Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Supporting Information

Reagent Based DOS:

A Click-Click-Cyclize Strategy to Probe Chemical Space

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Experimental Section

General procedures: All air and moisture sensitive reactions were carried out in flame- or oven-dried glassware under argon atmosphere using standard gas tight syringes, cannula, and septa. Microwave reactions were carried out using Biotage Initiator using 0.5-2.0 mL, 2.0 – 5.0 mL, and 10-20 mL vials. THF, CH_2Cl_2, CH_3CN were purified by passage through the Solv-Tek purification system employing activated Al_2O_3 (Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518-1520). Et_3N was purified by passage over basic alumina and stored over KOH. Flash column chromatography was performed with SiO_2 from Sorbent Technology (30930M-25, Silica Gel 60A, 40-63 um). Thin layer chromatography was performed on silica gel 60F254 plates (EM-5717, Merck). Deuterated solvents were purchased from Cambridge Isotope laboratories. ^1H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 NMR spectrometer operating at 400 MHz and 100 MHz respectively; or a Bruker Avance operating at 500 MHz and 125 MHz respectively. High-resolution mass spectrometry (HRMS) analyses were obtained on a VG Instrument ZAB double-focusing mass spectrometer.

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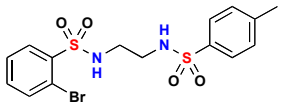
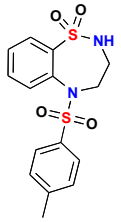


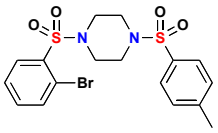
2-Bromo-*N*-(2-(4-methylphenylsulfonamido)ethyl)benzenesulfonamide (2)

In a round bottom flask under an Ar atmosphere was added *N*-(3-aminoethyl)-2-bromobenzenesulfonamide **1** (1.0 g, 3.58 mmol, 1.1 eq.), dry CH_2Cl_2 (6.5 mL) and Et_3N (0.9 mL, 6.5 mmol, 2 eq.). The reaction was cooled to 0 ºC, stirred for 20 minutes after which *p*-toluenesulfonyl chloride (0.62 g, 3.25 mmol, 1 eq.) was added cautiously. After stirring for 2 hours at RT monitored by TLC, the crude reaction was diluted with CH_2Cl_2 (5 mL) and quenched with 10% aq. HCl (10 mL). The organic layer was separated and washed with water (10 mL) and brine (10 mL). The combined organic was dried ($MgSO_4$), filtered and concentrated under reduced pressure to give **2** (1.48 g, 3.43 mmol, 96%) as a white solid. **(**FTIR (neat): 2951, 1448, 1158, 1200 cm^{-1}; δ ^1H (500 MHz, $CDCl_3$) 8.06 (1 H, dd, *J* = 7.7, 1.8 Hz), 7.72 (3 H, dd, *J* = 5.8, 4.2 Hz), 7.47 – 7.39 (2 H, m), 7.30 – 7.27 (2 H, m), 5.76 (1 H, t, *J* = 5.8 Hz), 5.29 (1 H, t, *J* = 5.9 Hz), 3.09 – 2.99 (4 H, m), 2.41 (3 H, s); δ ^{13}C (126 MHz, $CDCl_3$) 144.0, 138.3, 136.5, 135.4, 134.3, 131.8, 130.2, 128.2, 127.3, 120.1, 43.2, 21.8; HRMS calculated for $C_{15}H_{17}BrN_2O_4S_2Na$ $(M+Na)^+$ 454.9711; found 454.9708 (FAB).



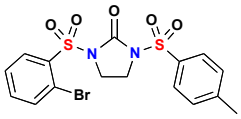
Sultam (3)

Into a microwave reaction vial was added 2-bromo-*N*-(2-(4 methylphenylsulfonamido)ethyl)-benzenesulfonamide **2** (100 mg, 0.23 mmol, 1 eq.), CuI (4.4 mg, 23 µmol, 0.1 eq.), 1,10-phenanthroline (8.3 mg, 46 µmol, 0.2 eq.), Cs_2CO_3 (149 mg, 0.46 mmol, 2 eq.) and dry DMF (0.46 mL, 0.5 M). The reaction was heated in the microwave at 150 ºC for 20 minutes. After such time, the crude reaction was directly loaded onto a silica column and was purified by flash chromatography [1:1 hexane:EtOAc, R_f = 0.4] to afford **13** (63.2 mg, 0.18 mmol, 78%) as a yellow oil. FTIR (neat): 2349, 1748, 1363, 1170 cm^{-1}. δ ^1H (500 MHz, $CDCl_3$) 7.86 (1 H, dd, *J* = 7.9, 1.5 Hz), 7.74 (2 H, d, *J* = 8.3 Hz), 7.52 (1 H, dd, *J* = 8.0, 1.2 Hz), 7.49 – 7.44 (1 H, m), 7.34 (1 H, td, *J* = 7.6, 1.3 Hz), 7.28 (2 H, t, *J* = 6.5 Hz), 5.12 (1 H, s), 2.92 (2 H, m), 2.82 (2 H, d, *J* = 0.5 Hz), 2.41 (3 H, s); δ ^{13}C (126 MHz, $CDCl_3$) 144.1, 140.5, 136.2, 133.0, 129.7, 128.4, 128.1, 127.9, 49.8, 43.7, 21.7; HRMS calculated for $C_{15}H_{16}N_2O_4S_2Na$ $(M+Na)^+$ 375.0449; found 375.0449 (FAB).



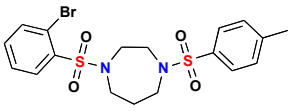
1-(2-Bromophenylsulfonyl)-4-tosylpiperazine (4)

In a 1 dram vial was added 2-bromo-*N*-(2-(4-methylphenylsulfonamido)ethyl)benzenesulfonamide **2** (50 mg, 0.11 mmol, 1 eq.), dry DMF (0.55 mL, 0.2 M), Cs_2CO_3 (71 mg, 0.22 mmol, 2 eq.) and 1,2-dibromoethane (11.3 µL, 0.13 mmol, 1.2 eq.). The reaction was heated at 60 ºC, stirred for 10 hours after which time the crude mixture was directly loaded onto a silica column and purified by flash chromatography (1:1 hexane:EtOAc, R_f = 0.55) to provide **4** (45 mg, 0.1 mmol, 90% yield) as a yellow oil. FTIR (neat): 2538, 1448, 1346, 1267, 1164 cm^{-1}; δ ^{1}H (500 MHz, $CDCl_3$) 8.02 (1 H, dd, *J* = 7.8, 1.8 Hz), 7.73 (1 H, dd, *J* = 7.8, 1.3 Hz), 7.62 – 7.59 (2 H, m), 7.42 (2 H, dddd, *J* = 17.0, 15.1, 7.5, 1.6 Hz), 7.34 (2 H, dd, *J* = 8.5, 0.6 Hz), 3.42 (4 H, dd, *J* = 12.0, 7.1 Hz), 3.11 – 3.05 (4 H, m), 2.45 (3 H, s); δ ^{13}C (126 MHz, $CDCl_3$) 144.2, 137.1, 135.9, 134.0, 132.3, 132.2, 130.0, 127.6, 120.3, 46.0, 45.4, 21.5; HRMS calculated for $C_{17}H_{19}BrN_2O_4S_2Na$ $(M+Na)^+$ 480.9867; found 480.9855 (FAB).



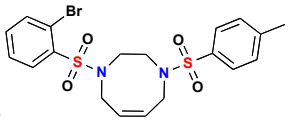
1-(2-Bromophenylsulfonyl)-3-tosylimidazolidin-2-one (5)

In a 1 dram vial was added 2-bromo-*N*-(2-(4-methylphenylsulfonamido)ethyl)benzenesulfonamide **2** (50 mg, 0.11 mmol, 1 eq.), 1,1'-carbonyldiimidazole (71.3 mg, 0.44 mmol, 4 eq.), Et_3N (30.6 µL, 0.22 mmol, 2 eq.) and dry DMF (0.55 mL, 0.2 M). The reaction was heated at 60 ºC, stirred for 10 hours after which time the crude mixture was diluted with CH_2Cl_2 (5 mL) and quenched with 10% aq. HCl (10 mL). The organic layer was separated and washed with water (10 mL) and brine (10 mL). The combined organic was dried ($MgSO_4$), filtered and concentrated under reduced pressure to give **5** (46 mg, 0.10 mmol, 92%) as a yellow oil. FTIR (neat): 2360, 1751, 1363, 1170 cm^{-1}. δ ^{1}H (500 MHz, $CDCl_3$) 8.28 – 8.25 (1 H, m), 7.83 – 7.80 (2 H, m), 7.68 (1 H, dd, *J* = 7.8, 1.3 Hz), 7.52 – 7.44 (2 H, m), 7.30 (2 H, dd, *J* = 8.5, 0.6 Hz), 4.19 – 4.14 (2 H, m), 3.97 – 3.92 (2 H, m), 2.44 (3 H, s); δ ^{13}C (126 MHz, $CDCl_3$) 148.7, 145.7, 136.8, 135.2, 135.1, 134.0, 133.8, 130.0, 128.1, 128.0, 120.0, 42.1, 41.8, 22.2; HRMS calculated for $C_{16}H_{15}BrN_2O_5S_2Na$ $(M+Na)^+$ 480.9503; found 480.9489 (FAB).



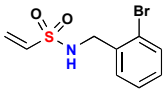
1-(2-Bromophenylsulfonyl)-4-tosyl-1,4-diazepane (6)

In a 1 dram vial was added 2-bromo-*N*-(2-(4-methylphenylsulfonamido)ethyl)benzenesulfonamide **2** (126 mg, 0.28 mmol, 1 eq.), dry DMF (0.55 mL, 0.2 M), Cs_2CO_3 (183 mg, 0.34 mmol, 1.2 eq.) and 1,2-dibromopropane (34 µL, 0.34 mmol, 1.2 eq.). The reaction was heated at 60 ºC, stirred for 10 hours after which time the crude mixture was directly loaded onto a silica column and purified by flash chromatography (1:1 hexane:EtOAc, R_f = 0.6) to provide **6** (112 mg, 0.24 mmol, 85% yield) as a yellow oil. FTIR (neat): 2537, 1442, 1345, 1264, 1160 cm^{-1}. δ ^{1}H (500 MHz, $CDCl_3$) 8.05 (1 H, dd, *J* = 7.8, 1.8 Hz), 7.72 (1 H, dd, *J* = 7.7, 1.4 Hz), 7.67 – 7.64 (2 H, m), 7.45 – 7.41 (1 H, m), 7.40 – 7.36 (1 H, m), 7.30 (2 H, d, *J* = 7.9 Hz), 3.56 (2 H, dd, *J* = 5.9, 3.9 Hz), 3.48 (2 H, t, *J* = 6.4 Hz), 3.41 (4 H, dd, *J* = 11.4, 5.7 Hz), 2.42 (3 H, s), 2.06 – 1.99 (2 H, m); δ ^{13}C (126 MHz, $CDCl_3$) 143.6, 138.3, 136.1, 135.7, 133.7, 132.2, 129.9, 127.5, 126.8, 120.0, 51.9, 51.8, 47.6, 47.2, 29.3, 21.5; HRMS calculated for $C_{18}H_{21}BrN_2O_4S_2Na$ $(M+Na)^+$ 495.0024; found 495.0020 (FAB).



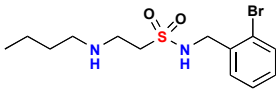
(Z)-1-(2-Bromophenylsulfonyl)-4-tosyl-1,2,3,4,5,8-hexahydro-1,4-diazocine (7)

In a 1 dram vial was added 2-bromo-*N*-(2-(4-methylphenylsulfonamido)ethyl)benzenesulfonamide **2** (50 mg, 0.11 mmol, 1 eq.), dry DMF (0.55 mL, 0.2 M), Cs_2CO_3 (107 mg, 0.33 mmol, 3 eq.) and allyl bromide (28 µL, 0.33 mmol, 3 eq.). The reaction was heated at 60 ºC, stirred for 10 hrs after which time the crude mixture was diluted with EtOAc (10 mL), filtered through a silica SPE and concentrated under reduced pressure. The crude mixture was then solvated in Ar degassed DCE (11 mL, 0.01M), to which Hoveyda-Grubbs generation II catalyst (2 mg, 3.3 µmol, 3 mol %) and the crude reaction mixture heated at 90 ºC for 6 hours. After such time, the crude mixture was filtered through a silica SPE, concentrated under reduced pressure and purified by flash chromatography (1:1 hexane:EtOAc, R_f = 0.4) to provide **7** (43 mg, 0.09 mmol, 88% yield, over 2 steps) as a yellow oil. FTIR (neat): 2526, 1448, 1345, 1270, 1165 cm^{-1}; δ ^{1}H (500 MHz, $CDCl_3$) 8.05 (1 H, dd, *J* = 7.8, 1.8 Hz), 7.76 – 7.73 (1 H, m), 7.68 – 7.65 (2 H, m), 7.47 – 7.42 (1 H, m), 7.42 – 7.37 (1 H, m), 7.32 (2 H, dd, *J* = 8.5, 0.5 Hz), 5.82 (1 H, dtt, *J* = 11.6, 6.6, 1.6 Hz), 5.71 – 5.65 (1 H, m), 4.14 (2 H, d, *J* = 6.5 Hz), 3.96 – 3.92 (2 H, m), 3.59 – 3.56 (2 H, m), 3.44 – 3.40 (2 H, m), 2.43 (3 H, s); δ ^{13}C (126 MHz, $CDCl_3$) 143.8, 138.4, 135.8, 135.0, 133.7, 132.2, 129.9, 128.2, 127.8, 127.6, 127.2, 120.1, 50.4, 49.6, 48.1, 45.6, 21.5; HRMS calculated for $C_{19}H_{21}BrN_2O_4S_2Na$ $(M+Na)^+$ 507.0023; found 507.0017 (FAB).



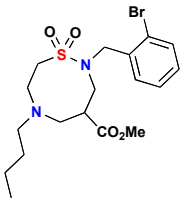
***N*-(2-Bromobenzyl)ethenesulfonamide (8)**

Into a round bottom flask was added 2-bromobenzylamine (1.0g, 5.4 mmol, 1.1 eq.), dry CH_2Cl_2 (10.8 mL, 0.5M) and Et_3N (2.24 mL, 16.1 mmol, 3 eq.). The crude mixture was cooled to 0 ºC and after stirring for 20 minutes, 2-chloroethanesulfonyl chloride (0.56 mL, 5.37 mmol, 1 eq.) was added drop wise to the reaction mixture cautiously (exothermic). The reaction mixture was stirred for an addition 20 minutes before being warmed to RT and stirred for 4 hrs. After such time, the reaction was quenched with 10% aq. HCl (10 mL). The organic layer was separated and washed with water (10 mL) and brine (10 mL). The combined organic was dried ($MgSO_4$), filtered and concentrated under reduced pressure to give **8** (1.42 g, 5.15 mmol, 96%) as a yellow oil. FTIR (neat): 2430, 1468, 1290, 1170 cm^{-1}; δ ^{1}H (500 MHz, $CDCl_3$) 7.53 (1 H, dd, *J* = 8.0, 1.2 Hz), 7.43 (1 H, dd, *J* = 7.7, 1.6 Hz), 7.29 (1 H, tt, *J* = 3.2, 1.6 Hz), 7.16 (1 H, tt, *J* = 4.1, 2.1 Hz), 6.44 – 6.37 (1 H, m), 6.21 – 6.15 (1 H, m), 5.84 (1 H, d, *J* = 9.9 Hz), 5.18 (1 H, t, *J* = 6.3 Hz), 4.28 (2 H, d, *J* = 6.5 Hz); δ ^{13}C (126 MHz, $CDCl_3$) 136.0, 135.9, 132.9, 130.5, 129.7, 127.8, 126.8, 123.5, 47.2; HRMS calculated for $C_9H_{11}BrNO_2S$ $(M+H)^+$ 275.9694; found 275.9698 (FAB).



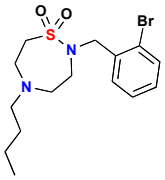
***N*-(2-Bromobenzyl)-2-(butylamino)ethanesulfonamide (9)**

Into a round bottom flask was added *N*-(2-Bromobenzyl)ethenesulfonamide **8** (0.84 g, 3.0 mmol, 1 eq.), dry MeOH (3.0 mL, 1M), *n*-butylamine (0.3 mL, 3.0 mmol, 1 eq.) and DBU (45.4 µL, 0.3 mmol, 0.1 eq.). The reaction was stirred for 4 hrs at RT, after which the crude reaction mixture was concentrated and the crude (yellow oil) was taken forward (96% conversion by crude ^{1}H NMR).



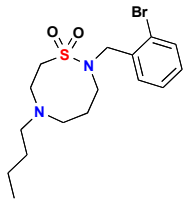
Sultam (10)

In a 1 dram vial was added *N*-(2-bromobenzyl)-2-(butylamino)ethanesulfonamide **9** (86 mg, 0.25 mmol, 1 eq.), dry DMF (1.24 mL, 0.2 M), Cs_2CO_3 (161 mg, 0.49 mmol, 2 eq.) and methyl 3-bromo-2-(bromomethyl)propionate (35 µL, 0.25 mmol, 1 eq.). The reaction was heated at 60 ºC, stirred for 10 hours after which time the crude mixture was directly loaded onto a silica column and purified by flash chromatography (1:1 hexane:EtOAc, $R_f = 0.6$) to provide **10** (71.5 mg, 0.16 mmol, 64% yield) as a yellow oil. FTIR (neat): 3100, 2360, 1735, 1320, 1180 cm^{-1}; δ ^1H (500 MHz, $CDCl_3$) 7.58 (1 H, dd, *J* = 7.8, 1.5 Hz), 7.52 (1 H, dd, *J* = 8.0, 1.1 Hz), 7.35 (1 H, td, *J* = 7.6, 1.2 Hz), 7.15 (1 H, td, *J* = 7.9, 1.7 Hz), 4.47 (2 H, q, *J* = 16.6 Hz), 3.91 – 3.82 (1 H, m), 3.61 (3 H, s), 3.48 – 3.41 (1 H, m), 3.24 – 3.18 (2 H, m), 3.12 – 3.02 (3 H, m), 2.93 (2 H, ddd, *J* = 11.4, 8.3, 4.5 Hz), 2.61 (2 H, dd, *J* = 8.5, 6.7 Hz), 1.53 – 1.46 (2 H, m), 1.39 – 1.30 (2 H, m), 0.94 (3 H, t, *J* = 7.3 Hz); δ ^{13}C (126 MHz, $CDCl_3$) 172.8, 134.9, 132.6, 129.2, 129.1, 128.1, 123.0, 57.1, 52.0, 51.6, 50.6, 49.8, 45.9, 41.9, 29.8, 20.4, 14.1; HRMS calculated for $C_{18}H_{28}BrN_2O_4S$ $(M+H)^+$ 447.0953; found 447.0962 (FAB).



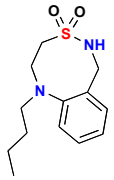
Sultam (11)

In a 1 dram vial was added *N*-(2-bromobenzyl)-2-(butylamino)ethanesulfonamide **9** (0.14 g, 0.38 mmol, 1 eq.), dry DMF (1.9 mL, 0.2 M), Cs_2CO_3 (250 mg, 0.77 mmol, 2 eq.) and 1,2-dibromoethane (33 µL, 0.38 mmol, 1 eq.). The reaction was heated at 60 ºC, stirred for 10 hrs after which time the crude mixture was directly loaded onto a silica column and purified by flash chromatography (1:1 hexane:EtOAc, $R_f = 0.7$) to provide **11** (121 mg, 0.32 mmol, 84% yield) as a yellow oil. FTIR (neat): 3105, 2360, 1363, 1218, 1170 cm^{-1}; δ ^1H (500 MHz, $CDCl_3$) 7.58 (1 H, dd, *J* = 7.7, 1.6 Hz), 7.54 – 7.52 (1 H, m), 7.36 – 7.31 (1 H, m), 7.17 – 7.12 (1 H, m), 4.62 (2 H, s), 3.31 (4 H, dt, *J* = 10.0, 4.1 Hz), 2.99 – 2.95 (4 H, m), 2.64 – 2.60 (2 H, m), 1.50 – 1.43 (2 H, m), 1.42 – 1.34 (2 H, m), 0.94 (3 H, t, *J* = 7.3 Hz). δ ^{13}C (126 MHz, $CDCl_3$) 135.7, 132.7, 129.8, 129.1, 127.9, 123.2, 57.3, 55.6, 53.1, 51.0, 47.9, 43.6, 29.9, 20.4, 14.0; HRMS calculated for $C_{15}H_{24}BrN_2O_2S$ $(M+H)^+$ 375.0742; found 375.0730 (FAB).



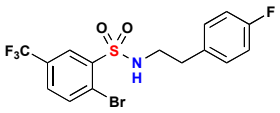
Sultam (12)

In a 1 dram vial was added *N*-(2-bromobenzyl)-2-(butylamino)ethanesulfonamide **9** (0.1 g, 0.28 mmol, 1 eq.), dry DMF (1.4 mL, 0.2 M), Cs_2CO_3 (186 mg, 0.57 mmol, 2 eq.) and 1,2-dibromopropane (34 µL, 0.34 mmol, 1.2 eq.). The reaction was heated at 60 ºC, stirred for 10 hrs after which time the crude mixture was directly loaded onto a silica column and purified by flash chromatography (1:1 hexane:EtOAc, R_f = 0.7) to provide **12** (85 mg, 0.22 mmol, 76% yield) as a yellow oil. FTIR (neat): 3115, 2361, 1360, 1215, 1169 cm^{-1}; δ ^{1}H (500 MHz, $CDCl_3$) 7.62 (1 H, dd, *J* = 7.8, 1.5 Hz), 7.54 – 7.51 (1 H, m), 7.37 – 7.32 (1 H, m), 7.14 (1 H, td, *J* = 7.9, 1.7 Hz), 4.50 (2 H, s), 3.43 – 3.37 (2 H, m), 3.20 (2 H, dd, *J* = 6.7, 4.4 Hz), 3.08 – 3.02 (2 H, m), 2.69 (2 H, dd, *J* = 12.8. 7.7 Hz), 2.63 – 2.56 (2 H, m), 1.67 (2 H, dt, *J* = 11.3, 5.7 Hz), 1.50 (2 H, tt, *J* = 7.5, 6.2 Hz), 1.37 (2 H, dq, *J* = 14.4, 7.3 Hz), 0.94 (3 H, t, *J* = 7.3 Hz); δ ^{13}C (126 MHz, $CDCl_3$) 135.5, 132.5, 129.6, 129.0, 128.0, 123.1, 57.4, 52.0, 51.7, 50.2, 49.3, 45.0, 30.2, 25.3, 20.5, 14.2; HRMS calculated for $C_{16}H_{26}BrN_2O_2S$ $(M+H)^+$ 389.0898; found 389.0901 (FAB).



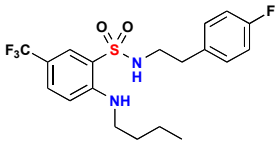
Sultam (13)

Into a microwave reaction vial was added *N*-(2-bromobenzyl)-2-(butylamino)ethanesulfonamide **9** (210 mg, 0.6 mmol, 1 eq.), CuI (11.4 mg, 65 µmol, 0.1 eq.), 1,10-phenanthroline (21 mg, 0.12 mmol, 0.2 eq.), K_2CO_3 (166 mg, 1.2 mmol, 2 eq.) and dry DMF (1.2 mL, 0.5 M). The reaction was heated in the microwave at 150 ºC for 13 minutes. After such time, the crude reaction was directly loaded onto a silica column and was purified by flash chromatography (1:1 hexane:EtOAc, R_f = 0.6) to afford **13** (90 mg, 0.33 mmol, 56%) as a yellow oil. FTIR (neat): 3335, 2345, 1363, 1170 cm^{-1}: δ ^{1}H (500 MHz, $CDCl_3$) 7.39 (1 H, ddd, *J* = 11.5, 6.7, 3.5 Hz), 7.33 – 7.29 (1 H, m), 7.28 – 7.26 (1 H, m), 7.21 (1 H, dd, *J* = 5.1, 1.1 Hz), 4.72 (1 H, t, *J* = 6.8 Hz), 4.44 (2 H, d, *J* = 7.0 Hz), 3.24 – 3.20 (2 H, m), 3.04 – 2.97 (4 H, m), 1.40 – 1.28 (4 H, m), 0.85 (3 H, t, *J* = 7.1 Hz); δ ^{13}C (126 MHz, CDCl3) 148.1, 137.5, 129.9, 129.0, 126.5, 124.2, 55.7, 52.6, 52.0, 44.8, 30.1, 20.5, 13.9; HRMS calculated for $C_{13}H_{21}N_2O_2S$ $(M+H)^+$ 269.1324; found 269.1329 (FAB).



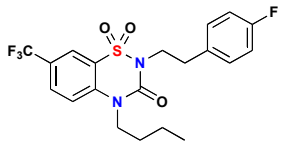
2-Bromo-*N*-(4-fluorophenethyl)-5-(trifluoromethyl)benzenesulfonamide (14)

In a round bottom flask under a Ar atmosphere was added 2-(4-fluorophenyl)ethanamine (0.47 g, 3.39 mmol, 1.1 eq.), dry CH_2Cl_2 (6.2 mL) and Et_3N (0.78 mL, 5.6 mmol, 2 eq.). The reaction was cooled to 0 ºC, stirred for 20 mins after which 2-bromo-5-(trifluoromethyl)benzene-1-sulfonyl chloride (1.0 g, 3.09 mmol, 1.0 eq.), was added cautiously. After stirring for 2 hours at RT monitored by TLC, the crude reaction was diluted with CH_2Cl_2 (5 mL) and quenched with 10% aq. HCl (10 mL). The organic layer was separated and washed with water (10 mL) and brine (10 mL). The combined organic was dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford **14** (1.13 g, 2.65 mmol, 86%) as a yellow oil. FTIR (neat): 3059, 2360, 1751, 1595 cm^{-1}; δ ^1H (500 MHz, $CDCl_3$) 8.33 (1 H, d, J = 2.0 Hz), 7.82 (1 H, d, J = 8.2 Hz), 7.66 – 7.62 (1 H, m), 7.09 – 7.04 (2 H, m), 6.96 – 6.90 (2 H, m), 5.16 (1 H, t, J = 6.0 Hz), 3.23 (2 H, q, J = 6.8 Hz), 2.79 (2 H, t, J = 6.8 Hz); δ ^{13}C (126 MHz, $CDCl_3$) 160.8 (d, $^1J_{C\text{-}F}$ = 243.5 Hz), 140.0, 135.8, 132.9 (d, $^3J_{C\text{-}F}$ = 3.2 Hz), 130.6 (d, $^2J_{C\text{-}F}$ = 8.8 Hz), 130.2, 130.1 (q, $^3J_{C\text{-}F}$ = 3.6 Hz), 128.3 (d, $^3J_{C\text{-}F}$ = 3.6 Hz), 123.0 (q, $^1J_{C\text{-}F}$ = 274.7 Hz), 115.7, 115.6, 44.5, 34.9. HRMS calculated for $C_{15}H_{12}BrF_4NO_2SNa$ $(M+Na)^+$ 447.9606; found 447.9617 (FAB).



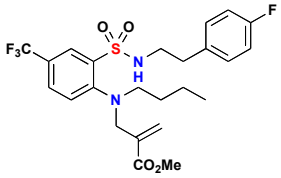
2-(Butylamino)-*N*-(4-fluorophenethyl)-5-(trifluoromethyl) benzenesulfonamide (15)

Into a microwave reaction vial was added 2-bromo-*N*-(4-fluorophenethyl)-5-(trifluoromethyl)benzene-sulfonamide **14** (270 mg, 0.64 mmol, 1 eq.), CuI (12.2 mg, 0.77 mmol, 0.1 eq.), 1,10-phenanthroline (23 mg, 0.128 mmol, 0.2 eq.), Cs_2CO_3 (0.42g, 1.28 mmol, 2 eq.), dry solvent (1.28 mL, 0.5 M), and *n*-butylamine (0.2 mmol, 1.2 eq.). The reaction was heated in the microwave at 150 ºC for 13 mins after such time, the crude reaction was directly loaded onto a silica column and was purified by flash chromatography [1:1 hexane:EtOAc, R_f = 0.6] to afford **15** (231 mg, 0.55 mmol, 86%) as a yellow oil. FTIR (neat): 3361, 3059, 2349, 1595 cm^{-1}; δ ^1H (500 MHz, $CDCl_3$) 7.96 (1 H, d, J = 1.3 Hz), 7.60 (1 H, dd, J = 8.8, 1.6 Hz), 6.99 (2 H, dt, J = 11.4, 5.8 Hz), 6.94 (2 H, t, J = 8.6 Hz), 6.75 (1 H, d, J = 8.8 Hz), 6.06 (1 H, d, J = 4.3 Hz), 4.49 (1 H, t, J = 6.1 Hz), 3.16 (2 H, q, J = 6.6 Hz), 3.11 (2 H, dd, J = 7.0, 12.3 Hz), 2.70 (2 H, t, J = 6.7 Hz), 1.62 – 1.55 (2 H, m), 1.40 (2 H, dq, J =14.6, 7.3 Hz), 0.96 (3 H, t, J = 7.3 Hz); δ ^{13}C (126 MHz, $CDCl_3$) 161.7 (d, $^1J_{C\text{-}F}$ = 248.3 Hz), 148.1, 133.0 (d, $^3J_{C\text{-}F}$ = 3.8 Hz), 131.2 (q, $^3J_{C\text{-}F}$ = 4.3 Hz), 130.1 (d, $^3J_{C\text{-}F}$ = 7.6 Hz), 127.7 (d, $^3J_{C\text{-}F}$ = 3.8 Hz), 124.4 (q, $^1J_{C\text{-}F}$ = 273.6 Hz), 119.9, 117.5 (q, $^2J_{C\text{-}F}$ = 34.4 Hz), 115.7, 112.1, 44.2, 43.0, 34.6, 30.8, 20.1, 13.7; HRMS calculated for $C_{19}H_{23}F_4N_2O_2S$ $(M+H)^+$ 419.1416; found 419.1417 (FAB).



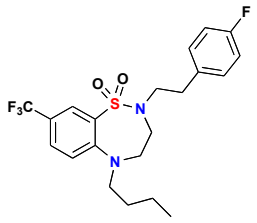
Sultam (16)

In a 1 dram vial was added 2-(butylamino)-*N*-(4-fluorophenethyl)-5-(trifluoromethyl)benzenesulfonamide **15** (40 mg, 95.5 µmol, 1 eq.), 1,1'-carbonyldiimidazole (62 mg, 0.38 mmol, 4 eq.), Et_3N (26 µL, 0.19 mmol, 2 eq.) and dry DMF (0.47 mL, 0.2 M). The reaction was heated at 60 ºC, stirred for 10 hours after which time the crude mixture was diluted with CH_2Cl_2 (5 mL) and quenched with 10% aq. HCl (10 mL). The organic layer was separated and washed with water (10 mL) and brine (10 mL). The combined organic was dried ($MgSO_4$), filtered and concentrated under reduced pressure to give **16** (40 mg, 91.6 µmol, 96%) as a yellow oil. FTIR (neat): 3361, 3059, 2349, 1732, 1595 cm^{-1} δ ^1H (500 MHz, $CDCl_3$) 8.09 (1 H, d, J = 1.6 Hz), 7.90 – 7.87 (1 H, m), 7.35 (1 H, d, J = 8.8 Hz), 7.15 – 7.11 (2 H, m), 6.93 – 6.87 (2 H, m), 4.12 – 4.08 (2 H, m), 4.07 – 4.03 (2 H, m), 3.04 – 2.99 (2 H, m), 1.74 – 1.66 (2 H, m), 1.43 (2 H, dq, J = 14.8, 7.4 Hz), 0.99 (3 H, t, J = 7.4 Hz); δ ^{13}C (126 MHz, $CDCl_3$) 161.7 (d, $^1J_{C\text{-}F}$ = 249.5 Hz), 150.2, 139.0, 133.1, 130.9 (q, $^3J_{C\text{-}F}$ = 33.4 Hz), 130.5 (d, $^2J_{C\text{-}F}$ = 8.2 Hz), 125.9, 125.2 (q, $^2J_{C\text{-}F}$ = 34.7 Hz), 123.1 (q, $^3J_{C\text{-}F}$ = 271.4 Hz), 120.7 (q, $^3J_{C\text{-}F}$ = 3.8 Hz), 116.7, 115.3 (d, $^2J_{C\text{-}F}$ = 21.7 Hz), 45.8, 44.1, 34.5, 29.1, 19.8, 13.6; HRMS calculated for $C_{20}H_{21}F_4N_2O_3S$ $(M+H)^+$ 445.4510; found 445.4514 (FAB).



Methyl 2-((butyl(2-(*N*-(4-fluorophenethyl)sulfamoyl)-4 -(trifluoromethyl)phenyl)amino)methyl)acrylate (17)

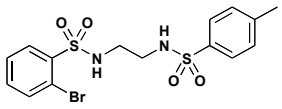
In a 1 dram vial was added 2-(butylamino)-*N*-(4-fluorophenethyl)-5-(trifluoromethyl)benzenesulfonamide **15** (50 mg, 0.19 mmol, 1 eq.), dry DMF (0.59 mL, 0.2 M), Cs_2CO_3 (78 mg, 0.23 mmol, 2 eq.) and methyl 3-bromo-2-(bromomethyl)propionate (20 µL, 0.14 mmol, 1.2 eq.). The reaction was heated at 60 ºC, stirred for 10 hours after which time the crude mixture was directly loaded onto a silica column and purified by flash chromatography (1:1 hexane:EtOAc, R_f = 0.6) to provide **17** (76.5 mg, 0.14 mmol, 78% yield) as a yellow oil. FTIR (neat): 3361, 3059, 2349, 1725, 1595 cm^{-1}; δ ^1H (500 MHz, $CDCl_3$) 7.92 (1 H, d, J = 1.5 Hz), 7.56 (1 H, dd, J = 8.8, 2.2 Hz), 7.03 – 6.98 (2 H, m), 6.95 – 6.90 (2 H, m), 6.72 (1 H, d, J = 8.8 Hz), 6.39 (1 H, t, J = 4.8 Hz), 6.31 (1 H, d, J = 0.7 Hz), 5.80 (1 H, d, J = 0.7 Hz), 4.13 (2 H, s), 3.74 (3 H, s), 3.42 – 3.36 (2 H, m), 3.15 (2 H, td, J = 7.1, 5.3 Hz), 2.74 – 2.69 (2 H, m), 1.66 – 1.59 (2 H, m), 1.47 – 1.38 (2 H, m), 0.98 – 0.93 (3 H, m); δ ^{13}C (126 MHz, $CDCl_3$) 166.2, 161.7 (d, $^1J_{C\text{-}F}$ = 242.1 Hz), 148.6, 135.2, 133.5 (d, $^3J_{C\text{-}F}$ = 3.6 Hz), 131.1 (q, $^3J_{C\text{-}F}$ = 4.8 Hz), 130.1 (d, $^3J_{C\text{-}F}$ = 8.0 Hz), 128.1 (q, $^3J_{C\text{-}F}$ = 3.6 Hz), 127.9, 124.0 (q, $^1J_{C\text{-}F}$ = 271.5 Hz), 120.1, 117.2 (q, $^2J_{C\text{-}F}$ = 33.9 Hz), 115.3, 113.3, 112.1, 52.1, 49.7, 47.9, 42.9, 33.8, 30.8, 20.2, 13.7; HRMS calculated for $C_{24}H_{29}F_4N_2O_4S$ $(M+H)^+$ 517.5567; found 517.5568 (FAB).



Sultam (19)

In a 1 dram vial was added 2-(butylamino)-*N*-(4-fluorophenethyl)-5-(trifluoromethyl)benzenesulfonamide **15** (40 mg, 9.55 x 10^{-5} mol, 1 eq.), dry DMF (0.48 mL, 0.2 M), Cs_2CO_3 (62 mg, 0.19 mmol, 2 eq.) and 1,2-dibromopropane (9.8 µL, 0.11 mmol, 1.2 eq.). The reaction was heated at 60 ºC, stirred for 10 hours after which time the crude mixture was directly loaded onto a silica column and purified by flash chromatography (1:1 hexane:EtOAc, R_f = 0.7) to provide **19** (36 mg, 8.31 x 10^{-5} mol, 87% yield) as a yellow oil. FTIR (neat): 3059, 2349, 1595, 1432 cm^{-1}; δ ^{1}H (500 MHz, $CDCl_3$) 7.87 (1 H, d, *J* = 1.5 Hz), 7.56 (1 H, dd, *J* = 8.8, 2.2 Hz), 7.09 – 7.05 (2 H, m), 7.00 – 6.94 (2 H, m), 6.92 – 6.84 (1 H, m), 6.74 (1 H, d, *J* = 8.9 Hz), 6.30 (1 H, t, *J* = 4.5 Hz), 4.39 (2 H, ddd, *J* = 17.3, 12.5, 1.6 Hz), 3.53 – 3.48 (2 H, m), 3.17 (2 H, td, *J* = 7.0, 5.2 Hz), 2.79 (2 H, dd, *J* = 9.2. 7.0 Hz), 1.69 – 1.61 (2 H, m), 1.49 – 1.40 (2 H, m), 0.97 (3 H, t, *J* = 7.4 Hz); δ ^{13}C (126 MHz, $CDCl_3$) 161.7 (d, $^1J_{C\text{-}F}$ = 244.4 Hz), 148.5, 133.5 (d, $^3J_{C\text{-}F}$ = 3.2 Hz), 131.4 (q, $^3J_{C\text{-}F}$ = 4.0 Hz), 131.2, 130.1 (d, $^2J_{C\text{-}F}$ = 8.5 Hz), 127.7 (q, $^3J_{C\text{-}F}$ = 4.0 Hz), 124.1 (q, $^1J_{C\text{-}F}$ = 268.1 Hz), 119.2, 117.3 (q, $^2J_{C\text{-}F}$ = 25.9 Hz), 115.6, 115.4, 112.4, 92.8, 46.3, 42.9, 32.1, 30.9, 20.1, 13.6; HRMS calculated for $C_{21}H_{25}F_4N_2O_2S$ $(M+H)^+$ 445.1573; found 444.1573 (FAB).

2-Bromo-*N*-(2-(4-methylphenylsulfonamido)ethyl)benzenesulfonamide (2)



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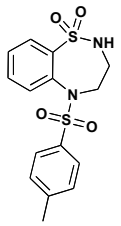

Sultam (3)

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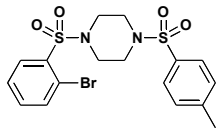

1-(2-Bromophenylsulfonyl)-4-tosylpiperazine (4)

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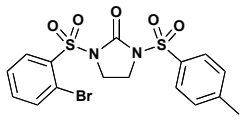
1-(2-Bromophenylsulfonyl)-3-tosylimidazolidin-2-one (5)



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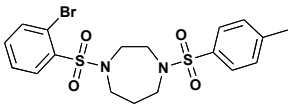
1-(2-Bromophenylsulfonyl)-4-tosyl-1,4-diazepane (6)



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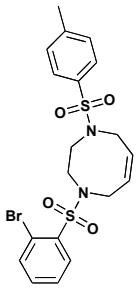

(*Z*)-1-(2-Bromophenylsulfonyl)-4-tosyl-1,2,3,4,5,8-hexahydro-1,4-diazocine (7)

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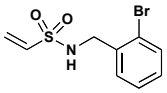
_N_-(2-Bromobenzyl)ethenesulfonamide (8)



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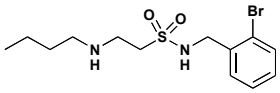

***N*-(2-Bromobenzyl)-2-(butylamino)ethanesulfonamide (9)**

^{1}H NMR crude mixture MeOD-4

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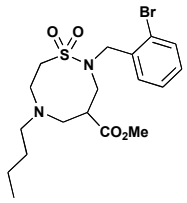

Sultam (10)

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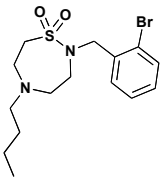

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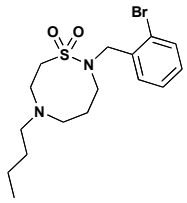

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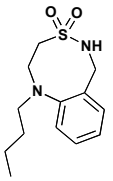
Sultam (13) 

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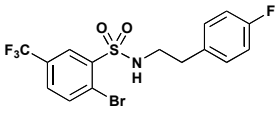
2-Bromo-*N*-(4-fluorophenethyl)-5-(trifluoromethyl)benzenesulfonamide (14)



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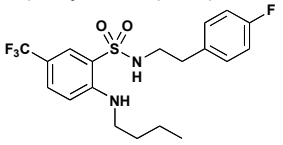
2-(Butylamino)-*N*-(4-fluorophenethyl)-5-(trifluoromethyl)benzenesulfonamide (15)



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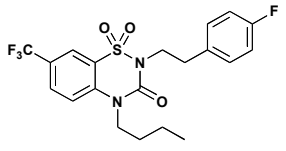

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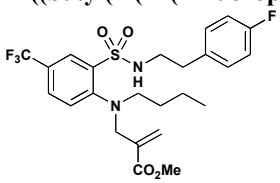
Methyl 2-((butyl(2-(*N*-(4-fluorophenethyl)sulfamoyl)-4-(trifluoromethyl)phenyl)amino)methyl)acrylate



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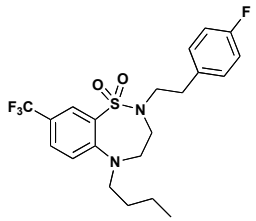

Sultam (19)

QuickTime™ and a
None decompressor
are needed to see this picture.

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are needed to see this picture.

In-Silico Analysis Data

Molecule	CLOGP	Mol.Wt	Acceptor	Donor	Rot Bond	LIP_VIOLS	DIVS	BBB	SOLY
1	1.08	279.15	3	2	5	0	1.64	-0.65	0.17
2	3.22	433.34	4	2	7	1	27.91	-0.02	0.01
3	2.44	352.43	5	1	2	0	37.36	0.50	0.06
4	3.82	459.38	4	0	4	0	27.91	0.46	0.00
5	3.62	459.33	5	0	2	0	2.50	0.29	0.00
6	3.75	473.40	4	0	4	0	27.91	0.00	0.00
7	4.03	485.42	4	0	4	0	30.96	-0.11	0.00
9	2.98	335.26	3	2	8	1	29.96	0.06	0.03
10	4.22	433.36	5	1	7	1	15.18	0.55	0.00
11	3.79	361.30	3	1	5	0	29.96	0.97	0.01
12	3.71	375.32	3	1	5	0	7.14	1.12	0.01
13	5.46	423.37	3	1	5	1	21.36	1.09	0.00
14	5.04	426.22	2	1	6	2	1.00	-0.45	0.01
15	5.95	418.45	3	2	10	2	21.55	0.22	0.00
16	5.98	444.44	3	0	5	1	15.05	-0.17	0.00
17	6.89	516.55	5	2	14	3	21.55	-0.52	0.00
19	7.50	472.54	3	1	7	2	21.55	-0.12	0.00

Molecule	CACO2	SP_S	SP_P	PB	VOLD	HERG	Sol_DMSO	METSTAB
1	0.49	0.71	0.31	56.76	-0.41	0.87	2.10	0.99
2	0.48	-0.25	0.52	84.27	-0.84	-0.18	0.79	-0.31
3	0.66	0.00	0.62	85.98	-0.69	0.62	0.94	0.34
4	0.98	-0.65	0.83	120.12	-0.75	-0.52	0.90	-0.80
5	0.51	-0.22	0.44	103.89	-0.51	-0.27	1.06	-0.70
6	0.85	-0.52	0.76	110.73	-0.99	-0.48	0.45	-1.12
7	0.95	-0.55	0.75	112.60	-1.02	-0.73	0.62	-1.10
9	0.91	0.31	0.49	73.14	-0.63	0.21	1.01	-0.05
10	1.12	-0.07	0.86	97.52	-0.55	0.24	1.07	-0.46
11	1.42	-0.09	1.01	98.68	-0.88	0.05	0.23	-0.64
12	1.48	-0.04	1.03	102.22	-0.73	0.09	0.26	-0.44
13	1.49	-0.44	1.10	115.01	-1.03	-0.45	-0.12	-0.84
14	0.04	-0.01	0.42	95.17	-0.83	0.41	0.91	-0.26
15	0.19	-0.14	0.43	106.74	-0.60	-0.02	0.28	-0.83
16	0.09	-0.15	0.24	100.15	-0.38	0.35	0.91	-0.55
17	0.03	-0.26	0.34	104.34	-0.92	0.29	0.69	-0.86
19	0.53	-0.60	0.66	122.17	-0.84	-0.30	0.47	-1.23

Polar Surface Area Calculations

	AREA	PSA	Fraction
Molecule	418.492	149.425	0.35705581
1	574.775	126.637	0.220324475
2	548.035	78.339	0.14294525
3	681.956	109.254	0.160206817
4	671.452	100.615	0.149846899
5	429.892	92.95	0.216217096
6	601.416	125.495	0.208665882
7	555.476	79.534	0.143181704
9	632.475	78.992	0.124893474
10	558.995	49.121	0.087873773
12	601.856	44.688	0.074250319
13	564.533	48.876	0.086577755
14	667.474	54.241	0.08126309
15	736.488	33.791	0.045881264
16	815.851	97.406	0.119391899
17	548.062	97.856	0.178549142
19	680.381	55.514	0.081592519

Tanimoto Similarity Matrix

	M02	M03	M04	M05	M06	M07	M09	M10	M11	M12	M13	M14	M15	M16	M17	M18	M19
M02	1	0.862	0.75	0.711	0.603	0.463	0.691	0.62	0.425	0.384	0.332	0.348	0.868	0.597	0.75	0.569	0.759
M03	0.862	1	0.872	0.827	0.701	0.556	0.803	0.647	0.462	0.419	0.372	0.399	0.773	0.586	0.687	0.603	0.704
M04	0.75	0.872	1	0.925	0.758	0.605	0.899	0.589	0.448	0.467	0.411	0.395	0.759	0.664	0.78	0.679	0.809
M05	0.711	0.827	0.925	1	0.743	0.588	0.856	0.623	0.484	0.514	0.44	0.429	0.79	0.72	0.85	0.711	0.829
M06	0.603	0.701	0.758	0.743	1	0.523	0.726	0.516	0.406	0.429	0.513	0.377	0.609	0.58	0.632	0.588	0.638
M07	0.463	0.556	0.605	0.588	0.523	1	0.568	0.428	0.602	0.603	0.527	0.525	0.476	0.447	0.489	0.576	0.5
M09	0.691	0.803	0.899	0.856	0.726	0.568	1	0.554	0.424	0.444	0.397	0.413	0.702	0.645	0.724	0.639	0.741
M10	0.62	0.647	0.589	0.623	0.516	0.428	0.554	1	0.7	0.628	0.541	0.561	0.618	0.489	0.582	0.527	0.573
M11	0.425	0.462	0.448	0.484	0.406	0.602	0.424	0.7	1	0.888	0.744	0.763	0.483	0.403	0.46	0.522	0.452
M12	0.384	0.419	0.467	0.514	0.429	0.603	0.444	0.628	0.888	1	0.81	0.769	0.448	0.455	0.52	0.582	0.506
M13	0.332	0.372	0.411	0.44	0.513	0.527	0.397	0.541	0.744	0.81	1	0.675	0.378	0.414	0.434	0.508	0.423
M14	0.348	0.399	0.395	0.429	0.377	0.525	0.413	0.561	0.763	0.769	0.675	1	0.405	0.489	0.413	0.483	0.407
M15	0.868	0.773	0.759	0.79	0.609	0.476	0.702	0.618	0.483	0.448	0.378	0.405	1	0.689	0.866	0.657	0.877
M16	0.597	0.586	0.664	0.72	0.58	0.447	0.645	0.489	0.403	0.455	0.414	0.489	0.689	1	0.794	0.633	0.767
M17	0.75	0.687	0.78	0.85	0.632	0.489	0.724	0.582	0.46	0.52	0.434	0.413	0.866	0.794	1	0.733	0.963
M18	0.569	0.603	0.679	0.711	0.588	0.576	0.639	0.527	0.522	0.582	0.508	0.483	0.657	0.633	0.733	1	0.74
M19	0.759	0.704	0.809	0.829	0.638	0.5	0.741	0.573	0.452	0.506	0.423	0.407	0.877	0.767	0.963	0.74	1