Synthesis and biological characterization of a series of 2-sulfonamidebenzamides as allosteric modulators of MrgX1

Swagat Sharma[a], Qi Peng[b], Anish K. Vadukoot[a], Christopher D. Aretz[a], Aaron A. Jensen[a], Alexander I. Wallick[a], Xinzhong Dong[b,c], Corey R. Hopkins[a,*]

[a]Department of Pharmaceutical Sciences, College of Pharmacy, University of Nebraska Medical Center, Omaha, NE USA 68198-6125
[b]The Solomon H. Snyder Department of Neuroscience, Center for Sensory Biology, Johns Hopkins University School of Medicine, Baltimore, MD 21205
[c]Howard Hughes Medical Institute, Johns Hopkins University School of Medicine, Baltimore, MD 21205

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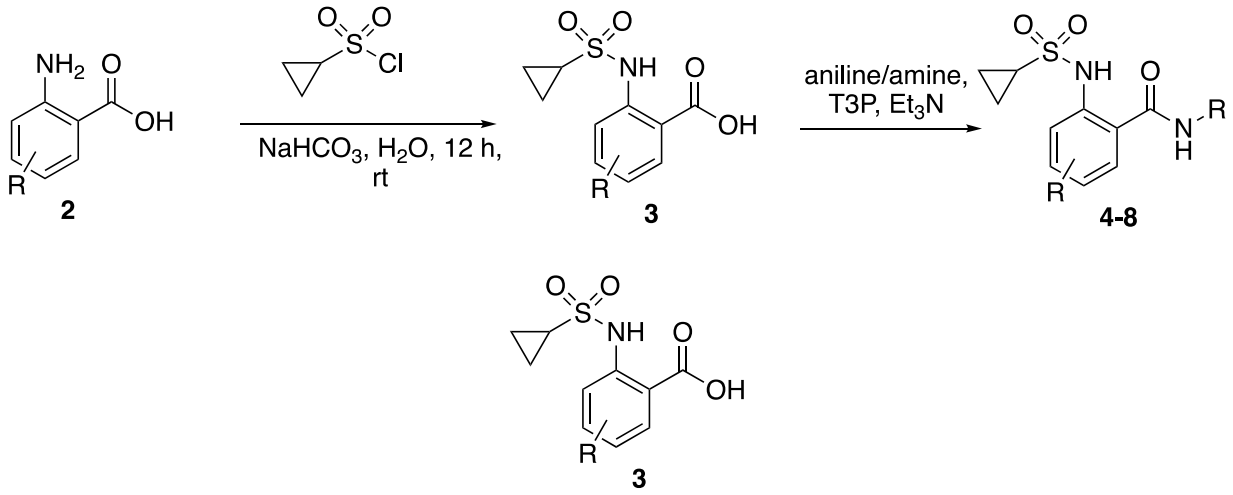
General Experimental Methods.

All ^{1}H & ^{13}C NMR spectra were recorded on Bruker AV-400 (500 MHz) instrument. Chemical shifts are reported in ppm relative to residual solvent peaks as an internal standard set to $\delta^{1}H$ 3.31 or $\delta^{13}C$ 49.00 (CD_3OD) or $\delta^{1}H$ 2.50 or $\delta^{13}C$ 39.52 ($(CD_3)_2SO$) or $\delta^{1}H$ 7.26 or $\delta^{13}C$ 77.23 ($CDCl_3$). Data are reported as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz), and integration. Low resolution mass spectra were obtained on an Agilent 1260 LCMS with electrospray ionization, with a gradient of 5-95% MeCN in 0.1% formic acid water over 4 min. Analytical thin layer chromatography was performed on LuxPlate silica gel 60 F254 plates. Visualization was accomplished with UV light, and/or the use of ninhydrin, anisaldehyde and ceric ammonium molybdate solutions followed by charring on a hotplate. Chromatography on silica gel was performed using Silica Gel 60Å (230-400 mesh) from Sorbent Technologies. Solvents for extraction, washing and chromatography were HPLC grade. All reagents were purchased from Aldrich Chemical Co. (or similar) and were used without purification. All reagents and solvents were commercial grade and purified prior to use when necessary.

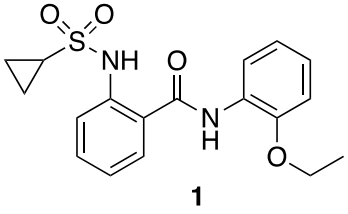
Final compounds were purified on a Gilson preparative reversed-phase HPLC system comprised of a 322 aqueous pump with solvent-selection valve, 334 organic pump, GX-271 liquid hander, two column switching valves, and a 159 UV detector. UV wavelength for fraction collection was user-defined, with absorbance at 254 nm always monitored. Column: Phenomenex Axia-packed Luna C18, 50 x 21.2 mm, 5 μm. For Acidic Method: Mobile phase: CH_3CN in H_2O (0.1% formic acid). Gradient conditions: 2.0 min equilibration, followed by user-defined gradient (starting organic percentage, ending organic percentage, duration, typically 15 mins), hold at 95% CH_3CN in H_2O (0.1% TFA) for 2 min, 20 mL/min, 23 °C. Final compounds were confirmed to be >95% purity based on HPLC and measured at 215 and 254 nm.

There were no unexpected or unusually high safety hazards encountered for the synthesis of these compounds.

General Procedures: A



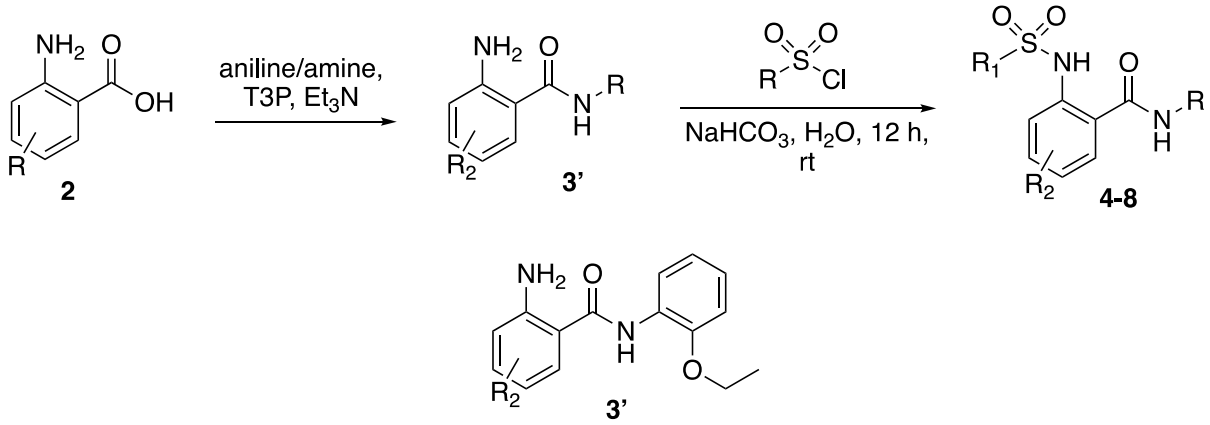
2-(Cyclopropanesulfonamido)benzoic acid (3). To an ice-cold solution of anthranilic acid (2.00 g, 14.6 mmol) and sodium bicarbonate (2.35 g, 29.2 mmol) in water (30.0 mL) was added cyclopropane sulfonyl chloride (1.70 mL, 16.8 mmol) dropwise. Reaction was stirred at RT for 12 hours. Crude was acidified up to pH 2 using concentrated HCl, acid product precipitates out, the solid was filtered and washed with cold water followed by hexane. Solids dried and used as such. Yield = 2.80 g (80%). LCMS: R_T = 2.14 min.; ESI-MS: *m/z* $[M + H]^+$, calc'd 242.05 for $C_{10}H_{12}NO_4S$, found 242.0. ^{1}H NMR (500 MHz, DMSO) δ 10.72 (s, 1H), 8.02 (d, *J* = 7.7 Hz, 1H), 7.67 – 7.61 (m, 2H), 7.24 – 7.17 (m, 1H), 2.86 – 2.79 (m, 1H), 1.05 – 0.97 (m, 4H). ^{13}C NMR (125 MHz, DMSO) δ 170.3, 141.0, 135.0, 132.0, 123.5, 119.2, 117.0, 30.4, 5.8.



2-(Cyclopropanesulfonamido)-*N*-(2-ethoxyphenyl)benzamide (1). To a solution of carboxylic acid (1.0 equiv.), substituted aniline (1.0 equiv.) and triethylamine (3.0 equiv.) in dichloromethane [0.1 M] was dropwise added T3P (50% wt/v in ethyl acetate) (1.50 equiv.). The reaction was stirred at RT for 6 hours. The reaction was concentrated under reduced pressure. The crude product was purified by flash column chromatography 0 to 50% ethyl acetate:hexanes to afford desired product. LCMS: R_T = 1.13 min, ESI-MS:

m/z $[M]^+$, calc'd 360.11 for $C_{18}H_{20}N_2O_4S$, found 360.1. ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 10.45 (s, 1H), 8.67 (s, 1H), 8.45-8.43 (m, 1H), 7.85 (d, *J* = 8.38 Hz, 1H), 7.64 (d, *J* = 8.02 Hz, 1H), 7.56-7.52 (m, 1H), 7.28-7.22 (m, 1H), 7.15-7.11 (m, 1H), 7.06-7.02 (m, 1H), 6.96-6.94 (m, 1H), 4.22-4.16 (m, 2H), 2.56-2.50 (m, 1H), 1.51 (t, *J* = 6.97 Hz, 3H), 1.27-1.25 (m, 2H), 0.95-0.92 (m, 2H).

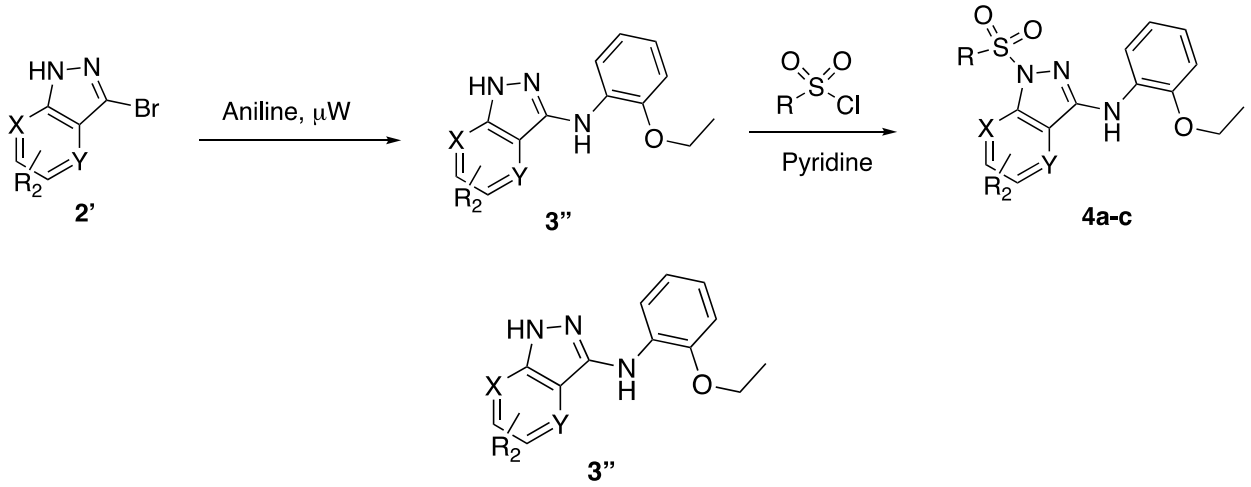
General Procedures: B



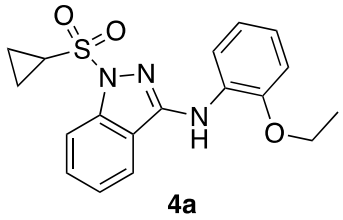
2-Amino-*N*-(2-ethoxyphenyl)benzamide (3'). To a solution of anthranilic acid (0.50 g, 3.6 mmol), *O*-Phenitidine (0.42 g, 3.1 mmol) and triethylamine (1.50 mL, 10.9 mmol) in dichloromethane (5.0 mL) was dropwise added T3P (50% wt/v in ethyl acetate) (3.0 mL, 4.7 mmol). The reaction was stirred at RT for 6 hours. To the reaction mixture was added 200 mL of aqueous 1N NaOH, the product was extracted with ethyl acetate (100 mL). Combined organic layer was washed with brine, concentrated and used as such. Yield = 0.60 g (65%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (s, 1H), 8.47 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.53 – 7.49 (m, 1H), 7.31 – 7.25 (m, 1H), 7.08 (td, *J* = 7.8, 1.7 Hz, 1H), 7.02 (td, *J* = 7.7, 1.1 Hz, 1H), 6.93 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.76 (t, *J* = 7.2 Hz, 2H), 5.61 (s, 2H), 4.17 (q, *J* = 7.0 Hz, 2H), 1.50 (t, *J* = 7.0 Hz, 3H).

Step 2. Respective anilines (1.0 equiv.) and carbonyl or sulfonyl chlorides (1.0 equiv.) in pyridine (0.5 M) were stirred from RT to 45 ºC over 12 hours. The crude was purified by Prep-HPLC (Water:ACN)

General Procedures: C

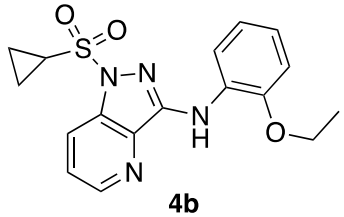


3-(2-Ethoxyphenyl)-1*H*-indazole (3"). 3-bromo-1*H*-indazole (0.20 g, 1.0 mmol) in *O*-phenetidine (0.2 mL) was subjected to microwave irradiation at 210 ºC for 2 hours. The crude was absorbed on silica gel and purified by flash chromatography 0 to 15% ethyl acetate:hexanes. Yield = 50.0 mg (19.6%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.30 (s, 1H), 8.11 (d, *J* = 7.9 Hz, 1H), 7.68 (d, *J* = 8.1 Hz, 1H), 7.44 – 7.39 (m, 2H), 7.15 (t, *J* = 7.1 Hz, 1H), 7.07 (s, 1H), 7.00 (t, *J* = 7.6 Hz, 1H), 6.95 – 6.87 (m, 2H), 4.22 (q, *J* = 7.0 Hz, 2H), 1.56 (t, *J* = 6.9 Hz, 3H).



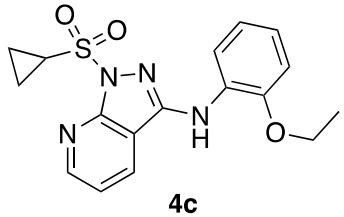
1-(Cyclopropylsulfonyl)-3-(2-ethoxyphenyl)-1*H*-indazole (4a). Cyclopropane sulfonyl chloride (28.8 μL, 0.280 mmol) was added to a solution of 3-(2-ethoxyphenyl)-1*H*-indazole (60.0 mg, 0.230 mmol) and pyridine (93.0 mg, 1.18 mmol) in ACN (1.5 mL). The reaction was heated at 45 ºC for 24 hours. All volatiles were evaporated and crude was purified via Prep-HPLC (water:ACN). Yield = 20.0 mg (23.8%). LCMS: R_T = 3.12 min., ESI-MS: *m/z* = 358.1 $[M + H]^+$, calc'd 358.12 for $C_{18}H_{20}N_3O_3S$, found 358.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (dd, *J* = 7.9, 1.1 Hz, 1H), 8.06 (d, *J* = 8.4 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.57 (t, *J*

= 7.8 Hz, 1H), 7.43 (s, 1H), 7.40 (t, *J* = 7.4 Hz, 1H), 7.07 (dd, *J* = 11.0, 4.2 Hz, 1H), 7.01 – 6.91 (m, 2H), 4.23 (q, *J* = 6.9 Hz, 2H), 2.69 – 2.63 (m, 1H), 1.57 (t, *J* = 7.0 Hz, 3H), 1.44 – 1.39 (m, 2H), 1.01 – 0.95 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.62, 146.40, 141.74, 129.79, 129.72, 123.69, 121.36, 121.25, 119.92, 118.62, 117.27, 114.21, 110.66, 64.30, 29.70, 15.01, 5.64.



4b

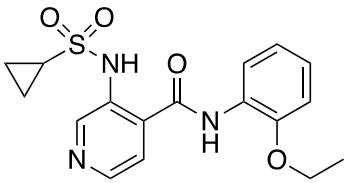
1-(Cyclopropylsulfonyl)-3-(2-ethoxyphenyl)-1*H*-pyrazolo[4,3-*b*]pyridine (4b). General Procedure C. Yield = 15.0 mg (21.7%). LCMS: R_T = 3.04 min., >95% @ 215 and 254 nm, *m/z* = 359.0 $[M + H]^+$.^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (dd, *J* = 4.5, 1.1 Hz, 1H), 8.56 (dd, *J* = 7.9, 1.3 Hz, 1H), 8.31 (dd, *J* = 8.4, 1.1 Hz, 1H), 8.07 (s, 1H), 7.49 (dd, *J* = 8.5, 4.5 Hz, 1H), 7.08 (dd, *J* = 11.1, 4.2 Hz, 1H), 7.01 (td, *J* = 7.8, 1.4 Hz, 1H), 6.97 – 6.94 (m, 1H), 4.25 (q, *J* = 7.0 Hz, 2H), 2.73 – 2.65 (m, 1H), 1.58 (t, *J* = 7.0 Hz, 3H), 1.46 – 1.41 (m, 2H), 1.06 – 1.01 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.7, 146.8, 137.4, 134.7, 129.4, 123.8, 121.8, 121.5, 121.2, 117.4, 110.8, 64.3, 29.9, 15.0, 5.9.



4c

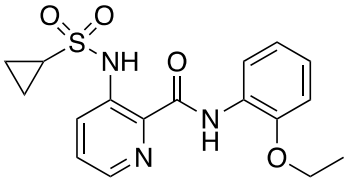
1-(Cyclopropylsulfonyl)-3-(2-ethoxyphenyl)-1*H*-pyrazolo[3,4-*b*]pyridine (4c). General Procedure C. Yield = 36.0 mg (27.8%). LCMS: R_T = 2.78 min., ESI-MS: *m/z* $[M + H]^+$, calc'd 359.12 for $C_{17}H_{19}N_4O_3S$, found 359.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.72 (dd, *J* = 4.6, 1.2 Hz, 1H), 8.34 (dd, *J* = 7.8, 1.3 Hz, 1H), 8.03 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.32 (dd, *J* = 7.7, 4.9 Hz, 2H), 7.05 – 7.01 (m, 1H), 6.98 (td, *J* = 7.7, 1.4 Hz, 1H), 6.92 (d, *J* = 7.9 Hz, 1H), 4.20 (q, *J* = 7.0 Hz, 2H), 2.93 – 2.86 (m, 1H), 1.58 – 1.51 (m, 5H), 1.06 –

1.01 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.7, 150.9, 146.8, 146.5, 129.4, 128.8, 121.7, 121.3, 118.7, 117.4, 111.8, 110.7, 64.3, 31.0, 15.0, 6.0.



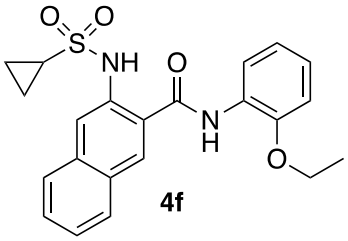
4d

3-(Cyclopropanesulfonamido)-*N*-(2-ethoxyphenyl)isonicotinamide (4d). General Procedure B. Yield = 15.0 mg (27.3%). LCMS: R_T = 2.37 min., ESI-MS: *m/z* $[M + H]^+$, calc'd 362.12 for $C_{17}H_{20}N_3O_4S$, found 362.0. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.03 (s, 1H), 9.15 (s, 1H), 8.76 (s, 1H), 8.55 (d, *J* = 5.1 Hz, 1H), 8.41 (d, *J* = 7.9 Hz, 1H), 7.45 (d, *J* = 5.1 Hz, 1H), 7.17 (td, *J* = 8.1, 1.3 Hz, 1H), 7.04 (t, *J* = 7.6 Hz, 1H), 6.97 (d, *J* = 8.2 Hz, 1H), 4.20 (q, *J* = 6.9 Hz, 2H), 2.62 – 2.53 (m, 1H), 1.52 (dd, *J* = 8.9, 5.1 Hz, 3H), 1.30 – 1.26 (m, 2H), 1.03 – 0.98 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.1, 147.7, 145.0, 144.5, 134.6, 128.3, 126.3, 125.5, 121.1, 120.3, 119.2, 111.1, 64.4, 30.9, 14.9, 6.0.



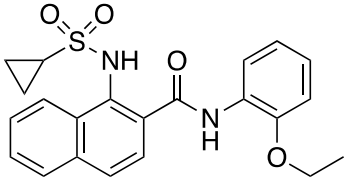
4e

3-(Cyclopropanesulfonamido)-*N*-(2-ethoxyphenyl)picolinamide (4e). General Procedure B. Yield = 17.0 mg (30.4%). LCMS: R_T = 2.97 min., ESI-MS: *m/z* $[M + H]^+$, calc'd 362.12 for $C_{17}H_{20}N_3O_4S$, found 362.0. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.69 (s, 1H), 10.92 (s, 1H), 8.49 (dd, *J* = 8.0, 1.4 Hz, 1H), 8.37 (dd, *J* = 4.4, 1.3 Hz, 1H), 8.26 (dd, *J* = 8.5, 1.2 Hz, 1H), 7.47 (dd, *J* = 8.5, 4.4 Hz, 1H), 7.13 (td, *J* = 8.0, 1.6 Hz, 1H), 7.04 (dd, *J* = 11.2, 4.3 Hz, 1H), 6.97 (d, *J* = 8.1 Hz, 1H), 4.20 (q, *J* = 7.0 Hz, 2H), 2.58 (td, *J* = 8.0, 4.0 Hz, 1H), 1.55 (t, *J* = 7.0 Hz, 3H), 1.33 – 1.28 (m, 2H), 1.03 – 0.98 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.7, 148.4, 142.6, 138.2, 134.3, 127.8, 127.5, 127.0, 124.7, 121.1, 119.9, 111.5, 64.5, 30.9, 14.9, 5.8.



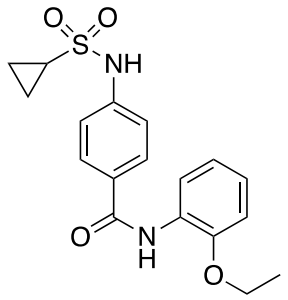
4f

3-(Cyclopropanesulfonamido)-*N*-(2-ethoxyphenyl)-2-naphthamide (4f). General Procedure A. Yield = 49 mg (70%). LCMS: R_T = 2.97 min., ESI-MS: *m/z* $[M + H]^+$, calc'd 411.14 for $C_{22}H_{23}N_2O_4S$, found 411.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.96 (s, 1H), 8.77 (s, 1H), 8.44 (dd, *J* = 8.0, 1.1 Hz, 1H), 8.18 (d, *J* = 7.6 Hz, 2H), 7.86 (t, *J* = 9.0 Hz, 2H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.18 – 7.10 (m, 1H), 7.04 (t, *J* = 7.7 Hz, 1H), 6.96 (d, *J* = 7.9 Hz, 1H), 4.20 (q, *J* = 7.0 Hz, 2H), 2.58 – 2.48 (m, 1H), 1.51 (t, *J* = 7.0 Hz, 3H), 1.25 – 1.19 (m, 2H), 0.93 – 0.84 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 148.1, 135.5, 135.0, 129.6, 129.3, 128.7, 128.3, 127.9, 127.3, 126.6, 125.3, 124.3, 121.5, 120.6, 119.8, 111.4, 64.7, 30.3, 15.2, 6.0.



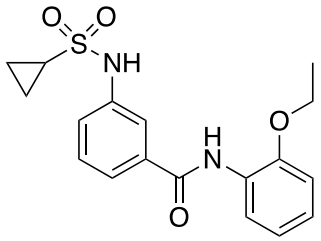
4g

1-(Cyclopropanesulfonamido)-*N*-(2-ethoxyphenyl)-2-naphthamide (4g). General Procedure A. Yield = 1 mg (3%) LCMS: R_T = 2.86 min., ESI-MS: *m/z* $[M + H]^+$, calc'd 411.14 for $C_{22}H_{23}N_2O_4S$, found 411.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.35 (s, 1H), 8.70 (dd, *J* = 8.5, 7.3 Hz, 2H), 8.52 (d, *J* = 7.9 Hz, 1H), 7.90 (d, *J* = 8.5 Hz, 1H), 7.88 – 7.83 (m, 1H), 7.71 – 7.59 (m, 3H), 7.14 (td, *J* = 7.9, 1.6 Hz, 1H), 7.05 (t, *J* = 7.2 Hz, 1H), 6.95 (dd, *J* = 8.1, 1.2 Hz, 1H), 4.18 (q, *J* = 7.0 Hz, 2H), 2.39 (ddd, *J* = 12.8, 8.0, 4.8 Hz, 1H), 1.50 (t, *J* = 7.0 Hz, 3H), 1.03 – 0.98 (m, 2H), 0.82 – 0.73 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.2, 148.0, 147.7, 135.9, 128.8, 128.5, 128.3, 126.0, 124.2, 123.9, 123.7, 121.9, 121.4, 120.2, 117.0, 111.4, 109.0, 64.6, 15.3.



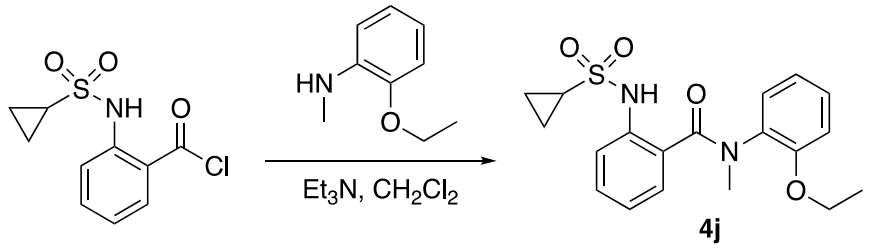
4h

4-(Cyclopropanesulfonamido)-*N*-(2-ethoxyphenyl)benzamide (4h). General Procedure A. Yield = 29.0 mg (21%). LCMS: R_T = 2.52 min, ESI-MS: $[M + H]^+$, calc'd 361.12 for $C_{18}H_{21}N_2O_4S$, found 361.0. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.45 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.88 – 7.77 (m, 2H), 7.44 – 7.31 (m, 2H), 7.06 (td, *J* = 7.7, 1.8 Hz, 1H), 6.99 (td, *J* = 7.8, 1.5 Hz, 1H), 6.91 (dd, *J* = 8.1, 1.6 Hz, 1H), 4.15 (q, *J* = 7.0 Hz, 2H), 2.60 – 2.39 (m, 3H), 1.49 (t, *J* = 7.0 Hz, 3H), 1.21 (dd, *J* = 5.0, 2.3 Hz, 2H), 1.04 – 0.91 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.6, 147.5, 147.5, 141.0, 130.7, 130.6, 128.4, 127.6, 127.5, 124.1, 121.0, 119.8, 119.7, 119.7, 111.0, 64.3, 50.0, 49.8, 49.6, 49.5, 49.3, 49.1, 48.9, 30.3, 30.3, 14.9, 5.6.



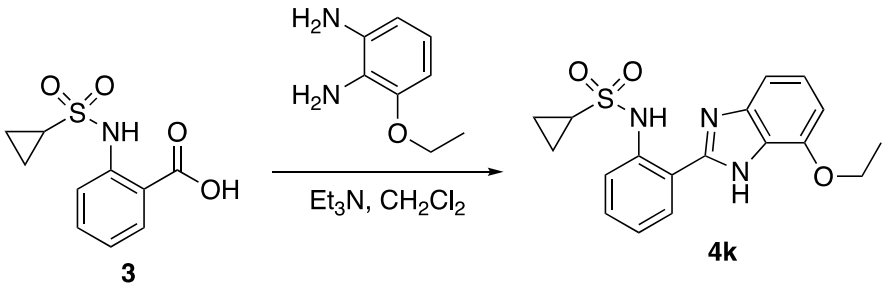
4i

3-(Cyclopropanesulfonamido)-*N*-(2-ethoxyphenyl)benzamide (4i). General Procedure A. Yield = 34.0 mg (25%). LCMS: R_T = 2.54 min, ESI-MS: *m/z* $[M + H]^+$, calc'd 361.12 for $C_{18}H_{21}N_2O_4S$, found 361.0. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.68 (s, 1H), 8.52 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.91 (t, *J* = 1.9 Hz, 1H), 7.66 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.56 (ddd, *J* = 8.2, 2.3, 1.1 Hz, 1H), 7.54 – 7.44 (m, 2H), 7.09 (td, *J* = 7.8, 1.7 Hz, 1H), 7.02 (td, *J* = 7.8, 1.4 Hz, 1H), 6.92 (dd, *J* = 8.1, 1.4 Hz, 1H), 4.16 (q, *J* = 7.0 Hz, 2H), 2.61 – 2.49 (m, 1H), 1.51 (t, *J* = 6.9 Hz, 3H), 1.20 (dd, *J* = 4.8, 2.2 Hz, 2H), 0.98 (dt, *J* = 7.9, 1.6 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.5, 147.6, 138.1, 136.5, 130.0, 127.5, 124.6, 124.2, 123.1, 121.1, 120.2, 119.9, 111.0, 64.4, 30.1, 14.9, 5.7.



4j

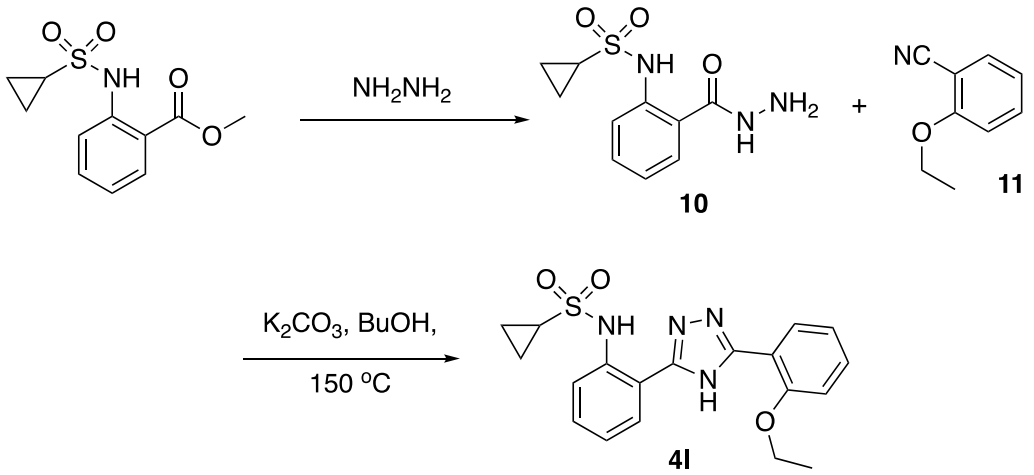
2-(Cyclopropanesulfonamido)-N-(2-methoxyphenyl)-*N*-methylbenzamide (4j). To a solution of 2-ethoxy-*N*-methylaniline (28.0 mg, 0.200 mmol) and TEA (57.0 µL, 0.410 mmol) in DCM (2.0 mL) was added 2-(cyclopropanesulfonamido)benzoyl chloride (50.0 mg, 0.200 mmol). the reaction was stirred at RT for 6 hours. Crude was purified by flash chromatography. Yield = 64.0 mg (86.5%). LCMS: R_T = 2.48 min., ESI-MS: *m/z* $[M + H - CH_3]^+$, calc'd 361.12 for $C_{18}H_{21}N_2O_4S$, found 361.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 – 8.26 (m, 1H), 7.55 (d, *J* = 7.1 Hz, 1H), 7.17 (s, 2H), 7.08 (d, *J* = 5.9 Hz, 2H), 7.00 (d, *J* = 5.5 Hz, 2H), 6.79 (dd, *J* = 29.5, 22.5 Hz, 3H), 3.76 (s, 3H), 3.38 (s, 3H), 2.67 (s, 1H), 1.24 (s, 2H), 1.01 (d, *J* = 6.6 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 154.0, 136.5, 132.7, 130.4, 129.0, 128.9, 128.5, 122.5, 121.1, 120.1, 111.8, 55.6, 37.1, 30.6, 6.3, 5.6.



3 **4k**

***N*-(2-(7-Ethoxy-1*H*-benzo[*d*]imidazol-2-yl)phenyl)cyclopropanesulfonamide (4k).** To a flask was added the carboxylic acid (121 mg; 0.500 mmol), HATU (228 mg; 0.600 mmol), 3-ethoxybenzene-1,2-diamine (76 mg; 0.50 mmol) followed by THF (2.7 mL) and iPr_2Net (0.74 mL; 1.3 mmol). The reaction mixture was stirred at rt for 16 h and then concentrated *in vacuo*. The residue was dissolved in AcOH (13.5 mL) and then heated at 80 °C for 16 h. The reaction was concentrated and then purified by flash column chromatography (Biotage Isolera, 0 – 100% EtOAc:Hexanes) to yield the desired product, **4k**. Yield = 166

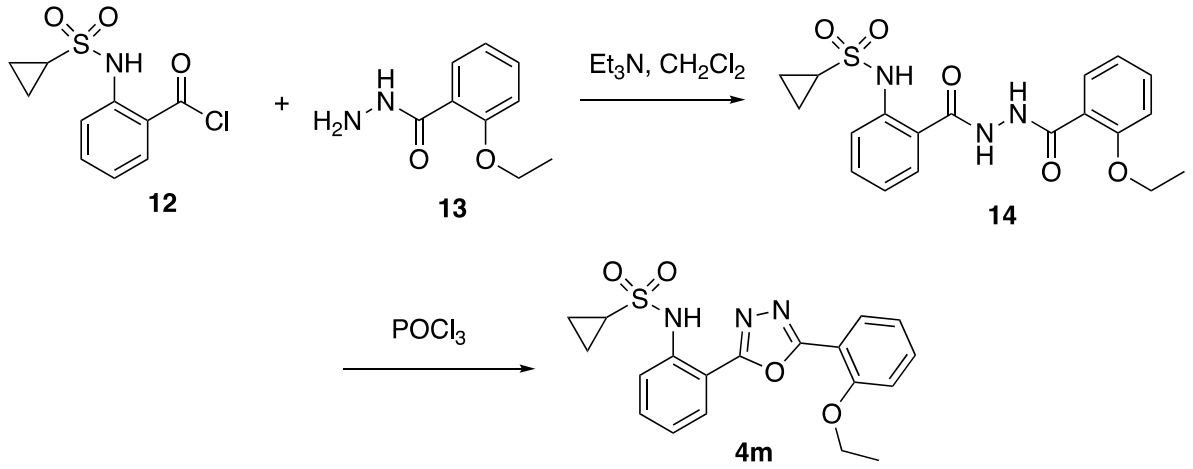
mg (93%). LCMS: R_T = 2.667 min., ESI-MS: *m/z* $[M + H]^+$., calc'd 358.12 for $C_{18}H_{20}N_3O_3S$, found 358.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 – 7.81 (m, 2H), 7.37 – 7.30 (m, 1H), 7.25 (d, *J* = 8.1 Hz, 1H), 7.18 – 7.10 (m, 2H), 6.72 (d, *J* = 7.9 Hz, 1H), 4.32 (dd, *J* = 13.8, 6.8 Hz, 2H), 2.50 (tt, *J* = 8.1, 4.8 Hz, 1H), 1.50 (t, *J* = 7.0 Hz, 3H), 1.21 (tt, *J* = 5.7, 2.9 Hz, 2H), 0.82 (qd, *J* = 5.8, 1.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 149.5, 138.3, 131.1, 127.0, 124.3, 123.8, 121.3, 117.3, 106.0, 65.0, 60.8, 53.8, 39.0, 30.7, 15.3, 5.9.



***N*-(2-(Hydrazinecarbonyl)phenyl)cyclopropanesulfonamide (10).** A solution of methyl 2-(cyclopropanesulfonamido)benzoate (0.15 g, 0.59 mmol) in hydrazine hydrate (80%) (117 µL, 2.35 mmol) and ethanol (0.20 mL) was subjected to microwave irradiation at 160 ºC for 1 hour. After TLC confirmation of starting material finish, volatiles were evaporated, and crude used as such.

***N*-(2-(5-(2-Ethoxyphenyl)-4*H*-1,2,4-triazol-3-yl)phenyl)cyclopropanesulfonamide (4l).** A solution of 2-ethoxybenzonitrile, **11**, (0.17 µL, 1.2 mmol), *N*-(2-(hydrazinecarbonyl)phenyl)cyclopropane sulfonamide, **10**, (0.10 g, 0.40 mmol) and K_2CO_3 (55.2 mg, 0.400 mmol) in tBuOH (0.10 mL)) was subjected to microwave irradiation at 150 ºC for 2 hour. Crude purified by Prep-HPLC. Yield = 10.0 mg (6.5%). LCMS: R_T = 2.92 min., ESI-MS: *m/z* $[M + H]^+$, calc'd 385.13 for $C_{19}H_{21}N_4O_3S$, found 385.0. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.85 (s, 1H), 11.16 (s, 1H), 8.41 (dd, *J* = 7.8, 1.6 Hz, 1H), 8.36 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.86 (d, *J* = 8.2 Hz, 1H), 7.53 – 7.47 (m, 1H), 7.45 – 7.41 (m, 1H), 7.28 – 7.23 (m, 1H), 7.21

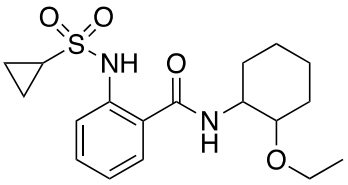
(t, *J* = 7.3 Hz, 1H), 7.11 (d, *J* = 8.4 Hz, 1H), 4.37 (q, *J* = 7.0 Hz, 2H), 2.49 – 2.43 (m, 1H), 1.68 (t, *J* = 7.0 Hz, 3H), 1.20 – 1.15 (m, 2H), 0.83 – 0.78 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.4, 156.3, 152.9, 136.8, 132.2, 130.3, 129.7, 128.2, 124.0, 122.0, 120.8, 119.3, 114.4, 112.1, 64.8, 29.9, 15.1, 5.4.



***N*-(2-(2-(2-Ethoxybenzoyl)hydrazine-1-carbonyl)phenyl)cyclopropanesulfonamide (14)** To a solution of 2-ethoxybenzohydrazide, **13**, (0.85 g, 0.47 mmol) and Et_3N in CH_2Cl_2 was added 2 (cyclopropanesulfonamido)benzoyl chloride, **12**, (0.13 g, 0.51 mmol) and the reaction was stirred for 2 hours at RT. Product was partitioned between Water and ethyl acetate, organic layer were collected, washed with brime, concentrated and used as such. Yield = 170.0 mg (crude). LCMS: R_T = 2.53 min., ESI-MS: *m/z* $[M + H]^+$, calc'd 404.13 for $C_{19}H_{22}N_3O_5S$, found 404.1.

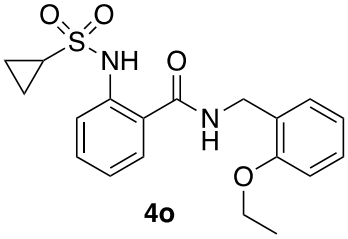
***N*-(2-(5-(2-Ethoxyphenyl)-1,3,4-oxadiazol-2-yl)phenyl)cyclopropanesulfonamide (4m).** A solution of *N*-(2-(2-(2-ethoxybenzoyl)hydrazine-1-carbonyl)phenyl)cyclopropanesulfonamide, **14**, (0.17 g crude) in $POCl_3$ was refluxed at 80º C for 12 hours. Volatiles were evaporated under vacuum; mixture was neutralized with saturated $NaHCO_3$ aqueous solution and product extracted with ethyl acetate. Organic layer purified by flash chromatography 0-80% Ethyl acetate:Hexane. Yield = 30.0 mg. LCMS: R_T = 2.96 min., ESI-MS: *m/z* $[M + H]^+$, calc'd 386.12 for $C_{19}H_{20}N_3O_4S$, found 386.0. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.46 (s, 1H), 8.10 (d, *J* = 7.6 Hz, 1H), 8.03 (d, *J* = 7.7 Hz, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 7.55 (dd, *J* = 12.9, 7.7 Hz, 2H), 7.26 (d, *J* = 7.6 Hz, 1H), 7.12 (dd, *J* = 15.0, 7.9 Hz, 2H), 4.26 (q, *J* = 6.9 Hz, 2H), 2.64 – 2.56 (m, 1H), 1.58

(t, J = 6.9 Hz, 3H), 1.33 – 1.27 (m, 2H), 0.97 – 0.91 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.4, 157.4, 137.9, 133.6, 132.6, 130.6, 127.9, 123.6, 120.8, 119.8, 113.0, 112.4, 111.8, 64.5, 30.7, 14.9, 5.8.



4n

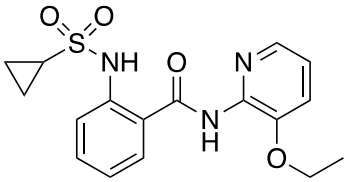
2-(Cyclopropanesulfonamido)-*N*-(2-ethoxycyclohexyl)benzamide (4n). General Procedure A. Yield = 17.0 mg (44%). LCMS: R_T = 2.78 min, ESI-MS: *m/z* $[M + H]^+$, calc'd 367.17 for $C_{18}H_{27}N_2O_4S$, found 367.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.72 (s, 1H), 7.81 (dd, J = 8.7, 1.2 Hz, 1H), 7.48 (ddd, J = 8.1, 6.5, 1.7 Hz, 2H), 7.15 (td, J = 7.6, 1.1 Hz, 1H), 6.77 (d, J = 8.6 Hz, 1H), 4.14 – 4.02 (m, 1H), 3.76 – 3.64 (m, 1H), 3.64 – 3.56 (m, 1H), 3.46 – 3.30 (m, 1H), 2.51 (tt, J = 8.0, 4.8 Hz, 1H), 2.11 – 1.96 (m, 1H), 1.83 – 1.59 (m, 4H), 1.59 – 1.35 (m, 5H), 1.30 – 1.18 (m, 6H), 1.01 – 0.88 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 139.6, 132.6, 126.7, 123.3, 121.5, 121.1, 75.5, 63.6, 50.5, 30.3, 27.8, 27.6, 24.1, 19.5, 15.7, 5.7, 5.6.



4o

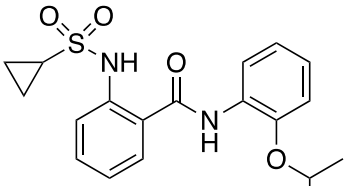
2-(Cyclopropanesulfonamido)-*N*-(2-ethoxybenzyl)benzamide (4o). General Procedures: A. Yield = 58.0 mg (77.3%). LCMS: R_T = 2.69 min., ESI-MS: *m/z* $[M + H]^+$, calc'd 375.14 for $C_{19}H_{23}N_2O_4S$, found 375.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.62 (s, 1H), 7.75 (d, J = 8.2 Hz, 1H), 7.49 (d, J = 7.8 Hz, 1H), 7.47 – 7.43 (m, 1H), 7.34 (d, J = 7.3 Hz, 1H), 7.31 – 7.25 (m, 1H), 7.16 – 7.12 (m, 1H), 7.00 (s, 1H), 6.94 (t, J = 7.4 Hz, 1H), 6.90 (d, J = 8.2 Hz, 1H), 4.63 (d, J = 5.8 Hz, 2H), 4.13 (q, J = 7.0 Hz, 2H), 2.37 – 2.31 (m, 1H),1.48

(t, J = 7.0 Hz, 3H), 1.11 (d, J = 2.4 Hz, 2H), 1.11 (d, J = 2.4 Hz, 2H), 0.80 – 0.74 (m, 2H).^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1, 157.0, 139.3, 132.6, 129.9, 129.3, 126.7, 125.6, 123.6, 122.1, 121.8, 120.7, 111.4, 63.7, 40.3, 30.1, 15.1, 5.5.



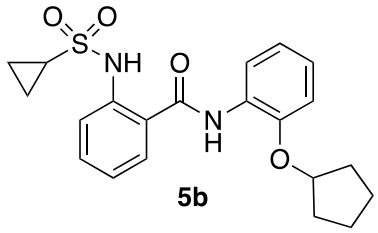
4p

2-(Cyclopropanesulfonamido)-*N*-(3-ethoxypyridin-2-yl)benzamide (4p) : General Procedures: A. Yield = 20.0 mg (21.0%). LCMS: R_T = 2.01 min., ESI-MS: *m/z* $[M + H]^+$, calc'd 362.12 for $C_{17}H_{20}N_3O_4S$, found 362.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.41 (s, 1H), 8.67 (s, 1H), 8.13 (s, 1H), 7.89 (d, J = 8.2 Hz, 1H), 7.71 (d, J = 6.9 Hz, 1H), 7.54 (t, J = 6.9 Hz, 1H), 7.22 (m, 2H), 7.12 (s, 1H), 4.19 (d, J = 6.6 Hz, 2H), 2.58 (s, 1H), 1.50 (t, J = 6.2 Hz, 3H), 1.23 (m, 2H), 0.94 (m, 2H).



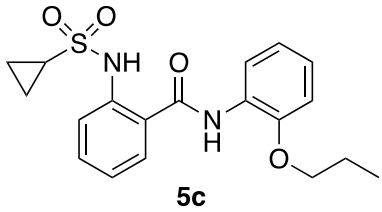
5a

2-**(Cyclopropanesulfonamido)-*N*-(2-isopropoxyphenyl)benzamide (5a).** General Procedure A. Yield = 31.0 mg (40.2%). LCMS: R_T = 2.82 min., ESI-MS: *m/z* $[M + H]^+$, calc'd 375.14 for $C_{19}H_{23}N_2O_4S$, found 375.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.49 (s, 1H), 8.71 (s, 1H), 8.46 (dd, J = 8.0, 1.4 Hz, 1H), 7.86 (dd, J = 8.3, 0.7 Hz, 1H), 7.64 (dd, J = 7.9, 1.2 Hz, 1H), 7.57 – 7.51 (m, 1H), 7.25 (td, J = 7.8, 1.0 Hz, 1H), 7.13 (td, J = 8.0, 1.6 Hz, 1H), 7.06 – 7.00 (m, 1H), 6.99 – 6.95 (m, 1H), 4.69 (hept, J = 6.0 Hz, 1H), 2.53 (tt, J = 8.0, 4.8 Hz, 1H), 1.44 (d, J = 6.1 Hz, 6H), 1.25 (tt, J = 5.7, 3.0 Hz, 2H), 0.94 (qd, J = 5.8, 1.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 146.6, 139.7, 133.0, 127.8, 126.6, 124.7, 123.8, 122.4, 121.8, 121.1, 120.2, 112.6, 71.5, 30.4, 22.3, 5.7.



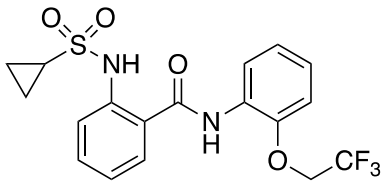
5b

***N*-(2-(Cyclopentyloxy)phenyl)-2-(cyclopropanesulfonamido)benzamide (5b).** General Procedure A. Yield = 45.0 mg (54.3%). LCMS: R_T = 2.99 min., ESI-MS: *m/z* $[M + H]^+$, calc'd 401.15 for $C_{21}H_{25}N_2O_4S$, found 401.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.52 (s, 1H), 8.67 (s, 1H), 8.44 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.86 (d, *J* = 8.3 Hz, 1H), 7.62 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.57 – 7.51 (m, 1H), 7.26 – 7.21 (m, 1H), 7.12 (td, *J* = 8.0, 1.5 Hz, 1H), 7.04 – 6.99 (m, 1H), 6.96 (d, *J* = 8.1 Hz, 1H), 2.53 (tt, *J* = 8.0, 4.8 Hz, 1H), 2.01 (dt, *J* = 13.6, 6.9 Hz, 2H), 1.96 – 1.89 (m, 2H), 1.87 – 1.78 (m, 2H), 1.77 – 1.70 (m, 2H), 1.26 – 1.23 (m, 2H), 0.97 – 0.92 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1, 146.8, 139.8, 133.0, 127.5, 126.5, 124.6, 123.8, 122.3, 121.8, 120.9, 120.1, 112.4, 80.6, 33.0, 30.4, 24.0, 5.7.



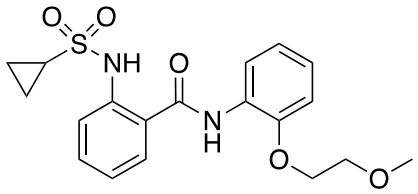
5c

2-(Cyclopropanesulfonamido)-*N*-(2-propoxyphenyl)benzamide (5c). General Procedure A. Yield = 27.0mg (35.0%). LCMS: R_T = 2.86 min., ESI-MS: *m/z* $[M + H]^+$, calc'd 375.14 for C19H23N2O4S, found 375.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.47 (s, 1H), 8.71 (s, 1H), 8.47 – 8.43 (m, 1H), 7.86 (d, *J* = 8.2 Hz, 1H), 7.65 (d, *J* = 7.7 Hz, 1H), 7.55 (dd, *J* = 11.5, 4.1 Hz, 1H), 7.24 (dd, *J* = 11.2, 3.9 Hz, 1H), 7.14 (td, *J* = 8.0, 1.3 Hz, 1H), 7.04 (t, *J* = 7.4 Hz, 1H), 6.96 (d, *J* = 8.0 Hz, 1H), 4.09 (t, *J* = 6.5 Hz, 2H), 2.56 – 2.50 (m, 1H), 1.91 (dt, *J* = 14.0, 7.0 Hz, 2H), 1.27 – 1.23 (m, 2H), 1.11 (t, *J* = 7.4 Hz, 3H), 0.96 – 0.91 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 147.8, 139.7, 133.0, 127.0, 126.5, 124.7, 123.8, 122.3, 121.9, 121.1, 120.0, 111.1, 70.2, 30.3, 22.6, 10.6, 5.7.



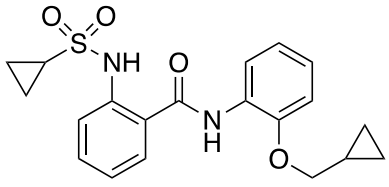
5d

2-(Cyclopropanesulfonamido)-*N*-(2-(2,2,2-trifluoroethoxy)phenyl)benzamide (5d). General Procedure A. Yield = 9.0 mg (12%). LCMS: R_T = 2.74 min, ESI-MS: *m/z* $[M + H]^+$, calc'd 415.09 for $C_{18}H_{18}F_3N_2O_4S$, found 415.0. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 10.40 (s, 1H), 8.62 – 8.47 (m, 2H), 7.88 (d, *J* = 8.3 Hz, 1H), 7.64 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.61 – 7.53 (m, 1H), 7.25 (t, *J* = 7.6 Hz, 1H), 7.18 (dd, *J* = 6.1, 3.5 Hz, 2H), 6.97 (dd, *J* = 6.1, 3.5 Hz, 1H), 4.52 (q, *J* = 7.9 Hz, 2H), 2.54 (tt, *J* = 8.0, 4.7 Hz, 1H), 1.31 – 1.18 (m, 3H), 0.95 (dd, *J* = 8.0, 2.4 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 146.3, 139.8, 133.3, 126.5, 124.9, 123.8, 123.5, 121.8, 121.1, 112.1, 66.9, 66.6, 30.4, 5.7. *Additional carbon peaks due to C-F coupling peaks however, these are overlapping with other aromatic peaks.



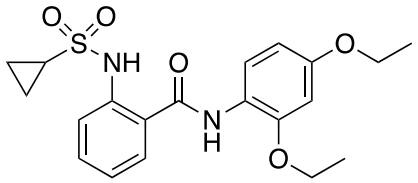
5e

2-(Cyclopropanesulfonamido)-*N*-(2-(2-methoxyethoxy)phenyl)benzamide (5e). General Procedure A. Yield = 38.1 mg (47%). LCMS: R_T = 2.65 min., ESI-MS: *m/z* $[M + H]^+$, calc'd 391.13 for $C_{19}H_{23}N_2O_5S$, found 391.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.49 (s, 1H), 9.01 (s, 1H), 8.46 (dd, *J* = 7.7, 1.9 Hz, 1H), 7.85 (d, *J* = 8.3 Hz, 1H), 7.77 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.56 – 7.50 (m, 1H), 7.25 – 7.20 (m, 1H), 7.12 (pd, *J* = 7.5, 1.7 Hz, 2H), 7.03 (dd, *J* = 7.6, 1.8 Hz, 1H), 4.27 – 4.23 (m, 2H), 3.75 – 3.72 (m, 2H), 3.39 (s, 3H), 2.53 (tt, *J* = 8.1, 4.8 Hz, 1H), 1.27 – 1.22 (m, 2H), 0.96 – 0.91 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 147.7, 139.7, 132.9, 128.8, 127.1, 124.7, 123.6, 122.7, 122.4, 121.7, 120.5, 114.5, 70.7, 69.9, 59.0, 30.3, 5.7.



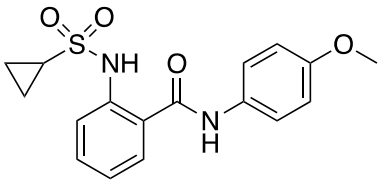
5f

2-(Cyclopropanesulfonamido)-*N*-(2-(cyclopropylmethoxy)phenyl)benzamide (5f). General Procedure A. Yield = 12.0 mg (15%). LCMS: R_T = 2.911 min, ESI-MS: *m/z* $[M + H]^+$, calc'd 387.14 for $C_{20}H_{23}N_2O_4S$, found 387.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.49 (s, 1H), 8.79 (s, 1H), 8.45 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.86 (dd, *J* = 8.4, 1.1 Hz, 1H), 7.70 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.55 (ddd, *J* = 8.5, 7.4, 1.5 Hz, 1H), 7.24 (td, *J* = 7.6, 1.2 Hz, 1H), 7.08 (dtd, *J* = 38.9, 7.8, 1.5 Hz, 2H), 6.94 (dd, *J* = 8.1, 1.4 Hz, 1H), 3.96 (d, *J* = 7.0 Hz, 2H), 2.54 (tt, *J* = 8.1, 4.8 Hz, 1H), 1.35 (tt, *J* = 7.4, 4.7 Hz, 1H), 1.25 (dd, *J* = 4.9, 2.2 Hz, 2H), 0.99 – 0.91 (m, 2H), 0.75 – 0.67 (m, 2H), 0.44 – 0.38 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 147.8, 139.7, 133.0, 127.3, 126.7, 124.7, 123.7, 122.3, 121.8, 121.3, 120.1, 111.6, 73.8, 30.4, 30.3, 10.3, 5.7, 3.2.



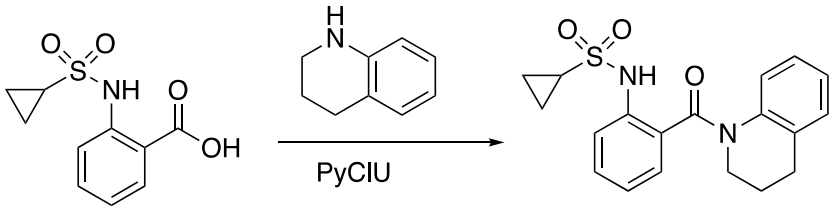
5g

2-(Cyclopropanesulfonamido)-*N*-(2,4-diethoxyphenyl)benzamide (5g). General Procedure A. Yield = 18.0 mg (42.8%). LCMS: R_T = 2.88 min., ESI-MS: *m/z* $[M + H]^+$, calc'd 405.15 for $C_{20}H_{25}N_2O_5S$, found 405.0. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.49 (s, 1H), 8.43 (s, 1H), 8.29 (d, *J* = 9.5 Hz, 1H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.63 (d, *J* = 7.1 Hz, 1H), 7.55 – 7.51 (m, 1H), 7.23 (t, *J* = 7.6 Hz, 1H), 6.53 (dd, *J* = 7.3, 2.3 Hz, 2H), 4.15 (q, *J* = 7.0 Hz, 2H), 4.06 (q, *J* = 7.0 Hz, 2H), 2.55 – 2.49 (m, 1H), 1.49 (t, *J* = 7.0 Hz, 3H), 1.44 (t, *J* = 7.0 Hz, 3H), 1.26 – 1.21 (m, 2H), 0.95 – 0.91 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.9, 156.5, 149.1, 139.5, 132.8, 126.6, 123.7, 122.5, 121.8, 121.1, 120.3, 104.5, 100.0, 64.3, 63.8, 30.3, 14.8, 5.7.



5h

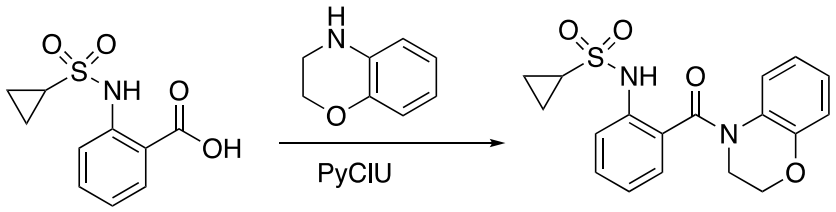
2-(Cyclopropanesulfonamido)-*N*-(4-methoxyphenyl)benzamide (5h). General Procedure A. Yield = 14.0 mg (19.1%). LCMS: R_T = 2.4 min., ESI-MS: *m/z* $[M - CH_2]^+$, calc'd 332.08 for $C_{16}H_{16}N_2O_4S$, found 332.0. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.35 (s, 1H), 8.23 (s, 1H), 7.73 (d, *J* = 8.3 Hz, 1H), 7.68 (d, *J* = 7.8 Hz, 1H), 7.50 (d, *J* = 8.8 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 1H), 7.17 (t, *J* = 7.6 Hz, 1H), 6.91 (d, *J* = 8.9 Hz, 2H), 3.82 (s, 3H), 2.50 – 2.44 (m, 1H), 1.21 – 1.15 (m, 2H), 0.96 – 0.88 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 157.2, 139.2, 132.9, 130.0, 127.3, 123.7, 122.9, 122.0, 121.3, 114.3, 55.5, 30.3, 5.8.



3 **5i**

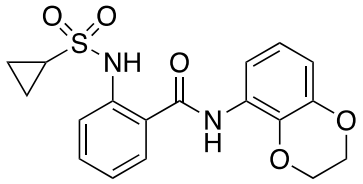
***N*-(2-(1,2,3,4-Tetrahydroquinoline-1-carbonyl)phenyl)cyclopropanesulfonamide (5i).** A solution of 2-(cyclopropanesulfonamido)benzoic acid, **3**, (50.0 mg, 0.220 mmol), PyClU (85.0 mg, 0.260 mmol) and DIPEA (117 µL, 0.660 mmol) in DMF (1.0 mL) was stirred for 15 minutes at RT followed by addition of 1,2,3,4-tetrahydroquinoline (29 mg, 0.22 mmol). The reaction was stirred at 50º C for 12h. Product was worked up between water (20.0 mL) and ethyl acetate (20.0 mL). Organic layer was washed with brine, dried over Na_2SO_4, concentrated and purified by flash chromatography. 0-50% hexane:ethyl acetate. Yield = 11.0 mg (14.2%). LCMS: R_T = 2.54 min., ESI-MS: *m/z* $[M + H]^+$, calc'd 357.13 for $C_{19}H_{21}N_2O_3S$, found 357.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (s, 1H), 7.73 (d, *J* = 8.3 Hz, 1H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.20 (d, *J* = 7.5 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 6.94 (t, *J* = 6.8 Hz, 1H), 6.89 (dd, *J* = 13.7, 6.5 Hz, 2H), 6.72 (d, *J* = 7.5 Hz, 1H), 3.94 (t, *J* = 6.5 Hz, 2H), 2.88 (t, *J* = 6.6 Hz, 2H), 2.67 – 2.61 (m, 1H), 2.09 (p, *J* = 6.6

Hz, 2H), 1.34 – 1.29 (m, 2H), 1.07 – 1.01 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0, 138.7, 137.6, 131.8, 131.4, 129.8, 128.7, 126.0, 125.3, 125.1, 123.2, 121.6, 44.5, 30.8, 26.8, 24.1, 6.0.



3 **5j**

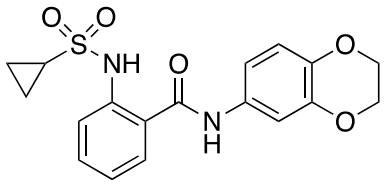
***N*-(2-(3,4-Dihydro-2H-benzo[*b*][1,4]oxazine-4-carbonyl)phenyl)cyclopropanesulfonamide (5j).** Same procedure as **5i**. Yield = 10.0 mg (13.5%). LCMS: R_T =3.28min., ESI-MS: *m/z* $[M + H]^+$, calc'd 359.11 for $C_{18}H_{19}N_2O_4S$, found 359.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.77 (d, *J* = 8.3 Hz, 1H), 7.45 (t, *J* = 7.9 Hz, 1H), 7.26 (d, *J* = 7.7 Hz, 1H), 7.07 – 7.03 (m, 2H), 6.95 (d, *J* = 8.2 Hz, 1H), 6.70 (t, *J* = 7.5 Hz, 1H), 4.42 (t, *J* = 4.6 Hz, 2H), 4.05 (s, 2H), 2.67 – 2.59 (m, 1H), 1.30 (tt, *J* = 8.3, 4.3 Hz, 2H), 1.06 – 1.00 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.3, 137.6, 132.0, 129.8, 126.4, 124.5, 124.2, 123.7, 122.4, 120.1, 117.6, 66.4, 30.8, 6.1.



5k

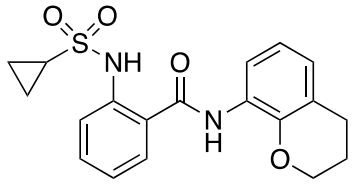
2-(Cyclopropanesulfonamido)-*N*-(2,3-dihydrobenzo[*b*][1,4]dioxin-5-yl)benzamide (5k). General Procedure A. Yield = 8.0 mg (12.3%). LCMS: R_T = 2.53 min., ESI-MS: *m/z* $[M + H]^+$, calc'd 375.10 for $C_{18}H_{19}N_2O_5S$, found 375.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.34 (s, 1H), 8.38 (s, 1H), 7.98 (d, *J* = 8.2 Hz, 1H), 7.86 (d, *J* = 8.3 Hz, 1H), 7.68 (d, *J* = 7.7 Hz, 1H), 7.55 (t, *J* = 7.8 Hz, 1H), 7.23 (t, *J* = 7.6 Hz, 1H), 6.93 (t, *J* = 8.3 Hz, 1H), 6.75 (d, *J* = 8.2 Hz, 1H), 4.42 – 4.37 (m, 2H), 4.36 – 4.31 (m, 2H), 2.57 – 2.50 (m,

1H), 1.28 – 1.23 (m, 2H), 0.98 – 0.92 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3, 143.3, 139.6, 133.1, 126.9, 123.6, 122.2, 121.8, 121.2, 113.3, 113.0, 64.9, 64.1, 30.4, 5.7.



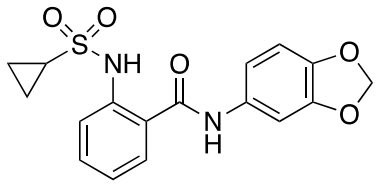
5l

2-(Cyclopropanesulfonamido)-*N*-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)benzamide (5l). General Procedure A. Yield = 31.0 mg (47.7%). LCMS: R_T = 2.45 min., ESI-MS: *m/z* $[M + H]^+$, calc'd 375.10 for $C_{18}H_{19}N_2O_5S$, found 375.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.27 (s, 1H), 7.93 (s, 1H), 7.79 (d, *J* = 8.3 Hz, 1H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.50 (t, *J* = 7.8 Hz, 1H), 7.23 (d, *J* = 2.3 Hz, 1H), 7.20 (t, *J* = 7.6 Hz, 1H), 6.99 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.88 (d, *J* = 8.7 Hz, 1H), 4.31 – 4.25 (m, 4H), 2.54 – 2.48 (m, 1H), 1.25 – 1.19 (m, 2H), 0.97 – 0.91 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 143.6, 141.3, 139.3, 133.0, 130.5, 127.0, 123.6, 121.9, 121.5, 117.4, 114.5, 110.8, 64.4, 64.3, 30.4, 5.8.



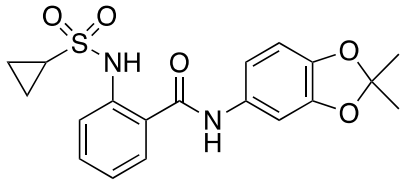
5m

***N*-(Chroman-8-yl)-2-(cyclopropanesulfonamido)benzamide (5m).** General Procedure A. Yield = 30.0 mg (38.9%). LCMS: R_T = 2.72 min., ESI-MS: *m/z* $[M + H]^+$, calc'd 373.12 for C19H21N2O4S, found 373.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.42 (s, 1H), 8.55 (s, 1H), 8.24 (d, *J* = 7.5 Hz, 1H), 7.84 (d, *J* = 8.3 Hz, 1H), 7.69 (d, *J* = 7.7 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.24 (t, *J* = 7.5 Hz, 1H), 6.90 (dd, *J* = 14.0, 7.3 Hz, 2H), 4.35 – 4.30 (m, 2H), 2.85 (t, *J* = 6.4 Hz, 2H), 2.55 – 2.47 (m, 1H), 2.11 – 2.04 (m, 2H), 1.25 – 1.20 (m, 2H), 0.95 – 0.89 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3, 143.9, 139.5, 132.9, 127.0, 126.2, 125.3, 123.8, 122.6, 122.1, 121.9, 120.2, 117.9, 67.3, 30.3, 24.5, 22.2, 5.7.



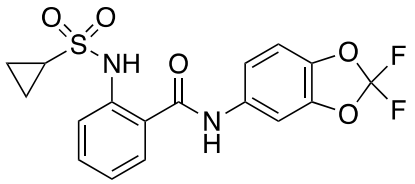
5n

***N*-(Benzo[*d*][1,3]dioxol-5-yl)-2-(cyclopropanesulfonamido)benzamide (5n).** General Procedure A. Yield = 20.0 mg (31.7%). LCMS: R_T = 2.47 min., ESI-MS: *m/z* $[M + H]^+$, calc'd 361.09 for $C_{17}H_{17}N_2O_5S$, found 361.0. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.25 (s, 1H), 7.95 (s, 1H), 7.80 (d, *J* = 8.3 Hz, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.51 (t, *J* = 7.8 Hz, 1H), 7.20 (t, *J* = 7.6 Hz, 1H), 6.91 (dd, *J* = 8.3, 1.9 Hz, 1H), 6.82 (d, *J* = 8.3 Hz, 1H), 6.01 (s, 2H), 2.56 – 2.49 (m, 1H), 1.26 – 1.21 (m, 2H), 0.98 – 0.92 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 148.0, 145.2, 139.4, 133.1, 131.1, 126.9, 123.6, 121.8, 121.4, 114.3, 108.2, 103.6, 101.5, 30.5, 5.8.



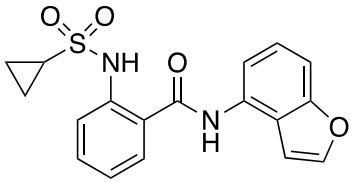
5o

2-(Cyclopropanesulfonamido)-*N*-(2,2-dimethylbenzo[d][1,3]dioxol-5-yl)benzamide (5o). General Procedure A. Yield = 23.0mg (33.8%). LCMS: R_T = 2.66 min., ESI-MS: *m/z* = 389.1 $[M + H]^+$, calc'd 389.12 for $C_{19}H_{21}N_2O_5S$, found 389.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.27 (s, 1H), 7.89 (s, 1H), 7.81 (d, *J* = 8.3 Hz, 1H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.51 (t, *J* = 7.8 Hz, 1H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.16 (d, *J* = 1.6 Hz, 1H), 6.85 (dd, *J* = 8.3, 1.9 Hz, 1H), 6.73 (d, *J* = 8.3 Hz, 1H), 2.56 – 2.49 (m, 1H), 1.71 (s, 6H), 1.26 – 1.21 (m, 2H), 0.98 – 0.92 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 147.9, 145.2, 139.4, 133.0, 130.4, 126.9, 123.6, 121.9, 121.5, 118.8, 113.9, 108.0, 103.5, 30.4, 25.9, 5.8.



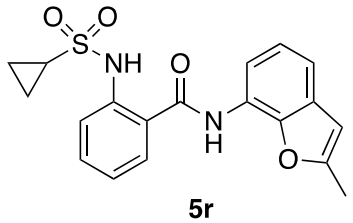
5p

2-(Cyclopropanesulfonamido)-*N*-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)benzamide (5p). General Procedure A. Yield = 8.0mg (12.3%). LCMS: R_T = 2.75 min., ESI-MS: *m/z* $[M + H]^+$, calc'd 397.07 for $C_{17}H_{15}F_2N_2O_5S$, found 397.0. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.11 (s, 1H), 8.02 (s, 1H), 7.81 (d, *J* = 8.3 Hz, 1H), 7.66 (dd, *J* = 8.7, 1.6 Hz, 1H), 7.56 – 7.51 (m, 2H), 7.24 – 7.20 (m, 1H), 7.14 – 7.10 (m, 1H), 7.08 (d, *J* = 8.5 Hz, 1H), 2.56 (tt, *J* = 8.0, 4.8 Hz, 1H), 1.29 – 1.24 (m, 2H), 0.98 (tt, *J* = 5.9, 2.9 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 144.0, 140.9, 139.5, 133.4, 133.1, 127.0, 123.6, 121.4, 121.3, 115.7, 109.5, 104.0, 30.6, 5.9. *Additional carbon peaks due to C-F coupling peaks however, these are overlapping with other aromatic peaks.



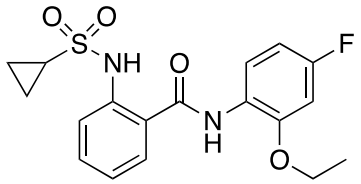
5q

***N*-(Benzofuran-4-yl)-2-(cyclopropanesulfonamido)benzamide (5q).** General Procedure A. Yield = 12.0 mg (25.5%). LCMS: R_T = 2.63 min., ESI-MS: *m/z* $[M + H]^+$, calc'd 357.09 for $C_{18}H_{17}N_2O_4S$, found 357.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.29 (s, 1H), 8.40 (s, 1H), 8.22 (d, *J* = 7.9 Hz, 1H), 7.89 (d, *J* = 8.3 Hz, 1H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.67 (d, *J* = 2.0 Hz, 1H), 7.58 (t, *J* = 7.9 Hz, 1H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.32 (t, *J* = 7.9 Hz, 1H), 7.29 (d, *J* = 4.0 Hz, 1H), 6.88 (d, *J* = 1.9 Hz, 1H), 2.58 – 2.52 (m, 1H), 1.28 – 1.24 (m, 2H), 0.98 – 0.92 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 145.3, 144.7, 139.7, 133.4, 127.8, 127.0, 123.8, 123.7, 122.5, 121.9, 121.7, 117.8, 115.9, 107.6, 30.4, 5.7.



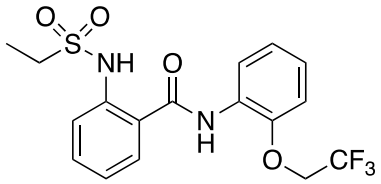
5r

2-(Cyclopropanesulfonamido)-*N*-(2-methylbenzofuran-7-yl)benzamide (5r). General Procedure A. Yield = 15.0 mg (19.5%). LCMS: R_T = 2.80 min., ESI-MS: *m/z* $[M + H]^+$, calc'd 371.11 for $C_{19}H_{19}N_2O_4S$, found 371.0. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.30 (s, 1H), 8.33 (s, 1H), 8.10 (d, *J* = 7.8 Hz, 1H), 7.89 (d, *J* = 8.2 Hz, 1H), 7.80 (d, *J* = 7.7 Hz, 1H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.28 (ddd, *J* = 21.6, 14.5, 7.6 Hz, 4H), 6.46 (s, 1H), 2.57 – 2.53 (m, 1H), 2.51 (s, 3H), 1.27 – 1.23 (m, 2H), 0.98 – 0.92 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 155.5, 144.9, 139.6, 133.3, 129.6, 127.0, 123.8, 123.3, 121.9, 121.9, 121.8, 116.9, 115.0, 103.6, 30.4, 14.1, 5.7.



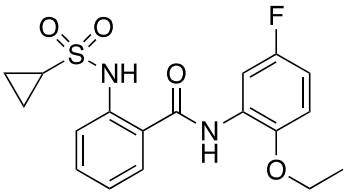
6a

2-(Cyclopropanesulfonamido)-*N*-(2-ethoxy-4-fluorophenyl)benzamide (6a). General Procedure A. Yield = 6.0 mg (10%). LCMS: R_T = 2.665 min, ESI-MS: *m/z* $[M]^+$, calc'd 378.10 for $C_{18}H_{19}FN_2O_4S$, found 378.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.27 (s, 1H), 8.08 (t, *J* = 9.1 Hz, 1H), 7.91 (s, 1H), 7.86 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.68 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.55 (ddd, *J* = 8.6, 7.5, 1.5 Hz, 1H), 7.23 (td, *J* = 7.6, 1.2 Hz, 1H), 6.82 – 6.70 (m, 2H), 4.05 (q, *J* = 7.0 Hz, 2H), 2.58 – 2.48 (m, 1H), 1.45 (t, *J* = 7.0 Hz, 4H), 1.27 – 1.21 (m, 2H), 0.96 (ddd, *J* = 8.0, 3.9, 2.7 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 157.1, 153.2, 139.6, 133.3, 126.9, 123.9, 123.7, 121.7, 121.5, 118.1, 110.2, 110.2, 102.5, 102.3, 64.1, 30.4, 14.7, 5.7. *Additional carbon peaks due to C-F coupling peaks however, these are overlapping with other aromatic peaks.



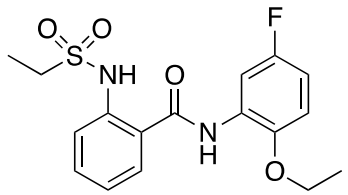
6b

2-(Ethylsulfonamido)-*N*-(4-fluoro-2-(2,2,2-trifluoroethoxy)phenyl)benzamide (6b). General Procedure A. Yield = 22.0 mg (50.3%). LCMS: R_T = 2.84 min., ESI-MS: *m/z* $[M + H]^+$, calc'd 403.09 for $C_{17}H_{18}F_3N_2O_4S$, found 403.0. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.57 (s, 1H), 8.57 (s, 1H), 8.50 – 8.46 (m, 1H), 7.85 (d, *J* = 8.3 Hz, 1H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 1H), 7.22 (t, *J* = 7.6 Hz, 1H), 7.17 (dt, *J* = 10.2, 3.8 Hz, 2H), 6.97 (dd, *J* = 6.0, 3.5 Hz, 1H), 4.52 (q, *J* = 7.9 Hz, 2H), 3.20 (q, *J* = 7.4 Hz, 2H), 1.39 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 146.4, 140.1, 133.6, 127.6, 126.8, 125.0, 123.5, 123.3, 121.2, 120.3, 119.7, 112.1, 66.8, 46.6, 8.2. *Additional carbon peaks due to C-F coupling peaks however, these are overlapping with other aromatic peaks.



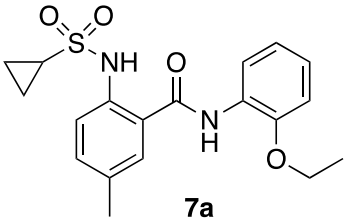
6c

2-(Cyclopropanesulfonamido)-*N*-(2-ethoxy-5-fluorophenyl)benzamide (6c). General Procedure A. Yield = 33.8 mg (40.2%). LCMS: R_T = 2.82 min., ESI-MS: *m/z* $[M + H]^+$, calc'd 379.11 for $C_{18}H_{20}FN_2O_4S$, found 379.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.39 (s, 1H), 8.72 (s, 1H), 8.31 (dd, *J* = 10.4, 2.9 Hz, 1H), 7.87 (d, *J* = 8.3 Hz, 1H), 7.64 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.58 – 7.54 (m, 1H), 7.27 – 7.22 (m, 1H), 6.88 – 6.85 (m, 1H), 6.84 – 6.78 (m, 1H), 4.17 (q, *J* = 7.0 Hz, 2H), 2.55 (ddd, *J* = 9.5, 6.4, 4.0 Hz, 1H), 1.51 (t, *J* = 7.0 Hz, 3H), 1.30 – 1.25 (m, 2H), 0.99 – 0.94 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3, 157.8, 143.7, 139.8, 133.3, 126.6, 123.7, 121.7, 121.7, 111.4, 111.4, 110.2, 110.1, 107.9, 107.7, 65.0, 30.5, 14.9, 5.8. *Additional carbon peaks due to C-F coupling peaks however, these are overlapping with other aromatic peaks.



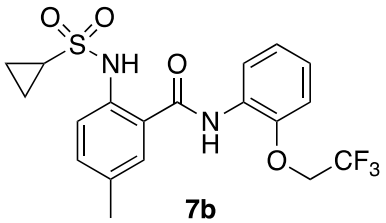
6d

***N*-(2-Ethoxy-5-fluorophenyl)-2-(ethylsulfonamido)benzamide (6d).** General Procedure A. Yield = 33.8 mg (40.2%). LCMS: R_T = 2.82 min., ESI-MS: *m/z* = 389.0 $[M + Na]^+$, calc'd 389.09 for $C_{17}H_{19}N_2O_4SNa$, found 389.0. ^1H NMR (500 MHz, $CDCl_3$) δ 10.54 (s, 1H), 8.73 (s, 1H), 8.30 (dd, *J* = 10.4, 3.0 Hz, 1H), 7.85 (d, *J* = 8.3 Hz, 1H), 7.64 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.58 – 7.53 (m, 1H), 7.24 – 7.19 (m, 1H), 6.87 (dd, *J* = 9.0, 4.9 Hz, 1H), 6.84 – 6.79 (m, 1H), 4.17 (q, *J* = 7.0 Hz, 2H), 3.21 (q, *J* = 7.4 Hz, 2H), 1.51 (t, *J* = 7.0 Hz, 3H), 1.40 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 157.8, 155.9, 143.7, 140.1, 133.5, 126.8, 123.2, 120.3, 119.7, 111.5, 111.4, 110.3, 110.1, 108.0, 107.7, 65.0, 46.7, 14.9, 8.2. *Additional carbon peaks due to C-F coupling peaks however, these are overlapping with other aromatic peaks.



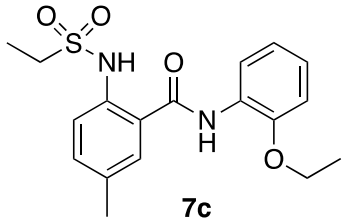
7a

2-(Cyclopropanesulfonamido)-*N*-(2-ethoxyphenyl)-5-methylbenzamide (7a). General Procedure A. LCMS: R_T = 2.96 min., ESI-MS: *m/z* = 375.1 $[M + H]^+$, calc'd 375.14 for $C_{19}H_{23}N_2O_4S$, found 375.1. ^1H NMR (500 MHz, $CDCl_3$) δ 10.16 (s, 1H), 8.65 (s, 1H), 8.43 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.45 (s, 1H), 7.35 (dd, *J* = 8.4, 1.3 Hz, 1H), 7.13 (td, *J* = 7.9, 1.5 Hz, 1H), 7.04 (dd, *J* = 11.2, 4.4 Hz, 1H), 6.95 (dd, *J* = 8.1, 0.8 Hz, 1H), 4.20 (q, *J* = 7.0 Hz, 2H), 2.48 (dq, *J* = 8.1, 4.8 Hz, 1H), 2.43 (s,3H), 1.52 (t, *J* = 7.0 Hz, 3H), 1.24 – 1.19 (m, 2H), 0.93 – 0.88 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3, 147.7, 136.9, 133.8, 133.6, 127.1, 127.0, 124.7, 123.0, 122.6, 121.2, 120.1, 111.0, 64.3, 30.1, 20.9, 14.9, 5.6.



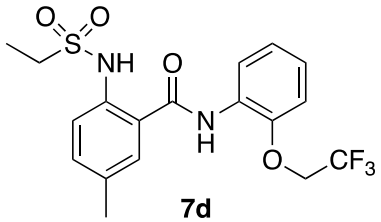
7b

2-(Cyclopropanesulfonamido)-5-methyl-N-(2-(2,2,2-trifluoroethoxy)phenyl)benzamide (7b). General Procedure A. Yield = 36.4 mg (43%). LCMS: R_T = 2.906 min., ESI-MS: *m/z* $[M + H]^+$, calc'd 429.11 for $C_{19}H_{20}F_3N_2O_4S$, found 429.0. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.15 (s, 1H), 8.56 (s, 1H), 8.49 – 8.41 (m, 1H), 7.72 (d, *J* = 8.4 Hz, 1H), 7.42 (s, 1H), 7.34 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.19 – 7.10 (m, 2H), 7.01 – 6.89 (m, 1H), 4.50 (q, *J* = 7.9 Hz, 2H), 2.46 (tt, *J* = 8.0, 4.8 Hz, 1H), 2.39 (s, 3H), 1.21 – 1.14 (m, 2H), 0.89 (qd, *J* = 5.8, 1.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 146.6, 137.4, 134.3, 134.3, 128.0, 127.4, 125.1, 123.9, 122.7, 122.6, 121.3, 112.4, 67.5, 67.2, 67.0, 66.7, 30.4, 21.1, 5.9. *Additional carbon peaks due to C-F coupling peaks however, these are overlapping with other aromatic peaks.



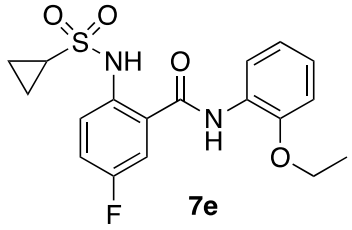
7c

***N*-(2-Ethoxyphenyl)-2-(ethylsulfonamido)-5-methylbenzamide (7c).** General Procedure A. LCMS: R_T = 2.96 min., ESI-MS: *m/z* $[M + H]^+$, calc'd 363.14 for $C_{18}H_{23}N_2O_4S$, found 363.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.36 (s, 1H), 8.67 (s, 1H), 8.42 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.45 (s, 1H), 7.35 (dd, *J* = 8.5, 1.3 Hz, 1H), 7.13 (td, *J* = 7.9, 1.5 Hz, 1H), 7.04 (dd, *J* = 11.2, 4.4 Hz, 1H), 6.95 (dd, *J* = 8.1, 0.8 Hz, 1H), 4.20 (q, *J* = 7.0 Hz, 2H), 3.15 (q, *J* = 7.4 Hz, 2H), 2.42 (s, 3H), 1.53 (t, *J* = 7.0 Hz, 3H), 1.36 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 147.7, 137.3, 133.9, 133.1, 127.3, 127.0, 124.7, 121.3, 121.2, 120.3, 120.1, 111.1, 64.3, 46.3, 20.9, 14.9, 8.1.



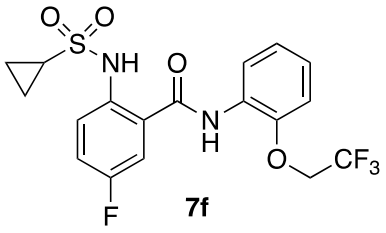
7d

2-(Ethylsulfonamido)-5-methyl-N-(2-(2,2,2-trifluoroethoxy)phenyl)benzamide (7d). General Procedure A. Yield = 55.8 mg (65%). LCMS: R_T = 2.88 min., ESI-MS: *m/z* $[M + H]^+$, calc'd 417.11 for $C_{18}H_{20}F_3N_2O_4S$, found 417.0. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.34 (s, 1H), 8.58 (s, 1H), 8.45 (dd, *J* = 5.9, 3.7 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.42 (s, 1H), 7.37 – 7.29 (m, 1H), 7.19 – 7.08 (m, 2H), 6.94 (dd, *J* = 5.9, 3.6 Hz, 1H), 4.50 (q, *J* = 7.9 Hz, 2H), 3.13 (q, *J* = 7.4 Hz, 2H), 2.38 (s, 3H), 1.34 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 146.6, 137.8, 134.5, 133.6, 128.0, 127.6, 125.2, 123.9, 121.3, 120.9, 120.6, 112.4, 67.6, 67.3, 67.0, 66.7, 46.7, 21.0, 8.5. *Additional carbon peaks due to C-F coupling peaks however, these are overlapping with other aromatic peaks.



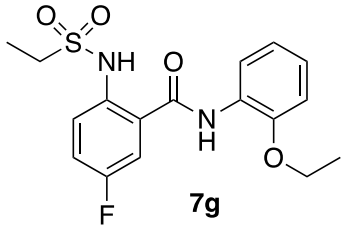
7e

2-(Cyclopropanesulfonamido)-*N*-(2-ethoxyphenyl)-5-fluorobenzamide (7e). General Procedure A. LCMS: R_T = 2.87 min., ESI-MS: *m/z* $[M + H]^+$, calc'd 379.11 for $C_{18}H_{20}FN_2O_4S$, found 379.0. ^{1}H NMR (500 MHz, CDCl3) δ 9.98 (s, 1H), 8.57 (s, 1H), 8.41 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.83 (dd, *J* = 9.1, 4.9 Hz, 1H), 7.35 (dd, *J* = 8.5, 2.9 Hz, 1H), 7.28 – 7.24 (m, 1H), 7.15 (td, *J* = 8.0, 1.6 Hz, 1H), 7.07 – 7.03 (m, 1H), 6.96 (dd, *J* = 8.2, 1.0 Hz, 1H), 4.20 (q, *J* = 7.0 Hz, 2H), 2.46 (tt, *J* = 8.0, 4.8 Hz, 1H), 1.52 (t, *J* = 7.0 Hz, 3H), 1.20 (tt, *J* = 5.7, 3.0 Hz, 2H), 0.92 (qd, *J* = 5.8, 1.0 Hz, 2H). ^{13}C NMR (125 MHz, CDCl3) δ 165.0, 159.8, 157.8, 147.7, 135.3, 135.3, 126.6, 125.2, 125.1, 121.1, 120.2, 120.0, 119.8, 113.4, 113.2, 111.1, 64.4, 30.1, 14.9, 5.6. *Additional carbon peaks due to C-F coupling peaks however, these are overlapping with other aromatic peaks.



7f

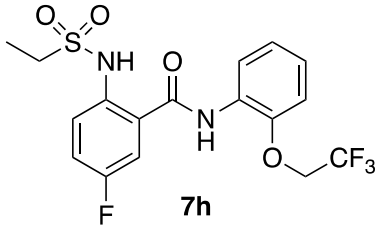
2-(Cyclopropanesulfonamido)-5-fluoro-N-(2-(2,2,2-trifluoroethoxy)phenyl)benzamide (7f). General Procedure A. Yield = 34.7 mg (42%). LCMS: R_T = 2.820 min., ESI-MS: *m/z* = 433.0 $[M + H]^+$, calc'd 433.08 for $C_{18}H_{17}F_4N_2O_4S$, found 433.0. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.91 (s, 1H), 8.42 (dd, *J* = 7.4, 2.1 Hz, 2H), 7.81 (dd, *J* = 9.1, 4.9 Hz, 1H), 7.31 (dd, *J* = 8.5, 2.8 Hz, 1H), 7.29 – 7.24 (m, 1H), 7.17 (pd, *J* = 7.5, 1.7 Hz, 2H), 6.96 (dd, *J* = 7.5, 1.8 Hz, 1H), 4.51 (q, *J* = 7.9 Hz, 2H), 2.49 – 2.38 (m, 1H), 1.21 – 1.14 (m, 2H), 0.98 – 0.86 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 165.5, 160.1, 158.2, 146.8, 135.8, 135.7, 127.6, 125.6, 125.4, 125.4, 124.6, 124.5, 124.5, 123.9, 122.4, 121.6, 120.7, 120.5, 113.7, 113.5, 112.6, 67.5, 67.3, 67.0, 66.7, 30.4, 6.0. *Additional carbon peaks due to C-F coupling peaks however, these are overlapping with other aromatic peaks.



7g

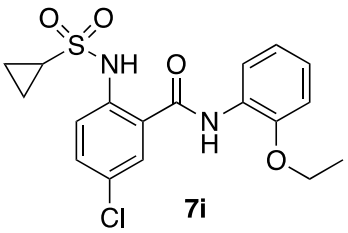
***N*-(2-Ethoxyphenyl)-2-(ethylsulfonamido)-5-fluorobenzamide (7g).** General Procedure A. LCMS: R_T = 2.86 min., ESI-MS: *m/z* $[M + H]^+$, calc'd 367.11 for $C_{17}H_{20}FN_2O_4S$ found 367.0. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (s, 1H), 7.84 (dd, *J* = 9.2, 4.9 Hz, 1H), 7.34 (dd, *J* = 8.6, 2.8 Hz, 1H), 7.28 – 7.24 (m, 1H), 7.15 (td, *J* = 8.0, 1.5 Hz, 1H), 7.05 (dd, *J* = 11.4, 4.1 Hz, 1H), 6.96 (d, *J* = 8.2 Hz, 1H), 4.21 (q, *J* = 7.0 Hz, 2H), 3.15 (q, *J* = 7.4 Hz, 2H), 1.53 (t, *J* = 7.0 Hz, 3H), 1.38 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.0, 159.2, 157.3, 147.7, 135.8, 135.8, 126.6, 125.1, 122.7, 122.6, 121.1, 120.2, 120.1, 113.6, 113.4,

111.1, 64.4, 46.6, 14.9, 8.1. *Additional carbon peaks due to C-F coupling peaks however, these are overlapping with other aromatic peaks.



7h

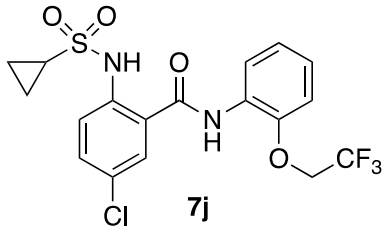
2-(Ethylsulfonamido)-5-fluoro-N-(2-(2,2,2-trifluoroethoxy)phenyl)benzamide (7h). General Procedure A. Yield = 54.5 mg (64%). LCMS: R_T = 2.812 min., ESI-MS: *m/z* $[M + H]^+$, calc'd 421.08 for $C_{17}H_{17}F_4N_2O_4S$, found 421.0. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.14 (s, 1H), 8.44 (s, 1H), 8.40 (dd, *J* = 7.7, 2.0 Hz, 1H), 7.82 (dd, *J* = 9.2, 4.8 Hz, 1H), 7.31 (dd, *J* = 8.6, 2.8 Hz, 1H), 7.26 (ddd, *J* = 9.3, 7.3, 2.9 Hz, 1H), 7.16 (dqd, *J* = 15.2, 7.6, 1.7 Hz, 2H), 6.96 (dd, *J* = 7.8, 1.6 Hz, 1H), 4.51 (q, *J* = 7.9 Hz, 2H), 3.13 (q, *J* = 7.4 Hz, 2H), 1.34 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 165.5, 159.6, 157.6, 146.8, 136.2, 136.2, 127.6, 125.7, 124.6, 123.9, 123.0, 122.9, 122.6, 122.5, 122.4, 121.6, 120.9, 120.7, 113.9, 113.7, 112.6, 67.6, 67.3, 67.0, 66.7, 47.0, 8.4. *Additional carbon peaks due to C-F coupling peaks however, these are overlapping with other aromatic peaks.



7i

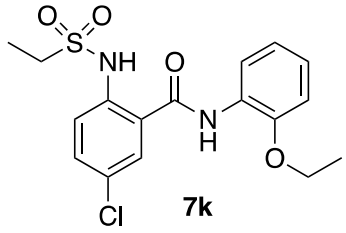
5-Chloro-2-(cyclopropanesulfonamido)-*N*-(2-ethoxyphenyl)benzamide (7i). General Procedure A. LCMS: R_T = 3.02 min., ESI-MS *m/z* $[M + H]^+$, calc'd 395.08 for $C_{18}H_{20}ClN_2O_4S$, found 395.0. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.23 (s, 1H), 8.59 (s, 1H), 8.38 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.82 (d, *J* = 8.9 Hz, 1H), 7.63 (d, *J* = 2.3 Hz, 1H), 7.50 (dd, *J* = 8.9, 2.3 Hz, 1H), 7.16 (td, *J* = 8.0, 1.5 Hz, 1H), 7.07 – 7.02 (m, 1H),

6.96 (dd, *J* = 8.2, 0.8 Hz, 1H), 4.21 (q, *J* = 7.0 Hz, 2H), 2.51 (tt, *J* = 8.0, 4.8 Hz, 1H), 1.53 (t, *J* = 7.0 Hz, 3H), 1.26 – 1.21 (m, 2H), 0.95 (tt, *J* = 5.9, 2.8 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.0, 147.8, 138.1, 132.8, 129.2, 126.7, 126.6, 125.1, 123.9, 123.4, 121.1, 120.3, 111.1, 64.4, 30.4, 14.9, 5.7.



7j

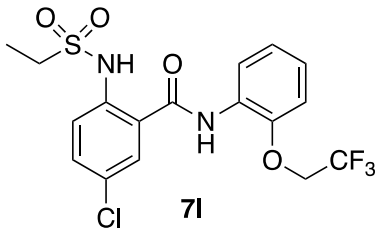
5-Chloro-2-(cyclopropanesulfonamido)-N-(2-(2,2,2-trifluoroethoxy)phenyl)benzamide (7j). General Procedure A. Yield = 49.6 mg (61%). LCMS: R_T = 2.948 min., ESI-MS: *m/z* $[M + H]^+$, calc'd 449.05 for $C_{18}H_{17}ClF_3N_2O_4S$, found 449.0. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.17 (s, 1H), 8.46 (s, 1H), 8.39 (dd, *J* = 7.7, 2.0 Hz, 1H), 7.79 (d, *J* = 8.9 Hz, 1H), 7.60 (d, *J* = 2.3 Hz, 1H), 7.48 (dd, *J* = 8.9, 2.3 Hz, 1H), 7.16 (pd, *J* = 7.5, 1.7 Hz, 2H), 6.96 (dd, *J* = 7.8, 1.6 Hz, 1H), 4.51 (q, *J* = 7.9 Hz, 2H), 2.48 (tt, *J* = 8.0, 4.8 Hz, 1H), 1.24 – 1.17 (m, 2H), 0.94 (qd, *J* = 5.9, 1.1 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 146.8, 138.5, 133.4, 129.7, 127.6, 127.0, 125.7, 123.9, 123.6, 123.6, 121.6, 112.6, 67.6, 67.3, 67.0, 66.7, 30.7, 6.3, 6.1. *Additional carbon peaks due to C-F coupling peaks however, these are overlapping with other aromatic peaks.



7k

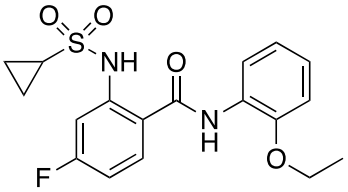
5-Chloro-*N*-(2-ethoxyphenyl)-2-(ethylsulfonamido)benzamide (7k). General Procedure A. LCMS: R_T = 3.02 min., ESI-MS: *m/z* $[M + H]^+$, calc'd 383.08 for $C_{17}H_{20}ClN_2O_4S$, found 383.0. ^{1}H NMR (500 MHz, CDCl3) δ 10.39 (s, 1H), 8.61 (s, 1H), 8.37 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.82 – 7.79 (m, 1H), 7.63 (d, *J* = 2.3 Hz, 1H), 7.49 (dd, *J* = 8.9, 2.3 Hz, 1H), 7.15 (td, *J* = 8.0, 1.5 Hz, 1H), 7.03 (dd, *J* = 11.3, 4.3 Hz, 1H), 6.96

(d, J = 8.2 Hz, 1H), 4.21 (q, 2H), 3.18 (q, J = 7.4 Hz, 2H), 1.54 (t, J = 7.0 Hz, 3H), 1.38 (t, J = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, CDCl3) δ 164.9, 147.8, 138.4, 133.0, 128.6, 126.9, 126.5, 125.2, 122.4, 121.3, 121.1, 120.3, 111.1, 64.4, 46.8, 14.9, 8.2.



7l

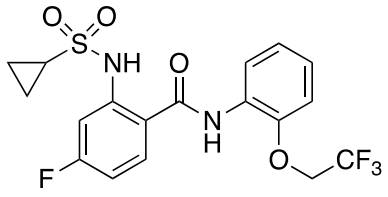
5-Chloro-2-(ethylsulfonamido)-N-(2-(2,2,2-trifluoroethoxy)phenyl)benzamide (7l). General Procedure A. Yield = 52 mg (64%). LCMS: R_T = 2.93 min., ESI-MS: *m/z* [M + H]$^+$, calc'd 437.05 for $C_{17}H_{17}ClF_3N_2O_4S$, found 437.0. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.33 (s, 1H), 8.47 (s, 1H), 8.40 (dd, J = 7.6, 2.0 Hz, 1H), 7.80 (d, J = 8.9 Hz, 1H), 7.60 (d, J = 2.2 Hz, 1H), 7.49 (dd, J = 8.9, 2.3 Hz, 1H), 7.17 (qd, J = 7.8, 6.0 Hz, 2H), 6.96 (dd, J = 7.7, 1.6 Hz, 1H), 4.51 (q, J = 7.9 Hz, 2H), 3.16 (q, J = 7.4 Hz, 2H), 1.36 (t, J = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.1, 146.5, 138.4, 133.3, 128.8, 127.2, 126.9, 125.3, 123.6, 121.7, 121.3, 121.2, 112.2, 67.3, 67.0, 66.7, 66.4, 46.8, 8.1. *Additional carbon peaks due to C-F coupling peaks however, these are overlapping with other aromatic peaks.



7m

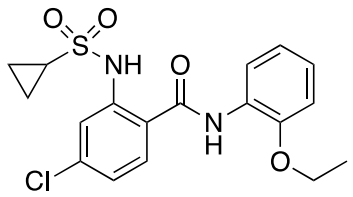
2-(Cyclopropanesulfonamido)-*N*-(2-ethoxyphenyl)-4-fluorobenzamide (7m). General Procedure A. LCMS: R_T = 2.95 min., ESI-MS: *m/z* [M + H]$^+$, calc'd 379.11 for $C_{18}H_{20}FN_2O_4S$, found 379.0. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.83 (s, 1H), 8.58 (s, 1H), 8.40 (dd, J = 8.0, 1.3 Hz, 1H), 7.67 – 7.61 (m, 2H), 7.14 (td, J = 8.0, 1.5 Hz, 1H), 7.04 (dd, J = 11.2, 4.3 Hz, 1H), 6.96 (d, J = 8.1 Hz, 1H), 6.93 – 6.88 (m, 1H), 4.20

(q, J = 7.0 Hz, 2H), 2.59 (tt, J = 8.1, 4.8 Hz, 1H), 1.52 (t, J = 7.0 Hz, 3H), 1.33 – 1.28 (m, 2H), 1.03 – 0.98 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1, 165.6, 164.0, 147.7, 142.4, 142.3, 128.8, 128.7, 126.8, 124.8, 121.1, 120.2, 117.5, 111.0, 110.6, 110.4, 108.0, 107.8, 64.4, 30.7, 14.9, 5.8. *Additional carbon peaks due to C-F coupling peaks however, these are overlapping with other aromatic peaks.



7n

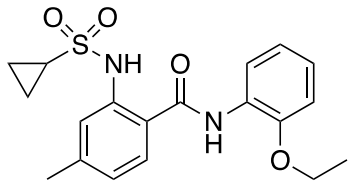
2-(Cyclopropanesulfonamido)-4-fluoro-*N*-(2-(2,2,2-trifluoroethoxy)phenyl)benzamide (7n). General Procedure A. Yield = 33.9 mg (41%). LCMS: R_T = 2.87 min., ESI-MS: *m/z* $[M + H]^+$, calc'd 433.08 for $C_{18}H_{17}F_4N_2O_4S$, found 433.0. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.76 (s, 1H), 8.44 (s, 1H), 8.40 (dd, J = 7.4, 2.3 Hz, 1H), 7.64 – 7.56 (m, 2H), 7.19 – 7.08 (m, 2H), 6.95 (dd, J = 7.5, 1.9 Hz, 1H), 6.93 – 6.84 (m, 1H), 4.50 (q, J = 7.9 Hz, 2H), 2.56 (dq, J = 8.0, 4.8 Hz, 1H), 1.33 – 1.21 (m, 2H), 1.04 – 0.94 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 166.1, 164.5, 146.7, 142.8, 142.7, 129.1, 129.0, 127.8, 125.4, 124.6, 123.8, 122.4, 121.5, 117.2, 117.2, 112.5, 111.1, 110.9, 108.3, 108.1, 67.5, 67.2, 66.9, 66.7, 31.0, 6.1. *Additional carbon peaks due to C-F coupling peaks however, these are overlapping with other aromatic peaks.



7o

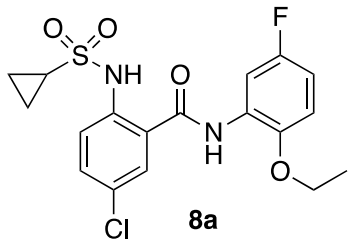
4-Chloro-2-(cyclopropanesulfonamido)-*N*-(2-ethoxyphenyl)benzamide (7o). General Procedure A. LCMS: R_T = 2.95 min., ESI-MS: *m/z* $[M + H]^+$, calc'd 395.08 for $C_{18}H_{20}ClN_2O_4S$, found 395.0. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.64 (s, 1H), 8.60 (s, 1H), 8.40 (dd, J = 8.0, 1.3 Hz, 1H), 7.90 (d, J = 2.0 Hz, 1H), 7.58 (d, J = 8.5 Hz, 1H), 7.20 (dd, J = 8.4, 2.0 Hz, 1H), 7.14 (td, J = 8.0, 1.5 Hz, 1H), 7.04 (dd, J = 11.2,

4.4 Hz, 1H), 6.95 (dd, *J* = 8.1, 0.8 Hz, 1H), 4.19 (q, *J* = 7.0 Hz, 2H), 2.59 (tt, *J* = 8.0, 4.8 Hz, 1H), 1.51 (t, *J* = 7.0 Hz, 3H), 1.30 (tt, *J* = 5.9, 3.0 Hz, 2H), 1.03 – 0.98 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 147.7, 141.0, 139.2, 127.7, 126.7, 124.9, 123.6, 121.2, 120.9, 120.2, 119.8, 111.0, 64.4, 30.7, 14.9, 5.9.



7p

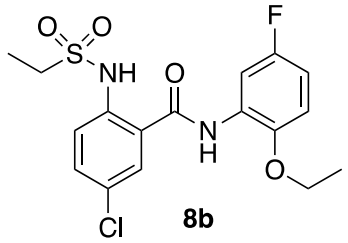
2-(Cyclopropanesulfonamido)-*N*-(2-ethoxyphenyl)-4-methylbenzamide (7p). General Procedure A. LCMS: R_T = 2.97 min., ESI-MS: *m/z* = 375.1 $[M + H]^+$, calc'd 375.14 for $C_{19}H_{23}N_2O_4S$, found 375.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.56 (s, 1H), 8.64 (s, 1H), 8.43 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.68 (s, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.12 (td, *J* = 7.9, 1.5 Hz, 1H), 7.03 (dd, *J* = 11.2, 4.3 Hz, 2H), 6.97 – 6.93 (m, 1H), 4.19 (q, *J* = 7.0 Hz, 2H), 2.54 (dq, *J* = 8.1, 4.8 Hz, 1H), 1.51 (t, *J* = 7.0 Hz, 3H), 1.27 – 1.23 (m, 2H), 0.97 – 0.92 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3, 147.6, 144.0, 139.8, 127.1, 126.6, 124.6, 124.6, 122.1, 121.1, 120.1, 119.5, 111.0, 64.3, 30.3, 21.8, 14.9, 5.7.



8a

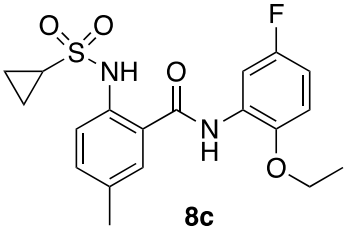
5-Chloro-2-(cyclopropanesulfonamido)-*N*-(2-ethoxy-5-fluorophenyl)benzamide (8a). General Procedure A. Yield = 18.0 mg (24.3%). LCMS: R_T = 3.02 min., ESI-MS: *m/z* $[M + H]^+$, calc'd 413.07 for $C_{18}H_{19}ClFN_2O_4S$, found 413.0. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.17 (s, 1H), 8.64 (s, 1H), 8.24 (dd, *J* = 10.2, 2.9 Hz, 1H), 7.82 (d, *J* = 8.9 Hz, 1H), 7.61 (d, *J* = 2.3 Hz, 1H), 7.51 (dd, *J* = 8.9, 2.3 Hz, 1H), 6.89 – 6.80 (m, 2H), 4.21 – 4.15 (m, 2H), 2.56 – 2.49 (m, 1H), 1.53 (dd, *J* = 9.1, 4.8 Hz, 3H), 1.26 (dt, *J* = 5.7, 4.5

Hz, 2H), 1.00 – 0.95 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.0, 157.8, 155.9, 143.8, 138.2, 133.1, 129.1, 127.4, 127.3, 126.7, 123.3, 123.2, 111.5, 111.5, 110.7, 110.5, 108.0, 107.8, 65.0, 30.5, 14.9, 5.8. *Additional carbon peaks due to C-F coupling peaks however, these are overlapping with other aromatic peaks.



8b

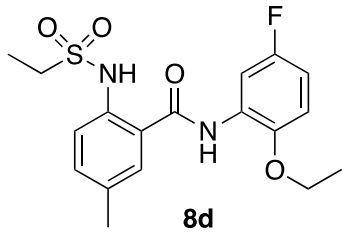
5-Chloro-*N*-(2-ethoxy-5-fluorophenyl)-2-(ethylsulfonamido)benzamide (8b). General Procedure A. Yield = 17.0 mg (23.4%). LCMS: R_T = 3.00 min., ESI-MS: *m/z* $[M + H]^+$, calc'd 401.07 for $C_{17}H_{19}ClFN_2O_4S$, found 401.0. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.32 (s, 1H), 8.65 (s, 1H), 8.23 (dd, *J* = 10.2, 2.9 Hz, 1H), 7.82 – 7.79 (m, 1H), 7.60 (d, *J* = 2.3 Hz, 1H), 7.50 (dd, *J* = 8.9, 2.3 Hz, 1H), 6.87 (dd, *J* = 9.0, 4.9 Hz, 1H), 6.85 – 6.80 (m, 1H), 4.18 (dt, *J* = 11.5, 4.8 Hz, 2H), 3.19 (q, *J* = 7.4 Hz, 2H), 1.55 – 1.51 (m, 3H), 1.39 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.0, 157.7, 155.8, 143.8, 138.5, 133.3, 128.6, 127.4, 127.3, 126.9, 121.8, 121.3, 111.5, 111.5, 110.7, 110.5, 108.0, 107.8, 65.0, 46.9, 14.9, 8.2. *Additional carbon peaks due to C-F coupling peaks however, these are overlapping with other aromatic peaks.



8c

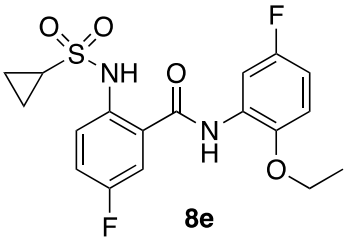
2**-(Cyclopropanesulfonamido)-*N*-(2-ethoxy-5-fluorophenyl)-5-methylbenzamide (8c).** General Procedure A. Yield = 19.0 mg (27.1%). LCMS: R_T = 2.98 min., ESI-MS: *m/z* = 393.0 $[M + H]^+$. ^{1}H NMR

(500 MHz, $CDCl_3$) δ 10.11 (s, 1H), 8.70 (s, 1H), 8.28 (dd, *J* = 10.3, 3.0 Hz, 1H), 7.75 – 7.70 (m, 1H), 7.42 (s, 1H), 7.38 – 7.33 (m, 1H), 6.86 (dd, *J* = 9.0, 4.9 Hz, 1H), 6.82 – 6.77 (m, 1H), 4.17 (q, *J* = 7.0 Hz, 2H), 2.48 (ddt, *J* = 11.0, 7.9, 3.9 Hz, 1H), 2.42 (s, 1H), 1.52 (t, *J* = 7.0 Hz, 3H), 1.25 – 1.20 (m, 2H), 0.95 – 0.89 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3, 157.8, 155.9, 143.7, 143.7, 137.1, 133.9, 133.8, 127.9, 127.8, 127.0, 122.4, 122.3, 111.5, 111.4, 110.2, 110.0, 107.8, 107.6, 65.0, 30.2, 20.9, 14.9, 5.7. *Additional carbon peaks due to C-F coupling peaks however, these are overlapping with other aromatic peaks.



8d

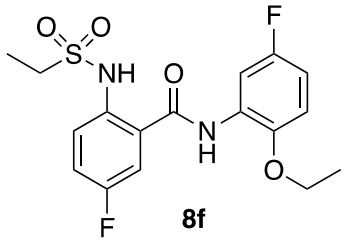
***N*-(2-Ethoxy-5-fluorophenyl)-2-(ethylsulfonamido)-5-methylbenzamide (8d).** General Procedure A. Yield = 22.0 mg (32.0%). LCMS: R_T = 2.97 min., ESI-MS: *m/z* $[M + H]^+$, calc'd 381.13 for $C_{18}H_{22}FN_2O_4S$, found 381.0. ^1H NMR (500 MHz, $CDCl_3$) δ 10.31 (s, 1H), 8.72 (s, 1H), 8.26 (dd, *J* = 10.4, 3.0 Hz, 1H), 7.72 (d, *J* = 8.5 Hz, 1H), 7.41 (s, 1H), 7.35 (d, *J* = 8.5 Hz, 1H), 6.86 (dd, *J* = 9.0, 4.9 Hz, 1H), 6.82 – 6.76 (m, 1H), 4.17 (q, *J* = 7.0 Hz, 2H), 3.15 (q, *J* = 7.4 Hz, 2H), 2.41 (s, 3H), 1.52 (t, *J* = 7.0 Hz, 3H), 1.36 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 157.8, 155.9, 143.8, 143.8, 137.4, 134.2, 133.1, 127.8, 127.7, 127.3, 120.6, 120.2, 111.5, 111.4, 110.2, 110.0, 107.8, 107.6, 65.0, 46.4, 20.8, 14.9, 8.1. *Additional carbon peaks due to C-F coupling peaks however, these are overlapping with other aromatic peaks.



8e

2-(Cyclopropanesulfonamido)-*N*-(2-ethoxy-5-fluorophenyl)-5-fluorobenzamide (8e). General Procedure A. Yield = 19.0 mg (26.5%). LCMS: R_T = 2.87 min., ESI-MS: *m/z* $[M + H]^+$, calc'd 397.10 for

$C_{18}H_{19}F_2N_2O_4S$, found 397.0. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.93 (s, 1H), 8.62 (s, 1H), 8.28 (dd, *J* = 10.2, 2.9 Hz, 1H), 7.84 (dd, *J* = 9.1, 4.9 Hz, 1H), 7.33 (dd, *J* = 8.5, 2.8 Hz, 1H), 7.31 – 7.27 (m, 1H), 6.88 (dd, *J* = 9.0, 5.0 Hz, 1H), 6.86 – 6.81 (m, 1H), 4.18 (q, *J* = 7.0 Hz, 2H), 2.51 – 2.44 (m, 1H), 1.52 (t, *J* = 7.0 Hz, 3H), 1.25 – 1.20 (m, 2H), 0.96 – 0.92 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.0, 159.7, 157.7, 155.8, 143.7, 135.5, 127.4, 127.4, 125.1, 125.0, 124.1, 124.1, 120.3, 120.1, 113.3, 113.2, 111.5, 111.4, 110.6, 110.4, 108.0, 107.7, 65.0, 30.2, 14.9, 5.7. *Additional carbon peaks due to C-F coupling peaks however, these are overlapping with other aromatic peaks.



8f

***N*-(2-Ethoxy-5-fluorophenyl)-2-(ethylsulfonamido)-5-fluorobenzamide (8f).** General Procedure A. Yield = 18.0 mg (25.8%). LCMS: R_T = 2.87 min., ESI-MS: *m/z* $[M + H]^+$, calc'd 385.10 for $C_{17}H_{19}F_2N_2O_4S$, found 385.0. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.15 (s, 1H), 8.64 (s, 1H), 8.24 (dd, *J* = 10.2, 2.9 Hz, 1H), 7.83 (dd, *J* = 9.1, 4.8 Hz, 1H), 7.32 (dd, *J* = 8.5, 2.8 Hz, 1H), 7.28 (ddd, *J* = 10.3, 6.7, 2.9 Hz, 1H), 6.90 – 6.85 (m, 1H), 6.85 – 6.79 (m, 1H), 4.18 (q, *J* = 7.0 Hz, 2H), 3.16 (q, *J* = 7.4 Hz, 2H), 1.52 (t, *J* = 7.0 Hz, 3H), 1.38 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.0, 164.9, 159.1, 157.7, 157.2, 155.8, 143.8, 143.8, 135.9, 135.9, 127.4, 127.3, 122.6, 122.6, 122.2, 122.2, 120.5, 120.4, 113.6, 113.4, 111.5, 111.4, 110.6, 110.5, 108.0, 107.8, 65.0, 46.7, 14.9, 8.1. *Additional carbon peaks due to C-F coupling peaks however, these are overlapping with other aromatic peaks.

In Vitro Pharmacology Methods

Cell based Ca2+ imaging assay to determine MrgX1 PAM activities. Ca^{2+} imaging assay was employed to determine the effect of PAMs on MrgX1 activation by its agonist BAM8-22 using a HEK293 cell line that stably expresses MrgX1 protein. The assay was developed and published in our previous study.[1] MrgX1-expressing HEK293 cells were plated into 96-well plates. On the following day, cells were incubated with Ca^{2+} sensitive dye Fluo4 solution at 37 °C for 30 min and at RT for 30 min after removing media. 5 μM PAM compounds were added to the assay buffer with dye for 80 sec followed by adding 10 nM BAM8-22 (EC_{20} of the agonist activating MrgX1) for 75 sec and recorded the change of fluorescence by Flexstation3 imaging plate reader. A previously characterized MrgX1 PAM ML382 was included on each plate as a positive control. PAM effect on MrgX1 activation was evaluated by the calculated fluorescence ratio and compared to the effect of ML382. If a new PAM compound exhibited a comparable or stronger effect as ML382 did, the EC_{50}s of the compound effect (i.e., enhancing MrgX1 activation by BAM8-22) was then determined from a dose response curve by repeating the assay with a series of 10 doses (from 0.04 nM to 10 μM) of the compound. The Emax of a new PAM was determined by normalizing its maximum effect with that of ML382.

1. Wen, W.; Wang, Y.; McManus, O. B.; Wu, M.; Li, M.; Lindsley, C. W.; Dong, X.; Hopkins, C. R. Discovery and characterization of 2-(cyclopropanesulfonamido)-*N*-(2-ethoxyphenyl)benzamide, ML382: a potent and selective positive allosteric modulator of MrgX1. *ChemMedChem* **2015**, *10*, 57-61.

Table S1. MrgX2 Selectivity

Cmpd	MrgX1, EC_{50} (μM)	MrgX2, %Activation
1	0.124	ND
5c	0.506	ND
5d	0.502	ND
5r	1.04	ND
6b	1.40	ND
6c	0.014	0.33 ± 30.7
7a	0.103	14.4 ± 26.5
7e	0.173	48.5 ± 25.9
7g	0.098	35.4 ± 3.7
7i	0.054	156.2 ± 3.0
8a	0.055	64.2 ± 24.0
8c	0.069	-8.8 ± 10.9
8d	0.080	-8.3 ± 18.7
8e	0.013	-2.1 ± 9.1
8f	0.031	9.2 ± 20.4

Table S2. MrgX1 PDSP Selectivity

Receptor	% Inhibition at 10 μM (Ki, nM)		
	6c	**8c**	**8e**
5-HT1A	-0.5	2.0	-16.5
5-HT1B	17.6	-10.3	-18.1
5-HT1D	1.2	3.1	-6.7
5-HT1E	-0.2	7.1	-4.1
5-HT2A	3.5	-0.4	2.9
5-HT2B	43.1	18.8	6.6
5-HT2C	45.1	16.4	16.0
5-HT3	-23.1	12.2	-12.8
5-HT5A	6.6	-7.5	-20.6
5-HT6	-6.0	17.5	11.7
5-HT7A	-28.2	-6.6	-39.9
Alpha1A	9.9	-9.0	-20.0
Alpha1B	-1.1	-12.6	-4.7
Alpha1D	-3.6	-3.4	-8.9
Alpha2A	4.9	8.4	-8.8
Alpha2B	8.8	10.3	7.1
Alpha2C	18.9	2.5	-0.9
Beta1	-3.0	-1.3	15.3
Beta2	11.3	-6.5	-3.5
Beta3	-3.1	-2.7	-19.0
BZP Rat Brain Site	13.6	19.4	20.2
D1	22.3	5.9	12.1
D2	-9.6	-10.9	-11.6
D3	1.7	43.3	16.5
D4	13.1	6.7	-0.4
D5	50.5 (4,131)	-6.6	18.9
DAT	-17.2	19.3	19.9
DOR	-1.6	-15.2	-12.1
GABAA	2.8	-4.9	19.5
H1	55.2 (5,569)	54.0 (1,089.4)	-20.3
H2	-1.2	5.8	-0.4
H3	-1.7	4.0	-4.7
H4	4.5	-8.7	-6.3
KOR	24.2	29.8	-9.4
M1	-3.2	22.1	4.7
M2	6.4	-1.8	30.6
M3	29.4	-25.9	-37.2
M4	42.7	-2.4	-5.1
M5	2.2	-16.6	2.8
MOR	-11.1	-0.2	-0.8
NET	7.7	-29.0	-34.0

PBR	94.6 (271)	92.1 (28.4)	96.4 (71.6)
SERT	-29.3	3.0	22.3
Sigma 1	18.2	36.5	47.3
Sigma 2	55.0 (5,169)	-11.0	-3.2