Supporting Information

Structure-Based Ligand Design of Novel Bacterial RNA Polymerase Inhibitors

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General Information and Instrumentation

All reactions were carried out under nitrogen unless otherwise specified. All reagents obtained from commercial suppliers (eg. Aldrich) were used without further purification. All solvents were distilled before use or obtained dry from commercial suppliers; petrol refers to petroleum ether (bp. 40-60 °C). Analytical TLC was performed using silica gel pre-coated plates (Merck) and visualized using UV irradiation. Flash column chromatography was carried out on silica gel 60 (230-400 mesh, Merck). Solvents were removed under reduced pressure using a Buchi rotary evaporator at diaphragm pump pressure. Samples were freed of remaining traces of solvents under high vacuum.

^{1}H and ^{13}C NMR spectra were measured on a Bruker DPX300 Fourier transform spectrometer or a Bruker Avance 500 using an internal deuterium lock. Chemical shifts were reported in parts per million (ppm) downfield from TMS in δ units and coupling constants (*J*) are given in hertz (Hz). TMS as defined as 0 ppm for ^{1}H NMR spectra and the centre line of the triplet of $CDCl_3$ was also defined as 77.10 ppm for ^{13}C NMR spectra. When displaying the ^{1}H NMR data the following abbreviations will be used; s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet. Proton and carbon assignment has been based on HMQC and HMBC spectra analysis where appropriate.

Infrared (IR) spectra were recorded as thin films using sodium chloride plates or solid samples on a Perkin Elmer Spectrum One FT-IR spectrophotometer. Vibrational frequencies are reported in wavenumbers (cm^{-1}).

Mass spectra (HRMS) was recorded in house using a Micromass GCT Premier, using electron impact ionization (EI) or a Bruker Daltonics micrOTOF, using electron spray ionization (ES). All quoted masses refer to the ^{79}Br isotope. Elemental analysis was carried out using a Carlo Erba 1108 Elemental Analyzer. Determination of halogens and sulfur were carried out using the Schoniger Oxygen Flask combustion method followed by the relevant titration for the particular halogen.

HPLC analyses were carried out on a Dionex HPLC system using a Thermo Electron Corporation Hyperprep HS C18 column (8 μm, 250 x 4.6 mm) and diode array as a detector. A gradient of water and acetonitrile (5-95 %) was used as solvent at a flow rate of 1 ml/min.

Preparative HPLC, unless otherwise stated, was carried out using a Gilson HPLC system. This consists of a Thermo Hypersil, Hyperprep HS C18 column (8 μm, 250 x 21.2 mm) or Thermo Hypersil-Keystone, Hyperprep C18 column (8 μm, 250 x 21.2 mm) and a diode array detector. A gradient of water and acetonitrile (5-95%) was used as solvent at a flow rate of 20 ml/ min. LCMS were recorded using an Agilent 1200 Series HPLC and Bruker HCT Ultra mass spectrometer, using Method A. Method A consists of a short C_{18} column using an acetonitrile-water mobile phase with a formic acid buffer and positive ion electrospray ionization.

Melting points were determined on a Reichert Hot Stage or Griffin Melting Point apparatus. Melting points obtained were uncorrected.

E. coli RNA Polymerase Assay

The ability of compounds to inhibit *E. coli* RNAP was determined using a 384-well plate (Greiner 781096) *in vitro* assay. Compounds, in a final concentration of 3% DMSO, were pre-incubated with buffer comprising 40mM TrisHCl, pH 7.5, 50 mM KCl, 10mM $MgCl_2$, 8mM DTT, 0.01% Triton X-100 with 20 U/ml *E. coli* core RNA polymerase and 125 ng/ml Kool^{TM} NC-45^{TM} Universal RNA polymerase template (Epicentre, Madison, WI, USA). The reaction was initiated with the addition of 0.5 mM rNTPs (Roche Diagnostics Ltd., UK) and incubated for 2 h at 37 ˚C. RNA products were detected using SYBR Green I dye (Invitrogen Ltd., UK) in a PerkinElmer 2103 Multilabel reader with excitation and emission at 485nm and 531 nm respectively. Assays were performed in duplicate and the % activity of compounds at 100 μM was determined after deduction of background (no rNTPs) and comparison with no compound/DMSO control, designated having 100% activity. The IC_{50} value against *E. coli* RNAP was determined using a 10-point 1:3 dilution series for each compound and the data was analyzed using GraphPad Prism 4. Table 1 (main text) shows, for each compound, the mean IC_{50} value $\pm$ SE of 3 independent measurements.

Strains and isolates for MIC determination

Strain	Description	Reference/Source
S. aureus SH1000	*rsbU*$^+$ derivative of 8325-4, common lab strain with genome sequenced.	Horsburgh *et al*,[1]
B. subtilis 1S34	Parental strain of *B. subtilis* antibiotic biosensors, asporogenous derivative of *B. subtilis* 168 (a commonly used lab strain).	B. G. S. C (Ohio)[2]
E. coli 1411	*lacI3, lacZ118, proB, trp, nalA, rpsL* Common lab strain.	Miller *et al,*[3]
E. coli SM1411	*lacI3, lacZ118, proB, trp, nalA, rpsL,* Δ*acrAB::Tn903kan*^{r} 1411 deficient in the AcrAB multidrug efflux pump component.	O'Neill *et al,*[4]

General Experimental Procedures

Method A: Nucleophilic aromatic substitution

To a stirred solution of the appropriate nitrogen heterocycle (1.10 eq) in anhydrous DMF at 0 °C was added NaH (1.20 eq) portion-wise. After 10 minutes, 2-chloro-5-nitropyridine **4** (1.00 eq) was added and the solution allowed to warm to R.T.. After the starting materials were consumed (TLC), the reaction was quenched with water. The resulting precipitate was collected via vacuum filtration, and washed thoroughly on the filter with excess water.

Method B: Hydrogenation of the aromatic nitro group

A catalytic amount of activated palladium on charcoal (50 mg) was added to a stirred solution of the appropriate nitro-compound in methanol. The mixture was stirred under an atmosphere of hydrogen until the starting material had been consumed (TLC). The reaction was filtered through celite (washed thoroughly with methanol) and the filtrate concentrated under reduced pressure.

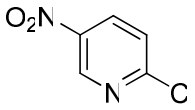
Method C: Amide coupling

The appropriate carboxylic acid (1.00 eq) was added to a stirred solution of HOBt.H_2O (1.50 eq) and EDC.HCl (1.50 eq) in anhydrous DMF. The mixture was stirred for 15 minutes before the appropriate aniline (1.00 eq) was added in anhydrous DMF. The mixture was heated to 40 °C until the starting materials had been consumed (TLC and/or LCMS). The reaction was quenched with water and either the resulting precipitate was filtered and washed thoroughly on the filter with excess water or, the resulting solution was extracted thrice with EtOAc, the combined organic extracts then washed with brine, and concentrated. The solid was subsequently purified by recrystallisation/trituration as appropriate.

Method D: Hydrolysis of nitrile of amide

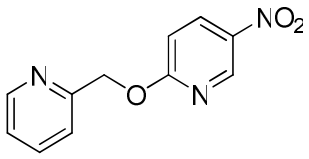
To a stirred solution of the appropriate nitrile (1.00 eq) in ethanol at R.T. was added H_2O_2 solution and 6M aq NaOH solution. The mixture was warmed to 55 °C and stirred for 3 hours to give a yellow solution, which was then adjusted to pH7 using 1M aq HCl. The reaction was concentrated under reduced pressure to give a yellow solid.

Preparation of 2-chloro-5-nitropyridine (4)



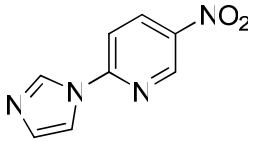
2-Hydroxy-5-nitropyridine (2.00 g, 14.3 mmol, 1.00 eq) was stirred in a solution of phosphorus oxychloride (25 ml) at reflux for 3 hours. The reaction mixture was cooled, concentrated and the residual oil taken up in DCM. This solution was added drop-wise to an ice-slurry of $NaHCO_3$ (aq.), extracted with DCM, dried (Na_2SO_4) and concentrated to give the title compound **4** (2.22 g, 14.1 mmol, 98%) as cream prisms, m.p. 110.2 – 111.8 °C (lit.105 – 108 °C)[5]; δ_H (300 MHz, $CDCl_3$); 9.25 (1H, s, 6-H), 8.44 (1H, dd, *J* 3.0 & 9.0, 4-H), 7.54 (1H, d, *J* 8.0, 3-H); δ_C (100 MHz, $CDCl_3$); 157.1 (2-C), 145.4 (6-C), 143.3 (5-C), 133.5 (4-C), 124.8 (3-C); ν_{max}/cm^{-1} (solid); 3094, 3051, 2934, 2863, 2512, 1589, 1501, 1437, 1377; *m/z* (*EI*) 158.0 (M); (Found: M, 157.9895. $C_5H_3N_2O_2Cl$ requires *M*, 157.9883).

Preparation of 2-(pyridin-2-ylmethoxy)-5-nitropyridine (5a)



2-pyridinemethanol (0.61 ml, 6.33 mmol, 1.00 eq) was added to a stirred solution of sodium hydride (0.16 g, 6.96 mmol, 1.10 eq) in DMF (10 ml). The mixture was allowed to stir for 20 minutes before 2-chloro-5-nitropyridine (1.00 g, 6.33 mmol, 1.00 eq) was added. The mixture was stirred at R.T. until the starting materials had been consumed (TLC). The reaction was quenched with water (10 ml) and the resulting precipitate isolated *via* vacuum filtration. Trituration with petroleum ether gave the title compound **5a** (925 mg, 4.00 mmol, 64%) as cream needles, m.p. 132.8 – 134.3 °C; R_f 0.12 (3:1 EtOAc–Petrol); LCMS (Method A), (RT = 1.43 min, *m/z* (ES) Found MH^+ 231.9); (Found: C, 56.7; H, 3.95; N, 18.0; $C_{11}H_9N_3O_3$ requires C, 57.1; H, 3.95; N, 18.2%); δ_H (300 MHz, $CDCl_3$); 9.08 (1H, d, *J* 3.0, 6-H), 8.62 (1H, d, *J* 4.0 6′-H), 8.39 (1H, dd, *J* 2.5 & 8.0 4-H), 7.72 (1H, t, *J* 7.5, 4′-H), 7.43 (1H, d, *J* 8.0, 3′-H) 7.26 (1H, t, *J* 7.5, 5′-H), 6.95 (1H, d, *J* 9.0, 3-H), 5.61 (2H, s, CH_2); δ_C (75 MHz, $CDCl_3$); 166.5 (2-C), 156.0 (2′-C), 149.6 (6′-C), 144.8 (6-C), 136.7 (4′-C) 134.1 (5-C), 123.0 (3′ & 5′-C), 121.9 (4-C), 111.5 (3-C), 69.6 (CH_2); ν_{max}/cm^{-1} (film); 3071, 2939, 1662, 1593, 1572, 1503, 1481, 1456, 1437, 1399; *m/z* (*EI*) 231.1 (M); (Found: M, 231.0645. $C_{11}H_9N_3O_3$ requires *M*, 231.0644).

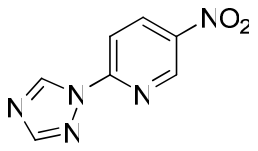
Preparation of 2-(1H-imidazol-1-yl)-5-nitropyridine (5b)



Prepared using Method A. Trituration with petroleum ether gave the title compound **5b** (1.05 g, 5.52 mmol, 87%) as a cream crystalline powder; m.p. 215.3 – 217.1 °C; R_f 0.05 (3:1 EtOAc–petrol); LCMS (Method A), (RT = 0.40 min, *m/z* (ES) Found MH^+ 191.0); (Found: C, 50.7; H, 3.20; N, 29.4; $C_8H_6N_4O_2$ requires C, 50.5; H, 3.18; N, 29.5%); δ_H (500 MHz, $CDCl_3$); 9.34 (1H, d, *J* 2.6, 6-H), 8.63 (1H, dd, *J* 2.6 & 9.5, 4-H), 8.47 (1H, s, 2′-H), 7.70 (1H, s, 5′-H), 7.51 (1H, d, *J* 8.3, 3-H), 7.27 (1H, s, 4′-H); δ_C (125 MHz, $CDCl_3$); 152.3 (2-C), 145.7 (6-C), 142.3 (5-C), 135.6 (2′-C), 134.7 (4-C), 132.1 (4′-C), 116.2 (3-C), 111.6 (5′-C); ν_{max}/cm^{-1} (solid); 3442, 3098,

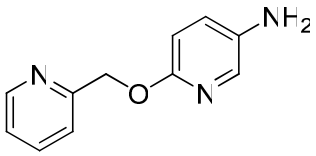
3032, 2846, 1629, 1604, 1583, 1517, 1481, 1407, 1371, 1344; *m/z* (*ES*) (Found: MH^+, 191.0559. $C_8H_7N_4O_2$ requires *MH*, 191.0564).

Preparation of 2-(1H-1,2,4-triazol-1-yl)-5-nitropyridine (5c)



Prepared using Method A. Trituration with petroleum ether gave the title compound **5c** (1.02 g, 5.34 mmol, 84%) as a cream crystalline powder; m.p. > 250 °C; R_f 0.11 (3:1 EtOAc–Petrol); LCMS (Method A), (RT = 1.38 min, *m/z* (ES) Found MH^+ 192.0); (Found: C, 44.2; H, 2.55; N, 36.9; $C_7H_5N_5O_2$ requires C, 44.0; H, 2.64; N, 36.6%); δ_H (500 MHz, $CDCl_3$); 9.32 (1H, d, *J* 2.5, 6-H), 9.25 (1H, s, 5′-H), 8.69 (1H, dd, *J* 2.5 & 9.0, 4-H), 8.17 (1H, s, 3′-H), 8.11 (1H, d, *J* 9.0, 3-H); δ_C (125 MHz, $CDCl_3$); 153.9 (3′-C), 152.4 (2-C), 145.0 (6-C), 143.2 (5-C), 142.8 (5′-C), 134.9 (4-C), 113.1 (3-C); ν_{max}/cm^{-1} (solid); 3131, 3054, 2851, 1769, 1733, 1610, 1580, 1525, 1478, 1429, 1344; *m/z* (*ES*) (Found: MH^+, 192.0512. $C_7H_6N_5O_2$ requires *MH*, 192.0516).

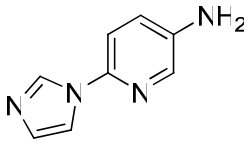
Preparation of 2-(pyridin-2-ylmethoxy)-5-aminopyridine (6a)



To a slurry of iron powder (0.77 g, 13.7 mmol, 7.00 eq) in MeOH/H_2O/AcOH (1 ml: 1 ml: 0.1 ml) was added 2-(pyridin-2-ylmethoxy)-5-nitropyridine **5a**. The reaction mixture was heated at reflux for one hour, cooled and 1M NaOH (3 ml) was added. The mixture was filtered through celite, washed with MeOH, and concentrated. The resulting oil was extracted with EtOAc, dried (Na_2SO_4), and concentrated to give the title compound **6a** (244 mg, 1.21 mmol, 62%) as a red oil; R_f 0.05 (3:1 EtOAc–Petrol); δ_H (300 MHz, $CDCl_3$); 8.61 (1H, d, *J* 5.0, 6′-H), 7.67 (2H, t, *J* 7.5, 4′ & 6-H), 7.45 (1H, d, *J* 7.5, 3′-H), 7.20 (1H, t, *J* 5.0, 5′-H), 7.04 (1H, dd, *J* 2.5 & 8.5, 4-H) 6.73 (1H, d, *J* 8.5, 3-H), 5.43 (2H, s, CH_2); δ_C (75 MHz, $CDCl_3$); 158.0 (2′-C), 157.1 (2-C), 149.0 (6′-C), 136.7 (4′ & 6-C), 133.0 (5-C) 127.6 (3′-C), 122.4 (4-C), 121.6 (5′-C), 111.0 (3-C),

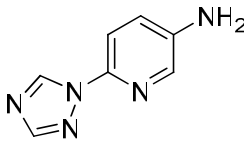
68.1 (CH_2); ν_{max}/cm^{-1} (film); 3340, 3019, 1596, 1575, 1490, 1437, 1418, 1365, 1275; *m/z* (*ES*) (Found: MH^+, 202.0977. $C_{11}H_{12}N_3O$ requires *MH*, 202.0975).

Preparation of 6-(imidazol-1-yl)-pyridin-3-yl amine (6b)



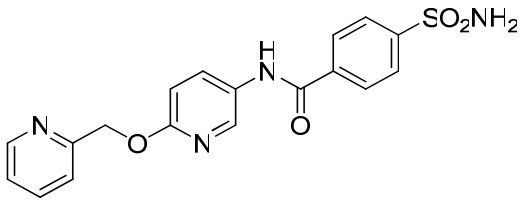
Prepared using Method B. Trituration with petroleum ether gave the title compound **6b** (0.38 g, 2.40 mmol, 91%) as a pale brown crystalline powder; m.p. 103.1 – 104.9 °C; R_f 0.05 (1:1 EtOAc–Petrol); HPLC (RT = 1.45 min); LCMS (Method A), (RT = 0.12 min, *m/z* (ES) Found MH^+ 161.0); δ_H (300 MHz, DMSO-*d6*); 8.27 (1H, s, 2′-H), 7.81 (1H, d, *J* 2.5, 2-H), 7.74 (1H, s, 5′-H), 7.44 (1H, d, *J* 9.0. 5-H), 7.10 (1H, dd, *J* 3.0 & 8.5, 4-H), 7.05 (1H, s, 4′-H), 5.49 (2H, s, NH_2); δ_C (75 MHz, DMSO-*d6*); 144.5 (6-C), 139.1 (3-C), 134.6 (2′-H), 134.1 (2-C), 129.6 (4′-C), 123.3 (4-C), 116.8 (5′-C), 113.8 (5-C); ν_{max}/cm^{-1} (solid); 3352, 3156, 2739, 1645, 1584, 1487, 1429, 1365, 1301; *m/z* (*ES*) (Found: MH^+, 161.0821. $C_8H_9N_4$ requires *MH*, 161.0822).

Preparation of 6-(1H-1,2,4-triazol-1yl)-pyridin-3-yl amine (6c)



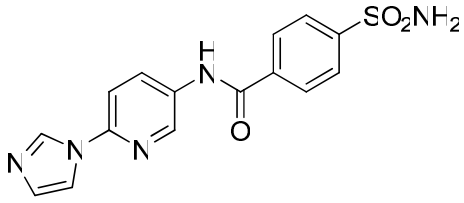
Prepared using Method B. Trituration with petroleum ether gave the title compound **6c** (0.37 g, 2.29 mmol, 88%) as a cream crystalline powder; m.p. >250 °C; R_f 0.1 (1:1 EtOAc–Petrol); HPLC (RT = 0.91 min); LCMS (Method A), (RT = 0.62 min, *m/z* (ES) Found MH^+ 162.0); δ_H (300 MHz, DMSO-*d6*); 9.10 (1H, s, 5′-H), 8.17 (1H, s, 3′-H), 7.82 (1H, d, *J* 2.5, 2-H), 7.54 (1H, d, *J* 8.5, 5-H), 7.15 (1H, dd, *J* 2.5 & 8.5, 4-H), 5.66 (2H, s, NH_2); δ_C (75 MHz, DMSO-*d6*); 152.3 (3′-C), 145.5 (3-C), 140.9 (5′-H), 139.3 (6-C), 133.7 (2-C), 123.1 (4-C), 114.1 (5-C); ν_{max}/cm^{-1} (solid); 3438, 3157, 3123, 1583, 1487, 1428, 1368, 1340, 1273; *m/z* (*ES*) (Found: MNa^+, 184.0600. $C_7H_7N_5Na$ requires *MNa*, 184.0594).

Preparation of *N*-(6-(pyridin-2-ylmethoxy)-pyridin-3-yl)-4-sulfamoyl-benzamide (7)



Prepared using Method C. Recrystallisation from ethanol, gave the title compound **7** (121 mg, 0.31 mmol, 63%) as a cream powder, m.p. > 250 °C; R_f 0.05 (3:1 EtOAc–Petrol); (Found: C, 56.4; H, 4.15; N, 14.5; S, 8.3; $C_{18}H_{16}N_4O_4S$ requires C, 56.2; H, 4.20; N, 14.6; S, 8.3%); δ_H (300 MHz, DMSO-*d6*); 10.48 (1H, s, NH), 8.56 (1H, d, *J* 4.5, 6″-H), 8.50 (1H, d, *J* 4.5, 2-H), 8.12 (3H, m, 3 &5 & 3″-H), 7.97 (2H, d, *J* 8.0, 2 & 6-H), 7.81 (1H, t, *J* 7.5, 4″-H), 7.53 (2H, s, NH_2), 7.45 (1H, d, *J* 7.5, 4′-H), 7.33 (1H, t, *J* 7.0, 5″-H), 7.00 (1H, d, *J* 9.5, 5′-H), 5.42 (2H, s, CH_2); δ_C (75 MHz, DMSO-*d6*); 165.4 (CONH), 160.2 (2′-C), 158.0 (6′-C), 150.0 (6″-C), 147.6 (3′-C), 139.9 (4-C), 138.3 (1-C), 137.7 (4″-C), 133.8 (2′-C), 131.1 (2 & 6-C), 129.3 (3 & 5-C), 126.7 (3″-C), 123.7 (4′-C), 122.3 (5″-C), 111.4 (5′-C), 69.7 (CH_2); ν_{max}/cm^{-1} (solid); 3336, 3267, 3106, 2949, 2613, 1931, 1641, 1599, 1573, 1531, 1468, 1461, 1394, 1334, 1302; *m/z* (*ES*) (Found: MH^+, 385.0977. $C_{18}H_{17}N_4O_4S$ requires *MH*, 385.0965).

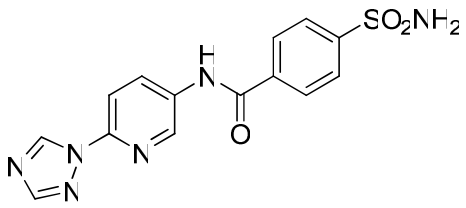
Preparation of 4-(aminosulfonyl)-*N*-[6-(1H-imidazol-1-yl)-3-pyridinyl]-benzamide (8)



Prepared using Method C. Trituration with hot methanol gave the title compound **8** (0.14 g, 0.40 mmol, 64%) as an off-white crystalline powder; m.p. > 250 °C; R_f 0.10 (EtOAc); HPLC (RT = 1.76 min, 95%); LCMS (Method A), (RT = 0.98 min, *m/z* (ES) Found MH^+ 344.0); δ_H (300 MHz, DMSO-*d6*); 10.79 (1H, s, NH), 8.88 (1H, d, *J* 1.0, 2′-H), 8.54 (1H, s, 5″-H), 8.40 (1H, dd, *J* 1.5 & 8.5, 4′-H), 8.16 (2H, d, *J* 8.0, 2 & 6-H), 8.00 (2H, d, *J* 9.0, 3 & 5-H), 7.96 (1H, s, 2″-H), 7.87 (1H, d, *J* 8.0, 5′-H), 7.56 (2H, s, NH_2), 7.16 (1H, s, 4″-H); δ_C (75 MHz, DMSO-*d6*); 165.2 (CONH), 147.2 (4-C), 144.8 (6′-C), 140.9 (2′-C), 137.4 (1-C), 134.8 (5″-C), 134.6 (3′-C), 131.2 (4′-C), 130.3 (4″-C), 128.9 (2 & 6-C), 126.1 (3 & 5-C), 116.9 (2″-C), 113.1 (5′-C); ν_{max}/cm^{-1}

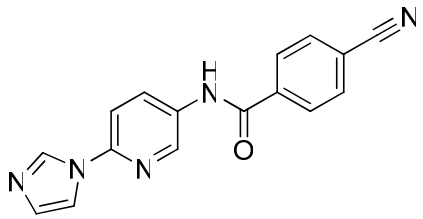
(solid); 3488, 3319, 3120, 1667, 1556, 1504, 1401, 1307, 1251; *m/z* (*ES*) (Found: MH^+, 344.0815. $C_{15}H_{14}N_5O_3S$ requires *MH*, 344.0812).

Preparation of 4-(aminosulfonyl)-*N*-[6-[1,2,4-triazol-1-yl)-3-pyridinyl]-benzamide (9)



Prepared using Method C. Trituration with hot methanol gave the title compound **9** (0.19 g, 0.55 mmol, 60%) as a colourless crystalline powder; m.p. > 250 °C; R_f 0.21 (EtOAc); HPLC (RT = 1.53 min); δ_H (300 MHz, DMSO-*d6*); 10.87 (1H, s, NH), 9.36 (1H, s, 5″-H), 8.92 (1H, d, *J* 2.5, 2′-H), 8.47 (1H, dd, *J* 2.5 & 8.5, 4′-H), 8.31 (1H, s, 3″-H), 8.16 (2H, d, *J* 8.5, 2 & 6-H), 8.00 (2H, d, *J* 8.0, 3 & 5-H), 7.94 (1H, d, *J* 9.5, 5′-H), 7.58 (2H, s, NH_2); δ_C (75 MHz, DMSO-*d6*); 165.3 (CO), 153.2 (3″-C), 147.3 (4-C), 144.9 (6′-C), 142.1 (5″-C), 140.6 (2′-C), 137.3 (1-C), 135.8 (3′-C), 131.4 (4′-C), 128.9 (2 & 6-C), 126.1 (3 & 5-C), 113.5 (5′-C); ν_{max}/cm^{-1} (solid); 3373, 1668, 1608, 1546, 1508, 1433, 1390; *m/z* (*ES*) (Found: MH^+, 345.0760. $C_{14}H_{13}N_6O_3S$ requires *MH*, 345.0764).

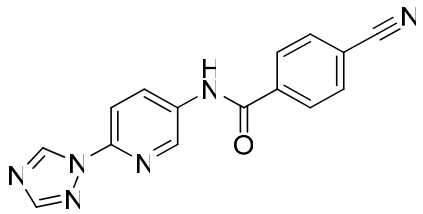
Preparation of *N*-[6-(1H-imidazol-1-yl)-3-pyridinyl]-4-cyanobenzamide (10)



Prepared using Method C. Trituration with hot methanol gave the title compound **10** (0.29 g, 0.99 mmol, 72%) as a cream crystalline powder; m.p. 245.1 – 247.8 °C; HPLC (RT = 1.48 min); δ_H (300 MHz, DMSO-*d6*); 10.85 (1H, s, NH), 8.86 (1H, d, *J* 2.5, 2′-H), 8.55 (1H, s, 5″-H), 8.37 (1H, dd, *J* 2.5 & 9.0, 4′-H), 8.15 (2H, d, *J* 8.5, 2 & 6-H), 8.07 (2H, d, *J* 8.5, 3 & 5-H), 7.96 (1H, s, 2″-H), 7.87 (1H, d, *J* 9.0, 5′-H), 7.16 (1H, s, 4″-H); δ_C (75 MHz, DMSO-*d6*); 164.8 (CO), 144.8 (6′-C), 140.9 (2′-C), 138.5 (1-C), 135.2 (5″-C), 134.5 (3′-C), 132.9 (3 & 5-C), 131.3 (4′-C), 130.1 (4″-C), 128.9 (2 & 6-C), 118.6 (CN), 117.0 (2″-C), 114.6 (4-C), 113.1 (5′-C); ν_{max}/cm^{-1}

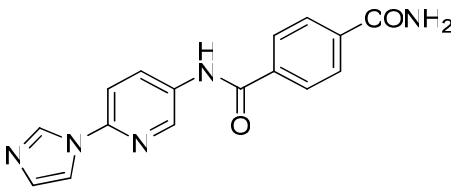
(solid); 2970, 2229, 1737, 1675, 1553, 1505, 1406, 1366, 1335; *m/z* (*ES*) (Found: MH^+, 290.1043. $C_{16}H_{12}N_5O$ requires *MH*, 290.1036).

Preparation of *N*-[6-[1,2,4-triazol-1-yl)-3-pyridinyl]-4-cyanobenzamide (11)



Prepared using Method C. Trituration with hot methanol gave the title compound **11** (84 mg, 0.29 mmol, 46%) as a yellow crystalline powder; m.p. > 250 °C; HPLC (RT = 17.3 min); δ_H (300 MHz, DMSO-*d6*); 10.91 (1H, s, NH), 9.34 (1H, s, 5″-H), 8.91 (1H, d, *J* 2.5, 2′-H), 8.46 (1H, dd, *J* 2.5 & 9.0, 4′-H), 8.31 (1H, s, 3″-H), 8.15 (2H, d, *J* 8.5, 2 & 6-H), 8.07 (2H, d, *J* 8.5, 3 & 5-H), 7.93 (1H, d, *J* 8.5, 5′-H); δ_C (75 MHz, DMSO-*d6*); 164.9 (CO), 153.2 (3″-C), 144.9 (6′-C), 142.1 (5″-C), 140.6 (2′-C), 138.4 (3′-C), 135.6 (1-C), 132.9 (3 & 5-C), 131.4 (4′-C), 128.9 (2 & 6-C), 118.6 (CN), 114.6 (4-C), 113.5 (5′-C); ν_{max}/cm^{-1} (solid); 3258, 3203, 3119, 3073, 2232, 1682, 1611, 1548, 1506, 1478, 1304; *m/z* (*ES*) (Found: MH^+, 291.0999. $C_{15}H_{11}N_6O$ requires *MH,* 291.0989).

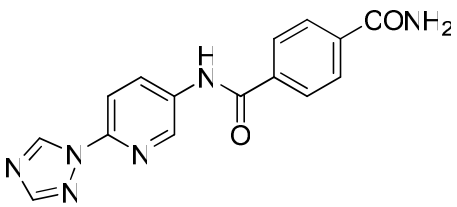
Preparation of *N*-(6-(1H-imidazol-1-yl)-pyridin-3-yl) terephthalamide (12)



Prepared using Method D. Trituration with hot acetonitrile gave the title compound **12** (102 mg, 0.35 mmol, 96%) as a cream crystalline powder; m.p. > 250 °C; HPLC (RT = 0.98 min); δ_H (300 MHz, DMSO-*d6*); 10.95 (1H, s, NH), 8.97 (1H, d, *J* 2.6, 2′-H), 8.84 (1H, broad s, 5″-H), 8.47 (1H, dd, *J* 2.5 & 9.0, 4′-H), 8.22 (1H, s, $CONH_2$), 8.13 (2H, d, *J* 8.5, 2 & 6-H), 8.08 (1H, broad s, 2″-H), 8.04 (2H, d, *J* 9.0, 3 & 5-H), 7.92 (1H, d, *J* 0.0, 5′-H), 7.60 (1H, s, $CONH_2$), 7.32 (1H, broad s, 4″-H); δ_C (75 MHz, DMSO-*d6*); 167.4 ($CONH_2$), 165.6 (CONH), 144.1 (6′-C), 141.0 (2′-C), 137.5 (4-C), 136.5 (1-C), 135.4 (3′-C), 131.2 (4′-C), 128.2 (2 & 6-C), 127.9 (3 & 5-C),

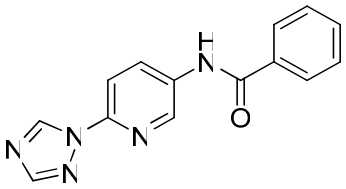
113.5 (5′-C), missing peaks for 2″-C, 4″-C, 5″-C; ν_{max}/cm^{-1} (solid); 3375, 3302, 1940, 1645, 1532, 1398, 1337, 1303; *m/z* (*ES*) (Found: MH^+, 308.1151. $C_{16}H_{14}N_5O_2$ requires *MH*, 308.1142).

Preparation of *N*-(6-[1,2,4-triazol-1-yl]-pyridin-3-yl) terephthalamide (13)



Prepared using Method D. Trituration with hot acetonitrile gave the title compound **13** (25.0 mg, 0.08 mmol, 47%) as a cream crystalline powder; m.p. > 250 °C; HPLC (RT = 1.21 min); δ_H (300 MHz, DMSO-*d6*); 10.82 (1H, broad s, NH), 9.35 (1H, s, 5″-H), 8.92 (1H, d, *J* 2.5, 2′-H), 8.48 (1H, dd, *J* 2.5 & 9.0, 4′-H), 8.30 (1H, s, 3″-H), 8.17 (1H, s, NH_2), 8.08 (2H, d, *J* 8.0, 2 & 6-H), 8.03 (2H, d, *J* 8.5, 3 & 5-H), 7.91 (1H, d, *J* 9.0, 5′-H), 7.58 (1H, s, NH_2); δ_C (75 MHz, DMSO-*d6*); 167.5 ($CONH_2$), 165.8 (CONH), 153.1 (3″-C), 144.6 (6′-C), 142.0 (5″-C), 140.7 (2′-C), 137.4 (4-C), 137.0 (1-C), 136.5 (3′-C), 131.4 (4′-C), 128.1 (2 & 6-C), 127.9 (3 & 5-C), 113.4 (5′-C); ν_{max}/cm^{-1} (solid); 3383, 3302, 3147, 1739, 1645, 1530, 1511, 1488, 1425, 1360; *m/z* (*ES*) (Found: MH^+, 309.1094. $C_{15}H_{13}N_6O_2$ requires *MH*, 309.1095).

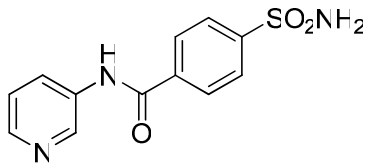
Preparation of *N*-(6-[1,2,4-triazol-1-yl]-pyridin-3-yl)-benzamide (14)



To a solution of 6-(1,2,4-triazol-1-yl)-pyridin-3-yl amine **6c** (50.0 mg, 0.31 mmol, 1.00 eq) in DCM (10 ml) was added benzoyl chloride (44.0 mg, 0.31 mmol, 1.00 eq), followed by triethylamine (0.10 ml, 0.63 mmol, 2.00 eq). The solution was stirred for 18 hours at R.T. until starting material had been consumed by TLC. The reaction was quenched with water (10 ml), concentrated in vacuo, and extracted with EtOAc (3 x 10 ml). The combined organic layers were washed with brine (30 ml), dried (Na_2SO_4) and concentrated to give a crude solid. Trituration with EtOAc gave the title compound **14** (21.0 mg, 0.08 mmol, 26%) as a colourless crystalline powder; m.p. 228.4 – 230.1 °C; R_f 0.72 (EtOAc); HPLC (RT = 2.11 min); LCMS (Method A),

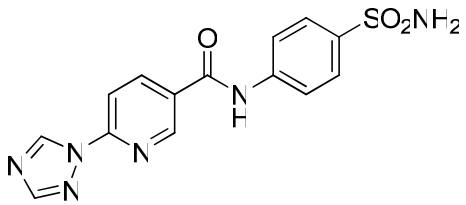
(RT = 1.61 min, *m/z* (ES) Found MH^+ 266.0); δ_H (300 MHz, DMSO-*d6*); 10.66 (1H, s, NH), 9.33 (1H, s, 5″-H), 8.91 (1H, d, *J* 2.5, 2′-H), 8.46 (1H, dd, *J* 2.5 & 9.0, 4′-H), 8.28 (1H, s, 3″-H), 8.00 (2H, d, *J* 7.0, 2 & 6-H), 7.90 (1H, d, *J* 9.0, 5′-H), 7.63 (1H, tt, *J* 1.5 & 7.5, 4-H), 7.56 (2H, m, 3 & 5-H); δ_C (75 MHz, DMSO-*d6*); 165.9 (CO), 152.7 (3″-C), 144.3 (6′-C), 141.6 (5″-C), 140.1 (2′-C), 135.7 (3′-C), 134.1 (1-C), 132.0 (4′-C), 130.8 (4-C), 128.5 (2 & 6-C), 127.7 (3 & 5-C), 113.0 (5′-C); ν_{max}/cm^{-1} (solid); 3329, 3149, 3065, 1649, 1604, 1581, 1521, 1420, 1357, 1314, 1314, 1291; *m/z* (*ES*) (Found: MH^+, 266.1033. $C_{14}H_{12}N_5O$ requires *MH*, 266.1036).

Preparation of *N*-(pyridin-3-yl)-4-sulfamoyl benzamide (15)



Prepared using Method C. Trituration with hot methanol gave the title compound **15** (0.21 g, 0.74 mmol, 47%) as a off-white crystalline powder; m.p. > 250 °C; R_f 0.12 (EtOAc); HPLC (RT = 1.38 min); LCMS (Method A), (RT = 0.54 min, *m/z* (ES) Found MH^+ 278.0); δ_H (300 MHz, DMSO-*d6*); 10.66 (1H, s, NH), 8.94 (1H, d, *J* 2.5, 2′-H), 8.35 (1H, dd, *J* 1.0 & 4.5, 6′-H), 8.21 (1H, ddd, *J* 1.5 & 2.5 & 8.5, 4′-H), 8.14 (2H, d, *J* 8.5, 2 & 6-H), 7.98 (2H, d, *J* 8.5, 3 & 5-H), 7.57 (2H, s, NH_2), 7.43 (1H, dd, *J* 4.5 & 8.0, 5′-H); δ_C (75 MHz, DMSO-*d6*); 165.3 (CO), 147.1 (4-C), 145.2 (6′-C), 142.2 (2′-C), 137.6 (1-C), 135.9 (3′-C), 128.8 (2 & 6-C), 127.8 (4′-C), 126.1 (3 & 5-C), 124.0 (5′-C); ν_{max}/cm^{-1} (solid); 3323, 1675, 1603, 1548, 1486, 1417, 1312; *m/z* (*ES*) (Found: MH^+, 278.0589. $C_{12}H_{12}N_3O_3S$ requires *MH*, 278.0594).

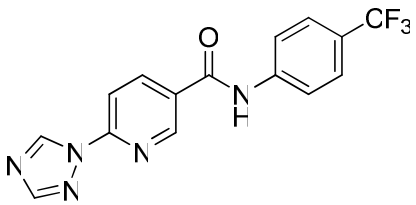
Preparation of (6-[1,2,4-triazol-1-yl]-*N*-(-4-sulfamoyl-phenyl)-nicotinamide (16)



Prepared using Method C. Prep HPLC gave the title compound **16** (20.0 mg, 0.06 mmol, 3%) as a colourless crystalline powder; m.p. > 250 °C; R_f 0.77 (EtOAc); HPLC (RT = 9.81 min); LCMS (Method A), (RT = 1.42 min, *m/z* (ES) Found MH^+ 345.0); δ_H (300 MHz, DMSO-*d6*); 10.82

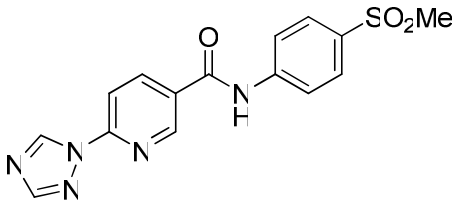
(1H, s, NH), 9.45 (1H, s, 5″-H), 9.08 (1H, d, *J* 2.0, 2-H), 8.59 (1H, dd, *J* 2.5 & 8.5, 4-H), 8.38 (1H, s, 3″-H), 8.03 (1H, d, *J* 8.5, 5-H), 7.94 (2H, d, *J* 9.0, 3′ & 5′-H), 7.83 (2H, d, *J* 9.0, 2′ & 6′-H), 7.29 (2H, s, NH_2); δ_C (75 MHz, DMSO-*d6*); 163.4 (CO), 153.5 (3″-C), 150.4 (6-C), 148.6 (2-C), 142.7 (5″-C), 141.7 (1′-C), 139.8 (4-C), 139.2 (4′-C), 129.6 (3-C), 126.6 (3′ & 5′-C), 119.9 (2′ & 6′-C), 112.4 (5-C); ν_{max}/cm^{-1} (solid); 3303, 2672, 1659, 1593, 1531, 1506, 1429, 1402, 1329; *m/z* (*ES*) (Found: MH^+, 345.0763. $C_{14}H_{13}N_6O_3S$ requires *MH*, 345.0764).

Preparation of 4-trifluoromethyl-*N*-(6-[1,2,4-triazol-1-yl]-pyridin-3-yl)-benzamide (17)



Prepared using Method C. Trituration with hot methanol gave the title compound **17** (23 mg, 0.07 mmol, 12%) as a cream crystalline powder; m.p. > 250 °C; R_f 0.74 (EtOAc); HPLC (RT 2.12 min); LCMS (Method A), (RT = 1.80 min, *m/z* (ES) Found MH^+ 334.0); δ_H (300 MHz, DMSO-*d6*); 10.91 (1H, s, NH), 9.36 (1H, s, 5″-H), 8.92 (1H, d, *J* 2.5, 2′-H), 8.47 (1H, dd, *J* 2.5 & 9.0, 4′-H), 8.31 (1H, s, 3″-H), 8.20 (2H, d, *J* 8.0, 2 & 6-H), 7.95 (3H, m (d + d overlap), 3 & 5-H +5′-H); δ_C (75 MHz, DMSO-*d6*); 165.1 (CO), 153.2 (3″-C), 144.9 (6′-C), 142.1 (5″-C), 140.6 (2′-C), 138.3 (1-C), 135.7 (3′-C), 131.7 (q, *J* 32, CF_3), 131.5 (4′-C), 129.1 (2 & 6-C), 125.9 (q, *J* 3.5, 3 & 5-C), 123.8 (q, *J* 273, 4-C), 113.5 (5′-C); ν_{max}/cm^{-1} (solid); 3332, 3164, 3115, 1656, 1583, 1532, 1490, 1375, 1327; *m/z* (*ES*) (Found: MH^+, 334.0923. $C_{15}H_{11}F_3N_5O$ requires *MH*, 334.0910).

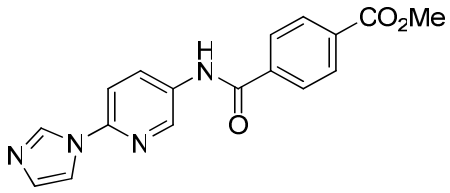
Preparation of 4-(methylsulfonyl)-*N*-(6-[1,2,4-triazol-1-yl]-pyridin-3-yl)-benzamide (18)



Prepared using Method C. Trituration with hot methanol gave the title compound **18** (42.0 mg, 0.12 mmol, 26%) as a peach crystalline powder; m.p. > 250 °C; R_f 0.18 (EtOAc); HPLC (RT =

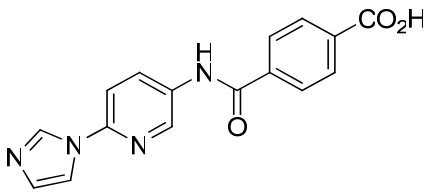
1.48 min); LCMS (Method A), (RT = 1.47 min, *m/z* (ES) Found MH^+ 344.0); δ_H (300 MHz, DMSO-*d6*); 10.95 (1H, s, NH), 9.36 (1H, s, 5″-H), 8.91 (1H, d, *J* 2.0, 2′-H), 8.48 (1H, dd, *J* 2.5 & 8.5, 4′-H), 8.31 (1H, s, 3″-H), 8.22 (2H, d, *J* 8.5, 2 & 6-H), 8.13 (2H, d, *J* 8.5, 3 & 5-H), 7.94 (1H, d, *J* 9.0, 5′-H), 3.28 (3H, s, CH_3); δ_C (75 MHz, DMSO-*d6*); 165.1 (CONH), 153.2 (3″-C), 144.9 (6′-C), 143.8 (4-C), 142.1 (5″-C), 140.6 (2′-C), 138.9 (1-C), 135.7 (3′-C), 131.4 (4′-C), 129.2 (2 & 6-C), 127.5 (3 & 5-C), 113.5 (5′-C), 43.6 (CH_3); ν_{max}/cm^{-1} (solid); 3363, 1668, 1533, 1489; *m/z* (*ES*) (Found: MH^+, 344.0801. $C_{15}H_{14}N_5O_3S$ requires *MH*, 344.0812).

Preparation of methyl 4-[6-(imidazol-1-yl)-pyridin-3-yl carbamoyl]-benzamide (19)



Prepared using Method C. Trituration with hot methanol gave the title compound **19** (0.31 g, 0.95 mmol, 76%) as a cream crystalline powder; m.p. 222.0 – 224.7 °C; HPLC (RT = 2.18 min); LCMS (Method A), (RT = 1.34 min, *m/z* (ES) Found MH^+ 323.0); δ_H (300 MHz, DMSO-*d6*); 10.81 (1H, s, NH), 8.86 (1H, d, *J* 2.5, 2′-H), 8.51 (1H, s, 5″-H), 8.38 (1H, dd, *J* 2.5 & 9.0, 4′-H), 8.13 (4H, collapsed s, 2 & 3 & 5 & 6-H), 7.94 (1H, s, 2″-H), 7.86 (1H, d, *J* 8.5, 5′-H), 7.13 (1H, s, 4″-H); δ_C (75 MHz, DMSO-*d6*); 166.0 (CO_2Me), 165.4 (CONH), 144.8 (6′-C), 140.9 (2′-C), 138.6 (aromatic quaternary C), 135.2 (5″-C), 134.6 (aromatic quaternary C), 132.7 (3′-C), 131.3 (4′-C), 130.4 (4″-C), 129.7 (aromatic CH), 128.5 (aromatic CH), 116.9 (2″-C), 113.1 (5′-C); ν_{max}/cm^{-1} (solid); 3585, 3130, 1727, 1607, 1567, 1510, 1406, 1316; *m/z* (*ES*) (Found: MH^+, 323.1141. $C_{17}H_{15}N_4O_3$ requires *MH*, 323.1139).

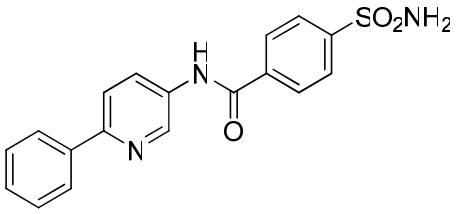
Preparation of 4-[6-(imidazol-1-yl)-pyridin-3-yl carbamoyl]-benzoic acid (20)



Methyl 4-[6-(imidazol-1-yl)-pyridin-3-yl carbamoyl]-benzamide **19** was stirred in a solution of 2M aq NaOH for 48 hours. The reaction was diluted with water (5 ml) and acidified to pH 2 with

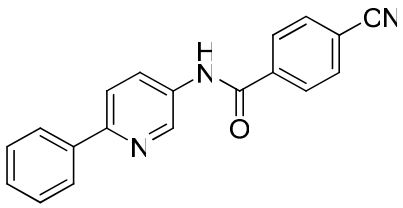
2M aq HCl. The precipitate was collected by vacuum filtration to give the title compound **20** (65.0 mg, 0.21 mmol, 45%) as colourless crystalline prisms; m.p. > 250 °C; HPLC (RT = 1.29 min); δ_H (300 MHz, DMSO-*d6*); 10.78 (1H, s, NH), 8.91 (1H, d, *J* 2.5, 2′-H), 8.87 (1H, s, 5″-H), 8.44 (1H, dd, *J* 2.5 & 9.0, 4′-H), 8.11 (4H, collapsed s, 2 & 3 & 5 & 6-H), 8.08 (1H, s, 2″-H), 8.07 (1H, s, OH), 7.92 (1H, d, *J* 9.0, 5′-H), 7.33 (1H, s, 4″-H); δ_C (75 MHz, DMSO-*d6*); 167.0 (CO_2H), 165.6 (CONH), 144.1 (6′-C), 140.9 (2′-C), 138.1 (4-C), 135.3 (3′-C), 135.0 (5″-C), 134.0 (1-C), 131.2 (4′-C), 129.8 (3 & 5-C), 128.4 (2 & 6-C), 128.1 (4″-C), 117.5 (2″-C), 113.5 (5′-C); ν_{max}/cm^{-1} (solid); 3300, 3127, 1668, 1538, 1410, 1394; *m/z* (*ES*) (Found: MH^+, 309.0987. $C_{16}H_{13}N_4O_3$ requires *MH*, 309.0982).

Preparation of *N*-(6-phenylpyridin-3-yl)-4-sulfamoyl benzamide (21)



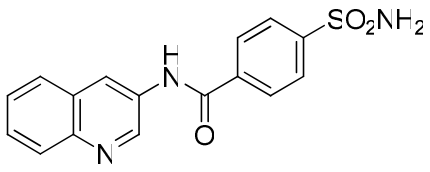
Prepared using Method C. Trituration with hot methanol gave the title compound **21** (0.13 g, 0.36 mmol, 62%) as a off-white crystalline powder; m.p. > 250 °C; HPLC (RT = 2.50 min); LCMS (Method A), (RT = 1.65 min, *m/z* (ES) Found MH^+ 354.0); δ_H (500 MHz, DMSO-*d6*); 10.74 (1H, s, NH), 9.04 (1H, d, *J* 2.5, 2′-H), 8.33 (1H, dd, *J* 2.5 & 8.5, 4′-H), 8.17 (2H, d, *J* 8.5, 2 & 6-H), 8.10 (2H, d, *J* 7.5, 2″ & 6″-H), 8.02 (3H, m, 5′-H + 3 & 5-H), 7.57 (2H, s, NH_2), 7.51 (2H, t, *J* 7.5, 3″ & 5″-H), 7.43 (1H, t, *J* 7.5, 4″-H); δ_C (75 MHz, DMSO-*d6*); 165.2 (CONH), 151.6 (6′-C), 147.2 (4-C), 142.0 (2′-C), 138.6 (1″-C), 137.6 (1-C), 135.0 (3′-C), 129.1 (aromatic CH), 128.9 (aromatic CH), 128.6 (4′-C), 126.5 (aromatic CH), 126.1 (aromatic CH), 120.4 (5′-C); ν_{max}/cm^{-1} (solid); 3331, 3254, 1651, 1588, 1575, 1500, 1385; *m/z* (*ES*) (Found: MH^+, 354.0916. $C_{18}H_{16}N_3O_3S$ requires *MH*, 354.0907).

Preparation of 4-cyano-*N*-(6-phenylpyridin-3-yl) benzamide (22)



Prepared using Method C. Trituration with hot methanol gave the title compound **22** (0.26 g, 0.88 mmol, 86%) as a colourless crystalline powder; m.p. > 250 °C; R_f 0.90 (EtOAc); HPLC (RT = 3.06 min); LCMS (Method A), (RT = 1.84 min, *m/z* (ES) Found MH^+ 300.0); δ_H (500 MHz, DMSO-*d6*); 10.80 (1H, s, NH), 9.03 (1H, d, *J* 2.5, 2′-H), 8.32 (1H, dd, *J* 2.5 & 8.5, 4′-H), 8.17 (2H, d, *J* 8.5, 2 & 6-H), 8.09 (4H, m, 3 & 5-H + 2″ & 6″-H), 8.03 (1H, d, *J* 8.5, 5′-H), 7.51 (2H, t, *J* 7.5, 3″ & 5″-H), 7.43 (1H, t, *J* 7.5, 4″-H); δ_C (75 MHz, DMSO-*d6*); 164.9 (CONH), 151.7 (6′-C), 142.0 (2′-C), 138.69 (1″-C), 138.58 (1-C), 134.9 (3′-C), 132.9 (2″ & 6″-C), 129.12 (aromatic CH), 129.05 (aromatic CH), 128.98 (aromatic CH), 128.6 (4′-C), 126.5 (3 & 5-C), 120.3 (5′-C), 118.7 (CN), 114.5 (4-C); ν_{max}/cm^{-1} (solid); 3224, 3067, 2229, 1673, 1534, 1480, 1372; *m/z* (*ES*) (Found: MH^+, 300.1139. $C_{19}H_{14}N_3O$ requires *MH*, 300.1131).

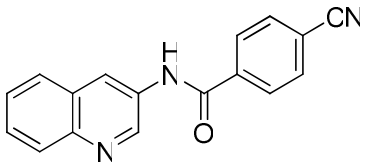
Preparation of *N*-(quinolin-3-yl)-4-sulfamoyl benzamide (23)



Prepared using Method C. Trituration with hot methanol gave the title compound **23** (0.15 g, 0.47 mmol, 67%) as a colourless crystalline powder; m.p. > 250 °C; R_f 0.34 (EtOAc); HPLC (RT = 1.43 min); LCMS (Method A), (RT = 1.49 min, *m/z* (ES) Found MH^+ 328.0); δ_H (300 MHz, DMSO-*d6*); 10.84 (1H, s, NH), 9.15 (1H, d, *J* 2.5, 2′-H), 8.87 (1H, d, *J* 2.5, 4′-H), 8.20 (2H, d, *J* 8.5, 2 & 6-H), 8.01 (4H, overlapped d + d, 3 & 5-H + 5′ & 8′-H), 7.70 (1H, dt, *J* 1.0 & 7.0, 7′-H), 7.65-7.55 (3H, m, 6′-H + NH_2); δ_C (75 MHz, DMSO-*d6*); 165.1 (CONH), 146.8 (4-C), 145.3 (2′-C), 144.5 (aromatic quaternary C), 137.1 (1-C), 132.6 (3′-C), 128.54 (2 & 6-C), 128.49 (aromatic CH), 128.2 (aromatic CH), 127.9 (7′-C), 127.1 (6′-C), 125.8 (3 & 5-C), 123.6 (4′-C); ν_{max}/cm^{-1}

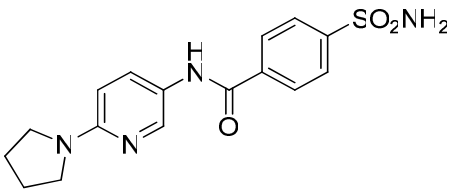
(solid); 3319, 3162, 1667, 1557, 1496, 1386, 1329; *m/z* (*ES*) (Found: MH^+, 328.0748. $C_{16}H_{14}N_3O_3S$ requires *MH*, 328.0750).

Preparation of 4-cyano-*N*-(quinolin-3-yl) benzamide (24)



Prepared using Method C. Trituration with hot methanol gave the title compound **24** (0.12 g, 0.42 mmol, 61%) as a colourless crystalline powder; m.p. > 250 °C; R_f 0.62 (EtOAc); HPLC (RT = 1.82 min); LCMS (Method A), (RT = 1.69 min, *m/z* (ES) Found MH^+ 274.0); δ_H (500 MHz, DMSO-*d6*); 10.96 (1H, s, NH), 9.15 (1H, d, *J* 2.5, 2′-H), 8.87 (1H, d, *J* 2.5, 4′-H), 8.21 (2H, d, *J* 8.5, 2 & 6-H), 8.10 (2H, d, *J* 8.5, 3 & 5-H), 8.01 (2H, d, *J* 8.5, 5′ & 8′-H), 7.71 (1H, t, *J* 8.0, 7′-H), 7.62 (1H, t, *J* 8.0, 6′-H); δ_C (75 MHz, DMSO-*d6*); 165.2 (CONH), 145.7 (2′-C), 144.9 (aromatic quaternary C), 138.7 (1-C), 133.0 (3 & 5-C), 132.9 (aromatic quaternary C), 129.0 (2 & 6-C), 128.9 (aromatic CH), 128.6 (aromatic CH), 128.3 (8′-C), 128.0 (aromatic quaternary C), 127.5 (5′-C), 124.0 (4′-C), 118.6 (CN), 114.6 (4-C); ν_{max}/cm^{-1} (solid); 3268, 3049, 2228, 1673, 1549, 1490, 1369, 1340; *m/z* (*ES*) (Found: MH^+, 274.0980. $C_{17}H_{12}N_3O_3$ requires *MH*, 274.0975).

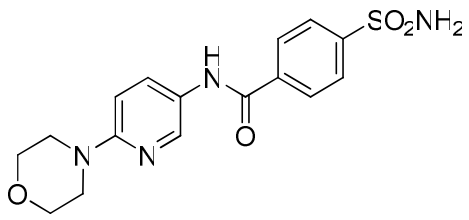
Preparation of *N*-[6-(pyrrolidin-1-yl)-pyridin-3-yl]-4-sulfamoyl benzamide (25)



To a slurry of iron powder (0.77 g, 13.7 mmol, 7.00 eq) in MeOH/H_2O/AcOH (1 ml: 1 ml: 0.1 ml) was added 5-nitro-2-(pyrrolidin-1-yl) pyridine **28**. The reaction mixture was heated to reflux for one hour, cooled and 1M NaOH (3 ml) was added. The mixture was filtered through celite (washed with MeOH) and concentrated. The oil was extracted with EtOAc, dried (Na_2SO_4), and concentrated to give 6-(pyrrolidin-1-yl)-pyridin-3-amine. This compound was then reacted according to Method C. Trituration with hot methanol gave the title compound **25** (0.17 g, 0.51 mmol, 55%) as a yellow crystalline powder; m.p. > 250 °C; HPLC (RT = 1.48 min); δ_H (500 MHz, DMSO-*d6*); 10.23 (1H, s, NH), 8.39 (1H, d, *J* 2.5, 2′-H), 8.11 (2H, d, *J* 8.5, 2 & 6-H), 7.96

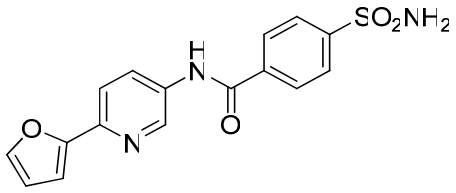
(2H, d, *J* 8.5, 3 & 5-H), 7.86 (1H, dd, *J* 2.5 & 9.0, 4′-H), 7.53 (2H, s, NH_2), 6.49 (1H, d, *J* 9.0, 5′-H), 3.38 (4H, broad s, 2″ & 5″-H), 1.96 (4H, broad s, 3″ & 4″-H); δ_C (75 MHz, DMSO-*d6*); 164.3 (CONH), 154.6 (6′-C), 146.7 (4-C), 141.9 (2′-C), 138.0 (1-C), 131.6 (4′-C), 128.6 (2 & 6-C), 126.0 (3 & 5-C), 124.8 (3′-C), 106.1 (5′-C), 46.9 (2″ & 5″-C), 25.4 (3″ & 4″-C); ν_{max}/cm^{-1} (solid); 3362, 3219, 1651, 1621, 1584, 1513, 1335; *m/z* (*ES*) (Found: MH^+, 347.1187. $C_{16}H_{19}N_4O_3S$ requires *MH*, 347.1172).

Preparation of *N*-[6-(morpholino)-pyridin-3-yl]-4-sulfamoyl benzamide (26)



Prepared using Method C. Trituration with hot methanol gave the title compound **26** (0.13 g, 0.36 mmol, 52%) as a pale pink crystalline powder; m.p. > 250 °C; R_f 0.66 (EtOAc); LCMS (Method A), (RT = 1.21 min, *m/z* (ES) Found MH^+ 363.0); δ_H (300 MHz, DMSO-*d6*); 10.35 (1H, s, NH), 8.49 (1H, d, *J* 2.5, 2′-H), 8.11 (2H, d, *J* 8.5, 2 & 6-H), 7.95 (3H, m, 3 & 5-H + 4′-H), 7.54 (2H, s, NH_2), 6.89 (1H, d, *J* 9.0, 5′-H), 3.71 (4H, m, OCH_2), 3.41 (4H, m, NCH_2); δ_C (75 MHz, DMSO-*d6*); 164.5 (CONH), 156.6 (6′-C), 146.8 (4-C), 140.6 (2′-C), 137.8 (1-C), 131.4 (3′-C), 128.6 (2 & 6-C), 127.1 (4′-C), 126.0 (3 & 5-C), 107.1 (5′-C), 66.3 (OCH_2), 45.8 (NCH_2); *m/z* (*ES*) (Found: MH^+, 363.1127. $C_{16}H_{19}N_4O_4S$ requires *MH*, 363.1122).

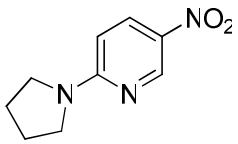
Preparation of [6-(2-furanyl)-pyridin-3-yl]-4-sulfamoyl benzamide (27)



Prepared using Method C. Trituration with hot methanol gave the title compound **27** (0.18 g, 0.53 mmol, 78%) as a off-white crystalline powder; m.p. > 250 °C; R_f 0.64 (EtOAc); HPLC (RT = 1.56 min); δ_H (300 MHz, DMSO-*d6*); 10.74 (1H, s, NH), 8.94 (1H, d, *J* 2.0, 2′-H), 8.31 (1H, dd, *J* 2.5 & 8.5, 4′-H), 8.15 (2H, d, *J* 8.5, 2 & 6-H), 7.99 (2H, d, *J* 8.5, 3 & 5-H), 7.83 (1H, d, *J*

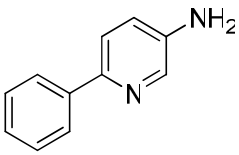
1.0, 5″-H), 7.78 (1H, dd, *J* 8.5, 5′-H), 7.57 (2H, s, NH_2), 7.06 (1H, d, *J* 3.0, 3″-H), 6.66 (1H, dd, *J* 2.0 & 3.5, 4″-H); δ_C (75 MHz, DMSO-*d6*); 164.8 (CONH), 153.0 (2″-C), 146.8 (4-C), 144.1 (6′-C), 143.8 (5″-C), 141.7 (2′-C), 137.1 (1-C), 134.3 (3′-C), 128.5 (2 & 6-C), 128.0 (4′-C), 125.7 (3 & 5-C), 118.1 (5′-C), 112.3 (4″-C), 108.0 (3″-C); ν_{max}/cm^{-1} (solid); 3393, 3309, 2945, 1669, 1582, 1530, 1504, 1399, 1326; *m/z* (*ES*) (Found: MH^+, 344.0715. $C_{16}H_{14}N_3O_4S$ requires *MH*, 344.0700).

Preparation of 5-nitro-2-(pyrrolidin-1-yl) pyridine (28)



Prepared using Method A. Trituration with petroleum ether gave the title compound **28** (0.39 g, 1.99 mmol, 91%) as yellow crystalline needles; m.p. 134.4 – 136.0 °C; R_f 0.21 (1:3 EtOAc–Petrol); LCMS (Method A), (RT = 1.72 min, *m/z* (ES) Found MH^+ 194.0); δ_H (300 MHz, DMSO-*d6*); 9.07 (1H, d, *J* 3.5, 6-H), 8.18 (1H, dd, *J* 2.5 & 9.5, 4-H), 6.32 (1H, d, *J* 9.0, 3-H), 3.71 (2H, broad s, 5′-H), 3.44 (2H, broad s, 2′-H), 2.08 (4H, broad s, 3′ & 4′-H); δ_C (75 MHz, DMSO-*d6*); 159.2 (2-C), 147.5 (6-C), 134.9 (5-H), 132.9 (4-C), 105.6 (3-C), 47.9 (2′ & 5′-C), 25.5 (3′ & 4′-C); ν_{max}/cm^{-1} (solid); 2977, 2876, 1614, 1566, 1524, 1481, 1330; *m/z* (*ES*) (Found: MH^+, 194.0932. $C_9H_{12}N_3O_2$ requires *MH*, 194.0924).

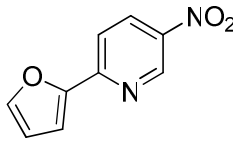
Preparation of 6-phenyl-pyridin-3-amine (29)



Tetrakis(triphenylphosphine) palladium (5.00 mol%), phenyl boronic acid (1.20 eq) and 2M Na_2CO_3 aqueous solution was added to a stirred solution of 2-chloro-5-nitropyridine **4** in THF. The reaction was stirred for 18 hours at 80°C, cooled and partitioned between EtOAc and water. The aqueous phase was separated and extracted (EtOAc), the combined organics washed with brine, dried and concentrated to give 5-nitro-2-(phenyl) pyridine. This compound was reacted according to Method B. Trituration with petroleum ether gave the title compound **29** (0.33 g,

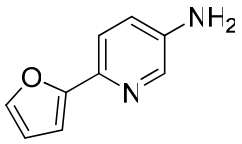
1.97 mmol, 89%) as brown crystalline prisms; m.p. 102.2 – 104.4 °C; R_f 0.1 (1:4 EtOAc–Petrol); HPLC (RT = 2.14 min); LCMS (Method A), (RT = 0.69 min, *m/z* (ES) Found MH^+ 171.1); δ_H (300 MHz, DMSO-*d6*); 8.02 (1H, d, *J* 2.5, 2-H), 7.91 (2H, dd, *J* 1.0 & 8.5, 2′ & 6′-H), 7.63 (1H, d, *J* 8.5, 5-H), 7.38 (2H, t, *J* 8.0, 3′ & 5′-H), 7.27 (1H, t, *J* 7.0 & 8.5, 4′-H), 7.00 (1H, dd, *J* 2.5 & 8.5, 4-H), 5.48 (2H, s, NH_2); δ_C (75 MHz, DMSO-*d6*); 144.5 (3-C), 144.0 (6-C), 139.7 (1′-H), 136.3 (2-C), 128.8 (3′ & 5′-C), 127.3 (4′-C), 125.3 (2′ & 6′-C), 120.9 (4-C), 120.6 (5-C); ν_{max}/cm^{-1} (solid); 3429, 3314, 3207, 1630, 1588, 1565, 1476, 1414; Spectroscopic data consistent with literature values.[6]

Preparation of 2-(2-furanyl)-5-nitropyridine (30)



Tetrakis(triphenylphosphine) palladium (5 mol%), the furanyl-2-boronic acid (1.20 eq) and 2M Na_2CO_3 aqueous solution was added to a stirred solution of 2-chloro-5-nitropyridine **4** in THF. The reaction was stirred for 18 hours at 80°C, cooled and partitioned between EtOAc and water. The aqueous phase was separated and extracted (EtOAc), the combined organics washed with brine, dried and concentrated to give a crude solid. Trituration with petroleum ether gave the title compound **30** (0.57 g, 2.99 mmol, 94%) as yellow crystalline needles; m.p. 167.7 – 171.9 °C; R_f 0.40 (1:8 EtOAc–Petrol); LCMS (Method A), (RT = 1.78 min, *m/z* (ES) Found MH^+ 191.0); δ_H (500 MHz, $CDCl_3$); 9.45 (1H, d, *J* 2.5, 6-H), 8.55 (1H, dd, *J* 2.5 & 9.0, 4-H), 7.88 (1H, d, *J* 8.5, 3-H), 7.70 (1H, m, 5′-H), 7.37 (1H, d, *J* 3.5, 3′-H), 6.68 (1H, dd, *J* 1.5 & 3.5, 4′-H); δ_C (75 MHz, $CDCl_3$); 170.8 (5-C), 153.6 (aromatic quaternary C), 152.1 (aromatic quaternary C), 145.7 (6-C + 5′-C overlap), 132.1 (4-H), 117.9 (3-C), 113.9 (3′-C), 113.1 (4′-C); ν_{max}/cm^{-1} (solid); 3071, 1606, 1577, 1519, 1486, 1335; Spectroscopic data consistent with literature values.[7]

Preparation of 6-(2-furanyl)-pyridin-3-amine (31)



To a slurry of iron powder (0.77 g, 13.7 mmol, 7.00 eq) in MeOH/H_2O/AcOH (1 ml: 1 ml: 0.1 ml) was added 2-(2-furanyl)-5-nitropyridine **30**. The reaction mixture was heated to reflux for one hour, cooled and 1M NaOH (3 ml) was added. The mixture was filtered through celite (washed with MeOH) and concentrated. The oil was extracted with EtOAc, dried (Na_2SO_4), and concentrated to give a crude solid. Trituration with petroleum ether gave the title compound **31** (0.12 g, 0.70 mmol, 53%) as a off-white crystalline powder; m.p. 102.3 – 104.3 °C; R_f 0.18 (1:1 EtOAc–Petrol); HPLC (RT = 1.85 min); δ_H (300 MHz, DMSO-*d6*); 7.94 (1H, d, *J* 1.5, 2-H), 7.65 (1H, d, *J* 1.0, 5′-H), 7.41 (1H, d, *J* 5.0, 5-H), 6.96 (2H, dd, *J* 2.0 & 5.0, 4-H), 6.72 (1H, d, *J* 2.0, 3′-H), 6.54 (1H, d, *J* 2.0, 4′-H), 5.52 (2H, s, NH_2); δ_C (75 MHz, DMSO-*d6*); 154.2 (2′-C), 144.0 (3-C), 141.8 (5′-H), 137.2 (6-C), 135.9 (2-C), 120.0 (4-C), 118.8 (5-C), 111.8 (4′-C), 104.3 (3′-C); ν_{max}/cm^{-1} (solid); 3437, 3180, 2531, 1615, 1504; *m/z* (*ESI*) 161.1 (100% MH^+).

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