

# Targeting Stat3 anti-apoptosis pathways with organic and hybrid organic–inorganic inhibitors.

*Matthew B. Minus<sup>4</sup>, Haopei Wang<sup>1</sup>, Jaime O. Munoz<sup>2</sup>, Alexandra M. Stevens<sup>2</sup>, Alicia E. Mangubat-Medina<sup>1</sup>, Michael J. Krueger<sup>2</sup>, Wei Liu<sup>2</sup>, Moses M. Kasembeli<sup>3</sup>, Julian C. Cooper<sup>1</sup>, Mikhail I. Kolosov<sup>5</sup>, David J. Tweardy<sup>3,6</sup>, Michele S. Redell<sup>2</sup>, Zachary T. Ball<sup>1\*</sup>*

<sup>1</sup>Department of Chemistry, Rice University, Houston, TX 77005 (USA).

<sup>2</sup>Baylor College of Medicine, Texas Children's Cancer Center, Houston, TX 77030 (USA).

<sup>3</sup>Department of Infectious Diseases, Infection Control and Employee Health and <sup>6</sup>Department of Molecule and Cellular Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030 (USA).

<sup>5</sup>Department of Medicine, Baylor College of Medicine, Houston, TX 77030 (USA)

<sup>4</sup>Prairieview A&M University, Prairie View, TX, 77446 (USA)

\* Corresponding Author

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### Experimental

#### 1.1. General Methods:

**Flash chromatography:** was performed with 40-63- $\mu\text{m}$  particle size silica gel.

**NMR Spectroscopy:** NMR data was acquired with Bruker Avance 400, Bruker Avance 500 MHz or, Bruker Avance 600 instrument.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were referenced relative to residual solvent or TMS.  $^{19}\text{F}$  NMR chemical shifts were determined relative to  $\text{C}_6\text{H}_5\text{F}$  in corresponding solvents.

**Mass spectroscopy:** ESI-MS was performed on Bruker Daltonics micro-TOF instrument.

**Chemicals:** The following chemicals were purchased and used as received: thiophenol (Aldrich), 4-hydroxythiophenol, 2-hydroxythiophenol, 4-tertbutylthiophenol, 2-naphthol, 4-nitronaphthylamine, 1,5-dinitronaphthalene, 1-naphthol, 4-amino-1-naphthol hydrochloride (TCI), pentafluorobenzene sulfonyl chloride (Sigma), diisopropylethylamine (Fisher),  $\text{Rh}_2(\text{OAc})_4$  (Pressure Chemical), 2,2,2-trifluoroethanol (Aldrich), iodobenzene diacetate (Aldrich), butyric acid (Acros), 2-bromo-4-nitro-1-naphthylamine, 2,4-dibromo-1-naphthylamine (Aldrich), 2,4-dibromo-1-naphthol (Aldrich), 2,4-dibromo-1-naphthol (compound **14**, TCI), 2,4-dibromonaphthalen-1-amine (compound **15**, Sigma), 2-Bromo-4-nitro-1-naphthalenamine (compound **16**, AmBeed),  $\text{Na}_2\text{SO}_4$  (Fisher), and  $\text{MgSO}_4$  (Fisher).

**Solvents:** All solvents were reagent grade. Solvents used in inert atmosphere reactions were purified and degassed by the glass contour solvent system from SG waters USA.

**Synthesis of known compounds:**  $\text{Rh}_2(\text{OAc})_3(\text{tfa})$ ,<sup>1</sup> *cis*-  $\text{Rh}_2(\text{OAc})_2(\text{tfa})_2$ ,<sup>1</sup>  $\text{Rh}_2(\text{tfa})_4$ ,<sup>2</sup> methyl 4-(chlorosulfonyl)butanoate,<sup>3</sup> methyl 5-(chlorosulfonyl)-2-hydroxybenzoate,<sup>4</sup> 3-(chlorosulfonyl)benzoic acid,<sup>5</sup> methyl 2-(4-(chlorosulfonyl)phenoxy)acetate,<sup>6</sup> compound **1a**,<sup>7</sup>

compound **1b**,<sup>8</sup> compound **1c**,<sup>7</sup> compound **3aa**,<sup>7</sup> compound **4a**,<sup>7</sup> compound **5**,<sup>9</sup> compound **6**,<sup>10</sup> compound **S2**,<sup>7</sup> compound **13ab**,<sup>7</sup> compound **13ac**,<sup>11</sup> and 1,8-difluoronaphthalene,<sup>9</sup> were prepared according to previously reported protocols.

**STAT3 expression:** The dimeric (pSTAT3) and monomeric (STAT3) recombinant core fragments of STAT3 (AA 127-722) were expressed, purified, and analyzed according to a previously described method.<sup>12</sup>

**HPLC:** HPLC was performed on a Shimadzu CBM-20A instrument with Phenomenex Jupiter 4  $\mu$  Proteo 90A (250 mm  $\times$  15  $\mu$ m) and Phenomenex Jupiter 4  $\mu$  Proteo 90A (250 mm  $\times$  4.6  $\mu$ m) columns. Flow rates of 8 mL/min and 1 mL/min were used for preparative and analytical columns, respectively. Analytical and preparative HPLC were performed with gradients of acetonitrile and water (no 2,2,2-trifluoroacetic acid). All samples were run on a gradient of increasing (40%  $\rightarrow$  90%) MeCN/H<sub>2</sub>O from 2-22 min unless otherwise noted in the synthesis section. The absorbance was monitored at 320 nm during each run unless otherwise noted in the synthesis section.

#### **Surface plasmon resonance (SPR) inhibition measurements:**

**a) Phosphopeptide binding.** The ability of molecules to inhibit STAT3 binding to phosphopeptide (P1068) was assessed by SPR analysis on a Biacore 3000 instrument as previously described.<sup>13</sup>

#### **Preparation of aqueous NMR samples for decomposition analysis**

DMSO-*d*<sub>6</sub> was purged with nitrogen for 0.5 h. Potassium Phosphate buffer (pH 6.8) was prepared by dissolving KH<sub>2</sub>PO<sub>4</sub> and K<sub>2</sub>HPO<sub>4</sub> in D<sub>2</sub>O (10 mL). C188-9 (100  $\mu$ L, 10 mM in DMSO-*d*<sub>6</sub>) and DMSO-*d*<sub>6</sub> (100  $\mu$ L) were added to deuterated potassium phosphate buffer (800  $\mu$ L). The final concentration of C188-9 (1 mM) is similar to previously reported *in vivo* dosing concentration. Air was bubbled through samples for 15 min. Samples were then incubated at 38 °C until analyzed by NMR and ESI-MS.

#### **STAT3 phosphorylation assay**

Cells were added in a 24-well plate (1 $\times$ 10<sup>5</sup> cells/well). Inhibitor was incubated with the cells for 1 h. After 1 h, Granulocyte-colony stimulating factor (G-CSF) (1  $\mu$ L, 100 ng/ $\mu$ L) was added into each well and incubated for 15 min. Paraformaldehyde was then added into eppendorf tubes to creating a 2% paraformaldehyde suspension. The cells were spun down, aspirated, and resuspended in phospho-flow buffer (500  $\mu$ L). The rinsing was repeated 2 more times. The resulting pellet was evenly mixed in phospho-flow buffer. Then 1 mL of ice-cold methanol was immediately added to the eppendorf tube. The tube was placed on ice for 30 min. To remove the methanol the eppendorf tube was spun and the supernatant was aspirated. The cells were resuspended into 500  $\mu$ L phospho-flow buffer. This step was repeated in order to remove trace amounts of methanol. Antibody solution (4  $\mu$ L p-stat3 antibody + 46  $\mu$ L phospho-flow buffer) was added to the eppendorf tube. The tube was allowed to rest at rt for 30 min in the dark. Phospho-flow buffer (500  $\mu$ L) was then added to cellular suspension. The eppendorf tube was spun and the supernatant was aspirated. The resulting cellular pellet was suspended in phospho-flow buffer (300  $\mu$ L). The suspension was transferred to a 5 mL flow tube through a strainer for further analysis.

- Cells were centrifuged at 200 rpm for 5 min.
- Phospho-flow buffer: 450 mL H<sub>2</sub>O, 50 mL 10x PBS, 1 g BSA, 450 mg Na Azide

### Cellular apoptosis

The human AML cells were grown in RPMI medium (ATCC) supplemented with 10% FBS and 1% penicillin-streptomycin. They were grown in a humidified 37 °C incubator with 5% CO<sub>2</sub>. AML cells were plated in growth medium and exposed to drug or vehicle for 24 h. Apoptosis was quantified based on Annexin V-FITC and propidium iodide using an LSRII flow cytometer and data were analyzed using FCS Express software

### Oxidative decay of C-188-9

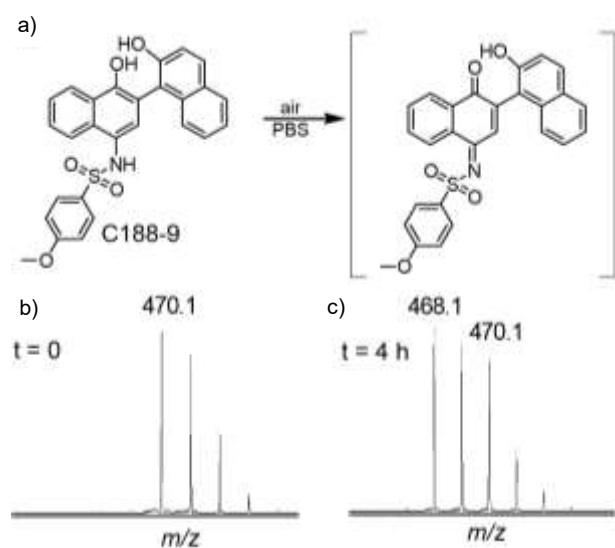


Figure S1. (a) Oxidation of C188-9 in PBS at 37°C, based on ESI-MS results. (b) ESI-MS spectrum (negative mode) of C188-9 before aqueous incubation. (c) ESI-MS spectrum (negative mode) of c188-9 after 4h of aqueous incubation.

Oxiativ decay of 4-hydroxynaphthylsulfonamdiess in aqueous buffer

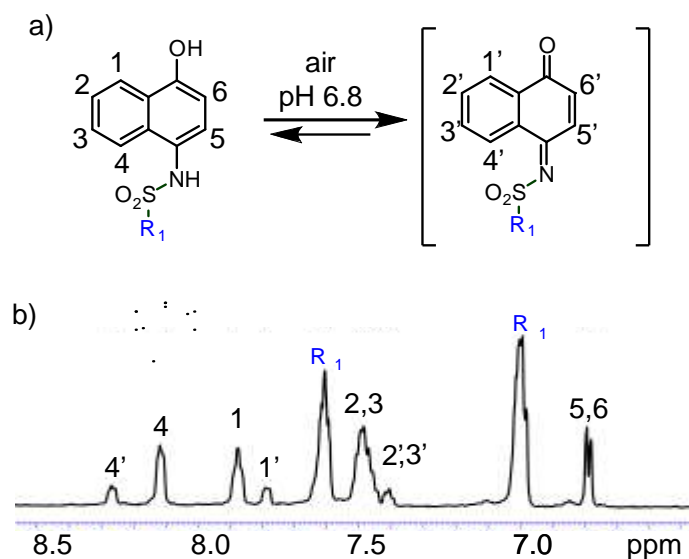
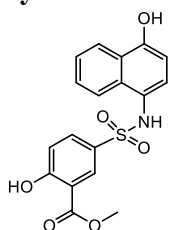


Figure S2. (a) Oxidation of 4-hydroxynaphthylsulfonamides in aqueous buffer (b) NMR spectrum of **1b** after 4 h of incubation (1 mM, 20% DMSO, 1x PBS, 38 °C).

## 1.2. Chemical synthesis and characterization

### *The general N-sulfonylation procedure*

#### Synthesis of sulfonamide compound **1e**

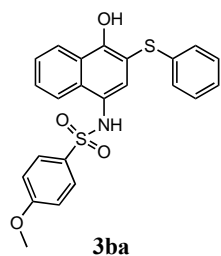


**1e**

Solid 4-amino-1-naphthol hydrochloride (971 mg, 4.9 mmol) and methyl 5-(chlorosulfonyl)-2-hydroxybenzoate (500 mg, 2 mmol) were placed in a round-bottomed flask containing  $\text{MgSO}_4$  (1.00 g) and a stir bar. The reaction vessel was evacuated and back-filled with nitrogen (3 $\times$ ). Both pyridine (10 mL) and acetonitrile (1 mL) were added by syringe to the round-bottomed flask. The reaction was monitored by TLC and was complete after 3 h. Upon completion, the reaction mixture was taken up in  $\text{CH}_2\text{Cl}_2$  and washed with aq HCl (3  $\times$  20 mL, 2 M). The organic layer was dried with  $\text{Na}_2\text{SO}_4$ , and filtered through cotton. Nitrogen gas was bubbled through the organic layer for 15 min. Then the organic layer was evaporated under vacuum. The resulting product was used without further purification (971 mg, 83%).

### *The general procedure for the oxidative coupling of thiols*

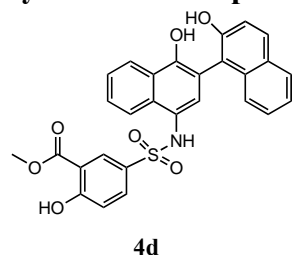
#### Synthesis of compound **3ba**



The naphtholsulfonamide **1b** (700 mg, 2.12 mmol) was dissolved into acetone (10 mL). Iodobenzene diacetate (750 mg, 2.3 mmol) was added to the reaction. After 1 h, the oxidation was complete by TLC (1:1 EtOAc/hexanes). Thiophenol (972 mg, 8.83 mmol) was added to the reaction mixture along with formic acid (1 mL). After 2 h, the reaction mixture was extracted with chloroform and washed thrice with 1M aq HCl. The organic layer was dried with Na<sub>2</sub>SO<sub>4</sub>, filtered through cotton, and dried onto silica gel. The crude was purified by silica gel chromatography (1:3 Et<sub>2</sub>O/hexanes) to afford **3ba** (350 mg, 37%).

### *The general procedure for the oxidative coupling of 2-naphthol*

#### Synthesis of compound 4d



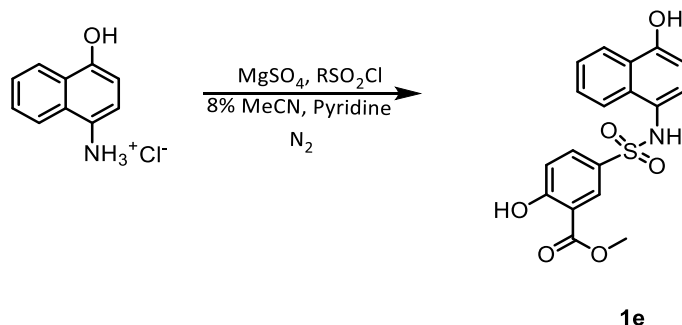
#### *i) Oxidation*

Naphthalene derivative **1e** (373 mg, 1 mmol) was placed in a 20-mL vial. Aq MeCN (10 mL, 50%) was added to the reaction vessel. The oxidant PhI(OAc)<sub>2</sub> (395 mg, 1.21 mmol) was added to the resulting solution. The solution was stirred with a magnetic stir bar for 0.5 h. The solution turned a deep red. The reaction was complete by TLC (1:1 EtOAc/hexanes). The reaction mixture was extracted thrice with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic extracts were washed twice with water, dried with Na<sub>2</sub>SO<sub>4</sub>, and filtered through cotton. The solvent was evaporated under vacuum to yield a brown solid crude which was taken to the next step without purification.

#### *ii) Oxidative addition*

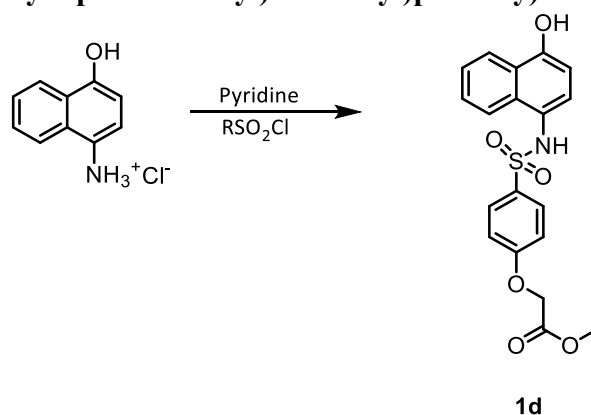
The 2-naphthol (1.00 g, 6.9 mmol) was added to the crude solid from part *i*) along with a magnetic stir bar. The flask was evacuated, and backfilled with nitrogen thrice. The dry solvent CH<sub>2</sub>Cl<sub>2</sub> (7 mL) was added to the reaction. BF<sub>3</sub>·Et<sub>2</sub>O (1.0 mL, 8.1 mmol) was added to the reaction mixture. The reaction was stirred at rt under nitrogen for 14 h. Once the quinone-imine intermediate was no longer visible by TLC (1:1 EtOAc/hexanes), the reaction was taken up in CH<sub>2</sub>Cl<sub>2</sub>. The organic solution was washed thrice with 1 M HCl, dried with Na<sub>2</sub>SO<sub>4</sub>, and filtered through cotton. Toluene was added to the solution. The solution was purged with nitrogen. The solvent was evaporated under vacuum. The dried crude was purified by silica gel chromatography (1:1 EtOAc/hexanes) to yield **4d** (237 mg, 46% over 2 steps).

**methyl 2-hydroxy-4-(N-(4-hydroxynaphthalen-1-yl)sulfamoyl)benzoate, 1e**



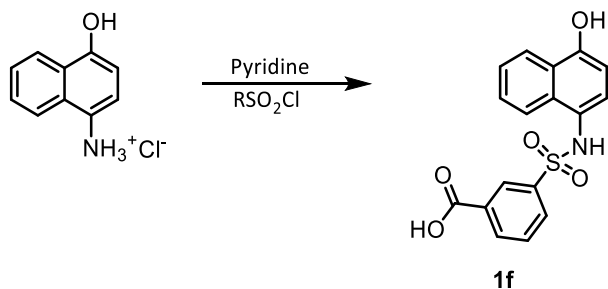
Product **1e** was sufficiently pure after extraction. (971 mg, 83%).  $^1\text{H}$  NMR (600 MHz, acetonitrile- $d_3$ )  $\delta$  10.98 (s, 1H), 8.05 (dd,  $J = 6.7, 2.8$  Hz, 1H), 7.94 (d,  $J = 2.6$  Hz, 1H), 7.81 – 7.77 (m, 1H), 7.76 (s, 1H), 7.65 – 7.58 (m, 2H), 7.41 – 7.30 (m, 3H), 6.91 (d,  $J = 8.9$  Hz, 1H), 6.86 (d,  $J = 8.0$  Hz, 1H), 6.66 (d,  $J = 8.1$  Hz, 1H), 3.81 (s, 3H).  $^{13}\text{C}$  NMR (151 MHz, acetonitrile- $d_3$ )  $\delta$  170.3, 165.2, 153.5, 135.1, 132.8, 131.6, 130.9, 127.6, 127.3, 126.2, 126.0, 124.4, 123.9, 123.0, 119.2, 113.4, 108.3, 53.6. MS (ESI)  $m/z$   $[\text{M}-\text{H}]^-$  calcd for  $\text{C}_{18}\text{H}_{15}\text{NO}_6\text{S}^-$  372.05, found 372.03. HPLC  $t_R$ : 6.7 min

#### methyl 2-(4-(N-(4-hydroxynaphthalen-1-yl)sulfamoyl)phenoxy)acetate, **1d**



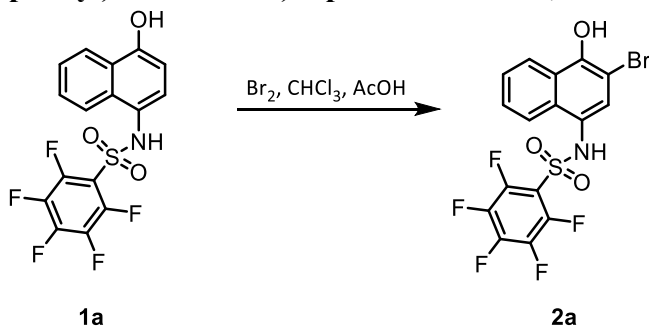
Sulfonamide **1d** was synthesized with the general N-sulfonylation procedure. Instead of column chromatography, the crude solid was dissolved in  $\text{CH}_2\text{Cl}_2$ . The product was precipitated by adding hexanes to the solution. The solid was filtered and dried to afford **1d** (281 mg, 48%).  $^1\text{H}$  NMR (600 MHz, acetonitrile- $d_3$ )  $\delta$  8.15 (d,  $J = 8.0$  Hz, 1H), 7.90 (d,  $J = 7.9$  Hz, 1H), 7.80 (s, 1H), 7.63 – 7.58 (m, 3H), 7.46 (q,  $J = 7.0$  Hz, 2H), 6.95 (dd,  $J = 14.3, 8.2$  Hz, 3H), 6.78 (d,  $J = 8.0$  Hz, 1H), 4.73 (s, 2H), 3.76 (s, 3H).  $^{13}\text{C}$  NMR (151 MHz, acetonitrile- $d_3$ )  $\delta$  170.0, 162.5, 153.7, 133.9, 133.2, 130.8, 127.97, 127.4, 126.6, 126.4, 125.1, 124.4, 123.4, 116.1, 108.7, 66.4, 53.2. MS (ESI)  $m/z$   $[\text{M}-\text{H}]^-$  calcd for  $\text{C}_{19}\text{H}_{16}\text{NO}_6\text{S}^-$  386.07, found 386.04. HPLC  $t_R$ : 6.4 min

#### 3-(N-(4-hydroxynaphthalen-1-yl)sulfamoyl)benzoic acid, **1f**



Sulfonamide **1f** was synthesized with the general N-sulfonylation procedure. Instead of column chromatography, the crude solid was dissolved in  $\text{CH}_2\text{Cl}_2$ . The product was precipitated by adding hexanes to the solution. The solid was filtered and dried to afford **1f** (600 mg, 32%).  $^1\text{H}$  NMR (500 MHz, acetone- $d_6$ )  $\delta$  8.39 (t,  $J = 1.8$  Hz, 1H), 8.19 (dt,  $J = 8.0, 1.2$  Hz, 2H), 8.05 – 7.96 (m, 1H), 7.86 – 7.78 (m, 1H), 7.57 (t,  $J = 7.8$  Hz, 1H), 7.47 – 7.34 (m, 2H), 6.98 (d,  $J = 8.1$  Hz, 1H), 6.79 (d,  $J = 8.1$  Hz, 1H).  $^{13}\text{C}$  NMR (151 MHz, acetone- $d_6$ )  $\delta$  171.5, 152.9, 139.6, 139.4, 133.7, 132.3, 129.0, 128.6, 127.9, 126.8, 126.3, 125.5, 125.3, 123.5, 123.4, 122.3, 107.5. MS (ESI)  $m/z$   $[\text{M}-\text{H}]^-$  calcd for  $\text{C}_{17}\text{H}_{12}\text{NO}_5\text{S}^-$  342.04, found 342.1. HPLC  $t_R$ : 5.9 min

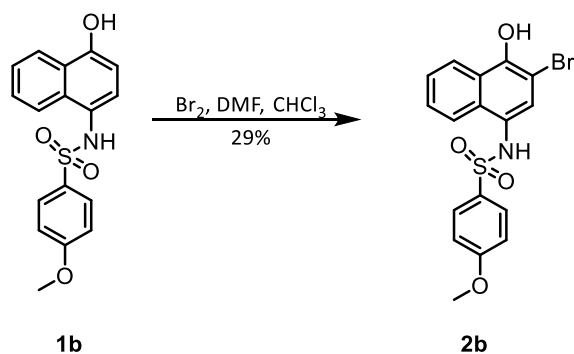
### 2-bromo-4-((perfluorophenyl)sulfonylamido)naphthalen-1-olate, **2a**



Sulfonamide **1a** (28 mg, 0.70 mmol) was placed in a scintillation vial and then dissolved in  $\text{CHCl}_3$  (1 mL). The vial was wrapped in foil and chilled to  $0^\circ\text{C}$ . A solution of  $\text{Br}_2$  (44  $\mu\text{L}$ , 9% in AcOH, 0.86 mmol) was added dropwise to the reaction mixture. After 0.5h, the reaction was complete by TLC. The reaction was washed thrice with water and once with  $\text{Na}_2\text{S}_2\text{SO}_3$ . The resulting organic layer was dried with  $\text{Na}_2\text{SO}_4$  and filtered through cotton. The organic solution was dried. The crude material was purified by silica gel chromatography (1:4, EtOAc/hexanes) to afford **2a** (22 mg, 66%).  $^1\text{H}$  NMR (600 MHz, acetone- $d_6$ )  $\delta$  8.68 (s, 0H), 8.23 (dd,  $J = 16.6, 7.8$  Hz, 2H), 7.93 (t,  $J = 7.5$  Hz, 1H), 7.87 (t,  $J = 7.9$  Hz, 1H).  $^{13}\text{C}$  NMR (151 MHz, acetone- $d_6$ )  $\delta$  177.2, 164.1, 141.4, 135.6, 135.1, 134.2, 133.3, 132.3, 128.6, 127.8. MS (ESI)  $m/z$   $[\text{M}-\text{H}]^-$  calcd for  $\text{C}_{16}\text{H}_6\text{BrF}_5\text{NO}_3\text{S}^-$  465.9, found 466.1.

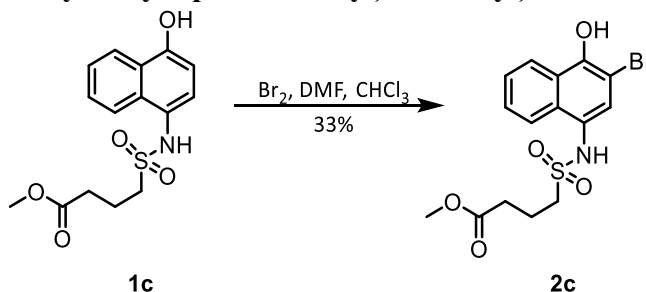
### N-(3-bromo-4-hydroxynaphthalen-1-yl)-4-methoxybenzenesulfonamide, **2b**





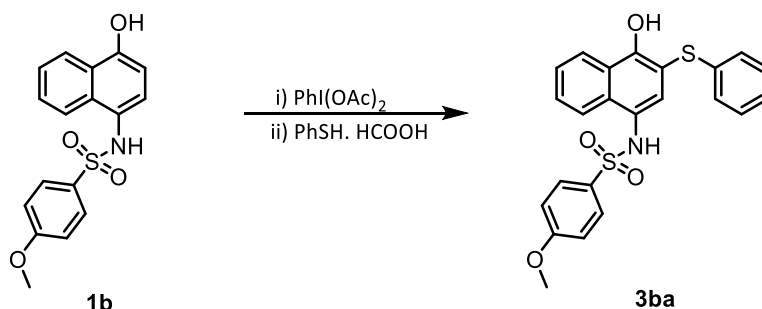
Compound **1b** (50 mg, 0.15 mmol) was charged into a 4-ml vial with a stir bar. DMF (500  $\mu$ L) was added to dissolve compound. Bromine (16  $\mu$ L, 0.30 mmol) was diluted in 500  $\mu$ L of  $\text{CHCl}_3$ , and then added slowly to the 4-ml vial at 0  $^\circ\text{C}$ . The reaction mixture was allowed to warm to rt, and stirred in the dark for 5 h. The crude reaction mixture was diluted in EtOAc (3.0 mL), and washed with saturated  $\text{Na}_2\text{S}_2\text{O}_3$ , water and brine. The organic layer was dried with  $\text{Na}_2\text{SO}_4$ , and filtered with filter paper. The solvent was removed with a stream of  $\text{N}_2$  gas. The crude mixture was purified with preparative HPLC (gradient: 40%  $\rightarrow$  90% MeCN with 0.1 % TFA from 4 to 29 min, absorbance 320 nm) to yield a bright yellow solid **2b** (18 mg, 29%). The product oxidized during synthesis, so all the characterizations were done for the oxidized product.  $^1\text{H}$  NMR (acetone- $d_6$ )  $\delta$  3.96 (s, 1H), 7.21- 7.23 (m, 2H), 7.82- 7.88 (m, 2H), 8.04- 8.05 (m, 2H), 8.17 (m, 2H), 8.94 (s, 1H).  $^{13}\text{C}$  NMR (acetone- $d_6$ )  $\delta$  56.83, 115.97, 127.77, 127.91, 128.62, 128.95, 131.10, 132.72, 133.47, 134.55, 135.31, 135.54, 135.84, 140.01, 141.80, 161.59, 165.35, 178.11. MS (ESI)  $m/z$   $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{17}\text{H}_{12}\text{BrNO}_4\text{S}^+$  (oxidized compound **2b**) 406.0, found 406.0.

#### methyl 4-(N-(3-bromo-4-hydroxynaphthalen-1-yl)sulfamoyl)butanoate, **2c**



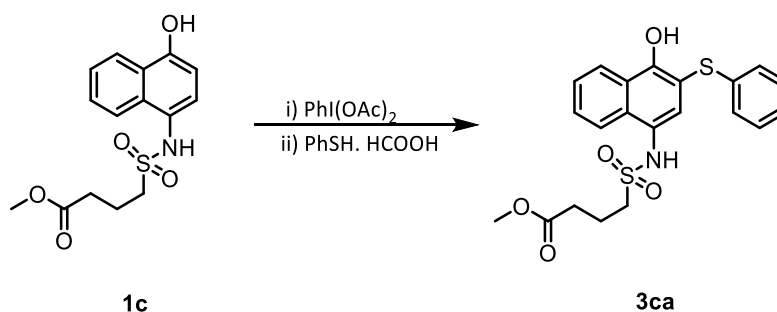
Compound **1c** (20 mg, 0.062 mmol) was charged into a 4-ml vial with a stir bar. DMF (500  $\mu$ L) was added to dissolve compound **3**. Bromine (3.0  $\mu$ L, 0.059 mmol) was diluted in 500  $\mu$ L of  $\text{CHCl}_3$ , and then added slowly to the 4-mL vial. The reaction mixture was stirred at rt in the dark for 16 h. The crude reaction mixture was diluted in EtOAc (3.0 mL), and washed with saturated  $\text{Na}_2\text{S}_2\text{O}_3$ , water and brine. The organic layer was dried with  $\text{Na}_2\text{SO}_4$ , and filtered with filter paper. The solvent was removed with a stream of  $\text{N}_2$  gas. The crude mixture was purified with preparative HPLC (gradient: 40%  $\rightarrow$  90% MeCN with 0.1% TFA from 4 to 29 min, absorbance 320 nm) to yield a dark green solid **2c** (8.3 mg, 33%).  $^1\text{H}$  NMR (acetone- $d_6$ )  $\delta$  2.29 (q,  $J=7.5$  Hz, 2H), 2.65 (t,  $J=7.3$  Hz, 2H), 3.59 (m, 2H), 3.67 (s, 3H), 7.90 (m, 2H), 8.19 (m, 1H), 8.35 (m, 1H), 8.66 (s, 1H).  $^{13}\text{C}$  NMR (acetone- $d_6$ )  $\delta$  20.65, 32.81, 52.39, 55.28, 127.92, 129.05, 132.80, 134.48, 135.09, 135.47, 135.66, 139.89, 162.87, 173.84, 178.10. MS (ESI)  $m/z$   $[\text{M}-\text{H}]^-$  calcd for  $\text{C}_{15}\text{H}_{16}\text{BrNO}_5\text{S}^-$  401.3, found 401.2.

#### N-(4-hydroxy-3-(phenylthio)naphthalen-1-yl)-4-methoxybenzenesulfonamide, **3ba**



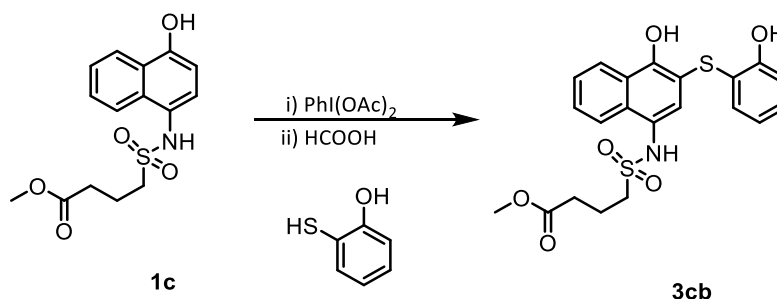
The thioether **3ba** was synthesized from **2** using the general oxidative coupling to thiols procedure. Tan solid (350 mg, 37%).  $^1\text{H}$  NMR (500 MHz, acetone- $d_6$ )  $\delta$  8.79 (s, 1H), 8.64 (s, 1H), 8.29 (dd,  $J = 7.8, 1.9$  Hz, 1H), 8.27 – 8.21 (m, 1H), 7.64 – 7.53 (m, 4H), 7.30 (t,  $J = 7.7$  Hz, 2H), 7.20 (t,  $J = 7.4$  Hz, 1H), 7.08 (s, 1H), 7.02 (d,  $J = 7.7$  Hz, 2H), 6.91 – 6.84 (m, 2H), 3.76 (s, 3H).  $^{13}\text{C}$  NMR (126 MHz, acetone- $d_6$ )  $\delta$  166.7, 158.2, 140.3, 136.9, 135.3, 135.1, 133.3, 133.0, 131.5, 130.8, 129.9, 129.3, 128.9, 127.7, 126.8, 117.8, 112.4, 59.0. MS (ESI)  $m/z$   $[\text{M}-\text{H}]^-$  calcd for  $\text{C}_{23}\text{H}_{18}\text{NO}_4\text{S}_2^-$  437.1, found 437.0

### methyl 4-(N-(4-hydroxy-3-(phenylthio)naphthalen-1-yl)sulfamoyl)butanoate, **3ca**



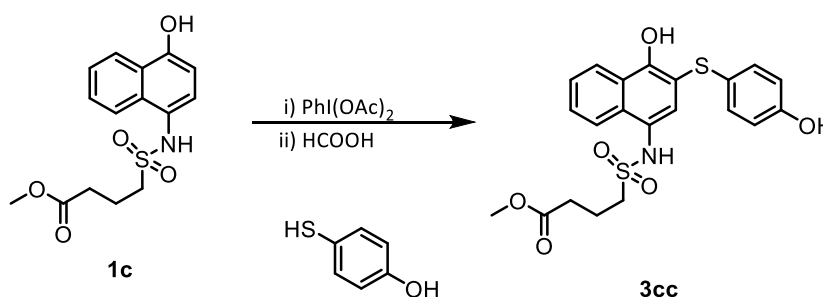
The naphthol sulfonamide **1c** (375 mg, 1.16 mmol) was dissolved into acetone. Iodobenzene diacetate (358 mg, 1.1 mmol) was subsequently added to the reaction. After 1 h, the reaction was complete by TLC (1:4 EtOAc/hexanes). The thiophenol (200 mg, 1.8 mmol) was added to the reaction mixture. The formic acid was subsequently added to the reaction mixture. After 2 h, the reaction mixture was extracted with chloroform and washed thrice with 1 M aq HCl. The organic layer was dried with  $\text{MgSO}_4$  and degassed with nitrogen. After degassing the solvent was evaporated under vacuum. The crude material was purified by silica gel chromatography (1:4, EtOAc/hexanes) to afford **3ca** (50 mg, 26%).  $^1\text{H}$  NMR (600 MHz, acetonitrile- $d_3$ )  $\delta$  8.28 (d, 1H,  $J = 8.4$  Hz), 8.21 (d, 1H,  $J = 8.4$  Hz), 7.69 (t, 1H,  $J = 7.7$  Hz), 7.62 (t, 1H,  $J = 7.7$  Hz), 7.54 (s, 1H), 7.28 (t, 2H,  $J = 7.7$  Hz), 7.20 (t, 1H,  $J = 7.4$  Hz), 7.15 (d, 2H,  $J = 8.0$  Hz), 3.57 (s, 3H), 3.13-3.10 (m, 2H), 2.38 (t, 2H,  $J = 7.2$  Hz), 2.04-1.99 (m, 2H).  $^{13}\text{C}$  NMR (151 MHz, acetonitrile- $d_3$ )  $\delta$  173.6, 155.1, 137.3, 133.7, 131.8, 130.3, 129.3, 128.3, 127.5, 127.3, 126.1, 125.7, 124.5, 124.1, 118.3, 110.3, 52.1, 51.6, 32.4, 20.0. MS (ESI)  $m/z$   $[\text{M}-\text{H}]^-$  calcd for  $\text{C}_{21}\text{H}_{20}\text{NO}_5\text{S}_2^-$  430.1, found 430.1. HPLC  $t_R$ : 12.2 min

### methyl 4-(N-(4-hydroxy-3-((2-hydroxyphenyl)thio)naphthalen-1-yl)sulfamoyl)butanoate, **3cb**



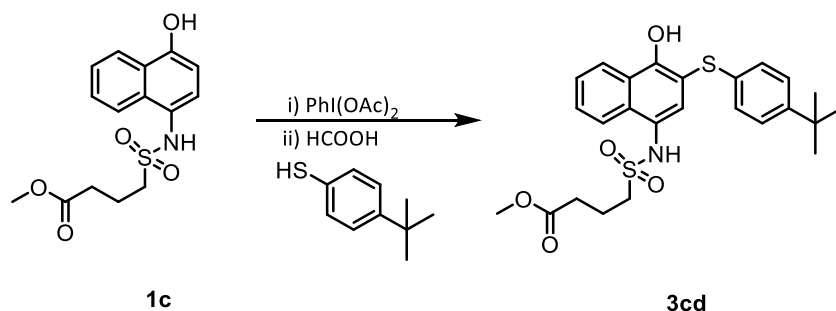
Sulfonamide **1c** was subjected to the general oxidative coupling of thiols procedure. The resulting crude material was purified by silica gel chromatography (Et<sub>2</sub>O/hexanes, 1:3) to afford **3cb** (20 mg, 50%). <sup>1</sup>H NMR (600 MHz, acetone-*d*<sub>6</sub>) δ 8.39 – 8.25 (m, 2H), 7.71 – 7.62 (m, 2H), 7.62 – 7.54 (m, 1H), 7.22 – 7.07 (m, 2H), 6.96 (d, *J* = 8.0 Hz, 1H), 6.80 (t, *J* = 7.5 Hz, 1H), 3.61 (s, 3H), 3.28 – 3.11 (m, 2H), 2.49 (t, *J* = 7.3 Hz, 2H), 2.15 – 2.09 (m, 2H). <sup>13</sup>C NMR (151 MHz, acetone-*d*<sub>6</sub>) δ 174.2, 157.3, 155.6, 134.4, 133.6, 132.3, 130.78, 129.4, 127.9, 126.9, 125.5, 124.7, 123.2, 122.5, 117.3, 112.7, 52.7, 52.3, 33.3, 21.0. MS (ESI) *m/z* [M-H]<sup>-</sup> calcd for C<sub>21</sub>H<sub>20</sub>NO<sub>6</sub>S<sub>2</sub><sup>-</sup> 446.1, found 446.1. HPLC *t*<sub>R</sub>:8.3 min

**methyl 4-(N-(4-hydroxy-3-((4-hydroxyphenyl)thio)naphthalen-1-yl)sulfamoyl)butanoate, 3cc**



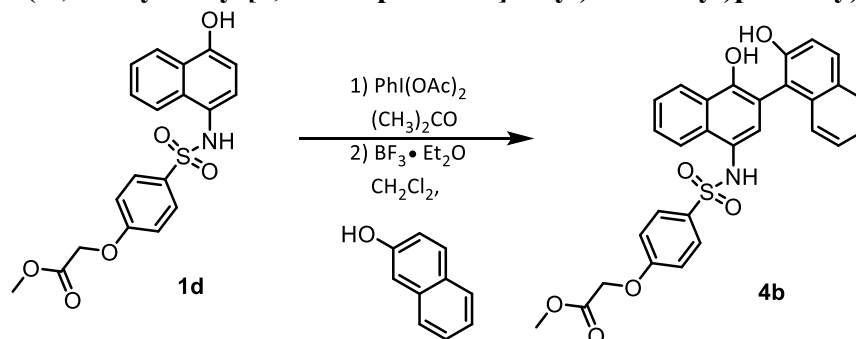
Sulfonamide **1c** was subjected to the general oxidative coupling of thiols procedure. The resulting crude material was purified by silica gel chromatography (Et<sub>2</sub>O/hexanes, 1:4) to afford **3cc** (6 mg, 36%). <sup>1</sup>H NMR (600 MHz, acetonitrile-*d*<sub>3</sub>) δ 8.24 (d, *J* = 8.4 Hz, 1H), 8.16 (d, *J* = 8.4 Hz, 1H), 7.72 (s, 1H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.61 – 7.55 (m, 2H), 7.47 (s, 1H), 7.41 (s, 1H), 7.20 (d, *J* = 8.6 Hz, 2H), 7.08 (s, 1H), 6.76 (d, *J* = 8.7 Hz, 2H), 3.59 (s, 3H), 3.14 – 3.03 (m, 2H), 2.38 (t, *J* = 7.2 Hz, 2H), 2.06 – 1.97 (m, 2H). <sup>13</sup>C NMR (151 MHz, acetonitrile-*d*<sub>3</sub>) δ 173.3, 157.2, 153.3, 132.8, 132.3, 130.4, 128.4, 127.0, 125.5, 125.4, 125.2, 124.1, 123.4, 116.9, 113.1, 51.7, 51.1, 32.0, 19.5. MS (ESI) *m/z* [M-H]<sup>-</sup> calcd for C<sub>21</sub>H<sub>20</sub>NO<sub>6</sub>S<sub>2</sub><sup>-</sup> 446.1, found 446.1. HPLC *t*<sub>R</sub>:8.3 min

**methyl 4-(N-(3-((4-(tert-butyl)phenyl)thio)-4-hydroxynaphthalen-1-yl)sulfamoyl)butanoate, 3cd**



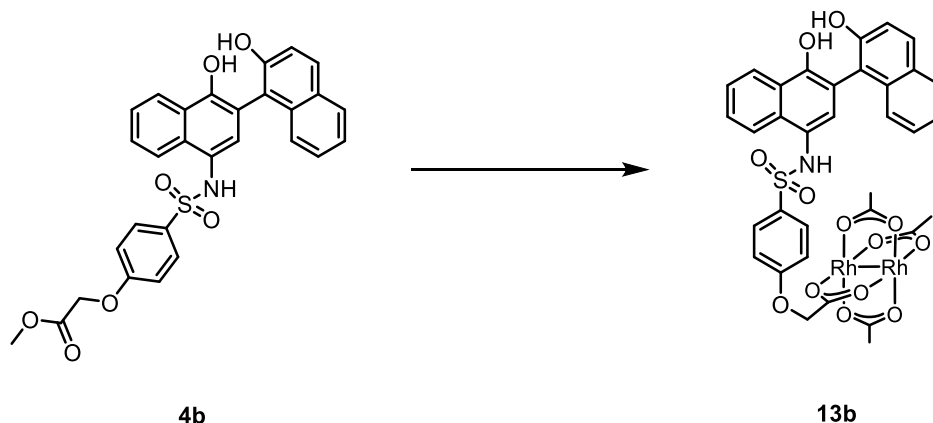
Sulfonamide **1c** was subjected to the general oxidative coupling of thiols procedure. The resulting crude material was purified by silica gel chromatography (Et<sub>2</sub>O/hexanes, 1:10) to afford **3cd** (50 mg, 35%).<sup>1</sup>H NMR (500 MHz, chloroform-*d*) δ 8.25 (dd, *J* = 8.3, 1.2 Hz, 1H), 8.09 – 8.01 (m, 1H), 7.64 – 7.58 (m, 2H), 7.52 (ddd, *J* = 8.2, 6.8, 1.2 Hz, 1H), 7.23 (s, 1H), 7.18 (t, *J* = 4.3 Hz, 2H), 7.00 (d, *J* = 8.5 Hz, 2H), 6.43 (s, 1H), 3.55 (s, 3H), 3.19 – 3.05 (m, 2H), 2.40 (t, *J* = 7.0 Hz, 2H), 2.11 (dq, *J* = 9.0, 7.0 Hz, 2H), 1.18 (s, 9H).<sup>13</sup>C NMR (126 MHz, chloroform-*d*) δ 172.8, 154.4, 149.9, 132.5, 130.9, 128.9, 127.4, 126.6, 126.4, 124.3, 123.9, 123.9, 122.3, 109.4, 51.8, 51.1, 34.5, 31.9, 31.2, 19.1. MS (ESI) *m/z* [M-H]<sup>-</sup> calcd for C<sub>25</sub>H<sub>28</sub>NO<sub>5</sub>S<sub>2</sub> 486.1, found 486.2. HPLC *t<sub>R</sub>*: 7.5 min

#### methyl 2-(4-(N-(1',2'-dihydroxy-[1,2'-binaphthalen]-4'-yl)sulfamoyl)phenoxy)acetate, **4b**



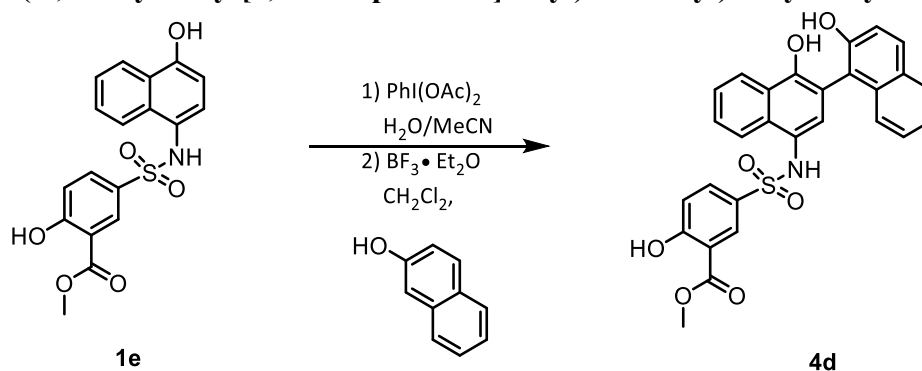
Sulfonamide **1d** was subjected to the general oxidative coupling of 2-naphthol procedure. The resulting crude material was purified by silica gel chromatography (Et<sub>2</sub>O/hexanes, 1:2) to afford **4b** (60 mg, 61%).<sup>1</sup>H NMR (500 MHz, acetone-*d*<sub>6</sub>) δ 8.32 (dd, *J* = 15.1, 8.6 Hz, 2H), 7.86 (t, *J* = 8.1 Hz, 3H), 7.82 – 7.76 (m, 1H), 7.71 (d, *J* = 8.2 Hz, 2H), 7.56 (p, *J* = 7.1 Hz, 2H), 7.39 (t, *J* = 7.2 Hz, 1H), 7.34 (t, *J* = 7.3 Hz, 1H), 7.28 (d, *J* = 8.9 Hz, 1H), 7.19 (d, *J* = 8.3 Hz, 1H), 7.11 (d, *J* = 8.1 Hz, 1H), 6.94 (d, *J* = 8.9 Hz, 2H), 6.85 (s, 1H), 4.67 (s, 2H), 3.74 (s, 3H). HPLC *t<sub>R</sub>*: 11 min

#### Rhodium conjugate, **13b**



Ester **4b** (10 mg, 0.018 mmol), was hydrolyzed according to procedures described in literature.<sup>7</sup> The metal complex  $\text{Rh}_2(\text{OAc})_3(\text{tfa})$  (6 mg, 0.012 mmol), the carboxylic acid of ester **4b**, and a stir bar were placed in a vial. The solid mixture was dissolved into 2,2,2-trifluoroethanol (1 mL). The resulting solution was purged with nitrogen for 15 min.  $^i\text{Pr}_2\text{EtN}$  (1.5 mg, 0.012 mmol) was added to the reaction and it was heated for 4 h at 50 °C while stirring. After 4 h, the reaction was complete by TLC (1:3, EtOAc/hexanes). The crude reaction mixture was evaporated onto silica and purified by silica gel chromatography (1:3, EtOAc/hexanes) to yield **13b** as a blue solid (4 mg, 37%).  $^1\text{H}$  NMR (500 MHz, acetone- $d_6$ )  $\delta$  8.36 – 8.25 (m, 2H), 7.84 (dd,  $J = 9.4, 6.5$  Hz, 2H), 7.65 – 7.59 (m, 2H), 7.59 – 7.49 (m, 2H), 7.37 – 7.29 (m, 2H), 7.25 (dd,  $J = 13.3, 8.2$  Hz, 2H), 7.21 – 7.11 (m, 2H), 6.82 (s, 1H), 6.62 (d,  $J = 8.9$  Hz, 1H), 4.28 – 4.17 (m, 2H), 1.70 (s, 9H). MS (ESI)  $m/z$   $[\text{M-H}]^-$  calcd for  $[\text{C}_{34}\text{H}_{28}\text{NO}_{13} \text{Rh}_2\text{S}]^-$  895.9, found 896.1

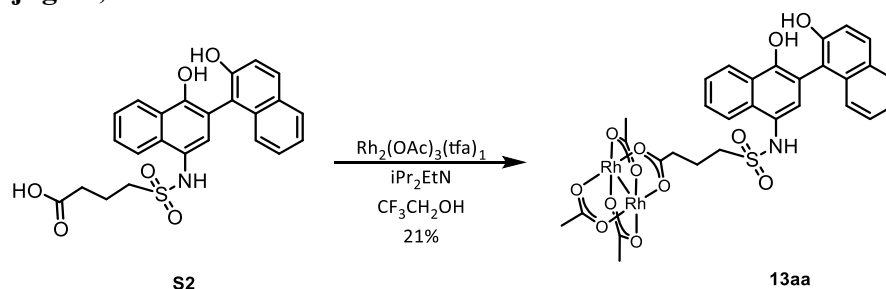
#### methyl 5-(N-(1',2-dihydroxy-[1,2'-binaphthalen]-4'-yl)sulfamoyl)-2-hydroxybenzoate, **4d**



Synthesis of **4d** was described in the general synthetic procedures section. White solid (240 mg, 46%).  $^1\text{H}$  NMR (600 MHz, acetonitrile- $d_3$ )  $\delta$  8.26 (d,  $J = 8.1$  Hz, 1H), 8.19 (d,  $J = 8.3$  Hz, 1H), 8.10 (d,  $J = 2.4$  Hz, 1H), 7.88 (dd,  $J = 11.4, 8.4$  Hz, 2H), 7.79 (dd,  $J = 8.8, 2.5$  Hz, 1H), 7.72 (s, 1H), 7.58 (dt,  $J = 18.8, 7.2$  Hz, 2H), 7.32 (dt,  $J = 24.8, 7.2$  Hz, 3H), 7.23 (d,  $J = 8.9$  Hz, 1H), 7.08 (d,  $J = 8.4$  Hz, 1H), 6.93 (d,  $J = 8.8$  Hz, 1H), 6.79 (s, 1H), 6.75 (s, 1H), 6.69 (s, 1H), 3.88 (s, 3H).  $^{13}\text{C}$  NMR (151 MHz, acetonitrile- $d_3$ )  $\delta$  169.9, 164.7, 153.6, 151.3, 134.9, 134.5, 132.7, 131.0, 130.8, 130.6, 129.7, 128.6, 127.4, 127.3, 126.4, 126.3, 124.6, 124.4, 124.1, 123.8, 123.1,

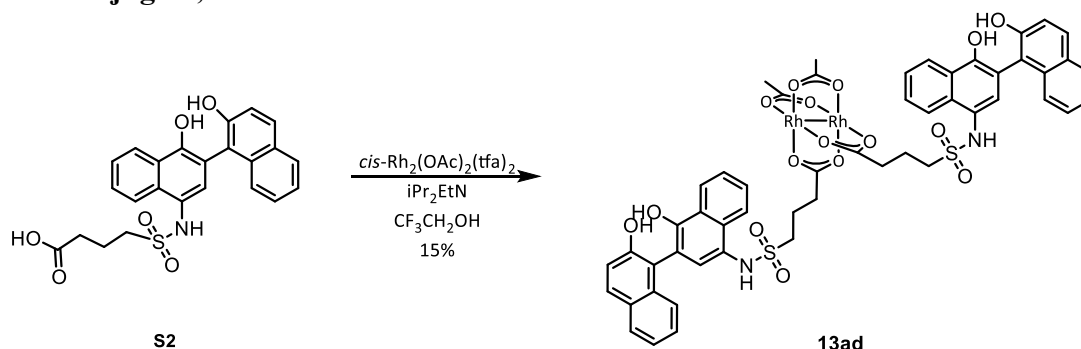
118.9, 118.9, 115.3, 114.5, 113.0, 53.3. MS (ESI)  $m/z$   $[M-H]^-$  calcd for  $[C_{28}H_{21}NO_7S]^-$  514.1, found 516.0. HPLC  $t_R$ : 12.5 min

### Rhodium conjugate, 13aa



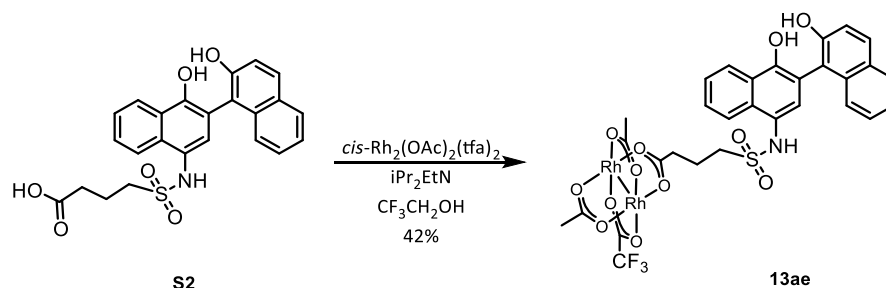
The metal complex  $\text{Rh}_2(\text{OAc})_3(\text{tfa})_1$  (1.4 mg, 0.0028 mmol), compound **S2** (1.4 mg, 0.0031 mmol), and a stir bar were placed in a vial. The solid mixture was dissolved into 2,2,2-trifluoroethanol (1.4 mL). The resulting solution was purged with nitrogen for 15 min.  $\text{iPr}_2\text{EtN}$  (0.4 mg, 0.0031 mmol) was added to the reaction and it was heated at 40 °C for 22 h while stirring. After 22 h, the reaction was purified by HPLC to yield **13aa** as a blue solid (0.5 mg, 21%).  $^1\text{H}$  NMR (500 MHz, acetone- $d_6$ )  $\delta$  8.45-8.37 (m, 3H), 7.87 (d, 2H,  $J = 8.3$ , Hz), 7.67-7.63 (m, 1H), 7.60-7.57 (m, 1H), 7.44 (m, 1H), 7.40-7.30 (m, 4H), 3.31-3.25 (m, 2H), 2.49-2.46 (m, 2H), 1.81-1.80 (m, 8H). MS (ESI),  $[M-H]^-$  calcd for  $[C_{30}H_{28}NO_{12}Rh_2S]^-$  831.9, found 831.7.

### Rhodium conjugate, 13ad



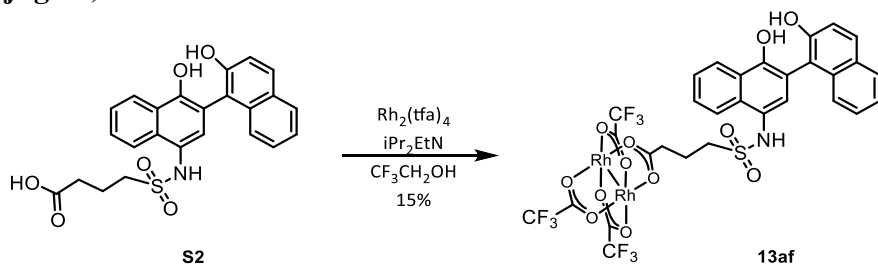
The metal complex *cis*- $\text{Rh}_2(\text{OAc})_2(\text{tfa})_2$  (86 mg, 0.16 mmol), compound **S2** (80 mg, 0.18 mmol), and a stir bar were placed in a vial. The solid mixture was dissolved into 2,2,2-trifluoroethanol (5 mL). The resulting solution was purged with nitrogen for 15 min.  $\text{iPr}_2\text{EtN}$  (18.5 mg, 0.14 mmol) was added to the reaction and it was heated for 4 h at 50 °C while stirring. After 4 h, the reaction was complete by TLC (1:3, EtOAc/hexanes). The crude reaction mixture was evaporated onto silica and purified by silica gel chromatography (1:3, EtOAc/hexanes) to yield **13ad** as a blue solid (30 mg, 15%).  $^1\text{H}$  NMR (600 MHz, DMSO- $d_6$ )  $\delta$  9.96 (s, 1H), 8.63 (d,  $J = 8.3$  Hz, 1H), 8.49 (s, 1H), 8.44 (d,  $J = 8.1$  Hz, 1H), 8.37 (d,  $J = 8.4$  Hz, 1H), 8.18 (d,  $J = 8.2$  Hz, 1H), 8.12 (d,  $J = 9.0$  Hz, 1H), 8.07 (d,  $J = 8.9$  Hz, 1H), 7.82 (t,  $J = 7.5$  Hz, 1H), 7.76 (t,  $J = 7.5$  Hz, 1H), 7.70 (t,  $J = 7.7$  Hz, 1H), 7.63 (t,  $J = 7.5$  Hz, 1H), 2.99 – 2.96 (m, 2H), 2.17 (t,  $J = 7.2$  Hz, 2H), 1.81 – 1.76 (m, 2H), 1.64 (s, 3H). MS (ESI),  $[M-H]^-$  calcd for  $[C_{52}H_{45}N_2O_{16}Rh_2S_2]^-$  1223.0, found 1223.1.

### Rhodium conjugate, 13ae



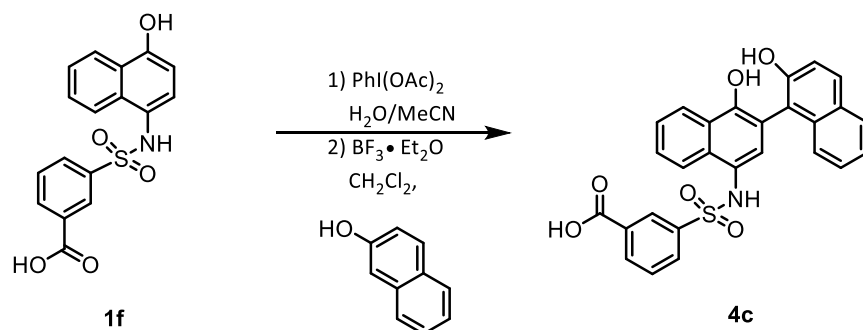
The metal complex  $\text{cis-Rh}_2(\text{OAc})_2(\text{tfa})_2$  (86 mg, 0.16 mmol), compound **S2** (80 mg, 0.18 mmol), and a stir bar were placed in a vial. The solid mixture was dissolved into 2,2,2-trifluoroethanol (5 mL). The resulting solution was purged with nitrogen for 15 min.  $\text{iPr}_2\text{EtN}$  (18.5 mg, 0.14 mmol) was added to the reaction and it was heated for 4 h at 50 °C while stirring. After 4 h, the reaction was complete by TLC (1:3, EtOAc/hexanes). The crude reaction mixture was evaporated onto silica and purified by silica gel chromatography (1:3, EtOAc/hexanes) to yield **13ae** as a blue solid (60 mg, 42%).  $^1\text{H}$  NMR (600 MHz,  $\text{DMSO-}d_6$ )  $\delta$  8.27 (d,  $J = 8.1$  Hz, 1H), 8.19 (d,  $J = 8.4$  Hz, 1H), 7.85 (t,  $J = 8.1$  Hz, 2H), 7.58 (t,  $J = 7.6$  Hz, 1H), 7.54 (t,  $J = 7.5$  Hz, 1H), 7.32 – 7.21 (m, 4H), 7.11 (s, 1H), 2.89 (t,  $J = 7.7$  Hz, 2H), 2.24 (d,  $J = 8.1$  Hz, 2H), 1.91 – 1.68 (m, 8H)  $^{13}\text{C}$  NMR (151 MHz,  $\text{DMSO-}d_6$ )  $\delta$  193.5, 193.1, 192.4, 172.7 (q,  $J = 38.4$  Hz), 153.5, 150.2, 134.1, 131.6, 129.6, 129.5, 128.6, 128.4, 126.6, 126.5, 126.4, 125.5, 124.7, 124.0, 123.1, 122.8, 119.1, 117.1, 116.8, 110.9 (q,  $J = 285.9$  Hz), 79.6, 50.1, 35.2, 30.1, 23.9 (d,  $J = 29.5$  Hz), 20.1. MS (ESI),  $[\text{M-H}]^-$  calcd for  $[\text{C}_{30}\text{H}_{25}\text{F}_3\text{NO}_{12}\text{Rh}_2\text{S}]^-$  885.9, found 885.9. HPLC (10% → 90% MeCN-20min, absorbance 254 nm)  $t_R$ : 16.9 min

### Rhodium conjugate, **13af**



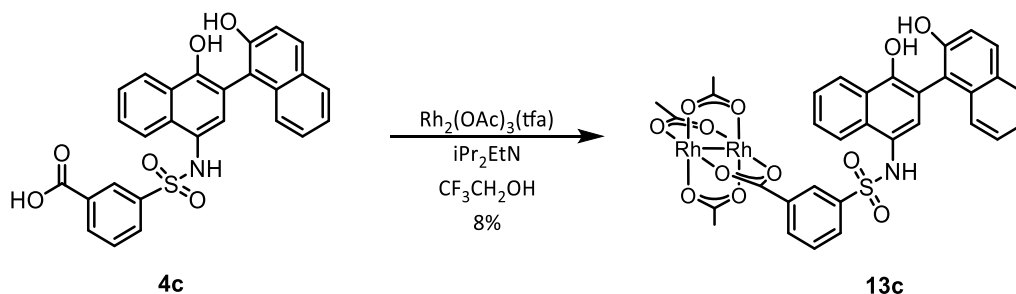
$\text{N,N}$ -Diisopropylethylamine (8.7  $\mu\text{L}$ , 0.050 mmol) was added to a solution of **S2** (22.6 mg, 0.050 mmol) and  $\text{Rh}_2(\text{tfa})_4$  (32.9 mg, 0.050 mmol) in 2,2,2-trifluoroethanol (0.5 mL) and stirred at 50 °C for 18 h. The crude reaction mixture was evaporated onto silica and purified using flash chromatography (EtOAc/hexanes, 1:5) to obtain **13af** as a green solid (7.3 mg, 15%).  $^1\text{H}$  NMR (600 MHz, chloroform- $d$ )  $\delta$  8.47 (d,  $J = 8.3$  Hz, 1H), 8.28 (d,  $J = 8.6$  Hz, 1H), 8.03 (d,  $J = 9.0$  Hz, 1H), 7.98 (d,  $J = 7.9$  Hz, 1H), 7.79 (t,  $J = 7.7$  Hz, 1H), 7.72 (t,  $J = 7.6$  Hz, 1H), 7.67 (d,  $J = 9.0$  Hz, 1H), 7.56 – 7.35 (m, 5H), 3.61 (m, 1.5H), 3.57 – 3.48 (m, 1.5H), 3.22 (m, 0.5H), 3.12 (m, 0.5H), 2.44 (dd,  $J = 7.4, 4.8$  Hz, 2H), 2.06 (s, 1H), 1.35 – 1.24 (m, 2H). MS (ESI),  $[\text{M-H}]^-$  calcd for  $[\text{C}_{30}\text{H}_{19}\text{F}_9\text{NO}_{12}\text{Rh}_2\text{S}]^-$  993.86 found 993.84

### 3-( $\text{N}$ -(1',2'-dihydroxy-[1,2'-binaphthalen]-4'-yl)sulfamoyl)benzoic acid, **4c**



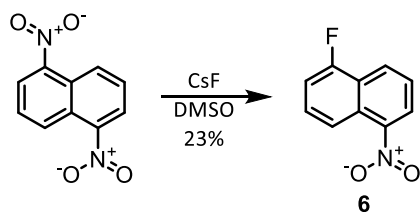
Sulfonamide **1f** was subjected to the general oxidative coupling of 2-naphthol procedure. The resulting crude material was purified by silica gel chromatography (Et<sub>2</sub>O/hexanes, 1:19) to afford **4c** (145 mg, 30%). <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>) δ 10.04 (s, 1H), 8.37 (s, 0H), 8.26 (d, *J* = 11.7 Hz, 2H), 8.12 (d, *J* = 8.6 Hz, 1H), 8.07 (d, *J* = 7.8 Hz, 1H), 7.90 (d, *J* = 7.9 Hz, 1H), 7.86 (t, *J* = 8.7 Hz, 2H), 7.63 – 7.58 (m, 1H), 7.54 (d, *J* = 7.8 Hz, 2H), 7.30 (t, *J* = 8.0 Hz, 3H), 7.01 (d, *J* = 8.2 Hz, 1H), 6.71 (s, 1H). <sup>13</sup>C NMR (151 MHz, DMSO-*d*<sub>6</sub>) δ 166.4, 153.4, 150.4, 140.6, 134.2, 133.5, 131.9, 131.5, 131.4, 130.0, 129.7, 129.5, 128.4, 128.3, 128.0, 126.5, 126.4, 126.2, 125.5, 124.3, 123.9, 123.3, 123.0, 122.8, 118.9, 116.7, 116.6, 79.6. MS (ESI) *m/z* [M-H]<sup>-</sup> calcd for [C<sub>27</sub>H<sub>18</sub>NO<sub>6</sub>S]<sup>-</sup> 484.1, found 485.9. HPLC *t*<sub>R</sub>: 8.9 min.

### Rhodium conjugate, **13c**



The metal complex Rh<sub>2</sub>(OAc)<sub>3</sub>(tfa) (0.3 mg, 0.0006 mmol), compound **18** (0.6 mg, 0.0012 mmol), and a stir bar were placed in a vial. The solid mixture was dissolved into 2,2,2-trifluoroethanol (124 μL) that had been purged with nitrogen for 15 min. A solution of iPr<sub>2</sub>EtN (24 μL, 0.0006 mmol, 25 mM in 2,2,2-trifluoroethanol) was subsequently added to this vial. The reaction was heated for 4 h at 40 °C with stirring. After 4 h, the reaction was purified by analytical HPLC to yield **13c** (0.04 mg, 8%). MS (ESI) *m/z* [M-H]<sup>-</sup> calcd for [C<sub>33</sub>H<sub>26</sub>NO<sub>12</sub>Rh<sub>2</sub>S]<sup>-</sup> 865.9, found 865.9. HPLC *t*<sub>R</sub>: 14.4 min.

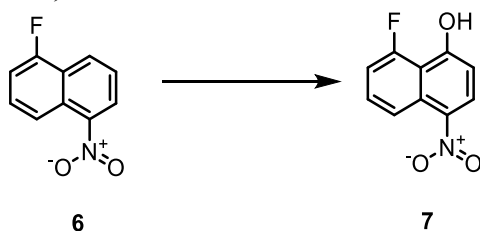
### 1-fluoro-5-nitronaphthalene, **6**





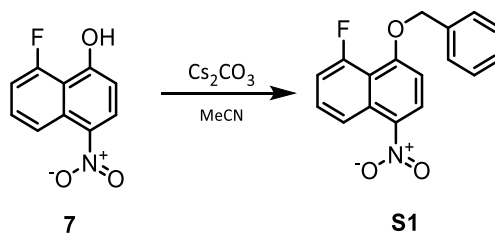
The aromatic compound 1,5-dinitronaphthalene (10 g, 45.9 mmol) was placed in a 20-mL vial in a nitrogen-atmosphere glovebox. Cesium fluoride (21 g, 139 mmol) and dry DMSO (70 mL, Sigma-Aldrich Sureseal) were added to the vial. The vial was then sealed and then taken out of the glovebox and heated at 100 °C for 4 h. The reaction vessel was then allowed to cool to rt. The mixture was diluted with water and washed thrice with ether. The organic layer were combined and washed once with water and once more with brine. The ether layer was dried with Na<sub>2</sub>SO<sub>4</sub> and filtered through cotton. The resulting solution was evaporated onto silica and purified using flash chromatography (CH<sub>2</sub>Cl<sub>2</sub>/hexanes, 1:4) to afford a yellow solid **6** (2 g, 23%). <sup>1</sup>H NMR (600 MHz, chloroform-*d*) δ 8.43 (d, *J* = 8.4 Hz, 1H), 8.35 (d, *J* = 8.8 Hz, 1H), 8.29 (d, *J* = 7.6 Hz, 1H), 7.66 – 7.60 (m, 2H), 7.30 (dd, *J*<sub>FH</sub> = 9.9 Hz, *J*<sub>HH</sub> = 7.8 Hz, 1H). <sup>13</sup>C NMR (151 MHz, chloroform-*d*) δ 158.8 (d, *J*<sub>CF</sub> = 253.7 Hz), 146.5 (d, *J*<sub>CF</sub> = 2.6 Hz), 129.6 (d, *J*<sub>CF</sub> = 8.7 Hz), 127.3 (d, *J*<sub>CF</sub> = 6.6 Hz), 126.5 (d, *J*<sub>CF</sub> = 3.8 Hz), 125.1, 125.1 (d, *J*<sub>CF</sub> = 17.5 Hz), 124.8, 119.3 (d, *J*<sub>CF</sub> = 4.4 Hz), 111.3 (d, *J*<sub>CF</sub> = 19.8 Hz). <sup>19</sup>F NMR (565 MHz, chloroform-*d*) δ -119.9 (dd, *J*<sub>FH</sub> = 9.9, 6.0 Hz). MS (GC) *m/z* [*M*<sup>+</sup>]<sup>+</sup> calcd for [C<sub>10</sub>H<sub>6</sub>FNO<sub>2</sub>]<sup>+</sup> 191.04, found 191.04

#### 8-fluoro-4-nitronaphthalen-1-ol, **7**



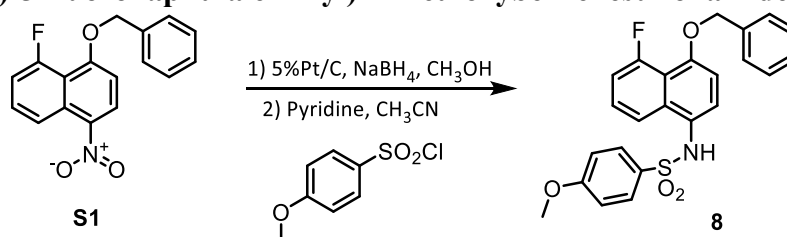
Liquid ammonia (30 mL) was added to a chilled round-bottomed flask (-78 °C). The fluorinated naphthalene **6** (750 mg, 3.9 mmol in 5 mL of THF) was added to the round bottomed flask, followed by addition of NaOH (1.00 g, 25.0 mmol) and 70% tBuOOH (1.5 mL, 987 mg, 11.0 mmol). The round-bottomed flask was removed from the dry ice/acetone bath. The reaction mixture was refluxed with a dry ice/acetone coldfinger (-78 °C) to condense the liquid ammonia. After 2 h, the reaction was complete by TLC (1:1, CH<sub>2</sub>Cl<sub>2</sub>/hexanes). The coldfinger was removed to allow the ammonia to evaporate. Once at rt, the reaction was quenched with 2 N HCl and extracted with ether. The ether extract was washed with 2 N HCl thrice. The organic layer was dried onto silica and purified by silica gel chromatography (1:1, CH<sub>2</sub>Cl<sub>2</sub>/hexanes) to afford **7** (450 mg, 55%). Yellow solid. <sup>1</sup>H NMR (600 MHz, chloroform-*d*) δ 8.63 (d, *J* = 8.8 Hz, 1H), 8.39 (d, *J* = 8.7 Hz, 1H), 7.78 (d, *J* = 31.4 Hz, 1H), 7.65 (td, *J* = 8.4, 6.1 Hz, 1H), 7.29 (dd, *J* = 15.2, 7.9 Hz, 1H), 7.01 (d, *J* = 8.7 Hz, 1H). <sup>13</sup>C NMR (151 MHz, chloroform-*d*) δ 159.7 (d, *J*<sub>CF</sub> = 243.5 Hz), 157.6, 139.1, 130.0 (d, *J*<sub>CF</sub> = 10.9 Hz), 129.4 (d, *J*<sub>CF</sub> = 2.1 Hz), 129, 121.1 (d, *J*<sub>CF</sub> = 4.4 Hz), 113.9 (d, *J*<sub>CF</sub> = 7.0 Hz), 111.6 (d, *J*<sub>CF</sub> = 23.0 Hz), 110.6 (d, *J*<sub>CF</sub> = 2.2 Hz). <sup>19</sup>F NMR (565 MHz, chloroform-*d*) δ -120.6 (s). MS (GC) *m/z* [*M*<sup>+</sup>]<sup>+</sup> calcd for C<sub>10</sub>H<sub>6</sub>FNO<sub>3</sub><sup>+</sup> 207.0, found 207.0

#### 4-(benzyloxy)-5-fluoro-1-nitronaphthalene, **S1**



The aromatic molecule **7** (150 mg, 0.72 mmol) was placed in a round bottomed flask along with  $\text{Cs}_2\text{CO}_3$  (600 mg, 1.84 mmol) and a magnetic stir bar. The air in the vial was evacuated and backfilled with nitrogen thrice. Acetonitrile (7 mL) was added to the reaction vessel. Benzyl bromide (1 mL, 8.42 mmol) was subsequently added to the vial. The reaction vessel was heated to 70 °C. After 14 h, the reaction was complete by TLC (1:2,  $\text{CH}_2\text{Cl}_2$ /hexanes). The reaction mixture was dried onto silica and purified by silica gel chromatography (1:2,  $\text{CH}_2\text{Cl}_2$ /hexanes) to yield **S1** (183 mg, 85%).  $^1\text{H}$  NMR (600 MHz, acetone- $d_6$ )  $\delta$  8.40 (d,  $J = 8.8$  Hz, 2H), 7.78 (ddd,  $J_{\text{HH}} = 8.2, 8.2, J_{\text{FH}} = 5.1$  Hz, 1H), 7.63 (d,  $J = 7.6$  Hz, 2H), 7.45 (t,  $J = 7.6$  Hz, 2H), 7.41 – 7.35 (m, 2H), 7.29 (d,  $J = 8.8$  Hz, 1H), 5.49 (s, 2H).  $^{13}\text{C}$  NMR (151 MHz, acetone- $d_6$ )  $\delta$  160.5 (d,  $J_{\text{CF}} = 4.3$  Hz), 160.3 (d,  $J_{\text{CF}} = 260.4$  Hz), 140.5 (d,  $J_{\text{CF}} = 3.3$  Hz), 137.2, 131.2 (d,  $J_{\text{CF}} = 9.8$  Hz), 129.9 (d,  $J_{\text{CF}} = 3.2$  Hz), 129.5, 129.0, 128.6, 128.2, 119.8 (d,  $J_{\text{CF}} = 4.4$  Hz), 116.7 (d,  $J_{\text{CF}} = 10.9$  Hz), 113.7 (d,  $J_{\text{CF}} = 22.4$  Hz), 106.3, 71.9.  $^{19}\text{F}$  NMR (565 MHz, acetone- $d_6$ )  $\delta$  -109.3 (dd,  $J_{\text{FH}} = 14.1, 5.9$  Hz). MS (GC)  $m/z$  [ $\text{M}^+$ ] calcd for  $\text{C}_{17}\text{H}_{12}\text{FNO}_3^+$  297.08, found 297.08

### N-(4-(benzyloxy)-5-fluoronaphthalen-1-yl)-4-methoxybenzenesulfonamide, **8**



#### Nitro reduction

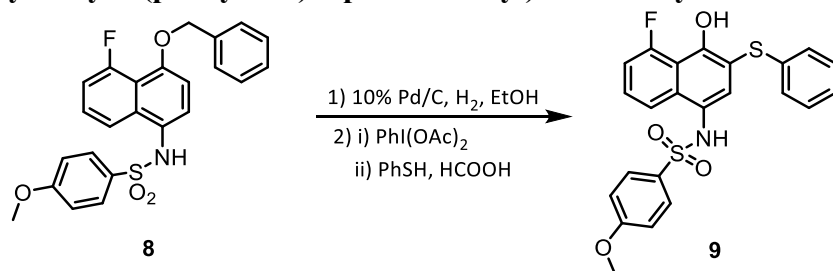
Molecule **S1** (70 mg, 0.24 mmol) was placed in scintillation vial along with 5% Pt/C (70 mg, 0.018 mmol). Methanol (4 mL) was added to the reaction vessel. The resulting slurry was degassed with nitrogen for 15 min. The reductant  $\text{NaBH}_4$  (50 mg, 1.35 mmol) was added to the reaction vessel. After 1h, the reaction was complete by TLC (1:2 EtOAc/hexanes). The crude reaction was filtered through celite. The resulting solution was purged with nitrogen, and the volatiles were removed under vacuum. The crude residue was taken to the next step without further purification.

#### N-sulfonylation

The crude sludge was already in a round-bottomed flask. The 4-methoxybenzenesulfonyl chloride (56 mg, 0.21 mmol) was added to the flask. The reaction vessel was evacuated and backfilled with nitrogen three times. A mixture of pyridine (4 mL) and acetonitrile (1 mL) was chilled in dry ice for 15 min and then transferred by syringe to the round-bottomed flask. The reaction was monitored by TLC (1:2 EtOAc/hexanes) and was complete after 2 h. The reaction mixture was taken up in  $\text{CH}_2\text{Cl}_2$  and washed with aq HCl (3  $\times$  20 mL, 2 M). The organic layer was purged with nitrogen gas. Compound was dry loaded and purified by silica gel chromatography (1:2, EtOAc/hexanes). The product fractions were collected and dried to yield **8** (78 mg, 46%). White solid.  $^1\text{H}$  NMR (600 MHz, acetone- $d_6$ )  $\delta$  7.90 (d,  $J = 8.6$  Hz, 1H), 7.65 – 7.55 (m, 4H), 7.45 – 7.37 (m, 3H), 7.35 (d,  $J = 7.4$  Hz, 1H), 7.16 (dd,  $J = 13.6, 7.9$  Hz, 2H), 7.02 (d,  $J = 8.4$  Hz, 1H), 7.00 – 6.94 (m, 2H), 5.29 (s, 2H), 3.85 (s, 3H).  $^{13}\text{C}$  NMR (151 MHz, acetone- $d_6$ )  $\delta$  163.9, 160.0 (d,  $J_{\text{CF}} = 258.2$  Hz), 154.7 (d,  $J_{\text{CF}} = 4.1$  Hz), 138.1, 135.5 (d,  $J_{\text{CF}} = 3.3$  Hz), 132.9, 130.3, 129.3, 128.6, 128.6 (d,  $J_{\text{CF}} = 4.4$  Hz), 128, 127.6, 127.5 (d,  $J_{\text{CF}} = 8.7$  Hz), 120.5 (d,  $J_{\text{CF}} = 4.8$  Hz), 117.1

(d,  $J_{CF} = 9.8$  Hz), 114.9, 112.3 (d,  $J_{CF} = 23.0$  Hz), 107.5 (d,  $J_{CF} = 2.2$  Hz), 71.1, 56.1. .  $^{19}\text{F}$  NMR (565 MHz, acetone- $d_6$ )  $\delta$  -111.9 (dd,  $J_{FH} = 12.3, 4.1$  Hz). HPLC  $t_R$ : 16.9 min

### N-(5-fluoro-4-hydroxy-3-(phenylthio)naphthalen-1-yl)-4-methoxybenzenesulfonamide, **9**



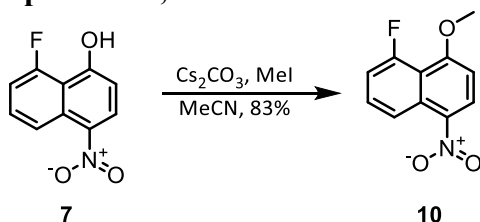
#### deprotection

The benzylether **8** (22 mg, 0.05 mmol) and 10% Pd/C (16 mg) were added to a scintillation vial. Ethanol (3 mL) was added to the vial. The vial was sealed and flushed with hydrogen gas. The solution was stirred overnight under hydrogen atmosphere (1 atm). The resulting mixture was filtered through celite. The organic solvent was evaporated under vacuum. The resulting crude was used directly in the next step.

#### oxidative coupling

The resulting crude solid was subjected to the general oxidative coupling to thiols procedure and then purified by silica gel chromatography (7:3, Et<sub>2</sub>O/Hex) to afford **9** (6 mg, 44% over 2 steps).  $^1\text{H}$  NMR (600 MHz, benzene- $d_6$ )  $\delta$  7.78 (d,  $J = 8.6$  Hz, 1H), 7.48 (d,  $J = 8.6$  Hz, 2H), 6.97 – 6.76 (m, 7H), 6.71 (dd,  $J = 12.9, 7.7$  Hz, 1H), 6.27 (d,  $J = 8.6$  Hz, 2H), 2.97 (s, 3H).  $^{13}\text{C}$  NMR (151 MHz, benzene- $d_6$ )  $\delta$  162.7, 159.2 (d,  $J_{CF} = 212.8$  Hz), 153.1, 135.6, 134.9, 132.0, 131.1, 129.6, 129.1, 128.0, 127.6, 127.3, 127.2, 126.4, 124.7, 120.0, 113.7, 111.7 (d,  $J_{CF} = 18.1$  Hz), 54.5. MS (ESI)  $m/z$   $[\text{M-H}]^-$  calcd for C<sub>23</sub>H<sub>17</sub>FNO<sub>4</sub>S<sub>2</sub><sup>-</sup> 454.1, found 455.7

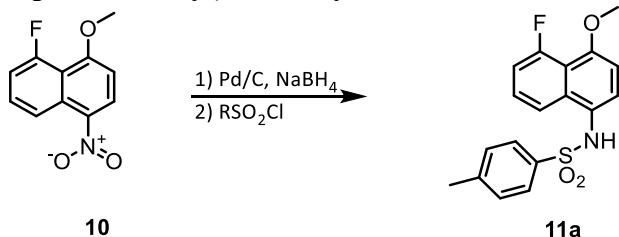
### 5-fluoro-4-methoxy-1-nitronaphthalene, **10**



The aromatic molecule **7** (49.7 mg, 0.24 mmol) was placed in a round bottomed flask along with K<sub>2</sub>CO<sub>3</sub> (132 mg, 0.96 mmol) and a magnetic stir bar. The air in the vial was evacuated and backfilled with nitrogen thrice. DMF (5 mL) was added to the reaction vessel. Iodomethane (0.3 mL, 4.8 mmol) was subsequently added to the vial. The reaction vessel was stirred at rt. After 14 h, the reaction was quenched by adding saturated sodium thiosulfate aqueous solution and HCl. The reaction mixture was then diluted with 100 mL of H<sub>2</sub>O and extracted with ether (3 × 30 mL). The organic layer was dried with MgSO<sub>4</sub>, filtered, and the solvent was removed in vacuo to yield **10** (61.9 mg, 84%). Characterization was in agreement with the literature.<sup>9</sup>  $^1\text{H}$  NMR (600 MHz, chloroform- $d$ )  $\delta$  8.46 (d, 1H,  $J = 8.8$  Hz), 8.32 (d, 1H,  $J = 8.8$  Hz), 7.60 (ddd,  $J_{FH} = 4.2$ ,  $J_{HH} =$

8.7, 7.9 Hz, 1H), 7.21 (dd, 1H,  $J_{FH} = 12.3$ ,  $J_{HH} = 7.8$  Hz), 6.81 (d, 1H,  $J = 8.8$  Hz), 4.06 (s, 3H).  $^{13}\text{C}$  NMR (151 MHz, chloroform-*d*)  $\delta$  161.2 (d,  $J_{CF} = 5.5$  Hz), 159.7 (d,  $J_{CF} = 260.9$  Hz), 139.5 (d,  $J_{CF} = 4.3$  Hz), 130.3 (d,  $J_{CF} = 9.8$  Hz), 129.3 (d,  $J_{CF} = 3.3$  Hz), 128.0, 119.4 (d,  $J_{CF} = 5.5$  Hz), 116.1 (d,  $J_{CF} = 10.4$  Hz), 113.0 (d,  $J_{CF} = 22.3$  Hz), 103.4 (d,  $J_{CF} = 2.2$  Hz), 56.7.  $^{19}\text{F}$  NMR (565 MHz, chloroform-*d*)  $\delta$  -109.2 (dd,  $J_{FH} = 12.3$ , 4.2). HPLC  $t_R$ : 13.6 min.

### N-(5-fluoro-4-methoxynaphthalen-1-yl)-4-methylbenzenesulfonamide, 11a



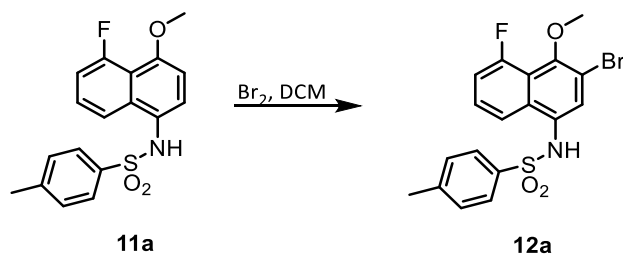
The aromatic compound **10** (60 mg, 0.27 mmol) was placed in a round bottomed flask along with 10% Pd/ C (35 mg, 0.03 mmol). Methanol (25 mL) was added to the reaction vessel. The resulting slurry was degassed with nitrogen for 15 min. The reductant NaBH<sub>4</sub> (50 mg, 1.32 mmol) was added to the reaction vessel. After 1 h, the reaction was complete by TLC (1:2 EtOAc/hexanes). A purple spot formed when the product was stained with ninhydrin. The crude reaction was filtered through celite. The resulting solution was purged with nitrogen and then condensed in a round bottom flask. The crude sludge was taken to the next step without further purification.

#### *N*-sulfonylation

The crude sludge was already in a round-bottomed flask. The electrophile para-toluenesulfonylchloride (57 mg, 0.31 mmol) was added to the flask. The reaction vessel was evacuated and back-filled with nitrogen three times. A mixture of pyridine (5 mL) and acetonitrile (5 mL) was chilled in dry ice for 15 min and then transferred by syringe to the round-bottomed flask. The reaction was monitored by TLC (1:2 EtOAc/hexanes) and was complete after 2 h. The reaction mixture was taken up in CH<sub>2</sub>Cl<sub>2</sub> and washed with aq HCl (3 × 20 mL, 2 M). The organic layer was purged with nitrogen gas. Compound was dry loaded and purified by silica gel chromatography (1:2, EtOAc/hexanes). The product fractions were collected and dried to yield **11a** (43 mg, 46%).  $^1\text{H}$  NMR (600 MHz, acetonitrile-*d*<sub>3</sub>)  $\delta$  7.72 (d, 1H,  $J = 8.4$  Hz), 7.69 (s, 1H), 7.54 (d, 2H,  $J = 8.4$  Hz), 7.35 (ddd,  $J_{FH} = 5.5$ ,  $J_{HH} = 8.7$ , 8.7 Hz, 1H), 7.25 (d, 2H,  $J = 8.1$  Hz), 7.10 (dd, 1H,  $J_{FH} = 13.6$ ,  $J_{HH} = 8.3$  Hz), 7.05 (d, 1H,  $J = 8.3$  Hz), 6.78 (d, 1H,  $J = 8.4$  Hz), 3.89 (s, 3H), 2.35 (s, 3H).

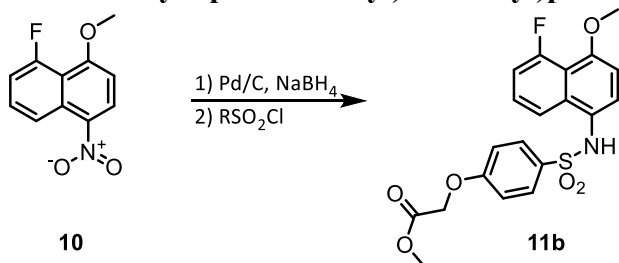
$^{13}\text{C}$  NMR (151 MHz, acetonitrile-*d*<sub>3</sub>)  $\delta$  160.0 (d,  $J_{CF} = 255.1$  Hz), 156.1 (d,  $J_{CF} = 5.4$  Hz), 144.9, 137.8, 135.3 (d,  $J_{CF} = 3.3$  Hz), 130.5, 128.2, 127.9, 127.8 (d,  $J_{CF} = 9.3$  Hz), 125.2 (d,  $J_{CF} = 3.4$  Hz), 120.3 (d,  $J_{CF} = 4.4$  Hz), 116.8 (d,  $J_{CF} = 10.9$  Hz), 112.4 (d,  $J_{CF} = 22.7$  Hz), 106.0 (d,  $J_{CF} = 2.1$  Hz), 56.7, 21.5.  $^{19}\text{F}$  NMR (565 MHz, acetonitrile-*d*<sub>3</sub>)  $\delta$  -112.6 (dd,  $J_{FH} = 13.6$ , 5.5 Hz). White solid. HPLC  $t_R$ : 18.4 min

### N-(3-bromo-5-fluoro-4-methoxynaphthalen-1-yl)-4-methylbenzenesulfonamide, 12a



Molecule **11a** (10 mg, 0.024 mmol) was placed in a round bottomed flask and dissolved in  $\text{CH}_2\text{Cl}_2$  (1 mL). A 10% solution of  $\text{Br}_2$  in  $\text{CH}_2\text{Cl}_2$  was added to the reaction vessel (12.4  $\mu\text{L}$ , 0.024 mmol). The reaction was stirred in the dark for 3 h. The resulting solution was taken up into ether. The ethereal layer was washed thrice with  $\text{NaS}_2\text{O}_3$  (aq) and then once with brine. The ether extract was dried with  $\text{Na}_2\text{SO}_4$ , filtered through cotton and dried onto silica gel. The dried crude with silica was loaded onto a silica gel column and purified by flash chromatography (1:3  $\text{Et}_2\text{O}$ /hexanes) to yield **12a** (8 mg, 75%), a white solid.  $^1\text{H}$  NMR (600 MHz, acetonitrile- $d_3$ )  $\delta$  7.95 (s, 1H), 7.77 (d,  $J = 8.6$  Hz, 1H), 7.60 (d,  $J = 8.1$  Hz, 2H), 7.45 (ddd,  $J_{\text{FH}} = 5.4$ ,  $J_{\text{HH}} = 8.2$ , 4.8 Hz, 1H), 7.35 (s, 1H), 7.33 – 7.24 (m, 3H), 3.91 (s, 3H), 2.40 (s, 3H).  $^{13}\text{C}$  NMR (151 MHz, acetonitrile- $d_3$ )  $\delta$  158.3 (d,  $J_{\text{CF}} = 250.3$  Hz), 152.0 (d,  $J_{\text{CF}} = 3.9$  Hz), 145.4, 137.2, 134.1 (d,  $J_{\text{CF}} = 2.1$  Hz), 130.7, 130.3, 130.2 (d,  $J_{\text{CF}} = 3.9$  Hz), 128.3, 128.2 (d,  $J_{\text{CF}} = 9.3$  Hz), 121.0 (d,  $J_{\text{CF}} = 3.8$  Hz), 120.5 (d,  $J_{\text{CF}} = 9.9$  Hz), 114.6, 114.0 (d,  $J_{\text{CF}} = 21.8$  Hz), 62.5, 21.5.  $^{19}\text{F}$  NMR (565 MHz, acetonitrile- $d_3$ )  $\delta$  -118.0 (dd,  $J_{\text{FH}} = 13.2$ , 5.4 Hz).

#### methyl 2-(4-(N-(5-fluoro-4-methoxynaphthalen-1-yl)sulfamoyl)phenoxy)acetate, **11b**



#### Reduction

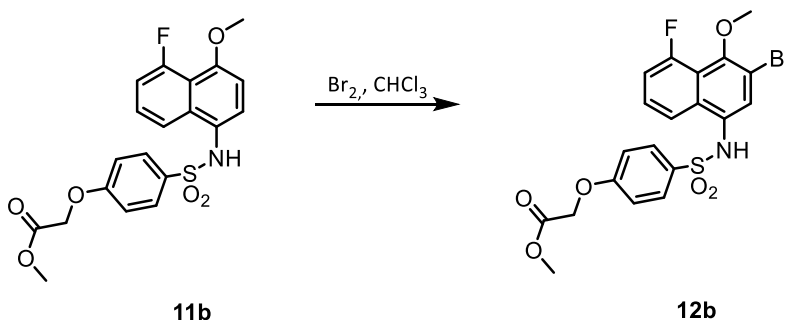
The aromatic compound **10** (40 mg, 0.18 mmol) was placed in a round bottomed flask along with 10% Pd/ C (15 mg, 0.01 mmol). Ethanol (4 mL) was added to the reaction vessel. The resulting slurry was degassed with nitrogen for 15 min. The reductant  $\text{NaBH}_4$  (37 mg, 1 mmol) was added to the reaction vessel. After 1 h, the reaction was complete by TLC (1:2  $\text{EtOAc}$ /hexanes). A purple spot formed when the product was stained with ninhydrin. The crude reaction was filtered through celite. The resulting solution was purged with nitrogen and then condensed in a round bottom flask. The crude sludge was taken to the next step without further purification.

#### N-sulfonylation

The crude sludge was already in a round-bottomed flask. Methyl 2-(4-(chlorosulfonyl)phenoxy)acetate (56 mg, 0.21 mmol) was added to the flask. The reaction vessel

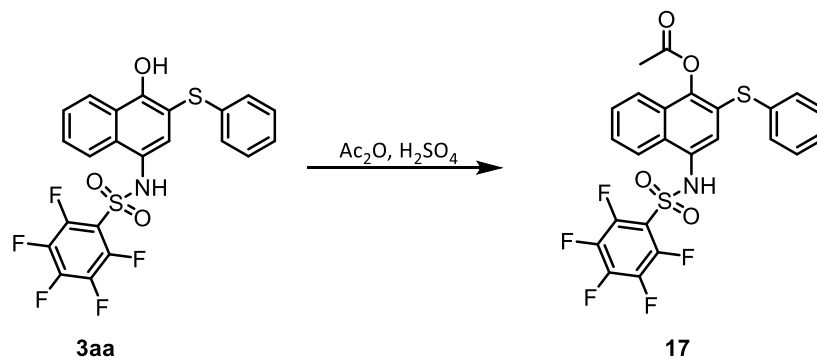
was evacuated and back-filled with nitrogen three times. Both pyridine (4 mL) and acetonitrile (1 mL) were transferred by syringe to the round-bottomed flask. The reaction was monitored by TLC (1:2 EtOAc/hexanes) and was complete after 2 h. The reaction mixture was taken up in  $\text{CH}_2\text{Cl}_2$  and washed with 1 M HCl thrice. The organic layer was purged with nitrogen gas. Compound was dry loaded and purified on a silica gel column (10%  $\text{Et}_2\text{O}$ /toluene). The product fractions were collected and dried to yield (35 mg, 46%) of **11b**.  $^1\text{H}$  NMR (600 MHz, acetone- $d_6$ )  $\delta$  7.85 (d,  $J = 8.6$  Hz, 1H), 7.62 (d,  $J = 8.5$  Hz, 2H), 7.38 (ddd,  $J_{\text{FH}} = 4.1$ ,  $J_{\text{HH}} = 8.1$ , 4.8 Hz, 1H), 7.21 – 7.07 (m, 2H), 7.03 – 6.98 (m, 2H), 6.90 (d,  $J = 8.4$  Hz, 1H), 4.82 (s, 2H), 3.95 (s, 3H), 3.74 (s, 3H).  $^{13}\text{C}$  NMR (151 MHz, acetone- $d_6$ )  $\delta$  169.3, 162.2, 160.0 (d,  $J_{\text{CF}} = 260.9$  Hz), 155.9 (d,  $J_{\text{CF}} = 5.0$  Hz), 135.4 (d,  $J_{\text{CF}} = 2.9$  Hz), 133.8, 130.3, 127.8, 127.5 (d,  $J_{\text{CF}} = 8.9$  Hz), 125.8 (d,  $J_{\text{CF}} = 5.7$  Hz), 120.4 (d,  $J_{\text{CF}} = 4.4$  Hz), 116.8 (d,  $J_{\text{CF}} = 10.3$  Hz), 115.6, 112.2 (d,  $J_{\text{CF}} = 21.7$  Hz), 105.9 (d,  $J_{\text{CF}} = 2.2$  Hz), 65.7, 56.3, 52.4.  $^{19}\text{F}$  NMR (565 MHz, acetone- $d_6$ )  $\delta$  -112.3 (dd,  $J_{\text{FH}} = 14.0$ , 4.1 Hz). HPLC  $t_{\text{R}}$ : 13.5 min

**methyl 2-(4-(N-(3-bromo-5-fluoro-4-methoxynaphthalen-1-yl)sulfamoyl)phenoxy)acetate, 12b**



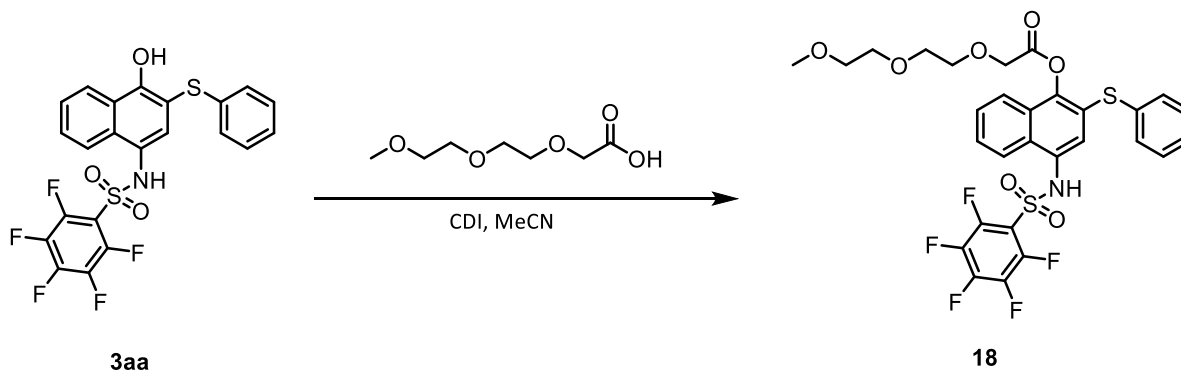
Molecule **12b** was synthesized with the same bromination process that yielded **12a**. The crude material was purified by flash chromatography (1:4, EtOAc/hexanes) and the preparative HPLC to afford a white solid **29** (9 mg, 19%).  $^1\text{H}$  NMR (600 MHz, chloroform- $d$ )  $\delta$  7.72 – 7.65 (m, 2H), 7.59 (d,  $J = 8.5$  Hz, 1H), 7.48 (s, 1H), 7.38 (td,  $J = 8.1$ , 4.7 Hz, 1H), 7.18 (dd,  $J = 12.7$ , 7.7 Hz, 1H), 6.89 (d,  $J = 8.9$  Hz, 2H), 6.55 (s, 1H), 4.66 (s, 2H), 3.93 (s, 3H), 3.80 (s, 3H).  $^{13}\text{C}$  NMR (151 MHz, chloroform- $d$ )  $\delta$  168.2, 161.4, 157.7 (d,  $J_{\text{CF}} = 213.0$  Hz), 151.4, 132.6, 131.7, 129.6, 129.5, 128.1, 127.3 (d,  $J_{\text{CF}} = 7.9$  Hz), 119.8 (d,  $J_{\text{CF}} = 8.1$  Hz), 118.6, 114.9 (d,  $J_{\text{CF}} = 8.2$  Hz), 113.6 (d,  $J_{\text{CF}} = 18.8$  Hz), 112.9, 65.2, 61.9, 52.5.

**4-((perfluorophenyl)sulfonamido)-2-(phenylthio)naphthalen-1-yl acetates, 17**



The STAT3 inhibitor **3aa** was placed in a vial (10 mg, 0.020 mmol). A solution of 10% acetic anhydride in sulfuric acid (2 mL) was subsequently added to this vial. After 30 minutes, the reaction was complete by TLC (1:10 EtOAc/hexanes). The reaction mixture was taken up into ether and washed thrice with water. The solution was dried with Na<sub>2</sub>SO<sub>4</sub>, filtered through cotton, and dried under vacuum to yield **17** (5.6 mg, 52%). Product was used without further purification. <sup>1</sup>H NMR (600 MHz, methanol-*d*<sub>4</sub>) δ 8.15 (d, *J* = 8.2 Hz, 1H), 7.87 (d, *J* = 8.2 Hz, 1H), 7.66 – 7.56 (m, 2H), 7.37 – 7.29 (m, 6H), 6.92 (s, 1H), 2.47 (s, 2H), 2.05 (s, 1H). <sup>13</sup>C NMR (151 MHz, methanol-*d*<sub>4</sub>) δ 169.1, 144.1, 132.9, 132.2, 130.2, 130.1, 129.1, 128.1, 127.9, 127.7, 126.9, 126.0, 124.7, 123.1, 121.3, 19.1. Due to extensive <sup>19</sup>F splitting, <sup>13</sup>C peaks in the perfluorophenyl region were not identified. <sup>19</sup>F NMR (565 MHz, methanol-*d*<sub>4</sub>) δ -138.3 (m), -148.5 (s), -161.6 (m). HPLC *t*<sub>R</sub>: 17.2 min

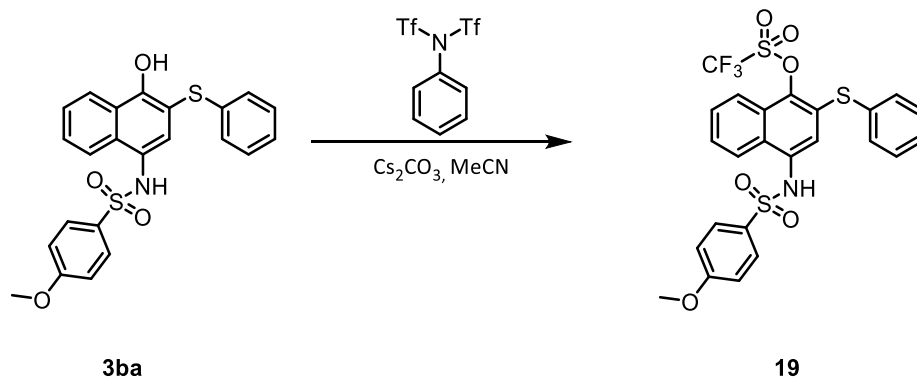
#### 4-((perfluorophenyl)sulfonamido)-2-(phenylthio)naphthalen-1-yl 2-(2-(2-methoxyethoxy)ethoxy)acetate, **18**



The coupling agent carbonyl diimidazole was taken out of the glovebox in a sealed 20-mL vial. The liquid 2-(2-(2-methoxyethoxy)ethoxy)acetic acid was added to the sealed flask while under nitrogen from a manifold. Gas bubbled from the reaction. After 10 min, a solution of **3aa** (100 mg, 0.20 mmol) in dry acetonitrile was added to the vial (4 mL). The reaction was complete by TLC after 30 min (1:5 EtOAc/hexanes). The reaction mixture was then taken up into ether and washed thrice with water. The organic layer was dried with Na<sub>2</sub>SO<sub>4</sub> and filtered through cotton. After filtration, the organic solution was dried onto silica and loaded onto a silica gel column where it was purified by elution on solvent (1:9 EtOAc/hexanes) to yield **18** (70 mg, 50%), a yellow oil. <sup>1</sup>H NMR (600 MHz, chloroform-*d*) δ 8.03 – 7.97 (m, 1H), 7.83 – 7.76 (m, 1H), 7.62 – 7.56 (m, 2H), 7.39 – 7.28 (m, 5H), 7.26 (s, 1H), 6.98 (s, 1H), 4.65 (s, 2H), 3.93 – 3.87 (m, 2H), 3.74 (dd, *J* = 5.7, 3.7 Hz, 2H), 3.69 – 3.62 (m, 2H), 3.58 – 3.50 (m, 2H), 3.37 (s, 2H). <sup>13</sup>C NMR

(151 MHz, chloroform-*d*)  $\delta$  168.6, 144.0, 132.7, 132.6, 129.4, 129.1, 128.6, 128.3, 128.3, 128.1, 127.9, 126.6, 124.2, 122.0, 121.9, 71.9, 70.7, 70.6, 68.4, 59.1, 22.5. Due to extensive  $^{19}\text{F}$  splitting,  $^{13}\text{C}$  peaks in the perfluorophenyl region were not identified.

**4-((perfluorophenyl)sulfonamido)-2-(phenylthio)naphthalen-1-yl trifluoromethanesulfonate, **19****

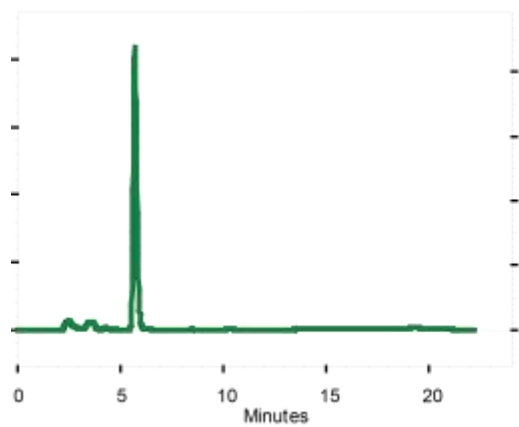


The sulfonamide **3ba** (50 mg, 0.11 mmol) was placed in a scintillation vial along N-Phenyl-bis(trifluoromethanesulfonyl)amine (50 mg, 0.14 mmol) and  $\text{Cs}_2\text{CO}_3$  (50 mg, 0.15 mmol). The air in the vial was evacuated and the vial was backfilled with nitrogen. Degassed MeCN (2 mL) from the solvent purification system was added to the sealed reaction vessel. The reaction was allowed to stir at rt. After 2 h, no starting material remained by TLC (1:2, EtOAc/hexanes). The reaction mixture was taken up into toluene and washed thrice with brine. The resulting organic layer was dried with  $\text{Na}_2\text{SO}_4$  and filtered through cotton. Solvent was removed to afford a crude orange solid. This material was purified by flash chromatography (1:4, EtOAc/hexanes) to afford a yellow solid **19**, (40 mg, 50%).  $^1\text{H}$  NMR (600 MHz, chloroform-*d*)  $\delta$  8.16 (d,  $J = 7.4$  Hz, 1H), 8.12 (d,  $J = 7.1$  Hz, 1H), 7.78 – 7.72 (m, 2H), 7.62 (s, 7H), 7.48 (s, 1H), 6.94 (d,  $J = 8.9$  Hz, 2H), 3.87 (s, 3H).  $^{13}\text{C}$  NMR (151 MHz, chloroform-*d*)  $\delta$  181.4, 163.5, 160.5, 156.1, 136.1, 134.3, 134.2, 133.3, 133.0, 132.0, 131.2, 130.8, 129.8, 127.5, 127.4, 127.2, 122.0, 114.4, 56.0. Due to extensive  $^{19}\text{F}$  splitting,  $^{13}\text{C}$  peak for  $\text{CF}_3$  was not identified.

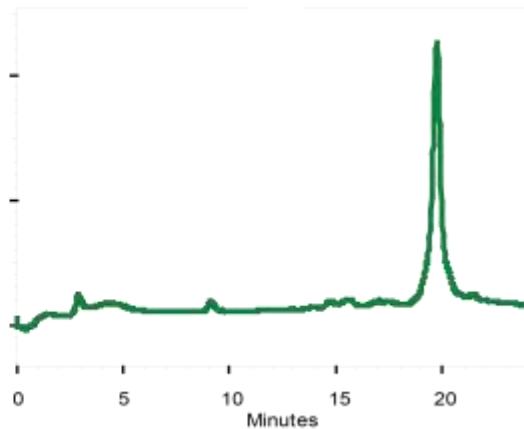


## 1.3. HPLC

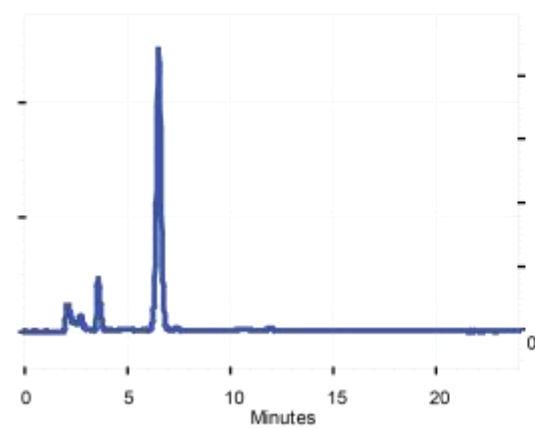
1d



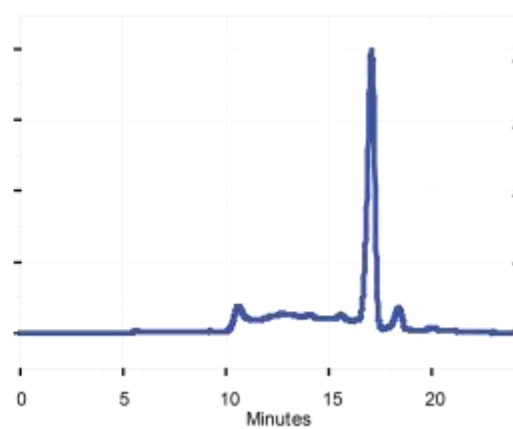
1f



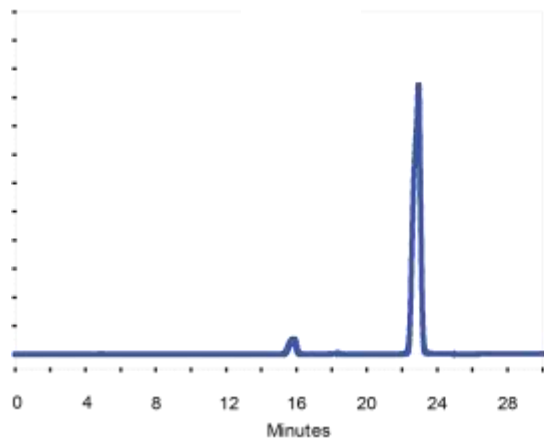
1c



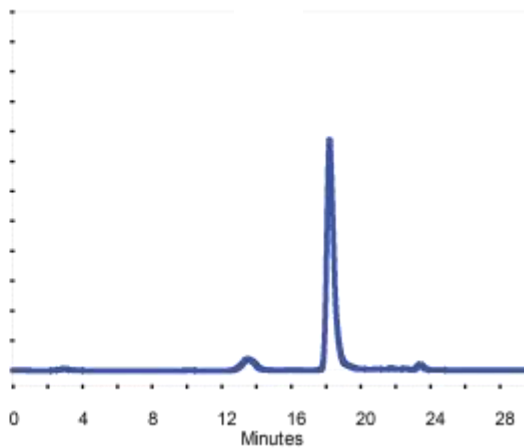
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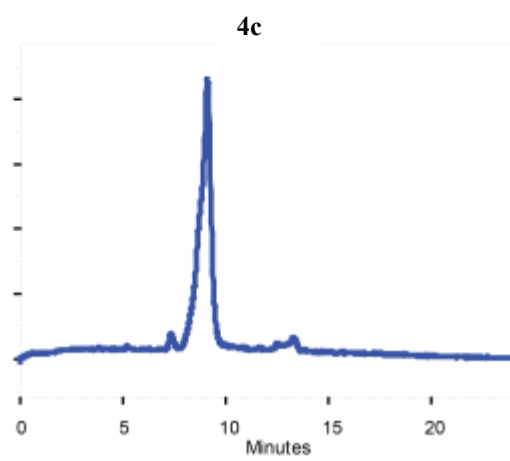
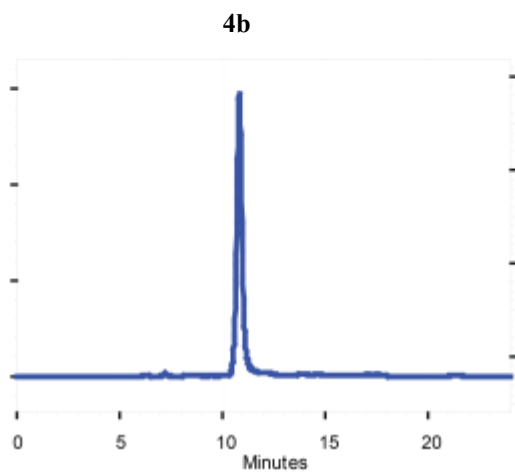
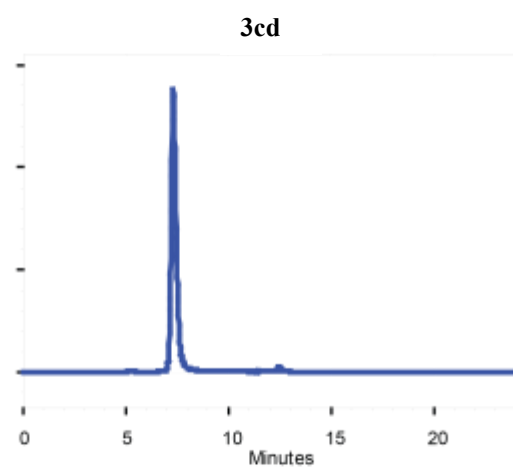
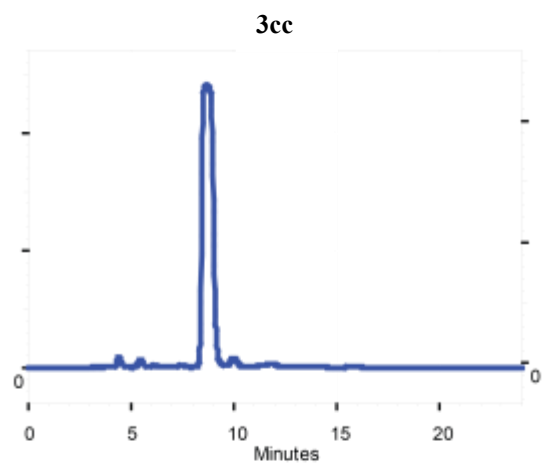
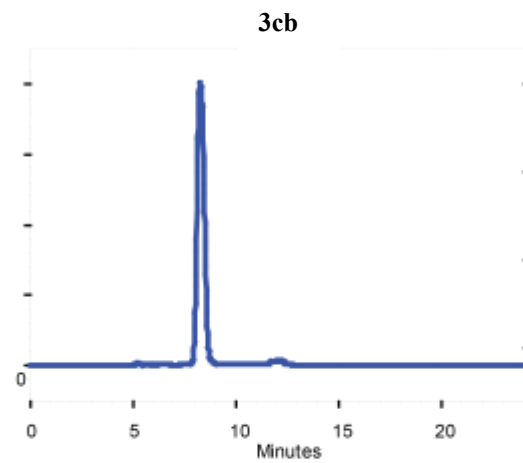
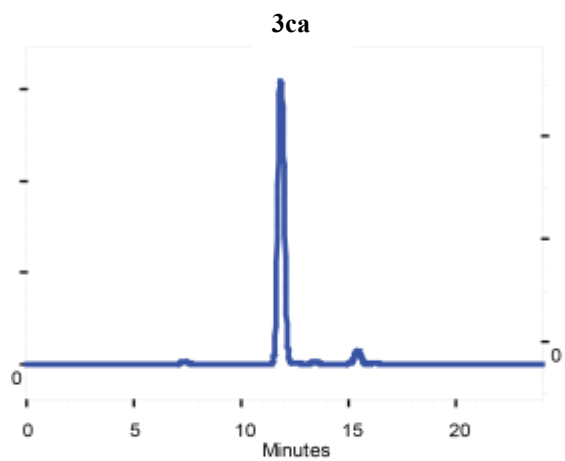


2b\*

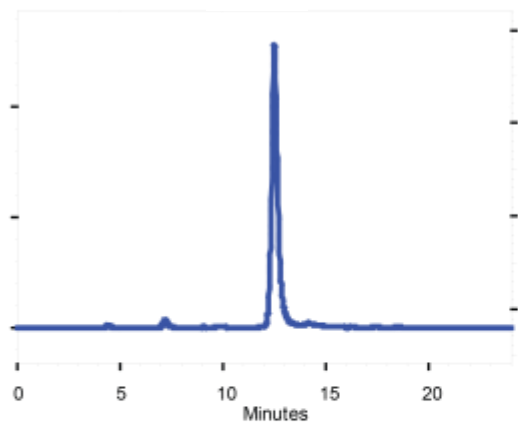


2c

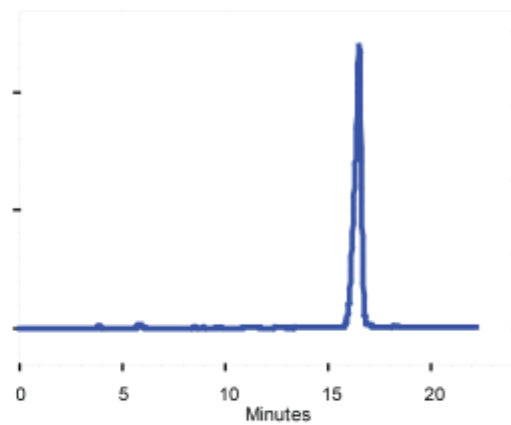




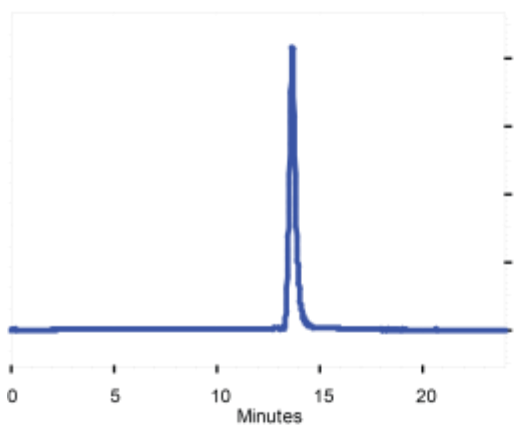
4d



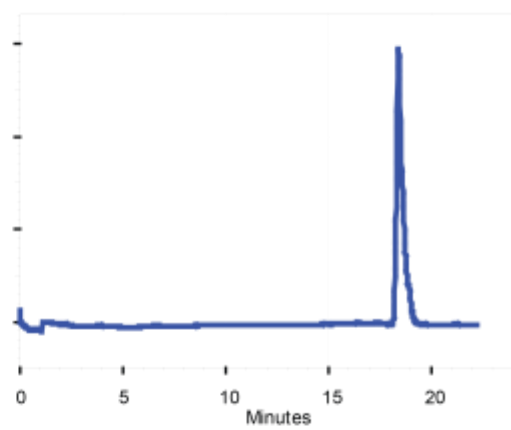
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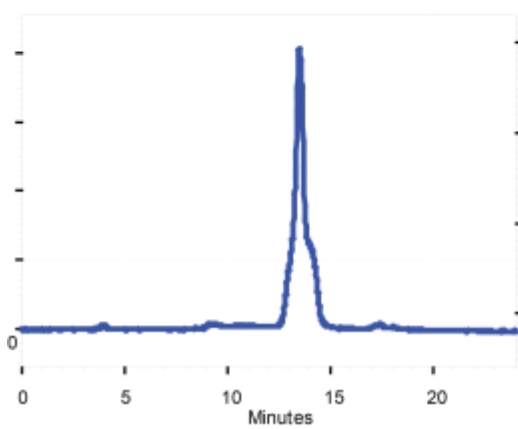
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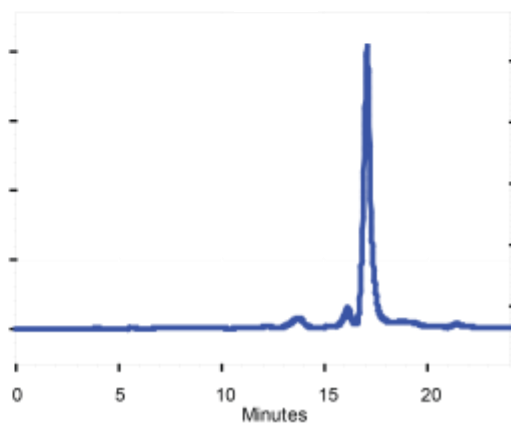
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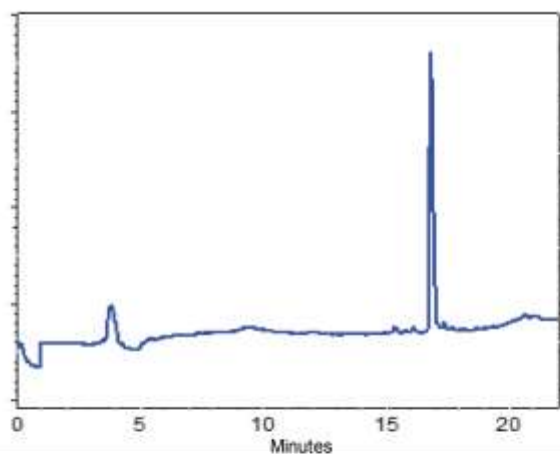
11b



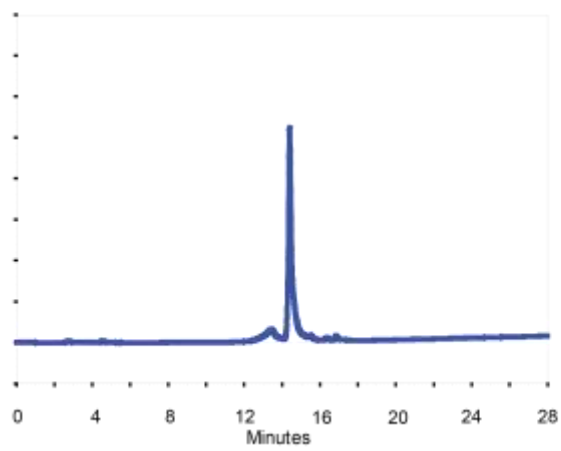
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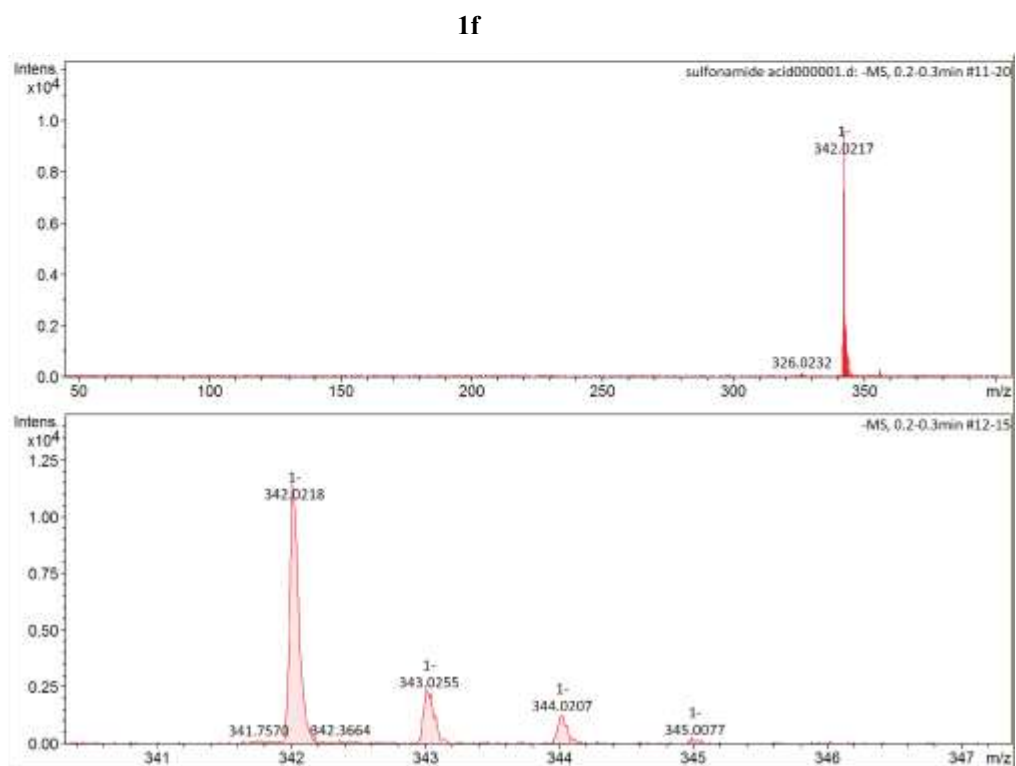
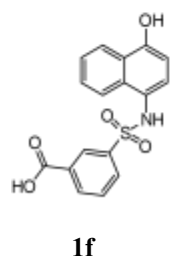
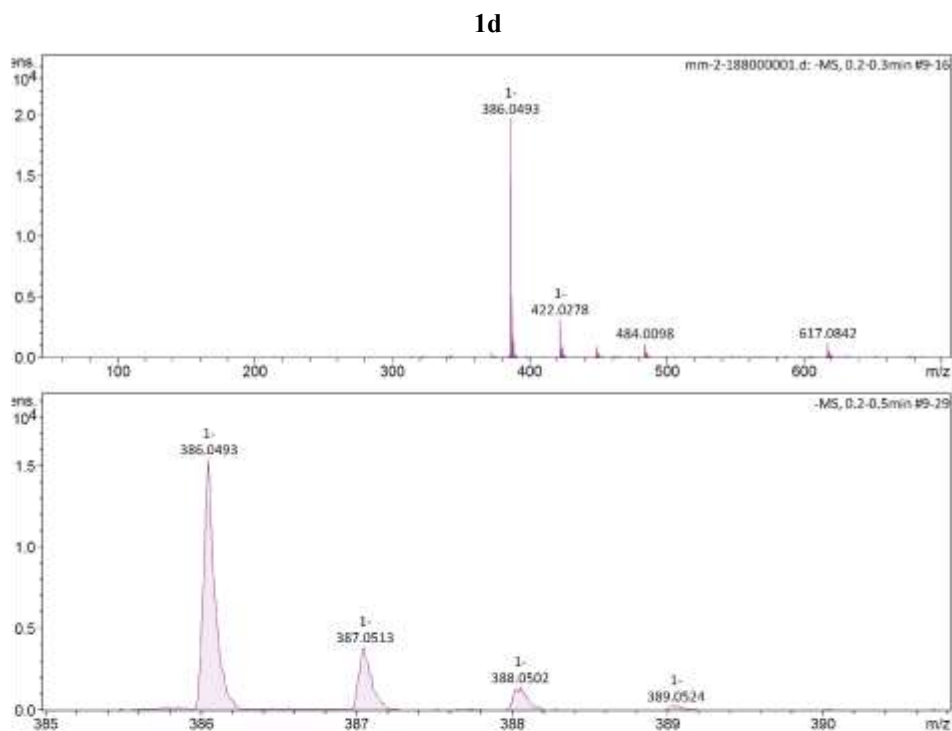
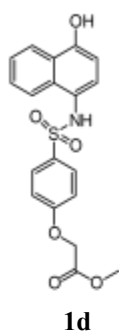
13ae

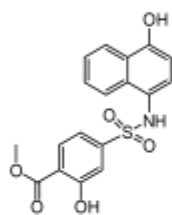
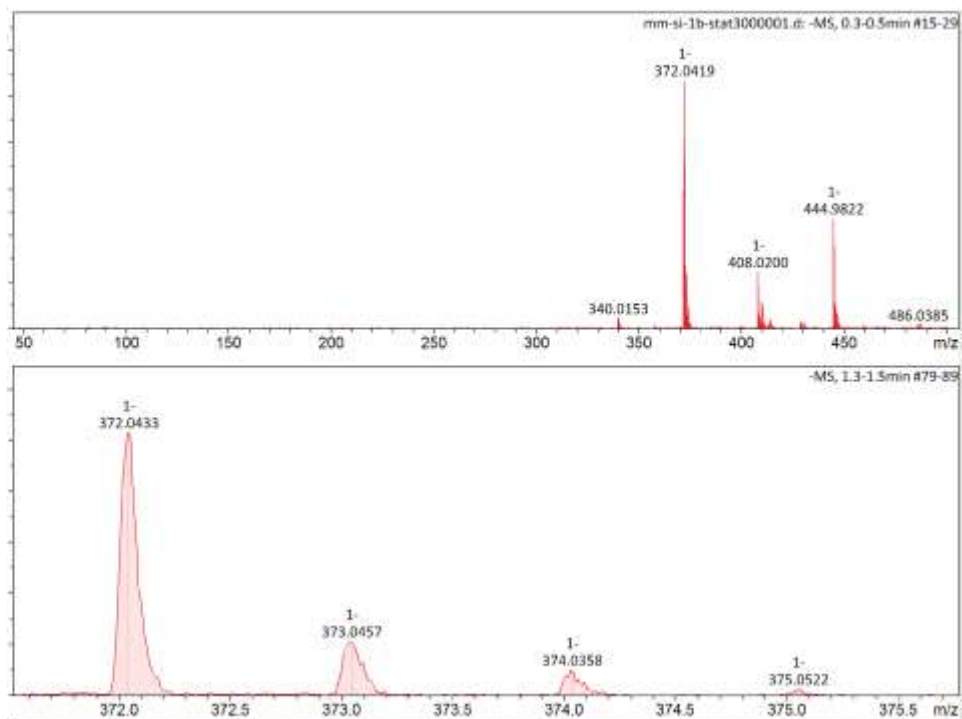
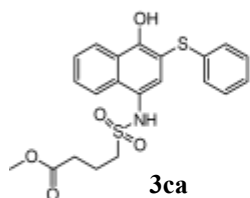
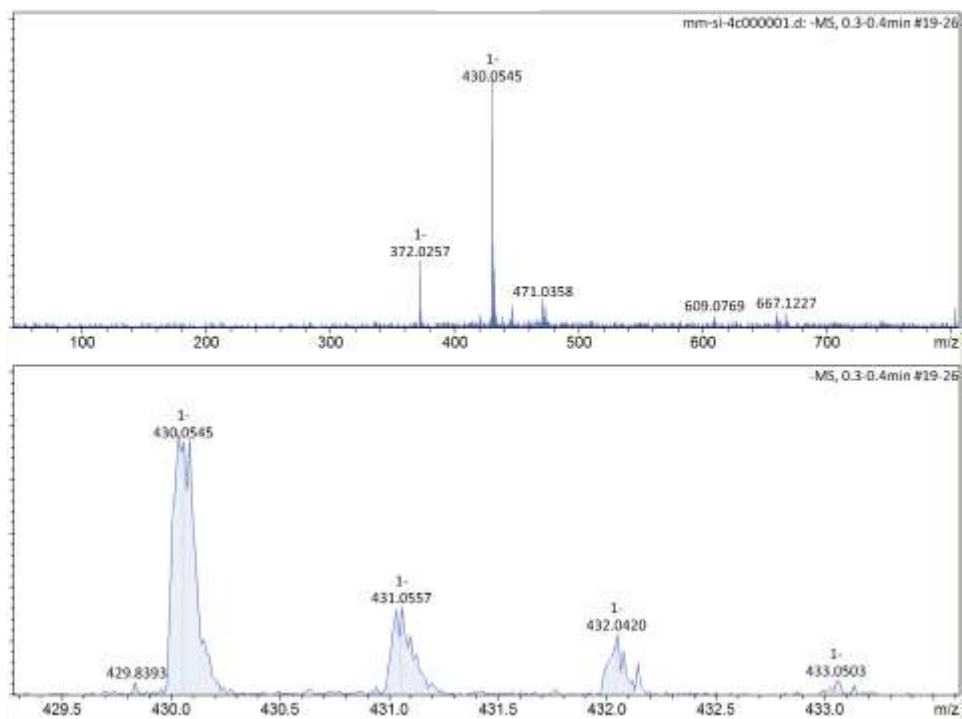


13c

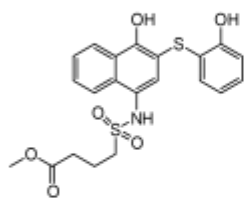


## 1.4. ESI-MS

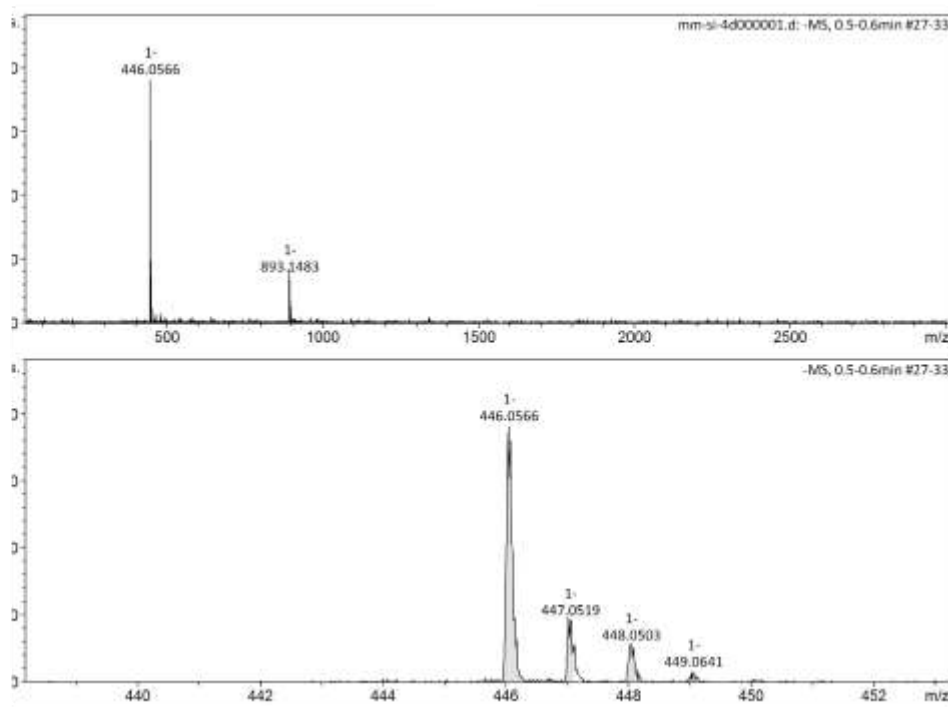


**1c****1c****3ca****3ca**

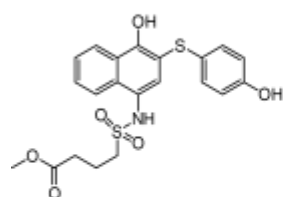
3b



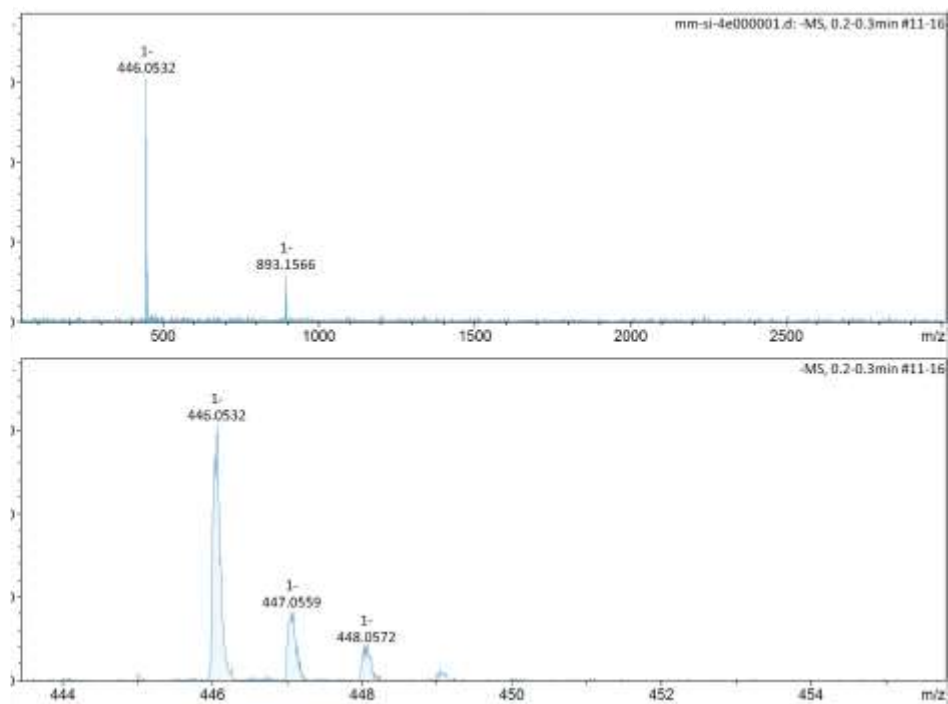
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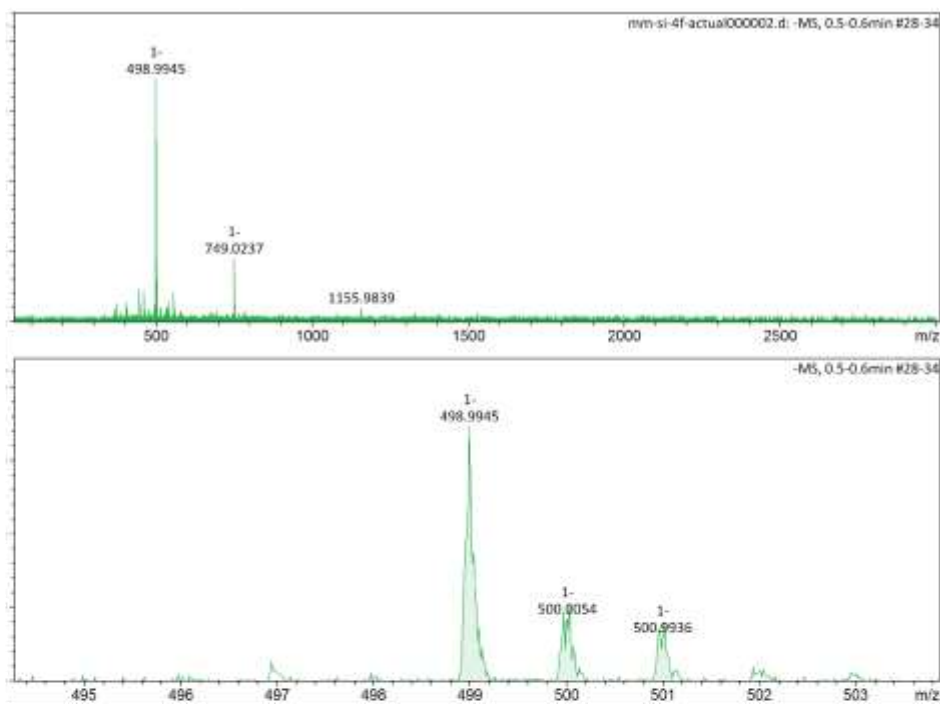
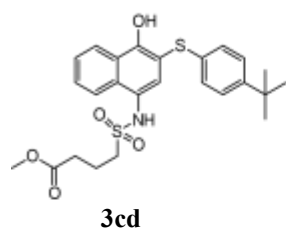
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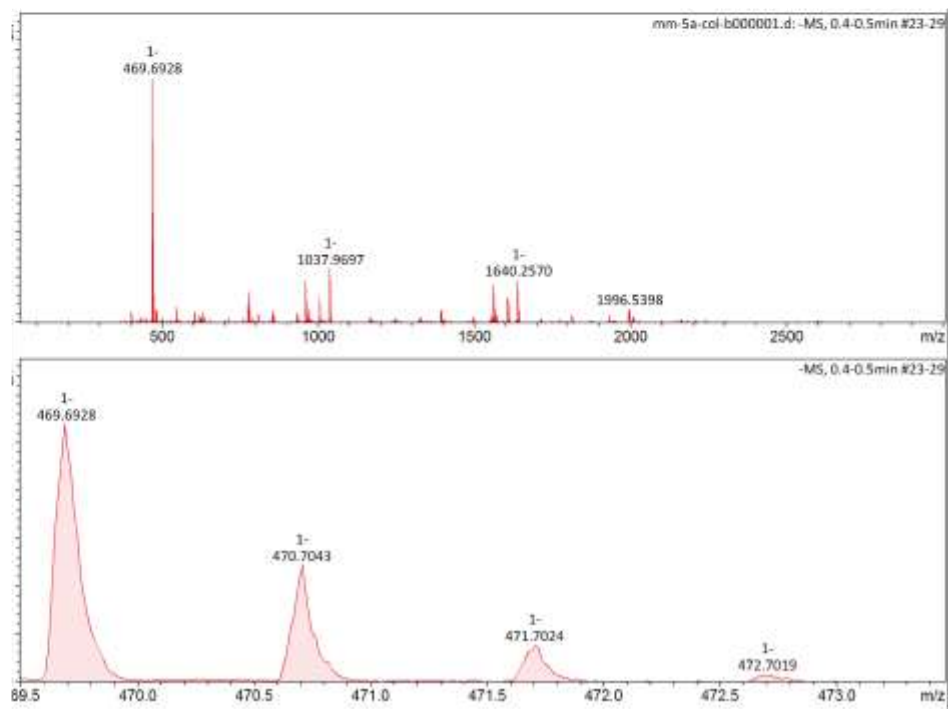
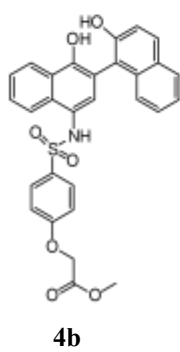
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## 3cd

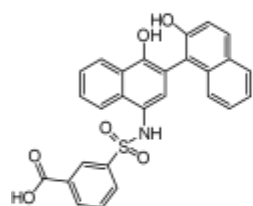


## 4b

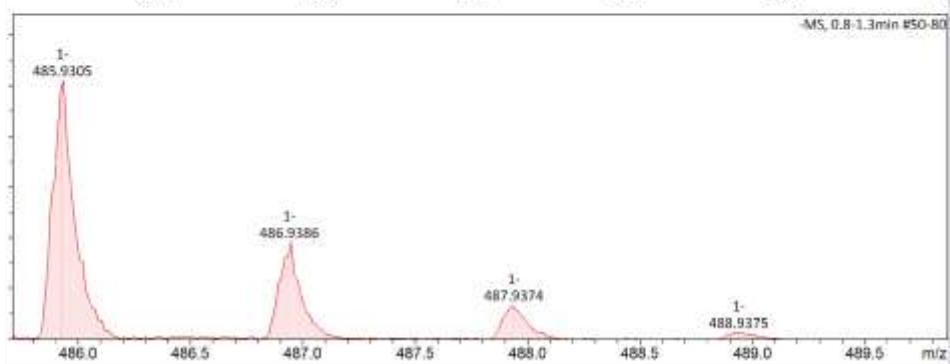
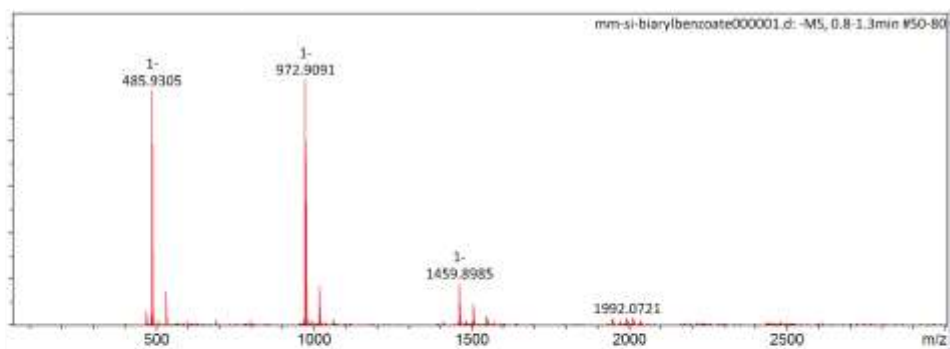




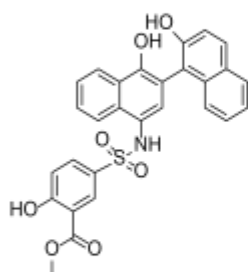
4c



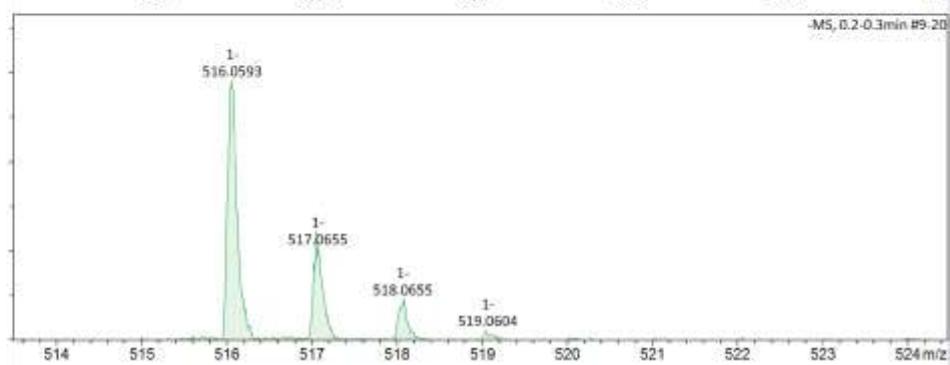
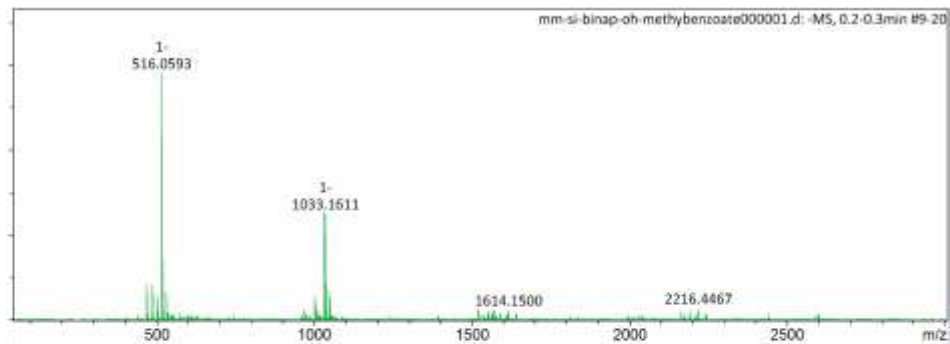
4c

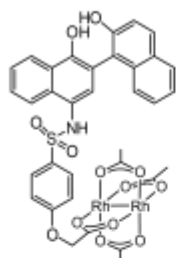
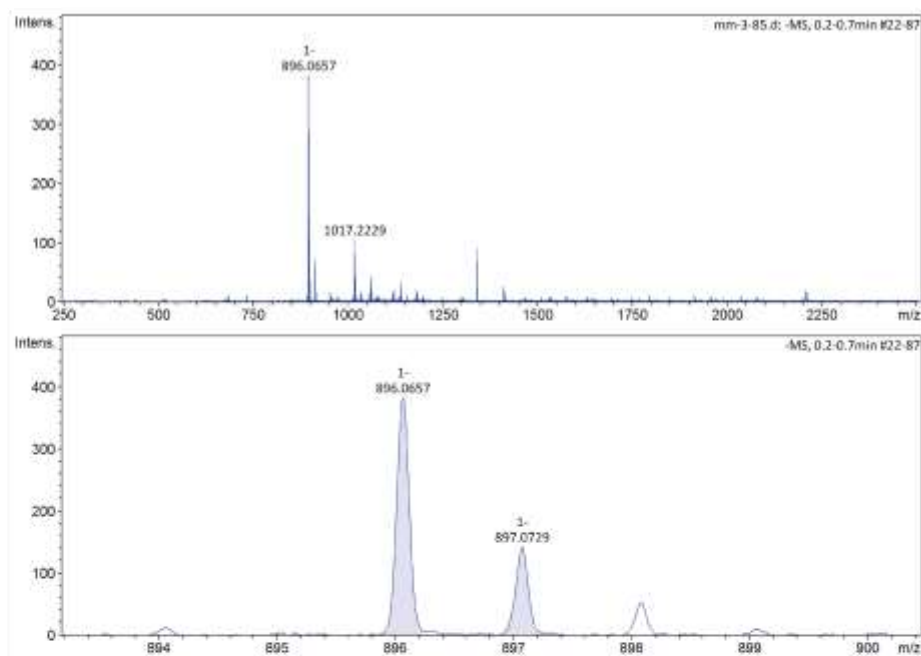
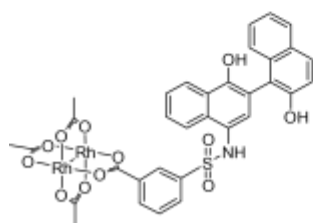
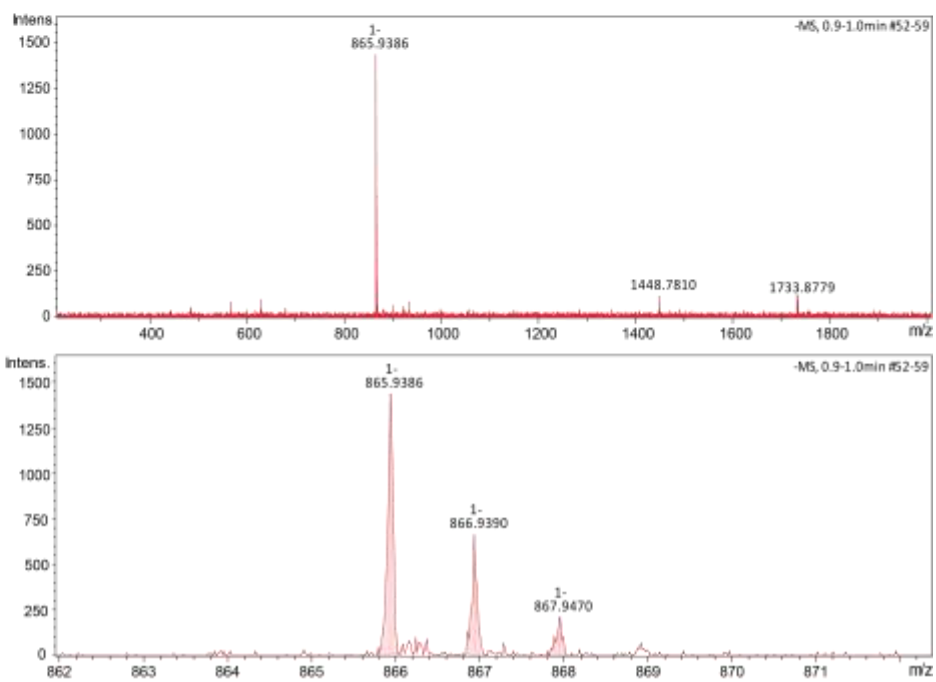


4d

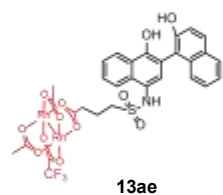


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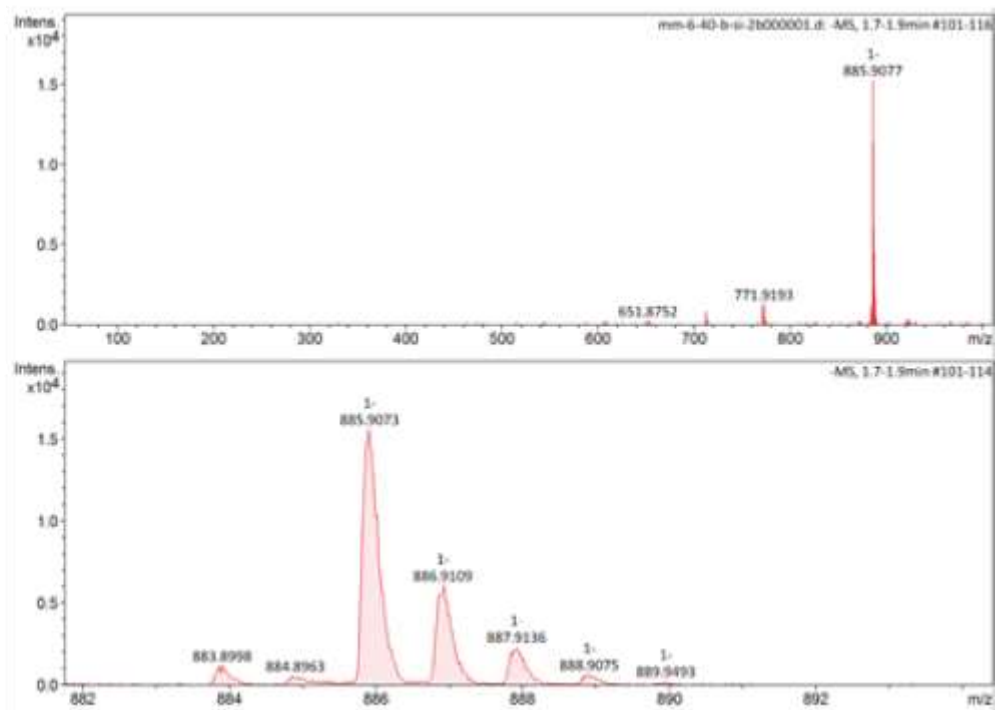


**13b****13b****13c****13c**

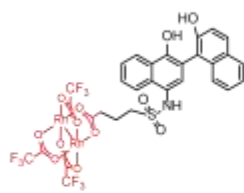
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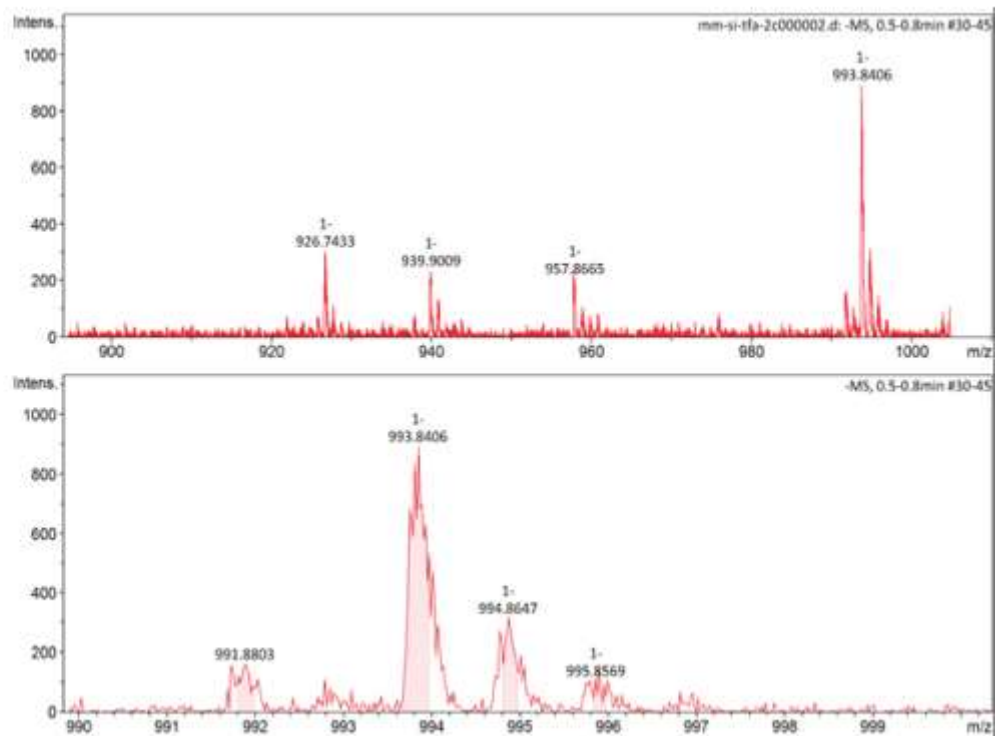
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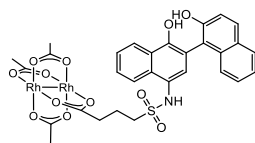
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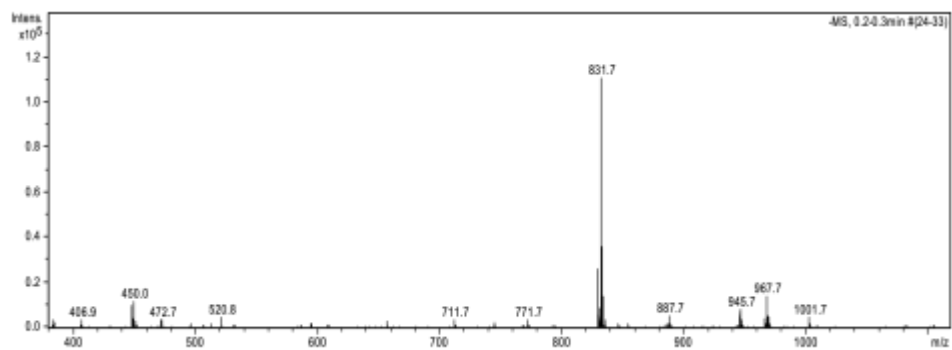
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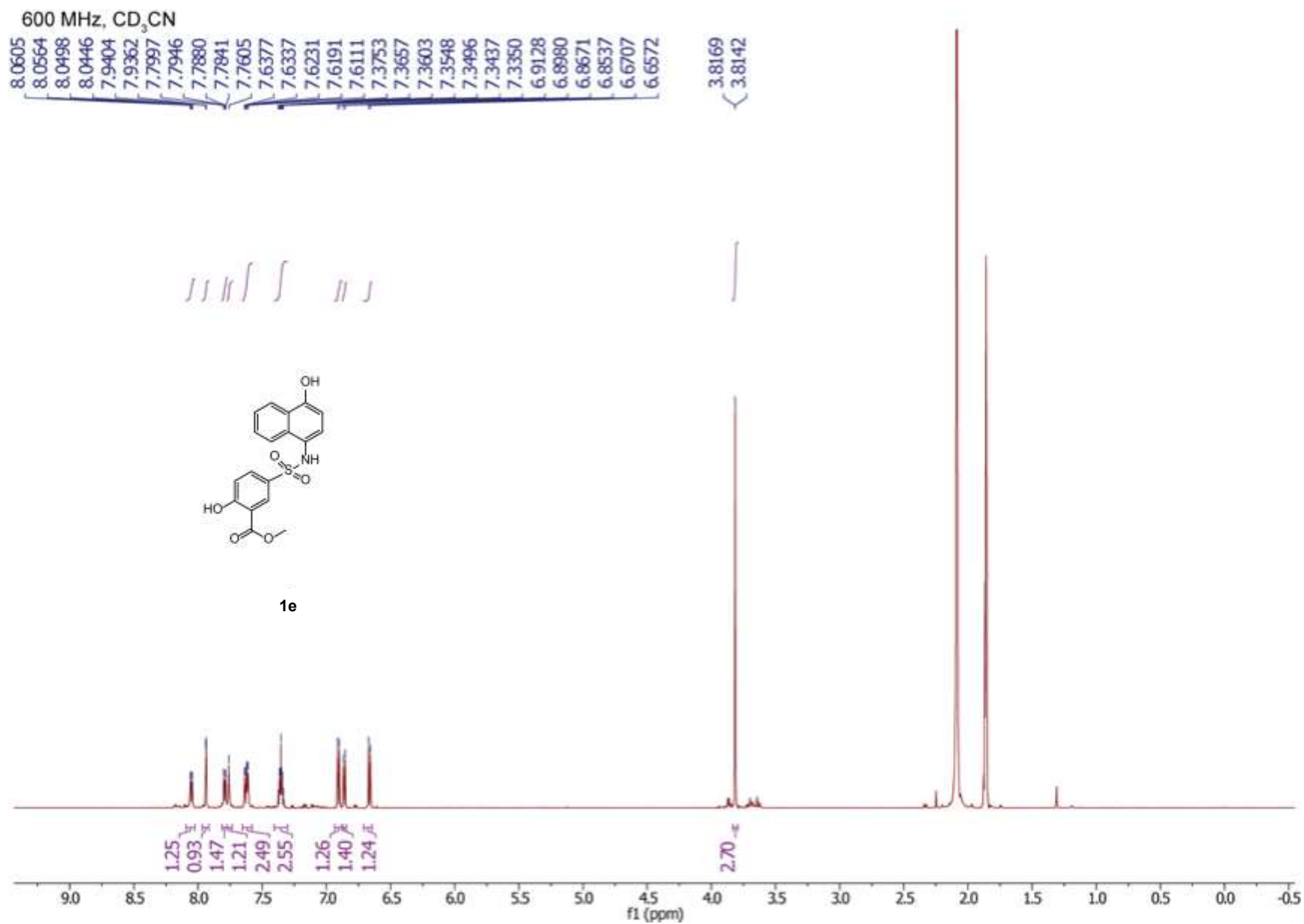
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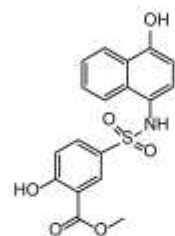


13aa

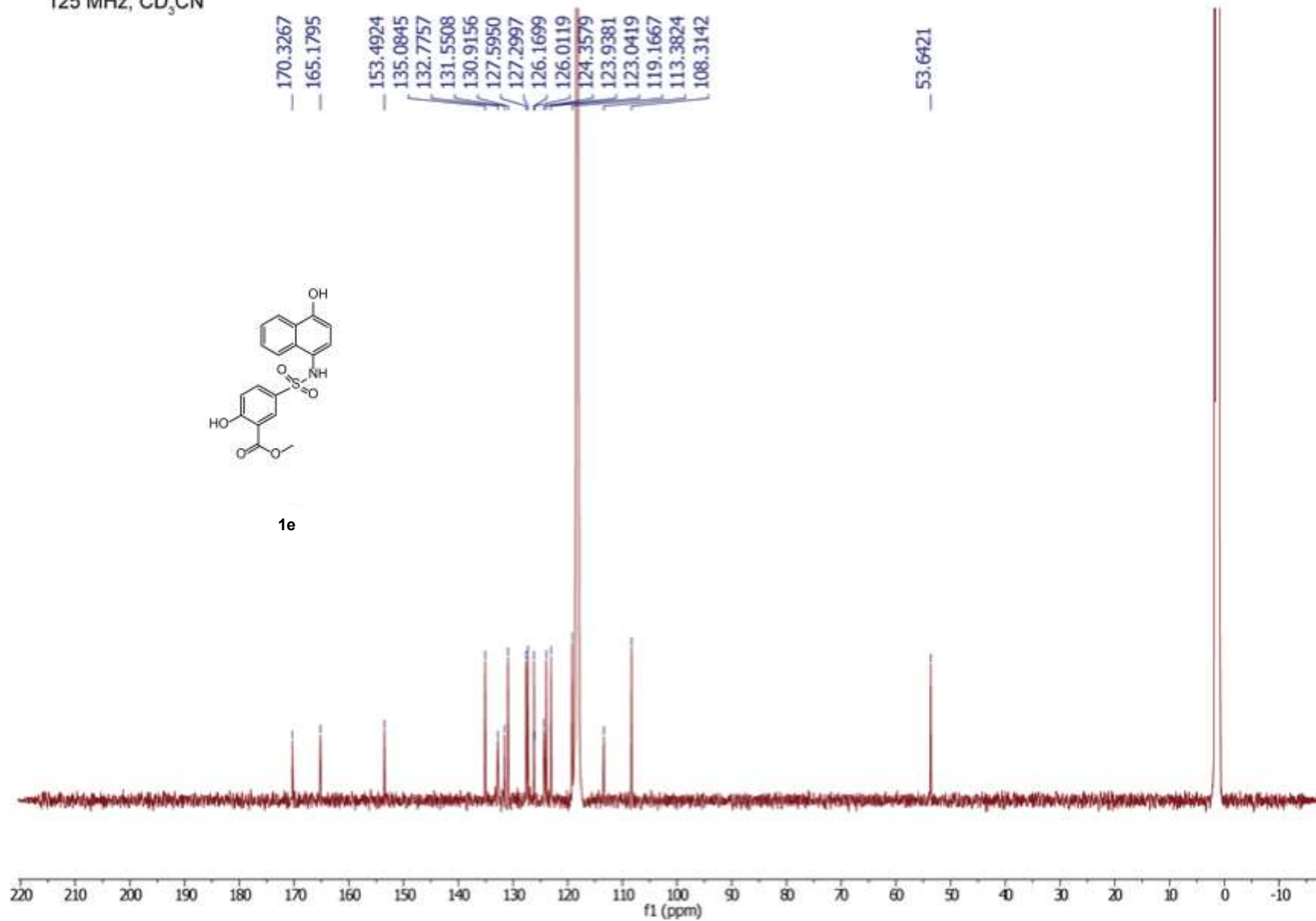


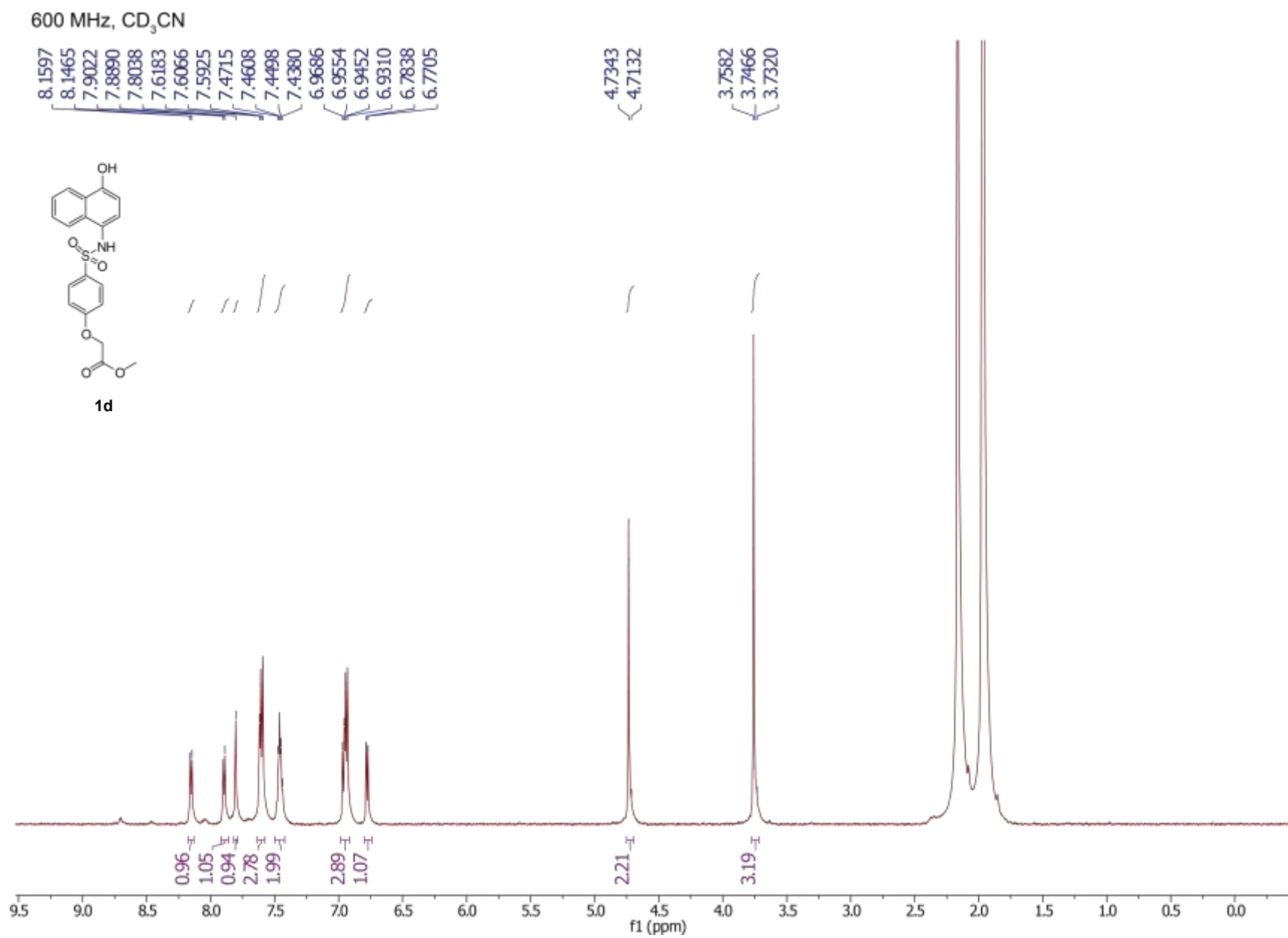
## 1.5. NMR Spectrum



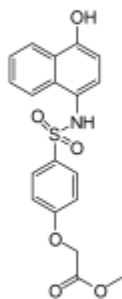
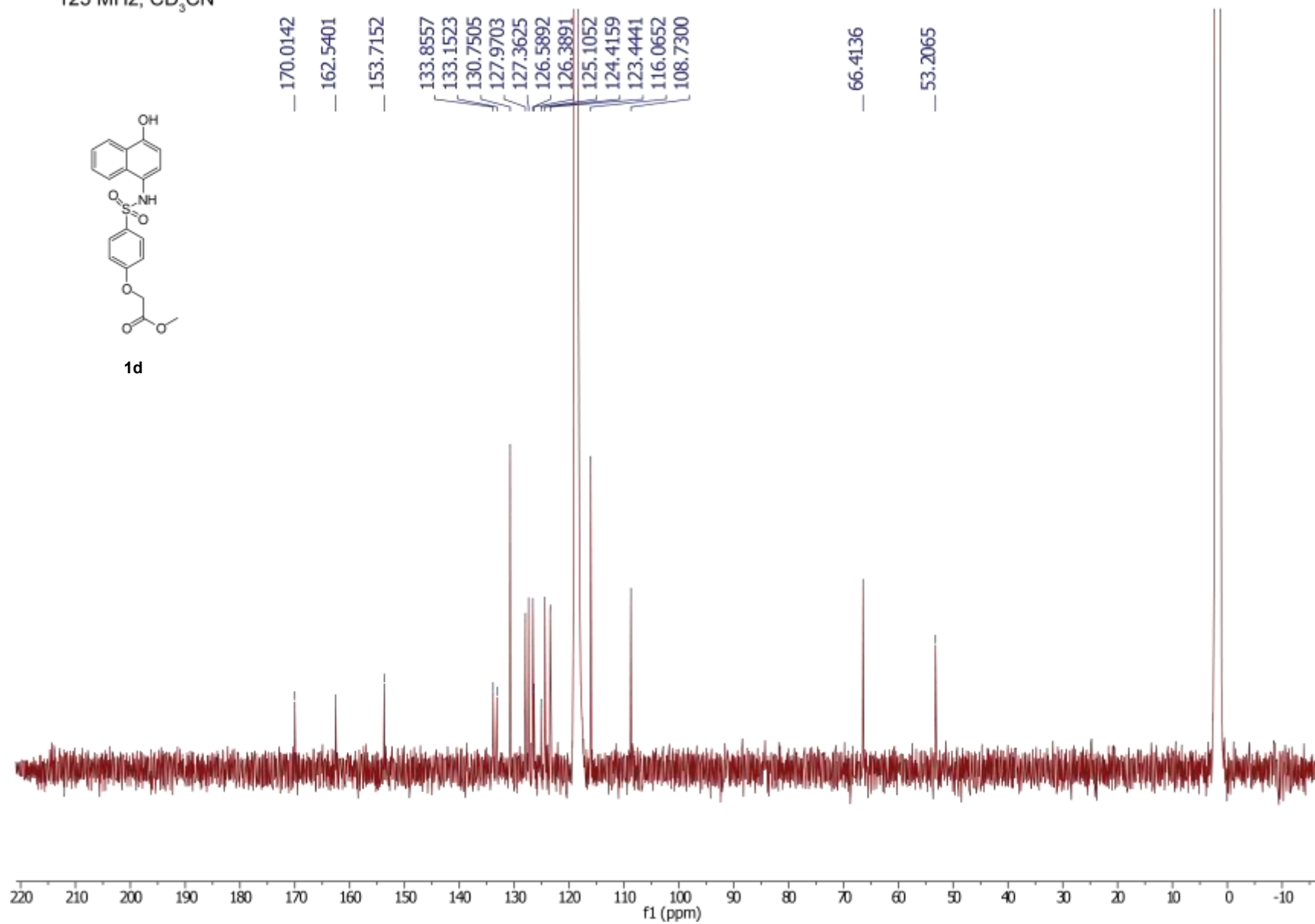
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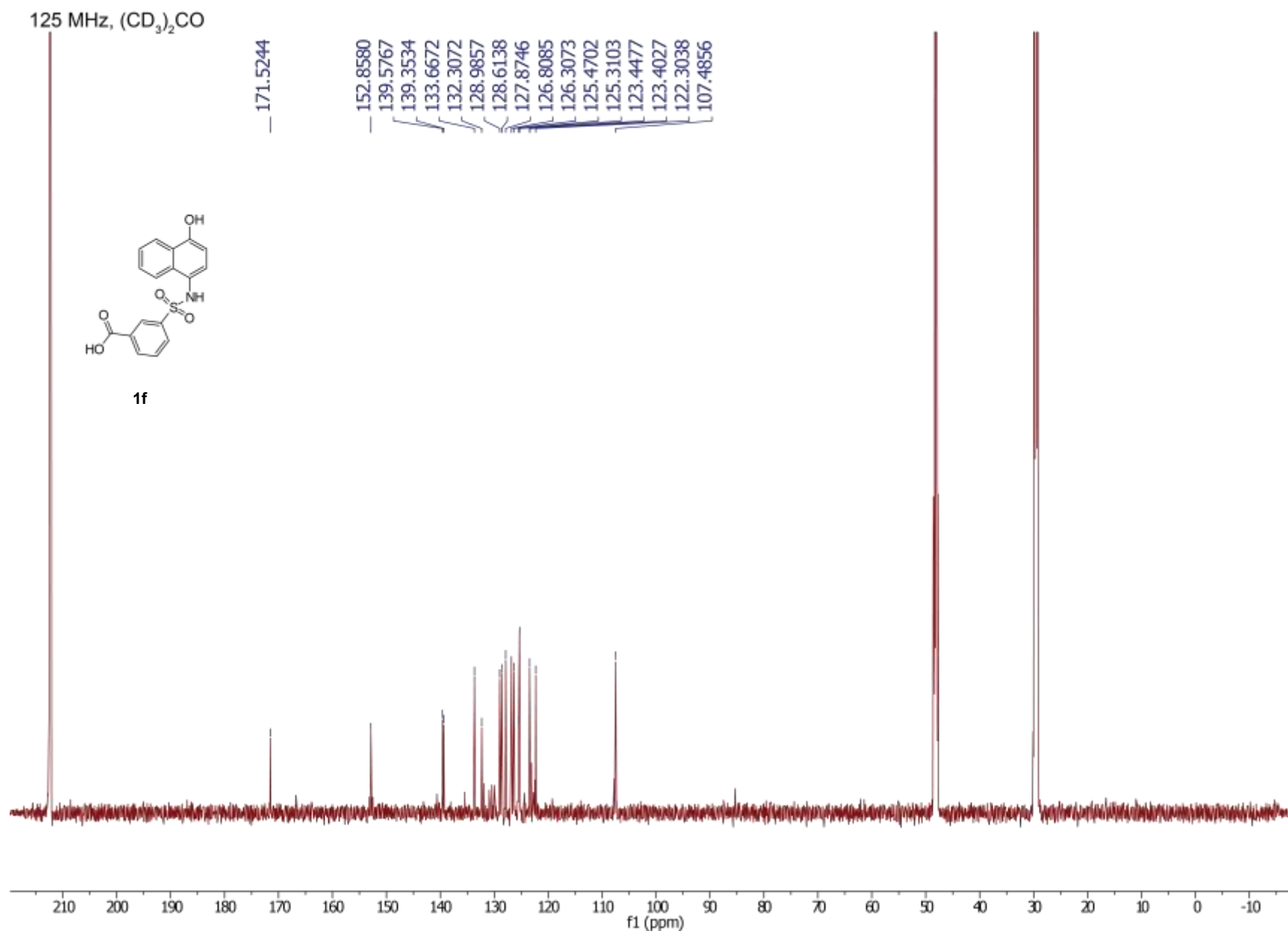
1e

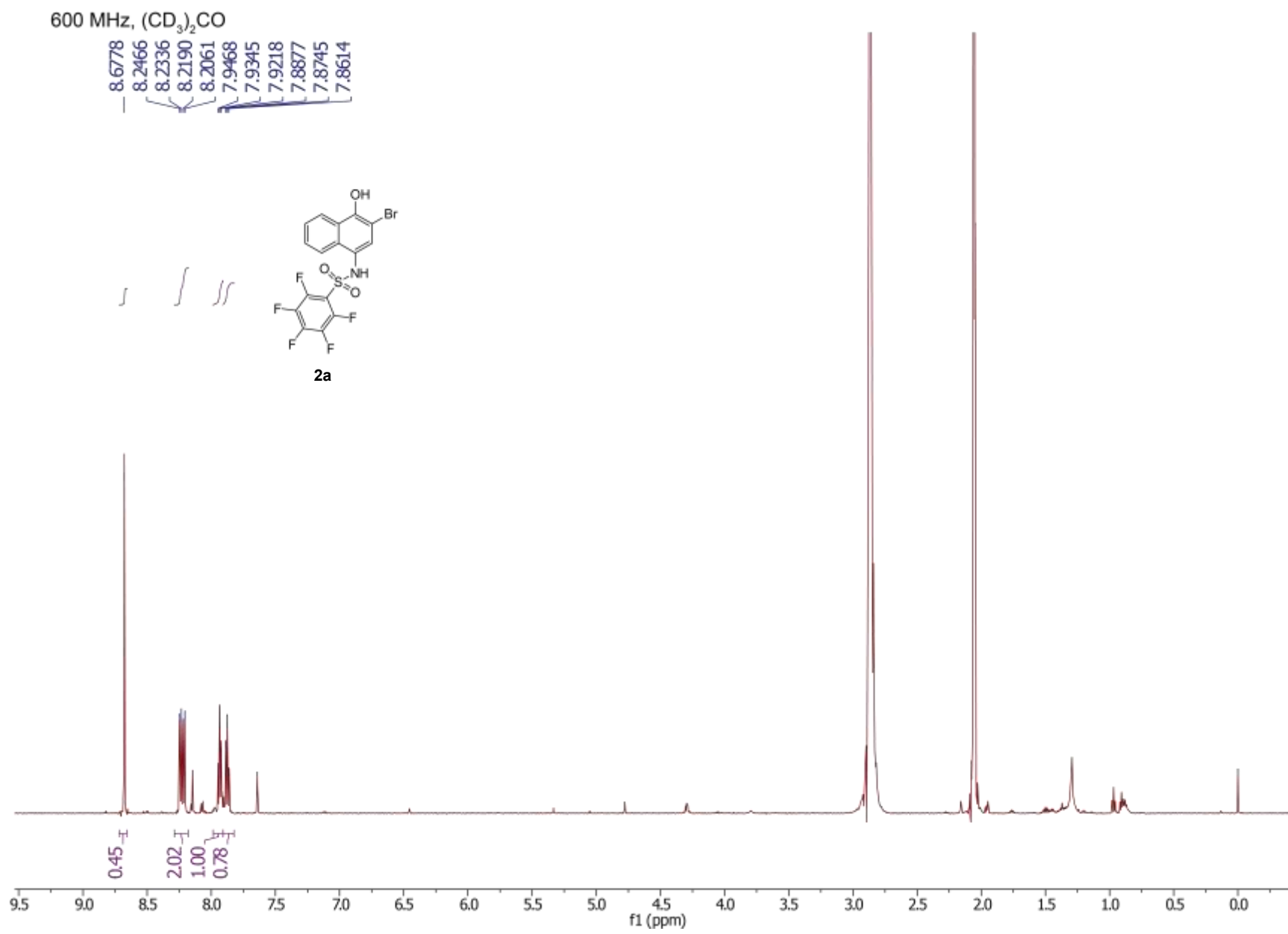


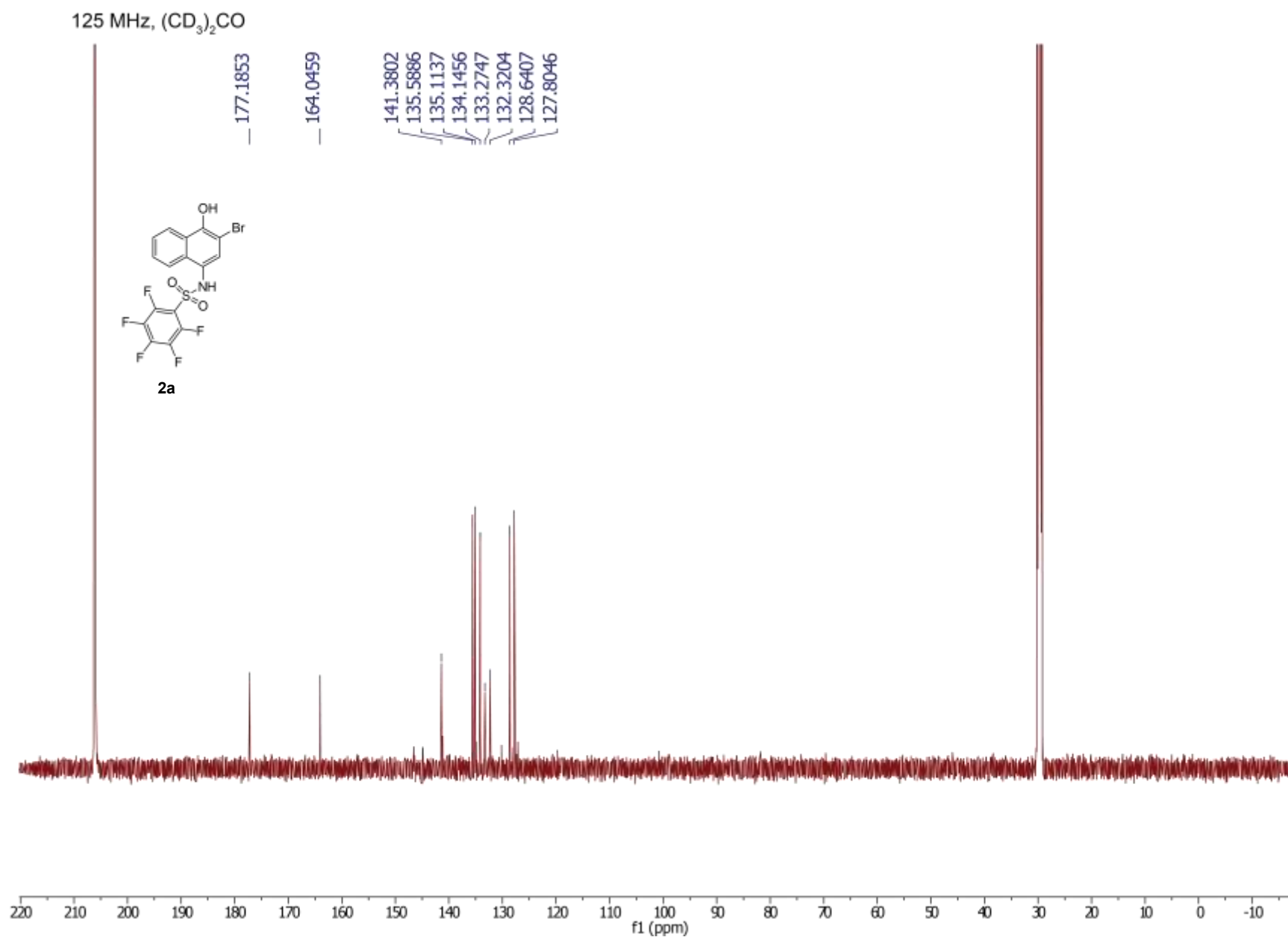


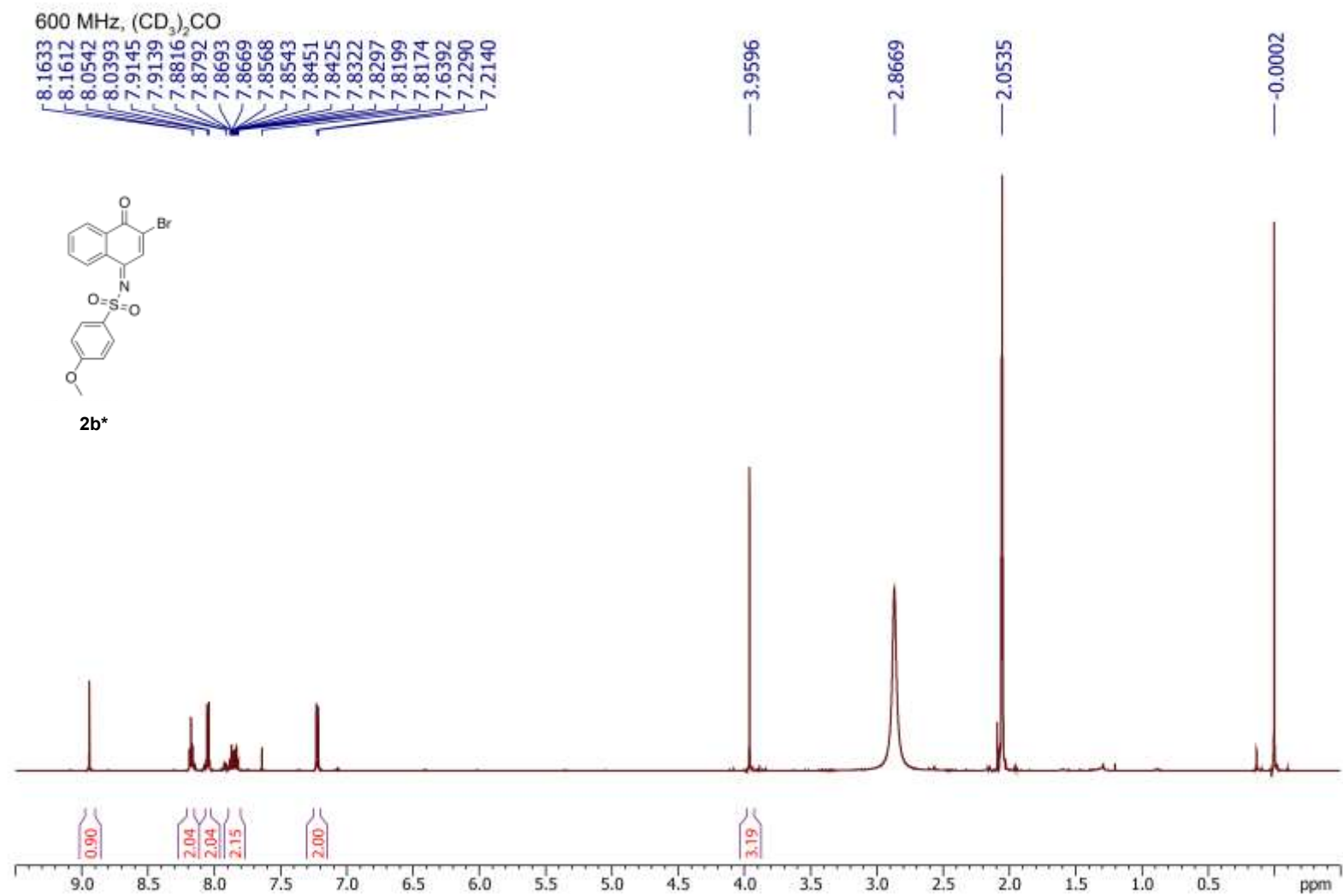


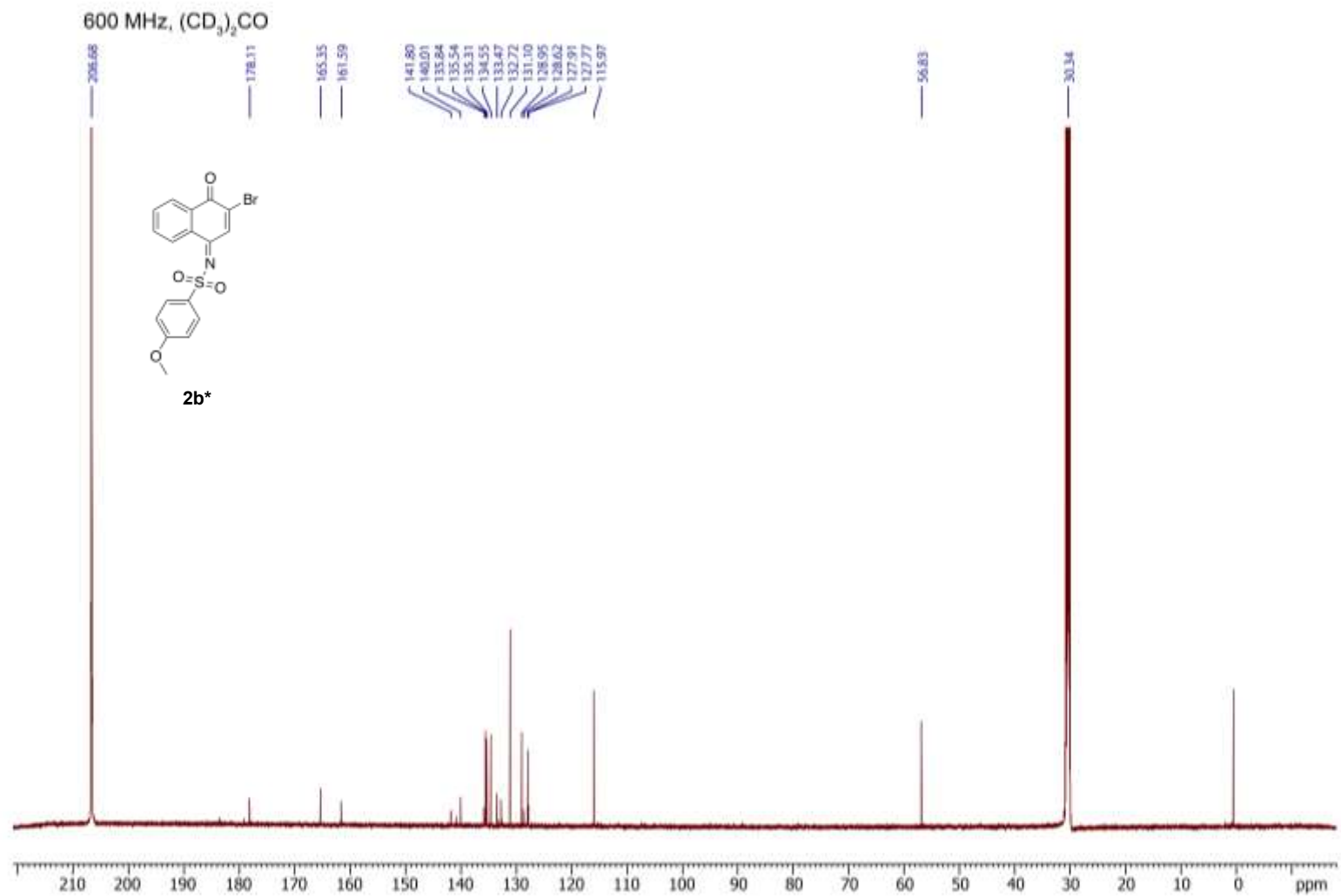
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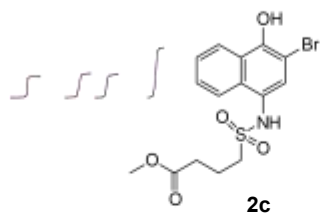




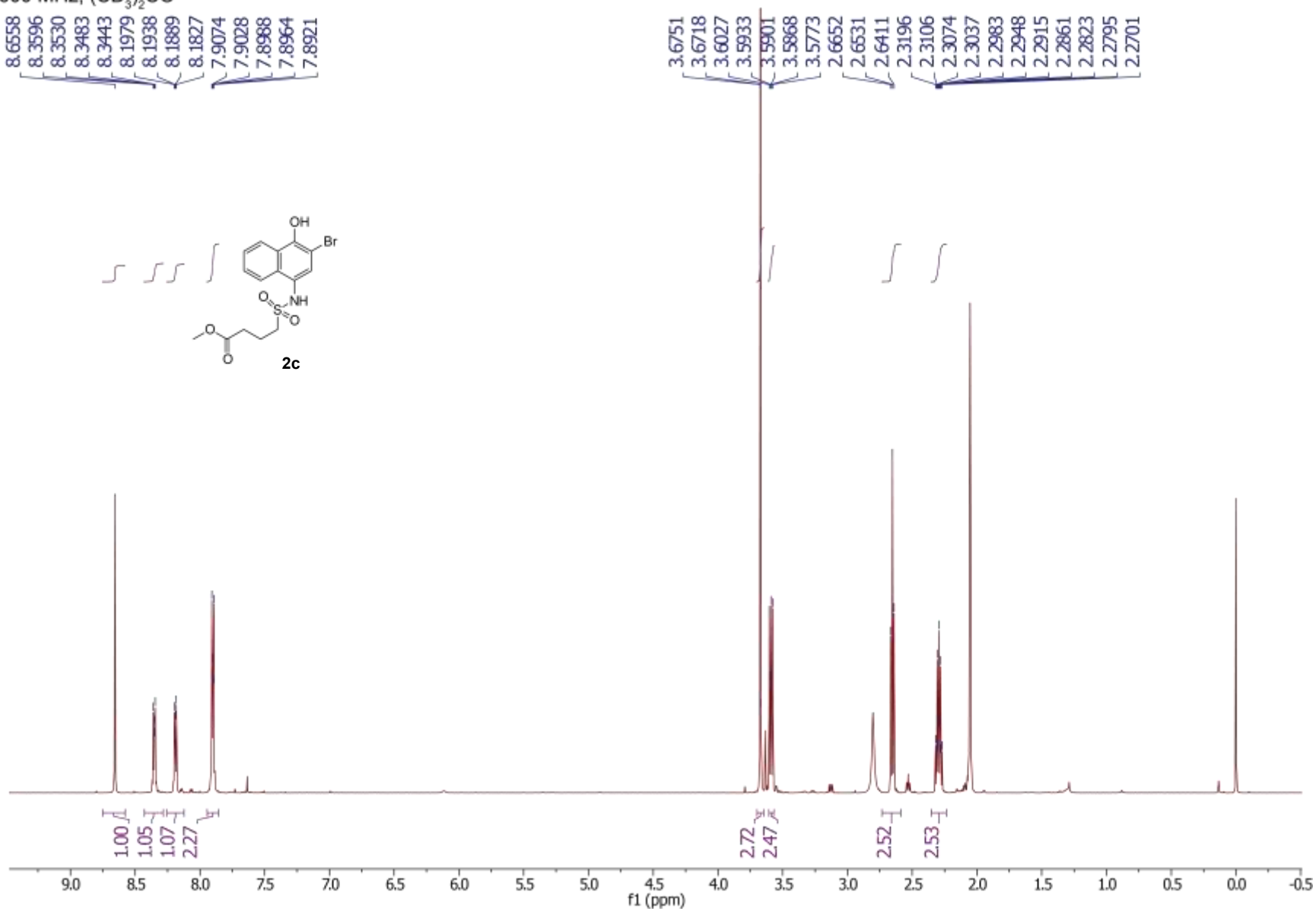
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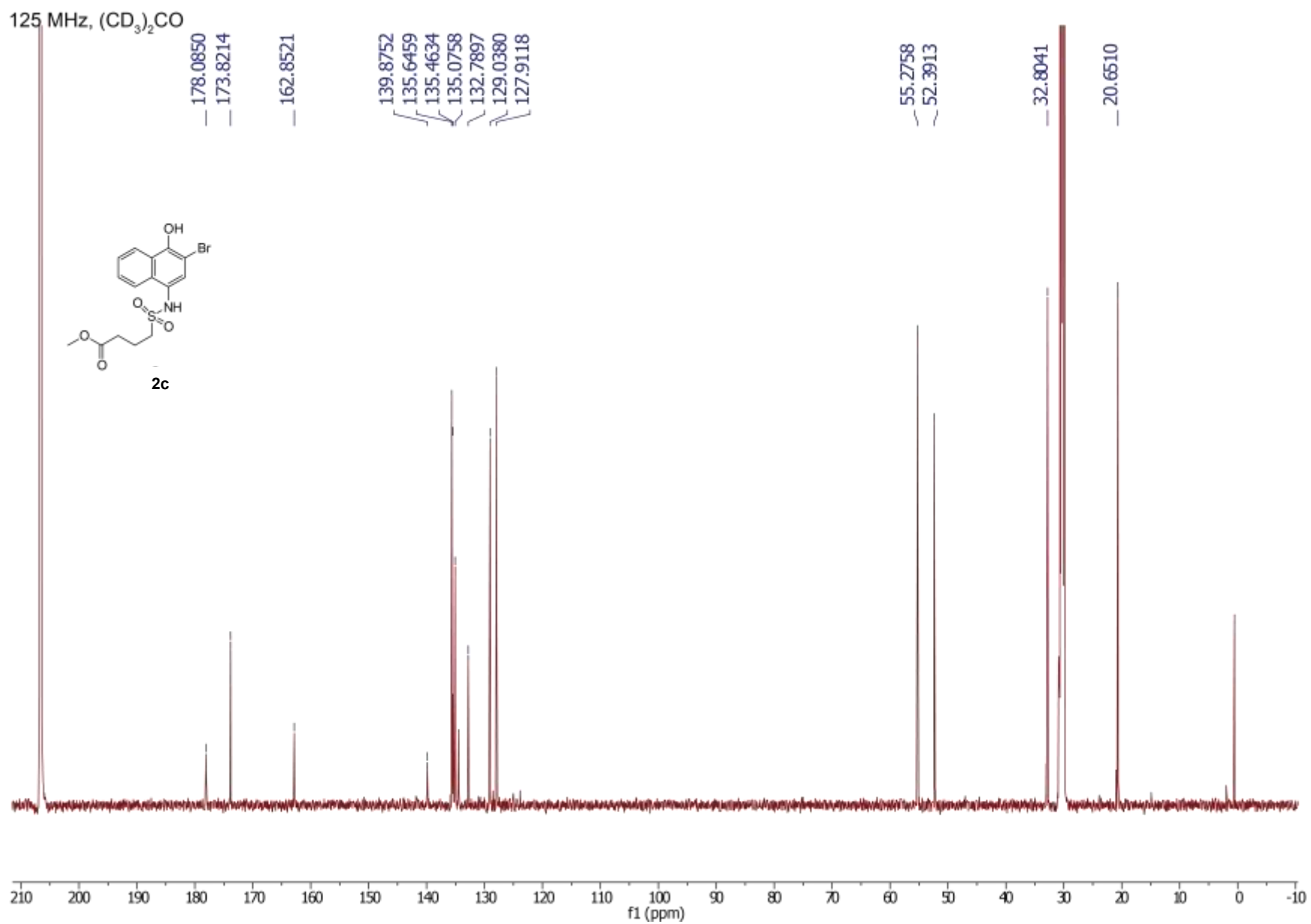
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2.3196  
2.3106  
2.3074  
2.3037  
2.2983  
2.2948  
2.2915  
2.2861  
2.2823  
2.2795  
2.2701

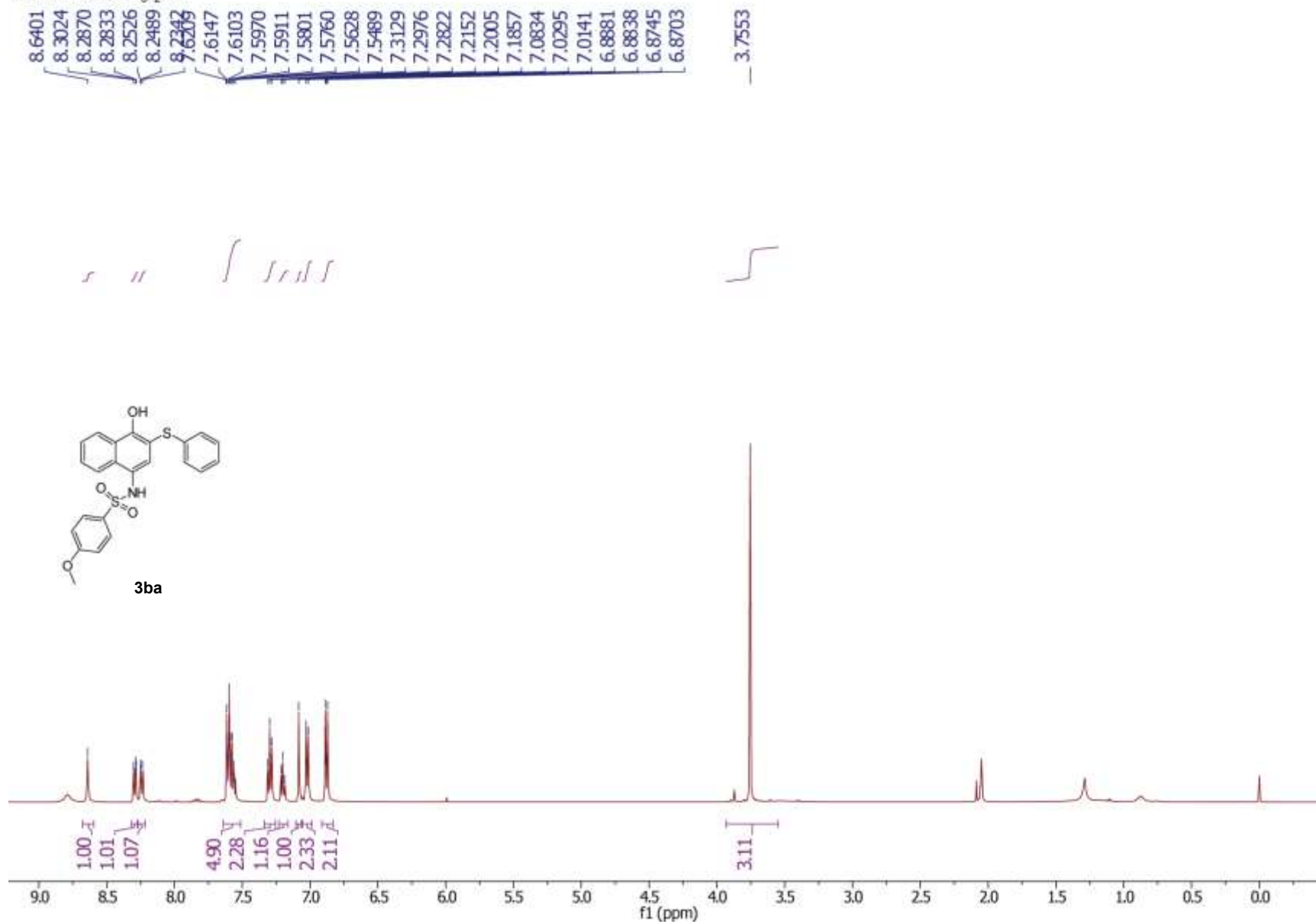


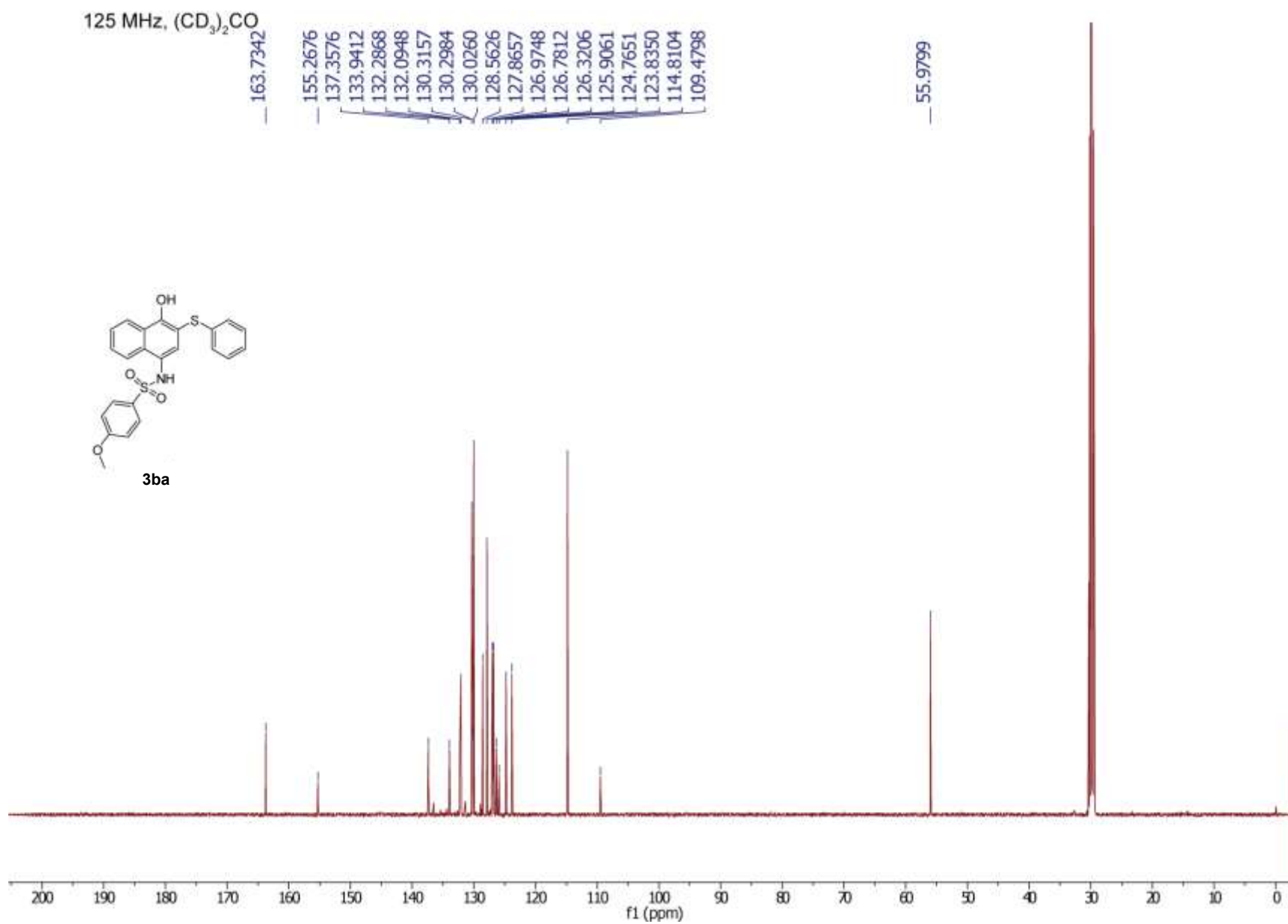
2c

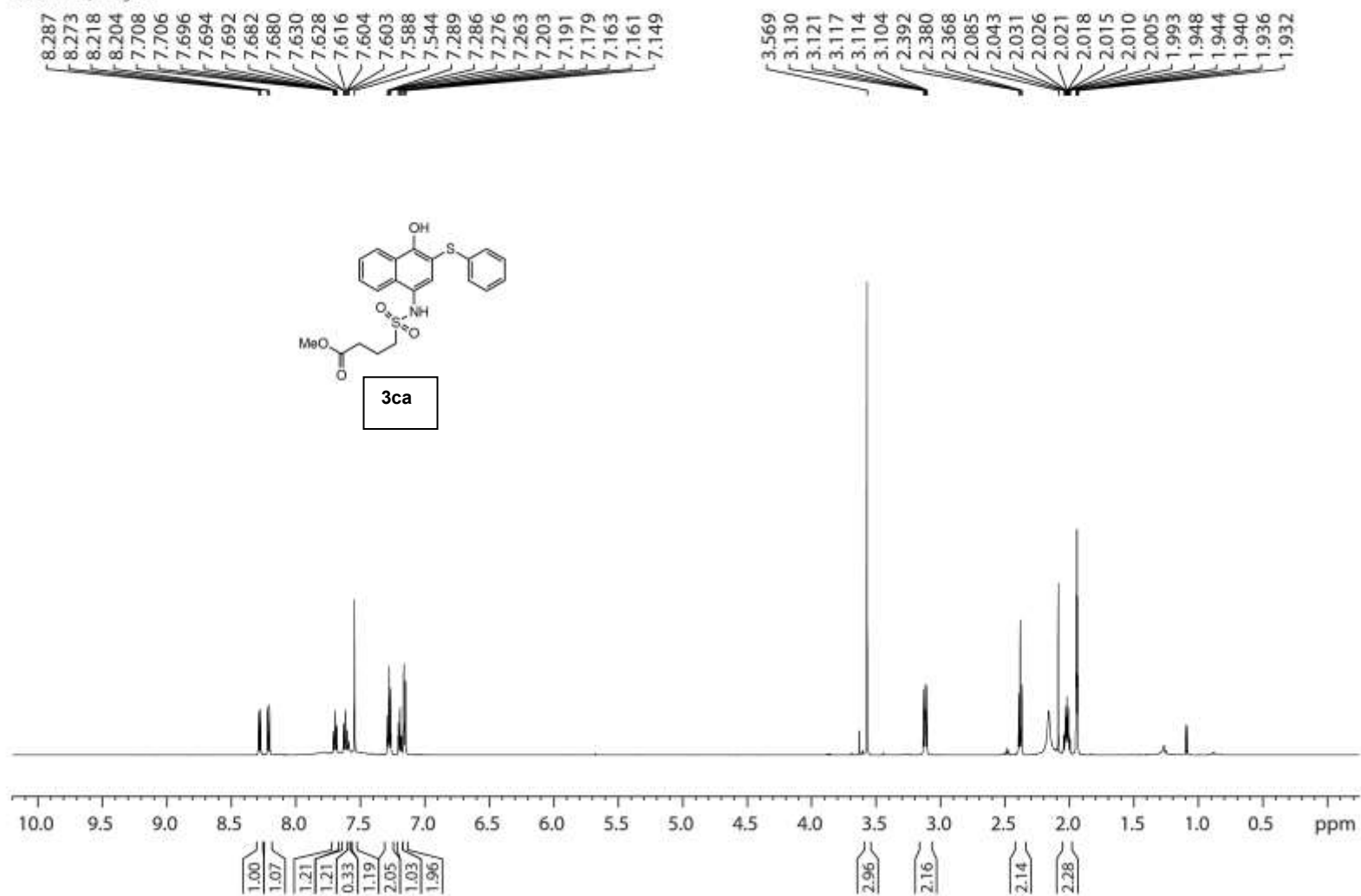


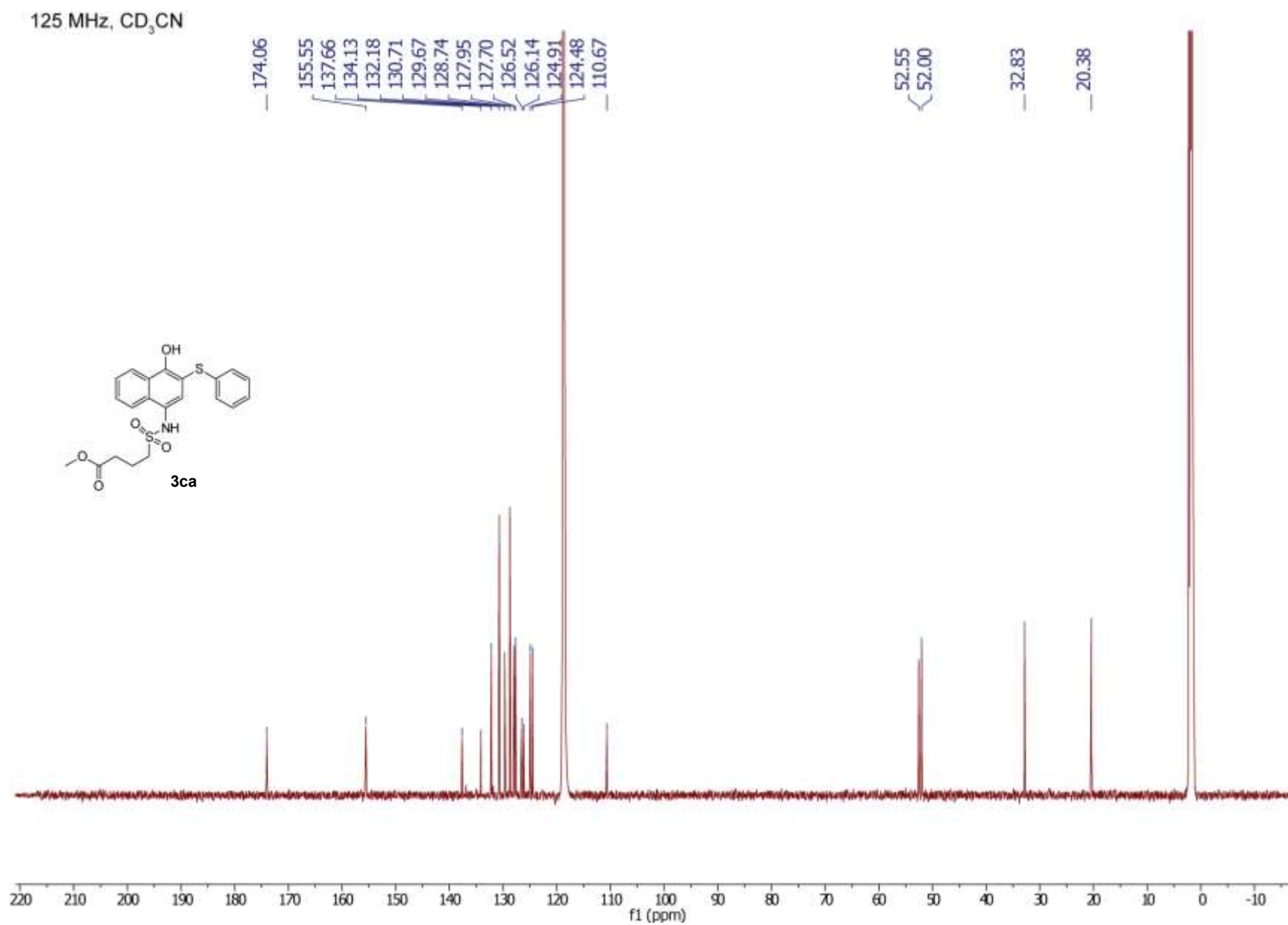


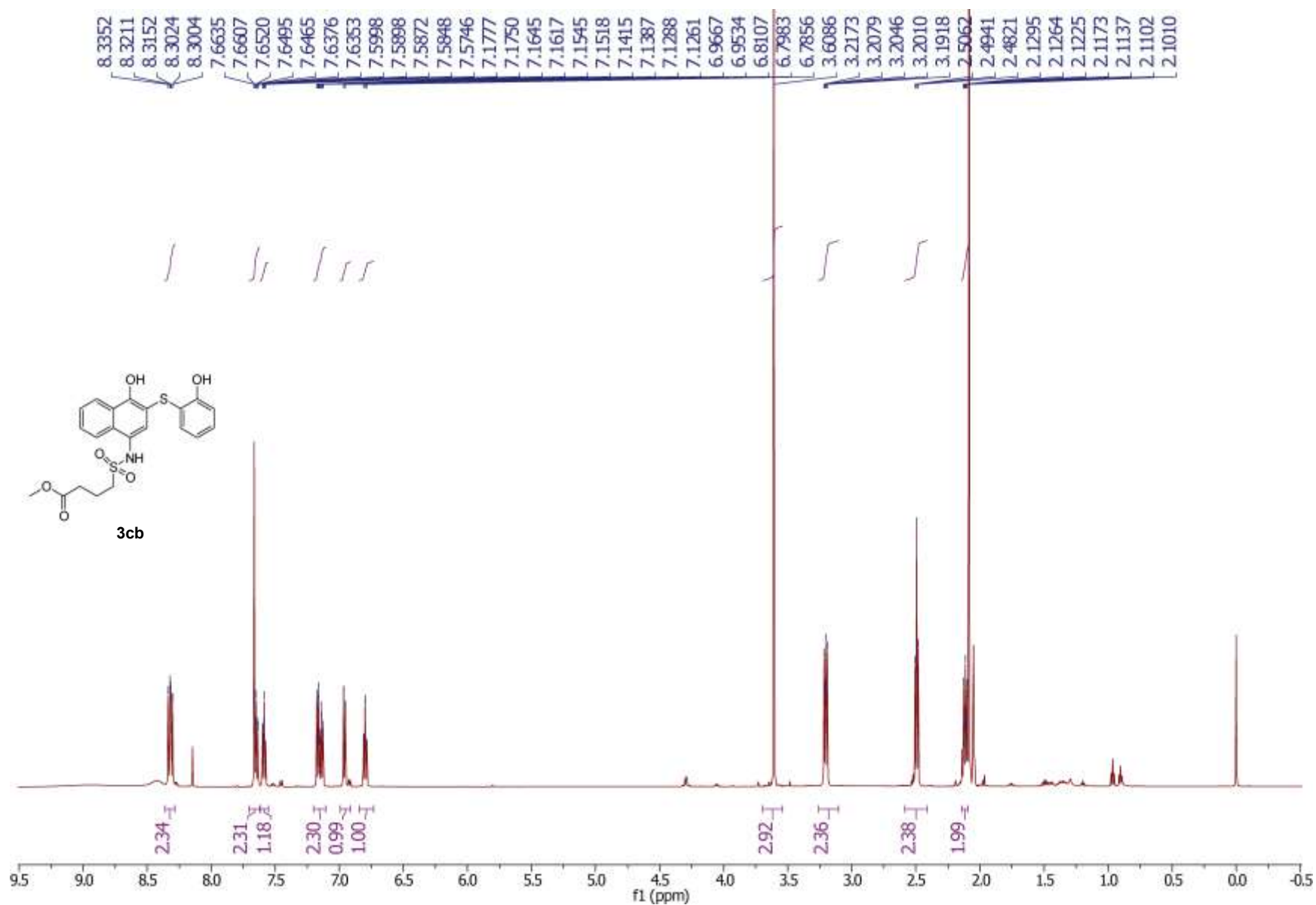


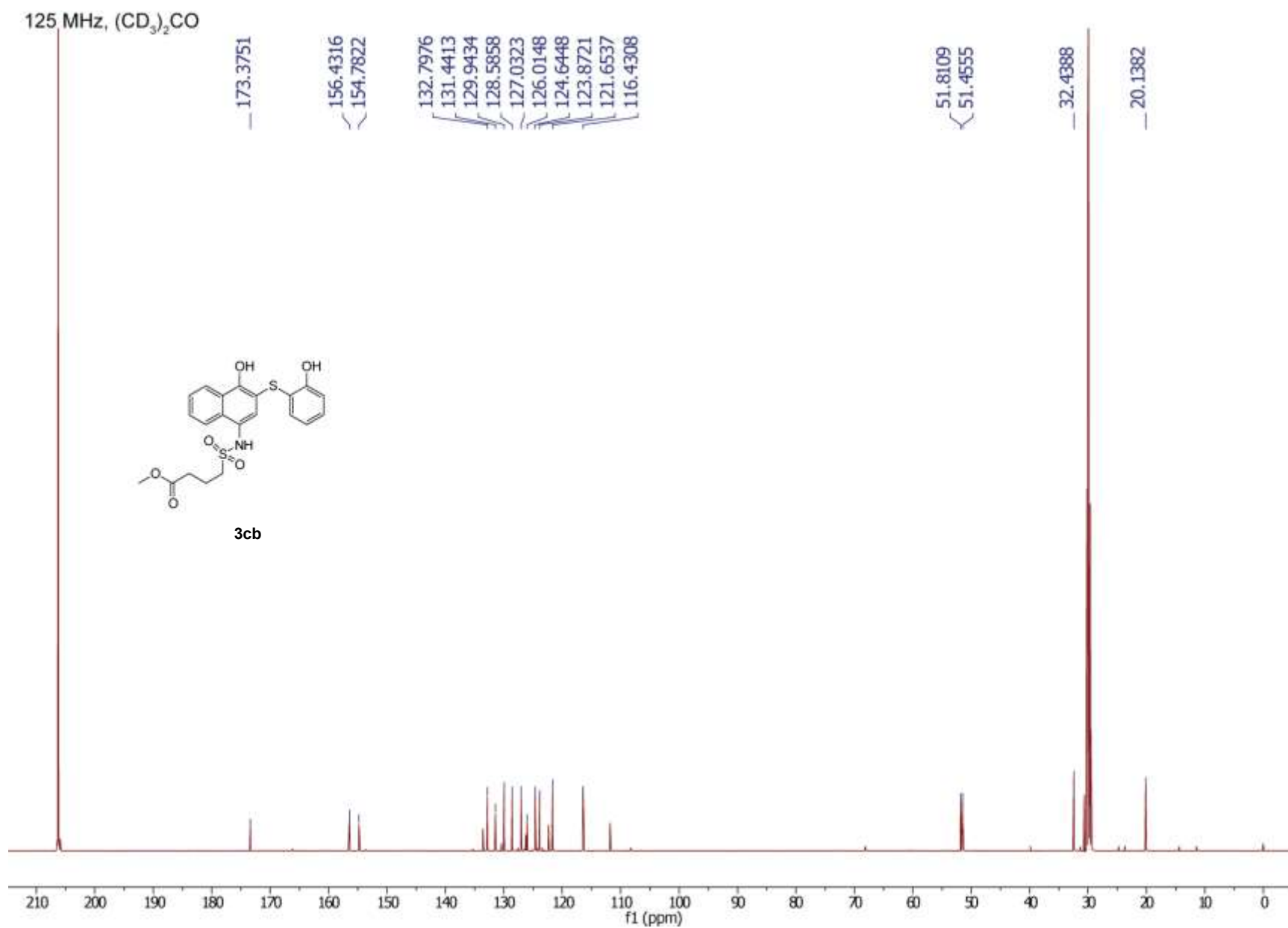
600 MHz, (CD<sub>3</sub>)<sub>2</sub>CO

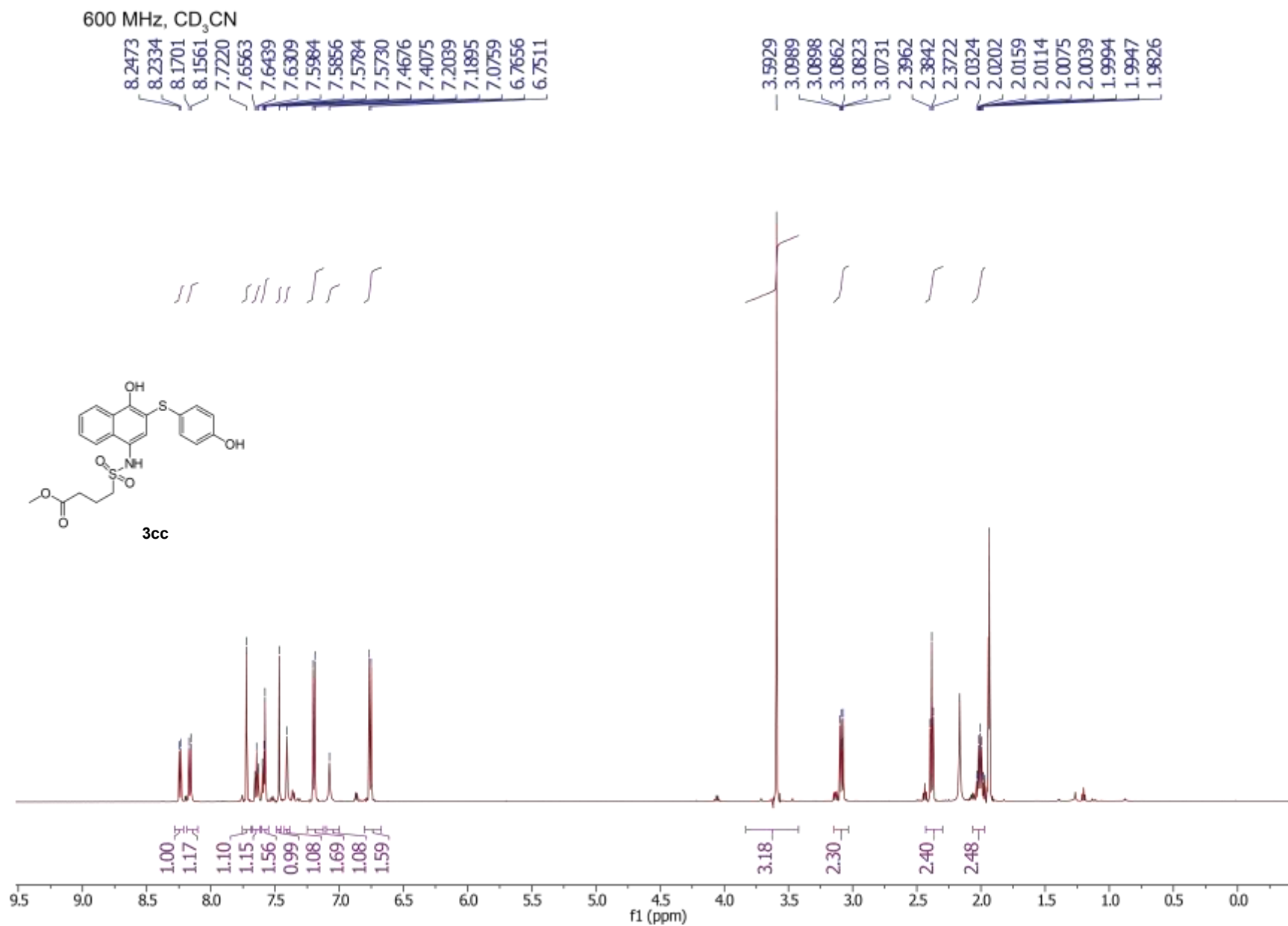


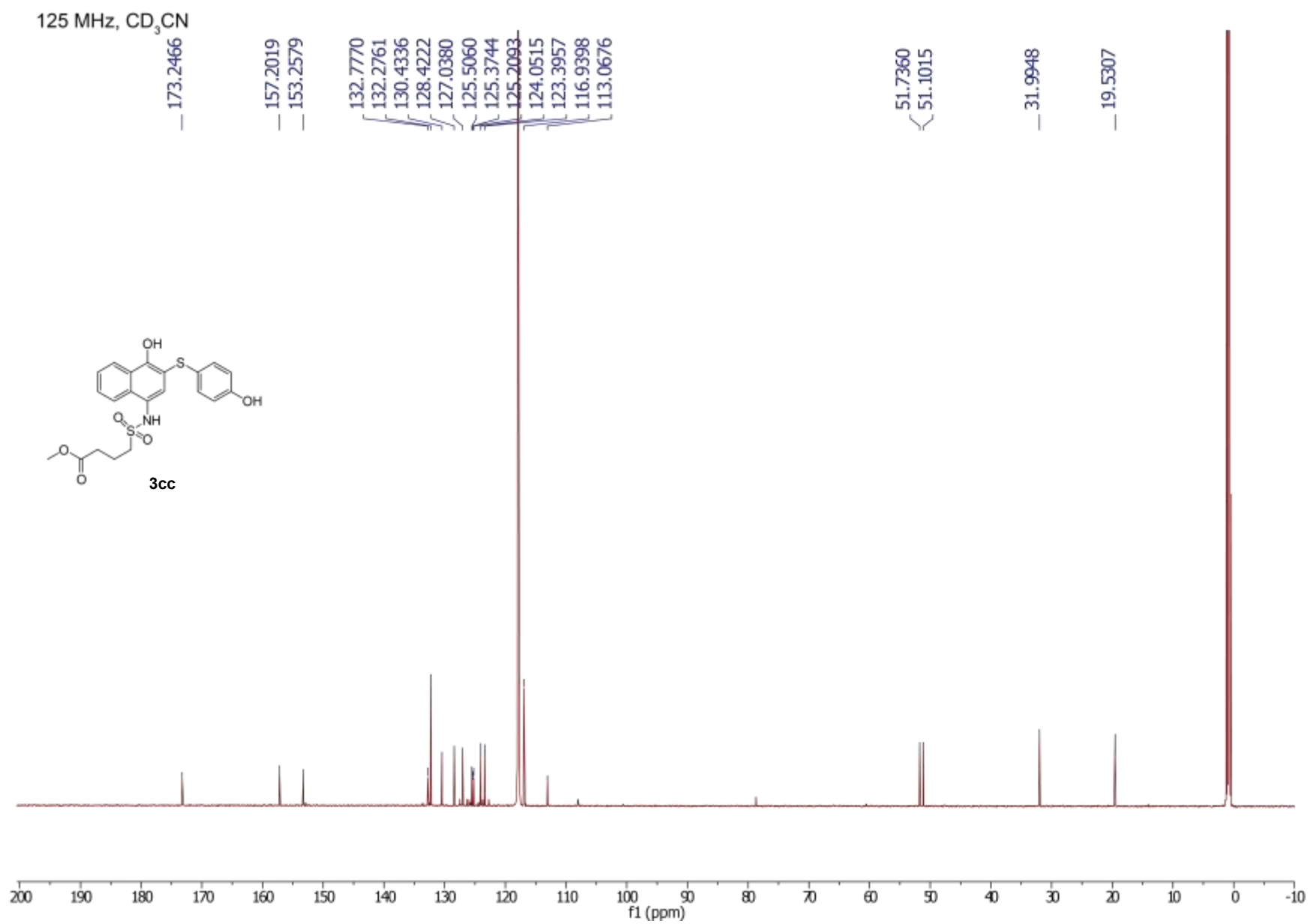
600 MHz, CD<sub>3</sub>CN



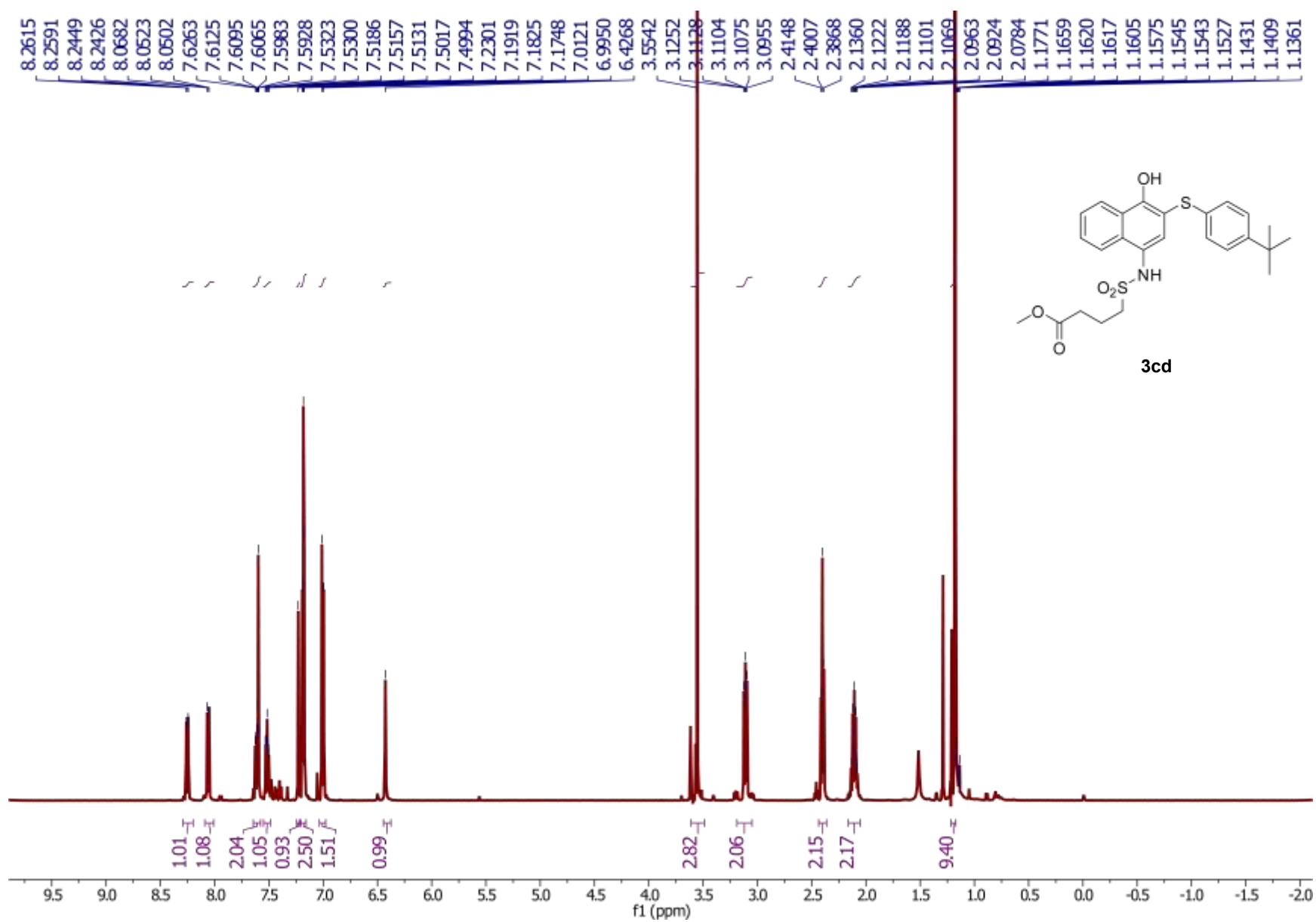


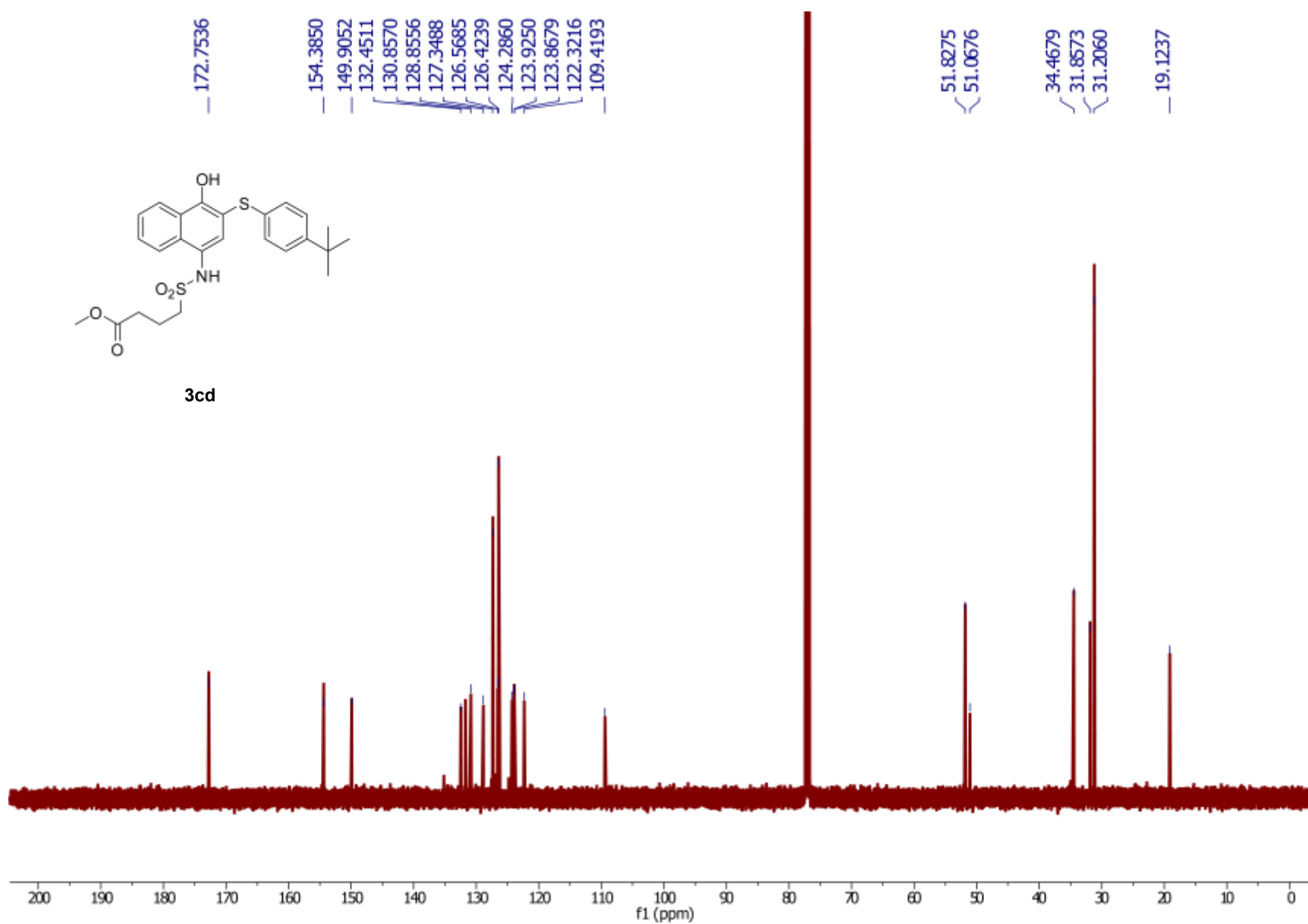


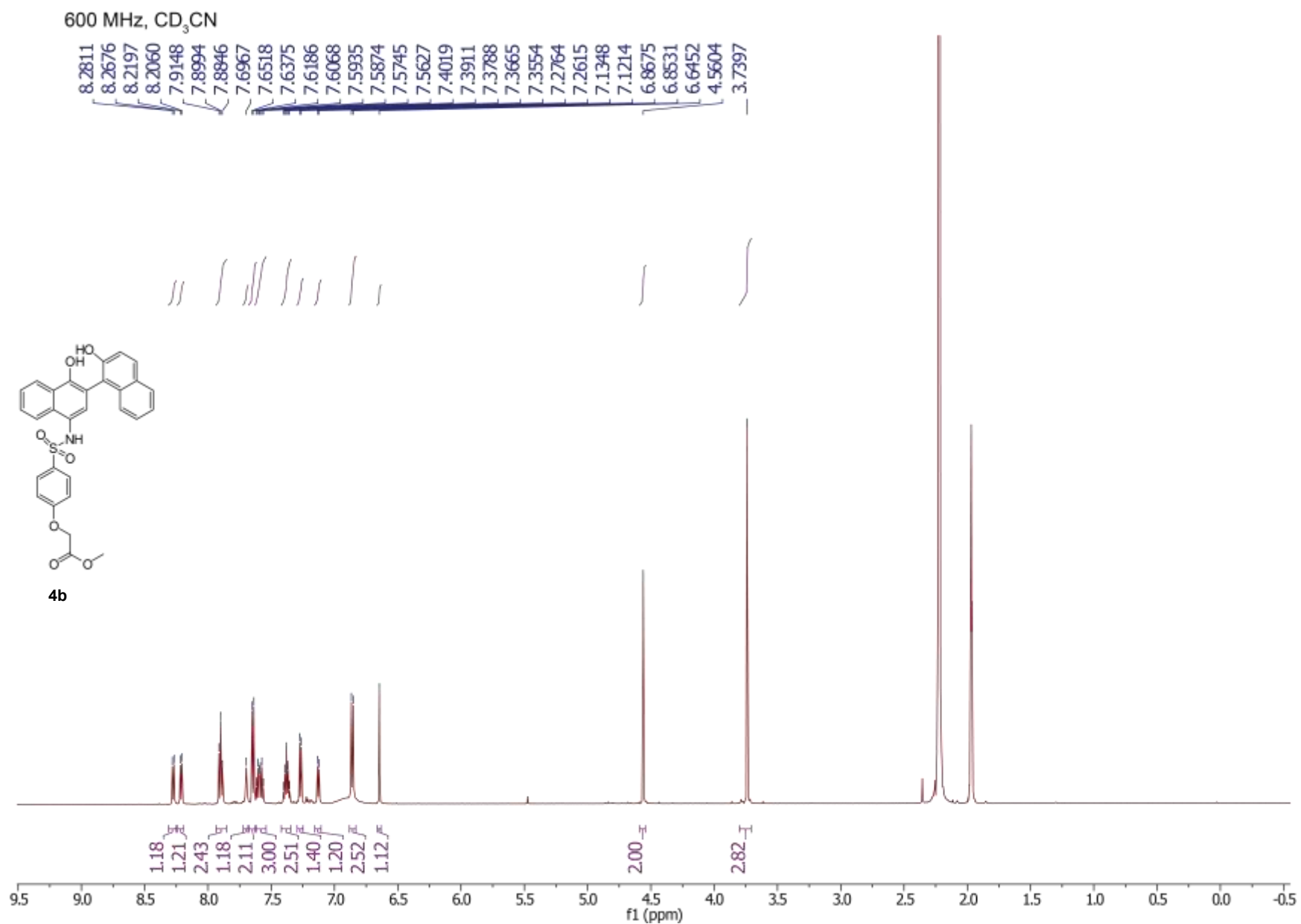






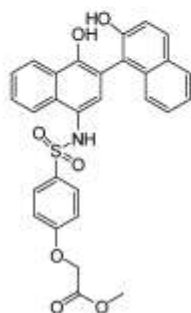




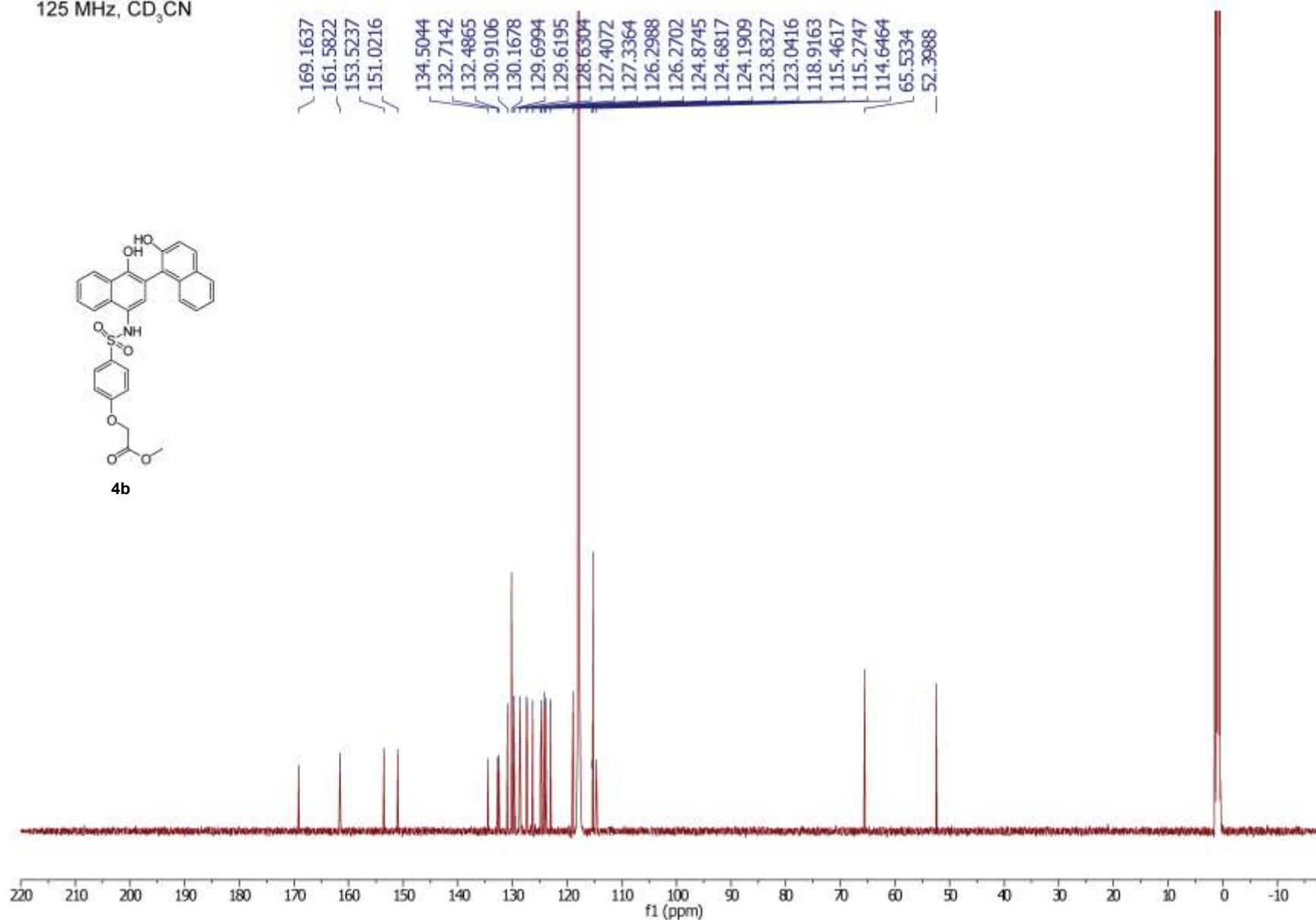


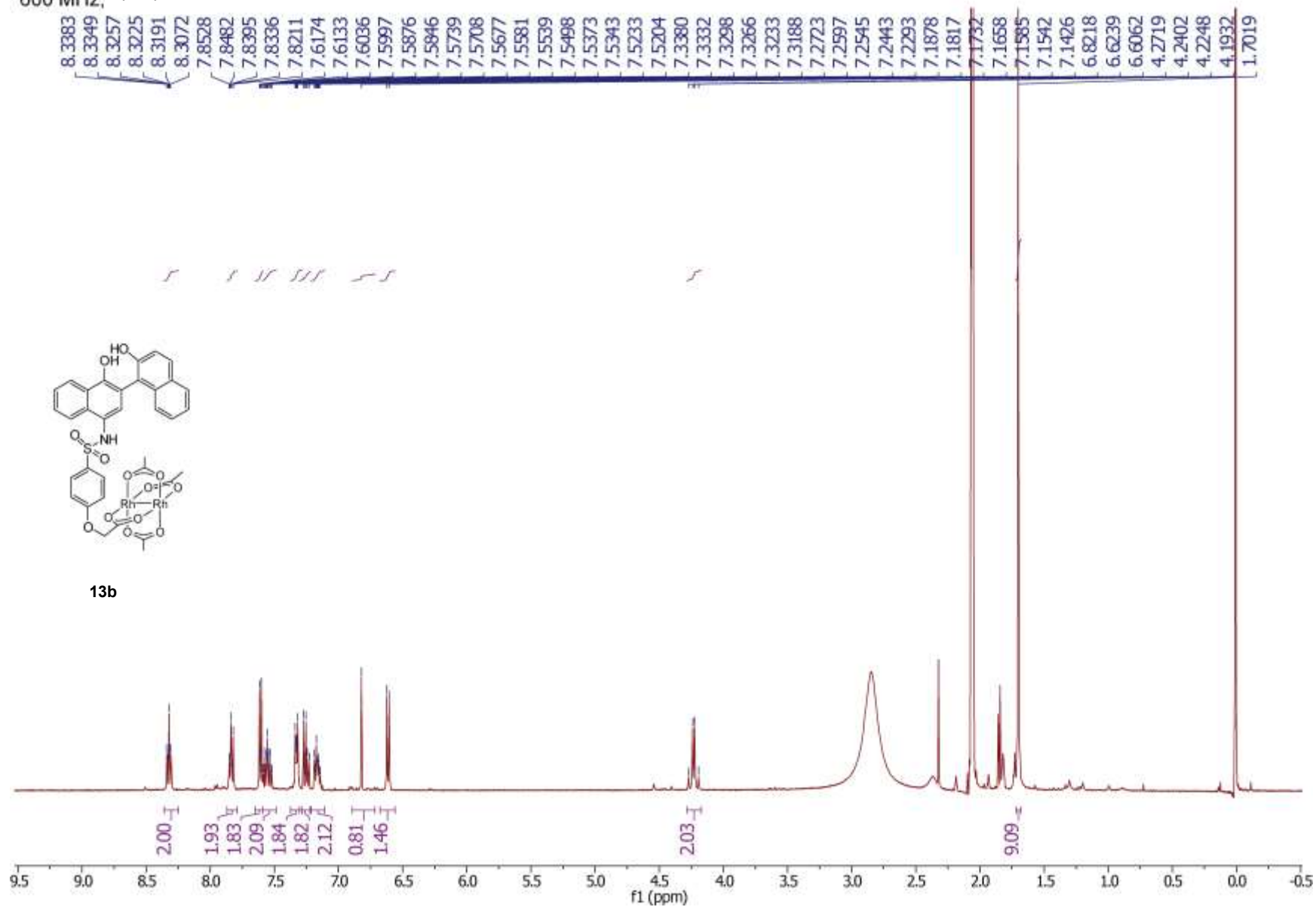
125 MHz, CD<sub>3</sub>CN

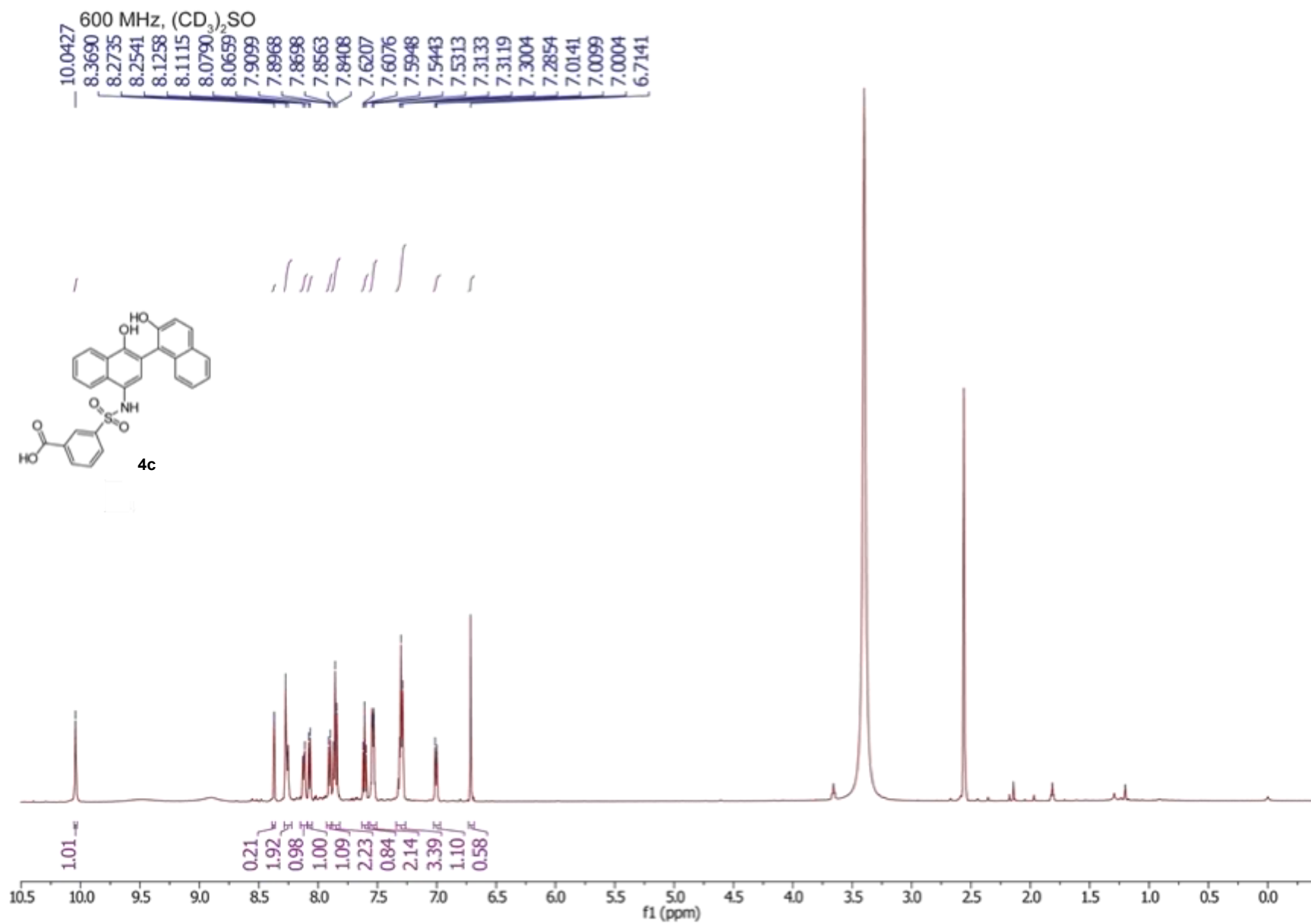
169.1637  
161.5822  
153.5237  
151.0216  
134.5044  
132.7142  
132.4865  
130.9106  
130.1678  
129.6994  
129.6195  
128.6304  
127.4072  
127.3364  
126.2988  
126.2702  
124.8745  
124.6817  
124.1909  
123.8327  
123.0416  
118.9163  
115.4617  
115.2747  
114.6464  
65.5334  
52.3988



4b

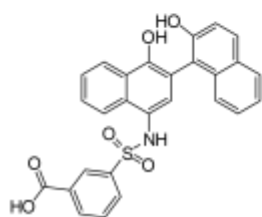


600 MHz, (CD<sub>3</sub>)<sub>2</sub>CO

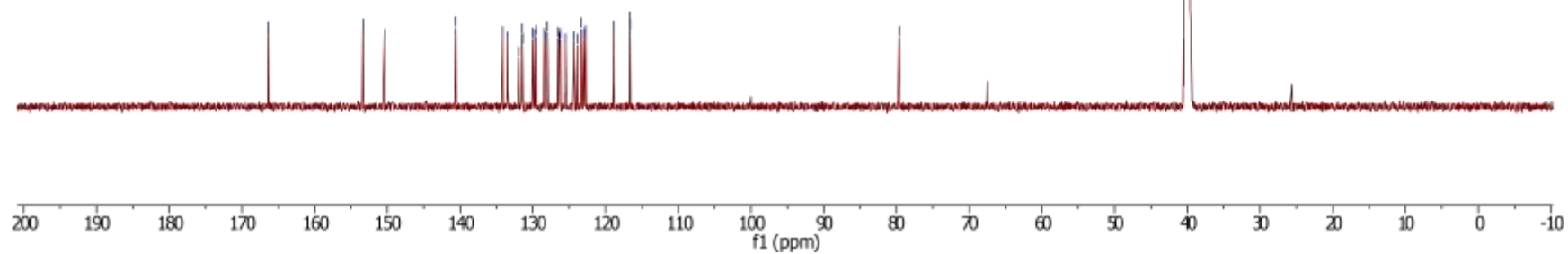


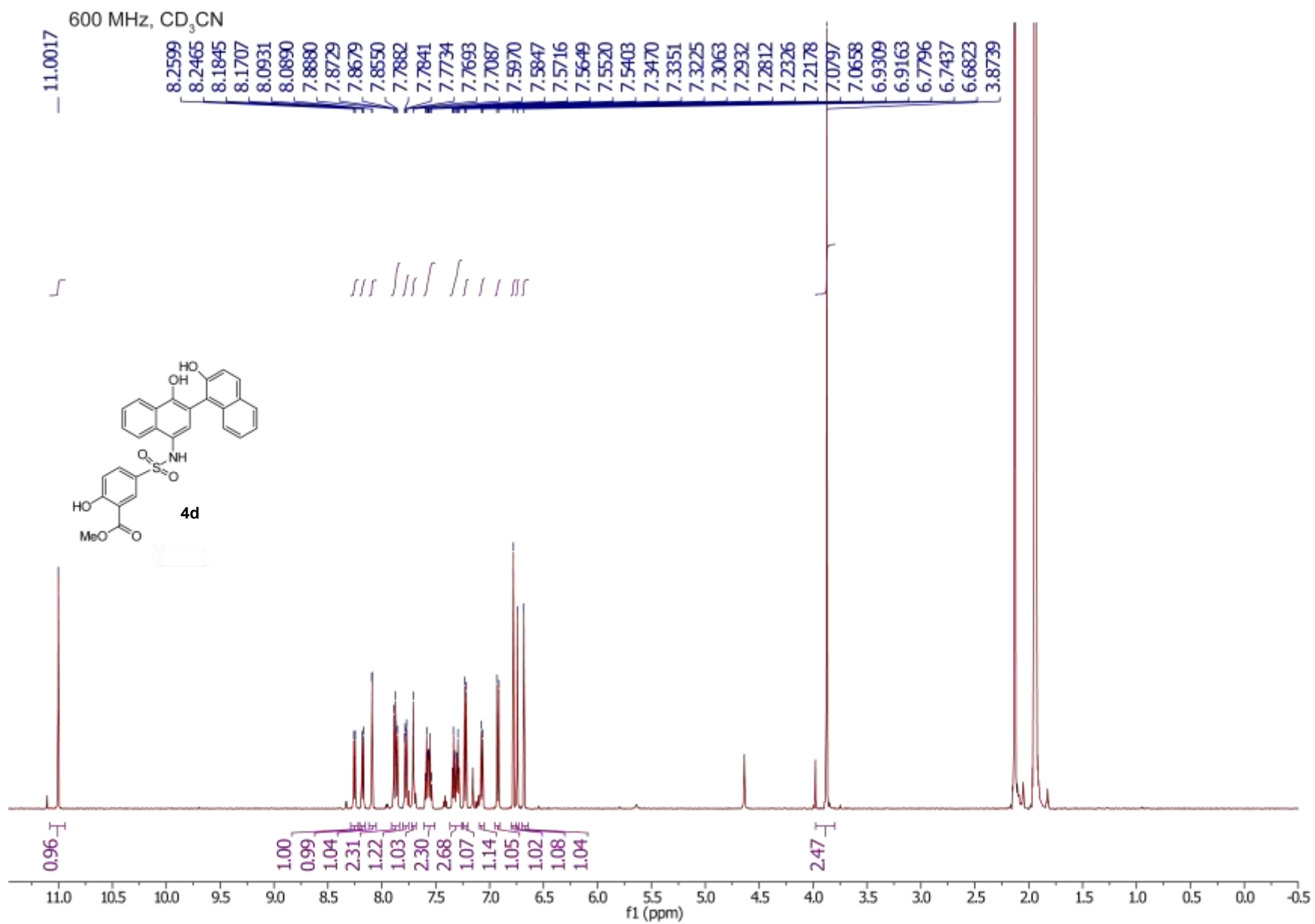
125 MHz, (CD<sub>3</sub>)<sub>2</sub>SO

166.3958  
153.3637  
150.3906  
140.6163  
134.1537  
133.4771  
131.9372  
131.4736  
131.3994  
130.0334  
129.6978  
129.5346  
128.4390  
128.3275  
127.9991  
126.5225  
126.3867  
126.2413  
125.4873  
124.3375  
123.9012  
123.3333  
122.9846  
122.7635  
118.8949  
116.6522  
116.6114  
79.6351

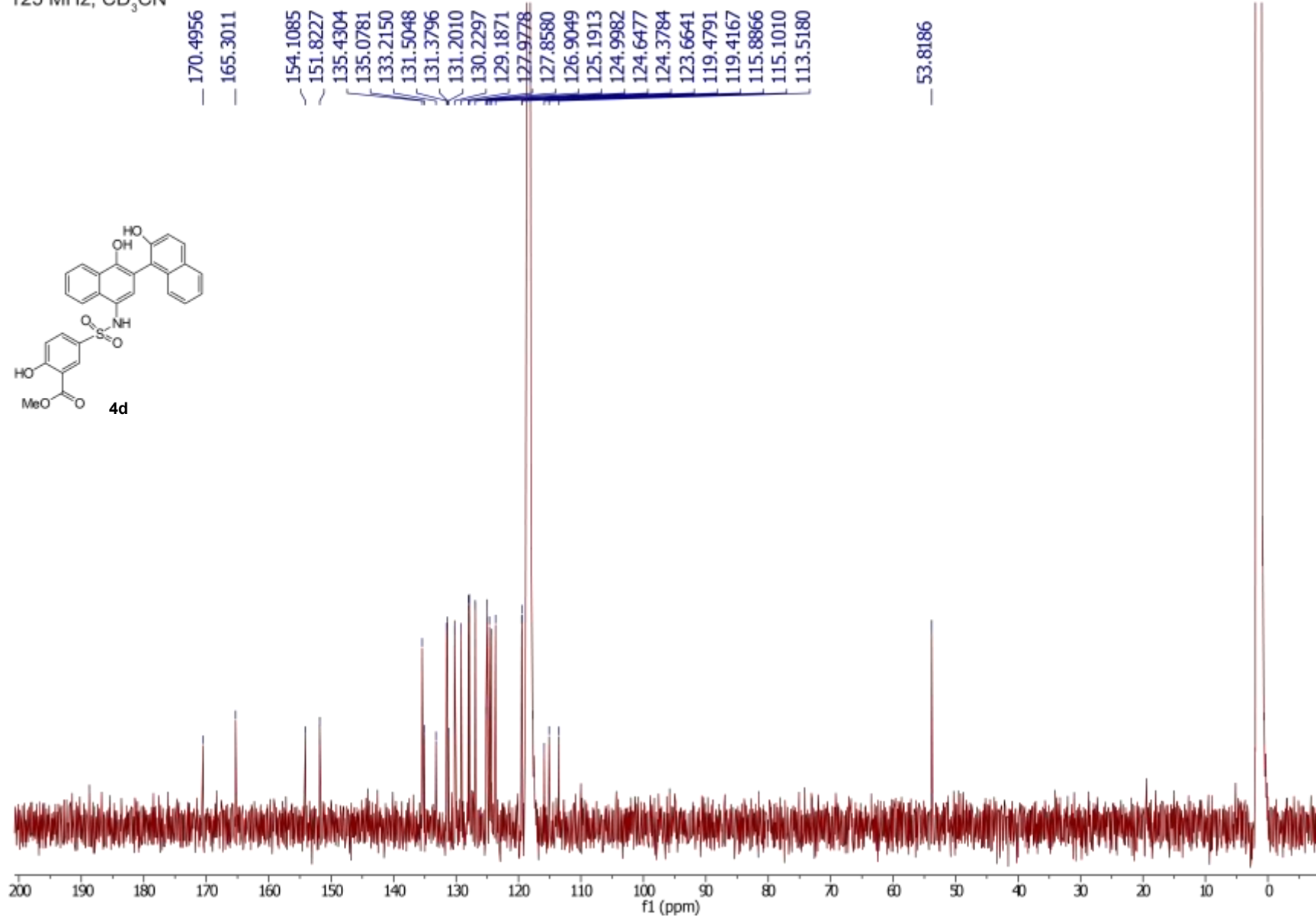


4c







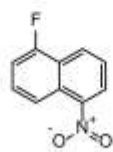
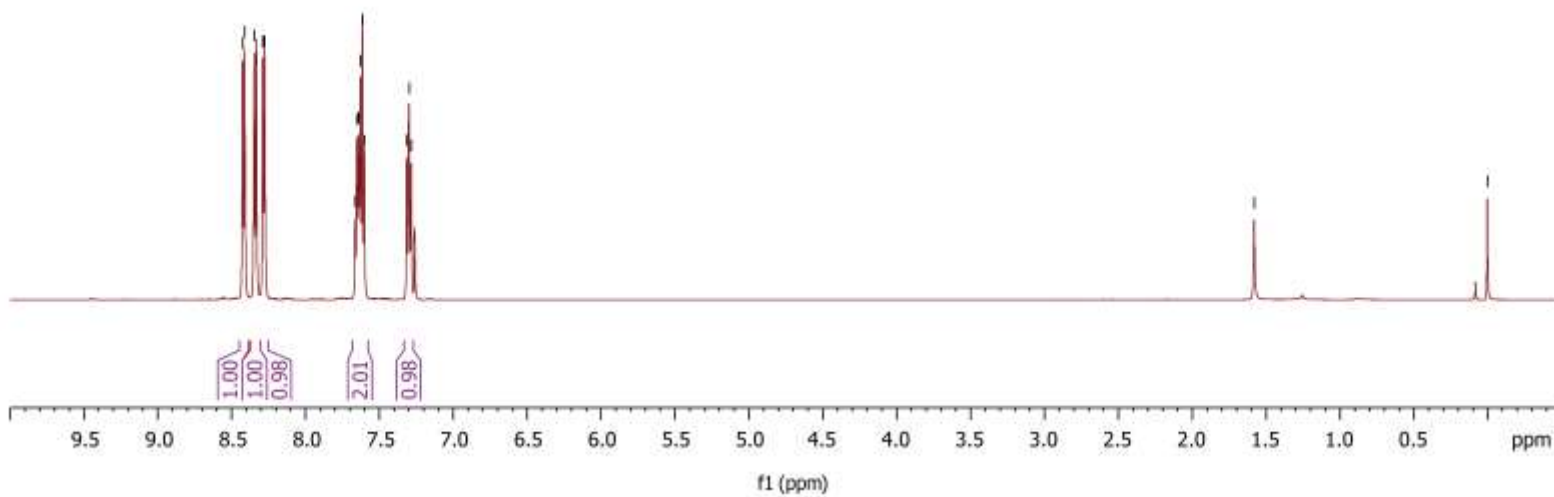
125 MHz, CD<sub>3</sub>CN

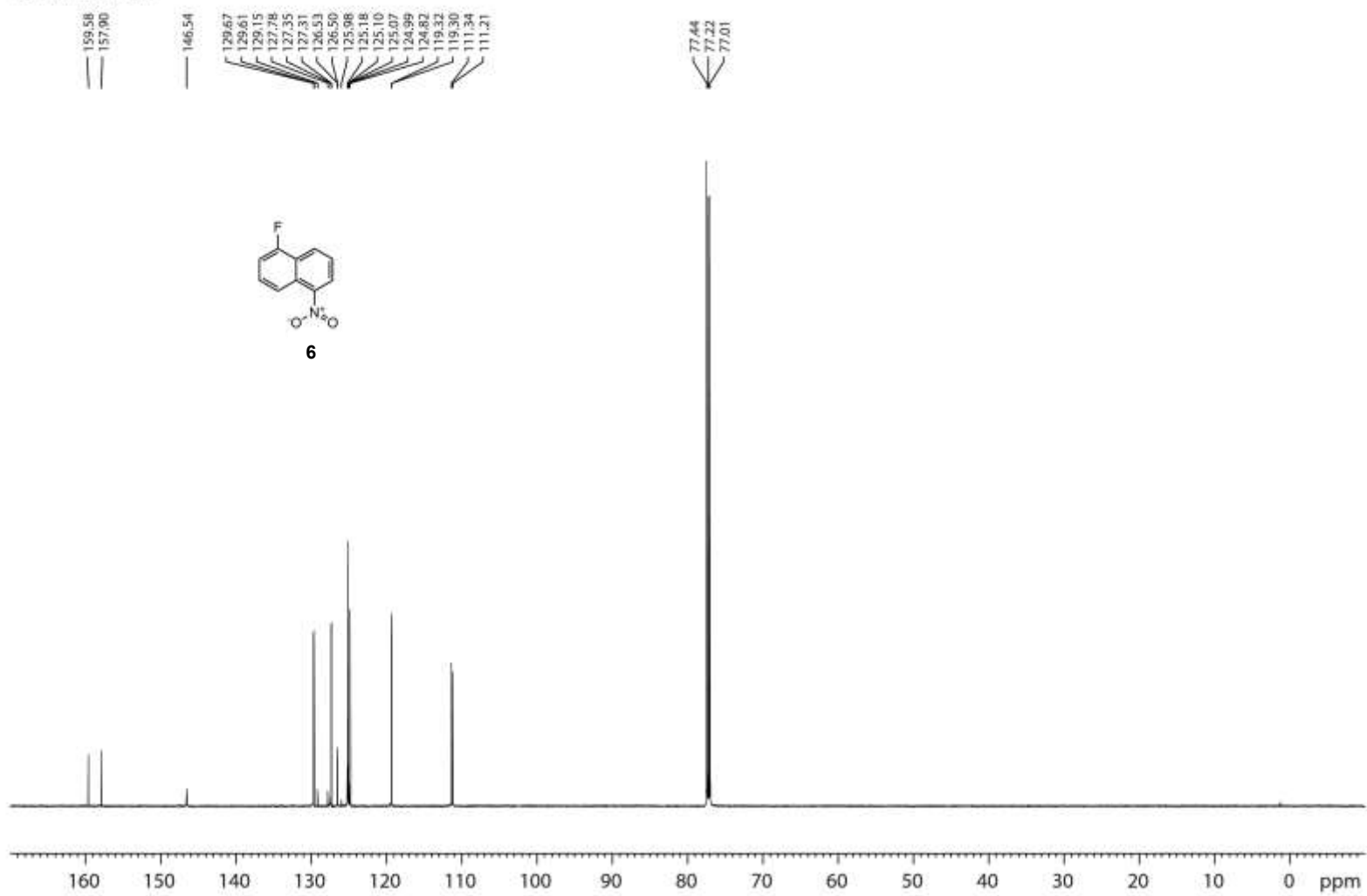
600 MHz, CDCl<sub>3</sub>

8.426  
8.412  
8.348  
8.334  
8.289  
8.277  
7.665  
7.651  
7.641  
7.629  
7.616  
7.603  
7.315  
7.299  
7.285  
7.260

—1.578

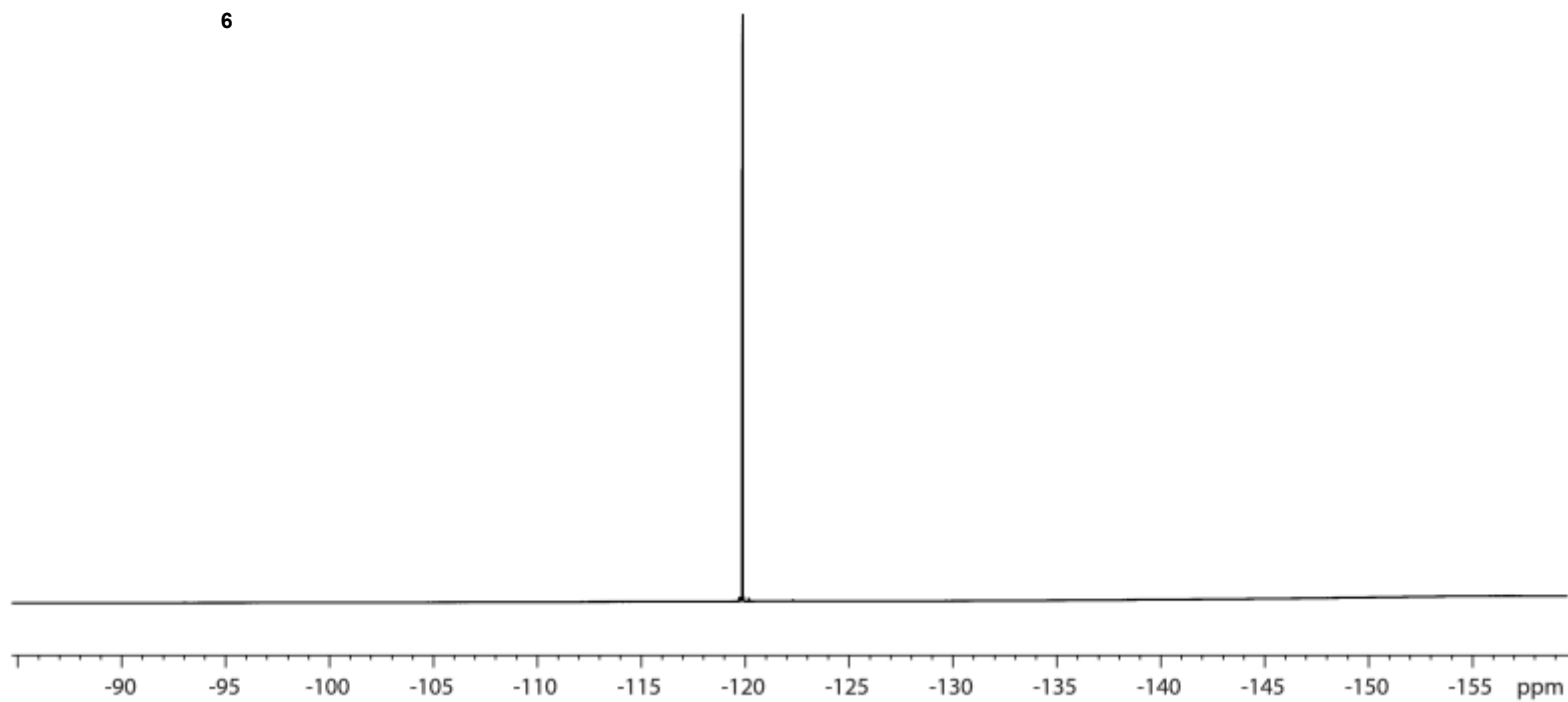
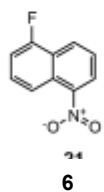
—0.000

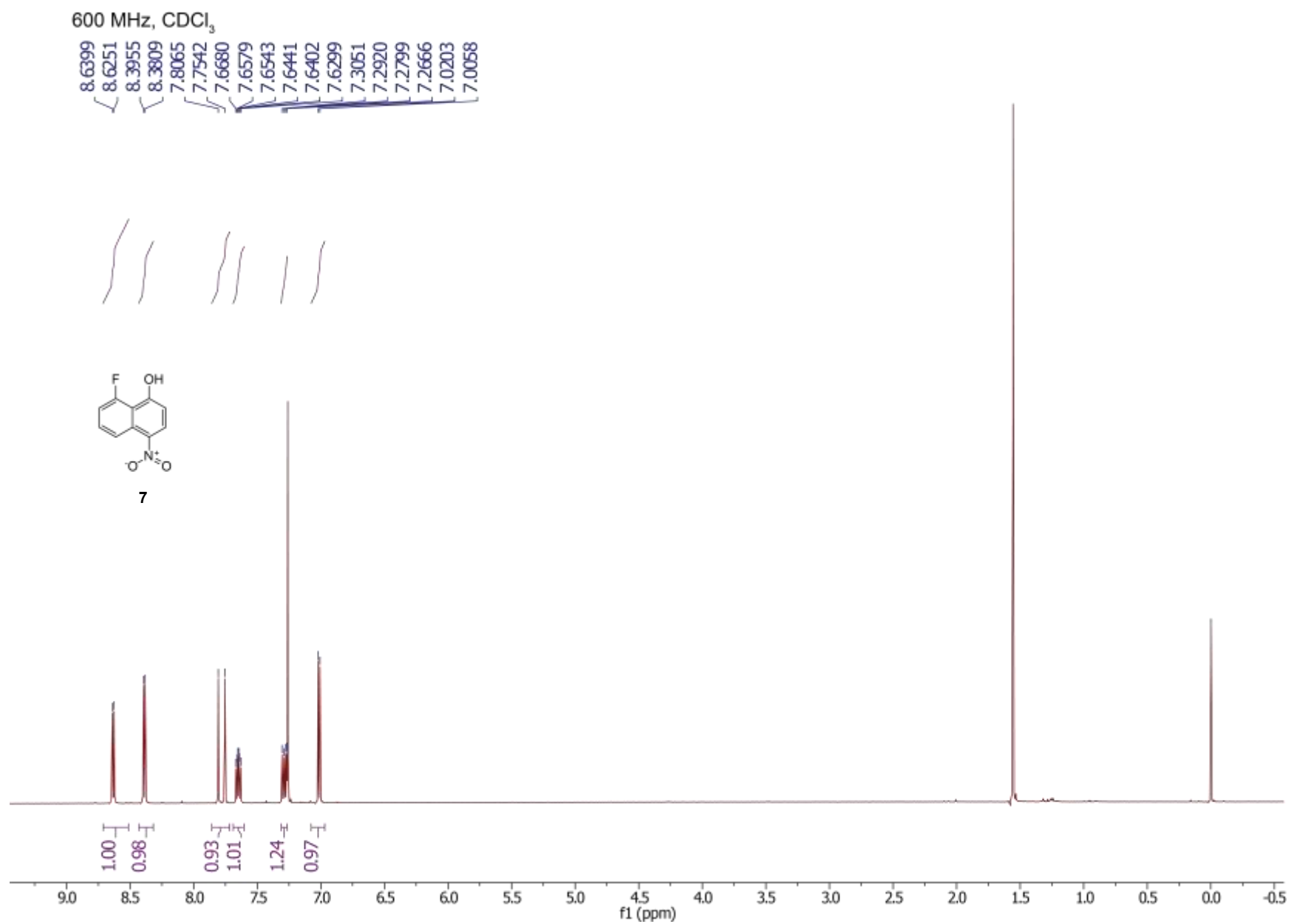
**6**

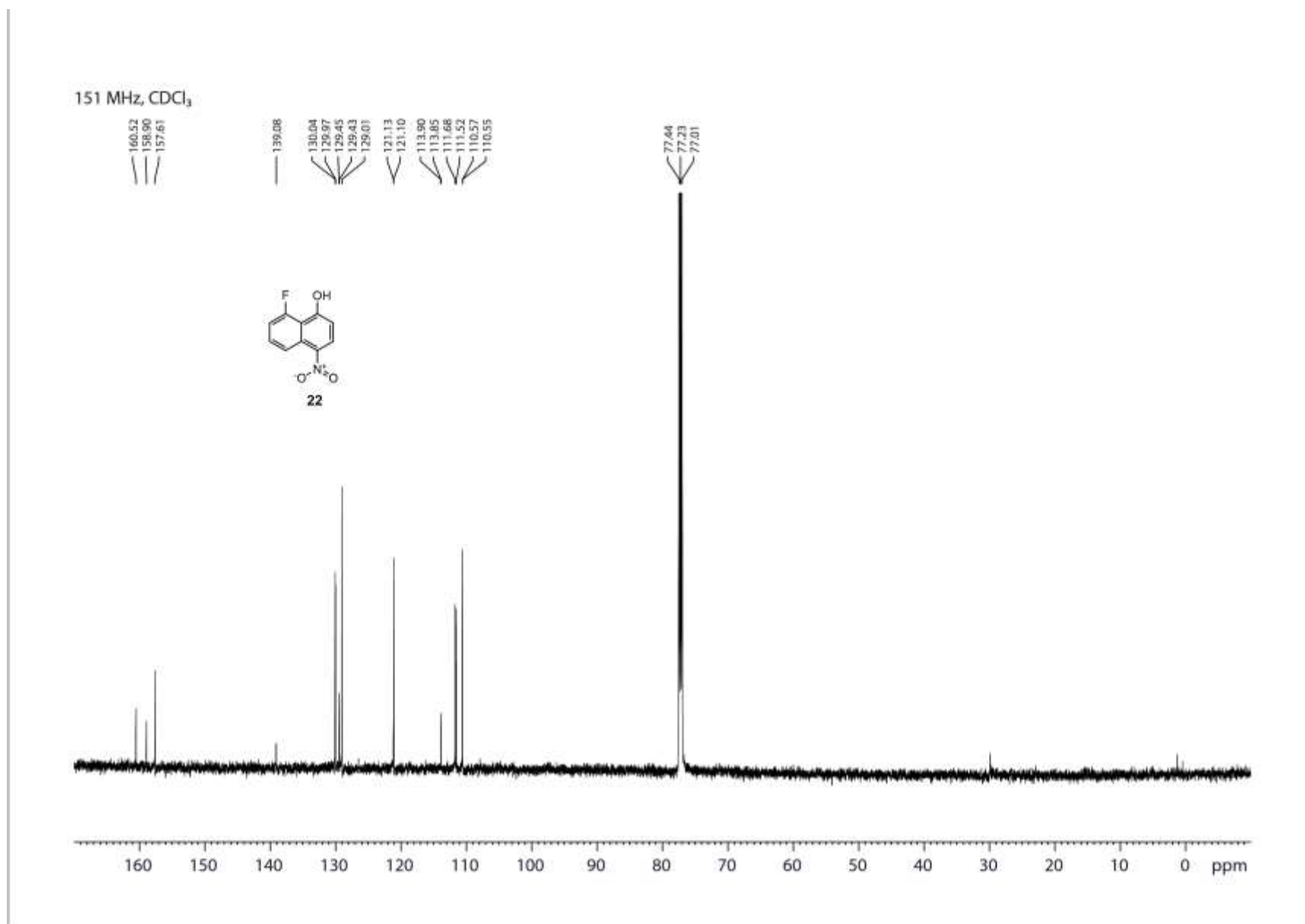
151 MHz, CDCl<sub>3</sub>

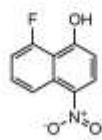
565 MHz, CDCl<sub>3</sub>

-119.87  
-119.88  
-119.89  
-119.90

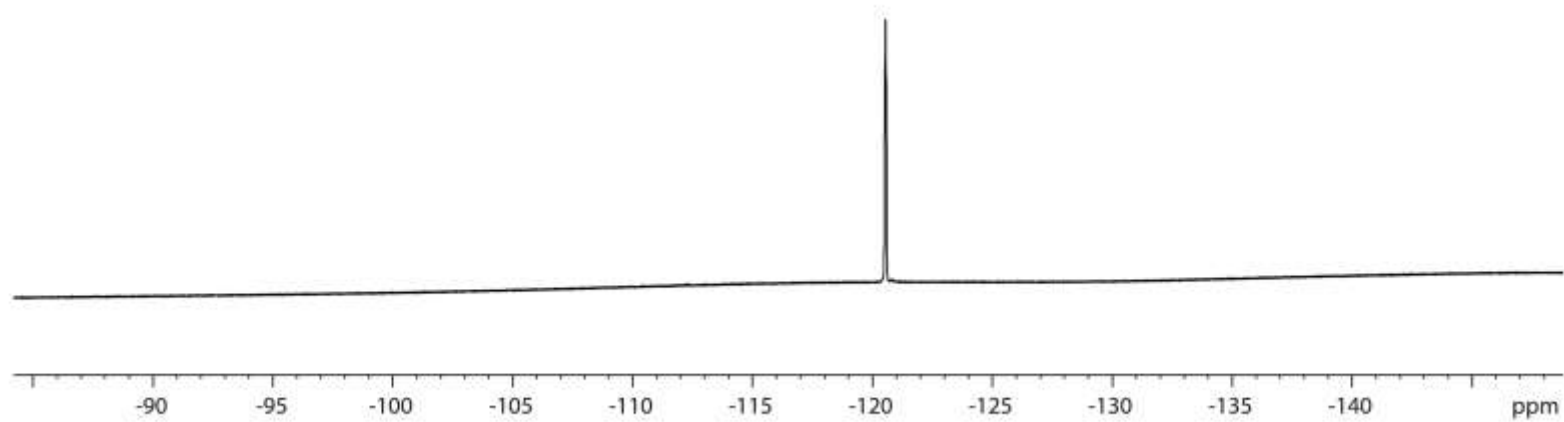


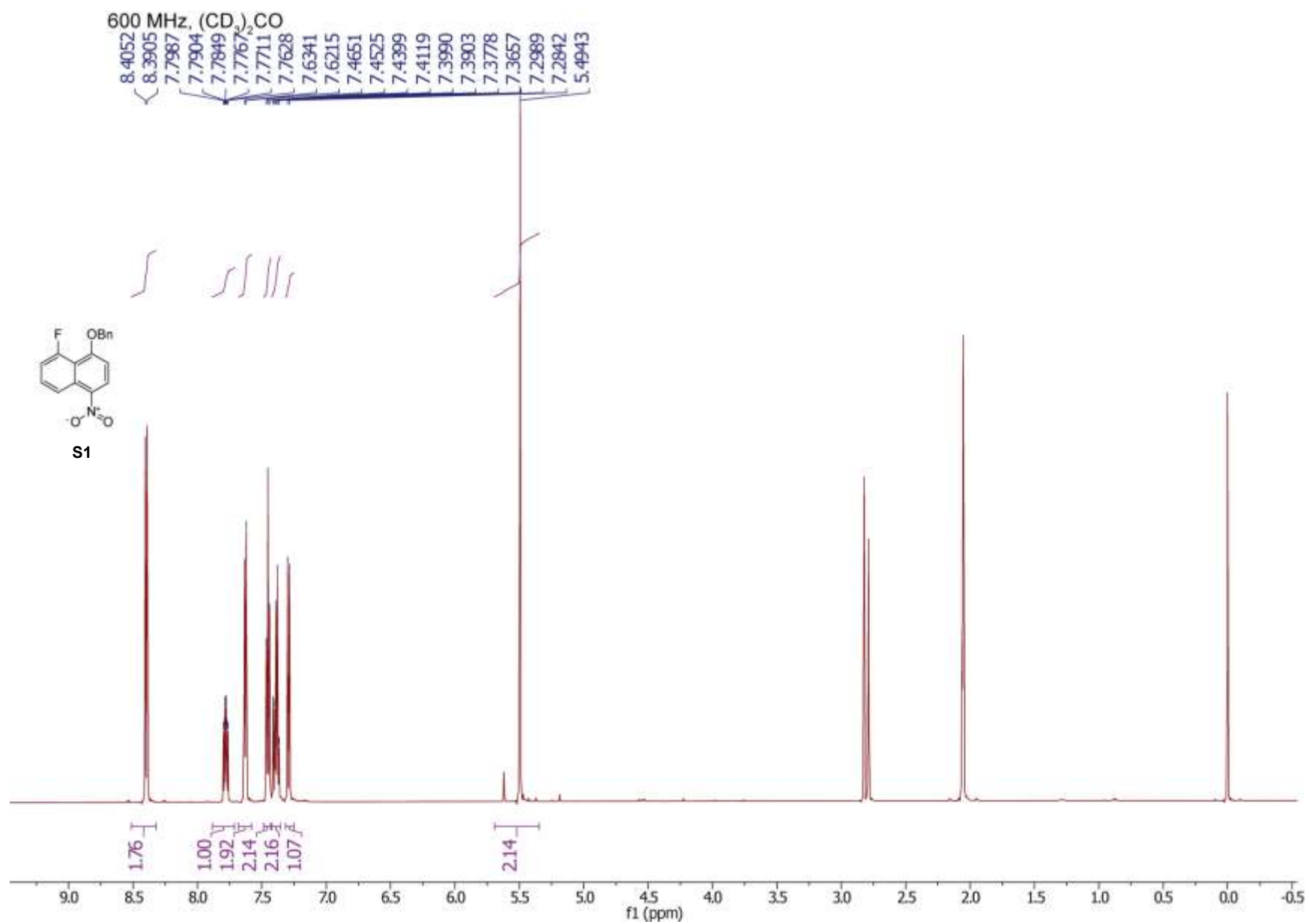




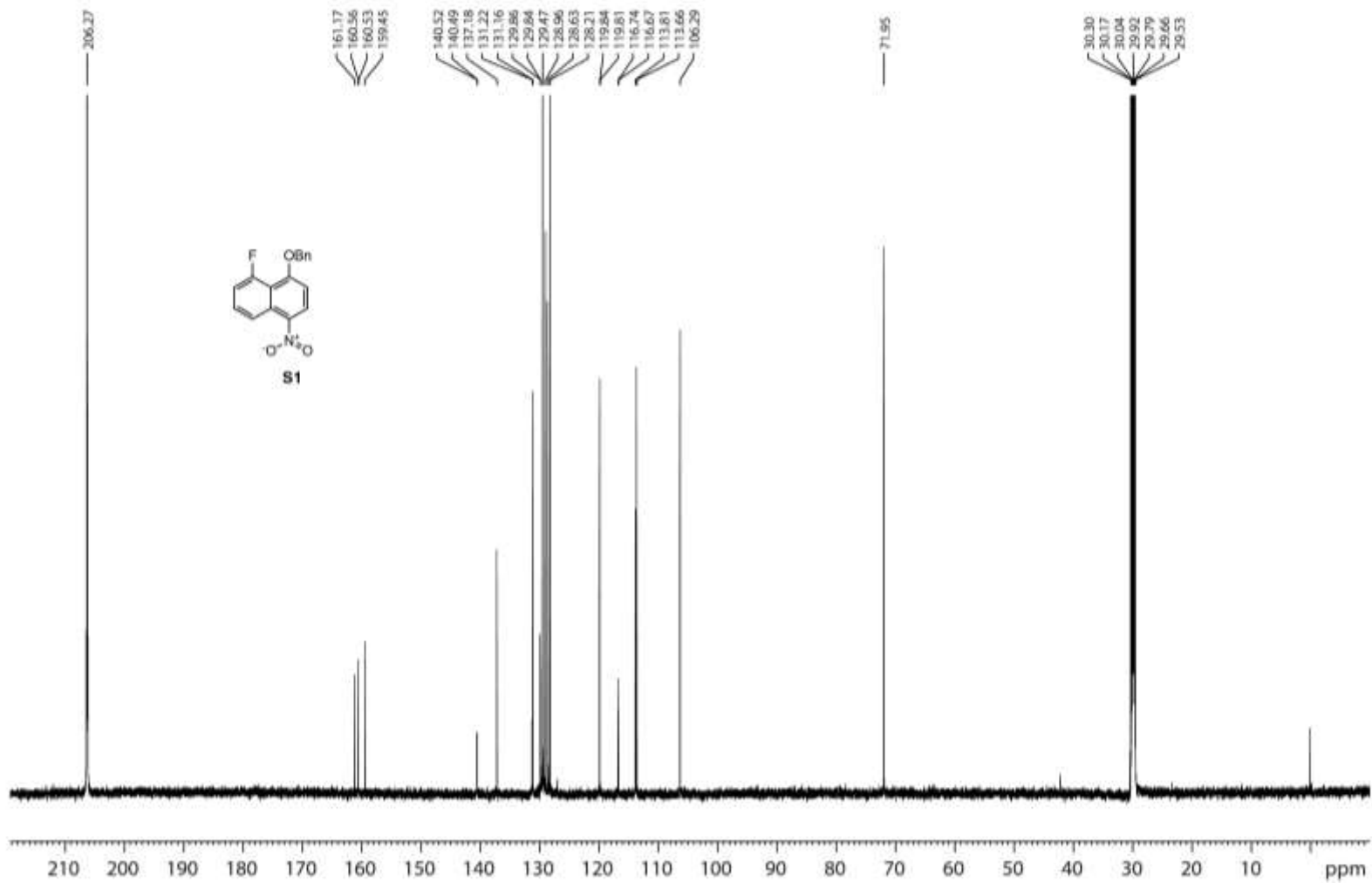
565 MHz, CDCl<sub>3</sub>**7**

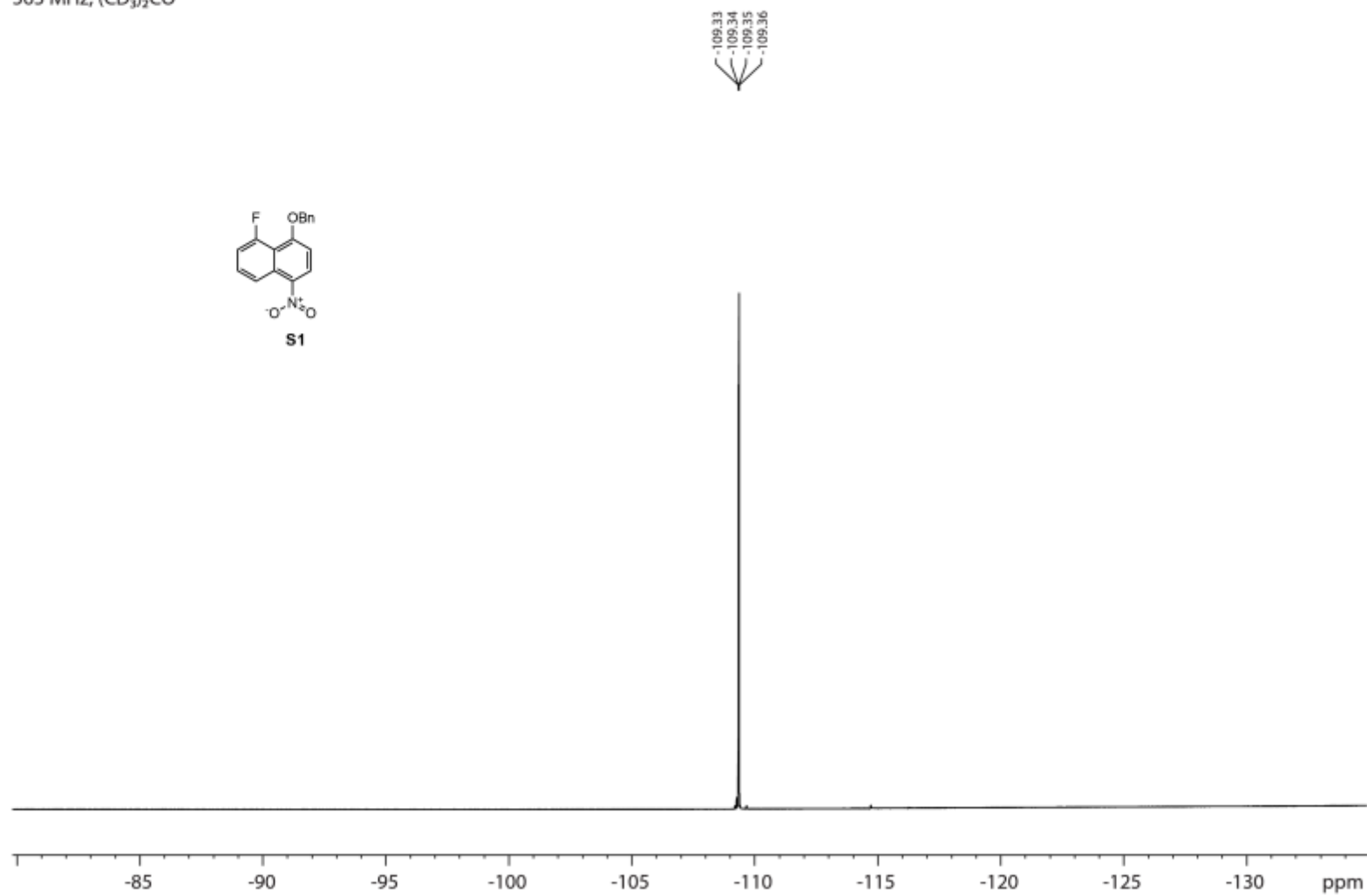
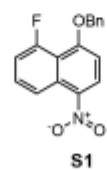
-120.56

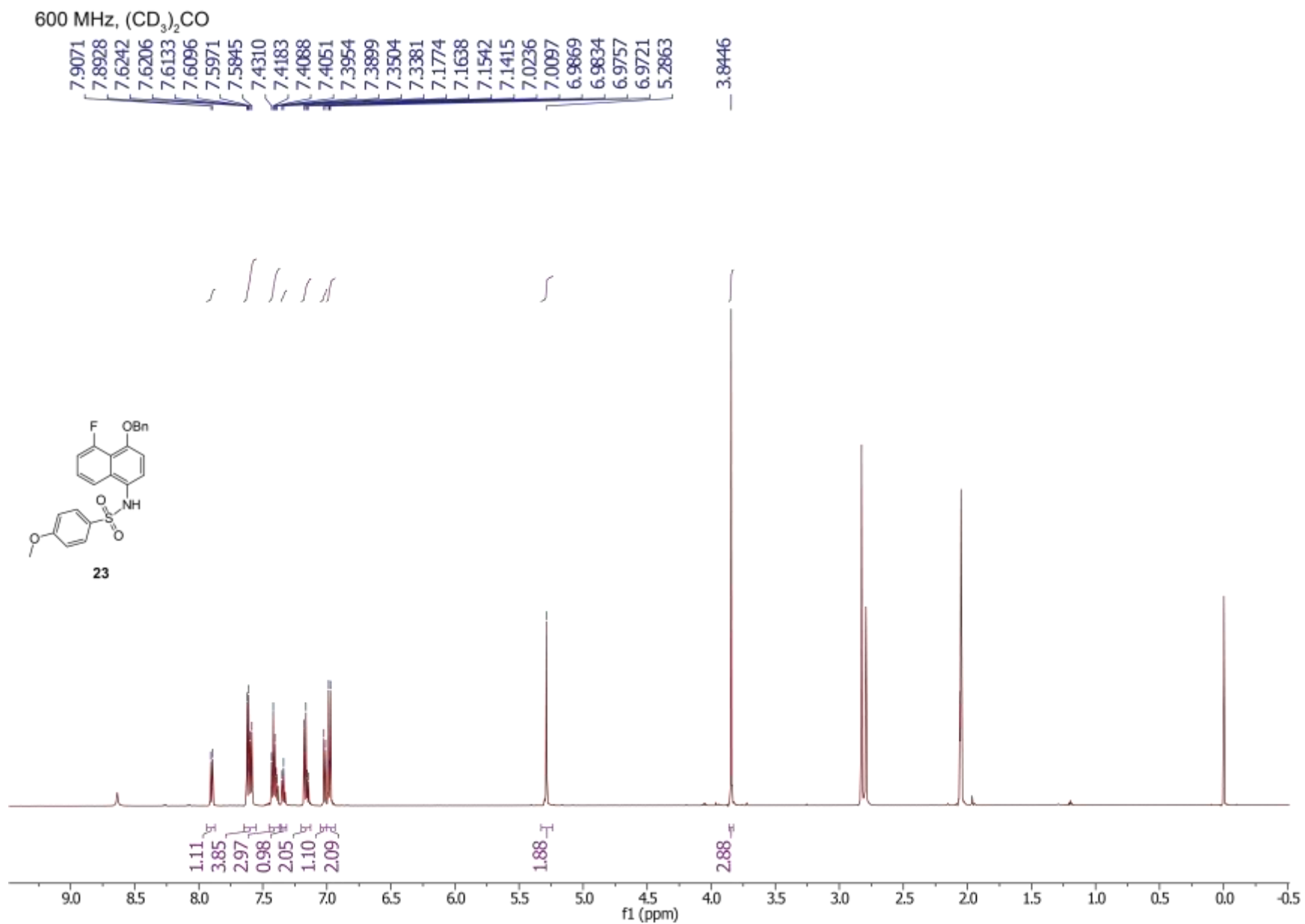


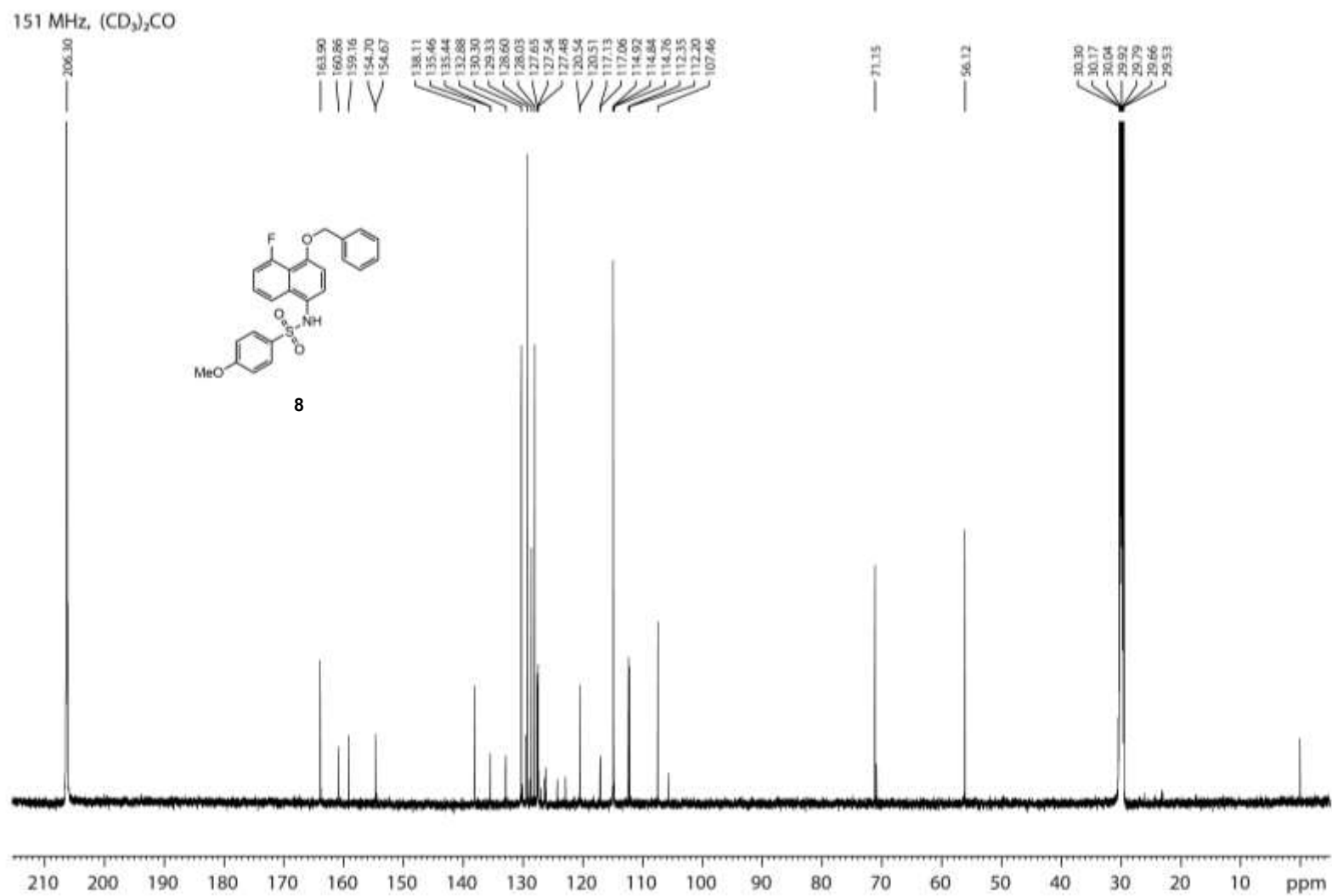




151 MHz (CD<sub>3</sub>)<sub>2</sub>CO

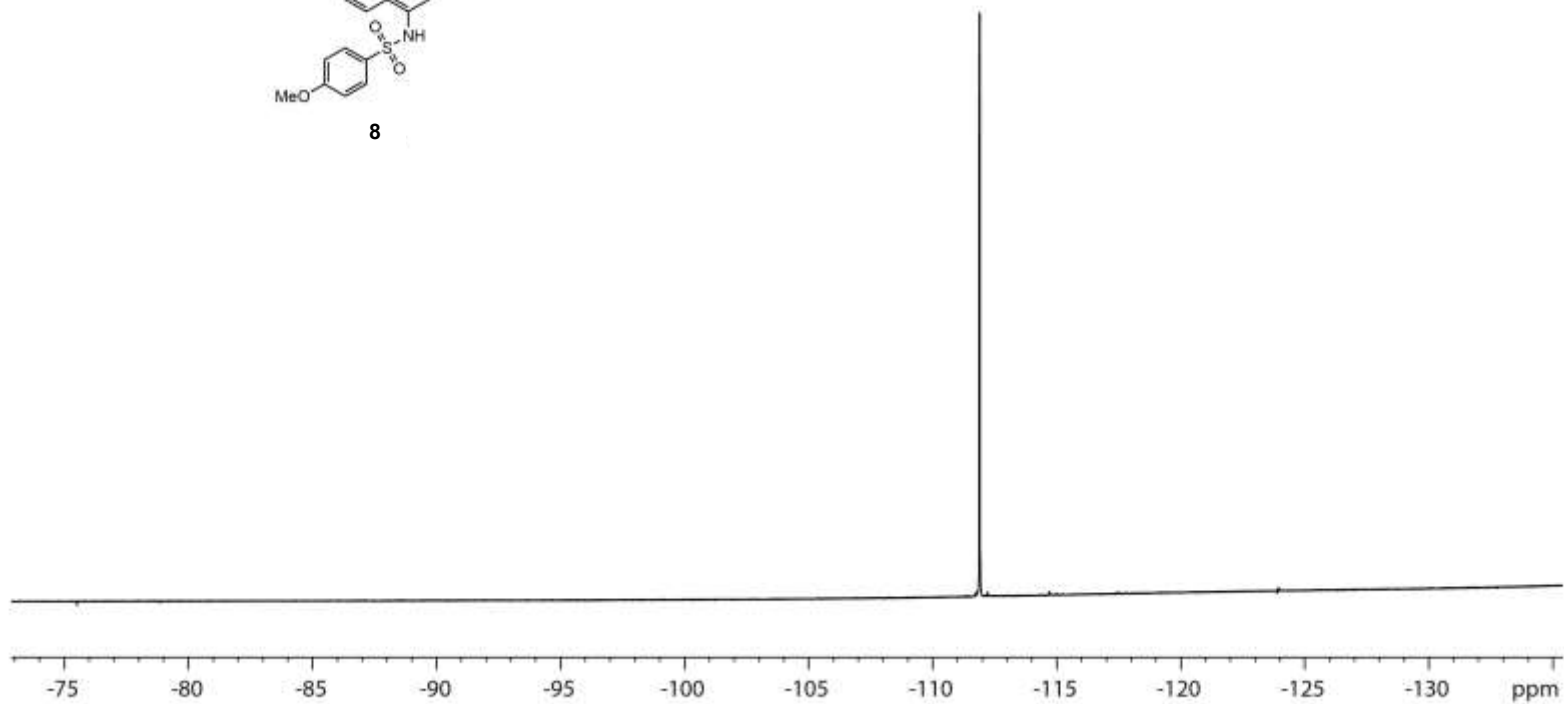
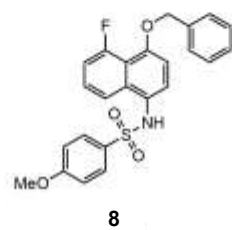
565 MHz, (CD<sub>3</sub>)<sub>2</sub>CO

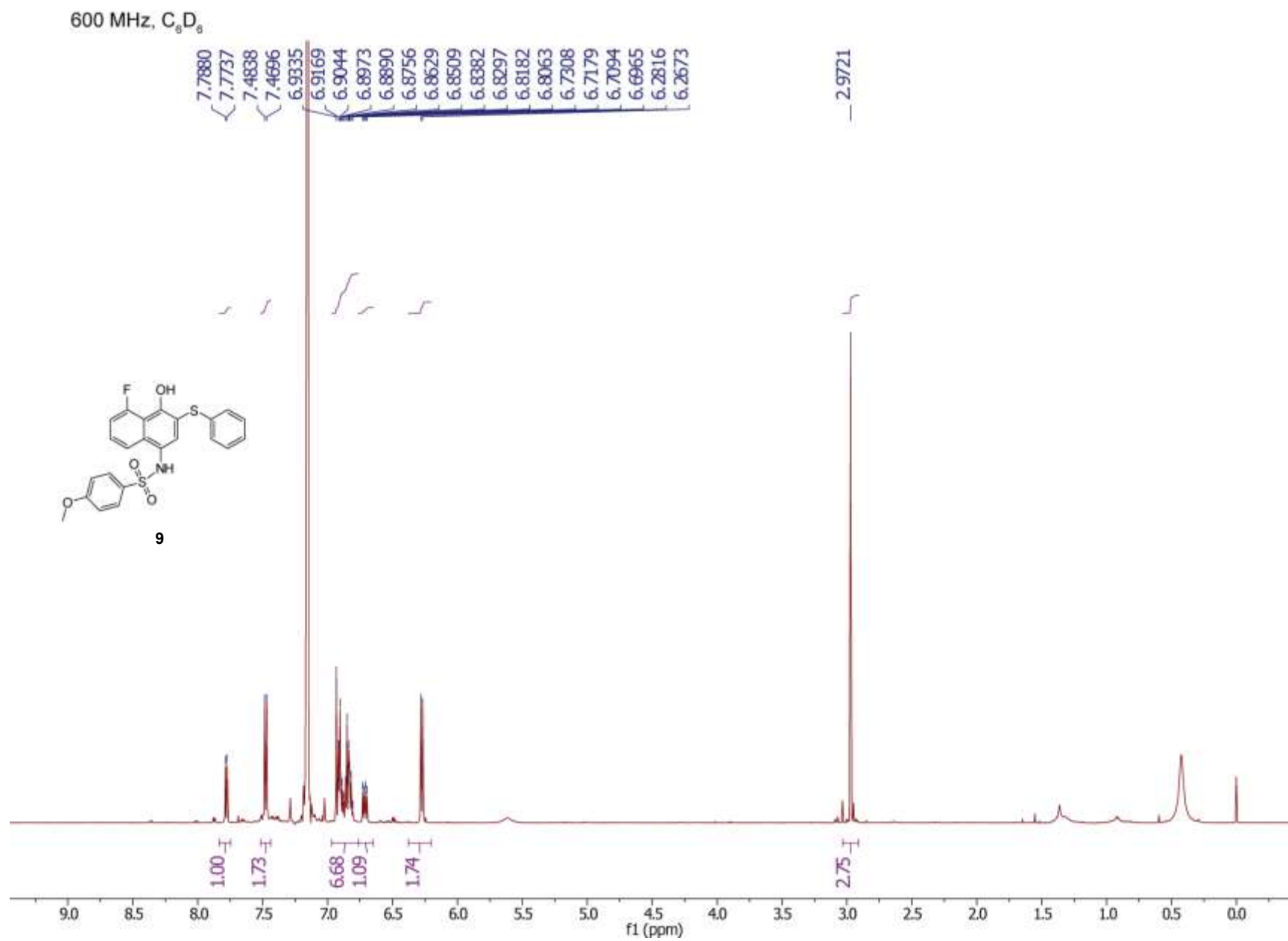


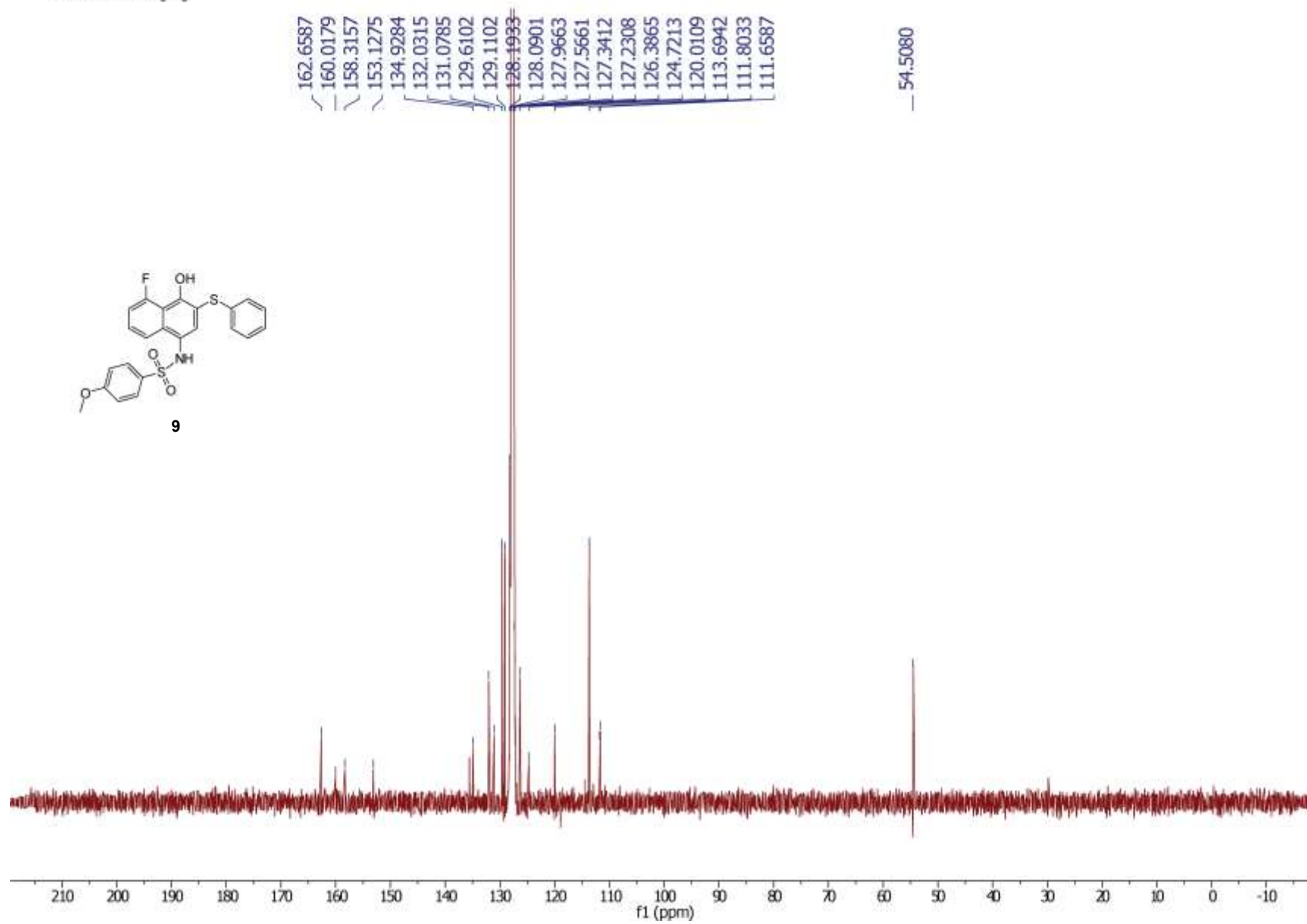


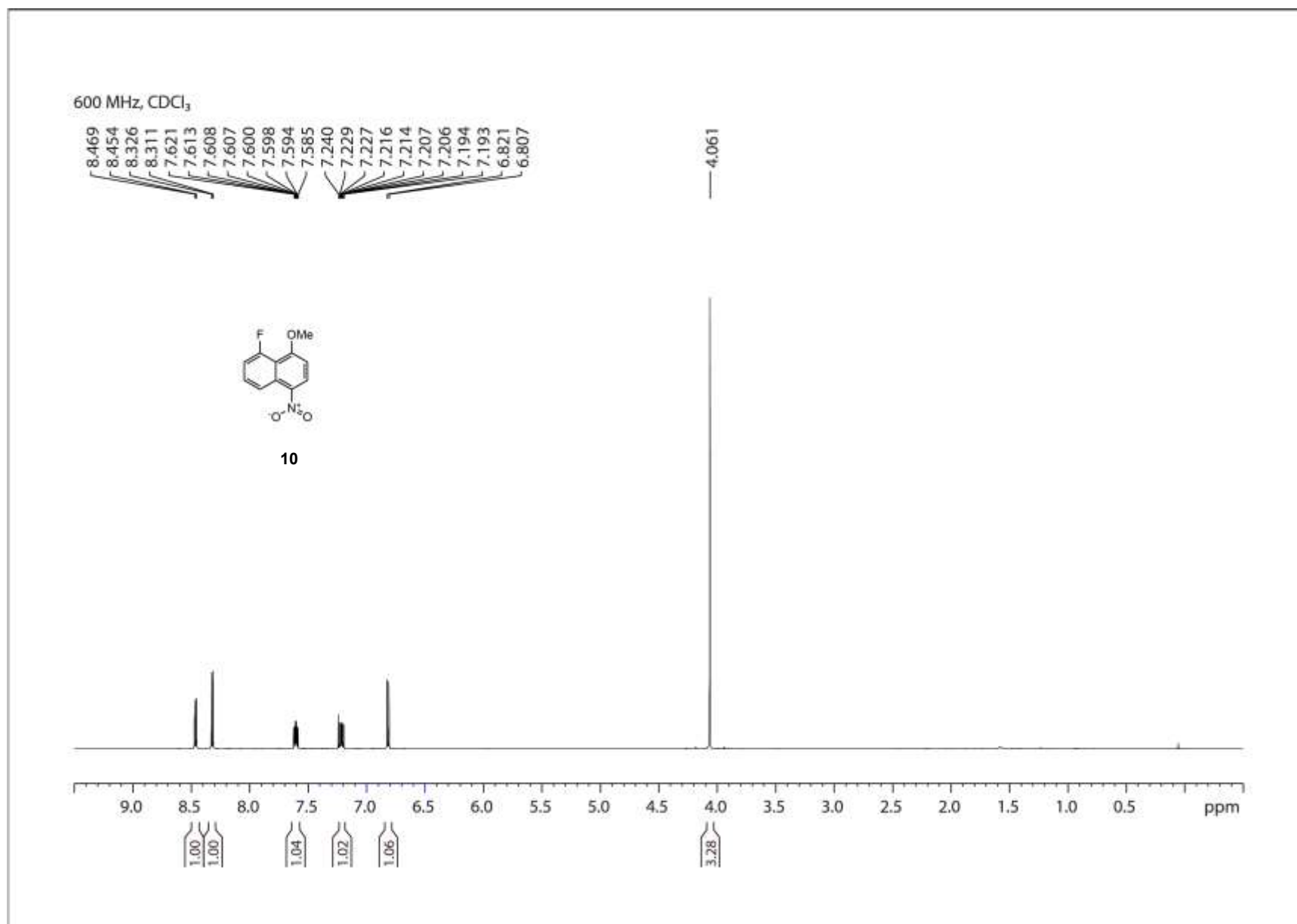
565 MHz, (CD<sub>3</sub>)<sub>2</sub>CO

-111.90  
-111.90  
-111.92  
-111.93





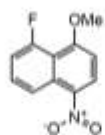
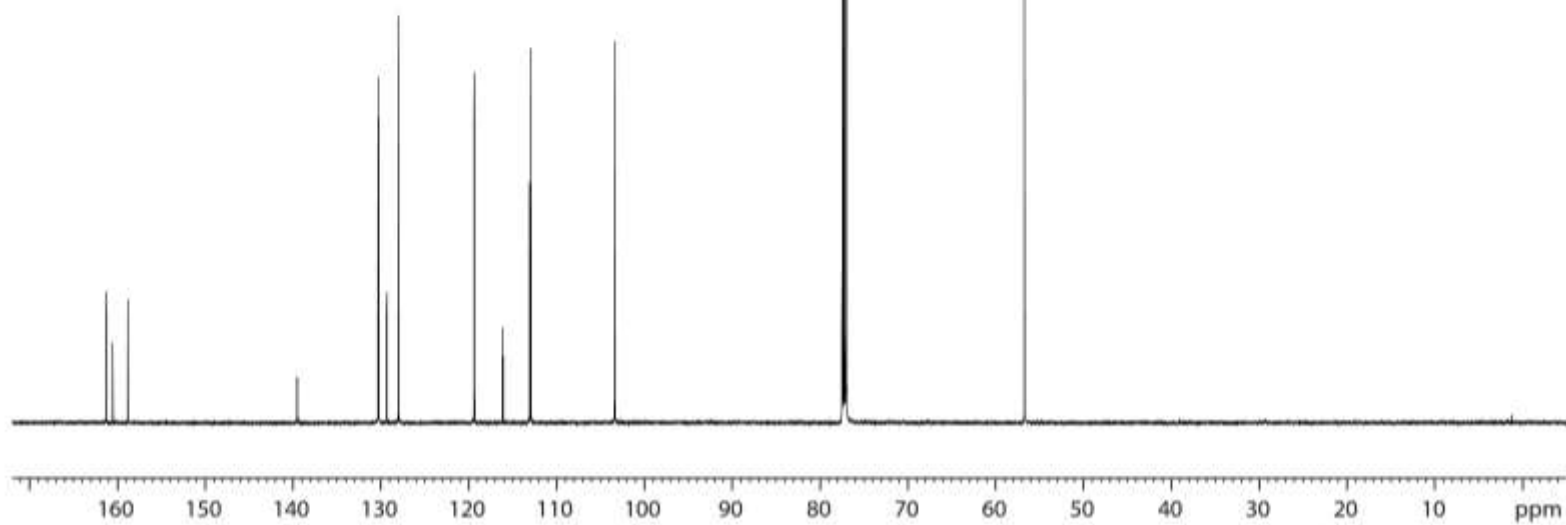
125 MHz, C<sub>6</sub>D<sub>6</sub>

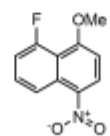




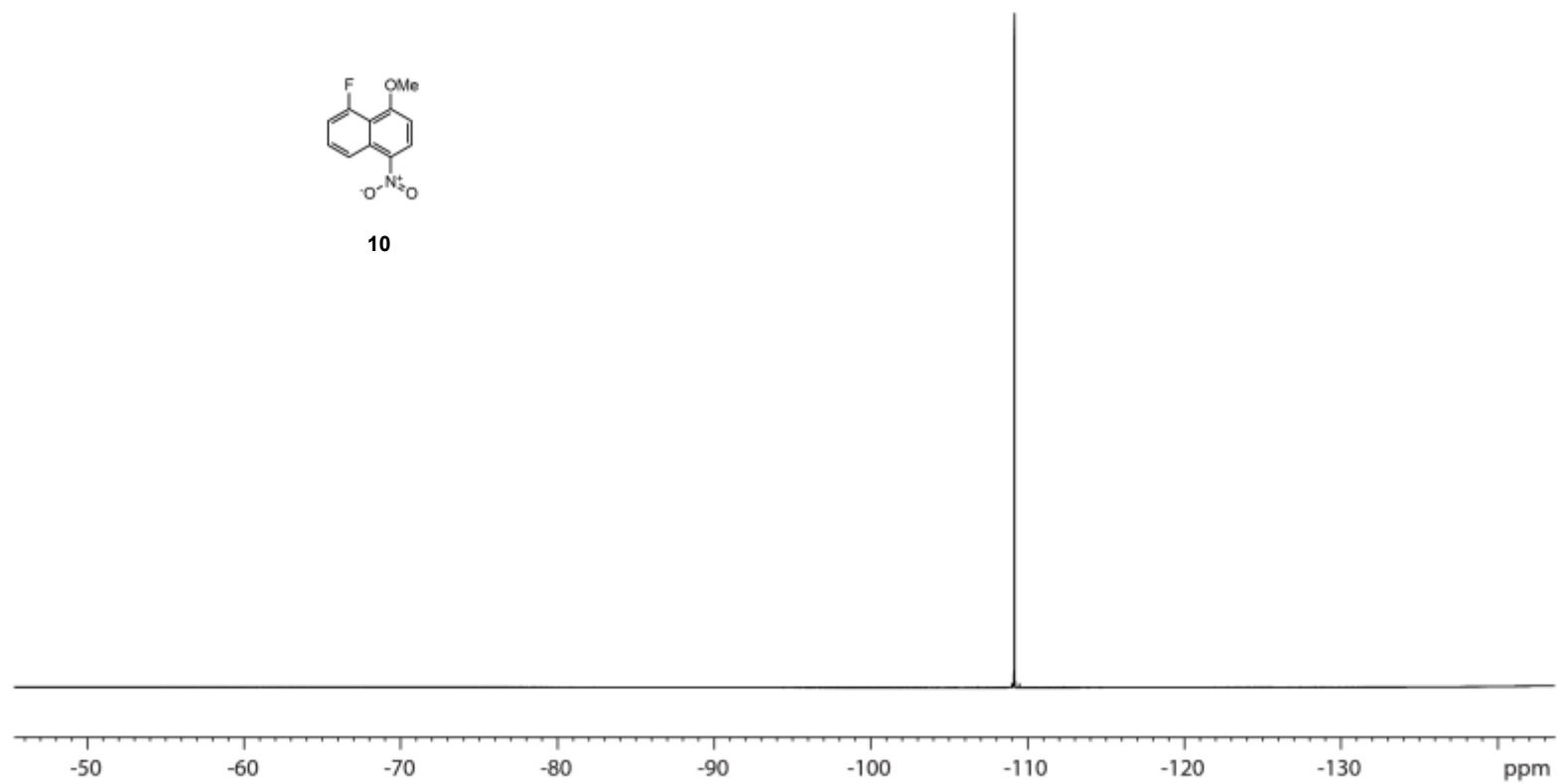
151 MHz, CDCl<sub>3</sub>161.25  
161.22  
160.53  
158.80139.52  
139.49130.31  
130.25  
129.31  
129.29  
127.98119.38  
119.34  
116.14  
116.07  
113.05  
112.90103.37  
103.3677.44  
77.23  
77.01

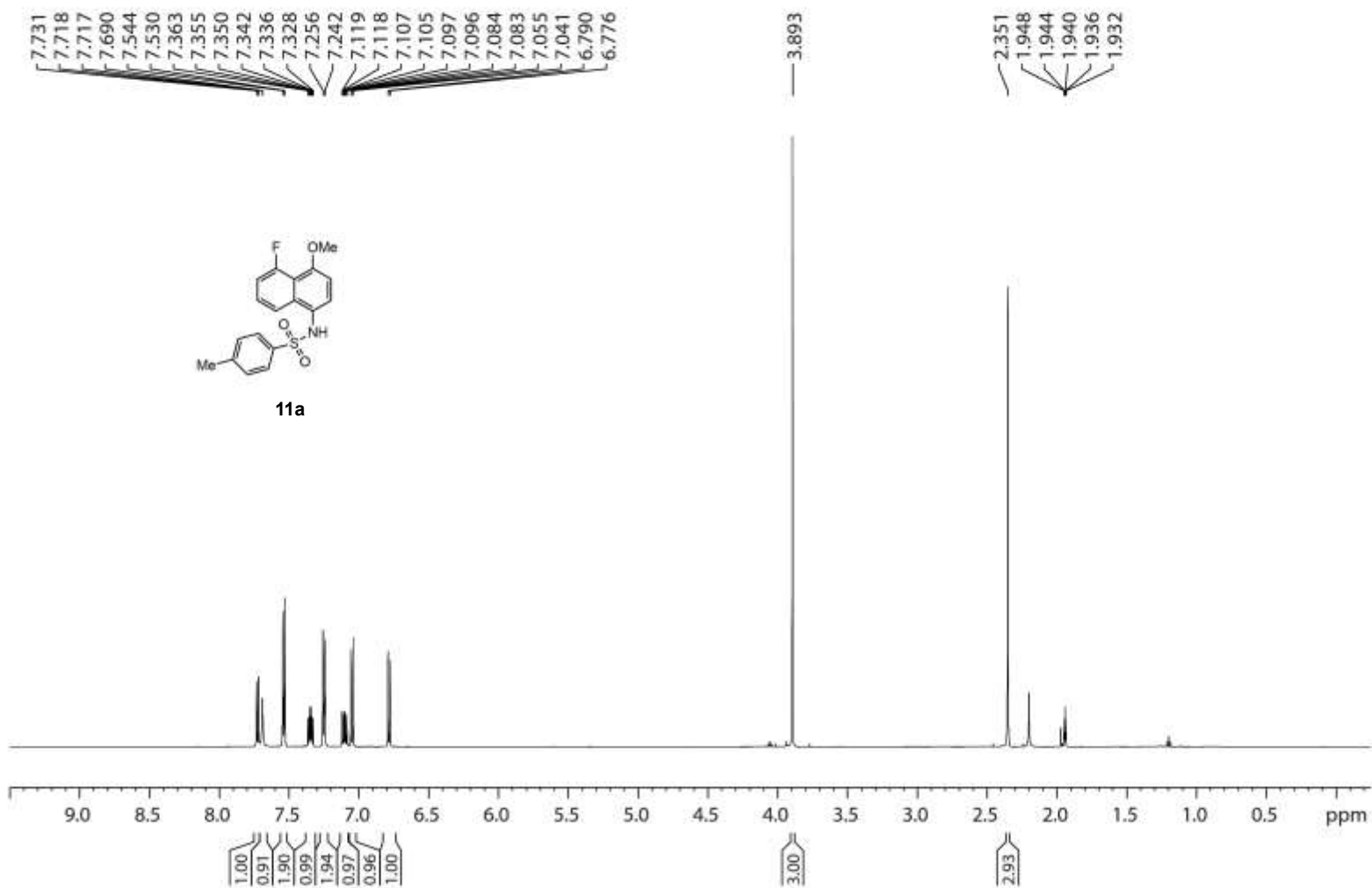
56.72

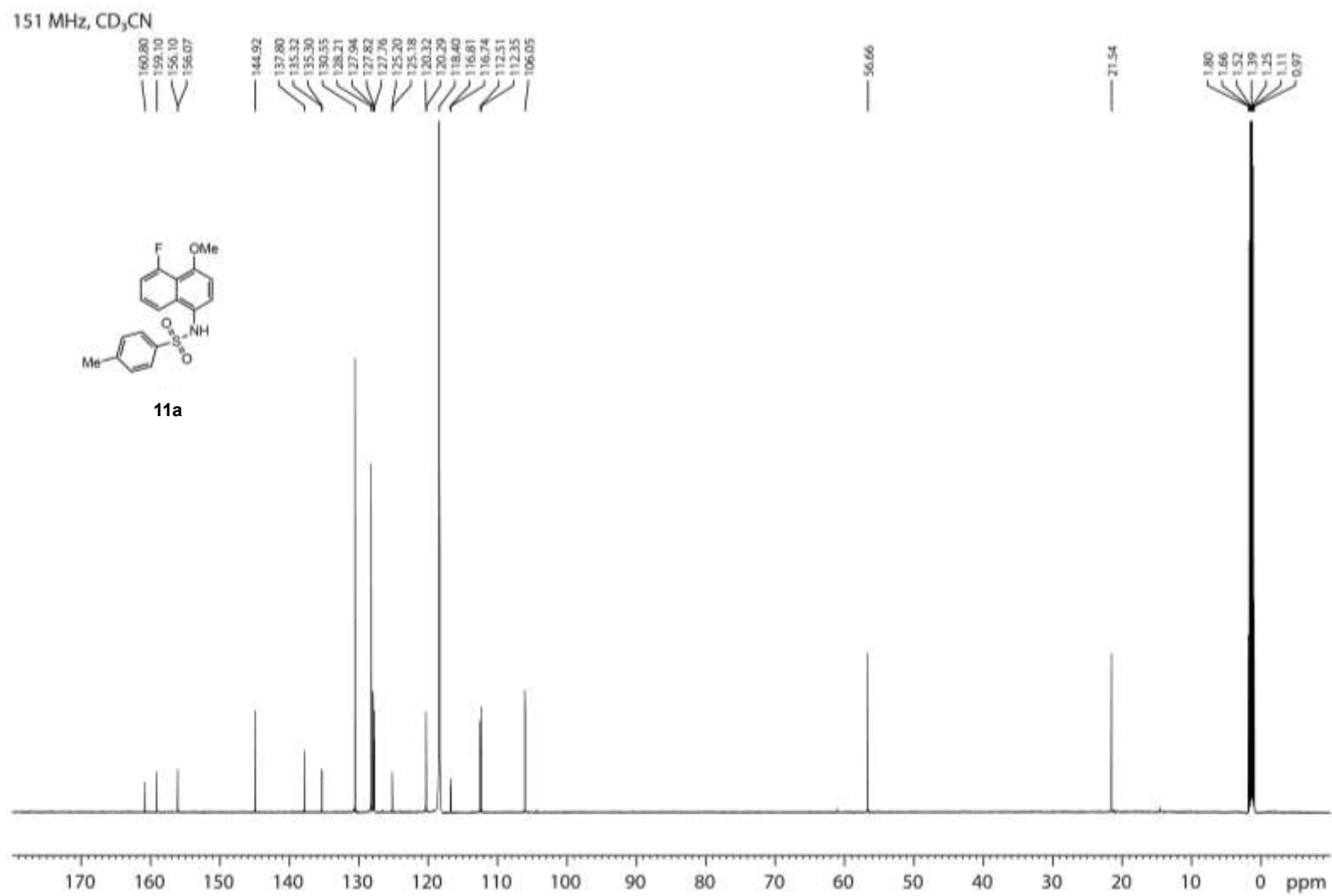
**10**

565 MHz, CDCl<sub>3</sub>**10**

-109.14  
-109.15  
-109.16  
-109.17

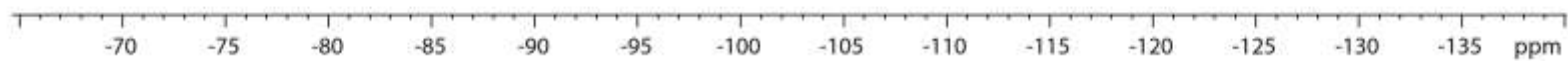
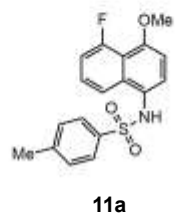


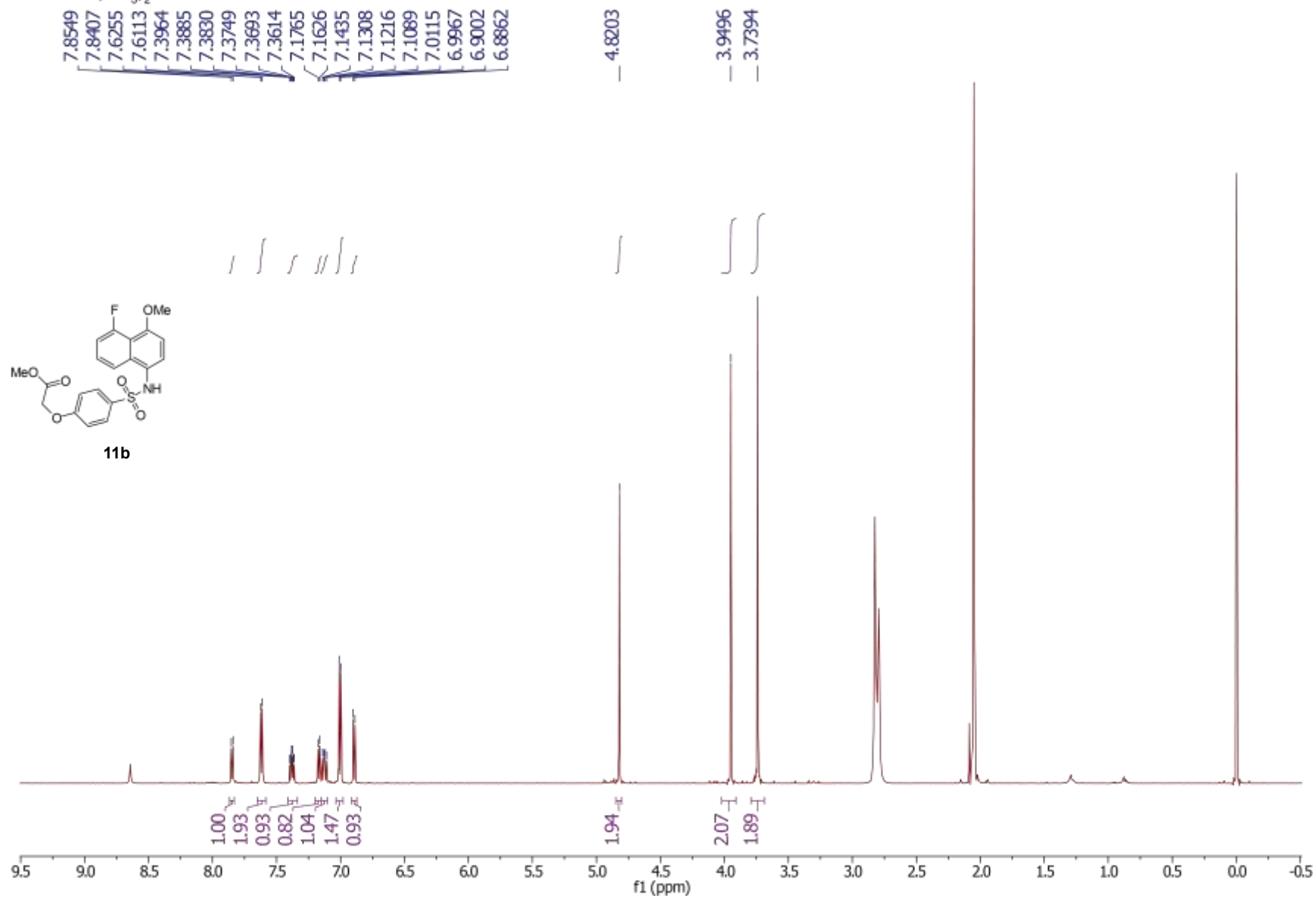
600 MHz, CD<sub>3</sub>CN

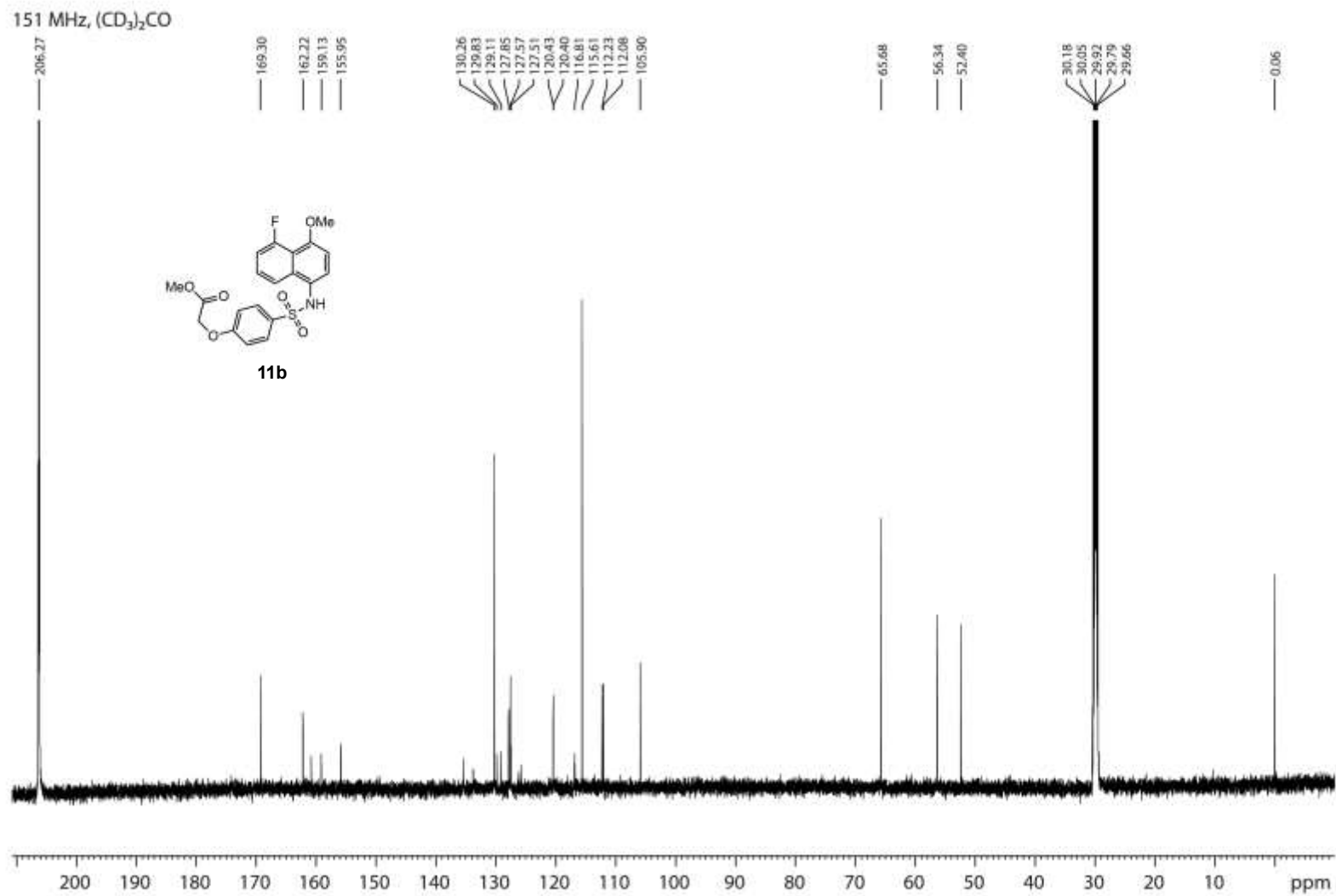


565 MHz, CD<sub>3</sub>CN

-112.55  
-112.56  
-112.57  
-112.58

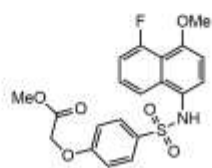
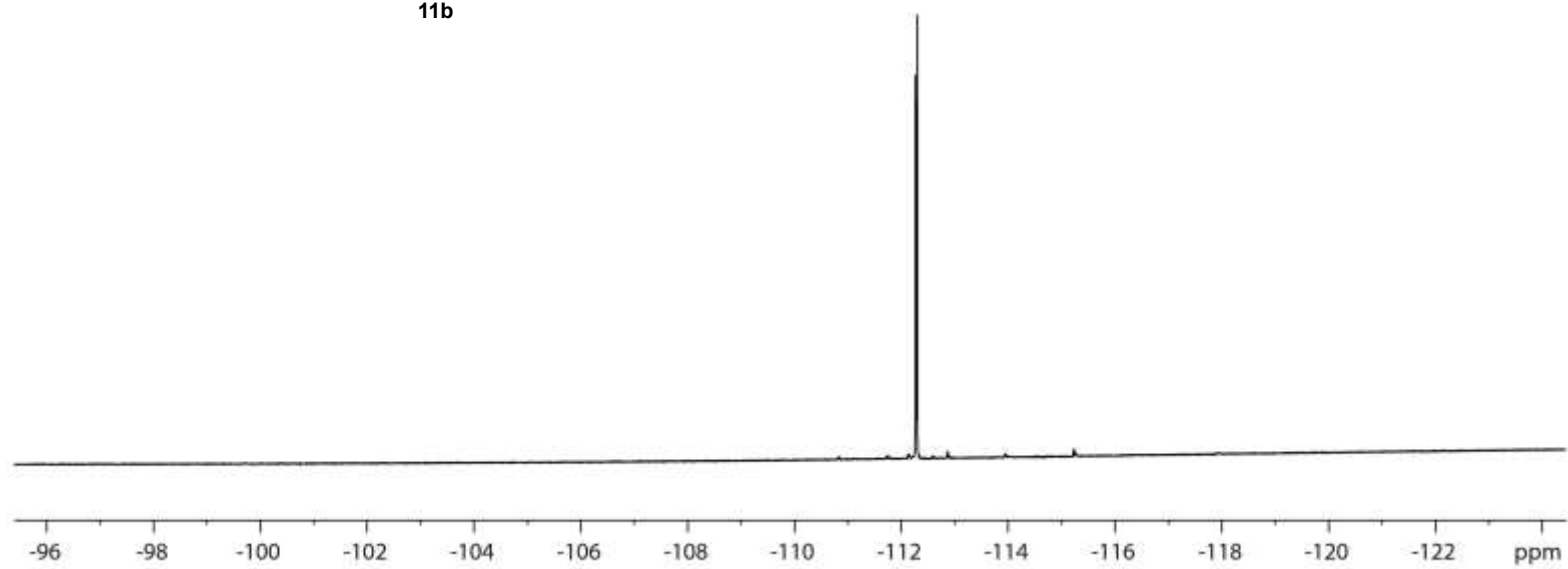


600 MHz, (CD<sub>3</sub>)<sub>2</sub>CO



565 MHz, (CD<sub>3</sub>)<sub>2</sub>CO

-112.27  
-112.28  
-112.29  
-112.30

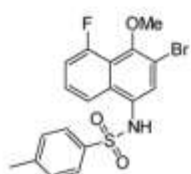
**11b**



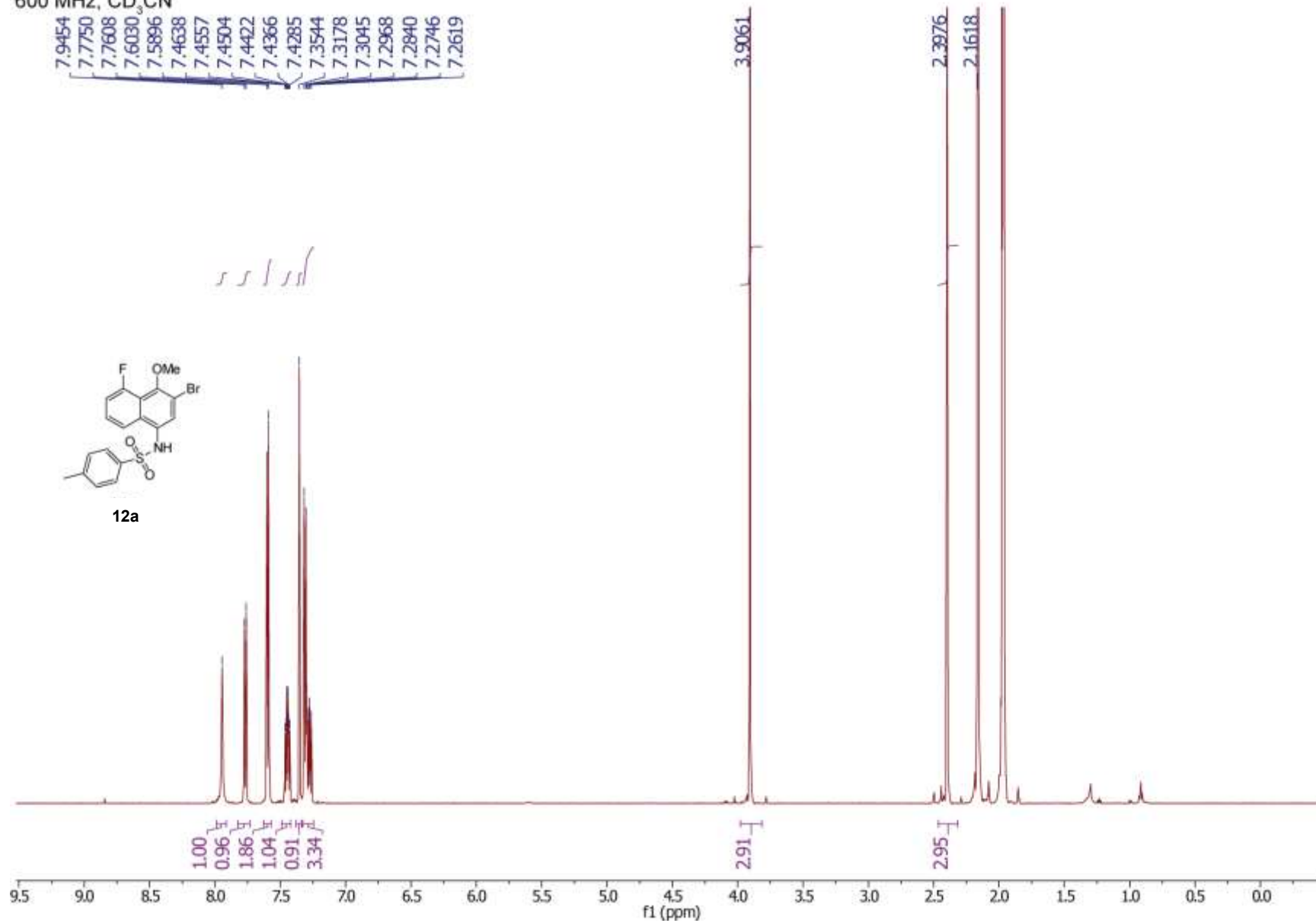
600 MHz, CD<sub>3</sub>CN

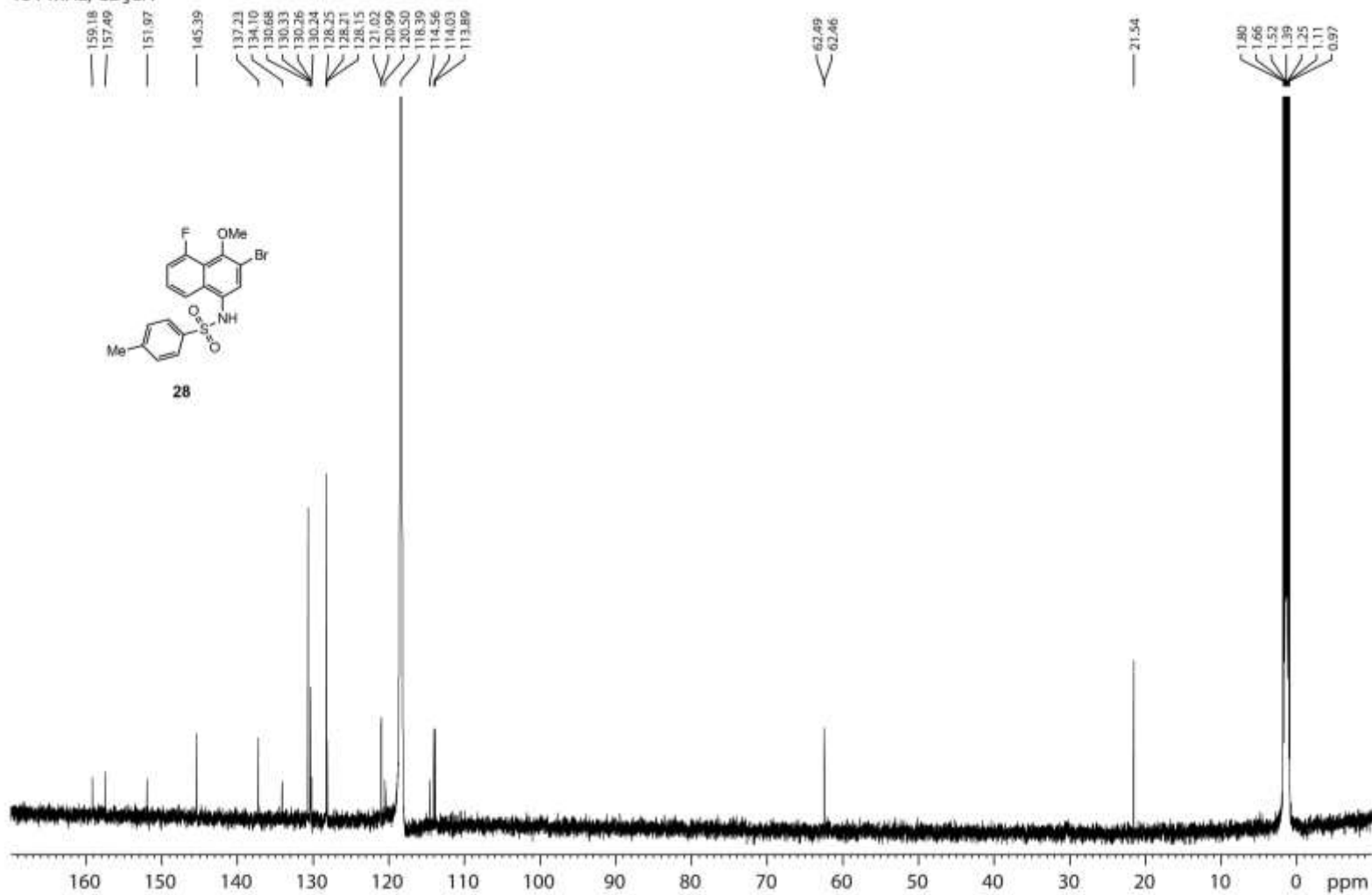
7.9454  
7.7750  
7.7608  
7.6030  
7.5896  
7.4638  
7.4557  
7.4504  
7.4422  
7.4366  
7.4285  
7.3544  
7.3178  
7.3045  
7.2968  
7.2840  
7.2746  
7.2619

*ssllll*



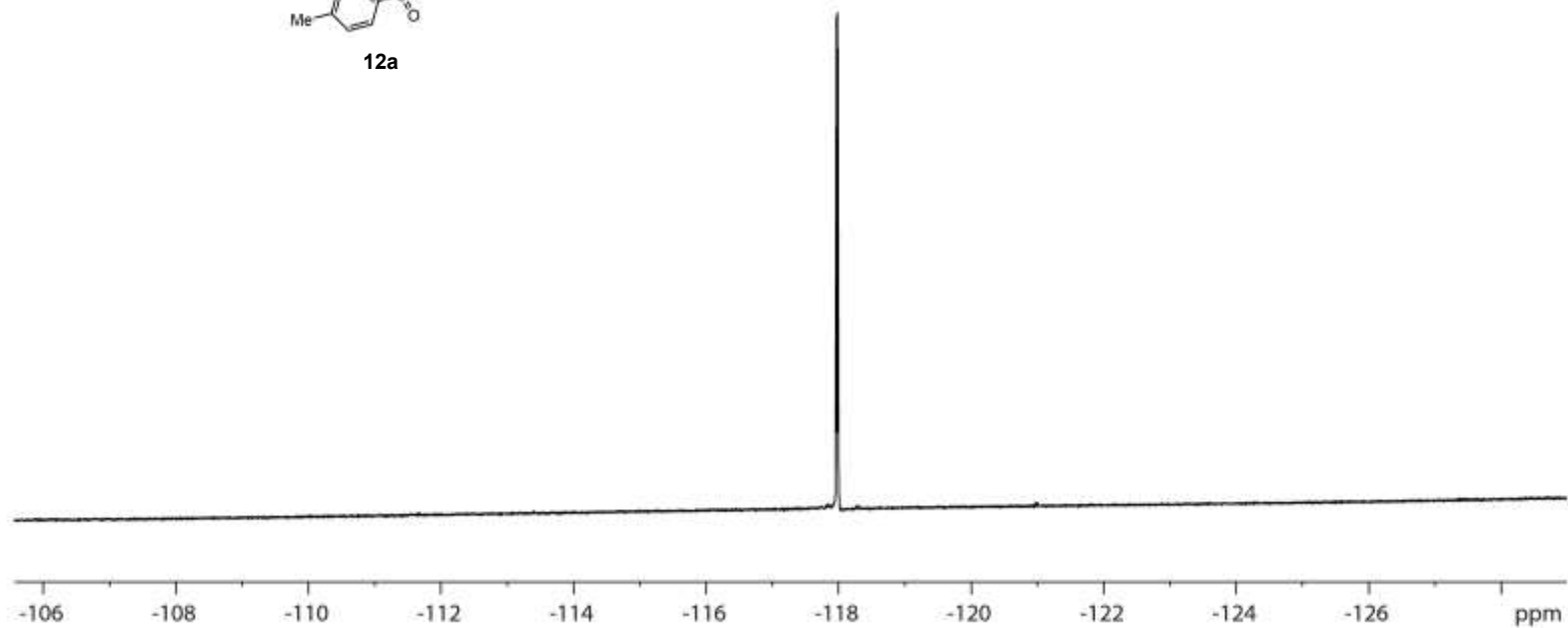
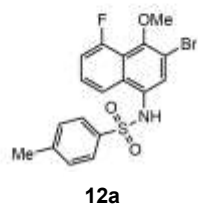
12a



151 MHz, CD<sub>3</sub>CN

565 MHz, CD<sub>3</sub>CN

-117.96  
-117.97  
-117.98  
-117.99

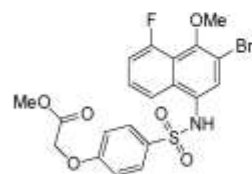




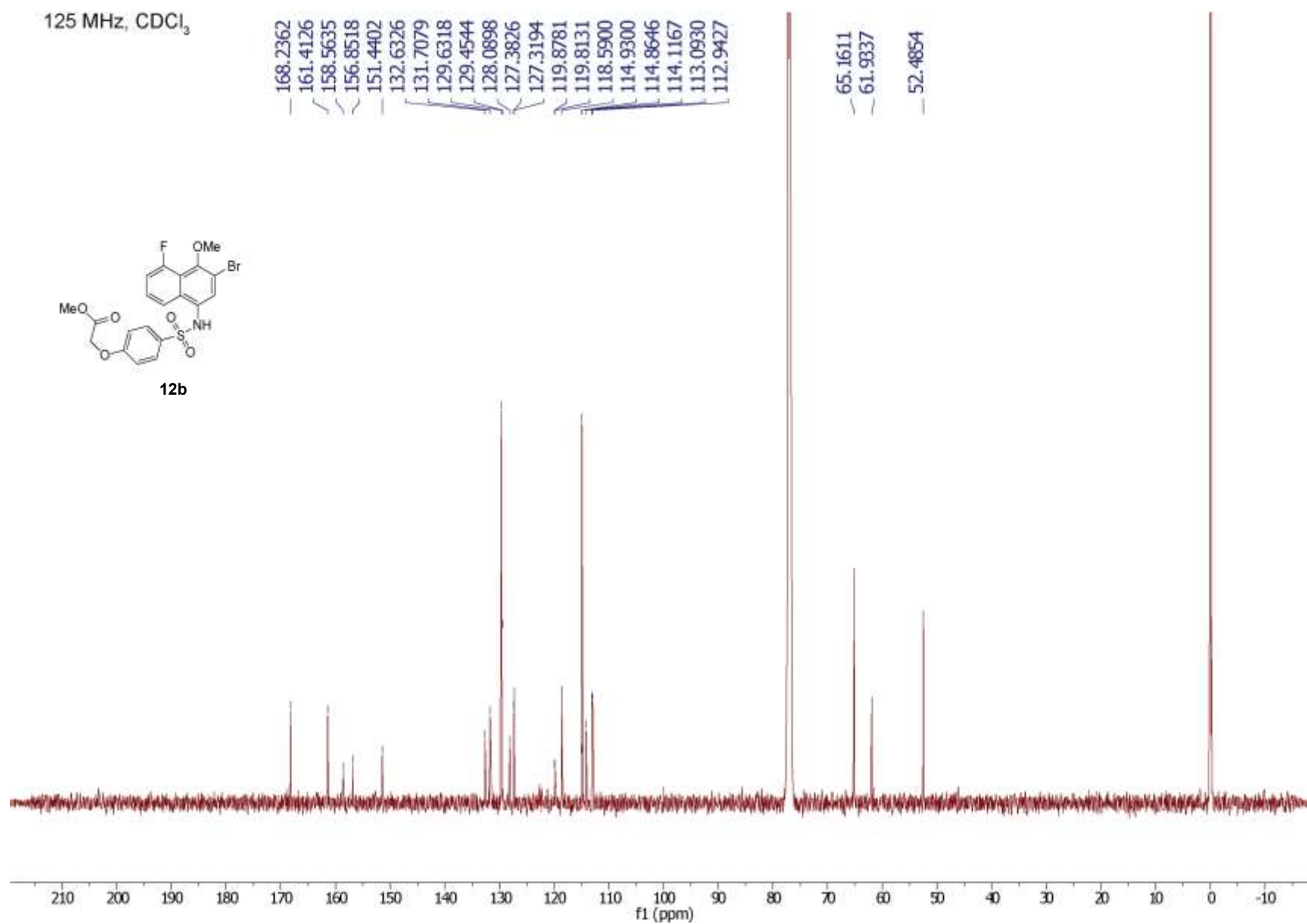
125 MHz, CDCl<sub>3</sub>

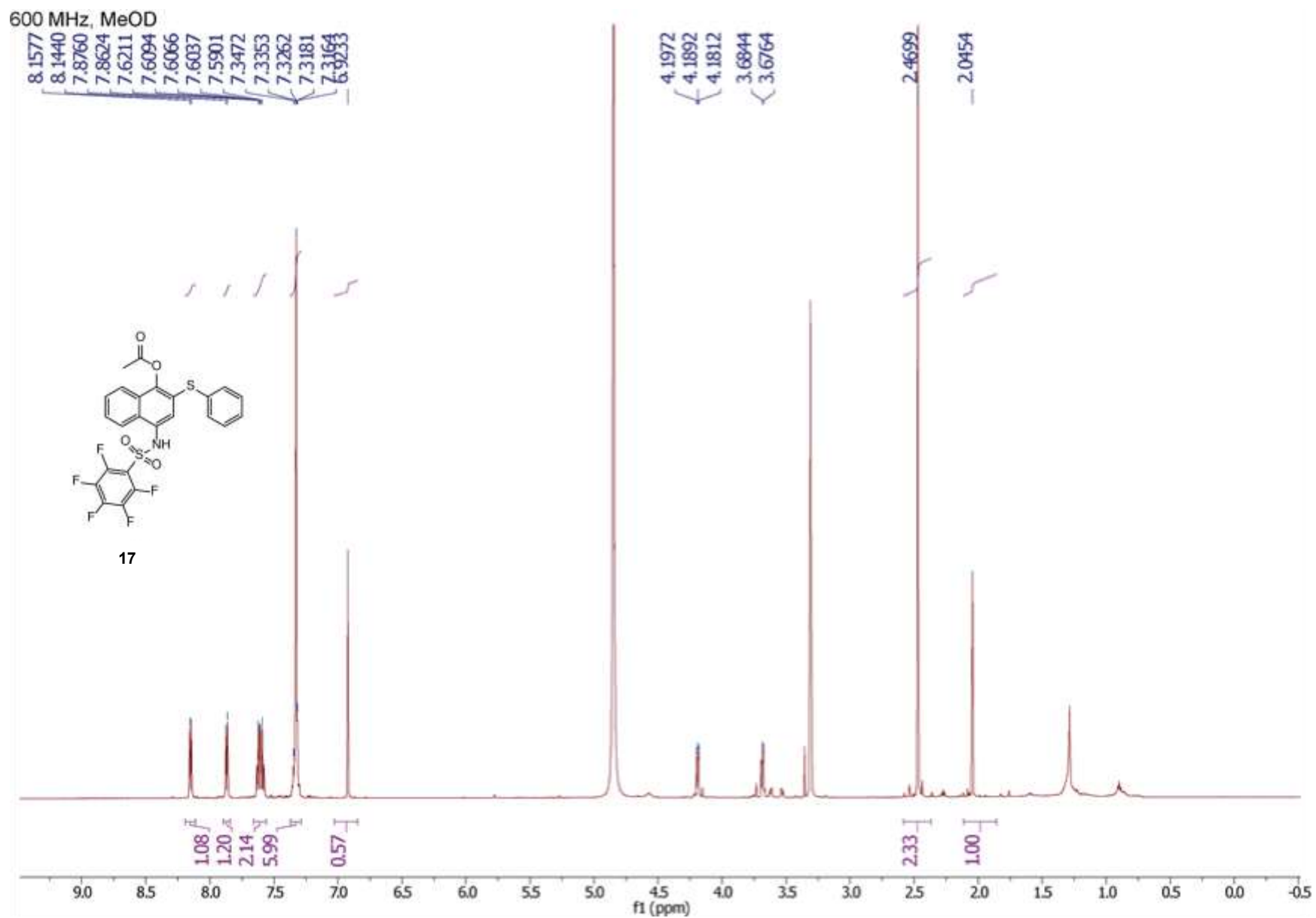
168.2362  
161.4126  
158.5635  
156.8518  
151.4402  
132.6326  
131.7079  
129.6318  
129.4544  
128.0898  
127.3826  
127.3194  
119.8781  
119.8131  
118.5900  
114.9300  
114.8646  
114.1167  
113.0930  
112.9427

65.1611  
61.9337  
52.4854

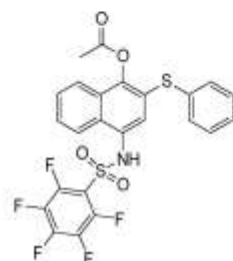


12b

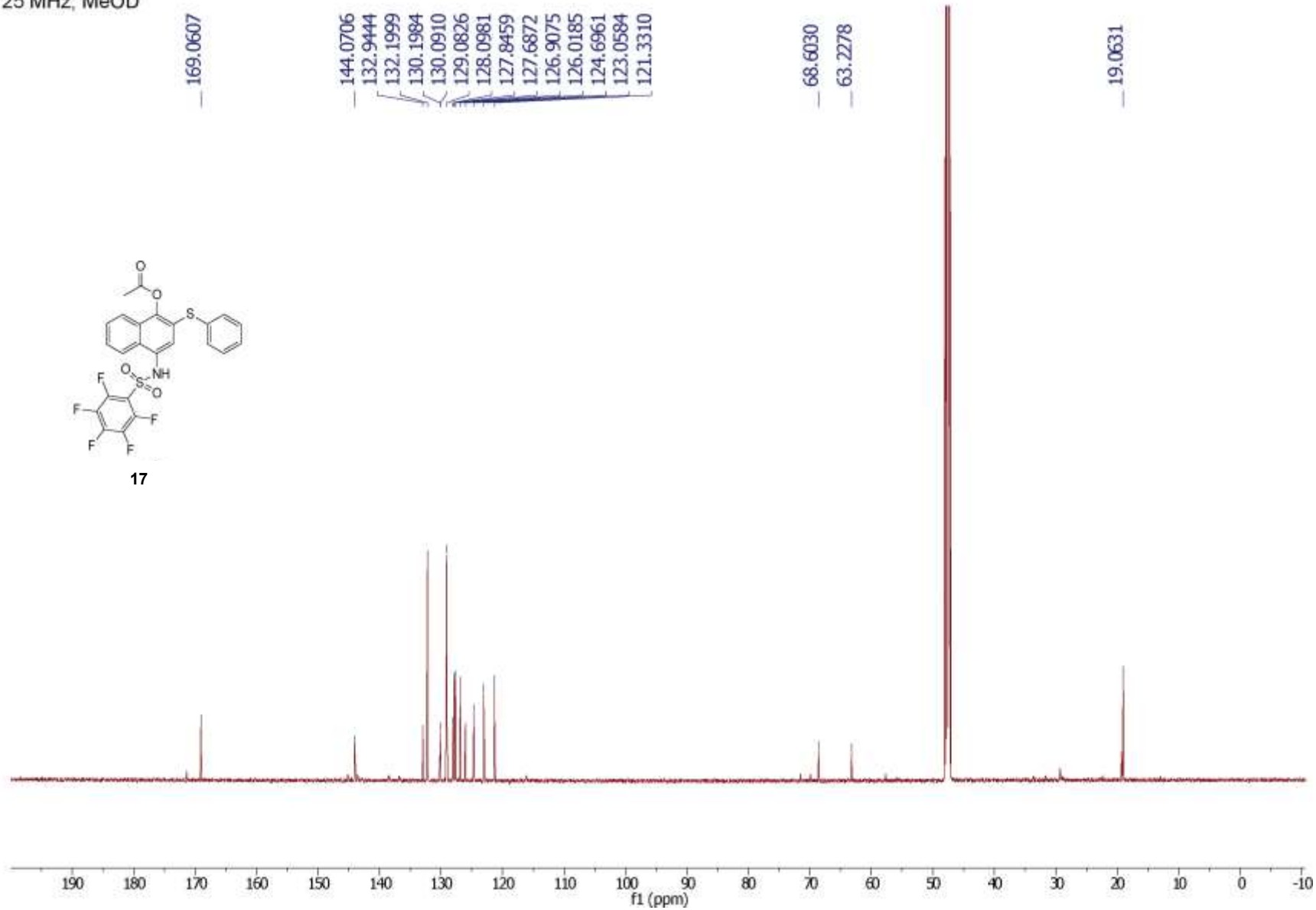




125 MHz, MeOD



17

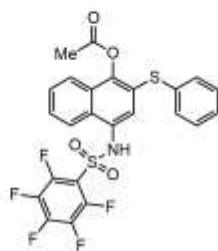


565 MHz, MeOD

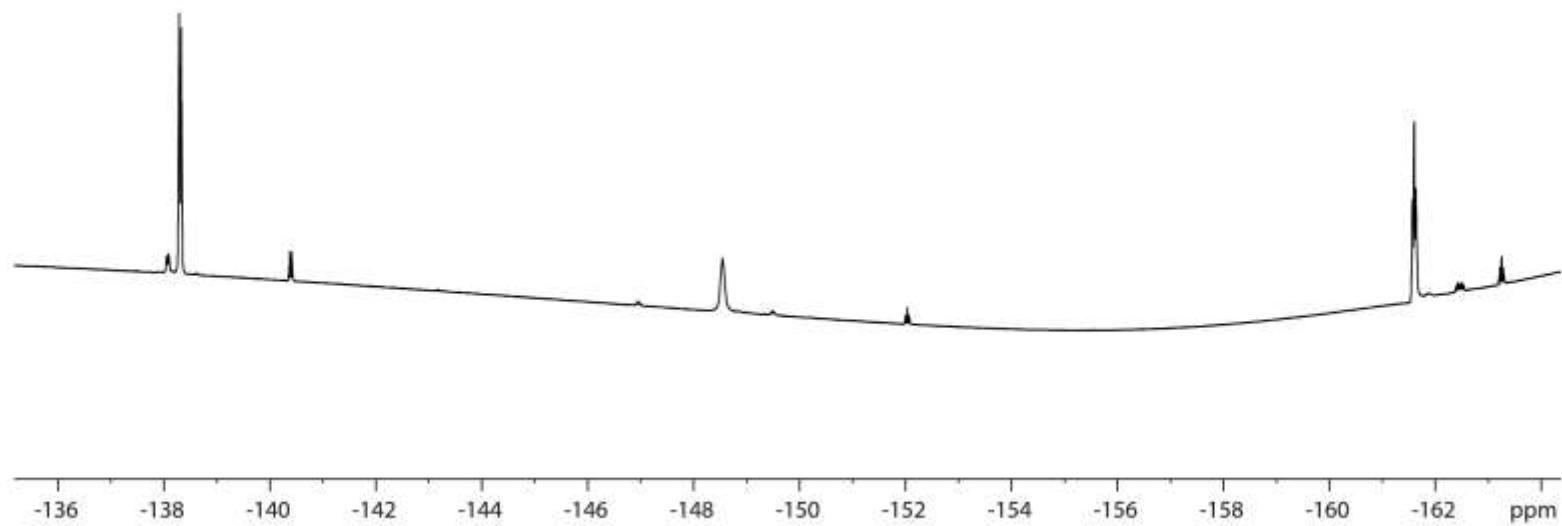
-138.27  
-138.29  
-138.30  
-138.32  
-138.33  
-138.33  
-138.35

-148.55

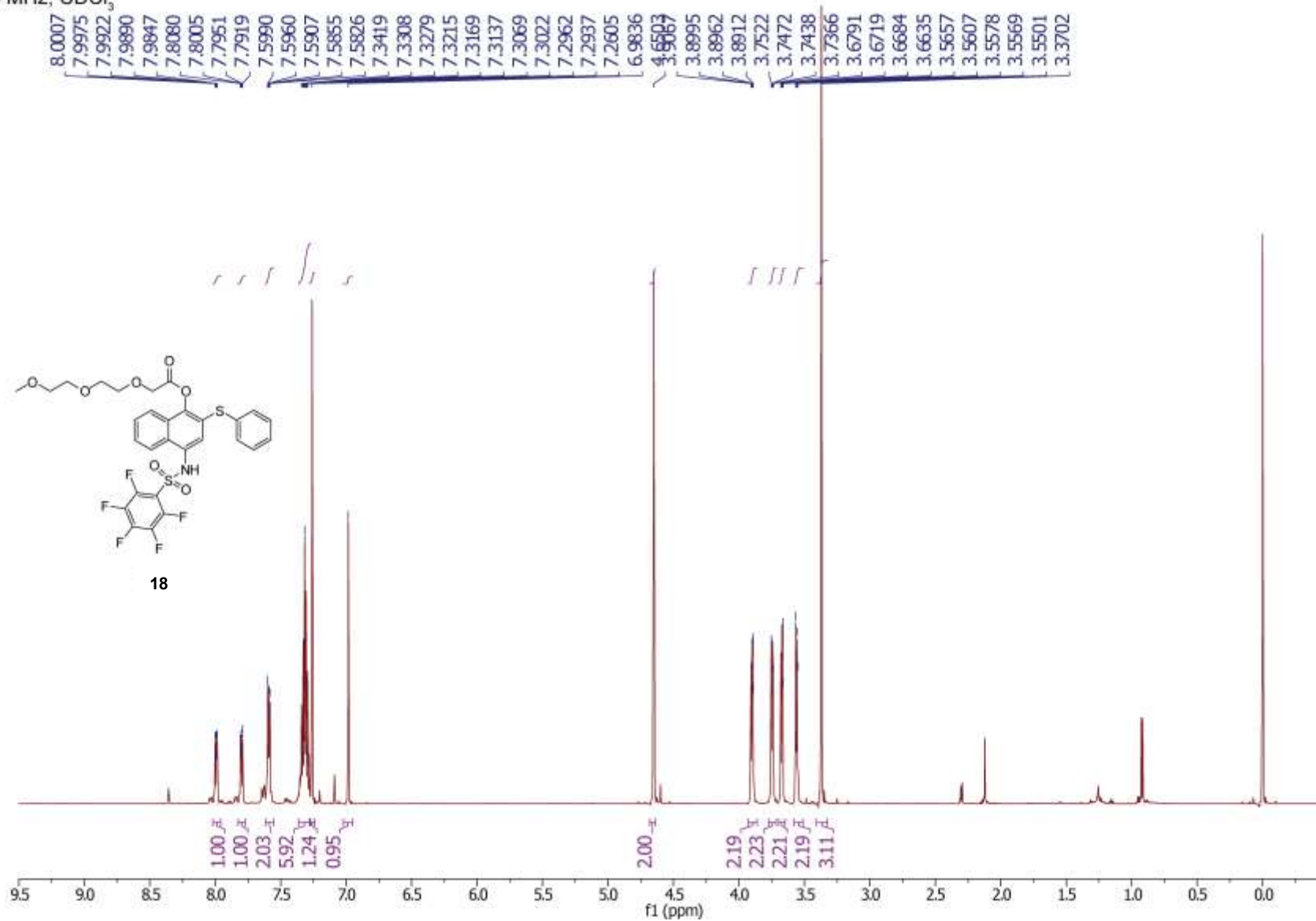
-161.58  
-161.61  
-161.64

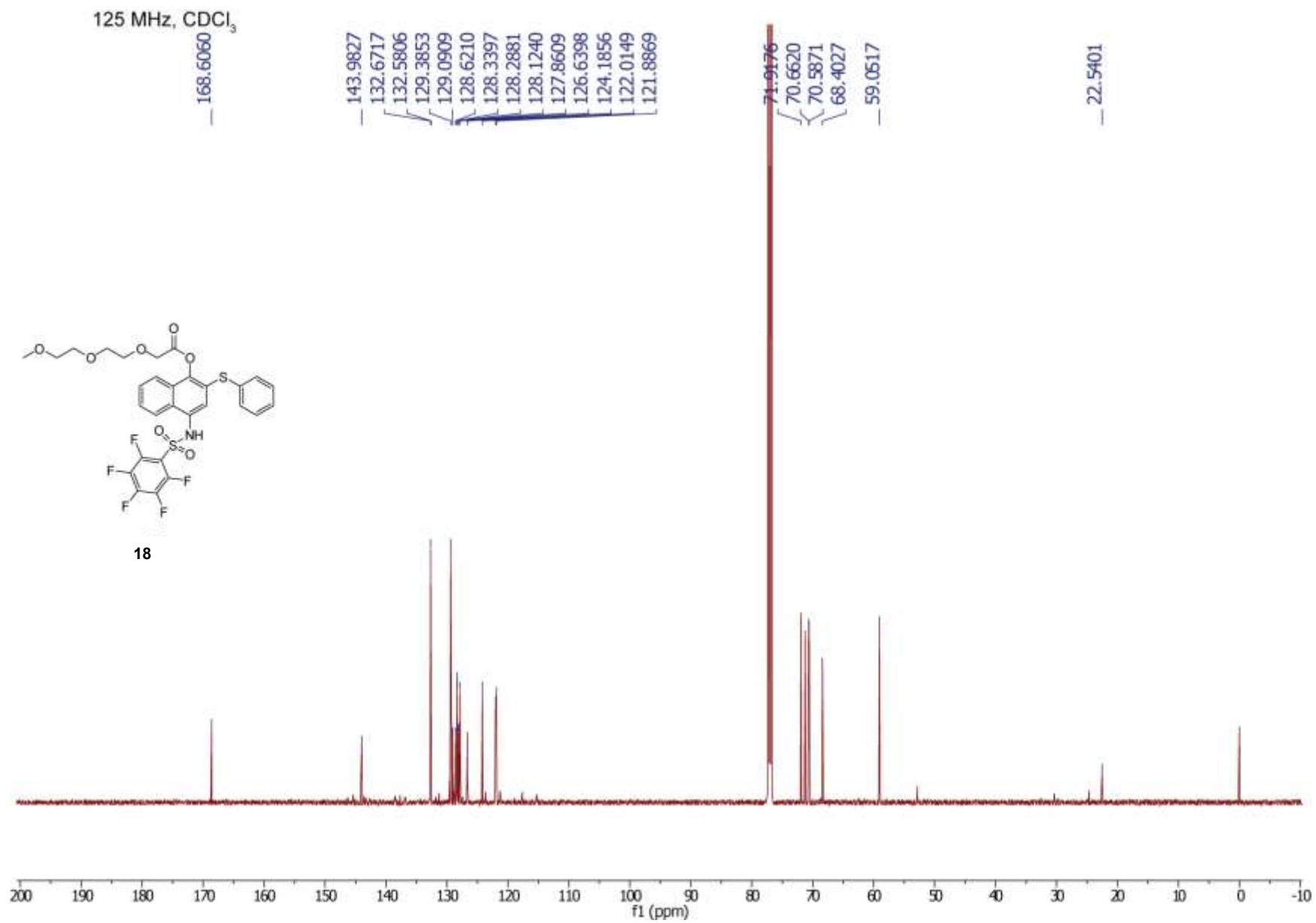


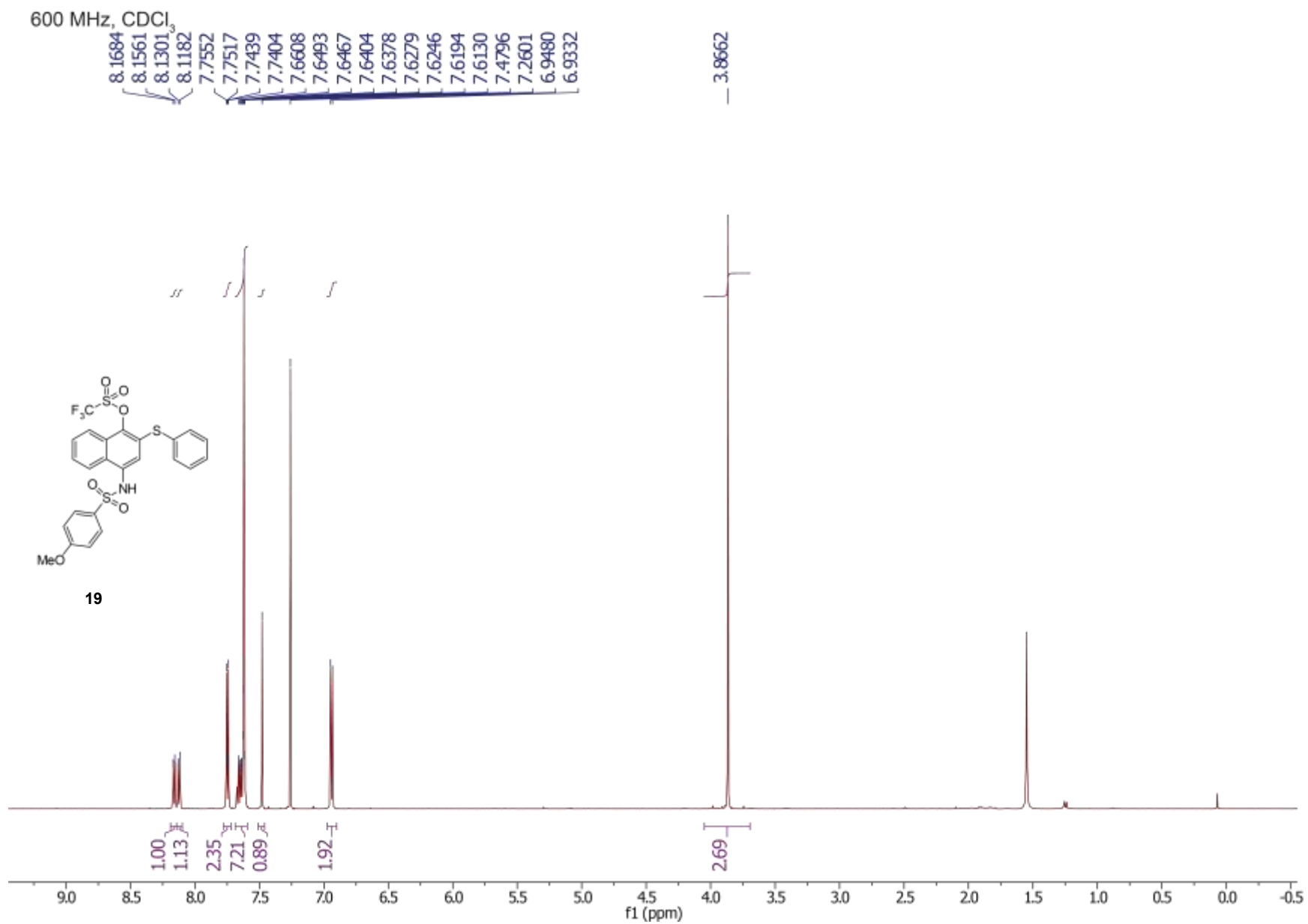
17

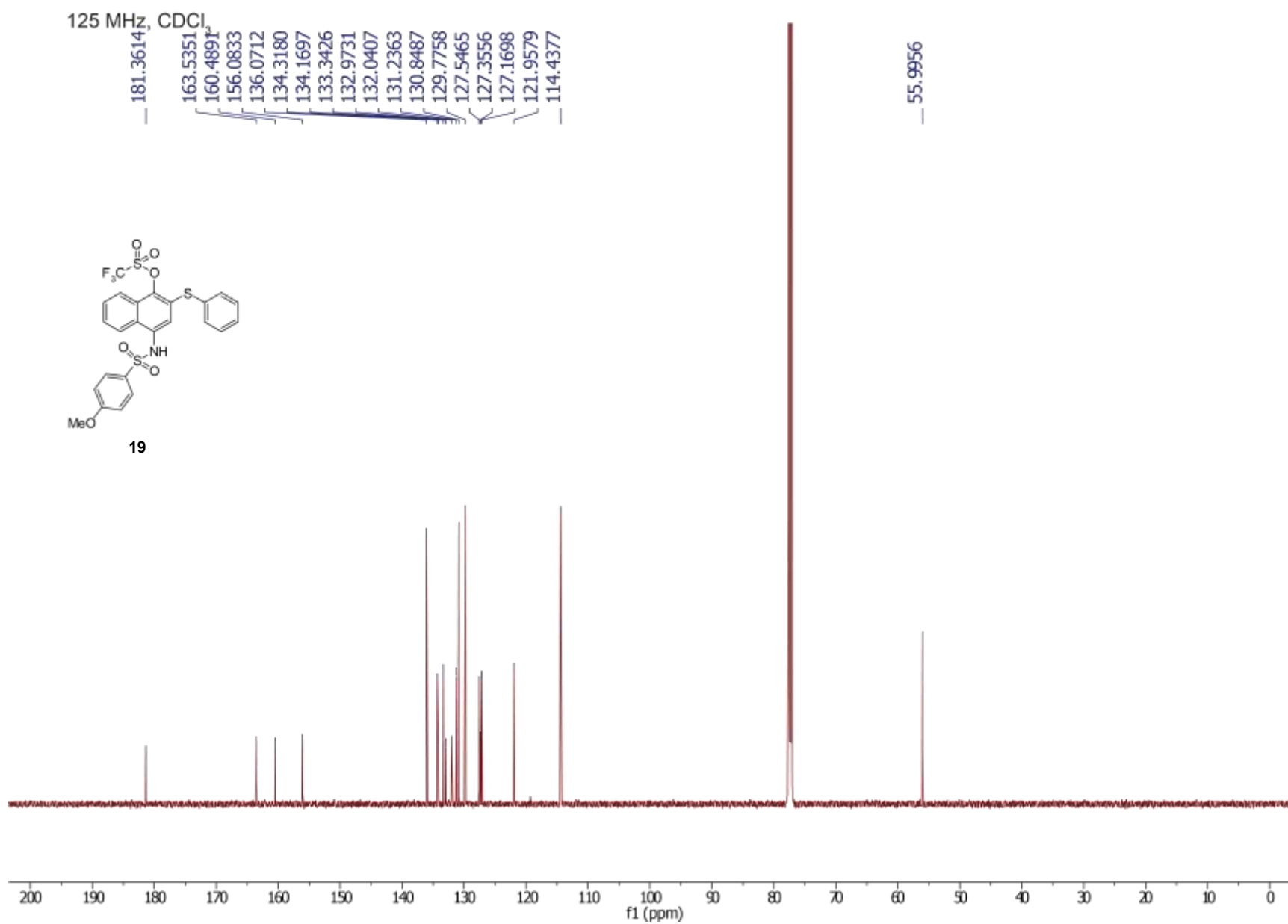




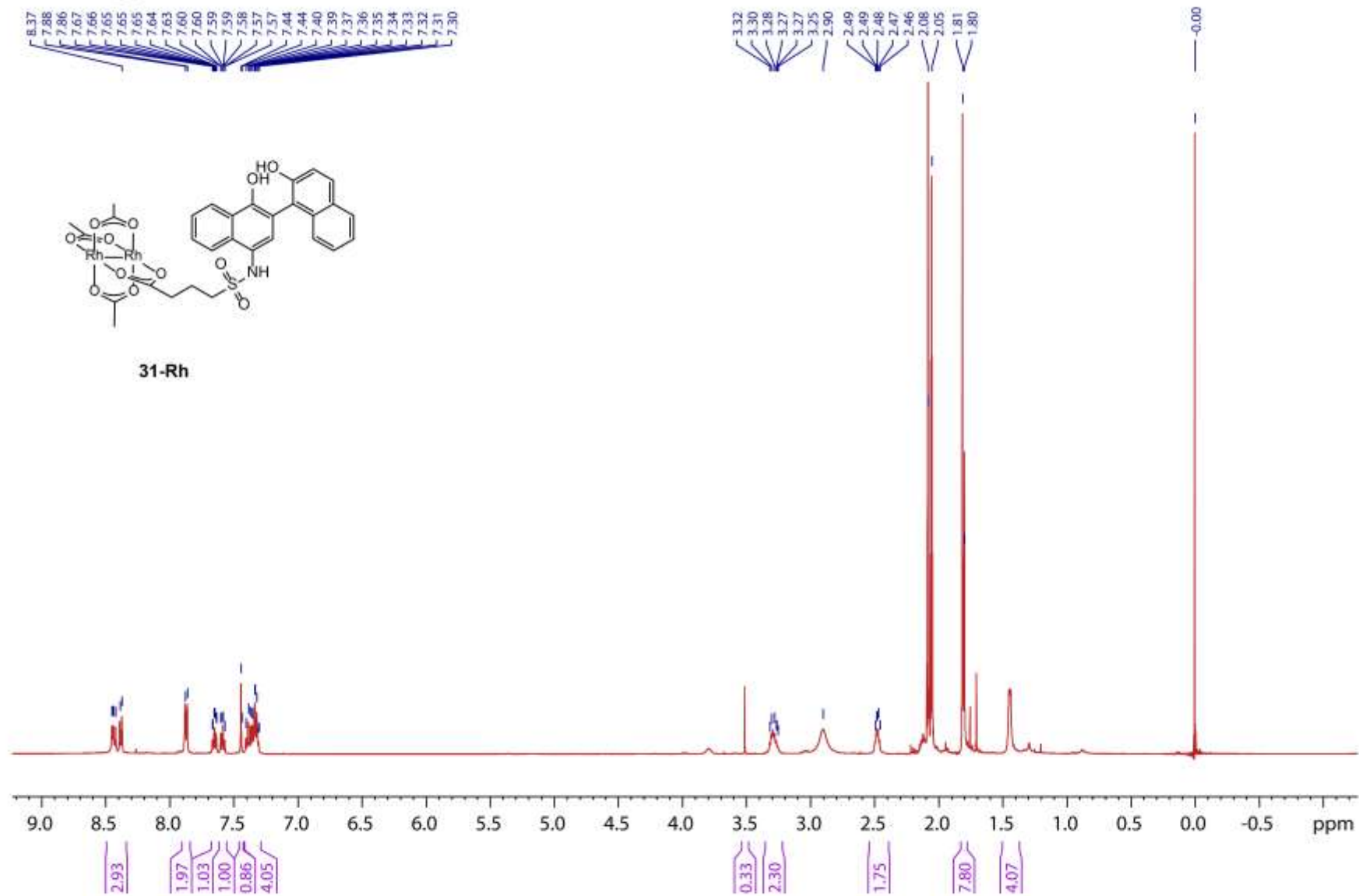
600 MHz, CDCl<sub>3</sub>

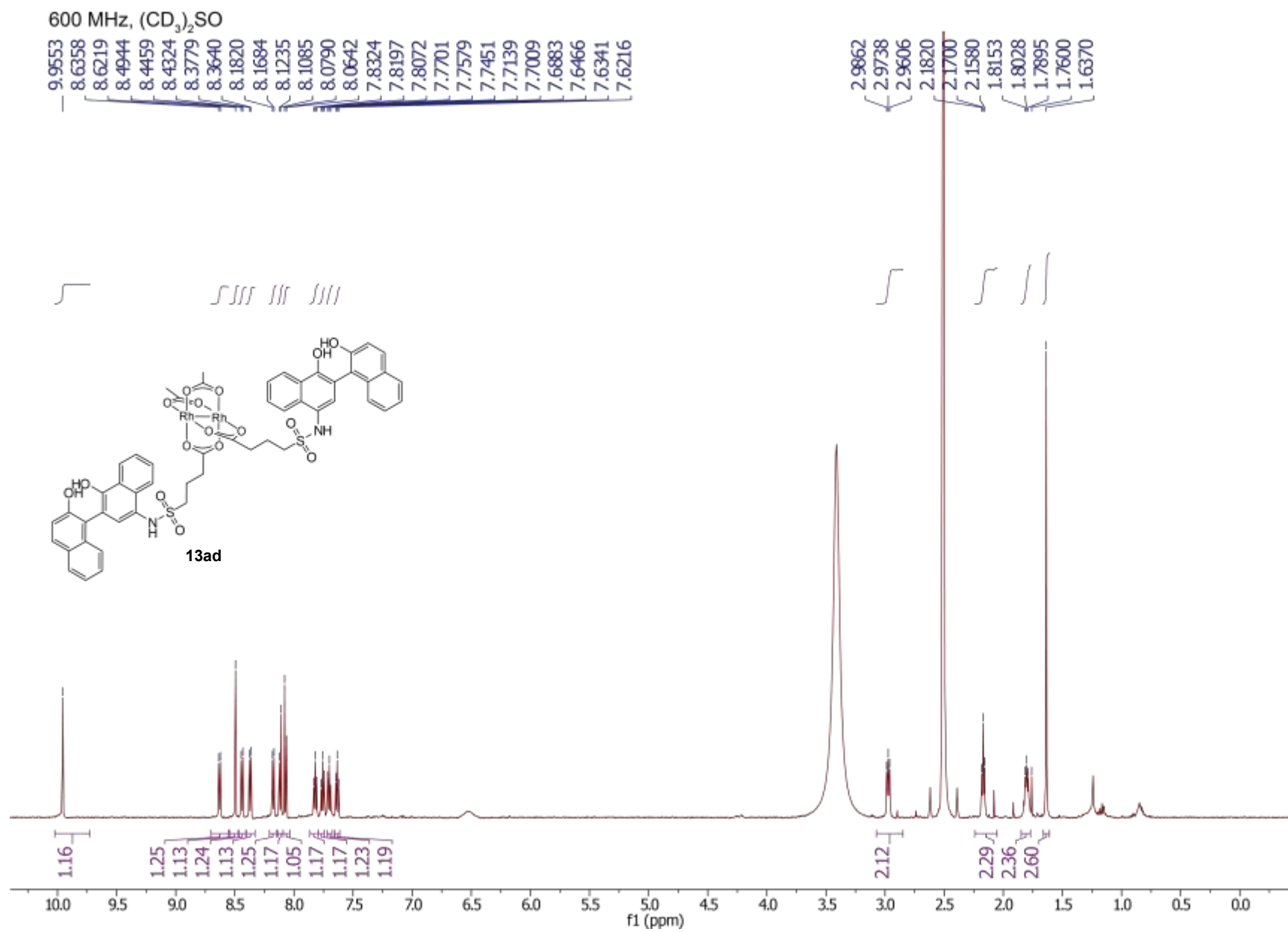


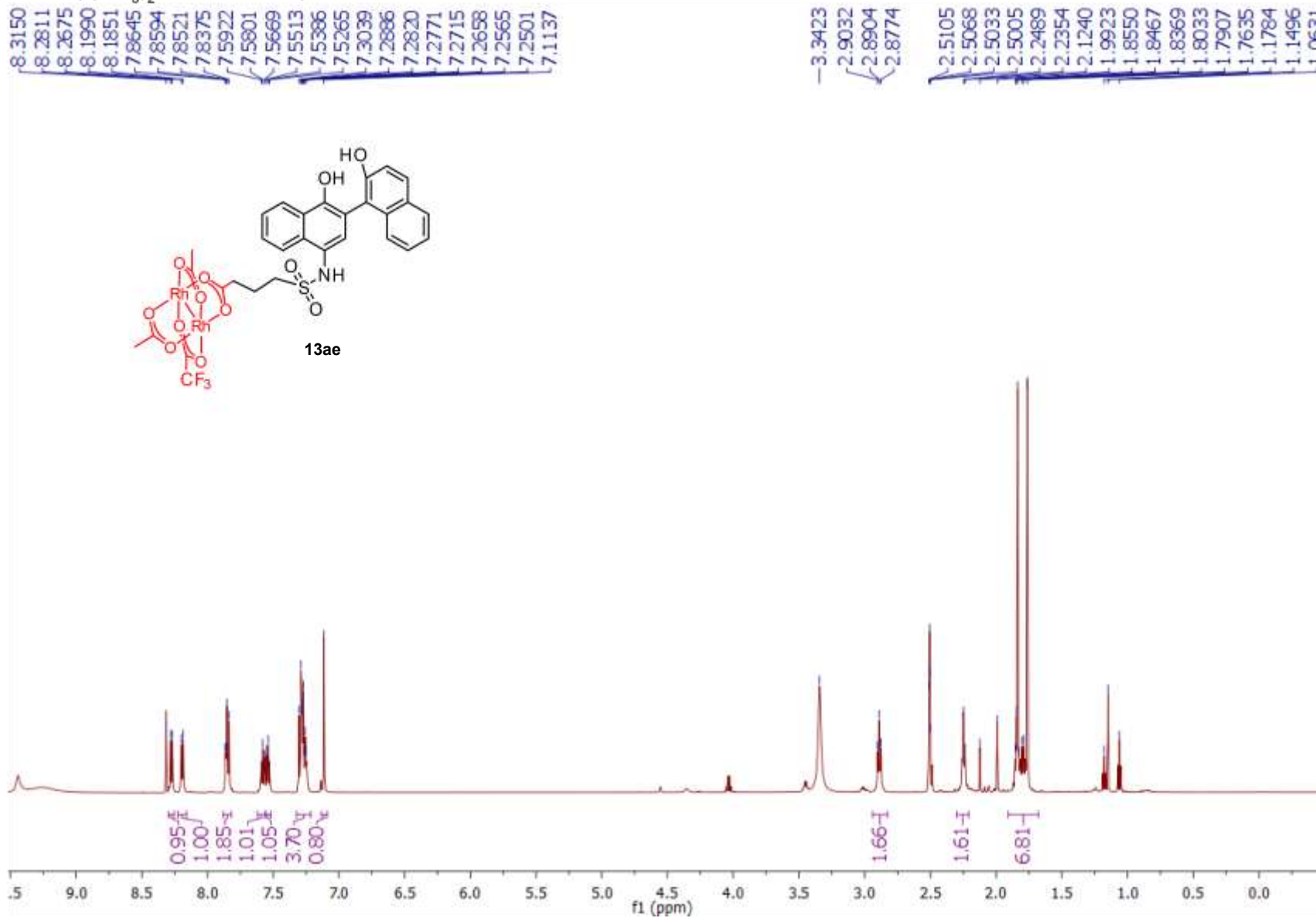




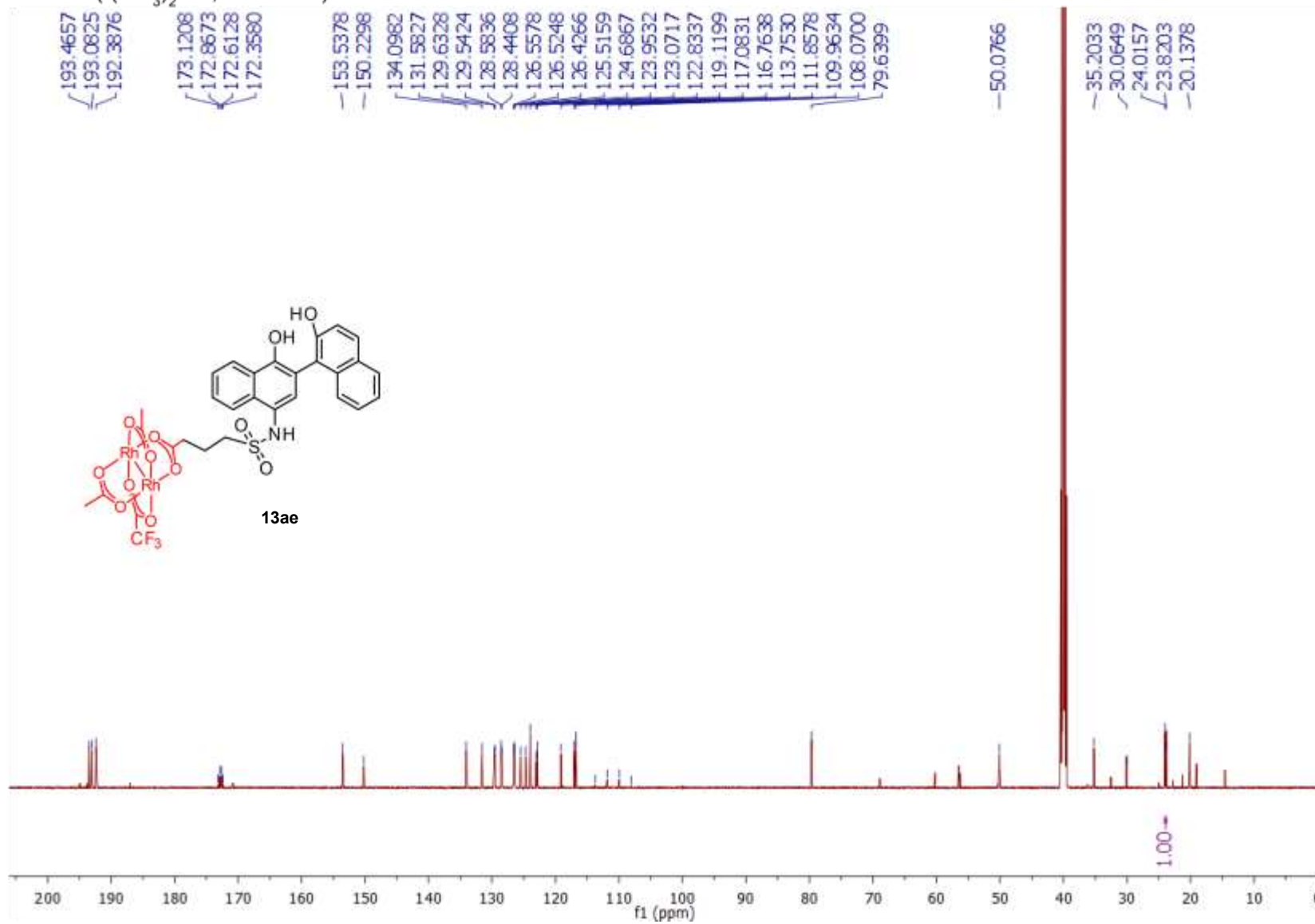
$^1\text{H NMR}$ ,  $(\text{CD}_3)_2\text{CO}$ , 500 MHz



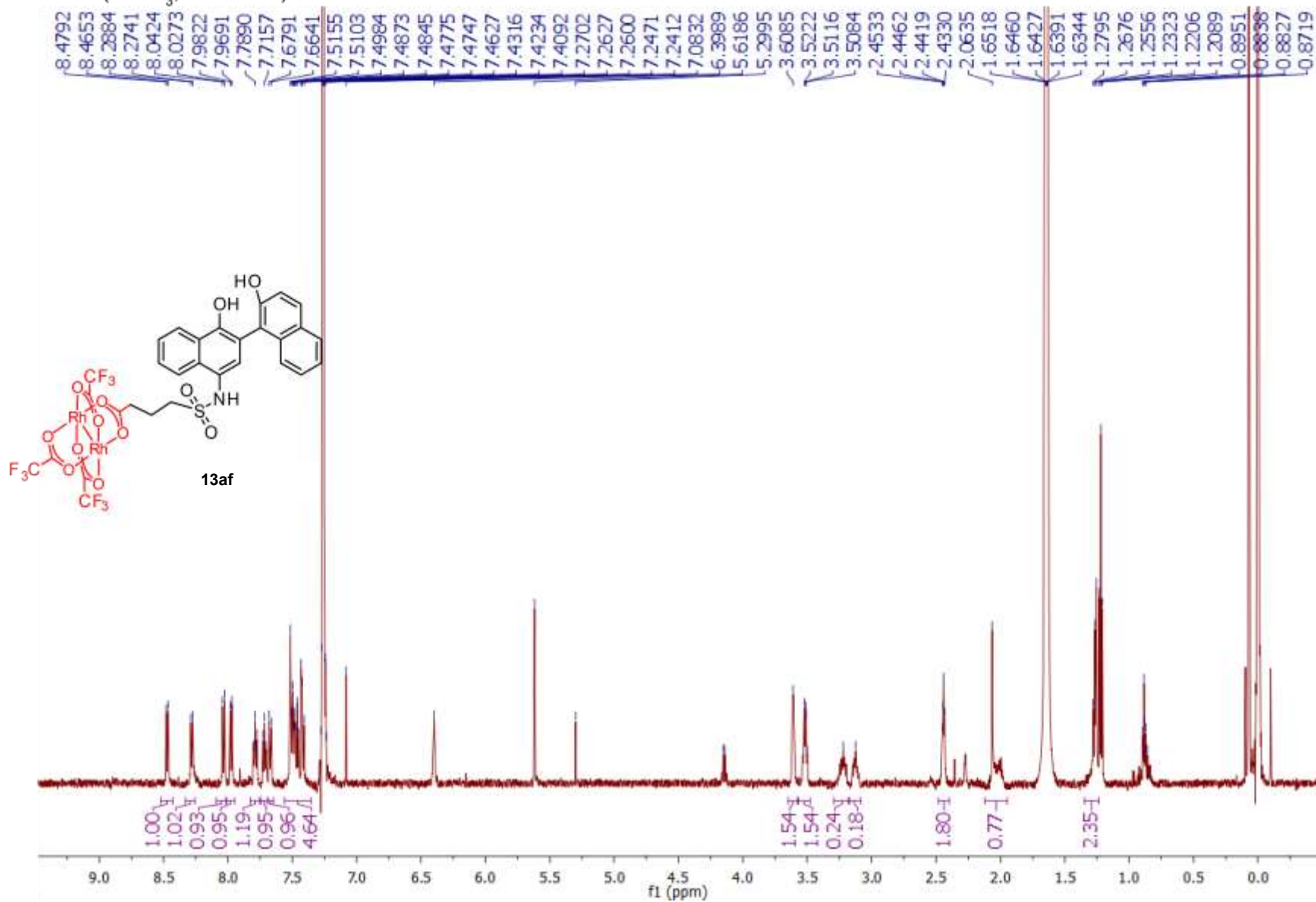


$^1\text{H NMR}$  ( $\text{CD}_3\text{SO}_2$ , 600 MHz)

Lorem ipsum

 $^{13}\text{C}$  NMR (  $\text{CD}_3\text{SO}$ , 150 MHz)



<sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz)

## 1.6. References

- (1) Martin, S. C.; Minus, M. B.; Ball, Z. T. Chapter One - Chemical Posttranslational Modification with Designed Rhodium(II) Catalysts. In *Methods in Enzymology*; Pecoraro, V. L., Ed.; Peptide, Protein and Enzyme Design; Academic Press, 2016; Vol. 580, pp 1–19.
- (2) Cotton, F. A.; Felthouse, T. R.; Klein, S. Crystal and Molecular Structures of the Bis(triphenylphosphine) and Bis(triphenylphosphite) Adducts of tetrakis(trifluoroacetato)dirhodium(II). *Inorg. Chem.* **1981**, *20* (9), 3037–3042. <https://doi.org/10.1021/ic50223a055>.
- (3) Backes, B. J.; Ellman, J. A. An Alkanesulfonamide “Safety-Catch” Linker for Solid-Phase Synthesis. *J. Org. Chem.* **1999**, *64* (7), 2322–2330. <https://doi.org/10.1021/jo981990y>.
- (4) Kim, D.-K.; Im, G.-J.; Choi, J.-Y. Pyrrolopyrimidinone Derivatives, Process for Preparation Thereof, and Method of Using and Composition Comprising Them. US2005/130983, June 16, 2005.
- (5) Thurber, T. C.; Prince, A.; Halpern, O. An Alternative Synthesis of Tiopinac. *J. Heterocycl. Chem.* **1982**, *19*, 961–965.
- (6) Garst, M. E.; Dolby, L. J.; Esfandiari, S.; MacKenzie, V. R.; Avey, A. A. J.; Muchmore, D. C.; Cooper, G. K.; Malone, T. C. United States Patent Application: 0050038076 - Process for Preparing Isomerically Pure Prodrugs of Proton Pump Inhibitors. 20050038076, A1.
- (7) Minus, M. B.; Liu, W.; Vohidov, F.; Kasembeli, M. M.; Long, X.; Krueger, M. J.; Stevens, A.; Kolosov, M. I.; Twardy, D. J.; Sison, E. A. R.; et al. Rhodium(II) Proximity-Labeling Identifies a Novel Target Site on STAT3 for Inhibitors with Potent Anti-Leukemia Activity. *Angew. Chem. Int. Ed.* **2015**, *54* (44), 13085–13089. <https://doi.org/10.1002/anie.201506889>.
- (8) Xu, F.; Xu, H.; Wang, X.; Zhang, L.; Wen, Q.; Zhang, Y.; Xu, W. Discovery of N-(3-((7H-Purin-6-Yl)thio)-4-Hydroxynaphthalen-1-Yl)-Sulfonamide Derivatives as Novel Protein Kinase and Angiogenesis Inhibitors for the Treatment of Cancer: Synthesis and Biological Evaluation. Part III. *Bioorg. Med. Chem.* **2014**, *22* (4), 1487–1495. <https://doi.org/10.1016/j.bmc.2013.11.052>.
- (9) Mallory, F. B.; Mallory, C. W.; Fedarko, M. C. Substituent Effects on through-Space Fluorine-19-Fluorine-19 Coupling in the 1,8-Difluoronaphthalene System. *J. Am. Chem. Soc.* **1974**, *96* (11), 3536–3542. <https://doi.org/10.1021/ja00818a029>.
- (10) Gege, C.; Steeneck, C.; Kinzel, O.; Kleymann, G.; Hoffmann, T. Carboxamide or Sulfonamide Substituted Thiazoles and Related Derivatives as Modulators for the Orphan Nuclear Receptor Ror[gamma]. WO/2013/178362, December 6, 2013.
- (11) Minus, M. B.; Kang, M. K.; Knudsen, S. E.; Liu, W.; Krueger, M. J.; Smith, M. L.; Redell, M. S.; Ball, Z. T. Assessing the Intracellular Fate of rhodium(II) Complexes. *Chem. Commun.* **2016**, *52* (78), 11685–11688. <https://doi.org/10.1039/C6CC05192H>.

- (12) Nkansah, E.; Shah, R.; Collie, G. W.; Parkinson, G. N.; Palmer, J.; Rahman, K. M.; Bui, T. T.; Drake, A. F.; Husby, J.; Neidle, S.; et al. Observation of Unphosphorylated STAT3 Core Protein Binding to Target dsDNA by PEMSA and X-Ray Crystallography. *FEBS Lett.* **2013**, *587* (7), 833–839. <https://doi.org/10.1016/j.febslet.2013.01.065>.
- (13) Xu, X.; Kasembeli, M. M.; Jiang, X.; Tweardy, B. J.; Tweardy, D. J. Chemical Probes That Competitively and Selectively Inhibit Stat3 Activation. *PLOS ONE* **2009**, *4* (3), e4783. <https://doi.org/10.1371/journal.pone.0004783>.