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Supporting Information Available. Table S1, elemental analyses. **Figure S1.** (Compounds **S5**, **S6**, **S7** and **S8** were reported previously and are pictured here for the reader's convenience.) This material is available free of charge via the Internet at http://pubs.acs.org.

Chemistry General. Melting points were determined using a Thomas-Hoover capillary melting point apparatus and are reported without correction. Mass spectrometric analysis was provided by the Emory University Mass Spectrometry Center. Routine proton and carbon NMR spectra measured during synthesis were obtained on a Varian Inova-400 (400 MHz). Solvents for NMR were deuteriochloroform ($CDCl_3$) (residual shifts: δ 7.26 for ^1H and δ 77.7 for ^{13}C) and deuteriomethyl sulfoxide (DMSO-d_6; residual shift: δ

2.5 for ^{1}H). The residual shifts were taken as internal references and reported in parts per million (ppm). TLC and preparative thin-layer chromatographies (PTLC) were performed on precoated, glass-backed plates (silica gel 60 F_{254}; 0.25 mm thickness) from EM Science and were visualized by UV lamp. Column chromatography was performed with silica gel (230-400 mesh ASTM) using the "flash" method. Elemental analyses were performed by Atlantic Microlab Inc. Norcross, Georgia. All solvents and other reagents were purchased from Aldrich Chemical Co., Milwaukee. The reagents were used as received. All reactions were performed under anhydrous nitrogen atmosphere in oven-dried glassware.

General procedures for synthesis of 4-amino-sulfonamide 7.

Pyridine (11.0 mmol, 1.1eq) was added to a solution of 4-nitro-benzenesulfonyl chloride (10.0 mmol, 2.22g) and amine (11.0 mmol, 1.1eq) in CH_2Cl_2 (20ml) at 0^{o}C. The reaction mixture was allowed to warm up to room temperature and stirred for 10h. The reaction was quenched by addition of 1N HCl (15ml) and extracted with CH_2Cl_2 (3x15ml). The organic solution was dried (Na_2SO_4) and evaporated to obtain 4-nitro-sulfonamide**.** The latter was subjected to reduction without further purification.

4-Nitro-sulfonamide (1.0 mmol) in EtOAc was stirred with $SnCl_2.2H_2O$ (5.0 mmol) at room temperature for at least 8h until starting material disappeared by TLC. The reaction mixture was poured into saturated aqueous $NaHCO_3$ (10 ml), extracted with EtOAc (3x20ml). The EtOAc extracts were washed with saturated aqueous $NaHCO_3$ (10ml) a second time and dried (Na_2SO_4). Products were purified by chromatography over silica gel.

Compounds 2a-o were synthesized by the same procedure as compound 1.

Compound 2a(ns-8): ^{1}H NMR (400 MHz, $CDCl_3$) δ1.79 (4H, t, J=6.8Hz), 3.26(4H,t, J=6.8Hz), 7.60-7.69 (4H, m), 7.76-7.86 (5H, m). Anal. Calcd for $C_{18}H_{17}F_3N_2O_3S$: C, 54.27; H,4.30 ; N, 7.03. Found: C, 54.26; H, 4.64; N, 7.74.

Compound 2b (ns-9): ^{1}H NMR (400 MHz, $CDCl_3$) δ1.78 (4H, t, J=6.8Hz), 3.26(4H,t, J=6.8Hz), 7.79-7.87 (6H, m), 8.0-8.02 (3H, m), 7.84-7.87 (3H, m). Anal. Calcd for $C_{18}H_{17}F_3N_2O_3S$: C, 54.27; H,4.30 ; N, 7.03. Found: C, 54.20; H, 4.32; N, 7.04.

Compound 2c (ns-10): ^{1}H NMR (400 MHz, $CDCl_3$) δ1.76-1.80 (4H, m), 3.26 (4H,t, J=6.8Hz), 7.69 (1H, t, J=8.0Hz)), 7.82-7.88 (5H, m), 8.0 (1H, s), 8.08 (1H, d, J=7.6Hz), 8.14 (s, 1H). Anal. Calcd for $C_{18}H_{17}F_3N_2O_3S$: C, 54.27; H, 4.30 ; N, 7.03. Found: C, 54.01; H, 4.37; N, 7.10.

Compound 2d (as-36b): ^{1}H NMR (600 MHz, $CDCl_3$) δ1.77 (4H, t, J=7.2Hz), 3.25 (4H,t, J=6.6 Hz), 4.65 (2H, s), 7.55 (2H, d, J=7.8Hz), 7.82 (2H, d, J=8.4Hz), 7.85 (2H, d, J=7.8Hz), 7.89 (2H, d, J=7.8Hz), 7.96 (s, 1H). Anal. Calcd for $C_{18}H_{19}ClN_2O_3S$: C, 57.06; H,5.05 ; N, 7.39. Found: C, 56.21; H, 5.18; N, 7.57.

Compound 2e (as-60a): ^{1}H NMR (400 MHz, $CDCl_3$) δ1.61 (4H, m), 3.09(4H, m), 7.05-7.11 (4H, m), 7.64-7.76 (5H, m). Anal. Calcd for $C_{17}H_{17}FN_2O_3S$: C, 58.61; H, 4.92 ; N, 8.04. Found: C, 58.14; H, 5.12; N, 8.08.

Compound 2f (as-36a): ^{1}H NMR (600 MHz, $CDCl_3$) δ1.77 (4H, t, J=6.6 Hz), 3.25 (4H, t, J=6.6Hz), 7.66 (2H, d, J=8.4Hz), 7.76 (2H, d, J=7.8Hz), 7.80-7.84 (4H, m), 8.0 (1H, s). Anal. Calcd for $C_{17}H_{17}BrN_2O_3S$: C, 49.89; H, 4.19 ; N, 6.84. Found: C, 49.75; H, 4.23; N, 6.84.

Compound 2g (as-40): ^{1}H NMR (400 MHz, $CDCl_3$) δ1.79 (4H, m), 3.23(4H, m), 7.37 (1H, dd, J=20Hz, J=11.2Hz), 7.83-7.89 (4H, m), 8.50 (1H, dd, J=2.4Hz, 6.0Hz), 8.57 (1H, d, J=11.2Hz). Anal. Calcd for $C_{18}H_{16}F_4N_2O_3S$: C, 51.92; H, 3.87 ; N, 6.73; Found: C, 51.69; H, 3.98; N, 6.57.

Compound 2h (as-60b): ^{1}H NMR (400 MHz, $CDCl_3$) δ1.78 (4H, t, J=6.4 Hz), 3.25 (4H, t, J=6.8Hz), 6.92 (1H, dd, J=3.2Hz, 8.8Hz), 7.23 (1H, d,

J=3.2Hz), 7.53 (1H, d, J=9.2Hz), 7.80-7.87 (4H, m), 7.96 (s, 1H). Anal. Calcd for $C_{18}H_{19}BrN_2O_4S$: C, 49.21; H, 4.36 ; N, 6.38; Found: C, 49.18; H, 4.29; N, 6.42.

Compound 2i (as-61d): ^{1}H NMR (400 MHz, DMSO-d_6) δ1.78 (4H, t, J=6.4 Hz), 3.12 (4H, t, J=6.4Hz), 6.55 (1H, dd, J=2.0Hz, 8.4Hz), 6.65 (1H, d, J=8.4Hz), 7.75 (2H, d, J=8.8Hz), 7.92 (4H, d, J=8.8Hz), 10.53 (s, 1H). Anal. Calcd for $C_{17}H_{18}ClN_3O_3S$: C, 53.75; H, 4.78 ; N, 11.06; Found: C, 53.38; H, 4.79; N, 10.44.

Compound 4 (as-101): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.74-1.78 (4H, m), 3.21-3.24 (4H, m), 4.25 (3H, s), 7.79-7.84 (4H, m), 8.66 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 25.41, 42.04, 48.15, 92.22, 120.32, 129.07, 133.34, 135, 20, 140.62, 155.94. Anal. Calcd for $C_{16}H_{16}BrF_3N_4O_3S$: C, 39.93; H, 3.35 ; N, 11.64. Found: C, 40.20; H, 3.36; N, 11.21.

Compound 9a (jm1-98): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (3H, d, J=7.0 Hz), 1.49-1.60 (9H, m), 2.98 (1H, td, J=13.3, 2.3 Hz), 3.69 (1H, bd, J=13.3 Hz), 4.23 (1H, m), 4.65 (2H, q, J=7.8 Hz), 6.94 (1H, s), 7.70 (2H, d, J=8.8 Hz), 7.81 (2H, d, J=8.8 Hz), 7.82 (1H, s). Anal. Calcd for $C_{16}H_{16}BrF_3N_4O_3S$: C, 51.34; H, 5.22 ; N, 12.61. Found: C, 52.45; H, 5.54; N, 11.58.

Compound 9b (jm1-89b): ^{1}H NMR (400 MHz, $CDCl_3$) δ1.06 (3H, d, J=7.0 Hz), 1.30-1.45 (2H, m), 1.53 (6H, d, J=7.0 Hz), 1.55-1.60 (4H, m), 2.97 (1H,

td, J=13.3, 2.3 Hz), 3.66 (1H, bd, J=13.3 Hz), 4.21 (1H, m), 5.48 (1H, m), 6.98 (1H, s), 7.68 (2H, d, J=8.6 Hz), 7.74 (2H, d, J=8.6 Hz), 8.12 (1H, s). Anal. Calcd for $C_{16}H_{16}BrF_3N_4O_3S$: C, 52.39; H, 5.50 ; N, 12.22. Found: C, 52.44; H, 5.51; N, 11.79.

Compound 9c (as-252): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.78 (4H, t, J=6.4Hz), 3.24(4H, t, J=6.8Hz), 5.84 (2H, s), 7.01 (1H, s), 7.28-7.35 (5H, m), 7.70 (2H, d, J=8.8Hz), 7.74 (1H,s), 7.83 (2H, d, J=8.8Hz). Anal. Calcd for $C_{24}H_{25}F_3N_4O_3S$: C, 56.91; H,4.97 ; N, 11.06. Found: C, 56.95; H, 5.09; N, 11.06.

Compound 13 (as-73b): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.71-1.74 (m, 4H), 3.19 (t, 4H, J=6.8Hz), 3.76 (s, 3H), 7.10 (s, 1H), 7.48 (dd, 1H, J=1.6Hz, 7.8Hz), 7.57 (d, 2H, J=8.8Hz), 7.62 (dd, 1H, J=1.2Hz, 7.6Hz), 7.67 (dd, 1H, J=1.6Hz, 7.6Hz), 7.75 (d, 2H, J=8.8Hz), 8.04 (dd, 1H, J=1.6Hz, 8.0Hz), 8.30 (s, 1H).

Anal. Calcd for $C_{23}H_{21}F_3N_4O_5S$: C, 52.87; H, 4.05. Found: C, 52.63; H, 4.60.

Compound 14 (as-77): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.74 (4H, t, J=6.8Hz), 3.2 (4H, t, J=6.8Hz), 7.15 (s, 1H), 7.52 (1H, d, J=8.0Hz), 7.59 (2H, d, J=8.8Hz), 7.64 (1H, d, J=6.8Hz), 7.71 (2H, d, J=8.4Hz), 7.75 (1H, dd, J=1.6Hz, 7.8Hz), 8.11 (1H, dd, J=1.2Hz, 7.8Hz), 8.33 (1H, s). Anal.

Calcd for $C_{22}H_{19}F_3N_4O_5S$. H_2O: C, 50.19; H, 4.02; N, 10.64. Found: C, 50.80; H, 4.20; N, 10.13.

Compound 15a (as-136a): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43-1.44 (m, 2H), 1.63-1.66 (m, 4H), 3.02 (t, 2H, J=3.6Hz), 4.28 (s, 3H), 6.98 (s, 1H), 7.75 (d, 1H, J=6.0Hz), 7.78 (d, 1H, J=6.0Hz), 7.84 (s, 1H). Anal. Calcd for $C_{17}H_{19}F_3N_4O_3S$: C, 49.03; H, 4.60 ; N, 13.45. Found: C, 49.14; H, 4.64; N, 13.40.

Compound 15b (as-125c): ^{1}H NMR (400 MHz, $CDCl_3$) δ1.07 (d, 3H, J=4.8Hz), 1.30-1.37 (m, 1H), 1.43 (d, 1H, J=6.0Hz), 1.51-1.56 (m, 1H), 2.98 (dt, 1H, J1=8.8 Hz, J2=1.6Hz), 3.64 (d, 1H, 8.0Hz), 7.16 (s, 1H), 7.78-7.81 (m, 4H), 8.57 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 15.61, 18.23, 25.33, 30.47, 40.54, 40.59, 48.91, 105.98, 120.02, 120.62, 121.81, 128.22, 136.38, 136.79, 141.00, 157.38. Anal. Calcd for $C_{18}H_{21}F_3N_4O_3S$: C, 50.23; H, 4.92; N, 13.02. Found: C, 50.34; H, 5.00; N, 12.71.

Compound 15c (as-127): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (d, 3H, J=3.6Hz), 1.33-1.36 (m, 4H), 1.76 (d, 2H, J=7.6Hz), 2.36 (t, 2H, J=7.8Hz), 3.79 (d, 2H, J=8.0Hz), 4.35 (s, 3H), 7.26 (s, 1H), 7.76 (d, 2H, J=6.0Hz), 7.89 (d, 2H, J=5.6Hz), 8.73 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 21.58, 30.20, 33.35, 40.60, 46.64, 106.03, 120.52, 128.92, 131.32, 141.54, 157.47.

Anal. Calcd for $C_{18}H_{21}F_3N_4O_3S$: C, 50.23; H, 4.92; N, 13.02. Found: C, 50.14; H, 4.99; N, 12.86.

Compound 15d (as-125b): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (6H, d, J=7.2Hz), 1.45-1.55 (m, 6H), 4.17-4.22 (m, 2H), 4.27 (s, 3H), 6.97 (s, 1H), 7.70 (d, 2H, J=8.8Hz), 7.80 (s, 1H), 7.83 (d, 2H, J=8.8Hz). Anal. Calcd for $C_{19}H_{23}F_3N_4O_3S$: C, 51.34; H, 5.22; N, 12.61. Found: C, 51.41; H, 5.34; N, 12.15.

Compound 15e (yy-0169a): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (3H, t, *J*=7.2 Hz), 1.41-1.69 (8H, m), 2.96-3.03 (1H, m), 3.73-3.77 (1H, m), 3.91-3.96 (1H, m), 4.27 (3H, s), 7.01 (1H, s), 7.70 (2H, d, *J*=8.8 Hz), 7.82 (2H, d, *J*=8.8 Hz), 7.95 (1H, s); Anal. Calcd for $C_{19}H_{23}F_3N_4O_3S$: C, 51.34; H, 5.22; N, 12.61. Found: C, 51.36; H, 5.24; N, 12.50.

Compound 15f (as-124a): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.56-1.59 (m, 4H), 1.66-1.70 (m, 4H), 3.26 (4H, t, J=6.0Hz), 4.26 (s, 3H), 7.10 (s, 1H), 7.69-7.73 (m, 4H), 8.27 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 27.07, 29.28, 40.68, 48.45, 120.62, 128.32, 135.52, 136.31, 140.73, 157.28. Anal. Calcd for $C_{18}H_{21}F_3N_4O_3S$: C, 50.23; H, 4.92; N, 13.02. Found: C, 49.71; H, 4.92; N, 12.78.

Compound 15g (as-124f): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62-1.71 (m, 10H), 3.12 (4H, t, J=4.0Hz), 4.25 (s, 3H), 7.14 (s, 1H), 7.65-7.69 (m, 4H),

8.42 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 25.19, 26.71, 27.88, 40.61, 48.95, 105.91, 120.81, 121.80, 128.37, 134.54, 136.34, 140.86, 157.36. Anal. Calcd for $C_{19}H_{23}F_3N_4O_3S$: C, 51.34; H, 5.22; N, 12.61. Found: C, 51.43; H, 5.27; N, 12.29.

Compound 15j (as-103): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.91 (t, 2H, J=8.0Hz), 3.93 (t, 2H, J=8.6Hz), 4.24 (s, 3H), 6.96 (d, 1H, J=7.2Hz), 7.0 (dd, 1H, J=1.2Hz, 7.6Hz), 7.09 (d, 1H, J=7.6Hz), 7.20 (t, 1H, J=7.6Hz), 7.62 (d, 1H, J=8.4Hz), 7.66-7.69 (m, 2H), 7.78-7.81 (m, 2H), 7.87 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 28.07, 40.61, 50.21, 105.34, 115.17, 120.14, 124.22, 125.45, 128.02, 128.97, 131.96, 141.35. Anal. Calcd for $C_{20}H_{17}F_3N_4O_3S$: C, 53.33; H, 3.80; N, 12.44. Found: C, 52.92; H, 3.57; N, 12.18.

Compound 15k (yy-0187a): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.63-1.66 (1H, m), 1.84-1.87 (1H, m), 1.99-2.04 (1H, m), 2.19-2.25 (2H, m), 2.23-2.25 (1H, m), 3.79-3.82 (1H, m), 3.96-3.98 (1H, m), 4.21-4.23 (1H, m), 4.26 (3H, s), 7.05 (1H, s), 7.73 (2H, d, *J*=8.8 Hz), 7.81 (2H, d, *J*=8.8 Hz), 8.20 (1H, s); Anal. Calcd for $C_{18}H_{18}F_6N_4O_3S$: C, 44.63; H, 3.75; N, 11.57. Found: C, 44.70; H, 3.76; N, 11.32.

Compound 15l (as-625): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (2H, t, J=6.0 Hz), 2.67 (2H, t, J=6.0Hz), 3.14 (2H, t, J=6.0Hz), 3.21 (2H, t, J=6.0Hz), 3.78

(3H, s), 4.27 (3H, s), 7.0(1H, s), 7.77 (4H, br), 7.88 (1H, s). HRMS calcd for $C_{18}H_{20}F_3N_5O_4S$: 457.12831; found: 458.11204 M+1. Anal. Calcd for $C_{18}H_{20}F_3N_5O_4S$: C, 47.06; H, 4.39; N, 15.24. Found: C, 46.51; H, 4.39; N, 14.57.

Compound 15m (yy-0233a): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.72 (6H, s), 4.28 (3H, s), 7.01 (1H, s), 7.76-7.80 (4H, s), 7.95 (1H, s); Anal. Calcd for $C_{14}H_{15}F_3N_4O_3S$: C, 44.68; H, 4.02; N, 14.89. Found: C, 44.86; H, 4.04; N, 14.62.

Compound 15n (as-154): ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.14 (t, 6H, J=7.2Hz), 3.24 (q, 4H, J=7.2Hz), 4.27 (s, 3H), 7.0 (s, 1H), 7.70 (d, 1H, J=8.4Hz), 7.79 (d, 1H, J=9.0Hz), 7.92 (s, 1H). Anal. Calcd for $C_{16}H_{19}F_3N_4O_3S$: C, 47.52; H, 4.74; N, 13.85. Found: C, 47.41; H, 4.72; N, 13.81.

Compound 15o (yy-0213a): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (12H, d, *J*=7.2 Hz), 3.68-3.71 (2H, m), 4.27 (3H, s), 7.05 (1H, s), 7.64 (2H, d, *J*=8.8 Hz), 7.80 (2H, d, *J*=8.8 Hz), 8.02 (1H, s); Anal. Calcd for $C_{18}H_{23}F_3N_4O_3S$: C, 49.99; H, 5.36; N, 12.96. Found: C, 50.18; H, 5.38; N, 12.86.

Compound 15p (yy-0237a): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (6H, t, *J*=7.6 Hz), 1.53-1.59 (4H, m), 3.06-3.10 (4H, m), 4.27 (3H, s), 7.00 (1H, s), 7.71 (2H, d, *J*=8.8 Hz), 7.80 (2H, d, *J*=8.8 Hz), 7.89 (1H, s); Anal. Calcd for

$C_{18}H_{23}F_3N_4O_3S$: C, 49.99; H, 5.36; N, 12.96. Found: C, 50.03; H, 5.40; N, 12.86.

Compound 15q (yy-0215a): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (12H, d, *J*=6.4 Hz), 1.88-1.91 (2H, m), 2.86 (4H, d, *J*=7.6 Hz), 7.02 (1H, s), 7.69 (2H, d, *J*=8.8 Hz), 7.76 (2H, d, *J*=8.8 Hz), 7.96 (1H, s); Anal. Calcd for $C_{20}H_{27}F_3N_4O_3S$: C, 52.16; H, 5.91; N, 12.17. Found: C, 52.18; H, 6.01; N, 12.04.

Compound 15r (yy-0247a): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (4H, d, *J*=6.8 Hz), 4.28 (3H, s), 5.14-5.18 (4H, m), 5.57-5.65 (2H, m), 6.99 (1H, s), 7.34 (2H, d, *J*=8.8 Hz), 7.83 (2H, d, *J*=8.8 Hz), 7.88 (1H, s); Anal. Calcd for $C_{18}H_{19}F_3N_4O_3S$: C, 50.46; H, 4.47; N, 13.08. Found: C, 50.33; H, 4.44; N, 12.83.

Compound 16 (as-140): ^{1}H NMR (400 MHz, $CDCl_3$) δ1.13-1.27 (m, 4H), 1.54-1.56 (m, 2H), 1.64-1.66 (m, 2H), 1.76-1.78(m, 2H), 3.15-3.16 (m, 1H), 4.27 (s, 3H), 4.34 (d, 1H, J=5.2Hz), 6.99 (s, 1H), 7.73 (d, 2H, J=5.6Hz), 7.87-7.90(m, 3H). Anal. Calcd for $C_{18}H_{21}F_3N_4O_3S$: C, 50.23; H, 4.92; N, 13.02. Found: C, 50.27; H, 5.03; N, 12.99.

Compound 17 (as-155): ^{1}H NMR (400 MHz, $CDCl_3$) δ1.22-1.31 (3H, m), 1.45-1.55 (3H, m), 1.68-1.78 (4H, m), 4.26 (3H, s), 4.51 (m, 1H), 7.1 (s, 1H), 7.77 (d, 1H, J=8.0Hz), 7.83 (d, 1H, J=8.0Hz), 8.30 (br, 1H). Anal.

Calcd for $C_{18}H_{20}F_3N_3O_4S$: C, 50.11; H, 4.67; N, 9.74. Found: C, 50.11; H, 4.58; N, 9.59.

Compound 18 (as-627-03): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38-1.42 (2H, m), 1.58-1.64 (4H, m), 2.88 (4H, t, J=5.2Hz), 3.49 (3H, s), 4.15 (3H, s), 5.59 (1H, s), 7.23 -7.26 (2H, m), 7.70-7.72 (2H, d, J=8.4Hz). Anal. Calcd for $C_{18}H_{21}F_3N_4O_3S$: C, 50.23; H, 4.92; N, 13.02. Found: C, 50.32; H, 4.90; N, 12.78.

Compound 19 (yy-0131b): ^{1}H NMR (400 MHz, $CDCl_3$) δ1.05 (3H, d, J=7.2Hz), 1.25-1.56 (6H, m), 2.96-3.04 (1H, m), 3.71-3.74 (1H, m), 4.22-4.27 (4H, m), 7.19 (1H, s), 7.50-7.54 (1H,m), 7.58-7.60 (1H, d, J=8.0Hz), 7.93-7.97(1H, m), 8.18 (1H, d, J=8.0Hz), 8.64 (1H, br). Anal. Calcd for $C_{18}H_{21}F_3N_4O_3S$: C, 50.23; H, 4.92; N, 13.02. Found: C, 50.29; H, 4.95; N, 13.05.

Compound 20 (yy-0131c): ^{1}H NMR (400 MHz, $CDCl_3$) δ1.11 (3H, d, J=7.2Hz), 1.25-1.55 (6H, m), 2.99-3.06 (1H, m), 3.60-3.63 (1H, m), 4.16-4.18 (1H, m), 4.31 (3H, s), 7.06 (1H, s), 7.26 (1H, t, J=8.4Hz), 7.60 (1H, t, J=8.4Hz), 7.86 (1H, d, J=8.4Hz), 8.56 (1H, d, J=8.4Hz), 10.43 (1H, br). Anal. Calcd for $C_{18}H_{21}F_3N_4O_3S$: C, 50.23; H, 4.92; N, 13.02. Found: C, 50.00; H, 4.92; N, 12.92.

Compound 23a (as-236): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.02 (4H, t, J=4.8Hz), 3.76 (4H, t, J=4.8Hz), 4.28 (s, 3H), 7.0 (s, 1H), 7.82-7.79 (m, 4H), 7.86 (s, 1H). Anal. Calcd for $C_{16}H_{17}F_3N_4O_4S$: C, 45.93; H, 4.10; N, 13.39. Found: C, 45.92; H, 4.19; N, 13.17.

Compound 23b (as-270): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.59-2.63 (6H, m), 3.05 (4H, br), 3.53-3.62 (6H, m), 4.27 (3H, s), 7.14 (1H, s), 7.65 (2H, d, J=8.8Hz), 7.75 (2H, d, J=8.8 Hz), 8.69 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 40.74, 46.02, 52.40, 54.19, 57.49, 61.93, 67.48, 72.14, 105.88, 120.17, 129.13, 130.72, 136.36, 141.90, 157.30. Anal. Calcd for $C_{20}H_{26}F_3N_5O_5S$. H_2O: C, 45.88; H, 5.39; N, 13.38. Found: C, 46.40; H, 5.08; N, 13.30.

Compound 23c (as-254): ^{1}H NMR (400 MHz, DMSO) δ 1.33 (9H, s), 2.84-2.85 (4H, m), 3.38 (4H, m), 4.17 (3H, s), 7.56 (1H, s), 7.75 (2H, d, J=8.8Hz), 8.01 (2H, d, J=8.8Hz), 10.80 (1H, s).

Compound 23d (yy-0168a): ^{1}H NMR (400MHz, $CDCl_3$) & 1.25-1.34 (2H, m), 1.43(9H, s), 1.75-1.80 (2H, m), 2.76-2.86 (2H, m), 3.30-3.33 (1H, m), 3.90-3.97 (2H, s), 4.28 (3H, s), 4.36 (1H, d, J=8Hz), 6.97 (1H, s), 7.76 (2H, d, J=7.2Hz), 7.89 (1H, s), 7.91 (2H, d, J=7.2Hz).

Compound 24e (as-244): ^{1}H NMR (400 MHz, CDCl3) δ 2.90-2.92 (4H, m), 2.96-2.98 (4H, m), 4.25 (3H, s), 5.28 (1H, s), 7.04 (1H, s), 7.71 (2H, d, J=9.2Hz), 7.76 (2H, d, J=9.2Hz), 8.17 (1H, s). Anal. Calcd for

$C_{16}H_{18}F_3N_5O_3S$: C, 46.04; H, 4.35; N, 16.78. Found: C, 45.58; H, 4.36; N, 16.26.

Compound 24f (yy-0251): ^{1}H NMR (400 MHz, Actone-d_6) δ 1.33-1.42 (2H, m), 1.65-1.69 (2H, m), 2.49-2.55 (2H, m), 2.93-2.97 (2H, m), 3.14-3.21 (1H, m), 4.25 (3H, s), 7.42 (1H, s), 7.88 (2H, d, *J*=8.4 Hz), 7.98 (2H, d, *J*=8.4 Hz), 9.96 (1H, s); Anal. Calcd for $C_{17}H_{20}F_3N_5O_3S$.0.5 EtOAc: C, 47.99; H, 5.09; N, 14.73. Found: C, 48.30; H, 5.19; N, 15.21.

Compound 28a (yy-0150a): ^{1}H NMR (400MHz, $CDCl_3$) δ 1.48-1.49 (1H, m), 1.58-1.77 (3H, m), 2.05-2.13 (1H, m), 3.16-3.24 (1H, m), 3.58 (3H, s), 3.75-3.77 (1H, m), 4.25 (3H, s), 4.75-4.77 (1H, m), 6.99 (1H, s), 7.22 (2H, d, J=6.8Hz), 7.78 (2H, d, J=6.8Hz), 7.91 (1H, s). Anal. Calcd for $C_{19}H_{21}F_3N_4O_5S$: C, 48.10; H, 4.46; N, 11.81. Found: C, 48.14; H, 4.50; N, 11.66.

Compound 28b (as-248): ^{1}H NMR (400MHz, $CDCl_3$) δ 1.38 (9H, s), 1.48-1.78 (5H, m), 2.12 (1H, d, J=13.6Hz)**,** 3.27 (1H, dt, J=12.8Hz, 3.2Hz), 3.74 (1H, d, J=9.2Hz), 4.27 (3H, s), 4.65 (1H, d, J=5.2Hz), 9.96 (1H, s), 7.71 (2H, d, J=8.8Hz), 7.81 (2H, d, J=8.8Hz).

Compound 28c (as-267): ^{1}H NMR (400MHz, $CDCl_3$) δ 1.23-1.62 (6H, m), 2.20 (1H, m), 3.08 (1H, t, J=13.2 Hz), 3.53-3.59 (1H, m), 3.77 (1H, d, J=14.0Hz), 3.84 (1H, t, J=10.4Hz), 4.00-4.06 (1H, m), 4.26 (3H, s), 7.11 (1H,

s), 7.74-7.81 (4H, m), 8.48 (1H, s).Anal. Calcd for $C_{18}H_{21}F_3N_4O_4S$: C, 48.43; H, 4.74; N, 12.55. Found: C, 48.33; H, 4.84; N, 12.23.

Compound 28d (yy-0194a): ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.38-1.41 (2H, m), 1.70-1.72 (2H, m), 2.66-2.70 (2H, m), 3.07-3.15 (2H, m), 3.45-3.52 (2H, m), 4.64 (1H, d, J=3.6 Hz), 7.52 (1H, s), 7.72 (2H, d, *J*=8.8 Hz), 7.96 (2H, d, *J*=8.8 Hz), 10.74 (1H, s). Anal. Calcd for $C_{17}H_{19}F_3N_4O_4S$: C, 47.22; H, 4.43; N, 12.96. Found: C, 47.43; H, 4.41; N, 12.72.

Compound 29e (as-251): ^{1}H NMR (400MHz, $CDCl_3$) δ 1.23-1.62 (6H, m), 2.20 (1H, m), 3.08 (1H, t, J=13.2 Hz), 3.53-3.59 (1H, m), 3.77 (1H, d, J=14.0Hz), 3.84 (1H, t, J=10.4Hz), 4.00-4.06 (1H, m), 4.26 (3H, s), 7.11 (1H, s), 7.74-7.81 (4H, m), 8.48 (1H, s).Anal. Calcd for $C_{18}H_{19}F_3N_4O_5S$: C, 46.95; H, 4.16; N, 12.17. Found: C, 47.10; H, 4.33; N, 11.54.

Compound 29f (yy-0173a): ^{1}H NMR (400MHz, $CDCl_3$) & 1.55-1.70 (2H, m), 1.81-1.96 (2H, m), 2.63-2.74 (2H, m), 2.84-2.89 (1H, m), 3.42-3.45 (1H, m), 3.65-3.67 (1H, m), 4.27 (3H, s), 7.00 (1H, s), 7.78-7.82 (4H, m), 7.94 (1H, broad). Anal. Calcd for $C_{18}H_{19}F_3N_4O_5S$ C, 46.95; H, 4.16; N, 12.17. Found: C, 46.71; H, 4.16; N, 11.42.

Computational Methods.

QSAR by Molecular Field Topology Analysis (MFTA).

MFTAWin software (version 3.0 beta17) was applied by first performing a topological alignment of the training set structures (compounds **1**, **2j**, 2**o**, **9a, 13, 14,** 1**5a**, 1**5c**-**15i**, **15k,** 1**5m**, **15o**, **15p**, **15r**, **23a**, **23d**, **28c**, and **28d**; plus **3s**, **5**, **7**, and **8** from a previous publication) to construct a molecular supergraph, providing a common reference framework for the chosen descriptor set. Then MFTA's PLS (partial least squares) regression function was used to build statistical models, the predictivity of which was assessed by the leave-25%-out cross validation procedure. A variety of descriptor sets were examined; the best results (high R and Q^2 values, low PLS factor count, small errors) were obtained with descriptors for Gasteiger-Marsili atomic charge (Q), the effective environment van der Waal radius (R_e), and group lipophilicity based on the sum of the Ghose-Crippen atomic contributions for an atom and attached hydrogens (L_g). The veracity of this model was checked by means of an explicit test set (compounds **2n**, **2k, 15b, 15n**, **24e, and 28a**; plus **6** from a previous publication). These compounds were selected based on their range of activities and diversity of structures. MFTA was used to map the test set to the previously generated molecular supergraph and to calculate their descriptor values. Then these values were applied to the previously generated QSAR equation and the test set activities predicted. The validity of the correlation was further checked by

randomizing the data and structures. MFTA was also used to generate color-coded molecular supergraphs reflecting the quantitative effect on activity of each descriptor in each position.

CF_3-bearing ligands bound to proteins. Identification of CF_3-substituted ligands was achieved by searching the Protein Data Bank (PDB[32]) with Relibase+.[33,34,35] The resulting 132 hits were individually inspected in ReliView and catalogued for the presence of protein side-chains, water, ions or other small molecules within 4 Å of the fluorine atoms. Selected examples were examined further with DeepView[36] and displayed with PyMOL[37] in the construction of **Figures 7-10.**