}$C NMR (CDCl$_3$, 101MHz): $\delta$ (ppm) 156.9, 145.7, 134.2, 132.5, 131.5, 129.9, 129.2, 128.6, 128.1, 126.4, 106.4, 21.7; IR (neat): 3145, 3062, 1595, 1533, 1500, 1454, 1380, 1324, 1303, 1191, 1176, 1149, 1091, 1069, 1033 cm$^{-1}$; HRMS (ESI): [M+H$^+$] Calcd for C$_{16}$H$_{13}$N$_2$O$_2$S: 299.0849; Found: 299.0848; M. p. = 143–144 oC.

5,6-Dichloro-1-(methylsulfonyl)-2-(methylthio)-1H-benzo[d]imidazole, 4j

The titled compound was prepared using Procedure 1, using 5,6-dichloro-2-(methylthio)-1H-benzo[d]imidazole as substrate (466 mg, 2 mmol), CH$_2$Cl$_2$ (6.7 ml, 0.3 M), NEt$_3$ (0.42 ml, 1.5 equiv), and MsCl (0.19 ml, 1.2 equiv). The mixture was allowed to stir at room temperature for 2 hours before quenching. The crude was obtained as an orange solid. The crude was purified by column chromatography (12 g cartridge, 0-50% EtOAc in heptane) to give the major isomer (colorless solid, 400 mg, 56%) and the minor isomer (colorless solid, 280 mg, 39%).
13C NMR (CDCl3, 101MHz): δ (ppm) 155.9, 142.4, 133.1, 128.1, 128.1, 119.8, 114.1, 41.1, 15.3; IR (neat): 3115, 3092, 3026, 2995, 2960, 2917, 1468, 1440, 1369, 1237, 1201, 1163, 1103, 1042, 983, 970, 879 cm⁻¹; HRMS (ESI): [M+H⁺] Calcd for C₉H₉Cl₂N₂O₂S₂: 310.9477; Found: 310.9474; M. p. = 209–212 °C (decomp).

4-Chloro-7-(methylsulfonyl)-7H-pyrrolo[2,3-d]pyrimidine, 4k

The titled compound was prepared using Procedure 1, using 4-chloro-7H-pyrrolo[2,3-d]pyrimidine as substrate (307 mg, 2 mmol), CH₂Cl₂ (6.7 ml, 0.3 M), NEt₃ (0.42 ml, 1.5 equiv), and MsCl (0.19 ml, 1.2 equiv). The mixture was allowed to stir at room temperature for 2 hours before quenching. The crude was obtained as an off-white solid. The crude was purified by column chromatography (12 g cartridge, 0-50% EtOAc in heptane) to give the product as a colorless highly crystalline solid (360 mg, 78%). 1H NMR (CDCl₃, 400MHz): δ (ppm) 8.85 (s, 1H), 7.71 (d, J = 3.9 Hz, 1H), 6.78 (d, J = 3.9 Hz, 1H), 3.63 (s, 3H); 13C NMR (CDCl₃, 101MHz): δ (ppm) 153.1, 152.3, 150.8, 126.6, 119.6, 102.4, 42.3; IR (neat): 3154, 3128, 3036, 3009, 2927, 1581, 1546, 1508, 1439, 1362, 1331, 1305, 1247, 1216, 1169, 1151, 1106, 1014, 967, 916, 848, 772 cm⁻¹; HRMS (ESI): [M+H⁺] Calcd for C₇H₇ClN₃O₂S: 231.9942; Found: 231.9941; M. p. = 125–126 °C.

1-(Methylsulfonyl)-1H-indazole, 4l

The titled compound was prepared using Procedure 1, using indazole (1180 mg, 10 mmol), CH₂Cl₂ (20 ml, 0.5 M), NEt₃ (1.54 ml, 1.1 equiv), and MsCl (0.82 ml, 1.05 equiv). The mixture was allowed to stir at room temperature for 16 hours before quenching. The crude was obtained as a yellow oil (1.7 g, 87%), and was used directly without further purification. Characterization data was consistent with literature. 1H NMR (CDCl₃, 400MHz): δ (ppm) 8.29 (d, J = 0.8 Hz, 1H), 8.06-8.11 (m, 1H), 7.78 (d, J = 8.2 Hz, 1H), 7.53-7.59 (m, 1H), 7.33-7.42 (m, 1H), 3.25 (s, 3H); M. p. = 37–38 °C.

1-Tosyl-1H-indole, 4m

The characterization of material is consistent with literature. 1H NMR (CDCl₃, 400MHz): δ (ppm) 8.00 (d, J = 8.2 Hz, 1H), 7.77 (d, J = 8.6 Hz, 2H), 7.57 (d, J = 3.9 Hz, 1H), 7.53 (d, J = 7.8 Hz, 1H), 7.31 (td, J = 7.8, 1.2 Hz, 1H), 7.20-7.25 (m, 3H), 6.66 (d, J = 3.5 Hz, 1H), 2.35 (s, 3H).

1-(1-Tosyl-1H-indol-3-yl)ethan-1-one, 4n

The characterization of material is consistent with literature. 1H NMR (CDCl₃, 400MHz): δ (ppm) 8.32-8.36 (m, 1H), 8.22 (s, 1H), 7.92-7.95 (m, 1H), 7.84 (d, J = 8.6 Hz, 2H), 7.38 (td, J = 7.0, 1.6 Hz, 1H), 7.35 (td, J = 7.0, 1.2 Hz, 1H), 7.29 (d, J = 8.2 Hz, 2H), 2.58 (s, 3H), 2.38 (s, 3H).

III. Experimental Procedures for Sulfonyl Transfer Reaction

General Procedure 2 (Conditions A, Table 2): Sulfonyl transfer reaction of sulfonylated azoles and alcohols

Meslypyrazole (0.72 mmol, 1.2 equiv), the alcohol (0.6 mmol, 1 equiv) and Cs₂CO₃ (0.72 mmol, 1.2 equiv) are weighed into a vial. The vial is fitted with a stirring bar and a screw cap with a septum. MeCN (2 ml, 0.3M) is added, the vial is sealed and heated overnight at 90 °C. No special precautions to exclude air or moisture are taken. After a 16-18 hour reaction time, the reaction is diluted with water and EtOAc, extracted into EtOAc. The aqueous phase is washed with EtOAc (2x). The combined organic phases are washed with brine, dried over MgSO₄, filtered, and concentrated to give the reaction crude. The crude is purified through column chromatography (typically 4g cartridge, EtOAc and heptanes as solvents).

General Procedure 3 (Conditions B, Table 2): Sulfonyl transfer reaction of sulfonylated azoles and alcohols using NaOt-Bu.

Meslypyrazole (0.72 mmol, 1.2 equiv), the alcohol (0.6 mmol, 1 equiv) and NaOt-Bu (0.72 mmol, 1.2 equiv) are weighed into a vial. The vial is fitted with a stirring bar and a screw cap with a septum. DMF (2 ml, 0.3M) is added, the vial is sealed and heated overnight at 90 °C. No special precautions to exclude air or moisture are taken. After a 16-18 hour reaction time, the reaction is diluted with water and EtOAc, extracted into EtOAc. The aqueous phase is washed with EtOAc (2x). The combined organic phases are washed...
with brine, dried over MgSO₄, and concentrated to give the reaction crude. The crude is purified through column chromatography (typically 4g cartridge, EtOAc and heptanes as solvents).

IV. Characterization Data for Alkylated Azoles

tert-Butyl 4-[(4-cyano-1H-pyrazol-1-yl)ethyl]piperazine-1-carboxylate, 3a

The titled compound was prepared using Procedure 2, using tert-butyl 4-(2-hydroxyethyl)piperazine-1-carboxylate (138 mg, 0.6 mmol), pyrazole 4a (123 mg, 0.72 mmol, 1.2 equiv), Cs₂CO₃ (237 mg, 0.72 mmol, 1.2 equiv) in MeCN (2 ml, 0.3M). The mixture was allowed to stir at 90 °C overnight. The crude was obtained as a pale yellow oil, which was purified by column chromatography (4g cartridge, 0-100% EtOAc in heptane) to give the desired product as a colorless oil, which solidified over time. (144 mg, 78%); ¹H NMR (CDCl₃, 400MHz): δ (ppm) 7.92 (s, 1H), 7.72 (s, 1H), 4.21 (t, J=6.2 Hz, 2H), 3.31-3.37 (m, 4H), 2.75 (t, J=6.0 Hz, 2H), 2.36 (br. m., 4H), 1.39 (s, 9H); ¹³C NMR (CDCl₃, 101MHz): δ (ppm) 154.5, 142.0, 134.8, 113.4, 91.9, 79.7, 57.0, 52.8, 50.1, 43.4 (br), 28.3; IR (neat): 3124, 2974, 2929, 2861, 2816, 2233, 1687, 1544, 1421, 1364, 1249, 1169, 1128, 1005 cm⁻¹; HRMS (EI): [M+H⁺] Calcd for C_{15}H_{24}F_{3}N_{4}O_{2}: 349.1846; Found: 349.1849; M. p. = 66–68 °C.

tert-Butyl 4-[(1H-pyrazol-1-yl)ethyl]piperazine-1-carboxylate 3b

The titled compound was prepared using Procedure 3, using tert-butyl 4-(2-hydroxyethyl)piperazine-1-carboxylate (78.8 mg, 0.34 mmol), pyrazole (50 mg, 0.41 mmol, 1.0 equiv), NaOt-Bu (40 mg, 0.41 mmol, 1.2 equiv) in DMF (1 ml, 0.3M). The mixture was allowed to stir at 90 °C overnight. The crude was obtained as a pale yellow oil, which was purified by column chromatography (4g cartridge, 0-100% EtOAc in heptane) to give the desired product as a colorless oil (83 mg, 87%); ¹H NMR (CDCl₃, 400MHz): δ (ppm) -56.27 (s, 3F); IR (neat): 2975, 2933, 2862, 3813, 1687, 1455, 1418, 1397, 1365, 1280, 1246, 1166, 1124, 1089, 1040, 1004, 865, 751 cm⁻¹; HRMS (ESI): [M+H⁺] Calcd for C_{15}H_{24}N_{5}O_{2}: 306.1925; Found: 306.1926; M. p. = 75–76 °C.

tert-Butyl 4-[(1H-pyrazol-1-yl)ethyl]piperazine-1-carboxylate, 3c

The titled compound was prepared using Procedure 3, using tert-butyl 4-(2-hydroxyethyl)piperazine-1-carboxylate (100 mg, 0.43 mmol), pyrazole 4c (102 mg, 0.48 mmol, 1.1 equiv), Cs₂CO₃ (172 mg, 0.52 mmol, 1.2 equiv) in MeCN (1.5 ml, 0.3M). The mixture was allowed to stir at 90 °C overnight. The crude was obtained as a yellow oil, which was purified by column chromatography (4g cartridge, 0-100% EtOAc in heptane) to give the desired product as a pale yellow oil (83 mg, 87%); ¹H NMR (CDCl₃, 400MHz): δ (ppm) 7.75 (s, 1H), 7.65 (s, 1H), 4.22 (t, J=6.2 Hz, 2H), 3.37 (br. m, J=5.1 Hz, 4H), 2.78 (t, J=6.4 Hz, 2H), 2.38 (br. t, J=4.7 Hz, 4H), 1.42 (s, 9H); ¹³C NMR (CDCl₃, 101MHz): δ (ppm) 154.6, 136.7 (q, J=38.1 Hz), 79.6, 57.3, 52.9, 50.1, 43.4 (br, m), 28.3; IR (neat): 3124, 2974, 2929, 2861, 2816, 2233, 1687, 1544, 1421, 1364, 1249, 1166, 1128, 1005 cm⁻¹; HRMS (EI): [M+H⁺] Calcd for C_{15}H_{22}N_{5}O_{2}: 306.1926; Found: 306.1926; M. p. = 75–76 °C.

tert-Butyl 4-[(1H-pyrazol-1-yl)ethyl]piperazine-1-carboxylate, 3d

The titled compound was prepared using Procedure 3, using tert-butyl 4-(2-hydroxyethyl)piperazine-1-carboxylate (100 mg, 0.43 mmol), pyrazole 4d (130 mg, 0.48 mmol, 1.1 equiv), NaOt-Bu (50 mg, 0.52 mmol, 1.2 equiv) in DMF (1.5 ml, 0.3M). The mixture was allowed to stir at 90 °C overnight. The crude was obtained as a yellow oil, which was purified by column chromatography (4g cartridge, 0-100% EtOAc in heptane) to give the desired product as a pale yellow oil (140 mg, 79%). Procedure 2 could also be used to prepare the material (124 mg, 70%); ¹H NMR (CDCl₃, 400MHz): δ (ppm) 7.47 (s, 1H), 7.43 (s, 1H), 4.18 (t, J=6.6 Hz, 2H), 3.35 (dd, J=5.9, 4.3 Hz, 4H), 2.73 (t, J=6.4 Hz, 2H), 2.35 (br. t, J=5.1 Hz, 4H), 1.40 (s, 9H); ¹³C NMR (CDCl₃, 101MHz): δ (ppm) 154.5, 144.0, 133.8, 79.5, 57.5, 55.6, 52.8, 50.0, 43.4 (br), 28.2; IR (neat): 3115, 2974, 2930, 2860, 2813, 1685, 1419, 1364, 1288, 1246, 1166, 1124, 1004, 940 cm⁻¹; HRMS (EI): [M+H⁺] Calcd for C_{14}H_{12}IN_{3}O_{2}: 407.0938; Found: 407.0941.
1-(2-(Pyridin-4-yl)ethyl)-1H-pyrazole-4-carbonitrile, 3e

The titled compound was prepared using Procedure 2, using 2-(pyridin-4-yl)ethan-1-ol (85.8 mg, 0.7 mmol), pyrazole 4a (131 mg, 0.77 mmol, 1.1 equiv), Cs2CO3 (275 mg, 0.84 mmol, 1.2 equiv) in MeCN (2.3 ml, 0.3M).

The mixture was allowed to stir at 90 °C overnight. The crude was obtained as a colorless oil, which was purified by column chromatography (4g cartridge, 0-100% EtOAc in heptane) to give the desired product as an off-white solid (91.7 mg, 66%). 1H NMR (CDCl3, 400MHz): δ (ppm) 8.27 (d, J=2.0 Hz, 1H), 7.92 (s, 1H), 7.75 (s, 1H), 7.52 (dd, J=8.2, 2.7 Hz, 1H), 7.26 (d, J=8.6 Hz, 1H), 5.28 (s, 2H); 13C NMR (CDCl3, 101MHz): δ (ppm) 151.6, 148.8, 142.7, 138.3, 134.5, 129.4, 124.4, 112.9, 92.7, 52.9; IR (neat): 3124, 2932, 2853, 2235, 1589, 1568, 1460, 1385, 1356, 1152, 1013, 982, 864 cm–1; HRMS (ESI): [M+H+] Calcd for C9H13N3O: 202.0952; Found: 202.0951.

1-((6-Chloropyridin-3-yl)methyl)-1H-pyrazole-4-carbonitrile, 3f

The titled compound was prepared using Procedure 2, using 6-chloropyridin-3-yl)methanol (100 mg, 0.7 mmol), pyrazole 4a (131 mg, 0.77 mmol, 1.1 equiv), Cs2CO3 (275 mg, 0.84 mmol, 1.2 equiv) in MeCN (2.3 ml, 0.3M).

The mixture was allowed to stir at 90 °C overnight. The crude was obtained as a colorless oil, which was purified by column chromatography (4g cartridge, 0-100% EtOAc in heptane) to give the desired product as a colorless solid (123 mg, 81%). 1H NMR (CDCl3, 400MHz): δ (ppm) 8.45 (d, J=5.9 Hz, 2H), 7.77 (s, 1H), 7.58 (s, 1H), 6.94 (d, J=6.2 Hz, 2H), 4.37 (t, J=6.8 Hz, 2H), 3.16 (t, J=6.8 Hz, 2H); 13C NMR (CDCl3, 101MHz): δ (ppm) 149.8, 145.8, 142.3, 134.4, 123.6, 113.0, 91.7, 52.7, 35.1; IR (neat): 3121, 3069, 3032, 2994, 2954, 2233, 1603, 1544, 1462, 1438, 1417, 1385, 1358, 1158, 999 cm–1; HRMS (EI): [M+H+] Calcd for C11H11N4: 199.0978; Found: 199.0978; M. p. = 101–103 °C.

1-(3-Hydroxy-3-methylbutyl)-1H-pyrazole-4-carbonitrile, 3g

The titled compound was prepared using Procedure 2, using 3-methylbutane-1,3-diol (31.2 mg, 0.3 mmol), pyrazole 4a (131 mg, 0.77 mmol, 1.1 equiv), Cs2CO3 (118 mg, 0.36 mmol, 1.05 equiv) in MeCN (1 ml, 0.3M).

The mixture was allowed to stir at 90 °C overnight. The crude was obtained as a colorless oil, which was purified by column chromatography (4g cartridge, 0-70% EtOAc in heptane) to give the desired product as a colorless oil (37 mg, 70%); 1H NMR (CDCl3, 400MHz): δ (ppm) 149.8, 145.8, 142.3, 134.4, 123.6, 113.0, 91.7, 52.7, 35.1; IR (neat): 3121, 3069, 3032, 2994, 2954, 2233, 1603, 1544, 1462, 1438, 1417, 1385, 1358, 1158, 999 cm–1; HRMS (ESI): [M+H+] Calcd for C9H12N3O: 162.1026; Found: 162.1022.

1-Cyclopentyl-1H-pyrazole-4-carbonitrile, 3h

The titled compound was prepared using Procedure 2, using cyclopentanol (51.7 mg, 0.6 mmol), pyrazole 4a (131 mg, 0.77 mmol, 1.1 equiv), Cs2CO3 (275 mg, 0.84 mmol, 1.2 equiv) in MeCN (2 ml, 0.3M).

The mixture was allowed to stir at 90 °C overnight. The crude was obtained as a colorless oil, which was purified by column chromatography (4g cartridge, 0-100% EtOAc in heptane) to give the desired product as a colorless solid (123 mg, 81%). 1H NMR (CDCl3, 400MHz): δ (ppm) 7.89 (s, 1H), 7.79 (s, 1H), 4.38 (ddd, J=14.05, 7.80, 6.63 Hz, 1 H), 2.06 - 2.23 (m, 2 H), 1.90 - 2.04 (m, 2 H), 1.77 - 1.90 (m, 2 H), 1.63 - 1.77 (m, 2 H); 13C NMR (CDCl3, 101MHz): δ (ppm) 141.8, 132.7, 113.5, 92.0, 69.5, 49.0, 42.8, 29.7; IR (neat): 3411, 2971, 2930, 2233, 1589, 1568, 1460, 1385, 1356, 1152, 1013, 982, 864 cm–1; HRMS (EI): [M+H+] Calcd for C10H15N3: 162.0951; Found: 162.0952.

1-(Tetrahydro-2H-pyran-4-yl)-1H-pyrazole-4-carbonitrile, 3i

The titled compound was prepared using Procedure 2, using tetrahydro-2H-pyran-4-ol (71.2 mg, 0.7 mmol), pyrazole 4a (131 mg, 0.77 mmol, 1.1 equiv), Cs2CO3 (275 mg, 0.84 mmol, 1.2 equiv) in MeCN (2.3 ml, 0.3M).

The mixture was allowed to stir at 90 °C overnight. The crude was obtained as a colorless oil, which was purified by column chromatography (4g cartridge, 0-10% EtOAc in heptane) to give the desired product as a colorless solid (71.2 mg, 58%); 1H NMR (CDCl3, 400MHz): δ (ppm) 7.89 (s, 1H), 7.79 (s, 1H), 4.38 (ddd, J=15.6, 10.9, 4.7 Hz, 1H), 4.05-4.13 (m, 2H), 3.52 (td, J=11.6, 2.9 Hz, 2H), 1.97-2.13 (m, 4H); 13C NMR (CDCl3, 101MHz): δ (ppm) 141.8, 131.9, 113.3, 91.7, 66.2, 58.8, 32.7; IR (neat): 3127, 2965, 2928, 2853, 2233, 1542, 1448, 1385, 1368, 1266, 1145, 1007, 982 cm–1; HRMS (ESI): [M+H+] Calcd for C10H12N3O: 178.0975; Found: 178.0975; M. p. = 101–103 °C.
The titled compound was prepared using Procedure 2, using (R)-2-hydroxy-1-(pyrrolidin-1-yl)propan-1-one (43 mg, 0.3 mmol), pyrazole 4a (61.6 mg, 0.36 mmol, 1.2 equiv), Cs$_2$CO$_3$ (118 mg, 0.36 mmol, 1.2 equiv) in MeCN (1 ml, 0.3M). The mixture was allowed to stir at 70 °C overnight. The crude was obtained as a colorless oil, which was purified by column chromatography (4g cartridge, 0-75% EtOAc in heptane) to give the desired product as a colorless solid (38 mg, 58%). $^1$H NMR (CDCl$_3$, 400MHz): δ (ppm) 8.15 (s, 1H), 7.76 (s, 1H), 5.35 (q, J = 7.0 Hz, 1H), 3.61 (dt, J = 9.8, 6.6 Hz, 1H), 3.52 (dt, J = 9.8, 7 Hz, 1H), 3.50 (t, J = 7.0 Hz, 2H), 1.96-2.06 (m, 2H), 1.85-1.95 (m, 2H), 1.71 (d, J = 7.4 Hz, 3H). $^{13}$C NMR (CDCl$_3$, 101MHz): δ (ppm) 166.7, 141.7, 133.4, 113.3, 93.0, 59.3, 46.7, 46.4, 26.1, 24.1, 18.2; IR (neat): 3115, 2975, 2929, 2879, 2232, 1645, 1542, 1438, 1386, 1359, 1342, 1229, 1188, 1161, 1072, 1004, 967 cm$^{-1}$; M. p. = 116–120 °C; HRMS (ESI): [M+H$^+$] Calcd for C$_{17}$H$_{18}$N$_{3}$O$_3$: 317.4, 313.4, 298.4, 128.4, 127.9, 127.8, 113.0, 92.8, 87.3, 81.1, 78.5, 72.8, 72.5, 71.0, 68.4; IR (neat): 3121, 3065, 3031, 2929, 2878, 2234, 1544, 1495, 1454, 1388, 1359, 1324, 1211, 1134, 1099, 1082, 1058, 1021, 984 cm$^{-1}$; HRMS (EI): [M+H$^+$] Calcd for C$_{17}$H$_{18}$N$_{3}$O$_3$: 312.1343; Found: 312.1342; M. p. = 113–114 °C.

**1-(β-(S,R)-β-(3,2-bj)hexahydrofuro[3,2-b]furan-3-yl)-1H-pyrazole-4-carbonitrile, 3k**

Using substrate 3e in reaction at 90 °C, the desired product was contaminated with some tosylated alcohol. $^1$H NMR (CDCl$_3$, 400MHz): δ (ppm) 7.92 (s, 1H), 7.82 (s, 1H), 7.28 - 7.40 (m, 5H), 4.88 - 4.93 (m, 1H), 4.82 (t, J = 4.70 Hz, 1H), 4.79 (d, J = 11.32 Hz, 1H), 4.70 (d, J = 4.68 Hz, 1H), 4.59 (d, J = 11.71 Hz, 1H), 4.37 (dd, J = 10.54, 5.46 Hz, 1H), 4.26 (dd, J = 10.15, 1.95 Hz, 1H), 4.12 (td, J = 6.63, 4.68 Hz, 1H), 3.91 (dd, J = 8.98, 6.24 Hz, 1H), 3.80 (dd, J = 9.37, 7.02 Hz, 1H). $^{13}$C NMR (CDCl$_3$, 101MHz): δ (ppm) 142.6, 137.4, 133.4, 128.4, 127.9, 127.8, 113.0, 92.8, 87.3, 81.1, 78.5, 72.8, 72.5, 71.0, 68.4; IR (neat): 3121, 3065, 3031, 2929, 2878, 2234, 1544, 1495, 1454, 1388, 1359, 1324, 1211, 1134, 1099, 1082, 1058, 1021, 984 cm$^{-1}$; HRMS (ESI): [M+H$^+$] Calcd for C$_{17}$H$_{18}$N$_{3}$O$_3$: 312.1343; Found: 312.1342; M. p. = 113–114 °C.

**[(S)-1-(1-Oxo-1-(pyrrolidin-1-yl)propan-2-yl)-1H-pyrazole-4-carbonitrile, 3j)**

The titled compound was prepared using Procedure 2, using (R)-2-hydroxy-1-(pyrrolidin-1-yl)propan-1-one (43 mg, 0.3 mmol), pyrazole 4a (61.6 mg, 0.36 mmol, 1.2 equiv), Cs$_2$CO$_3$ (118 mg, 0.36 mmol, 1.2 equiv) in MeCN (1 ml, 0.3M). The mixture was allowed to stir at 70 °C overnight. The crude was obtained as a colorless oil, which was purified by column chromatography (4g cartridge, 0-75% EtOAc in heptane) to give the desired product as a colorless solid (38 mg, 58%). $^1$H NMR (CDCl$_3$, 400MHz): δ (ppm) 7.81 (s, 1H), 7.08 (d, J = 1.2 Hz, 1H), 6.91 (d, J = 1.2 Hz, 1H), 5.58 (tt, J = 7.8, 4.7 Hz, 1H), 4.47 (dd, J = 11.3, 7.4 Hz, 1H), 4.30 (dd, J = 11.3, 4.7 Hz, 1H), 3.47 (dd, J = 16.6, 8.4 Hz, 1H), 3.27 (dd, J = 16.6, 4.9 Hz, 1H). $^{13}$C NMR (CDCl$_3$, 101MHz): δ (ppm) 155.8, 139.8, 129.8, 105.4, 79.5, 51.4, 40.8, 28.3; IR (neat): 3340, 2977, 2932, 1699, 1513, 1453, 1395, 1366, 1273, 1251, 1168, 1092, 1047 cm$^{-1}$; HRMS (ESI): [M+Na$^+$] Calcd for C$_{10}$H$_{17}$N$_{3}$NaO$_2$: 234.1213; Found: 234.1211; M. p. = 49–50 °C.
**tert-Butyl (3-(1H-pyrazol-1-yl)propyl)carbamate, 3n**

The titled compound was prepared using Procedure 2, using tert-butyl (2-hydroxypropyl)carbamate (52.6 mg, 0.3 mmol), pyrazole 4b (48.2 mg, 0.33 mmol, 1.1 equiv), Cs₂CO₃ (118 mg, 0.36 mmol, 1.2 equiv) in MeCN (1 ml, 0.3M). The mixture was allowed to stir at 90 °C overnight. The crude was obtained as a colorless oil, which was purified by column chromatography (4g cartridge, 0-45% EtOAc in heptane) to give the desired product as a colorless oil (45.3 mg, 87%); 1H NMR (CDCl₃, 400MHz): δ (ppm) 7.95 (br. s, 1H), 7.79 (s, 1H), 4.75 (br. m, 1H), 4.22 (t, J=6.6 Hz, 2H), 3.12 (q, J=6.2 Hz, 2H), 2.04 (quint, J=6.5 Hz, 2H), 1.44 (s, 9H); 13C NMR (CDCl₃, 101MHz): δ (ppm) 156.1, 142.3, 134.7, 113.4, 92.1, 79.6, 50.1, 37.2, 30.6, 28.3; IR (neat): 2974, 2928, 2858, 2811, 1687, 1501, 1457, 1416, 1365, 1280, 1247, 1166, 1128, 1004, 864 cm⁻¹; HRMS (ESI): [M+H⁺] Calcd for C₁₁H₁₉N₃O₂: 248.1371; Found: 248.1371; M. p. = 83–84 °C.

**tert-Butyl (3-(4-cyano-1H-pyrazol-1-yl)propyl)carbamate, 3o**

The titled compound was prepared using Procedure 2, using tert-butyl (2-hydroxyethyl)carbamate (48.4 mg, 0.3 mmol), pyrazole 4a (56.5 mg, 0.33 mmol, 1.1 equiv), Cs₂CO₃ (118 mg, 0.36 mmol, 1.2 equiv) in MeCN (1 ml, 0.3M). The mixture was allowed to stir at 90 °C overnight. The crude was obtained as a colorless oil, which was purified by column chromatography (4g cartridge, 0-45% EtOAc in heptane) to give the desired product as a colorless solid (62.5 mg, 83%); 1H NMR (CDCl₃, 400MHz): δ (ppm) 7.36 (d, J=1.6 Hz, 1H), 7.32 (d, J=2.3 Hz, 1H), 5.93-6.01 (m, 2H), 4.17 (ap. q, J=7.0 Hz, 4H), 3.41 (br. m., 8H, major), 2.42 (br. m., 8H, minor), 2.29 (s, 3H), 2.25 (s, 3H), 1.43 (s, 18H); 13C NMR (CDCl₃, 101MHz): δ (ppm) 154.6, 148.5, 138.5, 138.2, 130.2, 105.1, 104.9, 79.7, 57.8, 57.7, 53.1, 52.9, 49.3, 46.5, 43.3 (br), 28.3, 13.5, 11.1; IR (neat): 2975, 2930, 2863, 2813, 1687, 1454, 1416, 1365, 1280, 1247, 1166, 1128, 1004, 864 cm⁻¹; HRMS (ESI): [M+Na⁺] Calcd for C₁₁H₁₉N₃NaO₂: 248.1369; Found: 248.1371; M. p. = 83–84 °C.

**tert-Butyl 4-(2-(3-methyl-1H-pyrazol-1-yl)ethyl)piperazine-1-carboxylate, 3p-1, and tert-butyl 4-(2-(5-methyl-1H-pyrazol-1-yl)ethyl)piperazine-1-carboxylate, 3p-2**

The titled compounds were prepared using Procedure 3, using tert-butyl 4-(2-hydroxyethyl)piperazine-1-carboxylate (100 mg, 0.434 mmol), pyrazole 4g (76.4 mg, 0.48 mmol, 1.1 equiv, mixture of two regioisomers), NaOt-Bu (50.1 mg, 0.52 mmol, 1.2 equiv) in DMF (1.45 ml, 0.3M). The mixture was allowed to stir at 90 °C overnight. The crude was obtained as a colorless oil, which was purified by column chromatography (4g cartridge, 0-50% EtOAc in heptane) to give the desired products as a pale yellow gum (56.5 mg, 0.33 mmol, 1.1 equiv), Cs₂CO₃ (118 mg, 0.36 mmol, 1.2 equiv) in MeCN (1 ml, 0.3M). The mixture was allowed to stir at 90 °C overnight. The crude was obtained as a colorless oil, which was purified by column chromatography (4g cartridge, 0-50% EtOAc in heptane) to give the desired products as pale yellow gums (48.2 mg, 0.33 mmol, 1.1 equiv), Cs₂CO₃ (118 mg, 0.36 mmol, 1.2 equiv) in MeCN (1 ml, 0.3M). The mixture was allowed to stir at 90 °C overnight. The crude was obtained as a colorless oil, which was purified by column chromatography (4g cartridge, 0-50% EtOAc in heptane) to give the desired products as pale yellow solids (110.7 mg, 83%); 1H NMR (CDCl₃, 400MHz): δ (ppm) 7.98 (s, 1H), 7.79 (s, 1H), 4.75 (br. m, 1H), 4.22 (t, J=6.6 Hz, 2H), 3.12 (q, J=6.2 Hz, 2H), 2.04 (quint, J=6.5 Hz, 2H), 1.44 (s, 9H, major), 1.43 (s, 2.25H, minor); 13C NMR (CDCl₃, 101MHz): δ (ppm) 156.1, 142.3, 134.7, 113.4, 92.1, 79.6, 50.1, 37.2, 30.6, 28.3; IR (neat): 2975, 2932, 2875, 1692, 1514, 1453, 1395, 1366, 1276, 1250, 1166, 1091, 1044, 1004, 969 cm⁻¹; HRMS (ESI): [M+Na⁺] Calcd for C₁₂H₁₈N₄NaO₂: 273.1325; Found: 273.1325.
1-(2-(4-(Methylsulfonyl)piperazin-1-yl)ethyl)-1H-pyrazole-4-carbonitrile, 3

The titled compound was prepared using a modified Procedure 2, using 2-(piperazin-1-yl)ethan-1-ol (39.1 mg, 0.3 mmol), pyrazole 4b (113 mg, 0.66 mmol, 2.2 equiv), Cs₂CO₃ (217 mg, 0.66 mmol, 2.2 equiv) in MeCN (1 ml, 0.3M). The mixture was allowed to stir at 90 °C overnight. The crude was obtained as a colorless oil, which was purified by column chromatography (4g cartridge, 0-50% EtOAc in heptane) to give the desired product as a colorless solid (70.4 mg, 82%); ¹H NMR (CDCl₃, 400MHz): δ (ppm) 7.93 (s, 1H), 7.77 (s, 1H), 4.25 (t, J=5.9 Hz, 2H), 3.16–3.24 (m, 4H), 2.85 (t, J=5.9 Hz, 2H), 2.77 (s, 3H), 2.52–2.61 (m, 4H); ¹³C NMR (CDCl₃, 101MHz): δ (ppm) 142.0, 134.8, 113.5, 91.9, 56.6, 52.2, 50.0, 45.7, 34.3; IR (neat): 3340, 2977, 2932, 1699, 1513, 1453, 1395, 1366, 1273, 1251, 1168, 1092, 1047, 973 cm⁻¹; MS(ES⁺): 284.0 (M+H⁺), 306.1 (M+Na⁺).

1-(2-(4-(Methylsulfonyl)piperazin-1-yl)ethyl)-1H-pyrazole-4-carbonitrile, 9

The titled compound was prepared using Procedure 2, using tert-butyl 4-(2-hydroxyethyl)piperazine-1-carboxylate (69.1 mg, 0.3 mmol), sulfonylbenzimidazole 4j (112 mg, 0.36 mmol, 1.2 equiv) in MeCN (1 ml, 0.3M). The mixture was allowed to stir at 90 °C overnight. The crude was obtained as a colorless oil, which was purified by column chromatography (4g cartridge, 0-65% EtOAc in heptane) to give the desired product as a pale yellow solid (120 mg, 89%); ¹H NMR (CDCl₃, 400MHz): δ (ppm) 7.68 (s, 1H), 7.31 (s, 1H), 4.08 (t, J=6.6 Hz, 2H), 3.38 (t, J=4.7 Hz, 4H), 2.75 (s, 3H), 2.66 (t, J=6.6 Hz, 2H), 2.42 (br. s., 4H), 1.43 (s, 9H); ¹³C NMR (CDCl₃, 101MHz): δ (ppm) 155.5, 154.5, 142.7, 135.5, 125.6, 125.4, 119.2, 109.9, 79.6, 56.4, 53.2, 43.4 (br), 42.2, 28.3, 14.7; IR (neat): 2974, 2932, 2861, 2815, 1687, 1457, 1428, 1363, 1300, 1245, 1168, 1127, 1091, 1050, 1005, 864 cm⁻¹; HRMS (ESI): [M+H⁺] Calcd for C₁₉H₁₈Cl₂N₂O₂S: 374.1030; Found: 374.1028; M. p. = 193–196 °C.

tert-Butyl 4-(2-(5,6-dichloro-2-(methylthio)-1H-benzo[d]imidazol-1-yl)ethyl)piperazine-1-carboxylate, 8

The titled compound was prepared using Procedure 2, using (cis)-2-(6-chloro-9H-purin-9-yl)cyclopentan-1-ol (71.6 mg, 0.3 mmol), pyrazole 4a (56.5 mg, 0.36 mmol, 1.2 equiv), Cs₂CO₃ (118 mg, 0.36 mmol, 1.2 equiv) in MeCN (1 ml, 0.3M). The mixture was allowed to stir at 90 °C overnight. The crude was obtained as a colorless solid, which was purified by column chromatography (4g cartridge, 0-90% EtOAc in heptane) to give the desired product as a colorless solid (63.6 mg, 67%); ¹H NMR (CDCl₃, 400MHz): δ (ppm) 8.18 (s, 1H), 5.52–5.64 (m, 1H), 5.03 (td, J=9.0, 5.9 Hz, 1H), 2.91 (s, 3H), 2.47–2.58 (m, 1H), 2.38–2.47 (m, 2H), 1.99–2.23 (m, 3H); ¹³C NMR (CDCl₃, 101MHz): δ (ppm) 154.2, 151.7, 145.8, 145.5, 145.0, 136.2, 123.2, 112.4, 95.9, 83.6, 62.8, 38.1, 31.1, 29.3, 21.4; IR (neat): 3121, 2957, 2925, 2854, 2239, 1604, 1573, 1552, 1502, 1463, 1423, 1405, 1385, 1350, 1332, 1269, 1222, 1172, 1088, 1006, 938, 912, 875 cm⁻¹; HRMS (ESI): [M+H⁺] Calcd for C₁₅H₁₆N₇O₃S: 374.1028; Found: 374.1028; M. p. = 193–196 °C.

tert-Butyl 4-(2-(4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)ethyl)piperazine-1-carboxylate, 10

The titled compound was prepared using Procedure 2, using tert-butyl 4-(2-hydroxyethyl)piperazine-1-carboxylate (69.1 mg, 0.3 mmol), sulfonylpyrrolopyrimidine 4k (83.4 mg, 0.36 mmol, 1.2 equiv), Cs₂CO₃ (118 mg, 0.36 mmol, 1.2 equiv) in MeCN (1 ml, 0.3M). The mixture was allowed to stir at 90 °C overnight. The crude was obtained as a colorless oil, which was purified by column chromatography (4g cartridge, 0-100% EtOAc in heptane) to give the desired product as a colorless solid (63.3 mg, 58%); ¹H NMR (CDCl₃, 400MHz): δ (ppm) 8.60 (s, 1H), 7.33 (d, J=3.5 Hz, 1H), 6.57 (d, J=3.5 Hz, 1H), 4.37 (t, J=6.2 Hz, 2H), 3.31–3.41 (m, 4H), 2.76 (t, J=6.4 Hz, 2H), 2.44 (br t, J=4.3 Hz, 4H), 1.44 (s, 9H); ¹³C NMR (CDCl₃, 101MHz): δ (ppm) 154.6, 152.0, 151.0, 150.4, 129.6, 117.4, 99.2, 79.7, 57.6, 52.9, 43.6; IR (neat): 2975, 2931, 2861, 2814, 1693, 1588, 1544, 1511, 1458, 1420, 1352, 1245, 1169, 1127, 1005 cm⁻¹; HRMS (ESI): [M+H⁺] Calcd for C₁₇H₂₁ClN₀₂: 366.1691; Found: 366.1692; M. p. = 90–92 °C.

S9
**tetr-Butyl 4-(2-(1H-indazol-1-yl)ethyl)piperazine-1-carboxylate, 11**

The titled compound was prepared using Procedure 2, using tert-butyl 4-(2-hydroxyethyl)piperazine-1-carboxylate (100 mg, 0.43 mmol), sulfonylindazole 4i (93.6 mg, 0.48 mmol, 1.1 equiv), Cs₂CO₃ (172 mg, 0.52 mmol, 1.2 equiv) in MeCN (1.45 ml, 0.3M). The mixture was allowed to stir at 90 oC overnight. The crude was obtained as a colorless solid, which was purified by column chromatography (4g cartridge, 0-70% EtOAc in heptane) to give the desired product as an orange oil (70.3 mg, 49%); ¹H NMR (CDCl₃, 400MHz): δ (ppm) 7.97 (d, J=0.8 Hz, 1H), 7.70 (d, J=8.2 Hz, 1H), 7.44 (d, J=8.2 Hz, 1H), 7.36 (ddd, J=8.6, 6.6, 0.8 Hz, 1H), 7.12 (ddd, J=7.8, 6.6, 0.8 Hz, 1H), 4.55 (t, J=6.8 Hz, 2H), 3.40 (br. t., J=4.7 Hz, 4H), 2.94 (t, J=6.8 Hz, 2H), 2.48 (br. t., 4H), 1.43 (s, 9H); ¹³C NMR (CDCl₃, 101MHz): δ (ppm) 154.5, 139.5, 133.1, 126.2, 123.9, 121.0, 120.5, 108.9, 79.7, 57.0, 52.9, 46.3, 43.1 (br. m.), 28.3; IR (neat): 2976, 2931, 2863, 2814, 1687, 1616, 1500, 1461, 1418, 1365, 1243, 1167, 1128, 1003 cm⁻¹; HRMS (ESI): [M+Na⁺] Calcd for C₁₈H₂₆N₄O₂Na: 353.1948; Found: 353.1953.

**tetr-Butyl 4-(2-(1H-indol-1-yl)ethyl)piperazine-1-carboxylate, 12**

The titled compound was prepared using a modified Procedure 3, using tert-butyl 4-(2-hydroxyethyl)piperazine-1-carboxylate (57.6 mg, 0.25 mmol), N-toluenesulfonylindole 4m (81.4 mg, 0.3 mmol, 1.2 equiv), NaOt-Bu (29 mg, 0.3 mmol, 1.2 equiv) in DMF (0.83 ml, 0.3M). The mixture was allowed to stir at 55 oC overnight. In morning, the reaction was observed to be incomplete by LCMS, and was heated at 90°C for another 24h, at which time the mixture was subjected to the standard workup. The crude was obtained as an orange oil, which was purified by column chromatography (4g cartridge, 0-90% EtOAc in heptane) to give the desired product as an orange oil (73.1 mg, 88%); Conditions C furnished the product in 74% yield (68.7 mg); ¹H NMR (CDCl₃, 400MHz): δ (ppm) 8.6, 6.6, 0.8 Hz, 1H), 6.51 (d, J=3.1 Hz, 1H), 4.26 (t, J=4.7 Hz, 4H), 2.77 (t, J=6.8 Hz, 2H), 2.44 (br. s., 4H), 1.49 (s, 9H); ¹³C NMR (CDCl₃, 101MHz): δ (ppm) 154.6, 135.8, 128.5, 121.4, 120.5, 109.3, 101.2, 79.6, 57.7, 53.1, 44.1, 43.5 (br), 28.3; IR (neat): 2975, 2932, 2863, 2814, 1687, 1616, 1500, 1461, 1418, 1365, 1243, 1167, 1128, 1003 cm⁻¹; HRMS (ESI): [M+Na⁺] Calcd for C₁₉H₂₈N₄O₃Na: 372.2278; Found: 372.2278; M. p. = 107–108 °C.

**tetr-Butyl 4-(2-(3-acetyl-1H-indol-1-yl)ethyl)piperazine-1-carboxylate, 13**

The titled compound was prepared using a modified Procedure 2, using tert-butyl 4-(2-hydroxyethyl)piperazine-1-carboxylate (57.6 mg, 0.25 mmol), N-toluenesulfonyl-3-acetylindole 4n (94 mg, 0.3 mmol, 1.2 equiv), Cs₂CO₃ (98.7 mg, 0.3 mmol, 1.2 equiv) in MeCN (0.83 ml, 0.3M). The mixture was allowed to stir at 55 oC overnight. In morning, the reaction was observed to be incomplete by LCMS, and was heated at 90°C for another 24h, at which time the mixture was subjected to the standard workup. The crude was obtained as a colorless solid, which was purified by column chromatography (4g cartridge, 0-90% EtOAc in heptane) to give the desired product as a yellow solid (81 mg, 88%); Conditions C furnished the product in 74% yield (68.7 mg); ¹H NMR (CDCl₃, 400MHz): δ (ppm) 8.34-8.40 (m, 1H), 7.81 (s, 1H), 7.32-7.37 (m, 1H), 7.26-7.32 (m, 2H), 4.23 (t, J=6.6 Hz, 2H), 3.41 (br. t., J=4.3 Hz, 4H), 2.77 (t, J=6.4 Hz, 2H), 2.50 (s, 3H), 2.42 (br. s., 4H), 1.46 (s, 9H); ¹³C NMR (CDCl₃, 101MHz): δ (ppm) 192.8, 154.5, 136.6, 135.3, 126.1, 123.1, 122.5, 122.4, 116.9, 109.5, 79.6, 57.1, 53.0, 44.5, 43.5 (br), 28.3, 27.4; IR (neat): 2975, 2932, 2861, 2814, 1684, 1641, 1527, 1461, 1419, 1389, 1365, 1291, 1243, 1220, 1167, 1127, 1003, 921 cm⁻¹; HRMS (ESI): [M+H⁺] Calcd for C₁₉H₂₆N₄O₃: 372.2282; Found: 372.2278; M. p. = 107–108 °C.

**V. Supplementary Experiments on 3-Substituted Sulfonylpyrazoles**

Additional experiments utilizing 3- and 5-substituted sulfonylpyrazoles were conducted to establish whether sulfonylpyrazole regiosomeric ratio had any effect on the outcome of the alkylation reaction (Table 1). With 3-methyl pyrazole 4g nearly 1:1 regiosomeric mixtures of sulfonylated and alkylated pyrazole were obtained (3p, Entry 1). In the case of 3-phenyl pyrazole, sulfonylated regioisomers of 4h could be separated. Reacting single regioisomers of 4h (4h-1 and 4h-2) with 2a furnished products 3q-1 and 3q-2 in identical regiosomeric ratio, demonstrating that mesyl transfer and nucleophilic displacement were discrete reaction steps (Entries 2-4). The base and solvent used did affect the ratio of the two products, with Cs₂CO₃ offering worse regioselectivity (Entry 5). This trend was consistent in reaction of N-tosyl-3-phenylpyrazole 4i, even though a single tosylated regioisomer was formed upon tosylation (Entries 6,7). Further examination of the dependence of regioselectivity on the solvent and base could furnish more
insight into the observed trend. It is possible that better regiocontrol could be imposed in substrates bearing more sterically demanding or electronically biased substituents.

**Table 1**: Reaction of 3- and 5-substituted pyrazoles.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>4 (\text{rr}^b)</th>
<th>R</th>
<th>R'</th>
<th>Base, Solvent</th>
<th>Yield (%)</th>
<th>3x-1:3x-2(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1:1</td>
<td>Me</td>
<td>Me</td>
<td>NaOr-Bu, DMF</td>
<td>87</td>
<td>1.2:1</td>
</tr>
<tr>
<td>2</td>
<td>1:0</td>
<td>Me</td>
<td>Ph</td>
<td>NaOr-Bu, DMF</td>
<td>78</td>
<td>4.5:1</td>
</tr>
<tr>
<td>3</td>
<td>0:1</td>
<td>Me</td>
<td>Ph</td>
<td>NaOr-Bu, DMF</td>
<td>76</td>
<td>4.5:1</td>
</tr>
<tr>
<td>4</td>
<td>1.7:1</td>
<td>Me</td>
<td>Ph</td>
<td>NaOr-Bu, DMF</td>
<td>80</td>
<td>4.6:1</td>
</tr>
<tr>
<td>5</td>
<td>1:0</td>
<td>Me</td>
<td>Ph</td>
<td>Cs(_2)CO(_3), MeCN</td>
<td>-</td>
<td>2.7:1</td>
</tr>
<tr>
<td>6</td>
<td>1:0</td>
<td>(p)-Tol</td>
<td>Ph</td>
<td>NaOr-Bu, DMF</td>
<td>-</td>
<td>3.9:1</td>
</tr>
<tr>
<td>7</td>
<td>1:0</td>
<td>(p)-Tol</td>
<td>Ph</td>
<td>Cs(_2)CO(_3), MeCN</td>
<td>-</td>
<td>2.6:1</td>
</tr>
</tbody>
</table>

\(^a\) See Table 1 for reaction conditions; \(^b\) 4 \(\text{rr}\) refers to 3-R’ versus 5-R’ regioisomeric ratio of 4l, 4m, and 4n; \(^c\) Isolated yields; \(^d\) Regioisomer ratio determined from NMR of crude reaction mixture.

VI. References

1-(Methylsulfonyl)-1H-pyrazole-4-carbonitrile, 4a

$^1$H NMR

$^1$C NMR
1-(Methylsulfonyl)-1H-pyrazole, 4b

\[^1\text{H} \text{NMR}\]

```
\[\text{Chemical Shift (ppm)}\]
```

```
\[3.34\]
```

```
\[0.90\ 0.85\ 0.80\ 0.75\ 0.70\ 0.65\ 0.60\ 0.55\ 0.50\ 0.45\ 0.40\ 0.35\ 0.30\ 0.25\ 0.20\ 0.15\ 0.10\ 0.05\ 0.00\]
```

```
\[0\ 1.0\ 2.0\ 3.0\ 4.0\ 5.0\ 6.0\ 7.0\ 8.0\ 9.0\ 9.5\]
```

```
\[\text{Absolute Intensity}\]
```

```
\[\text{50.00}\ 6.00\ 7.00\ 8.00\ 8.50\ 9.00\ 9.50\ 10.00\]
```

```
\[\text{0.1}\ 0.2\ 0.3\ 0.4\ 0.5\ 0.6\ 0.7\ 0.8\ 0.9\ 1.0\]
```

```
\[\text{0.00}\ 0.05\ 0.10\ 0.15\ 0.20\ 0.25\ 0.30\ 0.35\ 0.40\ 0.45\ 0.50\ 0.55\ 0.60\ 0.65\ 0.70\ 0.75\ 0.80\ 0.85\ 0.90\ 0.95\ 1.00\]
```

```
\[\text{3.34}\]
```

```
\[\text{Chemical Shift (ppm)}\]
```

```
\[0.90\ 0.85\ 0.80\ 0.75\ 0.70\ 0.65\ 0.60\ 0.55\ 0.50\ 0.45\ 0.40\ 0.35\ 0.30\ 0.25\ 0.20\ 0.15\ 0.10\ 0.05\ 0.00\]
```
1-(Methylsulfonyl)-4-(trifluoromethyl)-1H-pyrazole, 4c

$^1$H NMR

$^{13}$C NMR
4-Iodo-1-(methylsulfonyl)-1H-pyrazole, 4d

$^1$H NMR

$^{13}$C NMR
1-Tosyl-1H-pyrazole-4-carbonitrile, 4e

$^1$H NMR

$^{13}$C NMR
1-((Trifluoromethyl)sulfonyl)-1\textit{H}-pyrazole-4-carbonitrile, 4f

\textbf{\textsuperscript{1}H NMR}

\textbf{\textsuperscript{13}C NMR}
5-Methyl-1-(methylsulfonyl)-1H-pyrazole and 3-methyl-1-(methylsulfonyl)-1H-pyrazole, 4g

**1H NMR**

![1H NMR graph](image)

**13C NMR**

![13C NMR graph](image)
1-(Methylsulfonyl)-3-phenyl-1H-pyrazole, 4h-1

\(^1\)H NMR

\(^1\)C NMR
1-(Methylsulfonyl)-5-phenyl-1H-pyrazole, 4h-2

$^1$H NMR

$^{13}$C NMR
3-Phenyl-1-tosyl-1H-pyrazole, 4i

$^1$H NMR

$^{13}$C NMR
5,6-Dichloro-1-(methylsulfonyl)-2-(methylthio)-1\textit{H}-benzo[\textit{d}]imidazole, 4j

\textbf{\textsuperscript{1}H NMR}

\textbf{\textsuperscript{13}C NMR}
4-Chloro-7-(methylsulfonyl)-7H-pyrrolo[2,3-d]pyrimidine, 4k

$^1$H NMR

$^{13}$C NMR
1-(Methylsulfonyl)-1H-indazole, 4l

$^1H$ NMR

Chemical Shift (ppm)
1-Tosyl-1H-indole, 4m

$^1$H NMR
1-(1-Tosyl-1H-indol-3-yl)ethan-1-one, 4n

$^1$H NMR
**tert-Butyl 4-(2-(4-cyano-1H-pyrazol-1-yl)ethyl)piperazine-1-carboxylate, 3a**

**$^1$H NMR**

$^1$H NMR spectrum showing various peaks at different chemical shifts.

**$^{13}$C NMR**

$^{13}$C NMR spectrum showing various peaks at different chemical shifts.
** tert-Butyl 4-(2-(1H-pyrazol-1-yl)ethyl)piperazine-1-carboxylate 3b **

$^{1}$H NMR

$^{13}$C NMR
**tert-Butyl 4-(2-(4-(trifluoromethyl)-1H-pyrazol-1-yl)ethyl)piperazine-1-carboxylate, 3c**

**$^1$H NMR**

![1H NMR spectrum](image)

**$^{13}$C NMR**

![$^{13}$C NMR spectrum](image)
tert-Butyl 4-(2-(4-iodo-1H-pyrazol-1-yl)ethyl)piperazine-1-carboxylate, 3d

$^1$H NMR

$^{13}$C NMR
1-(2-(Pyridin-4-yl)ethyl)-1H-pyrazole-4-carbonitrile, 3e

**1H NMR**

![1H NMR spectrum](image)

**13C NMR**

![13C NMR spectrum](image)
1-((6-Chloropyridin-3-yl)methyl)-1H-pyrazole-4-carbonitrile, 3f

$^1$H NMR

$^{13}$C NMR
1-(3-Hydroxy-3-methylbutyl)-1\textit{H}-pyrazole-4-carbonitrile, 3g

\textbf{\textsuperscript{1}H NMR}

\textbf{\textsuperscript{13}C NMR}
1-Cyclopentyl-1\textit{H}-pyrazole-4-carbonitrile, 3h

$^1$H NMR

$^1$C NMR
1-(Tetrahydro-2H-pyran-4-yl)-1H-pyrazole-4-carbonitrile, 3i

$^1$H NMR

$^1$C NMR
(S)-1-(1-Oxo-1-(pyrrolidin-1-yl)propan-2-yl)-1H-pyrazole-4-carbonitrile, 3j

$^1$H NMR

$^1$C NMR
1-((3S,6R)-6-(Benzyloxy)hexahydrofuro[3,2-b]furan-3-yl)-1H-pyrazole-4-carbonitrile, 3k

**$^1$H NMR**

![1H NMR spectrum](image)

**$^{13}$C NMR**

![$^{13}$C NMR spectrum](image)
(R)-1-(6,7-Dihydro-5H-pyrrolo[1,2-a]imidazol-6-yl)-1H-pyrazole-4-carbonitrile, 3l

$^1$H NMR

$^{13}$C NMR
tert-Butyl (2-(1H-pyrazol-1-yl)ethyl)carbamate, 3m

**$^1$H NMR**

![H NMR spectrum](image)

**$^{13}$C NMR**

![C NMR spectrum](image)
tert-Butyl (3-(1H-pyrazol-1-yl)propyl)carbamate, 3n

$^1$H NMR

$^{13}$C NMR
**tert-Butyl (3-(4-cyano-1H-pyrazol-1-yl)propyl)carbamate, 3o**

**$^1$H NMR**

[Chemical shift diagram for $^1$H NMR]

**$^{13}$C NMR**

[Chemical shift diagram for $^{13}$C NMR]
tert-butyl 4-(2-(3-methyl-1H-pyrazol-1-yl)ethyl)piperazine-1-carboxylate, 3p-1, and tert-butyl 4-(2-(5-methyl-1H-pyrazol-1-yl)ethyl)piperazine-1-carboxylate, 3p-2

$^1$H NMR

$^{13}$C NMR
**tert-Butyl 4-[(2-(3-phenyl-1H-pyrazol-1-yl)ethyl)piperazine-1-carboxylate, 3q-1 and tert-butyl 4-[(2-(5-phenyl-1H-pyrazol-1-yl)ethyl)piperazine-1-carboxylate, 3q-2**

**1H NMR**

![1H NMR spectrum]

**13C NMR**

![13C NMR spectrum]
1-(2-(4-(Methylsulfonyl)piperazin-1-yl)ethyl)-1H-pyrazole-4-carbonitrile, 3r

$^1$H NMR

$^{13}$C NMR
(1R,2R)-2-((4-Cyano-1H-pyrazol-1-yl)-9H-purin-9-yl)cyclopentyl methanesulfonate, 8

$^1$H NMR

$^{13}$C NMR
*tert*-Butyl 4-(2-(5,6-dichloro-2-(methylthio)-1H-benzo[d]imidazol-1-yl)ethyl)piperazine-1-carboxylate, 9

**1H NMR**

![1H NMR spectrum](image)

**13C NMR**

![13C NMR spectrum](image)
tert-Butyl 4-(2-(4-chloro-$7H$-pyrrolo[2,3-d]pyrimidin-7-yl)ethyl)piperazine-1-carboxylate, 10

$^1$H NMR

$^{13}$C NMR
tert-Butyl 4-(2-(1H-indazol-1-yl)ethyl)piperazine-1-carboxylate, 11

$^1$H NMR

$^{13}$C NMR
**tert-Butyl 4-(2-(1H-indol-1-yl)ethyl)piperazine-1-carboxylate, 12**

**$^1$H NMR**

![H NMR spectrum](image-url)

**$^{13}$C NMR**

![C NMR spectrum](image-url)
**tert-Butyl 4-(2-(3-acetyl-1H-indol-1-yl)ethyl)piperazine-1-carboxylate, 13**

**1H NMR**

**13C NMR**