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

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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 chromatography (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 °C. Method B) Waters ZQ 3100 using reverse phase HPLC (column: XBridge™ 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 °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 (M Braun SPS, Garching, Germany) based upon a technology originally described by Grubbs et al. 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 Arylsulphonamides (7a, 7b, 8-10).

To a magnetically stirred solution of amine (either S1 or cyclopentylamine) (1.1 equiv) in CH$_2$Cl$_2$ (5 mL per mmol of amine), under an atmosphere of N$_2$ at RT, was added arylsulphonyl 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$_2$Cl$_2$ 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.), aryloboronic 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 °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/CH₂Cl₂ 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 CH₂Cl₂ (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/CH₂Cl₂ 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 N₂ at RT was added cyclopentylamine (5.00 g, 58.7 mmol). After 30 min, the reaction mixture was cooled to 0 °C and NaBH₄ (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 (Na₂SO₄), filtered and concentrated under reduced pressure. The crude material was chromatographed (10-100%, EtOAc/cyclohexane). Concentration of the appropriate fractions (Rᵣ = 0.2, 100% EtOAc) afforded the title compound (S1) (14.02 g, quantitative) as a low melting pale yellow solid.¹H NMR: (600 MHz; CDCl₃): 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, tᵣ = 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. Rᵣ = 0.8, 1:1, v/v, EtOAc/cyclohexane. Yield: (2.85 g, 84%). Physical state: White solid.¹H
NMR: (600 MHz, CDCl₃): 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, tᵣ = 8.93 min, m/z = 484.1 [M+H]⁺.

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

![Structure of 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. Rᵣ = 0.9, 1:1, v/v, EtOAc/cyclohexane. Yield: (836 mg, 83%). Physical state: White solid. ¹H NMR: (600 MHz, CDCl₃): 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, tᵣ = 7.88 min, m/z = 468.1 [M+H]⁺.

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

![Structure of 8]

N-(2,4-dimethoxybenzyl)cyclopentanamine (S1) (400.7 mg, 1.70 mmol) was dissolved in CH₂Cl₂ (10 mL) at RT under N₂. Triethylamine (0.341 mL, 2.43 mmol) 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 CH₂Cl₂ (3 x 10 mL). Combined organics were washed with brine, dried (MgSO₄) and concentrated under reduced pressure to afford a light yellow oil. Recrystallization from Cyclohexane/CH₂Cl₂ afforded the title compound (8) (481 mg, 71%) as a white solid. ¹H NMR (600 MHz, CDCl₃) 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, 3H), 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, tᵣ = 5.99 min.

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

![Structure of 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. Rᵣ = 0.9, 1:1, v/v, EtOAc/cyclohexane. Yield: (3.50 g, 86%). Physical state: White solid. ¹H NMR: (600 MHz, CDCl₃): 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 \([\text{M+H}]^+\).

**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): \( \delta \) 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, \( \text{RT} = 7.25 \) min, m/z = 285.0 \([\text{M+H}]^+\).

**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, CDCl3): \( \delta \) 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 \([\text{M+H}]^+\).

**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, CDCl3): \( \delta \) 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 \([\text{M+H}]^+\).
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. Rt = 0.2, 100% EtOAc. Yield: (90 mg, 60%). Physical state: White powder. 1H NMR: (600 MHz, CDCl3): 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 = 8.4, 2.1 Hz, 1H), 6.40 (d, J = 8.5 Hz, 1H), 6.48 (dd, J = 8.5, 2.3 Hz, 1H), 6.40 (d, J = 8.5 Hz, 1H), 6.53 (s, 2H), 4.24 (m, 1H), 4.03 (s, 3H), 3.79 (s, 3H), 3.78 (s, 3H), 2.23 (s, 2H), 1.60-1.42 (m, 4H), 1.40-1.29 (m, 4H). LCMS: Method A, tR = 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-1H-pyrazole-4-boronic acid, pinacol ester (86 mg, 0.36 mmol). Chromatography conditions: CombiFlash, 1:1, v/v, EtOAc:cyclohexane. Rt = 0.2, 1:1, v/v, EtOAc:cyclohexane. Yield: (60 mg, 51%). Physical state: White solid. 1H 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), 2.23 (s, 2H), 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. Rt = 0.2, 1:1, v/v, EtOAc:cyclohexane. Yield: (67 mg, 62%). Physical state: White solid. 1H NMR:  δ 7.97 (d, J = 1.8 Hz, 1H), 7.80 (s, 2H), 7.57 (dd, J = 8.5, 1.8 Hz, 1H), 7.37 (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, tR = 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-1H-pyrazole-5-boronic acid, pinacol ester (62 mg, 0.30 mmol). Chromatography conditions: CombiFlash, 1:1, v/v, EtOAc:cyclohexane. Rt = 0.2, 1:1, v/v, EtOAc:cyclohexane. Yield: (102 mg, 60%). Physical state: White solid.
mg, 91%). **Physical state:** White solid. **^1H 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. **^1H 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. **^1H NMR:** δ 7.94 (d, J = 2.3 Hz, 1H), 7.48 (dd, 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-pyridylboronic 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. **^1H 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 = 484.3 [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-pyridylboronic acid (76 mg, 0.62 mmol, 2 equiv.). Chromatography conditions: CombiFlash, 0:1 to 1:0, v/v, EtOAc:cyclohexane. Rf = 0.2, 1:1, v/v, EtOAc:cyclohexane. Yield: (148 mg, >98%). Physical state: White solid. 1H 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, tR = 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, NH3:MeOH:CH2Cl2. Rf = 0.1, 1:1, v/v, EtOAc:cyclohexane. Yield: (96 mg, 84%). Physical state: White solid. 1H 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, tR = 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, NH3:MeOH:CH2Cl2. Rf = 0.1, 1:1, v/v, EtOAc:cyclohexane. Yield: (65 mg, 28%). Physical state: White solid. 1H NMR: (600 MHz, CD2OD): 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, tR = 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, NH₄OH:CH₂Cl₂. Rᵢ = 0.1, 1:1, v/v, EtOAc:cyclohexane. Yield: (98 mg, 79%). Physical state: White solid. ¹H NMR: (600 MHz, CDCl₃): 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: tᵢ = 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/v, NH₄OH:CH₂Cl₂. Rᵢ = 0.1, 1:1, v/v, EtOAc:cyclohexane. Yield: (75 mg, 61%). Physical state: White solid. ¹H NMR: (600 MHz, CDCl₃): 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, tᵢ = 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. Rᵢ = 0.5, 1:1, v/v, EtOAc:cyclohexane. Yield: (109 mg, 93%). Physical state: Tan solid. ¹H NMR: (600 MHz, CDCl₃): 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 (dd, 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, tᵢ = 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. Yield: (106 mg, 90%). Physical state: white solid. $^1$H NMR: (600 MHz, CDCl$_3$); δ 7.87 (d, J = 2.2 Hz, 1H), 7.47 (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), 3.52 (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. 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'-((methylsulphonamido)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. 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]$^+$. 

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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. Rt = 0.9, 1:1, v/v EtOAc/cyclohexane. Yield: (33 mg, 72%). Physical state: White powder. $^1$H NMR: (600 MHz, CDCl$_3$): 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. Rt = 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 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-1H-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. Rt = 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, 2H), 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-1H-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. Rt = 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]$^+ = 364.1689$. 

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N-Cyclopentyl-2-methoxy-5-{1H-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, NH₃:MeOH:CH₂Cl₂. Rf = 0.5,. 0.5:4.5:95, v/v, NH₃:MeOH:CH₂Cl₂. Yield: (31 mg, 69%).

Physical state: White solid. ¹H NMR: (600 MHz, CDCl₃): δ 8.05 (d, J = 2.3 Hz, 1H), 7.89 (s, 2H), 7.66 (dd, J = 8.5, 2.3 Hz, 1H), 7.57 (dd, J = 8.5 Hz, 1H), 6.38 (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, tR = 4.76, m/z = 322.4 [M+H]+. HRMS: found 322.1229. Calc [M+H]+ = 322.1220.

N-Cyclopentyl-2-methoxy-5-{1-methyl-1H-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. Rf = 0.2, 1:1, v/v, EtOAc:cyclohexane. Yield: (33 mg, 96%).

Physical state: White solid. ¹H NMR: (600 MHz, CDCl₃): 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, tR = 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. Rf = 0.5, 1:1, v/v, EtOAc:cyclohexane. Yield: (30 mg, 65%).

Physical state: White solid. ¹H NMR: (600 MHz, CDCl₃): 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, tR = 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. Rf = 0.6, 1:1, v/v, EtOAc:cyclohexane. Yield: (21 mg, 50%).

Physical state: White solid. ¹H NMR: (600 MHz, CDCl₃): 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)**

![Chemical structure](image)

Compound 18a was prepared using the **general procedure C** employing S9a (25 mg, 0.29 mmol). **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\(_2\)OD): \( \delta \) 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, \( J = 8.6 \), 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)**

![Chemical structure](image)

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\(_2\)OD): \( \delta \) 8.57 (dd, \( J = 4.6 \), 1.6 Hz, 2H), 8.21 (d, \( J = 2.4 \), 1H), 8.02 (dd, \( J = 8.6 \), 2.5 Hz, 1H), 7.70 (dd, \( J = 4.6 \), 1.7 Hz, 2H), 7.34 (d, \( J = 8.7 \), 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)**

![Chemical structure](image)

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\(_2\)Cl\(_2\). \( R_f = 0.1 \), 1:1, v/v, EtOAc:cyclohexane. **Yield:** (36 mg, 80%). **Physical state:** White solid. \(^1\)H NMR: (600 MHz, CDCl\(_3\)): \( \delta \) 8.25 (d, \( J = 2.2 \), 1H), 8.05 (d, \( J = 2.3 \), 1H), 7.67 (ddd, \( J = 17.5 \), 8.5, 2.4 Hz, 2H), 7.08 (d, \( J = 8.6 \), 1H), 6.61 (d, \( J = 8.6 \), 1H), 4.90 (d, \( J = 7.1 \), 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)**

![Chemical structure](image)

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\(_2\)Cl\(_2\). \( R_f = 0.1 \), 1:1, v/v, EtOAc:cyclohexane. **Yield:** (43 mg, 95%). **Physical state:** White solid. \(^1\)H NMR: (600 MHz, DMSO-d\(_6\)): \( \delta \) 8.50 (s, 2H), 7.84 (d, \( J = 2.3 \), 1H), 7.82-7.80 (m, 1H), 7.25 (d, \( J = 8.6 \), 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 513a (72 mg, 0.13 mmol). Chromatography conditions: CombiFlash, 0.5:4.5:95, v/v, NH₃:MeOH:CH₂Cl₂. Rᵣ = 0.1, 1:1, v/v, EtOAc:cyclohexane. Yield: (52 mg, 99%). Physical state: White solid. ¹H NMR: (600 MHz, CD₂OD): 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, tᵣ = 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 514a (55 mg, 0.10 mmol). Chromatography conditions: CombiFlash, EtOAc. Rᵣ = 0.1, 1:1, v/v, EtOAc:cyclohexane. Yield: (31 mg, 80%). Physical state: White solid. ¹H NMR: (600 MHz, CD₂OD): 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, tᵣ = 5.18, m/z = 389.4 [M+H]+. HRMS: found 389.1533. Calc [M+H]+ = 389.1530.

5′-Amino-N-cyclopentyl-4-methoxy-2′-methylibiphenyl-3-sulfonamide (24a)

Compound 24a was prepared using the general procedure C employing 515a (26 mg, 59 μmol). Chromatography conditions: CombiFlash, 1:2, v/v, EtOAc:cyclohexane. Rᵣ = 0.5, 1:1, v/v, EtOAc:cyclohexane. Yield: (8.4 mg, 39%). Physical state: White solid. ¹H NMR: (600 MHz, CDCl₃): 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, tᵣ = 4.57 min, m/z = 402.1 [M+CH₃CNH]+. HRMS: found 361.1589. Calc [M+H]+ = 361.1580.

4′-Amino-N-cyclopentyl-4-methoxy-2′-methylibiphenyl-3-sulfonamide (25a)

Compound 25a was prepared using the general procedure C employing 516a (63 mg, 0.12 mmol). Chromatography conditions: CombiFlash, 1:2 to 1:1, v/v, EtOAc:cyclohexane. Rᵣ = 0.5, 1:1, v/v, EtOAc:cyclohexane. Yield: (38 mg, 88%). Physical state: white solid. ¹H NMR: (600 MHz, CD₂OD): 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
(60 MHz, CDCl₃): 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 (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide (28)

A schlenk flask was purged with with N₂ then charged with PdCl₂(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 N₂ (3 cycles). Then a solution of 7a (1.350 g, 3.12 mmol) in DMSO (20 mL, which had been degassed with bubbling N₂ for 10 min) was added. The mixture was then heated at 80 °C for 12 h under N₂. 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 (MgSO₄), 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 (Rᵢ = 0.8, 1:1, v/v, EtOAc:cyclohexane) afforded the title compound 28 (629 mg, 38%) as a colourless solid. ¹H NMR (600 MHz, CDCl₃): 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, 1H).

**LCMS:** Method B, t<sub>R</sub> = 6.39 min, m/z = 555.1 [M+Na]<sup>+</sup>.

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**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 ester 28 (100 mg, 0.19 mmol). Chromatography conditions: CombiFlash, 0:1 to 1:0, v/v, EtOAc:cyclohexane. R<sub>f</sub> = 0.5, EtOAc. **Yield:** (68 mg, 71%). **Physical state:** White powder. **<sup>1</sup>H NMR:** (600 MHz, CDCl<sub>3</sub>): 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<sub>R</sub> = 4.59 min, m/z = 512.6 [M+H]<sup>+</sup>.

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**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<sub>f</sub> = 0.5, 1:1, v/v EtOAc/cyclohexane. **Yield:** (38 mg, 53%). **Physical state:** White solid. **<sup>1</sup>H NMR:** (600 MHz, CDCl<sub>3</sub>): 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<sub>R</sub> = 4.68 min, m/z = 362.2 [M+H]<sup>+</sup>. **HRMS:** found 362.1569. Calc [M+H]<sup>+</sup> = 362.1533.

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

A dry microwave vessel was purged with N<sub>2</sub> then charged with 7a (1.00 g, 2.07 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (120 mg, 0.103 mmol), and Cul (39 mg, 0.207 mmol) then capped with a rubber septum and evacuated and backfilled with N<sub>2</sub> (3 cycles). Triethylisilylacetylene (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<sub>f</sub> = 0.4, 1:19, v/v, EtOAc:cyclohexane) afforded the title alkyne 30 (704 mg, 63%) as a pale yellow solid. **<sup>1</sup>H NMR:** (600 MHz, CDCl<sub>3</sub>): 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
To a magnetically stirred solution of 30 (700 mg, 1.29 mmol) in THF (10 mL) at 0 °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. NaHCO3 (2.5 mL of a sat. aq. solution) was then added and the reaction mixture was extracted with EtOAc (3 x 10 mL), dried (MgSO4), 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 (Rf = 0.4, 1:1, v/v, EtOAc:cyclohexane) afforded the title compound 31 (483 mg, 87%) as a white solid. 1H NMR: (600 MHz, CDCl3): δ 8.01 (d, J = 2.1 Hz, 1H), 7.57 (dd, J = 8.5, 2.3 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, tR = 7.27 min, m/z = 430.3 [M+H]+.

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

A dry microwave vessel was charged with 31 (100 mg, 0.250 mmol) and Cul (2.4 mg, 12.5 µg) then capped with a rubber septum evacuated and backfilled with N2 (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 °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, 1:9 to 1:9, v/v, MeOH:CH2Cl2). Concentration of the appropriate fractions (Rf = 0.5, 1:19, v/v, MeOH:CH2Cl2) afforded the title triazole 32 (107 mg, 91%) as an off-white solid. 1H NMR: (600 MHz, DMSO-d6): 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, tR = 7.30 min, m/z = 473.1 [M+H]+.

N-Cyclopentyl-N-(2,4-dimethoxybenzyl)-2-methoxy-5-(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 N2 was added Na2CO3 (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 × 1 mL) and the aqueous was extracted with EtOAc (1 × 2 mL). The combined organic fractions were dried (MgSO₄), 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%) ¹H NMR: (600 MHz, CDCl₃); 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). ¹³C NMR: (150 MHz, CDCl₃); 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, 56.12, 55.3, 55.2, 55.1, 42.1, 41.8, 28.8, 23.4. LCMS: Method B, tᵣ = 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%) ¹H NMR: (600 MHz, CDCl₃); 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, J₁ = J₂ = 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). ¹³C NMR: (75 MHz, CDCl₃); 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, tᵣ = 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
N-Cyclopentyl-2-methoxy-5-(2-methyl-2H-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. Rf = 0.2, 1:1, v/v EtOAc/cyclohexane. Yield: (12.2 mg, 53%). Physical state: White solid. 1H NMR: (600 MHz, CDCl3): 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, J1 = J2 = 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, tR = 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-1H-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. Rf = 0.2, 1:1, v/v EtOAc/cyclohexane. Yield: (10.2 mg, 86%). Physical state: White solid. 1H NMR: (600 MHz, CDCl3): 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, J1 = J2 = 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, tR = 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 CH2Cl2 (0.5 mL) at RT, under an atmosphere of N2 was added meta-chloroperbenzoic acid (m-CPBA) (49 mg, 75% purity, 284 µmol) in CH2Cl2 (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:CH2Cl2). Concentration of the appropriate fractions (Rf = 0.3, 1:19, v/v, MeOH:CH2Cl2) afforded the title compound 37 (60 mg, 91%) as an off-white solid. 1H NMR: (600 MHz, CDCl3): 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, tR = 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 CH2Cl2 (0.5 mL) at RT, under an atmosphere of N2 was added m-CPBA (14 mg, 75% purity, 83 µmol) in CH2Cl2 (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:CH2Cl2). Concentration of the appropriate fractions (Rf = 0.3, 1:19, v/v, MeOH:CH2Cl2) afforded the title compound 38 (17 mg, 80%) as an off-white solid. 1H NMR: (600 MHz, CDCl3): 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, tR = 4.53 min, m/z = 349.5 [M+H]+.
**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 H2O (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 (MgSO4) 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. 1H NMR: (600 MHz, CDCl3) 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, tR = 7.34 min, m/z = 408.3 [M+H]+. HRMS: found 408.2225. Calc [M+H]+ = 408.2220.

**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 (MgSO4) and concentrated under reduced pressure. Recrystallisation from EtOAc/cyclohexane afforded the titled compound 40 (96 mg, 87%) as a light yellow solid. 1H NMR: (600 MHz, CDCl3) 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, tR = 5.94 min.
Compound 40 (80 mg, 0.17 mmol) was dissolved in DMSO (2 mL) at RT. Na$_2$CO$_3$ (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$_3$OD) 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$_3$) $\delta$ 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$_2$Cl$_2$ (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$_2$Cl$_2$ (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$_3$CN/H$_2$O + 0.1% formic acid) afforded the titled compound 43 (12 mg, 39%) as a light yellow oil. $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 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. ¹H NMR: (600 MHz, DMSO-d₆): 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, tᵢₚ = 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 CH₂Cl₂ (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 (Na₂SO₄), 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 (Rᵢ = 0.2, 1:1, v/v, EtOAc:cyclohexane) afforded the title compound S23 (728 mg, 66%) as an off-white solid. ¹H NMR: (600 MHz, DMSO-d₆): 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, tᵢₚ = 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. Rᵢ = 0.6, 1:1, v/v, EtOAc:cyclohexane. Yield: (68 mg, 92%). Physical state: White solid. ¹H NMR: (600 MHz, CD₂OD): 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, tᵢₚ = 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 CH₂Cl₂ (1 mL) at 0 °C under an atmosphere of N₂ 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 NaHCO₃ (sat. aq.) and the organic phase was separated, dried (Na₂SO₄), 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 ($R_t = 0.5, 1:1, v/v, EtOAc:cyclohexane)$ afforded the title compound S24 (123 mg, 91%) as a white solid. $^1$H NMR: (600 MHz, CDCl$_3$): $\delta$ 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 $[M+H]^+$. \[ \]

$\textbf{N-Cyclopentyl-2-methyl-5-(methylsulfonamido)benzenesulfonamide (46)}$

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. $R_t = 0.4, 1:1, v/v, EtOAc:cyclohexane$ Yield: (41 mg, 99%). Physical state: White solid. $^1$H NMR: (600 MHz, CDCl$_3$): $\delta$ 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]$^+ = 333.0937$. \[ \]

$\textbf{5-Amino-N-cyclopentyl-2-methylbenzenesulfonamide (47)}$

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$_3$): $\delta$ 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]$^+$. \[ \]

$\textbf{N-Cyclopentyl-2-methyl-5-(3-methyl-4H-1,2,4-triazol-4-yl)benzenesulfonamide (48)}$

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$_2$Cl$_2$). Concentration of the appropriate fractions ($R_t = 0.5, 1:9, v/v, MeOH:CH$_2$Cl$_2$) afforded the title compound 48 (331 mg, 66%) as a colourless solid. $^1$H NMR: (600 MHz, CDCl$_3$): $\delta$ 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,
N-Cyclopentyl-5-(3,5-dimethyl-4H-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:CH₂Cl₂). Concentration of the appropriate fractions (Rᵣ = 0.5, 1:9, v/v, MeOH:CH₂Cl₂) afforded the title compound 49 (223 mg, 42%) as a colourless solid. ¹H NMR: (600 MHz, CDCl₃): 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), 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, tᵣ = 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).¹

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.
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.

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4. Metabolism Studies

Metabolism studies were conducted as a contract service provided by Centre for Drug Candidate Optimisation (CDCO), Monash University, Parkville, Victoria, Australia.

**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 MS²E 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


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.

