Discovery of a Novel Class of Orally Active Trypanocidal *N*-Myristoyltransferase Inhibitors

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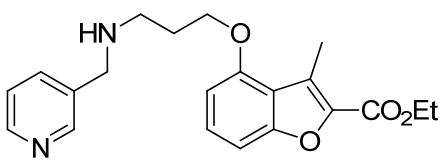
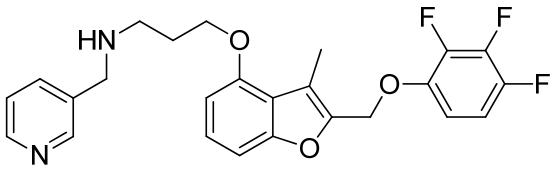
Chemicals and solvents were purchased from the Aldrich Chemical Company, Fluka, ABCR, VWR, Acros, Fisher Chemicals and Alfa Aesar and were used as received unless otherwise stated. Air- and moisture-sensitive reactions were carried out under an inert atmosphere of argon in oven-dried glassware. Analytical thin-layer chromatography (TLC) was performed on pre-coated TLC plates (layer 0.20 mm silica gel 60 with fluorescent indicator UV254, from Merck). Developed plates were air-dried and analyzed under a UV lamp (UV254/365 nm). Flash column chromatography was performed using pre-packed silica gel cartridges (230-400 mesh, 40–63 μm, from SiliCycle) using a Teledyne ISCO Combiflash Companion, or Combiflash Retrieve. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance II 500 spectrometer (^{1}H at 500.1 MHz, ^{13}C at 125.8 MHz) or a Bruker DPX300 spectrometer (^{1}H at 300.1 MHz). Chemical shifts (δ) are expressed in ppm recorded using the residual solvent as the internal reference in all cases. Signal splitting patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), pentet (p), multiplet (m), broad (br), or a combination thereof. Coupling constants (*J*) are quoted to the nearest 0.1 Hz. LC-MS analyses were performed with either an Agilent HPLC 1100 series connected to a Bruker Daltonics MicrOTOF, or an Agilent Technologies 1200 series HPLC connected to an Agilent Technologies 6130 quadrupole LC-MS, where both instruments were connected to an Agilent diode array detector. LC-MS chromatographic separations were conducted with a Waters Xbridge C18 column, 50 mm x 2.1 mm, 3.5 μm particle size; mobile phase, water/acetonitrile +0.1% HCOOH, or water/acetonitrile + 0.1% NH_3; linear gradient 80:20 to 5:95 over 3.5 min, and then held for 1.5 min; flow rate 0.5 mL min^{-1}. All assay compounds had a measured purity of ≥95% (by TIC and UV) as determined using this analytical LC-MS system. High resolution electrospray measurements were performed on a Bruker Daltonics MicrOTOF mass spectrometer. Microwave-assisted chemistry was performed using a Biotage Initiator Microwave Synthesizer.

Compounds **25**, **26**, **33** and **34** were purchased from Enamine as solids. Purity (>97%) and molecular mass were confirmed by HPLC high resolution mass spectrometry.



Ro-09-4609

*Tb*NMT, IC_{50} >100 μM



Ro-09-4879

*Tb*NMT, IC_{50} >100 μM

Figure S1: Structure and activity of literature anti-fungal NMT Inhibitors.

Prototypical procedure for preparation of a sulfonamide from an amine and a sulfonyl chloride:

4-Methoxy-2,3,6-trimethyl-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)benzenesulfonamide (1).

4-Methoxy-2,3,6-trimethylbenzenesulfonyl chloride (500 mg, 2.0 mmol) was added portionwise to a stirred solution of 4-amino-1,3,5-trimethyl-1*H*-pyrazole (250 mg, 2.0 mmol) in pyridine (10.0 ml) at rt. The reaction was stirred for 24 h then concentrated to dryness *in vacuo*. The resulting residue was diluted with DCM, washed with saturated aqueous $NaHCO_3$, the organic phase separated, dried ($MgSO_4$), filtered and concentrated to dryness *in vacuo*. Trituration from Et_2O and collection by vacuum filtration gave the title compound as a fine off-white solid (380 mg, 1.13 mmol, 57%). ^{1}H NMR (500MHz, DMSO-d_6): δ 8.87 (s, 1H), 6.67 (s, 1H), 3.48 (s, 3H), 3.28 (s, 3H), 2.33 (s, 3H), 2.21 (s, 3H), 2.01 (s, 3H), 1.77 (s, 3H), 1.54 (s, 3H). HRMS (*m/z*): [MH^+] calcd for $C_{16}H_{24}N_3SO_3$, 338.1533; found 338.1533.

***N*-(3,5-Dimethyl-1*H*-pyrazol-4-yl)-4-methoxy-2,3,6-trimethylbenzenesulfonamide (2).**

Prepared from 4-methoxy-2,3,6-trimethylbenzenesulfonyl chloride (1.0 g, 4.0 mmol) and 3,5-dimethyl-1H-pyrazol-4-amine (440 mg, 4.0 mmol) in pyridine (25.0 ml) according to the method of **1**, to give the title compound as an off-white solid (870 mg, 2.7 mmol, 67%). ^{1}H NMR (500MHz, DMSO-d_6): δ 12.10 (s, 1H), 8.80 (s, 1H), 6.73 (s, 1H), 3.81 (s, 3H), 2.41 (s, 3H), 2.26 (s, 3H), 2.08 (s, 3H), 1.77 (s, 3H), 1.67 (s, 3H). HRMS (*m/z*): [MH^+] calcd for $C_{15}H_{22}N_3SO_3$, 324.1376; found 324.1380.

Prototypical procedure for *N*-alkylation of 4-sulfonylamino-3,5-dimethyl-1*H*-pyrazole (2):

***N*-(1-Propyl-3,5-dimethyl-1*H*-pyrazol-4-yl)-4-methoxy-2,3,6-trimethylbenzenesulfonamide (3).**

A solution of *N*-(3,5-dimethyl-1*H*-pyrazol-4-yl)-4-methoxy-2,3,6-trimethylbenzenesulfonamide **2** (100 mg, 0.31 mmol), cesium carbonate (202 mg, 0.62 mmol) and 1-bromopropane (76 mg, 0.62 mmol) in DMF (10.0 ml) was heated to 80ºC for 1 h in a microwave. The reaction was partitioned between ethyl acetate (25 ml) and brine (25 ml), dried ($MgSO_4$), filtered and concentrated to dryness *in vacuo*. The resulting residue was purified by column chromatography (SiO_2, 1:1 ethyl acetate:hexane) to give the title compound as an off-white solid (27 mg, 0.07 mmol, 24%). ^{1}H NMR (500MHz, DMSO-d_6): . δ 8.67 (s, 1H), 6.45 (s, 1H), 4.46 (t, J = 6.9 Hz, 2H), 3.78 (s, 3H), 2.58 (s, 3H), 2.36 (s, 3H), 2.16 (s, 3H), 2.04 (s, 3H), 1.98 (m, 2H), 1.83 (s, 3H), 1.21 (t, J = 6.9 Hz, 3H). HRMS (*m/z*): [MH^+] calcd for $C_{18}H_{28}N_3SO_3$, 366.1846; found 366.1847.

***N*-(1-Isopropyl-3,5-dimethyl-1*H*-pyrazol-4-yl)-4-methoxy-2,3,6-trimethylbenzenesulfonamide (4).**

Prepared from *N*-(3,5-dimethyl-1*H*-pyrazol-4-yl)-4-methoxy-2,3,6-trimethylbenzenesulfonamide **2** (100 mg, 0.31 mmol), cesium carbonate (202 mg, 0.62 mmol) and 2-bromopropane (76 mg, 0.62 mmol) in DMF (5 ml) according to the method of **3** to give the title compound as an off-white solid (21 mg, 0.057 mmol, 19%). ^{1}H NMR (500MHz, DMSO-d_6): δ 8.34 (s, 1H), 6.38 (s, 1H), 4.80 (p, J = 6.8 Hz, 1H), 3.73 (s, 3H), 2.55 (s, 3H), 2.36 (s, 3H), 2.16 (s, 3H), 2.04 (s, 3H), 1.83 (s, 3H), 1.10 (d, J = 6.8 Hz, 6H). HRMS (*m/z*): [MH^+] calcd for $C_{18}H_{28}N_3SO_3$, 366.1846; found 366.1848.

***N*-(1,3-Dimethyl-5-morpholino-1*H*-pyrazol-4-yl)-4-methoxy-2,3,6-trimethylbenzene sulfonamide (5).**

Prepared from 4-methoxy-2,3,6-trimethylbenzenesulfonyl chloride (317mg, 1.27mmol) and 1,3-dimethyl-5-morpholino-1*H*-pyrazol-4-amine (250 mg, 1.27 mmol) in pyridine (3.0 ml) according to the method of **1**, to give the title compound as an off-white solid (320 mg, 0.78 mmol, 62%). ^{1}H NMR (500MHz, DMSO-d_6): δ 8.89 (s, 1H), 6.76 (s, 1H), 3.82 (s, 3H), 3.66-3.63 (m, 4H), 3.09-3.05 (m, 4H), 2.43 (s, 3H), 2.32 (s, 3H), 2.09 (s, 3H), 1.31 (s, 3H). HRMS (*m/z*): [MH^+] calcd for $C_{19}H_{29}N_4SO_4$, 409.1904; found 409.1911.

4-Methoxy-2,3,6-trimethyl-*N*-(1*H*-pyrazol-3-yl)benzenesulfonamide (6).

Prepared from 4-methoxy-2,3,6-trimethylbenzenesulfonyl chloride (100 mg, 0.4 mmol) and 1*H*-pyrazol-3-amine (33 mg, 0.4 mmol) in pyridine (3.0 ml) according to the method of **1**, to give the title compound as an off-white solid (23 mg, 0.078 mmol, 19%). ^{1}H NMR (500MHz, DMSO-d_6): δ 12.30 (s, 1H), 10.14 (s, 1H), 7.51 (s, 1H), 6.74 (s, 1H), 5.78 (s, 1H), 3.81 (s, 3H), 2.54 (s, 3H), 2.50 (s, 3H), 2.06 (s, 3H). HRMS (*m/z*): [MH^+] calcd for $C_{13}H_{18}N_3SO_3$, 296.1063; found 296.1066.

***N*-(Imidazo[1,2-a]pyridin-3-yl)-4-methoxy-2,3,6-trimethylbenzenesulfonamide (7).**

Prepared from 4-methoxy-2,3,6-trimethylbenzenesulfonyl chloride (248 mg, 1.0 mmol) and imidazo[1,2-a]pyridin-3-amine (133 mg, 1.0 mmol) in pyridine (10.0 ml) according to the method of **1**, to give the title compound as an off-white solid (121 mg, 0.35 mmol, 35%). ^{1}H NMR (500MHz, DMSO-d_6): δ 10.19 (br s, 1H), 8.20 (d, J = 7.1 Hz, 1H), 7.53 (d, J = 9.1 Hz, 1H), 7.32-7.28 (m, 1H), 7.00-6.96 (m 1H), 6.92 (s, 1H), 6.74 (s, 1H), 3.82 (s, 3H), 2.51 (s, 3H), 2.45 (s, 3H), 2.09 (s, 3H). HRMS (*m/z*): [MH^+] calcd for $C_{17}H_{20}N_3SO_3$, 346.1220; found 346.1221.

4-Methoxy-2,3,6-trimethyl-*N*-(pyridin-3-yl)benzenesulfonamide (8).

Prepared from 4-methoxy-2,3,6-trimethylbenzenesulfonyl chloride (248 mg, 1.0 mmol) and 3-aminopyridine (94 mg, 1.0 mmol) in pyridine (4.0 ml) according to the method of **1**, to give the title compound as an off-white solid (117 mg, 0.38 mmol, 38%). ^{1}H NMR (500MHz, DMSO-d_6): δ 10.48 (s, 1H), 8.20 (d, J = 1.4 Hz, 1H), 8.19 (d, J = 1.7 Hz, 1H), 7.33 (ddd, J = 8.3 Hz, 1.7 Hz, 1.5 Hz, 1H), 7.26 (dd, J = 8.3 Hz, 4.6 Hz, 1H), 6.82 (s, 1H), 3.82 (s, 3H), 2.58 (s, 3H), 2.52 (s, 3H), 2.05 (s, 3H). HRMS (*m/z*): [MH^+] calcd for $C_{15}H_{19}N_2SO_3$, 307.1111; found 307.1102.

4-Methoxy-2,3,6-trimethyl-*N*-(2-methylpyridin-3-yl)benzenesulfonamide (9).

Prepared from 4-methoxy-2,3,6-trimethylbenzenesulfonyl chloride (248 mg, 1.0 mmol) and 2-methyl-3-aminopyridine (107 mg, 1.0 mmol) in pyridine (4.0 ml) according to the method of **1**, to give the title compound as an off-white solid (110 mg, 0.34 mmol, 34%). ^{1}H NMR (500MHz, DMSO-d_6): δ 9.66 (s, 1H), 8.27 (dd, J = 4.6 Hz, 1.4 Hz, 1H), 7.33 (dd, J = 8.1 Hz, 1.4 Hz, 1H), 7.17 (dd, J = 7.9 Hz, 4.6 Hz, 1H), 6.76 (s, 1H), 3.82 (s, 3H), 2.42 (s, 3H), 2.31 (s, 3H), 2.23 (s, 3H), 2.08 (s, 3H). HRMS (*m/z*): [MH^+] calcd for $C_{16}H_{21}N_2SO_3$, 321.1267; found 321.1259.

***N*-(3,5-Dimethylisoxazol-4-yl)-4-methoxy-2,3,6-trimethylbenzenesulfonamide (10).**

Prepared from 4-methoxy-2,3,6-trimethylbenzenesulfonyl chloride (248 mg, 1.0 mmol) and 3,5-dimethylisoxazol-4-amine (112 mg, 1.0 mmol) in pyridine (4.0 ml) according to the method of **1**, to give the title compound as an off-white solid (212 mg, 0.65 mmol, 65%). ^{1}H NMR (500MHz, DMSO-d_6): δ 9.30 (s, 1H), 6.81 (s, 1H), 3.83 (s, 3H), 2.46 (s, 3H), 2.33 (s, 3H), 2.10 (s, 3H), 1.93 (s, 3H), 1.83 (s, 3H). HRMS (*m/z*): [MH^+] calcd for $C_{15}H_{21}N_2SO_4$, 325.1217; found 325.1201.

***N*-(3,4-Dimethylisoxazol-5-yl)-4-methoxy-2,3,6-trimethylbenzenesulfonamide (11).**

Prepared from 4-methoxy-2,3,6-trimethylbenzenesulfonyl chloride (248 mg, 1.0 mmol) and 3,4-dimethylisoxazol-5-amine (112 mg, 1.0 mmol) in pyridine (4.0 ml) according to the method of **1**, to give the title compound as white solid (72 mg, 0.22 mmol, 22%). ^{1}H NMR (500MHz, DMSO-d_6): δ 10.78 (s, 1H), 6.75 (s, 1H), 3.76 (s, 3H), 2.40 (s, 3H), 2.39 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H), 1.58 (s, 3H). HRMS (*m/z*): [MH^+] calcd for $C_{15}H_{21}N_2SO_4$, 325.1217; found 325.1208.

4-Methoxy-2,3,6-trimethyl-*N*-phenylbenzenesulfonamide (12).

Prepared from 4-methoxy-2,3,6-trimethylbenzenesulfonyl chloride (248 mg, 1.0 mmol) and aniline (93 mg, 1.0 mmol) in pyridine (3.0 ml) according to the method of **1**, to give the title compound as white solid (212 mg, 0.69 mmol, 69%). ^{1}H NMR (500MHz, DMSO-d_6): δ 10.15 (s, 1H), 7.19 (t, J =

7.5 Hz, 2H), 6.98-6.94 (m, 3H), 6.78 (s, 1H), 3.80 (s, 3H), 2.59 (s, 3H), 2.51 (s, 3H), 2.05 (s, 3H). HRMS (*m/z*): [MH^+] calcd for $C_{16}H_{20}NSO_3$, 306.1158; found 306.1144.

***N*-Benzyl-4-methoxy-2,3,6-trimethylbenzenesulfonamide (13).**

Prepared from 4-methoxy-2,3,6-trimethylbenzenesulfonyl chloride (248 mg, 1.0 mmol) and benzylamine (107 mg, 1.0 mmol) in pyridine (3.0 ml) according to the method of **1**, to give the title compound as an off-white solid (193 mg, 0.61 mmol, 62%). ^{1}H NMR (500MHz, DMSO-d_6): δ 7.92 (t, *J* = 6.5 Hz, 1H), 7.25-7.15 (m, 5H), 6.77 (s, 1H), 3.94 (d, *J* = 6.5 Hz, 2H), 3.82 (s, 3H), 2.58 (s, 3H), 2.46 (s, 3H), 2.05 (s, 3H). HRMS (*m/z*): [MH^+] calcd for $C_{17}H_{22}NSO_3$, 320.1315; found 320.1299.

4-Methoxy-2,3,6-trimethyl-*N*-((1,3,5-trimethyl-1*H*-pyrazol-4-yl)methyl)benzenesulfonamide (14).

Prepared from 4-methoxy-2,3,6-trimethylbenzenesulfonyl chloride (248 mg, 1.0 mmol) and 1,3,5-trimethyl-1*H*-pyrazol-4-yl)methanamine (139 mg, 1.0 mmol) in pyridine (4.0 ml) according to the method of **1**, to give the title compound as an off-white solid (312 mg, 0.89 mmol, 89%). ^{1}H NMR (500MHz, DMSO-d_6): δ 7.40 (t, *J* = 5.6 Hz, 1H), 6.80 (s, 1H), 3.84 (s, 3H), 3.63 (d, *J* = 5.6 Hz, 2H), 3.53 (s, 3H), 2.58 (s, 3H), 2.45 (s, 3H), 2.08 (s, 3H), 1.94 (s, 3H), 1.91 (s, 3H). HRMS (*m/z*): [MH^+] calcd for $C_{17}H_{26}N_3SO_3$, 352.1689; found 352.1690.

4-Bromo-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)benzenesulfonamide (15).

Prepared from 4-bromobenzenesulfonyl chloride (5.0 g, 19.6 mmol) and 3,5-dimethylisoxazol-4-amine (2.45 g, 19.6 mol) in pyridine (40.0 ml) according to the method of **1**, to give the title compound as an off-white solid (5.1 g, 14.8 mmol, 76%). ^{1}H NMR (500MHz, DMSO-d_6): δ 9.21 (1H, s), 7.79 (d, *J* = 8.5 Hz, 2H), 7.56 (d, *J* = 8.5 Hz, 2H), 3.56 (s, 3H), 1.82 (s, 3H), 1.61 (s, 3H). HRMS (*m/z*): [MH^+] calcd for $C_{12}H_{15}N_3SO_2Br$, 344.0063; found 344.0059.

Prototypical procedure for sulfonamide *N*-alkylation with an alkyl halide:

4-Bromo-*N*-methyl-N-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-benzenesulfonamide (16).

Sodium hydride (88 mg, 95 % w/w, 3.48 mmol) was added portionwise to a solution of 4-bromo-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-benzenesulfonamide (**15**) (1.0 g, 2.91 mmol) in DMF (10.0 ml) at 0°C. When effervescence had ceased, methyl iodide (217 µl, 3.48 mmol) was added dropwise and the reaction was allowed to warm to rt over 4 h. The reaction was concentrated to dryness *in vacuo*, diluted by addition of DCM (30 ml), washed with water (2 x 15 ml), dried ($MgSO_4$) and

concentrated *in vacuo*. The residue was triturated from Et_2O and collected by vacuum filtration to give the title compound as a fine off-white solid (557 mg, 1.56 mmol, 54%). ^{1}H NMR (500MHz, DMSO-d_6): δ 7.71 (d, *J* = 8.6 Hz, 2H), 7.61 (d, *J* = 8.6 Hz, 2H), 3.61 (s, 3H), 3.21 (s, 3H), 2.13 (s, 3H), 1.67 (s, 3H). HRMS (*m/z*): [MH^+] calcd for $C_{13}H_{17}N_3SO_2$, 358.0219; found 358.0210.

4-Bromo-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)benzamide (17).

4-Bromobenzoyl chloride (2.0 g, 9.13 mmol) was added to a stirred solution of 1,3,5-trimethyl-1*H*-pyrazol-4-amine (1.3 g, 10.4 mmol) in pyridine (20.0 ml) for 1 h at rt. The reaction was concentrated to dryness *in vacuo*, then diluted with DCM (100 ml), washed with saturated aqueous sodium hydrogencarbonate solution, the organic layer separated and dried ($MgSO_4$) and concentrated *in vacuo*. The resulting residue was recrystallised from ether to give the title compound as a white solid (1.98 g, 6.42 mmol, 70%). ^{1}H NMR (500MHz, DMSO-d_6): δ 9.60 (s, 1H), 7.91 (d, *J* = 8.6 Hz, 2H), 7.73 (d, *J* = 8.6 Hz, 2H), 3.66 (s, 3H), 2.08 (s, 3H), 1.99 (s, 3H). HRMS (*m/z*): [MH^+] calcd for $C_{13}H_{15}N_3OBr$, 308.0393; found 308.0404.

4-Bromo-*N*-isobutyl-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)benzamide (18).

Isobutyraldehyde (73 μL, 0.8 mmol) was added to an ice-cooled mixture of 1,3,5-trimethyl-1*H*-pyrazol-4-amine (100 mg, 0.8 mmol), acetic acid (137 μl, 2.4 mmol) and $NaBH(OAc)_3$ (424 mg, 2.0 mmol) in anhydrous DCM (10.0 mL). The reaction mixture was allowed to warm to rt and stirred for 6 h. The reaction was diluted with DCM (50 ml), washed with water, the organic layer separated and concentrated *in vacuo*. Chromatography (SiO_2, EtOAc) gave *N*-isobutyl-1,3,5-trimethyl-1H-pyrazol-4-amine as a low-melting white solid (92 mg, 0.51 mmol, 64 %). 4-Bromobenzoylchloride (90 mg, 0.41 mmol) was added to a solution of *N*-isobutyl-1,3,5-trimethyl-1H-pyrazol-4-amine (74 mg, 0.41 mmol) in DCM (5.0 mL) and pyridine (1.0 ml). The reaction mixture was stirred at rt for 5 h, concentrated *in vacuo* and purified by column chromatography (SiO_2, 1:1 EtOAc:Hexanes) to give the title compound (55 mg, 0.15 mmol, 37%). ^{1}H NMR (500MHz, DMSO-d_6): δ 7.43 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 3.49-3.55 (m, 1H), 3.51 (s, 3H), 3.38-3.43 (m, 1H), 2.00 (s, 3H), 1.90 (s, 3H,), 1.64-1.73 (m, 1H), 0.92 (dd, *J* = 4.1 Hz, 6.6 Hz, 6H). HRMS (*m/z*): [MH^+] calcd for $C_{17}H_{23}N_3O$, 364.1019; found 364.1033.

***N*-(4-Bromophenyl)-1,3,5-trimethyl-1*H*-pyrazole-4-sulfonamide (19).**

Prepared from 1,3,5-trimethyl-1H-pyrazole-4-sulfonyl chloride (122 mg, 0.58 mmol) and 4-bromoaniline (100 mg, 0.58 mmol) in pyridine (10.0 ml) according to the method of **1**, to give the title compound as an off-white solid (115 mg, 0.35 mmol, 60%). ^{1}H NMR (500MHz, DMSO-d_6): δ 10.22 (s, 1H), 7.45 (d, J = 8.8 Hz, 2H), 7.01 (d, J = 8.8 Hz, 2H), 3.63 (s, 3H), 2.33 (s, 3H), 2.17 (s, 3H). HRMS (*m/z*): [MH^+] calcd for $C_{12}H_{15}N_3SO_2Br$, 344.0063; found 344.0069.

4-(4-Bromophenyl)sulfonylmethyl-1,3,5-trimethyl-1*H*-pyrazole (20).

A stirred solution of (1,3,5-trimethyl-1*H*-pyrazol-4-yl)methanol (1.4 g, 10.0 mmol) in chloroform (20.0 ml) at rt was treated dropwise with thionyl chloride (2.9 mL, 40.0 mmol). The reaction was then heated to reflux for 1.5 h. Concentration to dryness *in vacuo* gave 4-(chloromethyl)-1,3,5-trimethyl-1*H*-pyrazole hydrochloride as a fine white powder (2.8 g, 10.0 mmol, 99%). 4-Bromobenzenesulfonyl chloride (5.0 g, 19.6 mmol) was added portionwise to a stirred solution of potassium phosphate (2.67 g, 19.6 mmol) and sodium sulfite (4.94 g, 39.2 mmol) in water (60.0 ml) at 30°C. The reaction was then heated to 60°C for 18 h. The reaction was concentrated to dryness *in* vacuo to give crude sulfinate salt. This material was then added portionwise to a solution of 4-(chloromethyl)-1,3,5-trimethyl-1H-pyrazole hydrochloride (559 mg, 2.0 mmol) in acetone (8.0 mL) and water (5 ml) and heated to 60°C for 2 h. Filtration followed by purification by column chromatography (SiO_2, 1:9 MeOH:DCM) gave the title compound as a fine off-white solid (103 mg, 0.3 mmol, 15%). ^{1}H NMR (300MHz, DMSO-d_6): δ 7.88 (d, J = 8.6 Hz, 2H), 7.62 (d, J = 8.6 Hz, 2H), 4.43 (s, 2H), 3.57 (s, 3H), 1.92 (s, 3H), 1.8 (s, 3H). HRMS (*m/z*): [MH^+] calcd for $C_{13}H_{16}N_2SO_2Br$, 343.0110; found 343.0110.

***N*-(4-Bromobenzyl)-1,3,5-trimethyl-1*H*-pyrazol-4-amine (21).**

A solution of 4-bromobenzyl bromide (502 mg, 2.01 mmol), potassium carbonate (600 mg, 4.3 mmol), potassium iodide (200 mg, 1.2 mmol) and 1,3,5-trimethyl-1*H*-4-aminopyrazole (256 mg, 2.04 mmol) in DMF (10.0 ml) was heated at 80ºC for 16 h. The reaction was concentrated *in vacuo*, diluted with water (5 ml) and stirred for a further 1 h at rt prior to extraction with EtOAc (3 x 25 ml). The extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. Chromatography (SiO_2, 1:10 MeOH:DCM) gave the title compound as a white solid (255mg, 0.86 mmol, 43%). ^{1}H NMR (500MHz, DMSO-d_6): δ 9.45 (s, 1H), 7.45 (d, J = 8.1 Hz, 2H), 7.18 (d, J = 8.1 Hz, 2H), 3.94 (s, 2H), 3.67 (s, 3H), 2.12 (s, 3H), 2.01 (s, 3H). HRMS (*m/z*): [MH^+] calcd for $C_{13}H_{17}N_3Br$, 294.0600; found 294.0552

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4-((4-Bromophenoxy)methyl)-1,3,5-trimethyl-1*H*-pyrazole (22).

A solution of 4-bromophenol (482 mg, 2.79 mmol) and (1,3,5-trimethyl-1*H*-pyrazol-4-yl)methanol (585 mg, 4.18 mmol) in THF (15.0 ml) was treated with polymer-supported triphenylphosphine (polystyrene, 2.2 mmol/g, 1.9 g, 4.18 mmol) followed by diisopropylazodicarboxylate (844 μl, 4.18 mmol) and heated to 70ºC for 5 h, prior to concentration *in vacuo*. Chromatography (SiO_2, 4:1 hexanes:EtOAc) gave the title compound as a white solid (474 mg, 1.6 mmol, 58%). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.9 Hz, 2H), 6.87 (d, *J* = 8.9 Hz, 2H) 4.79 (s, 2H), 3.75 (s, 3H), 2.26 (s, 3H), 2.24 (s, 3H). HRMS (*m/z*): [MH^+] calcd for $C_{13}H_{16}N_2OBr$, 295.0441; found 295.0438.

4-Bromo-*N*-((1,3,5-trimethyl-1*H*-pyrazol-4-yl)methyl)benzenesulfonamide (23).

Prepared from 4-bromobenzene-1-sulfonyl chloride (275 mg, 1.08 mmol) and (1,3,5-trimethyl-1H-pyrazol-4-yl)methanamine (150 mg, 1.08 mmol) in pyridine (5.0 ml) according to the method of **1**, to give the title compound as a white solid (279 mg, 0.78 mmol, 72%). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.84 (t, *J* = 5.7 Hz, 1H), 7.78 (d, *J* = 8.8 Hz, 2H), 7.65 (d, *J* = 8.8 Hz, 2H), 3.72 (d, *J* = 5.7 Hz, 2H), 3.52 (s, 3H), 1.99 (s, 3H), 1.94 (s, 3H). HRMS (*m/z*): [MH^+] calcd for $C_{13}H_{17}N_3SO_2Br$, 358.0219; found 358.0209.

***N*-(4-Bromophenyl)-1,3,5-trimethyl-1*H*-pyrazole-4-carboxamide (24).**

Prepared from 4-bromoaniline (100 mg, 0.58 mmol) and 1,3,5-trimethyl-1H-pyrazole-4-carbonyl chloride (100 mg, 0.59 mmol) in pyridine (5.0 ml) according to the method of **17**, to give the title compound as a white solid (112 mg, 0.38 mmol, 62%). ^{1}H NMR (500MHz, DMSO-d_6): δ 7.62 (d, *J* = 8.7 Hz, 2H), 7.21 (d, *J* = 8.7 Hz, 2H), 6.23 (s, 1H), 3.72 (s, 3H), 2.12 (s, 3H), 1.89 (s, 3H). HRMS (*m/z*): [MH^+] calcd for $C_{13}H_{15}N_3OBr$, 308.0393; found 308.0404.

4-Cyano-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)benzenesulfonamide (27).

Prepared from 4-cyanobenzene-1-sulfonyl chloride (201 mg, 1.0 mmol) and 4-amino-1,3,5-trimethyl-1*H*-pyrazole (125 mg, 1.0 mmol) in pyridine (3.0 ml) according to the method of **1**, to give the title compound as an off-white solid (172 mg, 0.59 mmol, 59%). ^{1}H NMR (500MHz, DMSO-d_6): δ 9.45 (s, 1H), 8.07 (d, *J* = 8.8 Hz, 2H), 7.79 (d, *J* = 8.8 Hz, 2H), 3.56 (s, 3H), 1.80 (s, 3H), 1.59 (s, 3H). HRMS (*m/z*): [MH^+] calcd for $C_{13}H_{15}N_4SO_2$, 291.0910; found 291.0904.

2,6-Dichloro-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)benzenesulfonamide (28).

Prepared from 2,6-dichlorobenzene-1-sulfonyl chloride (245 mg, 1.0 mmol) and 4-amino-1,3,5-trimethyl-1*H*-pyrazole (125 mg, 1.0 mmol) in pyridine (3.0 ml) according to the method of **1**, to give the title compound as an off-white solid (113 mg, 0.38 mmol, 39%). ^{1}H NMR (500MHz, DMSO-d_6): δ 9.82 (s, 1H), 7.58 (s, 1H), 7.57 (s, 1H), 7.50-7.47 (m, 1H), 3.64 (s, 3H), 2.17 (s, 3H), 2.06 (s, 3H). m/z (ES$^+$, 70V) 335.1 [MH$^+$].

4-Bromo-2,6-dichloro-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)- benzenesulfonamide (29).

Prepared from 4-bromo-2,6-dichlorobenzenesulfonyl chloride (5.0 g, 15.4 mmol) and 4-amino-1,3,5-trimethyl-1*H*-pyrazole (1.93 g, 15.4 mmol) in pyridine (35.0 ml) according to the method of **1**, to give the title compound as an off-white solid (5.64 g, 13.7 mmol, 89%). ^{1}H NMR (300MHz, DMSO-d_6): δ 9.75 (s, 1H), 8.00 (s, 2H), 3.57 (s, 3H), 1.93 (s, 3H), 1.72 (s, 3H). HRMS (*m/z*): [MH$^+$] calcd for $C_{12}H_{13}N_3SO_2Cl_2Br$, 411.9283; found 411.9282.

4-(1*H*-Pyrazol-1-yl)-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)benzenesulfonamide (30).

Prepared from 4-(1*H*-pyrazol-1-yl)benzene-1-sulfonyl chloride (242 mg, 1.0 mmol) and 4-amino-1,3,5-trimethyl-1*H*-pyrazole (125 mg, 1.0 mmol) in pyridine (3.0 ml) according to the method of **1**, to give the title compound as an off-white solid (215 mg, 0.65 mmol, 65%). ^{1}H NMR (500MHz, DMSO-d_6): δ 9.16 (s, 1H), 8.65 (d, J = 2.5 Hz, 1H), 8.05 (d, J = 8.9 Hz, 2H), 7.85 (d, J = 1.8 Hz, 1H), 7.72 (d, J = 8.9 Hz, 2H), 6.63 (dd, J = 2.7 Hz, 1.8 Hz, 1H), 3.56 (s, 3H), 1.83 (s, 3H), 1.61 (s, 3H). HRMS (*m/z*): [MH$^+$] calcd for $C_{15}H_{18}N_5SO_2$, 332.1176; found 332.1171.

6-Morpholino-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)pyridine-3-sulfonamide (31).

Prepared from 6-chloro-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)pyridine-3-sulfonamide **37** (150 mg, 0.5 mmol) and morpholine (0.25 ml) in ethanol (2.0 ml), according to the method of **42** to give the title compound as a pale yellow powder (112 mg, 0.32 mmol, 64%). ^{1}H NMR (500MHz, DMSO-d_6): δ 8.95 (s br, 1H), 8.20 (d, J = 2.5 Hz, 1H), 7.62 (dd, J = 2.5 Hz, 9.2 Hz, 1H), 6.93 (d, J = 9.2 Hz, 1H), 3.68 (m, 4H), 3.59 (m, 4H), 3.57 (s, 3H), 1.89 (s, 3H), 1.64 (s, 3H). HRMS (*m/z*): [MH$^+$] calcd for $C_{15}H_{22}N_5SO_3$, 352.1438; found 352.1435.

4-(2-Methylthiazol-4-yl)-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)benzenesulfonamide (32).

Prepared from 4-(2-methylthiazol-4-yl)benzene-1-sulfonyl chloride (249 mg, 1.0 mmol) and 4-amino-1,3,5-trimethyl-1*H*-pyrazole (125 mg, 1.0 mmol) in pyridine (3.0 ml) according to the method of **1**, to give the title compound as an off-white solid (247 mg, 0.68 mmol, 68%). ^{1}H NMR

(500MHz, DMSO-d_6): δ 9.12 (s, 1H), 8.17 (s, 1H), 8.12 (d, *J* = 8.6 Hz, 2H), 7.67 (d, *J* = 8.6 Hz, 2H), 3.55 (s, 3H), 2.74 (s, 3H), 1.81 (s, 3H), 1.59 (s, 3H). HRMS (*m/z*): [MH^+] calcd for $C_{16}H_{19}N_4S_2O_2$, 363.0944; found 363.0945.

***N*-(4-(*N*-(1,3,5-Trimethyl-1*H*-pyrazol-4-yl)sulfamoyl)phenyl)acetamide (35).**

Prepared from 4-acetamidobenzene-1-sulfonyl chloride (233 mg, 1.0 mmol) and 4-amino-1,3,5-trimethyl-1*H*-pyrazole (125 mg, 1.0 mmol) in pyridine (3.0 ml) according to the method of **1**, to give the title compound as an off-white solid (220 mg, 0.68 mmol, 68%). ^{1}H NMR (500MHz, DMSO-d_6): δ 10.34 (s, 1H), 8.96 (s, 1H), 7.73 (d, *J* = 8.8 Hz, 2H), 7.54 (d, *J* = 8.8 Hz, 2H), 3.55 (s, 3H), 2.09 (s, 3H), 1.81 (s, 3H), 1.58 (s, 3H). HRMS (*m/z*): [MH^+] calcd for $C_{14}H_{19}N_4SO_3$, 323.1172; found 323.1184.

3',5'-Dichloro-4'-(*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)sulfamoyl)-[1,1'-biphenyl]-3-carboxamide (36).

Prepared from 4-bromo-2,6-dichloro-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-benzenesulfonamide (**29**) (250 mg, 0.61 mmol), (3-carbamoylphenyl)boronic acid (164 mg, 1.0 mmol), tribasic potassium phosphate (155 mg, 0.73 mmol), and Pd(dppf)Cl_2.DCM (30 mg, 0.36 mmol) in DMF (2.5 ml) and water (0.5 ml), according to the method of **56**, to give the title compound as an off-white powder (178 mg, 0.39 mmol, 64%). ^{1}H NMR (500MHz, DMSO-d_6): δ 9.66 (s, 1H), 8.28 (s, 2H), 8.06 (s, 2H), 8.02 (d, *J* = 8.2 Hz, 1H), 7.97 (d, *J* = 8.2 Hz, 1H), 7.61 (t, *J* = 8.2 Hz, 1H), 7.55 (s, 1H), 3.58 (s, 3H), 1.95 (s, 3H), 1.74 (s, 3H). HRMS (*m/z*): [MH^+] calcd for $C_{19}H_{19}N_4SO_3Cl_2$, 454.0447; found 454.0467.

6-Chloro-pyridine-3-sulfonic acid (1,3,5-trimethyl-1*H*-pyrazol-4-yl)-amide (37).

Prepared from 6-chloropyridine-3-sulfonyl chloride (4.8 g, 22.7 mmol) and 4-amino-1,3,5-trimethyl-1*H*-pyrazole (2.84 g, 22.7 mmol) in pyridine (35.0 ml) according to the method of **1**, to give the title compound as an off-white solid (5.13 g, 17.1 mmol, 75%). ^{1}H NMR (500MHz, DMSO-d_6): δ 9.51 (s, 1H), 8.59 (d, *J* = 2.3 Hz, 1H), 8.03 (dd *J* = 7.6 Hz, 2.3 Hz, 1H), 7.77 (d, *J* = 7.6Hz, 1H), 3.58 (s, 3H), 1.84 (s, 3H), 1.63 (s, 3H). HRMS (*m/z*): [MH^+] calcd for $C_{11}H_{14}N_4SO_2Cl$, 301.0521; found 301.0523.

Prototypical procedure for preparation of a 2-aminopyridine by displacement reaction of a 2-chloropyridine with an alkylamine (thermal conditions):

6-[2-(4-Methyl-piperazin-1-yl)-ethylamino]-pyridine-3-sulfonic acid (1,3,5-trimethyl-1*H*-pyrazol-4-yl)-amide (42).

6-Chloro-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)pyridine-3-sulfonamide (**37**) (225 mg, 0.75 mmol) and 4-(2-aminoethyl)-methylpiperazine (215 mg, 1.5 mmol) in ethanol (2.0 ml), was heated at 155°C for 1 h by microwave in a sealed vessel. Dilution with DCM (25 ml), washing with saturated aqueous sodium hydrogencarbonate solution (2 x 5 ml), drying ($MgSO_4$) and concentration *in vacuo* gave a residual oil which was subjected to chromatography (SiO_2, 10:90 MeOH:EtOAc) to give the title compound as an off-white powder (198 mg, 0.49 mmol, 65%). ^{1}H NMR (300MHz, DMSO-d_6): δ 8.77 (s, 1H), 8.07 (d, *J* = 2.2 Hz, 1H), 7.45 (dd, *J* = 2.2 Hz, 8.9 Hz, 1H), 7.28 (s br, 1H), 6.54 (d, *J* = 8.9 Hz, 1H), 3.57 (s, 3H), 3.44-3.39 (m, 2H), 2.41 (t, *J* = 6.1 Hz, 2H), 2.41 (s br, 4H), 2.36-2.31 (s br, 4H and 3H), 2.16 (s, 3H), 1.89 (s, 3H), 1.67 (s, 3H). HRMS (*m/z*): [MH^+] calcd for $C_{18}H_{30}N_7SO_2$, 408.2176; found 408.2185.

6-(Benzylamino)-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)pyridine-3-sulfonamide (38).

Prepared from 6-chloro-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)pyridine-3-sulfonamide (**37**) (150 mg, 0.5 mmol) and benzylamine (268 mg, 2.5 mmol) in ethanol (1.5 ml), according to the method of **42** to give the title compound as a pale yellow powder (137 mg, 0.37 mmol, 74%). ^{1}H NMR (500MHz, DMSO-d_6): δ 8.76 (s br, 1H), 8.06 (d, *J* = 2.4 Hz, 1H), 7.98 (t, *J* = 5.9 Hz, 1H), 7.48 (dd, *J* = 8.9 Hz, 2.4 Hz, 1H), 7.34-7.23 (m, 5H), 6.58 (d, *J* = 8.3 Hz, 1H), 4.55 (d, *J* = 5.7 Hz, 2H), 3.55 (s, 3H), 1.85 (s, 3H), 1.64 (s, 3H). HRMS (*m/z*): [MH^+] calcd for $C_{18}H_{22}N_5SO_2$, 372.1489; found 372.1507.

6-(((1H-Indol-5-yl)methyl)amino)-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)pyridine-3-sulfonamide (39).

Prepared from 6-chloro-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)pyridine-3-sulfonamide (**37**) (130 mg, 0.43 mmol) and (1*H*-indol-5-yl)methanamine (314 mg, 2.15 mmol) in ethanol (2.0 ml), according to the method of **42**, to give the title compound as an off-white powder (105mg, 0.25mmol, 59%). ^{1}H NMR (500MHz, DMSO-d_6): δ 11.04 (s, 1H), 8.80 (s, 1H), 8.07 (d, *J* = 2.4 Hz, 1H), 7.91 (t, *J* = 5.7 Hz, 1H), 7.46 (dd, *J* = 9.0 Hz, 2.4 Hz, 1H), 7.44 (s, 1H), 7.35-7.31 (m, 2H), 7.0 (dd, *J* = 8.3 Hz, 1.6 Hz, 1H), 6.58-6.54 (m, 1H), 6.38-6.36 (m, 1H), 4.59 (s, 2H), 3.53 (s, 3H), 1.85 (s, 3H), 1.66 (s, 3H). HRMS (*m/z*): [MH^+] calcd for $C_{20}H_{23}N_6SO_2$, 411.1593; found 411.1605.

6-((4-((Dimethylamino)methyl)benzyl)(methyl)amino)-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)pyridine-3-sulfonamide (40).

Prepared from 6-chloro-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)pyridine-3-sulfonamide (**37**) (250 mg, 0.83 mmol) and *N*,*N*-dimethyl-1-(4-((methylamino)methyl)phenyl)methanamine (560 mg, 2.23 mmol) in ethanol (1.5 ml), according to the method of **42**, to give the title compound as an off-white powder (216 mg, 0.49 mmol, 59%). ^{1}H NMR (500MHz, DMSO-d_6): δ 8.90 (s, 1H), 8.18 (d, J = 2.6 Hz, 1H), 7.62 (dd, J = 9.0 Hz, 2.6 Hz, 1H), 7.51 (d, J = 8.2 Hz, 2H), 7.24 (d, J = 8.2 Hz, 2H), 6.77 (d, J = 9.2 Hz, 1H), 4.92 (s, 2H), 4.54 – 4.37 (s br, 6H), 4.34 (s, 2H), 3.57 (s, 3H), 2.68 (s, 3H), 2.67 (s, 3H), 1.90 (s, 3H). HRMS (*m/z*): [MH$^+$] calcd for $C_{22}H_{31}N_6SO_2$, 443.2224; found 443.2226.

6-((2-Morpholinoethyl)amino)-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)pyridine-3-sulfonamide (41).

Prepared from 6-chloro-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)pyridine-3-sulfonamide (**37**) (150 mg, 0.5 mmol) and 2-morpholinoethanamine (325 mg, 2.5 mmol) in ethanol (1.5 ml), according to the method of **42**, to give the title compound as a white powder (96 mg, 0.24 mmol, 49%). ^{1}H NMR (500MHz, DMSO-d_6): δ 8.78 (br s, 1H), 8.06 (d, J = 2.30 Hz, 1H), 7.47-7.44 (m, 1H), 7.37 (br s, 1H), 6.55 (d, J = 9.20 Hz, 1H), 3.58-3.55 (m, 7H), 3.45-3.40 (m, 2H), 2.45 (t, J = 6.72 Hz, 2H), 2.41-2.38 (m, 4H), 1.88 (s, 3H), 1.65 (s, 3H). HRMS (*m/z*): [MH$^+$] calcd for $C_{17}H_{27}N_6SO_3$, 395.1860; found 395.1876.

6-((2-(Piperazin-1-yl)ethyl)amino)-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)pyridine-3-sulfonamide (43).

Prepared from 6-chloro-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)pyridine-3-sulfonamide (**37**) (150 mg, 0.5mmol) and 2-(piperazin-1-yl)ethanamine (0.25ml) in ethanol (3.0 ml), according to the method of **42**, to give the title compound as a white powder (61 mg, 0.16 mmol, 31%). ^{1}H NMR (500MHz, DMSO-d_6): δ 8.18 (d, J = 2.3 Hz, 1H), 7.64 (dd, J = 8.8 Hz, 2.3 Hz, 1H), 6.65 (d, J = 8.8 Hz, 1H), 3.66 (s, 3H), 3.38 (t, J = 5.1 Hz, 2H), 3.14 (t, J = 5.1 Hz, 2H), 2.60 (s br, 4H), 2.02 (s, 3H), 1.79 (s, 3H) 1.73 (m br, 4H). HRMS (*m/z*): [MH$^+$] calcd for $C_{17}H_{28}N_7SO_2$, 394.2020; found 394.2036.

6-((2-(Piperidin-1-yl)ethyl)amino)-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)pyridine-3-sulfonamide (44).

Prepared from 6-chloro-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)pyridine-3-sulfonamide (**37**) (0.20 g, 0.66 mmol) and 2-(piperidin-1-yl)ethanamine (0.13 ml, 1.3 mmol) in ethanol (3.0 ml), according to the method of **42**, to give the title compound as a beige powder (218 mg, 0.56 mmol, 85%). ^{1}H

NMR (500MHz, DMSO-d_6): δ 8.39 (d, J = 2.3 Hz, 1H), 7.61 (dd, J = 8.8 Hz, 2.4 Hz, 1H), 6.46 (d, J = 8.8 Hz, 1H), 5.79 (s br, 1H NH), 3.70 (s, CH_3), 3.55 (s br, 2H), 2.74 (s br, 2H), 2.60 (s br, 4H), 2.13 (s, CH_3), 1.78 (s, CH_3), 1.73 (s br, 4H), 1.54 (s br, 2H). m/z (ES^+, 70V) 393.2 [MH^+].

6-((2-(4-Isopropylpiperazin-1-yl)ethyl)amino)-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)pyridine-3-sulfonamide (45).

Prepared from 6-chloro-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)pyridine-3-sulfonamide (**37**) (0.20 g, 0.66 mmol) and 2-(4-isopropylpiperazin-1-yl)ethanamine (0.1 ml) in ethanol (1.5 ml), according to the method of **42**, to give the title compound as a powder (97 mg, 0.22 mmol, 33%). ^{1}H NMR (500MHz, DMSO-d_6): δ 8.38 (d, J = 2.5 Hz, 1H), 7.60 (dd, J = 2.5 Hz, 9.2 Hz, 1H), 7.28 (d, J = 9.2 Hz, 1H), 3.68 (s, 3H), 3.40 (m br, 2H), 2.70 (m br, 2H), 2.63 (m br, 1H), 2.58 (m br, 8H), 2.12 (s, 3H), 1.79 (s, 3H), 1.08 (d, J = 8.1 Hz, 6H). HRMS (*m/z*): [MH^+] calcd for $C_{20}H_{34}N_7SO_2$, 436.2489; found 436.2485.

6-((3-(Dimethylamino)propyl)amino)-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)pyridine-3-sulfonamide (46).

Prepared from 6-chloro-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)pyridine-3-sulfonamide (**37**) (0.20 g, 0.66 mmol) and *N*, *N*-dimethylpropane-1,3-diamine (0.13 ml, 1.3mmol) in ethanol (1.5 ml), according to the method of **42** to give the title compound as an off-white powder (182 mg, 0.50 mmol, 76%). ^{1}H NMR (500MHz, $CDCl_3$): δ 8.37 (s, 1H), 7.60 (d, J = 8.5 Hz, 1H), 6.61 (s br, 1H), 6.44 (dd, J = 8.5 Hz, 3.0 Hz, 1H), 5.89 (s, 1H), 3.69 (d, J = 3.2 Hz, 3H), 3.52 (s br, rotamer, 2H NCH_2), 2.74 (s br, rotamer, 2H NCH_2), 2.49 (s, 6H,), 2.12 (d, J = 3.2 Hz, 3H), 2.07 (d, J = 3.2 Hz, 2H), 1.78 (d, J = 3.2 Hz, 3H). HRMS (*m/z*): [MH^+] calcd for $C_{16}H_{27}N_6SO_2$, 367.1911; found 367.1906.

6-[2-(1-Methyl-piperidin-4-yl)-ethylamino]-pyridine-3-sulfonic acid (1,3,5-trimethyl-1*H*-pyrazol-4-yl)-amide (47).

Prepared from 6-chloro-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)pyridine-3-sulfonamide (**37**) (528 mg, 1.8 mmol) and 2-(1-methylpiperidin-4-yl)ethanamine (500 mg, 3.5 mmol) in ethanol (1.5 ml), according to the method of **42**, to give the title compound as a white solid (190 mg, 0.5 mmol, 27%). ^{1}H NMR (300MHz, $CDCl_3$): δ 8.38 (d, J = 2.3 Hz, 1H), 7.60 (dd, J = 2.3 Hz, 9.0 Hz, 1H), 6.31 (d, J = 9.0 Hz, 1H), 5.80 (s, 1H), 4.97 (s br, 1H), 3.68 (s, 3H), 3.38-3.32 (m, 2H), 2.87-2.81 (m, 2H), 2.26 (s, 3H), 2.12 (s, 3H), 1.93-1.85 (m, 2H), 1.73 (s, 3H), 1.74-1.68 (m, 2H), 1.63-1.54

(m, 3H), 1.31-1.37 (m, 2H). HRMS (*m/z*): [MH^+] calcd for $C_{19}H_{31}N_6SO_2$, 407.2224; found 407.2222.

6-((2-(4-Phenylpiperazin-1-yl)ethyl)amino)-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)pyridine-3-sulfonamide (48).

Prepared from 6-chloro-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)pyridine-3-sulfonamide (**37**) (0.20 g, 0.66 mmol) and 2-(4-phenylpiperazin-1-yl)ethanamine (0.13 ml, 1.3 mmol) in ethanol (2.0 ml), according to the method of **42**, to afford the title compound as a beige solid (218 mg, 0.56 mmol, 85%). ^{1}H NMR (500MHz, $CDCl_3$): δ 8.41 (d, *J* = 2.0 Hz, 1H), 7.61 (dd, *J* = 8.9 Hz, 2.3 Hz, 1H), 7.30-7.27 (m, 2H), 6.97-6.93 (m, 2H), 6.90-6.87 (m, 1H), 6.46 (d, *J* = 8.9 Hz, 1H), 5.94 (s, 1H), 5.71 (s br, 1H NH), 3.70 (s, 3H), 3.50-3.45 (m, 2H), 3.25-3.22 (m, 4H), 2.72-2.66 (m, 6H), 2.13 (s, 3H), 1.78 (s, 3H). HRMS (*m/z*): [MH^+] calcd for $C_{23}H_{32}N_7SO_2$, 470.2333; found 470.2300.

6-((3-(4-Methylpiperazin-1-yl)propyl)amino)-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)pyridine-3-sulfonamide (49).

Prepared from 6-chloro-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)pyridine-3-sulfonamide (**37**) (0.20 g, 0.66 mmol) and 3-(4-methylpiperazin-1-yl)propan-1-amine (0.20 ml, 1.3 mmol), in ethanol (2.0 ml), according to the method of compound **42** to give the title compound as a pale orange solid (205 mg, 0.49 mmol, 74%). ^{1}H NMR (500MHz, $CDCl_3$): δ 8.37 (d, *J* = 2.4 Hz, 1H), 7.61 (dd, *J* = 8.9 Hz, 2.4 Hz, 1H), 6.42 (d, *J* = 8.9 Hz, 1H), 5.93 (s br, 1H NH), 3.70 (s, 3H), 3.53 (s br, 2H), 2.88 (s br, 8H CH_2-piperazine), 2.76 (s br, 2H), 2.53 (s, 3H), 2.13 (s, 3H), 1.96 (s, 2H), 1.77 (s, 3H). HRMS (*m/z*): [MH^+] calcd for $C_{19}H_{32}N_7SO_2$, 422.2333; found 422.2329.

6-((3-(1H-Imidazol-1-yl)propyl)amino)-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)pyridine-3-sulfonamide (50).

Prepared from 6-chloro-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)pyridine-3-sulfonamide (**37**) (0.20 g, 0.66 mmol) and 3-(1*H*-imidazol-1-yl)propan-1-amine (0.16 ml, 1.3 mmol) in ethanol (2.0 ml), according to the method of **42**, to give the title compound as an off-white powder (55 mg, 0.14 mmol, 21%). ^{1}H NMR (500MHz, $CDCl_3$): δ 8.32 (d, *J* = 2.4 Hz, 1H), 7.53 (dd, *J* = 8.9 Hz, 2.4 Hz, 1H), 7.44 (s, 1H), 7.02 (s, 1H,), 6.86 (t, *J* = 1.1 Hz, 1H), 6.22 (dd, *J* = 8.9 Hz, 0.5 Hz, 1H), 5.98 (s br, 1H NH), 4.99 (s, 1H), 3.99 (t, *J* = 6.7 Hz, 2H), 3.61 (s, 3H), 3.34 (dd, *J* = 12.9 Hz, 6.6 Hz, 2H), 2.08-2.02 (m, 5H), 1.65 (s, 3H). HRMS (*m/z*): [MH^+] calcd for $C_{17}H_{24}N_7SO_2$, 390.1707; found 390.1724.

(+,-)-6-(3-(Piperazin-1-yl)pyrrolidin-1-yl)-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)pyridine-3-sulfonamide (51).

Prepared from 6-chloro-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)pyridine-3-sulfonamide (**37**) (300 mg, 1.0mmol) and **(+,-)**-1-benzyl-4-(pyrrolidin-3-yl)piperazine (366 mg, 1.5 mmol) in ethanol (2.0 ml) according to the method of **42**, to give 6-(3-(4-benzylpiperazin-1-yl)pyrrolidin-1-yl)-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)pyridine-3-sulfonamide (178 mg, 0.35 mmol, 35 %). Hydrogenation of 150 mg of this material with Pd/C (5% w/w, 250mg) in ethanol (3.0 ml) at rt over 3 d and purification by column chromatography (SiO_2, 9:1 EtOAc:MeOH) gave the title compound as a white solid (20 mg, 0.05 mmol, 20%). ^{1}H NMR (500MHz, $CDCl_3$): δ 8.43 (d, *J* = 2.4 Hz, 1H), 7.61 (dd, *J* = 9.1 Hz, 2.4 Hz, 1H), 6.28 (d, *J* = 9.1 Hz, 1H), 5.75 (s br, 1H), 3.67 (s, 3H), 3.37-3.47 (m, 1H), 3.24-3.34 (m, 1H), 2.87-3.04 (m, 4H), 2.45-2.64 (m, 3H), 2.23-2.33 (m, 1H), 2.11 (s, 3H), 1.76-2.00 (m, 4H), 1.72 (s, 3H), 1.23-1.27 (m, 1H). HRMS (*m/z*): [MH^+] calcd for $C_{19}H_{30}N_7SO_2$, 420.2176; found 420.2166.

6-(3-(Piperazin-1-yl)piperidin-1-yl)-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)pyridine-3-sulfonamide (52).

Prepared from 6-chloro-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)pyridine-3-sulfonamide (**37**) (78 mg, 0.3 mmol) and *tert*-butyl 4-(piperidin-3-yl)piperazine-1-carboxylate (100 mg, 0.4 mmol) in ethanol (2.0 ml) according to the method of **42**, to give *tert*-butyl 4-(1-(5-(*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)sulfamoyl)pyridin-2-yl)piperidin-3-yl)piperazine-1-carboxylate (80 mg, 0.15 mmol, 50%). Stirring with TFA (0.25 ml) in DCM (2.0 ml) at rt for 18 h, followed by chromatography (SiO_2, 9:1 EtOAc:MeOH) gave the title compound as a white solid (45 mg, 0.1 mmol, 67%). ^{1}H NMR (500MHz, $CDCl_3$): δ 8.41 (d, *J* = 2.3 Hz, 1H), 7.60 (dd, *J* = 2.3 Hz, 9.1 Hz, 1H), 6.55 (d, *J* = 9.1 Hz, 1H), 6.03 (s br, 1H), 4.51 (d, *J* = 12.6 Hz, 1H), 4.15 (d, *J* = 12.6 Hz, 1H), 3.68 (s, 3H), 3.13-3.19 (m, 4H), 2.81-3.00 (m, 6H), 2.39-2.45, (m, 1H), 2.12 (s, 3H), 1.96-2.04 (m, 1H), 1.82-1.88 (m, 1H), 1.71 (s, 3H), 1.44-1.60 (m, 2H). HRMS (*m/z*): [MH^+] calcd for $C_{20}H_{32}N_7SO_2$, 434.2333; found 434.2320.

6-((2-(4-Benzylpiperazin-1-yl)ethyl)amino)-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)pyridine-3-sulfonamide (53).

Prepared from 6-chloro-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)pyridine-3-sulfonamide (**37**) (0.2 g, 0.67 mmol) and 2-(4-benzylpiperazin-1-yl)ethanamine (0.33 g, 1.5 mmol) in ethanol (2.0 ml), according to the method of **42**, to give the title compound as a yellow powder (175 mg, 0.36 mmol, 54%). ^{1}H NMR (500MHz, $CDCl_3$): δ 8.37 (d, *J* = 8.4 Hz, 1H), 7.58 (m, 1H), 7.32-7.31 (m, 5H),

6.37 (d, *J* = 8.4 Hz, 1H), 5.69 (s br, 2H), 3.67 (s, 3H), 3.53 (s, 3H), 3.38-3.35 (m, 2H), 2.63 (s br, 2H), 2.51 (s br, 8H), 2.11 (s, 3H), 1.73 (s, 2H). HRMS (*m/z*): [MH^+] calcd for $C_{24}H_{34}N_7O_2S$, 484.2489; found 484.2486.

***tert*-Butyl 4-(2-((5-(*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)sulfamoyl)pyridin-2-yl)amino)ethyl)piperazine-1-carboxylate (54).**

Prepared from 6-chloro-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)pyridine-3-sulfonamide (**37**) (0.2 g, 0.67 mmol) and *tert*-butyl 4-(2-aminoethyl)piperazine-1-carboxylate (0.30 g, 1.3 mmol) in ethanol (2.0 ml), according to the method of **42**, to give the title compound as a yellow powder (79 mg, 0.16 mmol, 24%). ^{1}H NMR (500MHz, $CDCl_3$): δ 8.38 (d, *J* = 2.4 Hz, 1H), 7.62 (dd, *J* = 8.7 Hz 2.4 Hz, 1H), 6.37 (d, *J* = 8.7 Hz, 1H), 6.15 (br s, 1H), 5.69 (br s, 1H), 3.67 (s, 3H), 3.53 (s, 3H), 3.47 (m, 2H), 2.64 (m, 2H), 2.48-2.42 (bs, 8H), 2.11 (s, 3H), 1.48 (s, 9H). HRMS (*m/z*): [MH^+] calcd for $C_{22}H_{36}N_7O_4S$, 494.2505; found 494.2510.

Prototypical procedure for the Suzuki reaction between an aryl bromide and a boronic acid/boronate ester:

2,6-Dichloro-4-(isoquinolin-5-yl)-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)benzenesulfonamide (56).

A solution of 4-bromo-2,6-dichloro-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-benzenesulfonamide (**29**) (250 mg, 0.61 mmol), isoquinolin-5-yl boronic acid (124 mg, 0.72 mmol), tribasic potassium phosphate (154 mg, 0.73 mmol), and Pd(dppf)Cl_2.DCM (30 mg, 0.36 mmol) in oxygen-free DMF (3.0 ml) and water (0.5 ml), was heated in a microwave at 110°C for 1 h. The reaction was concentrated to dryness *in vacuo*, diluted with DCM (100 ml), washed with saturated aqueous sodium hydrogencarbonate solution (2 x 25 ml), dried ($MgSO_4$) and concentrated *in vacuo* to give a residual oil. Chromatography (SiO_2, EtOAc) gave the title compound as a white solid (212 mg, 0.46 mmol, 75%). ^{1}H NMR (500MHz, DMSO-d_6): δ 9.73 (s, 1H), 9.45 (s, 1H,), 8.58 (d, *J* = 6.0 Hz, 1H), 8.28 (d, *J* = 7.9 Hz, 1H), 7.86 (dd, *J* = 7.3 Hz, 1.2 Hz, 1H), 7.83-7.80 (m, 3H), 7.59 (d, *J* = 6.1 Hz, 1H), 3.61 (s, 3H), 2.00 (s, 3H), 1.79 (s, 3H). HRMS (*m/z*): [MH^+] calcd for $C_{21}H_{19}N_4SO_2Cl_2$, 461.0600; found 461.0601.

3,5-Dichloro-4'-((4-methylpiperazin-1-yl)methyl)-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-[1,1'-biphenyl]-4-sulfonamide (57).

Prepared from 4-bromo-2,6-dichloro-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-benzenesulfonamide (**29**) (1.0 g, 2.43 mmol), 4-formylphenylboronic acid (440 mg, 2.91 mmol), tribasic potassium phosphate (620 mg, 2.91 mmol) and Pd(dppf)Cl_2.DCM (100 mg, 0.12 mmol) in water (0.5 ml) and oxygen-

free DMF (6.0 ml) at 130°C for 1 h according to the method of **56**, gave 3,5-dichloro-4'-formyl-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-[1,1'-biphenyl]-4-sulfonamide as a white solid (791 mg, 1.83 mmol, 75 %). ^{1}H NMR (500MHz, DMSO-d_6): δ 10.12 (1H, s), 9.68 (s, 1H), 8.31 (d, *J* = 7.1Hz, 2H), 8.07 (2H, s), 8.01 (d, *J* = 7.1Hz, 2H), 3.58 (s, 3H), 1.50 (s, 3H), 1.75 (s, 3H). m/z (ES$^+$, 70V) 439.2 (MH^+). Reductive amination of this intermediate (186 mg, 0.43 mmol) with 1-methylpiperazine (85 mg, 0.86 mmol), sodium triacetoxyborohydride (180 mg, 0.86 mmol), in $CHCl_3$ (10.0 ml), according to the method of **58**, gave the title compound as a white powder (182 mg, 0.35 mmol, 81%). ^{1}H NMR (500MHz, DMSO-d_6): δ 9.63 (s, 1H), 7.99 (s, 2H), 7.97-7.94 (m, 2H), 7.76-7.71 (m, 2H), 4.80-4.25 (m, 7H), 3.58 (s, 3H), 3.51-3.39 (s br, 6H), 1.95 (s, 3H), 1.73 (s, 3H). HRMS (*m/z*): [MH^+] calcd for $C_{24}H_{30}N_5SO_2Cl_2$, 522.1492; found 522.1498.

3,5-Dichloro-4'-((diethylamino)methyl)-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-[1,1'-biphenyl]-4-sulfonamide (58).

A solution of 3,5-dichloro-4'-formyl-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-[1,1'-biphenyl]-4-sulfonamide (195 mg, 0.45 mmol), and diethylamine (66 mg, 0.9 mmol), in $CHCl_3$ (4.0 ml) was stirred for 30 min at rt prior to the addition of sodium triacetoxyborohydride (284 mg, 1.35 mmol) and heating at 50°C for 16 h. Dilution with DCM (25 ml), washing with water (2 x 10 ml), drying ($MgSO_4$) and concentration *in vacuo* followed by chromatography (SiO_2, EtOAc) gave the title compound as a white powder (121 mg, 0.24 mmol, 54%). ^{1}H NMR (500MHz, DMSO-d_6): δ 9.63 (s, 1H), 8.00 (s, 2H), 7.97 (d, *J* = 8.6 Hz, 2H), 7.78 (d, *J* = 8.6 Hz, 2H), 4.36 (d, *J* = 5.8 Hz, 2H), 3.58 (s, 3H), 3.11-3.01 (m, 4H), 1.96 (s, 3H), 1.74 (s, 3H), 1.27 (t, *J* = 7.3 Hz, 6H). HRMS (*m/z*): [MH^+] calcd for $C_{23}H_{29}N_4SO_2Cl_2$, 495.1383; found 495.1366.

2,6-Dichloro-4-(6-(piperazin-1-yl)pyridin-3-yl)-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)benzenesulfonamide (59).

Prepared from 4-bromo-2,6-dichloro-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-benzenesulfonamide (**29**) (250 mg, 0.61 mmol), 1-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)piperazine (212 mg, 0.73 mmol), tribasic potassium phosphate (155 mg, 0.73 mmol), and Pd(dppf)Cl_2.DCM (30 mg, 0.36 mmol) in DMF (2.5 ml) and water (0.5 ml), according to the method of **56**, to give the title compound as an off-white powder (212 mg, 0.43 mmol, 72%). ^{1}H NMR (500MHz, DMSO-d_6): δ 9.43 (s, 1H), 8.67 (d, *J* = 2.6 Hz, 1H), 8.19 (dd, *J* = 9.1 Hz, 2.6 Hz, 1H), 7.96 (s, 2H), 7.10 (d, *J* = 9.1 Hz, 1H), 3.91-3.88 (m, 4H), 3.58 (s, 3H), 3.21-3.17 (m, 4H), 1.96 (s, 3H), 1.74 (s, 3H). HRMS (*m/z*): [MH^+] calcd for $C_{21}H_{25}N_6SO_2Cl_2$, 495.1131; found 495.1112.

2,6-Dichloro-4-(1,2,3,4-tetrahydroisoquinolin-5-yl)-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)benzenesulfonamide (60).

Prepared from 4-bromo-2,6-dichloro-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-benzenesulfonamide (**29**) (250 mg, 0.55 mmol), 5-bromo tetrahydroisoquinoline (175 mg, 0.83 mmol), tribasic potassium phosphate (180 mg, 0.6 mmol), and $Pd(PPh_3)_4$ (70 mg, 0.06 mmol) in oxygen-free DMF (2.5 ml) and water (0.5 ml), according to the method of **56**, to give the title compound as a white solid (176mg, 0.38 mmol, 69%). ^{1}H NMR (500MHz, DMSO-d_6): δ 7.33 (s, 2H), 7.00 (t, J = 7.9 Hz, 1H), 6.91 (d, J = 7.9 Hz, 1H), 6.85 (d, J = 7.9 Hz, 1H), 3.70 (s, 2H), 3.35 (s, 3H), 3.13-3.10 (m, 2H), 2.68-2.65 (m, 2H), 1.73 (s, 3H), 1.50 (s, 3H). HRMS (*m/z*): [MH^+] calcd for $C_{21}H_{23}N_4SO_2Cl_2$, 465.0913; found 465.0902.

3,5-Dichloro-3'-((4-methylpiperazin-1-yl)methyl)-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-[1,1'-biphenyl]-4-sulfonamide (61).

Reaction of 4-bromo-2,6-dichloro-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-benzenesulfonamide (**29**) (1.0 g, 2.43 mmol), 3-formylphenylboronic acid (440 mg, 2.91 mmol), tribasic potassium phosphate (620 mg, 2.91 mmol), Pd(dppf)Cl_2.DCM (100 mg, 0.12 mmol) and water (0.5 ml) in oxygen-free DMF (6.0 ml) according to the method of **56**, gave 3,5-dichloro-3'-formyl-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-[1,1'-biphenyl]-4-sulfonamide as a white solid (870 mg, 2.0 mmol, 82%). ^{1}H NMR (300MHz, DMSO-d_6): δ 10.12 (s, 1H), 9.68 (s, 1H), 8.42 (s, 1H), 8.21 (d, J = 7.9Hz, 1H), 8.07 (s, 2H), 8.01 (d, J = 7.5Hz, 1H), 7.74 (dd, J = 7.5Hz 7.9Hz, 1H), 3.58 (s, 3H), 1.50 (s. 3H), 1.75 (s, 3H). m/z (ES^+, 70V) 439.2 (MH^+). Reductive amination of this intermediate (150 mg, 0.34 mmol) with 1-methylpiperazine (0.133 ml, 1.02 mmol), in $CHCl_3$ (10.0 ml) and sodium triacetoxyborohydride (216 mg, 1.02 mmol), according to the method of **58**, gave the title compound as a colourless oil (84 mg, 0.16 mmol, 48%). ^{1}H NMR (300MHz, $CDCl_3$): δ 7.68 (s, 2H), 7.54 (s br, 1H), 7.49-7.41 (m, 3H), 6.68 (s br, 1H), 3.61 (s, 2H), 3.69 (s, 3H), 2.61 (s br, 4H), 2.39 (s, 3H), 2.27 (s br, 4H), 2.19 (s, 3H), 1.80 (s, 3H). HRMS (*m/z*): [MH^+] calcd for $C_{24}H_{30}N_5SO_2$, 522.1492; found 522.1486.

3,5-Dichloro-3'-((diethylamino)methyl)-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-[1,1'-biphenyl]-4-sulfonamide (62).

3,5-Dichloro-3'-formyl-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-[1,1'-biphenyl]-4-sulfonamide (210 mg, 0.52 mmol), and diethylamine (0.25 ml), in chloroform (3.0 ml), was stirred at rt for 2 h, prior to addition of sodium triacetoxyborohydride (220 mg, 1.04 mmol) and stirring for an additional 16 h. Dilution with DCM (25 ml), washing with water (2 x 10 ml), drying ($MgSO_4$), concentration *in*

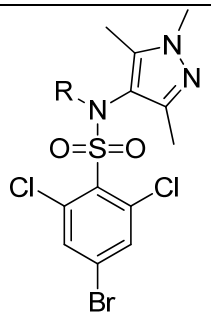
vacuo and chromatography (SiO_2, 80:20:1 EtOAc: MeOH: saturated aqueous ammonia solution) gave the title compound as a white powder (39 mg, 0.08 mmol, 15%). ^{1}H NMR (300MHz, $CDCl_3$): δ 7.65 (s, 2H), 7.53 (s, 1H), 7.43-7.37 (m, 3H), 6.62 (s, 1H), 3.64 (s, 3H), 3.60 (s, 2H), 2.52 (q, *J* = 6.8 Hz, 4H), 2.14 (s, 3H), 1.77 (s, 3H), 1.03 (t, *J* = 6.8 Hz, 6H). HRMS (*m/z*): [MH^+] calcd for $C_{23}H_{29}N_4SO_2Cl_2$, 495.1383; found 495.1374.

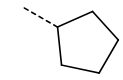
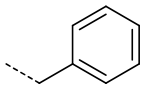
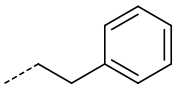
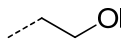
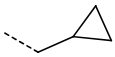
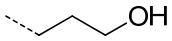
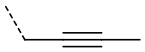
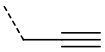
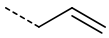
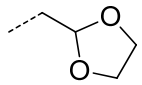
2,6-Dichloro-4-(2-piperazin-1-yl-pyridin-4-yl)-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-benzenesulfonamide (63).

A deoxygenated solution of 4-bromo-2,6-dichloro-*N*-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-benzenesulfonamide (**29**) (13.84 g, 33.3 mmol), 2-(1-piperazinyl)pyridine-4-boronic acid pinacol ester (11.57 g, 40.0 mmol), tribasic potassium phosphate (9.73 g, 44.0 mmol), and $Pd(PPh_3)_4$ (1.50 g, 0.96 mmol) in DMF (200 ml) and water (40 ml) in a round-bottomed flask under argon, was heated at 120ºC for 1 h. The reaction mixture was then concentrated *in vacuo*, diluted with DCM (400 ml), washed with saturated aqueous ammonia solution (2 x 100 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residual solid was triturated from Et_2O and collected by filtration to give a solid which was recrystallized from EtOAc to give the title compound **63** as an off-white powder (15.22 g, 30.7 mmol, 92%). ^{1}H NMR (500MHz, DMSO-d_6): δ 9.79 (s, 1H), 8.25 (d, *J* = 5.9 Hz, 1H), 8.20 (s, 2H), 7.61 (s, 1H), 7.40 (d, *J* = 5.9 Hz, 1H), 4.08 (s br, 4H), 3.63 (s, 3H), 3.28 (s br, 4H), 2.00 (s, 3H), 1.77 (s, 3H). ^{13}C-NMR (125MHz, DMSO-d_6): 147.5, 147.3, 143.8, 137.4, 136.3, 135.2, 129.8, 111.8, 111.7, 109.1, 108.9, 42.7, 42.0, 36.2, 10.4. HRMS (*m/z*): [MH^+] calcd for $C_{21}H_{25}N_6SO_2Cl_2$, 495.1131; found 495.1124.

SUPPLEMENTARY TABLES

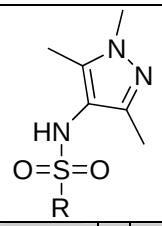
Table S1: Effect on activity against *Tb*NMT of substitution at the sulfonamide nitrogen of **29**.[a]

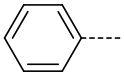
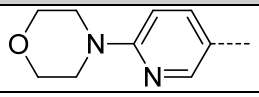
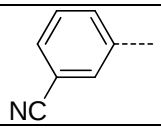
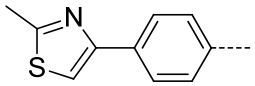
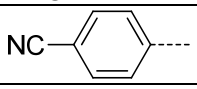
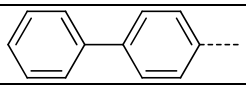
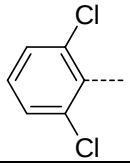
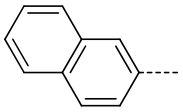
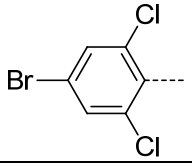
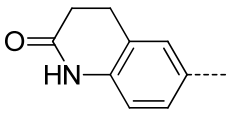
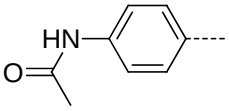
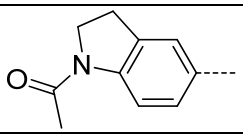
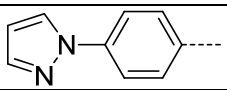
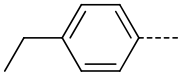
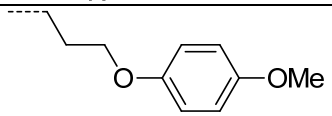
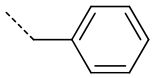
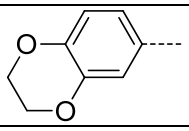
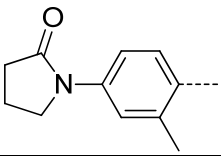
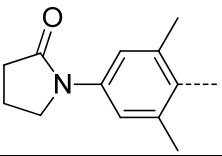
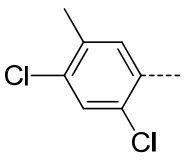
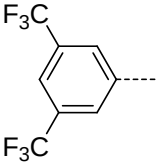


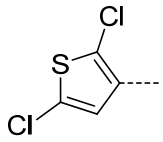
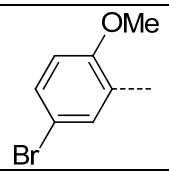
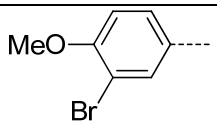
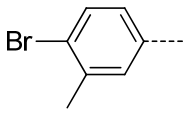
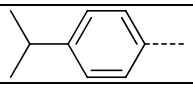
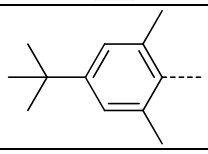
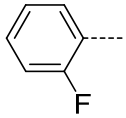
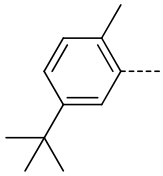
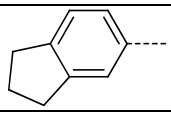
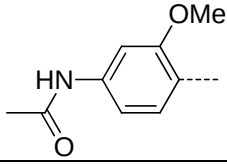
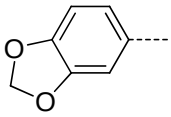
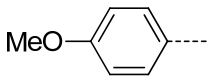
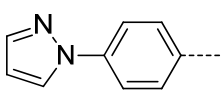
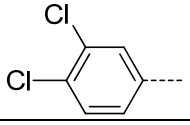
No	R	IC_{50} (μM)	No	R	IC_{50} (μM)
29	H	0.5		Me	0.35
	Et	0.5		^{n}Pr	1.8
		1.9			4.6
		4.9			1.1
		0.67			0.75
		9.3			1.6
		0.90			1.6

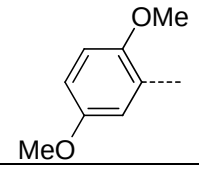
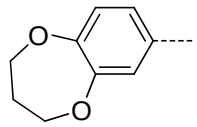
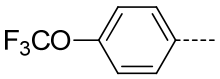
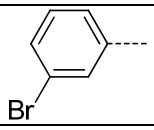
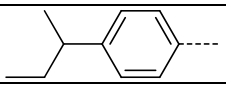
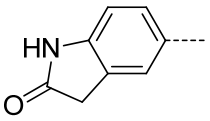
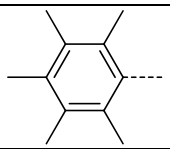
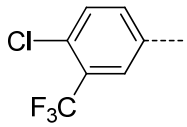
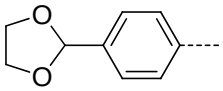
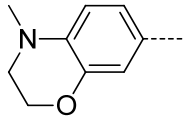
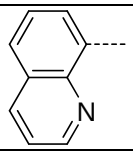
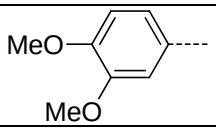
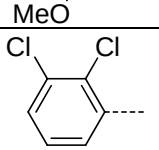
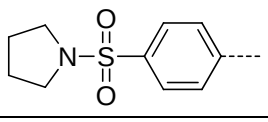
[a]IC_{50} values are shown as mean values of two or more determinations.

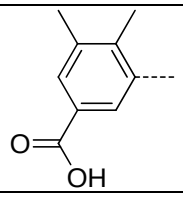
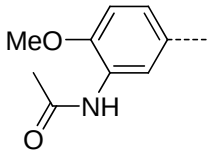
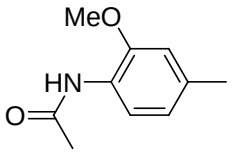
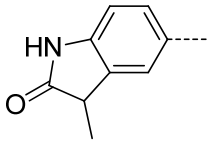
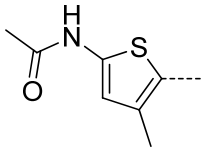
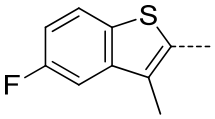
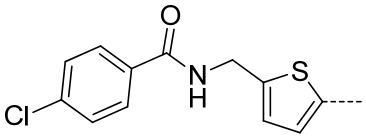
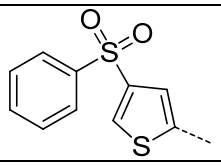
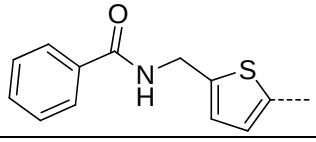
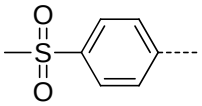
Table S2: Activity against *Tb*NMT of a library of pyrazole sulfonamides.[a]



No	R	IC_{50} (μM)	No	R	IC_{50} (μM)
25		12	**31**		1.9
26		28	**32**		12
27		32			12
28		1.0			8.4
29		0.34	**33**		3.3
35		2.8	**34**		8.8
30		4.8			4.6
		>50		^{n}Butyl	>50
		>50			4.0
		7.4			8.2
		16			>50

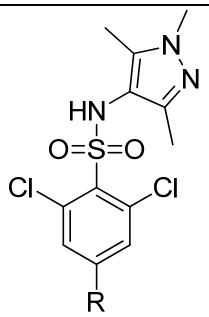
		6.4
		>50
		2.5
		5.3
		1.5
		0.49
		5.5
		>50
		5.6
		>50
		3.9
		9.7
		4.8
		9.8

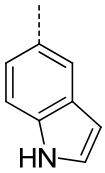
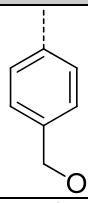
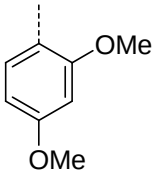
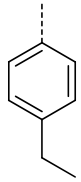
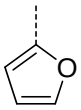
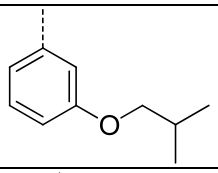
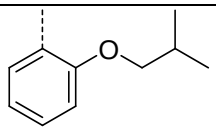
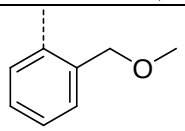
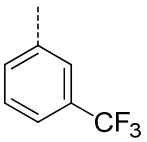
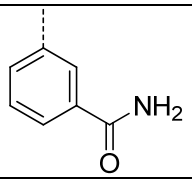
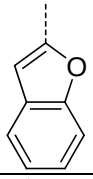
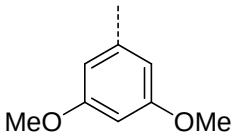
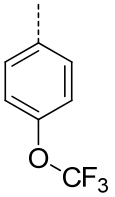
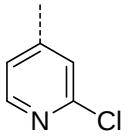
		>50
		3.5
		2.7
		8.0
		4.2
		15
		>50
		17
		9.5
		16
		7.3
		41
		3.2
		>50

		>50			41
		42			12
		>50			6.6
		1.5			10
		0.7			4.2

[a]IC_{50} values are shown as mean values of two or more determinations.

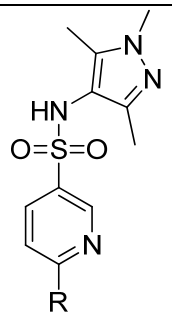
Table S3: Activity against *Tb*NMT of a library of biaryl compounds.[a]

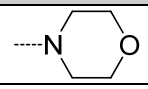
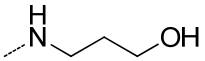
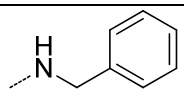
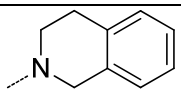
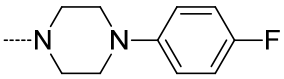
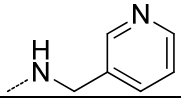
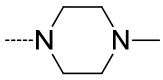
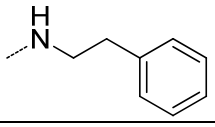
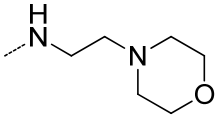
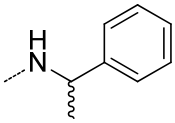
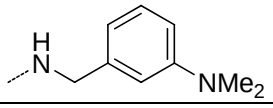
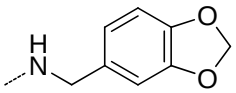
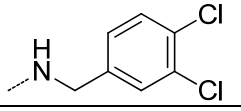
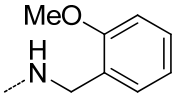
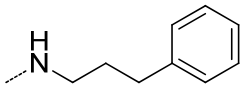
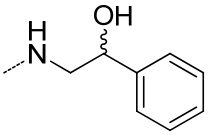
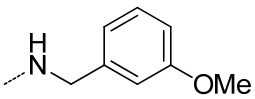
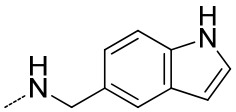
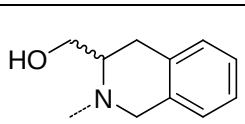
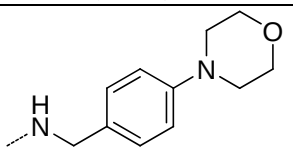
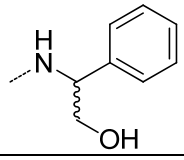
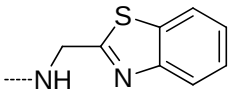
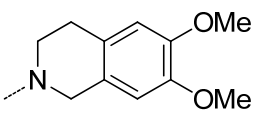
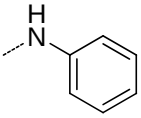


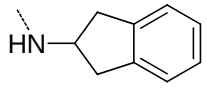
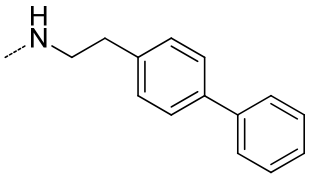
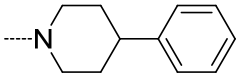
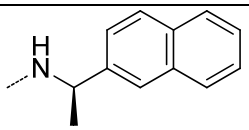
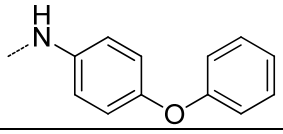
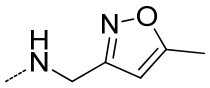
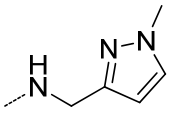
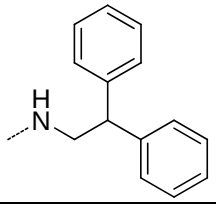
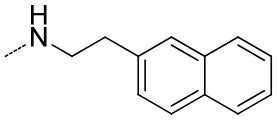
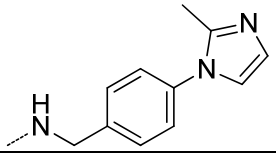
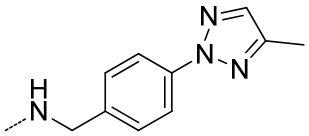
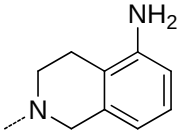
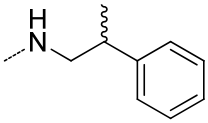
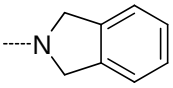
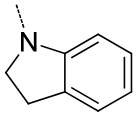
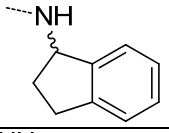
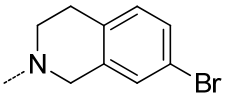
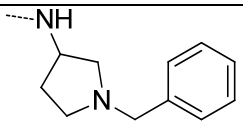
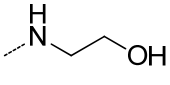
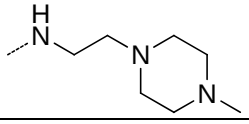
No	R	IC_{50} (μM)	No	R	IC_{50} (μM)
		6.7			0.92
		7.0			44
		3.6			35
		26			32
		40	**36**		0.90
		21			4.2
		>50			0.96

[a] IC_{50} values are shown as mean values of two or more determinations.

Table S4: Activity against *Tb*NMT of a library of aminopyridines.[a]



No	R	IC_{50} (μM)	No	R	IC_{50} (μM)
31		1.9			>100
38		1.3			0.87
		11			2.7
		12			1.1
41		38			0.86
		2.6			1.4
		13			2.4
		2.8			2.4
		1.6	**39**		0.29
		6.1			27
		>50			0.46
		7.1			4.3

		0.36			41
		25			2.7
		>50			9.9
		18			14
		12			9.6
		17			7.0
		1.0			18
		8.0			6.5
		2.4			>50
		>50	**42**		0.14

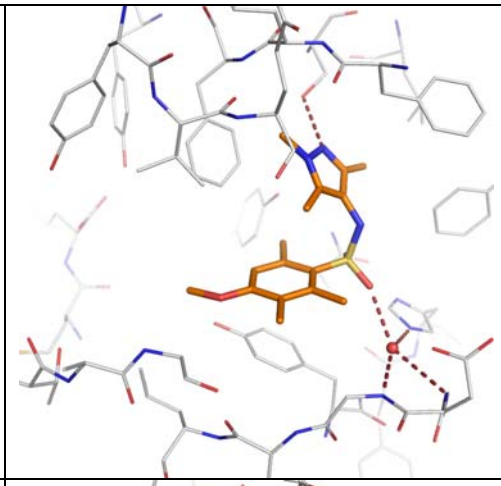
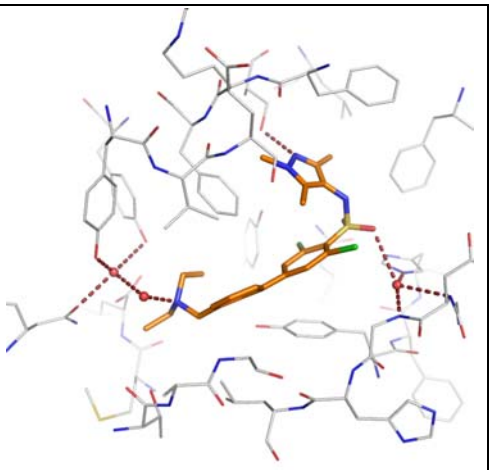
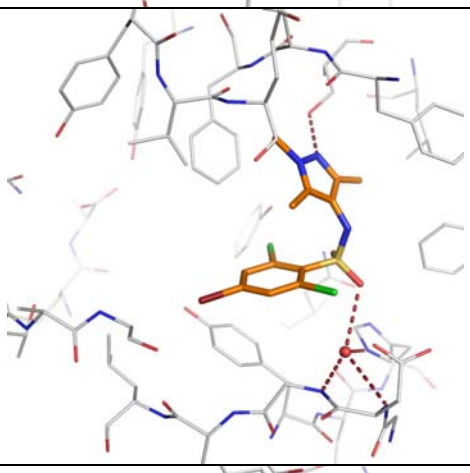
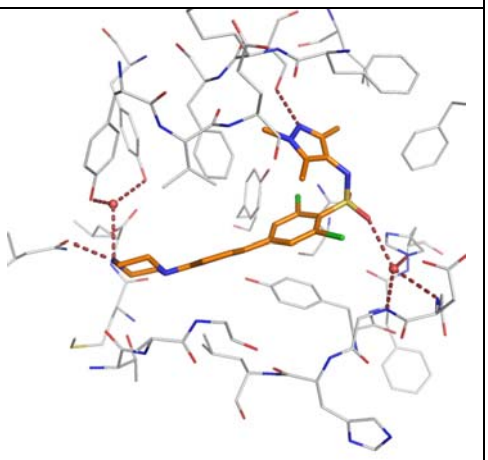
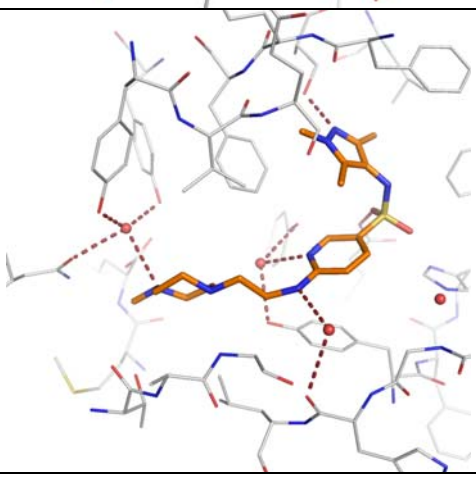
[a]IC_{50} values are shown as mean values of two or more determinations

Table S5: Details of data collection and structure refinement.

Details of Data Collection					
Ligand Complex PDB code	**1** 4A2Z	**29** 4A30	**42** 4A31	**62** 4A32	**59** 4A33
Space Group	$P2_1$	$P2_1$	$P2_1$	$P2_1$	$P2_1$
Unit Cell Dimensions (Å)	a = 48.50 b=90.98 c=53.46 β=114.05	a=48.63 b=90.68 c=53.51 β=114.02	a=47.01 b=90.38, c=52.89 β=111.88	a=48.86 b=91.25 c=53.84 β=113.86	a=48.23 b=91.33 c=53.38 β=113.52
Resolution Range (Å)	20.0-2.30 (2.38-2.3)	50.0 -1.5 (1.55-1.50)	20.0-2.10 (2.17-2.10)	30.0–2.20 (2.28–2.20)	20.0-2.40 (2.53-2.40)
Observations	62718	198840	75124	67210	54387
Unique Observations	17977	66101	22941	20985	16497
Redundancy	3.5 (2.2)	3.0 (2.9)	3.3 (2.7)	3.2 (2.4)	3.3 (3.3)
Completeness (%)	96.5 (79.2)	97.4 (93.8)	94.7 (73.1)	95.2 (78.9)	99.1 (99.9)
I/σI	17 (2.8)	29 (3.0)	12.2 (2.7)	13.5 (2.3)	8.8 (2.8)
R_{merge} [a] (%)	6.5 (23.4)	3.7 (22.8)	8.3 (27.4)	8.4 (35.3)	11.1 (47.7)
Refinement Statistics					
Resolution Range (Å)	20.0 – 2.30	20.0 – 1.50	20.0 – 2.10	20.0 – 2.20	20.0 - 2.40
R-factor [b] % (R_{work}/R_{free})	16.1/ 22.5	17.8/21.1	15.8 / 22.7	16.9 / 23.2	17.1 /25.9
Number of atoms [c]	3343/63/23/204	3360/63/21/361	3346/63/28/306	3343/63/32/234	3343/63/32/173
Mean B-factor [c] ($Å^2$)	26/16/24/30	20/16/19/31	20/12/21/29	25/17/30/30	26/17/31/27
RMS bond length deviation(Å)	0.019	0.029	0.015	0.017	0.016
RMS bond angle deviation (˚)	1.84	2.48	1.65	1.75	1.73

Values between brackets for the highest resolution shell.[a] Rmerge = $\sum|I - \langle I\rangle| / \sum\langle I\rangle$. [b] R-factor = $\sum F_o - F_c| / \sum F_o$. [c] Number of atoms of protein, co-factor, ligand and water molecules respectively.

Table S6: Structural analysis of the pyrazolesulfonamide inhibitors of NMT. Binding modes of compounds **1**, **29**, **42**, **59, 62** and **63** in *Lm*NMT.

1 **PDB** **4A2Z**		**62** **PDB** **4A32**	
29 **PDB** **4A30**		**59** **PDB** **4A33**	
42 **PDB** **4A31**		**63** **PDB** **2WSA**