A novel series of potential allosteric modulators was constructed involving a combination of structural elements from 4BP-TQS$^1$ and A867744$^2$. Both compounds contain an arylsulfonamide unit linked to a heterocyclic core, which has both a bromoarene and a second lipophilic group attached.

Five compounds were synthesised containing arylsulfonamide and bromoarene groups attached to a triazole ring but with a variety of groups attached at R (see figure).

1-Bromo-4-(nitromethyl)benzene$^3$

AgNO$_2$ (3 eq) was added to a solution of 4-bromobenzylbromide (1.5 g, 6.09 mmol) in Et$_2$O (20 mL). The solution was stirred in the dark for 18 h before the solid was filtered off and the solvent removed from the filtrate under reduced pressure. The residue was purified by flash chromatography to give the nitroalkane as a white solid.
White crystals, 720 mg, 55%; Mp 54–56 °C, [55–56 °C]3; νmax (film/cm⁻¹) 1552 (N-O), 1489 (Ar), 1370 (N-O); 1H NMR (500 MHz, CDCl₃) δ 7.58 (2H, d, J = 8.4, 2 × ArH), 7.34 (2H, d, J = 8.4, 2 × ArH), 5.39 (2H, s, CH₂); 13C NMR (125MHz, CDCl₃) δ 132.4, 131.7, 128.6, 124.7, 79.3; LRMS: (Cl): 169 ([M-NO₂]⁺, 100)  

(Z)-4-(2-((4-Bromophenyl)(nitro)methylene)hydrazinyl)benzenesulfonamide

Prepared according to a modified literature procedure.⁴  
Sulfanilamide (992 mg, 5.8 mmol) was added to stirring conc. HCl (5 mL) at RT then cooled to -5 °C. A solution of NaNO₂ (415 mg, 6.02 mmol) in water (3 mL) was added dropwise over 5 min, then the resulting solution allowed to stir for 30 mins. Sodium acetate (4.7 g, 58 mmol) was then added in one portion and the mixture stirred vigorously. An aliquot of the solution (7.5 mL) was added to a solution of 1-Bromo-4-(nitromethyl)benzene (300 mg, 1.40 mmol) and NaOH (58 mg, 1.4 mmol) in a solution of EtOH/H₂O (30 mL, 4:1). The solution was allowed to stir for 1 h before the precipitate was filtered and the solid was dried to give the nitrohydrazone as an orange solid.  

Orange solid; 437 mg, 79%; Mp 165–167 °C; νmax (film/cm⁻¹) 3385 (N-H), 3265 (N-H), 1588 (N-O), 1492 (Ar), 1157 (S=O); 1H NMR (500 MHz, DMSO-d₆) δ 12.03 (1H, s, NH) 7.97 (2H, d, J = 8.2, 2 × ArH) 7.63 (2H, d, J = 8.6, 2 × ArH) 7.57 (2H, d, J = 8.6, 2 × ArH) 7.45 (2H, d, J = 8.2, 2 × ArH) 4.76 (2H, s, NH₂); 13C NMR (125 MHz, DMSO-d₆) δ 163.7, 143.4, 142.4, 131.9, 130.1, 127.6, 127.3, 124.0, 116.9; LRMS: (ES): 497 ([M-H]⁺, 10), 369 (100); HRMS: Found (ES): [M-H]⁺ 396.9619, C₁₃H₁₀N₄O₄SBr requires 396.9606
General Procedure for synthesis of triazoles

The nitrohydrazone (1 eq) was added to a solution of triethylamine (TEA) (1.2 eq) and primary amine (1.2 eq) in MeCN (1 M) and stirred at RT for 15 h. After this time, the solvent was removed by rotary evaporation, before addition of MeCN (2 mL), tetrapropylammonium perruthenate (TPAP) (0.2 eq) and N-methylmorpholine oxide (NMO) (1.5 eq). The solution was stirred for 3 h and then the solvent was removed and the residue purified by flash chromatography to give the triazole.

4-(3-(4-Bromophenyl)-5-phenyl-1H-1,2,4-triazol-1-yl)benzenesulfonamide (TBS-345)

Yellow solid, 23 mg, 50%; Mp 182–186 °C; ν_max (film/cm\(^{-1}\)) 3315 (N-H), 2922 (C-H), 1599 (Ar), 1484 (Ar), 1342 (S=O), 1162 (S=O); \(^1\)H NMR (500 MHz, DMSO-d\(_6\)) δ 8.06 (2H, d, J = 8.4, 2 × ArH), 7.92 (2H, d, J = 8.5, 2 × ArH), 7.73 (2H, d, J = 8.4, 2 × ArH), 7.67 (2H, d, J = 8.5, 2 × ArH), 7.53 (2H, s, NH\(_2\)), 7.43 - 7.55 (5H, m, 5 × ArH); \(^{13}\)C NMR (125 MHz, DMSO-d\(_6\)) δ 160.2, 155.1, 144.3, 140.0, 132.0, 130.5, 129.4, 128.9, 128.8, 128.0, 127.3, 127.0, 126.0, 123.1; LRMS: (Cl): 454 ([M]+, 100), 353 (25), 170 (35), 106 (100); HRMS: Found (Cl): [M]+, 454.010788, C\(_{20}\)H\(_{15}\)O\(_2\)N\(_4\)SBr requires 454.00991.
4-(3-(4-Bromophenyl)-5-(4-methoxyphenyl)-1H-1,2,4-triazol-1-yl)benzenesulfonamide (TBS-346)

![Chemical Structure of TBS-346](image)

Yellow solid, 19 mg, 40%; Mp 290–294 °C; \( \nu_{\text{max}} \) (film/cm\(^{-1} \)) 3400 (N-H), 1655 (Ar), 1023 (S=O); \(^1\)H NMR (600 MHz, DMSO-\(d_6\)) \( \delta \) 8.05 (2H, d, \( J = 8.3, 2 \times \text{ArH} \)), 7.94 (2H, d, \( J = 8.5, 2 \times \text{ArH} \)), 7.73 (2H, d, \( J = 8.3, 2 \times \text{ArH} \)), 7.69 (2H, d, \( J = 8.5, 2 \times \text{ArH} \)), 7.56 (2H, s, NH\(_2\)), 7.47 (2H, d, \( J = 8.7, 2 \times \text{ArH} \)), 7.02 (2H, d, \( J = 8.7, 2 \times \text{ArH} \)) 3.80 (3H, s, CH\(_3\)); \(^{13}\)C NMR (150 MHz, DMSO-\(d_6\)) \( \delta \) 160.8, 160.1, 155.0, 144.3, 140.3, 132.0, 130.5, 129.5, 128.1, 127.1, 126.0, 123.1, 119.4, 114.3, 55.4; LRMS: (CI): 485 ([M+H]\(^+\), 30), 173 (35), 85 (100); HRMS: Found (CI): [M+H]\(^+\) 485.026337, \( C_{21}H_{18}O_3N_4SBr \) requires 485.02830.

4-(5-Benzyl-3-(4-bromophenyl)-1H-1,2,4-triazol-1-yl)benzenesulfonamide (TBS-516)

![Chemical Structure of TBS-516](image)

Yellow solid, 38 mg, 45%; Mp 203–205 °C; \( \nu_{\text{max}} \) (film/cm\(^{-1} \)) 3365 (N-H), 3266 (N-H), 1595 (Ar), 1494 (Ar), 1328 (S=O), 1157 (S=O); \(^1\)H NMR (600 MHz, DMSO-\(d_6\)) \( \delta \) 7.99 (2H, d, \( J = 8.7, 2 \times \text{ArH} \)), 7.98 (2H, d, \( J = 8.3, 2 \times \text{ArH} \)), 7.83 (2H, d, \( J = 8.7, 2 \times \text{ArH} \)), 7.70 (2H, d, \( J = 8.3, 2 \times \text{ArH} \)), 7.57 (2H, s, NH\(_2\)), 7.28 (2H, t, \( J = 7.3, 2 \times \text{ArH} \)), 7.22 (1H, t, \( J = 7.3, \text{ArH} \)), 7.17 (2H, d, \( J = 7.3, 2 \times \text{ArH} \)), 4.34 (2H, s, CH\(_2\)); \(^{13}\)C NMR (150 MHz, DMSO-\(d_6\)) \( \delta \) 159.9, 156.1, 144.3, 139.3, 135.8, 132.0, 129.5, 128.7, 128.6, 128.0, 127.1, 126.9, 125.4, 123.0, 32.1; LRMS: (CI): 469 ([M]\(^+\), 100); HRMS: Found (CI): [M]\(^+\) 469.030795, \( C_{21}H_{17}O_3N_4SBr \) requires 469.03338
4-(3-{4-Bromophenyl})-5-propyl-1H-1,2,4-triazol-1-yl)benzenesulfonamide (TBS-546)

Yellow solid, 24 mg, 29%; Mp 204–208 °C; \( \nu_{\text{max}} \) (film/cm\(^{-1} \)) 3321 (N-H), 3073 (C-H), 1597 (Ar), 1497 (Ar), 1340 (S=O), 1161 (S=O); \(^1\)H NMR (600 MHz, DMSO-d\(_6\)) \( \delta \) 8.02 (2H, d, \( J = 8.7 \)), 7.99 (2H, s, NH\(_2\)), 7.87 (2H, d, \( J = 8.5 \)), 7.70 (2H, d, \( J = 8.5 \)), 7.58 (2H, s, NH\(_2\)), 2.87 (2H, t, \( J = 7.5 \)), 1.75 (2H, sxt, \( J = 7.5 \)), 0.92 (3H, t, \( J = 7.5 \)); \(^{13}\)C NMR (150 MHz, DMSO-d\(_6\)) \( \delta \) 159.7, 157.4, 144.1, 139.4, 127.1, 125.3, 122.9, 28.0, 20.3, 13.6; LRMS: (CI): 421 ([M+H]\(^+\), 100), 343 (10); HRMS: Found (Cl): [M+H]\(^+\) 421.032564, \( \text{C}_{17}\text{H}_{18}\text{O}_{2}\text{N}_{4}\text{SBr} \) requires 421.03338

4-(3-{4-Bromophenyl})-5-phenethyl-1H-1,2,4-triazol-1-yl)benzenesulfonamide (TBS-556)

Orange powder, 32 mg, 33%; Mp 184–186 °C; \( \nu_{\text{max}} \) (film/cm\(^{-1} \)) 3282 (N-H), 3015 (C-H), 1495 (Ar), 1332 (S=O), 1159 (S=O); \(^1\)H NMR (600 MHz, DMSO-d\(_6\)) \( \delta \) 8.02 (2H, d, \( J = 8.7 \)), 7.98 (2H, d, \( J = 8.7 \)), 7.74 (2H, d, \( J = 8.5 \)), 7.72 (2H, d, \( J = 8.5 \)), 7.56 (2H, s, NH\(_2\)), 7.23 - 7.27 (2H, m, \( J = 2 \)), 7.16 - 7.20 (3H, m, \( J = 3 \)), 3.19 (2H, t, \( J = 7.8 \)), 3.09 (2H, t, \( J = 7.8 \)), 3.08 (2H, t, \( J = 7.8 \)), PhCH\(_2\)); \(^{13}\)C NMR (150 MHz, DMSO-d\(_6\)) \( \delta \) 159.7, 156.8, 144.1, 140.3, 139.3, 132.0, 129.6, 128.44, 128.38, 128.0, 127.1, 126.3, 125.2, 122.9, 32.7, 28.2; LRMS: (Cl): 483 ([M+H]\(^+\), 100), 111 (55); HRMS: Found (Cl): [M+H]\(^+\) 483.047112, \( \text{C}_{22}\text{H}_{20}\text{O}_{2}\text{N}_{4}\text{SBr} \) requires 483.04903
References


