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Supporting Information

Discovery and development of novel substituted monohydrazides as potent antifungal agents

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Table of content:

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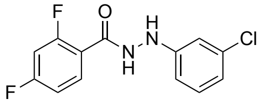
Materials and instrumentation. The chemicals used in this study were purchased from Sigma-Aldrich (St. Louis, MO), AK Scientific (Union City, CA), Acros Organics (New Jersey, NJ), TCI America (Portland, OR), Oakwood Chemicals (Estill, SC), Combi-Blocks (San Diego, CA), Accela Chembio (San Diego, CA), and Chem-Impex (Wood Dale, IL), and used without any further purification. Chemical reactions were monitored by thin layer chromatography (TLC) (Merck, silica gel 60 F_{254}) and visualized using UV light. Compounds were purified by SiO_2 flash chromatography (Dynamic Adsorbents Inc., flash SiO_2 gel 32-63μ). ^1H and ^{13}C NMR spectra were recorded on Agilent VNMRS-500, MR-400, or MR-600 (for both ^1H and ^{13}C) spectrometers using deuterated solvents, as specified. Chemical shifts (δ) are given in parts per million (ppm). Coupling constants (*J*) are given in Hertz (Hz), and conventional abbreviations used for signal shape are as follows: br s; broad singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublet of doublets; dt, doublet of triplets; m, multiplet; s, singlet; t, triplet; td, triplet of doublets; tt, triplet of triplets. High resolution-mass spectrometry (HRMS) was carried out using a Shimadzu prominence LC system equipped with an AB SCIEX Triple TOFTM 5600 mass spectrometer (Shimadzu manufacturing, Kyoto, Japan). HRMS $[M+H]^+$ signals were consistent with the expected molecular weights for all of the reported compounds. Further confirmation of purity for these final molecules was obtained by reversed-phase high-performance liquid chromatography (RP-HPLC) on an Agilent Technologies 1260 Infinity HPLC system by using the following general method:

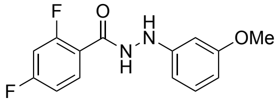
flow rate = 0.5 mL/min; λ = 254 nm; column = Vydac 201SP^{TM} C18, 250 × 4.6 mm, 90 Å; 5 µm; eluents: A = H_2O + 0.1% TFA, B = MeCN; gradient profile: starting from 5% B, increasing from 5% B to 100% B over 20 min, holding at 100% B for 7 min, decreasing from 100% B to 5% B in 3 min. Prior to each injection, the HPLC column was equilibrated for 15 min with 5% B. All compounds were at least 95% pure. Compounds **1a**, **1e**, **2a**, **2b**, **2c**, **2e**, **3a**, **3c**, **3d**, **3e**, **3f**, **4a**, **5a**, **5e**, **6a**, **7a**, **7e**, **8a**, **8e**, **9a**, and **9e** were prepared and purified as previously reported.[1]

Synthesis and characterization of compounds 1a-9j.



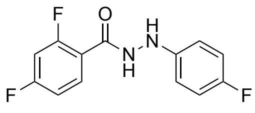
Synthesis of compound 1b (SGT1772). To a solution of 2,4-difluorobenzoic acid (100 mg, 0.63 mmol) in DMF (3 mL) at 0 °C, *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (157 mg, 0.82 mmol), 1-hydroxybenzotriazole hydrate (111 mg, 0.82 mmol), and *N*,*N*-diisopropylethyl amine (0.33 mL, 1.89 mmol) were added. The reaction mixture was stirred at 0 °C for 30 min followed by the addition of 3-chlorophenylhydrazine hydrochloride (147 mg, 0.82 mmol). The reaction mixture was stirred at room temperature for 12 h, and the progress of the reaction was monitored by TLC (2:3/EtOAc:Hexanes, R_f 0.63). The reaction was quenched with H_2O (60 mL) and extracted with EtOAc (80 mL). The organic layer was washed with H_2O (60 mL), brine (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (SiO_2, 1:4/EtOAc:Hexanes) to afford compound **1b** (122 mg, 69%) as a white solid: ^{1}H NMR (400 MHz, $(CD_3)_2SO$, Fig. S1) δ 10.26 (s, 1H), 8.32 (s, 1H), 7.74 (td, J_1 = 8.4 Hz, J_2 = 6.6 Hz, 1H), 7.43 (ddd, J_1 = 10.6 Hz, J_2 = 9.4 Hz, J_3 = 2.5 Hz, 1H), 7.26-7.20 (m, 1H), 7.19 (t, J = 8.0 Hz, 1H), 6.79-6.72 (m, 3H); ^{13}C NMR (150 MHz, $(CD_3)_2SO$, Fig. S2) δ 164.7 and 164.6 and 163.0 and 162.9 (dd, J_1 = 249.1 Hz, J_2 = 12.0 Hz), 163.5, 160.84 and 160.76 and 159.2

and 159.1 (dd, J_1 = 250.4 Hz, J_2 = 12.9 Hz), 150.7, 133.7, 131.99 and 131.96 and 131.92 and 131.89 (dd, J_1 = 10.1 Hz, J_2 = 4.3Hz), 130.7, 119.44 and 119.42 and 119.34 and 119.32 (dd, J_1 = 15.7 Hz, J_2 = 3.2 Hz), 118.4, 112.33 and 112.31 and 112.19 and 112.17 (dd, J_1 = 21.6 Hz, J_2 = 2.0 Hz), 111.7, 111.0, 105.1 and 104.9 and 104.7 (t, J = 26.9 Hz); HRMS *m/z* calcd for $C_{13}H_9ClF_2N_2O$ $[M+H]^+$: 283.0449; found 283.0446 (Fig. S3). The purity of the compound was further confirmed by HPLC: R_t = 16.15 min (99% pure; Fig. S4).



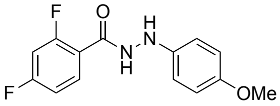
Synthesis of compound 1c (SGT1771). To a solution of 2,4-difluorobenzoic acid (125 mg, 0.79 mmol) in DMF (3 mL) at 0 °C, *N*-(3-dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride (182 mg, 0.95 mmol), 1-hydroxybenzotriazole hydrate (128 mg, 0.95 mmol), and *N*,*N*-diisopropylethyl amine (0.41 mL, 2.37 mmol) were added. The reaction mixture was stirred at 0 °C for 30 min followed by the addition of 3-methoxyphenylhydrazine hydrochloride (166 mg, 0.85 mmol). The reaction mixture was stirred at room temperature for 12 h, and the progress of the reaction was monitored by TLC (2:3/EtOAc:Hexanes, R*f* 0.68). The reaction was quenched with H_2O (100 mL) and extracted with EtOAc (70 mL). The organic layer was washed with H_2O (70 mL), brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (SiO_2, 2:3/EtOAc:Hexanes) to afford compound **1c** (46 mg, 21%) as a pale yellow solid: ^{1}H NMR (500 MHz, CD_3OD, Fig. S5) δ 7.84-7.80 (m, 1H), 7.17-7.08 (m, 3H), 6.51-6.47 (m, 2H), 6.41 (ddd, J_1 = 8.2 Hz, J_2 = 2.5 Hz, J_3 = 0.9 Hz, 1H), 3.75 (s, 3H); ^{13}C NMR (150 MHz, $(CD_3)_2SO$, Fig. S6) δ 164.4 and 164.3 and 162.7 and 162.6 (dd, J_1 = 248.2 Hz, J_2 = 12.0 Hz), 163.2, 160.65 and 160.56 and 159.0 and 158.9 (dd, J_1 = 250.2 Hz, J_2 = 13.0 Hz), 160.2, 150.5, 131.74 and 131.71 and 131.67 and 131.64 (dd, J_1 = 10.6 Hz, J_2 = 5.1 Hz), 129.6, 119.68

and 119.66 and 119.58 and 119.56 (dd, J_1 = 15.2 Hz, J_2 = 3.3 Hz), 112.09 and 112.06 and 111.94 and 111.92 (dd, J_1 = 21.6 Hz, J_2 = 3.9 Hz), 105.1 and 104.2 (d, J = 138.6 Hz), 104.9 and 104.7 and 104.5 (t, J = 26.0 Hz), 98.1, 54.7; HRMS m/z calcd for $C_{14}H_{12}F_2N_2O_2$ $[M+H]^+$: 279.0945; found 279.0935 (Fig. S7). The purity of the compound was further confirmed by HPLC: R_t = 15.40 min (95% pure; Fig. S8).



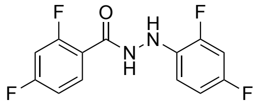
Synthesis of compound 1d (SGT1785). To a solution of 2,4-difluorobenzoic acid (100 mg, 0.63 mmol) in DMF (3 mL) at 0 °C, *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (157 mg, 0.82 mmol) and *N*,*N*-diisopropylethyl amine (0.33 mL, 1.89 mmol) were added. The reaction mixture was stirred at 0 °C for 30 min followed by the addition of 4-fluorophenylhydrazine hydrochloride (134 mg, 0.82 mmol). The reaction mixture was stirred at room temperature for 12 h, and the progress of the reaction was monitored by TLC (2:3/EtOAc:Hexanes, R_f 0.43). The reaction was quenched with H_2O (100 mL), extracted with EtOAc (150 mL), washed with brine (30 mL), and dried over $MgSO_4$. The organic layer was removed under reduced pressure, and the residue was purified by flash column chromatography (SiO_2, 3:7/EtOAc:Hexanes) to afford compound **1d** (144 mg, 86%) as a white solid: ^{1}H NMR (500 MHz, $(CD_3)_2SO$, Fig. S9) δ 10.21 (d, J = 2.9 Hz, 1H), 7.99 (d, J = 2.9 Hz, 1H), 7.73 (td, J_1 = 8.5 Hz, J_2 = 6.6 Hz, 1H), 7.41 (ddd, J_1 = 10.6 Hz, J_2 = 9.5 Hz, J_3 = 2.5 Hz, 1H), 7.24-7.19 (m, 1H), 7.02 (t, J = 8.9 Hz, 2H), 6.80 (dd, J_1 = 9.1 Hz, J_2 = 4.7 Hz, 2H); ^{13}C NMR (150 MHz, $(CD_3)_2SO$, Fig. S10) δ 164.4 and 164.3 and 162.8 and 162.7 (dd, J_1 = 248.2 Hz, J_2 = 12.0 Hz), 163.2, 160.7 and 160.6 and 159.0 and 158.9 (dd, J_1 = 250.9 Hz, J_2 = 13.0 Hz), 156.7 and 155.2 (d, J = 231.8 Hz), 145.6, 131.80 and 131.77 and 131.73 and 131.70 (dd, J_1 = 10.0 Hz, J_2 = 4.4 Hz), 119.56 and 119.53 and 119.5 and 119.4 (dd, J_1 = 15.3 Hz, J_2 = 4.2 Hz), 115.3 and

115.2 (d, J = 21.8 Hz), 113.5 and 113.4 (d, J = 7.8 Hz), 112.1 and 112.0 and 111.92 and 111.89 (dd, J_1 = 21.6 Hz, J_2 = 4.1 Hz), 104.9 and 104.7 and 104.6 (t, J = 26.5 Hz); HRMS *m/z* calcd for $C_{13}H_9F_3N_2O$ $[M+H]^+$: 267.0745; found 267.0741 (Fig. S11). The purity of the compound was further confirmed by HPLC: R_t = 15.63 min (98% pure; Fig. S12).



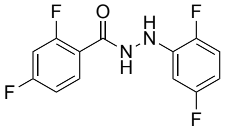
Synthesis of compound 1f (SGT1771). To a solution of 2,4-difluorobenzoic acid (100 mg, 0.63 mmol) in DMF (3 mL) at 0 °C, *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (157 mg, 0.82 mmol), 1-hydroxybenzotriazole hydrate (111 mg, 0.82 mmol), and *N*,*N*-diisopropylethyl amine (0.33 mL, 1.89 mmol) were added. The reaction mixture was stirred at 0 °C for 30 min followed by the addition of 4-methoxyphenylhydrazine hydrochloride (143 mg, 0.82 mmol). The reaction mixture was stirred at room temperature for 12 h, and the progress of the reaction was monitored by TLC (2:3/EtOAc:Hexanes, R_f 0.65). The reaction was quenched with H_2O (60 mL) and extracted with EtOAc (80 mL). The organic layer was washed with H_2O (60 mL), brine (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (SiO_2, 1:4/EtOAc:Hexanes) to afford compound **1f** (124 mg, 71%) as a yellow solid: ^{1}H NMR (500 MHz, $(CD_3)_2SO$, Fig. S13) δ 10.16 (d, J = 3.5 Hz, 1H), 7.71 (td, J_1 = 8.4 Hz, J_2 = 6.7 Hz, 1H), 7.68 (d, J = 3.3 Hz, 1H), 7.40 (ddd, J_1 = 10.6 Hz, J_2 = 9.5 Hz, J_3 = 2.5 Hz, 1H), 7.24-7.18 (m, 1H), 6.80 (d, J = 9.4 Hz, 2H), 6.77 (d, J = 9.3 Hz, 2H); ^{13}C NMR (150 MHz, $(CD_3)_2SO$, Fig. S14) δ 164.35 and 164.27 and 162.7 and 162.6 (dd, J_1 = 248.2 Hz, J_2 = 12.0 Hz), 163.2, 160.66 and 160.58 and 159.0 and 158.9 (dd, J_1 = 250.2 Hz, J_2 = 12.6 Hz), 152.8, 142.9, 131.8 and 131.73 and 131.69 and 131.66 (dd, J_1 = 10.0 Hz, J_2 = 4.4 Hz), 119.74 and 119.72 and 119.64 and 119.62 (dd, J_1 = 15.0 Hz, J_2 = 3.1 Hz), 114.3, 113.8, 112.03 and 111.99 and 111.88

and 111.86 (dd, J_1 = 21.5 Hz, J_2 = 3.9 Hz), 104.9 and 104.7 and 104.5 (t, J = 26.0 Hz), 55.3; HRMS *m/z* calcd for $C_{14}H_{12}F_2N_2O_2$ $[M+H]^+$: 279.0945; found 279.0947 (Fig. S15). The purity of the compound was further confirmed by HPLC: R_t = 15.29 min (99% pure; Fig. S16).



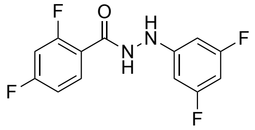
Synthesis of compound 1g (SGT1393). To a solution of 2,4-difluorobenzoic acid (100 mg, 0.63 mmol) in DMF (3 mL) at 0 °C, *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (157 mg, 0.82 mmol), 1-hydroxybenzotriazole hydrate (111 mg, 0.82 mmol), and *N*,*N*-diisopropylethyl amine (0.33 mL, 1.89 mmol) were added. The reaction mixture was stirred at 0 °C for 30 min followed by the addition of 2,4-difluorophenylhydrazine hydrochloride (148 mg, 0.82 mmol). The reaction mixture was stirred at room temperature for 12 h, and the progress of the reaction was monitored by TLC (1:4/EtOAc:Hexanes, R_f 0.31). The reaction was quenched with H_2O (100 mL), extracted with EtOAc (150 mL), washed with brine (30 mL), and dried over $MgSO_4$. The organic layer was removed under reduced pressure, and the residue was purified by flash column chromatography (SiO_2, 1:4/EtOAc:Hexanes) to afford compound **1g** (149 mg, 83%) as a white solid: ^{1}H NMR (500 MHz, $(CD_3)_2SO$, Fig. S17) δ 10.27 (s, 1H), 7.90 (s, 1H), 7.73 (td, J_1 = 8.4 Hz, J_2 = 6.6 Hz, 1H), 7.42 (ddd, J_1 = 10.6 Hz, J_2 = 9.4 Hz, J_3 = 2.5 Hz, 1H), 7.25-7.20 (m, 1H), 7.17 (ddd, J_1 = 11.7 Hz, J_2 = 8.9 Hz, J_3 = 2.8 Hz, 1H), 6.96-6.91 (m, 1H), 6.87 (td, J_1 = 9.4 Hz, J_2 = 5.8 Hz, 1H); ^{13}C NMR (150 MHz, $(CD_3)_2SO$, Fig. S18) δ 164.5 and 164.4 and 162.85 and 162.76 (dd, J_1 = 249.0 Hz, J_2 = 12.7 Hz), 163.33 and 163.32 (d, J = 1.6 Hz), 160.75 and 160.66 and 159.1 and 159.0 (dd, J_1 = 251.2 Hz, J_2 = 12.9 Hz), 155.7 and 155.6 and 154.13 and 154.06 (dd, J_1 = 235.1 Hz, J_2 = 10.8 Hz), 150.43 and 150.35 and 148.8 and 148.7 (dd, J_1 = 241.5 Hz, J_2 = 12.0 Hz), 133.42 and 133.41 and 133.36 and 133.34 (dd, J_1 = 10.9 Hz, J_2 = 2.9 Hz), 131.9 and 131.82 and 131.78 and 131.75 (dd,

J_1 = 10.1 Hz, J_2 = 4.6 Hz), 119.32 and 119.29 and 119.22 and 119.19 (dd, J_1 = 15.2 Hz, J_2 = 4.1 Hz), 114.18 and 114.15 and 114.12 and 114.09 (dd, J_1 = 8.8 Hz, J_2 = 4.4 Hz), 112.09 and 112.07 and 111.95 and 111.92 (dd, J_1 = 21.0 Hz, J_2 = 3.3 Hz), 110.98 and 110.96 and 110.84 and 110.81 (dd, J_1 = 21.6 Hz, J_2 = 3.7 Hz), 104.9 and 104.8 and 104.6 (t, J = 26.0 Hz), 104.0 and 103.80 and 103.77 and 103.6 (dd, J_1 = 27.0 Hz, J_2 = 22.6 Hz); HRMS *m/z* calcd for $C_{13}H_8F_4N_2O$ $[M+H]^+$: 285.0651; found 285.0632 (Fig. S19). The purity of the compound was further confirmed by HPLC: R_t = 16.02 min (99% pure; Fig. S20).



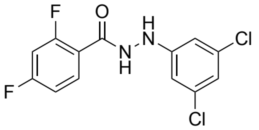
Synthesis of compound 1h (SGT1769). To a solution of 2,4-difluorobenzoic acid (100 mg, 0.63 mmol) in DMF (3 mL) at 0 °C, *N*-(3-dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride (157 mg, 0.82 mmol), 1-hydroxybenzotriazole hydrate (111 mg, 0.82 mmol), and *N*,*N*-diisopropylethyl amine (0.33 mL, 1.89 mmol) were added. The reaction mixture was stirred at 0 °C for 30 min followed by the addition of 2,5-difluorophenylhydrazine hydrochloride (148 mg, 0.82 mmol). The reaction mixture was stirred at room temperature for 12 h, and the progress of the reaction was monitored by TLC (2:3/EtOAc:Hexanes, R*f* 0.61). The reaction was quenched with H_2O (60 mL) and extracted with EtOAc (80 mL). The organic layer was washed with H_2O (60 mL), brine (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (SiO_2, 1:4/EtOAc:Hexanes) to afford compound **1h** (119 mg, 67%) as a white solid: ^{1}H NMR (500 MHz, $(CD_3)_2SO$, Fig. S21) δ 10.30 (s, 1H), 8.29 (s, 1H), 7.76 (td, J_1 = 8.5 Hz, J_2 = 6.6 Hz, 1H), 7.43 (ddd, J_1 = 10.7 Hz, J_2 = 9.6 Hz, J_3 = 2.5 Hz, 1H), 7.26-7.20 (m, 1H), 7.14 (ddd, J_1 = 11.4 Hz, J_2 = 8.9 Hz, J_3 = 5.1 Hz, 1H), 6.59 (ddd, J_1 = 10.2 Hz, J_2 = 6.9 Hz, J_3 = 3.1 Hz, 1H), 6.53 (tt, J_1 = 8.3 Hz, J_2 = 3.3 Hz, 1H); ^{13}C NMR (150 MHz, $(CD_3)_2SO$, Fig. S22) δ 164.6 and 164.5 and 162.9 and

162.8 (dd, J_1 = 249.1 Hz, J_2 = 12.5 Hz), 163.3, 160.8 and 160.7 and 159.1 and 159.0 (dd, J_1 = 250.3 Hz, J_2 = 12.9 Hz), 159.8 and 158.2 (d, J = 235.9 Hz), 146.98 and 146.97 and 145.42 and 145.41 (dd, J_1 = 233.9 Hz, J_2 = 1.3 Hz), 138.3 and 138.20 and 138.19 and 138.1 (dd, J_1 = 12.6 Hz, J_2 = 11.1 Hz), 131.90 and 131.87 and 131.83 and 131.80 (dd, J_1 = 10.6 Hz, J_2 = 5.0 Hz), 119.20 and 119.18 and 119.10 and 119.08 (dd, J_1 = 15.0 Hz, J_2 = 3.3Hz), 116.0 and 115.94 and 115.88 and 115.8 (dd, J_1 = 20.4 Hz, J_2 = 10.5 Hz), 112.15 and 112.12 and 112.0 and 111.98 (dd, J_1 = 21.6 Hz, J_2 =3.8 Hz), 105.0 and 104.8 and 104.6 (t, J = 26.1 Hz), 104.1 and 104.0 and 103.9 and 103.8 (dd, J_1 = 24.0 Hz, J_2 = 7.3 Hz), 100.19 and 100.16 and 99.99 and 99.97 (dd, J_1 = 29.1 Hz, J_2 = 3.9 Hz); HRMS *m/z* calcd for $C_{13}H_8F_4N_2O$ $[M+H]^+$: 285.0651; found 285.0654 (Fig. S23). The purity of the compound was further confirmed by HPLC: R_t = 15.86 min (100% pure; Fig. S24).

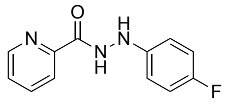


Synthesis of compound 1i (SGT1770). To a solution of 2,4-difluorobenzoic acid (100 mg, 0.63 mmol) in DMF (3 mL) at 0 °C, *N*-(3-dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride (157 mg, 0.82 mmol), 1-hydroxybenzotriazole hydrate (111 mg, 0.82 mmol), and *N*,*N*-diisopropylethyl amine (0.33 mL, 1.89 mmol) were added. The reaction mixture was stirred at 0 °C for 30 min followed by the addition of 3,5-difluorophenylhydrazine hydrochloride (148 mg, 0.82 mmol). The reaction mixture was stirred at room temperature for 12 h, and the progress of the reaction was monitored by TLC (2:3/EtOAc:Hexanes, R_f 0.64). The reaction was quenched with H_2O (60 mL) and extracted with EtOAc (80 mL). The organic layer was washed with H_2O (60 mL), brine (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (SiO_2, 1:4/EtOAc:Hexanes) to afford compound **1i** (99 mg, 55%) as a white solid: ^1H NMR (500 MHz, $(CD_3)_2SO$, Fig. S25) δ 10.32 (s, 1H), 8.61 (s, 1H), 7.77 (td, J_1 =

8.4 Hz, J_2 = 6.5 Hz, 1H), 7.43 (ddd, J_1 = 11.8 Hz, J_2 = 9.4 Hz, J_3 = 2.5 Hz, 1H), 7.25-7.20 (m, 1H), 6.48 (tt, J_1 = 9.4 Hz, J_2 = 2.3Hz, 1H), 6.39 (dd, J_1 = 10.0 Hz, J_2 = 2.3 Hz, 2H); ^{13}C NMR (150 MHz, $(CD_3)_2SO$, Fig. S26) δ 164.6 and 164.5 and 162.9 and 162.8 (dd, J_1 = 249.0 Hz, J_2 = 12.1 Hz), 164.2 and 164.1 and 162.6 and 162.5 (dd, J_1 = 241.2 Hz, J_2 = 16.1 Hz), 163.3, 160.7 and 160.6 and 159.1 and 159.0 (dd, J_1 = 250.3 Hz, J_2 = 12.6 Hz), 152.2 and 152.14 and 152.06 (t, J = 12.8 Hz), 131.93 and 131.90 and 131.86 and 131.83 (dd, J_1 = 10.6 Hz, J_2 = 4.3 Hz), 119.18 and 119.15 and 119.08 and 119.05 (dd, J_1 = 15.2 Hz, J_2 = 4.0 Hz), 112.2 and 112.1 and 112.02 and 111.99 (dd, J_1 = 21.5 Hz, J_2 = 3.6 Hz), 105.0 and 104.8 and 104.6 (t, J = 26.0 Hz), 95.0 and 94.8 (d, J = 29.0 Hz), 93.4 and 93.2 and 93.1 (t, J = 26.1 Hz); HRMS *m/z* calcd for $C_{13}H_8F_4N_2O$ $[M+H]^+$: 285.0651; found 285.0622 (Fig. S27). The purity of the compound was further confirmed by HPLC: R_t = 15.92 min (99% pure; Fig. S28).

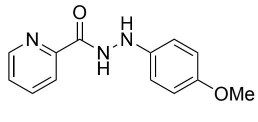


Synthesis of compound 1j (SGT1773). To a solution of 2,4-difluorobenzoic acid (100 mg, 0.63 mmol) in DMF (3 mL) at 0 °C, *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (157 mg, 0.82 mmol), 1-hydroxybenzotriazole hydrate (111 mg, 0.82 mmol), and *N*,*N*-diisopropylethyl amine (0.33 mL, 1.89 mmol) were added. The reaction mixture was stirred at 0 °C for 30 min followed by the addition of 3,5-dichlorophenylhydrazine hydrochloride (175 mg, 0.82 mmol). The reaction mixture was stirred at room temperature for 12 h, and the progress of the reaction was monitored by TLC (2:3/EtOAc:Hexanes, R*f* 0.71). The reaction was quenched with H_2O (60 mL) and extracted with EtOAc (80 mL). The organic layer was washed with H_2O (60 mL), brine (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (SiO_2, 1:4/EtOAc:Hexanes) to afford compound **1j** (102 mg, 51%) as a yellow solid: ^{1}H NMR (400 MHz, $(CD_3)_2SO$, Fig. S29) δ 10.33 (s, 1H), 8.61 (s, 1H), 7.76 (td, J_1 = 8.4 Hz, J_2 = 6.6 Hz, 1H), 7.44 (ddd, J_1 = 10.7 Hz, J_2 = 9.4 Hz, J_3 = 2.5 Hz, 1H), 7.27-7.20 (m, 1H), 6.87 (t, J = 1.8 Hz, 1H), 6.75 (d, J = 1.8 Hz, 2H); ^{13}C NMR (150 MHz, $(CD_3)_2SO$, Fig. S30) δ 164.6 and 164.5 and 162.9 and 162.8 (dd, J_1 = 249.7 Hz, J_2 = 12.8 Hz), 163.2, 160.7 and 160.6 and 159.1 and 159.0 (dd, J_1 = 250.2 Hz, J_2 = 11.9 Hz), 151.5, 134.5, 131.91 and 131.88 and 131.84 and 131.81 (dd, J_1 = 10.5 Hz, J_2 = 4.7 Hz), 119.1 and 119.0 and 118.96 and 118.93 (dd, J_1 = 14.9 Hz, J_2 = 2.9 Hz), 117.5, 112.22 and 112.20 and 112.08 and 112.06 (dd, J_1 = 22.0 Hz, J_2 = 2.9 Hz), 110.3, 105.0 and 104.8 and 104.6 (t, J = 26.1 Hz); HRMS *m/z* calcd for $C_{13}H_8Cl_2F_2N_2O$ $[M+H]^+$: 317.0060; found 317.0052 (Fig. S31). The purity of the compound was further confirmed by HPLC: R_t = 17.08 min (99% pure; Fig. S32).

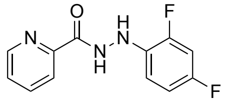


Synthesis of compound 2d (SGT1776). To a solution of 2-picolinic acid (100 mg, 0.81 mmol) in DMF (2 mL) at 0 °C, *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (203 mg, 1.06 mmol), 1-hydroxybenzotriazole hydrate (143 mg, 1.06 mmol), and *N*,*N*-diisopropylethyl amine (0.40 mL, 2.43 mmol) were added. The reaction mixture was stirred at 0 °C for 30 min followed by the addition of 4-fluorophenylhydrazine hydrochloride (172 mg, 1.06 mmol). The reaction mixture was stirred at room temperature for 12 h, and the progress of the reaction was monitored by TLC (2:3/EtOAc:Hexanes, R$_f$ 0.41). The reaction was quenched with H_2O (100 mL), extracted with EtOAc (150 mL), washed with brine (30 mL), and dried over $MgSO_4$. The organic layer was removed under reduced pressure, and the residue was purified by flash column chromatography (SiO_2, 2:3/EtOAc:Hexanes) to afford compound **2d** (148 mg, 79%) as a pale yellow solid: ^{1}H NMR (500 MHz, $(CD_3)_2SO$, Fig. S33) δ 10.58 (d, J = 3.3 Hz, 1H), 8.70-8.68 (m, 1H), 8.04-7.98 (m, 2H), 7.87 (d, J = 3.4 Hz, 1H), 7.64

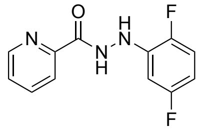
(ddd, J_1 = 8.3 Hz, J_2 = 4.8 Hz, J_3 = 3.3 Hz, 1H), 6.98 (t, J = 8.9 Hz, 2H), 6.76 (dd, J_1 = 9.1 Hz, J_2 = 4.7 Hz, 2H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$, Fig. S34) δ 164.0, 157.1 and 154.7 (d, J = 232.1 Hz), 149.7, 148.6, 145.79 and 145.78 (d, J = 1.8 Hz), 137.8, 126.8, 122.2, 115.2 and 115.0 (d, J = 22.3 Hz), 113.6 and 113.5 (d, J = 7.6 Hz); HRMS *m/z* calcd for $C_{12}H_{10}FN_3O$ $[M+H]^+$: 232.0886; found 232.0856 (Fig. S35). The purity of the compound was further confirmed by HPLC: R_t = 15.21 min (96% pure; Fig. S36).



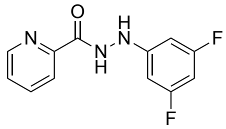
Synthesis of compound 2f (SGT1778). To a solution of 2-picolinic acid (100 mg, 0.81 mmol) in DMF (2 mL) at 0 °C, *N*-(3-dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride (203 mg, 1.06 mmol), 1-hydroxybenzotriazole hydrate (143 mg, 1.06 mmol), and *N*,*N*-diisopropylethyl amine (0.40 mL, 2.43 mmol) were added. The reaction mixture was stirred at 0 °C for 30 min followed by the addition of 4-methoxyphenylhydrazine hydrochloride (185 mg, 1.06 mmol). The reaction mixture was stirred at room temperature for 12 h, and the progress of the reaction was monitored by TLC (2:3/EtOAc:Hexanes, R_f 0.43). The reaction was quenched with H_2O (100 mL), extracted with EtOAc (150 mL), washed with brine (30 mL), and dried over $MgSO_4$. The organic layer was removed under reduced pressure, and the residue was purified by flash column chromatography (SiO_2, 2:3/EtOAc:Hexanes) to afford compound **2f** (162 mg, 82%) as an yellow solid: ^{1}H NMR (500 MHz, $(CD_3)_2SO$, Fig. S37) δ 10.50 (d, J = 3.8 Hz, 1H), 8.69-8.67 (m, 1H), 8.03-7.98 (m, 2H), 7.63 (ddd, J_1 = 8.0 Hz, J_2 = 4.8 Hz, J_3 = 3.1 Hz, 1H), 7.57 (d, J = 3.8 Hz, 1H), 6.78-6.72 (m, 4H), 3.33 (s, 3H); ^{13}C NMR (150 MHz, $(CD_3)_2SO$, Fig. S38) δ 163.9, 152.7, 149.8, 148.6, 143.1, 137.8, 126.7, 122.2, 114.2, 113.9, 55.3; HRMS *m/z* calcd for $C_{13}H_{13}N_3O_2$ $[M+H]^+$: 244.1086; found 244.1056 (Fig. S39). The purity of the compound was further confirmed by HPLC: R_t = 14.67 min (96% pure; Fig. S40).



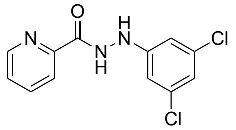
Synthesis of compound 2g (SGT1396). To a solution of 2-picolinic acid (100 mg, 0.81 mmol) in DMF (3 mL) at 0 °C, *N*-(3-dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride (203 mg, 1.06 mmol), 1-hydroxybenzotriazole hydrate (143 mg, 1.06 mmol), and *N*,*N*-diisopropylethyl amine (0.40 mL, 2.43 mmol) were added. The reaction mixture was stirred at 0 °C for 30 min followed by the addition of 2,4-difluorophenylhydrazine hydrochloride (191 mg, 1.06 mmol). The reaction mixture was stirred at room temperature for 12 h, and the progress of the reaction was monitored by TLC (2:3/EtOAc:Hexanes, R_f 0.38). The reaction was quenched with H_2O (100 mL), extracted with EtOAc (150 mL), washed with brine (30 mL), and dried over $MgSO_4$. The organic layer was removed under reduced pressure, and the residue was purified by flash column chromatography (SiO_2, 2:3/EtOAc:Hexanes) to afford compound **2g** (145 mg, 72%) as a yellow solid: ^{1}H NMR (500 MHz, $(CD_3)_2SO$, Fig. S41) δ 10.64 (d, J = 2.8 Hz, 1H), 8.69 (dt, J_1 = 4.8 Hz, J_2 = 1.3 Hz, 1H), 8.04-8.00 (m, 2H), 7.77 (very br s, 1H), 7.65 (ddd, J_1 = 6.0 Hz, J_2 = 4.8 Hz, J_3 = 2.9 Hz, 1H), 7.16 (ddd, J_1 = 11.8 Hz, J_2 = 8.9 Hz, J_3 = 2.8 Hz, 1H), 6.90-6.84 (m, 1H), 6.78 (td, J_1 = 9.5 Hz, J_2 = 5.8 Hz, 1H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$, Fig. S42) δ 164.1, 156.0 and 155.9 and 153.6 and 153.5 (dd, J_1 = 235.5 Hz, J_2 = 10.8 Hz), 150.9 and 150.8 and 148.5 and 148.3 (dd, J_1 = 241.4 Hz, J_2 = 12.1 Hz), 149.5, 148.7, 137.8, 133.7 and 133.65 and 133.57 and 133.5 (dd, J_1 = 13.8 Hz, J_2 = 3.0 Hz), 126.9, 122.3, 114.35 and 114.30 and 114.26 and 114.21 (dd, J_1 = 9.1 Hz, J_2 = 4.7 Hz), 110.91 and 110.88 and 110.69 and 110.66 (dd, J_1 = 21.7 Hz, J_2 = 3.5 Hz), 103.9 and 103.7 and 103.6 and 103.4 (dd, J_1 = 26.7 Hz, J_2 = 22.3 Hz); HRMS *m/z* calcd for $C_{12}H_9F_2N_3O$ $[M+H]^+$: 250.0792; found 250.0781 (Fig. S43). The purity of the compound was further confirmed by HPLC: R_t = 15.36 min (95% pure; Fig. S44).



Synthesis of compound 2h (SGT1789). To a solution of 2-picolinic acid (100 mg, 0.81 mmol) in DMF (3 mL) at 0 °C, *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (203 mg, 1.06 mmol) and *N*,*N*-diisopropylethyl amine (0.40 mL, 2.43 mmol) were added. The reaction mixture was stirred at 0 °C for 30 min followed by the addition of 2,5-difluorophenylhydrazine hydrochloride (191 mg, 1.06 mmol). The reaction mixture was stirred at room temperature for 12 h, and the progress of the reaction was monitored by TLC (3:2/EtOAc:Hexanes, R_f 0.32). The reaction was quenched with H_2O (100 mL), extracted with EtOAc (150 mL), washed with brine (30 mL), and dried over $MgSO_4$. The organic layer was removed under reduced pressure, and the residue was purified by flash column chromatography (SiO_2, 3:2/EtOAc:Hexanes) to afford compound **2h** (157 mg, 78%) as a pale yellow solid: ^{1}H NMR (500 MHz, $(CD_3)_2SO$, Fig. S45) δ 10.67 (br s, 1H), 8.70 (dt, J_1 = 4.7 Hz, J_2 = 1.5 Hz, 1H), 8.17 (br s, 1H), 8.04-8.01 (m, 2H), 7.69-7.64 (m, 1H), 7.16-7.10 (m, 1H), 6.52-6.44 (m, 2H); ^{13}C NMR (150 MHz, $(CD_3)_2SO$, Fig. S46) δ 164.1, 159.7 and 158.1 (d, J = 235.8 Hz), 149.5, 148.7, 147.0 and 145.5 (d, J = 233.4 Hz), 138.6 and 138.5 and 138.4 (t, J = 11.9 Hz), 137.8, 127.0, 122.4, 115.9 and 115.8 and 115.72 and 115.66 (dd, J_1 = 20.5 Hz, J_2 = 10.5 Hz), 103.8 and 103.7 and 103.6 and 103.5 (dd, J_1 = 24.2 Hz, J_2 = 7.2 Hz), 100.21 and 100.19 and 100.02 and 100.00 (dd, J_1 = 32.6 Hz, J_2 = 3.4 Hz); HRMS *m/z* calcd for $C_{12}H_9F_2N_3O$ $[M+H]^+$: 250.0792; found 250.0768 (Fig. S47). The purity of the compound was further confirmed by HPLC: R_t = 15.54 min (98% pure; Fig. S48).

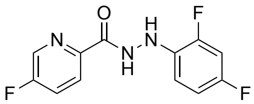


Synthesis of compound 2i (SGT1790). To a solution of 2-picolinic acid (100 mg, 0.81 mmol) in DMF (3 mL) at 0 °C, *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (203 mg, 1.06 mmol) and *N*,*N*-diisopropylethyl amine (0.40 mL, 2.43 mmol) were added. The reaction mixture was stirred at 0 °C for 30 min followed by the addition of 3,5-difluorophenylhydrazine hydrochloride (191 mg, 1.06 mmol). The reaction mixture was stirred at room temperature for 12 h, and the progress of the reaction was monitored by TLC (3:2/EtOAc:Hexanes, R_f 0.33). The reaction was quenched with H_2O (100 mL), extracted with EtOAc (150 mL), washed with brine (30 mL), and dried over $MgSO_4$. The organic layer was removed under reduced pressure, and the residue was purified by flash column chromatography (SiO_2, 3:2/EtOAc:Hexanes) to afford compound **2i** (147 mg, 73%) as a pale yellow solid: ^1H NMR (500 MHz, $(CD_3)_2SO$, Fig. S49) δ 10.72 (s, 1H), 8.70 (dt, J_1 = 4.8 Hz, J_2 = 1.4 Hz, 1H), 8.51 (br s, 1H), 8.04-8.01 (m, 2H), 7.66 (sextet, J = 4.6 Hz, 1H), 6.44 (ddd, J_1 = 11.6 Hz, J_2 = 4.5 Hz, J_3 = 2.2 Hz, 1H), 6.36-6.31 (m, 2H); ^{13}C NMR (150 MHz, $(CD_3)_2SO$, Fig. S50) δ 164.09 and 164.0 and 162.5 and 162.4 (dd, J_1 = 240.5 Hz, J_2 = 16.1 Hz), 164.1, 152.5 and 152.4 and 152.3 (t, J = 13.0 Hz), 149.4 and 148.7 (d, J = 106.0 Hz), 137.8, 127.0, 122.4, 94.9 and 94.7 (d, J = 29.1 Hz), 94.88 and 94.77 (d, J = 16.4 Hz), 93.1 and 92.9 and 92.7 (t, J = 26.1 Hz); HRMS *m/z* calcd for $C_{12}H_9F_2N_3O$ $[M+H]^+$: 250.0792; found 250.0770 (Fig. S51). The purity of the compound was further confirmed by HPLC: R_t = 15.48 min (98% pure; Fig. S52).



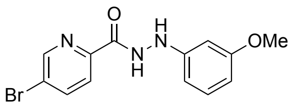
Synthesis of compound 2j (SGT1788). To a solution of 2-picolinic acid (100 mg, 0.81 mmol) in DMF (3 mL) at 0 °C, *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (203 mg, 1.06 mmol), 1-hydroxybenzotriazole hydrate (143 mg, 1.06 mmol), and *N*,*N*-diisopropylethyl amine (0.40 mL, 2.43 mmol) were added. The reaction mixture was stirred at 0 °C for 30 min followed by the addition of 3,5-dichlorophenylhydrazine hydrochloride (226 mg, 1.06 mmol). The reaction mixture was stirred at room temperature for 12 h, and the progress of the reaction was monitored by TLC (2:3/EtOAc:Hexanes, R_f 0.37). The reaction was quenched with H_2O (100 mL), extracted with EtOAc (150 mL), washed with brine

(30 mL), and dried over $MgSO_4$. The organic layer was removed under reduced pressure, and the residue was purified by flash column chromatography (SiO_2, 2:3/EtOAc:Hexanes) to afford compound **2j** (139 mg, 61%) as a yellow solid: ^{1}H NMR (500 MHz, $(CD_3)_2SO$, Fig. S53) δ 10.76 (br s, 1H), 8.70 (dt, J_1 = 4.7 Hz, J_2 = 1.4 Hz, 1H), 8.51 (d, J = 2.1 Hz, 1H), 8.04-8.02 (m, 2H), 7.67 (sextet, J = 4.6 Hz, 1H), 6.83 (t, J = 1.9 Hz, 1H), 6.69 (d, J = 1.9 Hz, 2H); ^{13}C NMR (150 MHz, $(CD_3)_2SO$, Fig. S54) δ 164.0, 151.7, 149.3, 148.7, 137.9, 134.3, 127.1, 122.4, 117.1, 110.3; HRMS *m/z* calcd for $C_{12}H_9Cl_2N_3O$ $[M+H]^+$: 282.0201; found 282.0168 (Fig. S55). The purity of the compound was further confirmed by HPLC: R_t = 16.82 min (99% pure; Fig. S56).



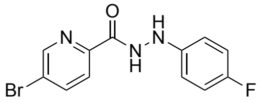
Synthesis of compound 3g (SGT1803). To a solution of 5-fluoro-2-pyridinecarboxylic acid (100 mg, 0.71 mmol) in DMF (3 mL) at 0 °C, *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (176 mg, 0.92 mmol), 1-hydroxybenzotriazole hydrate (124 mg, 0.92 mmol), and *N*,*N*-diisopropylethyl amine (0.37 mL, 2.13 mmol) were added. The reaction mixture was stirred at 0 °C for 30 min followed by the addition of 2,4-difluorophenylhydrazine hydrochloride (166 mg, 0.92 mmol). The reaction mixture was stirred at room temperature for 12 h, and the progress of the reaction was monitored by TLC (2:3/EtOAc:Hexanes, R_f 0.47). The reaction was quenched with H_2O (80 mL) and extracted with EtOAc (60 mL). The organic layer was washed with H_2O (50 mL), brine (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (SiO_2, 2:3/EtOAc:Hexanes) to afford compound **3g** (122 mg, 64%) as a pale yellow solid: ^{1}H NMR (500 MHz, $(CD_3)_2SO$, Fig. S57) δ 10.64 (s, 1H), 8.70 (d, J = 2.9 Hz, 1H), 8.10 (dd, J_1 = 8.5 Hz, J_2 = 4.7 Hz, 1H), 7.93 (td, J_1 = 8.8 Hz, J_2 = 2.9 Hz, 1H), 7.78 (s, 1H), 7.16 (ddd, J_1 = 11.8 Hz, J_2 = 8.9 Hz, J_3 = 2.8 Hz,1H), 6.90-6.84 (m, 1H), 6.77 (td, J_1 = 9.5 Hz, J_2

= 5.8 Hz, 1H); ^{13}C NMR (150 MHz, $(CD_3)_2SO$, Fig. S58) δ 163.1, 161.7 and 160.0 (d, *J* = 257.5 Hz), 155.6 and 155.5 and 154.02 and 153.94 (dd, J_1 = 235.0 Hz, J_2 = 10.6 Hz), 150.4 and 150.3 and 148.8 and 148.7 (dd, J_1 = 240.6 Hz, J_2 = 12.1 Hz), 146.3 and 146.2 (d, *J* = 4.2 Hz), 137.3 and 137.0 (d, *J* = 24.9 Hz), 133.60 and 133.58 and 133.53 and 133.50 (dd, J_1 = 10.8 Hz, J_2 = 3.1 Hz), 124.59, 124.55 and 124.46 (d, *J* = 12.1 Hz), 114.30 and 114.27 and 114.24 and 114.21 (dd, J_1 = 9.5 Hz, J_2 = 4.6 Hz), 110.87 and 110.85 and 110.72 and 110.70 (dd, J_1 = 21.7 Hz, J_2 = 3.3 Hz), 103.8 and 103.7 and 103.6 and 103.5 (dd, J_1 = 26.6 Hz, J_2 = 22.0 Hz); HRMS *m/z* calcd for $C_{12}H_8F_3N_3O$ $[M+H]^+$: 268.0697; found 268.0702 (Fig. S59). The purity of the compound was further confirmed by HPLC: R_t = 15.63 min (96% pure; Fig. S60).



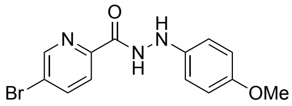
Synthesis of compound 4c (SGT1436). To a solution of 5-bromo-2-pyridinecarboxylic acid (100 mg, 0.50 mmol) in DMF (3 mL) at 0 °C, *N*-(3-dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride (123 mg, 0.64 mmol), 1-hydroxybenzotriazole hydrate (87 mg, 0.64 mmol), and *N*,*N*-diisopropylethyl amine (0.26 mL, 1.50 mmol) were added. The reaction mixture was stirred at 0 °C for 30 min followed by the addition of 3-methoxyphenylhydrazine hydrochloride (112 mg, 0.64 mmol). The reaction mixture was stirred at room temperature for 12 h, and the progress of the reaction was monitored by TLC (2:3/EtOAc:Hexanes, R_f 0.39). The reaction was quenched with H_2O (60 mL) and extracted with EtOAc (80 mL). The organic layer was washed with H_2O (60 mL), brine (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (SiO_2, 2:3/EtOAc:Hexanes) to afford compound **4c** (92 mg, 57%) as a pale yellow solid: ^{1}H NMR (500 MHz, $(CD_3)_2SO$, Fig. S61) δ 10.60 (d, *J* = 2.9 Hz, 1H), 8.82 (dd, J_1 = 2.4 Hz, J_2 = 0.7 Hz, 1H), 8.28 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H), 7.95 (dd, J_1 = 8.3 Hz, J_2 =

0.6 Hz, 1H), 7.92 (d, *J* = 2.8 Hz, 1H), 7.03 (dd, J_1 = 8.7 Hz, J_2 = 8.0 Hz, 1H), 6.35 (ddd, J_1 = 8.1 Hz, J_2 = 2.0 Hz, J_3 = 1.0 Hz, 1H), 6.32-6.28 (m, 2H), 3.66 (s, 3H); ^{13}C NMR (150 MHz, $(CD_3)_2SO$, Fig. S62) δ 163.3, 160.1, 150.6, 149.5, 148.5, 140.5, 129.5, 124.1, 123.7, 105.1, 103.9, 98.3, 54.8; HRMS *m/z* calcd for $C_{13}H_{12}BrN_3O_2$ $[M+H]^+$: 322.0191; found 322.0177 (Fig. S63). The purity of the compound was further confirmed by HPLC: R_t = 15.21 min (97% pure; Fig. S64).

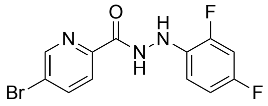


Synthesis of compound 4d (SGT1774). To a solution of 5-bromo-2-pyridinecarboxylic acid (100 mg, 0.50 mmol) in DMF (3 mL) at 0 °C, *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (123 mg, 0.64 mmol), 1-hydroxybenzotriazole hydrate (88 mg, 0.64 mmol), and *N*,*N*-diisopropylethyl amine (0.26 mL, 1.50 mmol) were added. The reaction mixture was stirred at 0 °C for 30 min followed by the addition of 4-fluorophenylhydrazine hydrochloride (104 mg, 0.64 mmol). The reaction mixture was stirred at room temperature for 12 h, and the progress of the reaction was monitored by TLC (2:3/EtOAc:Hexanes, R*f* 0.67). The reaction was quenched with H_2O (80 mL) and extracted with EtOAc (70 mL). The organic layer was washed with H_2O (60 mL), brine (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (SiO_2, 3:7/EtOAc:Hexanes) to afford compound **4d** (74 mg, 48%) as a white solid: ^{1}H NMR (400 MHz, $(CD_3)_2SO$, Fig. S65) δ 10.65 (d, *J* = 3.2 Hz, 1H), 8.82 (dd, J_1 = 2.3 Hz, J_2 = 0.7 Hz, 1H), 8.27 (dd, J_1 = 8.4 Hz, J_2 = 2.3 Hz, 1H), 7.95 (dd, J_1 = 8.4 Hz, J_2 = 0.7 Hz, 1H), 7.88 (d, *J* = 3.2 Hz, 1H), 6.98 (t, *J* = 8.9 Hz, 2H), 6.75 (dd, J_1 = 9.0 Hz, J_2 = 4.7 Hz, 2H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$, Fig. S66) δ 163.4, 157.1 and 154.7 (d, *J* = 232.3 Hz), 149.4, 148.5, 145.64 and 145.62 (d, *J* = 1.7 Hz), 140.5, 124.1, 123.7, 115.2 and 115.0 (d, *J* = 22.3 Hz), 113.6 and 113.5 (d, *J* = 7.6 Hz); HRMS *m/z* calcd for $C_{12}H_9BrFN_3O$ $[M+H]^+$: 309.9991; found

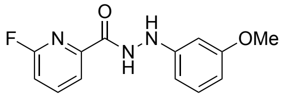
309.9977 (Fig. S67). The purity of the compound was further confirmed by HPLC: R_t = 16.23 min (95% pure; Fig. S68).



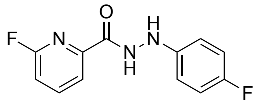
Synthesis of compound 4f (SGT1434). To a solution of 5-bromo-2-pyridinecarboxylic acid (100 mg, 0.50 mmol) in DMF (3 mL) at 0 °C, *N*-(3-dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride (123 mg, 0.64 mmol), 1-hydroxybenzotriazole hydrate (87 mg, 0.64 mmol), and *N*,*N*-diisopropylethyl amine (0.26 mL, 1.50 mmol) were added. The reaction mixture was stirred at 0 °C for 30 min followed by the addition of 4-methoxyphenylhydrazine hydrochloride (112 mg, 0.64 mmol). The reaction mixture was stirred at room temperature for 12 h, and the progress of the reaction was monitored by TLC (2:3/EtOAc:Hexanes, R_f 0.38). The reaction was quenched with H_2O (60 mL) and extracted with EtOAc (80 mL). The organic layer was washed with H_2O (60 mL), brine (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (SiO_2, 2:3/EtOAc:Hexanes) to afford compound **4f** (111 mg, 69%) as a pale yellow solid: ^{1}H NMR (500 MHz, $(CD_3)_2SO$, Fig. S69) δ 10.59 (d, *J* = 3.4 Hz, 1H), 8.81 (dd, J_1 = 2.3 Hz, J_2 = 0.7 Hz, 1H), 8.27 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H), 7.94 (dd, J_1 = 8.4 Hz, J_2 = 0.7 Hz, 1H), 7.58 (d, *J* = 3.5 Hz, 1H), 6.76 (d, *J* = 9.1 Hz, 2H), 6.73 (d, *J* = 9.3 Hz, 2H), 3.65 (s, 3H); ^{13}C NMR (150 MHz, $(CD_3)_2SO$, Fig. S70) δ 163.3, 152.8, 149.4, 148.6, 142.9, 140.4, 124.1, 123.6, 114.2, 113.9, 55.3; HRMS *m/z* calcd for $C_{13}H_{12}BrN_3O_2$ $[M+H]^+$: 322.0191; found 322.0120 (Fig. S71). The purity of the compound was further confirmed by HPLC: R_t = 16.01 min (99% pure; Fig. S72).



Synthesis of compound 4g (SGT1438). To a solution of 5-bromo-2-pyridinecarboxylic acid (100 mg, 0.50 mmol) in DMF (3 mL) at 0 °C, *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (123 mg, 0.64 mmol), 1-hydroxybenzotriazole hydrate (87 mg, 0.64 mmol), and *N*,*N*-diisopropylethyl amine (0.26 mL, 1.50 mmol) were added. The reaction mixture was stirred at 0 °C for 30 min followed by the addition of 2,4-difluorophenylhydrazine hydrochloride (116 mg, 0.64 mmol). The reaction mixture was stirred at room temperature for 12 h, and the progress of the reaction was monitored by TLC (2:3/EtOAc:Hexanes, R*f* 0.47). The reaction was quenched with H_2O (60 mL) and extracted with EtOAc (80 mL). The organic layer was washed with H_2O (60 mL), brine (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (SiO_2, 2:3/EtOAc:Hexanes) to afford compound **4g** (102 mg, 62%) as a white solid: ^{1}H NMR (500 MHz, $(CD_3)_2SO$, Fig. S73) δ 10.70 (s, 1H), 8.83 (dd, J_1 = 2.4 Hz, J_2 = 0.8 Hz, 1H), 8.28 (dd, J_1 = 8.5 Hz, J_2 = 2.4 Hz, 1H), 7.95 (dd, J_1 = 8.4 Hz, J_2 = 0.8 Hz, 1H), 7.79 (s, 1H), 7.16 (ddd, J_1 = 11.8 Hz, J_2 = 9.0 Hz, J_3 = 2.8 Hz, 1H), 6.90-6.84 (m, 1H), 6.77 (td, J_1 = 9.5 Hz, J_2 = 5.8 Hz, 1H); ^{13}C NMR (150 MHz, $(CD_3)_2SO$, Fig. S74) δ 163.4, 155.6 and 155.5 and 154.03 and 153.96 (dd, J_1 = 235.1 Hz, J_2 = 10.7 Hz), 150.43 and 150.35 and 148.8 and 148.7 (dd, J_1 = 241.4 Hz, J_2 = 12.6 Hz), 149.5, 148.3, 140.5, 133.51 and 133.49 and 133.43 and 133.42 (dd, J_1 = 10.7 Hz, J_2 = 2.1 Hz), 124.2, 123.8, 114.32 and 114.29 and 114.26 and 114.23 (dd, J_1 = 9.5 Hz, J_2 = 5.0 Hz), 110.87 and 110.85 and 110.72 and 110.71 (dd, J_1 = 21.8 Hz, J_2 = 2.6 Hz), 103.8 and 103.7 and 103.6 and 103.5 (dd, J_1 = 27.0 Hz, J_2 = 22.6 Hz); HRMS *m/z* calcd for $C_{12}H_8BrF_2N_3O$ $[M+H]^+$: 327.9897; found 327.9890 (Fig. S75). The purity of the compound was further confirmed by HPLC: R_t = 16.28 min (99% pure; Fig. S76).

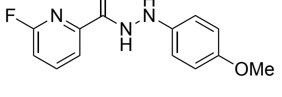


Synthesis of compound 5c (SGT1798). To a solution of 6-fluoro-2-pyridinecarboxylic acid (100 mg, 0.71 mmol) in DMF (3 mL) at 0 °C, *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (176 mg, 0.92 mmol), 1-hydroxybenzotriazole hydrate (124 mg, 0.92 mmol), and *N*,*N*-diisopropylethyl amine (0.37 mL, 2.13 mmol) were added. The reaction mixture was stirred at 0 °C for 30 min followed by the addition of 3-methoxyphenylhydrazine hydrochloride (161 mg, 0.92 mmol). The reaction mixture was stirred at room temperature for 12 h, and the progress of the reaction was monitored by TLC (2:3/EtOAc:Hexanes, R_f 0.42). The reaction was quenched with H_2O (80 mL) and extracted with EtOAc (60 mL). The organic layer was washed with H_2O (50 mL), brine (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (SiO_2, 2:3/EtOAc:Hexanes) to afford compound **5c** (85 mg, 46%) as a yellow solid: ^{1}H NMR (500 MHz, $(CD_3)_2SO$, Fig. S77) δ 10.54 (d, $J = 2.8$ Hz, 1H), 8.20 (td, $J_1 = 8.2$ Hz, $J_2 = 7.4$ Hz, 1H), 7.95 (ddd, $J_1 = 7.5$ Hz, $J_2 = 2.4$ Hz, $J_3 = 0.8$ Hz, 1H), 7.92 (d, $J = 2.7$ Hz, 1H), 7.46 (ddd, $J_1 = 8.3$ Hz, $J_2 = 2.4$ Hz, $J_3 = 0.8$ Hz, 1H), 7.04 (t, $J = 8.1$ Hz, 1H), 6.35 (ddd, $J_1 = 8.1$ Hz, $J_2 = 2.0$ Hz, $J_3 = 1.0$ Hz, 1H), 6.32-6.29 (m, 2H), 3.67 (s, 3H); ^{13}C NMR (150 MHz, $(CD_3)_2SO$, Fig. S78) δ 162.9, 162.6 and 161.0 (d, $J = 238.3$ Hz), 160.1, 150.5, 148.23 and 148.15 (d, $J = 11.9$ Hz), 143.74 and 143.69 (d, $J = 7.7$ Hz), 129.6, 120.5, 113.3 and 113.1 (d, $J = 36.2$ Hz), 105.2 and 104.0 (d, $J = 178.7$ Hz), 98.4, 54.8; HRMS *m/z* calcd for $C_{13}H_{12}FN_3O_2$ $[M+H]^+$: 262.0992; found 262.0986 (Fig. S79). The purity of the compound was further confirmed by HPLC: $R_t = 15.29$ min (96% pure; Fig. S80).

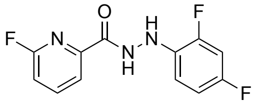


Synthesis of compound 5d (SGT1800). To a solution of 6-fluoro-2-pyridinecarboxylic acid (100 mg, 0.71 mmol) in DMF (3 mL) at 0 °C, *N*-(3-

dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (176 mg, 0.92 mmol), 1-hydroxybenzotriazole hydrate (124 mg, 0.92 mmol), and *N*,*N*-diisopropylethyl amine (0.37 mL, 2.13 mmol) were added. The reaction mixture was stirred at 0 °C for 30 min followed by the addition of 4-fluorophenylhydrazine hydrochloride (150 mg, 0.92 mmol). The reaction mixture was stirred at room temperature for 12 h, and the progress of the reaction was monitored by TLC (2:3/EtOAc:Hexanes, R_f 0.49). The reaction was quenched with H_2O (80 mL) and extracted with EtOAc (60 mL). The organic layer was washed with H_2O (50 mL), brine (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (SiO_2, 2:3/EtOAc:Hexanes) to afford compound **5d** (122 mg, 69%) as a yellow solid: ^{1}H NMR (500 MHz, $(CD_3)_2SO$, Fig. S81) δ 10.60 (d, J = 3.0 Hz, 1H), 8.20 (td, J_1 = 8.2 Hz, J_2 = 7.4 Hz, 1H), 7.95 (ddd, J_1 = 7.5 Hz, J_2 = 2.4 Hz, J_2 = 0.8 Hz, 1H), 7.89 (d, J = 3.2 Hz, 1H), 7.47 (ddd, J_1 = 8.3 Hz, J_2 = 2.5 Hz, J_2 = 0.8 Hz, 1H), 6.99 (t, J = 8.9 Hz, 2H), 6.76 (dd, J_1 = 9.1 Hz, J_2 = 4.7 Hz, 2H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$, Fig. S82) δ 162.9 and 160.5 (d, J = 238.3 Hz), 162.8, 157.1 and 154.7 (d, J = 232.3 Hz), 148.2 and 148.0 (d, J = 12.1 Hz), 145.60 and 145.58 (d, J = 1.9 Hz), 143.7 and 143.6 (d, J = 7.9 Hz), 120.50 and 120.46 (d, J = 3.7 Hz), 115.2 and 115.0 (d, J = 22.3 Hz), 113.64 and 113.56 (d, J = 7.6 Hz), 113.3 and 113.0 (d, J = 36.3 Hz); HRMS *m/z* calcd for $C_{12}H_9F_2N_3O$ $[M+H]^+$: 250.0792; found 250.0785 (Fig. S83). The purity of the compound was further confirmed by HPLC: R_t = 15.36 min (96% pure; Fig. S84).

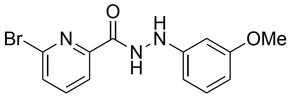


Synthesis of compound 5f (SGT1770). To a solution of 6-fluoro-2-pyridinecarboxylic acid (100 mg, 0.71 mmol) in DMF (3 mL) at 0 °C, *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (163 mg, 0.85 mmol), 1-hydroxybenzotriazole hydrate (115 mg, 0.85 mmol), and *N*,*N*-diisopropylethyl amine (0.37 mL, 2.13 mmol) were added. The reaction mixture was stirred at 0 °C for 30 min followed by the addition of 4-methoxyphenylhydrazine hydrochloride (148 mg, 0.85 mmol). The reaction mixture was stirred at room temperature for 12 h, and the progress of the reaction was monitored by TLC (2:3/EtOAc:Hexanes, R_f 0.49). The reaction was quenched with H_2O (100 mL) and extracted with EtOAc (70 mL). The organic layer was washed with H_2O (70 mL), brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (SiO_2, 2:3/EtOAc:Hexanes) to afford compound **5f** (109 mg, 59%) as a pale yellow solid: ^{1}H NMR (500 MHz, CD_3OD, Fig. S85) δ 8.13 (td, J_1 = 8.1 Hz, J_2 = 7.5 Hz, 1H), 8.02 (ddd, J_1 = 7.4 Hz, J_2 = 2.1 Hz, J_3 = 0.8 Hz, 1H), 7.31 (ddd, J_1 = 8.2 Hz, J_2 = 2.5 Hz, J_3 = 0.8 Hz, 1H), 6.85 (d, J = 9.2 Hz, 2H), 6.80 (d, J = 9.3 Hz, 2H), 3.72 (s, 3H); ^{13}C NMR (150 MHz, $(CD_3)_2SO$, Fig. S86) δ 162.7, 162.5 and 160.9 (d, J = 238.1 Hz), 152.8, 148.3 and 148.2 (d, J = 11.9 Hz), 143.7 and 143.6 (d, J = 7.6 Hz), 142.9, 120.43 and 120.41 (d, J = 3.9 Hz), 114.2, 114.0, 113.2 and 112.9 (d, J = 36.0 Hz), 55.3; HRMS *m/z* calcd for $C_{13}H_{12}FN_3O_2$ $[M+H]^+$: 262.0992; found 262.0983 (Fig. S87). The purity of the compound was further confirmed by HPLC: R_t = 15.01 min (97% pure; Fig. S88).

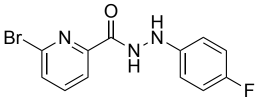


Synthesis of compound 5g (SGT1804). To a solution of 6-fluoro-2-pyridinecarboxylic acid (100 mg, 0.71 mmol) in DMF (3 mL) at 0 °C, *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (176 mg, 0.92 mmol), 1-hydroxybenzotriazole hydrate (124 mg, 0.92 mmol), and *N*,*N*-diisopropylethyl amine (0.37 mL, 2.13 mmol) were added. The reaction mixture was stirred at 0 °C for 30 min followed by the addition of 2,4-difluorophenylhydrazine hydrochloride (166 mg, 0.92 mmol). The reaction mixture was stirred at room temperature for 12 h, and the progress of the reaction was monitored by TLC

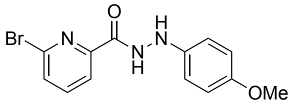
(2:3/EtOAc:Hexanes, R_f 0.46). The reaction was quenched with H_2O (80 mL) and extracted with EtOAc (60 mL). The organic layer was washed with H_2O (50 mL), brine (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (SiO_2, 2:3/EtOAc:Hexanes) to afford compound **5g** (133 mg, 70%) as a pale yellow solid: ^{1}H NMR (500 MHz, $(CD_3)_2SO$, Fig. S89) δ 10.63 (s, 1H), 8.21 (td, J_1 = 8.1 Hz, J_2 = 7.2 Hz, 1H), 7.96 (dd, J_1 = 7.5 Hz, J_2 = 1.6 Hz, 1H), 7.79 (s, 1H), 7.48 (dd, J_1 = 8.3 Hz, J_2 = 2.5 Hz, 1H), 7.16 (ddd, J_1 = 11.8 Hz, J_2 = 9.0 Hz, J_3 = 2.8 Hz,1H), 6.91-6.85 (m, 1H), 6.77 (td, J_1 = 9.8 Hz, J_2 = 5.8 Hz, 1H); ^{13}C NMR (150 MHz, $(CD_3)_2SO$, Fig. S90) δ 163.0, 162.6 and 161.0 (d, J = 238.3 Hz), 155.7 and 155.6 and 154.1 and 154.0 (dd, J_1 = 235.1 Hz, J_2 = 10.7 Hz), 150.5 and 150.4 and 148.9 and 148.8 (dd, J_1 = 240.5 Hz, J_2 = 11.9 Hz), 147.99 and 147.91 (d, J = 12.1 Hz), 143.81 and 143.75 (d, J = 7.7 Hz), 133.50 and 133.48 and 133.43 and 133.41 (dd, J_1 = 10.8 Hz, J_2 = 3.2 Hz), 120.61 and 120.59 (d, J = 3.7 Hz), 114.40 and 114.37 and 114.34 and 114.31 (dd, J_1 = 8.7 Hz, J_2 = 4.3 Hz), 113.5 and 113.2 (d, J = 36.0 Hz), 110.93 and 110.91 and 110.78 and 110.76 (dd, J_1 = 21.7 Hz, J_2 = 3.3 Hz), 103.9 and 103.71 and 103.68 and 103.5 (dd, J_1 =26.9 Hz, J_2 = 22.5 Hz); HRMS *m/z* calcd for $C_{12}H_8F_3N_3O$ $[M+H]^+$: 268.0697; found 268.0692 (Fig. S91). The purity of the compound was further confirmed by HPLC: R_t = 15.68 min (99% pure; Fig. S92).



Synthesis of compound 6c (SGT1437). To a solution of 6-bromo-2-pyridinecarboxylic acid (100 mg, 0.50 mmol) in DMF (3 mL) at 0 °C, *N*-(3-dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride (123 mg, 0.64 mmol), 1-hydroxybenzotriazole hydrate (87 mg, 0.64 mmol), and *N*,*N*-diisopropylethyl amine (0.26 mL, 1.50 mmol) were added. The reaction mixture was stirred at 0 °C for 30 min followed by the addition of 3-methoxyphenylhydrazine hydrochloride (112 mg, 0.64 mmol). The reaction mixture was stirred at room temperature for 12 h, and the progress of the reaction was monitored by TLC (2:3/EtOAc:Hexanes, R*f* 0.41). The reaction was quenched with H_2O (60 mL) and extracted with EtOAc (80 mL). The organic layer was washed with H_2O (60 mL), brine (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (SiO_2, 2:3/EtOAc:Hexanes) to afford compound **6c** (98 mg, 61%) as a pale yellow solid: ^{1}H NMR (500 MHz, $(CD_3)_2SO$, Fig. S93) δ 10.49 (d, *J* = 2.7 Hz, 1H), 8.01 (dd, J_1 = 7.6 Hz, J_2 = 1.1 Hz, 1H), 7.96 (t, *J* = 7.8 Hz, 1H), 7.92 (d, *J* = 2.5 Hz, 1H), 7.90 (dd, J_1 = 7.8 Hz, J_2 = 1.1 Hz, 1H), 7.05 (dd, J_1 = 8.6 Hz, J_2 = 8.5 Hz, 1H), 6.35 (ddd, J_1 = 8.1 Hz, J_2 = 2.1 Hz, J_3 = 1.0 Hz, 1H), 6.33-6.29 (m, 2H), 3.67 (s, 3H); ^{13}C NMR (150 MHz, $(CD_3)_2SO$, Fig. S94) δ 162.8, 160.1, 151.0, 150.5, 140.9, 140.4, 131.2, 129.5, 121.9, 105.2, 104.0, 98.4, 54.8; HRMS *m/z* calcd for $C_{13}H_{12}BrN_3O_2$ $[M+H]^+$: 322.0191; found 322.0187 (Fig. S95). The purity of the compound was further confirmed by HPLC: R_t = 16.05 min (96% pure; Fig. S96).

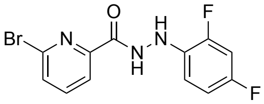


Synthesis of compound 6d (SGT1775). To a solution of 6-bromo-2-pyridinecarboxylic acid (100 mg, 0.50 mmol) in DMF (3 mL) at 0 °C, *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (123 mg, 0.64 mmol), 1-hydroxybenzotriazole hydrate (88 mg, 0.64 mmol), and *N*,*N*-diisopropylethyl amine (0.26 mL, 1.50 mmol) were added. The reaction mixture was stirred at 0 °C for 30 min followed by the addition of 4-fluorophenylhydrazine hydrochloride (104 mg, 0.64 mmol). The reaction mixture was stirred at room temperature for 12 h, and the progress of the reaction was monitored by TLC (2:3/EtOAc:Hexanes, R*f* 0.68). The reaction was quenched with H_2O (80 mL) and extracted with EtOAc (70 mL). The organic layer was washed with H_2O (60 mL), brine (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (SiO_2, 3:7/EtOAc:Hexanes) to afford compound **6d** (70 mg, 45%) as a white solid: ^{1}H NMR (400 MHz, $(CD_3)_2SO$, Fig. S97) δ 10.54 (d, *J* = 3.2 Hz, 1H), 8.02 (dd, J_1 = 7.5 Hz, J_2 = 1.2 Hz, 1H), 7.96 (t, *J* = 7.8 Hz, 1H), 7.89 (dd, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1H), 7.88 (s, 1H), 6.99 (t, *J* = 8.9 Hz, 2H), 6.76 (dd, J_1 = 9.0 Hz, J_2 = 4.6 Hz, 2H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$, Fig. S98) δ 162.9, 156.8 and 155.2 (d, *J* = 154.5 Hz), 151.0, 145.61 and 145.60 (d, *J* = 1.0 Hz), 141.0, 140.4, 131.3, 122.0, 115.3 and 115.1 (d, *J* = 15.0 Hz), 113.73 and 113.68 (d, *J* = 5.0 Hz); HRMS *m/z* calcd for $C_{12}H_9BrFN_3O$ $[M+H]^+$: 309.9991; found 309.9966 (Fig. S99). The purity of the compound was further confirmed by HPLC: R_t = 15.94 min (100% pure; Fig. S100).



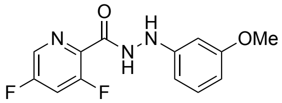
Synthesis of compound 6f (SGT1435). To a solution of 6-bromo-2-pyridinecarboxylic acid (100 mg, 0.50 mmol) in DMF (3 mL) at 0 °C, *N*-(3-dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride (123 mg, 0.64 mmol), 1-hydroxybenzotriazole hydrate (87 mg, 0.64 mmol), and *N*,*N*-diisopropylethyl amine (0.26 mL, 1.50 mmol) were added. The reaction mixture was stirred at 0 °C for 30 min followed by the addition of 4-methoxyphenylhydrazine hydrochloride (112 mg, 0.64 mmol). The reaction mixture was stirred at room temperature for 12 h, and the progress of the reaction was monitored by TLC (2:3/EtOAc:Hexanes, R_f 0.40). The reaction was quenched with H_2O (60 mL) and extracted with EtOAc (80 mL). The organic layer was washed with H_2O (60 mL), brine (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (SiO_2, 2:3/EtOAc:Hexanes) to afford compound **6f** (118 mg, 73%) as a pale yellow solid: ^{1}H NMR (500 MHz, $(CD_3)_2SO$, Fig. S101) δ 10.47 (d, *J* = 3.6 Hz, 1H), 8.01 (dd, J_1 = 7.5 Hz, J_2 = 1.1 Hz, 1H), 7.95 (t, *J* = 7.5 Hz, 1H), 7.89 (dd, J_1 = 7.9 Hz, J_2 = 1.1 Hz, 1H), 7.58 (d, *J* = 3.5 Hz, 1H), 6.77 (d, *J* = 9.4 Hz, 2H), 6.73 (d, *J* = 9.3 Hz, 2H), 3.66 (s, 3H); ^{13}C NMR

(150 MHz, $(CD_3)_2SO$, Fig. S102) δ 162.7, 152.8, 151.1, 142.8, 140.9, 140.4, 131.1, 121.8, 114.2, 114.0, 55.3; HRMS *m/z* calcd for $C_{13}H_{12}BrN_3O_2$ $[M+H]^+$: 322.0191; found 322.0151 (Fig. S103). The purity of the compound was further confirmed by HPLC: R_t = 15.87 min (98% pure; Fig. S104).

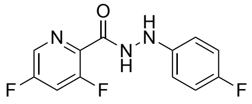


Synthesis of compound 6g (SGT1439). To a solution of 6-bromo-2-pyridinecarboxylic acid (100 mg, 0.50 mmol) in DMF (3 mL) at 0 °C, *N*-(3-dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride (123 mg, 0.64 mmol), 1-hydroxybenzotriazole hydrate (87 mg, 0.64 mmol), and *N*,*N*-diisopropylethyl amine (0.26 mL, 1.50 mmol) were added. The reaction mixture was stirred at 0 °C for 30 min followed by the addition of 2,4-difluorophenylhydrazine hydrochloride (116 mg, 0.64 mmol). The reaction mixture was stirred at room temperature for 12 h, and the progress of the reaction was monitored by TLC (2:3/EtOAc:Hexanes, R_f 0.44). The reaction was quenched with H_2O (60 mL) and extracted with EtOAc (80 mL). The organic layer was washed with H_2O (60 mL), brine (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (SiO_2, 2:3/EtOAc:Hexanes) to afford compound **6g** (116 mg, 71%) as a white solid: ^1H NMR (500 MHz, $(CD_3)_2SO$, Fig. S105) δ 10.58 (s, 1H), 8.02 (dd, J_1 = 7.5 Hz, J_2 = 1.1 Hz, 1H), 7.96 (t, J = 7.8 Hz, 1H), 7.91 (dd, J_1 = 7.9 Hz, J_2 = 1.2 Hz, 1H), 7.79 (s, 1H), 7.17 (ddd, J_1 = 11.8 Hz, J_2 = 8.9 Hz, J_3 = 2.8 Hz, 1H), 6.91-6.85 (m, 1H), 6.80 (td, J_1 = 9.6 Hz, J_2 = 5.8 Hz, 1H); ^{13}C NMR (150 MHz, $(CD_3)_2SO$, Fig. S106) δ 162.9, 155.63 and 155.56 and 154.1 and 154.0 (dd, J_1 = 235.1 Hz, J_2 = 10.8 Hz), 150.8, 150.44 and 150.36 and 148.83 and 148.75 (dd, J_1 = 241.4 Hz, J_2 = 11.9 Hz), 140.9, 140.4, 133.43 and 133.41 and 133.36 and 133.34 (dd, J_1 = 10.8 Hz, J_2 = 3.2 Hz), 131.3, 122.0, 114.44 and 114.41 and 114.38 and 114.35 (dd, J_1 = 8.8 Hz, J_2 =

4.4 Hz), 110.89 and 110.86 and 110.74 and 110.72 (dd, J_1 = 21.6 Hz, J_2 = 3.5 Hz), 103.8 and 103.67 and 103.63 and 103.5 (dd, J_1 = 26.6 Hz, J_2 = 21.8 Hz); HRMS *m/z* calcd for $C_{12}H_8BrF_2N_3O$ $[M+H]^+$: 327.9897; found 327.9889 (Fig. S107). The purity of the compound was further confirmed by HPLC: R_t = 16.19 min (100% pure; Fig. S108).

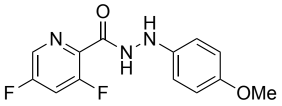


Synthesis of compound 7c (SGT1774). To a solution of 3,5-difluoro-2-pyridinecarboxylic acid (125 mg, 0.79 mmol) in DMF (3 mL) at 0 °C, *N*-(3-dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride (181 mg, 0.94 mmol), 1-hydroxybenzotriazole hydrate (127 mg, 0.94 mmol), and *N*,*N*-diisopropylethyl amine (0.41 mL, 2.37 mmol) were added. The reaction mixture was stirred at 0 °C for 30 min followed by the addition of 3-methoxyphenylhydrazine hydrochloride (164 mg, 0.94 mmol). The reaction mixture was stirred at room temperature for 12 h, and the progress of the reaction was monitored by TLC (2:3/EtOAc:Hexanes, R_f 0.42). The reaction was quenched with H_2O (100 mL) and extracted with EtOAc (70 mL). The organic layer was washed with H_2O (70 mL), brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (SiO_2, 2:3/EtOAc:Hexanes) to afford compound **7c** (38 mg, 18%) as a pale yellow solid: ^{1}H NMR (500 MHz, CD_3OD, Fig. S109) δ 8.49 (d, J = 2.3 Hz, 1H), 7.80-7.74 (m, 1H), 7.09 (td, J_1 = 8.1 Hz, J_2 = 0.6 Hz, 1H), 6.49 (ddd, J_1 = 7.9 Hz, J_2 = 2.2 Hz, J_3 = 0.9 Hz, 1H), 6.48-6.47 (m, 1H), 6.40 (ddd, J_1 = 8.2 Hz, J_2 = 2.4 Hz, J_3 = 0.9 Hz, 1H), 3.74 (s, 3H); ^{13}C NMR (150 MHz, $(CD_3)_2SO$, Fig. S110) δ 162.2 and 162.1 (d, J = 4.4 Hz), 160.74 and 160.70 and 158.99 and 158.95 (dd, J_1 = 261.2 Hz, J_2 = 5.6 Hz), 160.1, 158.2 and 158.1 and 156.4 and 156.3 (dd, J_1 = 267.5 Hz, J_2 = 7.5 Hz), 150.4, 136.86 and 136.84 and 136.79 and 136.76 (dd, J_1 = 10.7 Hz, J_2 = 4.2 Hz), 133.84 and 133.81 and 133.68 and 133.65 (dd, J_1 = 23.6 Hz, J_2 = 4.9 Hz), 129.6, 114.0 and 113.9 and 113.7 (t, *J* = 4.4 Hz), 105.1, 104.0, 98.2, 54.8; HRMS *m/z* calcd for $C_{13}H_{11}F_2N_3O_2$ $[M+H]^+$: 280.0897; found 280.0886 (Fig. S111). The purity of the compound was further confirmed by HPLC: R_t = 14.89 min (95% pure; Fig. S112).



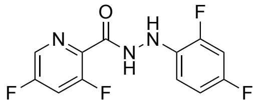
Synthesis of compound 7d (SGT1801). To a solution of 3,5-difluoro-2-pyridinecarboxylic acid (100 mg, 0.63 mmol) in DMF (3 mL) at 0 °C, *N*-(3-dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride (157 mg, 0.82 mmol), 1-hydroxybenzotriazole hydrate (111 mg, 0.82 mmol), and *N*,*N*-diisopropylethyl amine (0.33 mL, 1.89 mmol) were added. The reaction mixture was stirred at 0 °C for 30 min followed by the addition of 4-fluorophenylhydrazine hydrochloride (133 mg, 0.82 mmol). The reaction mixture was stirred at room temperature for 12 h, and the progress of the reaction was monitored by TLC (2:3/EtOAc:Hexanes, R*f* 0.51). The reaction was quenched with H_2O (80 mL) and extracted with EtOAc (60 mL). The organic layer was washed with H_2O (50 mL), brine (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (SiO_2, 2:3/EtOAc:Hexanes) to afford compound **7d** (109 mg, 65%) as a yellow solid: ^{1}H NMR (500 MHz, $(CD_3)_2SO$, Fig. S113) δ 10.47 (br s, 1H), 8.63 (m, 1H), 8.13 (ddd, J_1 = 10.5 Hz, J_2 = 9.2 Hz, J_2 = 2.4 Hz, 1H), 8.00 (br s, 1H), 7.02 (t, *J* = 8.9 Hz, 2H), 6.79 (dd, J_1 = 9.1 Hz, J_2 = 4.7 Hz, 2H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$, Fig. S114) δ 162.14 and 162.09 (d, *J* = 5.3 Hz), 161.23 and 161.17 and 158.7 and 158.6 (dd, J_1 = 251.9 Hz, J_2 = 6.1 Hz), 158.61 and 158.55 and 156.03 and 155.96 (dd, J_1 = 258.5 Hz, J_2 = 6.2 Hz), 157.1 and 154.8 (d, *J* = 232.3 Hz), 145.51 and 145.49 (d, *J* = 1.8 Hz), 136.65 and 136.61 and 136.54 and 136.50 (dd, J_1 = 10.2 Hz, J_2 = 4.1 Hz), 133.82 and 133.78 and 133.6 and 133.5 (dd, J_1 = 23.3 Hz, J_2 = 4.5 Hz), 115.3 and 115.1 (d, *J* = 22.2 Hz), 114.1 and 113.9 and 113.7 (t, *J* = 22.1 Hz), 113.5 and 113.4 (d, *J* = 7.6

Hz); HRMS *m/z* calcd for $C_{12}H_8F_3N_3O$ $[M+H]^+$: 268.0697; found 268.0690 (Fig. S115). The purity of the compound was further confirmed by HPLC: R_t = 15.24 min (95% pure; Fig. S116).



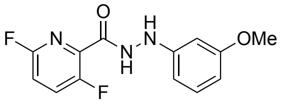
Synthesis of compound 7f (SGT1795). To a solution of 3,5-difluoro-2-pyridinecarboxylic acid (100 mg, 0.63 mmol) in DMF (3 mL) at 0 °C, *N*-(3-dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride (157 mg, 0.82 mmol), 1-hydroxybenzotriazole hydrate (111 mg, 0.82 mmol), and *N*,*N*-diisopropylethyl amine (0.33 mL, 1.89 mmol) were added. The reaction mixture was stirred at 0 °C for 30 min followed by the addition of 4-methoxyphenylhydrazine hydrochloride (143 mg, 0.82 mmol). The reaction mixture was stirred at room temperature for 12 h, and the progress of the reaction was monitored by TLC (2:3/EtOAc:Hexanes, R*f* 0.57). The reaction was quenched with H_2O (80 mL) and extracted with EtOAc (70 mL). The organic layer was washed with H_2O (60 mL), brine (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (SiO_2, 3:7/EtOAc:Hexanes) to afford compound **7f** (72 mg, 41%) as a white solid: ^{1}H NMR (500 MHz, $(CD_3)_2SO$, Fig. S117) δ 10.40 (d, *J* = 3.4 Hz, 1H), 8.62 (d, *J* = 2.3 Hz, 1H), 8.12 (ddd, J_1 = 10.6 Hz, J_2 = 9.2 Hz, J_3 = 2.4 Hz, 1H), 7.69 (d, *J* = 3.8 Hz, 1H), 6.79 (d, *J* = 9.3 Hz, 2H), 6.76 (d, *J* = 9.5 Hz, 2H), 3.67 (s, 3H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$, Fig. S118) δ 162.10 and 162.05 (d, *J* = 5.1 Hz), 161.15 and 161.09 (d, *J* = 6.1 Hz), 158.6 and 158.54 and 158.47 (t, *J* = 6.5 Hz), 155.93 and 155.86 (d, *J* = 7.1 Hz), 152.8, 142.8, 136.90 and 136.86 and 136.80 and 136.76 (dd, J_1 = 10.5 Hz, J_2 = 4.1 Hz), 133.8 and 133.7 and 133.6 and 133.5 (dd, J_1 = 23.3 Hz, J_2 = 4.6 Hz), 114.2 and 113.8 (d, *J* = 48.8 Hz), 114.1 and 113.9 and 113.6 (t, *J* = 22.2 Hz), 55.3; HRMS *m/z* calcd for $C_{13}H_{11}F_2N_3O_2$ $[M+H]^+$: 280.0897; found 280.0890 (Fig. S119).

The purity of the compound was further confirmed by HPLC: R_t = 14.98 min (97% pure; Fig. S120).



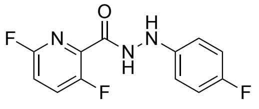
Synthesis of compound 7g (SGT1805). To a solution of 3,5-difluoro-2-pyridinecarboxylic acid (100 mg, 0.63 mmol) in DMF (3 mL) at 0 °C, *N*-(3-dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride (157 mg, 0.82 mmol), 1-hydroxybenzotriazole hydrate (111 mg, 0.82 mmol), and *N*,*N*-diisopropylethyl amine (0.33 mL, 1.89 mmol) were added. The reaction mixture was stirred at 0 °C for 30 min followed by the addition of 2,4-difluorophenylhydrazine hydrochloride (148 mg, 0.82 mmol). The reaction mixture was stirred at room temperature for 12 h, and the progress of the reaction was monitored by TLC (2:3/EtOAc:Hexanes, R_f 0.53). The reaction was quenched with H_2O (80 mL) and extracted with EtOAc (60 mL). The organic layer was washed with H_2O (50 mL), brine (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (SiO_2, 2:3/EtOAc:Hexanes) to afford compound **7g** (118 mg, 66%) as a pale yellow solid: ^{1}H NMR (500 MHz, $(CD_3)_2SO$, Fig. S121) δ 10.52 (s, 1H), 8.63 (d, J = 2.4 Hz, 1H), 8.14 (ddd, J_1 = 10.5 Hz, J_2 = 9.1 Hz, J_3 = 2.4 Hz,1H), 7.91 (s, 1H), 7.18 (ddd, J_1 = 11.8 Hz, J_2 = 9.0 Hz, J_3 = 2.8 Hz,1H), 6.96-6.90 (m, 1H), 6.84 (td, J_1 = 9.5 Hz, J_2 = 5.8 Hz, 1H); ^{13}C NMR (150 MHz, $(CD_3)_2SO$, Fig. S122) δ 162.13 and 162.09 (d, J = 5.3 Hz), 160.91 and 160.87 and 159.2 and 159.1 (dd, J_1 = 261.2 Hz, J_2 = 5.7 Hz), 158.42 and 158.37 and 156.63 and 156.58 (dd, J_1 = 268.6 Hz, J_2 = 7.5 Hz), 155.7 and 155.6 and 154.1 and 154.0 (dd, J_1 = 235.3 Hz, J_2 = 10.3 Hz), 150.44 and 150.36 and 148.83 and 148.75 (dd, J_1 = 241.5 Hz, J_2 = 12.6 Hz), 136.28 and 136.25 and 136.21 and 136.19 (dd, J_1 = 9.8 Hz, J_2 = 4.3 Hz), 133.83 and 133.80 and 133.7 and 133.6 (dd, J_1 = 22.9 Hz, J_2 = 4.4 Hz), 133.40 and 133.38 and 133.32 and 133.31 (dd, J_1 = 11.4 Hz,

J_2 = 2.6 Hz), 114.2 and 113.99 and 113.96 and 113.89 (dd, J_1 = 33.4 Hz, J_2 = 29.0 Hz), 114.0, 110.95 and 110.92 and 110.80 and 110.78 (dd, J_1 = 21.6 Hz, J_2 = 3.3 Hz), 103.9 and 103.79 and 103.76 and 103.6 (dd, J_1 = 26.9 Hz, J_2 = 22.0 Hz); HRMS *m/z* calcd for $C_{12}H_7F_4N_3O$ $[M+H]^+$: 286.0603; found 286.0591 (Fig. S123). The purity of the compound was further confirmed by HPLC: R_t = 15.35 min (95% pure; Fig. S124).



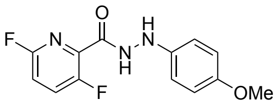
Synthesis of compound 8c (SGT1775). To a solution of 3,6-difluoro-2-pyridinecarboxylic acid (125 mg, 0.79 mmol) in DMF (3 mL) at 0 °C, *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (181 mg, 0.94 mmol), 1-hydroxybenzotriazole hydrate (127 mg, 0.94 mmol), and *N*,*N*-diisopropylethyl amine (0.41 mL, 2.37 mmol) were added. The reaction mixture was stirred at 0 °C for 30 min followed by the addition of 3-methoxyphenylhydrazine hydrochloride (164 mg, 0.94 mmol). The reaction mixture was stirred at room temperature for 12 h, and the progress of the reaction was monitored by TLC (2:3/EtOAc:Hexanes, R_f 0.41). The reaction was quenched with H_2O (100 mL) and extracted with EtOAc (70 mL). The organic layer was washed with H_2O (70 mL), brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (SiO_2, 2:3/EtOAc:Hexanes) to afford compound **8c** (43 mg, 19%) as a pale yellow solid: ^{1}H NMR (500 MHz, CD_3OD, Fig. S125) δ 7.49 (td, J_1 = 9.0 Hz, J_2 = 5.6 Hz, 1H), 7.35 (ddd, J_1 = 9.0 Hz, J_2 = 3.6 Hz, J_3 = 3.1 Hz, 1H), 7.09 (td, J_1 = 7.8 Hz, J_2 = 0.7 Hz, 1H), 6.49 (ddd, J_1 = 8.8 Hz, J_2 = 2.2 Hz, J_3 = 0.9 Hz, 1H), 6.48-6.47 (m, 1H), 6.41 (ddd, J_1 = 8.2 Hz, J_2 = 2.5 Hz, J_3 = 0.9 Hz, 1H), 3.75 (s, 3H); ^{13}C NMR (150 MHz, $(CD_3)_2SO$, Fig. S126) δ 161.6 and 161.5 (d, J = 4.4 Hz), 160.2, 158.0 and 156.4 (d, J = 235.9 Hz), 155.94 and 155.91 and 154.23 and 154.21 (dd, J_1 = 260.0 Hz, J_2 = 3.7 Hz), 150.3, 136.7 and 136.6 and 136.5 (t, J = 15.0 Hz), 132.05

and 131.99 and 131.90 and 131.8 (dd, J_1 = 22.8 Hz, J_2 = 8.7 Hz), 129.6, 114.4 and 114.3 and 114.11 and 114.07 (dd, J_1 = 41.0 Hz, J_2 = 6.1 Hz), 105.1, 104.2, 98.2, 54.8; HRMS *m/z* calcd for $C_{13}H_{11}F_2N_3O_2$ $[M+H]^+$: 280.0897; found 280.0886 (Fig. S127). The purity of the compound was further confirmed by HPLC: R_t = 14.91 min (99% pure; Fig. S128).



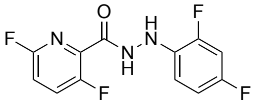
Synthesis of compound 8d (SGT1802). To a solution of 3,6-difluoro-2-pyridinecarboxylic acid (100 mg, 0.63 mmol) in DMF (3 mL) at 0 °C, *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (157 mg, 0.82 mmol), 1-hydroxybenzotriazole hydrate (111 mg, 0.82 mmol), and *N*,*N*-diisopropylethyl amine (0.33 mL, 1.89 mmol) were added. The reaction mixture was stirred at 0 °C for 30 min followed by the addition of 4-fluorophenylhydrazine hydrochloride (133 mg, 0.82 mmol). The reaction mixture was stirred at room temperature for 12 h, and the progress of the reaction was monitored by TLC (2:3/EtOAc:Hexanes, R*f* 0.50). The reaction was quenched with H_2O (80 mL) and extracted with EtOAc (60 mL). The organic layer was washed with H_2O (50 mL), brine (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (SiO_2, 2:3/EtOAc:Hexanes) to afford compound **8d** (116 mg, 69%) as a yellow solid: ^1H NMR (500 MHz, $(CD_3)_2SO$, Fig. S129) δ 10.51 (s, 1H), 8.14 (td, J_1 = 8.9 Hz, J_2 = 6.0 Hz, 1H), 8.01 (s, 1H), 7.53 (dt, J_1 = 8.6 Hz, J_2 = 3.2 Hz, 1H), 7.02 (t, J = 8.9 Hz, 2H), 6.78 (dd, J_1 = 9.1 Hz, J_2 = 4.6 Hz, 2H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$, Fig. S130) δ 161.6 and 161.5 (d, J = 4.7 Hz), 158.3 and 155.9 (d, J = 120.9 Hz), 157.2 and 154.8 (d, J = 232.6 Hz), 156.5 and 156.5 and 153.89 and 153.85 (dd, J_1 = 256.8 Hz, J_2 = 4.2 Hz), 145.35 and 145.33 (d, J = 1.8 Hz), 136.5 and 136.4 and 136.3 and 136.2 (dd, J_1 = 15.6 Hz, J_2 = 13.9 Hz), 132.2 and 132.1 and 131.9 and 131.8 (dd, J_1 = 22.9 Hz, J_2 = 8.8 Hz), 115.3 and 115.1 (d, J = 89.2 Hz), 114.6 and 114.5 and

114.2 and 114.1 (dd, J_1 = 41.0 Hz, J_2 = 6.1 Hz), 113.5 and 113.4 (d, J = 30.4 Hz); HRMS *m/z* calcd for $C_{12}H_{98}F_3N_3O$ $[M+H]^+$: 268.0697; found 268.0695 (Fig. S131). The purity of the compound was further confirmed by HPLC: R_t = 15.12 min (95% pure; Fig. S132).



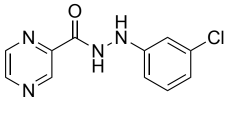
Synthesis of compound 8f (SGT1796). To a solution of 3,6-difluoro-2-pyridinecarboxylic acid (100 mg, 0.63 mmol) in DMF (3 mL) at 0 °C, *N*-(3-dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride (157 mg, 0.82 mmol), 1-hydroxybenzotriazole hydrate (111 mg, 0.82 mmol), and *N*,*N*-diisopropylethyl amine (0.33 mL, 1.89 mmol) were added. The reaction mixture was stirred at 0 °C for 30 min followed by the addition of 4-methoxyphenylhydrazine hydrochloride (143 mg, 0.82 mmol). The reaction mixture was stirred at room temperature for 12 h, and the progress of the reaction was monitored by TLC (2:3/EtOAc:Hexanes, R_f 0.51). The reaction was quenched with H_2O (80 mL) and extracted with EtOAc (70 mL). The organic layer was washed with H_2O (60 mL), brine (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (SiO_2, 2:3/EtOAc:Hexanes) to afford compound **8f** (74 mg, 42%) as an orange solid: ^1H NMR (500 MHz, $(CD_3)_2SO$, Fig. S133) δ 10.44 (d, J = 3.6 Hz, 1H), 8.13 (td, J_1 = 8.9 Hz, J_2 = 6.0 Hz, 1H), 7.71 (d, J = 3.6 Hz, 1H), 7.51 (ddd, J_1 = 9.0 Hz, J_2 = 3.4 Hz, J_3 = 2.8 Hz, 1H), 6.80 (d, J = 9.2 Hz, 2H), 6.76 (d, J = 9.1 Hz, 2H), 3.67 (s, 3H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$, Fig. S134) δ 161.50 and 161.46 (d, J = 4.7 Hz), 158.32 and 158.31 and 155.96 and 155.95 (dd, J_1 = 235.9 Hz, J_2 = 1.0 Hz), 156.35 and 156.31 and 153.78 and 153.74 (dd, J_1 = 256.2 Hz, J_2 = 4.1 Hz), 153.4, 152.9, 142.6, 141.9, 136.8 and 136.7 and 136.6 and 136.5 (dd, J_1 = 15.9 Hz, J_2 = 13.9 Hz), 132.1 and 132.0 and 131.84 and 131.75 (dd, J_1 = 23.0 Hz, J_2 = 8.9 Hz), 114.4 and 114.2 and 114.0 and 113.9 (dd, J_1 = 17.3 Hz, J_2 = 6.0 Hz), 114.3 and 113.8 (d, J = 49.3 Hz);

HRMS *m/z* calcd for $C_{13}H_{11}F_2N_3O_2$ $[M+H]^+$: 280.0897; found 280.0885 (Fig. S135). The purity of the compound was further confirmed by HPLC: R_t = 15.02 min (97% pure; Fig. S136).

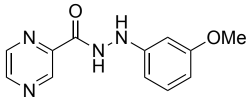


Synthesis of compound 8g (SGT1806). To a solution of 3,6-difluoro-2-pyridinecarboxylic acid (100 mg, 0.63 mmol) in DMF (3 mL) at 0 °C, *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (157 mg, 0.82 mmol), 1-hydroxybenzotriazole hydrate (111 mg, 0.82 mmol), and *N*,*N*-diisopropylethyl amine (0.33 mL, 1.89 mmol) were added. The reaction mixture was stirred at 0 °C for 30 min followed by the addition of 2,4-difluorophenylhydrazine hydrochloride (148 mg, 0.82 mmol). The reaction mixture was stirred at room temperature for 12 h, and the progress of the reaction was monitored by TLC (2:3/EtOAc:Hexanes, R*f* 0.51). The reaction was quenched with H_2O (80 mL) and extracted with EtOAc (60 mL). The organic layer was washed with H_2O (50 mL), brine (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (SiO_2, 2:3/EtOAc:Hexanes) to afford compound **8g** (109 mg, 61%) as a pale yellow solid: ^1H NMR (500 MHz, $(CD_3)_2SO$, Fig. S137) δ 10.55 (s, 1H), 8.15 (td, J_1 = 9.0 Hz, J_2 = 6.0 Hz, 1H), 7.93 (s, 1H), 7.53 (dt, J_1 = 8.9 Hz, J_2 = 2.9 Hz, 1H), 7.18 (ddd, J_1 = 11.8 Hz, J_2 = 8.9 Hz, J_3 = 2.8 Hz,1H), 6.97-6.91 (m, 1H), 6.84 (td, J_1 = 9.5 Hz, J_2 = 5.8 Hz, 1H); ^{13}C NMR (150 MHz, $(CD_3)_2SO$, Fig. S138) δ 161.6 and 161.5 (d, J = 4.7 Hz), 157.9 and 156.3 (d, J = 236.0 Hz), 156.2 and 156.1 and 154.44 and 154.41 (dd, J_1 = 256.9 Hz, J_2 = 4.3 Hz), 155.72 and 155.65 and 154.15 and 154.08 (dd, J_1 = 235.1Hz, J_2 = 10.7 Hz), 150.5 and 150.4 and 148.84 and 148.76 (dd, J_1 = 241.5 Hz, J_2 = 12.0 Hz), 136.1 and 136.0 and 135.9 (t, J = 14.3 Hz), 133.23 and 133.21 and 133.15 and 133.14 (dd, J_1 = 10.8 Hz, J_2 = 2.3 Hz), 132.24 and 132.19 and 132.1 and 132.03 (dd, J_1 = 22.9 Hz, J_2 = 8.8 Hz), 114.72 and 114.68 and 114.45 and 114.41 (dd, J_1 = 41.0 Hz, J_2

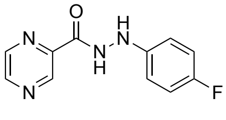
=6.3Hz), 114.1 and 114.03 and 114.00 and 113.97 (dd, J_1 = 9.0 Hz, J_2 = 4.4 Hz), 110.98 and 110.95 and 110.83 and 110.81 (dd, J_1 = 21.7 Hz, J_2 = 3.7 Hz), 104.0 and 103.81 and 103.78 and 103.6 (dd, J_1 = 26.5 Hz, J_2 = 22.1 Hz); HRMS *m/z* calcd for $C_{12}H_7F_4N_3O$ $[M+H]^+$: 286.0603; found 286.0600 (Fig. S139). The purity of the compound was further confirmed by HPLC: R_t = 15.38 min (98% pure; Fig. S140).



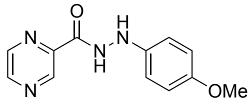
Synthesis of compound 9b (SGT1793). To a solution of pyrazinecarboxylic acid (100 mg, 0.81 mmol) in DMF (3 mL) at 0 °C, *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (201 mg, 1.05 mmol) and *N*,*N*-diisopropylethyl amine (0.40 mL, 2.43 mmol) were added. The reaction mixture was stirred at 0 °C for 30 min followed by the addition of 3-chlorophenylhydrazine hydrochloride (188 mg, 1.05 mmol). The reaction mixture was stirred at room temperature for 12 h, and the progress of the reaction was monitored by TLC (3:2/EtOAc:Hexanes, R_f 0.31). The reaction was quenched with H_2O (100 mL), extracted with EtOAc (150 mL), washed with brine (30 mL), and dried over $MgSO_4$. The organic layer was removed under reduced pressure, and the residue was purified by flash column chromatography (SiO_2, 3:2/EtOAc:Hexanes) to afford compound **9b** (137 mg, 68%) as a pale yellow solid: ^{1}H NMR (500 MHz, $(CD_3)_2SO$, Fig. S141) δ 10.83 (s, 1H), 9.18 (d, *J* = 1.5 Hz, 1H), 8.91 (d, *J* = 2.5 Hz, 1H), 8.78 (dd, J_1 = 2.3 Hz, J_2 = 1.5 Hz, 1H), 8.29 (s, 1H), 7.18-7.13 (m, 1H), 6.76-6.70 (m, 3H); ^{13}C NMR (150 MHz, $(CD_3)_2SO$, Fig. S142) δ 163.1, 150.6, 147.9, 144.6, 143.7, 143.6, 133.4, 130.4, 118.1, 111.5, 111.0; HRMS *m/z* calcd for $C_{11}H_9ClN_4O$ $[M+H]^+$: 249.0543; found 249.0546 (Fig. S143). The purity of the compound was further confirmed by HPLC: R_t = 15.00 min (97% pure; Fig. S144).



Synthesis of compound 9c (SGT1773). To a solution of pyrazinecarboxylic acid (125 mg, 1.01 mmol) in DMF (3 mL) at 0 °C, *N*-(3-dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride (232 mg, 1.21 mmol), 1-hydroxybenzotriazole hydrate (163 mg, 1.21 mmol), and *N*,*N*-diisopropylethyl amine (0.53 mL, 3.03 mmol) were added. The reaction mixture was stirred at 0 °C for 30 min followed by the addition of 3-methoxyphenylhydrazine hydrochloride (211 mg, 1.21 mmol). The reaction mixture was stirred at room temperature for 12 h, and the progress of the reaction was monitored by TLC (2:3/EtOAc:Hexanes, R_f 0.21). The reaction was quenched with H_2O (100 mL) and extracted with EtOAc (70 mL). The organic layer was washed with H_2O (70 mL), brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (SiO_2, 3:2/EtOAc:Hexanes) to afford compound **9c** (49 mg, 20%) as a pale yellow solid: ^{1}H NMR (500 MHz, CD_3OD, Fig. S145) δ 9.24 (d, J = 1.6 Hz, 1H), 8.83 (d, J = 2.5 Hz, 1H), 8.73 (dd, J_1 = 2.5 Hz, J_2 = 1.5 Hz, 1H), 7.09 (t, J = 8.1 Hz, 1H), 6.47 (ddd, J_1 = 8.0 Hz, J_2 = 2.2 Hz, J_3 = 0.9 Hz, 1H), 6.45 (t, J = 2.3 Hz, 1H), 6.41 (ddd, J_1 = 8.2 Hz, J_2 = 2.5 Hz, J_3 = 0.9 Hz, 1H), 3.73 (s, 3H); ^{13}C NMR (150 MHz, $(CD_3)_2SO$, Fig. S146) δ 163.0, 160.1, 150.5, 147.8, 144.8, 143.62, 143.59, 129.6, 105.2, 104.0, 98.3, 54.8; HRMS *m/z* calcd for $C_{12}H_{12}N_4O_2$ $[M+H]^+$: 245.1038; found 245.1027 (Fig. S147). The purity of the compound was further confirmed by HPLC: R_t = 14.14 min (97% pure; Fig. S148).

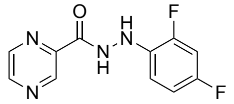


Synthesis of compound 9d (SGT1780). To a solution of pyrazinecarboxylic acid (100 mg, 0.81 mmol) in DMF (3 mL) at 0 °C, *N*-(3-dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride (201 mg, 1.05 mmol), 1-hydroxybenzotriazole hydrate (142 mg, 1.05 mmol), and *N*,*N*-diisopropylethyl amine (0.40 mL, 2.43 mmol) were added. The reaction mixture was stirred at 0 °C for 30 min followed by the addition of 4-fluorophenylhydrazine hydrochloride (171 mg, 1.05 mmol). The reaction mixture was stirred at room temperature for 12 h, and the progress of the reaction was monitored by TLC (1:2/EtOAc:Hexanes, R_f 0.21). The reaction was quenched with H_2O (100 mL), extracted with EtOAc (150 mL), washed with brine (30 mL), and dried over $MgSO_4$. The organic layer was removed under reduced pressure, and the residue was purified by flash column chromatography (SiO_2, 3:2/EtOAc:Hexanes) to afford compound **9d** (154 mg, 82%) as a yellow solid: ^{1}H NMR (500 MHz, $(CD_3)_2SO$, Fig. S149) δ 10.78 (s, 1H), 9.16 (d, *J* = 1.5 Hz, 1H), 8.90 (d, *J* = 2.5 Hz, 1H), 8.77 (dd, J_1 = 2.5 Hz, J_2 = 1.5 Hz, 1H), 7.96 (s, 1H), 6.99 (t, *J* = 9.0 Hz, 2H), 6.78 (dd, J_1 = 9.1 Hz, J_2 = 4.6 Hz, 2H); ^{13}C NMR (150 MHz, $(CD_3)_2SO$, Fig. S150) δ 163.1, 156.7 and 155.2 (d, *J* = 231.8 Hz), 147.8, 145.5, 144.8, 143.63, 143.58, 115.2 and 115.1 (d, *J* = 22.6 Hz), 113.7 and 113.6 (d, *J* = 7.6 Hz); HRMS *m/z* calcd for $C_{11}H_9FN_4O$ $[M+H]^+$: 233.0838; found 233.0817 (Fig. S151). The purity of the compound was further confirmed by HPLC: R_t = 14.38 min (97% pure; Fig. S152).



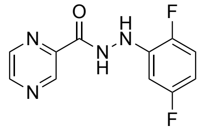
Synthesis of compound 9f (SGT1782). To a solution of pyrazinecarboxylic acid (100 mg, 0.81 mmol) in DMF (3 mL) at 0 °C, *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (201 mg, 1.05 mmol), 1-hydroxybenzotriazole hydrate (142 mg, 1.05 mmol), and *N*,*N*-diisopropylethyl amine (0.40 mL, 2.43 mmol) were added. The reaction mixture was stirred at 0 °C for 30 min followed by the addition of 4-methoxyphenylhydrazine hydrochloride (183 mg, 1.05 mmol). The reaction mixture was stirred at room temperature for 12 h, and the progress of the reaction was monitored by TLC (1:2/EtOAc:Hexanes, R_f 0.263). The reaction was quenched with H_2O (100 mL), extracted with

EtOAc (150 mL), washed with brine (30 mL), and dried over $MgSO_4$. The organic layer was removed under reduced pressure, and the residue was purified by flash column chromatography (SiO_2, 3:2/EtOAc:Hexanes) to afford compound **9f** (122 mg, 62%) as a brown solid: ^{1}H NMR (500 MHz, $(CD_3)_2SO$, Fig. S153) δ 10.71 (d, *J* = 3.7 Hz, 1H), 9.15 (d, *J* = 1.6 Hz, 1H), 8.90 (d, *J* = 2.5 Hz, 1H), 8.77 (dd, J_1 = 2.5 Hz, J_2 = 1.5 Hz, 1H), 7.65 (d, *J* = 3.7 Hz, 1H), 6.76 (d, *J* = 1.9 Hz, 4H), 3.66 (s, 3H); ^{13}C NMR (150 MHz, $(CD_3)_2SO$, Fig. S154) δ 163.0, 152.9, 147.7, 144.9, 143.6 (2C), 142.8, 114.2, 114.0, 55.3; HRMS *m/z* calcd for $C_{12}H_{12}N_4O_2$ $[M+H]^+$: 245.1038; found 245.1011 (Fig. S155). The purity of the compound was further confirmed by HPLC: R_t = 14.29 min (97% pure; Fig. S156).

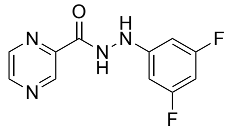


Synthesis of compound 9g (SGT1397). To a solution of pyrazinecarboxylic acid (100 mg, 0.81 mmol) in DMF (3 mL) at 0 °C, *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (201 mg, 1.05 mmol), 1-hydroxybenzotriazole hydrate (142 mg, 1.05 mmol), and *N*,*N*-diisopropylethyl amine (0.40 mL, 2.43 mmol) were added. The reaction mixture was stirred at 0 °C for 30 min followed by the addition of 2,4-difluorophenylhydrazine hydrochloride (190 mg, 1.05 mmol). The reaction mixture was stirred at room temperature for 12 h, and the progress of the reaction was monitored by TLC (2:4/EtOAc:Hexanes, R_f 0.24). The reaction was quenched with H_2O (100 mL), extracted with EtOAc (150 mL), washed with brine (30 mL), and dried over $MgSO_4$. The organic layer was removed under reduced pressure, and the residue was purified by flash column chromatography (SiO_2, 1:1/EtOAc:Hexanes) to afford compound **9g** (160 mg, 79%) as a yellow solid: ^{1}H NMR (500 MHz, $(CD_3)_2SO$, Fig. S157) δ 10.82 (s, 1H), 9.16 (d, *J* = 1.5 Hz, 1H), 8.91 (d, *J* = 2.5 Hz, 1H), 8.78 (dd, J_1 = 2.5 Hz, J_2 = 1.5 Hz, 1H), 7.87 (s, 1H), 7.17 (ddd, J_1 = 11.8 Hz, J_2 = 9.0 Hz, J_3

= 2.8 Hz, 1H), 6.90-6.85 (m, 1H), 6.81 (td, J_1 = 9.5 Hz, J_2 = 5.8 Hz, 1H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$, Fig. S158) δ 163.2, 156.1 and 156.0 and 153.7 and 153.6 (dd, J_1 = 235.5 Hz, J_2 = 10.7 Hz), 150.9 and 150.8 and 148.5 and 148.4 (dd, J_1 = 241.4 Hz, J_2 = 12.0 Hz), 147.9, 144.6, 143.7, 143.6, 133.42 and 133.39 and 133.31 and 133.28 (dd, J_1 = 10.9 Hz, J_2 = 3.0 Hz), 114.5 and 114.41 and 114.36 and 114.32 (dd, J_1 = 9.1 Hz, J_2 = 4.6 Hz), 110.94 and 110.90 and 110.72 and 110.69 (dd, J_1 = 21.8 Hz, J_2 = 3.6 Hz), 103.9 and 103.72 and 103.67 and 103.4 (dd, J_1 = 26.8 Hz, J_2 = 22.3 Hz); HRMS *m/z* calcd for $C_{11}H_8F_2N_4O$ $[M+H]^+$: 251.0744; found 251.0723 (Fig. S159). The purity of the compound was further confirmed by HPLC: R_t = 14.93 min (96% pure; Fig. S160).

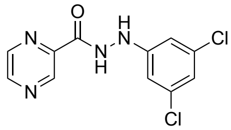


Synthesis of compound 9h (SGT1791). To a solution of pyrazinecarboxylic acid (100 mg, 0.81 mmol) in DMF (3 mL) at 0 °C, *N*-(3-dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride (201 mg, 1.05 mmol) and *N*,*N*-diisopropylethyl amine (0.40 mL, 2.43 mmol) were added. The reaction mixture was stirred at 0 °C for 30 min followed by the addition of 2,5-difluorophenylhydrazine hydrochloride (187 mg, 1.05 mmol). The reaction mixture was stirred at room temperature for 12 h, and the progress of the reaction was monitored by TLC (3:2/EtOAc:Hexanes, R*f* 0.28). The reaction was quenched with H_2O (100 mL), extracted with EtOAc (150 mL), washed with brine (30 mL), and dried over $MgSO_4$. The organic layer was removed under reduced pressure, and the residue was purified by flash column chromatography (SiO_2, 3:2/EtOAc:Hexanes) to afford compound **9h** (156 mg, 77%) as a pale yellow solid: ^{1}H NMR (500 MHz, $(CD_3)_2SO$, Fig. S161) δ 10.83 (s, 1H), 9.18 (d, J = 1.5 Hz, 1H), 8.92 (d, J = 2.5 Hz, 1H), 8.78 (dd, J_1 = 2.5 Hz, J_2 = 1.5 Hz, 1H), 8.25 (s, 1H), 7.13 (ddd, J_1 = 13.9 Hz, J_2 = 8.9 Hz, J_3 = 5.0 Hz, 1H), 6.56 (ddd, J_1 = 10.4 Hz, J_2 = 5.4 Hz, J_3 = 3.2 Hz, 1H), 6.52-6.46 (m, 1H); ^{13}C NMR (150 MHz, $(CD_3)_2SO$, Fig. S162) δ 163.2, 159.7 and 158.2 (d, J = 235.8 Hz), 147.9, 147.0, 145.5, 144.6, 143.8 and 143.6 (d, J = 27.0 Hz), 138.3 and 138.2 and 138.1 (t, J = 11.7 Hz), 115.9 and 115.8 and 115.74 and 115.67 (dd, J_1 = 20.4 Hz, J_2 = 10.6 Hz), 103.93 and 103.88 and 103.77 and 103.72 (dd, J_1 = 24.6 Hz, J_2 = 7.5 Hz), 100.39 and 100.37 and 100.21 and 100.18 (dd, J_1 = 29.1 Hz, J_2 = 4.1 Hz); HRMS *m/z* calcd for $C_{11}H_8F_2N_4O$ $[M+H]^+$: 251.0744; found 251.0739 (Fig. S163). The purity of the compound was further confirmed by HPLC: R_t = 14.89 min (98% pure; Fig. S164).



Synthesis of compound 9i (SGT1792). To a solution of pyrazinecarboxylic acid (100 mg, 0.81 mmol) in DMF (3 mL) at 0 °C, *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (201 mg, 1.05 mmol) and *N*,*N*-diisopropylethyl amine (0.40 mL, 2.43 mmol) were added. The reaction mixture was stirred at 0 °C for 30 min followed by the addition of 3,5-difluorophenylhydrazine hydrochloride (187 mg, 1.05 mmol). The reaction mixture was stirred at room temperature for 12 h, and the progress of the reaction was monitored by TLC (3:2/EtOAc:Hexanes, R_f 0.26). The reaction was quenched with H_2O (100 mL), extracted with EtOAc (150 mL), washed with brine (30 mL), and dried over $MgSO_4$. The organic layer was removed under reduced pressure, and the residue was purified by flash column chromatography (SiO_2, 3:2/EtOAc:Hexanes) to afford compound **9i** (148 mg, 73%) as a pale yellow solid: ^1H NMR (500 MHz, $(CD_3)_2SO$, Fig. S165) δ 10.87 (s, 1H), 9.18 (d, J = 1.5 Hz, 1H), 8.91 (d, J = 2.5 Hz, 1H), 8.78 (dd, J_1 = 2.5 Hz, J_2 = 1.5 Hz, 1H), 8.57 (s, 1H), 6.45 (tt, J_1 = 9.4 Hz, J_2 = 2.4 Hz, 1H), 6.40-6.35 (m, 2H); ^{13}C NMR (150 MHz, $(CD_3)_2SO$, Fig. S166) δ 164.1 and 164.0 and 162.5 and 162.4 (dd, J_1 = 240.6 Hz, J_2 = 16.0 Hz), 163.1, 152.2 and 152.1 and 152.0 (t, J = 12.9 Hz), 147.9, 144.5, 143.8 and 143.6 (d, J = 31.6 Hz), 95.04 and 94.85 (d, J = 28.7 Hz), 95.00 and 94.89 (d, J = 16.5 Hz), 93.3 and 93.1 and 92.9 (t, J = 26.3 Hz); HRMS *m/z* calcd for

$C_{11}H_8F_2N_4O$ $[M+H]^+$: 251.0744; found 251.0738 (Fig. S167). The purity of the compound was further confirmed by HPLC: R_t = 14.82 min (98% pure; Fig. S168).



Synthesis of compound 9j (SGT1794). To a solution of pyrazinecarboxylic acid (100 mg, 0.81 mmol) in DMF (3 mL) at 0 °C, *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (201 mg, 1.05 mmol) and *N*,*N*-diisopropylethyl amine (0.40 mL, 2.43 mmol) were added. The reaction mixture was stirred at 0 °C for 30 min followed by the addition of 3,5-dichlorophenylhydrazine hydrochloride (224 mg, 1.05 mmol). The reaction mixture was stirred at room temperature for 12 h, and the progress of the reaction was monitored by TLC (3:2/EtOAc:Hexanes, R_f 0.36). The reaction was quenched with H_2O (100 mL), extracted with EtOAc (150 mL), washed with brine (30 mL), and dried over $MgSO_4$. The organic layer was removed under reduced pressure, and the residue was purified by flash column chromatography (SiO_2, 3:2/EtOAc:Hexanes) to afford compound **9j** (147 mg, 64%) as a pale yellow solid: ^1H NMR (500 MHz, $(CD_3)_2SO$, Fig. S169) δ 10.91 (s, 1H), 9.18 (d, J = 1.5 Hz, 1H), 8.92 (d, J = 2.5 Hz, 1H), 8.78 (dd, J_1 = 2.5 Hz, J_2 = 1.5 Hz, 1H), 8.57 (s, 1H), 6.85 (t, J = 1.9 Hz, 1H), 6.73 (d, J = 1.9 Hz, 2H); ^{13}C NMR (150 MHz, $(CD_3)_2SO$, Fig. S170) δ 163.1, 151.5, 147.9, 144.4, 143.8, 143.6, 134.4, 117.3, 110.4; HRMS *m/z* calcd for $C_{11}H_8Cl_2N_4O$ $[M+H]^+$: 283.0153; found 283.0159 (Fig. S171). The purity of the compound was further confirmed by HPLC: R_t = 15.95 min (95% pure; Fig. S172).

BIOLOGICAL STUDIES

Reagents, fungal strains, and culture conditions. 10 mg/mL stock solutions of compounds **1a**-**9j** were prepared in dimethyl sulfoxide (DMSO) and were stored at -20 °C in the dark. The antifungal agent amphotericin B (AmB) was purchased from VWR (Radnor PA, USA). AmB was dissolved in DMSO at a final concentration of 5 mg/mL and was stored at -20 °C, protected from light. *Candida albicans* ATCC 10231 (strain *A*), *C. albicans* ATCC 64124 (*B*), and *C. albicans* ATCC MYA-2876 (*C*) were kindly provided by Dr. Jon Y. Takemoto (Utah State University, Logan, UT, USA). *C. albicans* ATCC 90819 (*D*), *C. albicans* ATCC MYA-2310 (*E*), *C. albicans* ATCC MYA-1237 (*F*), *C. albicans* ATCC MYA-1003 (*G*), *Candida glabrata* ATCC 2001 (*H*), *Candida krusei* ATCC 6258 (*I*), *Candida parapsilosis* ATCC 22019 (*J*), *Cryptococcus neoformans* ATCC MYA-895 (*M*), *Aspergillus terreus* ATCC MYA-3633 (*N*), and *Aspergillus flavus* ATCC MYA-3631 (*O*) were obtained from the American Type Culture Collection (ATCC; Manassas, VA, USA). *Aspergillus nidulans* ATCC 38163 (*P*) was received from Dr. Jon S. Thorson (University of Kentucky, Lexington, KY, USA). Clinically derived *Aspergillus fumigatus* NRRL 163 (*Q*), *A. fumigatus* NRRL 5109 (*R*), and *A. fumigatus* NRRL 6113 (*S*) were obtained from Northern Regional Research Laboratory (NRRL). *Candida auris* 384 (*K*), *C. auris* 390 (*L*), and fungal strains 381-400 (including 10 *C. auris* (AR Bank # 381-390), 3 *Candida duobushaemulonii* (AR Bank # 391, AR Bank # 392, and AR Bank # 394), 2 *Candida haemulonii* (AR Bank # 393 and AR Bank # 395), 1 *Kodameae ohmeri* (AR Bank # 396), 1 *C. krusei* (AR Bank # 397), 1 *Candida lusitaniae* (AR Bank # 398), and 2 *Saccharomyces cerevisiae* strains (AR Bank # 399 and AR Bank # 400)) were part of a larger fungal library from the AR Bank maintained by the Centers for Disease Control and Prevention (CDC; Atlanta, GA, USA). Filamentous fungi and yeasts were cultivated at 35 °C in RPMI 1640 medium (with L-glutamine, without sodium biocarbonate, Sigma-Aldrich, St. Louis, MO) buffered to a pH of 7.0 with 0.165 M morpholinepropanesulfonic acid (MOPS) buffer (Sigma-Aldrich). For cytotoxicity assays, HepG2 and the mouse macrophage cell line J774A.1 were provided by Profs. Vincent J. Venditto

(University of Kentucky, Lexington, KY) and David J. Feola (University of Kentucky, Lexington, KY), respectively. The human embryonic kidney cell line, HEK-293, was bought from the ATCC. Mammalian cells were grown in Dulbecco's Modified Eagle's Medium (DMEM) (from VWR) with 10% fetal bovine serum (FBS) (from VWR) and 1% Pen/Strep (from ATCC). Cell lines were cultured at 37 °C with 5% CO_2 and passaged by trypsinization with 0.05% trypsin:0.53 mM EDTA (from Sigma-Aldrich).

MIC value determination by *in vitro* antifungal assays. The MIC values of compounds **1a-9j** against yeast cells (strains *A*-*P* and 381-400) were determined in 96-well plates as described in the CLSI documents M27-A3 and M38-A2 with minor modifications.[2] A single colony of freshly prepared yeast cells was used to inoculate 5 mL of yeast extract peptone dextrose (YPD) broth prior to incubation overnight with shaking at 200 rpm at 35 °C. From the actively growing yeast culture, 100 μL were then transferred to 900 μL of RPMI 1640 medium and re-adjusted to achieve OD_{600} of 0.12 (~1×10^6 CFU/mL). The cell suspension was further diluted to achieve 1:100 in RPMI 1640 medium. 100 μL of cells were added to the wells of a 96-well microtiter plates that contained 100 μL of the compound solution to obtain concentrations of 0.06-31.3 μg/mL of compounds **1a-9j** or AmB prior to incubation for 48 h at 35 °C.

***In vitro* cytotoxicity assays.** Cytotoxicity assays were performed as previously described with slight modifications.[3] HepG2, J774A.1, and HEK-293 cells were first thawed from frozen stocks kept in liquid N_2 and grown in Dulbecco's modified Eagles's medium (DMEM) containing 10% fetal bovine serum (FBS) and 1% Pen/Strep. The adherent cells (HepG2 and HEK-293) were then treated with trypsin using 0.05% trypsin-0.53 mM EDTA and resuspended in fresh DMEM (*Note*:

the trypsin treatment is not needed for J774A.1 cells). Once the cells were 80% confluent, they were transferred to a 96-well microtiter plate at density of 10,000 cells/well for J774A.1, HEK-293, and HepG2. The 96-well plates were incubated 37 °C with 5% CO_2 overnight. The fresh powders of compounds **2a**, **2b**, **2d**, **2g**, **2i**, **9a**, **9b**, **9c**, **9f**, **9g**, as well as controls AmB and VRC were prepared as 6.26 mg/mL stock solutions in molecular biology grade DMSO (200× the highest final concentration). The stock solutions were diluted in 1.5 mL eppendorf tubes to achieve concentrations of 6.26-0.024 mg/mL (200×). 5 μL of these 200× compound stock solutions were then added to 495 μL of DMEM in 1.5 mL eppendorf tubes to obtain concentrations of 62.6-0.24 μg/mL (2×). The medium in the 96-well plates containing the cells was aspirated and replaced by fresh DMEM (100 μL). The serially diluted monohydrazides **2a**, **2b**, **2d**, **2g**, **2i**, **9a**, **9b**, **9c**, **9f**, **9g**, as well as controls AmB and VRC were added to the 96-well plates to obtain final concentrations of 31.3-0.12 μg/mL. The 96-well plates were further incubated for 24 h at 37 °C with 5% CO_2 overnight. To evaluate cell survival, each well was treated with 10 μL (2 mM) of resazurin sodium salt (Sigma-Aldrich, St. Louis, MO, USA) and was incubated for another 6 h. Metabolically active cells can convert resazurin to the highly fluorescent dye, resorufin, and be detected at λ_{560} excitation and λ_{590} emission using a SpectraMax M5 plate reader (Molecular Devices, San Jose, CA, USA). Triton X-100® (1%, *v*/*v*) was used as positive control; the negative control consisted of cells treated with the delivery vehicle (0.05% DMSO), and the blank control was only the culture medium with 0.05% DMSO without cells. The experiments were performed in quadruplicate. The 100% normalized data are reported in Fig. 3 and the corresponding non-normalized data are reported in Fig S173.

Time-kill assays. Time-kill assays were used to assess the inhibitory efficiency of compound **2b** against *C. albicans* ATCC 10231 (strain *A*, Fig. 4). The yeast culture was grown overnight in YPD medium at 35 °C with shaking at 200 rpm. A working stock of fungal cells was made by diluting cultures in RPMI 1640 medium to an OD_{600} of 0.125. From the working stock, 100 μL of cells were added to 4.9 mL of RPMI 1640 medium in sterile culture tubes, making the starting fungal cell concentration ~1×10^5 CFU/mL. Compounds were then added to the fungal cells. The treatment conditions included growth control, AmB (positive control), and compound **2b** at 1× and 4× MIC. For *C. albicans* ATCC 10231 (strain *A*), the concentration of AmB was 0.98 μg/mL and the concentrations of compound **2b** were 0.12 (1× MIC) and 0.48 (4× MIC) μg/mL. The treated fungal cultures were incubated at 35 °C with shaking at 200 rpm for 24 h. Samples were aliquoted from the different treatments at regular time points (0, 3, 6, 9, 12, 18, and 24 h) and plated in duplicate. For each time point, cultures were vortexed, 100 μL of each culture were aspirated, and 10-fold serial dilutions were made in RPMI 1640 medium. From the appropriate dilutions, 100 μL of fungal suspension was spread onto potato dextrose agar (PDA) plates and incubated at 35 °C for 48 h before colony were counted. Experiments were performed in duplicate.

Biofilm disruption assays. Biofilm disruption assays were performed to assess the effectiveness of compounds **2a**-**2j** against *C. albicans* ATCC 10231 (strain *A*, Fig. 5A). AmB was used as a positive control. Biofilm assays were performed in 96-well plates using XTT [2,3-bis(2-methoxy-4-nitro-5-sulfophenyl)-2*H*-tetrazolium-5-carboxanilide] to measure the viability of the cells in the biofilm, as previously described.[4] An overnight culture of the yeast cells was grown at 35 °C in YPD medium with shaking at 200 rpm. The overnight culture was diluted in RPMI 1640 medium to an OD_{600} between 0.12 and 0.15 to make a working stock. The working stock was transferred to 96-well plates in 100 μL aliquots, leaving one column empty for the sterile controls. The plates were incubated at 37 °C for 24 h to allow the biofilm to form. The medium and planktonic cells from the plate were then aspirated. Phosphate buffered saline (PBS) was then used to wash remaining planktonic cells from wells 3 times. After washing, RPMI 1640 medium and the compound were added to the plate, in a similar fashion to that described in the MIC assays. Plates were incubated at 37 °C for 24 h. Finally, the plates were washed 3 times with PBS before adding 100 μL of XTT dye (0.5 mg/mL) with 1 μM menadione. The XTT was prepared by dissolving XTT at 0.5 mg/mL concentration in sterile PBS. After addition of XTT (containing menadione), the plates were incubated for 3 h at 37 °C in the dark. 80 μL of liquid from each well was transferred to new plates. Absorbance at 450 nm was then measured with a SpectraMax M5 plate reader (Molecular Devices, Sunnyvale, CA, USA).

Prevention of biofilm formation assays. Biofilm prevention assays were set up identically to the ordinary MIC experiment, where compounds were diluted, and the fungi added. After overnight growth, the plates were washed as in the biofilm disruption assay and stained and measured in the same fashion. The resulting data are reported in Fig. 5B.

Development of resistance. To determine if the fungi would become resistant to the compounds, the change in the MIC of compounds **2a** and **2b** over 15 serial passages was monitored using *C. albicans* ATCC 10231 (strain *A*; Fig. 6). MIC assays were performed as described above. For the serial passages, cells were selected from a well representing ½× the MIC concentration and used to start an overnight culture for the following MIC value determination.

References

(1) Green, K. D.; Thamban Chandrika, N.; Vu, L. Y.; Pang, A. H.; Tsodikov, O. V.; Garneau-Tsodikova, S. Aromatic hydrazides: A potential solution for *Acinetobacter baumannii* infections. *Eur. J. Med. Chem.* **2023**, *249*, 115165. DOI: 10.1016/j.ejmech.2023.115165.

(2) (a) Clinical and Laboratory Standards Institute. Reference method for Broth Dilution Antifungal Susceptibility Testing of Yeasts - Approved Standard. (b) Clinical and Laboratory Standards Institute; Wayne, PA, USA: 2008. CLSI Document M27-A3. Clinical and Laboratory Standards Institute. Reference method for Broth Dilution Antifungal Susceptibility Testing of Filamentous Fungi: Approved Standard - Second Edition. Clinical and Laboratory Standards Institute; Wayne, PA, USA: 2008. CLSI Document M38-A2.

(3) Shrestha, S. K.; Fosso, M. Y.; Green, K. D.; Garneau-Tsodikova, S. Amphiphilic tobramycin analogues as antibacterial and antifungal agents. *Antimicrob. Agents Chemother.* **2015**, *59* (8), 4861-4869. DOI: 10.1128/AAC.00229-15.

(4) Pierce, C. G.; Uppuluri, P.; Tristan, A. R.; Wormley, F. L., Jr.; Mowat, E.; Ramage, G.; Lopez-Ribot, J. L. A simple and reproducible 96-well plate-based method for the formation of fungal biofilms and its application to antifungal susceptibility testing. *Nat. Protoc.* **2008**, *3* (9), 1494-1500. DOI: 10.1038/nport.2008.141.

Supplementary Figures S1-S173

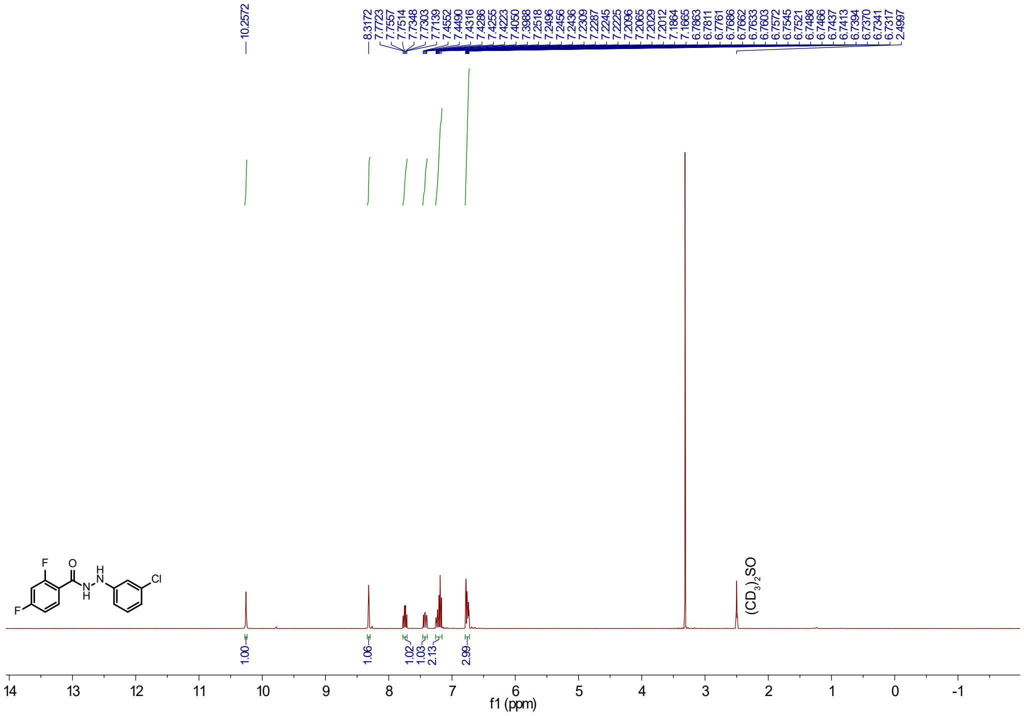


Fig. S1: ^{1}H NMR spectrum for compound **1b** (**SGT1772**) in $(CD_3)_2SO$ (400 MHz).

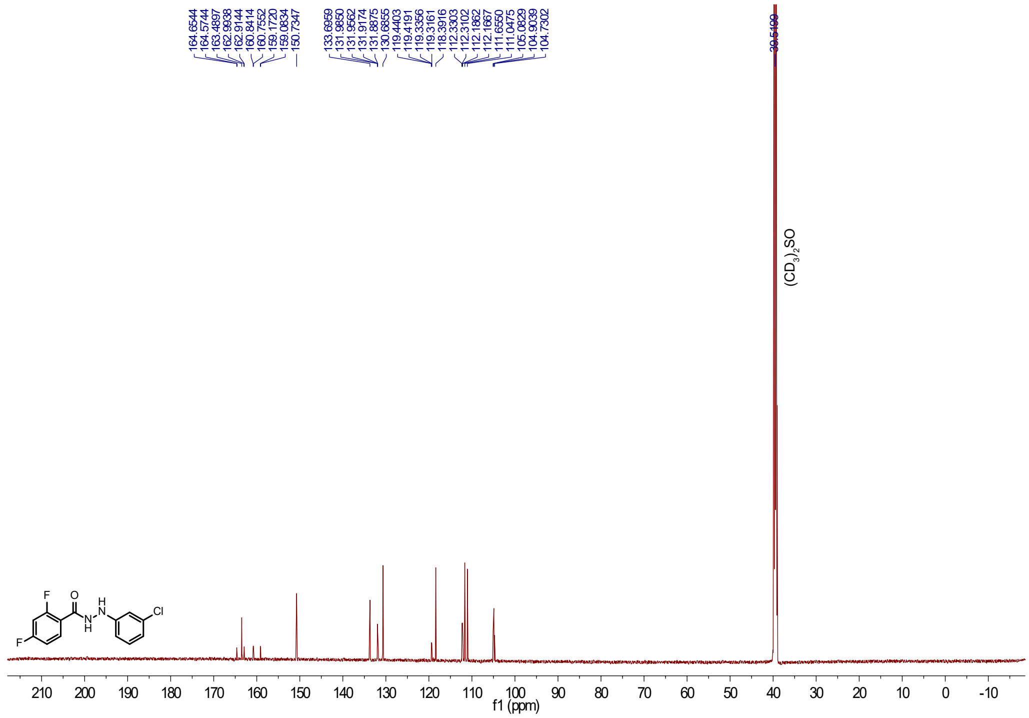


Fig. S2: ^{13}C NMR spectrum for compound **1b** (**SGT1772**) in $(CD_3)_2SO$ (150 MHz).

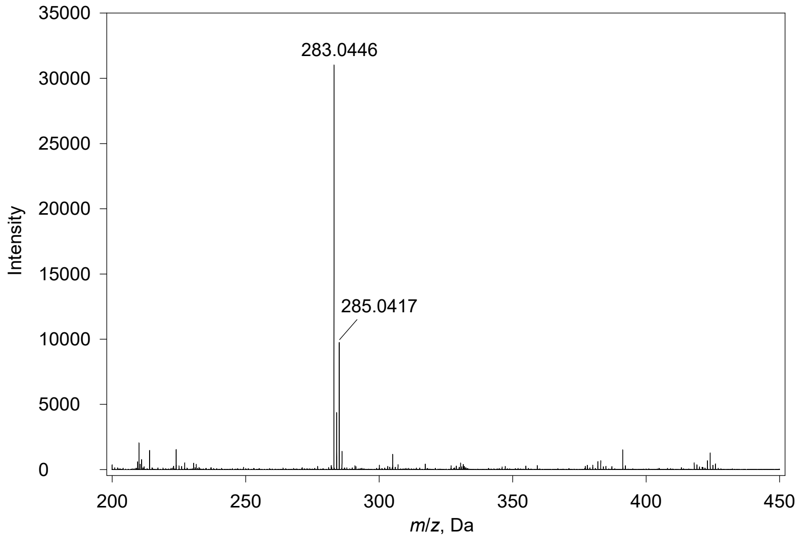


Fig. S3: HRMS spectrum for compound **1b** (**SGT1772**). *m/z* found 283.0446 $[M+H]^+$.

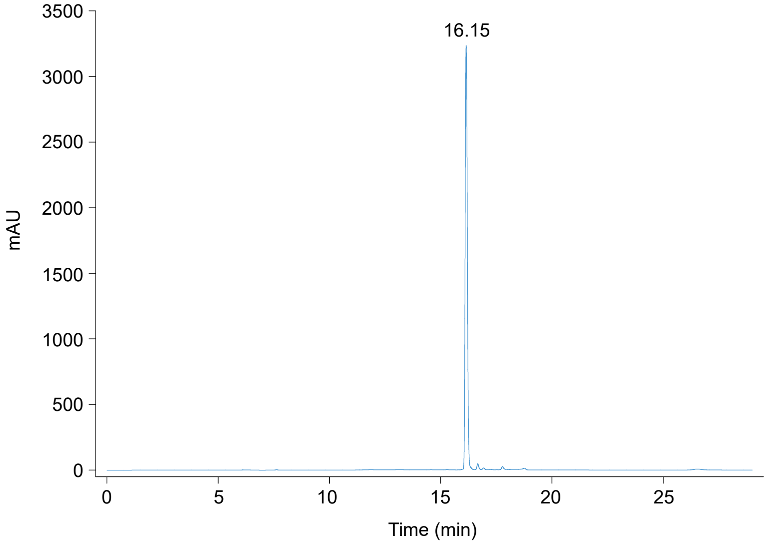


Fig. S4: HPLC trace for compound **1b** (**SGT1772**). R_t = 16.15 min.

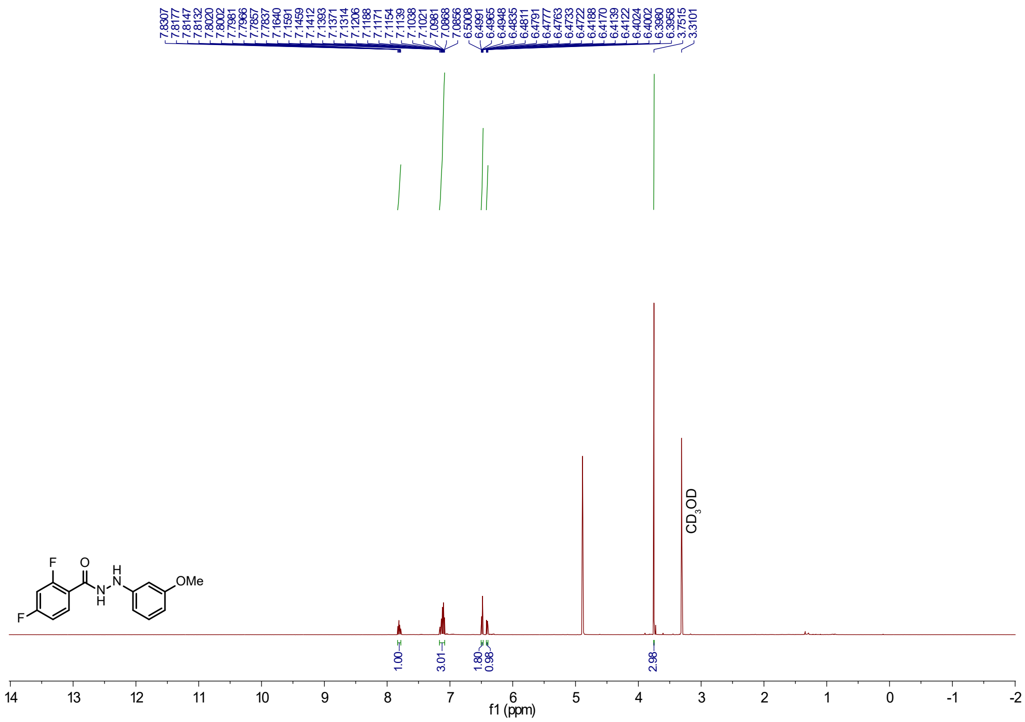


Fig. S5: ^{1}H NMR spectrum for compound **1c** (**SGT1772**) in CD_3OD (500 MHz).

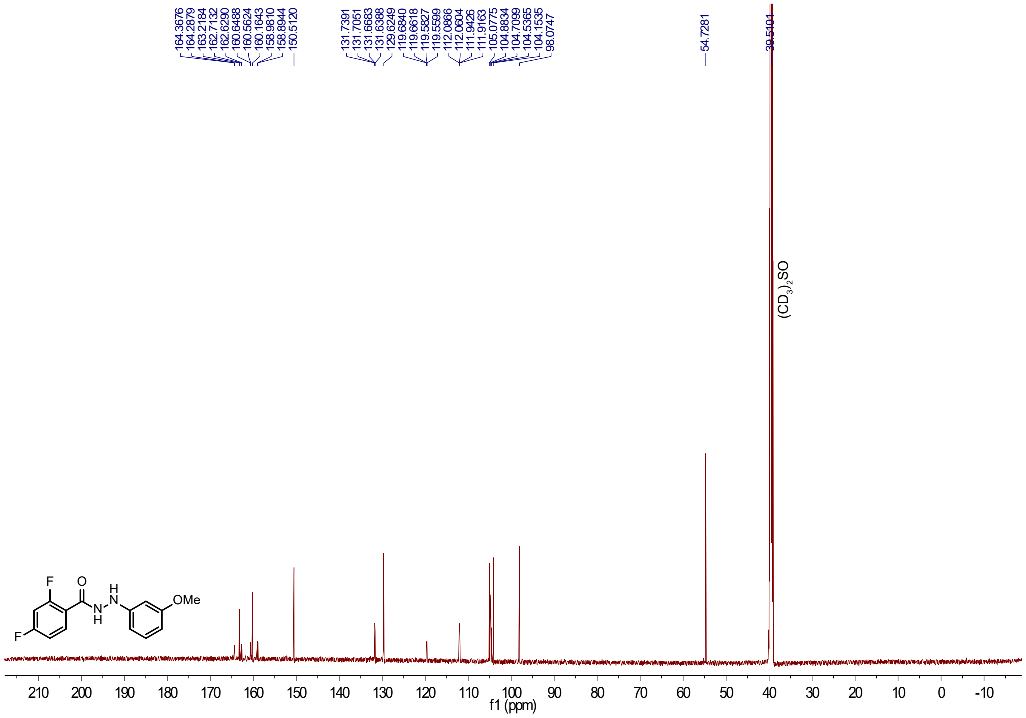


Fig. S6: ^{13}C NMR spectrum for compound **1c** (**SGT1772**) in $(CD_3)_2SO$ (150 MHz).

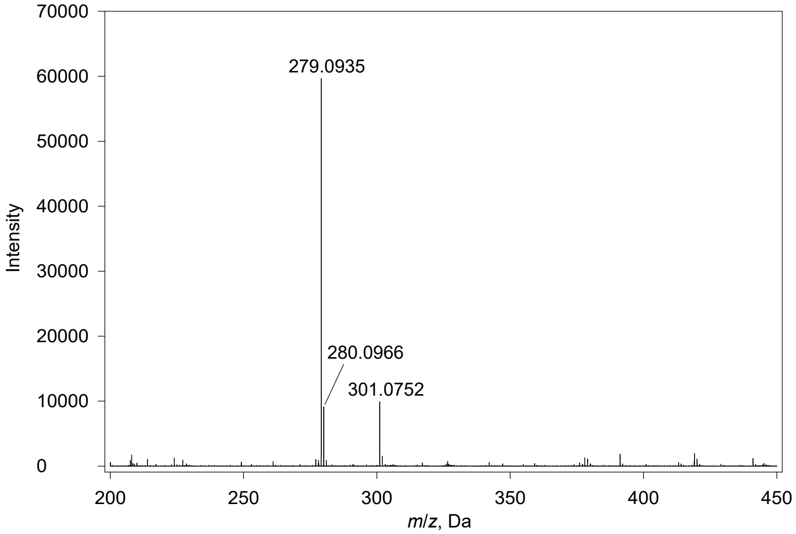


Fig. S7: HRMS spectrum for compound **1c** (**SGT1772**). *m/z* found 279.0935 $[M+H]^+$.

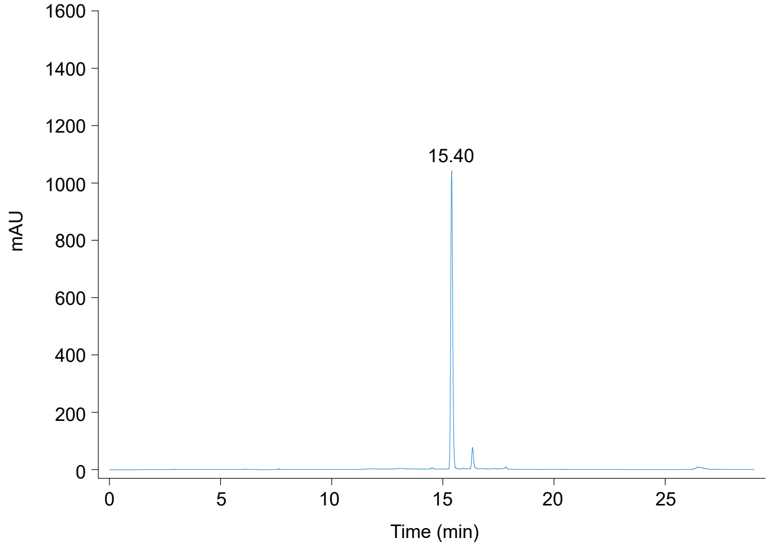


Fig. S8: HPLC trace for compound **1c** (**SGT1772**). R_t = 15.40 min.

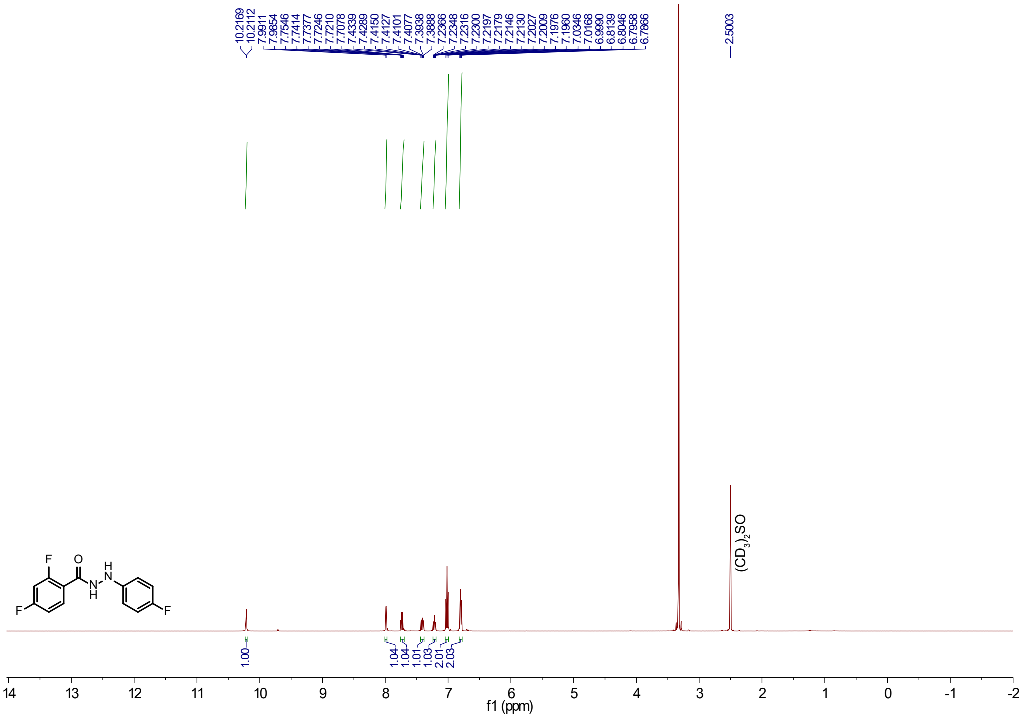


Fig. S9: ^{1}H NMR spectrum for compound **1d** (**SGT1785**) in $(CD_3)_2SO$ (500 MHz).

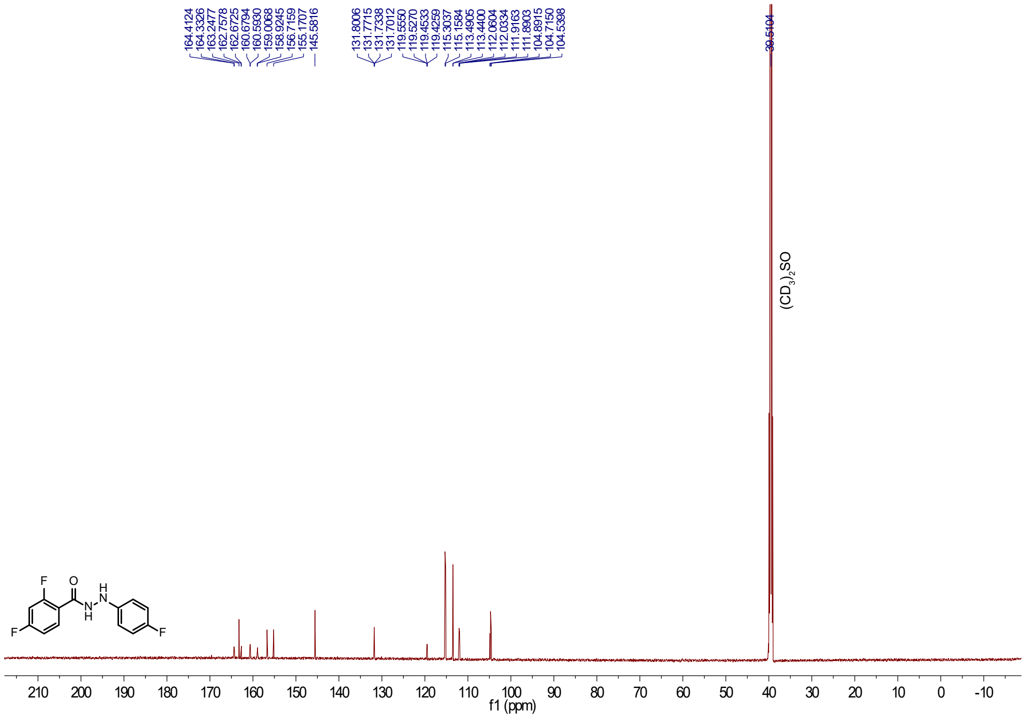


Fig. S10: ^{13}C NMR spectrum for compound **1d** (**SGT1785**) in $(CD_3)_2SO$ (150 MHz).

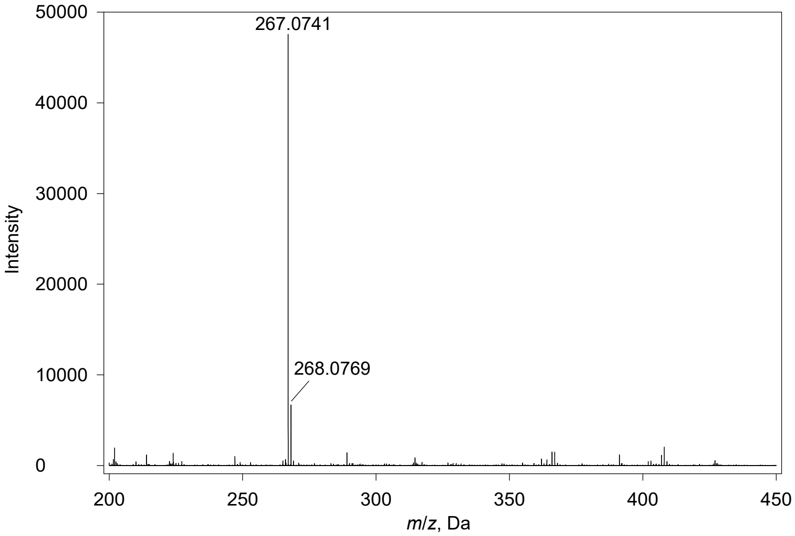


Fig. S11: HRMS spectrum for compound **1d** (**SGT1785**). *m/z* found 267.0741 $[M+H]^+$.

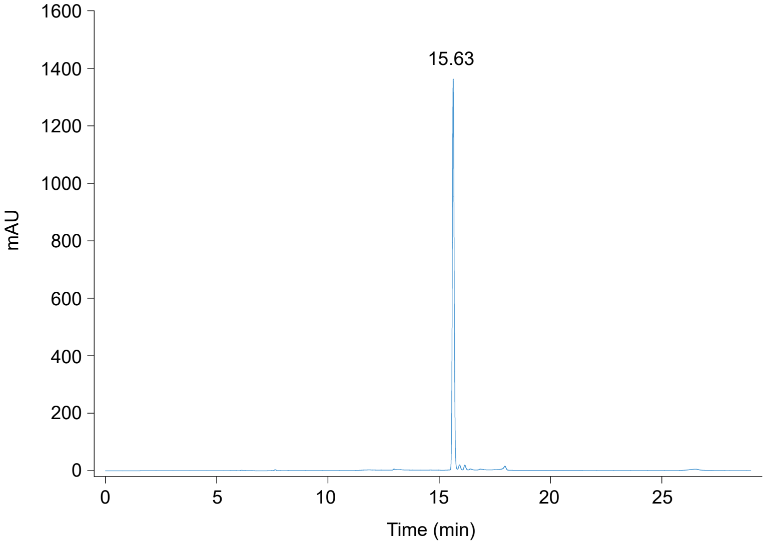


Fig. S12: HPLC trace for compound **1d** (**SGT1785**). R_t = 15.63 min.

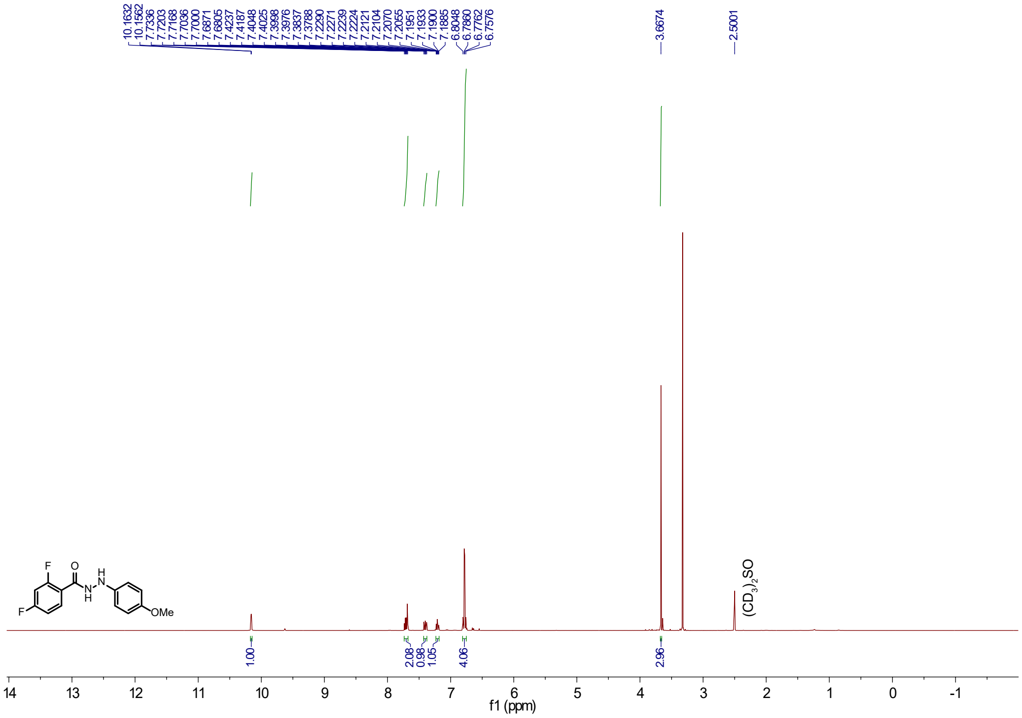


Fig. S13: ^{1}H NMR spectrum for compound **1f** (**SGT1771**) in $(CD_3)_2SO$ (500 MHz).

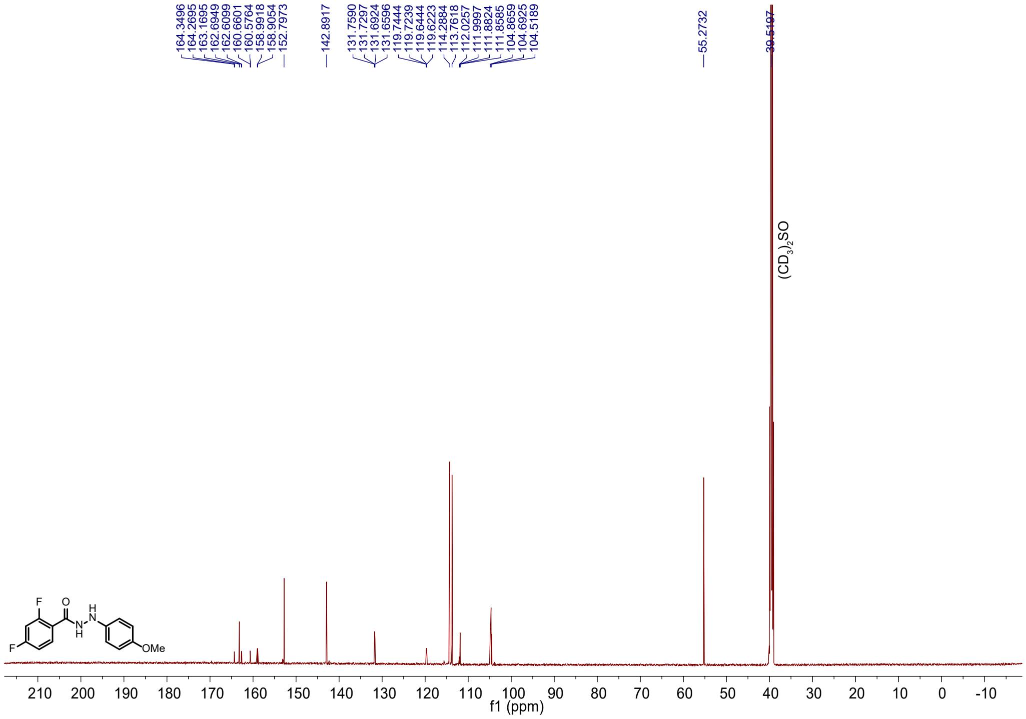


Fig. S14: ^{13}C NMR spectrum for compound **1f** (**SGT1771**) in $(CD_3)_2SO$ (150 MHz).

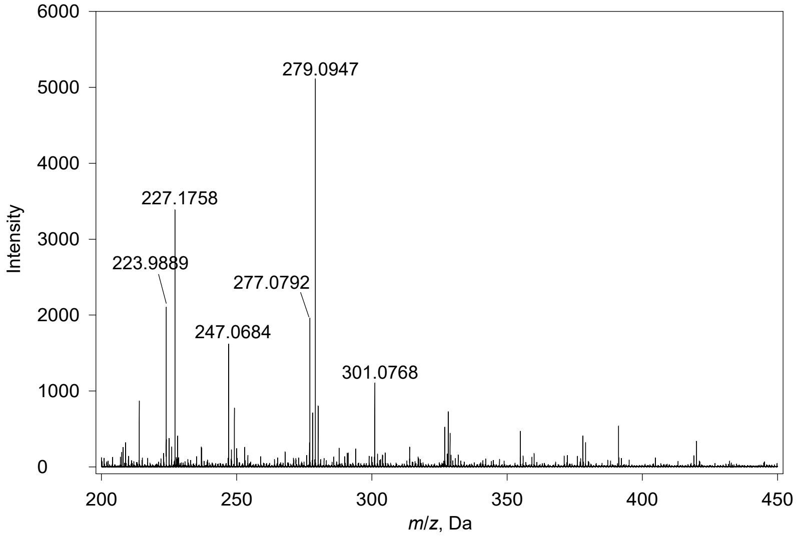


Fig. S15: HRMS spectrum for compound **1f** (**SGT1771**). *m/z* found 279.0947 $[M+H]^+$.

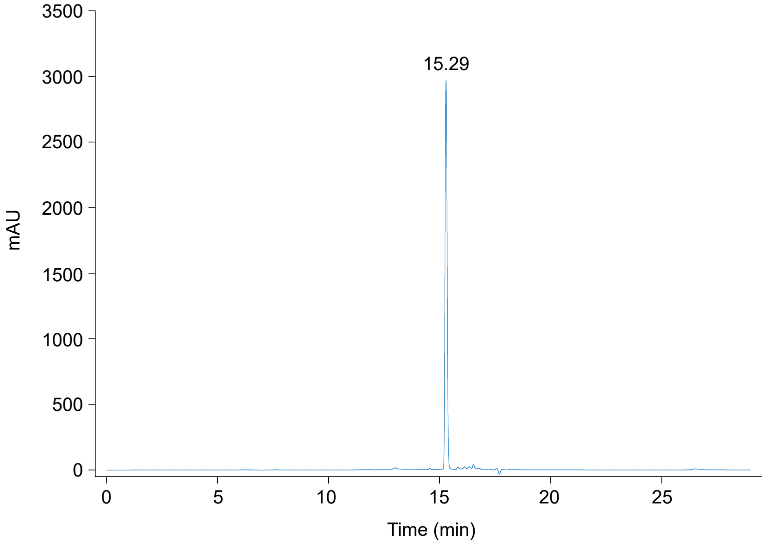


Fig. S16: HPLC trace for compound **1f** (**SGT1771**). R_t = 15.29 min.

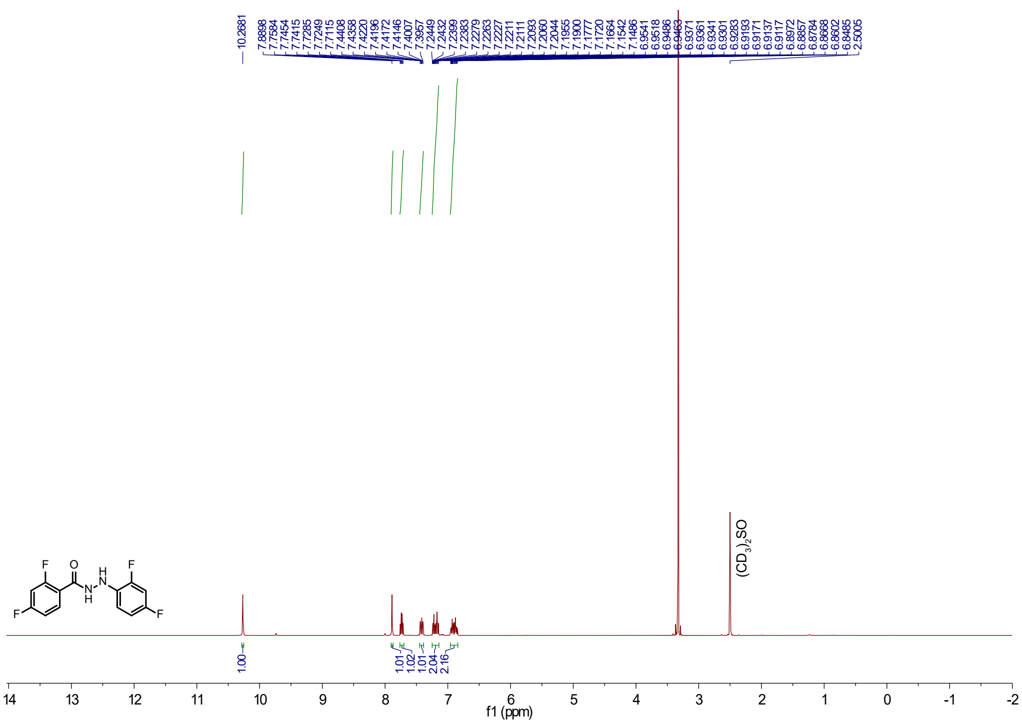


Fig. S17: ^{1}H NMR spectrum for compound **1g** (**SGT1393**) in $(CD_3)_2SO$ (500 MHz).

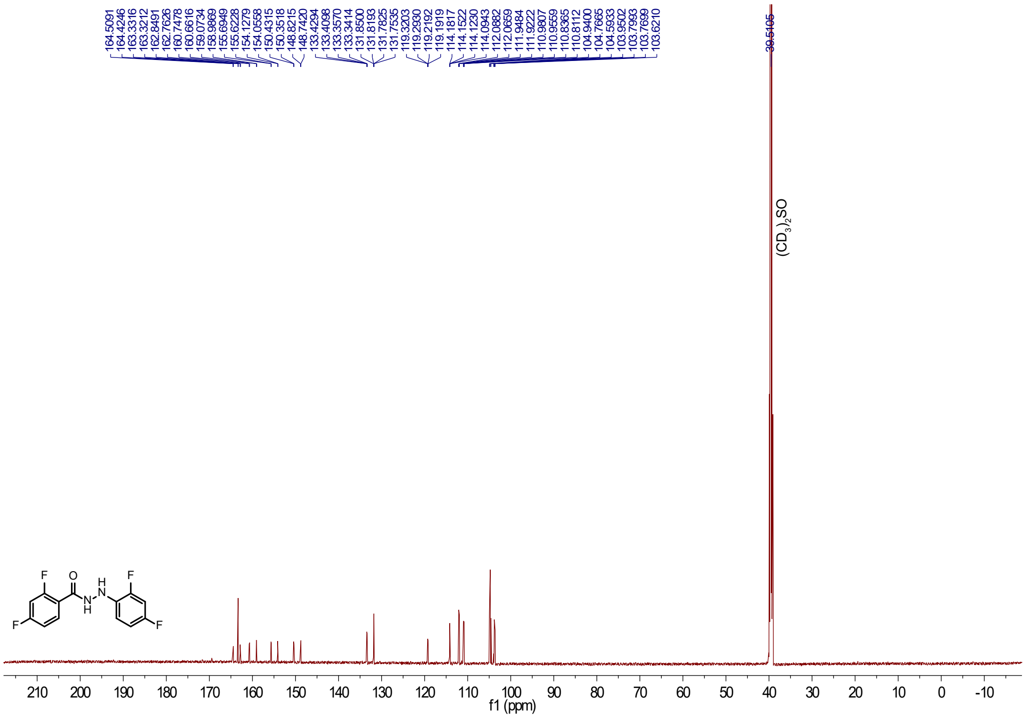


Fig. S18: ^{13}C NMR spectrum for compound **1g** (**SGT1393**) in $(CD_3)_2SO$ (150 MHz).

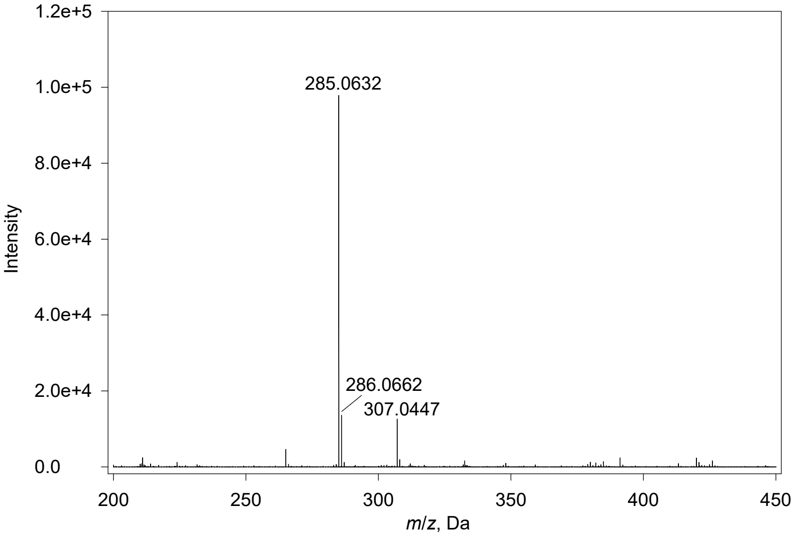


Fig. S19: HRMS spectrum for compound **1g** (**SGT1393**). *m/z* found 285.0632 [M+H]$^+$.

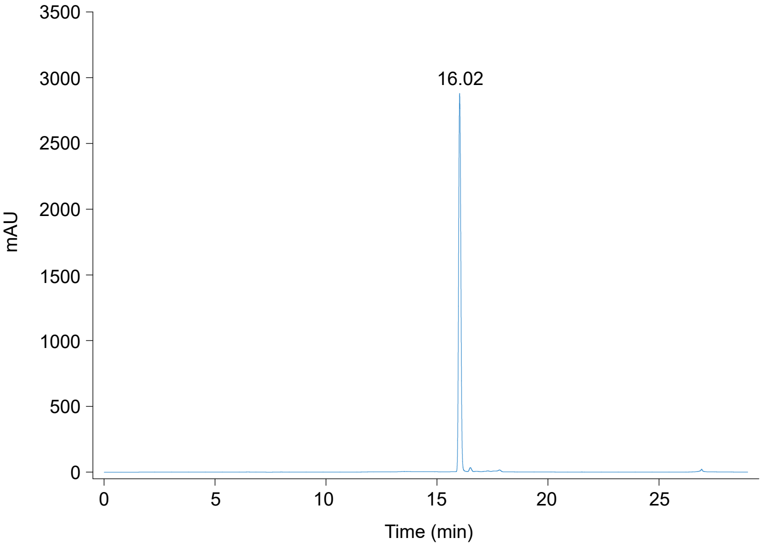


Fig. S20: HPLC trace for compound **1g** (**SGT1393**). R_t = 16.02 min.

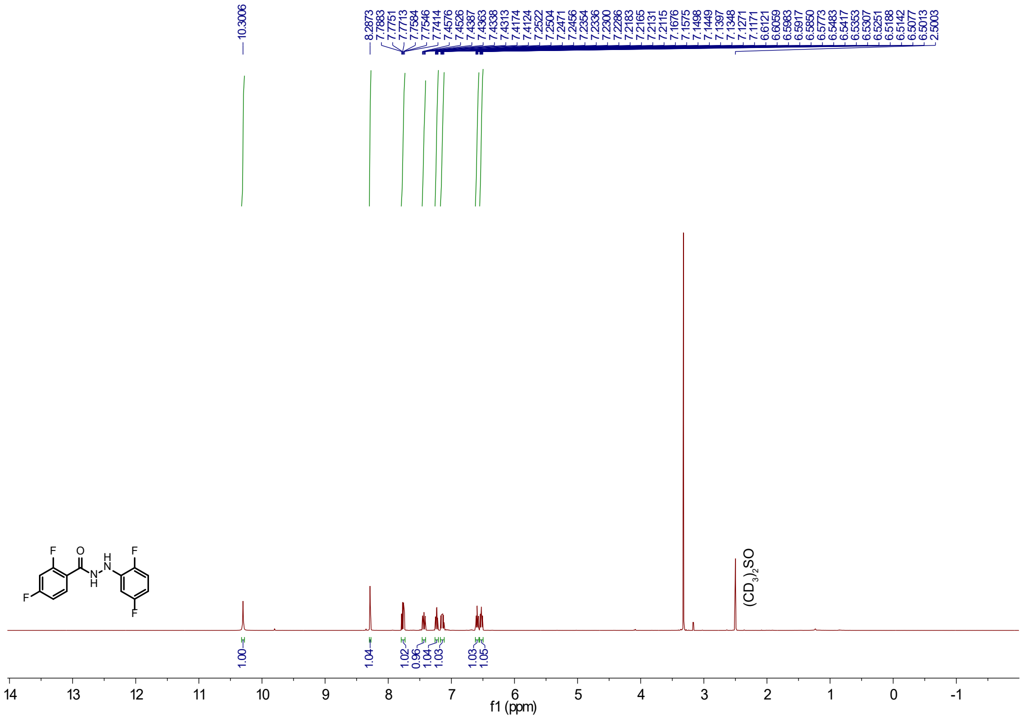


Fig. S21: ^{1}H NMR spectrum for compound **1h** (**SGT1769**) in $(CD_3)_2SO$ (500 MHz).

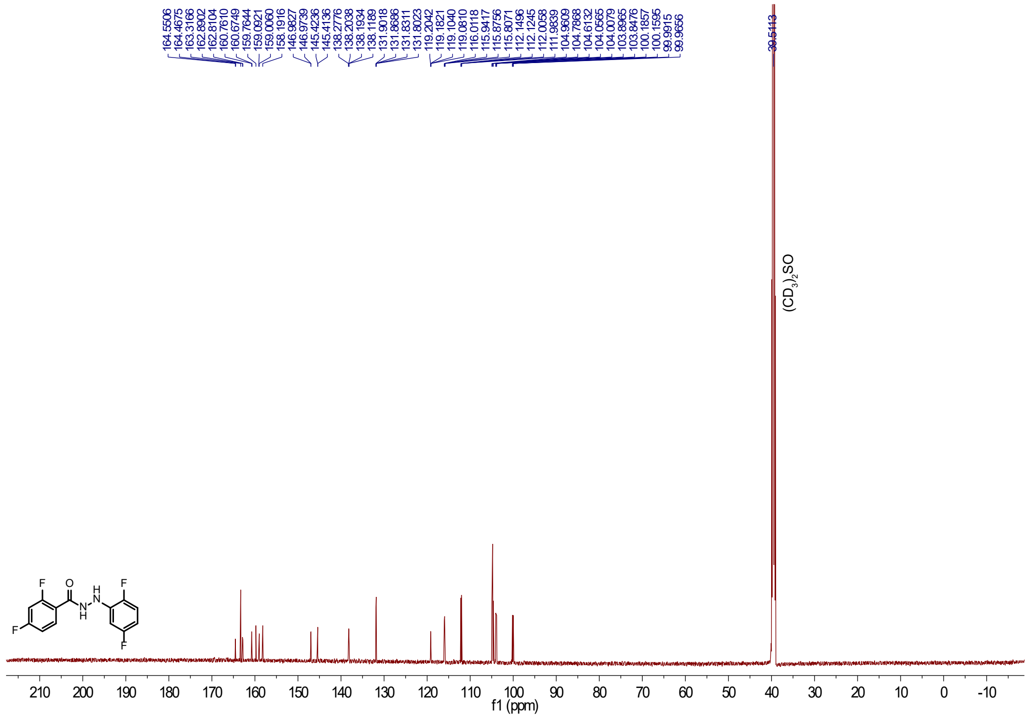


Fig. S22: ^{13}C NMR spectrum for compound **1h** (**SGT1769**) in $(CD_3)_2SO$ (150 MHz).

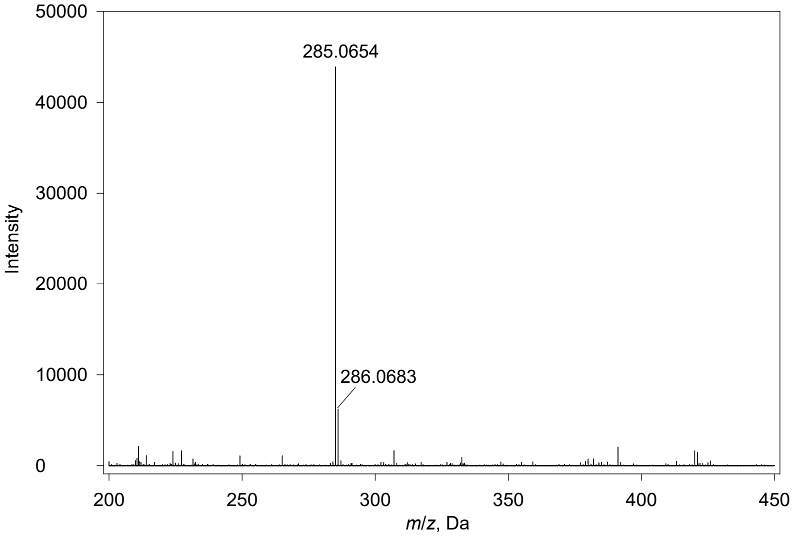


Fig. S23: HRMS spectrum for compound **1h** (**SGT1769**). *m/z* found 285.0654 $[M+H]^+$.

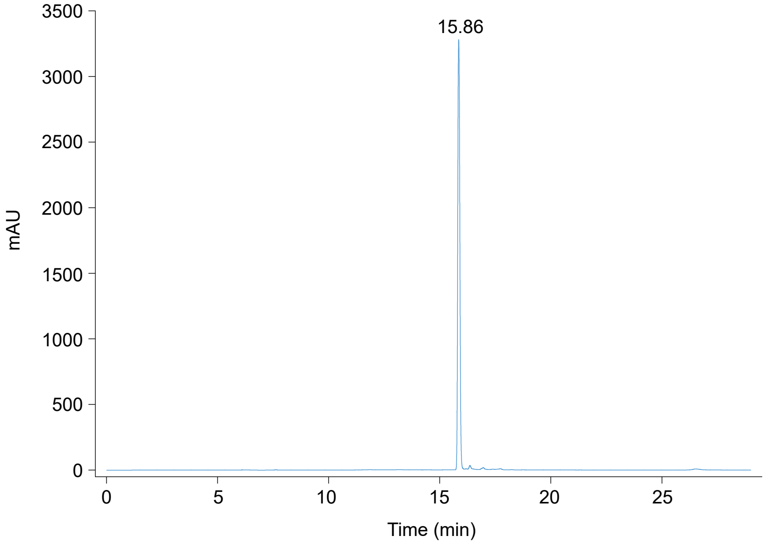


Fig. S24: HPLC trace for compound **1h** (**SGT1769**). R_t = 15.86 min.

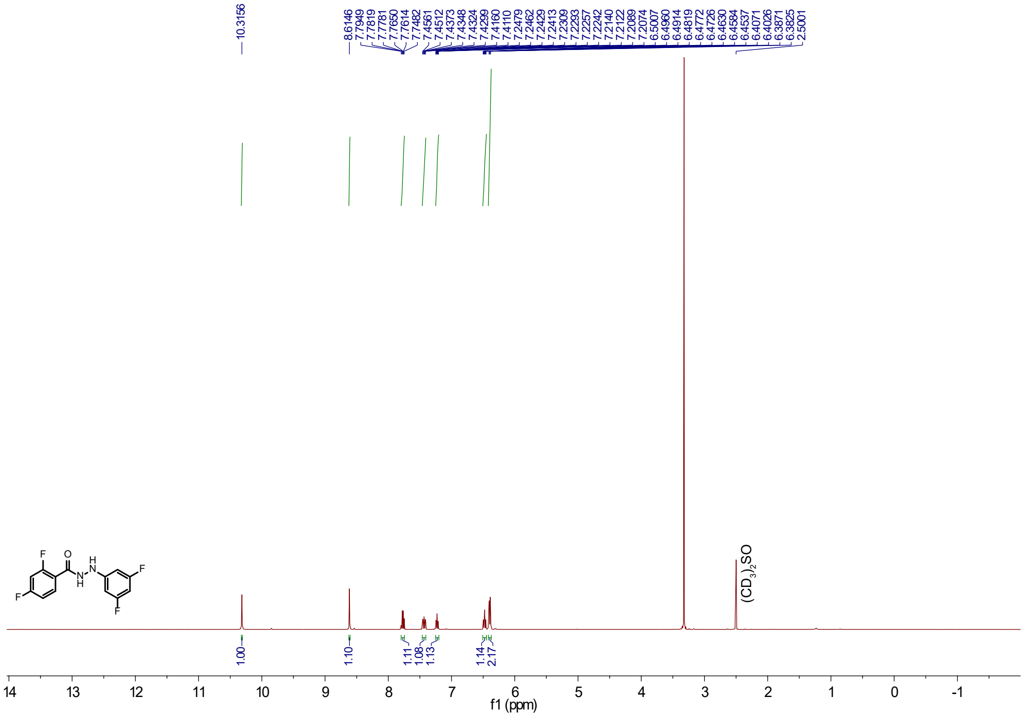


Fig. S25: ^{1}H NMR spectrum for compound **1i** (**SGT1770**) in $(CD_3)_2SO$ (500 MHz).

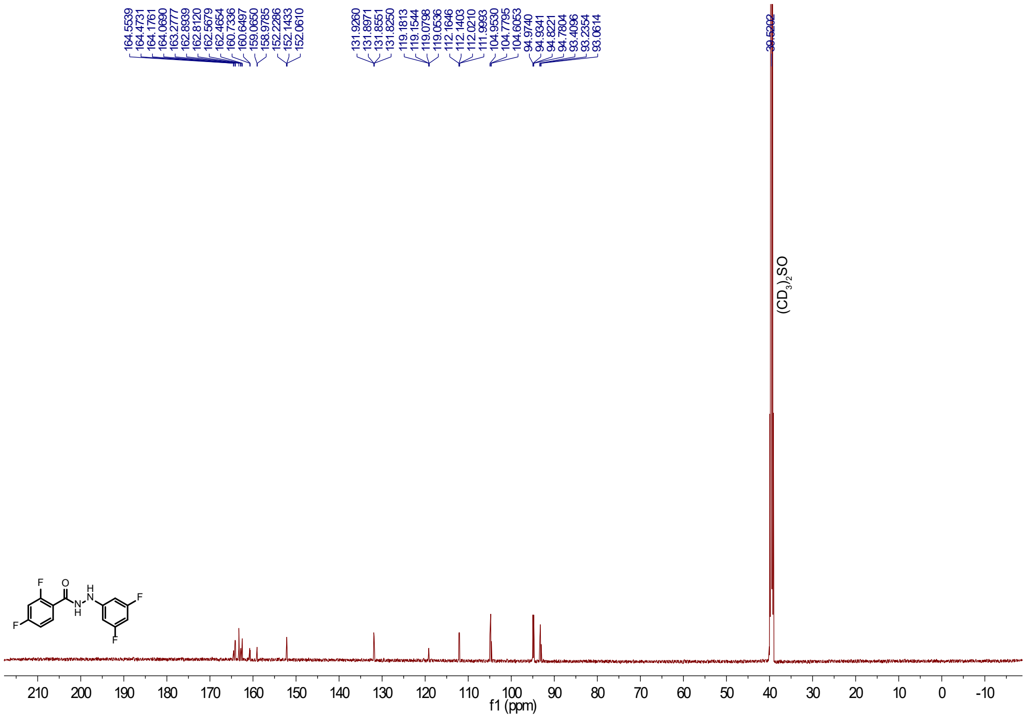


Fig. S26: ^{13}C NMR spectrum for compound **1i** (**SGT1770**) in $(CD_3)_2SO$ (150 MHz).

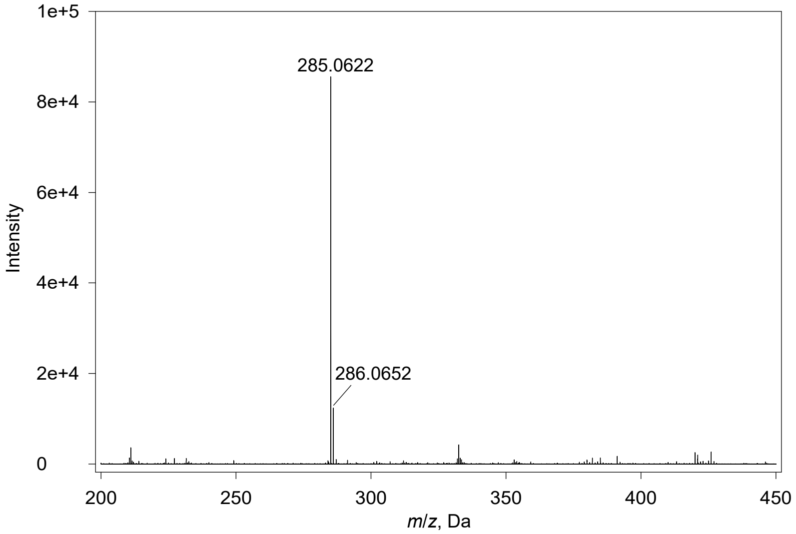


Fig. S27: HRMS spectrum for compound **1i** (**SGT1770**). *m/z* found 285.0622 $[M+H]^+$.

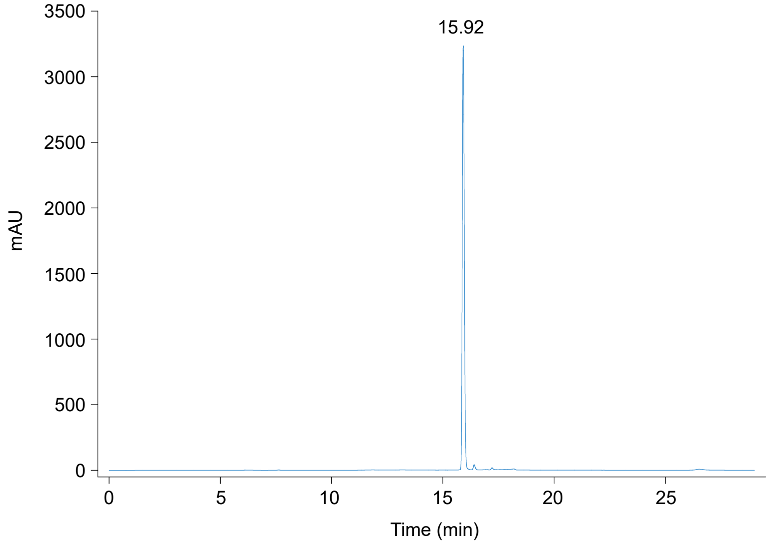


Fig. S28: HPLC trace for compound **1i** (**SGT1770**). R_t = 15.92 min.

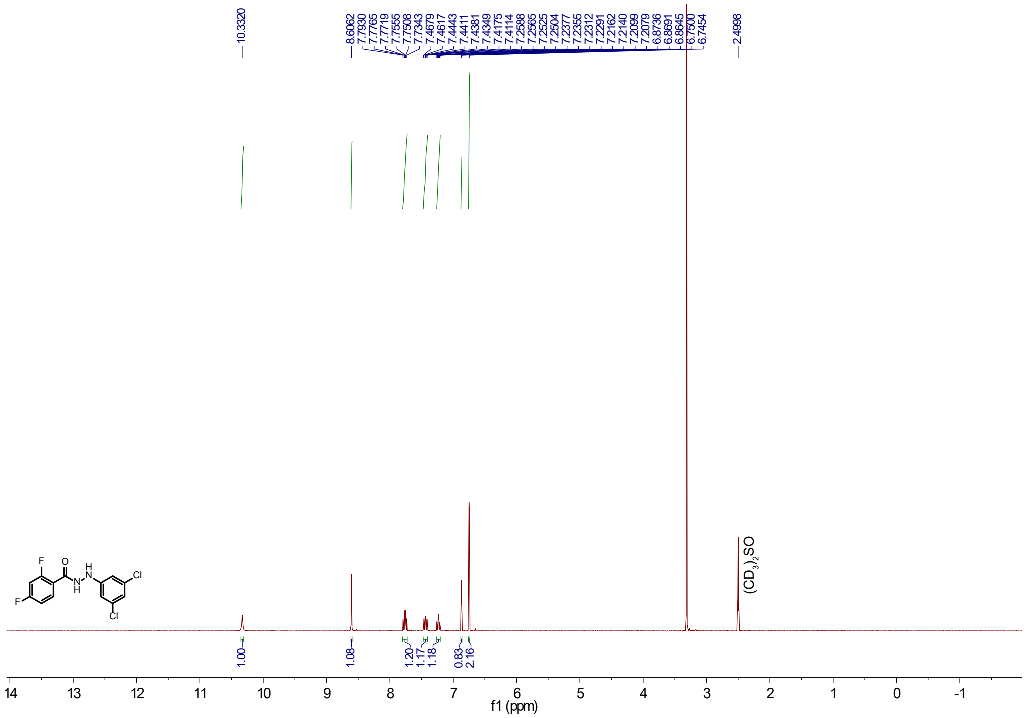


Fig. S29: ^{1}H NMR spectrum for compound **1j** (**SGT1773**) in $(CD_3)_2SO$ (400 MHz).

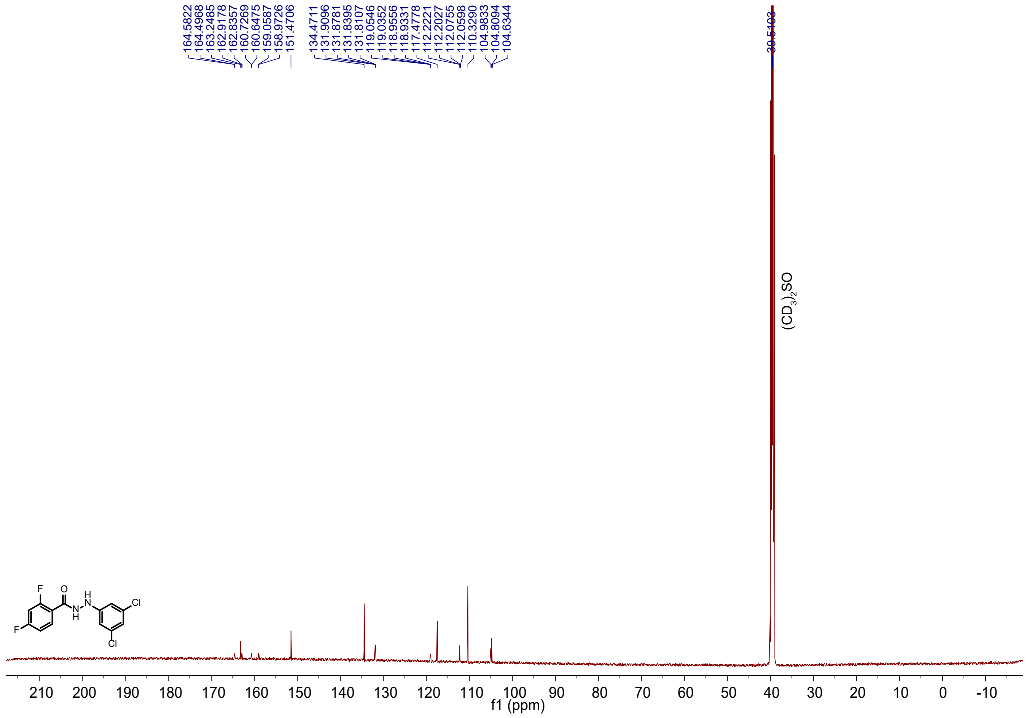


Fig. S30: ^{13}C NMR spectrum for compound **1j** (**SGT1773**) in $(CD_3)_2SO$ (150 MHz).

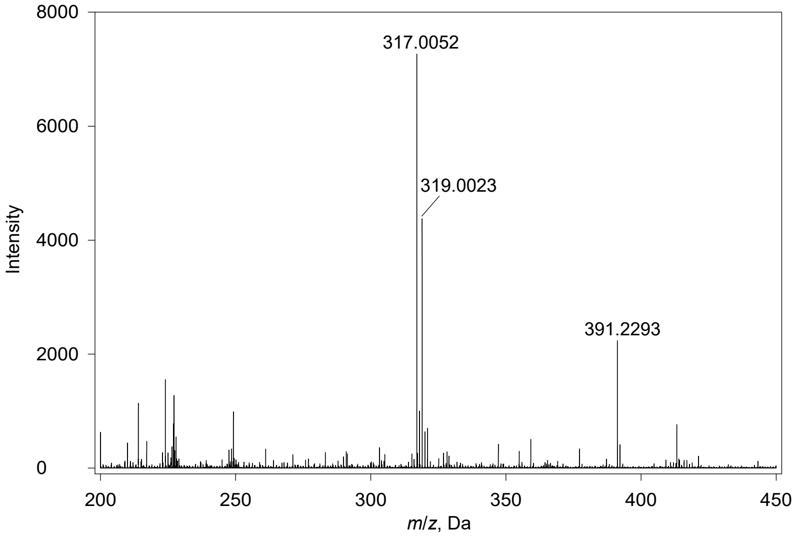


Fig. S31: HRMS spectrum for compound **1j** (**SGT1773**). *m/z* found 317.0052 [M+H]$^+$.

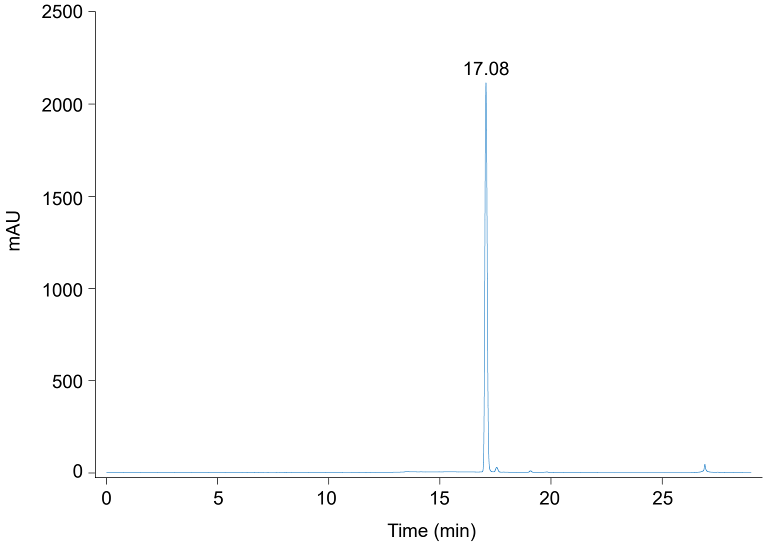


Fig. S32: HPLC trace for compound **1j** (**SGT1773**). R_t = 17.08 min.

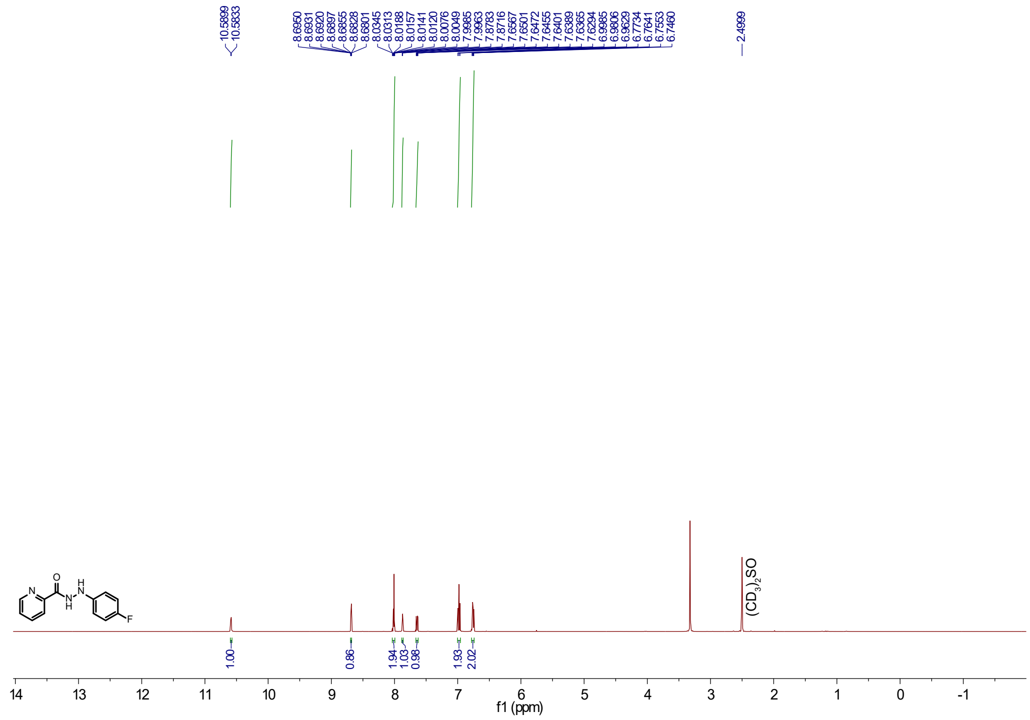


Fig. S33: ^{1}H NMR spectrum for compound **2d** (**SGT1776**) in (CD$_3$)$_2$SO (500 MHz).

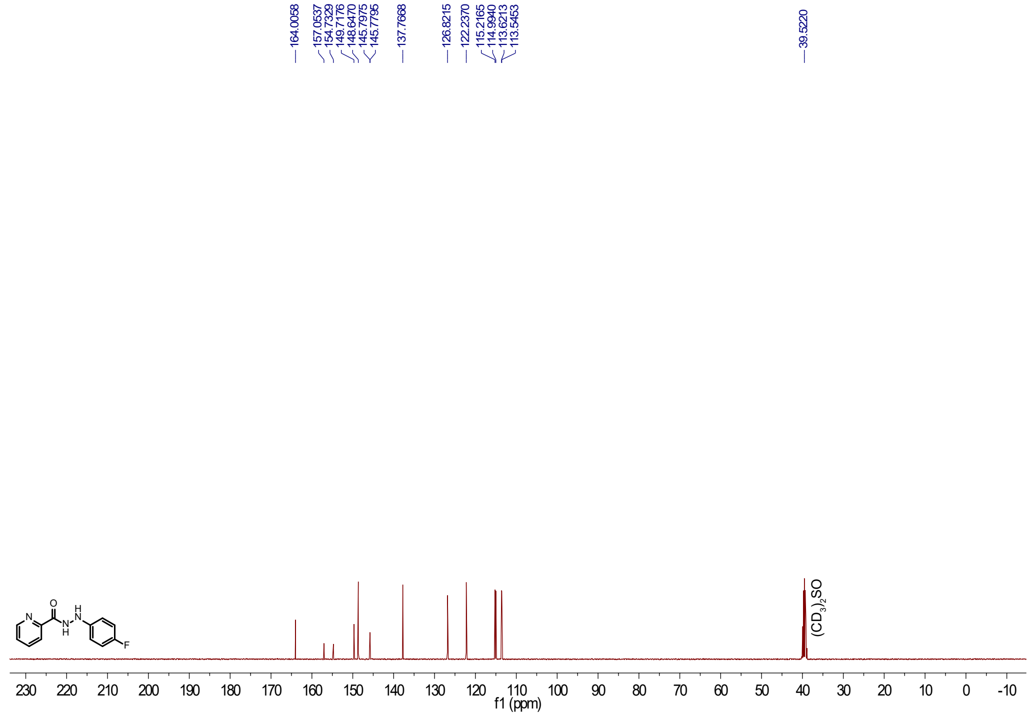


Fig. S34: ^{13}C NMR spectrum for compound **2d** (**SGT1776**) in (CD$_3$)$_2$SO (100 MHz).

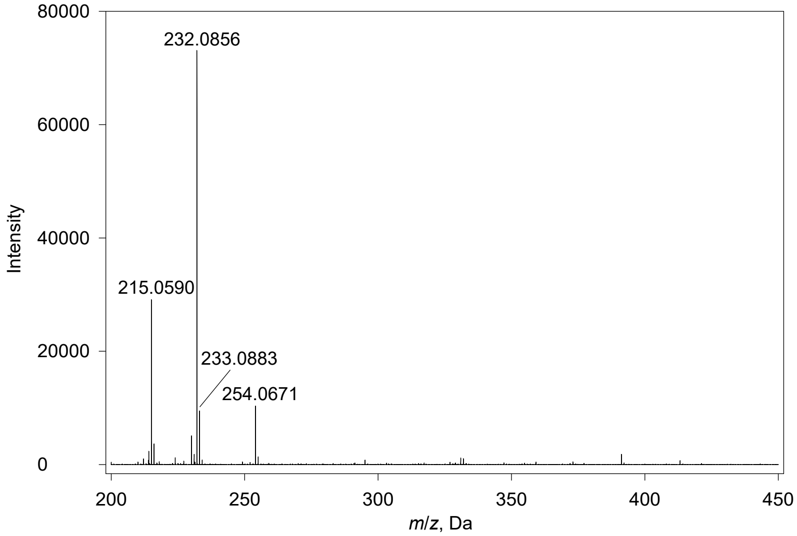


Fig. S35: HRMS spectrum for compound **2d** (**SGT1776**). *m/z* found 232.0856 $[M+H]^+$.

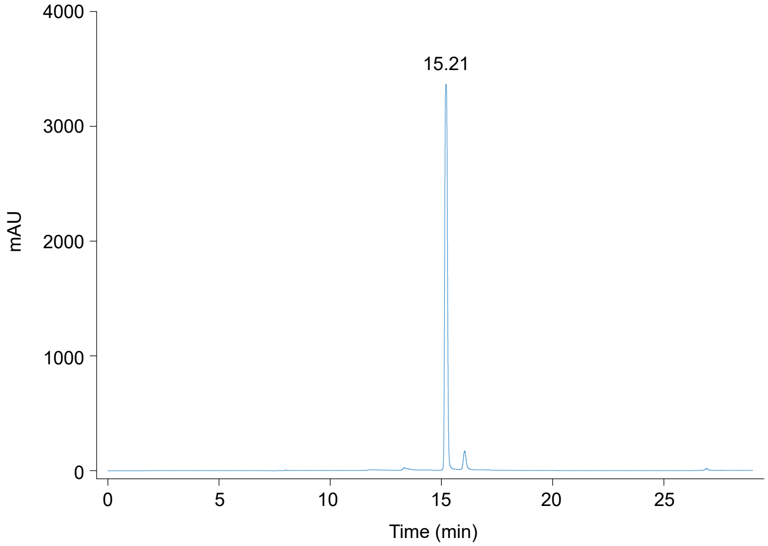


Fig. S36: HPLC trace for compound **2d** (**SGT1776**). R_t = 15.21 min.

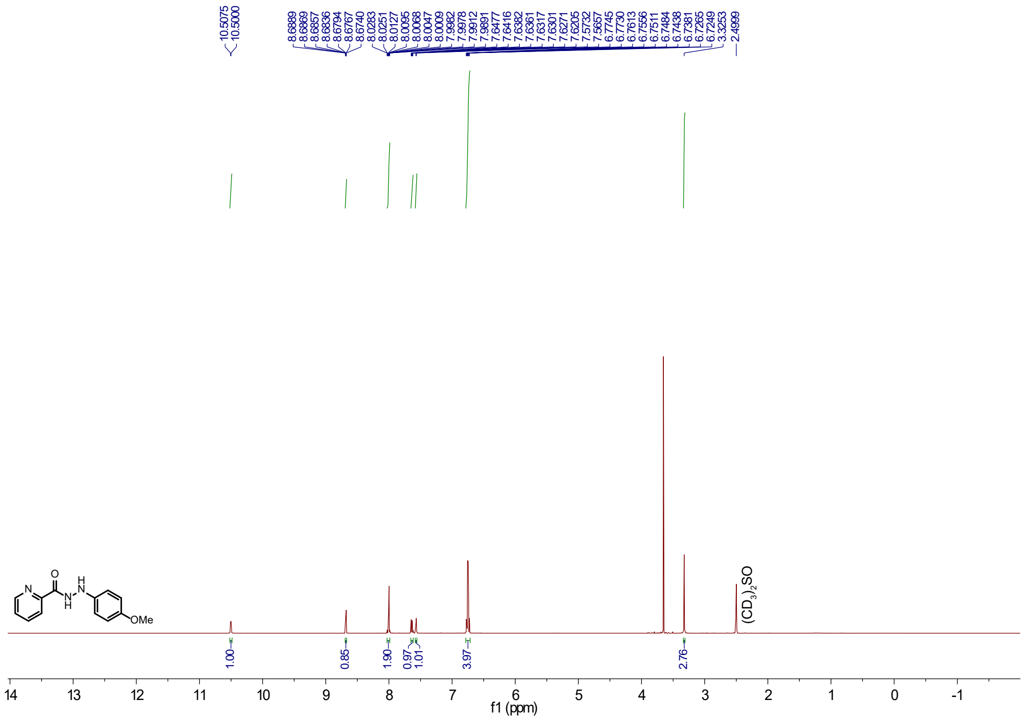


Fig. S37: ^{1}H NMR spectrum for compound **2f** (**SGT1778**) in $(CD_3)_2SO$ (500 MHz).

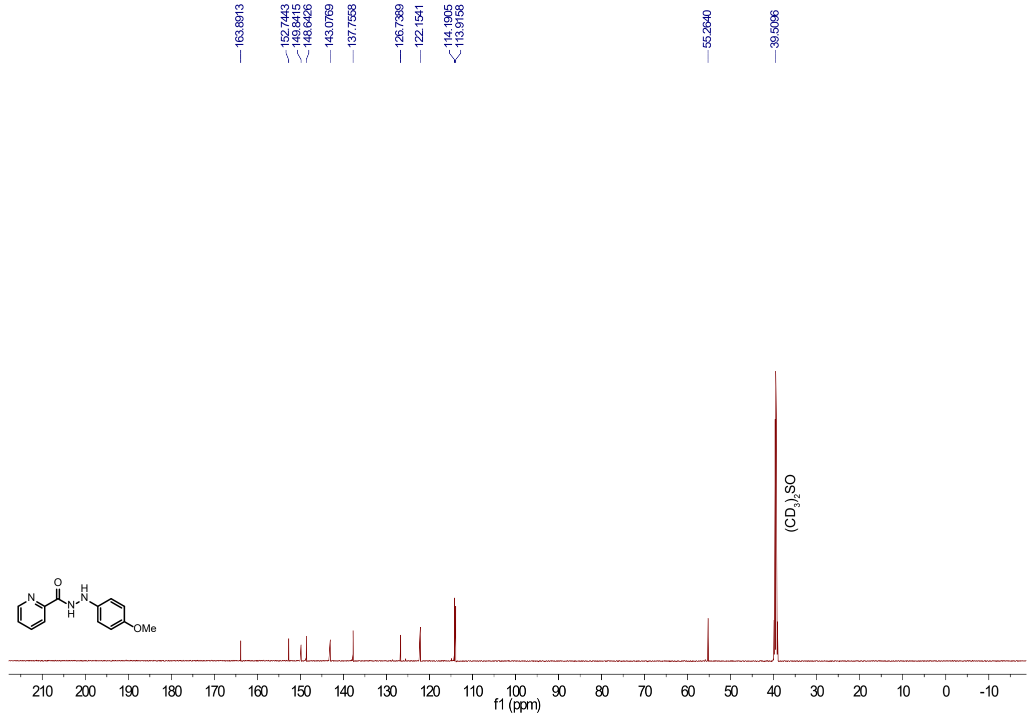


Fig. S38: ^{13}C NMR spectrum for compound **2f** (**SGT1778**) in $(CD_3)_2SO$ (150 MHz).

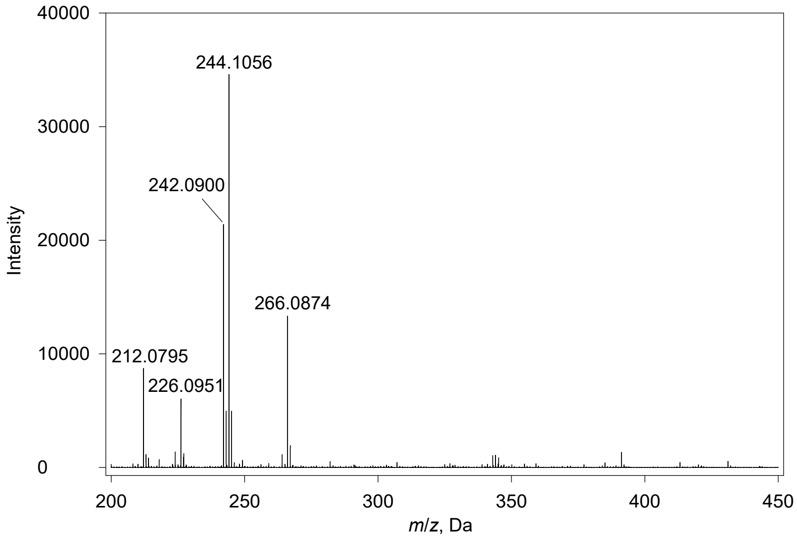


Fig. S39: HRMS spectrum for compound **2f** (**SGT1778**). *m/z* found 244.1056 $[M+H]^+$.

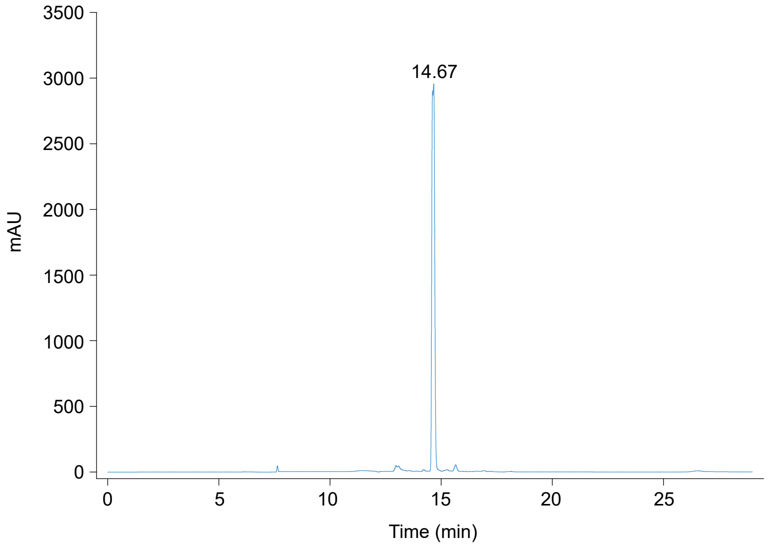


Fig. S40: HPLC trace for compound **2f** (**SGT1778**). R_t = 14.67 min.

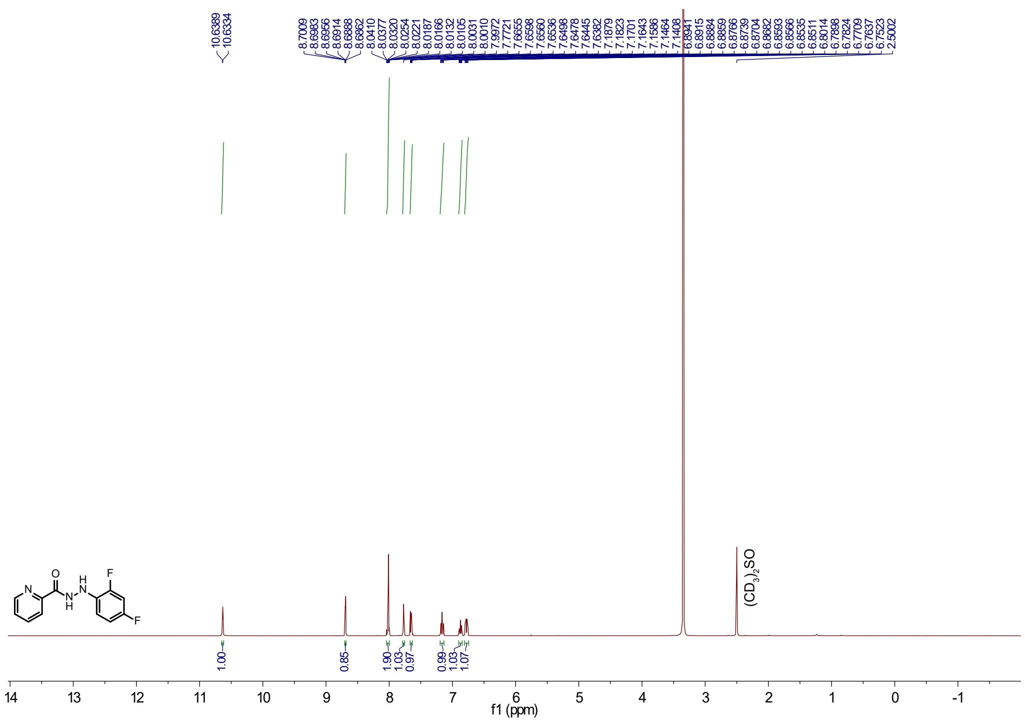


Fig. S41: ^{1}H NMR spectrum for compound **2g** (**SGT1396**) in $(CD_3)_2SO$ (500 MHz).

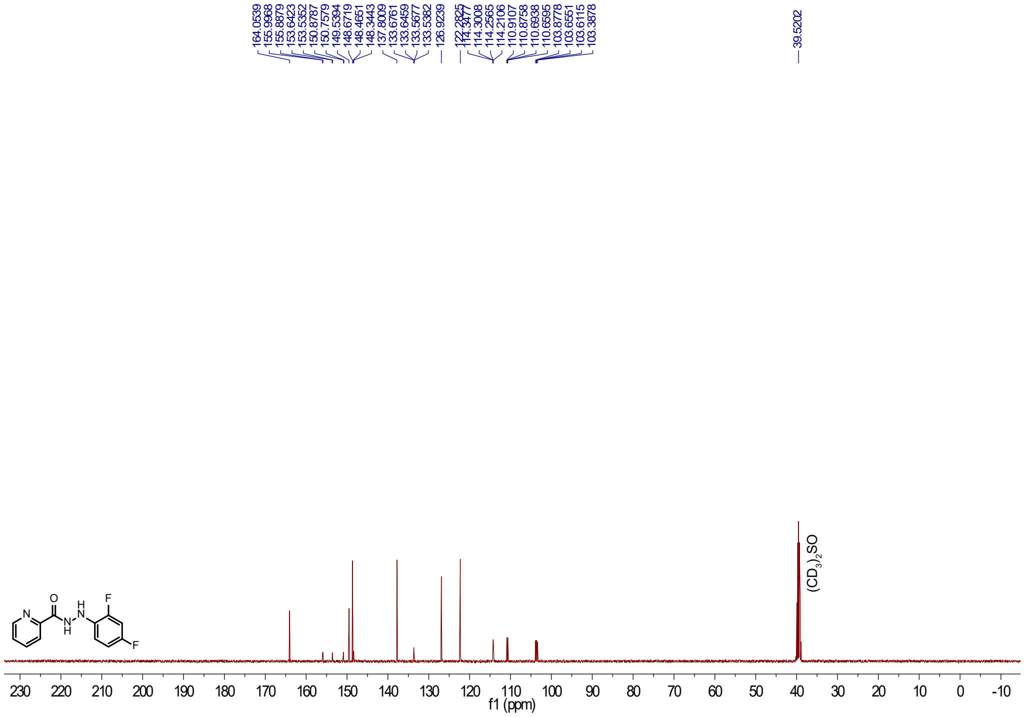


Fig. S42: ^{13}C NMR spectrum for compound **2g** (**SGT1396**) in $(CD_3)_2SO$ (100 MHz).

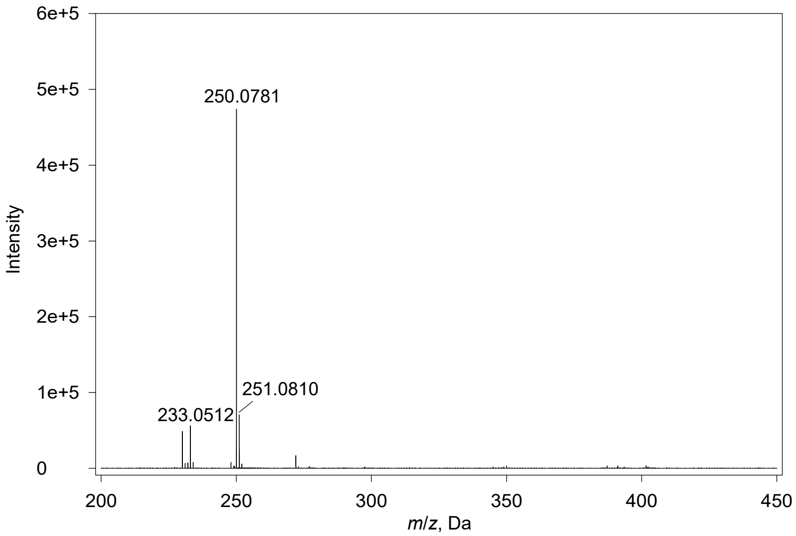


Fig. S43: HRMS spectrum for compound **2g** (**SGT1396**). *m/z* found 250.0781 $[M+H]^+$.

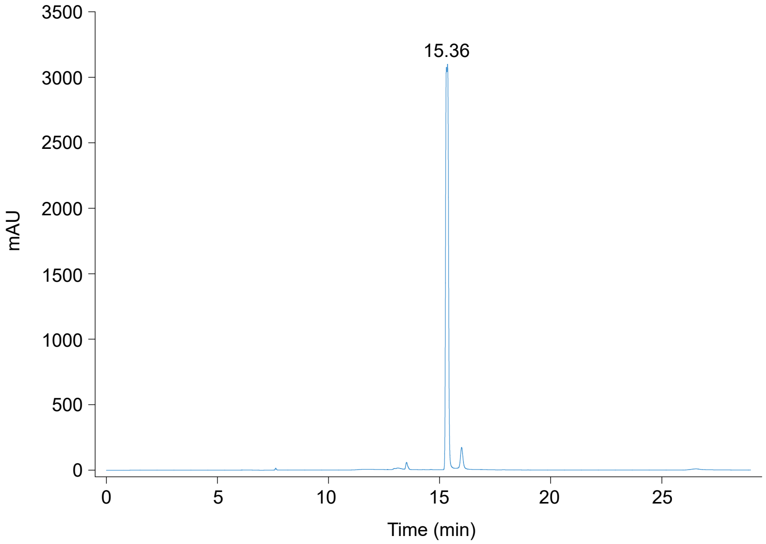


Fig. S44: HPLC trace for compound **2g** (**SGT1396**). R_t = 15.36 min.

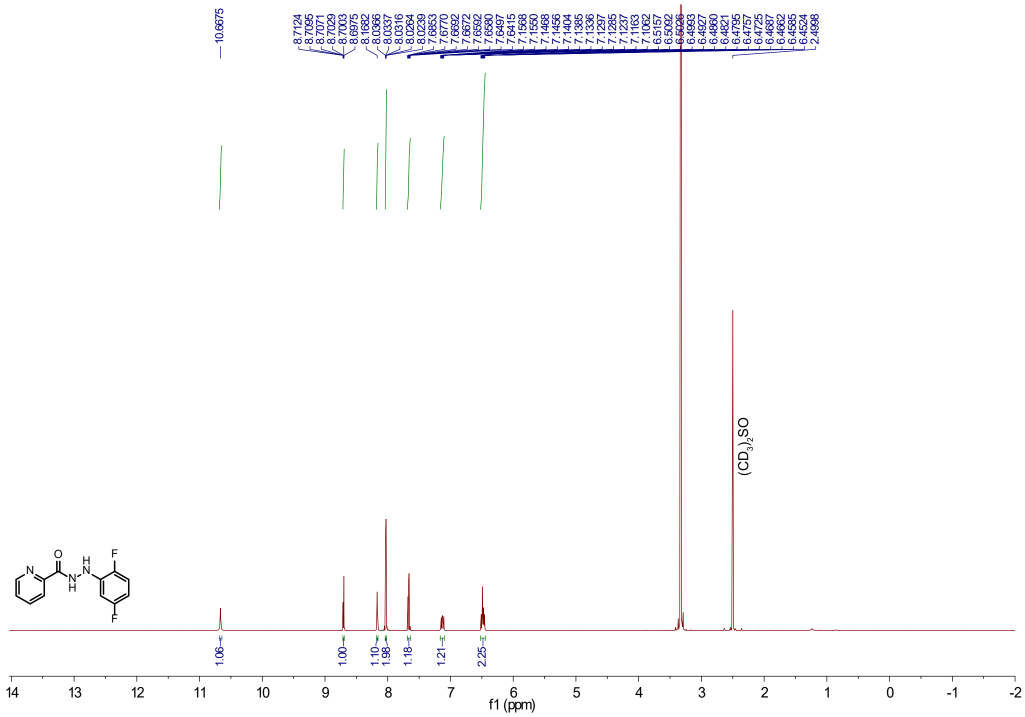


Fig. S45: ^{1}H NMR spectrum for compound **2h** (**SGT1789**) in $(CD_3)_2SO$ (500 MHz).

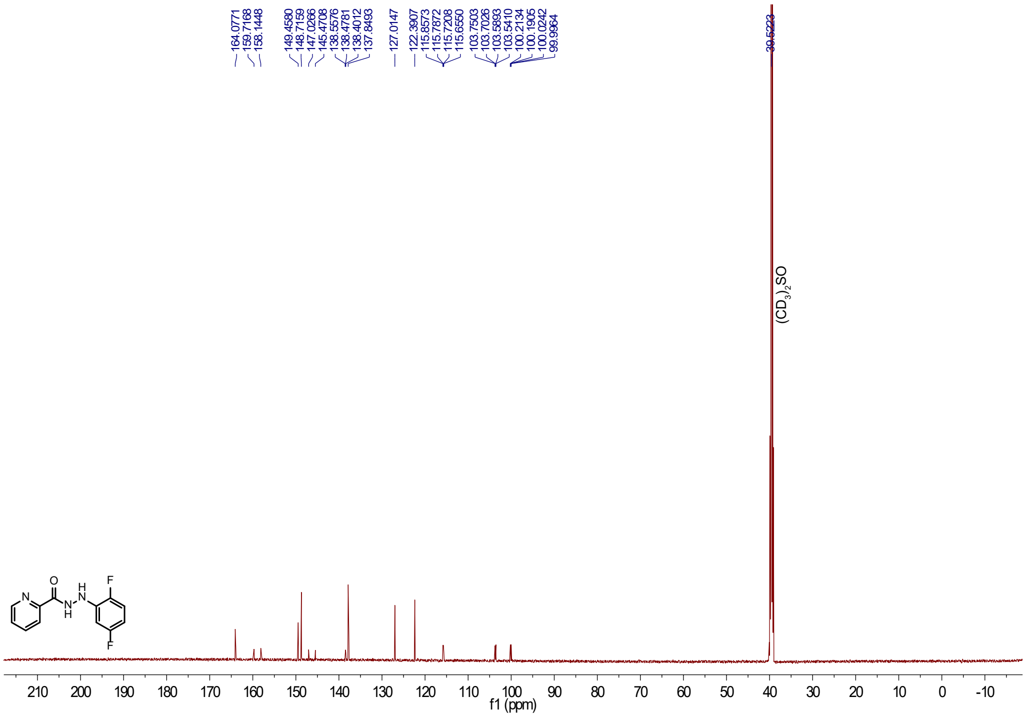


Fig. S46: ^{13}C NMR spectrum for compound **2h** (**SGT1789**) in $(CD_3)_2SO$ (150 MHz).

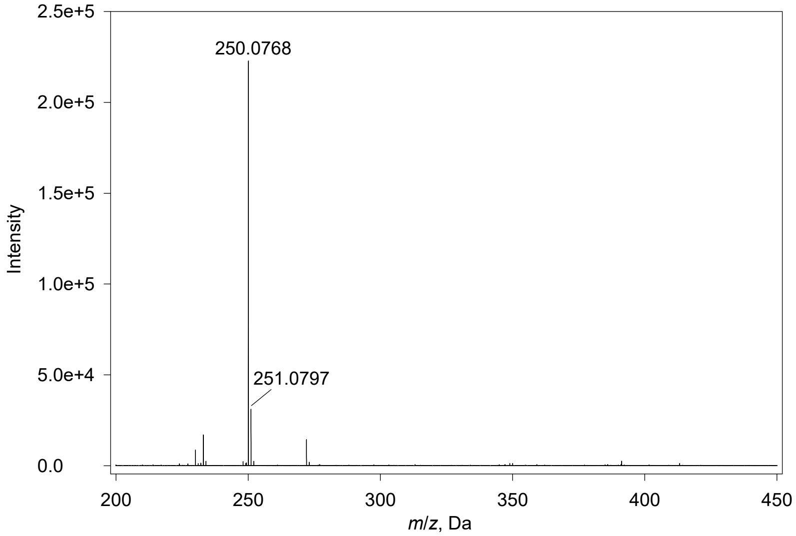


Fig. S47: HRMS spectrum for compound **2h** (**SGT1789**). *m/z* found 250.0768 $[M+H]^+$.

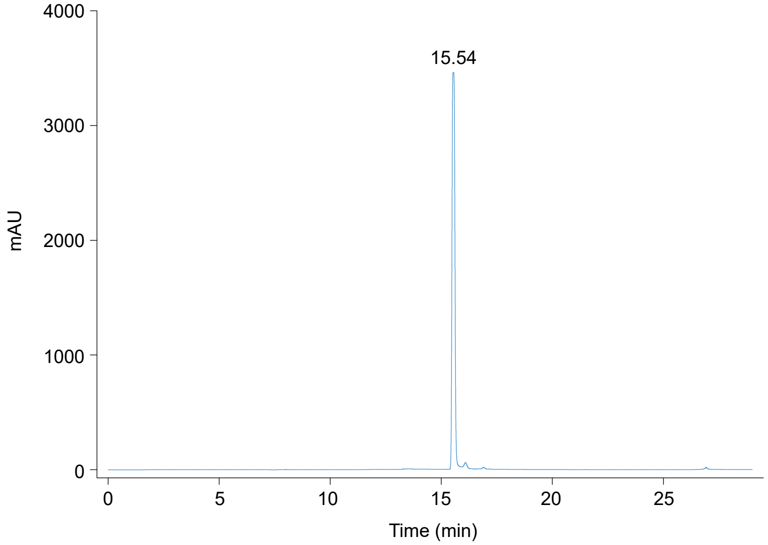


Fig. S48: HPLC trace for compound **2h** (**SGT1789**). R_t = 15.54 min.

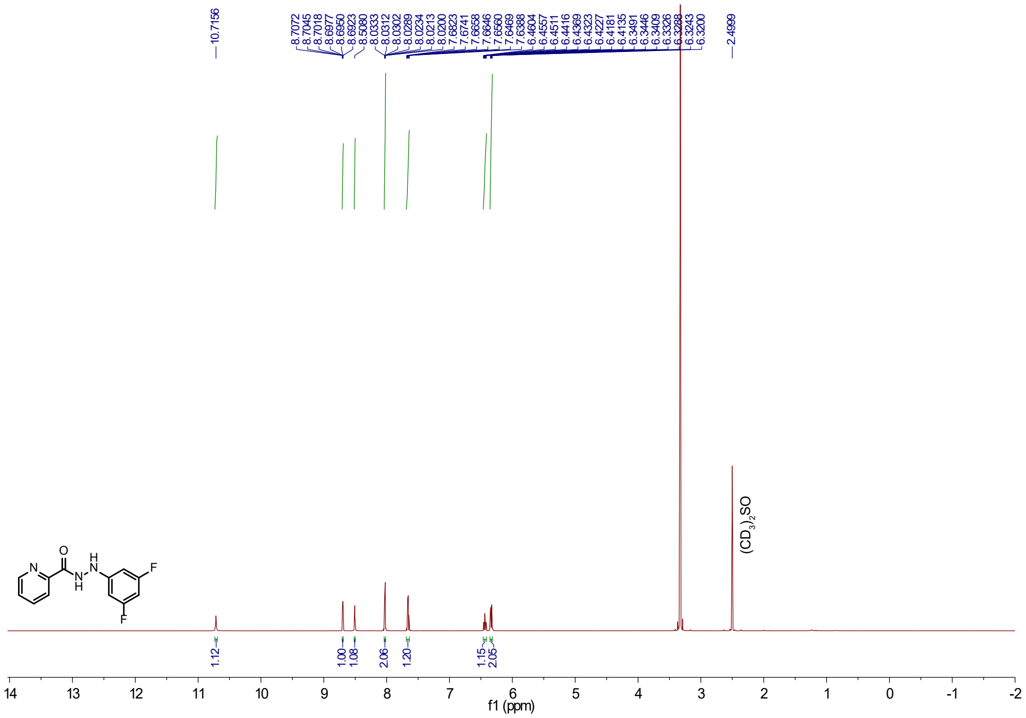


Fig. S49: ^{1}H NMR spectrum for compound **2i** (**SGT1790**) in (CD$_3$)$_2$SO (500 MHz).

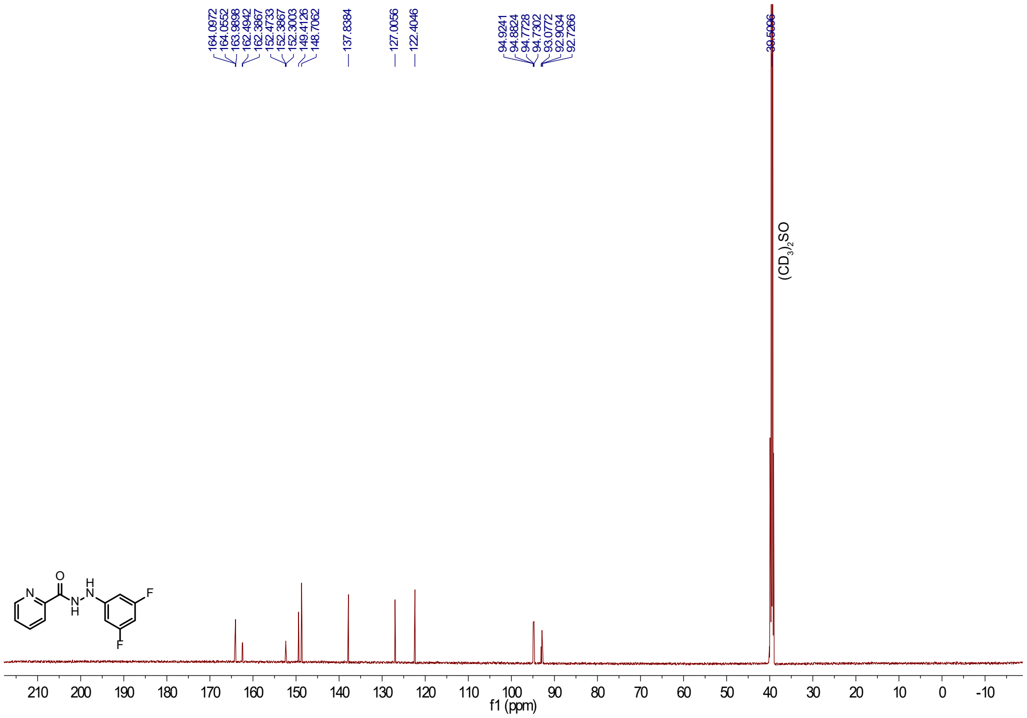


Fig. S50: ^{13}C NMR spectrum for compound **2i** (**SGT1790**) in (CD$_3$)$_2$SO (150 MHz).

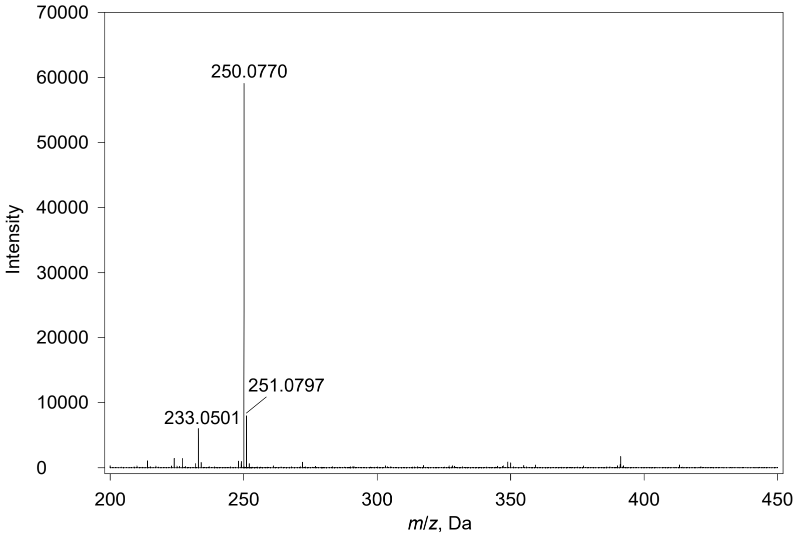


Fig. S51: HRMS spectrum for compound **2i** (**SGT1790**). *m/z* found 250.0770 [M+H]$^+$.

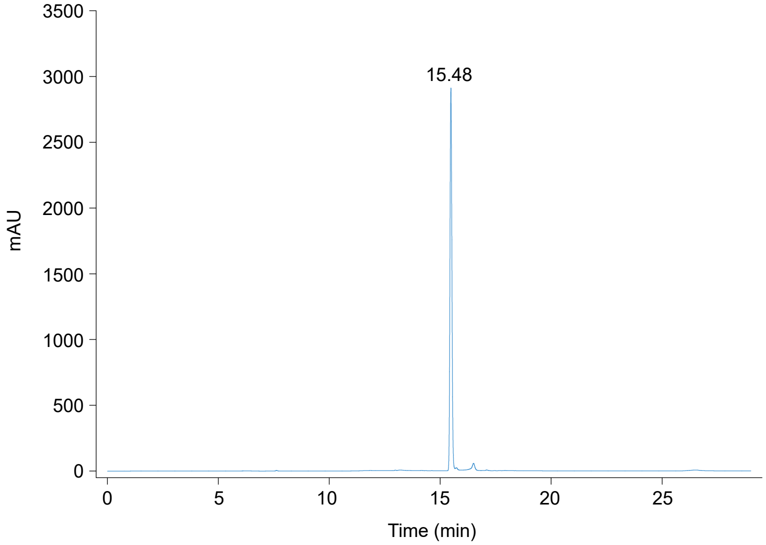


Fig. S52: HPLC trace for compound **2i** (**SGT1790**). R_t = 15.48 min.

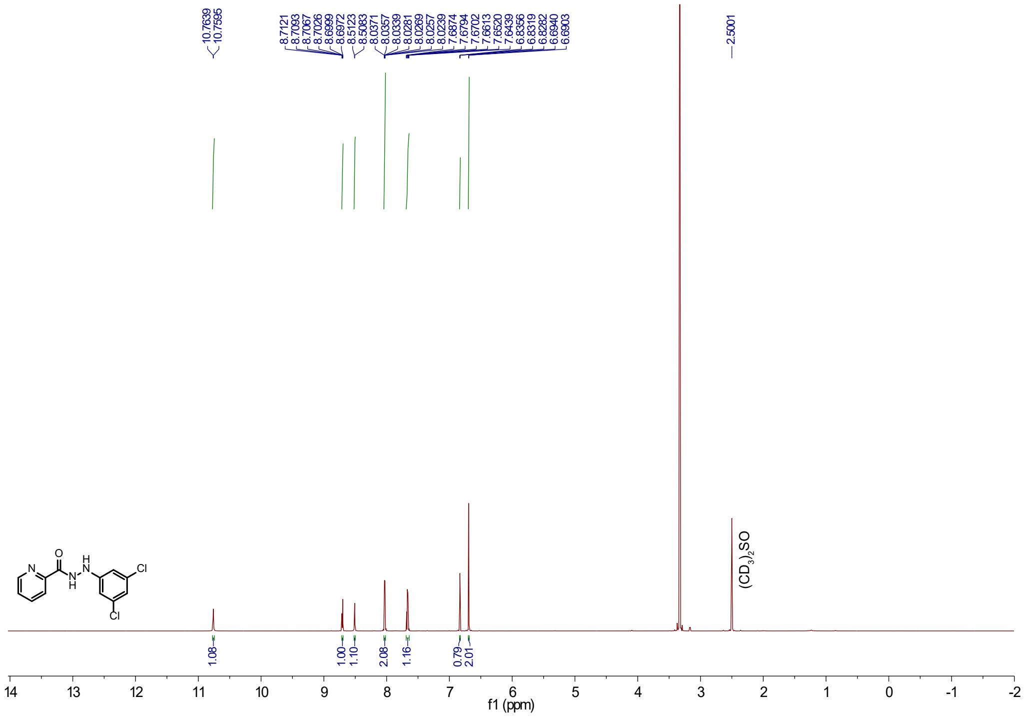


Fig. S53: ^{1}H NMR spectrum for compound **2j** (**SGT1788**) in $(CD_3)_2SO$ (500 MHz).

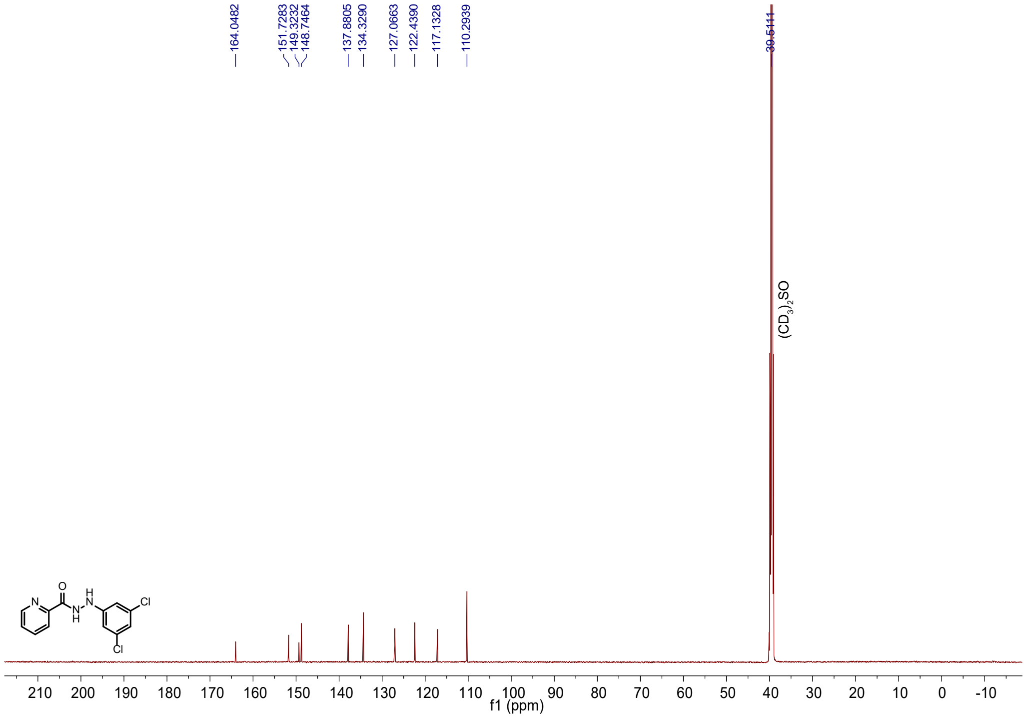


Fig. S54: ^{13}C NMR spectrum for compound **2j** (**SGT1788**) in $(CD_3)_2SO$ (150 MHz).

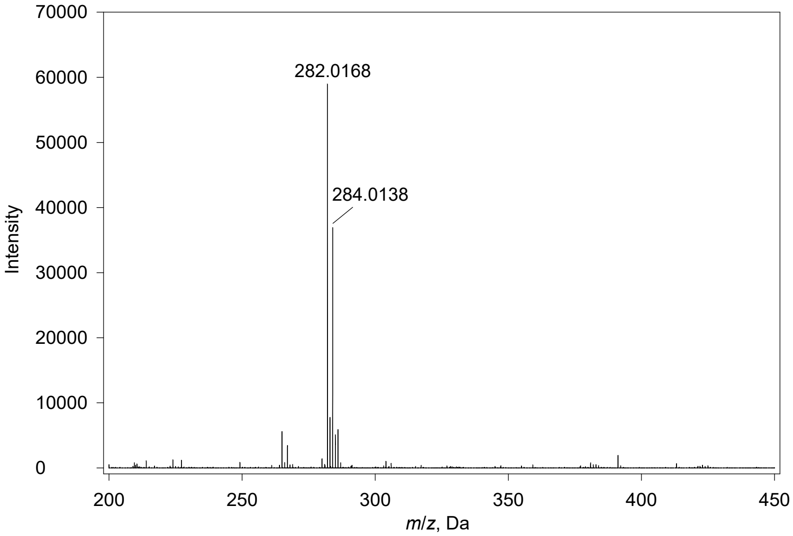


Fig. S55: HRMS spectrum for compound **2j** (**SGT1788**). *m/z* found 282.0168 [M+H]$^+$.

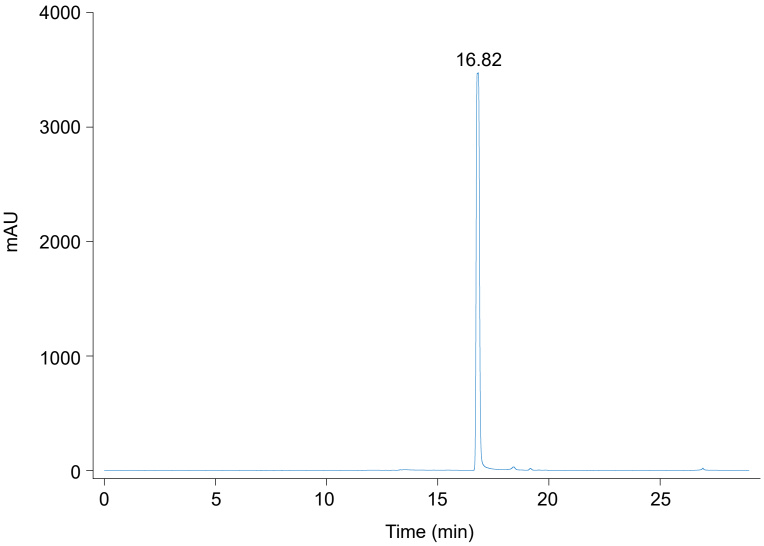


Fig. S56: HPLC trace for compound **2j** (**SGT1788**). R_t = 16.82 min.

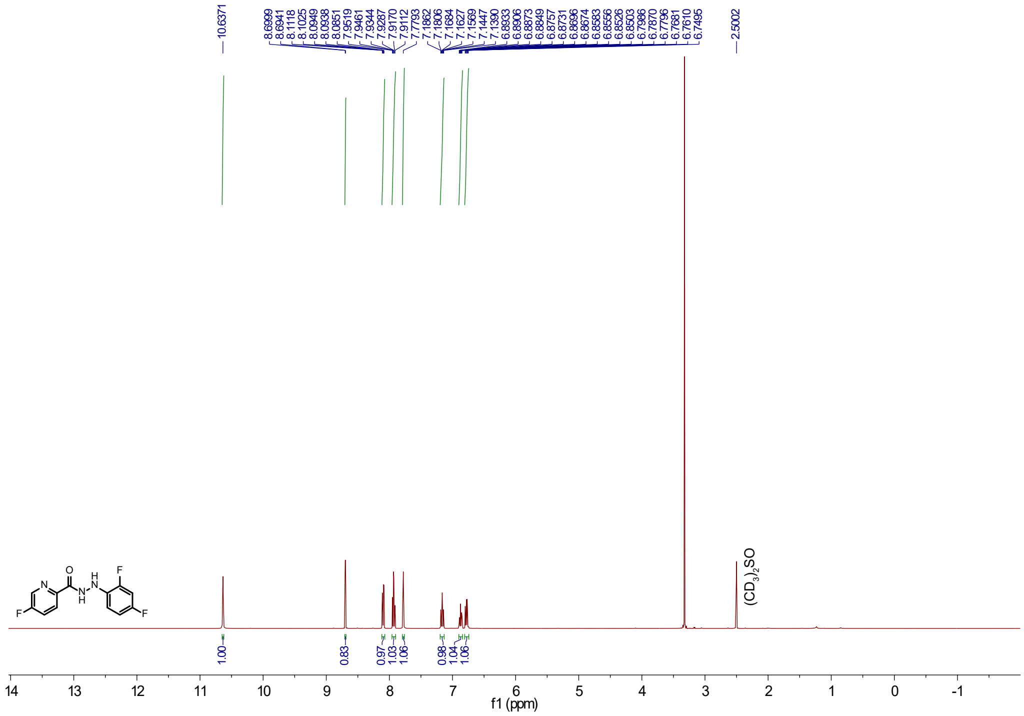


Fig. S57: ^{1}H NMR spectrum for compound **3g** (**SGT1803**) in $(CD_3)_2SO$ (500 MHz).

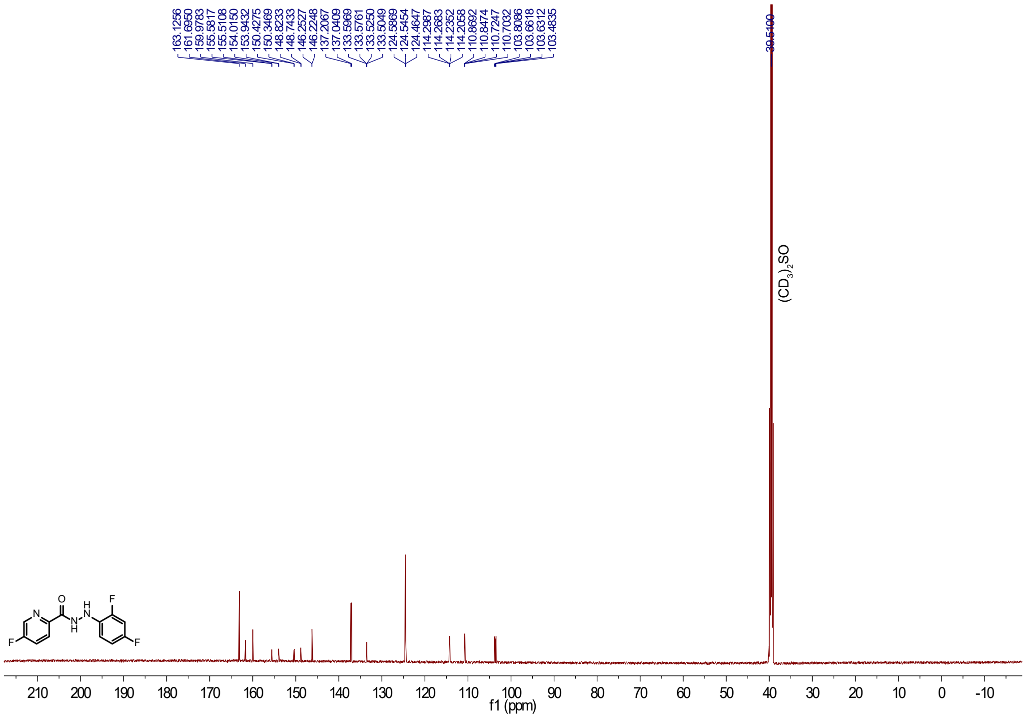


Fig. S58: ^{13}C NMR spectrum for compound **3g** (**SGT1803**) in $(CD_3)_2SO$ (150 MHz).

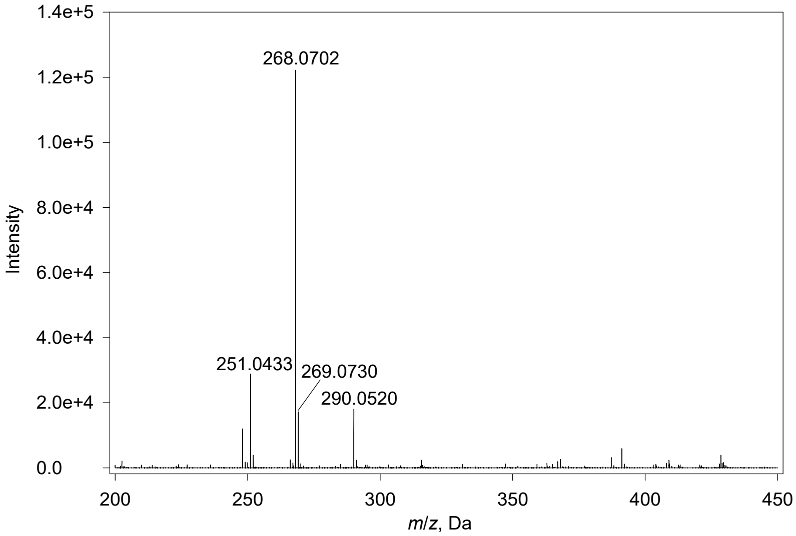


Fig. S59: HRMS spectrum for compound **3g** (**SGT1803**). *m/z* found 268.0702 $[M+H]^+$.

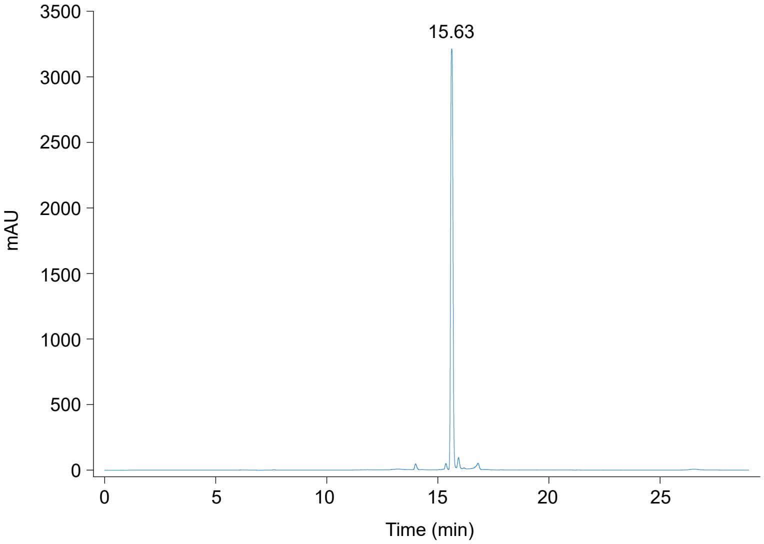


Fig. S60: HPLC trace for compound **3g** (**SGT1803**). R_t = 15.63 min.

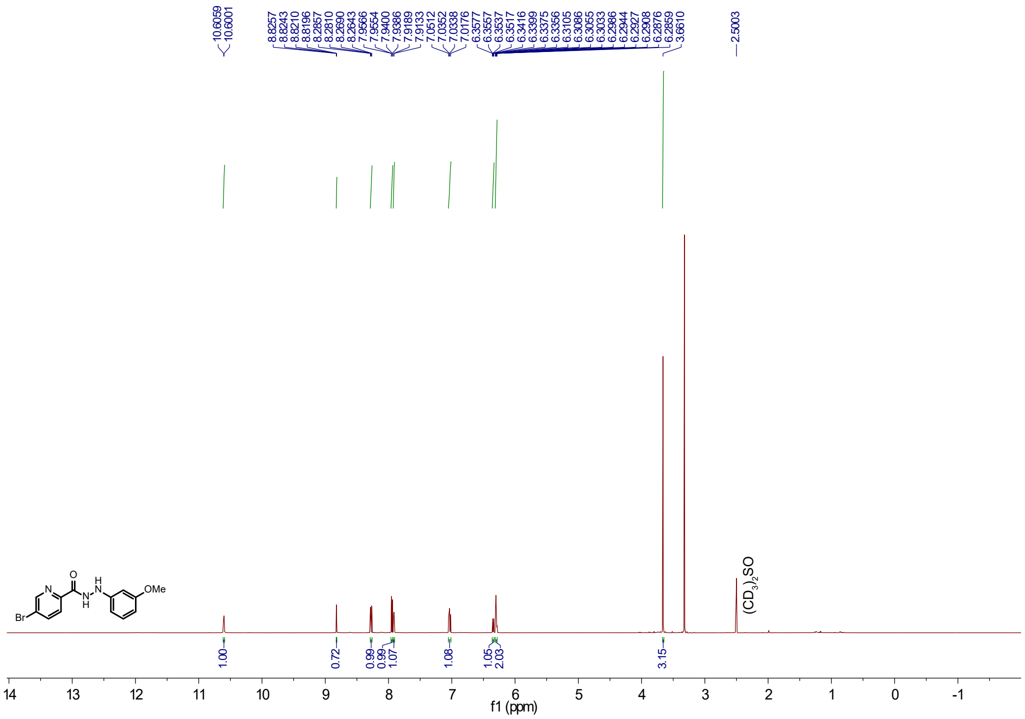


Fig. S61: ^{1}H NMR spectrum for compound **4c** (**SGT1436**) in $(CD_3)_2SO$ (500 MHz).

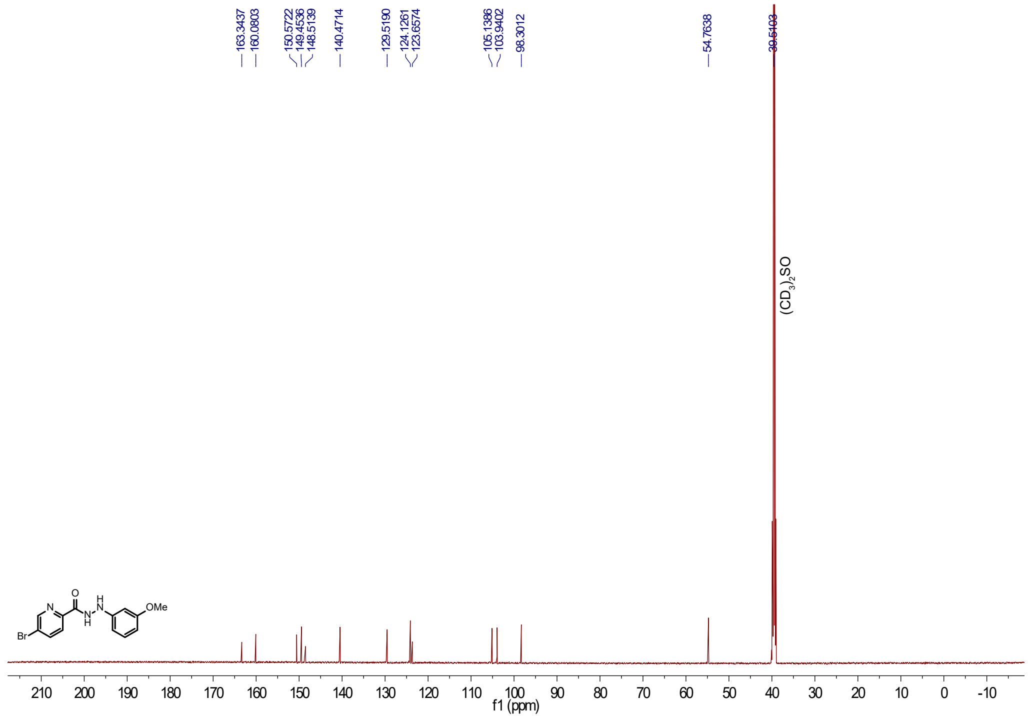


Fig. S62: ^{13}C NMR spectrum for compound **4c** (**SGT1436**) in $(CD_3)_2SO$ (150 MHz).

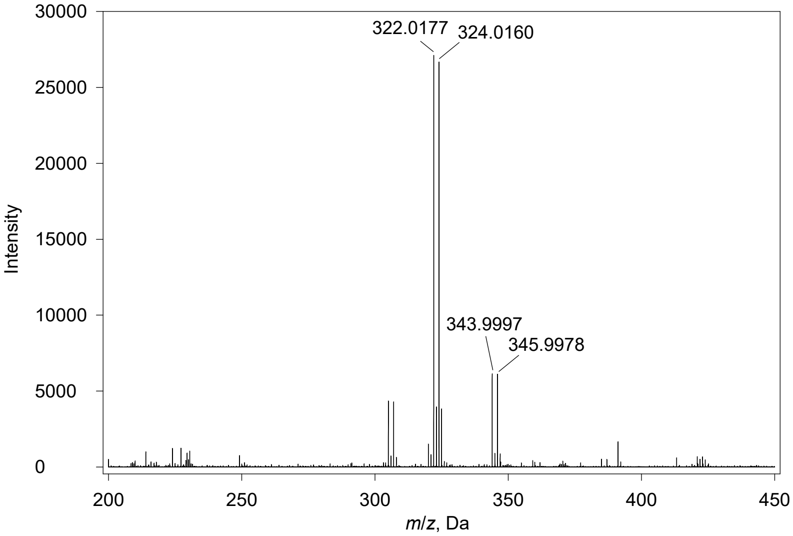


Fig. S63: HRMS spectrum for compound **4c** (**SGT1436**). *m/z* found 322.0177 $[M+H]^+$.

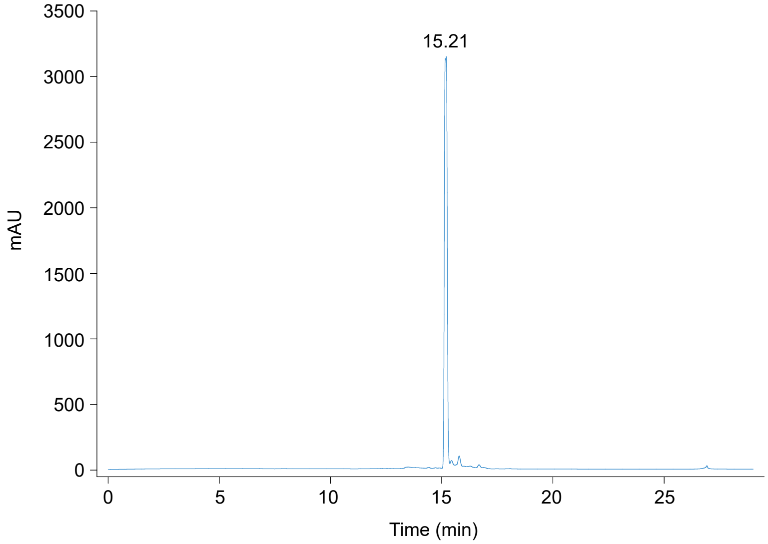


Fig. S64: HPLC trace for compound **4c** (**SGT1436**). R_t = 15.21 min.

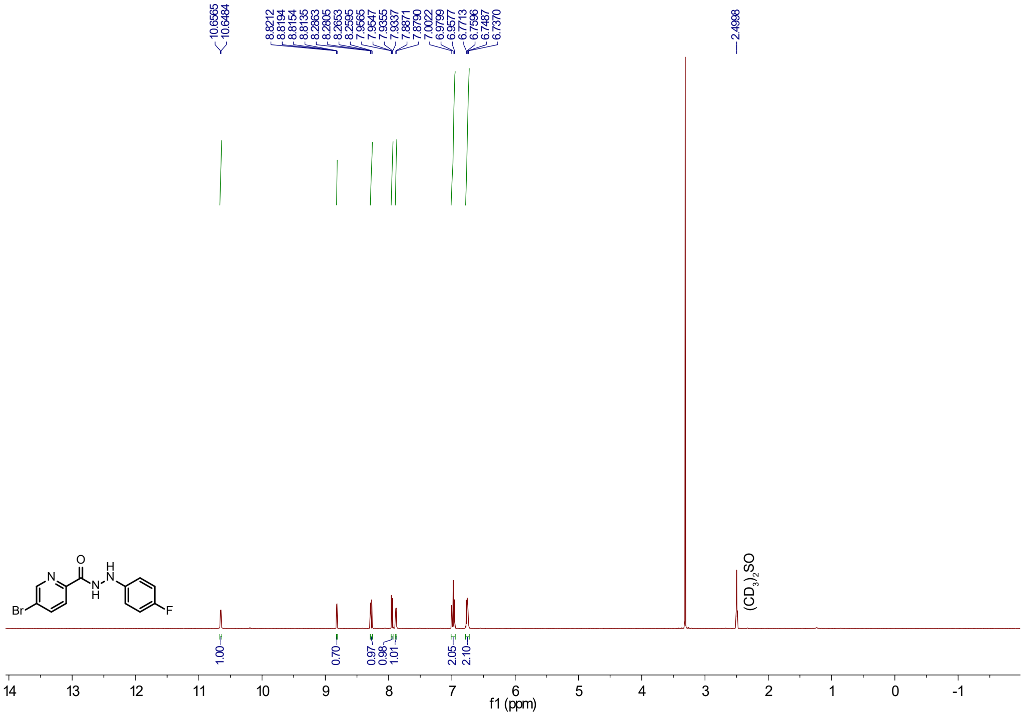


Fig. S65: ^{1}H NMR spectrum for compound **4d** (**SGT1774**) in $(CD_3)_2SO$ (400 MHz).

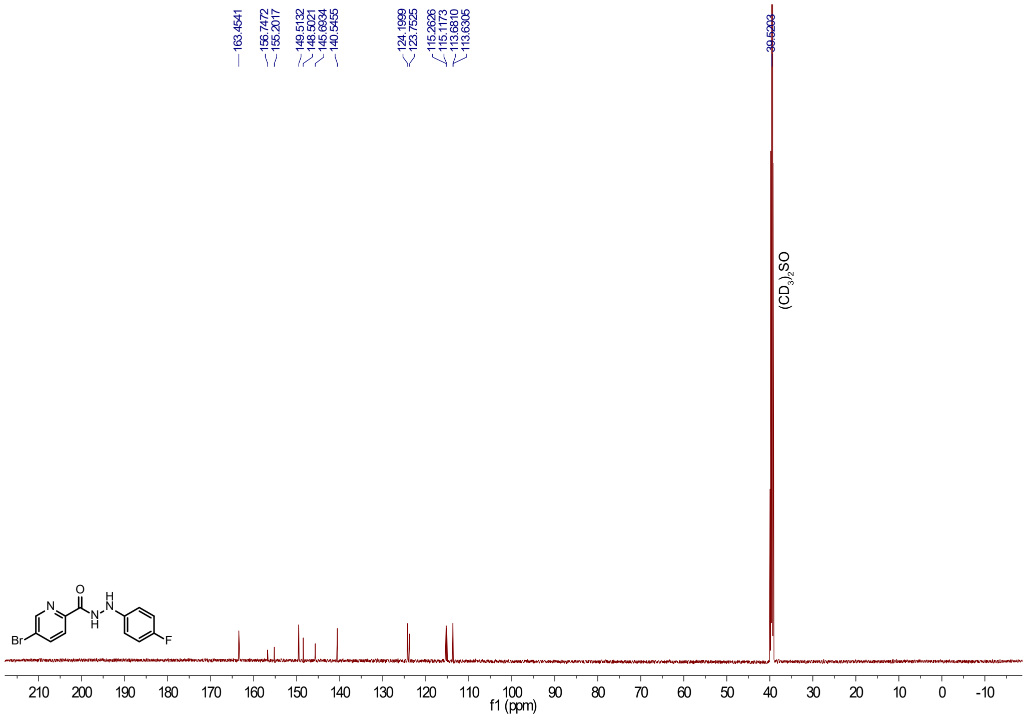


Fig. S66: ^{13}C NMR spectrum for compound **4d** (**SGT1774**) in $(CD_3)_2SO$ (100 MHz).

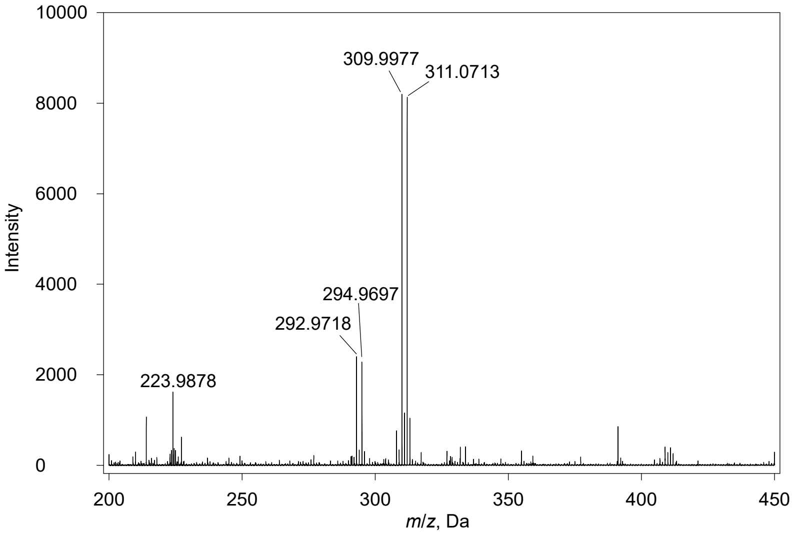


Fig. S67: HRMS spectrum for compound **4d** (**SGT1774**). *m/z* found 309.9977 $[M+H]^+$.

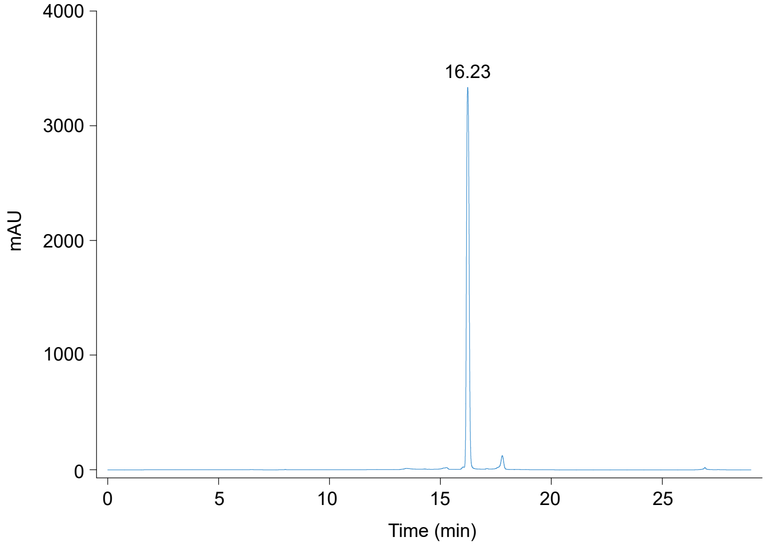


Fig. S68: HPLC trace for compound **4d** (**SGT1774**). R_t = 16.23 min.

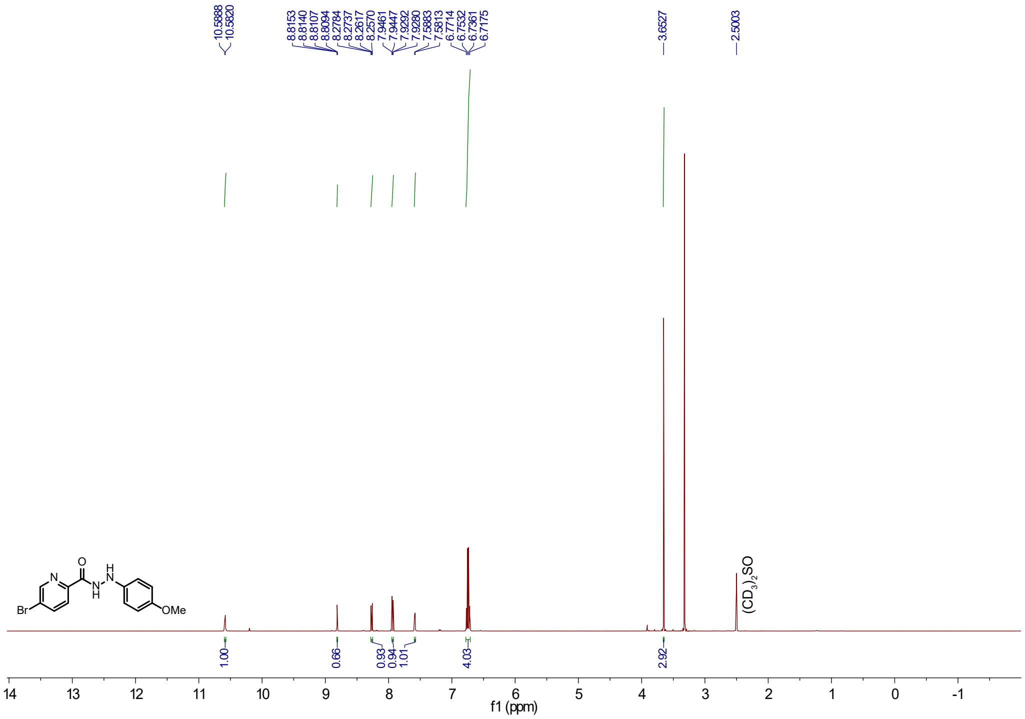


Fig. S69: ^{1}H NMR spectrum for compound **4f** (**SGT1434**) in $(CD_3)_2SO$ (500 MHz).

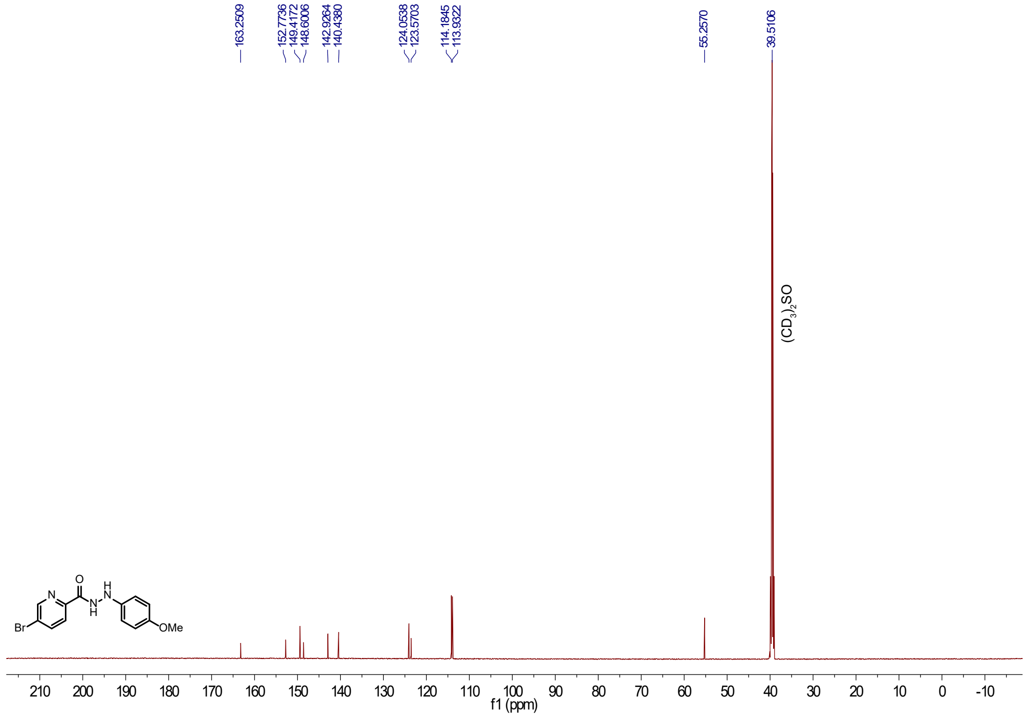


Fig. S70: ^{13}C NMR spectrum for compound **4f** (**SGT1434**) in $(CD_3)_2SO$ (150 MHz).

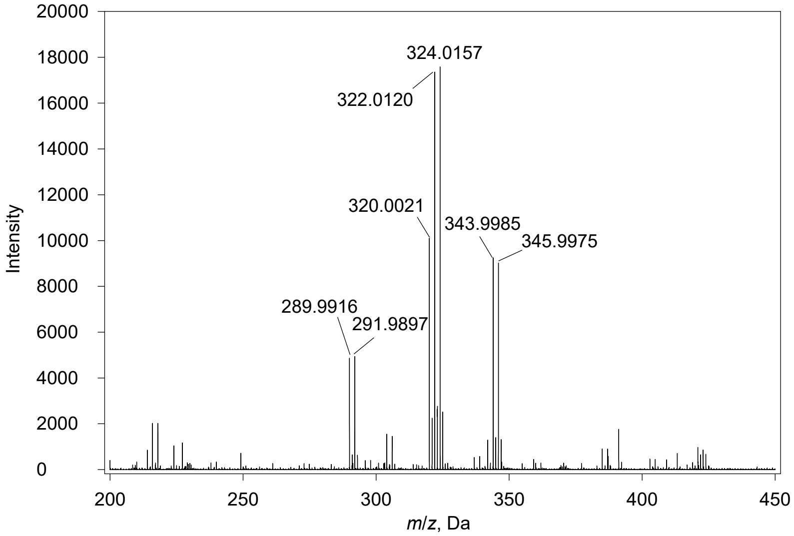


Fig. S71: HRMS spectrum for compound **4f** (**SGT1434**). *m/z* found 322.0120 $[M+H]^+$.

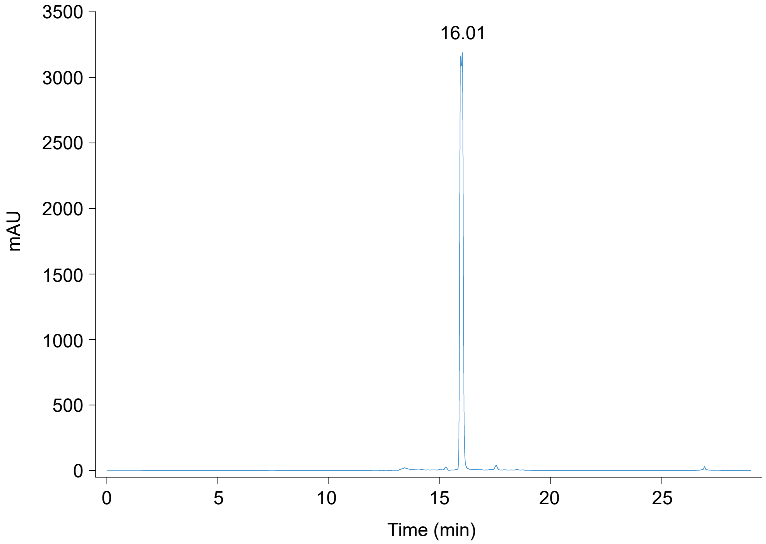


Fig. S72: HPLC trace for compound **4f** (**SGT1434**). R_t = 16.01 min.

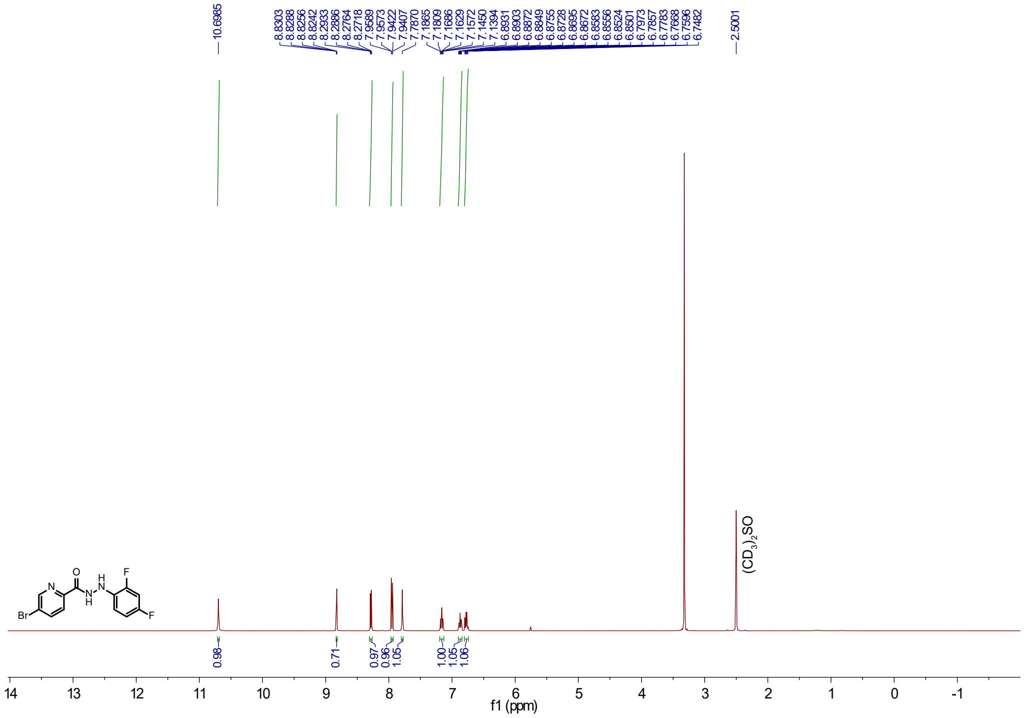


Fig. S73: ^{1}H NMR spectrum for compound **4g** (**SGT1438**) in (CD$_3$)$_2$SO (500 MHz).

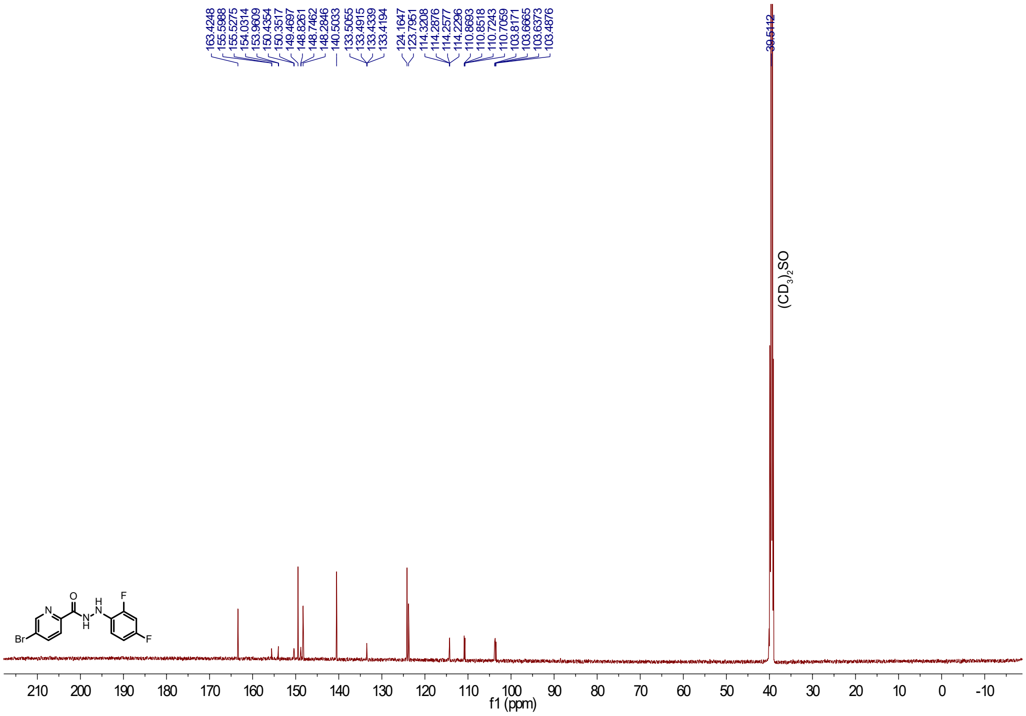


Fig. S74: ^{13}C NMR spectrum for compound **4g** (**SGT1438**) in (CD$_3$)$_2$SO (150 MHz).

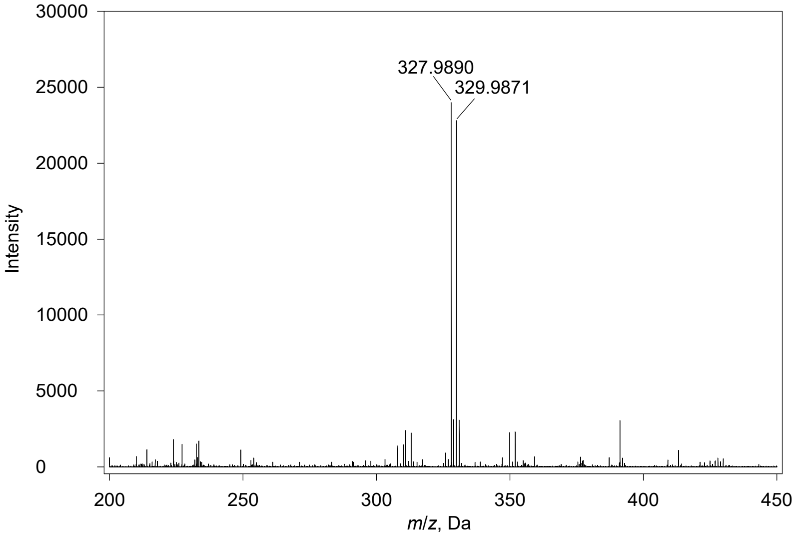


Fig. S75: HRMS spectrum for compound **4g** (**SGT1438**). *m/z* found 327.9890 $[M+H]^+$.

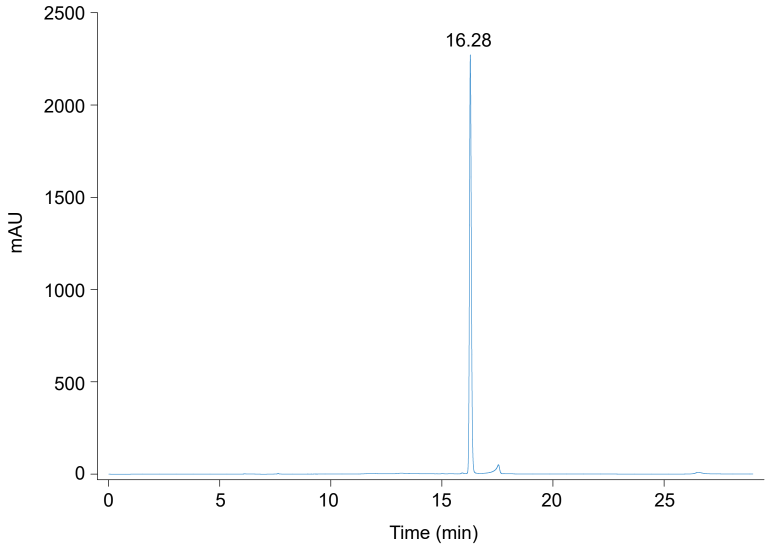


Fig. S76: HPLC trace for compound **4g** (**SGT1438**). R_t = 16.28 min.

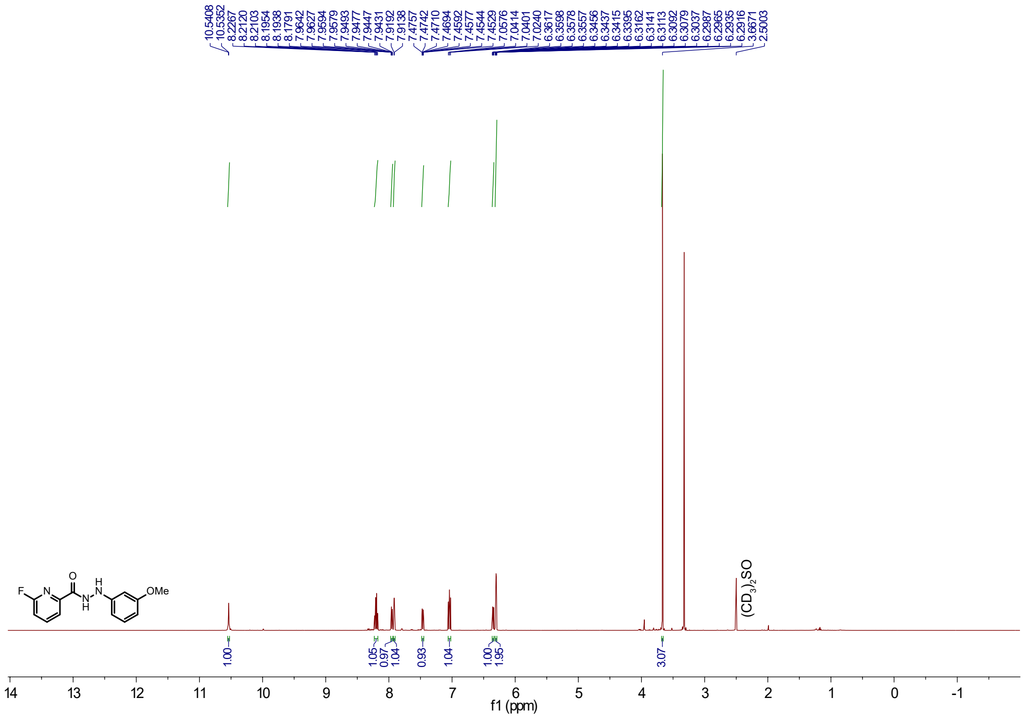


Fig. S77: ^{1}H NMR spectrum for compound **5c** (**SGT1798**) in $(CD_3)_2SO$ (500 MHz).

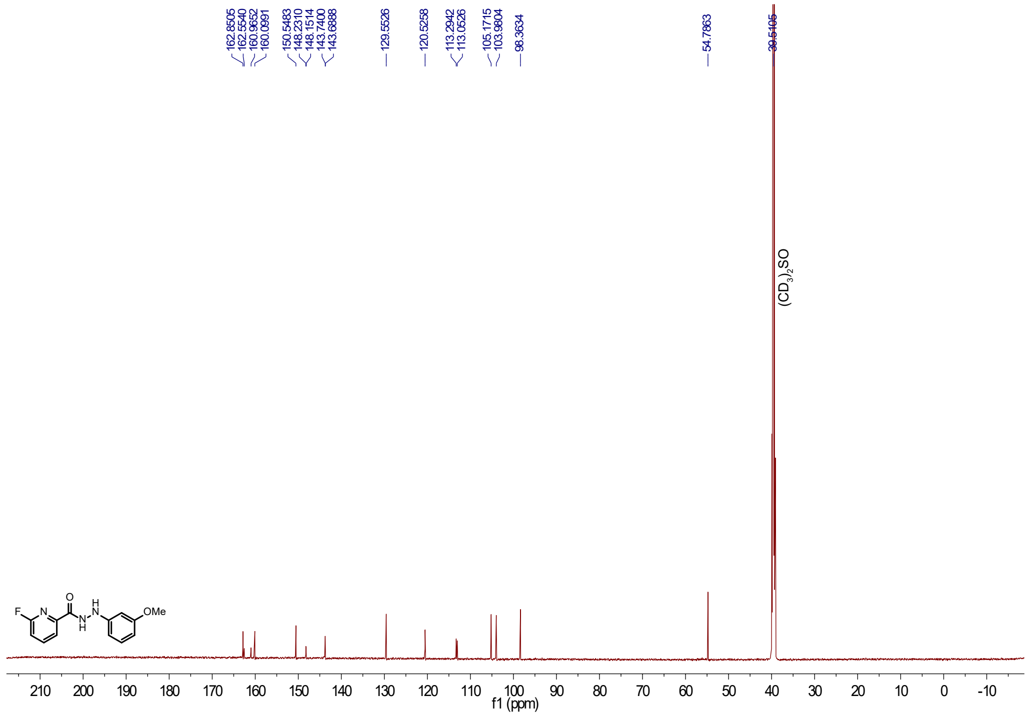


Fig. S78: ^{13}C NMR spectrum for compound **5c** (**SGT1798**) in $(CD_3)_2SO$ (150 MHz).

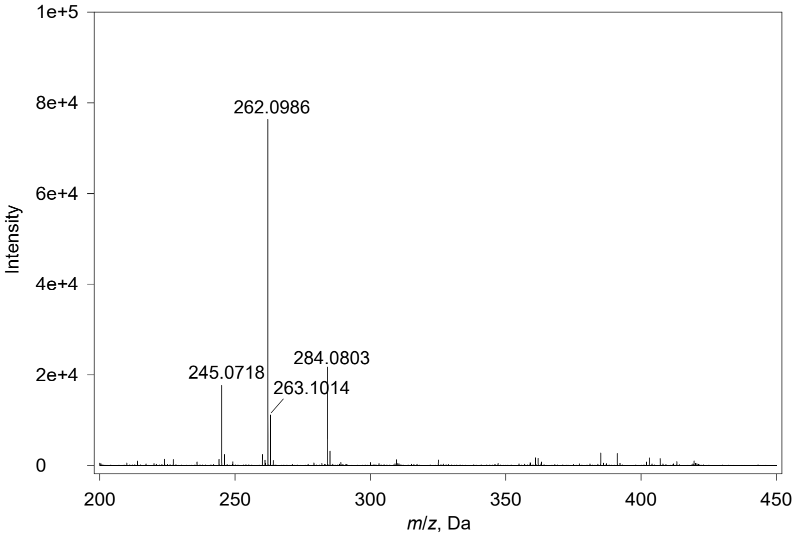


Fig. S79: HRMS spectrum for compound **5c** (**SGT1798**). *m/z* found 262.0986 $[M+H]^+$.

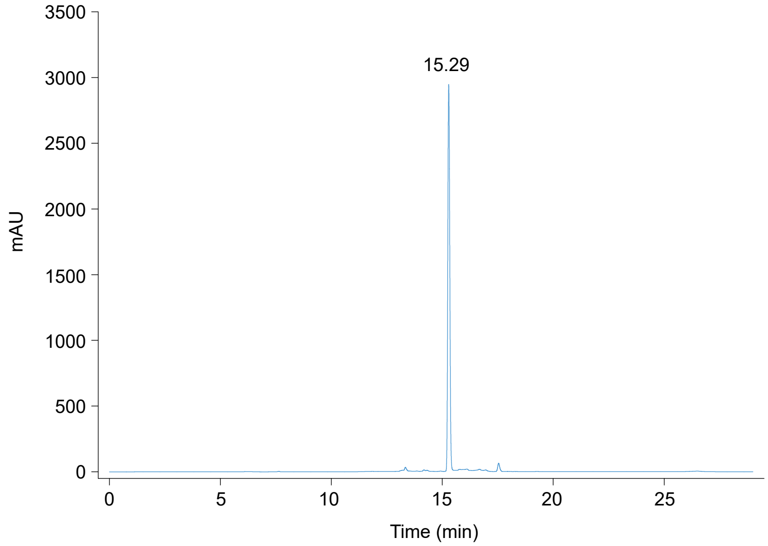


Fig. S80: HPLC trace for compound **5c** (**SGT1798**). R_t = 15.29 min.

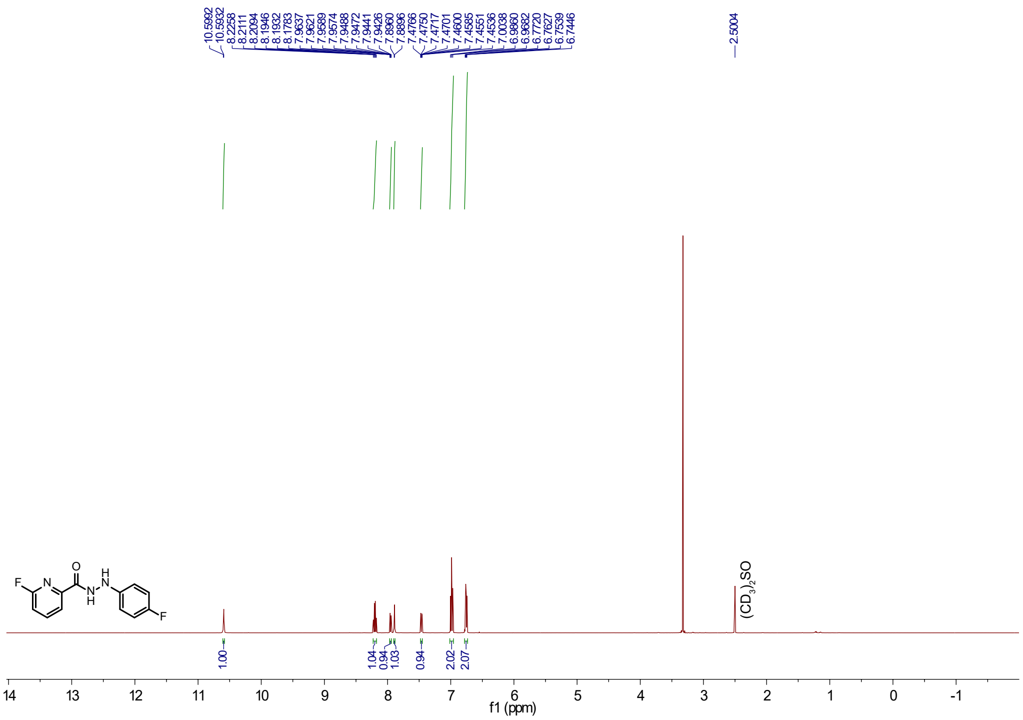


Fig. S81: ^{1}H NMR spectrum for compound **5d** (**SGT1800**) in $(CD_3)_2SO$ (500 MHz).

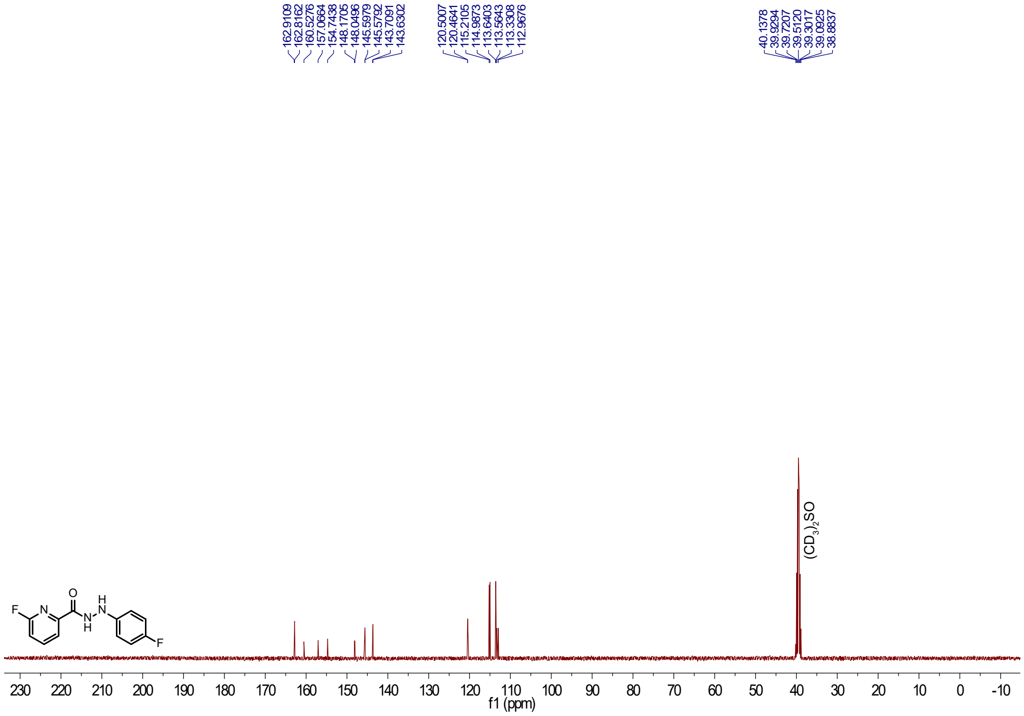


Fig. S82: ^{13}C NMR spectrum for compound **5d** (**SGT1800**) in $(CD_3)_2SO$ (100 MHz).

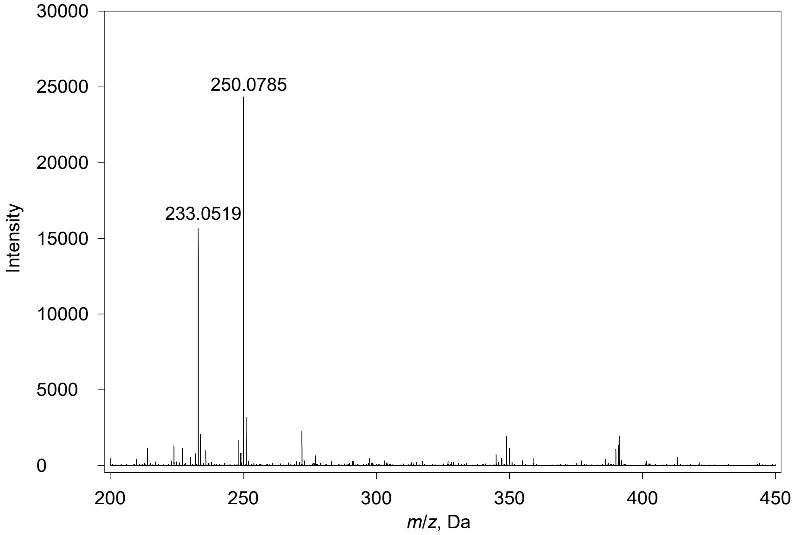


Fig. S83: HRMS spectrum for compound **5d** (**SGT1800**). *m/z* found 250.0785 $[M+H]^+$.

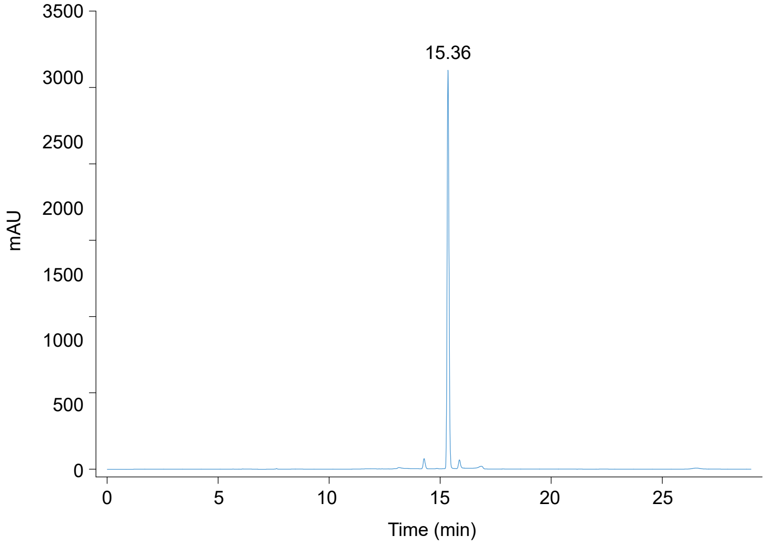


Fig. S84: HPLC trace for compound **5d** (**SGT1800**). R_t = 15.36 min.

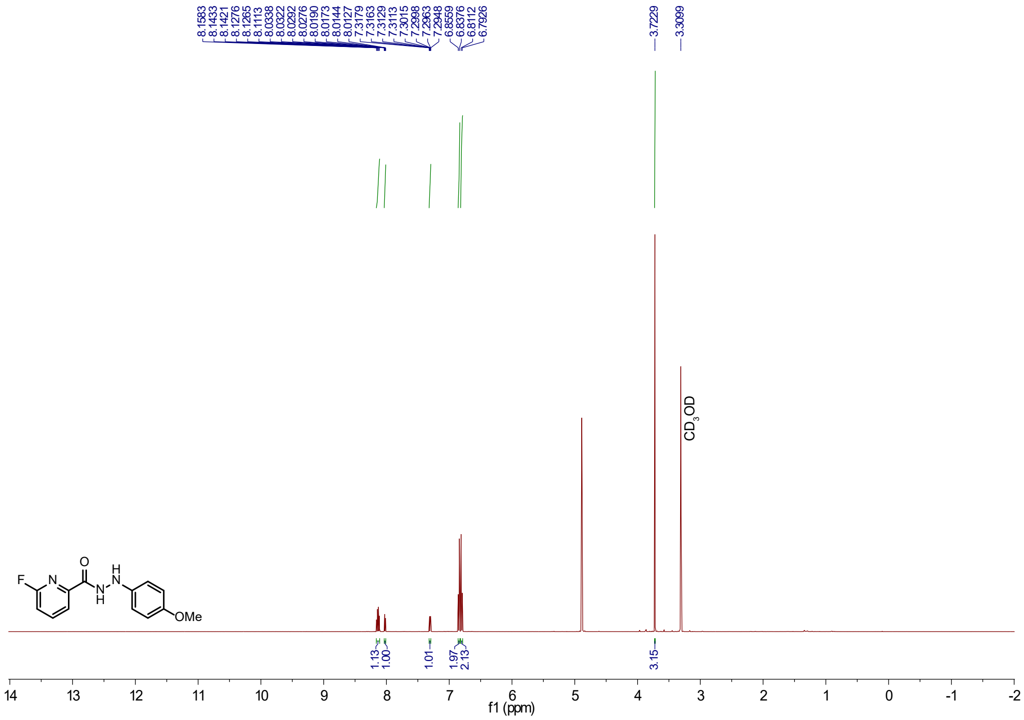


Fig. S85: ^{1}H NMR spectrum for compound **5f** (**SGT1770**) in CD$_3$OD (500 MHz).

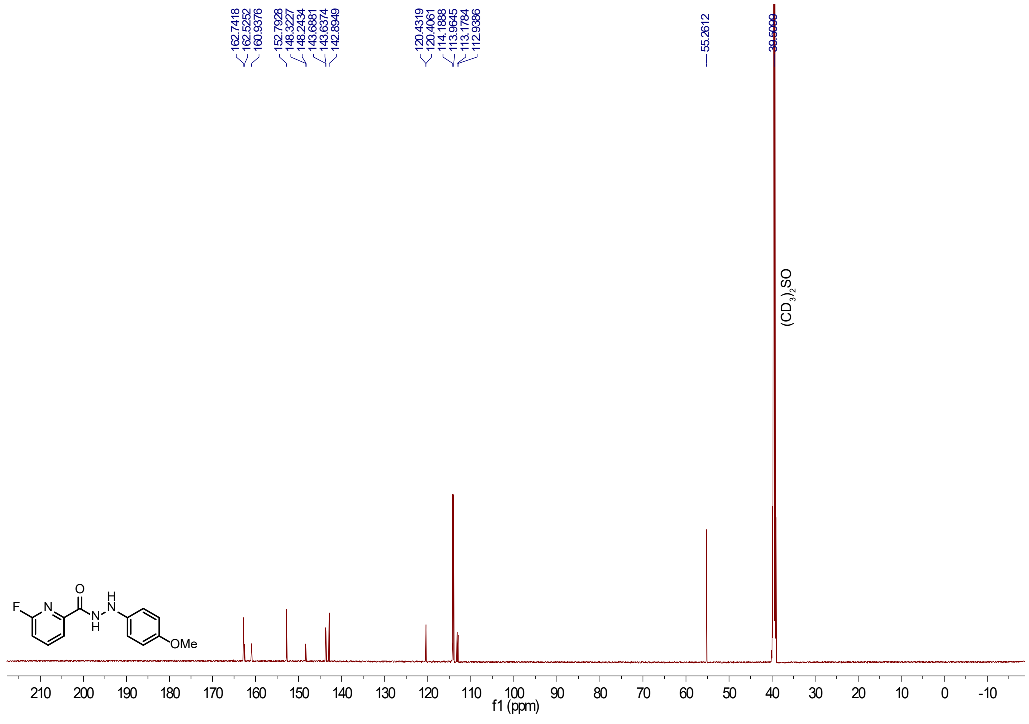


Fig. S86: ^{13}C NMR spectrum for compound **5f** (**SGT1770**) in (CD$_3$)$_2$SO (150 MHz).

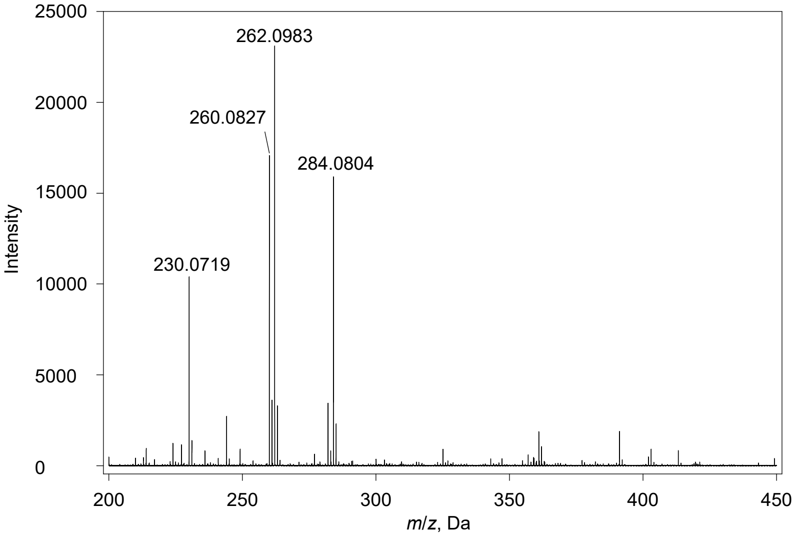


Fig. S87: HRMS spectrum for compound **5f** (**SGT1770**). *m/z* found 262.0983 $[M+H]^+$.

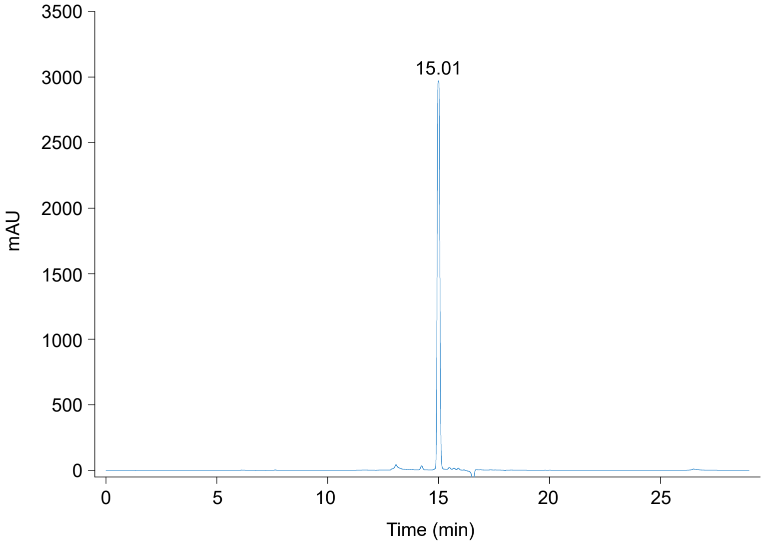


Fig. S88: HPLC trace for compound **5f** (**SGT1770**). R_t = 15.01 min.

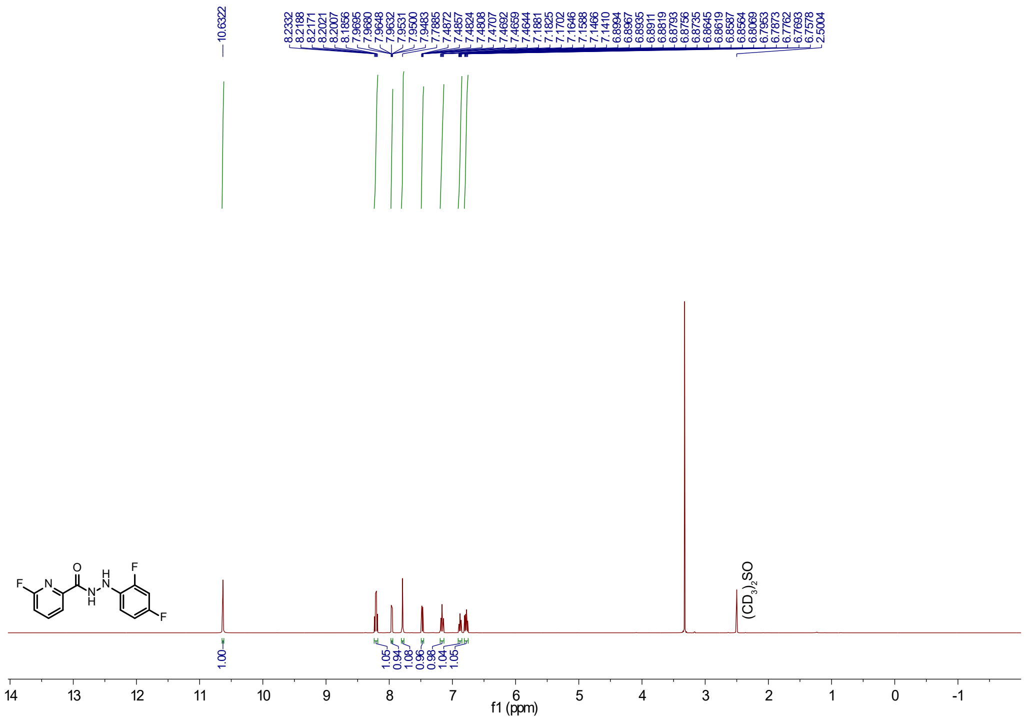


Fig. S89: ^{1}H NMR spectrum for compound **5g** (**SGT1804**) in $(CD_3)_2SO$ (500 MHz).

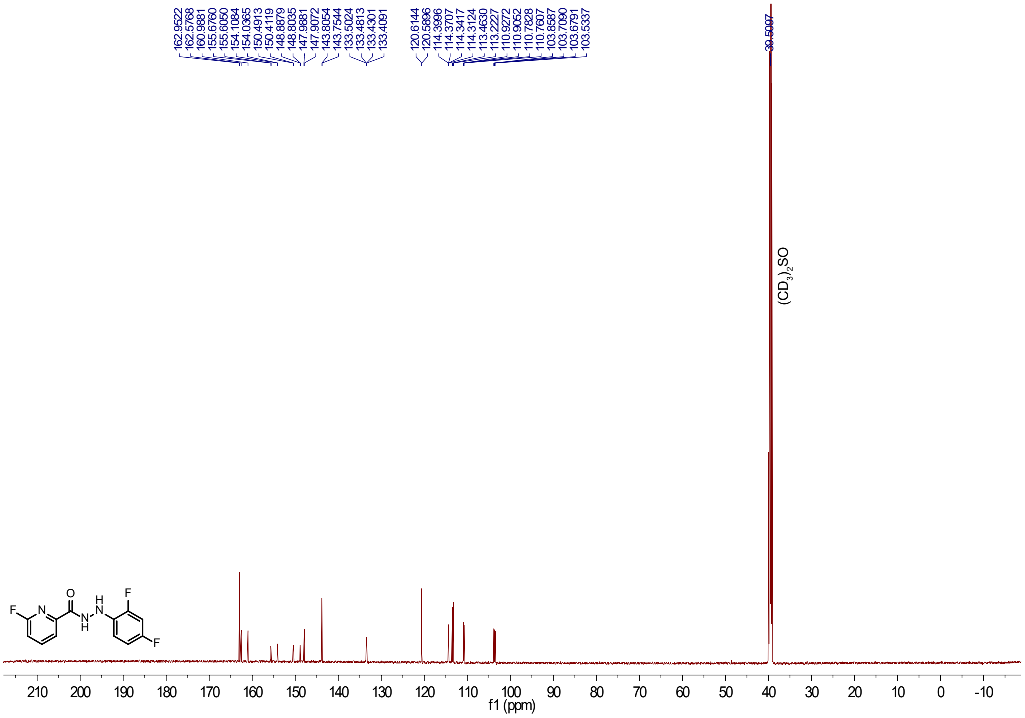


Fig. S90: ^{13}C NMR spectrum for compound **5g** (**SGT1804**) in $(CD_3)_2SO$ (150 MHz).

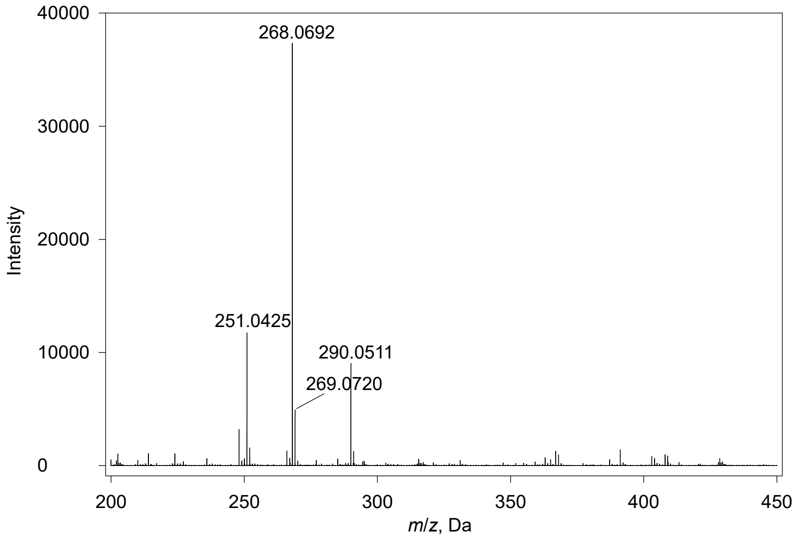


Fig. S91: HRMS spectrum for compound **5g** (**SGT1804**). *m/z* found 268.0692 $[M+H]^+$.

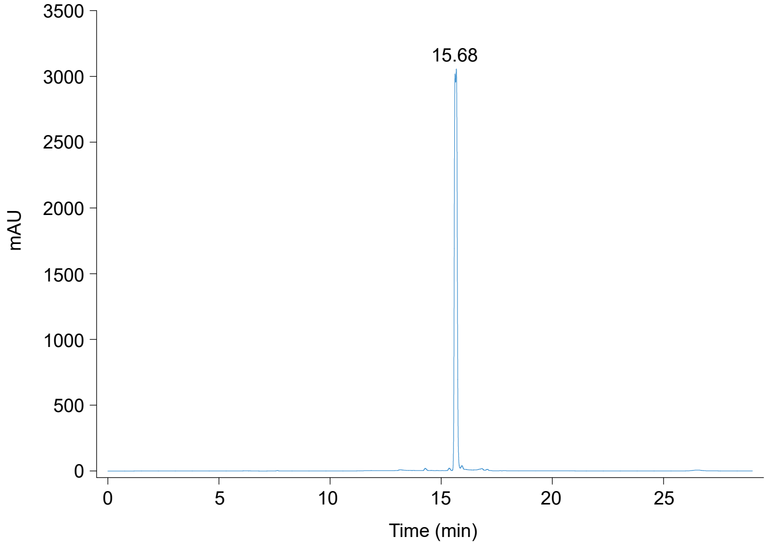


Fig. S92: HPLC trace for compound **5g** (**SGT1804**). R_t = 15.68 min.

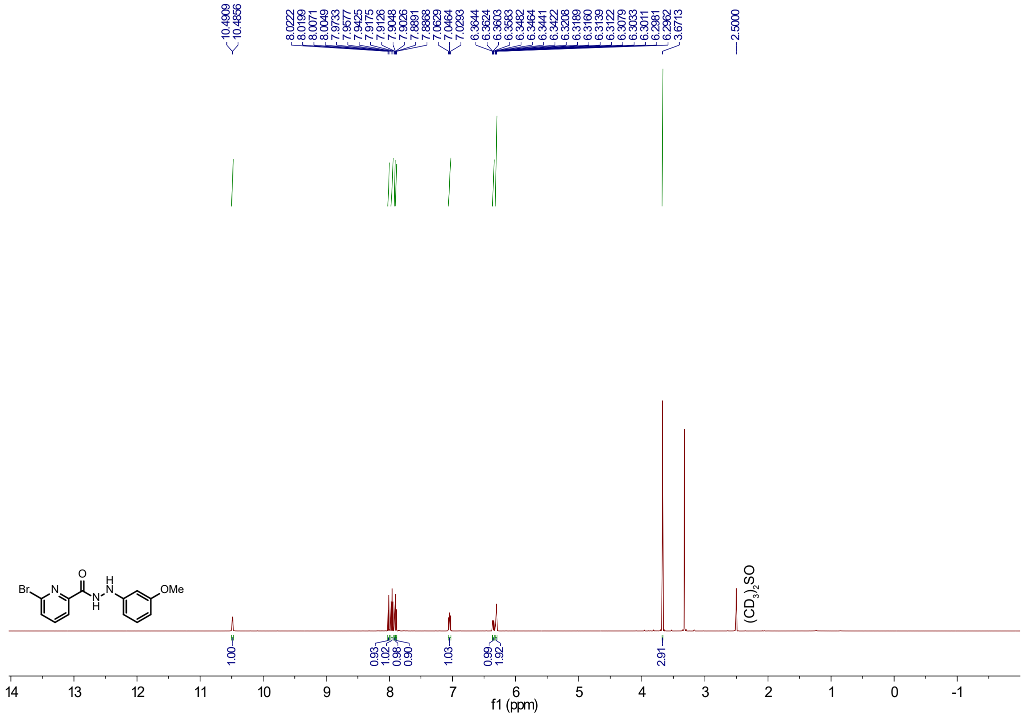


Fig. S93: ^{1}H NMR spectrum for compound **6c** (**SGT1437**) in $(CD_3)_2SO$ (500 MHz).

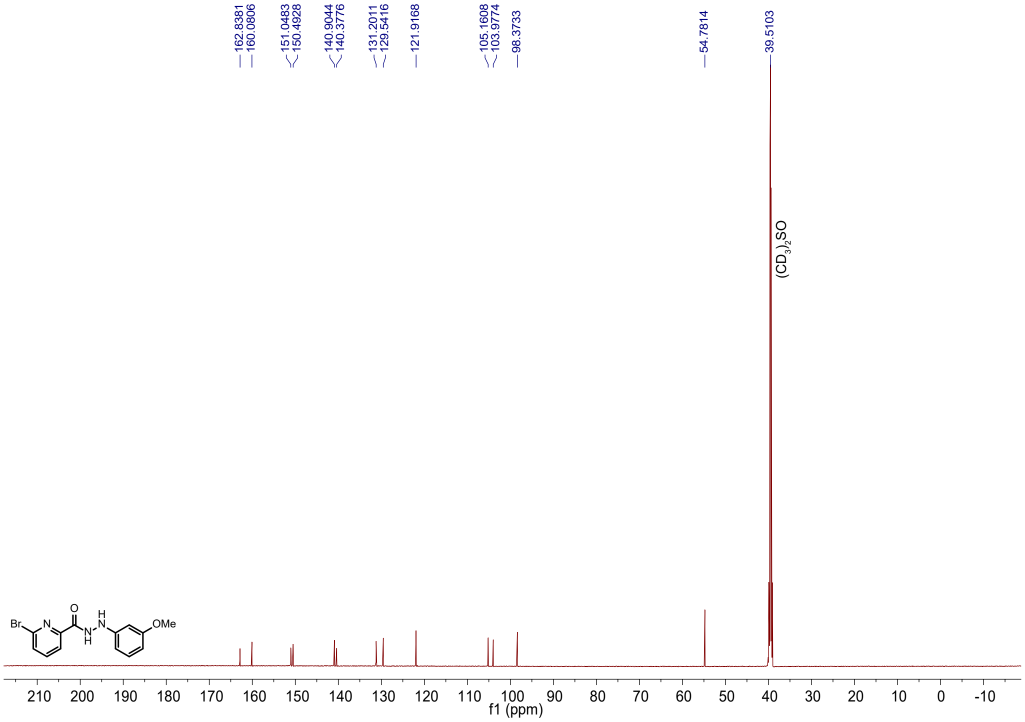


Fig. S94: ^{13}C NMR spectrum for compound **6c** (**SGT1437**) in $(CD_3)_2SO$ (150 MHz).

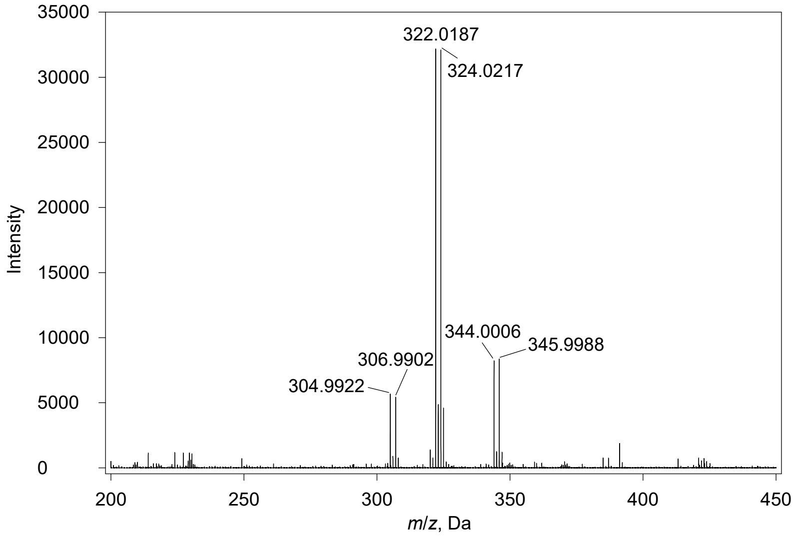


Fig. S95: HRMS spectrum for compound **6c** (**SGT1437**). *m/z* found 322.0187 $[M+H]^+$.

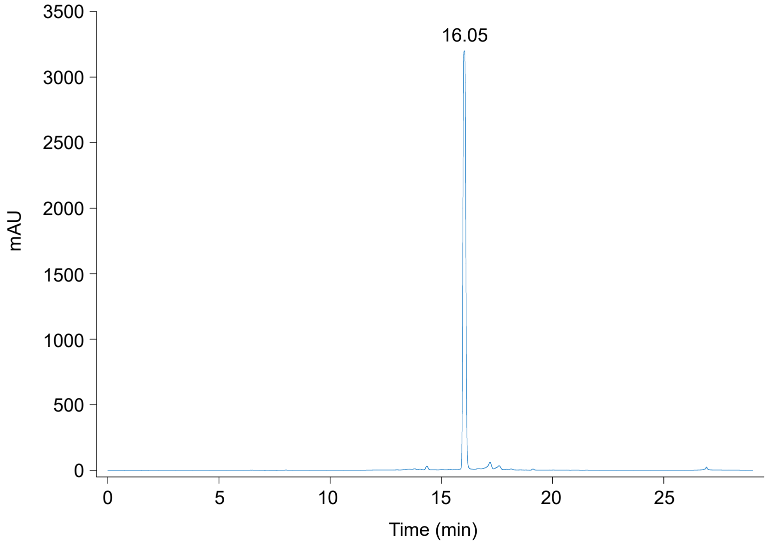


Fig. S96: HPLC trace for compound **6c** (**SGT1437**). R_t = 16.05 min.

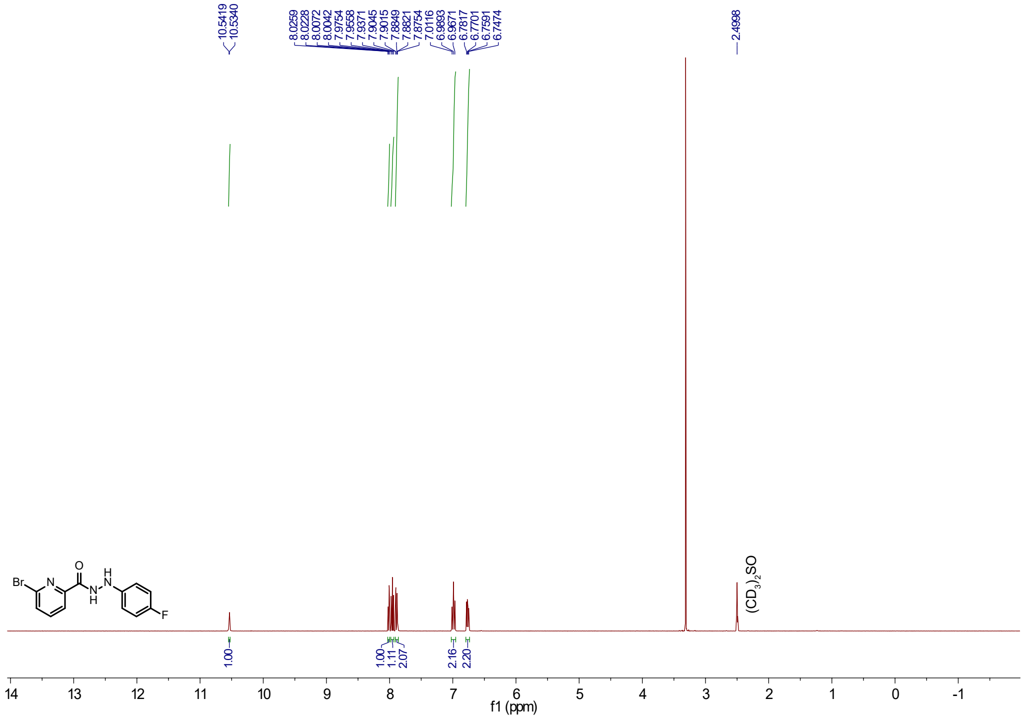


Fig. S97: ^{1}H NMR spectrum for compound **6d** (**SGT1775**) in $(CD_3)_2SO$ (400 MHz).

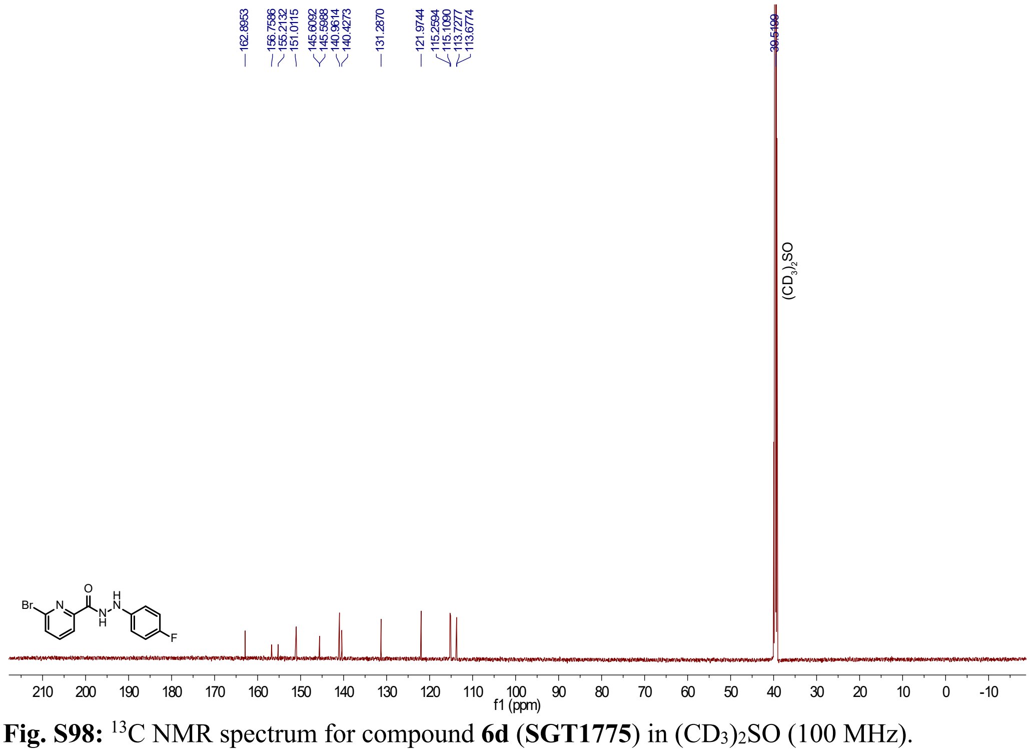


Fig. S98: ^{13}C NMR spectrum for compound **6d** (**SGT1775**) in $(CD_3)_2SO$ (100 MHz).

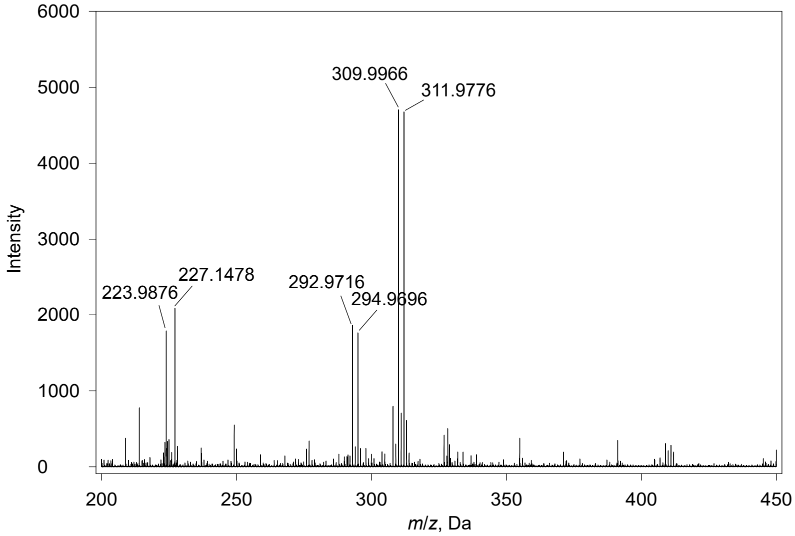


Fig. S99: HRMS spectrum for compound **6d** (**SGT1775**). *m/z* found 309.9966 [M+H]$^+$.

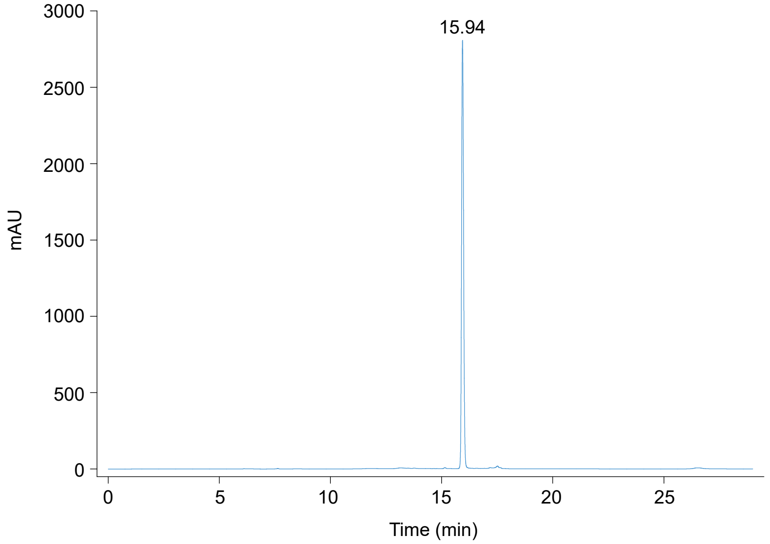


Fig. S100: HPLC trace for compound **6d** (**SGT1775**). R_t = 15.94 min.

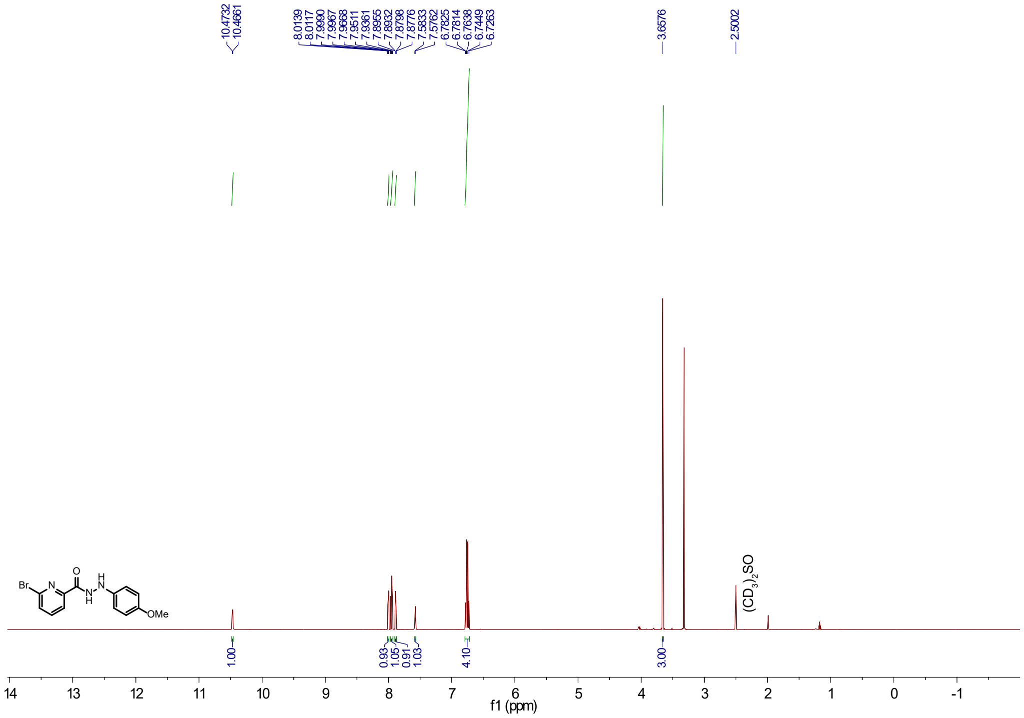


Fig. S101: ^{1}H NMR spectrum for compound **6f** (**SGT1435**) in $(CD_3)_2SO$ (500 MHz).

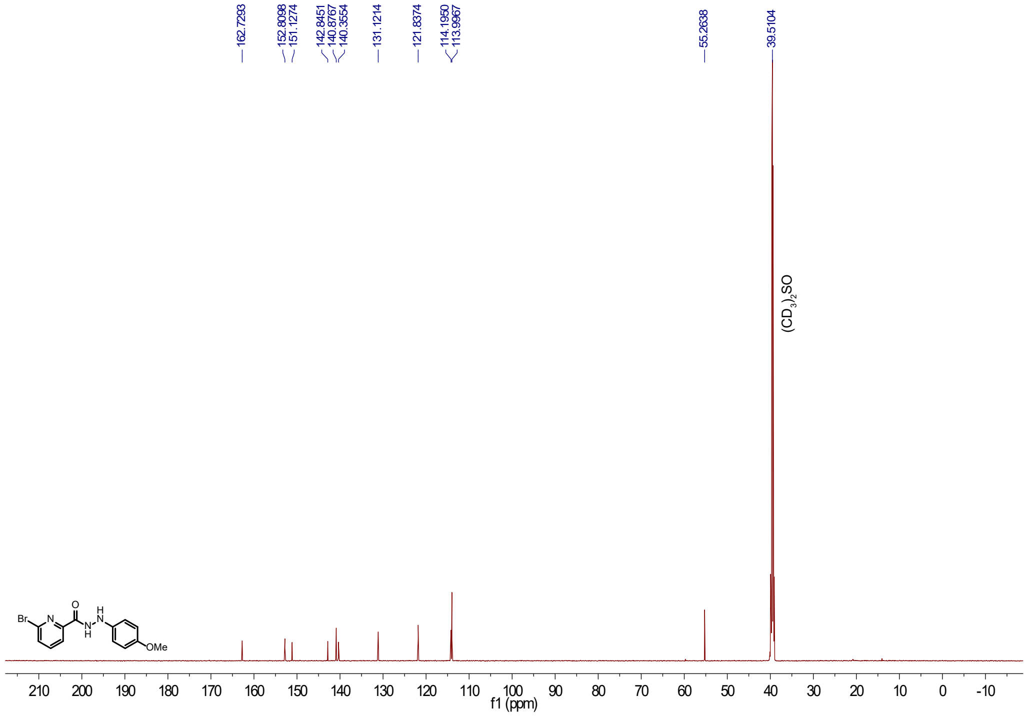


Fig. S102: ^{13}C NMR spectrum for compound **6f** (**SGT1435**) in $(CD_3)_2SO$ (150 MHz).

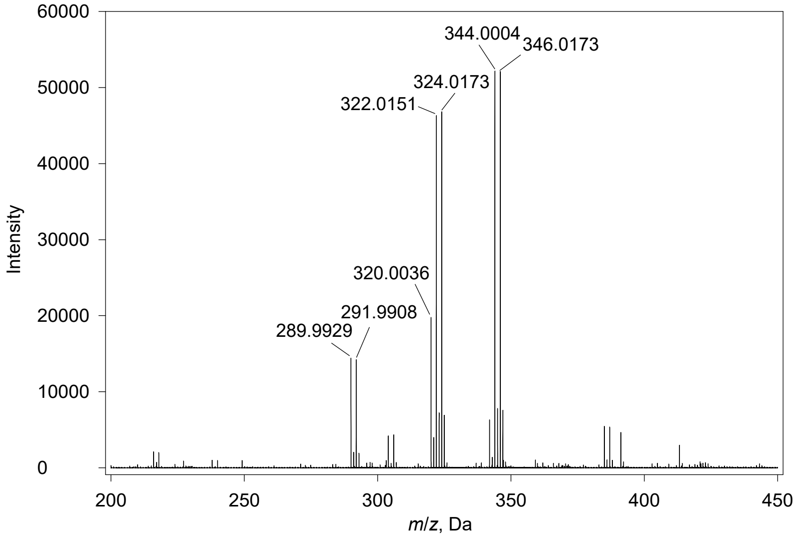


Fig. S103: HRMS spectrum for compound **6f** (**SGT1435**). *m/z* found 322.0151 $[M+H]^+$.

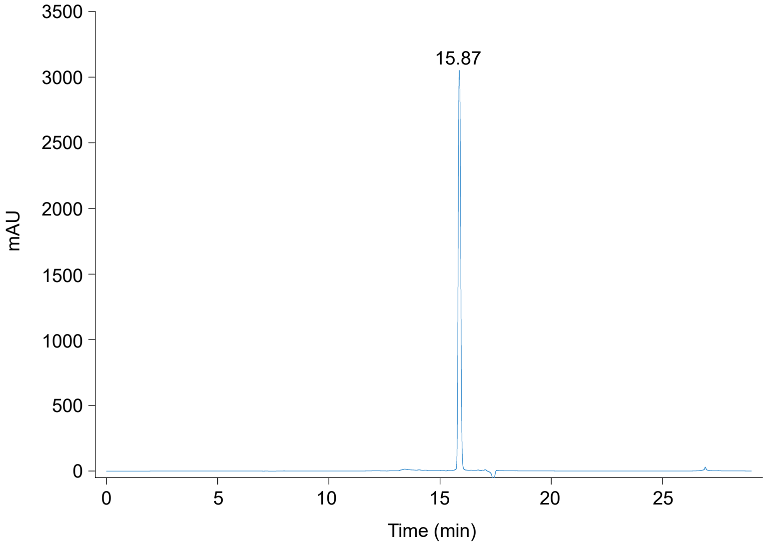


Fig. S104: HPLC trace for compound **6f** (**SGT1435**). R_t = 15.87 min.

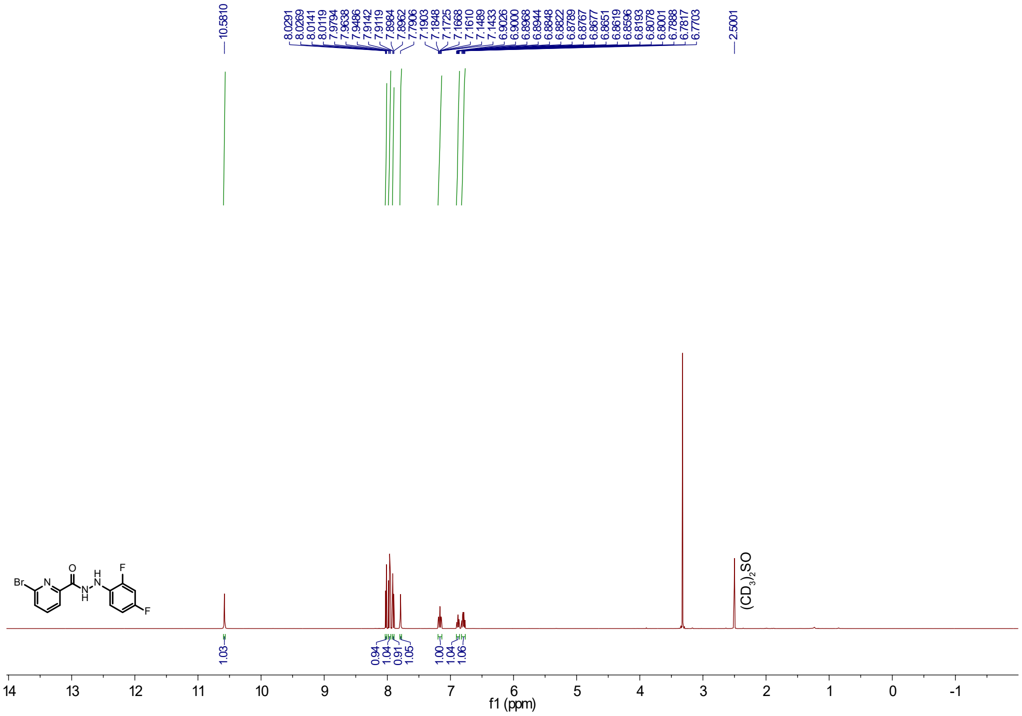


Fig. S105: ^{1}H NMR spectrum for compound **6g** (**SGT1439**) in $(CD_3)_2SO$ (500 MHz).

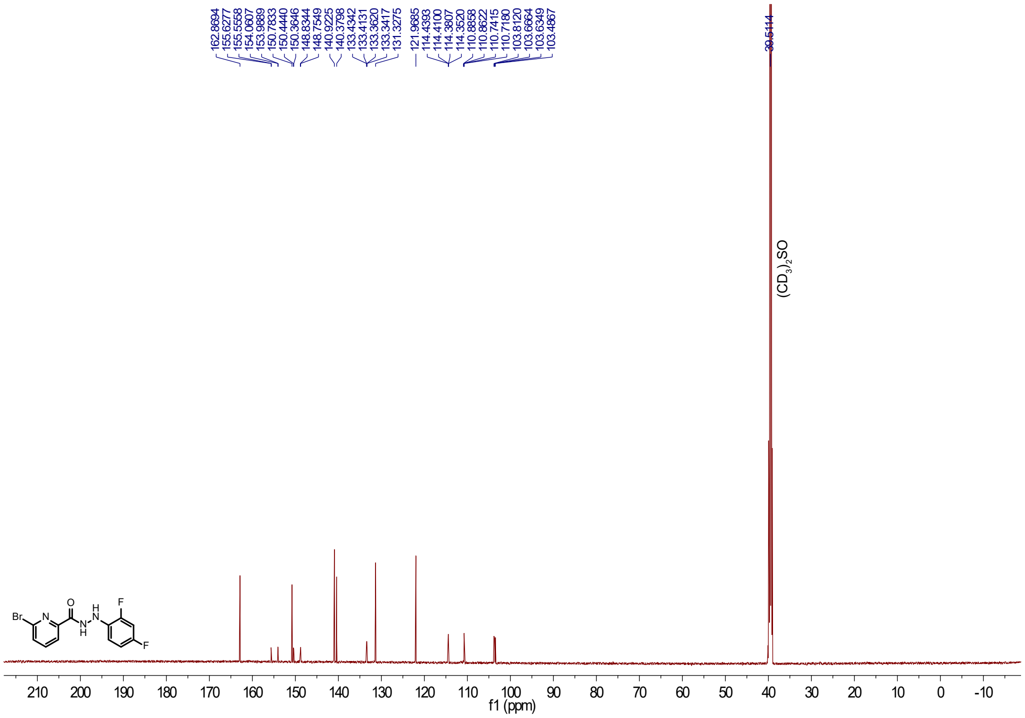


Fig. S106: ^{13}C NMR spectrum for compound **6g** (**SGT1439**) in $(CD_3)_2SO$ (150 MHz).

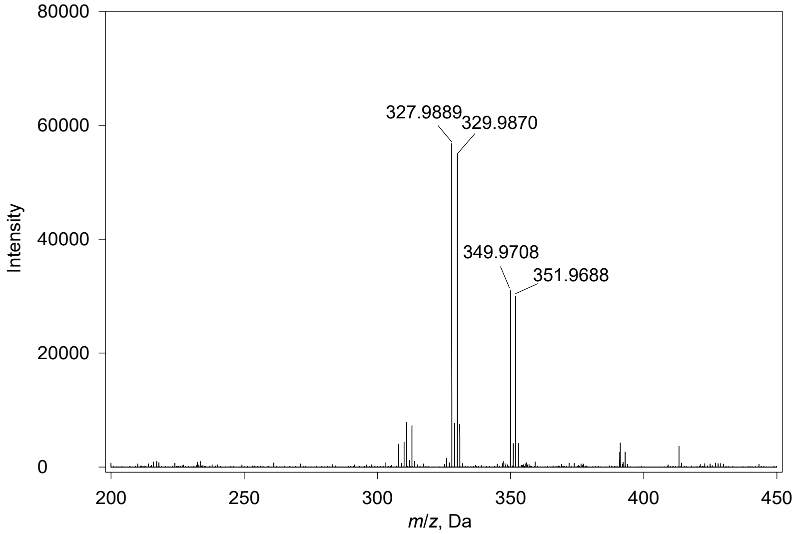


Fig. S107: HRMS spectrum for compound **6g** (**SGT1439**). *m/z* found 327.9889 $[M+H]^+$.

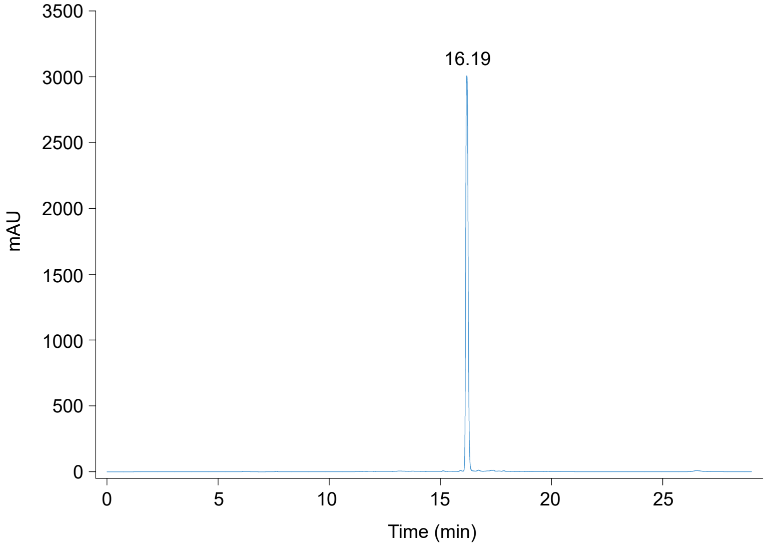


Fig. S108: HPLC trace for compound **6g** (**SGT1439**). R_t = 16.19 min.

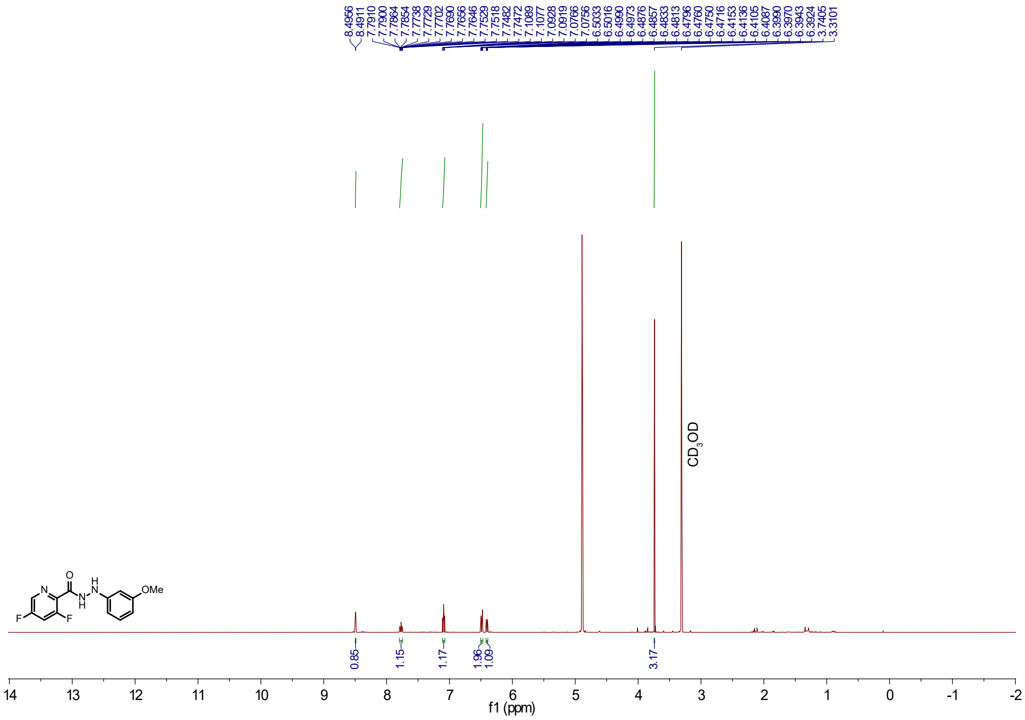


Fig. S109: ^{1}H NMR spectrum for compound **7c** (**SGT1774**) in CD$_3$OD (500 MHz).

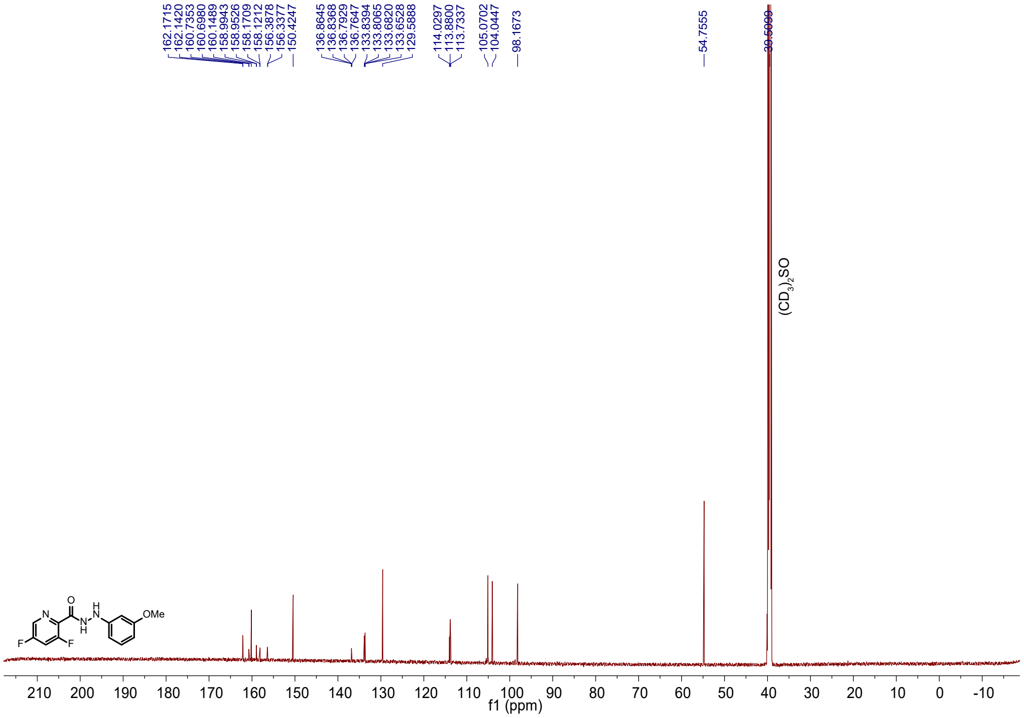


Fig. S110: ^{13}C NMR spectrum for compound **7c** (**SGT1774**) in (CD$_3$)$_2$SO (150 MHz).

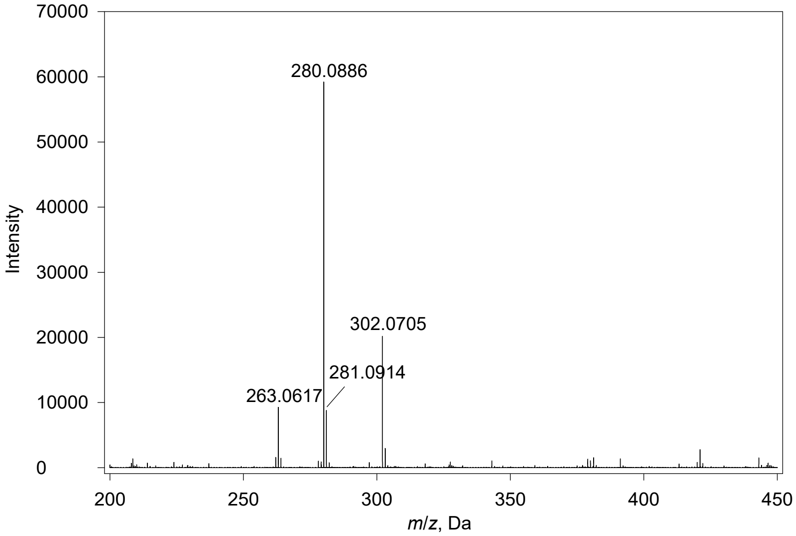


Fig. S111: HRMS spectrum for compound **7c** (**SGT1774**). *m/z* found 280.0886 [M+H]$^+$.

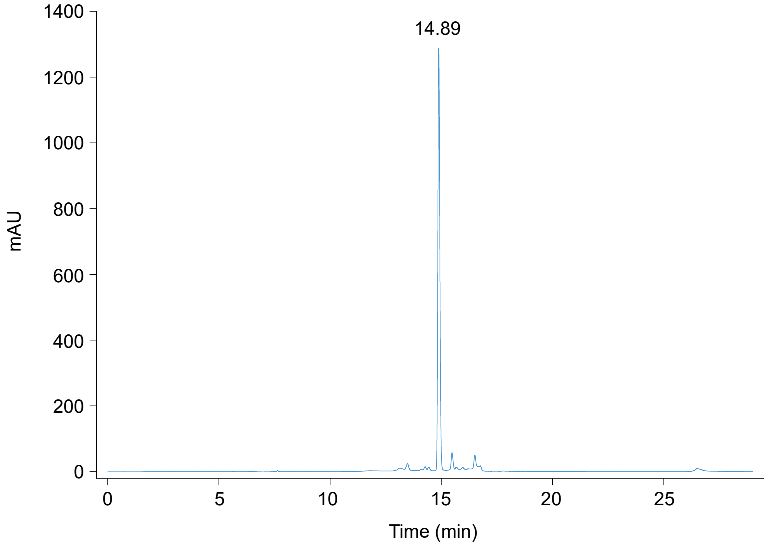


Fig. S112: HPLC trace for compound **7c** (**SGT1774**). R_t = 14.89 min.

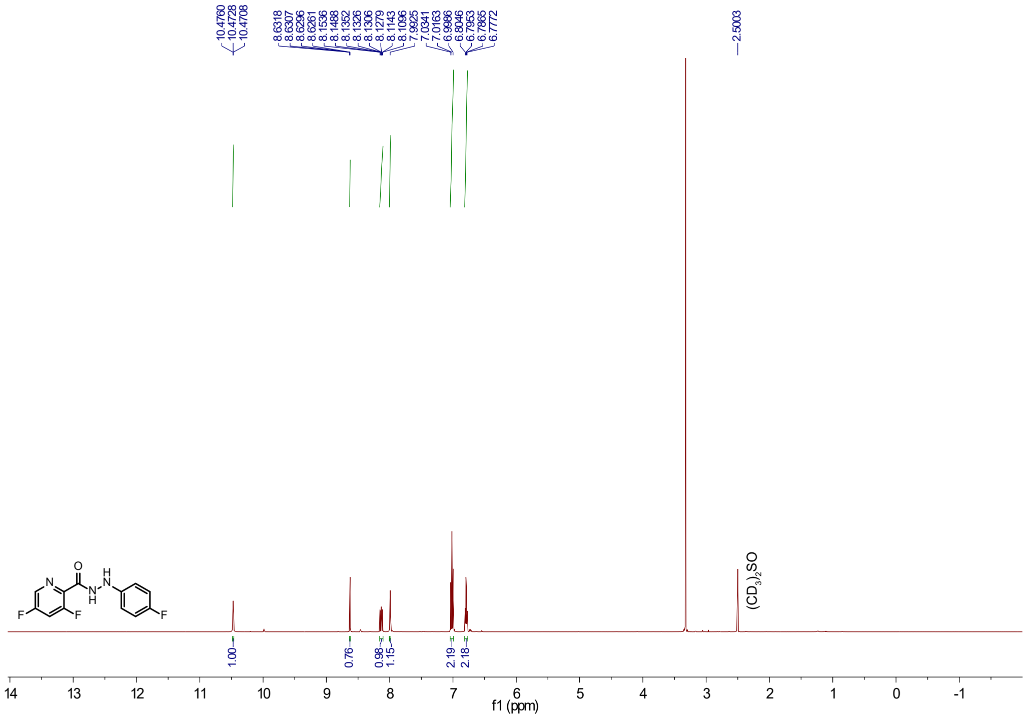


Fig. S113: ^{1}H NMR spectrum for compound **7d** (**SGT1801**) in $(CD_3)_2SO$ (500 MHz).

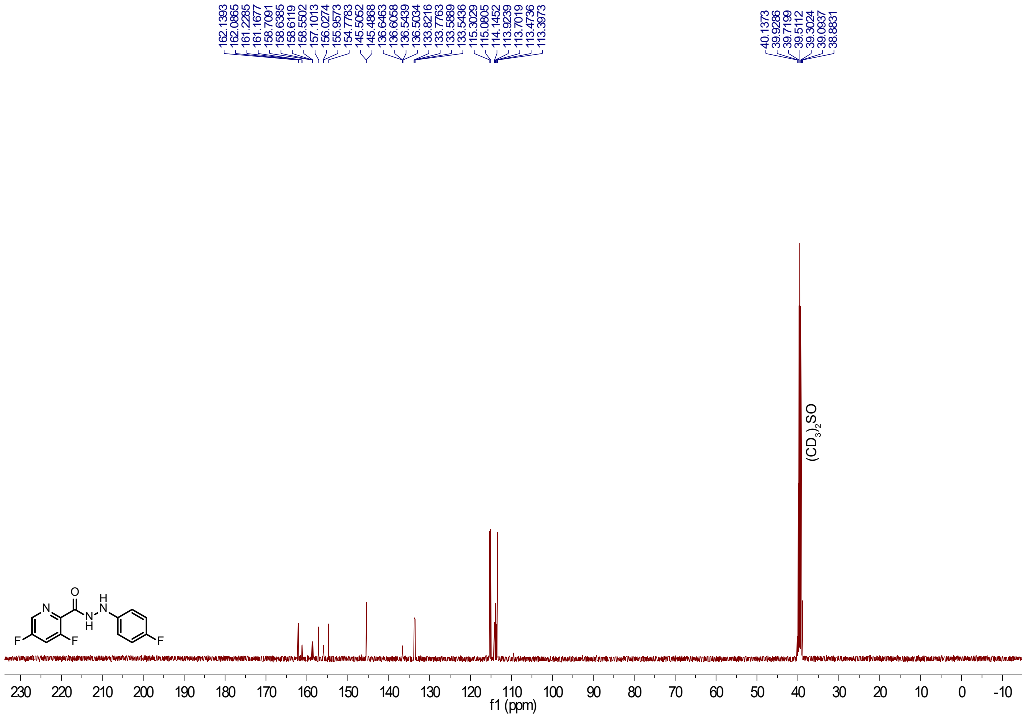


Fig. S114: ^{13}C NMR spectrum for compound **7d** (**SGT1801**) in $(CD_3)_2SO$ (100 MHz).

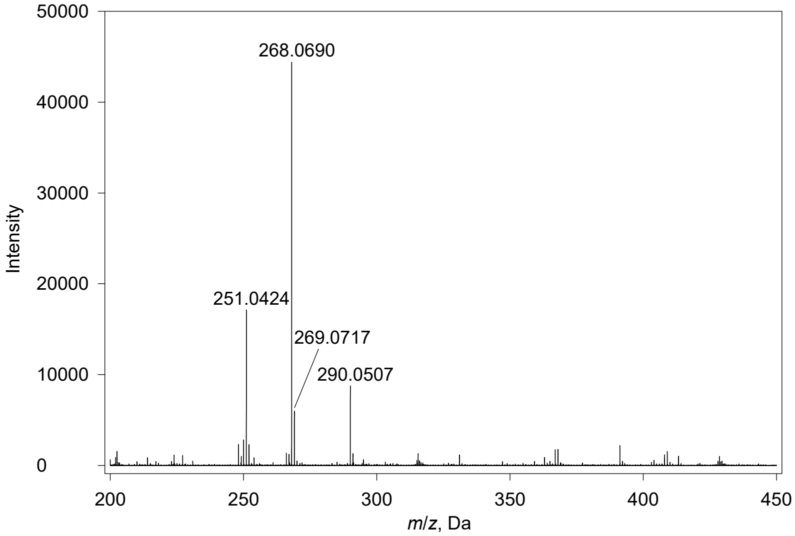


Fig. S115: HRMS spectrum for compound **7d** (**SGT1801**). *m/z* found 268.0690 $[M+H]^+$.

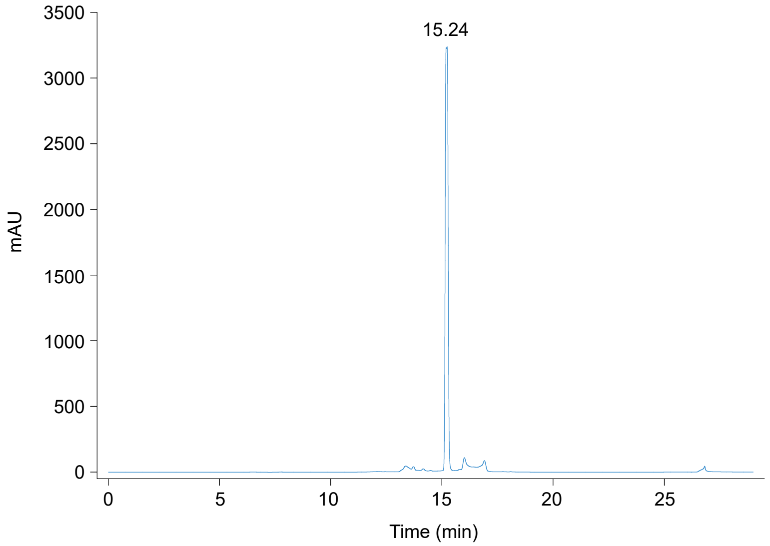


Fig. S116: HPLC trace for compound **7d** (**SGT1801**). R_t = 15.24 min.

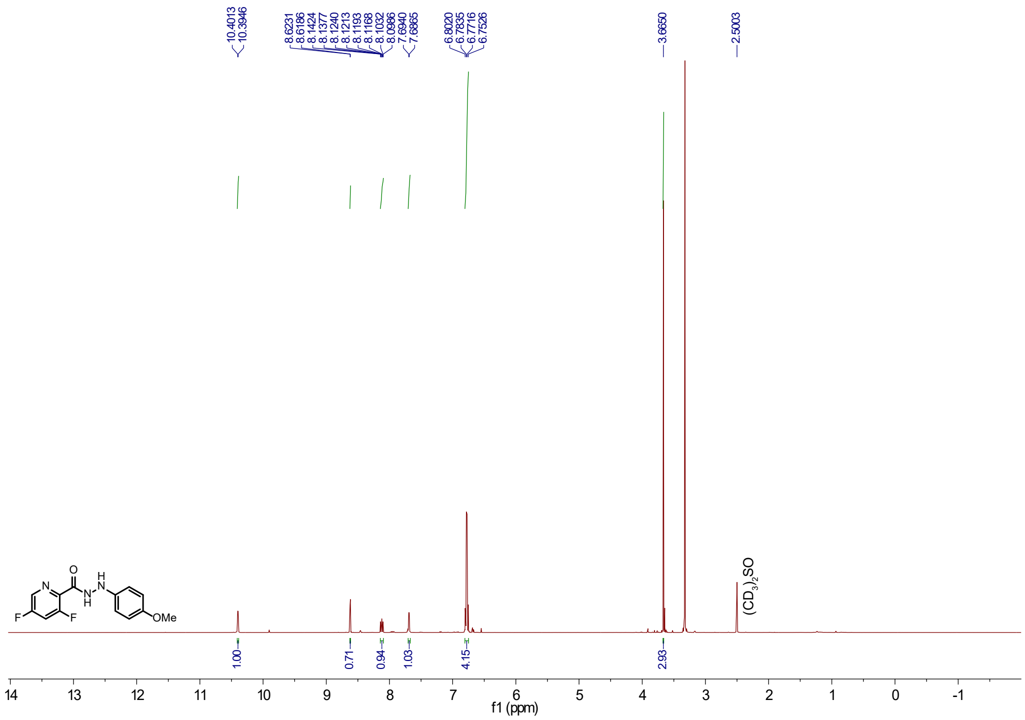


Fig. S117: ^{1}H NMR spectrum for compound **7f** (**SGT1795**) in $(CD_3)_2SO$ (500 MHz).

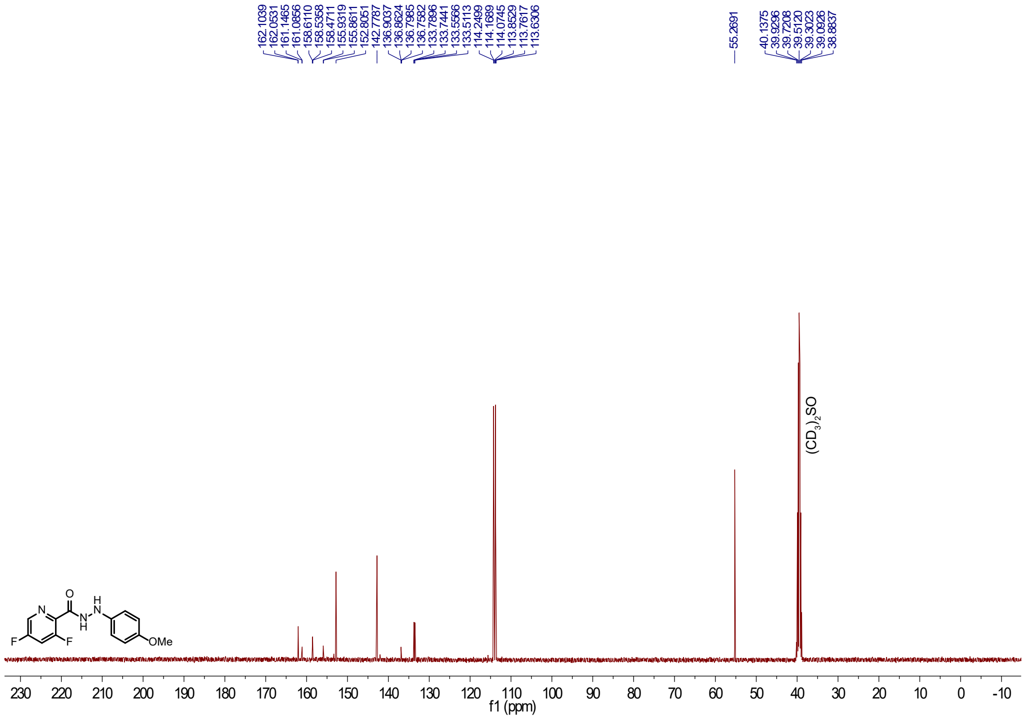


Fig. S118: ^{13}C NMR spectrum for compound **7f** (**SGT1795**) in $(CD_3)_2SO$ (100 MHz).

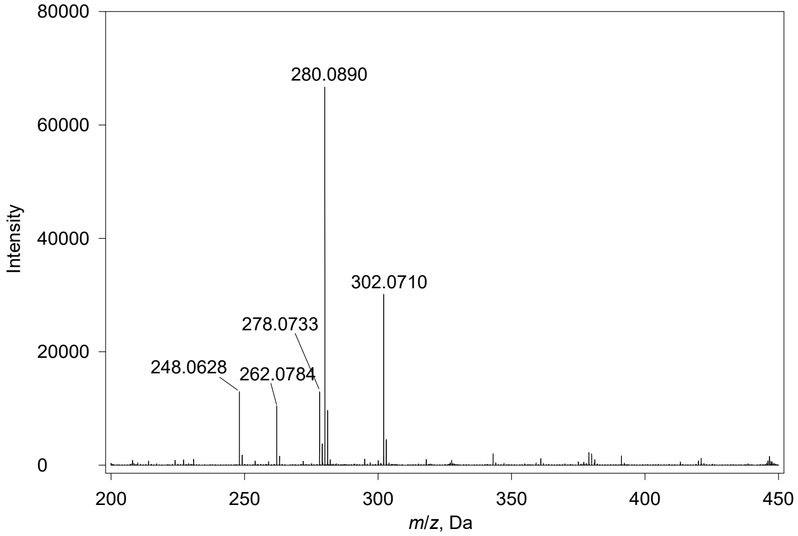


Fig. S119: HRMS spectrum for compound **7f** (**SGT1795**). *m/z* found 280.0890 $[M+H]^+$.

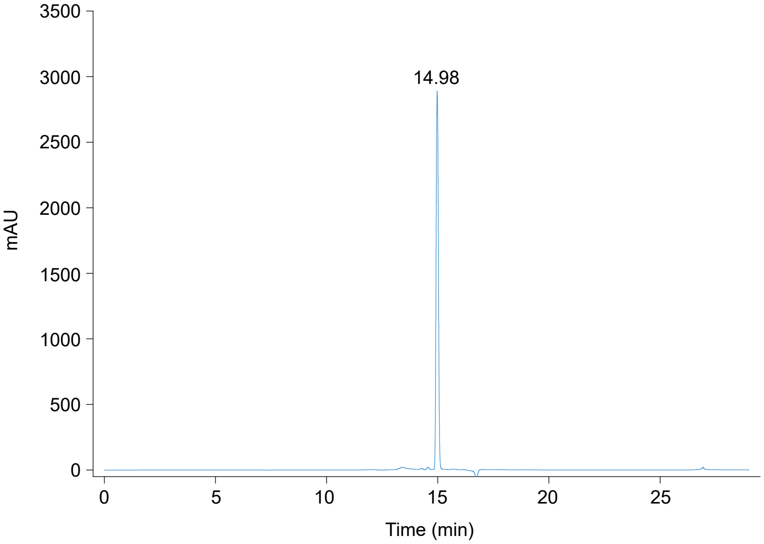


Fig. S120: HPLC trace for compound **7f** (**SGT1795**). R_t = 14.98 min.

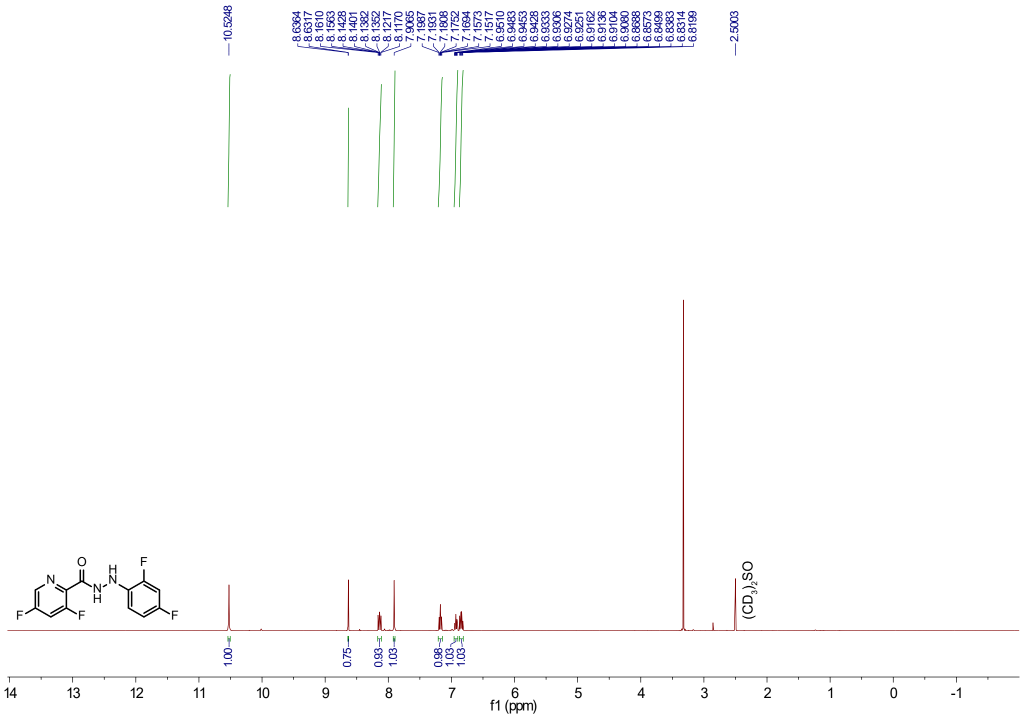


Fig. S121: ^{1}H NMR spectrum for compound **7g** (**SGT1805**) in $(CD_3)_2SO$ (500 MHz).

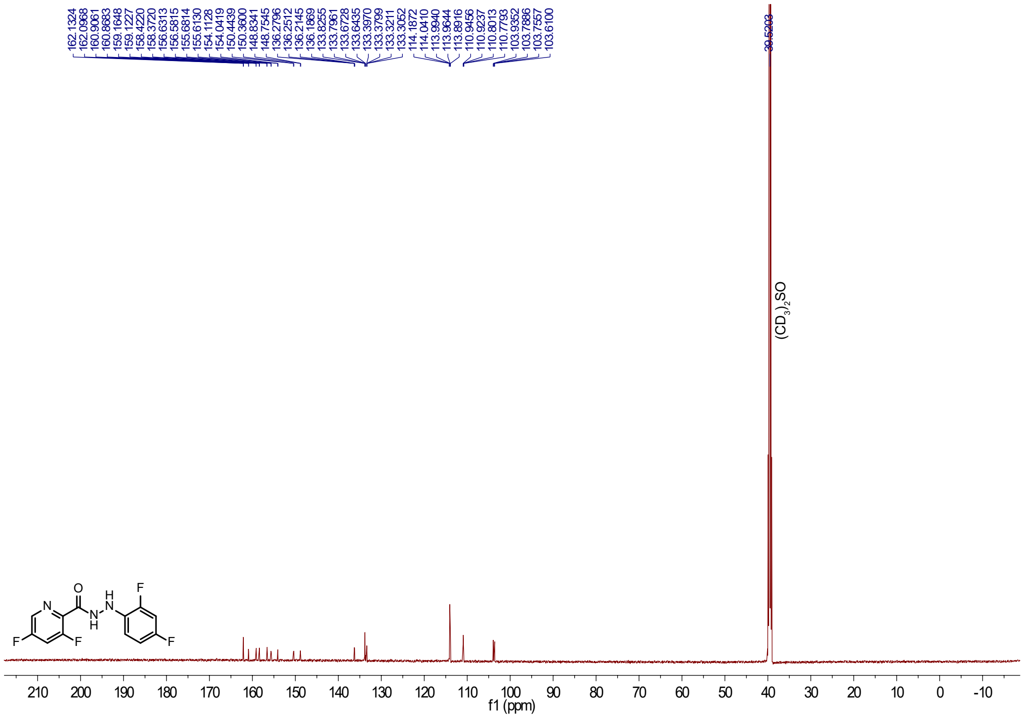


Fig. S122: ^{13}C NMR spectrum for compound **7g** (**SGT1805**) in $(CD_3)_2SO$ (150 MHz).

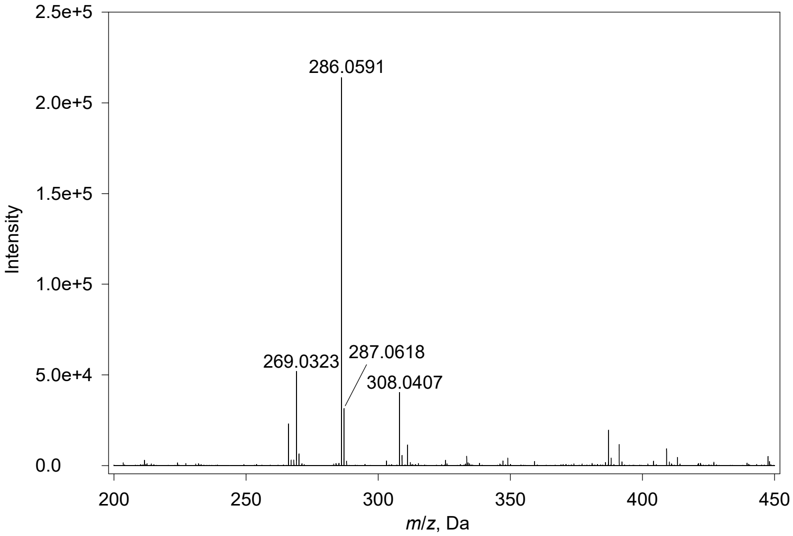


Fig. S123: HRMS spectrum for compound **7g** (**SGT1805**). *m/z* found 286.0591 $[M+H]^+$.

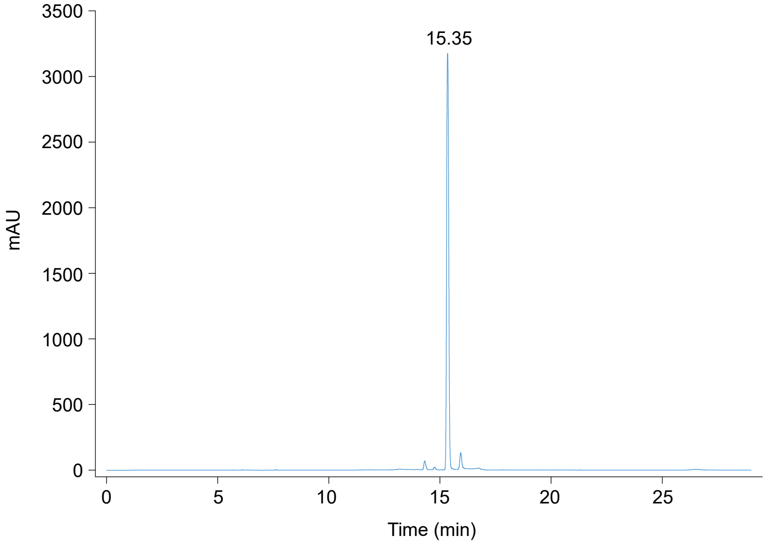


Fig. S124: HPLC trace for compound **7g** (**SGT1805**). R_t = 15.35 min.

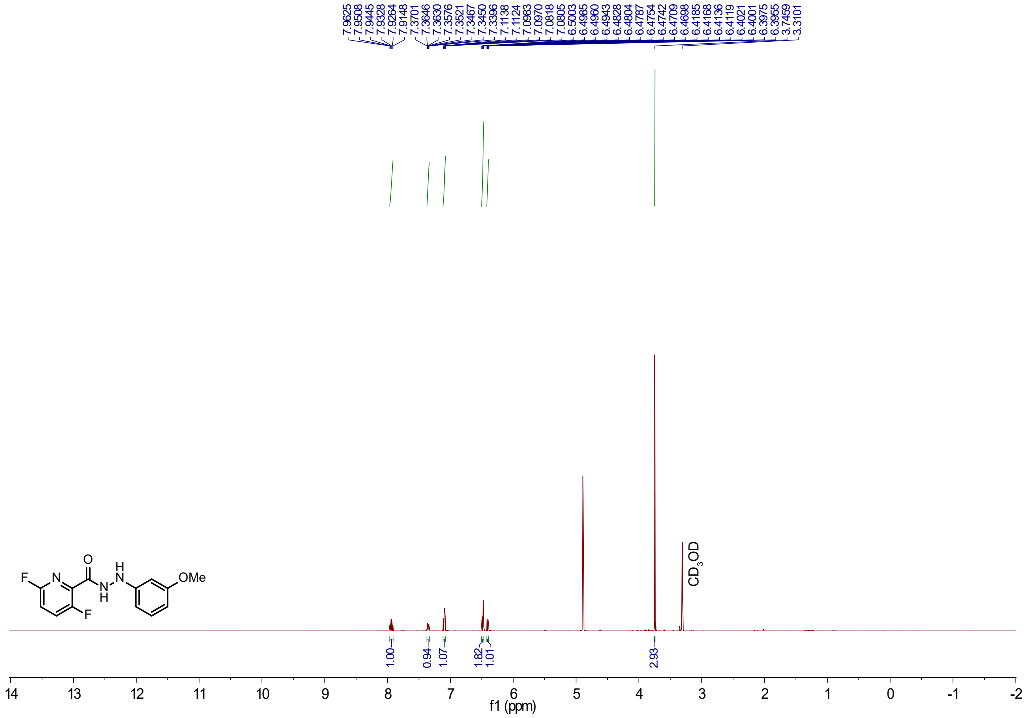


Fig. S125: ^{1}H NMR spectrum for compound **8c** (**SGT1775**) in CD_3OD (500 MHz).

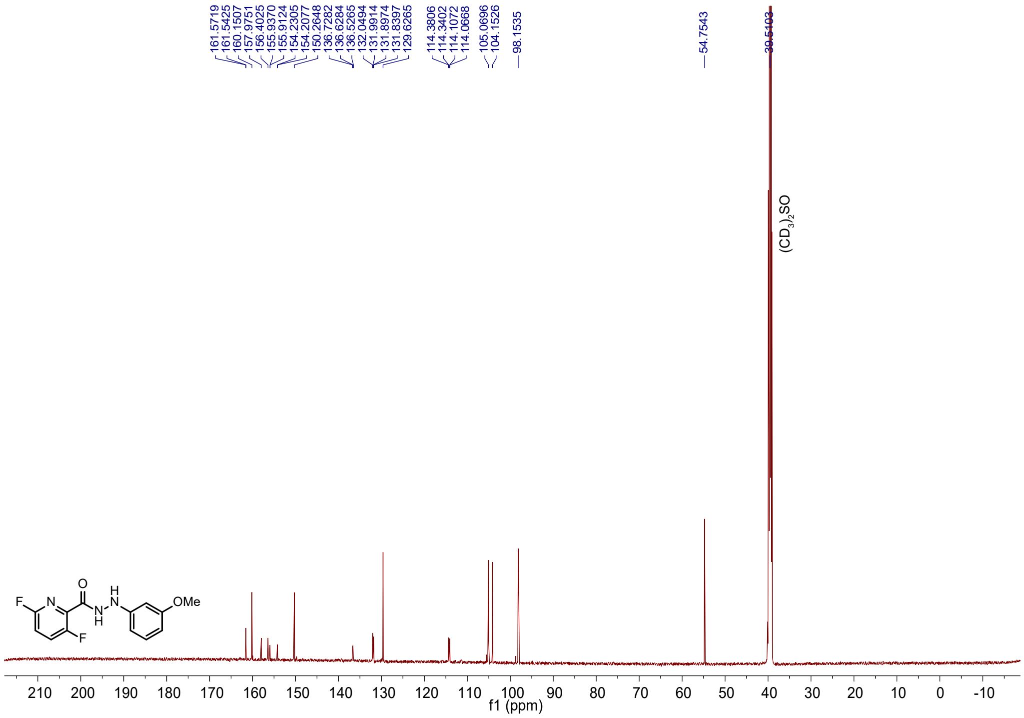


Fig. S126: ^{13}C NMR spectrum for compound **8c** (**SGT1775**) in $(CD_3)_2SO$ (150 MHz).

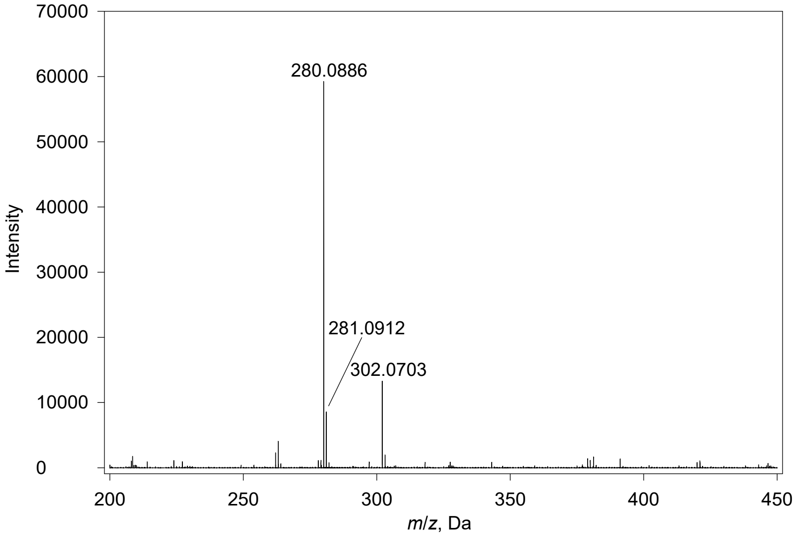


Fig. S127: HRMS spectrum for compound **8c** (**SGT1775**). *m/z* found 280.0886 $[M+H]^+$.

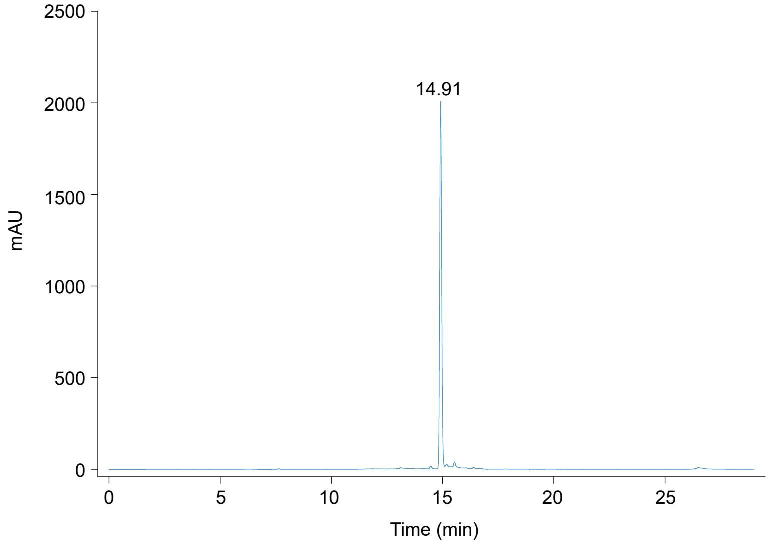


Fig. S128: HPLC trace for compound **8c** (**SGT1775**). R_t = 14.91 min.

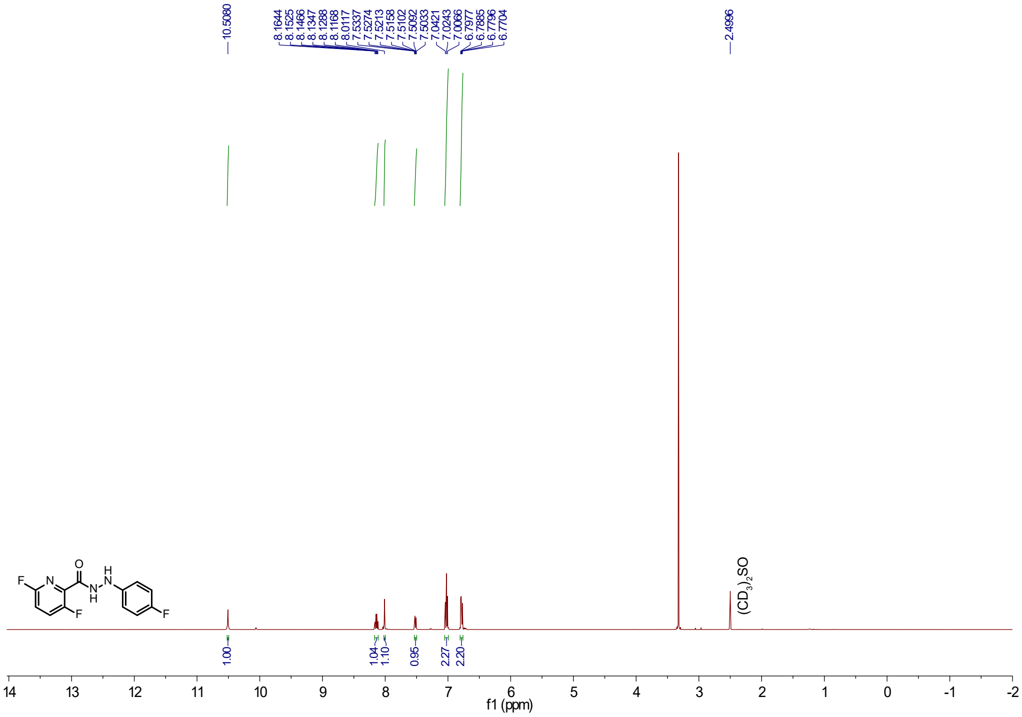


Fig. S129: ^{1}H NMR spectrum for compound **8d** (**SGT1802**) in (CD$_3$)$_2$SO (500 MHz).

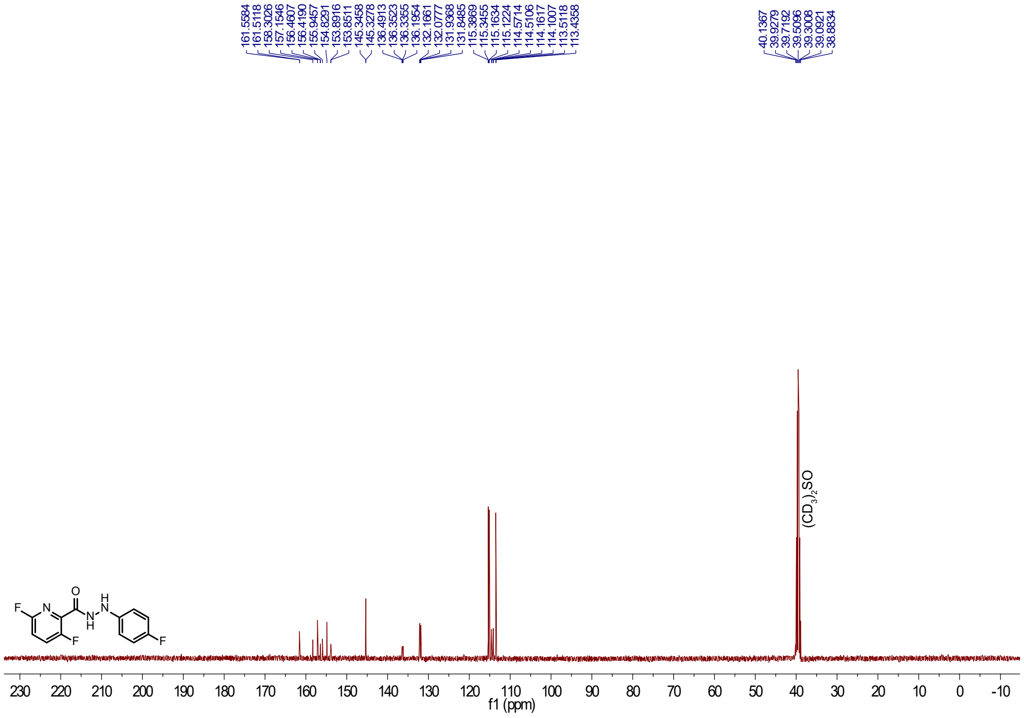


Fig. S130: ^{13}C NMR spectrum for compound **8d** (**SGT1802**) in (CD$_3$)$_2$SO (100 MHz).

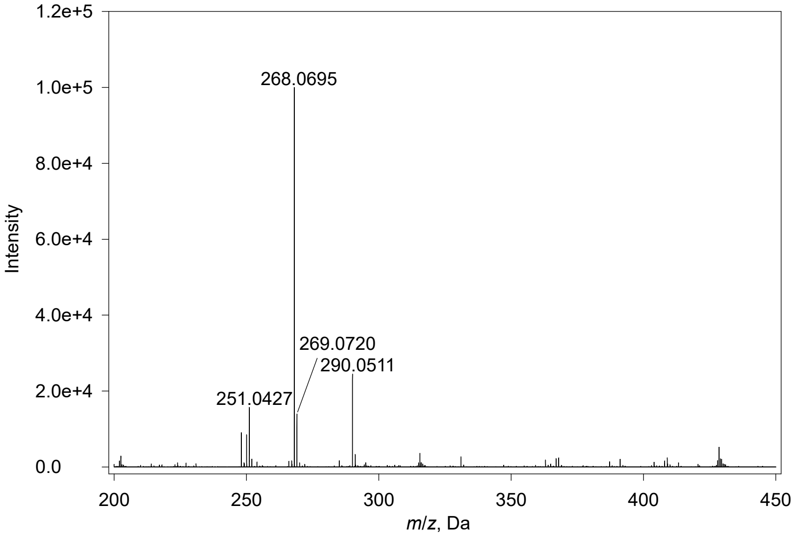


Fig. S131: HRMS spectrum for compound **8d** (**SGT1802**). *m/z* found 268.0695 $[M+H]^+$.

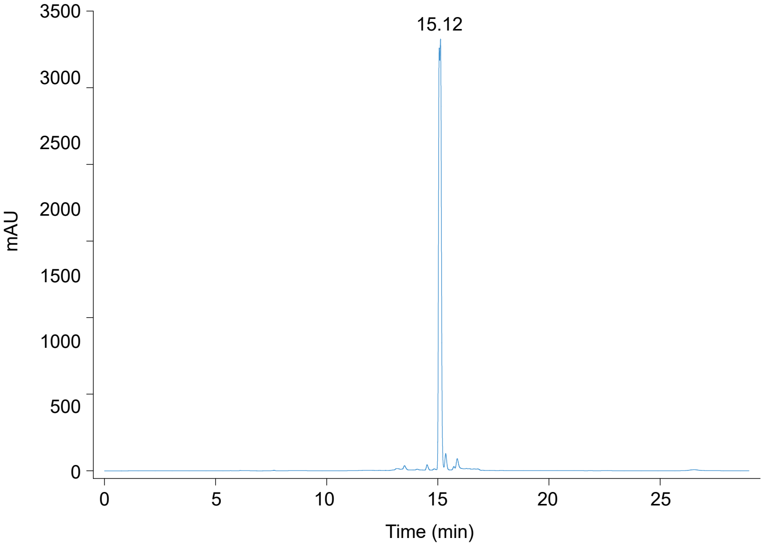


Fig. S132: HPLC trace for compound **8d** (**SGT1802**). R_t = 15.12 min.

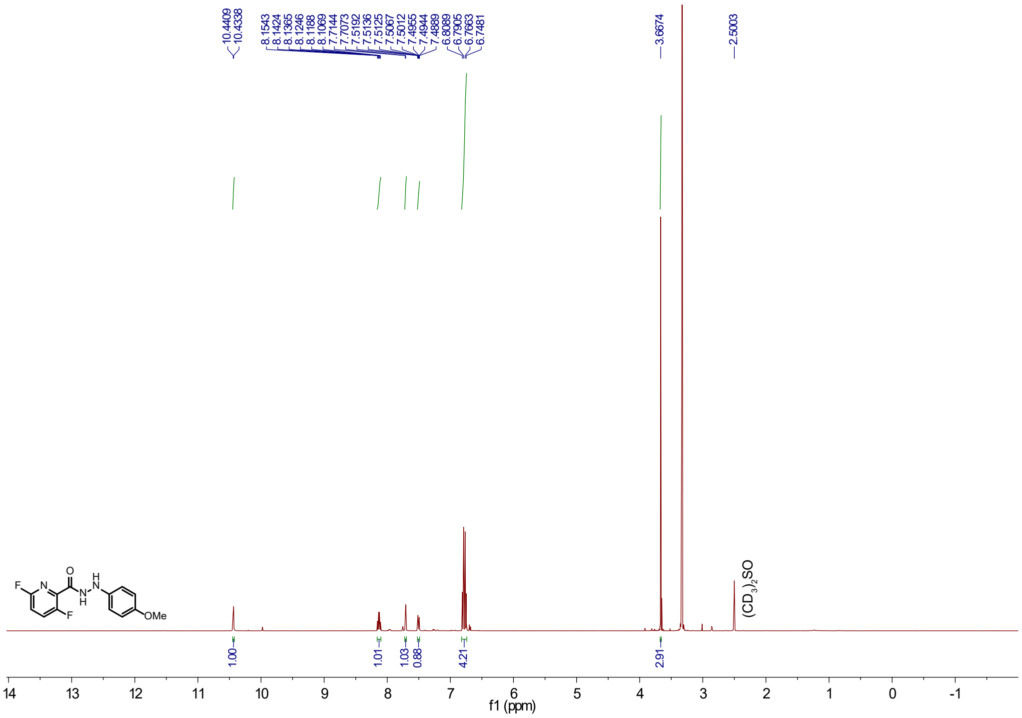


Fig. S133: ^{1}H NMR spectrum for compound **8f** (**SGT1796**) in $(CD_3)_2SO$ (500 MHz).

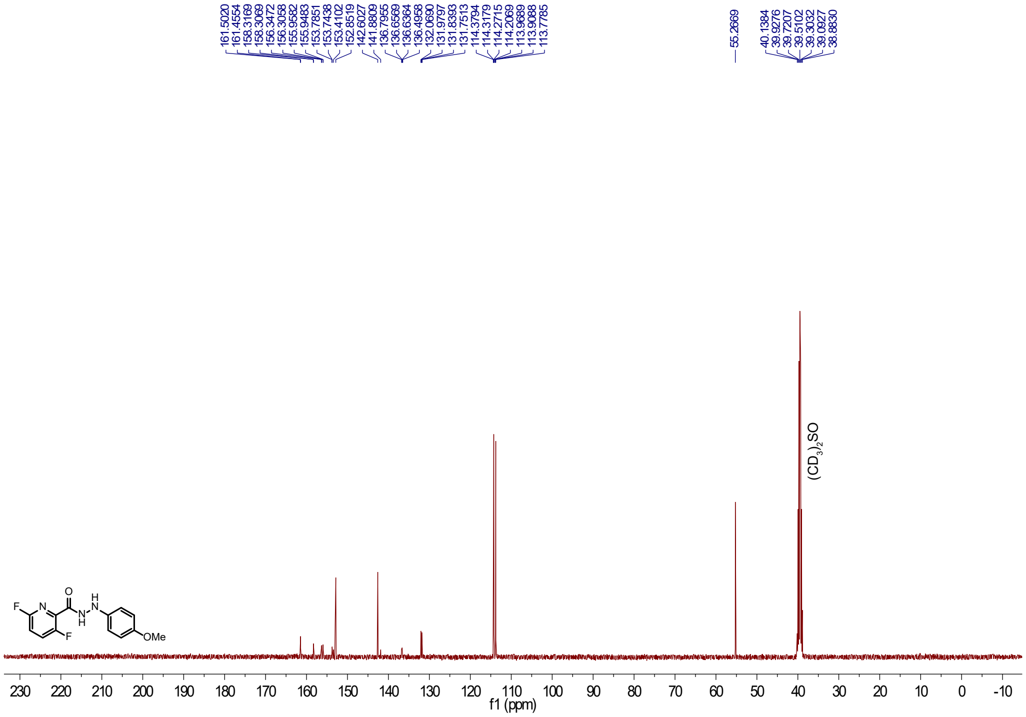


Fig. S134: ^{13}C NMR spectrum for compound **8f** (**SGT1796**) in $(CD_3)_2SO$ (100 MHz).

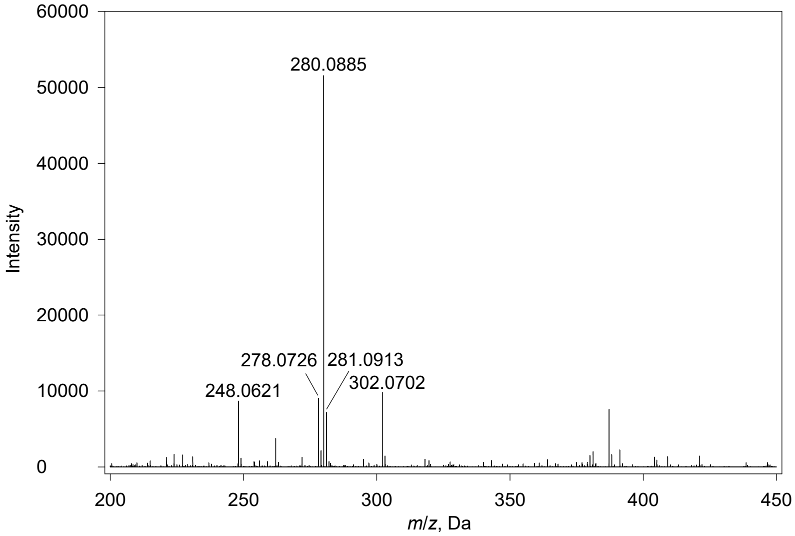


Fig. S135: HRMS spectrum for compound **8f** (**SGT1796**). *m/z* found 280.0885 [M+H]$^+$.

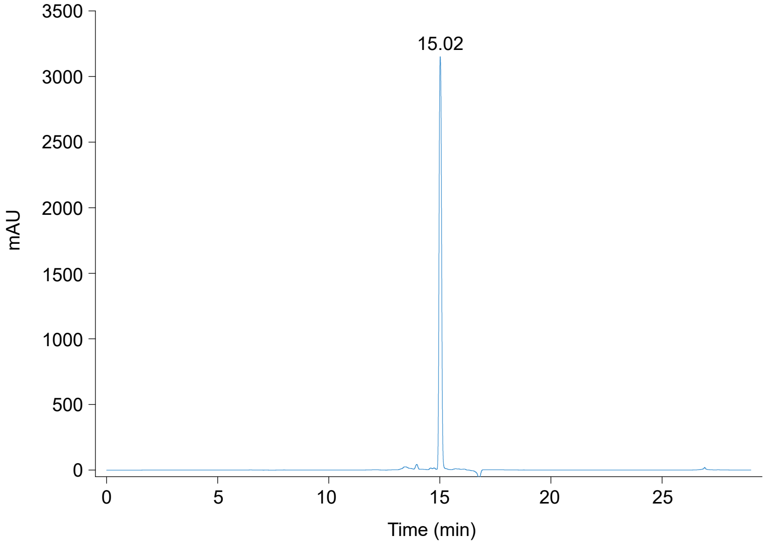


Fig. S136: HPLC trace for compound **8f** (**SGT1796**). R_t = 15.02 min.

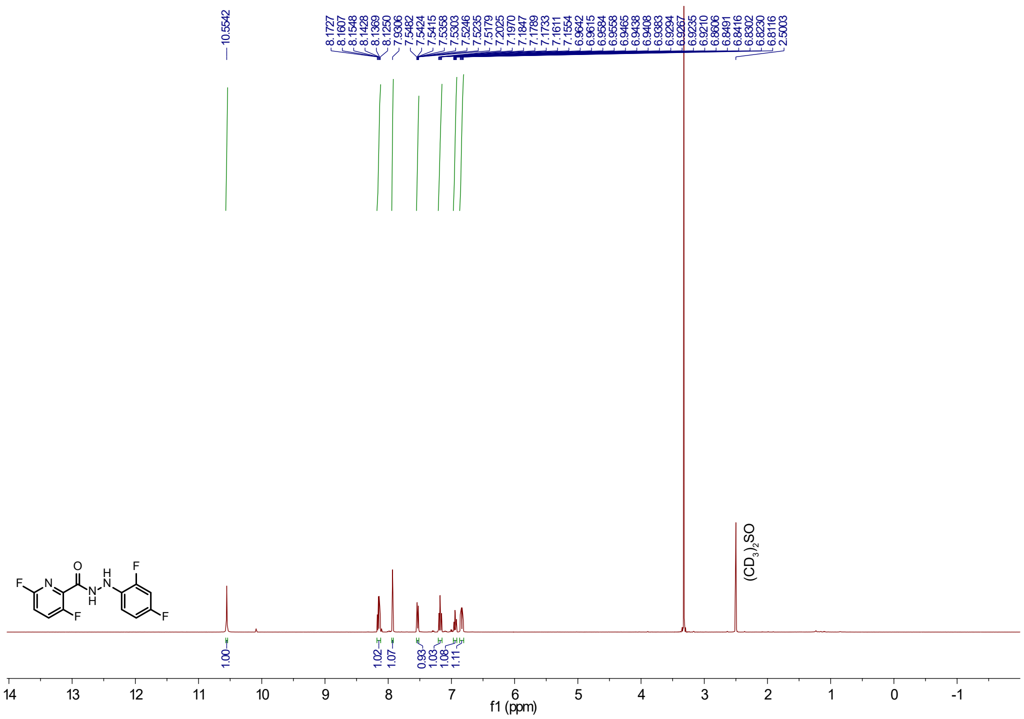


Fig. S137: ^{1}H NMR spectrum for compound **8g** (**SGT1806**) in $(CD_3)_2SO$ (500 MHz).

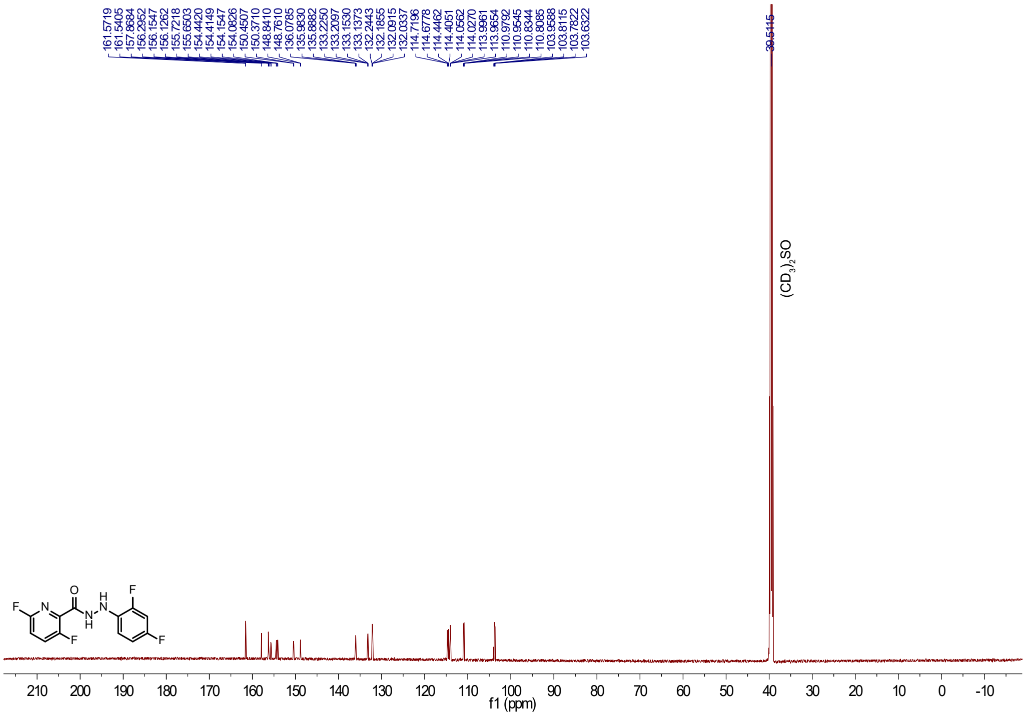


Fig. S138: ^{13}C NMR spectrum for compound **8g** (**SGT1806**) in $(CD_3)_2SO$ (150 MHz).

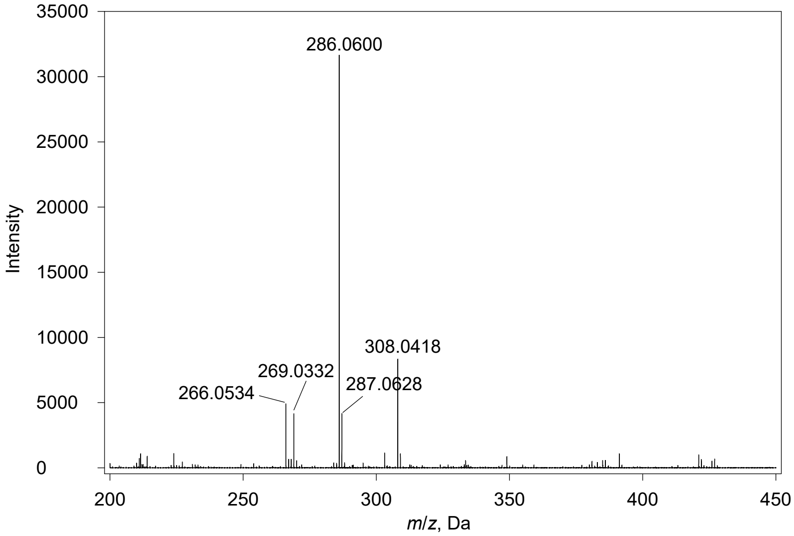


Fig. S139: HRMS spectrum for compound **8g** (**SGT1806**). *m/z* found 286.0600 $[M+H]^+$.

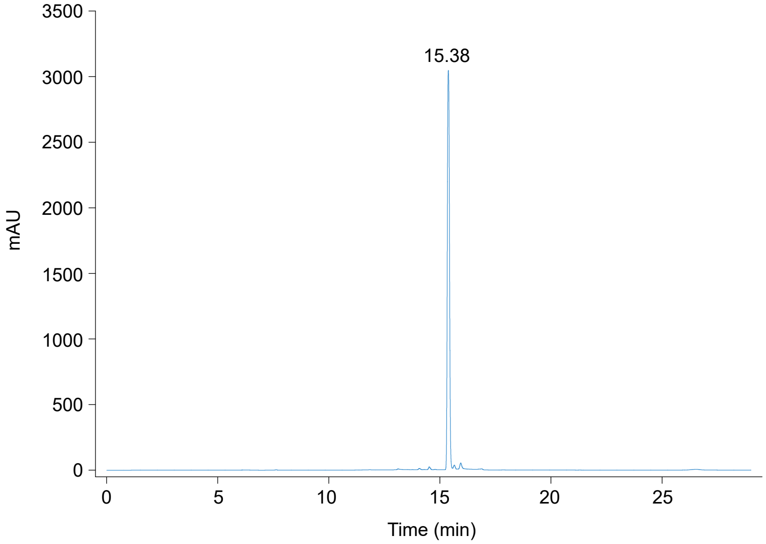


Fig. S140: HPLC trace for compound **8g** (**SGT1806**). R_t = 15.38 min.

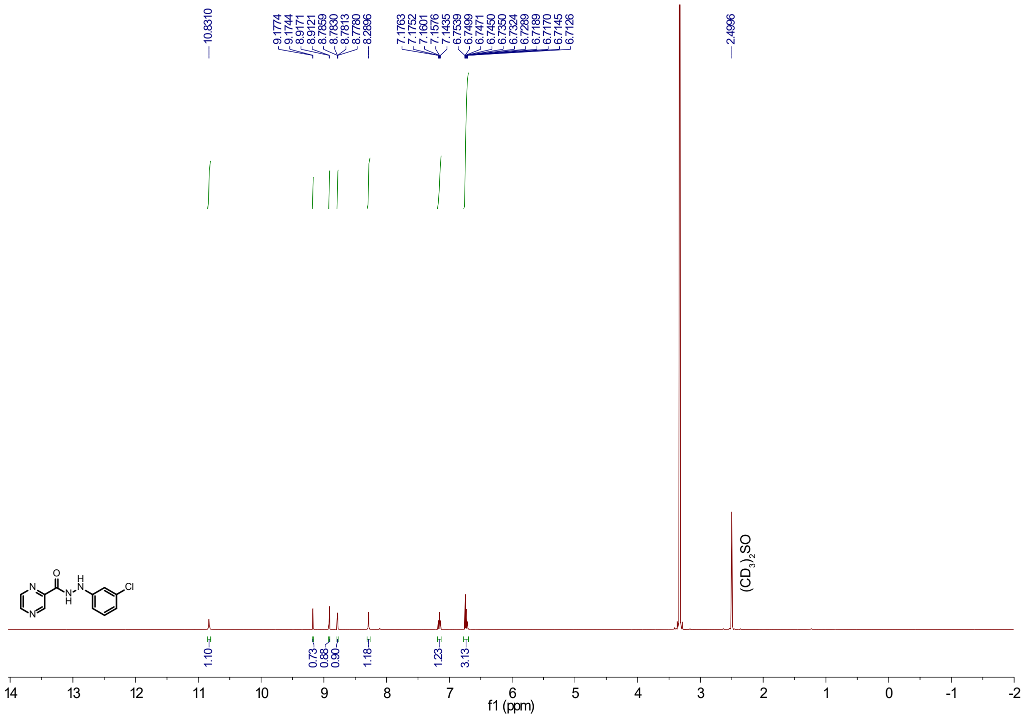


Fig. S141: ^{1}H NMR spectrum for compound **9b** (**SGT1793**) in $(CD_3)_2SO$ (500 MHz).

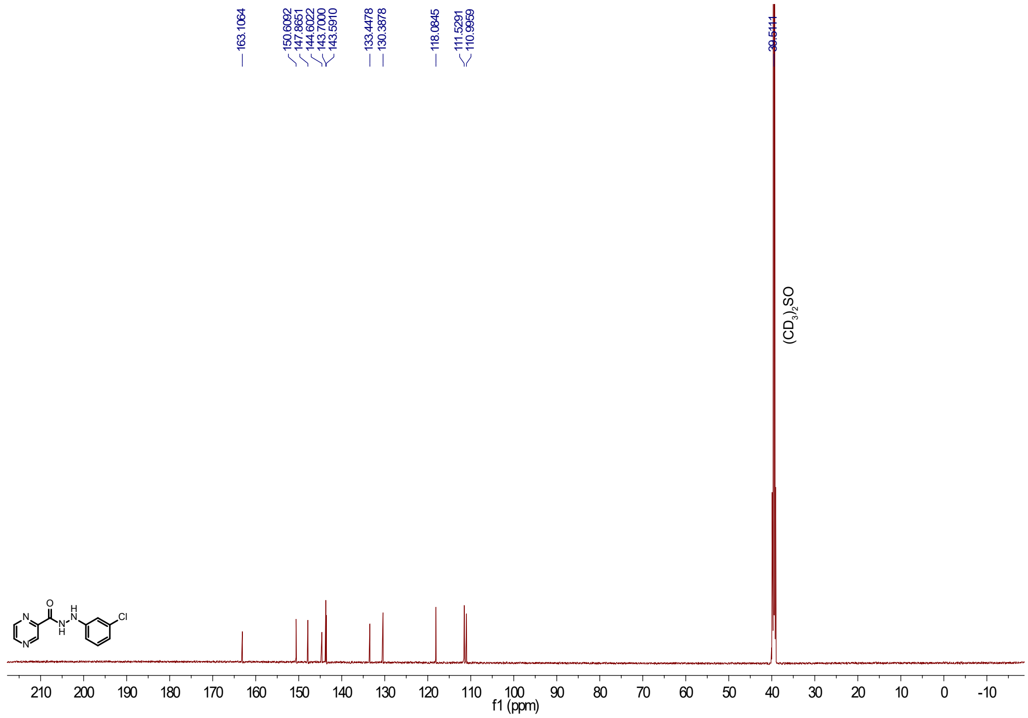


Fig. S142: ^{13}C NMR spectrum for compound **9b** (**SGT1793**) in $(CD_3)_2SO$ (150 MHz).

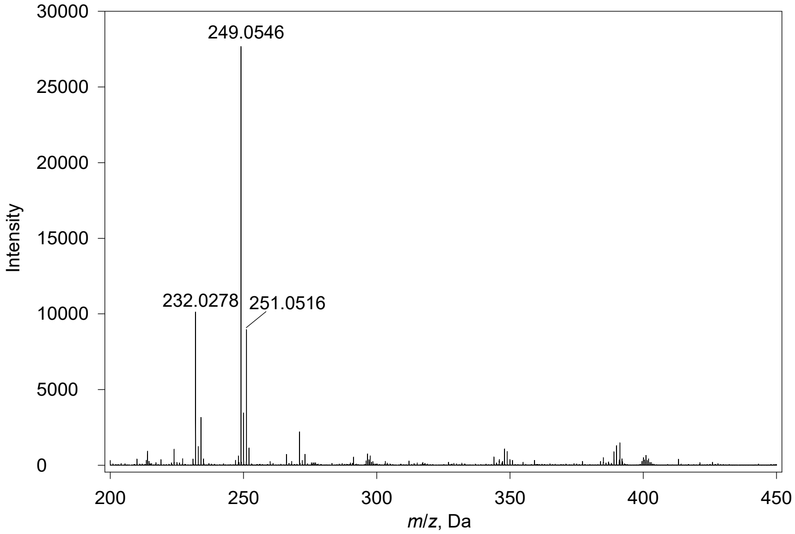


Fig. S143: HRMS spectrum for compound **9b** (**SGT1793**). *m/z* found 249.0546 $[M+H]^+$.

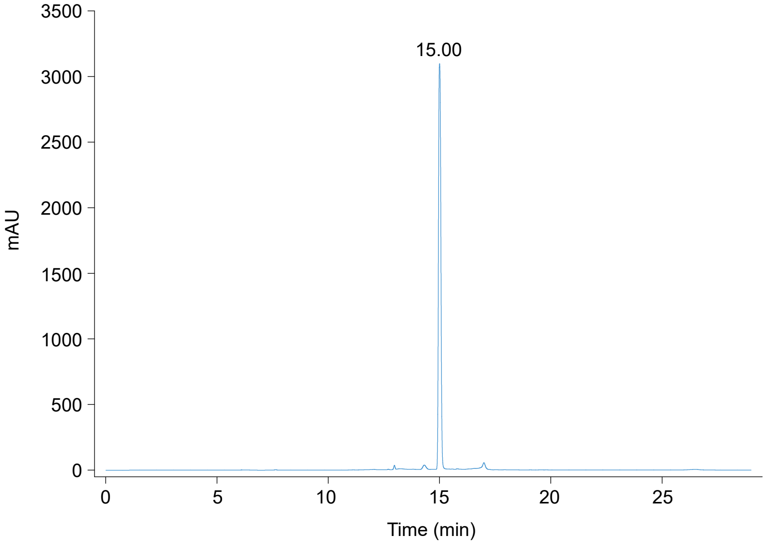


Fig. S144: HPLC trace for compound **9b** (**SGT1793**). R_t = 15.00 min.

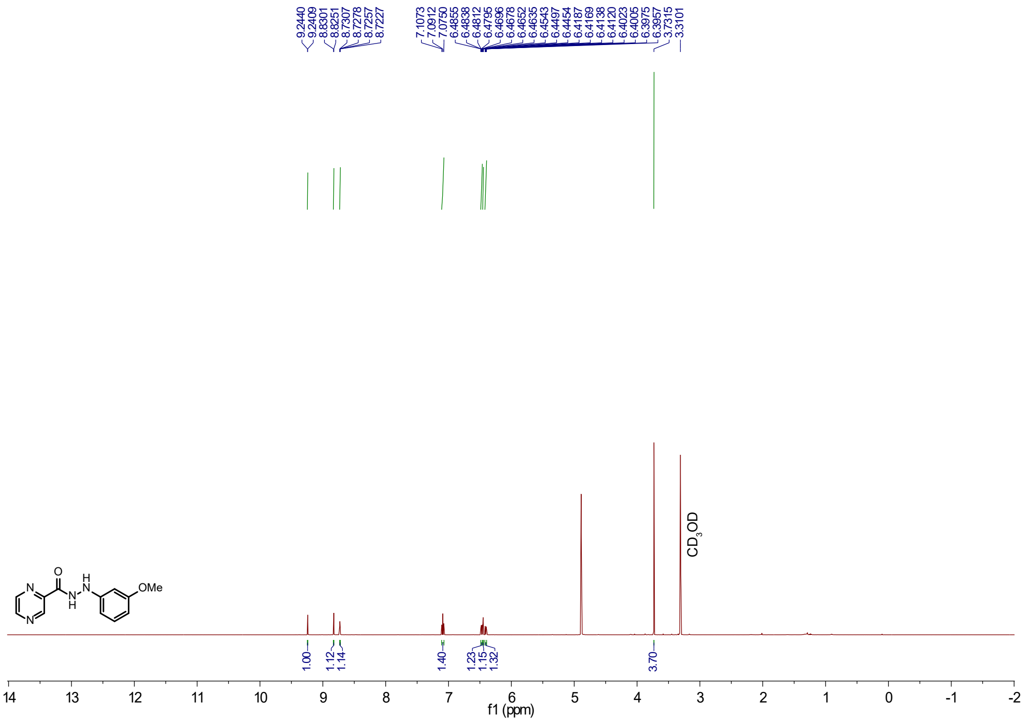


Fig. S145: ^{1}H NMR spectrum for compound **9c** (**SGT1773**) in CD$_3$OD (500 MHz).

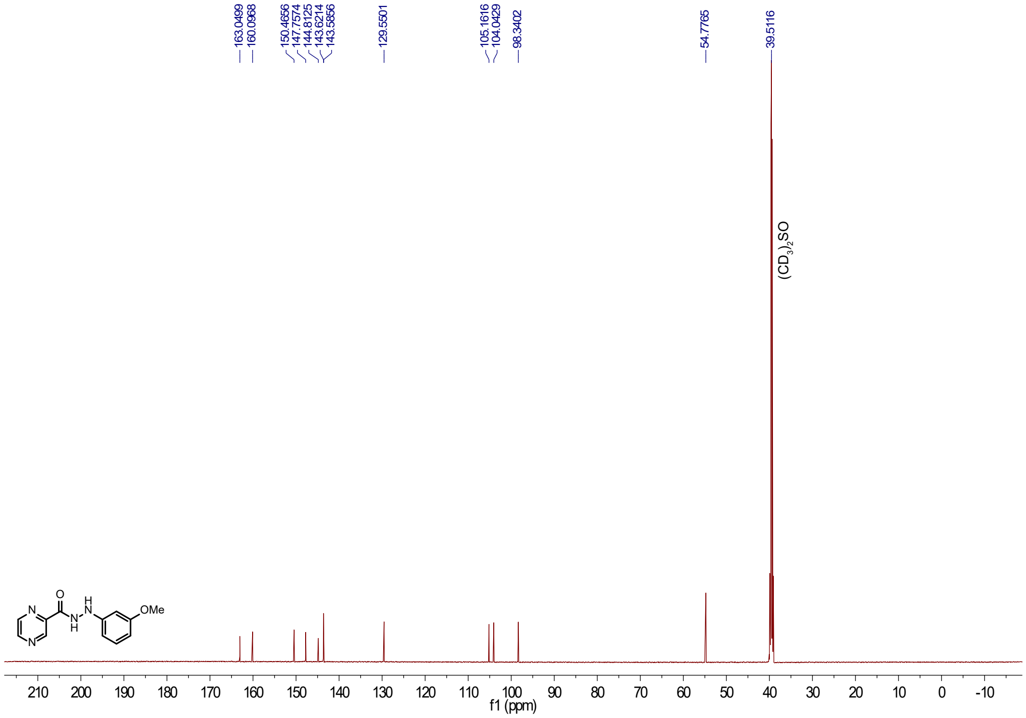


Fig. S146: ^{13}C NMR spectrum for compound **9c** (**SGT1773**) in (CD$_3$)$_2$SO (150 MHz).

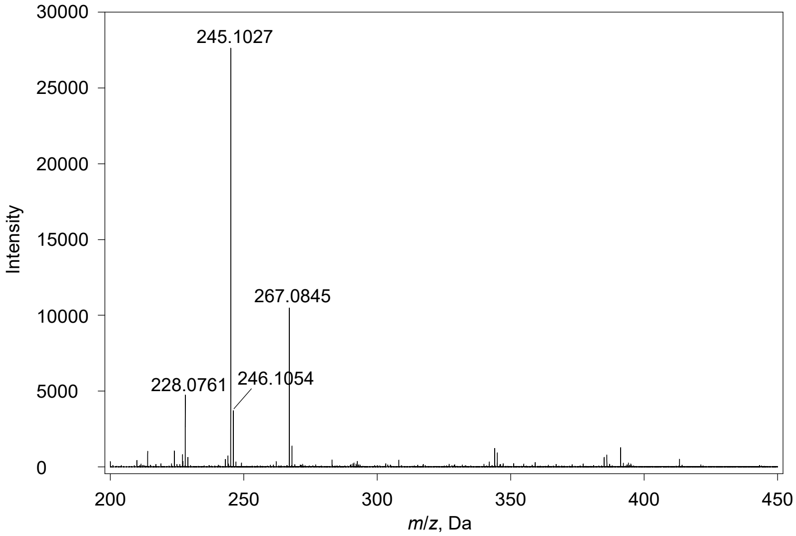


Fig. S147: HRMS spectrum for compound **9c** (**SGT1773**). *m/z* found 245.1027 $[M+H]^+$.

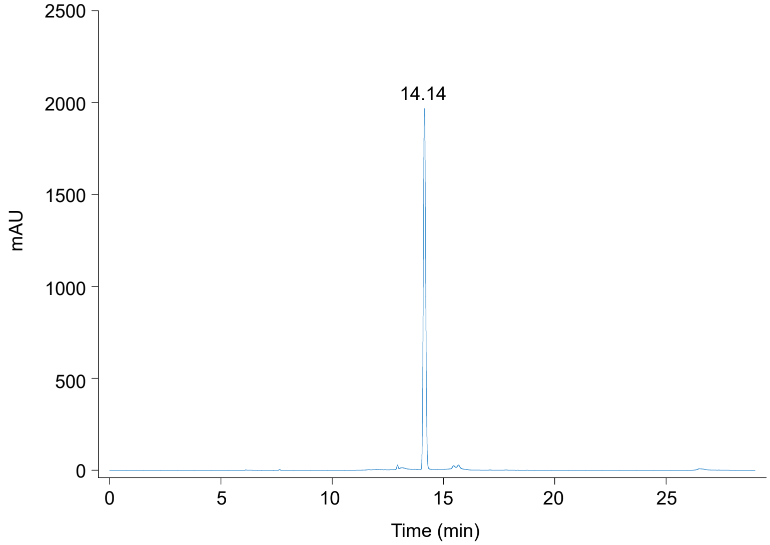


Fig. S148: HPLC trace for compound **9c** (**SGT1773**). R_t = 14.14 min.

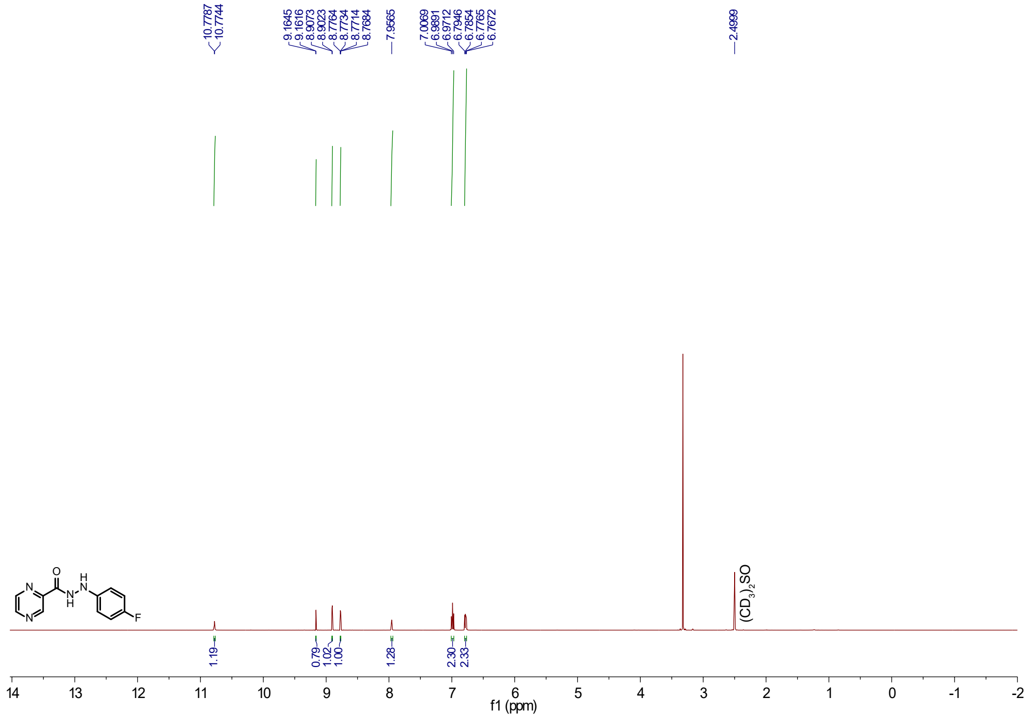


Fig. S149: ^{1}H NMR spectrum for compound **9d** (**SGT1780**) in $(CD_3)_2SO$ (500 MHz).

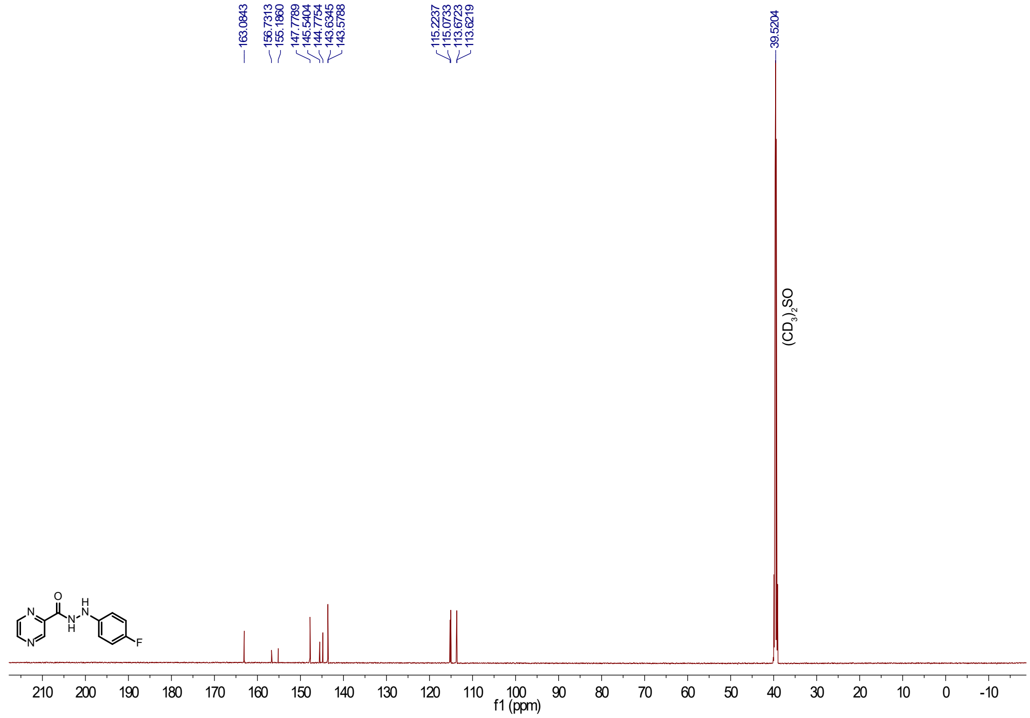


Fig. S150: ^{13}C NMR spectrum for compound **9d** (**SGT1780**) in $(CD_3)_2SO$ (150 MHz).

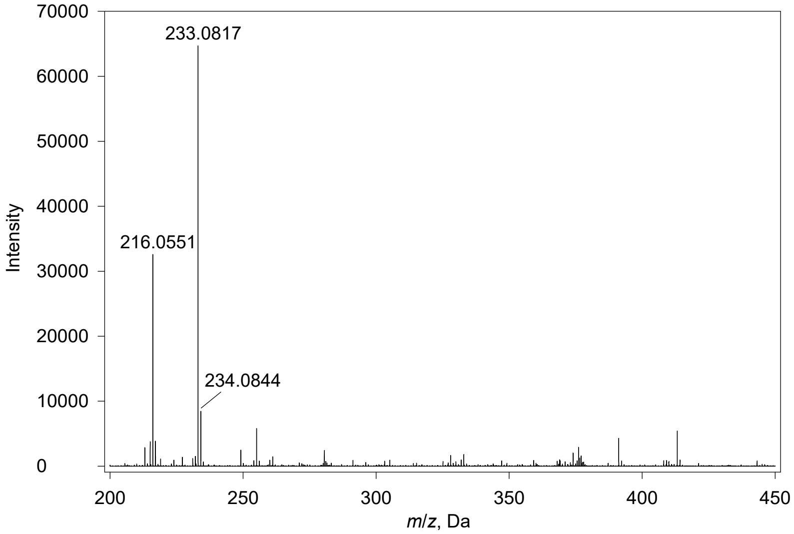


Fig. S151: HRMS spectrum for compound **9d** (**SGT1780**). *m/z* found 233.0817 [M+H]$^+$.

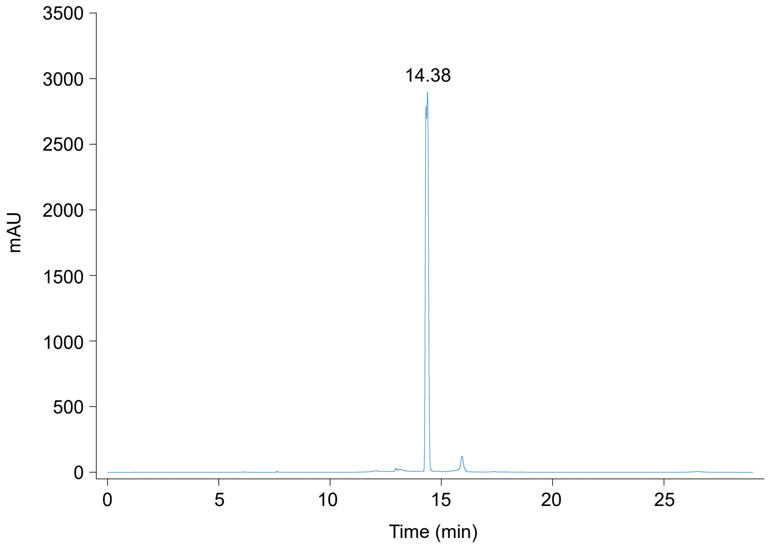


Fig. S152: HPLC trace for compound **9d** (**SGT1780**). R_t = 14.38 min.

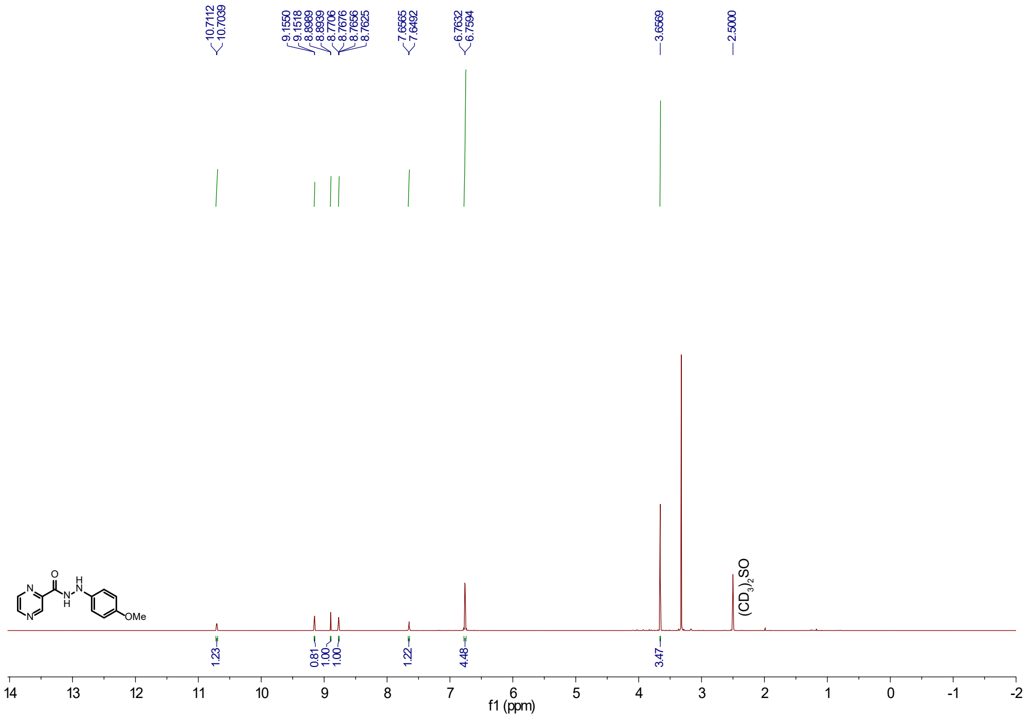


Fig. S153: ^{1}H NMR spectrum for compound **9f** (**SGT1782**) in (CD$_3$)$_2$SO (500 MHz).

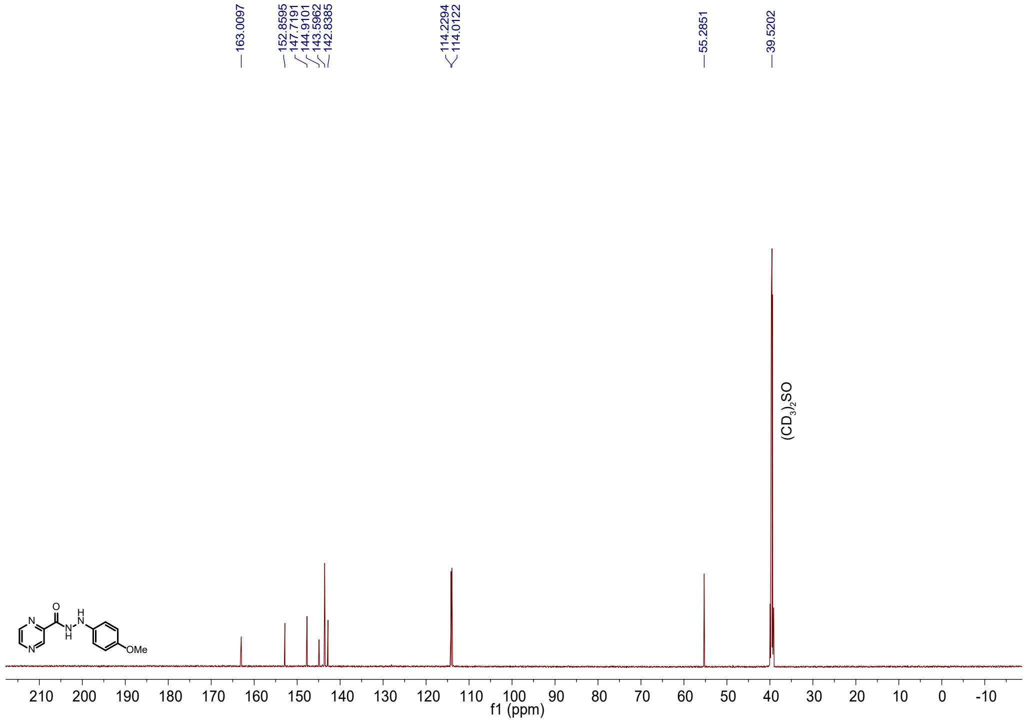


Fig. S154: ^{13}C NMR spectrum for compound **9f** (**SGT1782**) in (CD$_3$)$_2$SO (150 MHz).

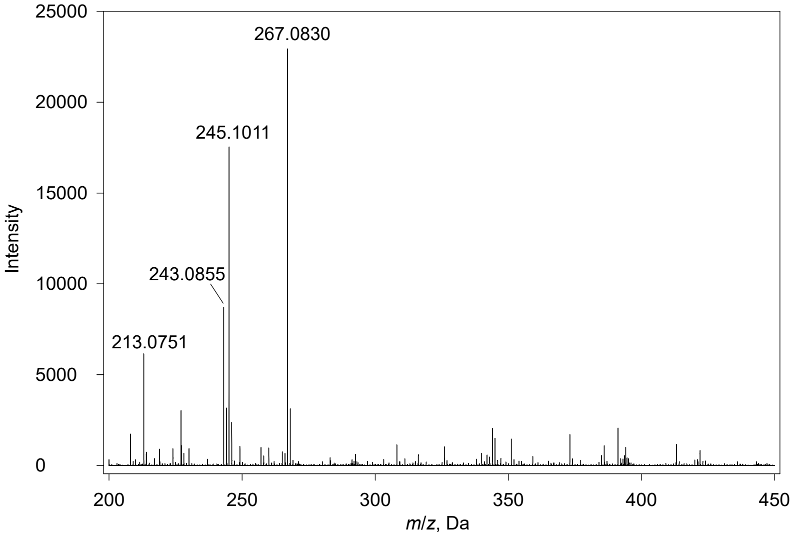


Fig. S155: HRMS spectrum for compound **9f** (**SGT1782**). *m/z* found 245.1011 $[M+H]^+$.

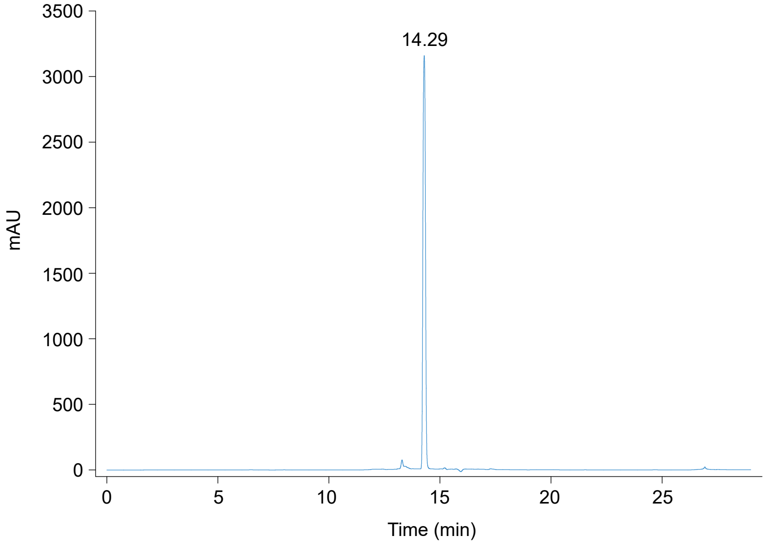


Fig. S156: HPLC trace for compound **9f** (**SGT1782**). R_t = 14.29 min.

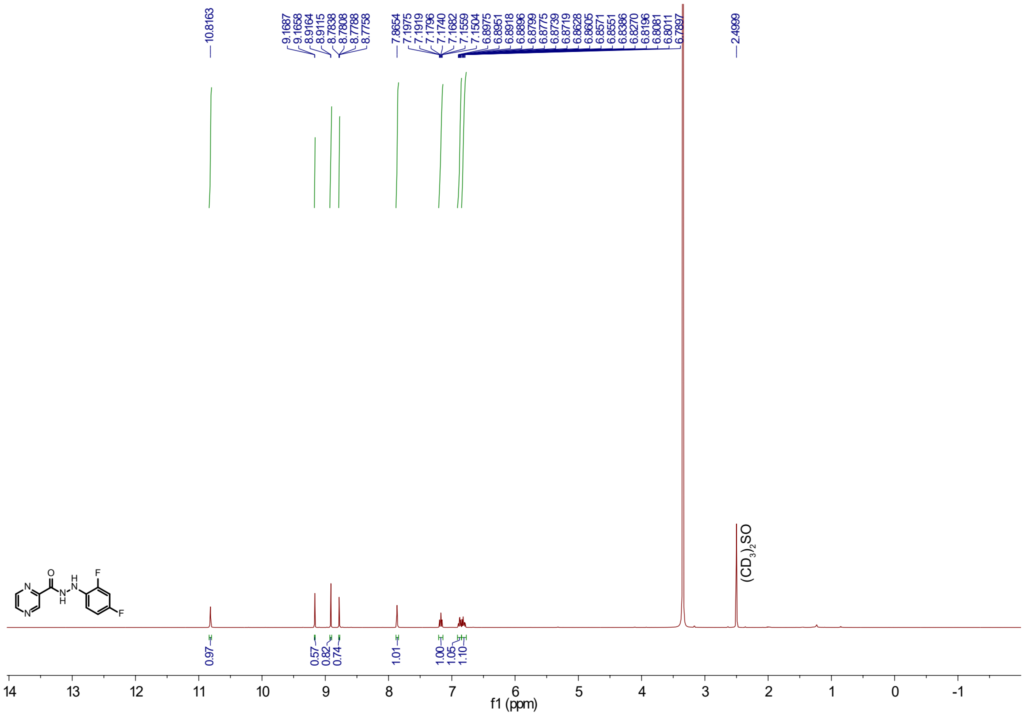


Fig. S157: ^{1}H NMR spectrum for compound **9g** (**SGT1397**) in $(CD_3)_2SO$ (500 MHz).

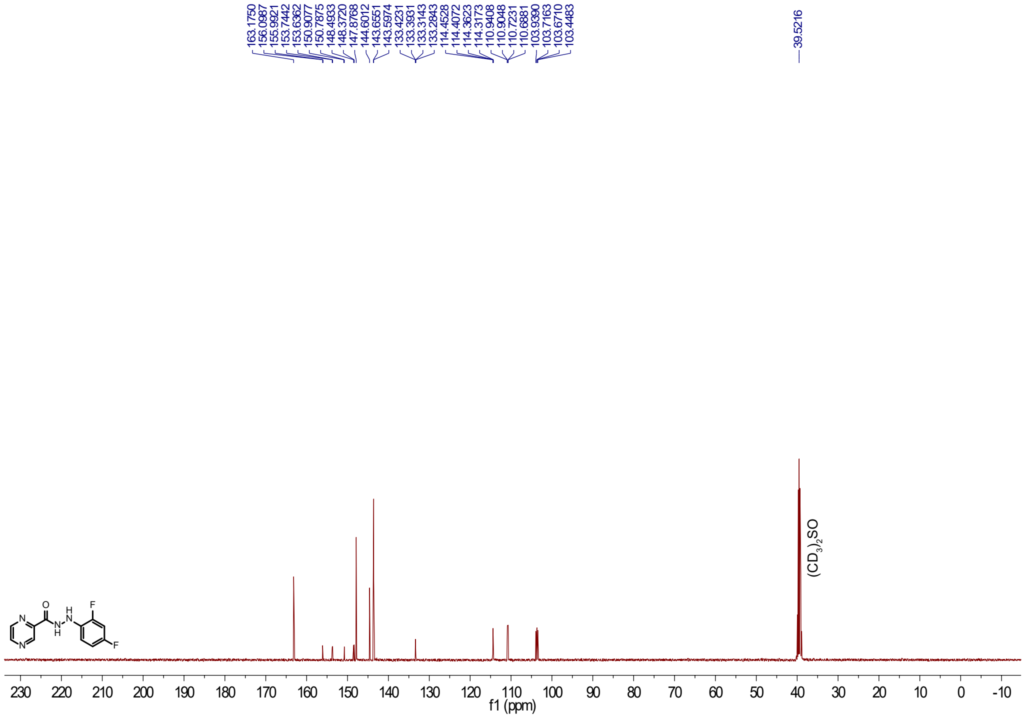


Fig. S158: ^{13}C NMR spectrum for compound **9g** (**SGT1397**) in $(CD_3)_2SO$ (100 MHz).

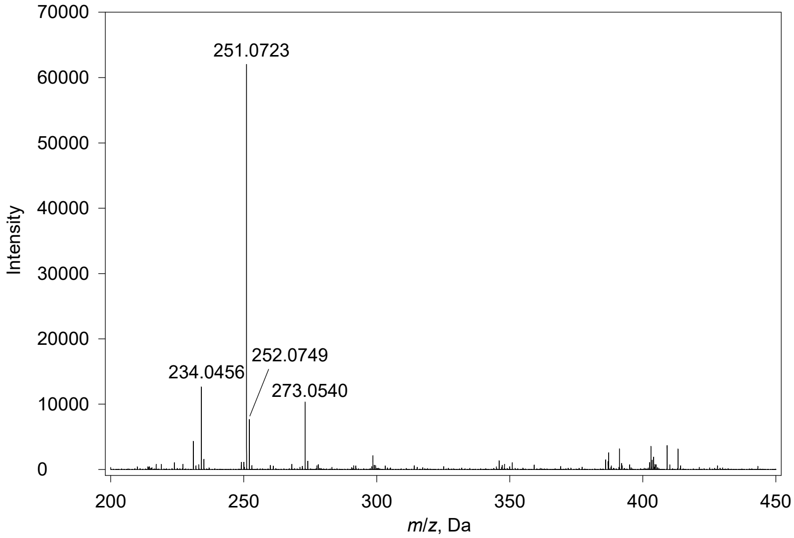


Fig. S159: HRMS spectrum for compound **9g** (**SGT1397**). *m/z* found 251.0723 $[M+H]^+$.

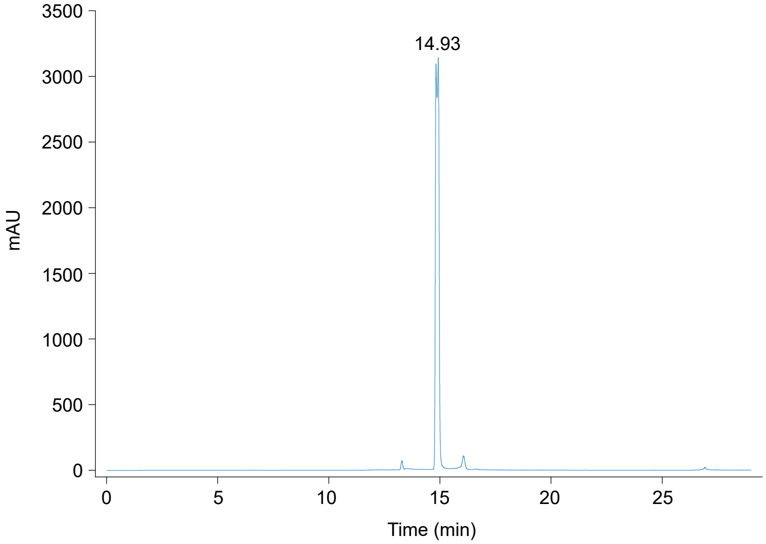


Fig. S160: HPLC trace for compound **9g** (**SGT1397**). R_t = 14.93 min.

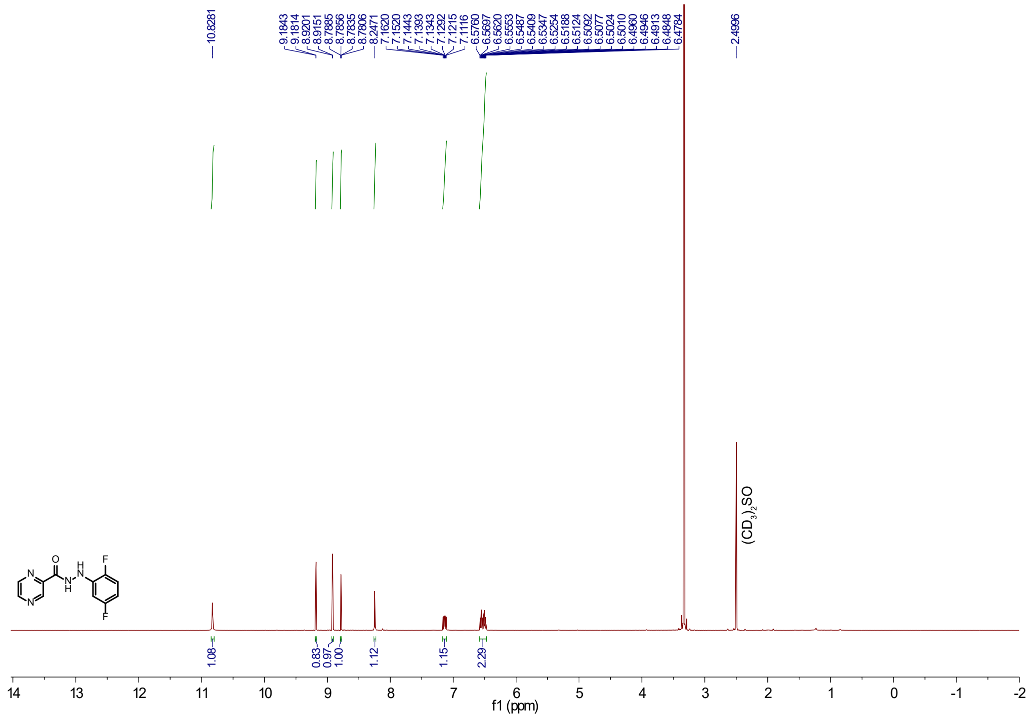


Fig. S161: ^{1}H NMR spectrum for compound **9h** (**SGT1791**) in $(CD_3)_2SO$ (500 MHz).

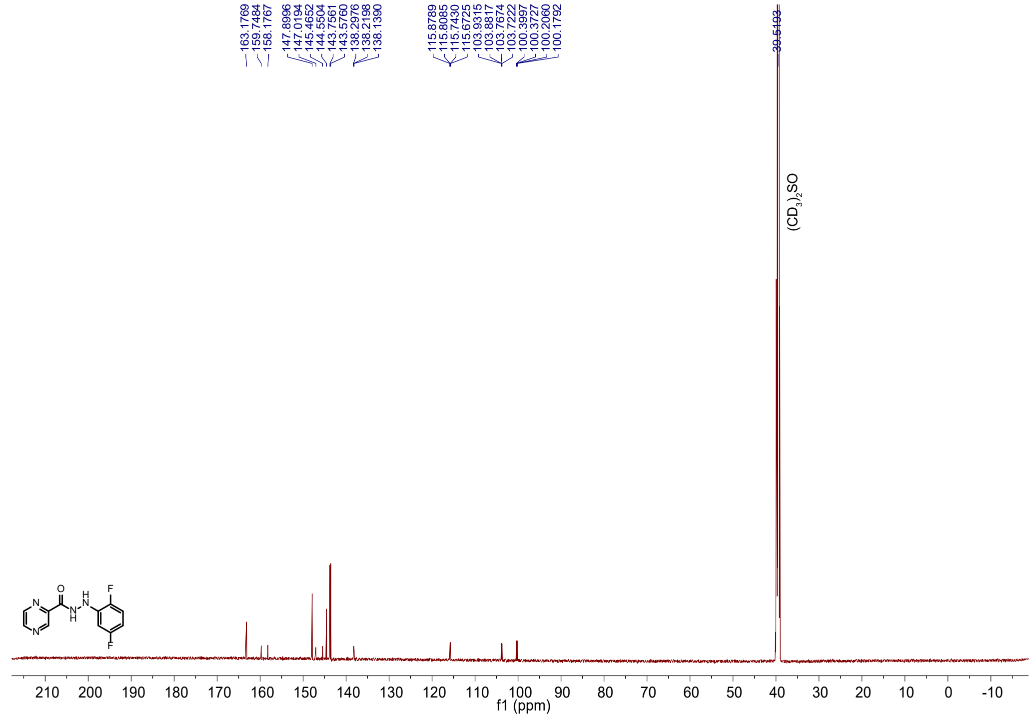


Fig. S162: ^{13}C NMR spectrum for compound **9h** (**SGT1791**) in $(CD_3)_2SO$ (150 MHz).

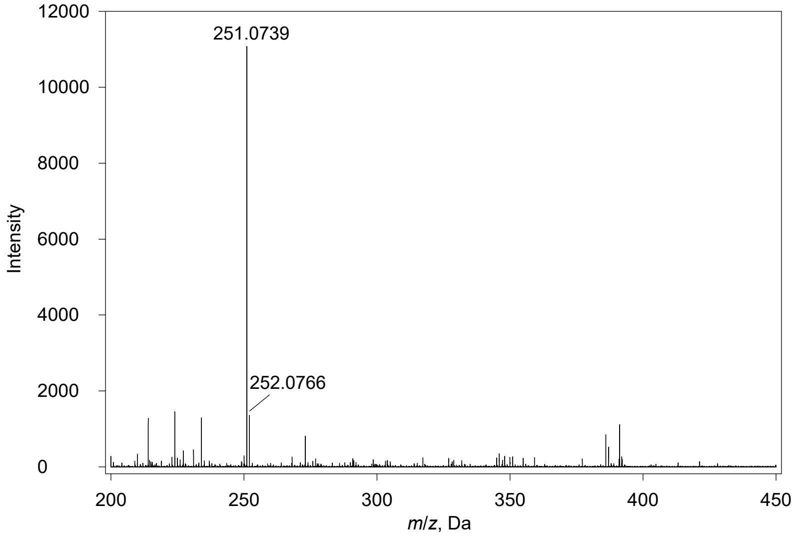


Fig. S163: HRMS spectrum for compound **9h** (**SGT1791**). *m/z* found 251.0739 $[M+H]^+$.

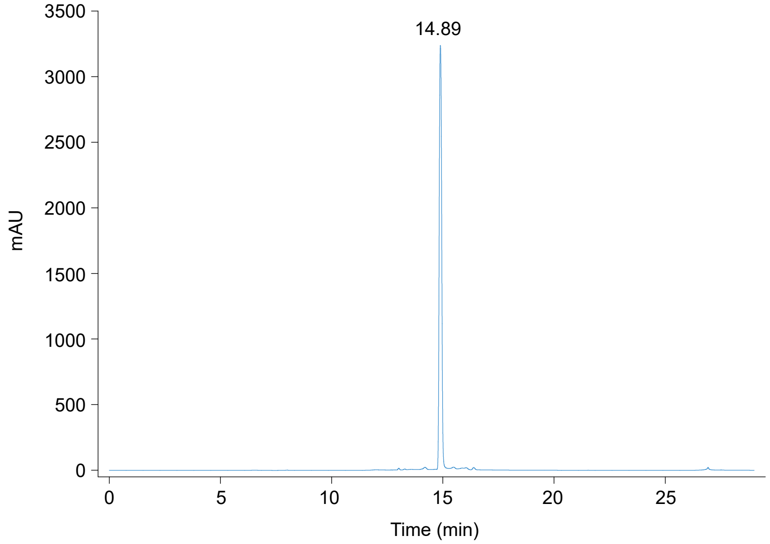


Fig. S164: HPLC trace for compound **9h** (**SGT1791**). R_t = 14.89 min.

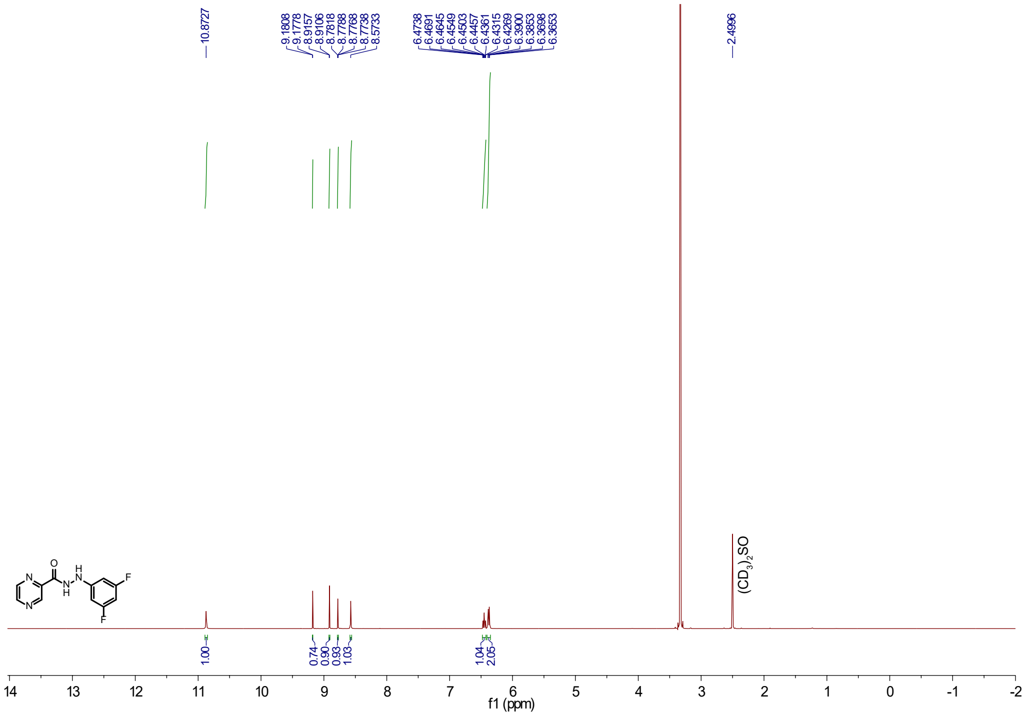


Fig. S165: ^{1}H NMR spectrum for compound **9i** (**SGT1792**) in $(CD_3)_2SO$ (500 MHz).

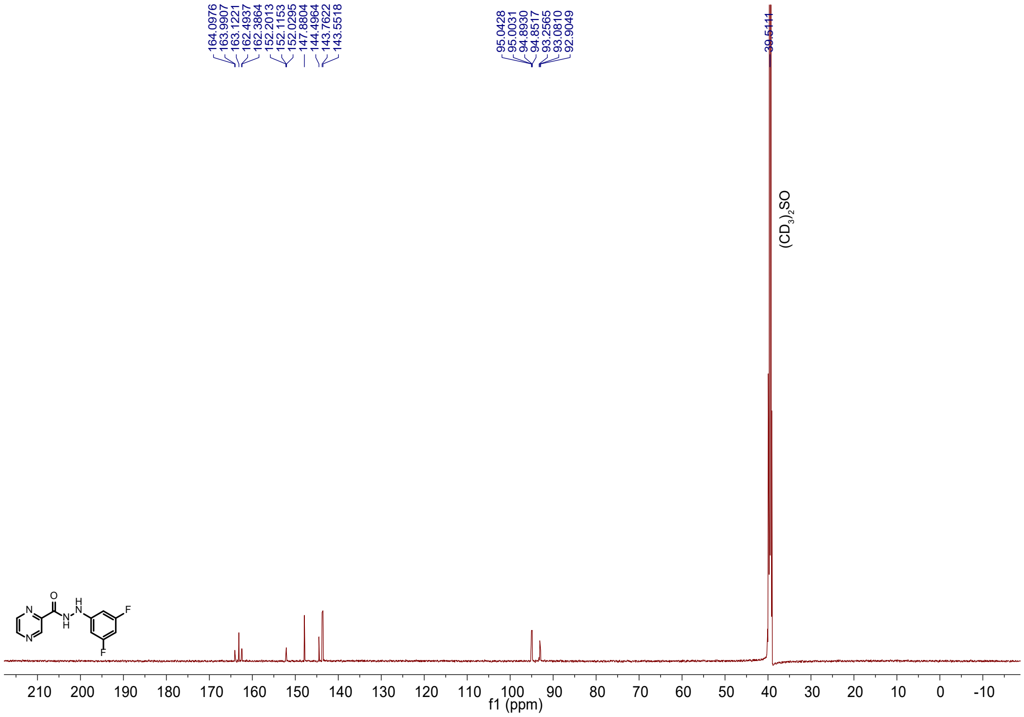


Fig. S166: ^{13}C NMR spectrum for compound **9i** (**SGT1792**) in $(CD_3)_2SO$ (150 MHz).

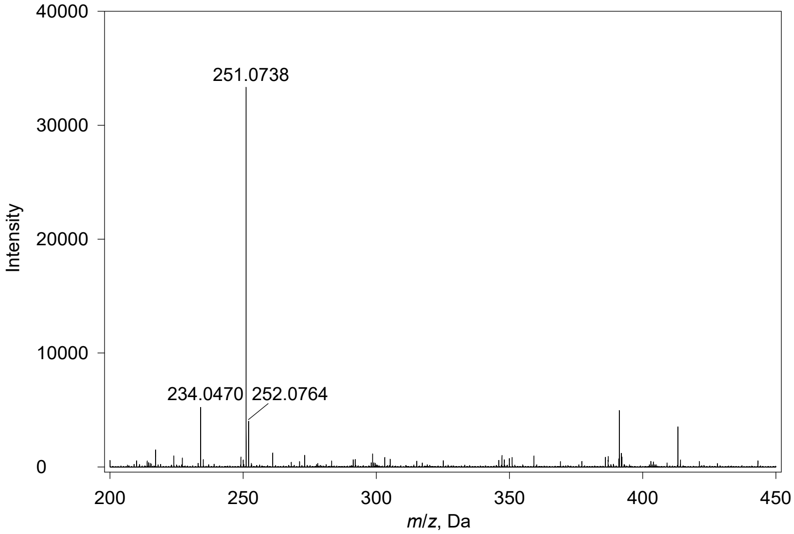


Fig. S167: HRMS spectrum for compound **9i** (**SGT1792**). *m/z* found 251.0738 $[M+H]^+$.

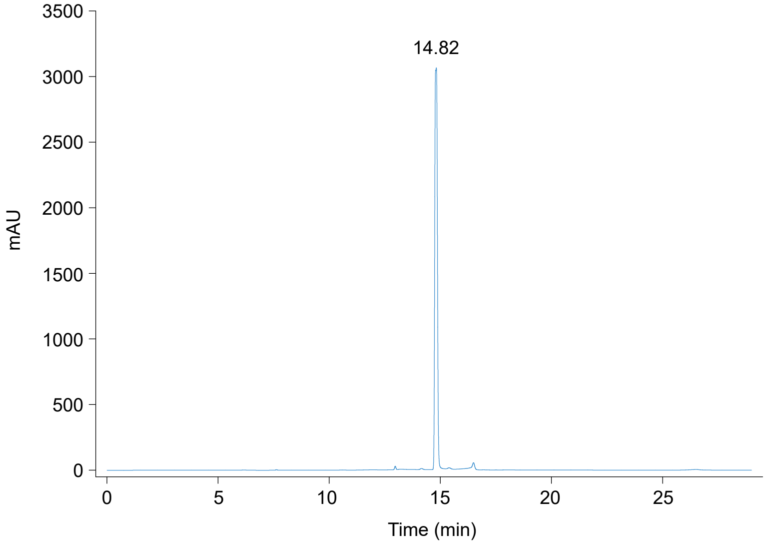


Fig. S168: HPLC trace for compound **9i** (**SGT1792**). R_t = 14.82 min.

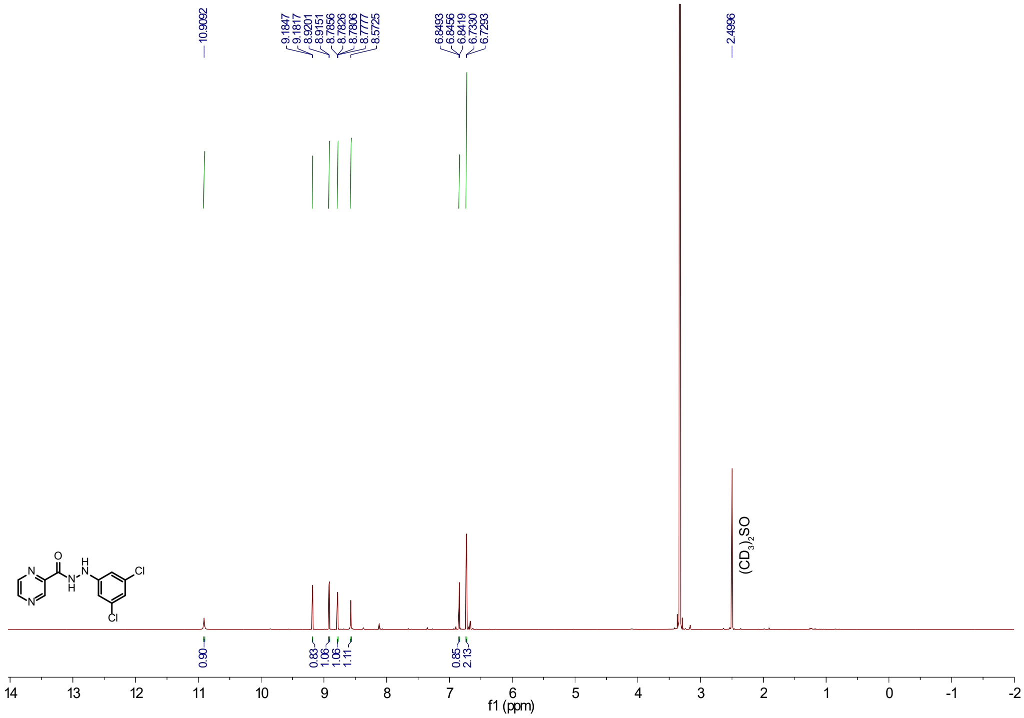


Fig. S169: ^{1}H NMR spectrum for compound **9j** (**SGT1794**) in $(CD_3)_2SO$ (500 MHz).

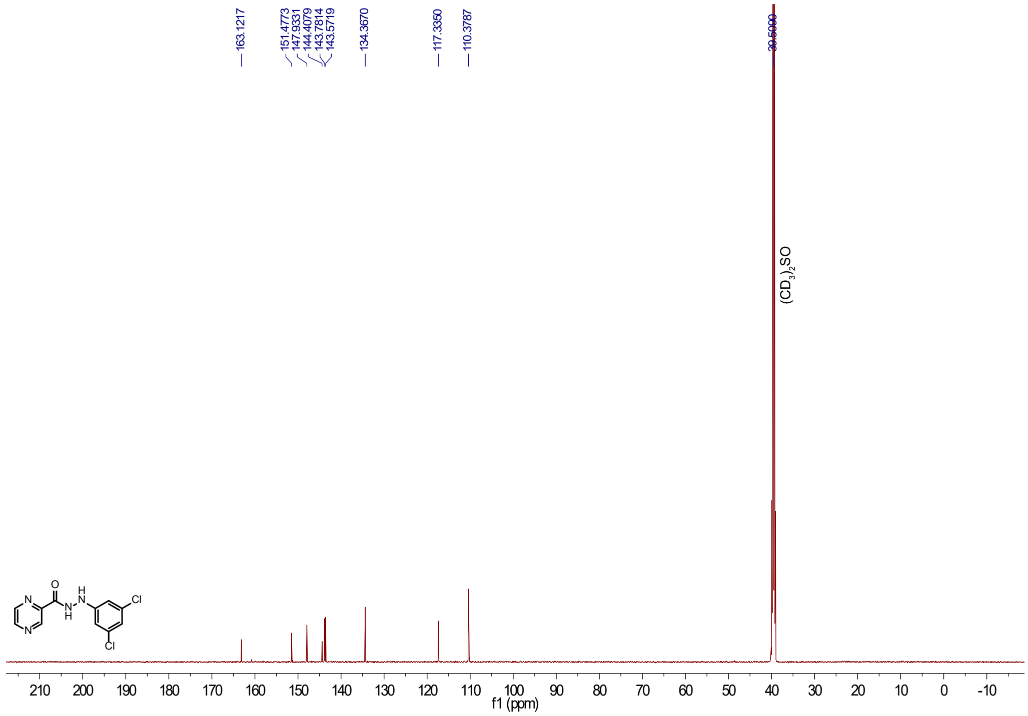


Fig. S170: ^{13}C NMR spectrum for compound **9j** (**SGT1794**) in $(CD_3)_2SO$ (150 MHz).

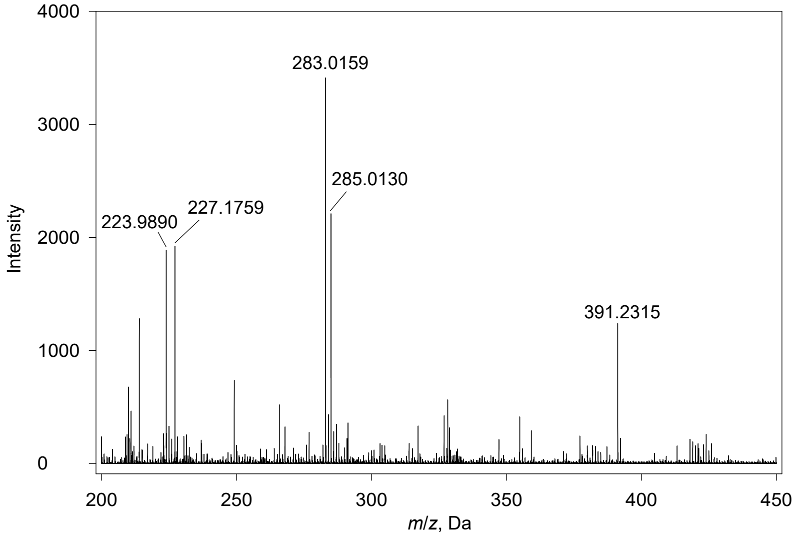


Fig. S171: HRMS spectrum for compound **9j** (**SGT1794**). *m/z* found 283.0159 $[M+H]^+$.

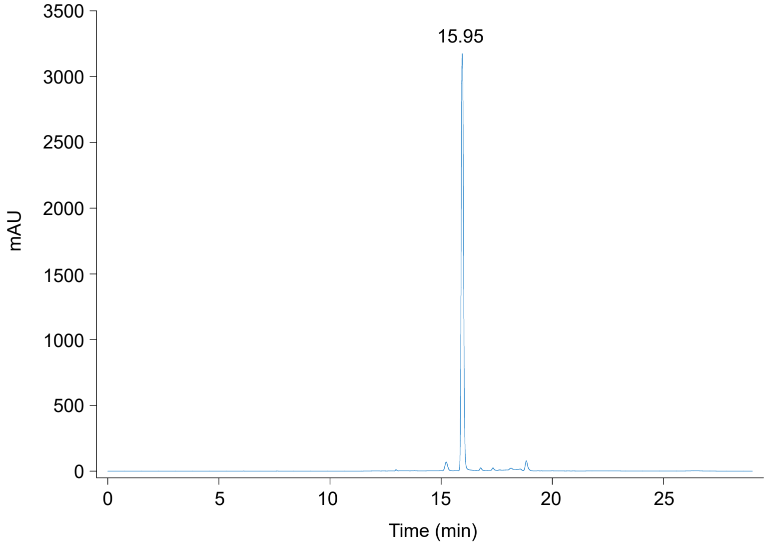


Fig. S172: HPLC trace for compound **9j** (**SGT1794**). R_t = 15.95 min.

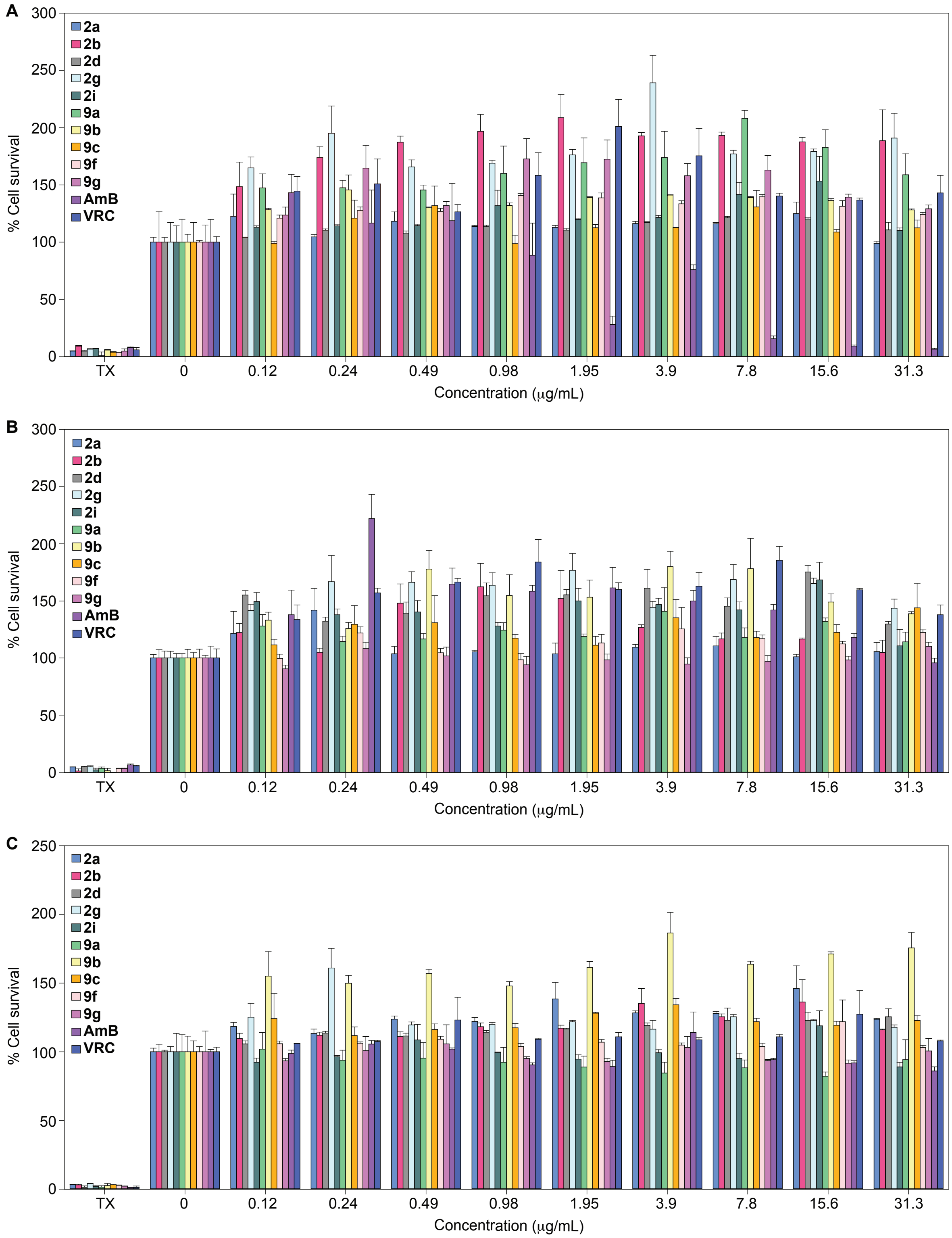


Fig. S173: Non-normalized 2D bar graphs depicting the dose-dependent cytotoxic activity of monohydrazides **2a**, **2b**, **2d**, **2g**, **2i**, **9a**, **9b**, **9c**, **9f**, **9g**, as well as AmB and VRC against **A.** J774A.1, **B.** HEK-293, and **C.** HepG2 cell lines. *Note*: For Triton X-100® (TX) the eight bars are colored differently and correspond to colors of the respective compounds for which TX was used as a positive control. *Note*: The corresponding data normalized at 100% are presented in Fig. 3.

Supplementary Tables S1-S6

Table S1. MIC values (in µg/mL) for remaining compounds from **1a-9j** and AmB against a variety of *Candida albicans*, non-*albicans Candida*, and non-*Candida* fungal strains.

	Fungal strain															
	Candida albicans							**non-*albicans Candida***					**non-*Candida***			
Cpd #	*A*	*B*	*C*	*D*	*E*	*F*	*G*	*H*	*I*	*J*	*K*	*L*	*M*	*N*	*O*	*P*
1b	1.95	7.8	7.8	15.6	7.8	3.9	3.9	>31.3	0.98	3.9	15.6	7.8	1.95	7.8	>31.3	3.9
1c	0.98	1.95	3.9	3.9	3.9	3.9	1.95	31.3	0.98	7.8	1.95	1.95	0.49	3.9	>31.3	3.9
1e	1.95	15.6	15.6	3.9	7.8	1.95	7.8	3.9	15.6	31.3	7.8	>31.3	1.95	31.3	>31.3	31.3
1g	1.95	1.95	3.9	3.9	>31.3	1.95	0.98	1.95	7.8	7.8	15.6	7.8	0.49	31.3	>31.3	1.95
1h	3.9	15.6	31.3	31.3	31.3	31.3	31.3	>31.3	3.9	31.3	31.3	15.6	0.98	>31.3	15.6	3.9
1i	3.9	15.6	15.6	15.6	15.6	7.8	15.6	>31.3	1.95	15.6	15.6	15.6	0.49	>31.3	>31.3	7.8
1j	3.9	>31.3	>31.3	>31.3	>31.3	15.6	7.8	>31.3	1.95	>31.1	>31.3	>31.3	7.8	>31.3	>31.3	15.6
3d	0.49	1.95	3.9	1.95	3.9	1.95	1.95	15.6	0.49	3.9	3.9	0.98	0.98	3.9	15.6	0.98
3e	1.95	1.95	1.95	3.9	1.95	1.95	0.98	7.8	0.98	31.3	7.8	7.8	3.9	>31.3	>31.3	15.6
3g	0.49	1.95	1.95	1.95	1.95	1.95	0.98	31.3	0.98	31.3	7.8	3.9	0.98	3.9	15.6	0.98
4d	1.95	7.8	7.8	7.8	7.8	7.8	3.9	>31.3	0.98	7.8	7.8	3.9	0.98	7.8	15.6	1.95
4f	3.9	3.9	1.95	3.9	3.9	0.98	1.95	1.95	0.98	3.9	1.95	1.95	1.95	7.8	>31.3	15.6
4g	3.9	15.6	0.98	3.9	>31.3	1.95	15.6	7.8	0.49	3.9	3.9	31.3	1.95	3.9	>31.3	3.9
5a	0.49	0.49	3.9	7.8	1.95	1.95	1.95	31.3	0.24	7.8	1.95	3.9	≤0.06	1.95	>31.3	0.98
5e	1.95	1.95	1.95	3.9	1.95	0.98	0.98	3.9	1.95	15.6	3.9	7.8	1.95	31.3	>31.3	7.8
5g	0.98	1.95	1.95	3.9	1.95	1.95	0.98	31.3	0.98	31.3	7.8	3.9	0.49	3.9	31.3	0.49
6a	0.49	1.95	1.95	7.8	3.9	3.9	3.9	>31.3	0.49	1.95	3.9	1.95	≤0.06	3.9	31.3	1.95
6d	0.98	1.95	3.9	3.9	3.9	3.9	1.95	>31.3	0.49	7.8	3.9	0.98	0.98	3.9	15.6	0.98
6f	1.95	3.9	1.95	3.9	3.9	0.98	3.9	1.95	0.98	3.9	1.95	1.95	1.95	7.8	>31.3	3.9
6g	3.9	15.6	0.98	3.9	31.3	1.95	15.6	15.6	0.98	7.8	3.9	31.3	0.49	7.8	>31.3	1.95
7c	0.98	1.95	3.9	7.8	3.9	3.9	1.95	15.6	15.6	15.6	7.8	15.6	15.6	31.3	>31.3	15.6
7e	3.9	3.9	3.9	7.8	1.95	0.49	1.95	3.9	1.95	15.6	3.9	7.8	1.95	>31.3	>31.3	7.8
7g	0.98	3.9	3.9	3.9	3.9	3.9	1.95	>31.3	0.98	31.3	7.8	1.95	0.98	7.8	>31.3	0.98
8c	0.98	1.95	3.9	7.8	3.9	1.95	1.95	15.6	15.6	7.8	15.6	15.6	7.8	31.3	>31.3	7.8
8e	3.9	7.8	3.9	7.8	3.9	>31.3	3.9	3.9	3.9	15.6	7.8	7.8	1.95	>31.3	>31.3	7.8
8g	0.98	1.95	1.95	3.9	1.95	1.95	0.98	15.6	0.49	15.6	3.9	1.95	0.49	31.3	>31.3	0.49
9d	0.24	1.95	7.8	0.98	7.8	0.98	1.95	3.9	0.49	3.9	0.49	0.98	0.24	1.95	15.6	0.49
9e	0.98	1.95	3.9	0.98	1.95	0.98	1.95	1.95	3.9	7.8	1.95	3.9	0.98	7.8	>31.3	1.95
9h	0.24	7.8	3.9	3.9	>31.3	3.9	1.95	15.6	0.49	7.8	0.49	1.95	0.49	1.95	>31.3	1.95
9i	0.24	3.9	7.8	3.9	15.6	1.95	1.95	7.8	0.49	3.9	0.49	1.95	0.24	1.95	3.9	1.95
9j	0.49	3.9	3.9	1.95	7.8	1.95	3.9	15.6	0.98	3.9	15.6	7.8	0.49	3.9	>31.3	7.8
AmB	1.95	1.95	1.95	0.98	0.98	1.95	0.98	0.98	0.98	0.98	1.95	1.95	7.8	3.9	31.3	15.6

Strains: *A* = *C. albicans* ATCC 10231, *B* = *C. albicans* ATCC 64124, *C* = *C. albicans* ATCC MYA-2876(S), *D* = *C. albicans* ATCC 90819(R), *E* = *C. albicans* ATCC MYA-2310(S), *F* = *C. albicans* ATCC MYA-1237(R), *G* = *C. albicans* ATCC MYA-1003(R), *H* = *C. glabrata* ATCC 2001, *I* = *C. krusei* ATCC 6258, *J* = *C. parapsilosis* ATCC 22019, *K* = *C. auris* AR Bank # 0384, *L* = *C. auris* AR Bank # 0390, *M* = *C. neoformans* ATCC MYA-895, *N* = *A. terreus* ATCC MYA-3633, *O* = *A. flavus* ATCC MYA-3631, *P* = *A. nidulans* ATCC 38163, NOTE: Here, the (S) and (R) indicate that ATCC reports these strains to be susceptible (S) and resistant (R) to itraconazole (ITC) and fluconazole (FLC).

Table S2. MIC values (in µg/mL) for compounds selected as well as AmB against a variety of *Candida auris* fungal strains.

	***C. auris* fungal strain (AR Bank #)**									
Cpd #	*381*	*382*	*383*	*384 (K)*	*385*	*386*	*387*	*388*	*389*	*390 (L)*
1b	3.9	3.9	15.6	7.8	3.9	7.8	7.8	3.9	3.9	7.8
1j	>31.3	15.6	>31.3	15.6	31.3	>31.3	>31.3	>31.3	>31.3	>31.3
3c	0.98	0.49	0.98	0.49	0.49	0.98	0.98	0.98	0.98	3.9
3d	1.95	0.98	1.95	0.98	0.98	1.95	0.98	1.95	1.95	3.9
3e	7.8	7.8	3.9	7.8	1.95	7.8	7.8	7.8	7.8	7.8
3g	1.95	1.95	1.95	0.98	0.49	1.95	0.98	1.95	1.95	3.9
4d	3.9	3.9	7.8	1.95	1.95	3.9	3.9	1.95	3.9	7.8
5c	0.98	0.49	1.95	0.49	0.98	0.98	0.49	0.98	0.98	3.9
5d	0.98	0.98	1.95	0.49	0.49	0.98	0.49	0.49	0.98	1.95
5e	7.8	7.8	3.9	3.9	3.9	7.8	7.8	7.8	7.8	7.8
5g	3.9	0.98	1.95	0.98	0.98	1.95	1.95	0.98	3.9	3.9
6d	1.95	0.98	1.95	0.98	0.98	1.95	0.98	0.98	1.95	3.9
7d	1.95	0.98	1.95	0.49	0.49	0.98	0.49	0.49	1.95	3.9
7e	7.8	15.6	3.9	7.8	7.8	15.6	15.6	7.8	7.8	7.8
7f	0.98	0.98	0.98	0.98	0.49	0.98	0.98	0.98	0.98	31.3
7g	3.9	1.95	3.9	0.98	0.98	1.95	1.95	3.9	3.9	7.8

8d	0.98	0.98	0.98	0.49	0.24	0.98	0.49	0.49	0.98	1.95
8e	7.8	7.8	7.8	7.8	3.9	15.6	7.8	15.6	7.8	7.8
8f	0.98	0.98	1.95	0.98	0.49	0.98	0.98	0.98	0.98	31.3
8g	1.95	1.95	1.95	0.98	0.49	1.95	0.98	0.98	1.95	31.3
AmB	0.98	0.98	1.95	1.95	1.95	0.98	0.98	1.95	1.95	1.95

Table S3. MIC values (in µg/mL) for compounds **1a-9j** and AmB against a variety of *Candida albicans*, non-*albicans Candida*, and non-*Candida* fungal strains.

	Fungal strain															
	Candida albicans							**non-*albicans Candida***					**non-*Candida***			
Cpd #	*A*	*B*	*C*	*D*	*E*	*F*	*G*	*H*	*I*	*J*	*K*	*L*	*M*	*N*	*O*	*P*
1a	0.24	1.95	3.9	7.8	3.9	0.98	1.95	7.8	1.95	3.9	1.95	0.24	1.95	1.95	>31.3	3.9
1b	1.95	7.8	7.8	15.6	7.8	3.9	3.9	>31.3	0.98	3.9	15.6	7.8	1.95	7.8	>31.3	3.9
1c	0.98	1.95	3.9	3.9	3.9	3.9	1.95	31.3	0.98	7.8	1.95	1.95	0.49	3.9	>31.3	3.9
1d	0.49	7.8	7.8	1.95	3.9	1.95	1.95	7.8	1.95	15.6	1.95	1.95	0.49	3.9	>31.3	3.9
1e	1.95	15.6	15.6	3.9	7.8	1.95	7.8	3.9	15.6	31.3	7.8	>31.3	1.95	31.3	>31.3	31.3
1f	0.98	1.95	1.95	1.95	1.95	1.95	1.95	3.9	0.98	7.8	1.95	1.95	0.98	31.3	>31.3	1.95
1g	1.95	1.95	3.9	3.9	>31.3	1.95	0.98	1.95	7.8	7.8	15.6	7.8	0.49	31.3	>31.3	1.95
1h	3.9	15.6	31.3	31.3	31.3	31.3	31.3	>31.3	3.9	31.3	31.3	15.6	0.98	>31.3	15.6	3.9
1i	3.9	15.6	15.6	15.6	15.6	7.8	15.6	>31.3	1.95	15.6	15.6	15.6	0.49	>31.3	>31.3	7.8
1j	3.9	>31.3	>31.3	>31.3	>31.3	15.6	7.8	>31.3	1.95	>31.1	>31.3	>31.3	7.8	>31.3	>31.3	15.6
2a	≤0.06	0.98	0.98	0.49	1.95	0.98	0.98	1.95	0.24	1.95	1.95	0.24	0.12	1.95	7.8	0.49
2b	0.12	0.98	0.98	0.49	0.98	0.98	0.49	1.95	0.49	1.95	0.98	0.98	0.12	0.98	>31.3	0.24
2c	0.24	0.98	0.98	1.95	1.95	1.95	0.98	15.6	0.49	3.9	0.98	0.98	0.24	3.9	>31.3	1.95
2d	0.12	0.98	3.9	0.98	1.95	1.95	0.49	1.95	0.12	1.95	3.9	0.98	0.24	1.95	31.3	0.49
2e	0.12	0.98	1.95	0.24	0.98	0.98	0.98	1.95	1.95	3.9	1.95	1.95	0.49	3.9	31.3	0.49
2f	0.12	0.98	1.95	0.49	0.98	0.98	0.98	0.98	0.49	3.9	3.9	0.12	0.49	31.3	>31.3	0.49
2g	0.12	1.95	0.98	0.98	31.3	0.49	0.49	0.98	0.49	1.95	0.49	0.12	0.24	0.98	15.6	0.49
2h	0.12	1.95	3.9	0.98	1.95	1.95	0.98	3.9	0.24	3.9	0.24	0.98	0.49	0.98	3.9	0.49
2i	≤0.06	0.98	0.98	0.98	0.98	1.95	0.49	7.8	0.24	1.95	0.24	0.49	0.24	0.98	1.95	0.49
2j	0.24	1.95	1.95	0.98	1.95	3.9	1.95	7.8	0.98	1.95	7.8	1.95	0.49	1.95	>31.3	0.49
3a	0.49	0.49	3.9	3.9	3.9	3.9	1.95	31.3	0.24	1.95	1.95	1.95	≤0.06	1.95	7.8	0.98
3c	0.24	0.98	0.49	3.9	1.95	1.95	0.98	15.6	0.24	3.9	1.95	0.98	0.24	3.9	>31.3	1.95
3d	0.49	1.95	3.9	1.95	3.9	1.95	1.95	15.6	0.49	3.9	3.9	0.98	0.98	3.9	15.6	0.98
3e	1.95	1.95	1.95	3.9	1.95	1.95	0.98	7.8	0.98	31.3	7.8	7.8	3.9	>31.3	>31.3	15.6
3f	0.24	0.98	0.98	0.98	0.98	0.49	0.49	1.95	0.24	3.9	3.9	0.49	≤0.06	31.3	>31.3	1.95
3g	0.49	1.95	1.95	1.95	1.95	1.95	0.98	31.3	0.98	31.3	7.8	3.9	0.98	3.9	15.6	0.98
4a	0.49	0.49	1.95	3.9	3.9	3.9	0.98	>31.3	0.24	7.8	1.95	1.95	0.06	0.98	15.6	1.95
4c	0.98	3.9	0.98	1.95	3.9	0.98	3.9	3.9	0.24	1.95	0.98	1.95	0.49	1.95	>31.3	3.9
4d	1.95	7.8	7.8	7.8	7.8	7.8	3.9	>31.3	0.98	7.8	7.8	3.9	0.98	7.8	15.6	1.95
4f	3.9	3.9	1.95	3.9	3.9	0.98	1.95	1.95	0.98	3.9	1.95	1.95	1.95	7.8	>31.3	15.6
4g	3.9	15.6	0.98	3.9	>31.3	1.95	15.6	7.8	0.49	3.9	3.9	31.3	1.95	3.9	>31.3	3.9
5a	0.49	0.49	3.9	7.8	1.95	1.95	1.95	31.3	0.24	7.8	1.95	3.9	≤0.06	1.95	>31.3	0.98
5c	0.98	0.98	0.49	3.9	1.95	1.95	0.98	15.6	0.24	3.9	1.95	0.98	0.49	3.9	>31.3	1.95
5d	0.24	0.98	1.95	1.95	3.9	1.95	0.98	15.6	0.49	3.9	1.95	0.98	0.49	1.95	7.8	0.98
5e	1.95	1.95	1.95	3.9	1.95	0.98	0.98	3.9	1.95	15.6	3.9	7.8	1.95	31.3	>31.3	7.8
5f	0.24	1.95	0.98	1.95	0.98	0.98	0.98	0.98	0.49	7.8	1.95	1.95	0.24	15.6	>31.3	1.95
5g	0.98	1.95	1.95	3.9	1.95	1.95	0.98	31.3	0.98	31.3	7.8	3.9	0.49	3.9	31.3	0.49
6a	0.49	1.95	1.95	7.8	3.9	3.9	3.9	>31.3	0.49	1.95	3.9	1.95	≤0.06	3.9	31.3	1.95
6c	1.95	3.9	0.49	1.95	7.8	0.98	3.9	7.8	0.24	0.98	0.98	1.95	0.98	1.95	>31.3	3.9
6d	0.98	1.95	3.9	3.9	3.9	3.9	1.95	>31.3	0.49	7.8	3.9	0.98	0.98	3.9	15.6	0.98
6f	1.95	3.9	1.95	3.9	3.9	0.98	3.9	1.95	0.98	3.9	1.95	1.95	1.95	7.8	>31.3	3.9
6g	3.9	15.6	0.98	3.9	31.3	1.95	15.6	15.6	0.98	7.8	3.9	31.3	0.49	7.8	>31.3	1.95
7a	0.24	0.98	1.95	3.9	1.95	3.9	1.95	31.3	0.24	1.95	1.95	1.95	≤0.06	3.9	>31.3	0.98
7c	0.98	1.95	3.9	7.8	3.9	3.9	1.95	15.6	15.6	15.6	7.8	15.6	15.6	31.3	>31.3	15.6
7d	0.98	1.95	1.95	1.95	3.9	1.95	0.98	15.6	0.49	3.9	1.95	0.98	0.49	3.9	7.8	0.49
7e	3.9	3.9	3.9	7.8	1.95	0.49	1.95	3.9	1.95	15.6	3.9	7.8	1.95	>31.3	>31.3	7.8
7f	1.95	1.95	1.95	1.95	1.95	0.98	0.98	7.8	0.98	7.8	3.9	0.98	1.95	31.3	>31.3	1.95
7g	0.98	3.9	3.9	3.9	3.9	3.9	1.95	>31.3	0.98	31.3	7.8	1.95	0.98	7.8	>31.3	0.98
8a	0.98	0.98	1.95	3.9	1.95	1.95	0.98	15.6	0.49	7.8	1.95	1.95	≤0.06	3.9	>31.3	1.95
8c	0.98	1.95	3.9	7.8	3.9	1.95	1.95	15.6	15.6	7.8	15.6	15.6	7.8	31.3	>31.3	7.8
8d	0.24	0.98	0.98	0.98	0.98	0.98	0.49	15.6	0.24	7.8	1.95	0.98	0.49	1.95	7.8	0.49
8e	3.9	7.8	3.9	7.8	3.9	>31.3	3.9	3.9	3.9	15.6	7.8	7.8	1.95	>31.3	>31.3	7.8
8f	1.95	1.95	1.95	1.95	1.95	0.98	0.98	7.8	0.98	7.8	3.9	0.98	0.98	31.3	>31.3	1.95

8g	0.98	1.95	1.95	3.9	1.95	1.95	0.98	15.6	0.49	15.6	3.9	1.95	0.49	31.3	>31.3	0.49
9a	0.24	1.95	3.9	0.98	7.8	0.98	0.98	7.8	0.49	3.9	0.98	0.98	0.12	0.98	15.6	0.98
9b	0.24	1.95	1.95	3.9	7.8	0.98	0.98	3.9	0.24	1.95	1.95	0.98	0.24	0.98	>31.3	0.98
9c	0.49	0.98	1.95	1.95	1.95	1.95	0.98	7.8	0.49	1.95	1.95	0.98	0.49	1.95	>31.3	1.95
9d	0.24	1.95	7.8	0.98	7.8	0.98	1.95	3.9	0.49	3.9	0.49	0.98	0.24	1.95	15.6	0.49
9e	0.98	1.95	3.9	0.98	1.95	0.98	1.95	1.95	3.9	7.8	1.95	3.9	0.98	7.8	>31.3	1.95
9f	0.49	0.98	1.95	0.98	1.95	0.98	1.95	0.98	0.98	3.9	0.49	0.49	0.98	>31.3	>31.3	0.98
9g	0.24	0.98	0.98	0.98	3.9	0.49	0.49	0.98	0.24	3.9	3.9	0.98	0.24	0.98	7.8	0.49
9h	0.24	7.8	3.9	3.9	>31.3	3.9	1.95	15.6	0.49	7.8	0.49	1.95	0.49	1.95	>31.3	1.95
9i	0.24	3.9	7.8	3.9	15.6	1.95	1.95	7.8	0.49	3.9	0.49	1.95	0.24	1.95	3.9	1.95
9j	0.49	3.9	3.9	1.95	7.8	1.95	3.9	15.6	0.98	3.9	15.6	7.8	0.49	3.9	>31.3	7.8
AmB	1.95	1.95	1.95	0.98	0.98	1.95	0.98	0.98	0.98	0.98	1.95	1.95	7.8	3.9	31.3	15.6

Strains: *A* = *C. albicans* ATCC 10231, *B* = *C. albicans* ATCC 64124, *C* = *C. albicans* ATCC MYA-2876(S), *D* = *C. albicans* ATCC 90819(R), *E* = *C. albicans* ATCC MYA-2310(S), *F* = *C. albicans* ATCC MYA-1237(R), *G* = *C. albicans* ATCC MYA-1003(R), *H* = *C. glabrata* ATCC 2001, *I* = *C. krusei* ATCC 6258, *J* = *C. parapsilosis* ATCC 22019, *K* = *C. auris* AR Bank # 0384, *L* = *C. auris* AR Bank # 0390, *M* = *C. neoformans* ATCC MYA-895, *N* = *A. terreus* ATCC MYA-3633, *O* = *A. flavus* ATCC MYA-3631, *P* = *A. nidulans* ATCC 38163, NOTE: Here, the (S) and (R) indicate that ATCC reports these strains to be susceptible (S) and resistant (R) to itraconazole (ITC) and fluconazole (FLC).

Table S4. Physicochemical properties of selected compounds **2a-2j**, **9a-9c**, **9f**, and **9g** used in this study.

Cpd #	TPSA	Log S	Log P	Lipinski
2a	54.02	-2.212	1.957	Yes
2b	54.02	-2.839	2.505	Yes
2c	63.25	-2.172	1.844	Yes
2d	54.02	-2.325	1.913	Yes
2e	54.02	-2.925	2.502	Yes
2f	63.25	-2.227	1.773	Yes
2g	54.02	-2.739	2.016	Yes
2h	54.02	-2.874	2.091	Yes
2i	54.02	-2.281	2.073	Yes
2j	54.02	-3.59	3.309	Yes
9a	66.91	-1.762	1.134	Yes
9b	66.91	-2.404	1.781	Yes
9c	76.41	-1.649	1.061	Yes
9f	76.41	-1.782	1.0	Yes
9g	66.91	-2.179	1.168	Yes

TPSA = Topological polar surface area
Log S = log of aqueous solubility
Log P = Log of octanol/water partition coefficient

Table S5. Predicted ADME/T properties of selected compounds **2a-2j**, **9a-9c**, **9f**, and **9g** used in this study.

Cpd #	HIA	Pgp-inhibitor	Pgp-substrate	BBB	PPB%	VD	CL	hERG Blockers	Carcinogenicity	H-HT
2a	0.007	0.002	0.003	0.997	72.03	0.643	7.206	0.006	0.88	0.923
2b	0.008	0.004	0.003	0.998	89.95	0.721	4.406	0.005	0.668	0.776
2c	0.009	0.002	0.003	0.998	75.68	0.67	7.354	0.008	0.844	0.912
2d	0.006	0.002	0.003	0.995	79.56	0.551	6.19	0.004	0.879	0.927
2e	0.007	0.004	0.003	0.997	86.84	0.664	4.074	0.004	0.726	0.725
2f	0.007	0.001	0.003	0.996	72.03	0.643	7.206	0.006	0.875	0.897
2g	0.004	0.008	0.001	0.974	84.72	0.667	6.236	0.004	0.907	0.976
2h	0.004	0.009	0.002	0.965	86.51	0.71	5.986	0.006	0.894	0.98
2i	0.004	0.012	0.003	0.976	88.84	0.641	6.39	0.01	0.885	0.957
2j	0.006	0.018	0.004	0.973	97.55	0.895	3.882	0.008	0.608	0.778
9a	0.007	0.0	0.006	0.646	55.85	0.92	7.903	0.013	0.178	0.944
9b	0.01	0.001	0.01	0.725	66.37	0.945	7.134	0.014	0.128	0.862
9c	0.008	0.0	0.006	0.649	52.21	0.947	9.438	0.016	0.221	0.935
9f	0.007	0.0	0.008	0.734	48.59	0.901	9.231	0.016	0.193	0.932
9g	0.005	0.001	0.002	0.534	63.50	1.049	8.017	0.011	0.204	0.98

HIA = Human intestinal absorption
Pgp = P-glycoprotein
BBB = Blood-brain barrier
PPB = Plasma protein binding (Optimal < 90%)
VD = Volume distribution (Optimal 0.04-20 L/Kg)

CL = Clearance (High: >15 mL/min/Kg; Moderate: 5-15 mL/min/Kg; Low: <5 mL/min/Kg)
hERG = human *Ether-à-go-go*-related
H-HT = Human hepatotoxicity
The output value represent probability.

Table S6. Predicted inhibition of cytochrome P450 (CYP) monooxygenase by compounds **2a**-**2j**, **9a**-**9c**, **9f**, and **9g**.

Cpd #	CYP1A2	CYP2C19	CYP2C9	CYP2D6	CYP3A4
2a	Yes	No	No	No	No
2b	Yes	No	No	No	No
2c	Yes	No	No	No	No
2d	Yes	No	No	No	No
2e	Yes	No	No	No	No
2f	Yes	No	No	No	No
2g	Yes	No	No	No	No
2h	Yes	No	No	No	No
2i	No	No	No	No	No
2j	Yes	Yes	No	Yes	No
9a	Yes	No	No	No	No
9b	Yes	No	No	No	No
9c	Yes	No	No	No	No
9f	Yes	No	No	No	No
9g	Yes	No	No	No	No