Supporting Information

Development of Novel Diclofenac Analogs Designed to Avoid Metabolic Activation and Hepatocyte Toxicity

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General Information and Instruments

^{1}H NMR spectra were measured using an Agilent 400 NMR, Brucker 500 NMR instrument operating at 400 or 500 MHz; tetramethylsilane (TMS, δ=0.00) in $CDCl_3$ or DMSO-d_6 was used as an internal standard for ^{1}H and ^{13}C experiments, and tribromofluoromethane ($CFBr_3$, δ=7.40) in $CDCl_3$ or DMSO-d_6 was used as an internal standard for ^{19}F experiments. For the ^{19}F experiment in DMSO-d_6, $CFBr_3$ dissolved in $CDCl_3$ was added. Mass spectra were recorded using a JEOL JMS-T100 LP (ESI-MS) instrument. Column chromatography was performed using silica gel 60 (Merck, Darmstadt, Germany). Medium pressure preparative liquid chromatography (MPLC) was performed with a Yamazen AI-580S equipped with a Universal Column (silica gel, 40 μm, 60 Å) (Yamazen, Tokyo, Japan). All of the other reagents used for experiments were of analytical grade or of the highest quality commercially available.

Synthetic Procedures of Diclofenac Analogs

Synthesis of 2-(2-((2,6-dichloro-4-fluorophenyl)amino)phenyl)acetic acid (1b):

*2-(2-Iodophenyl)-N,N-dimethylacetamide (**7a**).* To a solution of 2-iodophenylacetic acid (2.65 g, 10 mmol) in anhydrous dichloromethane (20 mL) was added dropwise thionyl chloride (5.0 mL, 69 mmol) and stirred at room temperature for 3 h and evaporated. The residue was cooled to 0°C, and 40% w/w aqueous dimethylamine (10 mL) was added. After stirring for 30 min, saturated sodium bicarbonate solution was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and then evaporated to obtain the title compound as brown oil (2.08 g, 71% yield). This product was used without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.01 (s, 3H), 3.04 (s, 3H), 3.80 (s, 2H), 6.94 (dt, 1H, *J*=7.5, 1.8 Hz), 7.26 (dd, 1H, *J*=7.6, 2.0 Hz), 7.31 (dt, 1H, *J*=7.4, 1.2 Hz), 7.84 (dd, 1H, *J*=8.0, 1.2 Hz).

*2-(2-((2,6-Dichloro-4-fluorophenyl)amino)phenyl)-N,N-dimethylacetamide (**8b**).* A mixture of **7a** (1.1 g, 3.7 mmol), 2,6-dichloro-4-fluoroaniline (1.6 g, 8.7 mmol), potassium carbonate (953 mg, 6.9 mmol), copper powder (224 mg, 3.5 mmol), cupric iodide (68 mg, 0.35 mmol) and toluene (14 mL) was refluxed for 62 h. The mixture was poured into saturated ammonium chloride solution, adjusted to pH 8 with 10% NaOH *aq.*, and then extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated. The residue was purified using silica gel column chromatography (*n*-hexane/ethyl acetate=2/1) to obtain the title compound as a brown paste (826 mg, 66% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.99 (s, 3H), 3.21 (s, 3H), 3.84 (s, 2H), 6.41 (d, 1H, *J*=8.0 Hz), 6.87 (dt, 1H, *J*=7.4, 1.2 Hz), 7.08 (dt, 1H, *J*=7.7, 1.4 Hz), 7.14 (d, 2H, *J*=8.0 Hz), 7.15 (dd, 1H, *J*=7.4, 1.2 Hz), 7.79 (br, 1H). LRMS-ESI (*m/z*): $[M+Na+4]^+$ 367, $[M+Na+2]^+$ 365, $[M+Na]^+$ 363.

*2-(2-((2,6-dichloro-4-fluorophenyl)amino)phenyl)acetic acid (**1b**).* A mixture of **8b** (268 mg, 0.78 mmol), ethanol (8.0 mL), 5 M NaOH *aq.* (7.0 mL) was refluxed for 2.5 h. The reaction mixture was acidified with 6 M HCl and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated to give the title compound as a brown solid (222 mg, 91% yield). Recrystallization from ethyl acetate yielded a beige plate. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.83 (s, 2H), 6.47 (d, 1H, *J*=8.0 Hz), 6.65 (br, 1H), 6.96 (dt, 1H, *J*=7.4, 1.2 Hz), 7.14 (dd, 1H, *J*=7.6, 1.6 Hz), 7.15 (d, 2H, *J*=7.8 Hz), 7.24 (dd, 1H, *J*=7.4, 1.4 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 38.2, 116.4 (d, *J*=25 Hz), 117.4, 122.0, 123.0, 128.4, 130.7 (d, *J*=12 Hz), 131.1, 134.3 (d, *J*=3.8 Hz), 142.8, 157.8 (d, *J*=249

Hz), 178.2. ^{19}F NMR ($CDCl_3$, 376 MHz): δ -116.4 (t, *J*=8.2 Hz). HRMS-ESI (*m/z*): $[M\text{-}COOH]^-$ calcd for $C_{13}H_9Cl_2NF$, 268.0096; found, 268.0103 (+0.7 mmu).

Synthesis of 2-(2-((2,6-dichloro-4-fluorophenyl)amino)phenyl)acetic acid (1c):

2-Amino-5-fluorophenyl acetic acid. A mixture of 5-fluoro-2-nitrophenyl acetic acid (2.0 g, 10 mmol), 5% palladium on charcoal (200 mg) and methanol (100 mL) was stirred at room temperature under a hydrogen atmosphere for 3 h. The reaction mixture was filtered through Celite and washed with methanol, and the filtrate was evaporated to obtain the title compound as a brown solid (1.7 g, quantitative yield). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 3.43 (s, 2H), 6.64 (dd, 1H, *J*=8.6, 5.2 Hz), 6.78 (dd, 1H, *J*=8.6, 3.0 Hz), 6.82 (dd, 1H, *J*=9.8, 3.0 Hz). ^{19}F NMR (DMSO-d_6, 471 MHz): δ -122.5 (dt, *J*=9.6, 5.2 Hz). LRMS-ESI (*m/z*): $[M\text{-}COOH]^-$ 124.

*5-Fluoro-2-iodophenyl acetic acid (**6b**).* To a solution of 2-amino-5-fluorophenyl acetic acid (10 mmol) in water (50 mL), sulfuric acid (98%, 10 mL) and sodium nitrite (828 mg, 12 mmol) in water (12 mL) were added at 0°C and stirred for 10 min. Then, the solution was added dropwise to a solution of 1.0 M potassium iodide *aq.* (20 mL) at 0°C. The mixture was stirred for 30 min and extracted with ethyl acetate. The organic layer was washed with 0.5 M sodium thiosulfate *aq.* and brine and dried over sodium sulfate. The solvent was evaporated to obtain the title compound as a yellow solid (2.6 g, 94% yield). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.74 (s, 2H), 6.94 (dt, 1H, *J*=8.6, 3.1 Hz), 7.30 (dd, 1H, *J*=9.8, 3.1 Hz), 7.85 (dd, 1H, *J*=8.6, 5.9 Hz). ^{19}F NMR (DMSO-d_6, 378 MHz): δ -108.23 (dt, *J*=9.5, 5.5 Hz).

*2-(5-Fluoro-2-iodophenyl)-N,N-dimethylacetamide (7**b**).* To a solution of **6b** (2.6 g, 9.4 mmol), in anhydrous dichloromethane (20 mL) was added dropwise thionyl chloride (4.8 mL, 65 mmol) and stirred at 50°C for 1 h and evaporated. The residue was cooled to 0°C, and 40% w/w aqueous dimethylamine (15 mL) was added. After stirring for 30 min, saturated sodium bicarbonate solution was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and then evaporated. The residue was purified using MPLC (silica gel, *n*-hexane/ethyl acetate=64/36→43/57) to yield the title compound as a brown solid (2.4 g, 83% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.01 (s, 3H), 3.06 (s, 3H), 3.78 (s, 2H), 6.73 (dt, 1H, *J*=8.4, 2.9 Hz), 7.03 (dd, 1H, *J*=9.4, 2.9 Hz), 7.77 (dd, 1H, *J*=8.6, 5.7 Hz). ^{19}F NMR ($CDCl_3$, 378 MHz): δ -113.8 (dt, *J*=9.5, 5.5 Hz).

LRMS-ESI (*m/z*): $[M+Na]^+$ 330.

*2-(2-((2,6-Dichlorophenyl)amino)-5-fluorophenyl)-N,N-dimethylacetamide (**8c**).* A mixture of **7b** (1.5 g, 5.0 mmol), 2,6-dichloroaniline (2.3 g, 13 mmol), potassium carbonate (1.4 g, 10 mmol), copper powder (318 mg, 5.0 mmol), cupric iodide (190 mg, 1.0 mmol) and toluene (20 mL) was refluxed for 63 h. The mixture was poured into saturated ammonium chloride solution, adjusted to pH 8 with 10% NaOH *aq.*, and then extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated. The residue was purified using MPLC (silica gel, *n*-hexane/ethyl acetate=93/7→72/28) to obtain the title compound as an orange solid (1.4 g, 80% yield). ^{1}H NMR($CDCl_3$, 500 MHz): δ 3.01 (s, 3H), 3.19 (s, 3H), 3.82 (s, 2H), 6.50 (dd, 1H, *J*=8.8, 5.0 Hz), 6.80 (dt, 1H, *J*=8.5, 2.9 Hz), 6.88 (dd, 1H, *J*=9.0, 2.9 Hz), 6.93 (t, 1H, *J*=8.0 Hz), 7.31 (d, 2H, *J*=8.0 Hz), 7.38 (br, 1H). LRMS-ESI (*m/z*): $[M+Na+4]^+$ 367, $[M+Na+2]^+$ 365, $[M+Na]^+$ 363.

*2-(2-((2,6-Dichlorophenyl)amino)-5-fluorophenyl)acetic acid (**1c**).* A mixture of **8c** (178 mg, 0.52 mmol), ethanol (6.0 mL), 5 M NaOH *aq.* (6.0 mL) was refluxed for 4 h. The reaction mixture was acidified with 6 M HCl and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated to give the title compound as a yellow solid (162 mg, 99% yield). Recrystallization from ethyl acetate/*n*-hexane yielded a yellow plate. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.85 (s, 2H), 6.54 (dd, 1H, *J*=8.8, 4.9 Hz), 6.56 (br, 1H), 6.85 (dd, 1H, *J*=8.4, 2.9 Hz), 6.97 (t, 1H, *J*=8.0 Hz), 6.98 (dd, 1H *J*=8.8, 2.9 Hz), 7.33 (d, 2H, *J*=8.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 37.9, 114.7 (d, *J*=22 Hz), 117.5 (d, *J*=24 Hz), 120.4 (d, *J*=8.4 Hz), 123.9, 126.1 (d, *J*=7.6 Hz), 128.8, 128.9, 138.0, 138.8 (d, *J*=2.2 Hz), 158.2 (d, *J*=242 Hz), 175.8. ^{19}F NMR ($CDCl_3$, 376 MHz): δ -121.0 (dt, *J*=8.2, 5.5 Hz). HRMS-ESI (*m/z*): $[M-H]^-$ calcd for $C_{14}H_9Cl_2NFO_2$, 311.9994 ; found, 311.9971 (-2.3 mmu).

Synthesis of 2-(2-((2,6-dichloro-4-fluorophenyl)amino)-5-fluorophenyl)acetic acid (1d):

*2-(2-((2,6-Dichloro-4-fluorophenyl)amino)-5-fluorophenyl)-N,N-dimethylacetamide (**8d**).* A mixture of **7b** (247 mg, 0.80 mmol), 2,6-dichloro-4-fluoroaniline (362 mg, 2.0 mmol), potassium carbonate (221 mg, 1.6 mmol), copper powder (51 mg, 0.80 mmol), cupric iodide (20 mg, 0.16 mmol) and toluene (4.0 mL) was refluxed for 64 h. The mixture was poured into saturated ammonium chloride solution, adjusted to pH 8 with 10% NaOH *aq.*, and then

extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated. The residue was purified using MPLC (silica gel, *n*-hexane/ethyl acetate=88/12→67/33) to obtain the title compound as a red-purple solid (261 mg, 90% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.00 (s, 3H), 3.21 (s, 3H), 3.82 (s, 2H), 6.40 (dd, 1H, *J*=8.8, 5.0 Hz), 6.79 (dt, 1H, *J*=8.4, 2.9 Hz), 6.88 (dd, 1H, *J*=8.9, 2.9 Hz), 7.13 (d, 2H, *J*=8.0 Hz), 7.41 (br, 1H). LRMS-ESI (*m/z*): $[M+Na+4]^+$ 385, $[M+Na+2]^+$ 383, $[M+Na]^+$ 381.

*2-(2-((2,6-Dichloro-4-fluorophenyl)amino)-5-fluorophenyl)acetic acid (**1d**).* A mixture of **8d** (224 mg, 0.66 mmol), ethanol (7.0 mL), 5 M NaOH *aq.* (7.0 mL) was refluxed for 3.0 hr. The reaction mixture was acidified with 6 M HCl and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated to give the title compound as a light brown solid (197 mg, 90% yield). Recrystallization from dichloromethane/*n*-hexane yielded a colorless needle. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.83 (s, 2H), 6.43 (br, 1H), 6.46 (dd, 1H, *J*=8.8, 4.9 Hz), 6.85 (dt, 1H, *J*=8.6, 2.9 Hz), 6.98 (dd, 1H, *J*=8.8, 2.9 Hz), 7.14 (d, 1H, *J*=7.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 38.0, 114.9 (d, *J*=22 Hz), 116.4 (d, *J*=25 Hz), 117.6 (d, *J*=24 Hz), 119.3 (d, *J*=8.4 Hz), 125.4 (d, *J*=7.6 Hz), 130.0 (d, *J*=12 Hz), 134.6 (d, *J*=3.8 Hz), 138.9 (d, *J*=2.3 Hz), 157.6 (d, *J*=248 Hz), 158.1 (d, *J*=242 Hz), 177.6. ^{19}F NMR ($CDCl_3$, 376 MHz): δ -116.5 (t, *J*=8.2 Hz), -121.3 (dt, *J*=8.2, 5.5 Hz). HRMS-ESI (*m/z*): $[M-H]^-$ calcd for $C_{14}H_9Cl_2NF_2O_2$, 329.9900 ; found, 329.9872 (-2.8 mmu).

Synthesis of 2-(2-((2,6-dichlorophenyl)amino)phenyl)-2,2-difluoroacetic acid (2a):

*Ethyl 2-(2-((2,6-dichlorophenyl)amino)phenyl)acetate (**9a**).* Sulfuric acid (98%, 1.0 mL) was added to a solution of diclofenac (1.2 g, 4.0 mmol) in ethanol (15 mL), and the mixture was refluxed for 2 h. The solvent was evaporated, and the residue was dissolved in chloroform. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate and evaporated. The crude product was purified using MPLC (silica gel, *n*-hexane/ethyl acetate=88/12→67/33) to obtain the title compound as a white solid (906 mg, 70% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.29 (t, 3H, *J*=7.1 Hz), 3.80 (s, 2H), 4.20 (q, 2H, *J*=7.1 Hz), 6.55 (d, 1H, *J*=8.0 Hz), 6.94–6.97 (m, 2H), 6.98 (t, 1H, *J*=8.1 Hz), 7.12 (dt, 1H, *J*=7.7, 1.5 Hz), 7.23 (dd, 1H, *J*=7.5, 1.4 Hz), 7.34 (d, 2H, *J*=8.1 Hz).

*1-(2,6-dichlorophenyl)-3,3-difluoroindoline-2-one (**10a**).* A solution of **14a** (324 mg, 1.0 mmol) in anhydrous tetrahydrofuran (THF, 6.0 mL) was cooled to -78°C. To the mixture lithium bis(trimethylsilyl)amide (1.1 mol/L in THF, 2.0 mL) was added. After 20 min, *N*-fluorobenzenesulfonimide (694 mg, 2.2 mmol) dissolved in anhydrous THF (2.0 mL) was added, and the resulting mixture was stirred for 2 h. 0.2 M HCl was added to quench the reaction, and the mixture was extracted by chloroform. The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated to obtain the title compound as a pink solid (316 mg, quantitative yield). This product was used without further purification. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.49 (d, 1H, *J*=8.0 Hz), 7.25 (t, 1H, *J*=7.7 Hz), 7.43 (dd, 1H, *J*=8.8, 7.5 Hz), 7.44 (dt, 1H, *J*=7.8, 1.3 Hz), 7.529 (d, 1H, *J*=7.6 Hz), 7.530 (d, 1H, *J*=8.4 Hz), 7.67 (dd, 1H, *J*=7.5, 1.4 Hz). ^{19}F NMR ($CDCl_3$, 471 MHz): δ -109.9.

*2-(2-((2,6-dichlorophenyl)amino)phenyl)-2,2-difluoroacetic acid (**2a**).* To a solution of **10a** (115 mg, 0.37 mmol) in water (1.0 mL) and methanol (2.0 mL) was added 1.0 M NaOH *aq.* (366 μL, 0.37 mmol). After stirring at room temperature for 2 h, the solvent was evaporated, and the crude product was purified using MPLC (ODS, water/methanol=84/16→59/41) to obtain the title compound as a light yellow solid (110 mg, 90% yield). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 6.22 (d, 1H, *J*=8.1 Hz), 6.78 (t, 1H, *J*=7.4 Hz), 7.12 (t, 1H, *J*=7.3 Hz), 7.16 (t, 1H, *J*=8.1 Hz), 7.35 (dd, 1H, *J*=7.8, 1.4 Hz), 7.49 (d, 1H, *J*=8.1 Hz), 10.15 (br, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 114.7, 115.3 (t, *J*=254 Hz), 118.0, 122.8, (t, *J*=26 Hz), 125.3, 125.7 (t, *J*=9.0 Hz), 129.0, 129.5, 130.6, 136.5, 142.4 (t, *J*=4.0 Hz), 165.9 (t, *J*=28 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz): δ -101.9. HRMS-ESI (*m/z*): $[M-H]^-$ calcd for $C_{14}H_8Cl_2NF_2O_2$, 329.9900 ; found, 329.9859 (-4.2 mmu).

Synthesis of 2-(2-((2,6-dichloro-4-fluorophenyl)amino)phenyl)-2,2-difluoroacetic acid (2b):

*Ethyl 2-(2-((2,6-dichloro-4-fluorophenyl)amino)phenyl)acetate (**9b**).* Sulfuric acid (98%, 0.5 mL) was added to a solution of **1b** (620 mg, 2.0 mmol) in ethanol (8.0 mL), and the mixture was refluxed for 1 h. The solvent was evaporated and the residue was dissolved in chloroform. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate and evaporated. The crude product was purified using MPLC (silica gel, *n*-hexane/ethyl acetate=88/12→67/33) to obtain the title compound as a cream solid (496 mg, 73% yield). ^{1}H

NMR ($CDCl_3$, 500 MHz): δ 1.28 (t, 3H, *J*=7.1 Hz), 3.78 (s, 2H), 4.19 (q, 2H, *J*=7.1 Hz), 6.45 (d, 1H, *J*=8.0 Hz), 6.83 (br, 1H), 6.92 (dt, 1H, *J*=7.5, 0.9 Hz), 7.10 (dt, 1H, *J*=7.9, 1.5 Hz), 7.14 (d, 2H, *J*=7.9 Hz), 7.22 (dd, 1H, *J*=7.5, 1.5 Hz).

*1-(2,6-dichloro-4-fluorophenyl)-3,3-difluoroindoline-2-one (**10b**).* A solution of **14b** (398 mg, 1.2 mmol) in anhydrous THF (6.0 mL) was cooled to -78°C. To the mixture lithium bis(trimethylsilyl)amide (1.1 mol/L in THF, 2.3 mL) was added. After 20 min, *N*-fluorobenzenesulfonimide (807 mg, 2.6 mmol) dissolved in anhydrous THF (3.0 mL) was added, and the resulting mixture was stirred for 2 h. 0.2 M HCl was added to quench the reaction, and the mixture was extracted by chloroform. The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated. The residue was purified using MPLC (silica gel, *n*-hexane/ethyl acetate=98/2→90/10) to obtain the title compound as a pink solid (189 mg, 49% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.50 (d, 1H, *J*=8.0 Hz), 7.25 (t, 1H, *J*=7.6 Hz), 7.30 (d, 2H, *J*=7.8 Hz), 7.45 (dt, 1H, *J*=7.9, 1.1 Hz), 7.66 (dd, 1H, *J*=7.5, 1.2 Hz). ^{19}F NMR ($CDCl_3$, 471 MHz): δ -105.7 (t, *J*=7.8 Hz), -109.8.

*2-(2-((2,6-dichloro-4-fluorophenyl)amino)phenyl)-2,2-difluoroacetic acid (**2b**).* To a solution of **10b** (123 mg, 0.37 mmol) in water (1.0 mL) and methanol (2.0 mL) was added 1.0 M NaOH *aq.* (370 μL, 0.37 mmol). After stirring at room temperature for 2 h, the solvent was evaporated, and the crude product was purified using MPLC (ODS, water/methanol=72/23→47/53) to obtain the title compound as a yellow solid (132 mg, 96% yield). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 6.16 (d, 1H, *J*=8.1 Hz), 6.76 (t, 1H, *J*=7.6 Hz), 7.10 (t, 1H, *J*=8.0 Hz), 7.34 (dd, 1H, *J*=7.8, 1.4 Hz), 7.55 (d, 2H, *J*=8.4 Hz), 10.14 (br, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 113.9, 115.3 (t, *J*=254 Hz), 116.7 (d, *J*=26 Hz), 117.7, 122.5, (t, *J*=26 Hz), 125.8 (t, *J*=9.0 Hz), 129.7, 132.1 (d, *J*=12 Hz), 133.6 (d, *J*=3.8 Hz), 142.9 (t, *J*=4.0 Hz), 157.7 (d, *J*=246 Hz), 165.7 (t, *J*=28 Hz). ^{19}F NMR (DMSO-d_6, 471 MHz): δ -94.6, -109.0 (t, *J*=8.4 Hz). HRMS-ESI (*m/z*): $[M-H]^-$ calcd for $C_{14}H_7Cl_2NF_3O_2$, 347.9806 ; found, 347.9768 (-3.8 mmu).

Synthesis of 2-(2-((2,6-dichlorophenyl)amino)-5-fluorophenyl)-2,2-difluoroacetic acid (2c):

*Ethyl 2-(2-((2,6-dichlorophenyl)amino)-5-fluorophenyl)acetate (**9c**).* Sulfuric acid (98%, 0.5

mL) was added to a solution of **1c** (628 mg, 2.0 mmol) in ethanol (8.0 mL), and the mixture was refluxed for 30 min. The solvent was evaporated and the residue was dissolved in chloroform. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate and evaporated. The crude product was purified using MPLC (silica gel, *n*-hexane/ethyl acetate=95/5→85/15) to obtain the title compound as a colorless paste (545 mg, 80% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.30 (t, 3H, *J*=7.1 Hz), 3.79 (s, 2H), 4.21 (q, 2H, *J*=7.1 Hz), 6.53 (dd, 1H, *J*=8.8, 5.0 Hz), 6.72 (br, 1H), 6.83 (dt, 1H, *J*=8.4, 3.0 Hz), 6.96 (t, 1H, *J*=8.1 Hz), 6.97 (dd, 1H, *J*=8.8, 3.3 Hz), 7.33 (d, 2H, *J*=8.1 Hz).

*1-(2,6-dichlorophenyl)-3,3,5-trifluoroindoline-2-one (**10c**).* A solution of **14c** (545 mg, 1.6 mmol) in anhydrous THF (15 mL) was cooled to -78°C. To the mixture lithium bis(trimethylsilyl)amide (1.1 mol/L in THF, 3.6 mL) was added. After 20 min, *N*-fluorobenzenesulfonimide (1.5 g, 4.8 mmol) dissolved in anhydrous THF (5.0 mL) was added, and the resulting mixture was stirred for 1 h. 0.2 M HCl was added to quench the reaction, and the mixture was extracted by ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated. The residue was purified using MPLC (silica gel, chloroform) to obtain the title compound as a pink solid (416 mg, 79% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.51 (dd, 1H, *J*=8.7, 3.8 Hz), 7.15 (t, 1H, *J*=8.7 Hz), 7.41 (d, 1H, *J*=9.0 Hz), 7.42 (t, 1H, *J*=8.8, 7.6 Hz), 7.5432 (d, 1H, *J*=7.9 Hz), 7.5433 (d, 1H, *J*=8.4 Hz). ^{19}F NMR ($CDCl_3$, 471 MHz): δ -110.0, -116.6 (dt, *J*=8.6, 3.5 Hz).

*2-(2-((2,6-dichlorophenyl)amino)-5-fluorophenyl)-2,2-difluoroacetic acid (**2c**).* To a solution of **10c** (166 mg, 0.50 mmol) in methanol (5.0 mL) was added 1.0 M NaOH *aq.* (500 μL, 0.50 mmol). After stirring at room temperature for 2 h, the solvent was evaporated, and the crude product was purified using MPLC (ODS, water/methanol=72/23→47/53) to obtain the title compound as a yellow solid (128 mg, 73% yield). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 6.24 (dd, 1H, *J*=8.9, 4.8 Hz), 7.00 (dt, 1H, *J*=8.5, 3.1 Hz), 7.10 (dd, 1H, *J*=9.8, 3.1 Hz), 7.14 (t, 1H, *J*=8.1 Hz), 7.48 (d, 2H, *J*=8.1 Hz), 10.10 (br, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 112.2–112.4 (m), 114.4, 116.0 (d, *J*=7.6 Hz), 116.4 (d, *J*=7.8 Hz), 124.3 (dt, *J*=27, 6.3 Hz), 125.0, 129.1, 130.0, 136.5, 155.1 (d, *J*=235 Hz), 164.9 (t, *J*=28 Hz). ^{19}F NMR (DMSO-d_6, 471 MHz): δ -95.1, -119.1 (dt, *J*=8.4, 5.0 Hz). HRMS-ESI (*m/z*): $[M-H]^-$ calcd for $C_{14}H_7Cl_2NF_3O_2$, 347.9806 ; found, 347.9782 (-2.4 mmu).

Synthesis of 2-(2-((2,6-dichloro-4-fluorophenyl)amino)-5-fluorophenyl)-2,2-difluoroacetic acid (2d):

*Ethyl 2-(2-((2,6-dichloro-4-fluorophenyl)amino)-5-fluorophenyl)acetate (**9d**).* Sulfuric acid (98%, 0.1 mL) was added to a solution of **1d** (228 mg, 0.7 mmol) in ethanol (5.0 mL), and the mixture was refluxed for 30 min. The solvent was evaporated and the residue was dissolved in chloroform. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate and evaporated. The crude product was purified using MPLC (silica gel, *n*-hexane/ethyl acetate=88/12→67/33) to obtain the title compound as a yellow paste (228 mg, 92% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.30 (t, 3H, *J*=7.1 Hz), 3.78 (s, 2H), 4.21 (q, 2H, *J*=7.1 Hz), 6.43 (dd, 1H, *J*=8.8, 4.9 Hz), 6.63 (br, 1H), 6.82 (dt, 1H, *J*=8.4, 3.0 Hz), 6.96 (dd, 1H, *J*=8.8, 2.9 Hz), 7.14 (d, 2H, *J*=7.9 Hz).

*1-(2,6-dichloro-4-fluorophenyl)-3,3,5-trifluoroindoline-2-one (**10d**).* A solution of **14d** (228 mg, 0.63 mmol) in anhydrous THF (15 mL) was cooled to -78°C. To the mixture lithium bis(trimethylsilyl)amide (1.1 mol/L in THF, 3.6 mL) was added. After 20 min, *N*-fluorobenzenesulfonimide (1.5 g, 4.8 mmol) dissolved in anhydrous THF (5.0 mL) was added, and the resulting mixture was stirred for 1 h. 0.2 M HCl was added to quench the reaction, and the mixture was extracted by chloroform. The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated. The residue was purified using MPLC (silica gel, chloroform) to obtain the title compound as a pink solid (154 mg, 69% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.46 (dd, 1H, *J*=8.6, 3.7 Hz), 7.17 (dt, 1H, *J*=8.7, 1.4 Hz), 7.32 (d, 2H, *J*=7.7 Hz), 7.41 (dd, 1H, *J*=6.8, 1.5 Hz). ^{19}F NMR ($CDCl_3$, 471 MHz): δ -105.2 (t, *J*=7.7 Hz), -109.9, -116.6 (dt, *J*=6.9, 3.4 Hz).

*2-(2-((2,6-dichloro-4-fluorophenyl)amino)-5-fluorophenyl)-2,2-difluoroacetic acid (**2d**).* To a solution of **10d** (154 mg, 0.44 mmol) in methanol (3.0 mL) was added 1.0 M NaOH *aq.* (440 μL, 0.44 mmol). After stirring at room temperature for 2 h, the solvent was evaporated, and the crude product was purified using MPLC (ODS, water/methanol=72/23→47/53) to obtain the title compound as a white solid (146 mg, 90% yield). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 6.19 (dd, 1H, *J*=8.8, 4.7 Hz), 6.99 (dt, 1H, *J*=8.5, 2.9 Hz), 7.10 (dd, 1H, *J*=9.7, 2.9 Hz), 7.56 (d, 2H, *J*=8.4 Hz), 9.98 (br, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 112.2–112.7 (m), 114.5 (t, *J*=255 Hz), 115.7 (d, *J*=7.6 Hz), 116.3 (d, *J*=22 Hz), 116.7 (d, *J*=25 Hz), 123.9 (dt, *J*=26, 6.4 Hz), 131.7 (d, *J*=12 Hz), 133.7 (d, *J*=3.6 Hz), 139.4, 155.0 (d, *J*=234 Hz), 157.60 (d,

J=246 Hz), 165.0 (t, *J*=28 Hz). ^{19}F NMR (DMSO-d_6, 471 MHz): δ -95.0, -109.0 (t, *J*=8.5 Hz), -119.5 (dt, *J*=8.6, 5.2 Hz). HRMS-ESI (*m/z*): $[M-H]^-$ calcd for $C_{14}H_6Cl_2NF_4O_2$, 365.9712 ; found, 365.9691 (-2.1 mmu).

Synthesis of *N*-(2-((1*H*-tetrazol-5-yl)methyl)phenyl)-2,6-dichloroaniline (3a):

*2-Iodo-N,N-dimethylbenzamide (**11a**).* To a solution of 2-iodobenzoic acid (5.0 g, 20 mmol) in anhydrous dichloromethane (40 mL) was added dropwise thionyl chloride (10 mL, 138 mmol) and stirred at 50°C for 2.5 h and evaporated. The residue was cooled to 0°C, and 40% w/w aqueous dimethylamine (20 mL) was added. After stirring for 30 min, saturated sodium bicarbonate solution was added and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and then evaporated to obtain the title compound as yellow oil (5.2 g, 95% yield). This product was used without further purification. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.85 (s, 3H), 3.14 (s, 3H), 7.06 (dt, 1H, *J*=7.6, 1.7 Hz), 7.21 (dd, 1H, *J*=7.6, 1.6 Hz), 7.39 (dt,1H, *J*=7.5, 1.1 Hz), 7.82 (dd, 1H, *J*=8.0, 0.8 Hz). LRMS-ESI (*m/z*): $[M+H]^+$ 276.

*2-((2,6-Dichlorophenyl)amino)-N,N-dimethylbenzamide (**12a**).* A mixture of **11a** (2.8 g, 10 mmol), 2,6-dichloroaniline (4.1 g, 25 mmol), potassium carbonate (2.8 g, 20 mmol), copper powder (636 mg, 10 mmol), cupric iodide (190 mg, 0.1 mmol) and toluene (40 mL) was refluxed for 90 h. The mixture was poured into saturated ammonium chloride solution, adjusted to pH 8 with 10% NaOH *aq.*, and then extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated. The residue was purified using MPLC (silica gel, *n*-hexane/ethyl acetate=71/29→50/50) to obtain the title compound as a brown paste (2.5 g, 82% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.12 (br, 6H), 6.47 (d, 1H, *J*=8.2 Hz), 6.88 (dt, 1H, *J*=7.6, 1.0 Hz), 7.03 (t, 1H, *J*=8.1 Hz), 7.17 (dt, 1H, *J*=7.7, 1.5 Hz), 7.21 (dd, 1H, *J*=7.6, 1.5 Hz), 7.31 (br, 1H), 7.36 (d, 2H, *J*=8.1 Hz). LRMS-ESI (*m/z*): $[M+Na+4]^+$ 335, $[M+Na+2]^+$ 333, $[M+Na]^+$ 331.

*2-((2,6-Dichlorophenyl)amino)benzoic acid (**13a**).* A mixture of **12a** (2.5 g, 8.2 mmol), ethanol (40 mL), water (40 mL), and sodium hydroxide (20 g, 489 mmol) was refluxed for 18 h. After evaporating ethanol, the reaction mixture was acidified with 2 M HCl and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated to give the title compound as an orange solid (2.0 g, 86% yield). ^{1}H

NMR (DMSO-d_6, 500 MHz): δ 6.22 (d, 1H, *J*=8.4 Hz), 6.79 (t, 1H, *J*=8.0 Hz), 7.33 (dt, 1H, *J*=8.6, 1.6 Hz), 7.37 (t, 1H, *J*=8.1 Hz), 7.62 (d, 2H, *J*=8.1 Hz), 7.90 (dd, 1H, *J*=7.9, 1.5 Hz), 9.54 (br, 1H), 13.14 (br, 1H). LRMS-ESI (*m/z*): $[M-H+4]^-$ 284, $[M-H+2]^-$ 282, $[M-H]^-$ 280.

*(2-((2,6-Dichlorophenyl)amino)phenyl)methanol (**14a**)*. A solution of **13a** (564 mg, 2.0 mmol) in anhydrous tetrahydrofuran (20 mL) was added slowly to lithium aluminum hydride (380 mg, 10 mmol) at 0°C under a nitrogen atmosphere. After warming to room temperature, the reaction mixture was refluxed for 9 h, and sodium sulfate was added to destroy excess $LiAlH_4$. The resulting mixture was filtered through Celite and washed with ethyl acetate, and the filtrate was evaporated. The residue was purified using MPLC (silica gel, *n*-hexane/ethyl acetate=87/13→66/34) to obtain the title compound as a cream solid (444 mg, 83% yield). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 4.61 (d, 2H, *J*=5.2 Hz), 5.49 (t, 1H, *J*=5.2 Hz), 6.21 (d, 1H, *J*=7.9 Hz), 6.80 (dt, 1H, *J*=7.4, 1.0 Hz), 7.06 (dt, 1H, *J*=7.6, 1.4 Hz), 7.22 (t, 1H, *J*=8.1 Hz), 7.23 (dd, 1H, *J*=7.4, 1.3 Hz), 7.43 (br, 1H), 7.55 (d, 2H, *J*=8.1 Hz).

*(2-((2,6-Dichlorophenyl)amino)phenyl)acetonitrile (**15a**)*. To a solution of **14a** (536 mg, 2.0 mmol) in anhydrous THF (20 mL), anhydrous pyridine (969 μL, 12 mmol) and thionyl chloride (859 μL, 12 mmol) were added. The reaction mixture was stirred at room temperature for 30 min, and 2 M HCl was added. The mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated to yield crude chloride intermediate. Then, the crude product was dissolved in anhydrous DMSO (15 mL) and added to sodium cyanide (404 mg, 8.2 mmol) under a nitrogen atmosphere. After stirring at 40°C for 1.5 h, saturated sodium bicarbonate *aq.* was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated. The residue was purified using MPLC (silica gel, *n*-hexane/ethyl acetate=95/5→74/26) to obtain the title compound as a yellow paste (385 mg, 69% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.85 (s, 2H), 5.59 (br, 1H), 6.60 (d, 1H, *J*=8.0 Hz), 7.01 (t, 1H, *J*=8.1 Hz), 7.07 (t, 1H, *J*=7.4 Hz), 7.20 (dt, 1H, *J*=6.6, 1.2 Hz), 7.34 (d, 2H, *J*=8.1 Hz), 7.39 (d, 1H, *J*=6.8 Hz). LRMS-ESI (*m/z*): $[M+H+4]^+$ 281, $[M+H+2]^+$ 279, $[M+H]^+$ 277.

*N-(2-((1H-Tetrazol-5-yl)methyl)phenyl)-2,6-dichloroaniline (**3a**).* A mixture of **15a** (385 mg, 1.4 mmol), sodium azide (903 mg, 14 mmol), ammonium chloride (743 mg, 14 mmol) and anhydrous *N*,*N*-dimethylformamide (DMF, 8.0 mL) was stirred at 120°C under a nitrogen

atmosphere. After 8.5 h, 2 M HCl was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated. The residue was purified using MPLC (silica gel, *n*-hexane/ethyl acetate=20/80→0/100) to obtain the title compound as a brown solid (339 mg, 81% yield). Recrystallization from toluene yielded a light orange needle. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.45 (s, 2H), 6.20 (br, 1H), 6.52 (d, 1H, *J*=8.1 Hz), 6.99 (t, 1H, *J*=7.5 Hz), 7.09 (t, 1H, *J*=8.1 Hz), 7.17 (dt, 1H, *J*=7.9, 1.4 Hz), 7.31 (dd, 1H, *J*=7.5, 1.2 Hz), 7.39 (d, 2H, *J*=8.1 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 27.2, 117.7, 122.8, 123.9, 125.7, 129.07, 129.10, 130.5, 131.0, 136.7, 141.8. HRMS-ESI (*m/z*): $[M-H]^-$ calcd for $C_{14}H_{10}Cl_2N_5$, 318.0313 ; found, 318.0268 (-4.2 mmu).

Synthesis of *N*-(2-((1*H*-tetrazol-5-yl)methyl)phenyl)-2,6-dichloro-4-fluoroaniline (3b):

*2-((2,6-Dichloro-4-fluorophenyl)amino)-N,N-dimethylbenzamide (**12b**).* A mixture of **11a** (550 mg, 2.0 mmol), 2,6-dichloro-4-fluoroaniline (900 mg, 5.0 mmol), potassium carbonate (553 mg, 4.0 mmol), copper powder (127 mg, 2.0 mmol), cupric iodide (79 mg, 0.4 mmol) and toluene (8.0 mL) was refluxed for 96 h. The mixture was poured into saturated ammonium chloride solution, adjusted to pH 8 with 10% NaOH *aq.*, and then extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated. The residue was purified using MPLC (silica gel, *n*-hexane/ethyl acetate=87/13→66/34) to obtain the title compound as a brown paste (580 mg, 89% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.12 (br, 6H), 6.39 (d, 1H, *J*=8.2 Hz), 6.86 (dt, 1H, *J*=7.5, 1.0 Hz), 7.16 (d, 2H, *J*=8.0 Hz), 7.18 (dd, 1H, *J*=7.6, 1.2 Hz), 7.22 (dd, 1H, *J*=7.6, 1.5 Hz), 7.23 (br, 1H). ^{19}F NMR ($CDCl_3$, 471 MHz): δ -114.9 (t, *J*=8.1 Hz). LRMS-ESI (*m/z*): $[M+Na+4]^+$ 353, $[M+Na+2]^+$ 351, $[M+Na]^+$ 349.

*2-((2,6-Dichloro-4-fluorophenyl)amino)benzoic acid (**13b**).* A mixture of **12b** (580 mg, 1.8 mmol), ethanol (10 mL), water (10 mL), and sodium hydroxide (4.3 g, 108 mmol) was refluxed for 17 h. After evaporating ethanol, the reaction mixture was acidified with 2 M HCl and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated to give the title compound as a red orange solid (603 mg, quantitative yield). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 6.02 (d, 1H, *J*=8.1 Hz), 6.58 (t, 1H, *J*=7.6 Hz), 7.02 (t, 1H, *J*=7.2 Hz), 7.13 (br, 1H), 7.59 (d, 2H, *J*=8.4 Hz), 7.86 (d, 1H,

J=7.6 Hz), 11.97 (br, 1H). LRMS-ESI (*m/z*): $[M-H+4]^-$ 302, $[M-H+2]^-$ 300, $[M-H]^-$ 298.

*(2-((2,6-Dichloro-4-fluorophenyl)amino)phenyl)methanol (**14b**)*. A solution of **13b** (390 mg, 1.3 mmol) in anhydrous tetrahydrofuran (10 mL) was added slowly to lithium aluminum hydride (247 mg, 6.5 mmol) at 0°C under a nitrogen atmosphere. After warming to room temperature, the reaction mixture was refluxed for 9 h, and sodium sulfate was added to destroy excess $LiAlH_4$. The resulting mixture was filtered through Celite and washed with ethyl acetate, and the filtrate was evaporated. The residue was purified using MPLC (silica gel, *n*-hexane/ethyl acetate=100/0→92/8→75/25) to obtain the title compound as a brown solid (154 mg, 41% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.81 (d, 2H, *J*=5.2 Hz), 6.36 (d, 1H, *J*=8.0 Hz), 6.85 (dt, 1H, *J*=7.4, 1.0 Hz), 6.90 (br, 1H), 7.13 (dt, 1H, *J*=7.9, 1.9 Hz), 7.16 (d, 2H, *J*=7.9 Hz), 7.17 (dd, 1H, *J*=7.4, 1.4 Hz).

*(2-((2,6-Dichloro-4-fluorophenyl)amino)phenyl)acetonitrile (**15b**)*. To a solution of **14b** (154 mg, 0.54 mmol) in anhydrous THF (10 mL), anhydrous pyridine (261 μL, 3.2 mmol) and thionyl chloride (231 μL, 3.2 mmol) were added. The reaction mixture was stirred at room temperature for 30 min, and 2 M HCl was added. The mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated to yield crude chloride intermediate. Then, the crude product was dissolved in anhydrous DMSO (5.0 mL) and added to sodium cyanide (109 mg, 2.2 mmol) under a nitrogen atmosphere. After stirring at 40°C for 1 h, saturated sodium bicarbonate *aq.* was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated. The residue was purified using MPLC (silica gel, *n*-hexane/ethyl acetate=100/0→75/25) to obtain the title compound as a yellow paste (93 mg, 59% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.83 (s, 2H), 5.42 (br, 1H), 6.50 (d, 1H, *J*=8.0 Hz), 7.03 (t, 1H, *J*=7.4 Hz), 7.17 (d, 2H, *J*=8.0 Hz), 7.20 (d, 1H, *J*=7.6 Hz), 7.37 (d, 1H, *J*=7.6 Hz).

*N-(2-((1H-Tetrazol-5-yl)methyl)phenyl)-2,6-dichloro-4-fluoroaniline (**3b**).* A mixture of **15b** (93 mg, 0.32 mmol), sodium azide (205 mg, 3.2 mmol), ammonium chloride (169 mg, 3.2 mmol) and anhydrous DMF (2.0 mL) was stirred at 120°C under a nitrogen atmosphere. After 24 h, 2 M HCl was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated. The residue was

purified using MPLC (silica gel, *n*-hexane/ethyl acetate/mehtanol=87/13/0→66/34/0 → 0/100/0→0/90/10) to obtain the title compound as a brown solid (61 mg, 58% yield). Recrystallization from toluene yielded a brown needle. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 4.37 (s, 2H), 6.19 (d, 1H, *J*=7.9 Hz), 6.82 (dd, 1H, *J*=7.4, 1.0 Hz), 7.02 (d, 1H, *J*=7.6 Hz), 7.05 (t, 1H, *J*=7.5 Hz), 7.32 (br, 1H), 7.62 (d, 2H, *J*=8.4 Hz). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 25.3, 114.7, 116.6 (d, *J*=26 Hz), 120.1, 123.4, 127.9, 129.7, 132.7 (d, *J*=12 Hz), 133.9 (d, *J*=4.1 Hz), 142.8, 158.1 (d, *J*=247 Hz). ^{19}F NMR (DMSO-d_6, 471 MHz): δ -107.8 (t, *J*=8.3 Hz). HRMS-ESI (*m/z*): $[M-H]^-$ calcd for $C_{14}H_9Cl_2FN_5$, 336.0219 ; found, 336.0183 (-3.6 mmu).

Synthesis of *N*-(2-((1*H*-tetrazol-5-yl)methyl)-4-fluorophenyl)-2,6-dichloroaniline (3c):

*5-Fluoro-2-iodo-N,N-dimethylbenzamide (**11b**).* To a solution of 5-fluoro-2-iodobenzoic acid (4.0 g, 15 mmol) in anhydrous dichloromethane (30 mL) was added dropwise thionyl chloride (7.6 mL, 105 mmol) and stirred at 50°C for 2 h and evaporated. The residue was cooled to 0°C, and 40% w/w aqueous dimethylamine (15 mL) was added. After stirring for 30 min, saturated sodium bicarbonate solution was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and then evaporated to obtain the title compound as an orange paste (4.1 g, 93% yield). This product was used without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.86 (s, 3H), 3.14 (s, 3H), 6.83 (dt, 1H, *J*=8.8, 2.9 Hz), 6.97 (dd, 1H, *J*=8.2, 2.9 Hz), 7.76 (dd,1H, *J*=8.8, 5.3 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz): δ -112.64 (dt, 1H, *J*=8.2, 5.5 Hz).

*2-((2,6-Dichlorophenyl)amino)-5-fluoro-N,N-dimethylbenzamide (**12c**).* A mixture of **11b** (1.2 g, 4.0 mmol), 2,6-dichloroaniline (1.4 g, 10 mmol), potassium carbonate (1.1 g, 8.0 mmol), copper powder (255 mg, 4.0 mmol), cupric iodide (152 mg, 0.8 mmol) and toluene (16 mL) was refluxed for 85 h. The mixture was poured into saturated ammonium chloride solution, adjusted to pH 8 with 10% NaOH *aq.*, and then extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated. The residue was purified using MPLC (silica gel, *n*-hexane/ethyl acetate=90/10→69/31) to obtain the title compound as a brown paste (835 mg, 64% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.11 (br,

6H), 6.44 (dd, 1H, *J*=8.9, 4.6 Hz), 6.90 (dt, 1H, *J*=8.5, 3.0 Hz), 6.94 (dd, 1H, *J*=8.3, 2.9 Hz), 6.99 (br, 1H), 7.03 (t, 1H, *J*=8.1 Hz), 7.35 (d, 2H, *J*=8.1 Hz). ^{19}F NMR ($CDCl_3$, 471 MHz): δ -123.7 (dt, *J*=8.7, 5.2 Hz). LRMS-ESI (*m/z*): $[M+Na+4]^+$ 353, $[M+Na+2]^+$ 351, $[M+Na]^+$ 349.

*2-((2,6-Dichlorophenyl)amino)-5-fluorobenzoic acid (**13c**).* A mixture of **12c** (835 mg, 2.6 mmol), ethanol (20 mL), water (20 mL), and sodium hydroxide (6.1 g, 153 mmol) was refluxed for 12 h. After evaporating ethanol, the reaction mixture was acidified with 2 M HCl and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated to give the title compound as a white solid (736 mg, 96%). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 6.24 (dd, 1H, *J*=9.2, 4.5 Hz), 7.25 (ddd, 1H, *J*=9.1, 8.0, 3.2 Hz), 7.37 (t, 1H, *J*=8.1 Hz), 7.620 (dd, *J*=9.5, 4.6 Hz), 7.624 (d, 2H, *J*=8.1 Hz), 9.34 (br, 1H), 13.50 (br, 1H). LRMS-ESI (*m/z*): $[M-H+4]^-$ 302, $[M-H+2]^-$ 300, $[M-H]^-$ 298.

*(2-((2,6-Dichlorophenyl)amino)-5-fluorophenyl)methanol (**14c**).* A solution of **13c** (300 mg, 1.0 mmol) in anhydrous tetrahydrofuran (10 mL) was added slowly to lithium aluminum hydride (190 mg, 5.0 mmol) at 0°C under a nitrogen atmosphere. After warming to room temperature, the reaction mixture was refluxed for 30 min, and sodium sulfate was added to destroy excess $LiAlH_4$. The resulting mixture was filtered through Celite and washed with ethyl acetate, and the filtrate was evaporated to obtain the title compound as a yellow solid (277 mg, 97% yield). This compound was used without further purification. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.91 (br, 1H), 4.81 (br, 2H), 6.42 (dd, 1H, *J*=8.8, 4.7 Hz), 6.78 (br, 1H), 6.85 (dt, 1H, *J*=8.5, 3.0 Hz), 6.97 (dd, 1H, *J*=8.6, 3.0 Hz), 7.03 (t, 1H, *J*=8.1 Hz), 7.36 (d, 2H, *J*=8.1 Hz).

*(2-((2,6-Dichlorophenyl)amino)-5-fluorophenyl)acetonitrile (**15c**).* To a solution of **14c** (277 mg, 0.97 mmol) in anhydrous THF (10 mL), anhydrous pyridine (468 μL, 5.8 mmol) and thionyl chloride (416 μL, 5.8 mmol) were added. The reaction mixture was stirred at room temperature for 30 min, and 2 M HCl was added. The mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated to yield crude chloride intermediate. Then, the crude product was dissolved in anhydrous DMSO (8.0 mL) and added to sodium cyanide (192 mg, 3.9 mmol) under a nitrogen atmosphere. After stirring at 40°C for 1.5 h, saturated sodium bicarbonate *aq.* was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated. The residue was purified using MPLC (silica gel, *n*-hexane/ethyl acetate=98/2→90/10) to obtain the title compound as a

yellow paste (155 mg, 54% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.87 (s, 2H), 5.46 (br, 1H), 6.35 (dd, 1H, *J*=8.8, 4.9 Hz), 6.92 (dt, 1H, *J*=8.5, 2.9 Hz), 7.00 (t, 1H, *J*=8.1 Hz), 7.17 (dd, 1H, *J*=8.6, 2.9 Hz), 7.36 (d, 2H, *J*=8.1 Hz).

*N-(2-((1H-tetrazol-5-yl)methyl)-4-fluorophenyl)-2,6-dichloroaniline (**3c**).* A mixture of **15c** (155 mg, 0.53 mmol), sodium azide (341 mg, 5.3 mmol), ammonium chloride (281 mg, 5.3 mmol) and anhydrous DMF (3.3 mL) was stirred at 120°C under a nitrogen atmosphere. After 10 h, 2 M HCl was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated. The residue was purified using MPLC (silica gel, *n*-hexane/ethyl acetate =40/60→0/100) to obtain the title compound as a light brown solid (127 mg, 71% yield). Recrystallization from toluene yielded a white needle. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 4.41 (s, 2H), 6.31 (dd, 1H, *J*=8.8, 5.0 Hz), 6.94 (dt, 1H, *J*=8.6, 3.0 Hz), 7.02 (dd, 1H, *J*=9.4, 3.0 Hz), 7.17 (br, 1H), 7.17 (t, 1H, *J*=8.0 Hz), 7.50 (d, 2H, *J*=8.1 Hz). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 26.0, 114.7 (d, *J*=22 Hz), 117.1 (d, *J*=23 Hz), 118.8 (d, *J*=8.3 Hz), 126.1, 127.8 (d, *J*=7.5 Hz), 129.7, 130.5, 138.0, 139.6 (d, *J*=2.3 Hz), 155.0, 157.3 (d, *J*=237 Hz). ^{19}F NMR (DMSO-d_6, 471 MHz): δ -115.92 (dt, *J*=8.7, 5.2 Hz). HRMS-ESI (*m/z*): $[M-H]^-$ calcd for $C_{14}H_9Cl_2FN_5$, 336.0219 ; found, 336.0171 (-4.2 mmu).

Synthesis of *N*-(2-((1*H*-tetrazol-5-yl)methyl)-4-fluorophenyl)-2,6-dichloro-4-fluoroaniline (3d):

*2-((2,6-Dichloro-4-fluorophenyl)amino)-5-fluoro-N,N-dimethylbenzamide (**12d**).* A mixture of **11b** (1.5 g, 5.0 mmol), 2,6-dichloro-4-fluoroaniline (2.3 g, 13 mmol), potassium carbonate (1.4 g, 10 mmol), copper powder (318 mg, 5.0 mmol), cupric iodide (190 mg, 1.0 mmol) and toluene (20 mL) was refluxed for 84 h. The mixture was poured into saturated ammonium chloride solution, adjusted to pH 8 with 10% NaOH *aq.*, and then extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated. The residue was purified using MPLC (silica gel, *n*-hexane/ethyl acetate=61/39→40/60) to obtain the title compound as a brown paste (1.5 g, 88% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.12 (br, 6H), 6.35 (dd, 1H, *J*=8.9, 4.5 Hz), 6.90 (dt, 1H, *J*=8.5, 2.9 Hz), 6.92 (br, 1H), 6.95 (dd, 1H, *J*=8.3, 2.9 Hz), 7.16 (d, 2H, *J*=7.9 Hz). ^{19}F NMR ($CDCl_3$, 471 MHz): δ -114.9 (t, *J*=8.2 Hz), -123.7 (dt, *J*=8.6, 5.1 Hz). LRMS-ESI (*m/z*): $[M+Na+4]^+$ 371,

$[M+Na+2]^+$ 369, $[M+Na]^+$ 367.

*2-((2,6-Dichloro-4-fluorophenyl)amino)-5-fluorobenzoic acid (**13d**).* A mixture of **12d** (1.5 g, 4.4 mmol), ethanol (25 mL), water (25 mL), and sodium hydroxide (11 g, 264 mmol) was refluxed for 13 h. After evaporating ethanol, the reaction mixture was acidified with 2 M HCl and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated to give the title compound as a light purple solid (1.3 g, 91%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.26 (dd, 1H, *J*=9.2, 4.4 Hz), 7.10 (ddd, 1H, *J*=9.2, 7.5, 3.1 Hz), 7.22 (d, 2H, *J*=7.9 Hz), 7.75 (dd, 1H, *J*=9.2, 3.1 Hz), 8.87 (br, 1H). LRMS-ESI (*m/z*): $[M-H+4]^-$ 320, $[M-H+2]^-$ 318, $[M-H]^-$ 316.

*(2-((2,6-Dichloro-4-fluorophenyl)amino)-5-fluorophenyl)methanol (**14d**)*. A solution of **13d** (318 mg, 1.0 mmol) in anhydrous tetrahydrofuran (10 mL) was added slowly to lithium aluminum hydride (114 mg, 3.0 mmol) at 0°C under a nitrogen atmosphere. After warming to room temperature, the reaction mixture was stirred for 7 h at 45°C, 1 h at 55°C, and 1 h at 60°C. After that, sodium sulfate was added to destroy excess $LiAlH_4$. The resulting mixture was filtered through Celite and washed with ethyl acetate, and the filtrate was evaporated. The residue was purified using MPLC (silica gel, *n*-hexane/ethyl acetate=87/13) to obtain the title compound as a white solid (78 mg, 26% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.80 (s, 2H), 6.32 (dd, 1H, *J*=8.8, 4.7 Hz), 6.67 (br, 1H), 6.85 (dt, 1H, *J*=8.5, 3.0 Hz), 6.96 (dd, 1H, *J*=8.6, 3.0 Hz), 7.17 (d, 2H, *J*=7.9 Hz).

*(2-((2,6-Dichloro-4-fluorophenyl)amino)-5-fluorophenyl)acetonitrile (**15d**)*. To a solution of **14d** (152 mg, 0.50 mmol) in anhydrous THF (5.0 mL), anhydrous pyridine (242 μL, 3.0 mmol) and thionyl chloride (215 μL, 3.0 mmol) were added. The reaction mixture was stirred at room temperature for 30 min, and 2 M HCl was added. The mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated to yield crude chloride intermediate. Then, the crude product was dissolved in anhydrous DMSO (4.0 mL) and added to sodium cyanide (98 mg, 2.0 mmol) under a nitrogen atmosphere. After stirring at 40°C for 1 h, saturated sodium bicarbonate *aq.* was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated. The residue was purified using MPLC (silica gel, *n*-hexane/ethyl acetate=100/0→79/21) to obtain the title compound as a yellow paste (86 mg, 55% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.86 (s, 2H), 5.30 (br, 1H), 6.53 (dd, 1H, *J*=8.8, 4.9 Hz), 6.91 (dt, 1H, *J*=8.3, 2.9 Hz), 7.14 (d, 2H, *J*=7.9 Hz), 7.15 (dd, 1H, *J*=8.6, 2.9

Hz).

*N-(2-((1H-Tetrazol-5-yl)methyl)-4-fluorophenyl)-2,6-dichloro-4-fluoroaniline (**3d**).* A mixture of **15d** (86 mg, 0.27 mmol), sodium azide (179 mg, 2.7 mmol), ammonium chloride (147 mg, 2.7 mmol) and anhydrous DMF (1.5 mL) was stirred at 120°C under a nitrogen atmosphere. After 11 h, 2 M HCl was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated. The residue was purified using MPLC (silica gel, *n*-hexane/ethyl acetate =20/80→0/100) to obtain the title compound as brown a paste (69 mg, 70% yield). Recrystallization from toluene yielded a brown needle. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 4.40 (s, 2H), 6.25 (dd, 1H, *J*=8.8, 5.0 Hz), 6.91 (dt, 1H, *J*=8.6, 3.0 Hz), 6.98 (dd, 1H, *J*=9.4, 3.0 Hz), 7.14 (br, 1H), 7.59 (d, 2H, *J*=8.4 Hz). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 25.4, 114.3 (d, *J*=22 Hz), 116.68 (d, *J*=23 Hz), 116.71 (d, *J*=26 Hz), 117.1 (d, *J*=8.2 Hz), 126.3 (d, *J*=7.4 Hz), 131.8 (d, *J*=12 Hz), 134.4 (d, *J*=4.0 Hz), 139.4, 156.6 (d, *J*=237 Hz), 157.9 (d, *J*=247 Hz). ^{19}F NMR (DMSO-d_6, 471 MHz): δ -108.3 (t, *J*=8.6 Hz), -116.7 (dt, *J*=8.5, 5.0 Hz). HRMS-ESI (*m/z*): $[M-H]^-$ calcd for $C_{14}H_8Cl_2F_2N_5$, 336.0125 ; found, 354.0079 (-4.6 mmu).

Synthesis of (2-((2,6-dichlorophenyl)amino)phenyl)methanesulfonic acid (4a):

Phosphorus tribromide (274 mg, 1.0 mmol) was added to a solution of **14a** (247 mg, 0.92 mmol) in anhydrous dichloromethane (4.0 mL) at 0°C. The reaction mixture was stirred at room temperature for 15 h, and then the reaction was quenched by several drops of water. The mixture was dried with anhydrous sodium sulfate and evaporated. The resulting crude bromide intermediate was dissolved in acetone (12 mL), and a solution of sodium sulfite (139 mg, 1.1 mmol) in water (6.0 mL) was added. After stirring at 100°C for 24 h, the mixture was filtered. The filtrate was acidified with 2 M HCl and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated to obtain the title compound as a cream solid (81 mg, 26% yield). Recrystallization from acetone yielded the pink needle. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 3.91 (s, 2H), 6.33 (d, 1H, *J*=7.9 Hz), 6.87 (t, 1H, *J*=7.4 Hz), 7.03 (dt, 1H, *J*=7.6, 1.4 Hz), 7.08 (t, 1H *J*=8.0 Hz), 7.16 (dd, 1H, *J*=7.5, 1.4 Hz), 7.46 (d, 1H, *J*=8.1 Hz), 8.42 (br, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 55.1, 116.9, 120.8, 123.9, 125.2, 126.8, 128.3, 129.0, 132.2, 137.8, 143.0. HRMS-ESI (*m/z*): $[M-H]^-$ calcd for $C_{13}H_{10}Cl_2NO_3S$, 329.9758; found, 329.9714 (-4.5 mmu).

Synthesis of (2-((2,6-dichlorophenyl)amino)phenyl)methanesulfonamide (5a).

*2-Nitrobenzylsulfonamide (**16**).* A mixture of 2-nitrobenzyl chloride (513 mg, 3.0 mmol) and thiourea (274 mg, 3.6 mmol) in ethanol (5.0 mL) was refluxed for 4.5 h. After evaporating ethanol, the crude product was added to a mixture of *N*-chlorosuccinimide (1.6 g, 12 mmol), 2 M HCl (1.0 mL) and acetonitrile (20 mL). The mixture was stirred for 16 h in a water bath, then ethyl acetate (50 mL) and water (20 mL) were added, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated. The obtained product was dissolved in THF (5.0 mL), and 28% aqueous ammonia (4.0 mL) was added to the solution. After stirring at room temperature for 1 h, ethyl acetate (20 mL) and saturated ammonium chloride *aq.* (20 mL) was added. After acidification with 2 M HCl, the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated to obtain the title compound as a white solid (282 mg, 43% yield). This product was used without further purification. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 4.77 (s, 2H), 7.06 (br, 2H), 7.60 (dd, 1H, *J*=7.7, 1.2 Hz), 7.63 (dt, 1H, *J*=8.0, 1.3 Hz), 7.75 (dt, 1H, *J*=7.6, 1.3 Hz), 8.00 (dd, 1H, *J*=8.1, 1.2 Hz). LRMS-ESI (*m/z*): $[M-H]^-$ 215.

*2-Aminobenzylsulfonamide (**17**).* A mixture of **16** (253 mg, 1.2 mmol), ammonium chloride (94 mg, 1.8 mmol), Fe powder (198 mg, 3.5 mmol), ethanol (15 mL) and water (15 mL) was refluxed for 1.5 h. After removal of iron by filtration, the filtrate was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated to obtain the title compound as a light yellow paste (180 mg, 83% yield). This product was used without further purification. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.35 (s, 2H), 4.88 (br, 2H), 6.75 (dd, 1H, *J*=7.5, 1.1 Hz), 6.81 (dt, 1H, *J*=8.0, 0.9 Hz), 7.15 (dd, 1H, *J*=7.6, 1.3 Hz), 7.18 (dd, 1H, *J*=8.0, 1.5 Hz). LRMS-ESI (*m/z*): $[M-H]^-$ 185.

*(2-((2,6-Dichlorophenyl)amino)phenyl)methanesulfonamide (**5a**)***:*** A mixture of **17** (180 mg, 0.97 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (441 mg, 2.9 mmol), 2,6-dichloroboronic acid (240 mg, 1.3 mmol), copper(II) acetate monohydrate (193 mg, 1.1 mmol) and 1,4-dioxane (10 mL) was stirred at room temperature for 3 h. The mixture was poured into saturated ammonium chloride *aq.* (20 mL), 10% NaOH *aq.* was added to adjust the pH 8 and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated. The residue was purified using MPLC (silica gel, *n*-hexane/ethyl acetate=87/13→66/34) to obtain the title compound as a white solid (72 mg, 22% yield). Recrystallization from toluene yielded a white needle. ^{1}H NMR (DMSO-d_6, 500

MHz): δ 4.47 (s, 2H), 6.41 (d, 1H, *J*=8.0 Hz), 7.00 (t, 1H, *J*=7.5 Hz), 7.11 (br, 2H), 7.15–7.20 (m, 5H), 7.28 (br, 1H), 7.32 (dt, 1H, *J*=7.5, 1.4 Hz), 7.52 (d, 2H, *J*=8.1 Hz). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 57.4, 117.5, 120.5, 121.7, 125.2, 128.8, 128.9, 129.2, 132.9, 137.0, 143.2. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{13}H_{12}Cl_2N_2NaO_2S$, 352.9894; found, 352.9941 (+4.7 mmu).

NMR spectra

Compound 1b

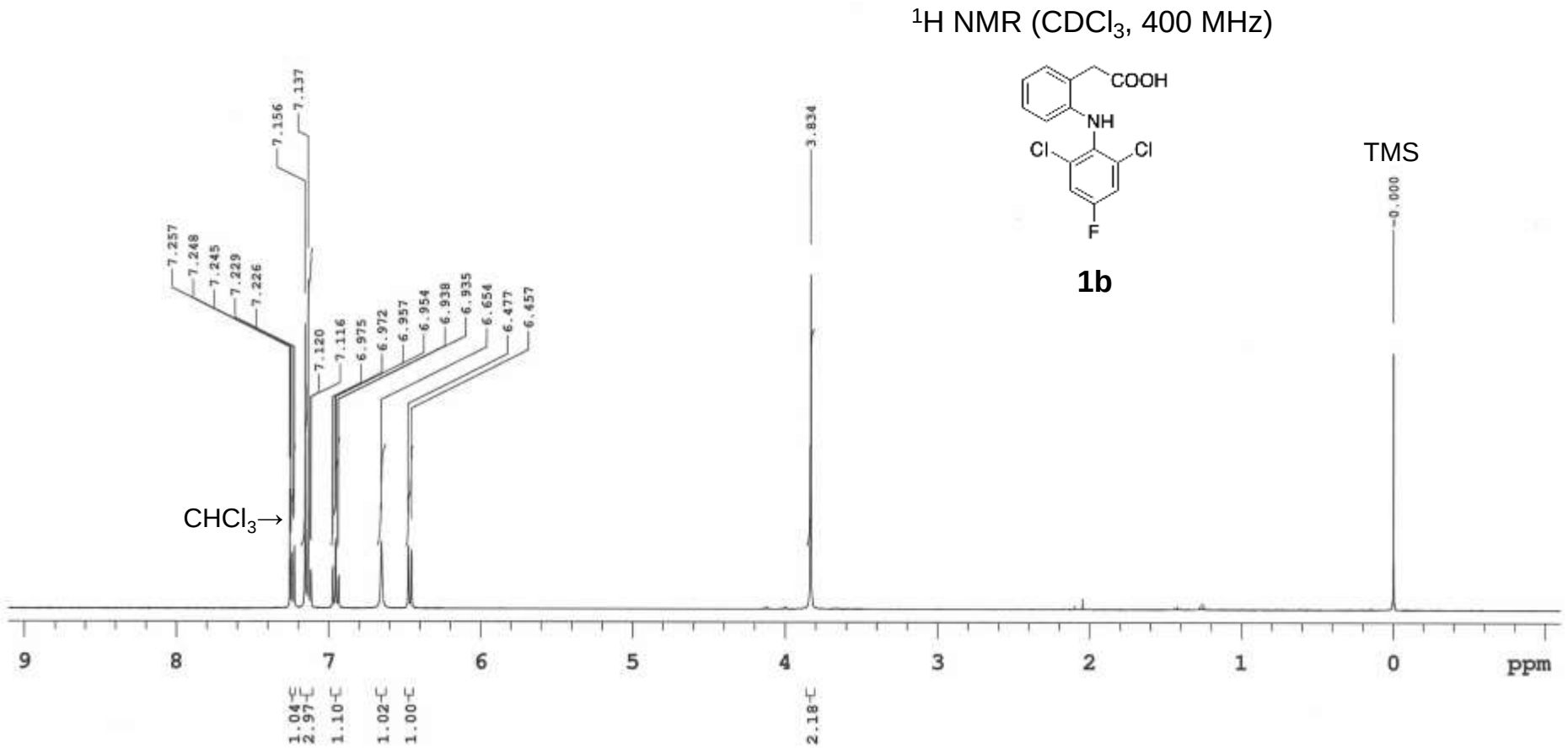

Figure S1 ^{1}H NMR spectra of **1b**

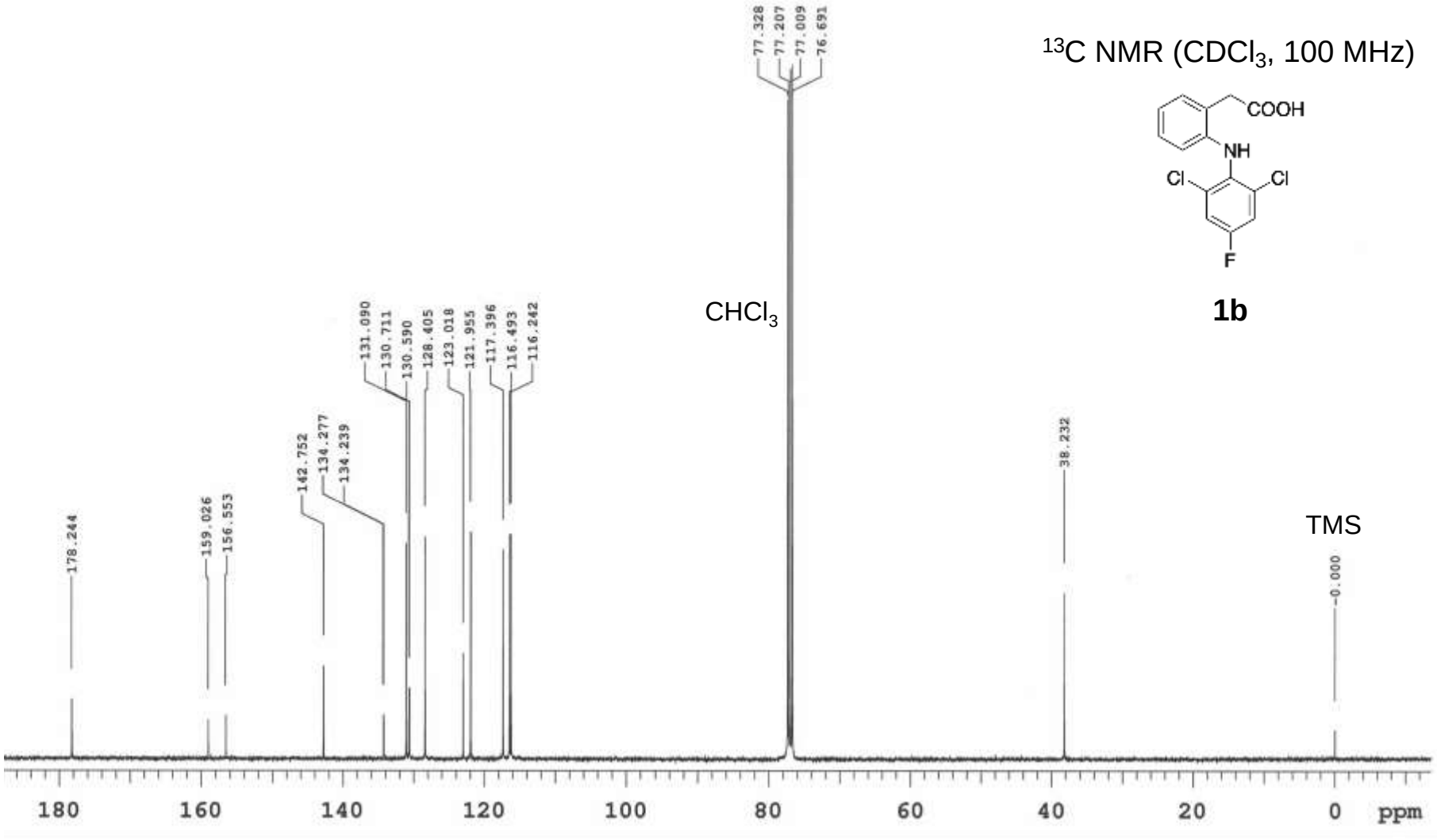

Figure S2 ^{13}C NMR spectra of **1b**

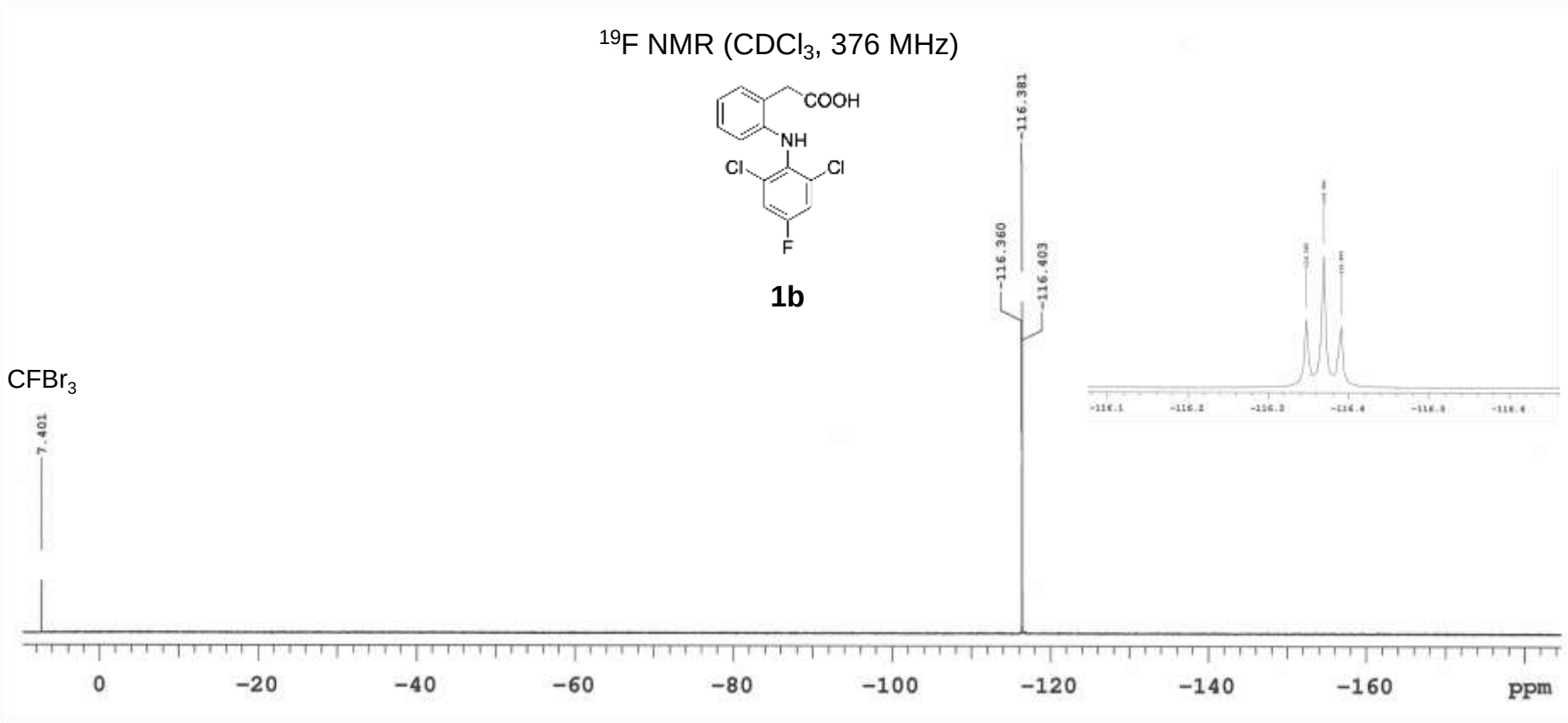

Figure S3 ^{19}F NMR spectra of **1b**

Compound 1c

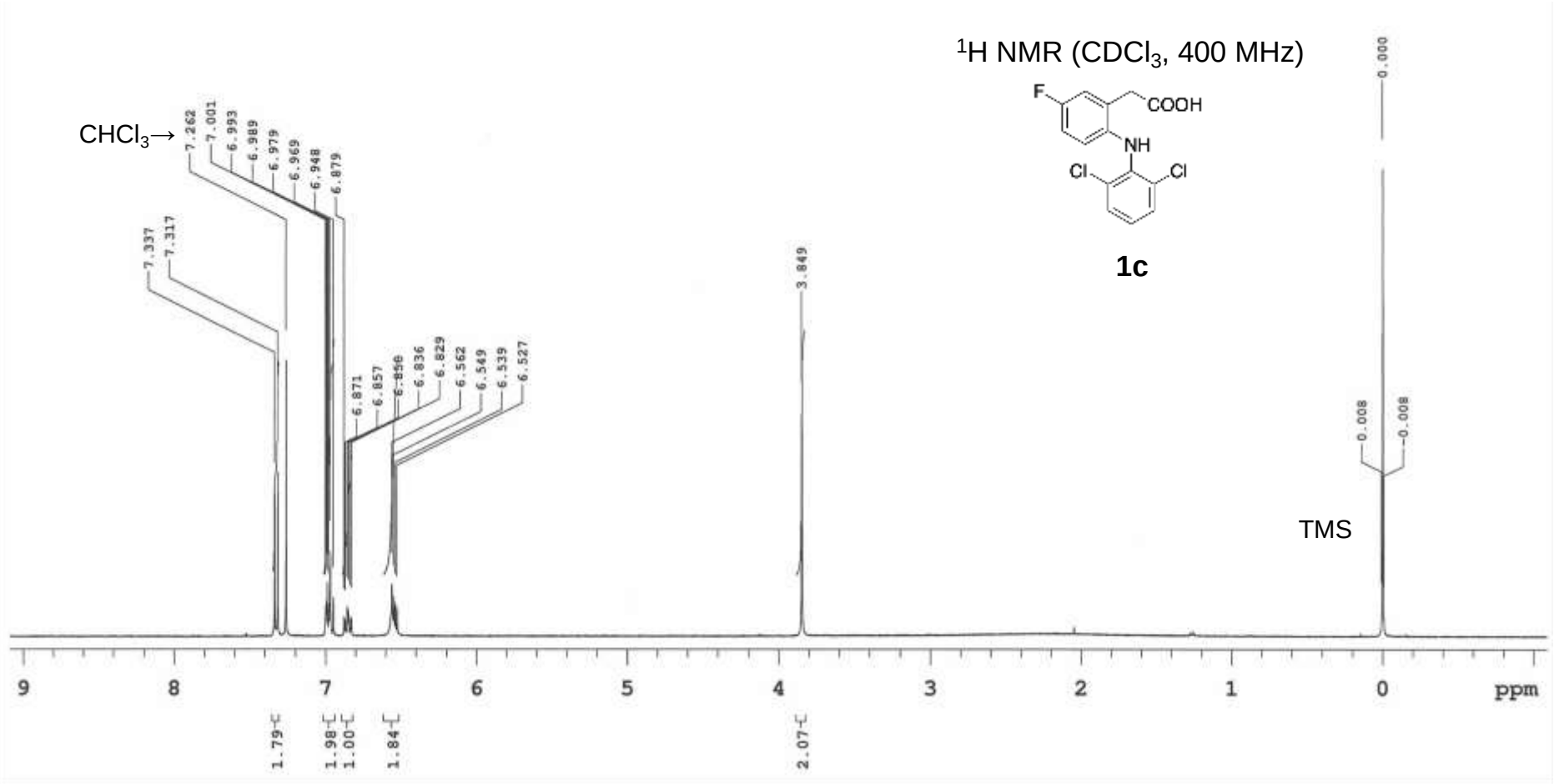

Figure S4 ^{1}H NMR spectra of **1c**

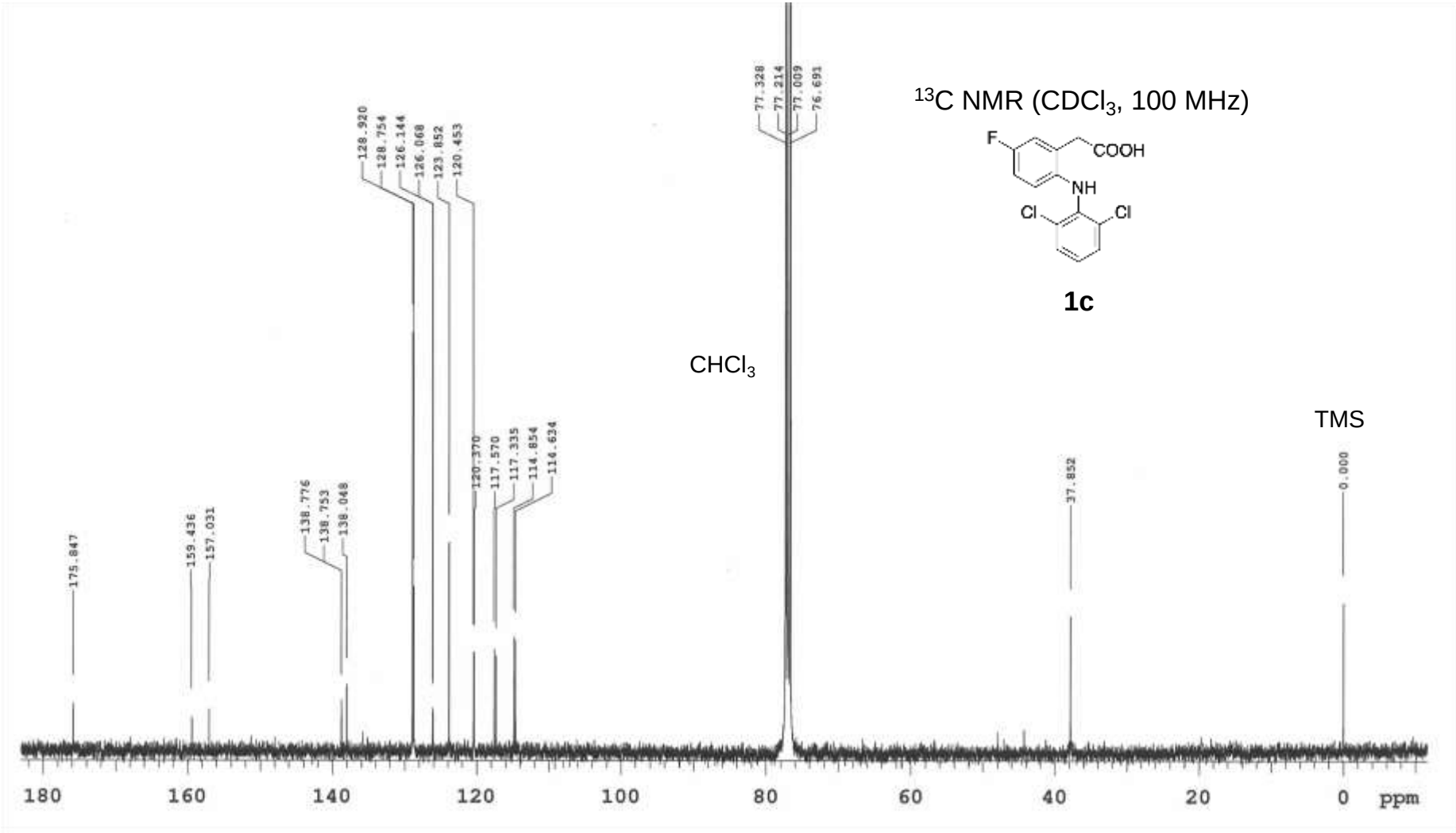

Figure S5 ^{13}C NMR spectra of **1c**

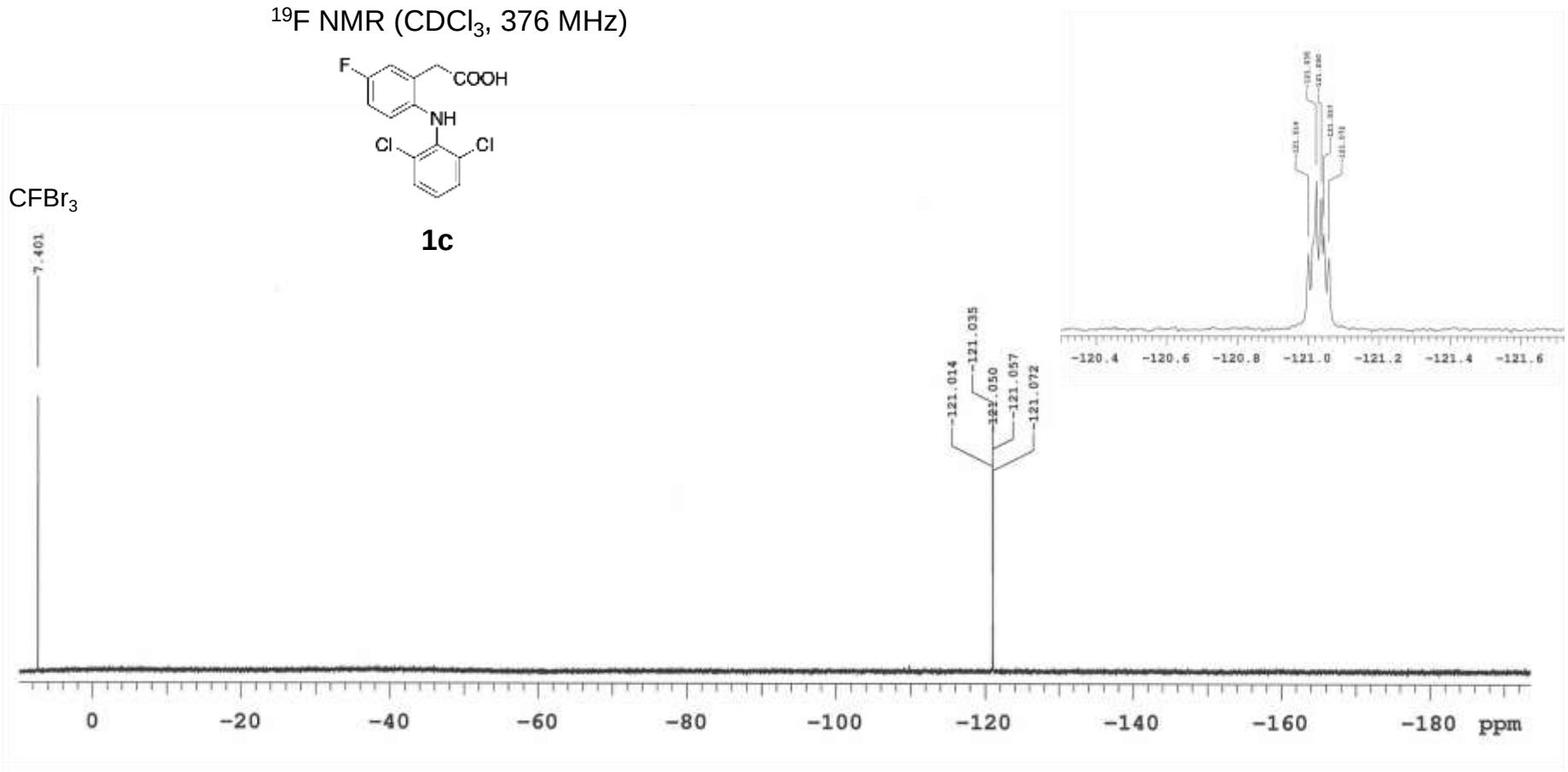

Figure S6 ^{19}F NMR spectra of **1c**

Compound 1d

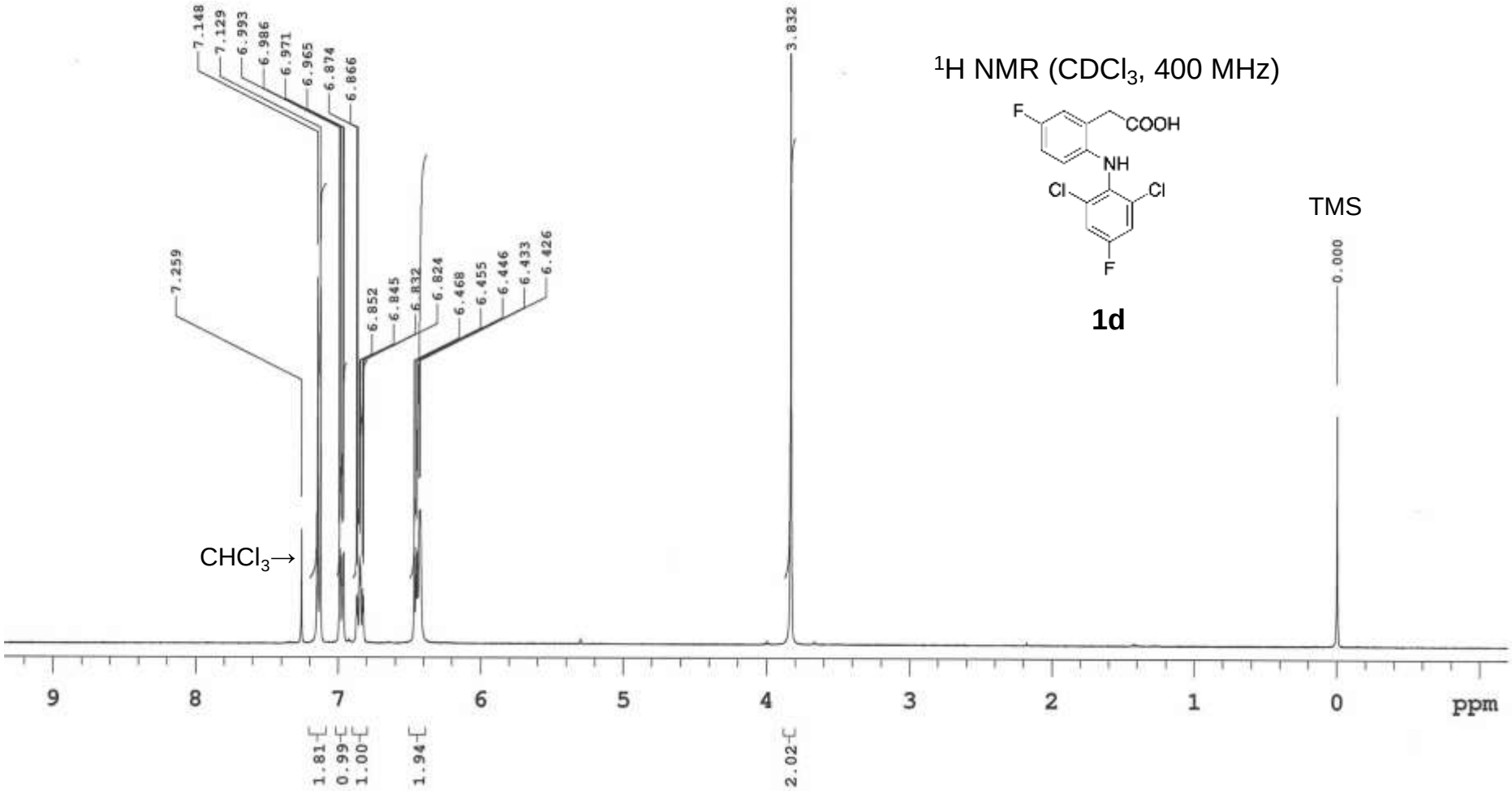

Figure S7 ^{1}H NMR spectra of **1d**

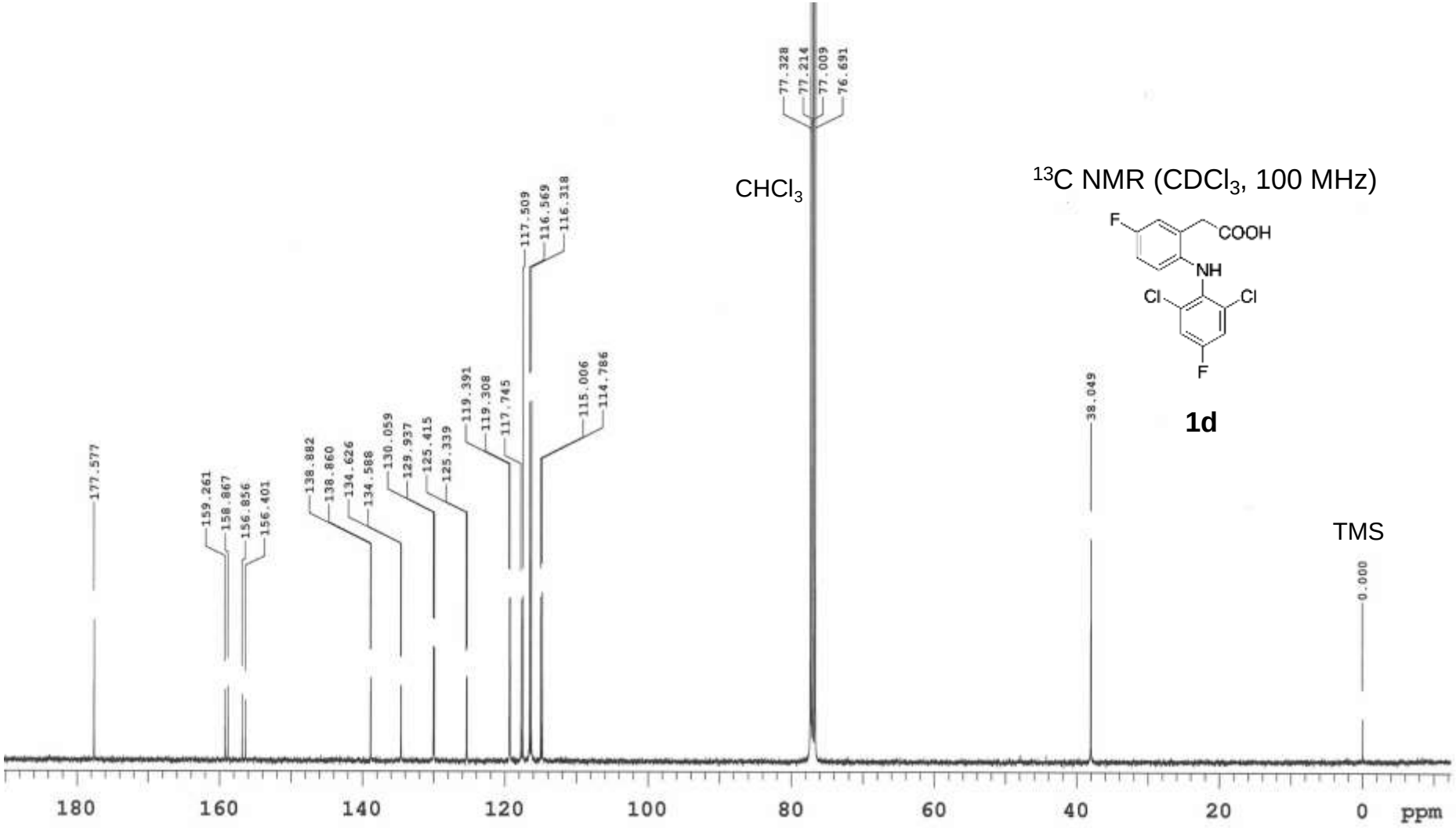

Figure S8 ^{13}C NMR spectra of **1d**

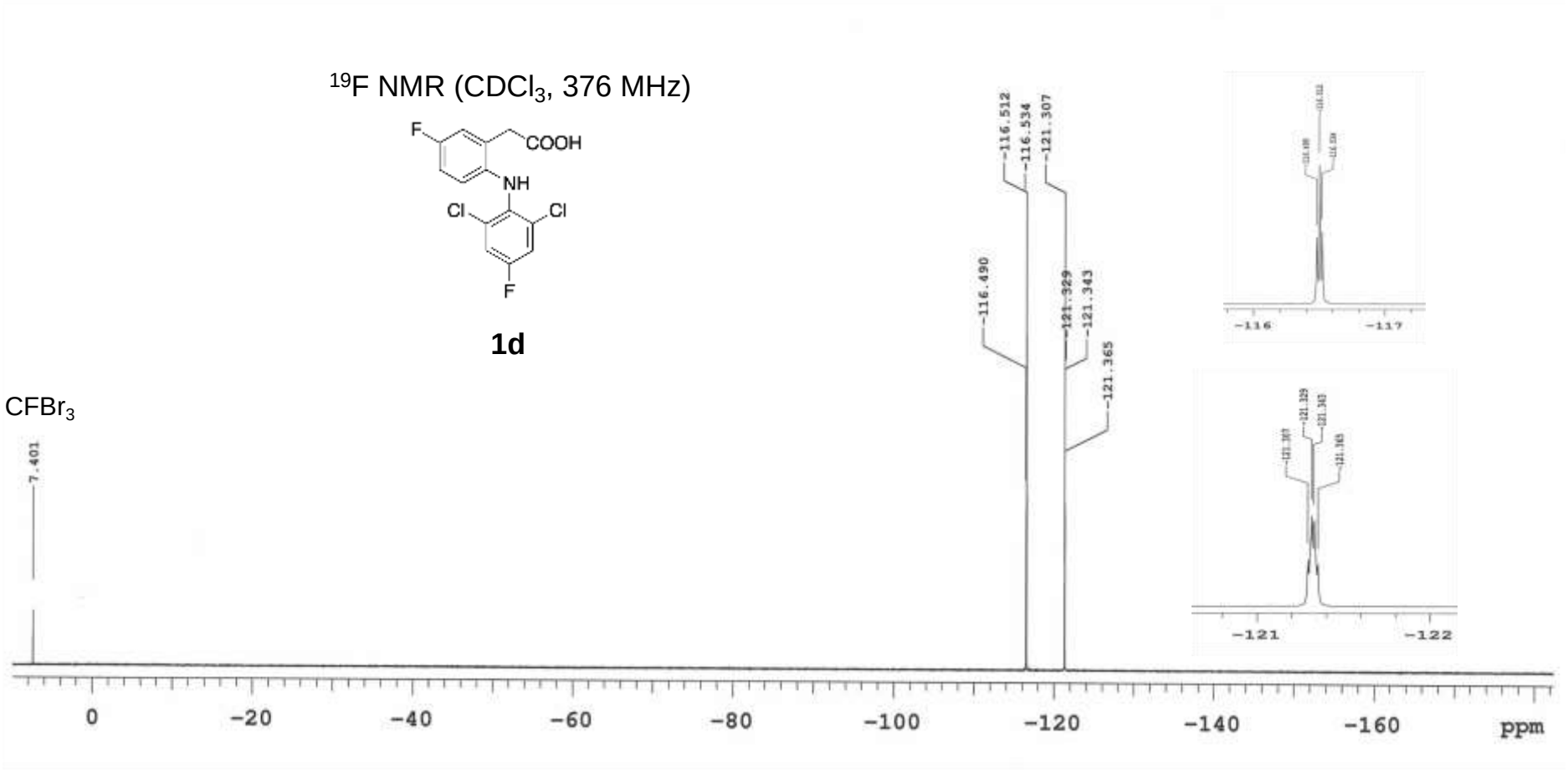

Figure S9 ^{19}F NMR spectra of **1d**

Compound 2a

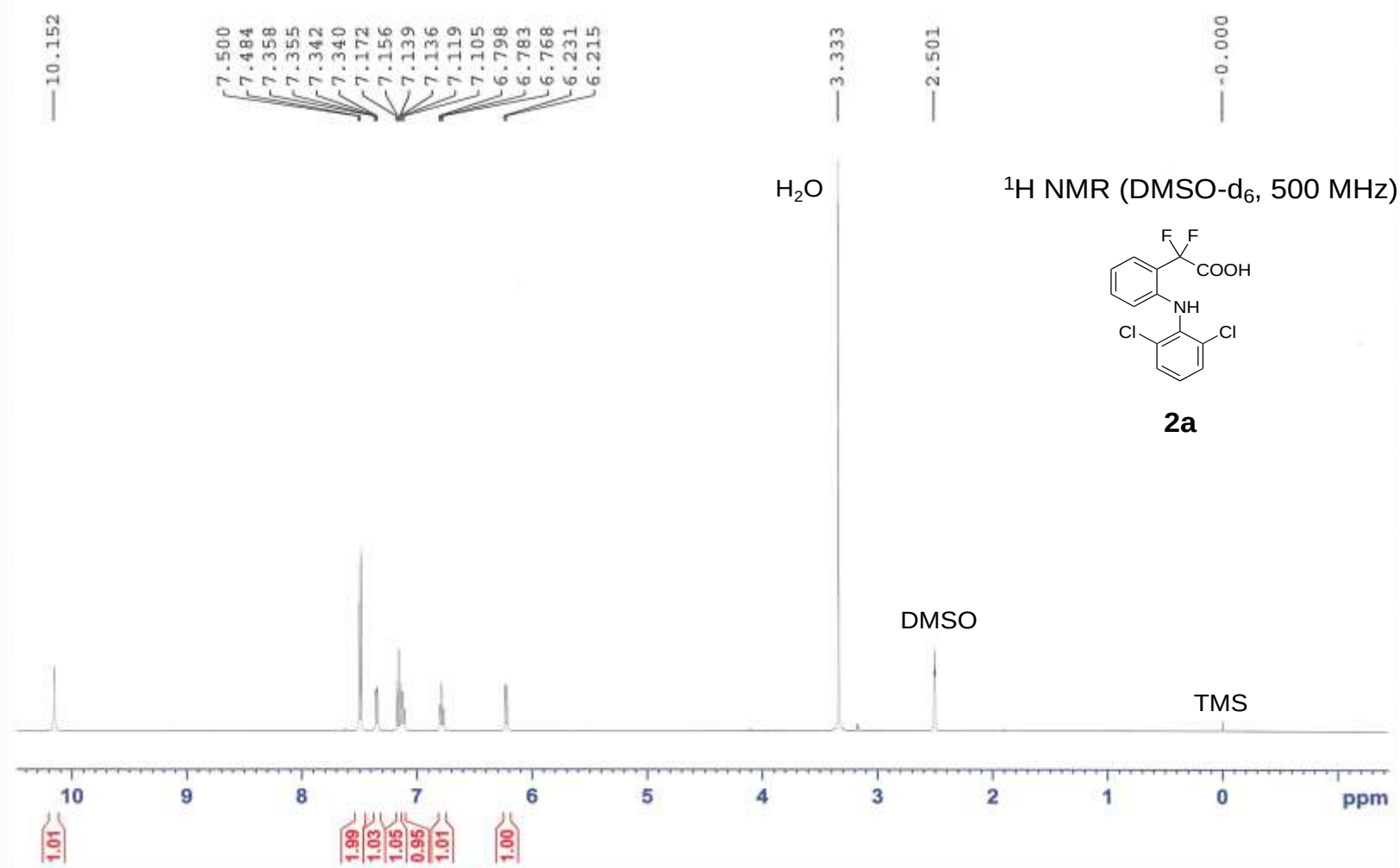

Figure S10 ^{1}H NMR spectra of **2a**

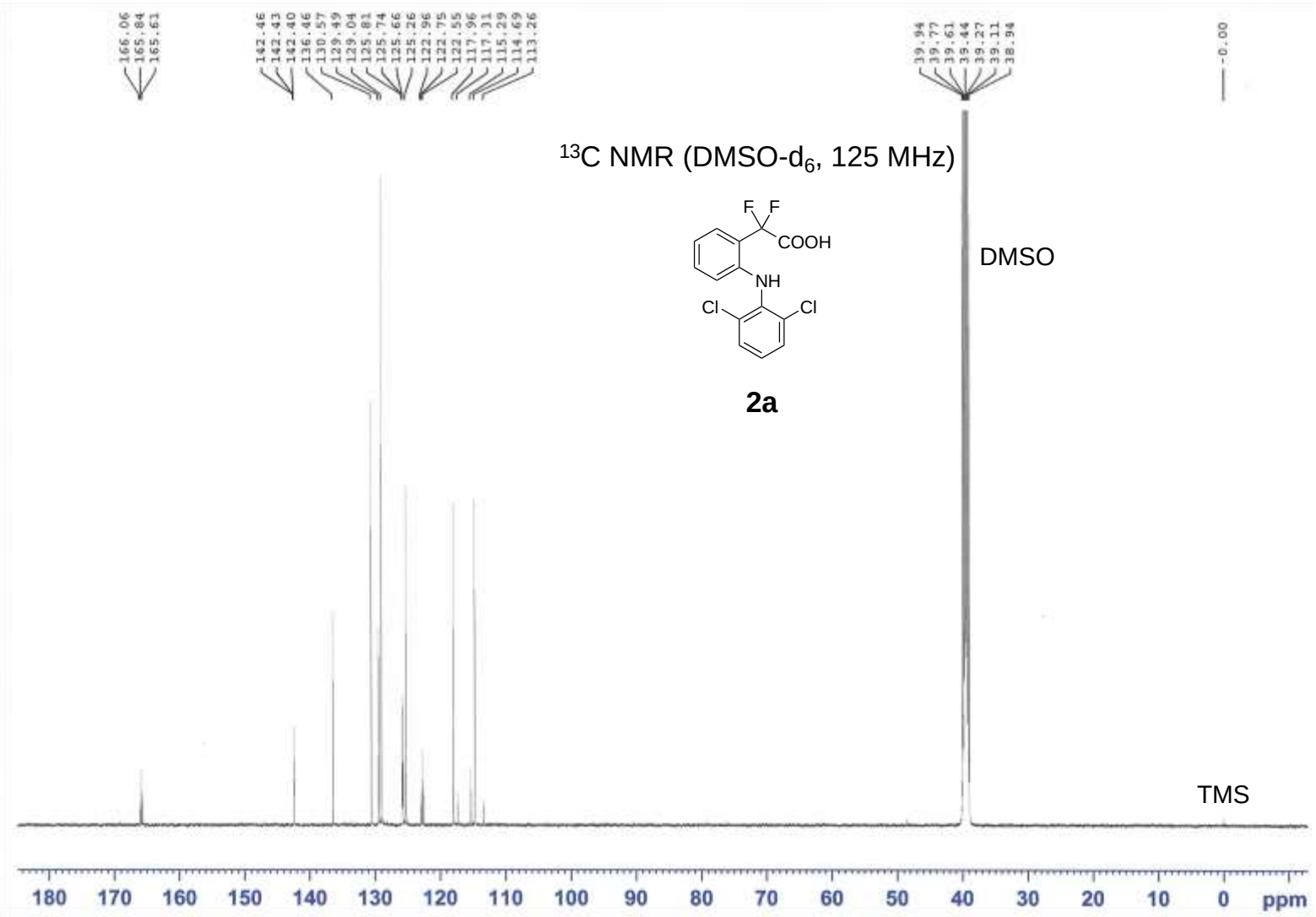

Figure S11 ^{13}C NMR spectra of **2a**

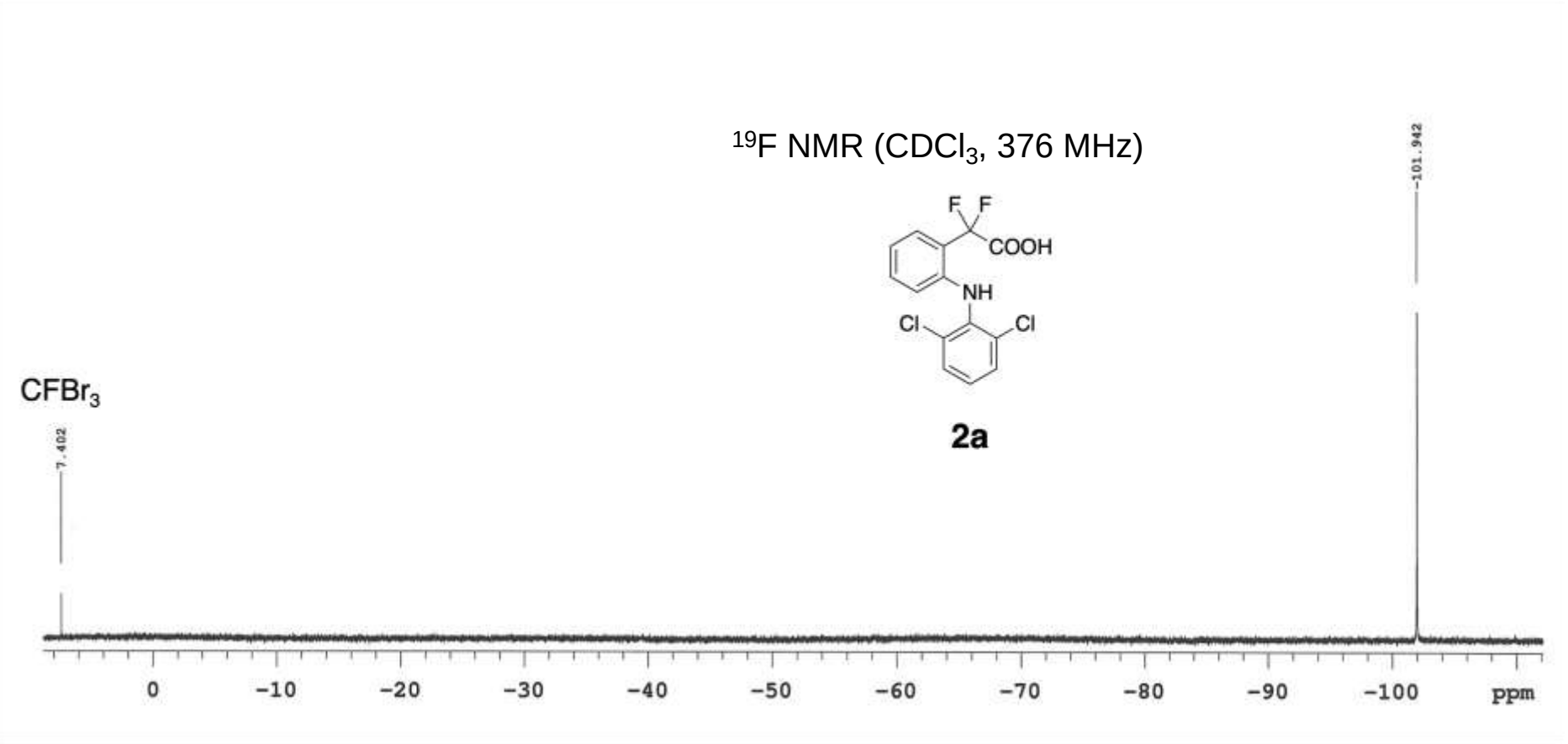

Figure S12 ^{19}F NMR spectra of **2a**

Compound 2b

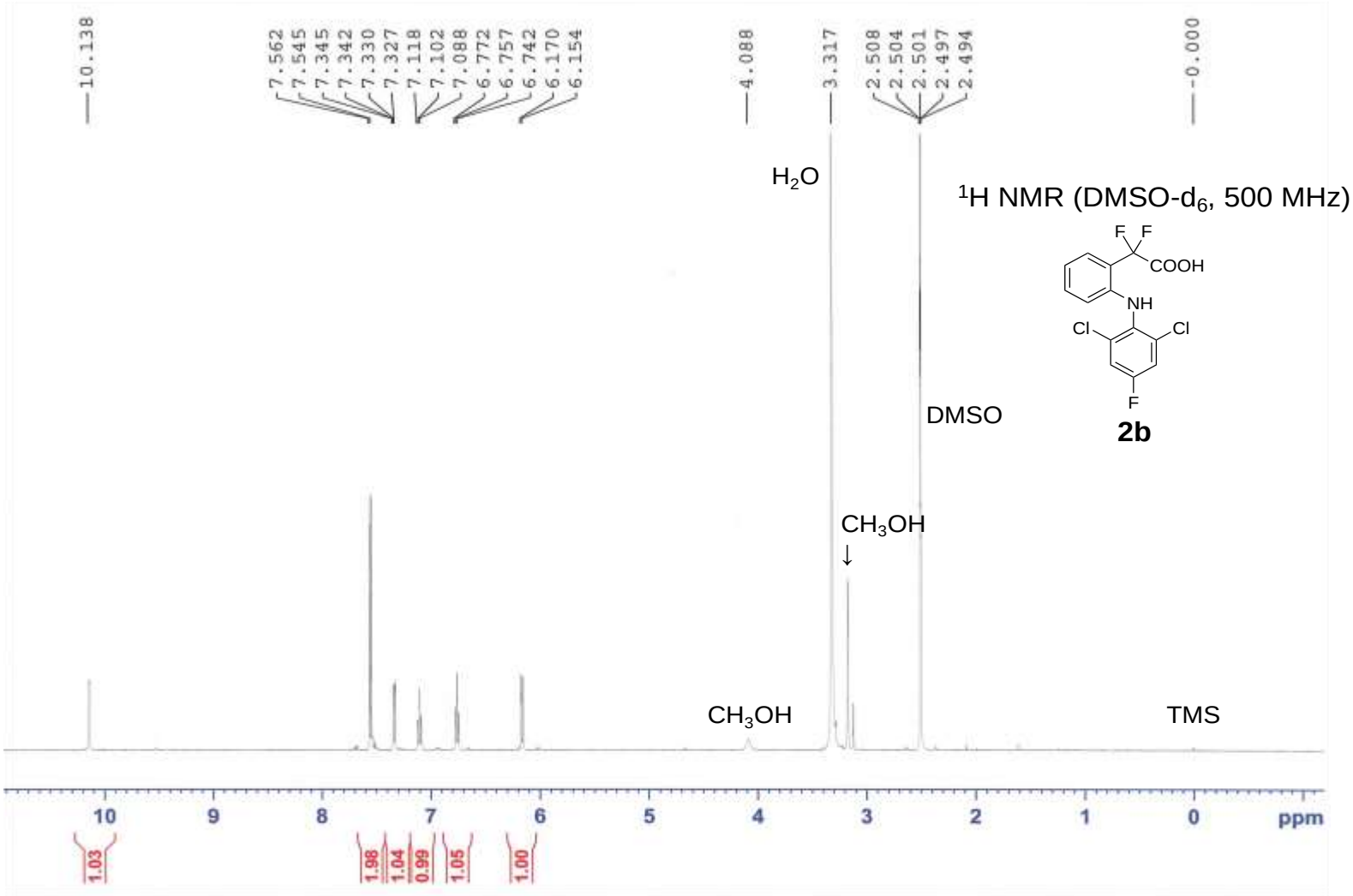

Figure S13 ^{1}H NMR spectra of **2b**

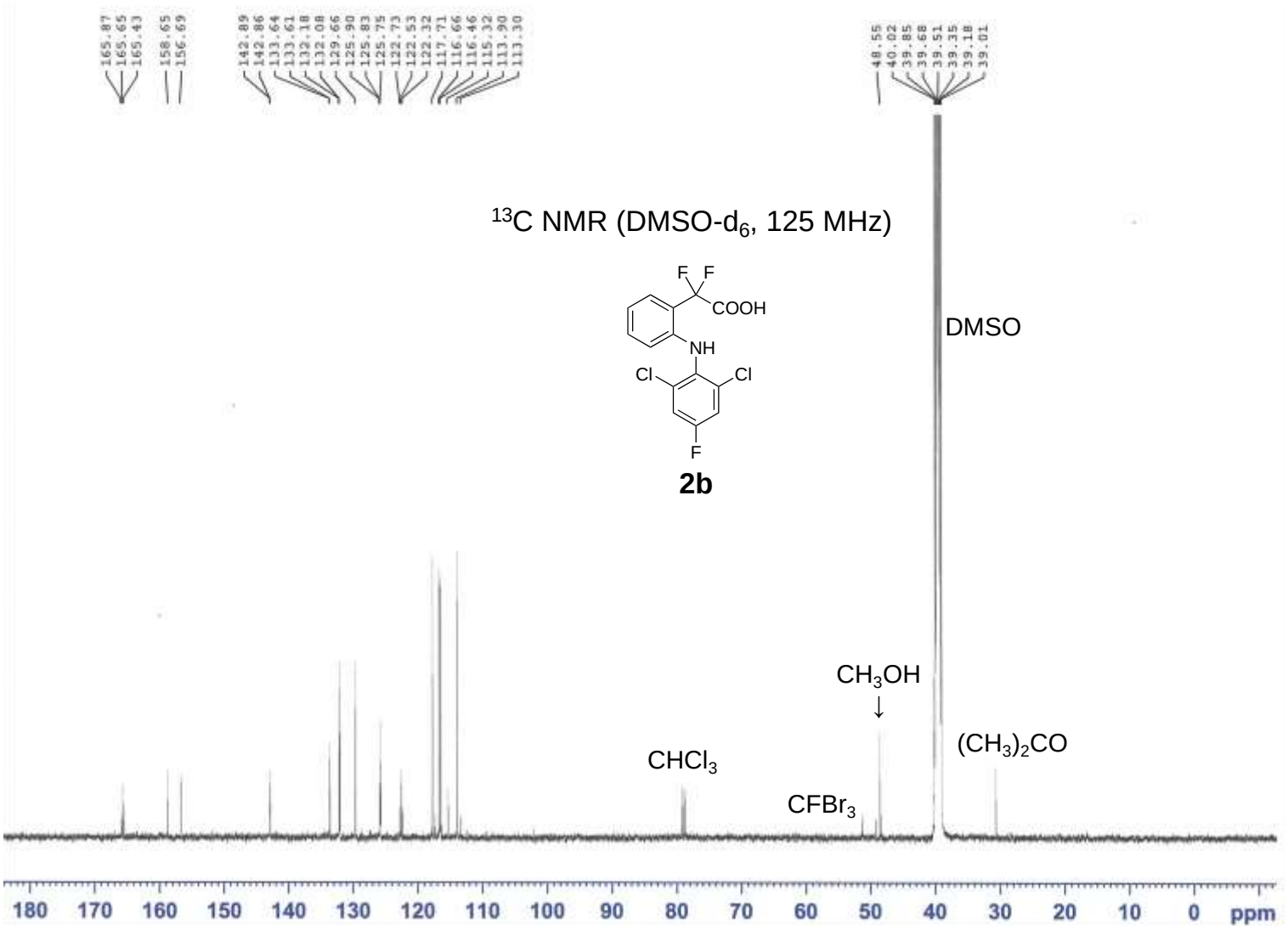

Figure S14 ^{13}C NMR spectra of **2b**

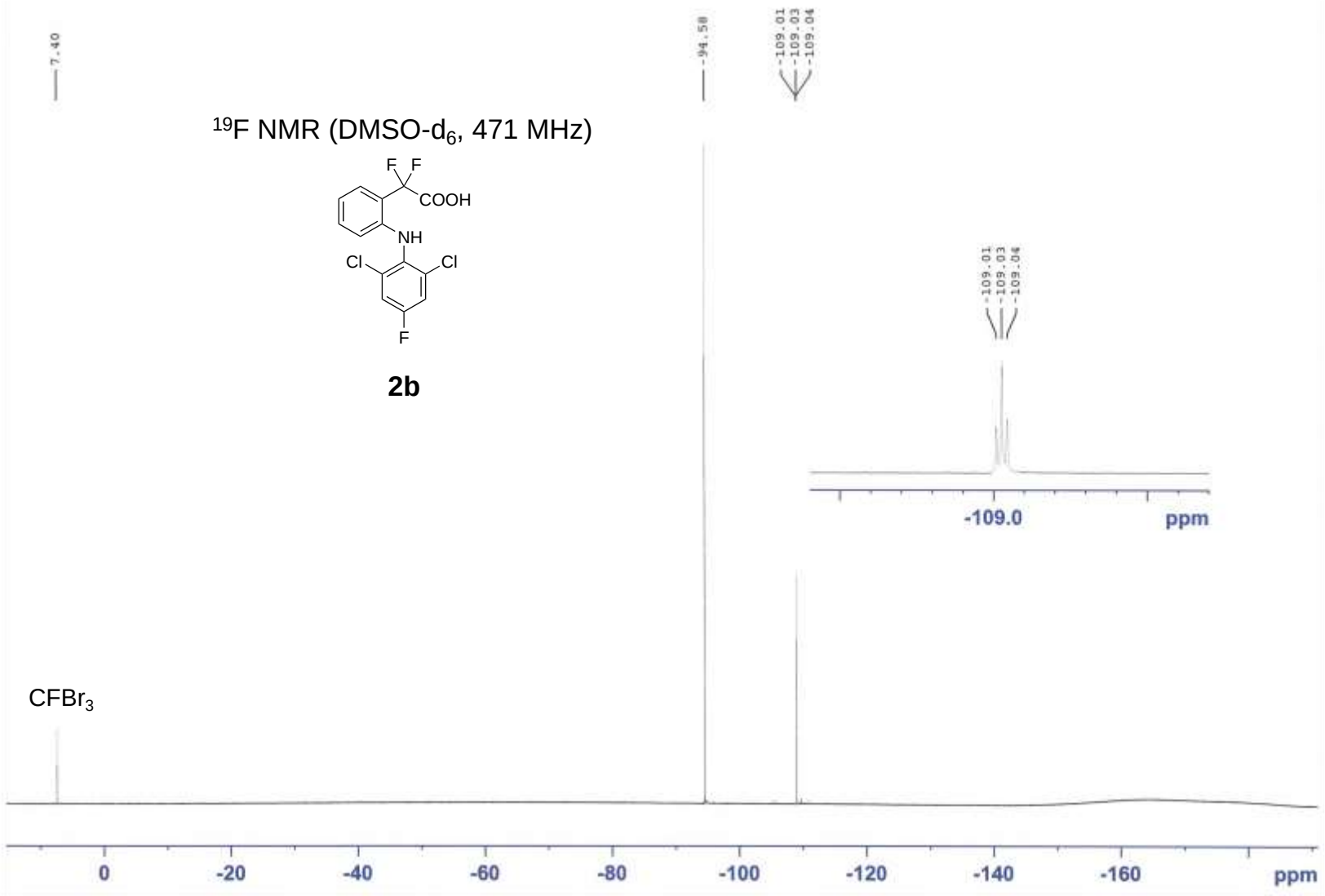

Figure S15 ^{19}F NMR spectra of **2b**

Compound 2c

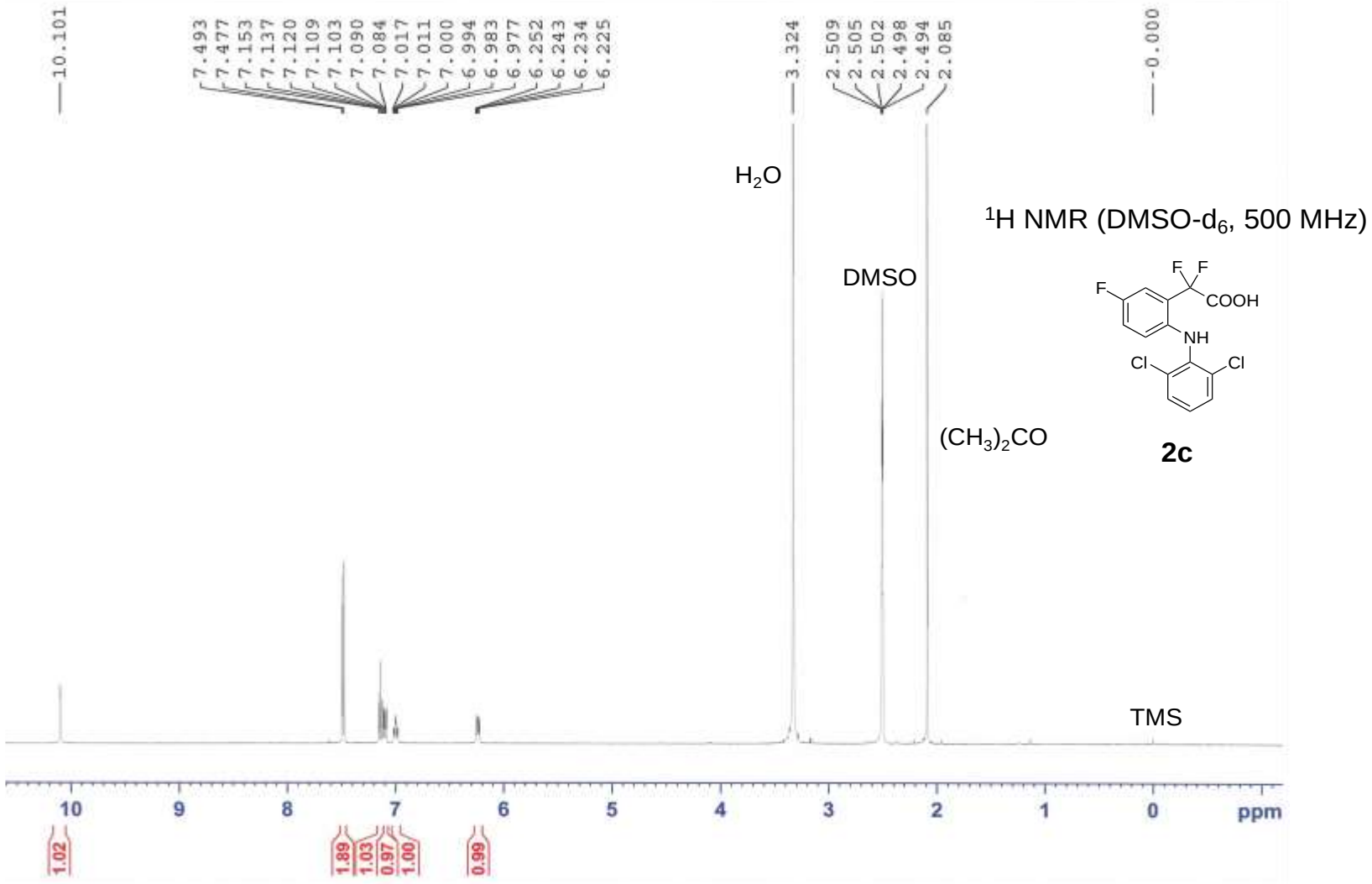

Figure S16 ^{1}H NMR spectra of **2c**

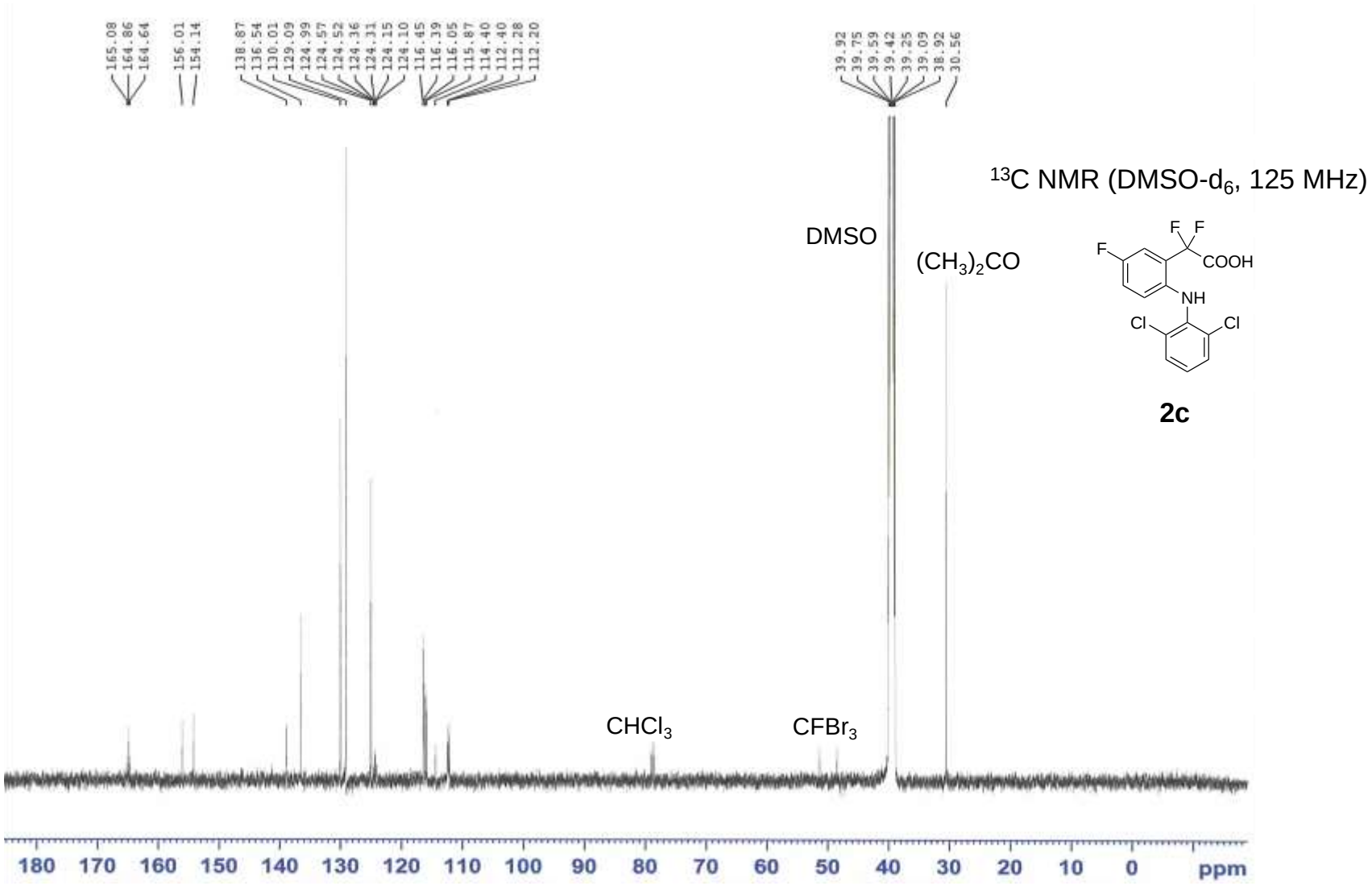

Figure S17 ^{13}C NMR spectra of **2c**

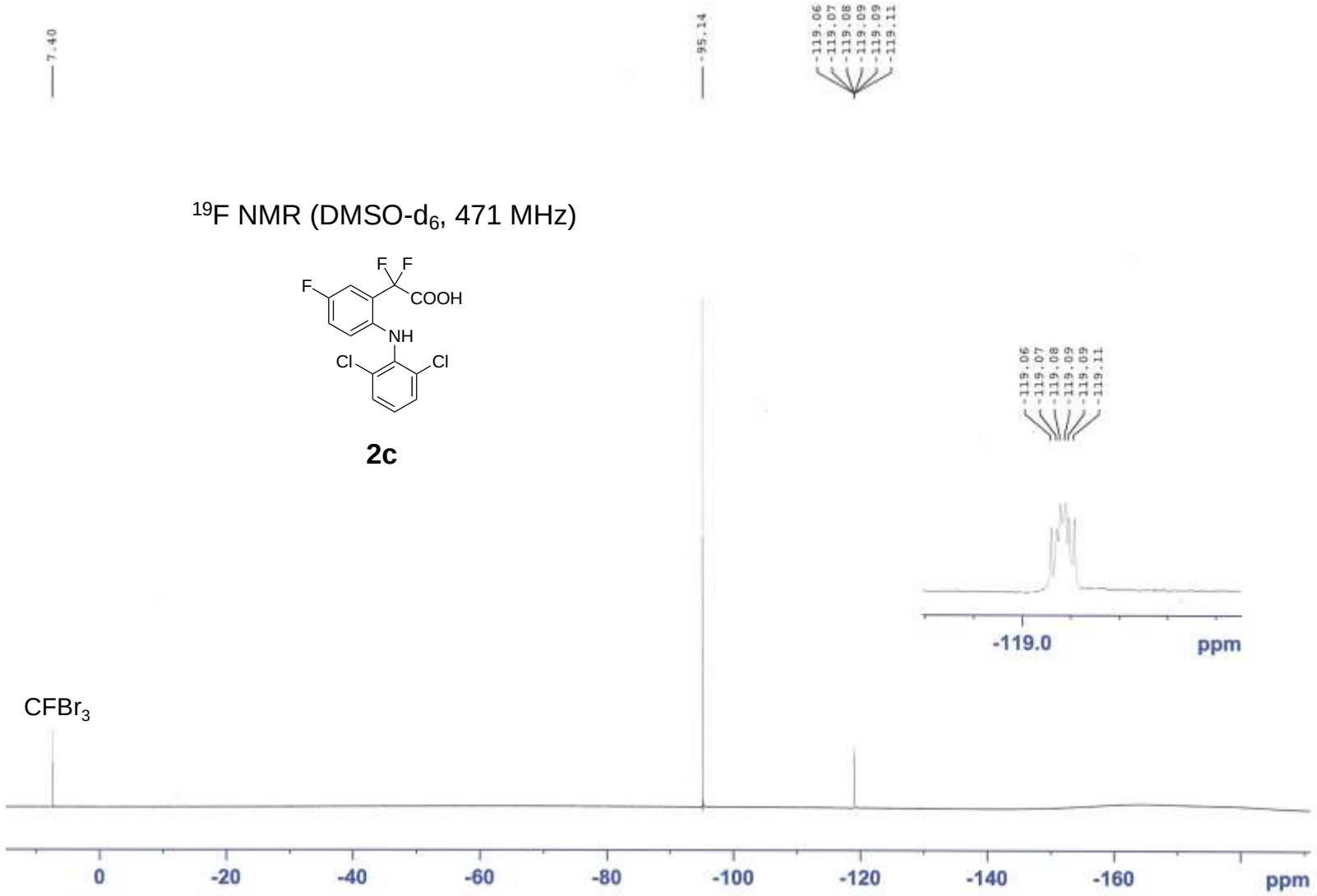

Figure S18 ^{19}F NMR spectra of **2c**

Compound 2d

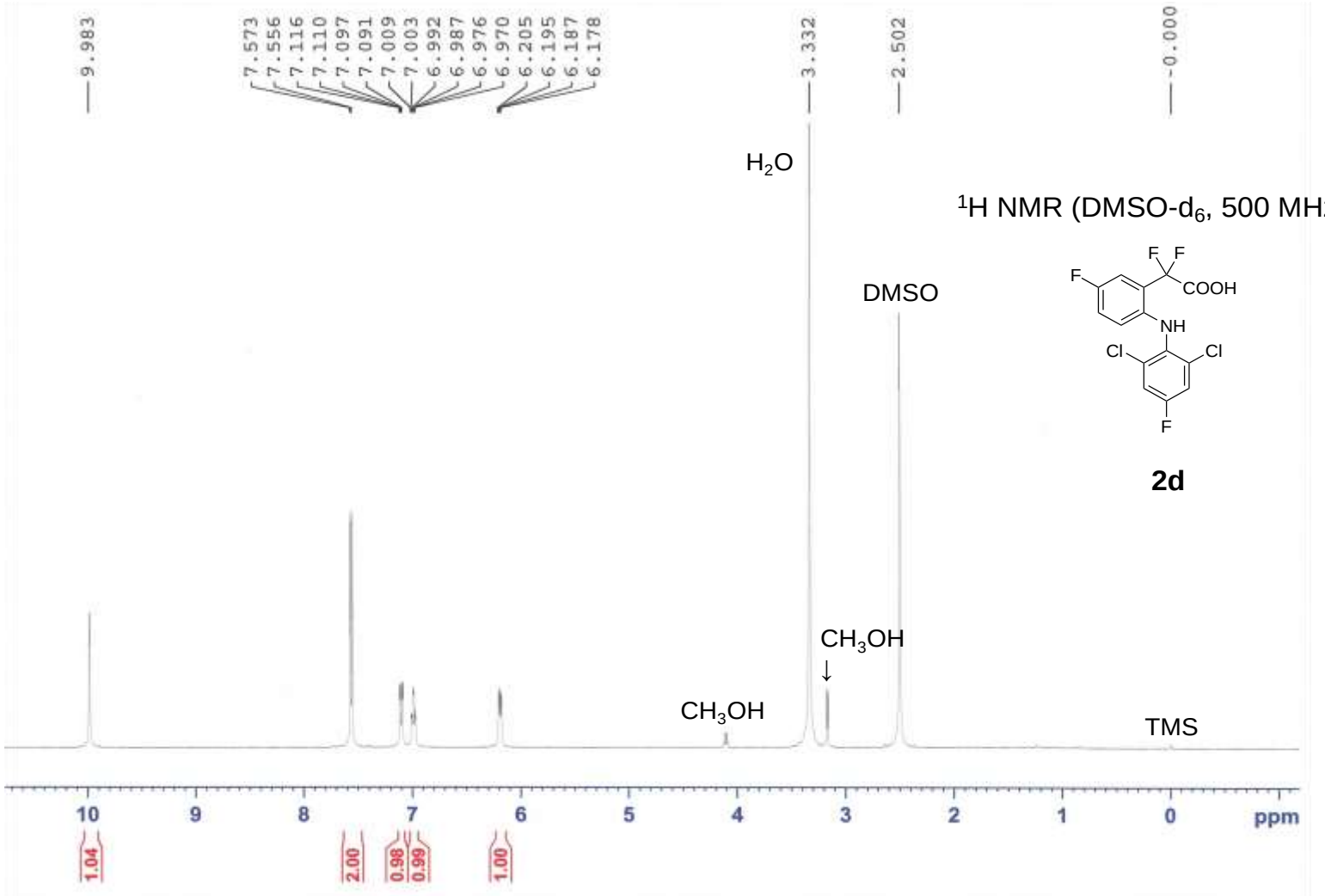

Figure S19 ^{1}H NMR spectra of **2d**

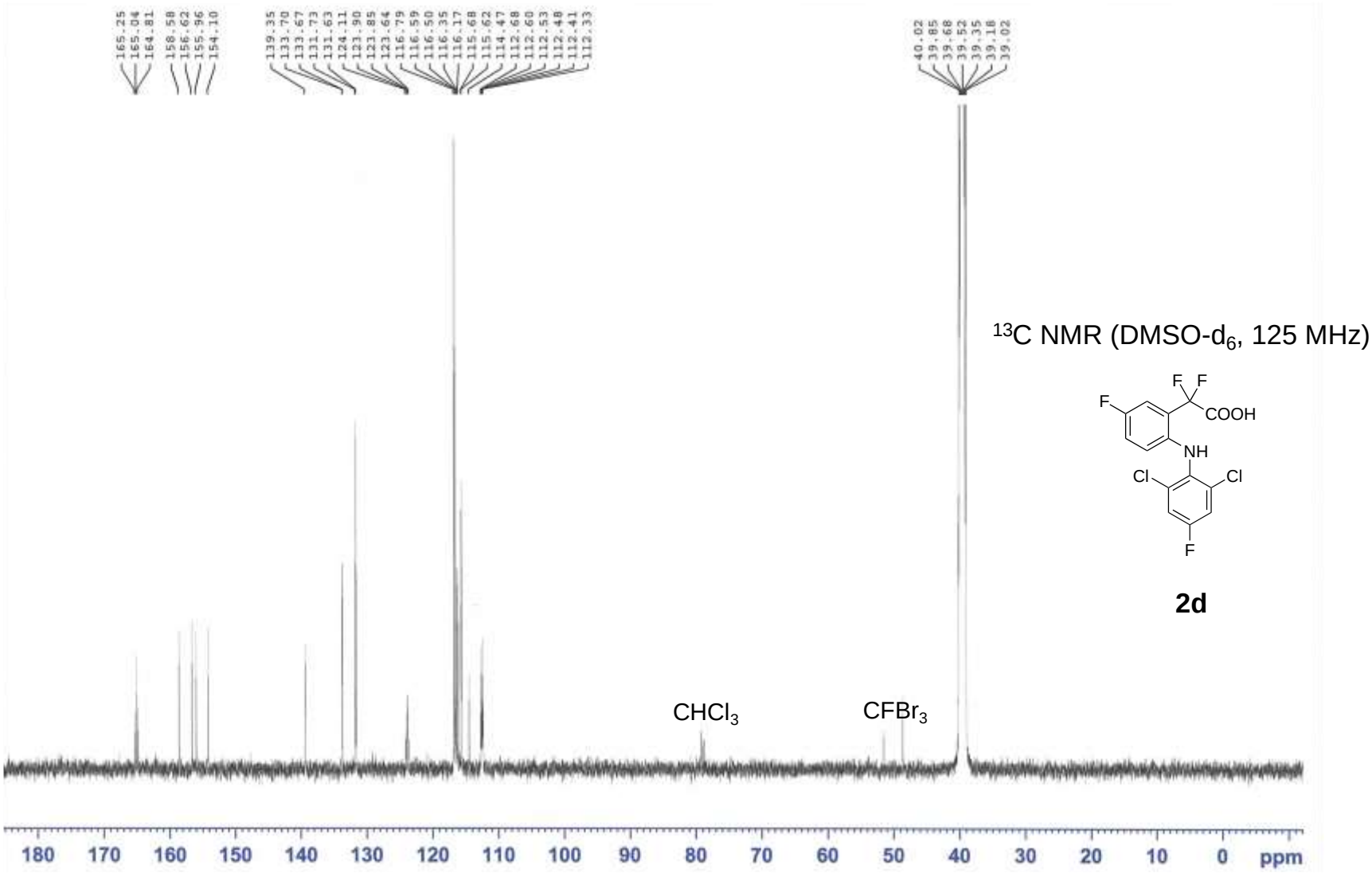

Figure S20 ^{13}C NMR spectra of **2d**

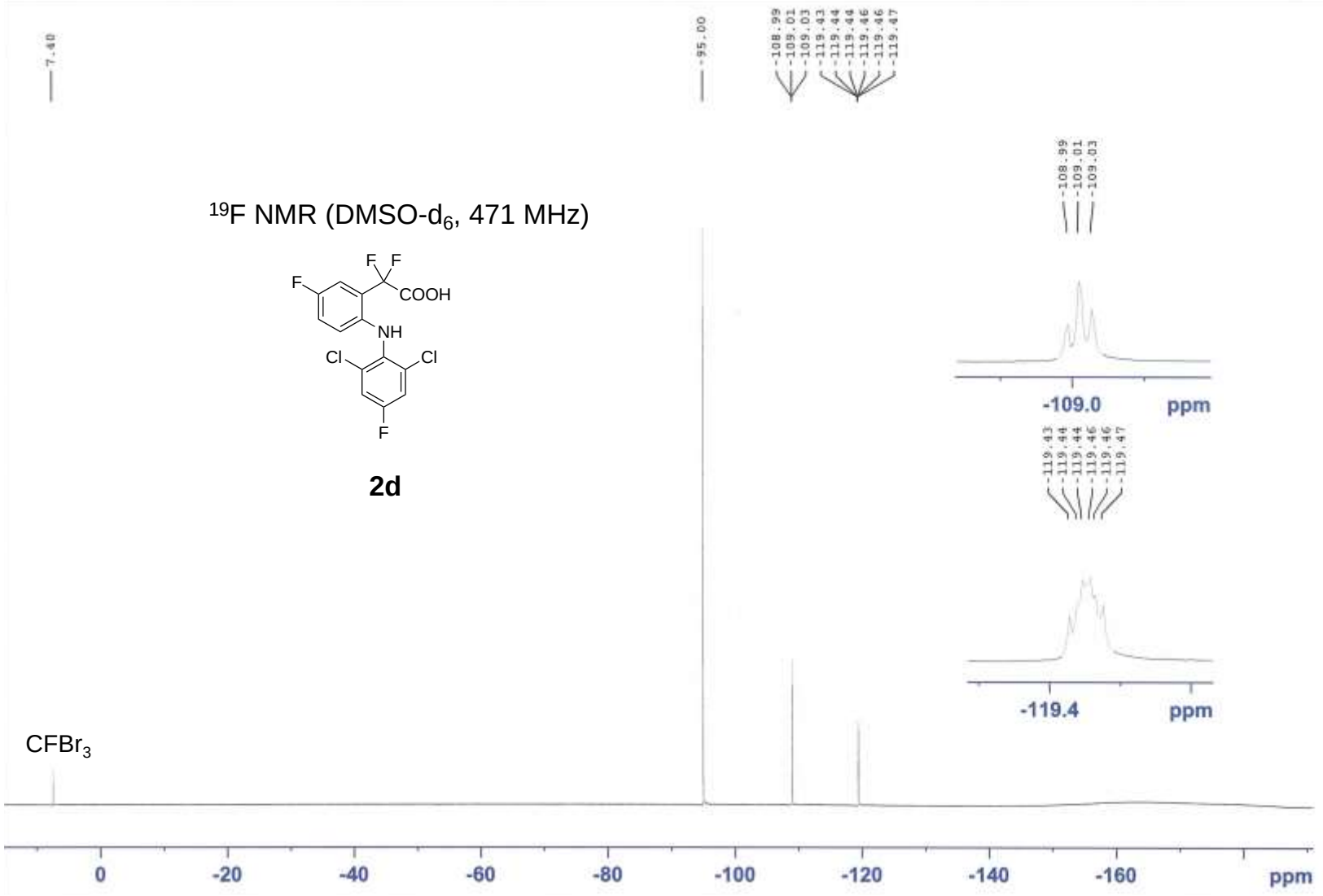

Figure S21 ^{19}F NMR spectra of **2d**

Compound 3a

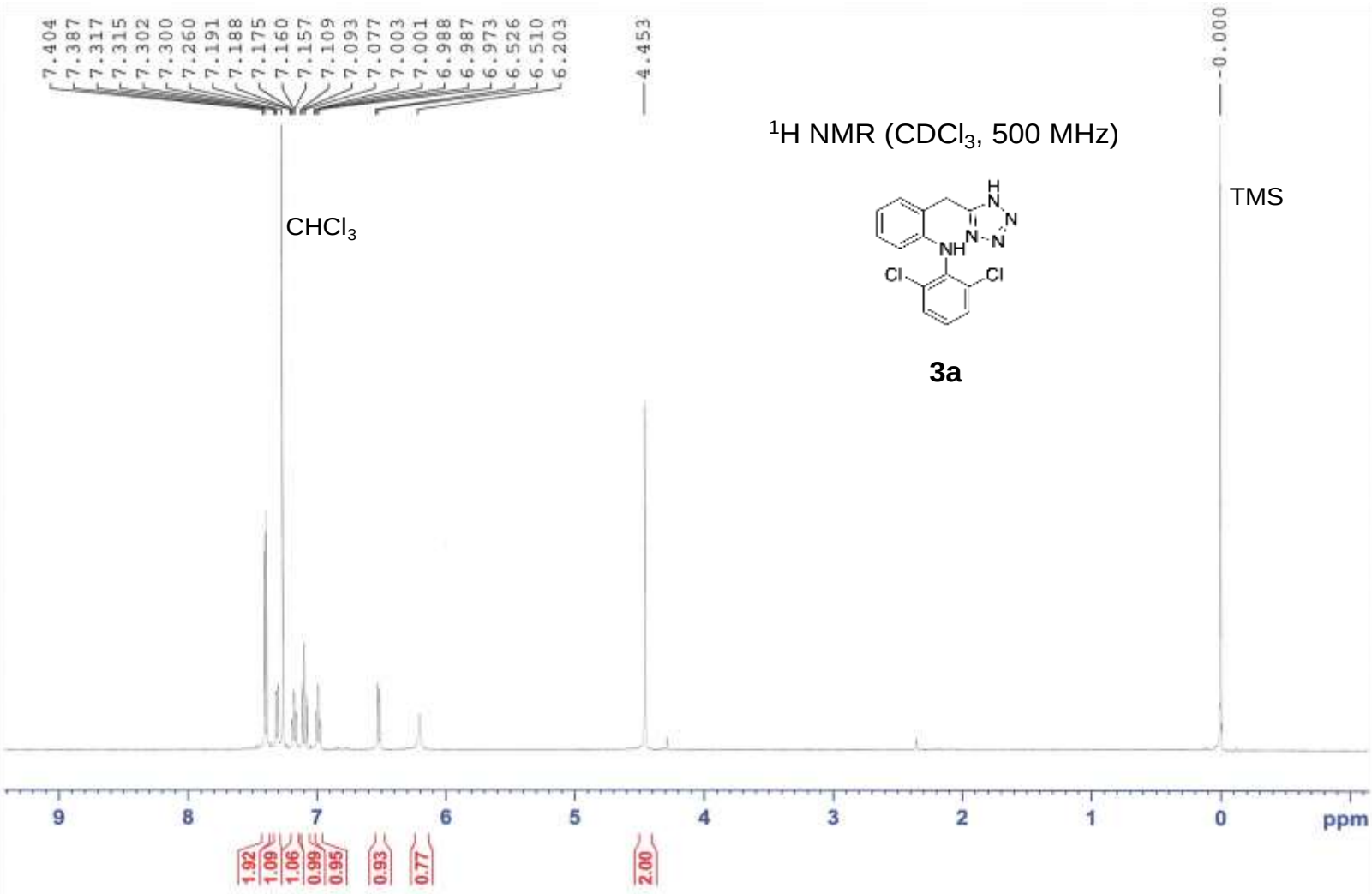

Figure S 22 ^{1}H NMR spectra of **3a**

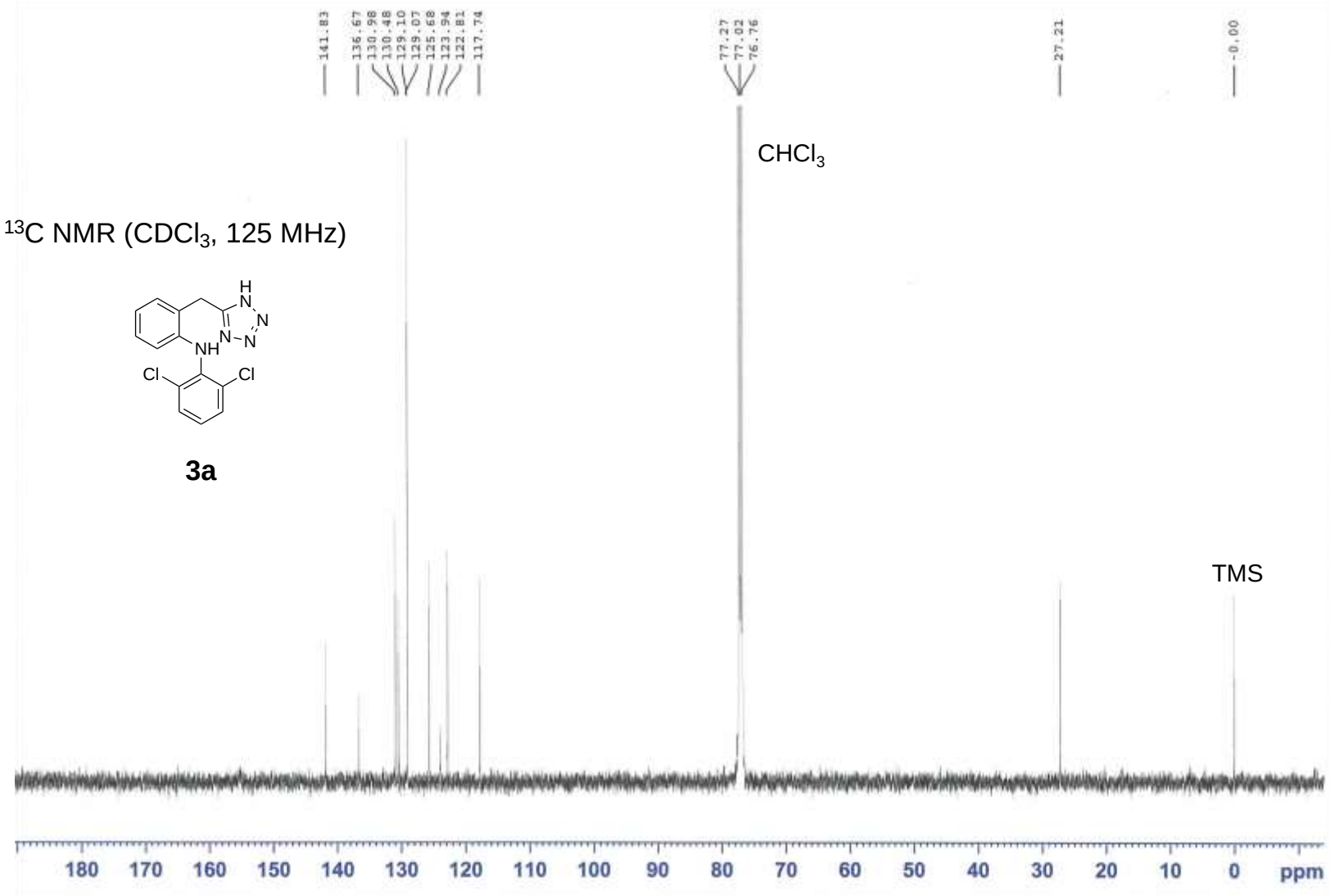

Figure S23 ^{13}C NMR spectra of **3a**

Compound 3b

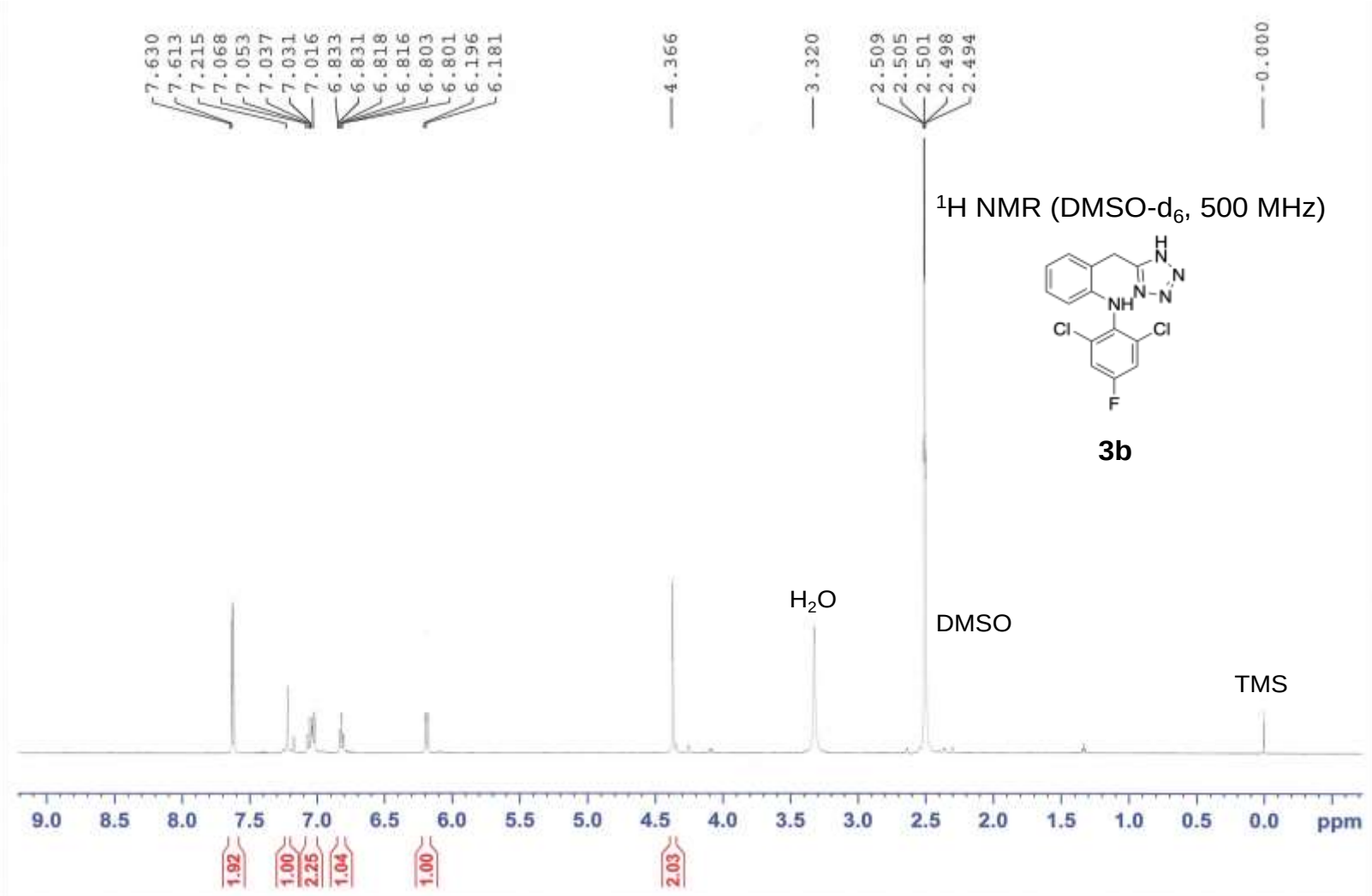

Figure S24 ^{1}H NMR spectra of **3b**

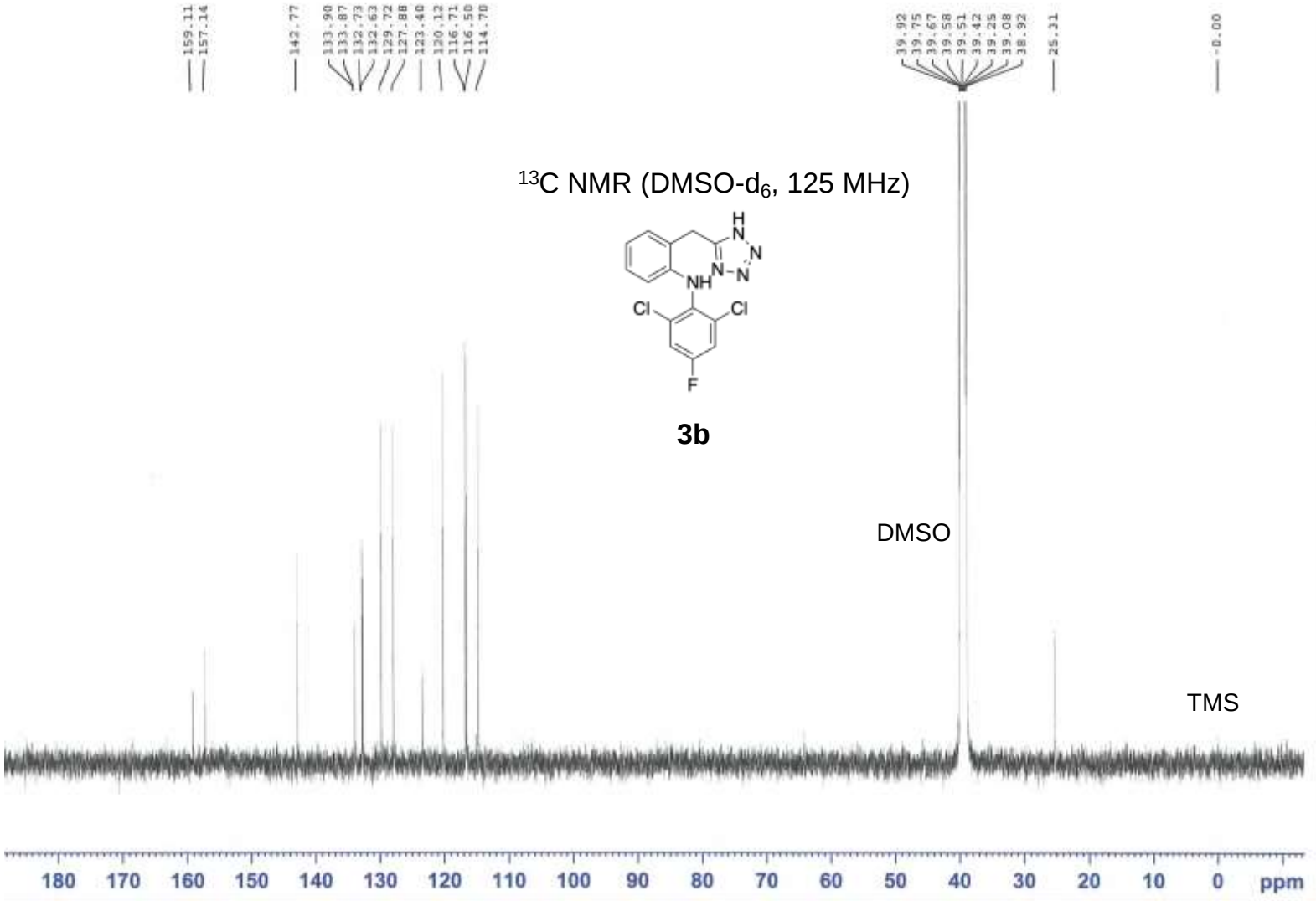

Figure S25 ^{13}C NMR spectra of **3b**

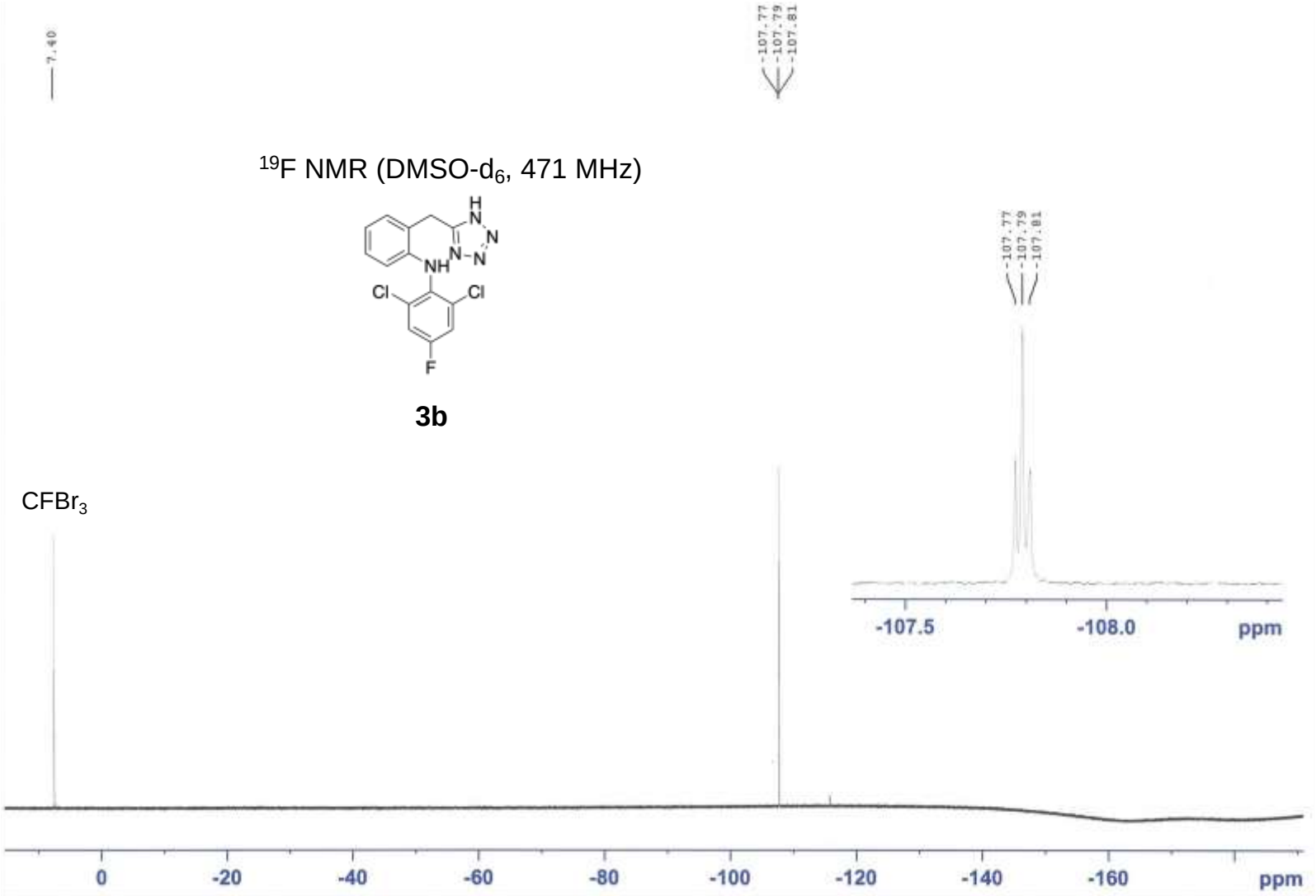

Figure S26 ^{19}F NMR spectra of **3b**

Compound 3c

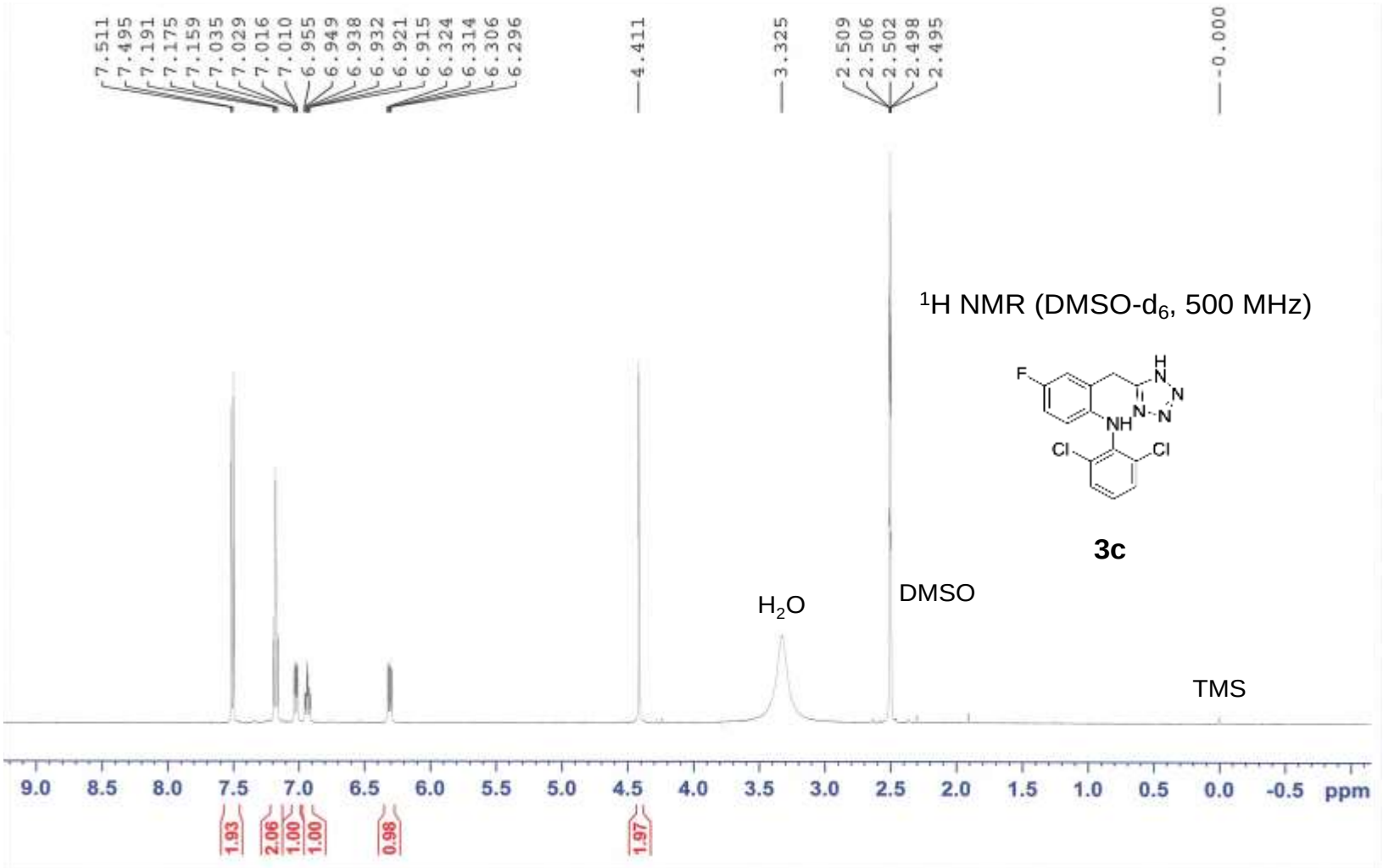

Figure S27 ^{1}H NMR spectra of **3c**

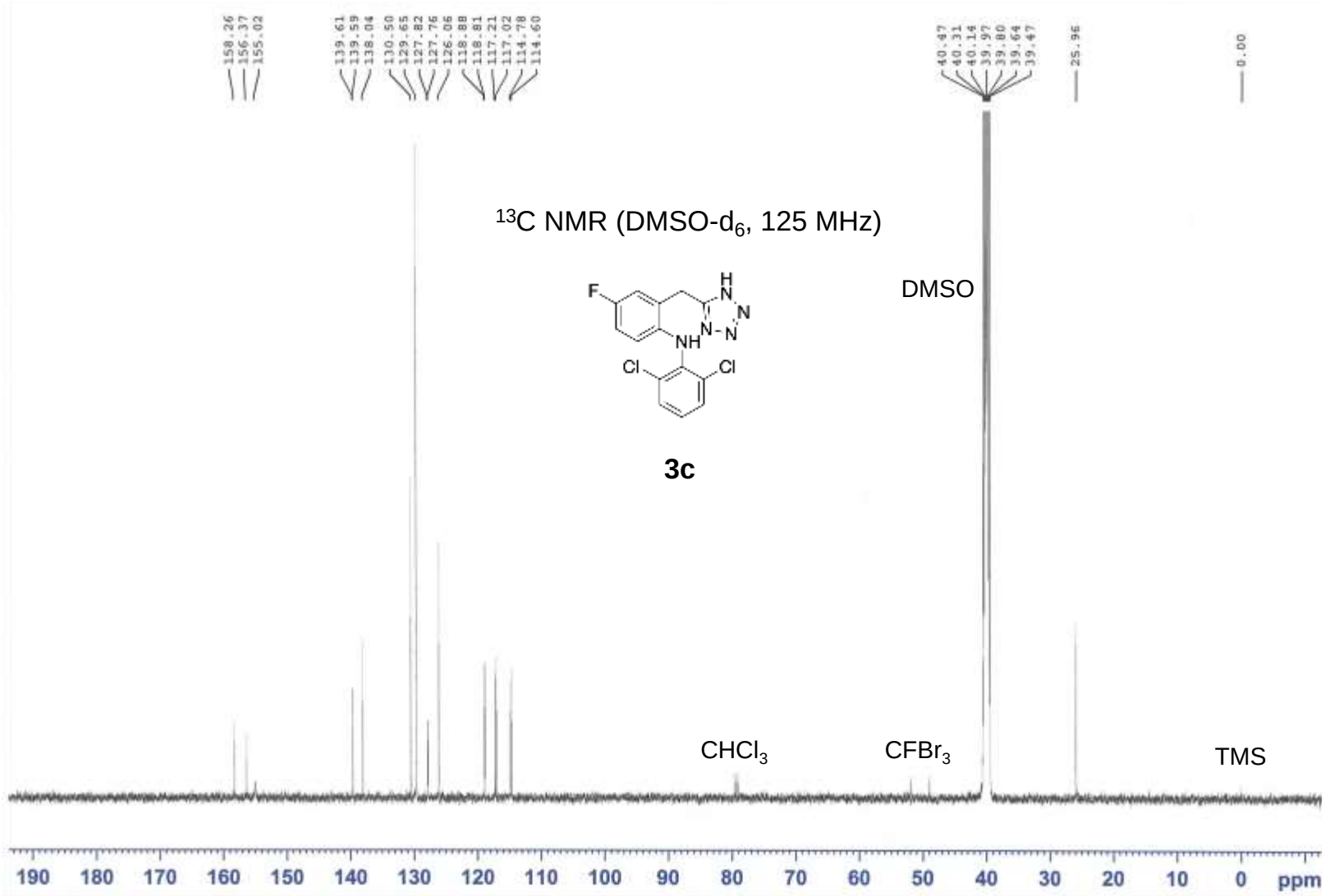

Figure S28 ^{13}C NMR spectra of **3c**

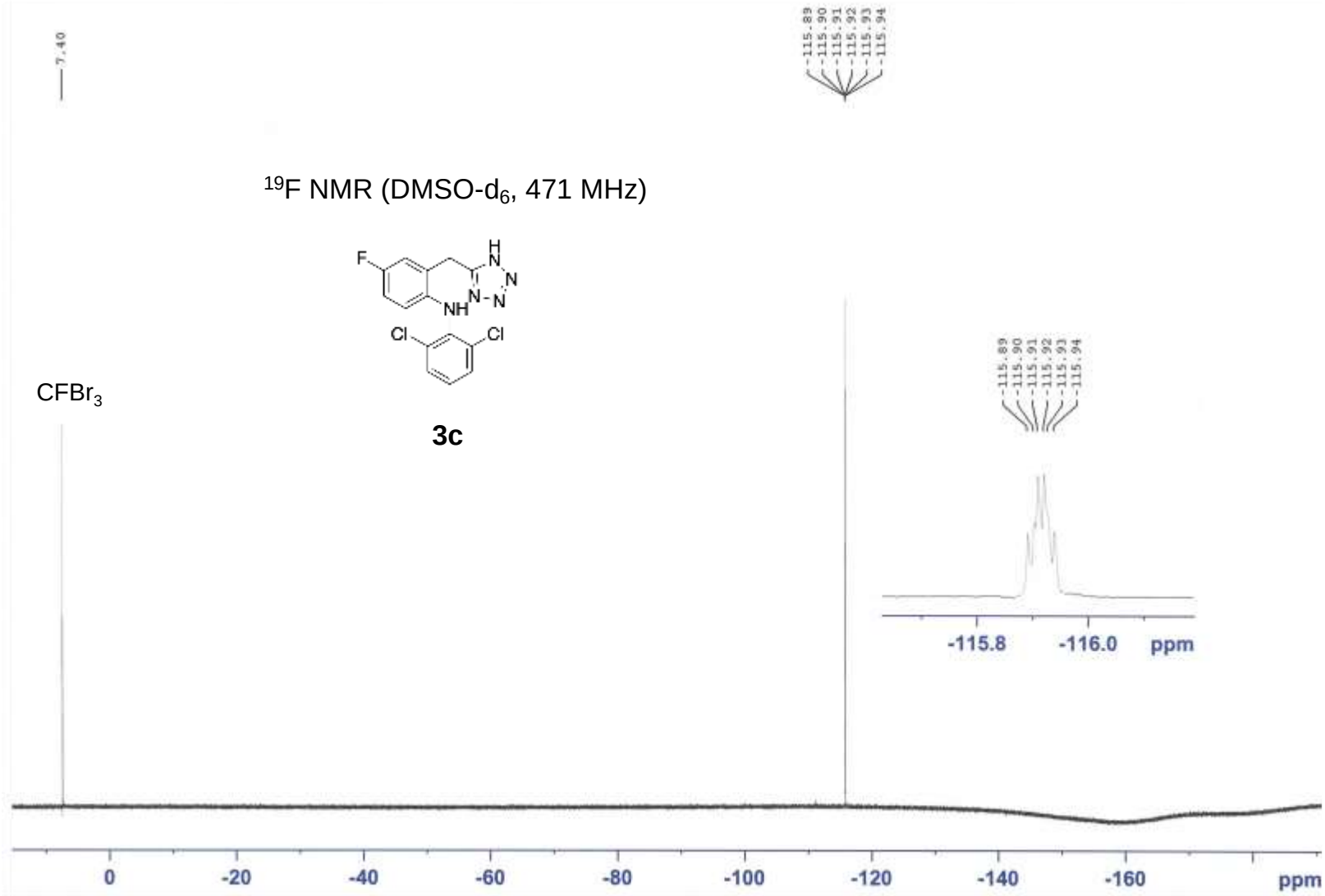

Figure S29 ^{19}F NMR spectra of **3c**

Compound 3d

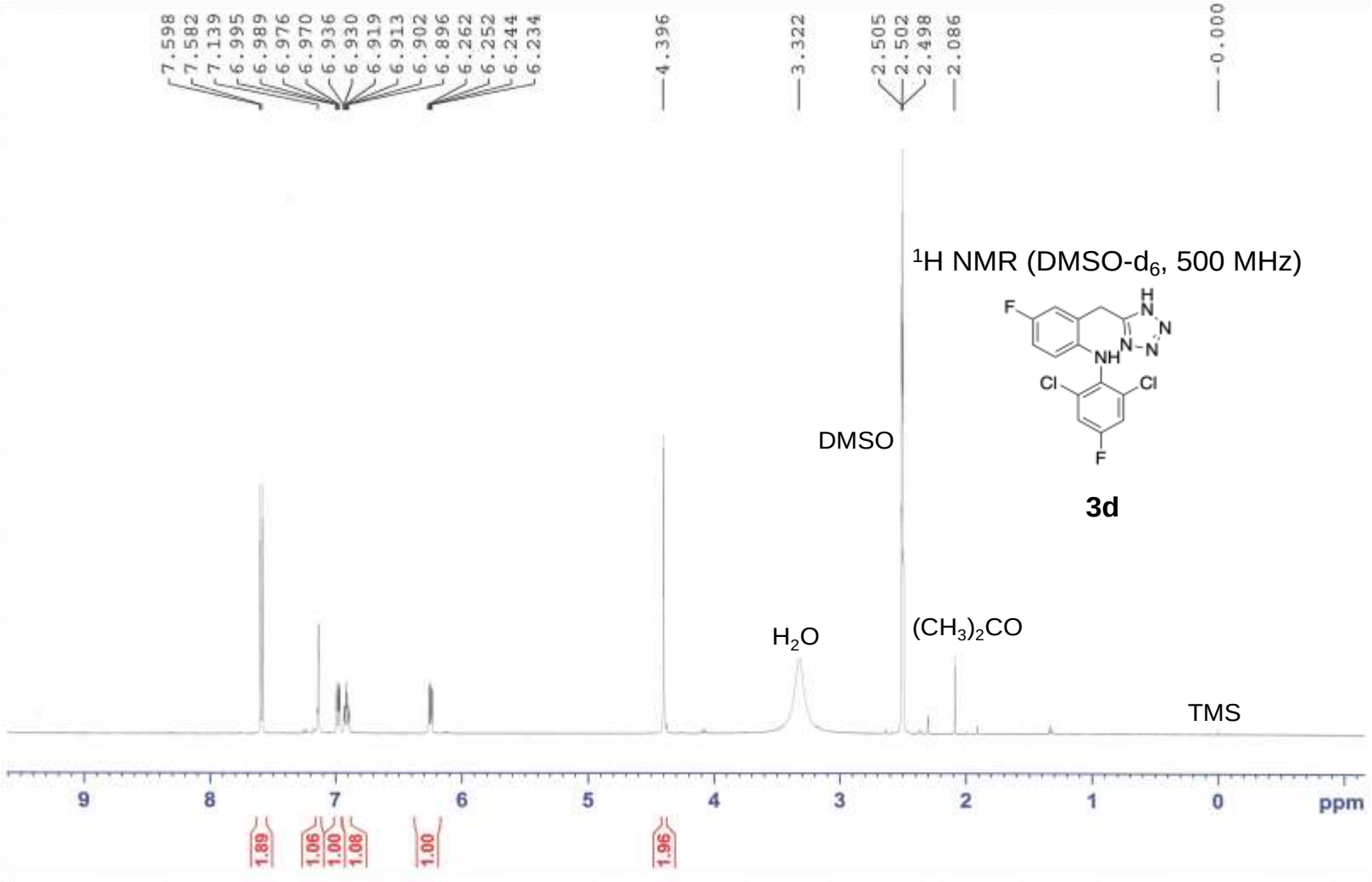

Figure S30 ^{1}H NMR spectra of **3d**

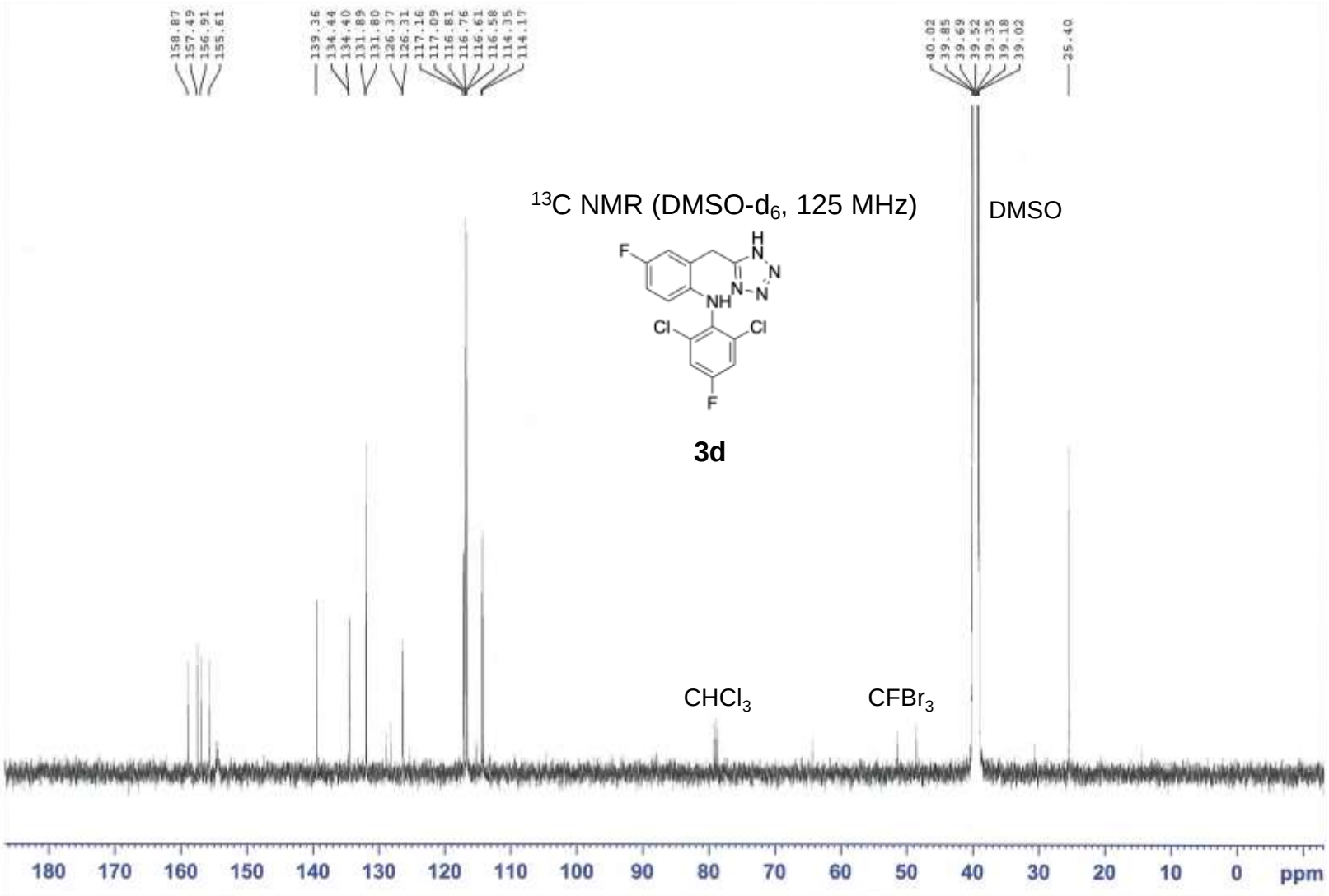

Figure S31 ^{13}C NMR spectra of **3d**

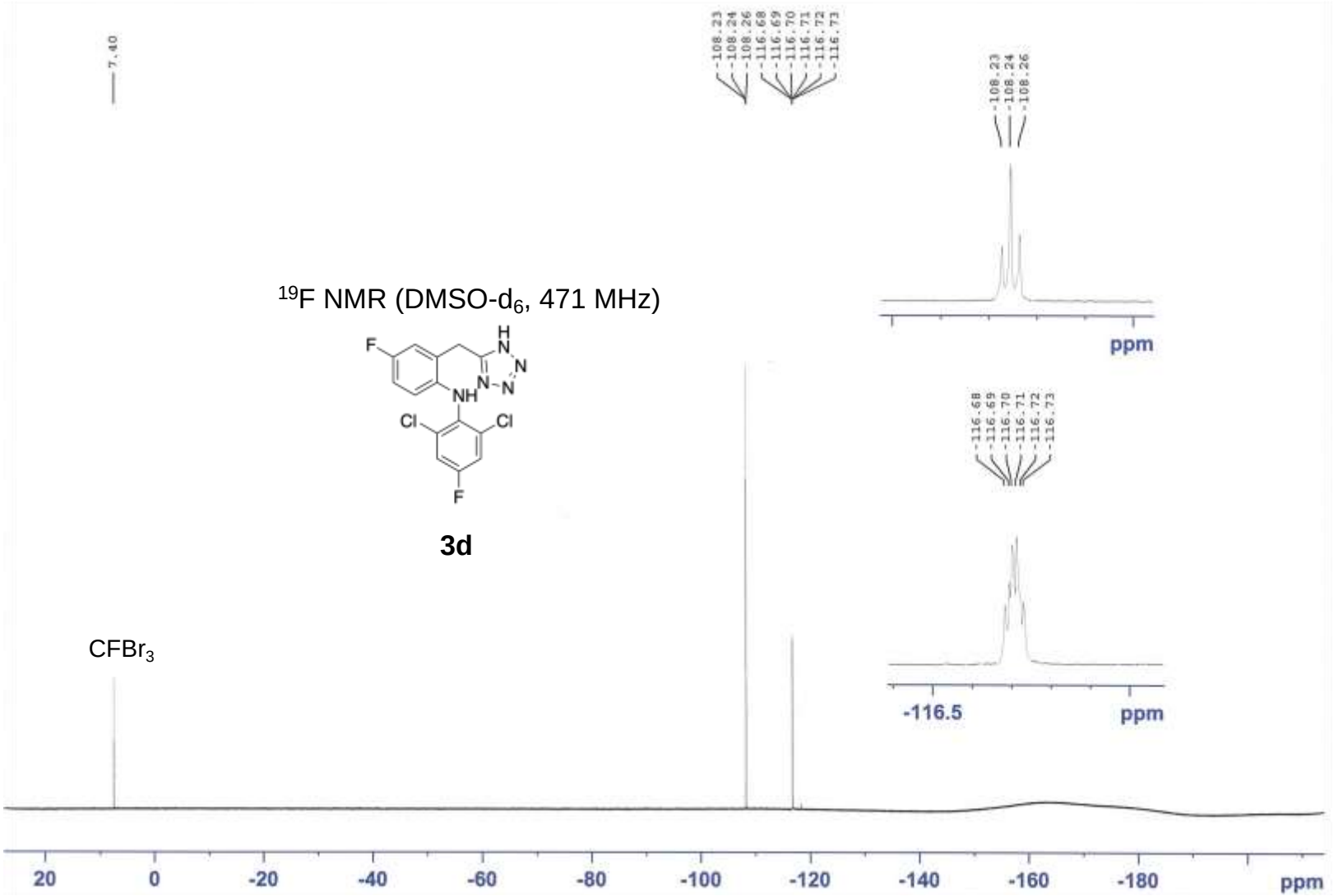

Figure S32 ^{19}F NMR spectra of **3d**

Compound 4a

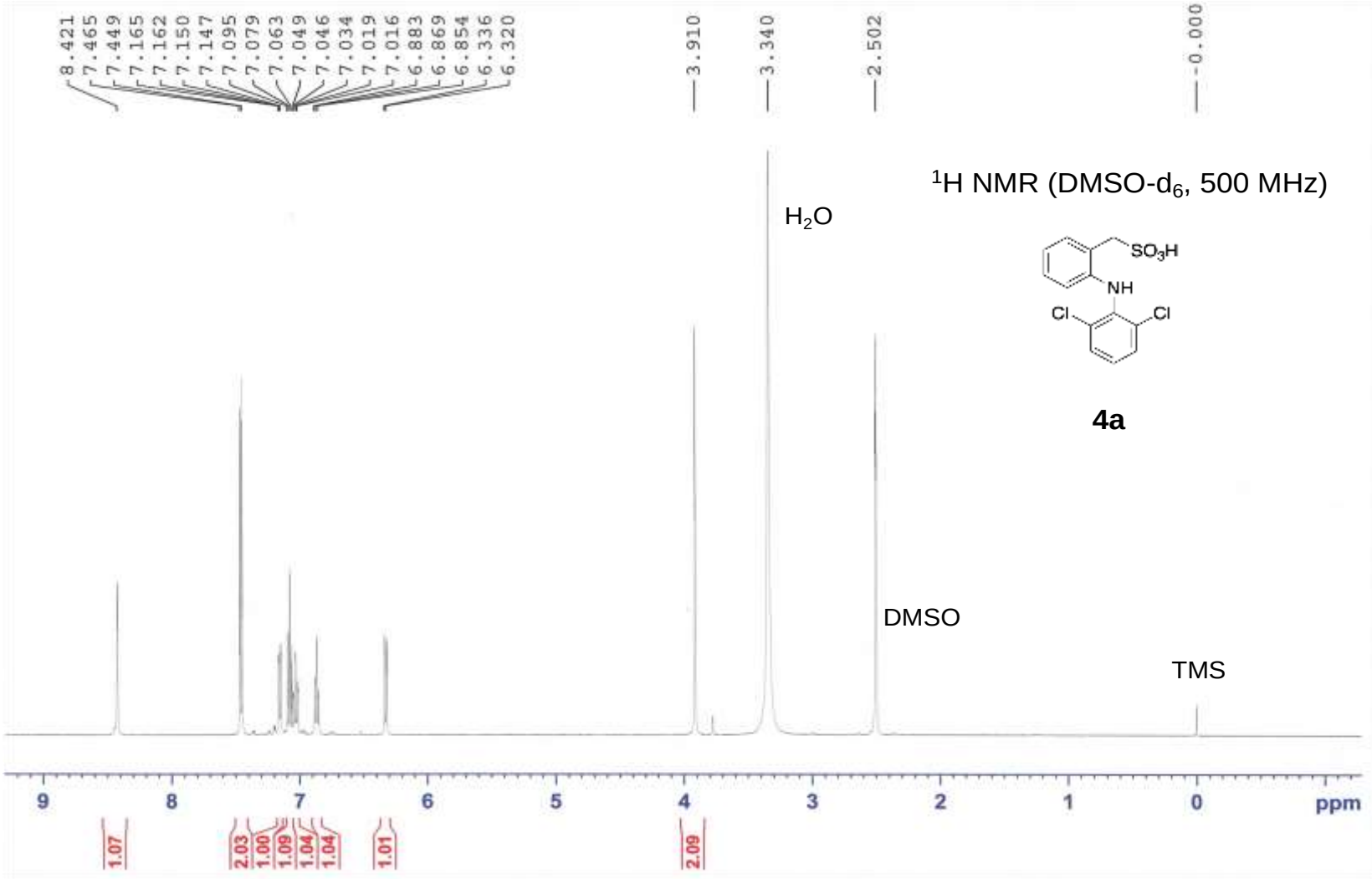

Figure S33 ^{1}H NMR spectra of **4a**

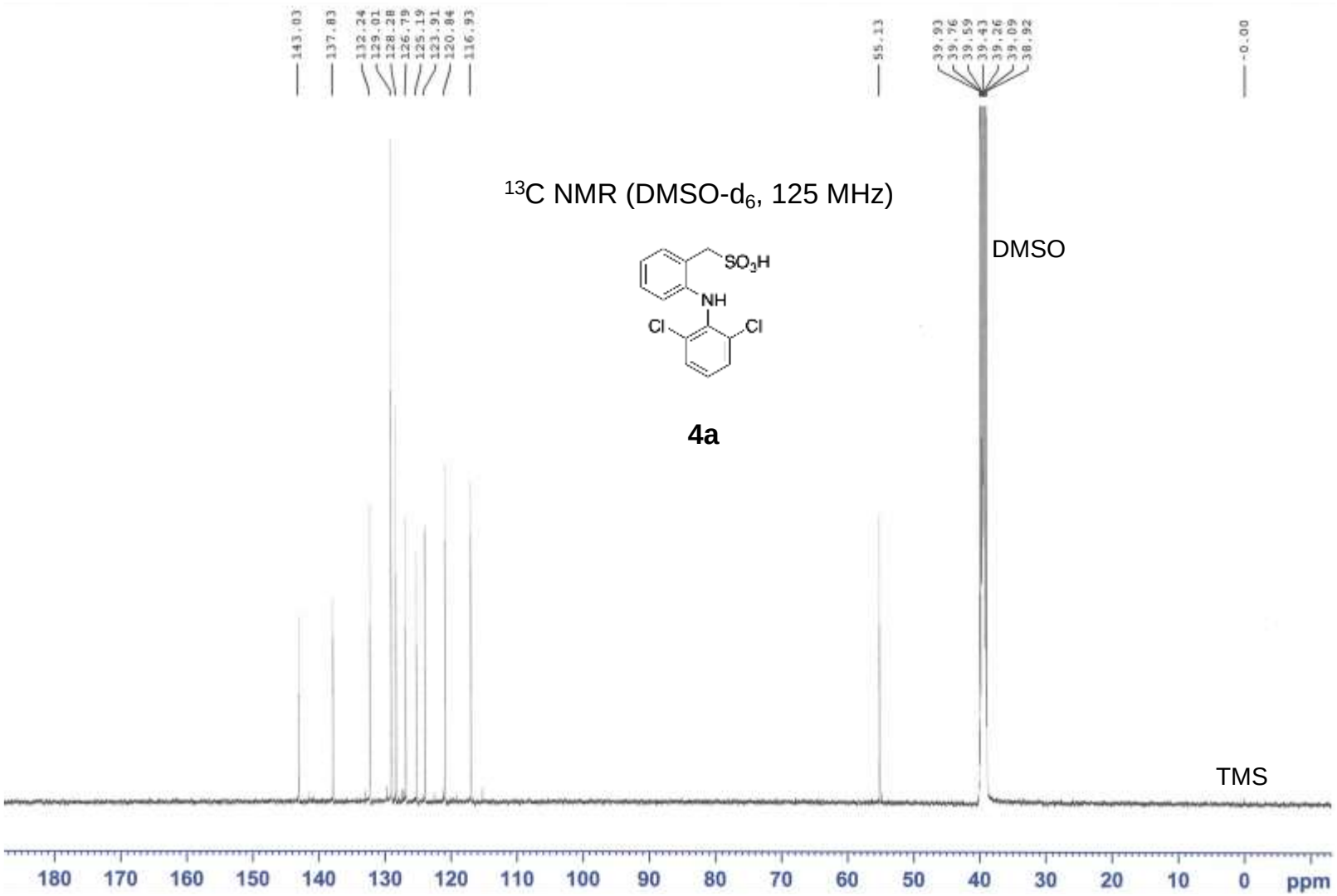

Figure S34 ^{13}C NMR spectra of **4a**

Compound 5a

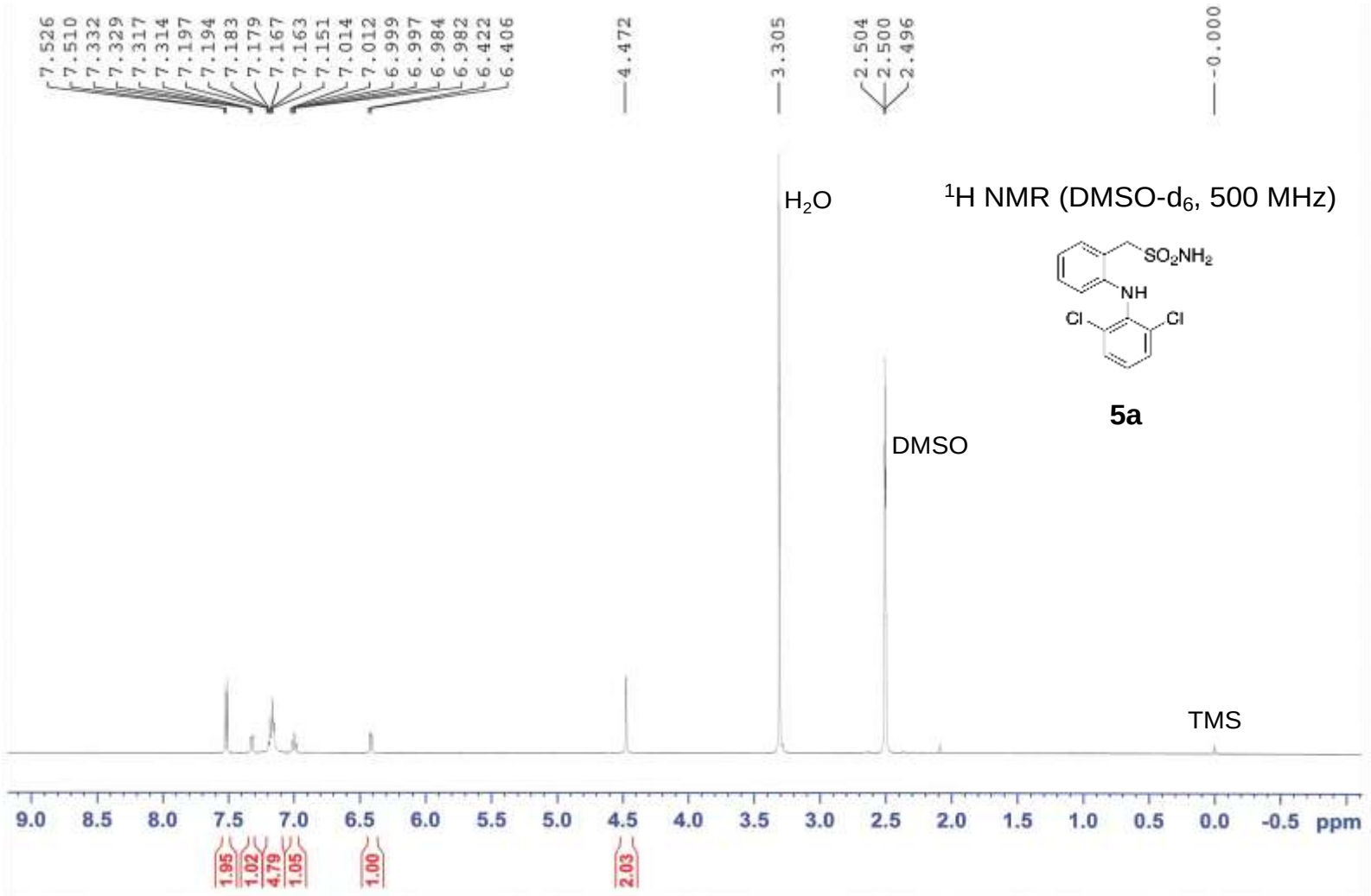

Figure S35 ^{1}H NMR spectra of **5a**

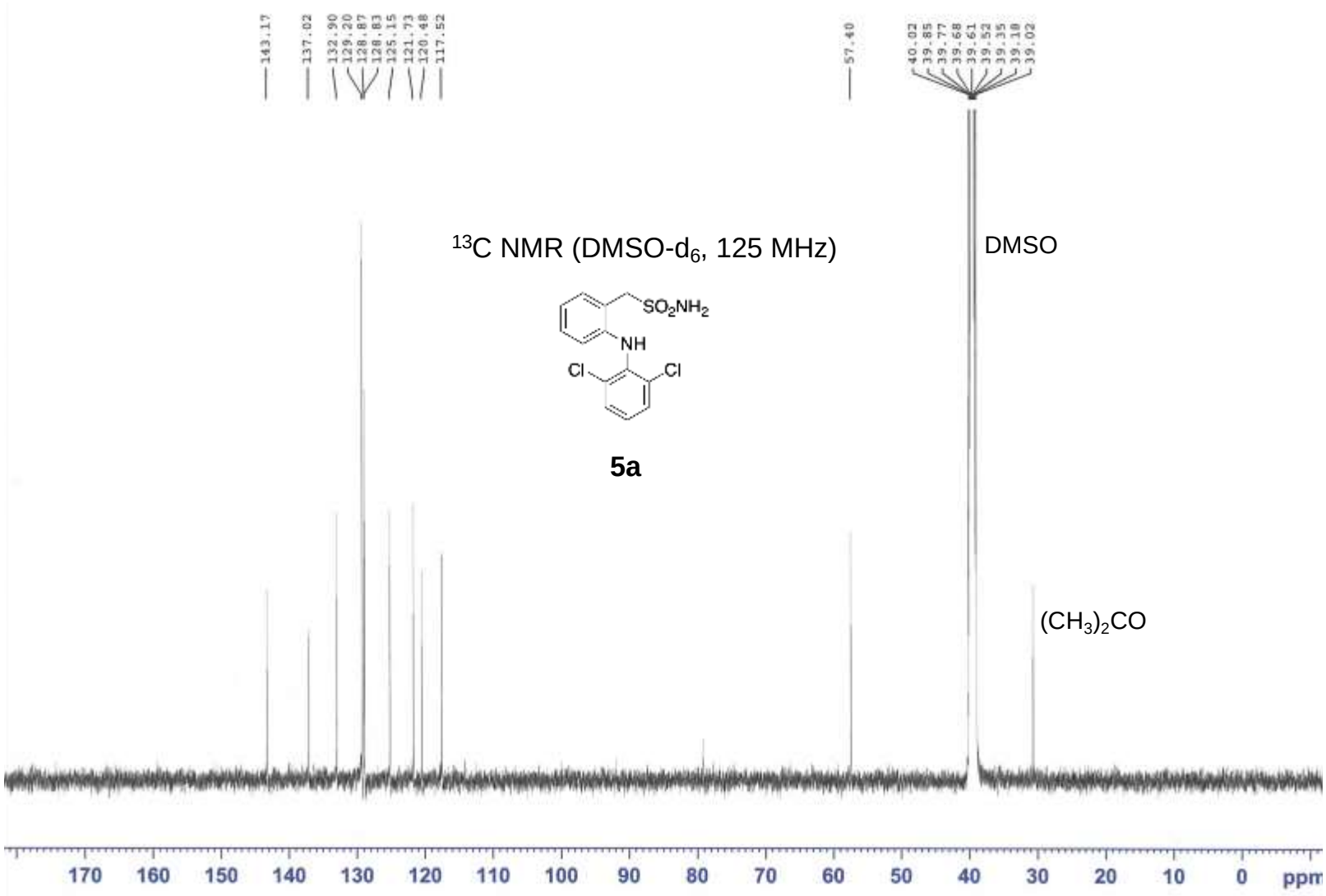

Figure S36 ^{13}C NMR spectra of **5a**

LC/MS Chromatogram of DCF

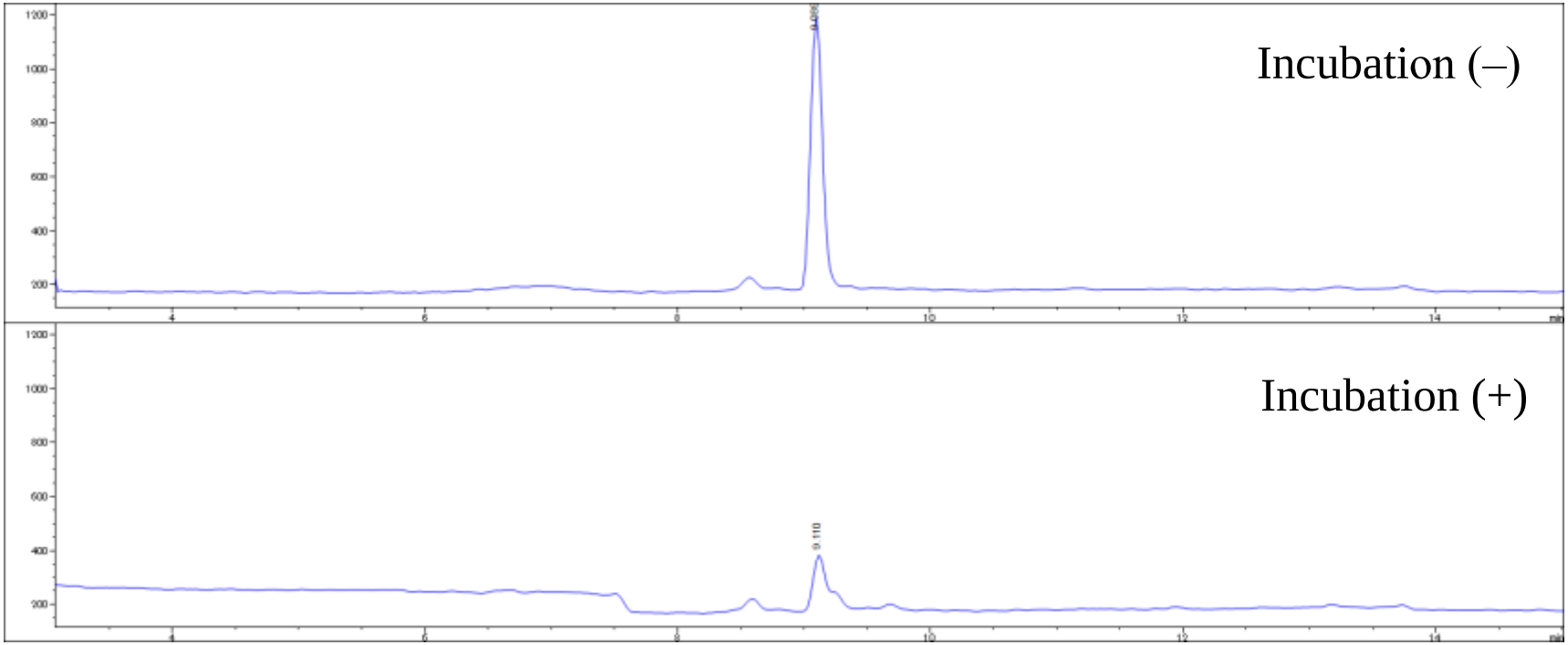

Figure S37 SIM chromatogram of DCF (*m/z* 294 $[M-H]^-$) after incubation with human liver microsomes fortified with an NADPH-generating system.

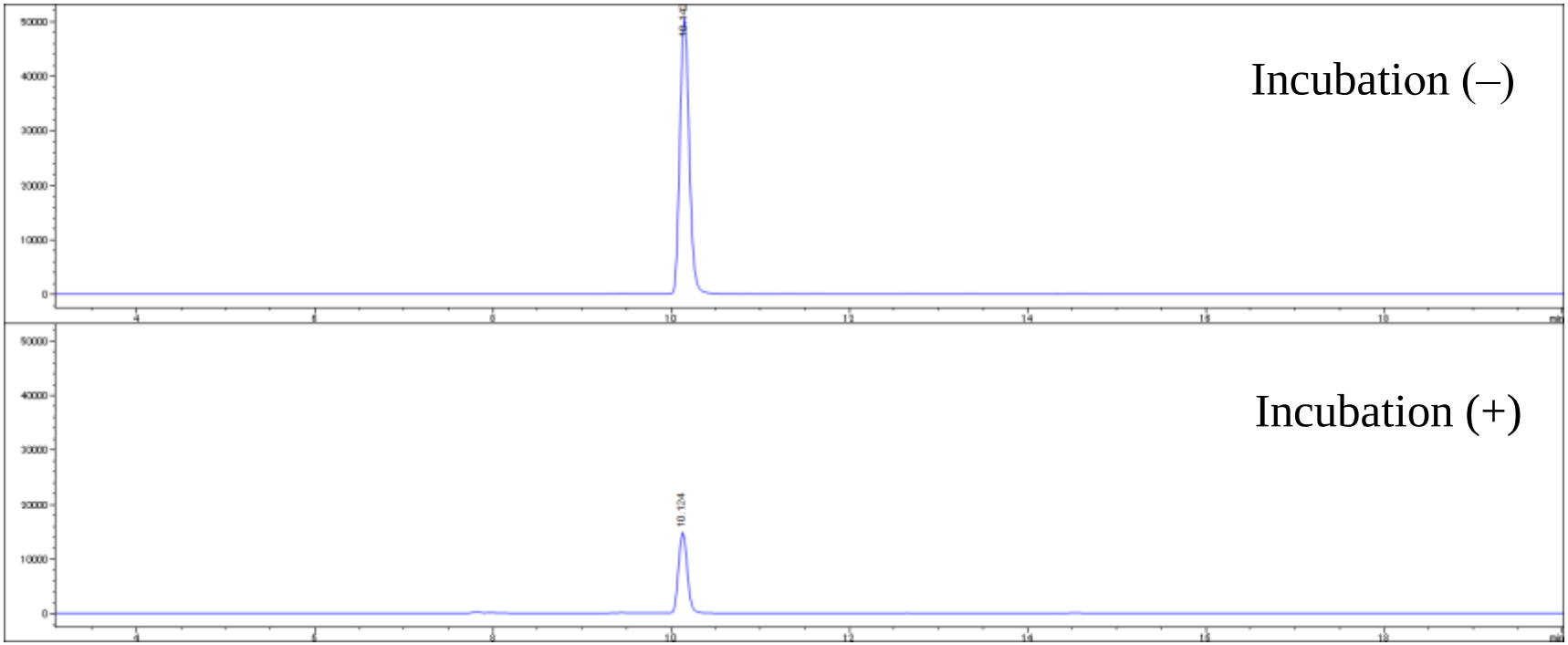

Figure S38 SIM chromatogram of DCF (*m/z* 294 $[M-H]^-$) after incubation with human liver microsomes fortified with UDPGA.