Supporting Information

Novel *N*-Aryl- and Heteroaryl-Sulfamide Synthesis *via* Palladium Cross Coupling

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General

Anhydrous dioxane was purchased from Fluka, Cs_2CO_3 (99.9%) and $\text{Pd}_2(\text{dba})_3$ from Aldrich and phosphine ligands from Strem. The secondary sulfamides employed in the palladium coupling reaction were prepared following literature procedures. Solvent removal was carried out using a rotary evaporator connected to a dry ice condenser. Purification was performed by flash column chromatography on silica cartridges or by preparative HPLC using a Waters Fraction Lynx system with Micromass ZQ (MS) and an Xterra Prep MS C_8 column, 5 μm , 19 x 50mm.

Melting points are uncorrected. ^1H and ^{13}C NMR spectra were obtained from either a 300 MHz (^1H : 300 MHz, ^{13}C : 75 MHz) or 400 MHz (^1H : 400 MHz, ^{13}C : 100 MHz) Varian Unity Inova spectrometer. ^1H and ^{13}C shifts are given in ppm, δ scale and are measured relative to tetramethylsilane as standard. Mass spectra were recorded on a Hewlett Packard HP 6890 or HP5973 MSD instrument.

General procedure: A 25 ml round bottom flask was charged with sulfamide **3** (166 mg, 1 mmol), 6-chloronicotinonitrile **4** (138 mg, 1 mmol), Cs_2CO_3 (456 mg, 1.4 mmol), N,P ligand **7** (30 mg, 75 μmol) and $\text{Pd}_2(\text{dba})_3$ (23 mg, 25 μmol). The flask was flushed with N_2 for 30s and charged with anhydrous dioxane (2.5 ml). The flask was heated at 80°C for 18 h under nitrogen atmosphere. The reaction mixture was then allowed to cool to room temperature, diluted with dichloromethane (5 ml) and acetic acid was added (500 μl). After filtration through a cotton wool plug, the crude mixture was concentrated under *vacuum* and purified by reverse phase HPLC to afford the product **5** in 74% yield.

***N*-(5-cyanopyridin-2-yl)morpholine-4-sulfonamide**

^1H NMR (300 MHz, DMSO) δ 8.65 (d, J = 2.3 Hz, 1H), 8.06 (dd, J = 8.8, 2.3 Hz, 1H), 7.08 (d, J = 8.8 Hz, 1H), 3.60 (t, J = 4.7 Hz, 4H), 3.16 (t, J = 4.7 Hz, 4H); ^{13}C NMR (75 MHz, DMSO) δ 155.85, 151.69, 141.11, 126.51, 117.67, 111.75, 65.58, 46.19; HRMS (ES) m/z calcd for $(\text{C}_{10}\text{H}_{12}\text{N}_4\text{O}_3\text{S} + \text{H})^+$ 269.0708, found 269.0716. Pale yellow solid m.p. 228-230 °C.

***N'*-(5-cyanopyridin-2-yl)-*N,N*-dimethylsulfamide**

^1H NMR (400 MHz, DMSO) δ 8.68 (d, J = 2.1 Hz, 1H), 8.09 (dd, J = 8.7, 2.1 Hz, 1H), 7.06 (d, J = 8.7 Hz, 1H), 2.80 (s, 6H); ^{13}C NMR (100 MHz, DMSO/ ND_4OD) δ 164.4, 152.6, 137.5, 120.0, 113.4, 92.7, 38.5; HRMS (ES) m/z calcd for $(\text{C}_8\text{H}_{10}\text{N}_4\text{O}_2\text{S} + \text{H})^+$ 227.0602, found 269.0612. Pale yellow solid m.p. 191-193 °C.

***N'*-(5-cyanopyridin-2-yl)-*N*-[2-(dimethylamino)ethyl]-*N*-methylsulfamide**

^1H NMR (300 MHz, DMSO) δ 8.31 (d, J = 2.5 Hz, 1H), 6.75 (d, J = 9.0 Hz, 1H), 7.56 (dd, J = 9.0, 2.5 Hz, 1H), 3.09 (t, J = 6.7 Hz, 2H), 2.61 (s, 3H), 2.52 (t, J = 6.7 Hz, 2H), 2.26 (s, 6H); ^{13}C NMR (75 MHz, DMSO) δ 172.2, 163.5, 152.6, 137.9, 119.7, 113.4, 56.74, 47.8, 44.7, 35.9; HRMS (ES) m/z calcd for $(\text{C}_{11}\text{H}_{17}\text{N}_5\text{O}_2\text{S} + \text{H})^+$ 284.1181, found 284.1172. Colourless solid m.p. 143-145 °C.

1-[[5-(5-cyanopyridin-2-yl)amino]sulfonyl]-*N,N*-dimethylprolinamide

^1H NMR (300 MHz, DMSO) δ 11.10 (s, 1H), 8.77 (d, J = 2.1 Hz, 1H), (dd, J = 8.9, 2.1 Hz, 1H), 7.05 (d, J = 8.9 Hz, 1H), 5.22 (d, J = 5.7 Hz, 1H), 3.43-3.25 (m, 3H), 3.06 (s, 3H), 2.82 (s, 3H), 2.12-1.68 (m, 4H); ^{13}C NMR (75 MHz, DMSO) δ 171.1, 154.6, 152.1, 141.4, 117.4, 111.2, 101.5, 59.1, 48.5, 36.6, 35.4, 30.1, 24.4. HRMS (ES) m/z calcd for $(\text{C}_{13}\text{H}_{17}\text{N}_5\text{O}_3\text{S} + \text{H})^+$ 324.1130, found 324.1125. Colourless solid m.p. 77-79 °C.

***N*-benzyl-*N'*-(5-cyanopyridin-2-yl)-*N*-methylsulfamide**

^1H NMR (300 MHz, DMSO) δ 8.74 (d, J = 2.2 Hz, 1H), 8.13 (dd, J = 8.8, 2.2 Hz, 1H), 7.37 - 7.27 (m, 5H), 7.06 (d, J = 8.8 Hz, 1H), 4.40 (s, 2H), 4.40 (s, 2H); ^{13}C NMR (75 MHz, DMSO) δ 154.9, 152.1, 141.5, 136.7, 128.5, 128.2, 127.9, 127.5, 117.4, 111.1, 54.2, 34.9; HRMS (ES) m/z calcd for $(\text{C}_{14}\text{H}_{14}\text{N}_4\text{O}_2\text{S} + \text{H})^+$ 303.0915, found 303.0910. Pale yellow solid m.p. 209-211 °C.

***N'*-(5-cyanopyridin-2-yl)-*N*-methyl-*N*-phenylsulfamide**

^1H NMR (300 MHz, DMSO) δ 8.75 (d, J = 1.7 Hz, 1H), 8.09 (dd, J = 8.8, 2.3 Hz, 1H), 7.39 - 7.23 (m, 5H), 6.95 (d, J = 8.7 Hz, 1H), 3.37 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ 154.5, 151.9, 141.5, 141.4, 129.1, 126.9, 125.9, 117.3, 111.2, 101.9, 39.1; HRMS (ES) m/z calcd for $(\text{C}_{13}\text{H}_{12}\text{N}_4\text{O}_2\text{S} + \text{H})^+$ 289.0759, found 289.0773. Colourless solid m.p. 191-193 °C.

***N*-(5-nitropyridin-2-yl)morpholine-4-sulfonamide**

^1H NMR (400 MHz, DMSO) δ 11.68 (s, 1H), 9.08 (d, J = 2.6 Hz, 1H), 8.47 (dd, J = 9.2, 2.6 Hz, 1H), 7.14 (d, J = 9.2 Hz, 1H), 3.61 (t, J = 4.7 Hz, 1H), 3.22 (t, J = 4.7 Hz, 1H); ^{13}C NMR (100 MHz, DMSO) δ 189.2, 156.7, 149.1, 137.3, 114.2, 65.5, 46.3. HRMS (ES) m/z calcd for $(\text{C}_9\text{H}_{12}\text{N}_4\text{O}_5\text{S} + \text{H})^+$ 289.0606, found 289.0596. Pale yellow solid m.p. 246-248 °C.

Ethyl 6-[(morpholin-4-ylsulfonyl)amino]nicotinate

^1H NMR (300 MHz, DMSO) δ 11.75 (bs, 1H), 8.62 (bs, 1H), 8.14 (dd, J = 8.9, 2.3 Hz, 1H), 7.17 (d, J = 8.9 Hz, 1H), 4.30 (q, J = 7.1 Hz, 2H), 3.60 (t, J = 4.7 Hz, 5H), 3.14 (t, J

= 4.7 Hz, 5H), 1.31 (t, J = 7.1 Hz, 4H); ^{13}C NMR (75 MHz, DMSO) δ 164.1, 155.9, 146.81, 139.4, 117.6, 112.6, 65.5, 60.8, 46.2, 14.1; HRMS (ES) m/z calcd for $(\text{C}_{12}\text{H}_{17}\text{N}_3\text{O}_5\text{S} + \text{H})^+$ 316.0967, found 316.0965. Colourless solid m.p. 130-132 °C.

***N*-(5-formylpyridin-2-yl)morpholine-4-sulfonamide**

^1H NMR (400 MHz, DMSO) δ 9.83 (s, 1H), 8.63 (d, 2.1 Hz, 1H), 8.07 (dd, J = 9.0, 2.1 Hz, 1H), 7.24 (d, J = 9.0 Hz, 1H), 3.63 (t, J = 4.7 Hz, 1H), 3.13 (q, J = 4.7 Hz, 1H); ^{13}C NMR (100 MHz, DMSO/ ND_4OD) δ 189.1, 166.2, 154.9, 134.0, 120.9, 113.8, 65.7, 46.5; HRMS (ES) m/z calcd for $(\text{C}_{10}\text{H}_{13}\text{N}_3\text{O}_4\text{S} + \text{H})^+$ 272.0705, found 269.0723. Pale yellow solid m.p. 216-218 °C.

***N*-[4-(trifluoromethyl)pyrimidin-2-yl]morpholine-4-sulfonamide**

^1H NMR (300 MHz, DMSO) δ 11.74 (s, 1H), 8.94 (d, J = 5.0 Hz, 1H), 7.56 (d, J = 5.0 Hz, 1H), 3.61 (t, J = 4.7 Hz, 4H), 3.30 (t, J = 4.7 Hz, 5H); ^{13}C NMR (75 MHz, DMSO) δ 162.2, 158.1, 154.7, 120.4, 110.78, 65.83, 46.31; HRMS (ES) m/z calcd for $(\text{C}_{12}\text{H}_{17}\text{N}_3\text{O}_5\text{S} + \text{H})^+$ 313.0582, found 313.0585. Colourless solid m.p. 191-193 °C.

***N*-[2-(1H-imidazol-1-yl)pyrimidin-4-yl]morpholine-4-sulfonamide**

^1H NMR (300 MHz, DMSO) δ 8.38 (s, 1H), 7.93 (d, J = 6.2 Hz, 1H), 7.79 (s, 1H), 7.01 (s, 1H), 6.68 (d, J = 6.2 Hz, 1H), 3.59 (t, J = 4.6 Hz, 4H), 2.96 (t, J = 4.6 Hz, 4H); ^{13}C NMR (75 MHz, DMSO) δ 167.43, 154.20, 135.27, 129.05, 126.42, 116.57, 108.66, 65.75, 46.56; HRMS (ES) m/z calcd for $(\text{C}_{11}\text{H}_{14}\text{N}_6\text{O}_3\text{S} + \text{H})^+$ 311.0926, found 311.0942. Pale yellow solid m.p. 99-101 °C.

***N*-thieno[2,3-*d*]pyrimidin-4-ylmorpholine-4-sulfonamide**

¹H NMR (400 MHz, DMSO) δ 8.13 (s, 1H), 7.26 (d, *J* = 5.9 Hz, 1H), 7.21 (d, *J* = 5.9 Hz, 1H), 3.61 (t, *J* = 4.7 Hz, 4H), 3.04 (t, *J* = 4.7 Hz, 4H); ¹³C NMR (100 MHz, DMSO/ND₄OD) δ 164.8, 160.9, 153.6, 121.5, 121.3, 119.7, 65.8, 46.9; HRMS (ES) *m/z* calcd for (C₁₀H₁₂N₄O₃S₂ + H)⁺ 301.0429, found 301.0437. Pale yellow solid m.p. 227-229 °C.

***N*-(2,6-dimethoxypyrimidin-4-yl)morpholine-4-sulfonamide**

¹H NMR (400 MHz, DMSO) δ 11.00 (s, 1H), 3.87 (s, 3H), 3.86 (s, 3H) 3.61 (t, *J* = 4.7 Hz, 4H), 3.10 (t, *J* = 4.7 Hz, 4H); ¹³C NMR (75 MHz, DMSO) δ 171.7, 164.2, 160.7, 84.5, 65.5, 54.5, 53.8, 46.2; HRMS (ES) *m/z* calcd for (C₁₀H₁₆N₄O₅S + H)⁺ 305.0919, found 305.0922. Colourless solid m.p. 190-191 °C.

***N*-(3-cyanopyrazin-2-yl)morpholine-4-sulfonamide**

¹H NMR (300 MHz, DMSO/ND₄OD) δ 8.08 (d, *J* = 2.3 Hz, 1H), 7.62 (d, *J* = 2.3 Hz, 1H), 3.61 (t, *J* = 4.7 Hz, 4H), 3.00 (t, *J* = 4.7 Hz, 4H); ¹³C NMR (100 MHz, DMSO/ND₄OD) δ 159.4, 145.9, 130.5, 118.2, 117.7, 65.7, 46.8; HRMS (ES) *m/z* calcd for (C₉H₁₁N₅O₃S + H)⁺ 270.0661, found 270.0661. Pale yellow solid m.p. 222-224 °C.

***N*-[3-(trifluoromethyl)quinoxalin-2-yl]morpholine-4-sulfonamide**

¹H NMR (300 MHz, DMSO) δ 7.94 (d, 7.79, *J* = 7.6 Hz), 7.75 (d, 7.79, *J* = 7.6 Hz), 1H (t, *J* = 7.6 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 1H), 3.69 (t, *J* = 4.7 Hz, 4H), 3.09 (t, *J* = 4.7 Hz, 4H); HRMS (ES) *m/z* calcd for (C₁₃H₁₃F₃N₄O₃S + H)⁺ 363.0738, found 363.0721. Pale yellow solid m.p. 193-195 °C.

***N*-(4-nitrophenyl)morpholine-4-sulfonamide**

^1H NMR (300 MHz, DMSO) δ 10.91 (s, 1H), 8.21 (d, J = 9.2 Hz, 2H), 7.35 (d, J = 9.2 Hz, 2H), 3.56 (t, J = 4.7 Hz, 4H), 3.13 (t, J = 4.7 Hz, 4H); ^{13}C NMR (75 MHz, DMSO) δ 145.54, 141.81, 125.32, 117.70, 65.33, 45.92 (s, 2H); HRMS (ES) m/z calcd for ($\text{C}_{10}\text{H}_{13}\text{N}_3\text{O}_5\text{S} + \text{H}$) $^+$ 288.0654, found 228.0650. Pale yellow solid m.p. 195-197 °C.

***N*-(4-cyanophenyl)morpholine-4-sulfonamide**

^1H NMR (300 MHz, DMSO) δ 10.68 (s, 1H), 7.77 (d, J = 8.7 Hz, 2H), 7.31 (d, J = 8.7 Hz, 2H), 3.55 (t, J = 4.7 Hz, 4H), 3.10 (t, J = 4.7 Hz, 4H); ^{13}C NMR (75 MHz, DMSO) δ 143.1, 133.6, 118.9, 118.2, 104.6, 63.3, 45.9; HRMS (ES) m/z calcd for ($\text{C}_{11}\text{H}_{13}\text{N}_3\text{O}_3\text{S} + \text{H}$) $^+$ 268.0756, found 268.0764. Colourless solid m.p. 161-163 °C.

***N*-(4-formylphenyl)morpholine-4-sulfonamide**

^1H NMR (300 MHz, DMSO) δ 9.58 (s, 1H), 7.50 (d, J = 8.7 Hz, 2H), 6.97 (d, J = 8.7 Hz, 2H), 3.54 (t, J = 4.7 Hz, 5H), 2.91 (t, J = 4.7 Hz, 4H); ^{13}C NMR (75 MHz, DMSO) δ 189.5, 172.5, 130.7, 119.7, 119.1, 65.8, 46.5; HRMS (ES) m/z calcd for ($\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_4\text{S} + \text{H}$) $^+$ 271.0752, found 271.0754. Pale yellow solid m.p. 135-137 °C.

Ethyl 4-[(morpholin-4-ylsulfonyl)amino]benzoate

^1H NMR (300 MHz, DMSO) δ 10.52 (s, 1H), 7.90 (d, J = 8.8 Hz, 2H), 7.29 (d, J = 8.8 Hz, 2H), 4.28 (q, J = 7.1 Hz, 2H), 3.53 (t, J = 4.7 Hz, 4H), 3.10 (t, J = 4.7 Hz, 4H), 1.30 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, DMSO) δ 165.3, 143.0, 130.5, 124.1, 117.82,

65.3, 60.5, 45.9, 14.22; HRMS (ES) m/z calcd for $(C_{13}H_{18}N_2O_2S + H)^+$ 315.1014, found 315.1007. Pale yellow solid m.p. 93-95 °C.