Electronic Supplementary Material (ESI) for Medicinal Chemistry Communications.

Evaluation of Functional Groups as Acetyl-Lysine Mimetics for BET Bromodomain Inhibition

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Supporting Information

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Experimental Section

1. General Remarks

Nuclear magnetic resonance (^{1}H NMR, 600 MHz and 300 MHz and ^{13}C NMR, 150 MHz and 75 MHz) spectra were obtained at 300 K with $CDCl_3$ as the solvent unless otherwise indicated. Chemical shifts are reported in ppm on the δ scale and referenced to the appropriate solvent peak. Liquid chromatography mass spectroscopy (LCMS) was carried out using one of either two different methods; Method A) Finnigan LCQ Advantage Max using reverse phase high performance liquid chromatorgraphy (HPLC) analysis (column: Gemini 3µ C18 20 x 4.0 mm 110A) Solvent A: Water 0.1% Formic Acid, Solvent B: Acetonitrile 0.1% Formic Acid, Gradient: 10-100% B over 10 min Detection: 100-600 nm and electrospray ionisation (ESI) in positive mode with source temperature 300 ^{o}C. Method B) Waters ZQ 3100 using reverse phase HPLC (column: XBridge^{TM} C18 5 µm 4.6 x 100 mm), Solvent A: Water 0.1% Formic Acid, Solvent B: Acetonitrile 0.1% Formic Acid, Gradient: 10-100% B over 10 min, Flow rate: 1.5 ml/min Detection: 100-600 nm and ESI in positive mode with source temperature 150 ^{o}C. All compounds submitted for biochemical assay were assessed to have purity ≥ 95% as measured by HPLC analysis at 254 nm UV absorbance. High Resolution Mass Spectrometry (HRMS) was conducted on an Agilent Q-TOF 6200 using positive mode electrospray ionisation (ESI). Analytical thin-layer chromatography (TLC) was performed on Merck silica gel 60 F254 aluminium-backed plates and visualized with short wavelength UV (254 nm) absorbance or by staining with vanillin dip (15 g vanillin, in 250 mL of 2% Conc. sulfuric acid, 98% ethanol solution). Chromatography was performed using either the CombiFlash® Rf purification system (Teledyne, ISCO, Lincon, NE, USA) with pre-packed silica gel columns (particle size 0.040-0.063 mm) or using a Flash chromatography employing a glass column with silica gel 60 (particle size 0.040-0.063 mm). Anhydrous solvents were dried using an automated solvent purification system (MBraun SPS, Garching, Germany) based upon a technology originally described by Grubbs et al.[1] All commercial reagents were used as received. TFA = 2,2,2-trifluoroacetic acid, DMB = 2,4-dimethoxybenzyl and RT = room temperature.

2. Synthetic Procedures

2.1. General Procedure A: Synthesis of Arylsulfonamides (7a, 7b, 8-10).

To a magnetically stirred solution of amine (either **S1** or cyclopentylamine) (1.1 equiv) in CH_2Cl_2 (5 mL per mmol of amine), under an atmosphere of N_2 at RT, was added arylsulfonyl chloride (1.0 equiv) followed by triethylamine (1.1 equiv). The mixture was stirred for 18 h then concentrated under reduced pressure and the crude material was subjected to chromatography. The product was eluted with appropriate mixtures of either EtOAc/cyclohexane or MeOH/CH_2Cl_2 as described for each example below.

2.2. General Procedure B: Suzuki-Miyuara Cross-coupling Reaction

A microwave reaction vessel containing a magnetic stirring bar was charged with aryl bromide **7a** or **7b** (1 equiv.), arylboronic acid or pinacol ester (1.2-2.0 equiv.), cesium carbonate (1.5 equiv.), dioxane (0.46 mL per mmol of aryl bromide), deionized water (0.092 mL per mmol of aryl bromide)

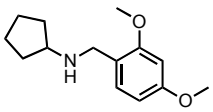
and N,N-dimethylformamide (0.092 mL per mmol of aryl bromide) then capped with a rubber septum. Nitrogen was bubbled through the solution for 10 min then PEPPSI-SIPr (0.05 equiv.) was added and nitrogen bubbling was continued for a further 5 min. The rubber septum was quickly replaced with a Teflon microwave vessel cap and the reaction mixture was then subjected to microwave irradiation in a CEM microwave reactor at 90 ^{o}C for 12 h (2 min ramp time and variable power not exceeding 200 W). The cooled reaction mixture was diluted in 5 volumes of EtOAc and concentrated onto chromatography grade silica. The ensuing free-flowing powder was subjected to Flash chromatography and the product was eluted with appropriate mixtures of either EtOAc/cyclohexane or MeOH/CH_2Cl_2 as described for each example below.

2.3. General Procedure C: Removal of 2,4-dimethoxybenzyl protecting group

To a magnetically stirred solution of sulfonamide (1 equiv.) in CH_2Cl_2 (0.1 M) at RT was added TFA (6 equiv.). The reaction mixture was stirred at RT until TLC indicated consumption of the starting material (reaction mixture appeared dark pink at about 0.5 - 2 h reaction time). The reaction mixture was subsequently quenched by the drop-wise addition of ammonia (7 M in MeOH) until the solution became colourless. Chromatography grade silica was then added and the resultant slurry was concentrated under reduced pressure. The ensuing free-flowing powder was then subjected to flash chromatography using appropriate mixtures of EtOAc/cyclohexane or MeOH/CH_2Cl_2 as described below.

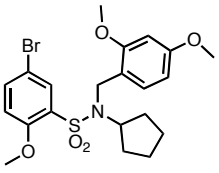
2.4. Synthetic procedures and analytical compound data

N-*Cyclopentyl*-N-*(2,4-dimethoxybenzyl)amine* (S1)



Compound **S1** was prepared following procedures described by Heald *et. al*.[2] Thus, to a magnetically stirred solution of 2,4-dimethoxybenzaldehyde (10.70 g, 64.4 mmol) in MeOH (200 mL) under an atmosphere of N_2 at RT was added cyclopentylamine (5.00 g, 58.7 mmol). After 30 min, the reaction mixture was cooled to 0 ^{o}C and $NaBH_4$ (2.95 g, 77.9 mmol) was added. After a further 30 min water (50 mL) was carefully added and the aqueous fraction was separated and extracted with EtOAc (3 x 20 mL). The combined organic fractions were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude material was chromatographed (10-100%, EtOAc/cyclohexane). Concentration of the appropriate fractions (R_f = 0.2, 100% EtOAc) afforded the title compound (**S1**) (14.02 g, quantitative) as a low melting pale yellow solid. **^{1}H NMR**: (600 MHz; $CDCl_3$): δ 7.40 (d, *J* = 8.9 Hz, 1H), 6.42-6.41 (m, 2H), 3.89 (s, 2H), 3.85 (s, 3H), 3.73 (s, 3H), 3.16 (quintet, *J* = 7.1 Hz, 1H), 1.90-1.86 (m, 2H), 1.79-1.74 (m, 4H), 1.46 (dd, *J* = 6.2, 3.5 Hz, 2H). **LCMS**: Method A, t_R = 4.44 min, m/z = 236.3 $[M+H]^+$.

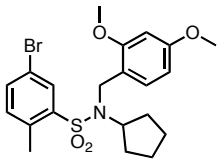
***5-Bromo*-N-*cyclopentyl*-N-*(2,4-dimethoxybenzyl)-2-methoxybenzenesulfonamide* (7a)**



Compound **7a** was prepared using the ***general procedure A*** described above employing (5-bromo-2-methoxyphenyl)sulfonyl chloride (2.00 g, 7.00 mmol) and amine **S1**. **Chromatography conditions:** 1:1, v/v, EtOAc:cyclohexane. R_f = 0.8, 1:1, v/v, EtOAc/cyclohexane. **Yield:** (2.85 g, 84%). **Physical state:** White solid. **^{1}H**

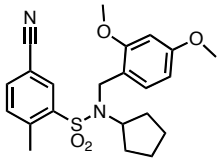
NMR: (600 MHz, $CDCl_3$): δ 7.80 (d, *J* = 2.5 Hz, 1H), 7.40 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 1H), 6.70 (d, *J* = 8.7 Hz, 1H), 6.33 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.17 (d, *J* = 2.4 Hz, 1H), 4.31 (s, 2H), 4.08 (quintet, *J* = 8.4 Hz, 1H), 3.80 (s, 3H), 3.66 (s, 3H), 3.61 (s, 3H), 1.45-1.35 (m, 4H), 1.29-1.26 (m, 4H). **LCMS:** Method B, t_R = 8.93 min, m/z = 484.1 $[M+H]^+$.

***5-Bromo*-N-*cyclopentyl*-N-*(2,4-dimethoxybenzyl)-2-methylbenzenesulfonamide* (7b)**



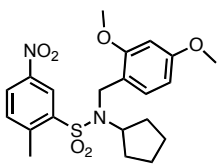
Compound **7b** was prepared using the ***general procedure A*** described above employing (5-bromo-2-methylphenyl)sulfonyl chloride (580 mg, 2.15 mmol) and amine **S1**. **Chromatography conditions:** CombiFlash, 0:1 to 1:1, v/v, EtOAc:cyclohexane. R_f = 0.9, 1:1, v/v, EtOAc/cyclohexane. **Yield:** (836 mg, 83%). **Physical state:** White solid. **^{1}H NMR:** (600 MHz, $CDCl_3$): δ 7.71 (d, *J* = 2.1 Hz, 1H), 7.38 (dd, *J* = 8.1, 2.1 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 1H), 7.02 (d, *J* = 8.1 Hz, 1H), 6.40 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.12 (d, *J* = 2.4 Hz, 1H), 4.39-4.32 (m, 1H), 4.33 (s, 2H), 3.77 (s, 3H), 3.65 (s, 3H), 2.51 (s, 3H), 1.79-1.74 (m, 2H), 1.66-1.59 (m, 4H), 1.51-1.48 (m, 2H). **LCMS:** Method B, t_R = 7.88 min, m/z = 468.1 $[M+H]^+$.

***5-Cyano*-N-*cyclopentyl*-N-*(2,4-dimethoxybenzyl)-2-methylbenzenesulfonamide* (8)**



N-(2,4-dimethoxybenzyl)cyclopentanamine (**S1**) (400.7 mg, 1.70 mmol) was dissolved in CH_2Cl_2 (10 mL) at RT under N_2. Triethylamine (0.341mL, 2.43mmol) was added drop-wise, followed by 5-cyano-2-methylbenzene-1-sulfonyl chloride (350 mg, 1.624 mmol) and the reaction mixture was stirred for 3 h. An aqueous solution of ammonium chloride was added and the organics were extracted with CH_2Cl_2 (3 x 10 mL). Combined organics were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to afford a light yellow oil. Recrystallization from Cyclohexane/CH_2Cl_2 afforded the *title compound* (**8**) (481mg, 71%) as a white solid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.48 (d, *J* = 7.9 Hz, 1H), 7.23 (m, 1H), 6.38 (dd, *J* = 8.4, 2.2 Hz, 1H), 5.98 (d, *J* = 2.5 Hz, 1H), 4.48 (m, 1H), 4.28 (s, 2H), 3.79 (s, 3H), 3.58 (s, 3 H), 2.62 (s, 3H), 1.80 - 1.87 (m, 2H), 1.71 - 1.78 (m, 2H), 1.63 - 1.70 (m, 2H), 1.51 - 1.59 (m, 2H). **LCMS:** Method A, t_R = 5.99 min.[3]

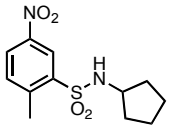
***5-Nitro*-N-*cyclopentyl*-N-*(2,4-dimethoxybenzyl)-2-methylbenzenesulfonamide* (9)**



Compound **9** was prepared using the ***general procedure A*** described above employing (2-methyl-5-nitrophenyl)sulfonyl chloride (2.20 g, 9.34 mmol) and amine **S1**. **Chromatography conditions:** 1:9 to 1:1, v/v, EtOAc:cyclohexane. R_f = 0.9, 1:1, v/v, EtOAc/cyclohexane. **Yield:** (3.50 g, 86%). **Physical state:** White solid. **^{1}H NMR:** (600 MHz, $CDCl_3$): δ 8.22 (d, *J* = 2.4 Hz, 1H), 8.06 (dd, *J* = 7.8, 2.4 Hz, 1H), 7.28 (d, *J* = 7.8 Hz, 1H), 7.24 (d, *J* = 8.4 Hz, 1H), 6.30 (dd, *J* = 8.4, 2.4 Hz, 1H), 5.92 (d, *J* = 2.4 Hz, 1H), 4.53 (quintet, *J* = 8.4 Hz, 1H), 4.30 (s, 2H), 3.67 (s, 3H), 3.57 (s, 3H), 2.66 (s, 3H), 1.87-1.85

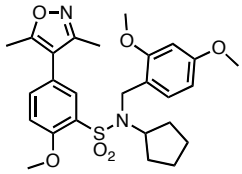
(m, 2H), 1.79-1.77 (m, 2H), 1.68-1.66 (m, 2H), 1.56-1.55 (m, 2H). **LCMS:** Method A, t_R = 6.62 min, m/z = 435.3 $[M+H]^+$.

***5-Nitro*-N-*cyclopentyl-2-methylbenzenesulfonamide* (10)**



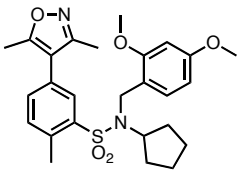
Compound **10** was prepared using the ***general procedure A*** described above employing (2-methyl-5-nitrophenyl)sulfonyl chloride (2.00 g, 8.49 mmol) and cyclopentylamine. **Chromatography conditions:** 1:9 to 1:1, v/v, EtOAc:cyclohexane. R_f = 0.9, 1:1, v/v EtOAc/cyclohexane. **Yield:** (2.39 g, 99%). **Physical state:** White solid. **^{1}H NMR:** (600 MHz, DMSO-d6): δ 8.54 (d, *J* = 2.5 Hz, 1H), 8.33 (dd, *J* = 8.4, 2.5 Hz, 1H), 8.08 (d, *J* = 0.3 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 1H), 3.45-3.42 (m, 1H), 2.67 (s, 3H), 1.60-1.57 (m, 2H), 1.52 (m, 2H), 1.37-1.29 (m, 4H). **LCMS:** Method B, RT = 7.25 min, m/z = 285.0 $[M+H]^+$.

N-*Cyclopentyl*-N-*(2,4-dimethoxybenzyl)-5-(3,5-dimethylisoxazol-4-yl)-2-methoxybenzenesulfonamide* (S2a)



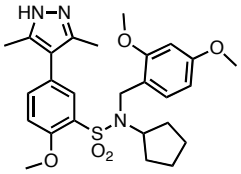
Compound **S2a** was prepared using the ***general procedure B*** employing aryl bromide **7a** (100 mg, 0.21 mmol) and 3,5-dimethylisoxazole-4-boronic acid (42 mg, 0.30 mmol). **Chromatography conditions:** 1:9 to 1:1, v/v, EtOAc:cyclohexane. R_f = 0.3, 1:1, v/v EtOAc/cyclohexane. **Yield:** (104 mg, 98%). **Physical state:** White powder. **^{1}H NMR:** (600 MHz, $CDCl_3$): δ 7.77 (d, *J* = 2.3 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.34 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.04 (d, *J* = 8.5 Hz, 1H), 6.43 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.33 (d, *J* = 2.3 Hz, 1H), 4.49 (s, 2H), 4.27-4.21 (m, 1H), 4.00 (s, 3H), 3.76 (s, 3H), 3.75 (s, 3H), 2.37 (s, 3H), 2.23 (s, 3H), 1.57-1.50 (m, 4H), 1.43-1.36 (m, 4H). **LCMS:** Method B, t_R = 7.15 min, m/z = 501.3 $[M+H]^+$.

N-*Cyclopentyl*-N-*(2,4-dimethoxybenzyl)-5-(3,5-dimethylisoxazol-4-yl)-2-methylbenzenesulfonamide* (S2b)



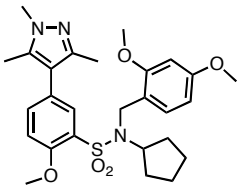
Compound **S2b** was prepared using the ***general procedure B*** employing aryl bromide **7b** (250 mg, 0.54 mmol) and 3,5-dimethylisoxazole-4-boronic acid (250 mg, 0.54 mmol). **Chromatography conditions:** 0:1 to 1:0, v/v, EtOAc:cyclohexane. R_f = 0.3, 1:1, v/v EtOAc/cyclohexane. **Yield:** (121 mg, 84%). **Physical state:** White powder. **^{1}H NMR:** (600 MHz, $CDCl_3$): δ 7.63 (d, *J* = 1.9 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.22 (dd, *J* = 7.7, 1.9 Hz, 1H), 6.32 (dd, *J* = 8.4, 2.3 Hz, 1H), 6.21 (d, *J* = 2.3 Hz, 1H), 4.40 (s, 2H), 4.31-4.26 (m, 1H), 3.68 (s, 3H), 3.68 (s, 3H), 2.65 (s, 3H), 2.37 (s, 3H), 2.23 (s, 3H), 1.72-1.67 (m, 2H), 1.58-1.53 (m, 4H), 1.46-1.43 (m, 2H). **LCMS:** Method B, t_R = 7.59 min, m/z = 485.3 $[M+H]^+$.

N-*Cyclopentyl*-N-*(2,4-dimethoxybenzyl)-5-(3,5-dimethyl-1H-pyrazol-4-yl)-2-methoxybenzenesulfonamide* (S3a)



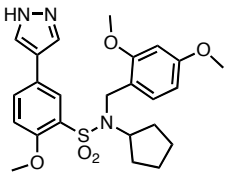
Compound **S3a** was prepared using the ***general procedure B*** employing aryl bromide **7a** (100 mg, 0.21 mmol) and 1-*tert*-butoxycarbonyl-3,5-dimethylpyrazole-4-boronic acid, pinacol ester (97 mg, 0.30 mmol). The Boc group was cleaved under the reaction conditions. **Chromatography conditions:** CombiFlash, 100% EtOAc. R_f = 0.2, 100% EtOAc. **Yield:** (90 mg, 60%). **Physical state:** White powder. **^{1}H NMR:** (600 MHz, $CDCl_3$): δ 7.83 (d, *J* = 2.2 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.36 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.02 (d, *J* = 8.5 Hz, 1H), 6.44 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.35 (d, *J* = 2.3 Hz, 1H), 4.51 (s, 2H), 4.20 (q, *J* = 8.4 Hz, 1H), 3.97 (s, 3H), 3.76 (s, 3H), 3.74 (s, 3H), 2.27 (s, 6H), 1.53-1.46 (m, 4H), 1.40-1.32 (m, 4H). **LCMS:** Method A, t_R = 6.37 min, m/z = 500.4 $[M+H]^+$.

N-*Cyclopentyl*-N-*(2,4-dimethoxybenzyl)-2-methoxy-5-(1,3,5-trimethyl-1H-pyrazol-4-yl)benzenesulfonamide* (S4a)



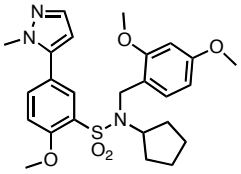
Compound **S4a** was prepared using the ***general procedure B*** employing aryl bromide **7a** (131 mg, 3.0 mmol) and 1,3,5-trimethyl-1*H*-pyrazole-4-boronic acid, pinacol ester (86 mg, 0.36 mmol). **Chromatography conditions:** CombiFlash, 1:1, v/v, EtOAc:cyclohexane. R_f = 0.2, 1:1, v/v, EtOAc:cyclohexane. **Yield:** (60 mg, 51%). **Physical state:** White solid. **^{1}H NMR:** 7.80 (d, *J* = 2.1 Hz, 1H), 7.49 (d, *J* = 8.4 Hz, 1H), 7.37 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.10 (d, *J* = 8.5 Hz, 1H), 6.48 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.40 (d, *J* = 2.3 Hz, 1H), 4.53 (s, 2H), 4.24 (m, 1H), 4.03 (s, 3H), 3.79 (s, 3H), 3.78 (s, 3H), 3.76 (s, 3H), 2.23 (s, 3H), 2.22 (s, 2H), 1.60-1.42 (m, 4H), 1.40-1.29 (m, 4H).

N-*Cyclopentyl*-N-*(2,4-dimethoxybenzyl)-2-methoxy-5-(1H-pyrazol-4-yl)benzenesulfonamide* (S5a)



Compound **S5a** was prepared using the ***general procedure B*** employing aryl bromide **7a** (100 mg, 0.21 mmol) and 1-*tert*-butoxycarbonyl-4-pyrazoleboronic acid, pinacol ester (88 mg, 0.30 mmol). The Boc group was cleaved under the reaction conditions. **Chromatography conditions:** CombiFlash, 1:1, v/v, EtOAc:cyclohexane. R_f = 0.2, 1:1, v/v, EtOAc:cyclohexane. **Yield:** (67 mg, 62%). **Physical state:** White solid. **^{1}H NMR:** δ 7.97 (d, *J* = 1.8 Hz, 1H), 7.80 (s, 2H), 7.57 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.47 (d, *J* = 8.5 Hz, 1H), 6.94 (d, *J* = 8.5 Hz, 1H), 6.45 (d, *J* = 8.5 Hz 1H), 6.31 (s, 1H), 4.48 (s, 2H), 4.22 (dt, *J* = 16.4, 8.1 Hz, 1H), 3.95 (s, 3H), 3.73 (s, 3H), 3.71 (d, 3H), 1.53-1.47 (m, 4H), 1.41-1.33 (m, 4H). **LCMS:** Method B, t_R = 5.42 min, m/z = 472.6 $[M+H]^+$.

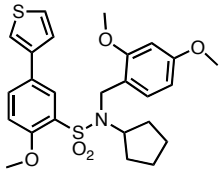
N-*Cyclopentyl*-N-*(2,4-dimethoxybenzyl)-2-methoxy-5-(1-methyl-1H-pyrazol-5-yl)benzenesulfonamide* (S6a)



Compound **S6a** was prepared using the ***general procedure B*** employing aryl bromide **7a** (100 mg, 0.21 mmol) and 1-methyl-1*H*-pyrazole-5-boronic acid, pinacol ester (62 mg, 0.30 mmol). **Chromatography conditions:** CombiFlash, 1:1, v/v, EtOAc:cyclohexane. R_f = 0.2, 1:1, v/v, EtOAc:cyclohexane. **Yield:** (102

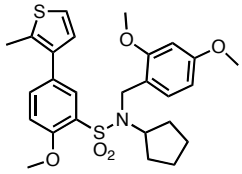
mg, 91%). **Physical state:** White solid. **^{1}H NMR:** δ 7.90 (d, *J* = 2.3 Hz, 1H), 7.50 (d, *J* = 2.3 Hz, 1H), 7.49 (s, 1H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.04 (d, *J* = 8.5 Hz, 1H), 6.41 (dd, *J* = 8.4, 2.3 Hz, 1H), 6.30 (d, *J* = 2.0 Hz, 1H), 6.28 (d, *J* = 2.0 Hz, 1H), 4.47 (s, 2H), 4.25 (quintet, *J* = 8.4 Hz, 1H), 4.00 (s, 3H), 3.84 (s, 3H), 3.74 (s, 3H), 3.73 (s, 3H), 1.58-1.50 (m, 4H), 1.45-1.36 (m, 4H). **LCMS:** Method A, t_R = 6.77 min, m/z = 486.3 $[M+H]^+$.

N-*Cyclopentyl*-N-*(2,4-dimethoxybenzyl)-2-methoxy-5-(thiophen-3-yl)benzenesulfonamide* (S7a)



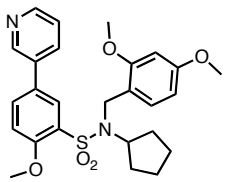
Compound **S7a** was prepared using the ***general procedure B*** employing aryl bromide **7a** (100 mg, 0.21 mmol) and thiophen-3-ylboronic acid (38 mg, 0.30 mmol). **Chromatography conditions:** CombiFlash, 1:2, v/v, EtOAc:cyclohexane. R_f = 0.6, 1:1, v/v, EtOAc:cyclohexane. **Yield:** (104 mg, 92%). **Physical state:** White solid. **^{1}H NMR:** δ 8.10 (d, *J* = 2.4 Hz, 1H), 7.68 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.48 (d, *J* = 8.4 Hz, 1H), 7.41 (td, *J* = 1.7, 0.8 Hz, 1H), 7.39-7.35 (m, 2H), 6.98 (d, *J* = 8.5 Hz, 1H), 6.45 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.31 (d, *J* = 2.4 Hz, 1H), 4.49 (s, 2H), 4.26-4.20 (m, 1H), 3.98 (s, 3H), 3.75 (s, 3H), 3.72 (s, 3H), 1.56-1.47 (m, 4H), 1.40-1.35 (m, 4H). **LCMS:** Method A, t_R = 7.65 min, m/z = 488.3 $[M+H]^+$.

N-*Cyclopentyl*-N-*(2,4-dimethoxybenzyl)-2-methoxy-5-(2-methylthiophen-3-yl)benzenesulfonamide* (S8a)



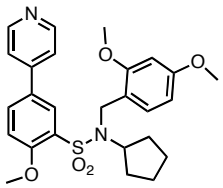
Compound **S8a** was prepared using the ***general procedure B*** employing aryl bromide **7a** (100 mg, 0.21 mmol) and 2-Methylthiophene-3-boronic acid, pinacol ester (67 mg, 0.30 mmol). **Chromatography conditions:** CombiFlash, 1:2, v/v, EtOAc:cyclohexane. R_f = 0.6, 1:1, v/v, EtOAc:cyclohexane. **Yield:** (78 mg, 68%). **Physical state:** White solid. **^{1}H NMR:** δ 7.94 (d, *J* = 2.3 Hz, 1H), 7.48 (dt, *J* = 8.4, 4.2 Hz, 2H), 7.10 (d, *J* = 5.2 Hz, 1H), 7.02-7.00 (m, 2H), 6.45 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.34 (d, *J* = 2.3 Hz, 1H), 4.50 (s, 2H), 4.25-4.19 (m, 1H), 3.99 (s, 3H), 3.76 (s, 3H), 3.75 (s, 3H), 2.47 (s, 3H), 1.55-1.47 (m, 4H), 1.40-1.35 (m, 4H). **LCMS:** Method A: t_R = 7.88 min, m/z = 502.3 $[M+H]^+$.

N-*Cyclopentyl*-N-*(2,4-dimethoxybenzyl)-2-methoxy-5-(pyridin-3-yl)benzenesulfonamide* (S9a)



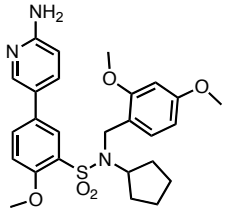
Compound **S9a** was prepared using the ***general procedure B*** employing aryl bromide **7a** (100 mg, 0.21 mmol) and 3-pyridinylboronic acid (36 mg, 0.30 mmol). **Chromatography conditions:** CombiFlash, 1:1, v/v, EtOAc:cyclohexane. R_f = 0.2, 1:1, v/v, EtOAc:cyclohexane. **Yield:** (27 mg, 24%). **Physical state:** White solid. **^{1}H NMR:** δ 8.79 (s, 1H), 8.57 (d, *J* = 4.4 Hz, 1H), 8.04 (dd, *J* = 2.3, 1.3 Hz, 1H), 7.84 (ddd, *J* = 7.9, 2.4, 1.5 Hz, 1H), 7.67 (ddd, *J* = 8.5, 2.3, 1.3 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 1H), 7.36 (dd, *J* = 7.9, 4.4 Hz, 1H), 7.06 (d, *J* = 8.6 Hz, 1H), 6.41 (dd, *J* = 8.4, 2.3 Hz, 1H), 6.27 (d, *J* = 2.3 Hz, 1H), 4.47 (s, 2H), 4.27 (quintet, *J* = 8.4 Hz, 1H), 4.04-3.96 (m, 3H), 3.76-3.71 (m, 3H), 3.67-3.65 (m, 3H), 1.59-1.52 (m, 2H), 1.51-1.47 (m, 2H), 1.46-1.40 (m, 2H), 1.39-1.36 (m, 2H). **LCMS:** Method B: t_R = 5.12 min, m/z = 483.4 $[M+H]^+$.

N-*Cyclopentyl*-N-*(2,4-dimethoxybenzyl)-2-methoxy-5-(pyridin-4-yl)benzenesulfonamide* (S10a)



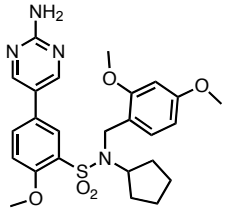
Compound **S10a** was prepared using the ***general procedure B*** employing aryl bromide **7a** (150 mg, 0.31 mmol) and 4-pyridinylboronic acid (76 mg, 0.62 mmol, 2 equiv.). **Chromatography conditions:** CombiFlash, 0:1 to 1:0, v/v, EtOAc:cyclohexane. R_f = 0.2, 1:1, v/v, EtOAc:cyclohexane. **Yield:** (148 mg, >98%). **Physical state:** White solid. **^{1}H NMR:** δ 8.61 (d, *J* = 5.3 Hz, 2H), 8.08 (d, *J* = 2.3 Hz, 1H), 7.72 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.44 (d, *J* = 5.9 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.04 (d, *J* = 8.6 Hz, 1H), 6.38 (dd, *J* = 8.4, 2.3 Hz, 1H), 6.24 (d, *J* = 2.3 Hz, 1H), 4.45 (s, 2H), 4.26 (quintet, *J* = 8.4 Hz, 1H), 3.98 (s, 3H), 3.69 (s, 3H), 3.64 (s, 3H), 1.57-1.53 (m, 2H), 1.50 (dt, *J* = 13.7, 7.0 Hz, 2H), 1.43 (ddt, *J* = 11.6, 8.8, 5.9 Hz, 2H), 1.36 (dt, *J* = 11.7, 6.0 Hz, 2H). **LCMS:** Method B: t_R = 4.71 min, m/z = 483.5 $[M+H]^+$.

***5-(6-Aminopyridin-3-yl)*-N-*cyclopentyl*-*N*-*(2,4-dimethoxybenzyl)-2-methoxybenzenesulfonamide* (S11a)**



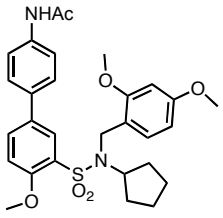
Compound **S11a** was prepared using the ***general procedure B*** employing aryl bromide **7a** (100 mg, 0.21 mmol) and 2-Aminopyridine-5-boronic acid, pinacol ester (66 mg, 0.30 mmol). **Chromatography conditions:** CombiFlash, 0.5:4.5:95, v/v, NH_3:MeOH:CH_2Cl_2. R_f = 0.1, 1:1, v/v, EtOAc:cyclohexane. **Yield:** (96 mg, 84%). **Physical state:** White solid. **^{1}H NMR:** δ 8.24 (d, *J* = 2.5 Hz, 1H), 7.97 (d, *J* = 2.4 Hz, 1H), 7.61 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.58 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.00 (d, *J* = 8.6 Hz, 1H), 6.56 (d, *J* = 8.5 Hz, 1H), 6.43 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.30 (d, *J* = 2.3 Hz, 1H), 4.59 (broad s, 2H), 4.48 (s, 2H), 4.23 (quintet, *J* = 8.4 Hz, 1H), 3.97 (s, 3H), 3.73 (s, 3H), 3.72 (s, 3H), 1.56-1.52 (m, 2H), 1.49 (dd, *J* = 8.4, 4.4 Hz, 2H), 1.42-1.34 (m, 4H). **LCMS:** Method B, t_R = 4.58 min, m/z = 498.5 $[M+H]^+$.

***5-(2-Aminopyrimidin-5-yl)*-N-*cyclopentyl*-N-*(2,4-dimethoxybenzyl)-2-methoxybenzenesulfonamide* (S12a)**



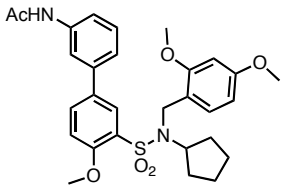
Compound **S12a** was prepared using the ***general procedure B*** employing aryl bromide **7a** (200 mg, 0.42 mmol) and 2-Aminopyrimidine-5-boronic acid, pinacol ester (153 mg, 0.69 mmol, 1.5 equiv.). **Chromatography conditions:** CombiFlash, 0.5:4.5:95, v/v/v, NH_3:MeOH:CH_2Cl_2. R_f = 0.1, 1:1, v/v, EtOAc:cyclohexane. **Yield:** (65 mg, 28%). **Physical state:** White solid. **1H NMR:** (600 MHz, CD_3OD): δ 8.53 (s, 2H), 7.72 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.68 (d, *J* = 2.3 Hz, 1H), 7.28 (d, *J* = 8.4 Hz, 1H), 7.23 (d, *J* = 8.6 Hz, 1H), 6.37 (dd, *J* = 8.4, 2.3 Hz, 1H), 6.24 (d, *J* = 2.3 Hz, 1H), 4.41 (s, 2H), 4.36-4.32 (m, 1H), 4.00 (s, 3H), 3.68 (s, 3H), 3.64 (s, 3H), 1.62-1.54 (m, 4H), 1.47-1.43 (m, 4H). **LCMS:** Method A, t_R = 7.12 min, m/z = 499.3 $[M+H]^+$.

N-*(3'-(*N-*Cyclopentyl-N-(2,4-dimethoxybenzyl)sulfamoyl)-4'-methoxybiphenyl-4-yl)acetamide* (S13a)



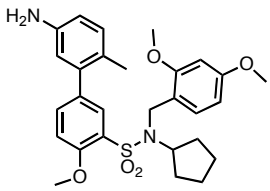
Compound **S13a** was prepared using the ***general procedure B*** employing aryl bromide **7a** (100 mg, 0.21 mmol) and 4-acetamidophenylboronic acid, pinacol ester (54 mg, 0.30 mmol). **Chromatography conditions:** CombiFlash, 0.5:4.5:95, v/v/v, NH_3:MeOH:CH_2Cl_2. R_f = 0.1, 1:1, v/v, EtOAc:cyclohexane. **Yield:** (98 mg, 79%). **Physical state:** White solid. **^{1}H NMR:** (600 MHz, $CDCl_3$): δ 8.21 (s, 1H), 8.05 (d, *J* = 2.3 Hz, 1H), 7.63 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.46-7.42 (m, 3H), 6.99 (d, *J* = 8.6 Hz, 1H), 6.41 (dd, *J* = 8.4, 2.3 Hz, 1H), 6.30 (d, *J* = 2.3 Hz, 1H), 4.49 (s, 2H), 4.21 (quintet, *J* = 8.4 Hz, 1H), 3.96 (s, 3H), 3.72 (s, 3H), 3.69 (s, 3H), 2.15 (s, 3H), 1.54-1.46 (m, 4H), 1.43-1.33 (m, 4H). **LCMS:** Method A: t_R = 6.77 min, m/z = 539.3 $[M+H]^+$.

N-*(3'-(*N-*Cyclopentyl-N-(2,4-dimethoxybenzyl)sulfamoyl)-4'-methoxybiphenyl-3-yl)acetamide* (S14a)



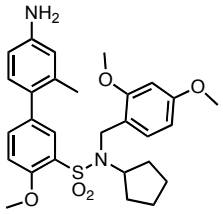
Compound **S14a** was prepared using the ***general procedure B*** employing aryl bromide **7a** (100 mg, 0.21 mmol) and 3-acetamidophenylboronic acid (54 mg, 0.30 mmol). **Chromatography conditions:** CombiFlash, 0.5:4.5:95, v/v, NH_3:MeOH:CH_2Cl_2. R_f = 0.1, 1:1, v/v, EtOAc:cyclohexane. **Yield:** (75 mg, 61%). **Physical state:** White solid. **^{1}H NMR:** (600 MHz, $CDCl_3$): δ 8.04 (d, *J* = 2.3 Hz, 1H), 7.68 (d, *J* = 8.5 Hz, 1H), 7.54 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.46 (d, *J* = 8.5 Hz, 1H), 7.42 (s, 1H), 7.31 (t, *J* = 7.9 Hz, 1H), 7.21 (d, *J* = 7.9 Hz, 1H), 6.85 (d, *J* = 8.5 Hz, 1H), 6.43 (dd, *J* = 8.4, 2.3 Hz, 1H), 6.31 (d, *J* = 2.3 Hz, 1H), 4.48 (s, 2H), 4.21 (dq, *J* = 14.4, 6.9 Hz, 1H), 3.83 (s, 3H), 3.73 (s, 3H), 3.71 (s, 3H), 2.11 (s, 3H), 1.54-1.48 (m, 4H), 1.41-1.32 (m, 4H). **LCMS:** Method A, t_R = 6.89 min, m/z = 539.3 $[M+H]^+$.

***5'-Amino*-N-*cyclopentyl*-N-*(2,4-dimethoxybenzyl)-4-methoxy-2'-methylbiphenyl-3-sulfonamide* (S15a)**



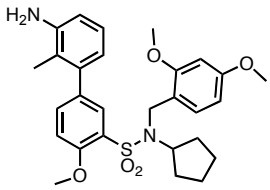
Compound **S15a** was prepared using the ***general procedure B*** employing aryl bromide **7a** (100 mg, 0.21 mmol) and 4-Methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (70 mg, 0.30 mmol). **Chromatography conditions: CombiFlash**, 1:2, v/v, EtOAc:cyclohexane. R_f = 0.5, 1:1, v/v, EtOAc:cyclohexane. **Yield:** (109 mg, 93%). **Physical state:** Tan solid. **^{1}H NMR:** (600 MHz, $CDCl_3$): δ 7.86 (d, *J* = 2.3 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.41 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.05 (d, *J* = 8.1 Hz, 1H), 6.99 (d, *J* = 8.5 Hz, 1H), 6.72 (dd, *J* = 8.1, 2.4 Hz, 1H), 6.65 (d, *J* = 2.4 Hz, 1H), 6.45 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.36 (d, *J* = 2.3 Hz, 1H), 4.51 (s, 2H), 4.23-4.18 (m, 1H), 3.99 (s, 3H), 3.76 (s, 3H), 3.76 (s, 3H), 2.12 (s, 3H), 1.55-1.46 (m, 4H), 1.39-1.33 (m, 4H). **LCMS:** Method A, t_R = 6.38 min, m/z = 511.4 $[M+H]^+$.

***4'-Amino*-N-*cyclopentyl*-N-*(2,4-dimethoxybenzyl)-4-methoxy-2'-methylbiphenyl-3-sulfonamide* (S16a)**



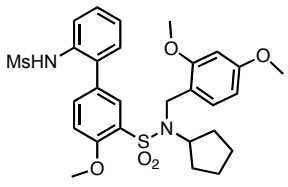
Compound **S16a** was prepared using the ***general procedure B*** employing aryl bromide **7a** (100 mg, 0.21 mmol) and 3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (70 mg, 0.30 mmol). **Chromatography conditions:** CombiFlash, 1:2 to 1:1, v/v, EtOAc:cyclohexane. R_f = 0.5, 1:1, v/v, EtOAc:cyclohexane. **Yield:** (106 mg, 90%). **Physical state:** white solid. **^{1}H NMR:** (600 MHz, $CDCl_3$): δ 7.87 (d, *J* = 2.2 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.41 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.02-6.98 (m, 2H), 6.60 (dd, *J* = 8.1, 2.4 Hz, 1H), 6.53 (d, *J* = 2.4 Hz, 1H), 6.44 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.36 (d, *J* = 2.3 Hz, 1H), 4.52 (s, 2H), 4.21 (quintet, *J* = 8.2 Hz, 1H), 3.98 (s, 3H), 3.76 (s, 3H), 3.75 (s, 3H), 3.52 (broad s, 2H), 2.10 (s, 3H), 1.55-1.47 (m, 4H), 1.41-1.33 (m, 4H). **LCMS:** Method A, t_R = 6.38 min, m/z = 511.4 $[M+H]^+$.

***3'-Amino*-N-*cyclopentyl*-N-*(2,4-dimethoxybenzyl)-4-methoxy-2'-methylbiphenyl-3-sulfonamide* (S17a)**



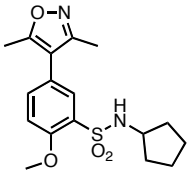
Compound **S17a** was prepared using the ***general procedure B*** employing aryl bromide **7a** (100 mg, 0.21 mmol) and 2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (70 mg, 0.30 mmol). **Chromatography conditions:** CombiFlash, 1:2 to 1:1, v/v, EtOAc:cyclohexane. R_f = 0.5, 1:1, v/v, EtOAc:cyclohexane. **Yield:** (112 mg, 95%). **Physical state:** white solid. **^{1}H NMR:** (600 MHz, $CDCl_3$): δ 7.88 (d, *J* = 2.3 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.41 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.04 (t, *J* = 7.7 Hz, 1H), 7.01 (d, *J* = 8.4 Hz, 1H), 6.69 (d, *J* = 7.9 Hz, 1H), 6.64 (d, *J* = 7.7 Hz, 1H), 6.45 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.37 (d, *J* = 2.3 Hz, 1H), 4.53 (s, 2H), 4.21 (quintet, *J* = 8.4 Hz, 1H), 3.99 (s, 3H), 3.77 (s, 3H), 3.76 (s, 3H), 2.01 (s, 3H), 1.56-1.47 (m, 4H), 1.42-1.34 (m, 4H). **LCMS:** Method A, t_R = 6.87 min, m/z = 511.4 $[M+H]^+$.

N-*Cyclopentyl*-N-*(2,4-dimethoxybenzyl)-4-methoxy-2'-(methylsulfonamido)biphenyl-3-sulfonamide* (S18a)



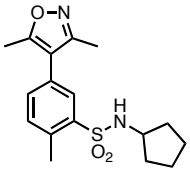
Compound **S18a** was prepared using the ***general procedure B*** employing aryl bromide **7a** (100 mg, 0.21 mmol) and 2-[(methylsulphonyl)amino]benzeneboronic acid, pinacol ester (89 mg, 0.30 mmol). **Chromatography conditions:** CombiFlash, 1:2, v/v, EtOAc:cyclohexane. R_f = 0.5, 1:1, v/v, EtOAc:cyclohexane. **Yield:** (75 mg, 61%). **Physical state:** White solid. **^{1}H NMR:** (600 MHz, $CDCl_3$): δ 7.87 (d, *J* = 2.3 Hz, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.48 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.38 (ddd, *J* = 8.4, 6.1, 2.5 Hz, 1H), 7.22 (t, *J* = 6.1 Hz, 1H), 7.09 (d, *J* = 8.5 Hz, 1H), 6.44 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.35 (d, *J* = 2.3 Hz, 1H), 6.23 (broad s, 1H), 4.50 (s, 2H), 4.26-4.21 (m, 1H), 4.03 (s, 3H), 3.76 (s, 6H), 2.95 (s, 3H), 1.58-1.49 (m, 4H), 1.46-1.39 (m, 4H). **LCMS:** Method B, t_R = 5.76 min, m/z = 597.8 $[M+Na]^+$.

N-*Cyclopentyl-5-(3,5-dimethylisoxazol-4-yl)-2-methoxybenzenesulfonamide* (11a)



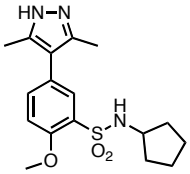
Compound **11a** was prepared using the ***general procedure C*** employing **S2a** (63 mg, 0.13 mmol). **Chromatography conditions:** 1:9 to 1:1, v/v, EtOAc:cyclohexane. R_f = 0.9, 1:1, v/v EtOAc/cyclohexane. **Yield:** (33 mg, 72%). **Physical state:** White powder. **^{1}H NMR:** (600 MHz, CD_3OD): δ 7.76 (d, *J* = 2.2 Hz, 1H), 7.56 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.29 (d, *J* = 8.5 Hz, 1H), 4.00 (s, 3H), 3.54-3.50 (m, 1H), 2.39 (s, 3H), 2.23 (s, 3H), 1.68-1.61 (m, 4H), 1.46-1.40 (m, 4H). **LCMS:** Method B, t_R = 5.24 min, m/z = 351.0 $[M+H]^+$. **HRMS:** Found 351.1375, Calc $[M+H]^+$ = 351.1373.

N-*Cyclopentyl-5-(3,5-dimethylisoxazol-4-yl)-2-methylbenzenesulfonamide* (5)



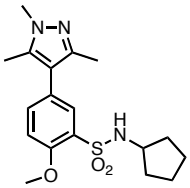
Compound **5** was prepared using the ***general procedure C*** employing **S2b** (50 mg, 0.10 mmol). **Chromatography conditions:** 0:1 to 1:2, v/v, EtOAc:cyclohexane. R_f = 0.5, 1:1, v/v EtOAc/cyclohexane. **Yield:** (34 mg, 96%). **Physical state:** White powder. **^{1}H NMR:** (600 MHz, $CDCl_3$): δ 7.93 (d, *J* = 1.8 Hz, 1H), 7.40 (d, *J* = 7.8 Hz, 1H), 7.36 (dd, *J* = 7.8, 1.8 Hz, 1H), 4.58 (d, *J* = 7.2 Hz, 1H), 3.64 (sextet, *J* = 6.8 Hz, 1H), 2.69 (s, 3H), 2.28 (s, 3H), 1.84-1.78 (m, 2H), 1.68-1.61 (m, 2H), 1.55-1.48 (m, 2H), 1.44-1.37 (m, 2H). **LCMS:** Method A, t_R = 4.43 min, m/z = 335.0 $[M+H]^+$. **HRMS:** Found 335.1422, Calc $[M+H]^+$ = 335.1424.

N-*Cyclopentyl-5-(3,5-dimethyl-1*H*-pyrazol-4-yl)-2-methoxybenzenesulfonamide* (12a)



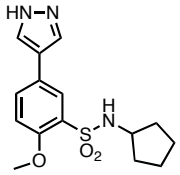
Compound **12a** was prepared using the ***general procedure C*** employing **S3a** (45 mg, 90 µmol). **Chromatography conditions:** CombiFlash, EtOAc. R_f = 0.2, EtOAc. **Yield:** (13 mg, 41%). **Physical state:** White powder. **^{1}H NMR:** (600 MHz, $CDCl_3$): δ 8.63 (broad s, 1H), 7.82 (d, *J* = 1.8 Hz, 1H), 7.41 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.07 (d, *J* = 8.5 Hz, 1H), 5.18 (d, *J* = 7.0 Hz, 1H), 3.97 (s, 3H), 3.56 (sextet, *J* = 6.7 Hz, 1H), 2.27 (broad s, 6H), 1.75-1.70 (m, 2H), 1.64-1.59 (m, 2H), 1.47 (m, 2H), 1.41-1.35 (m, 2H). **LCMS:** Method B, t_R = 4.71 min, m/z = 350.3 $[M+H]^+$. **HRMS:** found 350.1540. Calc $[M+H]^+$ = 350.1533.

N-*Cyclopentyl-2-methoxy-5-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)benzenesulfonamide* (13a)



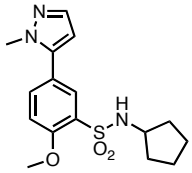
Compound **13a** was prepared using the ***general procedure C*** employing **S4a** (60 mg, 0.12 mmol). **Chromatography conditions:** CombiFlash, 1:1, v/v, EtOAc:cyclohexane. R_f = 0.2, 1:1, v/v, EtOAc:cyclohexane. **Yield:** (41mg, 98%). **Physical state:** White solid. **^{1}H NMR:** (600 MHz, $CDCl_3$): δ 7.78 (d, *J* = 2.3 Hz, 1H), 7.38 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.06 (d, *J* = 8.5 Hz, 1H), 4.89 (d, *J* = 7.1 Hz, 1H), 3.99 (s, 3H), 3.77 (s, 3H), 3.55 (sextet, *J* = 6.8 Hz, 1H), 2.21 (s, 6H), 1.75-1.70 (m, 2H), 1.65-1.58 (m, 2H), 1.50-1.43 (m, 2H), 1.39-1.34 (m, 2H). **LCMS:** Method A, RT = 6.33 min, m/z = 364.3 $[M+H]^+$. **HRMS:** found 364.1703. Calc $[M+H]^+$ = 364.1689.

N-*Cyclopentyl-2-methoxy-5-(1*H-*pyrazol-4-yl)benzenesulfonamide* (14a)



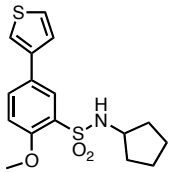
Compound **14a** was prepared using the ***general procedure C*** employing **S5a** (67 mg, 0.14 mmol). **Chromatography conditions:** CombiFlash, 0.5:4.5:95, v/v, NH_3:MeOH:CH_2Cl_2. R_f = 0.5,. 0.5:4.5:95, v/v, NH_3:MeOH:CH_2Cl_2. **Yield:** (31 mg, 69%). **Physical state:** White solid. **^{1}H NMR:** (600 MHz, $CDCl_3$): δ 8.05 (d, *J* = 2.3 Hz, 1H), 7.89 (s, 2H), 7.66 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.05 (d, *J* = 8.5 Hz, 1H), 5.38 (broad s, 1H), 4.95-4.94 (m, 1H), 3.98 (s, 3H), 3.59-3.54 (m, 1H), 1.77-1.71 (m, 2H), 1.64-1.59 (m, 2H), 1.51-1.46 (m, 2H), 1.40-1.35 (m, 2H). **LCMS:** Method B, t_R = 4.76, m/z = 322.4 $[M+H]^+$. **HRMS:** found 322.1229. Calc $[M+H]^+$ = 322.1220.

N-*Cyclopentyl-2-methoxy-5-(1-methyl-1*H-*pyrazol-5-yl)benzenesulfonamide* (15a)



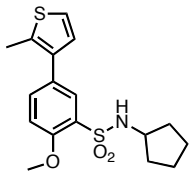
Compound **15a** was prepared using the ***general procedure C*** employing **S6a** (50 mg, 0.10 mmol). **Chromatography conditions: CombiFlash**, 1:1, v/v, EtOAc:cyclohexane. R_f = 0.2, 1:1, v/v, EtOAc:cyclohexane. **Yield:** (33 mg, 96%). **Physical state:** White solid. **^{1}H NMR:** (600 MHz, $CDCl_3$): δ 7.98 (d, *J* = 2.1 Hz, 1H), 7.57 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.51 (broad s, 1H), 7.11 (d, *J* = 8.6 Hz, 1H), 6.32 (broad s, 1H), 4.95 (d, *J* = 7.2 Hz, 1H), 4.03 (s, 3H), 3.87 (broad s, 3H), 3.56 (sextet, *J* = 6.8 Hz, 1H), 1.76-1.71 (m, 2H), 1.64-1.58 (m, 2H), 1.51-1.44 (m, 2H), 1.40-1.34 (m, 2H). **LCMS:** Method B, t_R = 5.01, m/z = 336.3 $[M+H]^+$. **HRMS:** found 336.1391. Calc $[M+H]^+$ = 336.1376.

N-*Cyclopentyl-2-methoxy-5-(thiophen-3-yl)benzenesulfonamide* (16a)



Compound **16a** was prepared using the ***general procedure C*** employing **S7a** (70 mg, 0.14 mmol). **Chromatography conditions:** CombiFlash, 1:2, v/v, EtOAc:cyclohexane. R_f = 0.5, 1:1, v/v, EtOAc:cyclohexane. **Yield:** (30 mg, 65%). **Physical state:** White solid. **^{1}H NMR:** (600 MHz, $CDCl_3$): δ 8.15 (d, *J* = 1.7 Hz, 1H), 7.74 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.45 (dd, *J* = 1.5, 1.1 Hz, 1H), 7.40-7.37 (m, 2H), 7.05 (d, *J* = 8.6 Hz, 1H), 4.90 (d, *J* = 5.0 Hz, 1H), 4.00 (s, 3H), 3.55 (q, *J* = 6.3 Hz, 1H), 1.74-1.71 (m, 2H), 1.62-1.57 (m, 2H), 1.48-1.45 (m, 2H), 1.39-1.35 (m, 2H). **LCMS:** Method B, t_R = 5.59 min, m/z = 338.1 $[M+H]^+$. **HRMS:** found 338.0883. Calc $[M+H]^+$ = 338.0879.

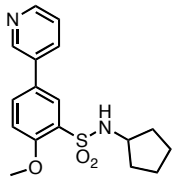
N-*Cyclopentyl-2-methoxy-5-(2-methylthiophen-3-yl)benzenesulfonamide* (17a)



Compound **17a** was prepared using the ***general procedure C*** employing **S8a** (62 mg, 0.12 mmol). **Chromatography conditions:** CombiFlash, 1:2, v/v, EtOAc:cyclohexane. R_f = 0.6, 1:1, v/v, EtOAc:cyclohexane. **Yield:** (21 mg, 50%). **Physical state:** White solid. **^{1}H NMR:** (600 MHz, $CDCl_3$): δ 7.96 (d, *J* = 2.3 Hz, 1H), 7.54 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.11 (d, *J* = 5.2 Hz, 1H), 7.07 (d, *J* = 8.5 Hz, 1H), 7.02

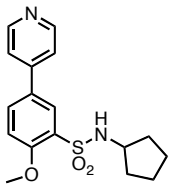
(d, *J* = 5.2 Hz, 1H), 4.90 (d, *J* = 6.9 Hz, 1H), 4.00 (s, 4H), 3.55 (sextet, *J* = 6.7 Hz, 1H), 2.49 (s, 3H), 1.76-1.70 (m, 2H), 1.64-1.58 (m, 2H), 1.51-1.44 (m, 2H), 1.40-1.34 (m, 2H). **LCMS:** Method B, t_R = 5.79, m/z = 352.3 $[M+H]^+$. **HRMS:** found 352.1039. Calc $[M+H]^+$ = 352.1036.

N-*Cyclopentyl-2-methoxy-5-(pyridin-3-yl)benzenesulfonamide* (18a)



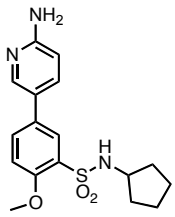
Compound **18a** was prepared using the ***general procedure C*** employing **S9a** (25 mg, 52 µmol). **Chromatography conditions:** CombiFlash, 1:1, v/v, EtOAc:cyclohexane. R_f = 0.2, 1:1, v/v, EtOAc:cyclohexane. **Yield:** (15 mg, 87%). **Physical state:** White solid. **^{1}H NMR:** (600 MHz, CD_3OD): δ 8.79 (s, 1H), 8.52 (broad s, 1H), 8.10-8.08 (m, 2H), 7.91 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.52 (dd, *J* = 7.6, 5.0 Hz, 1H), 7.33 (d, *J* = 8.6 Hz, 1H), 4.02 (s, 3H), 3.55-3.51 (m, 1H), 1.69-1.60 (m, 4H), 1.48-1.39 (m, 4H). **LCMS:** Method B, t_R = 4.20, m/z = 333.1 $[M+H]^+$. **HRMS:** found 333.1277. Calc $[M+H]^+$ = 333.1267.

N-*Cyclopentyl-2-methoxy-5-(pyridin-4-yl)benzenesulfonamide* (19a)



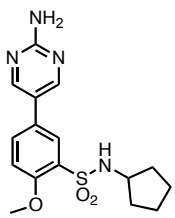
Compound **19a** was prepared using the ***general procedure C*** employing **S10a** (140 mg, 0.29 mmol). **Chromatography conditions:** CombiFlash, 0:1 to 1:0, v/v, EtOAc:cyclohexane. R_f = 0.2, 1:1, v/v, EtOAc:cyclohexane. **Yield:** (91 mg, 94%). **Physical state:** White solid. **^{1}H NMR:** (600 MHz, CD_3OD): δ 8.57 (dd, *J* = 4.6, 1.6 Hz, 2H), 8.21 (d, *J* = 2.4 Hz, 1H), 8.02 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.70 (dd, *J* = 4.6, 1.7 Hz, 2H), 7.34 (d, *J* = 8.7 Hz, 1H), 4.03 (s, 3H), 3.55-3.50 (m, 1H), 1.70-1.59 (m, 4H), 1.46-1.40 (m, 4H). **LCMS:** Method B, t_R = 4.51 min, m/z = 333.1 $[M+H]^+$.

***5-(6-Aminopyridin-3-yl)-N-cyclopentyl-2-methoxybenzenesulfonamide* (20a)**



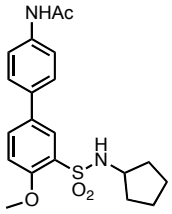
Compound **20a** was prepared using the ***general procedure C*** employing **S11a** (65 mg, 0.13 mmol). **Chromatography conditions: CombiFlash**, 0.5:4.5:95, v/v, NH_3:MeOH:CH_2Cl_2. R_f = 0.1, 1:1, v/v, EtOAc:cyclohexane. **Yield:** (36 mg, 80%). **Physical state:** White solid. **^{1}H NMR:** (600 MHz, $CDCl_3$): δ 8.25 (d, *J* = 2.2 Hz, 1H), 8.05 (d, *J* = 2.3 Hz, 1H), 7.67 (ddd, *J* = 17.5, 8.5, 2.4 Hz, 2H), 7.08 (d, *J* = 8.6 Hz, 1H), 6.61 (d, *J* = 8.6 Hz, 1H), 4.90 (d, *J* = 7.1 Hz, 1H), 4.82-4.67 (m, 1H), 4.00 (s, 3H), 3.59-3.53 (m, 1H), 1.76-1.71 (m, 2H), 1.63-1.59 (m, 2H), 1.50-1.46 (m, 2H), 1.40-1.34 (m, 2H). **LCMS:** Method B, t_R = 4.03 min, m/z = 348.3 $[M+H]^+$. **HRMS:** found 348.1389. Calc $[M+H]^+$ = 348.1376.

***5-(2-Aminopyrimidin-5-yl)-N-cyclopentyl-2-methoxybenzenesulfonamide* (21a)**



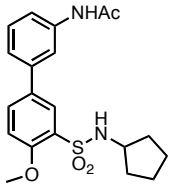
Compound **21a** was prepared using the ***general procedure C*** employing **S12a** (64 mg, 0.13 mmol). **Chromatography conditions:** CombiFlash, 0.5:4.5:95, v/v, NH_3:MeOH:CH_2Cl_2. R_f = 0.1, 1:1, v/v, EtOAc:cyclohexane. **Yield:** (43 mg, 95%). **Physical state:** White solid. **^{1}H NMR:** (600 MHz, DMSO-d_6): δ 8.50 (s, 2H), 7.84 (d, *J* = 2.3 Hz, 1H), 7.82-7.80 (m, 1H), 7.25 (d, *J* = 8.6 Hz, 2H), 6.76 (s, 2H), 3.90 (s, 3H), 3.43-3.40 (m, 1H), 1.55-1.49 (m, 4H), 1.36-1.29 (m, 4H). **LCMS:** Method A, t_R = 5.57 min, m/z = 349.2 $[M+H]^+$. **HRMS:** found 349.1343. Calc $[M+H]^+$ = 349.1329.

N-*(3'-(*N-*Cyclopentylsulfamoyl)-4'-methoxybiphenyl-4-yl)acetamide* (22a)



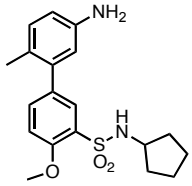
Compound **22a** was prepared using the ***general procedure C*** employing **S13a** (72 mg, 0.13 mmol). **Chromatography conditions: CombiFlash**, 0.5:4.5:95, v/v, NH_3:MeOH:CH_2Cl_2. R_f = 0.1, 1:1, v/v, EtOAc:cyclohexane. **Yield:** (52 mg, 99%). **Physical state:** White solid. **^{1}H NMR:** (600 MHz, CD_3OD): δ 8.03 (d, *J* = 2.4 Hz, 1H), 7.82 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.63 (d, *J* = 8.8 Hz, 2H), 7.54 (d, *J* = 8.8 Hz, 2H), 7.24 (d, *J* = 8.7 Hz, 1H), 3.98 (s, 3H), 3.53-3.48 (m, 1H), 2.13 (s, 3H), 1.69-1.59 (m, 4H), 1.47-1.40 (m, 4H). **LCMS:** Method B: t_R = 5.07 min, m/z = 389.4 $[M+H]^+$. **HRMS:** found 389.1532. Calc $[M+H]^+$ = 389.1530.

N-*(3'-(*N-*Cyclopentylsulfamoyl)-4'-methoxybiphenyl-3-yl)acetamide* (23a)



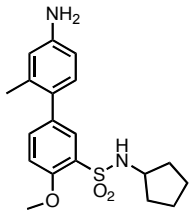
Compound **23a** was prepared using the ***general procedure C*** employing **S14a** (55 mg, 0.10 mmol). **Chromatography conditions: CombiFlash**, EtOAc. R_f = 0.1, 1:1, v/v, EtOAc:cyclohexane. **Yield:** (31 mg, 80%). **Physical state:** White solid. **^{1}H NMR:** (600 MHz, CD_3OD): δ 8.06 (d, *J* = 2.4 Hz, 1H), 7.82 (dt, *J* = 8.6, 4.3 Hz, 2H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.37 (t, *J* = 7.9 Hz, 1H), 7.31 (d, *J* = 7.8 Hz, 1H), 7.25 (d, *J* = 8.6 Hz, 1H), 3.99 (s, 3H), 3.50 (qd, *J* = 7.9, 6.3 Hz, 1H), 2.13 (s, 3H), 1.69-1.59 (m, 4H), 1.46-1.39 (m, 4H). **LCMS:** Method B, t_R = 5.18, m/z = 389.4 $[M+H]^+$. **HRMS:** found 389.1533. Calc $[M+H]^+$ = 389.1530.

***5'-Amino*-N-*cyclopentyl-4-methoxy-2'-methylbiphenyl-3-sulfonamide* (24a)**



Compound **24a** was prepared using the ***general procedure C*** employing **S15a** (26 mg, 59 µmol). **Chromatography conditions: CombiFlash**, 1:2, v/v, EtOAc:cyclohexane. R_f = 0.5, 1:1, v/v, EtOAc:cyclohexane. **Yield:** (8.4 mg, 39%). **Physical state:** White solid. **^{1}H NMR:** (600 MHz, $CDCl_3$): δ 7.88 (d, *J* = 2.3 Hz, 1H), 7.47 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.04 (t, *J* = 7.3 Hz, 2H), 6.62 (dd, *J* = 8.0, 2.5 Hz, 1H), 6.57 (d, *J* = 2.4 Hz, 1H), 4.92 (d, *J* = 7.2 Hz, 1H), 4.00 (s, 3H), 3.56 (dq, *J* = 13.7, 6.8 Hz, 2H), 2.13 (s, 3H), 1.75-1.70 (m, 2H), 1.64-1.58 (m, 2H), 1.50-1.44 (m, 2H), 1.39-1.33 (m, 2H). **LCMS:** Method B, t_R = 4.57 min, m/z = 402.1 $[M+CH_3CN+H]^+$. **HRMS:** found 361.1589. Calc $[M+H]^+$ = 361.1580.

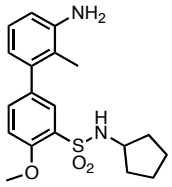
***4'-Amino*-N-*cyclopentyl-4-methoxy-2'-methylbiphenyl-3-sulfonamide* (25a)**



Compound **25a** was prepared using the ***general procedure C*** employing **S16a** (63 mg, 0.12 mmol). **Chromatography conditions: CombiFlash**, 1:2 to 1:1, v/v, EtOAc:cyclohexane. R_f = 0.5, 1:1, v/v, EtOAc:cyclohexane. **Yield:** (38 mg, 88%). **Physical state:** white solid. **^{1}H NMR:** (600 MHz, CD_3OD): δ 7.73 (d, *J* = 2.1 Hz, 1H), 7.51 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.22 (d, *J* = 8.5 Hz, 1H), 7.01 (d, *J* = 8.1 Hz, 1H), 6.67 (dd, *J* = 8.1, 2.2 Hz, 1H), 6.61 (d, *J* = 2.3 Hz, 1H), 3.99 (s, 3H), 3.52-3.48 (m, 1H), 2.09

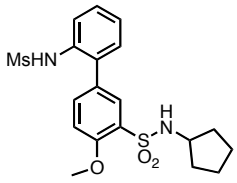
(s, 3H), 1.68-1.62 (m, 4H), 1.46-1.39 (m, 4H). **LCMS:** Method B, t_R = 4.53 min, m/z = 361.3 $[M+H]^+$. **HRMS:** found 361.1593. Calc $[M+H]^+$ = 361.1580.

***3'-Amino*-N-*cyclopentyl-4-methoxy-2'-methylbiphenyl-3-sulfonamide* (26a)**



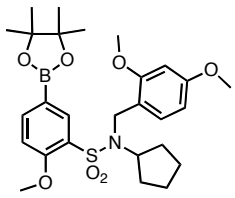
Compound **26a** was prepared using the ***general procedure C*** employing **S17a** (55 mg, 0.11 mmol). **Chromatography conditions: Chromatography conditions: CombiFlash**, 1:2 to 1:1, v/v, EtOAc:cyclohexane. R_f = 0.5, 1:1, v/v, EtOAc:cyclohexane. **Yield:** (30 mg, 76%). **Physical state:** white solid. **^{1}H NMR:** (600 MHz, $CDCl_3$): δ 7.88 (d, *J* = 2.2 Hz, 1H), 7.46 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.09-7.04 (m, 2H), 6.73 (d, *J* = 7.7 Hz, 1H), 6.67 (d, *J* = 7.5 Hz, 1H), 4.90 (d, *J* = 7.2 Hz, 1H), 4.05 (s, 3H), 3.59-3.54 (m, 1H), 2.09 (s, 3H), 1.76-1.71 (m, 2H), 1.65-1.58 (m, 2H), 1.51-1.44 (m, 2H), 1.42-1.34 (m, 2H). **LCMS:** Method B, t_R = 4.91 min, m/z = 361.6 $[M+H]^+$. **HRMS:** found 361.1596. Calc $[M+H]^+$ = 361.1580.

N-*Cyclopentyl-4-methoxy-2'-(methylsulfonamido)biphenyl-3-sulfonamide* (27a)



Compound **27a** was prepared using the ***general procedure C*** employing **S18a** (60 mg, 0.17 mmol). **Chromatography conditions: CombiFlash**, 1:2, v/v, EtOAc:cyclohexane. R_f = 0.5, 1:1, v/v, EtOAc:cyclohexane. **Yield:** (20 mg, 99%). **Physical state:** White solid. **^{1}H NMR:** (600 MHz, $CDCl_3$): δ 7.91 (d, *J* = 2.3 Hz, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.55-7.53 (m, 1H), 7.41-7.38 (m, 1H), 7.26 (dd, *J* = 8.5, 1.0 Hz, 2H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.14 (d, *J* = 8.5 Hz, 1H), 6.29 (s, 1H), 4.93 (dd, *J* = 3.7, 3.0 Hz, 1H), 4.04 (s, 3H), 3.58 (m, 1H), 2.98 (s, 3H), 1.79-1.74 (m, 2H), 1.67-1.58 (m, 2H), 1.53-1.49 (m, 2H), 1.42-1.36 (m, 2H). **LCMS:** Method B, t_R = 4.91 min, No molecular ion observed. **HRMS:** found 425.1205. Calc $[M+H]^+$ = 425.1199.

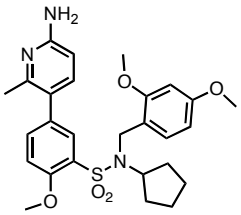
N-*Cyclopentyl*-N-*(2,4-dimethoxybenzyl)-2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide* (28)



A schlenk flask was purged with with N_2 then charged with $PdCl_2$(dppf) (112 mg, 0.155 mmol), potassium acetate (763 mg, 7.77 mmol) and bis(pinacolato)diboron (807 mg, 3.42 mmol), evacuated and backfilled with N_2 (3 cycles). Then a solution of **7a** (1.350 g, 3.12 mmol) in DMSO (20 mL, which had been degassed with bubbling N_2 for 10 min) was added. The mixture was then heated at 80 ^oC for 12 h under N_2. The reaction mixture was then cooled, and poured into toluene (100 mL) and washed with water (2 x 50 mL). The aqueous portions were extracted with toluene and the combined toluene fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude solid was dissolved in EtOAc and concentrated onto chromatography grade silica. The ensuing free flowing powder was chromatographed (CombiFlash, silca, 0:1 to 1:2, v/v, EtOAc:cyclohexane). Concentration of the appropriate fractions (R_f = 0.8, 1:1, v/v, EtOAc:cyclohexane) afforded the *title compound* **28** (629 mg, 38%) as a colourless solid. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.37 (d, *J* = 1.6 Hz, 1H), 7.90 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.51 (d, *J* = 8.4 Hz, 1H), 6.94

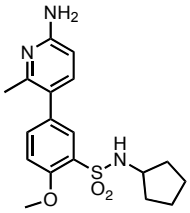
(d, *J* = 8.4 Hz, 1H), 6.49 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.36 (d, *J* = 2.4 Hz, 1H), 4.49 (s, 2H), 4.17 (quintet, *J* = 7.2 Hz, 1H), 3.97 (s, 3H), 3.79 (s, 3H), 3.77 (s, 3H), 1.46 (m, 4H), 1.33 (m, *J* = 16.1 Hz, 16H). **LCMS:** Method B, t_R = 6.39 min, m/z = 555.1 $[M+Na]^+$.

***5-(6-Amino-2-methylpyridin-3-yl)*-N-*cyclopentyl*-N-*(2,4-dimethoxybenzyl)-2-methoxybenzenesulfonamide* (S19)**



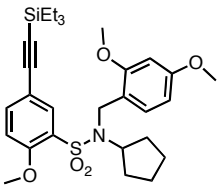
Compound **S19** was prepared using the ***general procedure B*** employing 2-amino-5-bromo-6-methylpyridine (70 mg, 0.38 mmol) and boronate etser **28** (100 mg, 0.19 mmol). **Chromatography conditions:** CombiFlash, 0:1 to 1:0, v/v, EtOAc:cyclohexane. R_f = 0.5, EtOAc. **Yield:** (68 mg, 71%). **Physical state:** White powder. **^{1}H NMR:** (600 MHz, $CDCl_3$): δ 7.81 (d, *J* = 2.3 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 1H), 7.36 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.24 (d, *J* = 8.3 Hz, 1H), 6.99 (d, *J* = 8.4 Hz, 1H), 6.43 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.38 (d, *J* = 8.3 Hz, 1H), 6.34 (d, *J* = 2.3 Hz, 1H), 4.55 (s, 2H), 4.49 (s, 2H), 4.21 (t, *J* = 8.4 Hz, 1H), 3.98 (s, 3H), 3.77 (s, 3H), 3.75 (s, 3H), 2.29 (s, 3H), 1.54-1.47 (m, 4H), 1.40-1.33 (m, 4H). **LCMS:** Method B, t_R = 4.59 min, m/z = 512.6 $[M+H]^+$.

***5-(6-Amino-2-methylpyridin-3-yl)*-N-*cyclopentyl-2-methoxybenzenesulfonamide* (29)**



Compound **29** was prepared using the ***general procedure C*** described above employing 100 mg (0.20 mmol) of **S1**. **Chromatography conditions:** CombiFlash, 0:1 to 1:0, v/v, EtOAc:cyclohexane. R_f = 0.5, 1:1, v/v EtOAc/cyclohexane. **Yield:** (38 mg, 53%). **Physical state:** White solid. **^{1}H NMR:** (600 MHz, $CDCl_3$): δ 7.84 (d, *J* = 2.1 Hz, 1H), 7.44 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.35 (d, *J* = 8.3 Hz, 1H), 7.06 (d, *J* = 8.5 Hz, 1H), 6.48 (d, *J* = 8.3 Hz, 1H), 4.97 (broad s, 2H), 4.88 (d, *J* = 7.1 Hz, 1H), 4.01 (s, 3H), 3.57 (q, *J* = 6.8 Hz, 1H), 2.37 (s, 3H), 1.75-1.73 (m, 2H), 1.63-1.61 (m, 2H), 1.50-1.47 (m, 2H), 1.39-1.36 (m, 2H). **LCMS:** Method A, t_R = 4.68 min, m/z = 362.2 $[M+H]^+$. **HRMS:** found 362.1569. Calc $[M+H]^+$ = 362.1533.

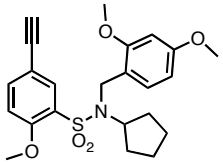
N-*Cyclopentyl*-N-*(2,4-dimethoxybenzyl)-2-methoxy-5-((triethylsilyl)ethynyl)benzenesulfonamide* (30)



A dry microwave vessel was purged with N_2 then charged with **7a** (1.00 g, 2.07 mmol), $Pd(PPh_3)_4$ (120 mg, 0.103 mmol), and CuI (39 mg, 0.207 mmol) then capped with a rubber septum and evacuated and backfilled with N_2 (3 cycles). Triethylsilylacetylene (0.741 mL, 4.14 mmol), THF (5.0 mL) and triethylamine (5.0 mL) were then added and the reaction vessel was capped with a microwave reaction cap and subjected to microwave irradiation at 90 °C for 12 h. The reaction mixture was concentrated onto silica and the ensuing free flowing powder was chromatographed (CombiFlash, 0-20%, EtOAc/heptane). Concentration of the appropriate fractions (R_f = 0.4, 1:19, v/v, EtOAc:cyclohexane) afforded the *title alkyne* **30** (704 mg, 63%) as a pale yellow solid. **^{1}H NMR:** (600 MHz, $CDCl_3$): δ 8.03 (d, *J* = 2.1 Hz, 1H), 7.56 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.47 (d, *J* = 8.5 Hz, 1H), 6.88 (d, *J*

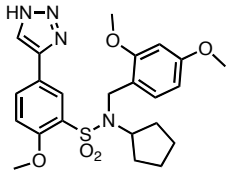
= 8.6 Hz, 1H), 6.48 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.35 (d, *J* = 2.3 Hz, 1H), 4.47 (s, 2H), 4.15 (dd, *J* = 10.9, 6.7 Hz, 1H), 3.95 (s, 3H), 3.78 (s, 3H), 3.77 (s, 3H), 1.49 (d, *J* = 10.3 Hz, 4H), 1.36 (d, *J* = 3.8 Hz, 4H), 1.04 (t, *J* = 7.9 Hz, 9H), 0.67 (q, *J* = 7.9 Hz, 6H).

N-*Cyclopentyl*-N-*(2,4-dimethoxybenzyl)-5-ethynyl-2-methoxybenzenesulfonamide* (31)



To a magnetically stirred solution of **30** (700 mg, 1.29 mmol) in THF (10 mL) at 0 ^{o}C using an ice bath was added TBAF (1.47 mL of a 1.0 M solution in THF, 1.42 mmol) and after 5 min the ice bath was removed and the mixture was warmed to RT over 0.5 h. $NaHCO_3$ (2.5 mL of a sat. aq. solution) was then added and the reaction mixture was extracted with EtOAc (3 x 10 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude residue was chromatographed (CombiFlash, 0:1 to 1:2, v/v, EtOAc:n-heptane). Concentration of the appropriate fractions (R_f = 0.4, 1:1, v/v, EtOAc:cyclohexane) afforded the *title compound* **31** (483 mg, 87%) as a white solid. **^{1}H NMR:** (600 MHz, $CDCl_3$): δ 8.01 (d, *J* = 2.1 Hz, 1H), 7.57 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 6.90 (d, *J* = 8.5 Hz, 1H), 6.47 (dd, *J* = 8.4, 2.3 Hz, 1H), 6.33 (d, *J* = 2.3 Hz, 1H), 4.46 (s, 2H), 4.18 (quintet, *J* = 7.8 Hz, 1H), 3.96 (s, 3H), 3.79 (s, 3H), 3.75 (s, 3H), 3.03 (s, 1H), 1.54-1.48 (m, 4H), 1.40-1.35 (m, 4H). **LCMS:** Method A, t_R = 7.27 min, m/z = 430.3 $[M+H]^+$.

N-*Cyclopentyl*-N-*(2,4-dimethoxybenzyl)-2-methoxy-5-(2H-1,2,3-triazol-4-yl)benzenesulfonamide* (32)

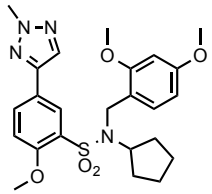


A dry microwave vessel was charged with **31** (100 mg, 0.250 mmol) and CuI (2.4 mg, 12.5 μg) then capped with a rubber septum evacuated and backfilled with N_2 (3 cycles). Then DMF (1.8 mL, anhydrous) and MeOH (0.2 mL, anhydrous) were added followed by (trimethylsilyl)azide (49 μL, 0.373 mmol). The solution was heated 90 ^{o}C under microwave irradiation for 12 h. The solution was then concentrated under reduced pressure, redissolved in MeOH and concentrated onto silica and chromatographed (CombiFlash, 1:99 to 1:9, v/v, MeOH:CH_2Cl_2). Concentration of the appropriate fractions (R_f = 0.5, 1:19, v/v, MeOH:CH_2Cl_2) afforded the *title triazole* **32** (107 mg, 91%) as an off-white solid. **^{1}H NMR:** (600 MHz, DMSO-d_6): δ 8.16 (broad s, 1H), 8.04 (d, *J* = 8.7 Hz, 1H), 7.93 (s, 1H), 7.31 (d, *J* = 8.7 Hz, 1H), 7.27 (d, *J* = 8.4 Hz, 1H), 6.48 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.43 (d, *J* = 2.2 Hz, 1H), 4.37 (s, 2H), 4.08-4.05 (m, 1H), 3.95 (s, 3H), 3.74 (s, 3H), 3.67 (s, 3H), 1.41-1.39 (m, 4H), 1.31-1.28 (m, 4H). **LCMS:** Method A, t_R = 7.30 min, m/z = 473.1 $[M+H]^+$.

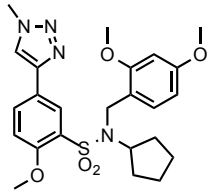
N-*Cyclopentyl*-N-*(2,4-dimethoxybenzyl)-2-methoxy-5-(2-methyl-2H-1,2,3-triazol-4-yl)benzenesulfonamide* (33) and N-*cyclopentyl*-N-*(2,4-dimethoxybenzyl)-2-methoxy-5-(1-methyl-1H-1,2,3-triazol-4-yl)benzenesulfonamide* (34).

To a magnetically stirred solution of **32** (100 mg, 0.234 mmol) in DMSO (0.5 mL, anhydrous) under N_2 was added Na_2CO_3 (74 mg, 0.70 mmol, anhydrous) and after 5 min stirring iodomethane (44 μL, 0.70 mmol) was added and the reaction was stirred at RT for 24 h. The mixture was then diluted in EtOAc

(5 mL), washed with water (4 X 1 mL) and the aqueous was extracted with EtOAc (1 x 2 mL). The combined organic fractions were dried ($MgSO_4$), concentrated onto silica and chromatographed (comiflash, 0:1 to 2:3, v/v, EtOAc:cyclohexane) which afforded two fractions.

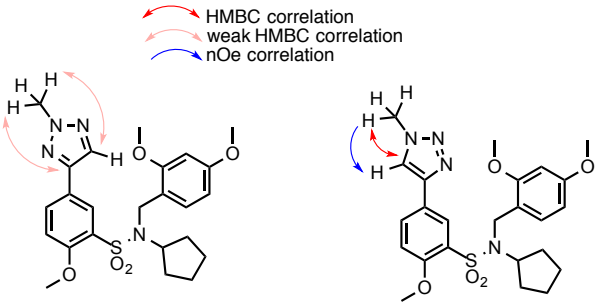


Fraction A: Compound **33** (Rf = 0.6, 50% EtOAc/cyclohexane) was isolated as a colourless solid (33 mg, 29%) **^{1}H NMR:** (600 MHz, $CDCl_3$): δ 8.21 (d, *J* = 2.2 Hz, 1H), 7.89 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.77 (s, 1H), 7.48 (d, *J* = 8.4 Hz, 1H), 7.01 (d, *J* = 8.6 Hz, 1H), 6.45 (dd, *J* = 8.4, 2.3 Hz, 1H), 6.30 (d, *J* = 2.3 Hz, 1H), 4.48 (s, 2H), 4.25-4.20 (m, 4H), 3.98 (s, 3H), 3.74 (s, 3H), 3.71 (s, 3H), 1.54-1.46 (m, 4H), 1.43-1.33 (m, 4H). **^{13}C NMR:** (150 MHz, $CDCl_3$): δ 159.8, 157.1, 156.6, 146.4, 131.1, 130.7, 129.9, 129.7, 128.9, 123.1, 120.0, 112.4, 104.0, 97.9, 59.1, 56.14, 56.12, 55.3, 55.2, 55.1, 42.1, 41.8, 28.8, 23.4. **LCMS:** Method B, t_R = 6.95 min, m/z = 487.3 $[M+H]^+$.



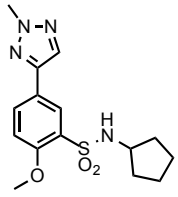
Fraction B: Compound **34** (Rf = 0.4, 50%, EtOAc/cyclohexane) was isolated as a colourless solid (19 mg, 17%) **^{1}H NMR:** (600 MHz, $CDCl_3$): δ 8.13 (dd, *J* = 8.5, 2.2 Hz, 1H), 8.10 (d, *J* = 2.2 Hz, 1H), 7.75 (s, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.04 (d, *J* = 8.5 Hz, 1H), 6.45 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.31 (d, *J* = 2.4 Hz, 1H), 4.48 (s, 2H), 4.19 (quintet, $J_1 = J_2$ = 8.4 Hz, 1H), 4.12 (s, 3H), 3.98 (s, 3H), 3.74 (s, 3H), 3.72 (s, 3H), 1.53-1.47 (m, 4H), 1.40-1.33 (m, 4H). **^{13}C NMR:** (75 MHz, $CDCl_3$): δ 159.6, 156.9, 156.2, 146.3, 130.7,129.4, 123.0, 120.6, 119.8, 112.3, 103.9, 97.6, 58.9, 55.9, 55.1, 55.04, 55.01, 55.0, 41.9, 36.7, 28.5, 23.1. **LCMS:** Method B, t_R = 6.47 min, m/z = 487.3 $[M+H]^+$.

The identities of regioisomeric compounds **33** and **34** were assigned based on the analysis of the correlation NMR experiments illustrated below. Other spectroscopic aspects of these materials, such as the relative chemical shift of the methyl group as well as the ratio of products generated from these reactions is consistent with similar examples described in the literature.[4]



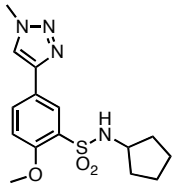
33 **34**

N-*Cyclopentyl-2-methoxy-5-(2-methyl-2*H-*1,2,3-triazol-4-yl)benzenesulfonamide* (35)



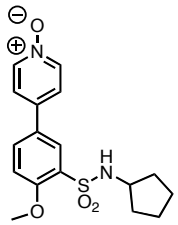
Compound **35** was prepared using the ***general procedure C*** described above employing 17 mg (35 μmol) of **33**. **Chromatography conditions:** CombiFlash, 0:1 to 1:1, v/v, EtOAc:cyclohexane. R_f = 0.2, 1:1, v/v EtOAc/cyclohexane. **Yield:** (12.2 mg, 53%). **Physical state:** White solid. **^{1}H NMR:** (600 MHz, $CDCl_3$): δ 8.29 (d, *J* = 2.2 Hz, 1H), 7.95 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.80 (s, 1H), 7.08 (d, *J* = 8.61 Hz, 1H), 4.89 (d, *J* = 7.2 Hz, 1H), 4.19 (s, 3H), 3.98 (s, 3H), 3.56 (dquintet, $J_1 = J_2$ = 6.9 Hz, 1H), 1.75-1.70 (m, 2H), 1.63-1.56 (m, 3H), 1.49-1.42 (m, 2H), 1.38-1.31 (m, 3H). **LCMS:** Method A, t_R = 5.21 min, m/z = 337.1 $[M+H]^+$. **HRMS:** found 337.1341. Calc $[M+H]^+$ = 337.1329.

N-*Cyclopentyl-2-methoxy-5-(1-methyl-1*H-*1,2,3-triazol-4-yl)benzenesulfonamide* (36)



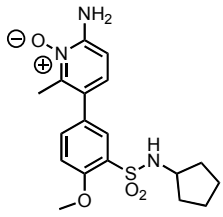
Compound **36** was prepared using the ***general procedure C*** described above employing 17 mg (35 μmol) of **34**. **Chromatography conditions:** CombiFlash, 0:1 to 1:1, v/v, EtOAc:cyclohexane. R_f = 0.2, 1:1, v/v EtOAc/cyclohexane. **Yield:** (10.2 mg, 86%). **Physical state:** White solid. **^{1}H NMR:** (600 MHz, $CDCl_3$): δ 8.18 (dd, *J* = 8.6, 2.2 Hz, 1H), 8.15 (d, *J* = 2.2 Hz, 1H), 7.79 (s, 1H), 7.10 (d, *J* = 8.6 Hz, 1H), 4.90 (d, *J* = 7.2 Hz, 1H), 4.14 (s, 3H), 4.00 (s, 3H), 3.53 (dq, $J_1 = J_2$ = 6.8 Hz, 1H), 1.74-1.68 (m, 2H), 1.63-1.57 (m, 2H), 1.49-1.42 (m, 2H), 1.38-1.33 (m, 2H). **LCMS:** Method A, t_R = 4.85 min, m/z = 337 $[M+H]^+$. **HRMS:** found 337.1335. Calc $[M+H]^+$ = 337.1329.

***4-(3-(*N-*Cyclopentylsulfamoyl)-4-methoxyphenyl)pyridine 1-oxide* (37)**



To a magnetically stirred suspension of **19a** (63 mg, 190 μmol) in CH_2Cl_2 (0.5 mL) at RT, under an atmosphere of N_2 was added *meta*-chloroperbenzoic acid (*m*-CPBA) (49 mg, 75% purity, 284 μmol) in CH_2Cl_2 (0.5 mL). The mixture was stirred for 2 h then concentrated onto silica (chromatography grade) under reduced pressure and the ensuing free-flowing solid was chromatographed (CombiFlash, 0:1 to 1:9, v/v, MeOH:CH_2Cl_2). Concentration of the appropriate fractions (Rf = 0.3, 1:19, v/v, MeOH:CH_2Cl_2) afforded the *title compound* **37** (60 mg, 91%) as an off-white solid. **^{1}H NMR:** (600 MHz, $CDCl_3$): δ 8.39 (d, *J* = 6.4 Hz, 2H), 8.25 (d, *J* = 1.2 Hz, 1H), 8.06-8.04 (m, 1H), 7.88 (d, *J* = 6.4 Hz, 2H), 7.38 (d, *J* = 8.6 Hz, 1H), 4.06 (s, 3H), 3.58-3.53 (m, 1H), 1.71-1.66 (m, 4H), 1.47-1.43 (m, 4H). **LCMS:** Method A, t_R = 4.53 min, m/z = 349.5 $[M+H]^+$.

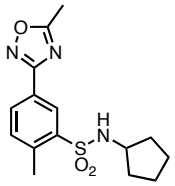
***6-Amino-3-(3-(*N-*cyclopentylsulfamoyl)-4-methoxyphenyl)-2-methylpyridine 1-oxide* (38)**



To a magnetically stirred suspension of **29** (20 mg, 55 μmol) in CH_2Cl_2 (0.5 mL) at RT, under an atmosphere of N_2 was added *m*-CPBA (14 mg, 75% purity, 83 μmol) in CH_2Cl_2 (0.5 mL). The mixture was stirred for 2 h then concentrated onto silica (chromatography grade) under reduced pressure and the ensuing free flowing solid was chromatographed (CombiFlash, 0:1 to 1:9, v/v, MeOH:CH_2Cl_2). Concentration of the appropriate fractions (R_f = 0.3, 1:19, v/v, MeOH:CH_2Cl_2) afforded the *title compound* **38** (17 mg, 80%) as an off-white solid. **^{1}H NMR:** (600

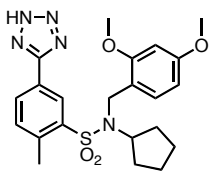
MHz, CD_3OD): δ 7.75 (d, *J* = 2.3 Hz, 1H), 7.54 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.27 (d, *J* = 8.6 Hz, 1H), 7.23 (d, *J* = 8.7 Hz, 1H), 6.87-6.86 (m, 1H), 4.03-3.97 (m, 3H), 3.52 (m, 1H), 2.45 (s, 3H), 1.70-1.59 (m, 4H), 1.48-1.38 (m, 4H). **LCMS:** Method A, t_R = 4.60 min. **HRMS:** found 378.1491. Calc $[M+H]^+$ = 378.1482.

N-*Cyclopentyl-2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)benzenesulfonamide (39)*



Compound **8** (100 mg, 0.24 mmol) was dissolved in EtOH (2 mL) at RT. Hydroxylamine hydrochloride (50 mg, 0.72 mmol), sodium carbonate (130 mg, 1.2 mmol) and H_2O (2 mL) were added and the reaction mixture was heated at 70°C for 3h. Hydroxylamine hydrochloride (50mg, 0.72 mmol) was added and the reaction mixture was heated at 70°C for 16h, cooled to RT and partitioned between an aqueous solution of ammonium chloride and EtOAc. Combined organics were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude oil (115 mg) was dissolved in toluene (2 mL) at RT and N, N-dimethylacetamide (67uL, 0.72 mmol) was added and the mixture was heated at 90 °C for 16h. The solvent was removed *in vacuo* and the crude oil was purified by flash chromatography column (CombiFlash, 1:9 to 3:7, v/v, EtOAc:cyclohexane). Concentration of the appropriate fractions afforded a light yellow gum (92 mg). The crude material was dissolved in dioxane (1 mL) and a solution of HCl in dioxane (4 M, 2 mL) was added at RT. The reaction mixture was stirred for 16 hours, and concentrated *in vacuo*. Purification by flash chromatography column (CombiFlash, 1:9 to 3:7, v/v, EtOAc:cyclohexane) afforded the *title compound* **39** (32 mg, 42% over 3 steps) as a white solid. **^{1}H NMR:** (600 MHz, $CDCl_3$) δ 8.88 (d, *J* = 2.0 Hz, 1H), 8.12 (dd, *J* = 7.9, 2.0 Hz, 1H), 7.42 (d, *J* = 7.9 Hz, 1H), 4.61 (m, 1H), 4.45 (broad s, 1H), 3.85 (m, 1H), 2.70 (s, 3H), 2.66 (s, 3H), 1.78 - 1.85 (m, 2H), 1.61 - 1.66 (m, 2H), 1.48 - 1.52 (m, 2H), 1.36 - 1.41 (m, 2H). **LCMS:** Method B, t_R = 7.34 min, m/z = 643.3 $[2M+H]^+$. **HRMS:** found 322.1225. Calc $[M+H]^+$ = 322.1220.

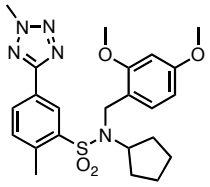
N-*Cyclopentyl-N-(2,4-dimethoxybenzyl)-2-methyl-5-(1H-tetrazol-5-yl)benzenesulfonamide (40)*



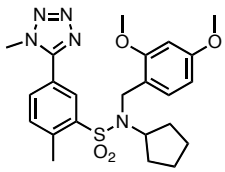
Compound **8** (100 mg, 0.24 mmol) was dissolved in DMSO (2 mL) at RT. Sodium azide (23.5 mg, 0.361 mmol) was added, followed by copper sulfate pentahydrate (1.2 mg, 0.005 mmol). The reaction mixture was heated at 120 °C for 2h and cooled to RT. An aqueous solution of HCl (1M) was added and the organics were extracted with EtOAc (3 x 3 mL). Combined organics were washed with brine, dried ($MgSO_4$) and concentrated under reduced proessure. Recrystallisation from EtOAc/cyclohexane afforded the *titled compound* **40** (96 mg, 87%) as a light yellow solid. **^{1}H NMR:** (600 MHz, $CDCl_3$) δ 8.12 (m, 1H), 7.36 (d, *J* = 7.9 Hz, 1H), 7.20 (m, 1H), 6.40 (m, 1H), 5.93 (m, 1H), 4.51 (m, 1H), 4.31 (s, 2H), 3.55 (s, 3H), 3.47 (s, 3H), 2.71 (s, 3H), 2.62 (s, 3H), 1.80 - 1.89 (m, 2H), 1.71 - 1.79 (m, 2H), 1.63 - 1.70 (m, 2H), 1.51 - 1.58 (m, 2H). **LCMS:** Method B, t_R = 5.94 min.[3]

N-*Cyclopentyl-N-(2,4-dimethoxybenzyl)-2-methyl-5-(2-methyl-2H-tetrazol-5-yl)benzenesulfonamide (S20) and* N-*Cyclopentyl-N-(2,4-dimethoxybenzyl)-2-methyl-5-(1-methyl-1H-tetrazol-5-yl)benzenesulfonamide* (S21)

Compound **40** (80 mg, 0.17 mmol) was dissolved in DMSO (2 mL) at RT. Na_2CO_3 (55.6 mg, 0.525 mmol) was added, followed by MeI (33 μL, 0.525 mmol) and the reaction mixture was stirred at RT for 16 h. An aqueous solution of ammonium chloride was added and the organics were extracted with EtOAc (3 x 3 mL). Combined organics were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash chromatography (8:2 to 7:3, v/v, EtOAc:cyclohexane) afforded 2 fractions.

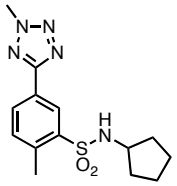


Fraction A: **S20** (56 mg, 69%), yellow solid. **^{1}H NMR** (600 MHz, CD_3OD) δ 8.13 (d, *J* = 1.6 Hz, 1H), 8.02 (dd, *J*= 7.8, 1.8 Hz, 1H), 7.37 (d, *J* = 7.8 Hz, 1H), 7.19 (d, *J* = 8.4 Hz, 1H), 6.22 (d, *J* = 8.4 Hz, 1H), 6.01 (m, 1H), 4.48 (m, 1H), 4.42 (s, 3H), 3.60 (s, 3H), 3.46 (s, 3H), 2.61 (s, 3H), 1.84 - 1.89 (m, 2H), 1.76 - 1.82 (m, 2H), 1.63 - 1.68 (m, 2H), 1.52 - 1.56 (m, 2H). **LCMS:** Method B, t_R = 8.67 min, m/z = 471.5 $[M+H]^+$.



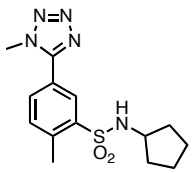
Fraction B: **S21** (12 mg, 15%), yellow solid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.91 (m, 1H), 7.39 (d, *J* = 7.8 Hz, 1H), 7.39 (d, *J* = 8.1 Hz, 1H), 7.24 (m, 1H), 6.24 (d, *J* = 6.2, 2.3 Hz, 1H), 6.06 (m, 1H), 4.41 (m, 1H), 4.35 (s, 2H), 4.13 (s, 3H), 3.61 (m, 6H), 3.55 (s, 3H), 2.69 (s, 3H), 1.78 - 1.82 (m, 2H), 1.51 - 1.70 (m, 6H). **LCMS:** Method A, t_R = 8.15 min, m/z = 471.5 $[M+H]^+$.

N-*Cyclopentyl-2-methyl-5-(2-methyl-2H-tetrazol-5-yl)benzenesulfonamide (41)*



To a magnetically stirred solution of tetrazole **S20** (55 mg, 0.117 mmol) in dioxane (1 mL) was added HCl in dioxane (4 M, 1 mL) at RT. The reaction mixture was stirred for 16 hours then concentrated under reduced pressure. Purification by flash chromatography (8:2 to 6:4, v/v, EtOAc:cyclohexane) afforded the *title compound* **41** (24 mg, 65%) as a yellow solid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.74 (d, *J* = 2.0 Hz, 1H), 8.21 (dd, *J* = 7.80, 2.0 Hz, 1H), 7.44 (d, *J* = 7.9 Hz, 1H), 4.52 (broad s, 1H), 4.40 (s, 3H), 3.65 (m, 1H), 2.70 (s, 3H), 1.78 - 1.84 (m, 2H), 1.61 - 1.66 (m, 2H), 1.47 - 1.55 (m, 2H), 1.37 - 1.41 (m, 2H). **LCMS:** Method B, t_R = 7.05 min, m/z = 322.2 $[M+H]^+$. **HRMS:** found 322.1337. Calc $[M+H]^+$ = 322.1332.

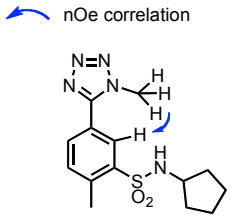
N-Cyclopentyl-2-methyl-5-(1-methyl-1H-tetrazol-5-yl)benzenesulfonamide (42)



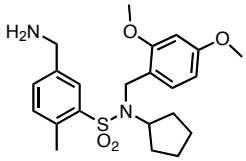
To a magnetically stirred solution of tetrazole **S21** (12 mg, 0.025 mmol) in dioxane (1 mL) was added HCl in dioxane (4 M, 1 mL) at RT. The reaction mixture was stirred for 16 h then concentrated under reduced pressure. Purification by flash chromatography (9:1 to 7:3, v/v, EtOAc:cyclohexane) afforded the *title compound* **42** (7.2 mg, 88%) as a yellow solid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.34 (d, *J* = 1.8 Hz, 1H), 7.92 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 4.61 (broad s, 1H), 4.20

(s, 3H), 3.62 (m, 1H), 2.74 (s, 3H), 1.79 - 1.82 (m, 2H), 1.61 - 1.65 (m, 2H), 1.48 - 1.54 (m, 2H), 1.36 - 1.41 (m, 2H). **LCMS:** Method B, t_R = 6.35 min, m/z = 322.2 $[M+H]^+$. **HRMS:** found 322.1225. Calc $[M+H]^+$ = 322.1220.

The identity of compound **42** was assigned based on the analysis of the nOe correlation NMR experiments illustrated below.

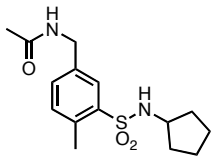


***5-(Aminomethyl)*-N-*cyclopentyl*-N-*(2,4-dimethoxybenzyl)*-2-methylbenzenesulfonamide (S22)**



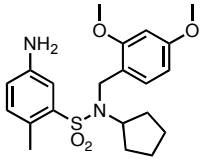
A solution of **8** (200 mg, 0.48 mmol) in EtOAc (40 mL) and hydrogenated ('H-cube' flow reactor, 50 bar, 70 °C, flow rate 1 mL/min). The reaction mixture was concentrated under reduced pressure and the crude oil was purified with SCX-2 cartridge (eluted with MeOH then NH_3:MeOH 2 M) to afford the *title compound* **S22** (96 mg, 48%) as a light yellow oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.32 (d, *J* = 9.0 Hz 1H), 7.28 (m, 1H), 7.16 (d, *J* = 8.4 Hz, 1H), 6.37 (d, *J* = 9.0 Hz, 1H), 6.17 (m, 1H), 5.27 (s, 2H), 4.26 (m, 1H), 3.73 (s, 3H) 3.66 (s, 3H), 2.56 (s, 3H), 1.93 - 1.98 (m, 2H), 1.86 - 1.90 (m, 2H), 1.53 - 1.56 (m, 2H) 1.41 - 1.44 (m, 2H). **LCMS:** Method B, t_R = 4.52 min, m/z = 419.6 $[M+H]^+$.

N-*(3-(*N-*Cyclopentylsulfamoyl)-4-methylbenzyl)acetamide* (43)



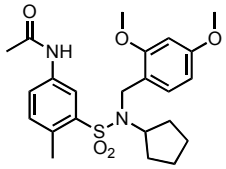
To a magnetically stirred solution of **S22** (40 mg, 0.095 mmol) in CH_2Cl_2 (2 mL) at RT was added triethylamine (41 μL, 0.286 mmol) followed by the drop-wise addition of acetyl chloride (13.6 μL, 0.191 mmol). The reaction mixture was stirred for 16 h and an aqueous solution of ammonium chloride was added. The organics were extracted with CH_2Cl_2 (3 x 2 mL). Combined organics were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crude oil (44 mg) was dissolved in dioxane (1 mL) and a solution of HCl in dioxane (4 M, 1 mL) was added at RT. The reaction mixture was stirred for 16 hours, and concentrated *in vacuo*. Purification by reverse phase preparative HPLC (CH_3CN/H_2O + 0.1% formic acid) afforded the *titled compound* **43** (12 mg, 39%) as a light yellow oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.87 (d, *J* = 1.1 Hz, 1H), 7.38 (d, *J* = 7.8, 1.1 Hz, 1H), 7.26 (m, 1H), 5.95 (broad s, 1H), 4.54 (broad d, *J* = 5.9 Hz, 1H), 4.44 (d, *J* = 5.9 Hz, 2H), 3.56 (m, 1H), 2.60 (s, 3H), 2.03 (s, 3H), 1.74 - 1.80 (m, 2H), 1.58 - 1.63 (m, 2H), 1.46 - 1.51 (m, 2H), 1.32 - 1.38 (m, 2H). **LCMS:** Method B, t_R = 4.65 min, m/z = 621.3 $[2M+H]^+$.

***5-Amino*-N-*cyclopentyl*-N-*(2,4-dimethoxybenzyl)-2-methylbenzenesulfonamide* (44)**



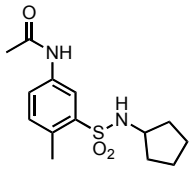
Nitroarene **9** (145 mg, 0.33 mmol) was dissolved in MeOH (10 mL) and the solution was subjected to hydrogenation ('H-cube' flow reactor, Pd/C (5%) cartridge, 1 mL/min, 40 °C) and the flow line was eluted with an additional aliquot of MeOH (5 mL). The ensuing solution was concentrated to afford the *title compound* **44** (130 mg, 97%) as an off-white solid. **^{1}H NMR:** (600 MHz, DMSO-d_6): δ 7.26 (d, *J* = 8.3 Hz, 1H), 7.08 (d, *J* = 2.4 Hz, 1H), 6.98 (d, *J* = 8.1 Hz, 1H), 6.64 (dd, *J* = 8.1, 2.4 Hz, 1H), 6.50-6.47 (m, 2H), 4.30 (s, 2H), 3.96-3.93 (m, 1H), 3.75 (s, 3H), 3.72 (s, 3H), 2.32 (s, 3H), 1.46-1.42 (m, 4H), 1.34-1.28 (m, 4H). **LCMS:** Method A, t_R = 7.98 min, m/z = 405.3 $[M+H]^+$.

N-*(3-(*N-*Cyclopentyl-N-(2,4-dimethoxybenzyl)sulfamoyl)-4-methylphenyl)acetamide (*S23)



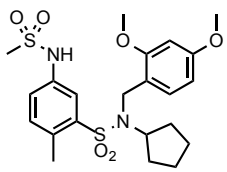
To a magnetically stirred solution of **44** (930 mg, 2.30 mmol) in CH_2Cl_2 (30 mL) and DMF (10 mL) at RT was added acetic anhydride (12 mL) followed by HCl (2 drops of a concentrated aqueous solution). The mixture was stirred for 3 h then diluted with EtOAc (200 mL) and washed with water (3 x 100 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude material was chromatographed (1:1, v/v, EtOAc:cyclohexane then 1:9, v/v, MeOH:EtOAc). Concentration of the appropriate fractions (R_f = 0.2, 1:1, v/v, EtOAc:cyclohexane) afforded the *title compound* **S23** (728 mg, 66%) as an off-white solid. **^{1}H NMR:** (600 MHz, DMSO-d_6): δ 10.09 (s, 1H), 7.97 (d, *J* = 2.1 Hz, 1H), 7.70 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.27-7.22 (m, 2H), 6.46 (dd, *J* = 8.4, 2.3 Hz, 1H), 6.40 (d, *J* = 2.3 Hz, 1H), 4.31 (s, 2H), 4.05-4.00 (m, 1H), 3.71 (s, 3H), 3.70 (s, 3H), 2.43 (s, 3H), 2.02 (d, *J* = 5.2 Hz, 3H), 1.54-1.49 (m, 2H), 1.48-1.36 (m, 4H), 1.36-1.30 (m, 2H). **LCMS:** Method A, t_R = 5.83 min, m/z = 447.3 $[M+H]^+$.

N-*(3-(*N-*Cyclopentylsulfamoyl)-4-methylphenyl)acetamide* (45)



Compound **45** was prepared using the ***general procedure C*** employing **S23** (111 mg, 0.25 mmol). **Chromatography conditions: CombiFlash**, 0:1 to 1:2, v/v, EtOAc:cyclohexane. R_f = 0.6, 1:1, v/v, EtOAc:cyclohexane. **Yield:** (68 mg, 92%). **Physical state:** White solid. **^{1}H NMR:** (600 MHz, CD_3OD): δ 8.16 (d, *J* = 2.2 Hz, 1H), 7.67 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.28 (d, *J* = 8.2 Hz, 1H), 3.48 (quintet, *J* = 6.8 Hz, 1H), 2.56 (s, 3H), 2.11 (s, 3H), 1.70 (dt, *J* = 12.3, 6.3 Hz, 2H), 1.63-1.60 (m, 2H), 1.46-1.37 (m, 4H). **LCMS:** Method A, t_R = 5.92 min, m/z = 297.3 $[M+H]^+$. **HRMS:** found 297.1270. Calc $[M+H]^+$ = 297.1267.

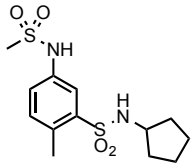
N-*Cyclopentyl*-N-*(2,4-dimethoxybenzyl)-2-methyl-5-(methylsulfonamido)benzenesulfonamide* (S24)



To a magnetically stirred solution of **44** (114 mg, 0.28 mmol), in CH_2Cl_2 (1 mL) at 0 °C under an atmosphere of N_2 was added methanesulfonyl chloride (30 μL, 0.34 mmol). After 0.5 h the mixture was warmed to RT and stirred for 3 days. The reaction was quenched with $NaHCO_3$ (sat. aq.) and the organic phase was separated, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude material was chromatographed (1:2 to 1:1, v/v, EtOAc:cyclohexane). Concentration of the

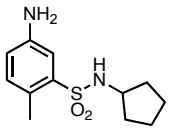
appropriate fractions (R_f = 0.5, 1:1, v/v, EtOAc:cyclohexane) afforded the *title compound* **S24** (123 mg, 91%) as a white solid. **^{1}H NMR:** (600 MHz, $CDCl_3$): δ 7.48 (d, *J* = 2.4 Hz, 1H), 7.35 (dd, *J* = 8.2, 2.4 Hz, 1H), 7.26-7.25 (m, 1H), 7.18-7.16 (m, 1H), 6.38 (dd, *J* = 8.4, 2.3 Hz, 1H), 6.16 (d, *J* = 2.3 Hz, 1H), 4.36 (s, 2H), 4.31 (t, *J* = 8.3 Hz, 1H), 3.74 (s, 3H), 3.65 (s, 3H), 2.93 (s, 3H), 2.55 (s, 3H), 1.75-1.70 (m, 2H), 1.61-1.55 (m, 4H), 1.47-1.44 (m, 2H). **LCMS:** Method A, t_R = 7.95 min, m/z = 483.2 $[M+H]^+$.

N-*Cyclopentyl-2-methyl-5-(methylsulfonamido)benzenesulfonamide* (46)



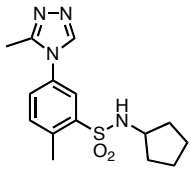
Compound **46** was prepared using the ***general procedure C*** employing **S24** (60 mg, 0.12 mmol). **Chromatography conditions:** 1:2 to 1:1, v/v, EtOAc:cyclohexane. R_f = 0.4, 1:1, v/v, EtOAc:cyclohexane) **Yield:** (41 mg, 99%). **Physical state:** White solid. **^{1}H NMR:** (600 MHz, $CDCl_3$): δ 7.80 (d, *J* = 2.2 Hz, 1H), 7.44 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.29 (d, *J* = 8.2 Hz, 1H), 7.05 (s, 1H), 4.76 (d, *J* = 7.3 Hz, 1H), 3.60 (sextet, *J* = 6.9 Hz, 1H), 3.02 (s, 3H), 2.60 (s, 3H), 1.82-1.76 (m, 2H), 1.66-1.59 (m, 2H), 1.52-1.46 (m, 2H), 1.40-1.35 (m, 2H). **LCMS:** Method B, t_R = 4.91 min. Molecular ion not observed. **HRMS:** found 333.0932. Calc $[M+H]^+$ = 333.0937.

***5-Amino*-N-*cyclopentyl-2-methylbenzenesulfonamide* (47)**



Nitroarene **10** (1.93 g, 6.79 mmol) was dissolved in MeOH (150 mL) and the solution was subjected to hydrogenation ('H-cube' flow reactor, Pt/C (5%) cartridge, 1 mL/min, 40 °C) and the flow line was eluted with an additional aliquot of MeOH (10 mL). The ensuing solution was concentrated to afford the *title compound* **47** (1.61 g, 93%) as an off-white solid. **^{1}H NMR:** (600 MHz, $CDCl_3$): δ 7.41 (d, *J* = 2.5 Hz, 1H), 7.06 (d, *J* = 8.1 Hz, 1H), 6.81 (dd, *J* = 8.1, 2.5 Hz, 1H), 4.58 (d, *J* = 7.3 Hz, 1H), 4.29 (broad s, 2H), 3.55 (sextet, *J* = 6.9 Hz, 1H), 2.49 (s, 3H), 1.79-1.73 (m, 2H), 1.63-1.56 (m, 2H), 1.50-1.44 (m, 2H), 1.38-1.32 (m, 2H). **LCMS:** Method B, t_R = 4.43 min, m/z = 255.1 $[M+H]^+$.

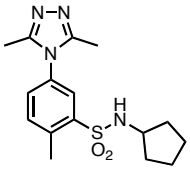
N-*Cyclopentyl-2-methyl-5-(3-methyl-4*H-*1,2,4-triazol-4-yl)benzenesulfonamide* (48)



To magnetically stirred solution of acetyl hydrazide (140 mg, 1.89 mmol) in acetonitrile (1 mL) was added *N*,*N*-dimethylformamide dimethylacetal (251 μL, 1.89 mmol) the reaction mixture was stirred at 50 °C for 3 h in an open flask. A solution of aniline **47** (400 mg, 1.58 mmol) in acetonitrile (1 mL) was then added followed by acetic acid (3 mL). The reaction flask was then fitted with a reflux condenser and the mixture was heated at 120 °C (oil bath temperature) for 24 h. The mixture was then cooled and the solvents were removed under reduced pressure and the crude material was subjected to chromatography (CombiFlash, 0:1 to 1:9, v/v, MeOH:CH_2Cl_2). Concentration of the appropriate fractions (R_f = 0.5, 1:9, v/v, MeOH:CH_2Cl_2) afforded the *title compound* **48** (331 mg, 66%) as a colourless solid. **^{1}H NMR:** (600 MHz, $CDCl_3$): δ 8.42 (s, 1H), 8.02 (d, *J* = 1.0 Hz, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.46 (dd, *J* = 8.1, 1.7 Hz, 1H), 5.11 (d, *J* = 7.3 Hz, 1H), 3.68-3.62 (m, 1H), 2.73 (s, 3H), 2.51 (s,

3H), 1.85-1.79 (m, 2H), 1.66-1.62 (m, 2H), 1.53-1.51 (m, 2H), 1.45-1.39 (m, 2H). **LCMS:** Method B, t_R = 4.94 min, m/z = 321.3 $[M+H]^+$. **HRMS:** found 321.1396. Calc $[M+H]^+$ = 321.1380.

N-*Cyclopentyl-5-(3,5-dimethyl-4*H-*1,2,4-triazol-4-yl)-2-methylbenzenesulfonamide* (49)



To magnetically stirred solution of acetyl hydrazide (140 mg, 1.89 mmol) in acetonitrile (1 mL) was added *N*,*N*-dimethylacetamide dimethylacetal (267 μL, 1.89 mmol) the reaction mixture was stirred at 50 °C for 3 h in an open flask. A solution of aniline **47** (400 mg, 1.58 mmol) in acetonitrile (1 mL) was then added followed by acetic acid (3 mL). the reaction flask was then fitted with a reflux condenser and the mixture was heated at 120 °C (oil bath temperature) for 24 h. The mixture was then cooled and the solvents were removed under reduced pressure and the crude material was subjected to chromatography (CombiFlash, 0:1 to 1:9, v/v, MeOH:CH_2Cl_2). Concentration of the appropriate fractions (R_f = 0.5, 1:9, v/v, MeOH:CH_2Cl_2) afforded the *title compound* **49** (223 mg, 42%) as a colourless solid. **^{1}H NMR**: (600 MHz, $CDCl_3$): δ 7.94 (d, *J* = 2.1 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.40 (dd, *J* = 8.0, 2.0 Hz, 1H), 5.06 (d, *J* = 7.3 Hz, 1H), 3.67 (sextet, *J* = 6.8 Hz, 1H), 2.75 (s, 3H), 2.33 (s, 6H), 1.83-1.77 (m, 2H), 1.63 (dtd, *J* = 13.0, 6.6, 2.7 Hz, 2H), 1.55-1.49 (m, 2H), 1.44-1.38 (m, 2H). **LCMS:** Method B, t_R = 4.85 min, m/z = 335.3 $[M+H]^+$. **HRMS:** found 335.1539. Calc $[M+H]^+$ = 335.1536.

3. ALPHAscreen™ Reader Assay Protocol

ALPHAscreen™ assays were conducted as a contract service provided by Reaction Biology Corp™ (Malvern, PA, USA).[5]

Assay format:

The reader assay is a binding assay using ALPHAscreen™ technology FRET assay. The singlet oxygen transfer from the Streptavidin-coated donor beads to the AlphaScreen™ Ni-chelate acceptor beads monitors the biotinylated peptide binding to the reader domain of His-tagged protein. **Reagent:** Reaction buffer: 50 mM Hepes, pH7.5, 100 mM NaCl, 0.05% CHAPS, 0.1 % BSA, and 1% DMSO.
Ligand: Histone H4 peptide (1-21) K5/8/12/16Ac-Biotin

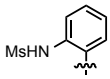
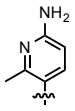
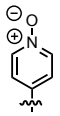
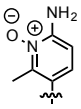
Procedure:

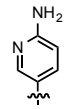
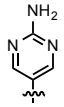
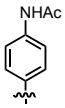
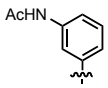
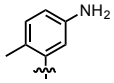
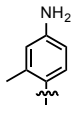
1. Deliver 4X BRD in wells of reaction plate except No BRD control wells. Add buffer instead.
2. Deliver compounds in 100% DMSO into the BRD mixture by Acoustic technology (Echo550; nanoliter range). Spin down and pre-incubation for 30 min.
3. Deliver 4X Ligand. Spin and shake.
4. Incubate for 30 min at RT with gentle shaking.
5. Deliver 4X donor beads. Spin and shake.
6. Deliver 4X acceptor beads. Spin and shake. Then gentle shaking in the dark for 60 min.
7. Alpha measurement (Ex/Em=680/520-620 nm) in Enspire.

3.1. Table S1. ALPHAscreen™ data

Table S1. Raw ALPHAscreen data (% binding relative to DMSO control). Averages of unnormalized duplicate single points at 5 µM compound concentration.

	Fg	R	BRD2	BRD3	BRD4
11a		MeO	16.47	0.02	1.00
5		Me	26.99	-0.07	2.34
12a		MeO	44.77	1.99	11.01
13a		MeO	100.76	95.34	81.35
14a		MeO	101.87	105.33	73.49
15a		MeO	79.71	19.55	55.73
16a		MeO	101.95	106.96	73.64
17a		MeO	98.57	78.05	83.18
18a		MeO	91.37	50.12	52.29
19a		MeO	97.71	69.07	78.16

	Fg	R	BRD2	BRD3	BRD4
26a		MeO	100.44	82.79	80.50
27a		MeO	112.75	124.96	98.36
29		MeO	99.66	62.71	40.95
35		MeO	100.73	73.32	23.28
36		MeO	100.76	85.77	73.64
37		MeO	95.58	80.17	89.58
38		MeO	78.42	39.08	38.60
39		Me	119.64	125.50	101.76
41		Me	113.86	114.43	91.03
42		Me	96.26	104.02	106.39

20a		MeO	99.07	69.47	64.40
21a		MeO	103.61	109.55	94.55
22a		MeO	90.64	73.99	68.15
23a		MeO	96.73	88.60	82.10
24a		MeO	98.29	97.15	82.39
25a		MeO	108.92	114.46	88.64
43		Me	103.57	111.83	68.92
45		Me	90.64	73.99	68.15
46		Me	103.60	118.64	74.03
48		Me	102.16	86.05	85.13
49		Me	98.25	73.52	76.53

4. Metabolism Studies

Metabolism studies were conducted as a contract service provided by Centre for Drug Candidate Optimisation (CDCO), Monash University, Parkville, Victoria, Australia.[6] **Incubation methods:** The metabolic stability assay was performed by incubating each test compound (at 1 µM) with human, rat and mouse liver microsomes (Xenotech, Lot# 1210057, 1110427 and 1310028, respectively) at 37 °C and 0.4 mg/mL protein concentration. The metabolic reaction was initiated by the addition of an NADPH-regenerating system (i.e. NADPH is the cofactor required for CYP450-mediated metabolism) and quenched at various time points over the 60 min incubation period by the addition of acetonitrile. Control samples (containing no NADPH) were included and quenched at selected time points to monitor for potential degradation in the absence of cofactor.

Analytical Conditions:

Instrument:	Waters Micromass Xevo G2QTOF coupled to a Waters Acquity UPLC
Detection:	Positive electrospray ionisation under MS^E mode
Cone Voltage	30 or 20
Column:	Ascentis Express Amide column (50 x 2.1 mm, 2.7 µm)
LC conditions:	Gradient cycle time: 6 minutes; Injection volume: 5 µL; Flow rate: 0.4 mL/min
Mobile phase:	Acetonitrile-water gradient with 0.05% formic acid

Notes and references

1. A. B. Pangborn, M. A. Giardello, R. H. Grubbs, R. K. Rosen and F. J. Timmers, *Organometallics,* 1996, **15**, 1518.

2. R. A. Heald and A. D. Morley, Astrazeneca LTD, International patent WO2007148064, 2007.

3. In the case of some *N*-2,4-dimethoxybenzyl-protected sulfonamides the molecular ion was not observed in the ESI-MS. Instead, only the ion corresponding to the 2,4-dimethoxybenzyl cation (m/z = 151.1) was observed.

4. T. Balle, J. Perregaard, M. T. Ramirez, A. K. Larsen, K. K. Søby, T. Liljefors and K. Andersen, *J. Med. Chem*., 2003, **46***,* 265.

5. Reaction Biology Corp. Malvern, PA, USA. http://www.reactionbiology.com/webapps/site/ Accessed March 2014.

6. CDCO, Monash Institute of Pharmaceutical Sciences, Melbourne, Victoria, Australia. http://www.monash.edu.au/pharm/research/areas/optimisation/. Accessed March 2014.