

On-Demand Generation and Use in Continuous Synthesis of the Ambiphilic Nitrogen Source Chloramine

Kelley E. Danahy¹, Evan D. Styduhar^{1,2}, Aria M. Fodness¹, Laurel M. Heckman^{1,3},
Timothy F. Jamison^{*,1}

¹ Department of Chemistry, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Cambridge MA 01239

² Current address: Incyte Research Institute, 1801 Augustine Cut-off, Wilmington DE 19803

³ Current address: FM Kirby Neurobiology Research Center, Boston Children's Hospital, 300 Longwood Avenue, Boston, MA 02115

tfj@mit.edu

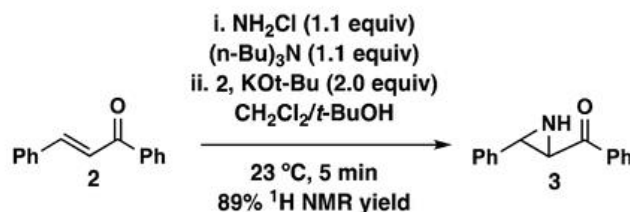
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General Considerations

All reactions were performed with commercial reagents and solvents that were used as received, unless otherwise specified. Reagents and starting materials were purchased from Sigma Aldrich, Alfa Aesar, Combi-Blocks, TCI America, and/or Ark Pharm; solvents were purchased from Fischer or Sigma-Aldrich. Concentration and removal of solvents was performed using a Buchi R-210 rotary evaporator with a dry ice/acetone condenser. Column chromatography was carried out using a prepackaged RediSep High-Performance silica column on a Biotage Isolera One flash chromatography system. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker (400 MHz or 500 MHz) using chloroform-*d* (CDCl₃). Chemical shifts are given in parts per million (ppm) from trimethylsilane (0.00) and measured relative to the solvent signal (¹H NMR: δ 7.26 for CDCl₃, ¹³C NMR: δ 77.16 for CDCl₃). Coupling constants (*J* values) are reported in Hertz (Hz) to the nearest 0.1 Hz. ¹H NMR spectra are given in the following order: multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet), coupling constants, number of protons. ¹³C NMR spectra are reported in terms of chemical shift (at 100 or 126 MHz). HRMS was performed using a Jeol AccuTOF LC-plus 4G mass spectrometer equipped with an ESI source. Melting points were obtained using an EZ-Melt automated melting point system manufactured by Stanford Research Systems. Continuous-flow reactions were carried out in high-purity perfluoroalkoxy (HPFA) tubing, purchased from IDEX Health and Science Technologies. Harvard Apparatus syringe pumps were used to continuously deliver reagents, with either Harvard Apparatus stainless steel syringes or SGE Analytical Science glass syringes. Variable back-pressure regulators were purchased from Zaiput Flow Technologies. For in-line extraction, Pall Zeflur PTFE microfiltration membranes (0.5 μm pore size) were placed inside liquid-liquid separators from Zaiput Flow Technologies. For chloramine generation, reservoirs of bleach and an ammonium hydroxide/ammonium chloride solution were pumped through a Vapourtec E-Series Integrated Flow Chemistry System. The concentration of chloramine was then obtained by iodometric titration against a standardized 0.2 M aqueous sodium thiosulfate solution, typically giving concentrations of 0.16–0.18 M.

Procedure for Batch Aziridine Synthesis

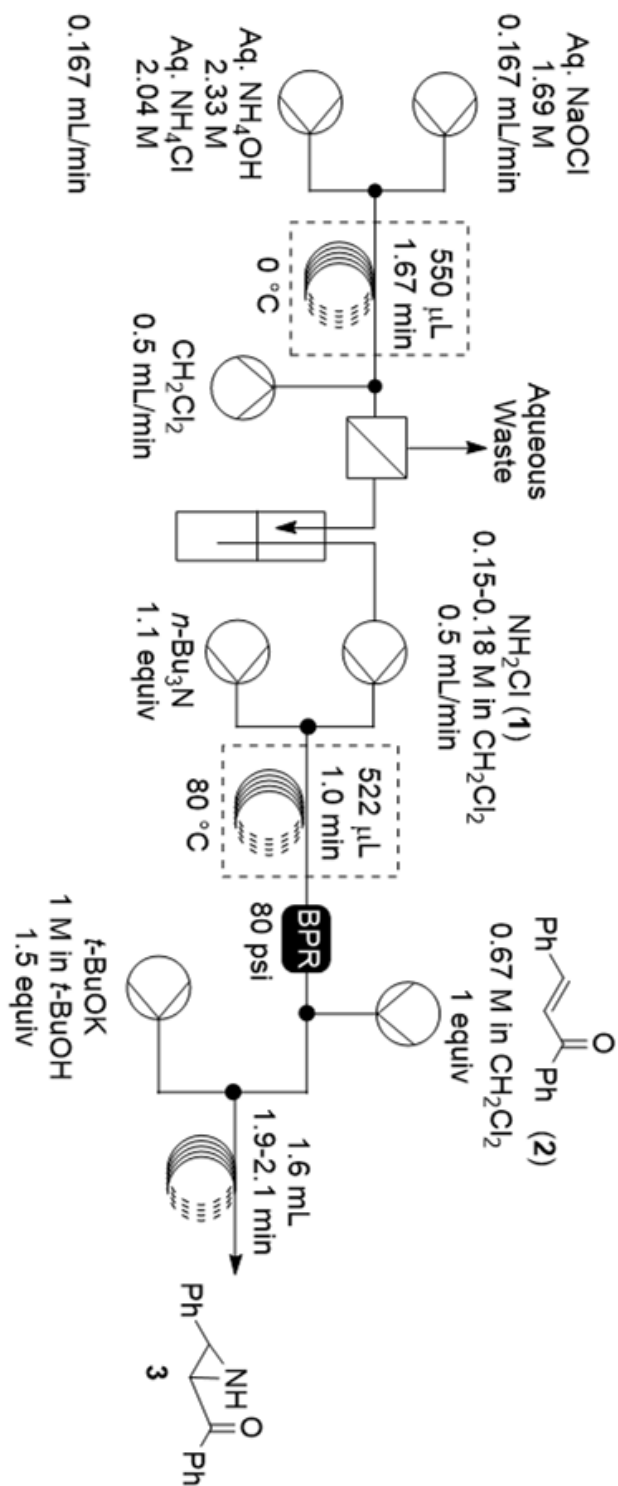


Aziridine 3 To a solution of chloramine prepared in flow as reported in the main text (0.19 M in CH_2Cl_2 , 1 mL, 0.19 mmol, 1.1 equiv) was added tri-*n*-butylamine (42 μL , 0.19 mmol, 1.1 equiv) and allowed to stir at 23 °C. After 30 min, *trans*-chalcone **2** (0.032 g, 0.171 mmol, 1.0 equiv) was added, followed by dropwise addition of potassium *t*-butoxide (1.0 M in *t*-butanol, 285 μL , 0.285 mmol, 2.0 equiv) and allowed to stir at 23 °C. After 3 minutes, the reaction was then quenched with a solution of saturated aqueous NH_4Cl (2 mL). The resulting biphasic mixture was then transferred to a separatory funnel with CH_2Cl_2 (1 mL) and extracted with CH_2Cl_2 (1 x 2 mL), followed by extraction with EtOAc (2 x 2 mL). The organic layers were combined, dried over MgSO_4 , and evaporated under reduced pressure, and the yield of 89% was determined by ^1H NMR analysis with 1,3,5- trimethoxybenzene as an external standard.

Procedure for the Continuous-flow Synthesis of Aziridine 3

Stock Solution Preparation and Reactor Setup: All solutions were prepared in a chemical fume hood. Stock solution **A** was obtained directly from a bottle of 10–15% aqueous sodium hypochlorite, by which the exact concentration of 1.69 M was determined by iodometric titration against a standardized aqueous sodium thiosulfate solution. Based on the concentration of sodium hypochlorite (1.69 M), stock solution **B** was prepared by addition of ammonium hydroxide (1.4 equiv with regard to NaOCl) and ammonium chloride (1.2 equiv with regard to NaOCl) in a dry 250 mL volumetric flask followed by dilution with DI H₂O. Stock solution **F** was prepared by adding chalcone **2** (6.67 mmol) to a 10- mL volumetric flask followed by dilution with DCM. Stock solutions **C**, **E**, and **G** were obtained directly from the reagent bottles.

Procedure: Stock solutions **A** and **B** were separately loaded into 100 mL glass jar reservoirs. Dichloromethane **C** was loaded into a 25 mL SGE glass syringe. Stock solutions **A** and **B** were pumped from a Vapourtec E-Series Integrated Flow Chemistry System at a rate of 167 μ L/min each and combined for a residence time of 1.66 min in **R1** at 0 °C. Dichloromethane (**C**) was pumped from a Harvard Apparatus PhD Ultra syringe pump at a rate of 0.5 mL/min to combine with the outlet of **R1** at 0 °C before entering a membrane-based liquid-liquid separator and the resulting solution of chloramine in CH₂Cl₂ was collected. The system equilibrated for 15 min prior to collecting into a surge 25 mL flask. After collecting for an additional 5 min, the concentration of chloramine was then obtained by iodometric titration against a standardized 0.2 M aqueous sodium thiosulfate solution, giving a concentration of 0.17 M. The organic solution **D** containing NH₂Cl (0.5 mL/min, 0.17 M, 1.1 equiv) was then pumped through the system. Flow rates of solutions **E** (1.1 equiv, 0.1, 0.02 mL/min), **F** (0.67 M, 1.0 equiv, 0.11 mL/min), and **G** (1.0 M, 1.5 equiv, 0.11 mL/min) were calculated by the concentration of chloramine **D** (1.1 equiv). Using the flow rate and concentration of stream **F**, a collection time was calculated that would correspond to 2 mmol of starting chalcone pumped through the system (26 min 15s). The product stream flowed into an aqueous saturated ammonium chloride solution (40 mL). When collection was complete, aqueous saturated brine (20 mL) and DCM (20 mL) were added. The organic layer was extracted. Next, the aqueous was extracted with EtOAc (2 x 30 mL). The crude residue was purified via flash column chromatography on silica gel (0-15% ethyl acetate in hexanes) to afford the desired aziridine.



S1. Continuous-flow scheme for aziridine synthesis.

Procedure for the Continuous-flow Synthesis of Nitriles

Stock Solution Preparation and Reactor Setup: All solutions were prepared in a chemical fume hood. Stock solution **A** was obtained directly from a bottle of 10–15% aqueous sodium hypochlorite, by which the exact concentration was determined by iodometric titration against a standardized aqueous sodium thiosulfate solution. Based on the concentration of sodium hypochlorite, stock solution **B** was prepared by addition of ammonium hydroxide (1.39 equiv with regard to NaOCl) and ammonium chloride (1.21 equiv with regard to NaOCl) in a dry 250 mL volumetric flask followed by dilution with distilled water. Stock solution **F** was prepared by dissolving the desired aldehyde (25 mmol) in 5- mL volumetric flask followed by dilution with DCM. Stock solutions **E** and **G** were obtained directly from the reagent bottles.

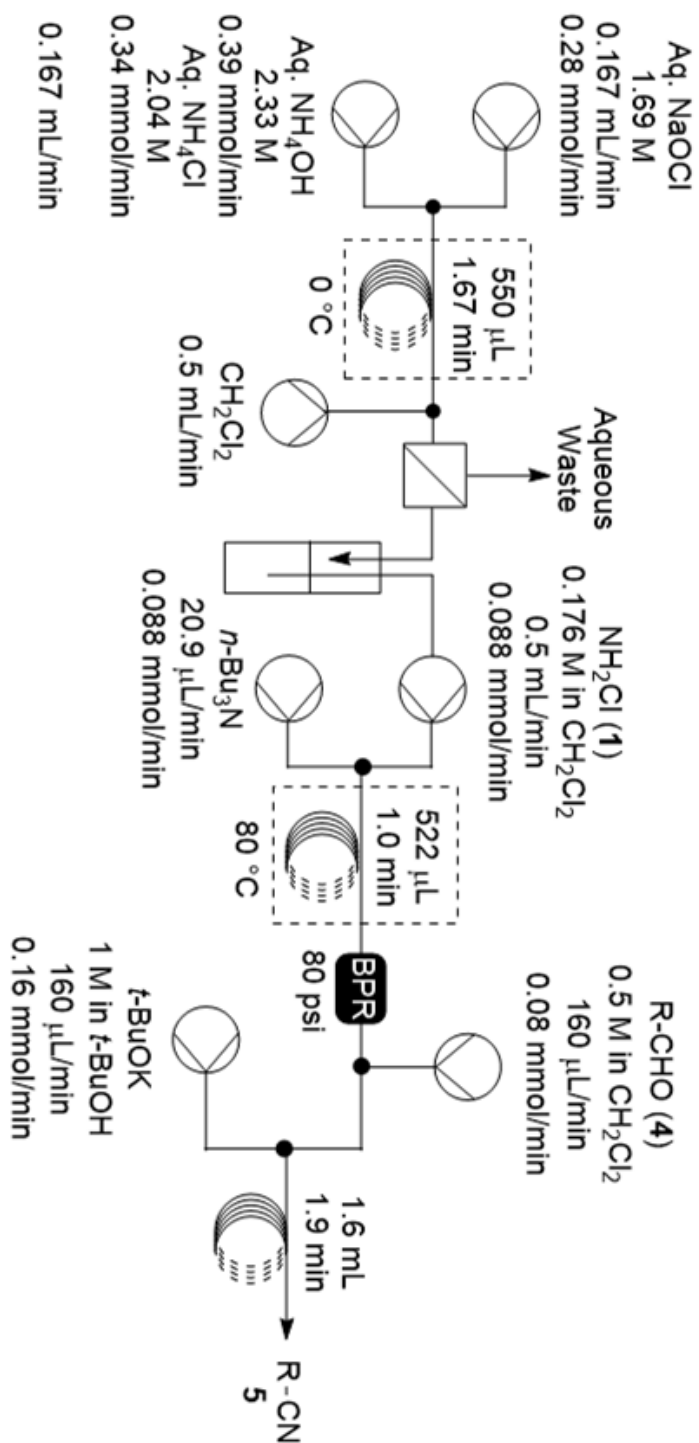
Procedure: Stock solutions **A** and **B** were separately loaded into 100 mL glass jar reservoirs. Dichloromethane (**C**) was loaded into a 25 mL SGE glass syringe. Stock solutions **A** and **B** were pumped from a Vapourtec E-Series Integrated Flow Chemistry System at a rate of 167 $\mu\text{L}/\text{min}$ each and combined for a residence time of 1.66 min in **R1** at 0 °C. Dichloromethane (**C**) was pumped from a Harvard Apparatus PhD Ultra syringe pump at a rate of 500 $\mu\text{L}/\text{min}$ to combine with the outlet of **R1** at 0 °C before entering a membrane-based liquid-liquid separator and the resulting solution of chloramine in CH_2Cl_2 was collected. The concentration of chloramine was then obtained by iodometric titration against a standardized 0.2 M aqueous sodium thiosulfate solution, typically giving concentrations of 0.15–0.18 M. Flow rates of solutions **E** (1.1 equiv), **F** (0.5 M, 1.0 equiv), and **G** (1.0 M, 2.0 equiv) were calculated by the concentration of chloramine (1.1 equiv). Using the flow rate and concentration of stream **F**, a collection time was calculated that would correspond to 2 mmol of starting aldehyde pumped through the system. The product stream flowed into an aqueous saturated ammonium chloride solution (40 mL). When collection was complete, aqueous saturated brine (20 mL) and DCM (20 mL) were added. The organic layer was extracted. Next, the aqueous was extracted with EtOAc (2 x 30 mL). The crude residue was purified via flash column chromatography on silica gel (0-15% ethyl acetate in hexanes) to afford the desired nitrile.

For 4-nitrobenzaldehyde and 1-methylindole-2-carboxyaldehyde, clogging was observed upon addition of KO t -Bu at the Y-mixer of **R3**. Thus, it was replaced with a tube-in-tube reactor and no further clogging was observed.

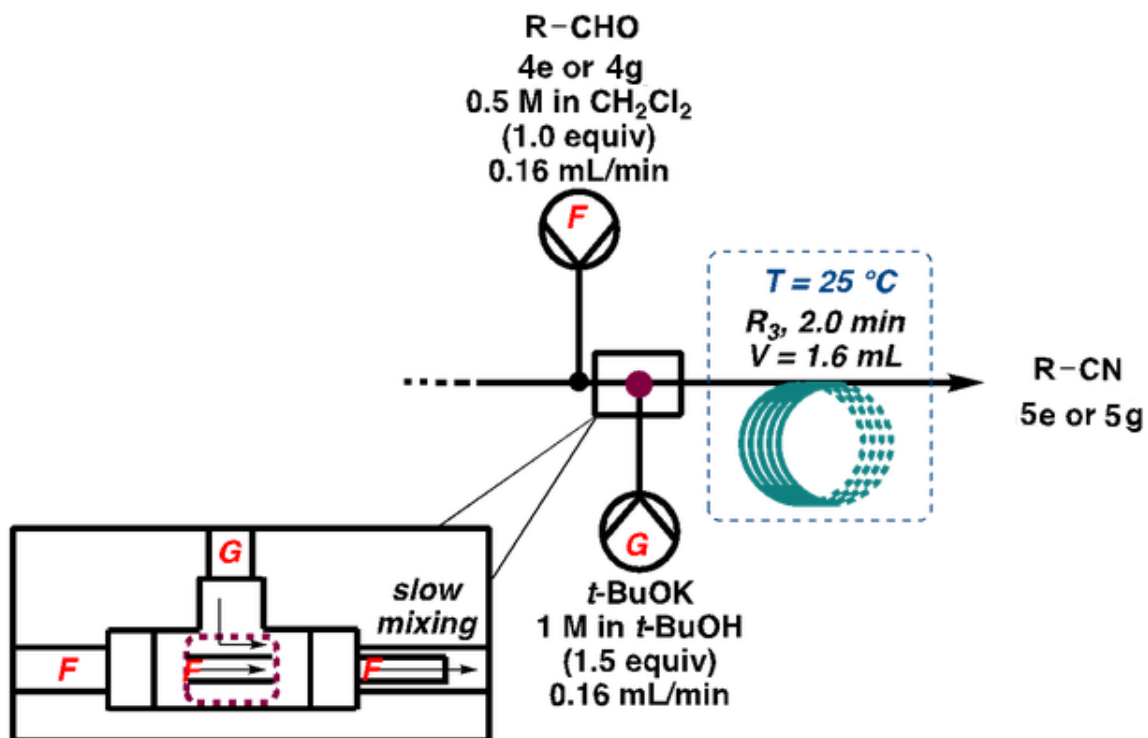
Example Procedure for the Continuous-flow Synthesis of Nitrile 5a

Stock Solution Preparation and Reactor Setup: Stock solution **A** was obtained directly from a bottle of 10–15% aqueous sodium hypochlorite, by which the exact concentration of 1.69 M was determined by iodometric titration against a standardized aqueous sodium thiosulfate solution. Based on the concentration of sodium hypochlorite, stock solution **B** was prepared by addition of ammonium hydroxide (0.583 mol, from aqueous solution) and ammonium chloride (0.51 mol, 27.28 g) in a dry 250 mL volumetric flask followed by dilution with distilled water to 250 mL to provide a solution 2.33 M in ammonium hydroxide (1.39 equiv with regard to NaOCl) and 2.04 M in ammonium chloride (1.21 equiv with regard to NaOCl). A 0.5 M solution of cinnamaldehyde was prepared by dissolving cinnamaldehyde (**4a**) (3.15 mL, 25 mmol) in a 5-mL volumetric flask followed by dilution with DCM to 5 mL.

Procedure: Stock solutions **A** and **B** were separately loaded into 100 mL glass jar reservoirs. Dichloromethane (**C**) was loaded into a 25 mL SGE glass syringe. Stock solutions **A** and **B** were pumped from a Vapourtec E-Series Integrated Flow Chemistry System at a rate of 167 $\mu\text{L}/\text{min}$ each and combined for a residence time of 1.66 min in **R1** at 0 °C. Dichloromethane (**C**) was pumped from a Harvard Apparatus PhD Ultra syringe pump at a rate of 500 $\mu\text{L}/\text{min}$ to combine with the outlet of **R1** at 0 °C before entering a membrane-based liquid-liquid separator and the resulting solution of chloramine in CH_2Cl_2 was collected in a surge tank. The concentration of chloramine was then obtained by iodometric titration against a standardized 0.2 M aqueous sodium thiosulfate solution, giving a concentration of 0.176 M. This chloramine solution was pumped at a rate of 0.5 mL/min (0.088 mmol/min, 1.1 equiv), and *n*-Bu₃N was flowed at 20.9 $\mu\text{L}/\text{min}$ (0.088 mmol/min, 1.1 equiv), and they were combined for a residence time of 1 minute in **R2** at 80 °C. The outlet of **R2** was connected to a BPR set to 80 PSI, which is connected to **R3**. Cinnamaldehyde (0.5 M in DCM) was flowed at 160 $\mu\text{L}/\text{min}$ (0.080 mmol/min, 1 equiv wrt chloramine), and *t*-BuOK (1 M in *t*-BuOH) was flowed at 160 $\mu\text{L}/\text{min}$ (0.160 mmol/min, 2 equiv wrt chloramine), into **R3**, where they combined for a residence time of 1 minute 54 seconds (1.9 minutes) at room temperature. The output of **R3** was then flowed into an aqueous saturated ammonium chloride solution (40 mL) for 25 minutes. The collection time of 25 minutes was calculated based on the time taken to allow 2 mmol of aldehyde to have been reacted and flowed through the system, based on the molar flow rate of cinnamaldehyde of 0.08 mmol/min. When collection was complete, aqueous saturated brine (20 mL) and DCM (20 mL) were added. The organic layer was extracted. Next, the aqueous was extracted with EtOAc (2 x 30 mL). The crude residue was purified via flash column chromatography on silica gel (0-15% ethyl acetate in hexanes) to afford cinnamonitrile (**5a**) in 94% yield.

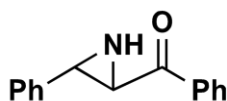


S2. Representative continuous-flow setup for nitrile synthesis.



S3. Tube-in-tube mixer for aldehydes **4e** and **4g** prevented clogging. The inner diameter of the outer tube was 0.093" and the inner diameter of the inner tube was 0.03".

Characterization of Aziridine and Nitrile Products

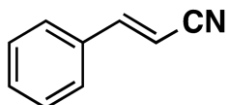


2-Benzoyl-3-Phenylaziridine (3)

The titled compound was prepared via the previously described procedure for the continuous-flow synthesis of aziridine and purified via flash chromatography on SiO₂ (ethyl acetate/hexanes, 0%→15% gradient elution) to yield **3** as a white solid (332 mg, 1.49 mmol, 74% yield).

¹H NMR (400 MHz, CDCl₃) δ 8.03 – 7.97 (m, 2H), 7.64 – 7.58 (m, 1H), 7.52 – 7.45 (m, 2H), 7.42 – 7.29 (m, 5H), 3.52 (dd, J = 8.0, 2.1 Hz, 1H), 3.19 (dd, J = 9.3, 2.0 Hz, 1H), 2.73 – 2.64 (m, 1H) ppm; **¹³C NMR (100 MHz, CDCl₃)** δ 195.8, 138.5, 136.0, 133.9, 128.9, 128.6, 128.4, 128.0, 126.3, 44.2, 43.6 ppm.

The ¹H and ¹³C NMR spectra are in agreement with those reported in the literature.¹

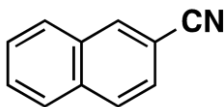


Cinnamitrile (5a)

The titled compound was prepared via the previously described example procedure for the continuous-flow synthesis of nitriles and purified via flash chromatography on SiO₂ (ethyl acetate/hexanes, 0%→15% gradient elution) to yield **5a** as a colorless oil (243 mg, 1.88 mmol, 94% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.51 – 7.32 (m, 6H), 5.87 (d, J = 16.6 Hz, 1H) ppm; **¹³C NMR (100 MHz, CDCl₃)** δ 150.6, 133.5, 131.3, 129.1, 127.4, 118.2, 96.4 ppm.

The ¹H and ¹³C NMR spectra are in agreement with those reported in the literature.²



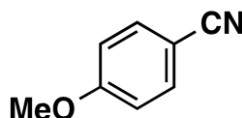
Naphthalene-2-carbonitrile (5b)

The titled compound was prepared via the previously described procedure for the continuous-flow synthesis of nitriles and purified via flash chromatography on SiO₂ (ethyl

acetate/hexanes, 0%→15% gradient elution) to yield **5b** as a white solid (303 mg, 1.98 mmol, 99% yield).

¹H NMR (400 MHz, CDCl₃) δ 8.23 (s, 1H), 7.94 – 7.86 (m, 3H), 7.70 – 7.55 (m, 3H) ppm;
¹³C NMR (100 MHz, CDCl₃) δ 134.6, 134.1, 132.2, 129.2, 129.1, 128.4, 128.1, 127.7, 126.3, 119.3, 109.3 ppm.

The ¹H and ¹³C NMR spectra are in agreement with those reported in the literature.³

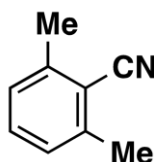


4-Methoxybenzonitrile (**5c**)

The titled compound was prepared via the previously described procedure for the continuous-flow synthesis of nitriles and purified via flash chromatography on SiO₂ (ethyl acetate/hexanes, 0%→15% gradient elution) to yield **5c** as a white solid (239 mg, 1.80 mmol, 90% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.61 – 7.53 (m, 2H), 6.96 – 6.90 (m, 2H), 3.84 (s, 3H) ppm;
¹³C NMR (100 MHz, CDCl₃) δ 162.9, 134.0, 119.3, 114.8, 104.0, 55.6 ppm.

The ¹H and ¹³C NMR spectra are in agreement with those reported in the literature.³

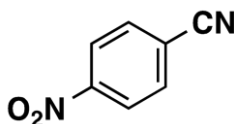


2,6-Dimethylbenzonitrile (**5d**)

The titled compound was prepared via the previously described procedure for the continuous-flow synthesis of nitriles and purified via flash chromatography on SiO₂ (ethyl acetate/hexanes, 0%→15% gradient elution) to yield **5d** as a white solid (185 mg, 1.41 mmol, 71% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.34 (t, *J* = 7.7 Hz, 1H), 7.11 (d, *J* = 7.7 Hz, 2H), 2.52 (s, 6H) ppm; **¹³C NMR (100 MHz, CDCl₃)** δ 142.2, 132.2, 127.4, 117.4, 113.4, 20.9 ppm.

The ¹H and ¹³C NMR spectra are in agreement with those reported in the literature.⁴

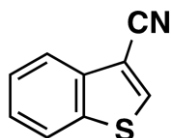


4-Nitrobenzonitrile (5e)

The titled compound was prepared via the previously described procedure for the continuous-flow synthesis of nitriles, required a tube-in-tube mixer, and was purified via flash chromatography on SiO₂ (ethyl acetate/hexanes, 0%→15% gradient elution) to yield **5e** as a white solid (272 mg, 1.84 mmol, 92%).

¹H NMR (400 MHz, CDCl₃) δ 8.35 (d, J = 8.8 Hz, 1H), 7.89 (d, J = 8.8 Hz, 1H) ppm; **¹³C NMR (100 MHz, CDCl₃)** δ 150.1, 133.6, 124.4, 118.4, 116.9 ppm.

The ¹H and ¹³C NMR spectra are in agreement with those reported in the literature.²

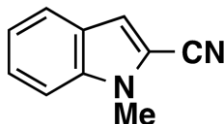


Benzo[b]thiophene-2-carbonitrile (5f)

The titled compound was prepared via the previously described procedure for the continuous-flow synthesis of nitriles and purified via flash chromatography on SiO₂ (ethyl acetate/hexanes, 0%→15% gradient elution) to yield **5f** as a colorless oil (256 mg, 1.61 mmol, 80% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.96 – 7.82 (m, 3H), 7.57 – 7.45 (m, 2H) ppm; **¹³C NMR (100 MHz, CDCl₃)** δ 141.1, 137.3, 134.9, 127.8, 125.6, 125.2, 122.2, 114.4, 109.4 ppm.

The ¹H and ¹³C NMR spectra are in agreement with those reported in the literature.⁵

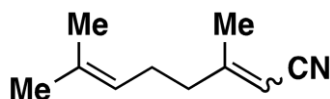


1-Methylindole-2-carbonitrile (5g)

The titled compound was prepared via the previously described procedure for the continuous-flow synthesis of nitriles, required a tube-in-tube mixer, and was purified via flash chromatography on SiO₂ (ethyl acetate/hexanes, 0%→15% gradient elution) to yield **5g** as a white solid (284 mg, 1.82 mmol, 91%).

¹H NMR (400 MHz, CDCl₃) δ 7.67 (d, J = 8.1 Hz, 1H), 7.42 (t, J = 7.7 Hz, 1H), 7.33 (d, J = 8.4 Hz, 1H), 7.23 (t, J = 7.5 Hz, 1H), 7.13 (s, 1H), 3.85 (s, 3H) ppm; **¹³C NMR (100 MHz, CDCl₃)** δ 137.9, 126.1, 125.8, 122.3, 121.4, 113.6, 112.6, 110.2, 110.1, 31.4 ppm.

The ¹H and ¹³C NMR spectra are in agreement with those reported in the literature.³



Geranonitrile (**5h**)

The titled compound was prepared via the previously described procedure for the continuous-flow synthesis of nitriles and purified via flash chromatography on SiO₂ (ethyl acetate/hexanes, 0%→15% gradient elution) to yield **5h** as a colorless oil (217 mg, 1.45 mmol, 73%, *E/Z* = 1.2:1).

¹H NMR (400 MHz, CDCl₃) δ 5.08 (s, 3.2H), 5.00 (t, *J* = 5.8 Hz, 1.2H), 2.40 (t, *J* = 7.6 Hz, 2H), 2.23 – 2.09 (m, 6.8H), 2.02 (s, 3.6H), 1.88 (s, 3H), 1.66 (s, 6.6H), 1.59 (d, *J* = 7.5 Hz, 6.6H) ppm; **¹³C NMR (100 MHz, CDCl₃)** δ 165.1, 165.0, 133.3, 133.2, 122.3, 122.2, 117.3, 117.0, 95.9, 95.3, 38.6, 36.3, 26.2, 25.68, 25.67, 25.65, 22.9, 21.0, 17.7, 17.9 ppm.

The ¹H and ¹³C NMR spectra are in agreement with those reported in the literature.⁶

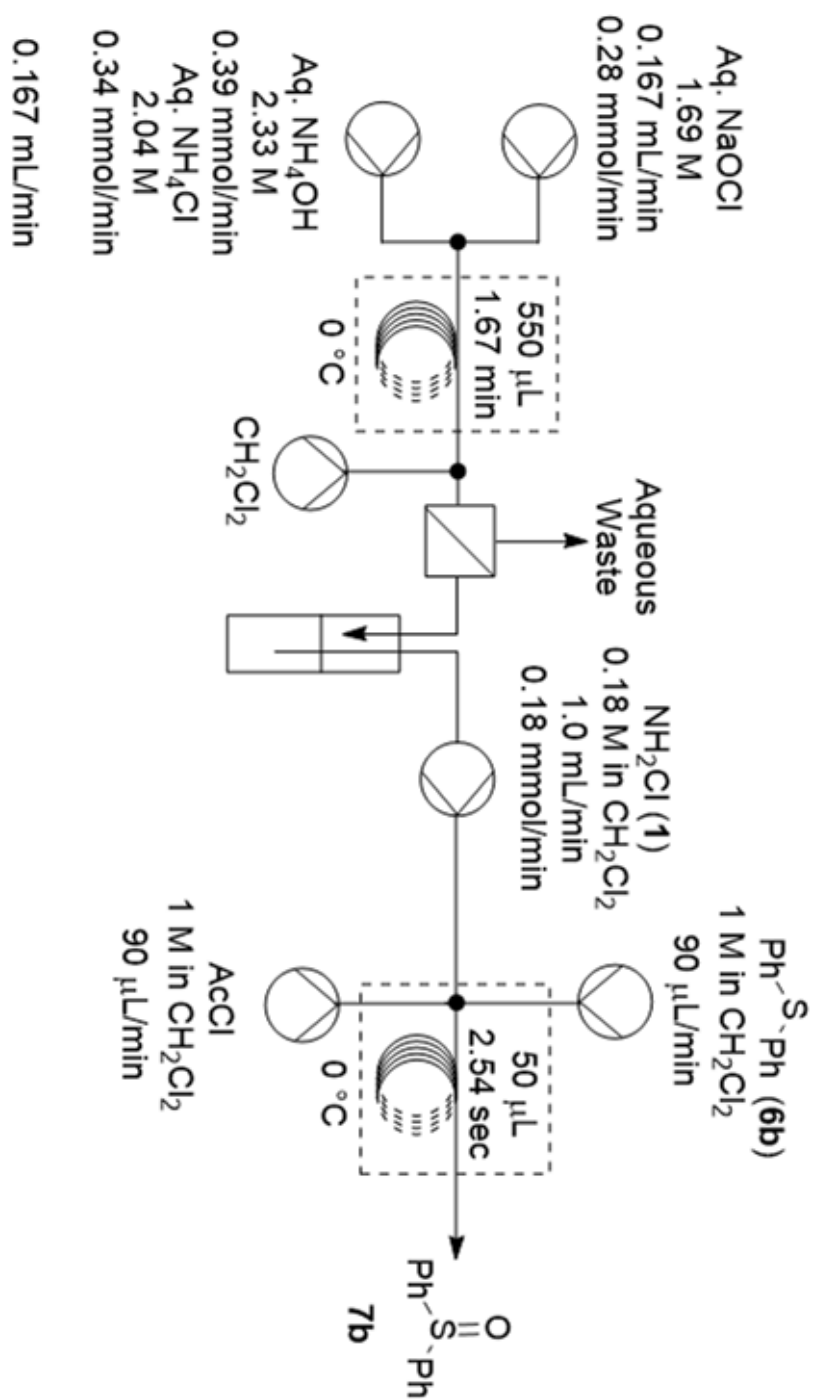
Procedure for the Continuous-flow Synthesis of Sulfoxides:

Stock solution preparation: Stock solution **A** was obtained from a bottle of 10–15% aqueous sodium hypochlorite, by which the exact concentration was determined by iodometric titration against a standardized aqueous sodium thiosulfate solution. Based on the concentration of sodium hypochlorite, stock solution **B** was prepared by addition of ammonium hydroxide (1.39 equiv with regard to NaOCl) and ammonium chloride (1.21 equiv with regard to NaOCl) in a dry 250 mL volumetric flask followed by dilution with distilled water. For stock solution **E**, a 2 mL volumetric flask was charged with 2 mmol of the desired commercially available thioether, with the exception of **6c**, which was obtained as a gift from Dr. Bryan Ingoglia of the Buchwald group and matched previously reported spectra.⁷ Dichloromethane was added to reach a volume of 2 mL. For stock solution **F**, 143 mL (2 mmol) of acetyl chloride were dissolved in dichloromethane up to 2 mL using a volumetric flask.

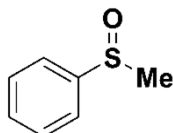
Procedure: Stock solutions **A** and **B** were separately loaded into glass jar reservoirs. Dichloromethane (**C**) was loaded into a 25 mL SGE glass syringe. Stock solutions **A** and **B** were pumped from a Vapourtec E-Series Integrated Flow Chemistry System at a rate of 167 $\mu\text{L}/\text{min}$ each and combined for a residence time of 1.66 min in **R1** at 0 °C. Dichloromethane (**C**) was pumped from a Harvard Apparatus PhD Ultra syringe pump at a rate of 500 $\mu\text{L}/\text{min}$ to combine with the outlet of **R1** at 0 °C before entering a membrane-based liquid-liquid separator. The resulting solution of chloramine in CH_2Cl_2 was collected. The concentration of chloramine was then obtained by iodometric titration against a standardized 0.2 M aqueous sodium thiosulfate solution, typically giving concentrations of 0.15–0.18 M. Flow rates of solutions **E** (1 M, 1 equiv) and **F** (1 M, 1 equiv) were calculated by the concentration

of chloramine (2 equiv). A collection time was calculated that would correspond to 1 mmol of starting thioether pumped into the system. Before collection, ten seconds were allowed to pass for equilibration. The heterogeneous product stream flowed into an Erlenmeyer flask filled with methanol as a mild quench (10 mL).

The solution was evaporated on a rotary evaporator, and the sulfoxide re-suspended in dichloromethane. The suspension was transferred to a separatory funnel, and washed with saturated aqueous sodium bicarbonate. The organic layer was dried over sodium sulfate, filtered, and the dichloromethane evaporated. The crude sulfoxide was then purified via column chromatography with ethyl acetate and hexanes, using a RediSep High-Performance silica column on a Biotage Isolera One flash chromatography system.



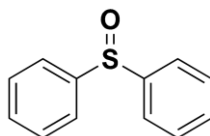
S4. Representative continuous-flow setup for sulfoxide synthesis



(Methylsulfinyl)benzene (7a): The titled compound was prepared via the previously described procedure for the continuous-flow synthesis of sulfoxides and was purified via flash chromatography on SiO₂ (ethyl acetate/hexanes, 25%→100% gradient elution) to yield **7a** as a yellow oil (90 mg, 0.64 mmol, 64% yield).

¹H NMR (500MHz, CDCl₃) δ: 7.65 (dd, *J* = 8.1, *J* = 1.6 Hz, 2H), 7.56 – 7.47 (m, 3H), 2.72 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ: 131.2, 129.5, 123.6, 44.1.

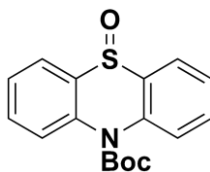
The ¹H and ¹³C NMR spectra are in agreement with those reported in the literature.⁸



Sulfinyldibenzene (7b): 62%, The titled compound was prepared via the previously described procedure for the continuous-flow synthesis of sulfoxides and was purified via flash chromatography on SiO₂ (ethyl acetate/hexanes, 25%→100% gradient elution) to yield **7b** as an off-white solid (126 mg, 0.62 mmol, 62% yield).

¹H NMR (500MHz, CDCl₃) δ: 7.65 (dd, *J* = 7.9, *J* = 1.7 Hz, 1H), 7.51 – 7.39 (m, 2H); ¹³C NMR (126 MHz, CDCl₃) δ: 131.2, 129.5, 124.9.

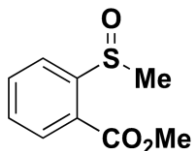
The ¹H and ¹³C NMR spectra are in agreement with those reported in the literature.⁹



tert-Butyl 10H-phenothiazine-10-carboxylate 5-oxide (7c): The titled compound was prepared via the previously described procedure for the continuous-flow synthesis of sulfoxides and was purified via flash chromatography on SiO₂ (ethyl acetate/hexanes, 15%→100% gradient elution) to yield **7c** as an off-white solid (145 mg, 0.46 mmol, 46%) with a melting point of 162.7–163.9 °C.

¹H NMR (400MHz, CDCl₃) δ: 7.84 (dd, *J* = 7.6, *J* = 1.7 Hz, 2H), 7.74 (dd, *J* = 7.9, 1.3 Hz, 2H), 7.46 (ddd, *J* = 14.8, *J* = 7.7, *J* = 1.5 Hz, 4H), 1.54 (s, 9H); ¹³C NMR (126 MHz, CDCl₃) δ: 151.5, 138.8, 133.5, 130.2, 126.9, 126.4, 124.2, 83.6, 28.3; HRMS (ESI-TOF) [*M* + *H*]⁺ *m/z*: Calcd for (C₁₇H₁₇NO₃S) 316.1002; Found 316.1019.

The ¹H and ¹³C NMR spectra are in agreement with those reported in the literature.¹⁰



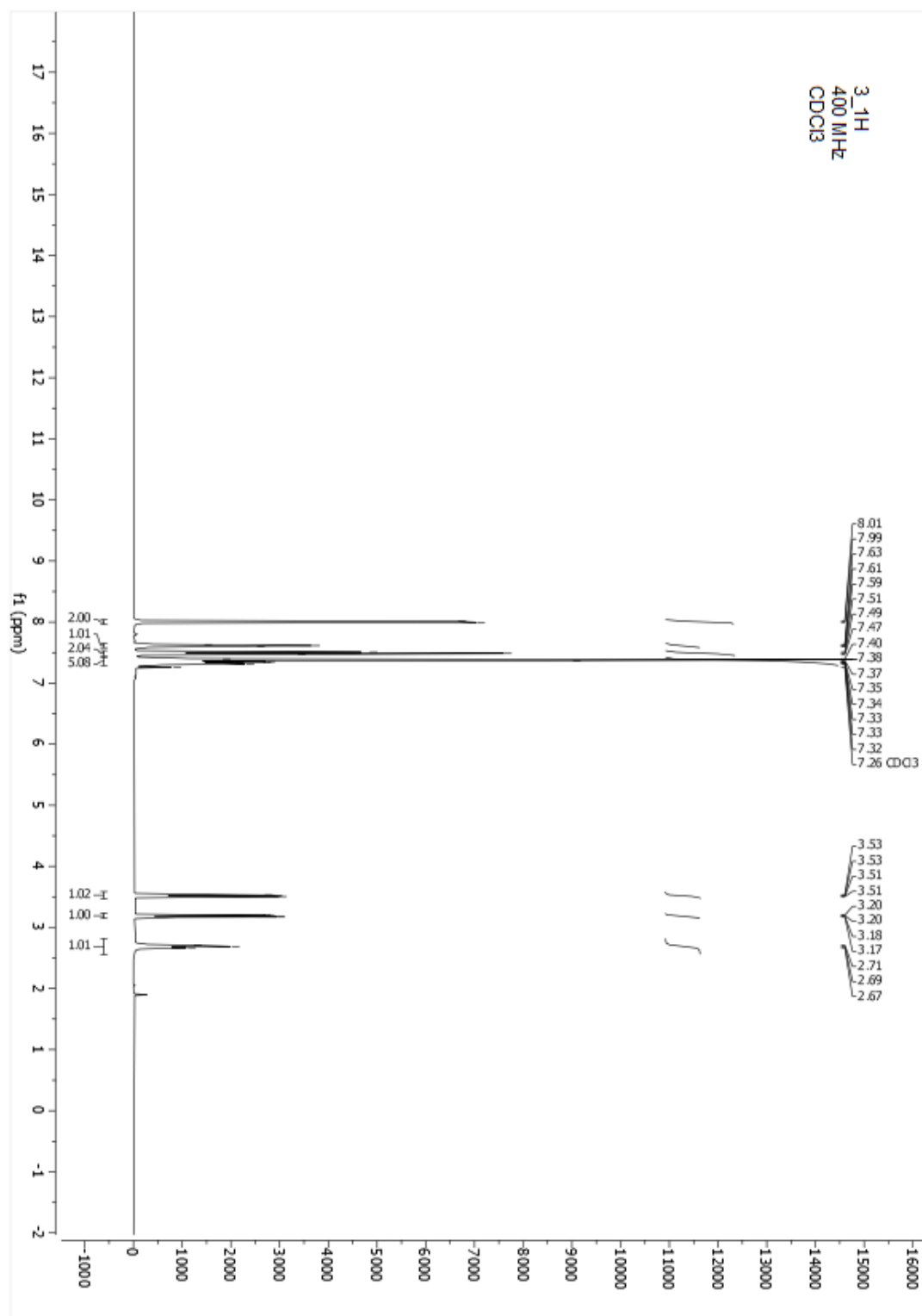
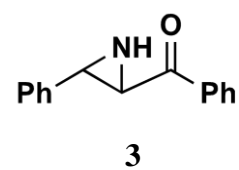
Methyl 2-(methylsulfinyl)benzoate (7d): The titled compound was prepared via the previously described procedure for the continuous-flow synthesis of sulfoxides and was purified via flash chromatography on SiO₂ (ethyl acetate/hexanes, 25%→100% gradient elution) to yield **7d** as a clear oil (73 mg, 0.37 mmol, 37%). Mass balance was a mixture of products resulting from reaction between the preformed sulfilimines and the adjacent methyl ester.

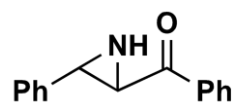
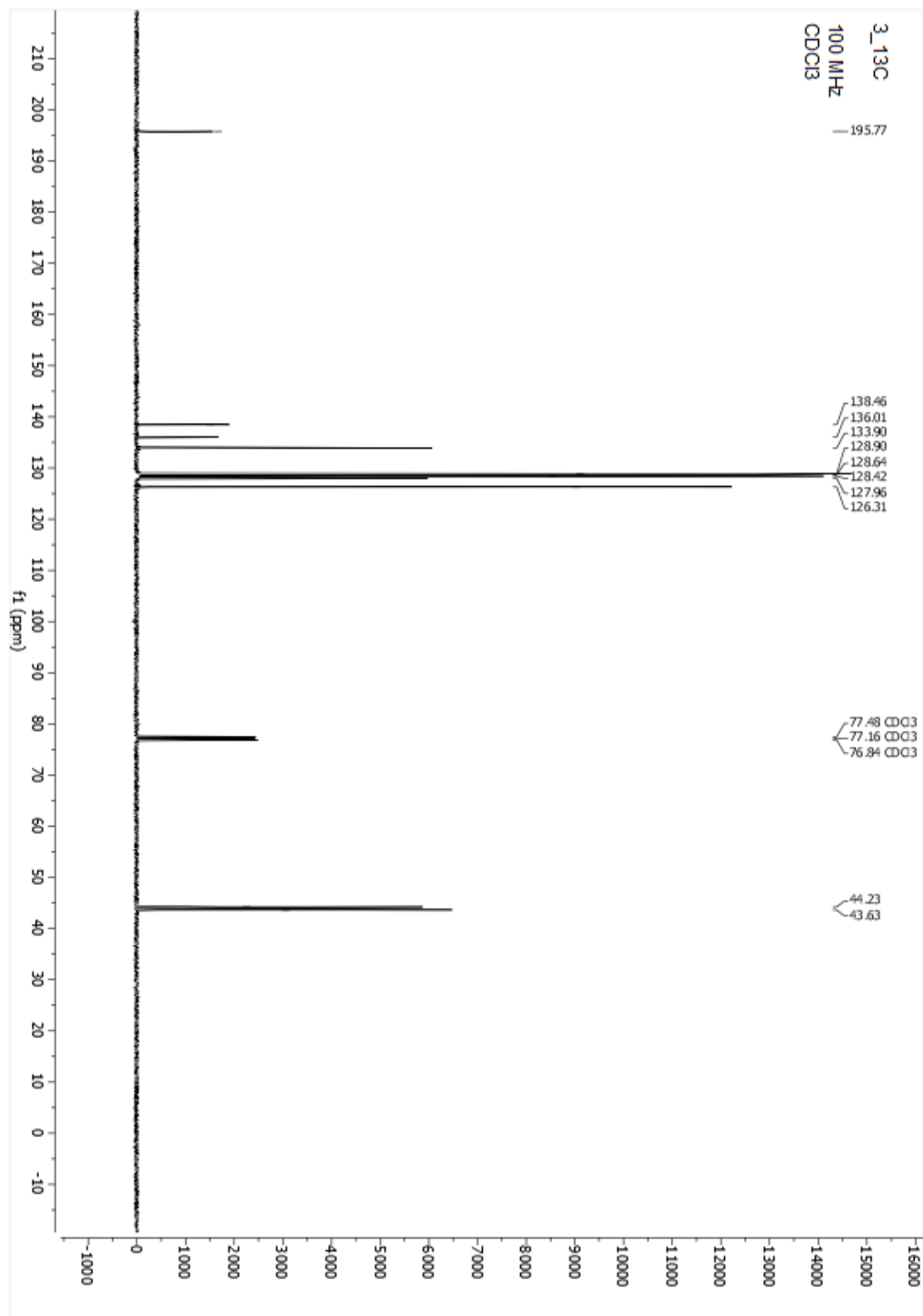
¹H NMR (400MHz, CDCl₃) δ : 8.32 (dd, $J = 8.0$ Hz, $J = 1.2$ Hz, 1H), 8.09 (dd, $J = 7.7$ Hz, $J = 1.3$ Hz, 1H), 7.83 (d, $J = 1.3$ Hz, 1H), 7.58 (dd, $J = 7.5$ Hz, $J = 1.3$ Hz, 1H), 3.95 (s, 3H), 2.85 (s, 3H); **¹³C NMR (125MHz, CDCl₃)** δ : 165.9, 150.6, 134.3, 130.9, 130.3, 126.6, 124.3, 52.8, 44.2.

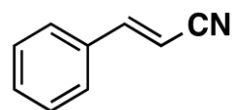
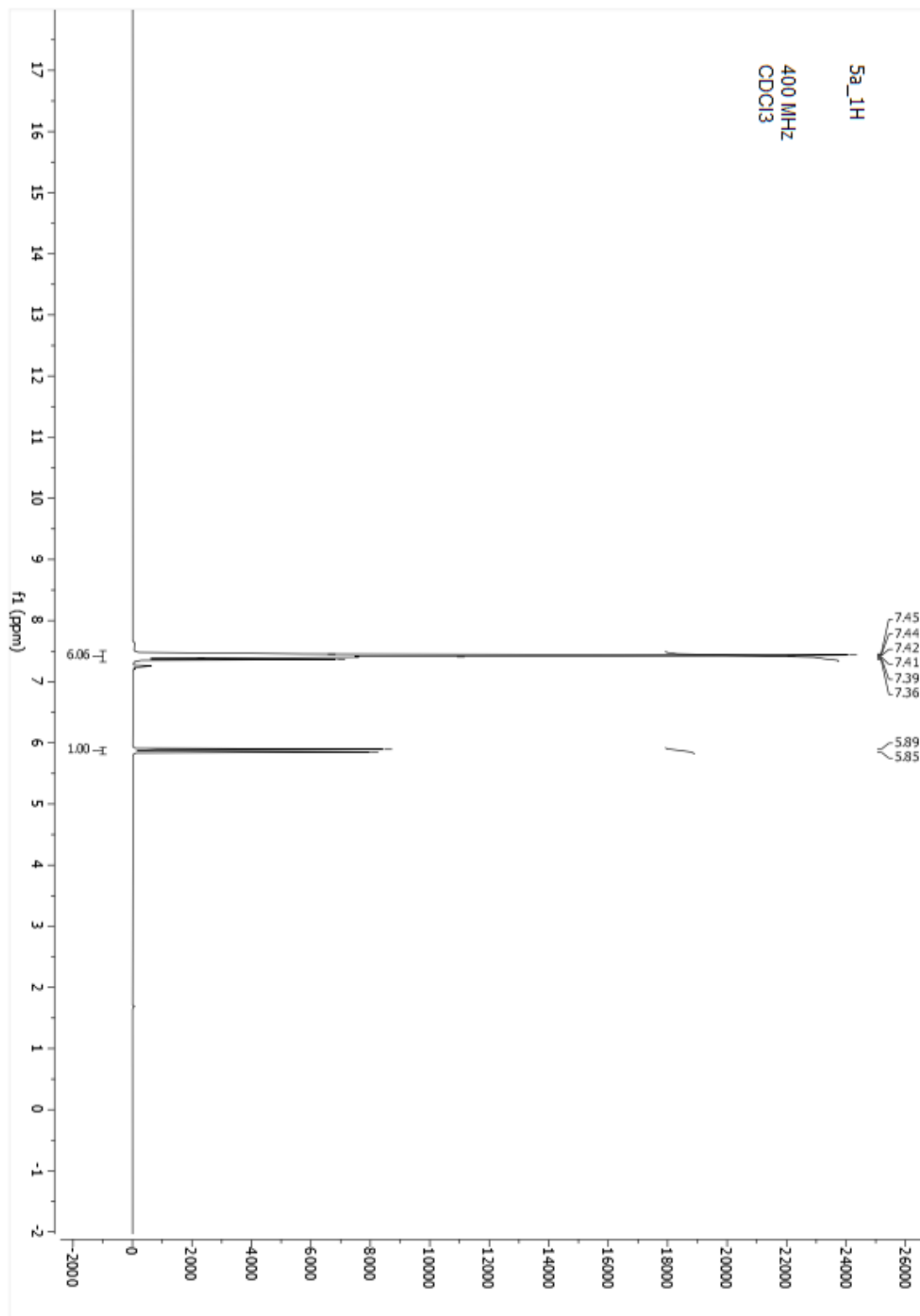
The ¹H and ¹³C NMR spectra are in agreement with those reported in the literature.¹¹

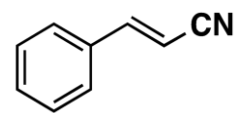
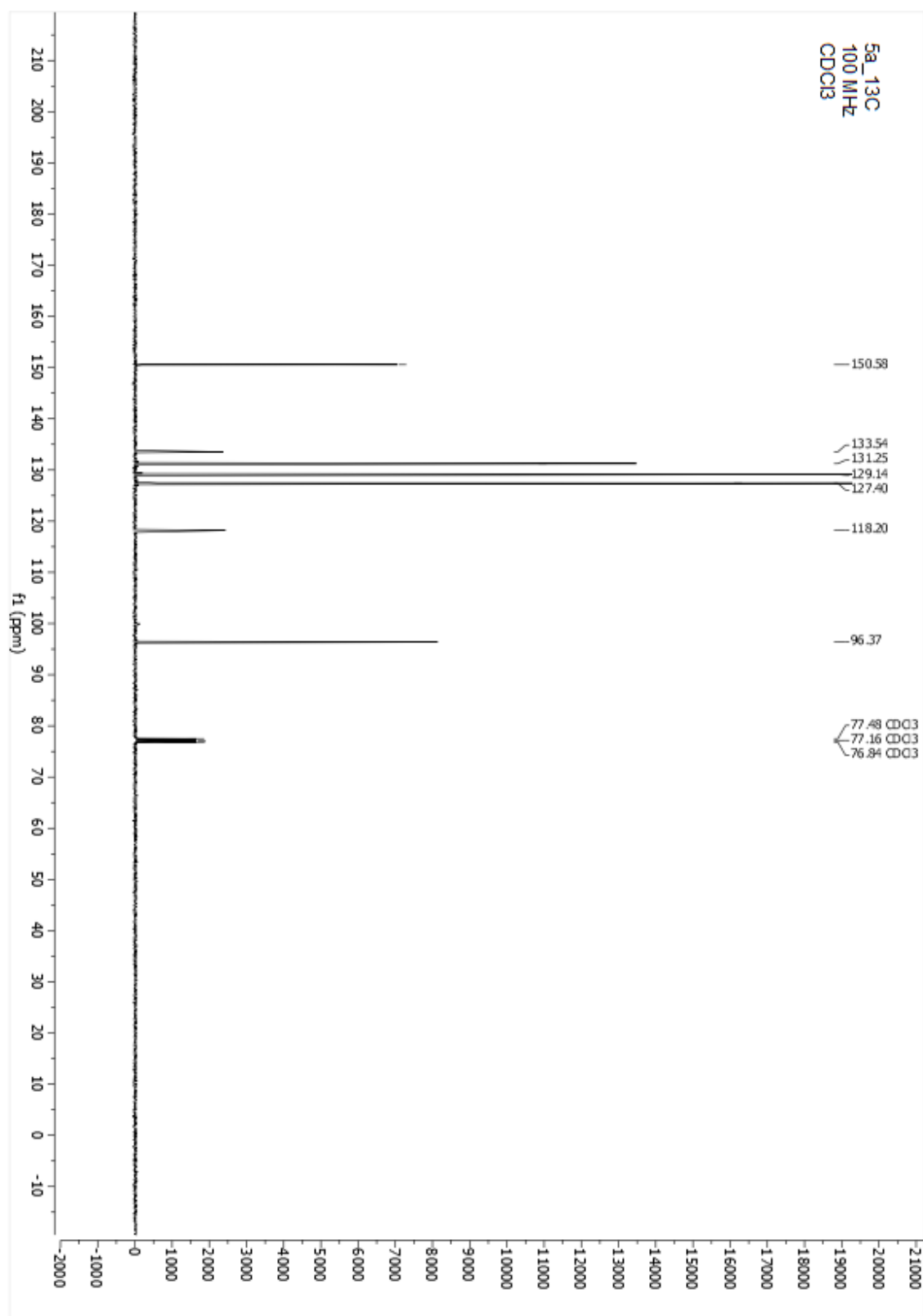
References

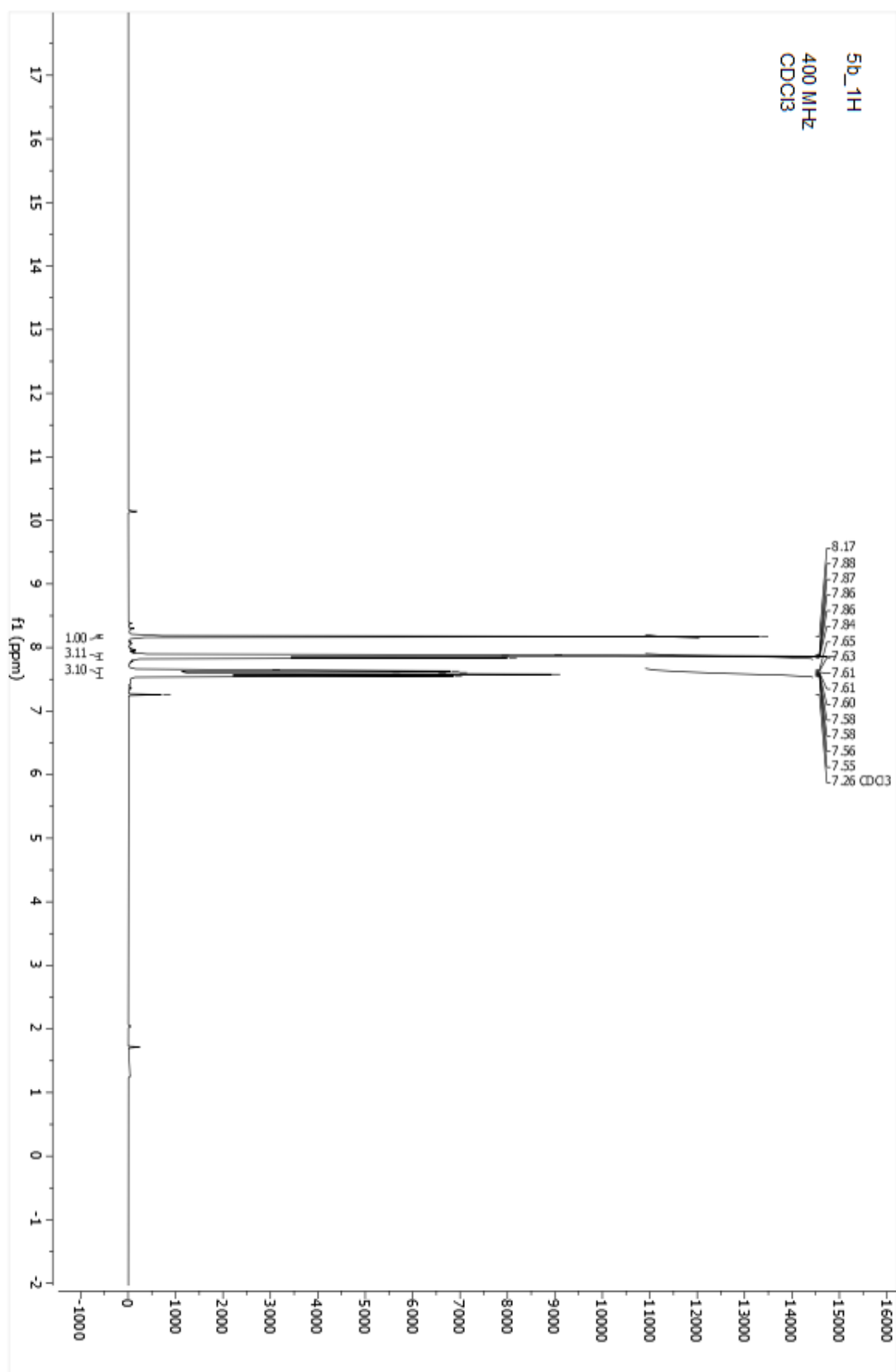
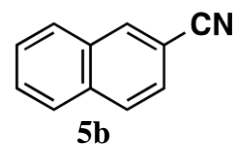
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^1H and ^{13}C SpectraS5. ^1H NMR spectrum of **3**.

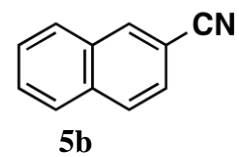
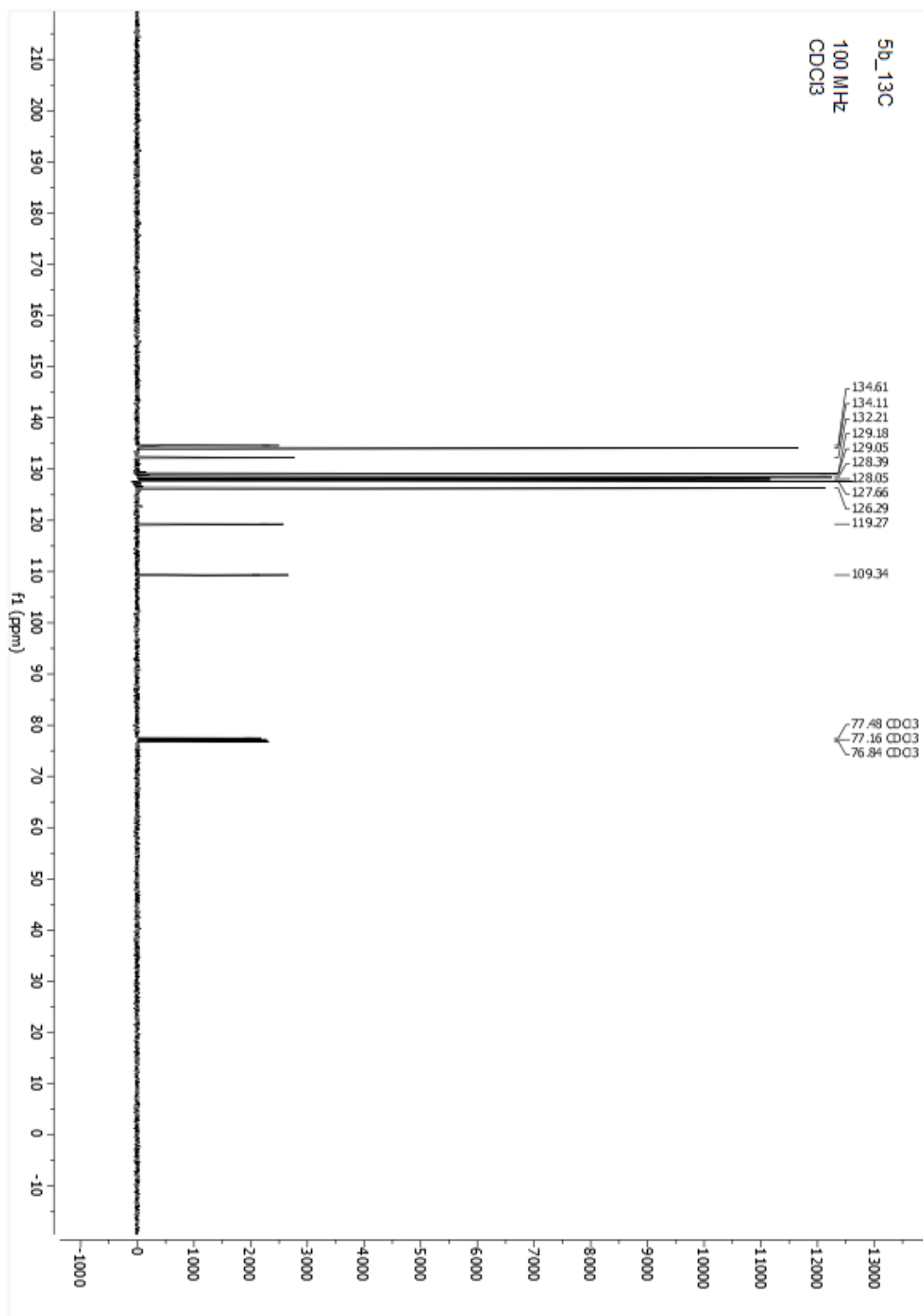
**3****S6.** ¹³C NMR spectrum of **3**.

**5a****S7.** ¹H NMR Spectrum of **5a**.

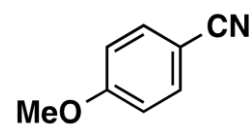
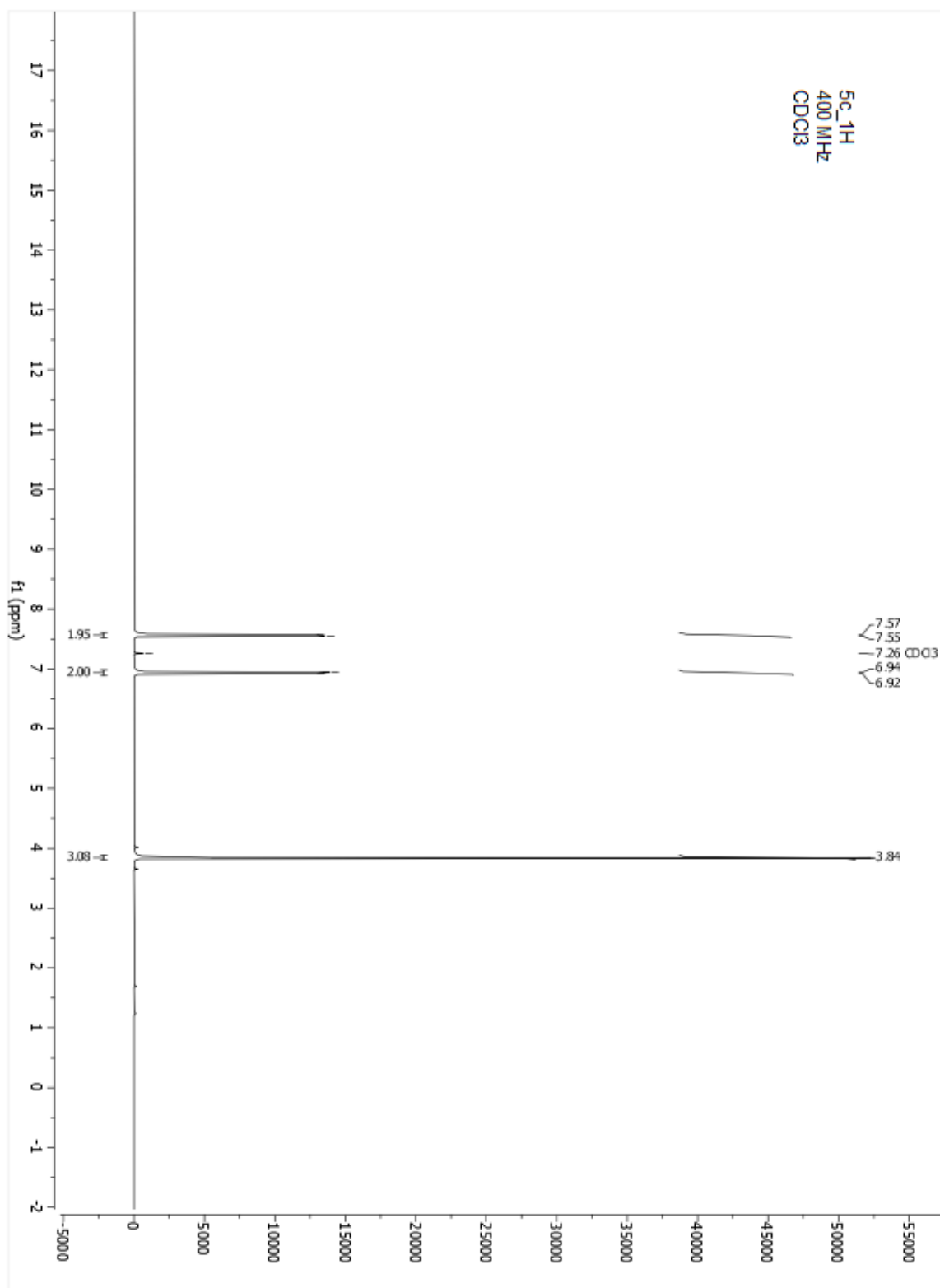
**5a****S8.** ¹³C NMR Spectrum of **5a**.

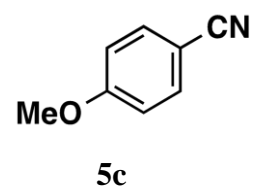
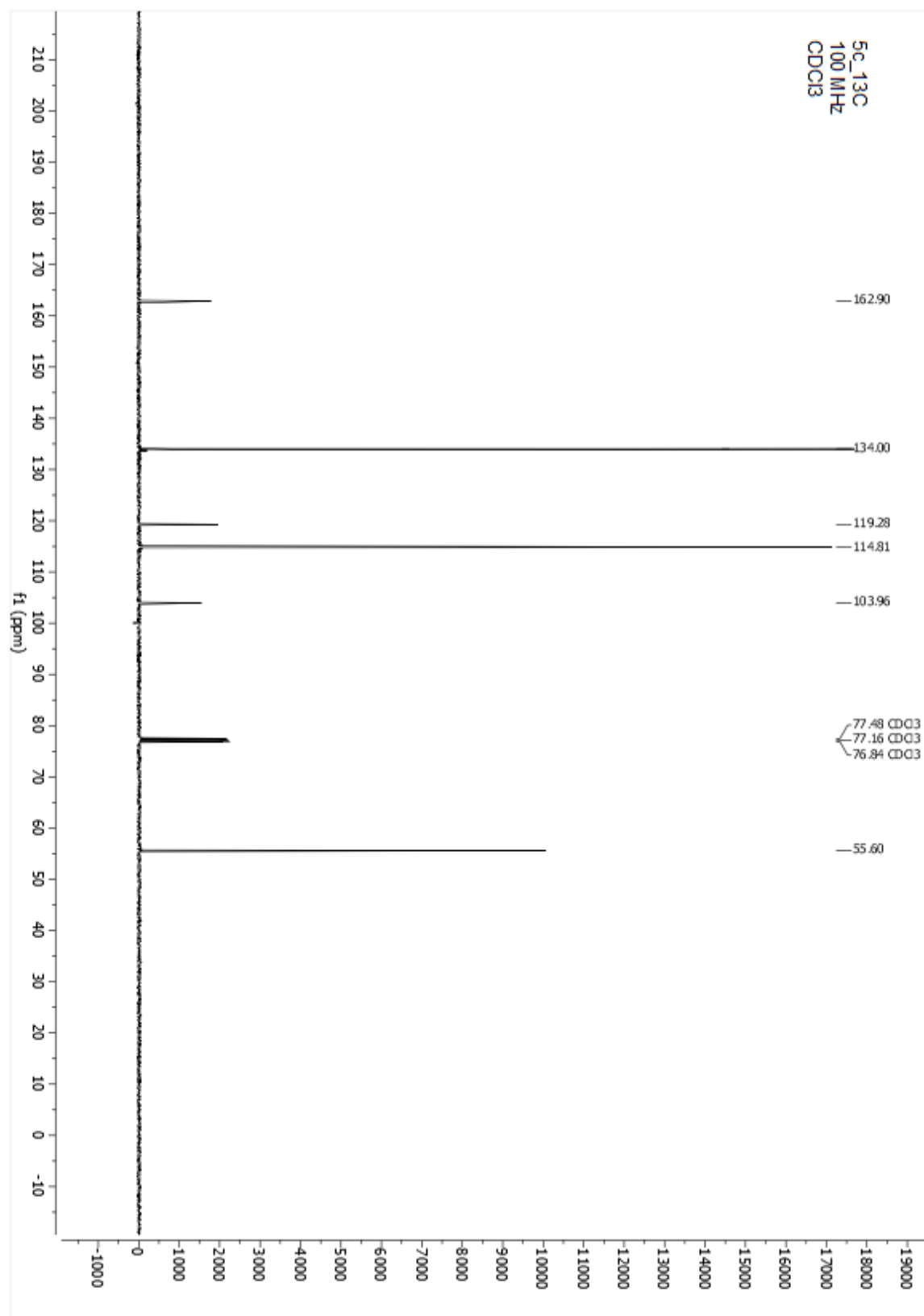


S9. ¹H NMR Spectrum of **5b**.

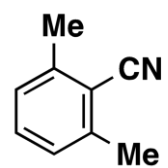
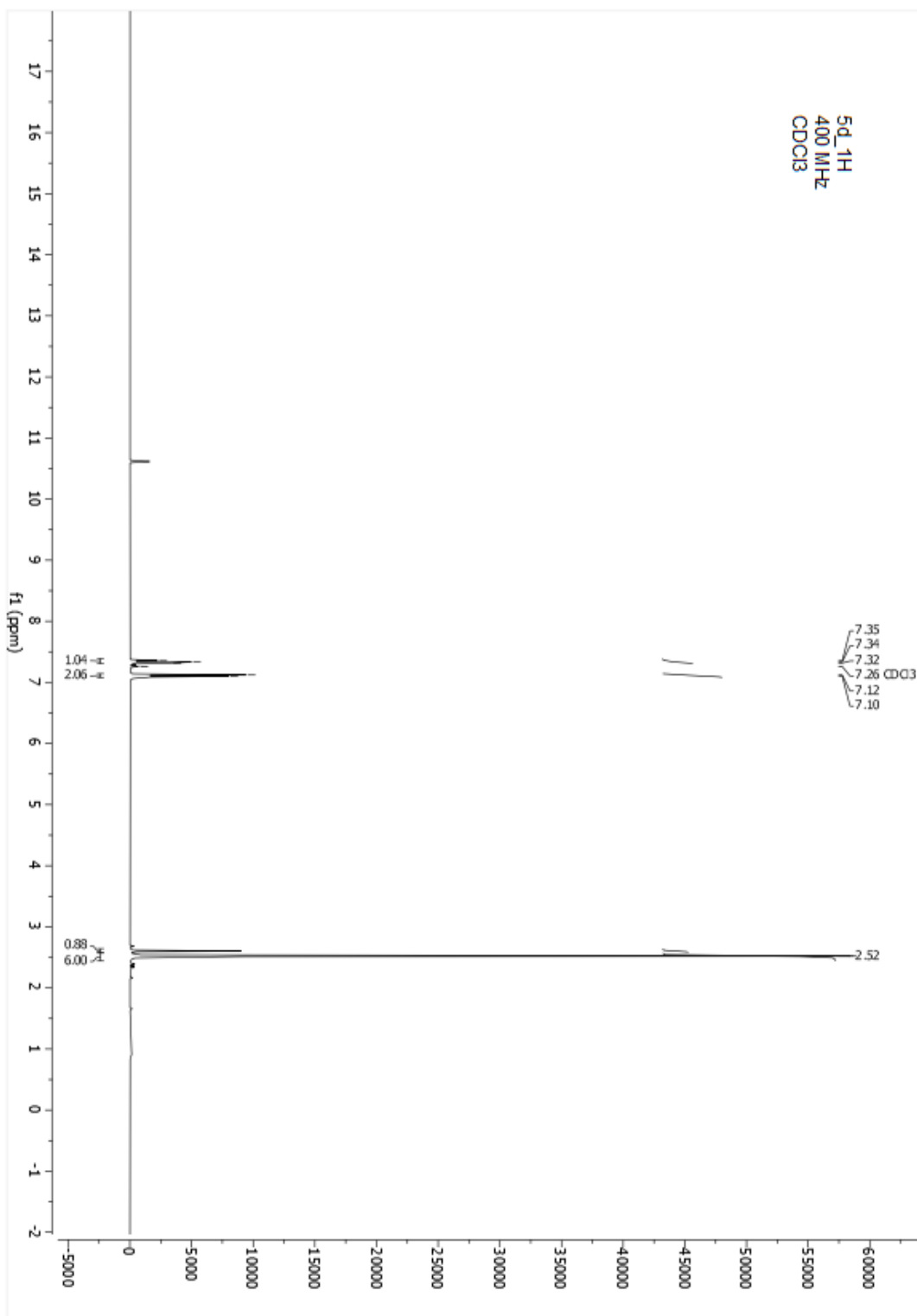


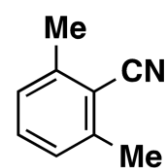
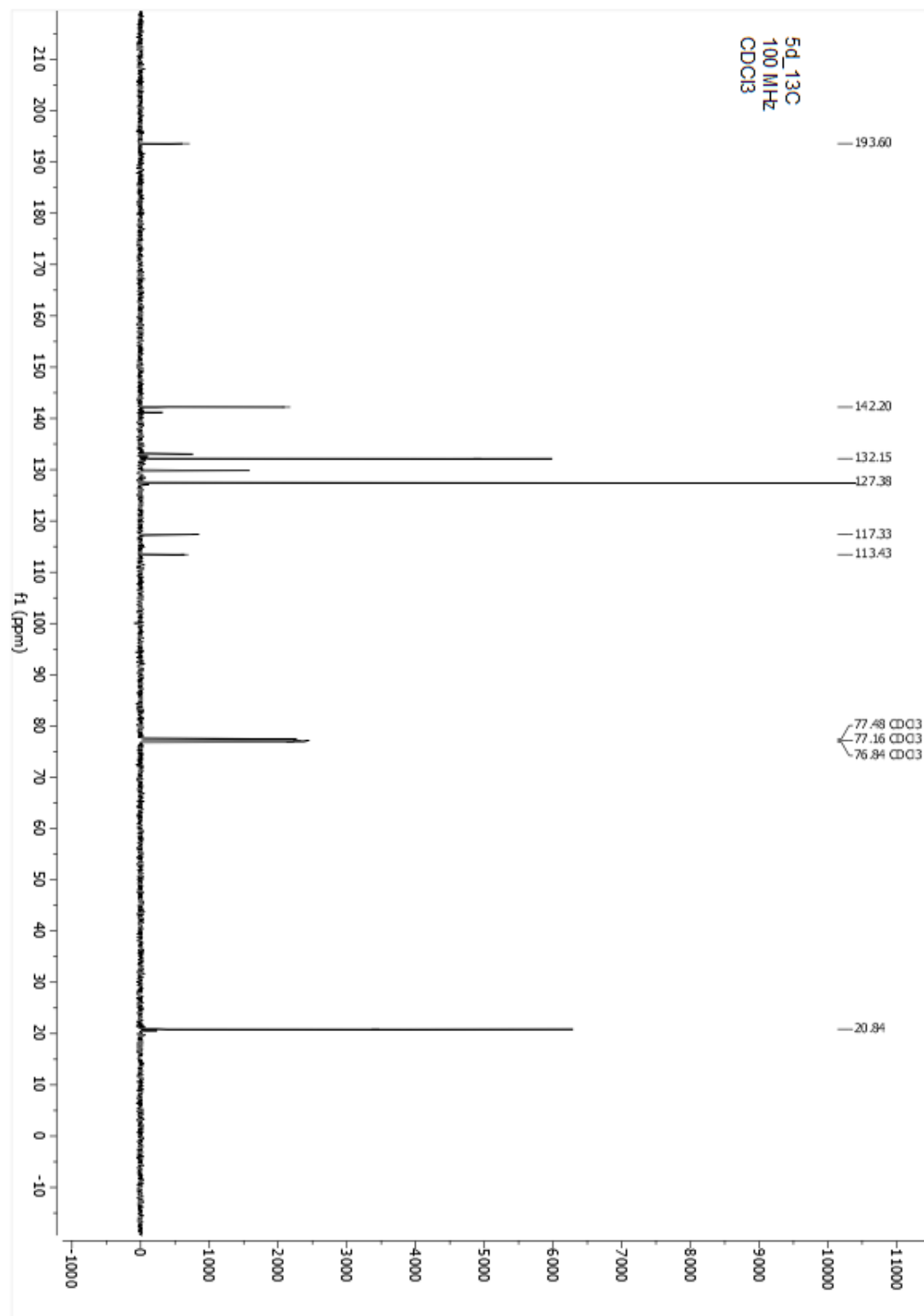
S10. ¹³C NMR Spectrum of **5b**.

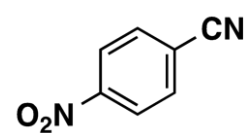
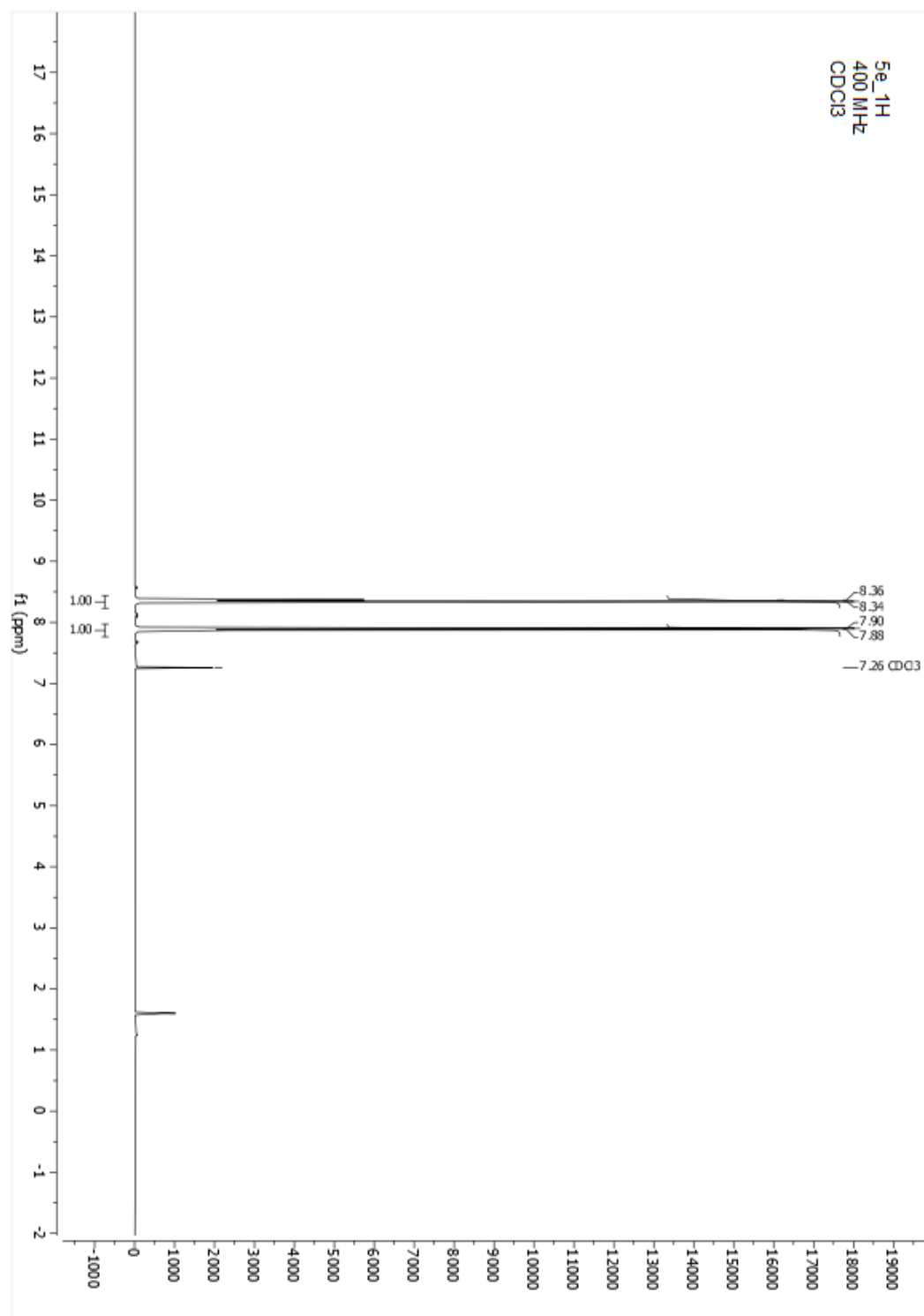
**5c****S11.** ¹H NMR Spectrum of **5c**.

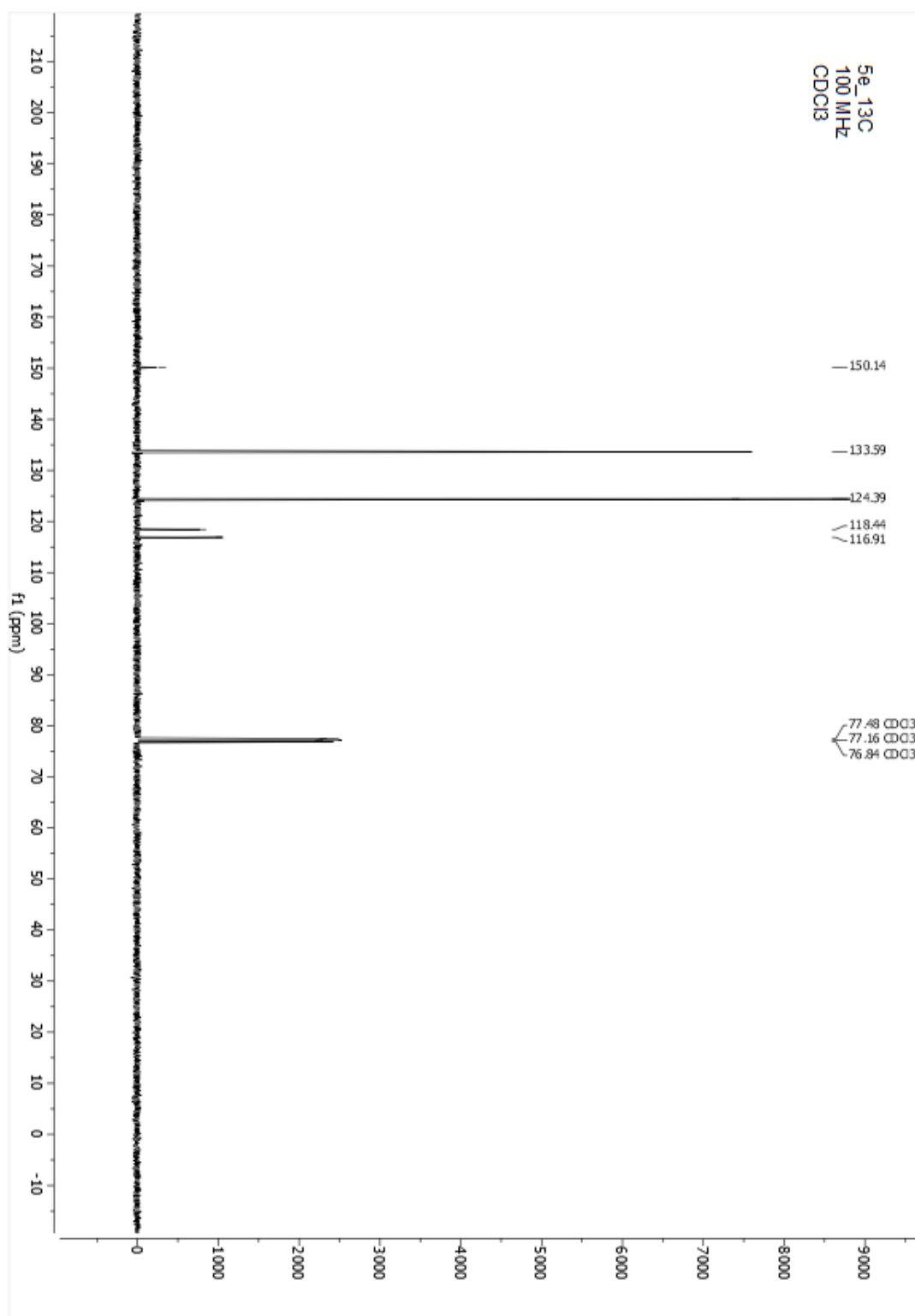
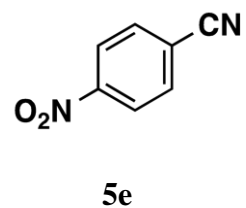


S12. ¹³C NMR Spectrum of 5c.

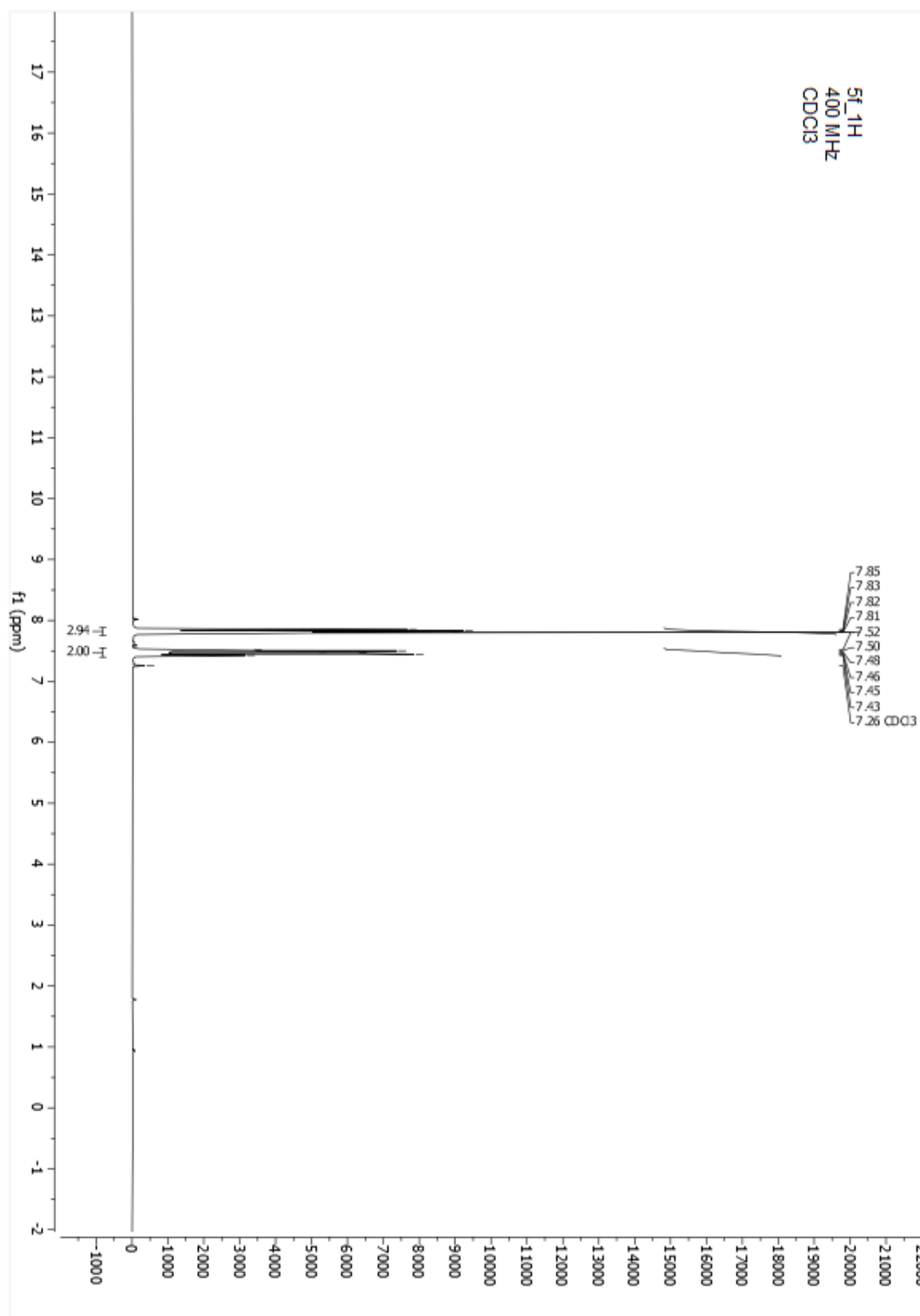
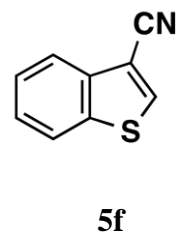
**5d****S13.** ¹H NMR Spectrum of **5d**.

**5d****S14.** ^{13}C NMR Spectrum of **5d**.

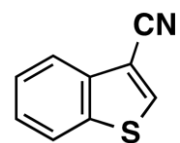
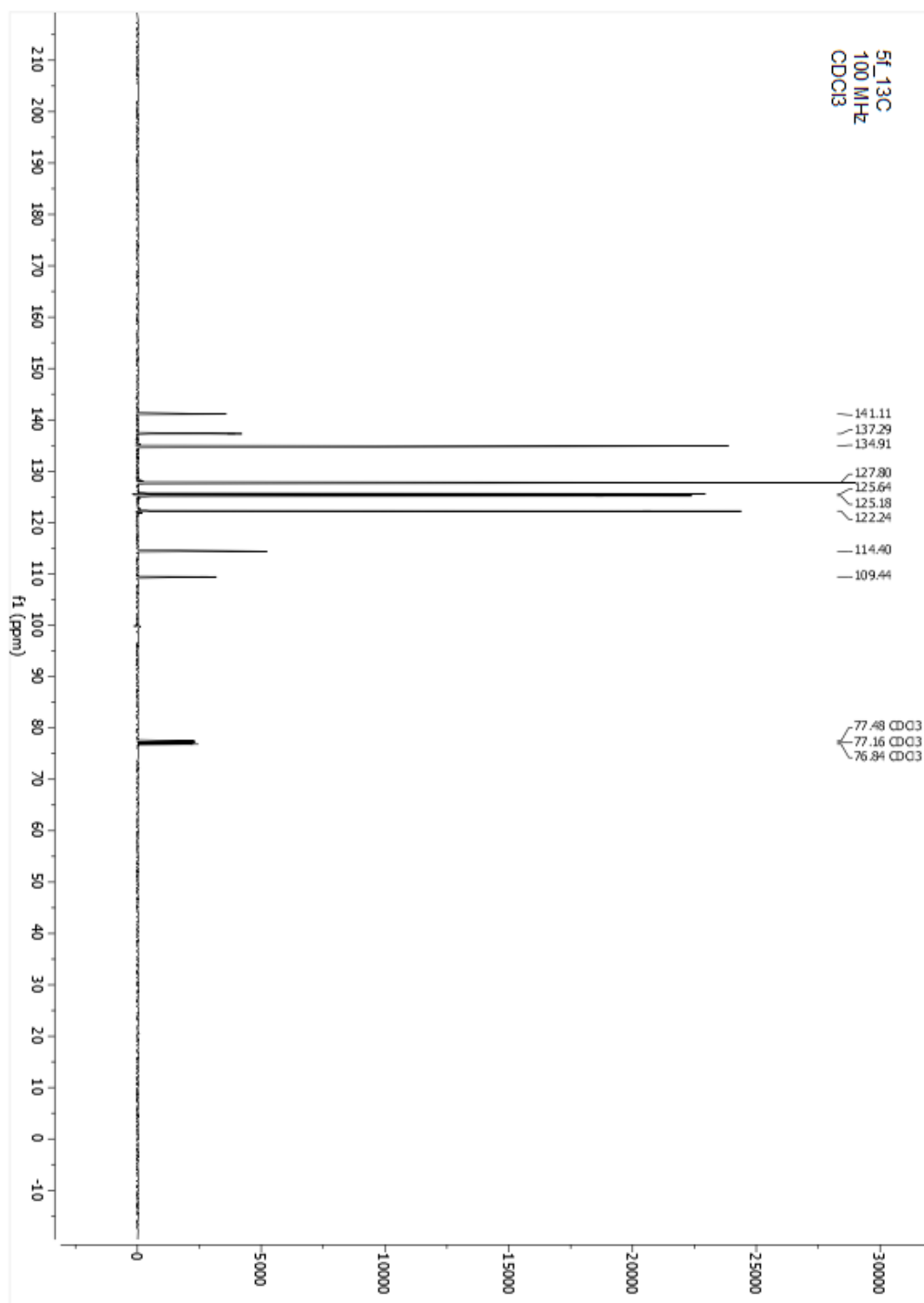
**5e****S15.** ¹H NMR Spectrum of **5e**.

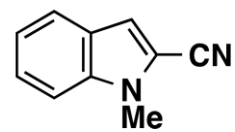
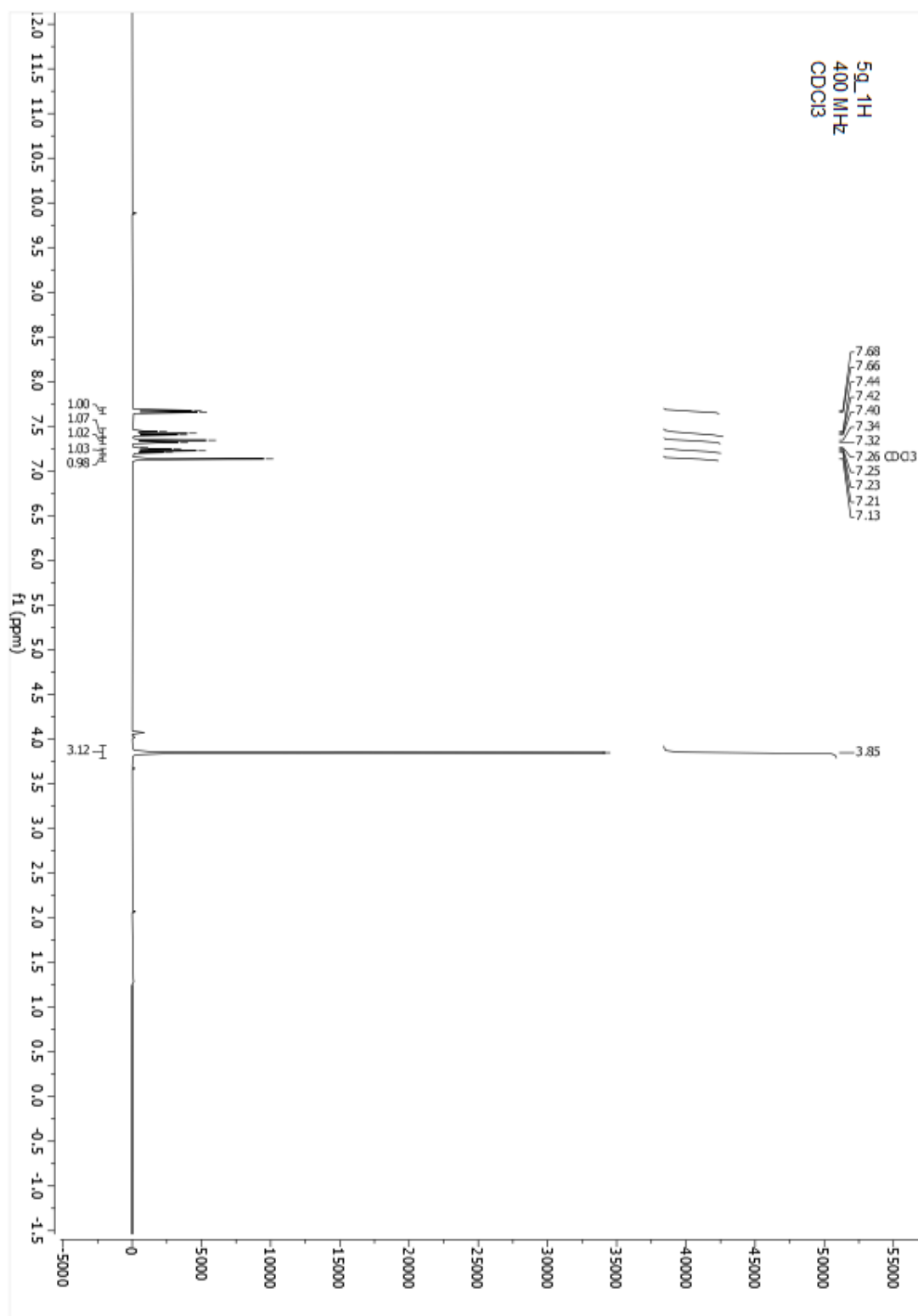


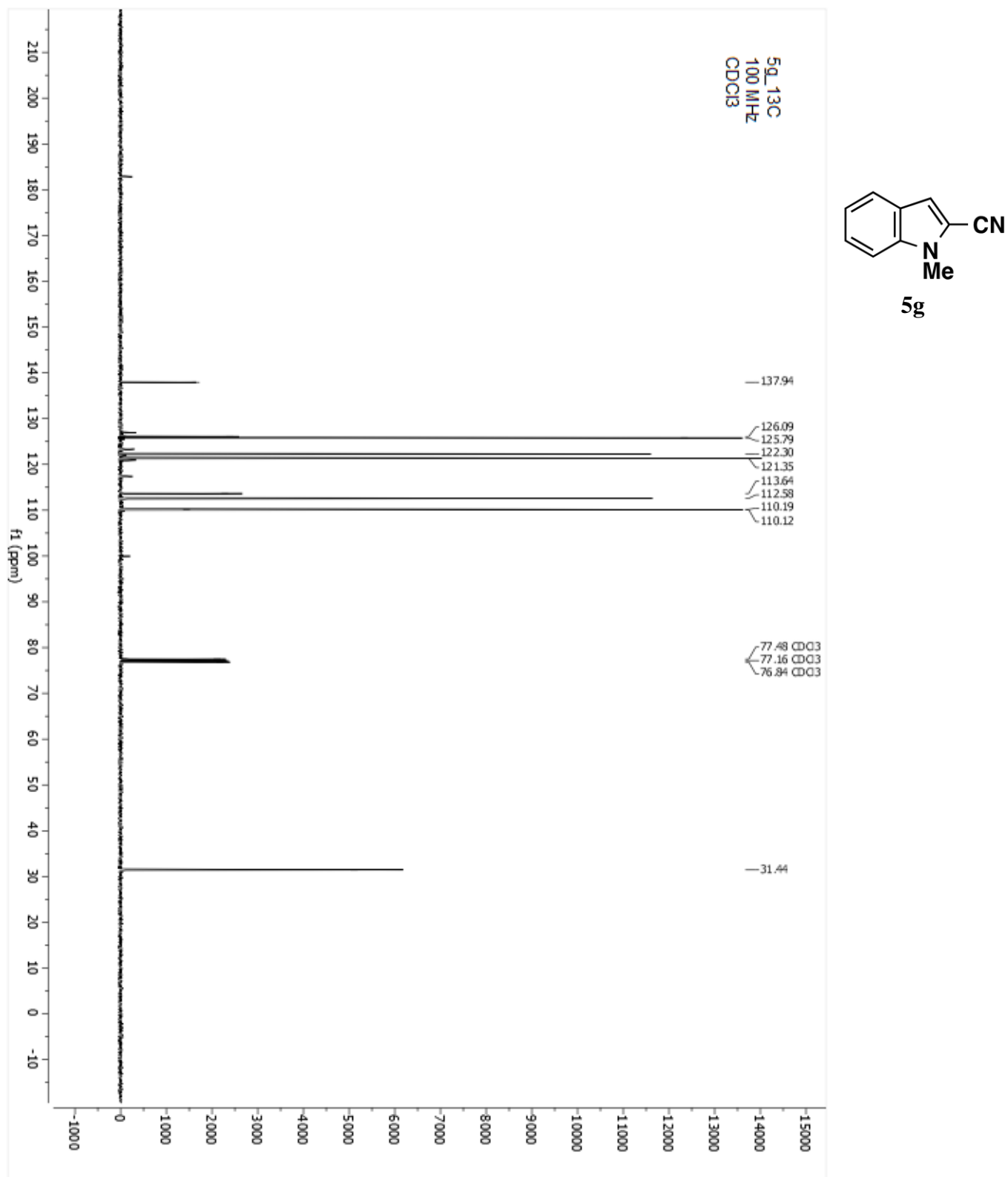
S16. ¹³C NMR Spectrum of **5e**.



S17. ¹H NMR Spectrum of **5f**.

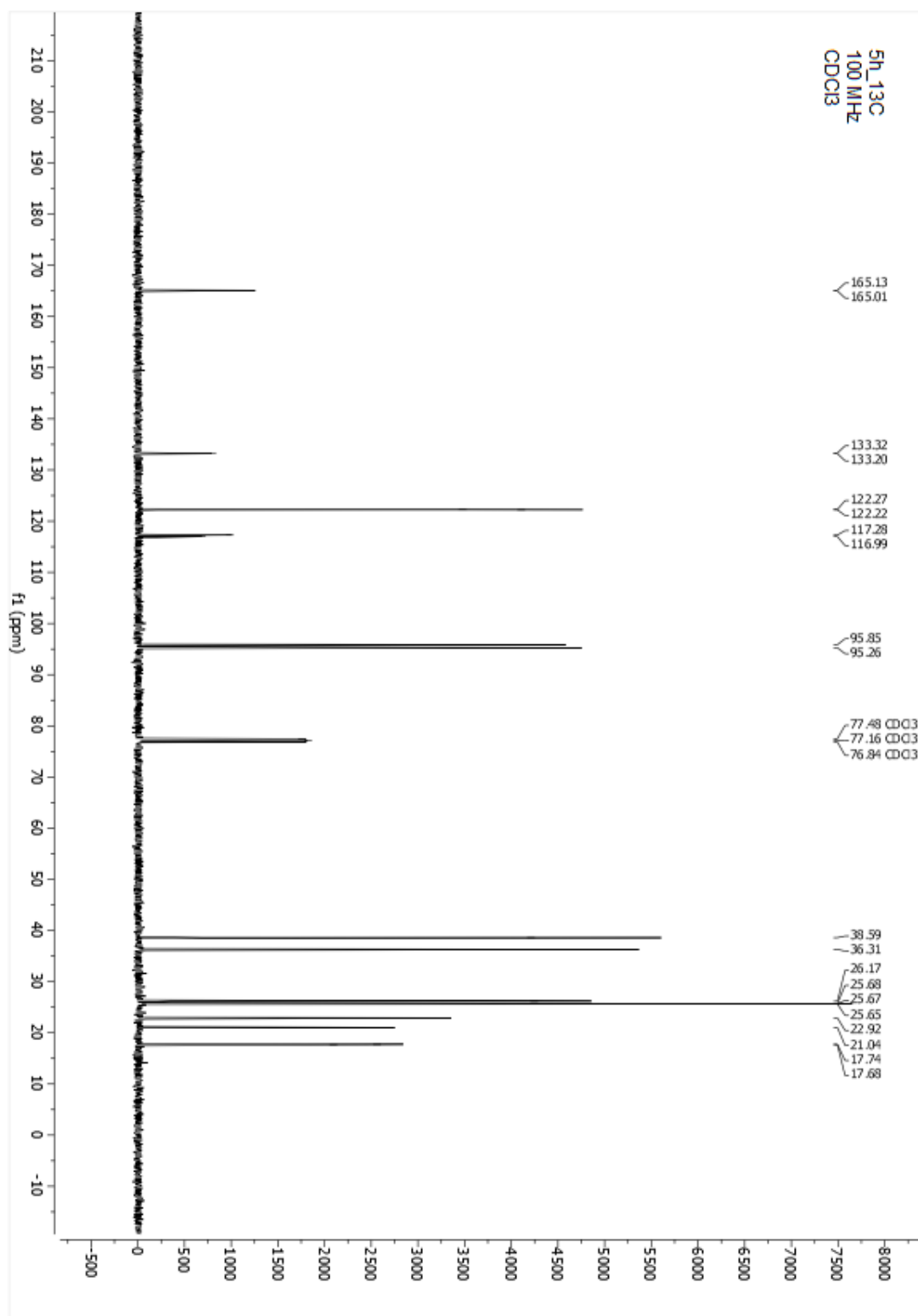
**5f****S18.** ¹³C NMR Spectrum of **5f**.

**5g****S19.** ¹H NMR Spectrum of **5g**.

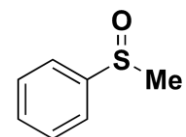
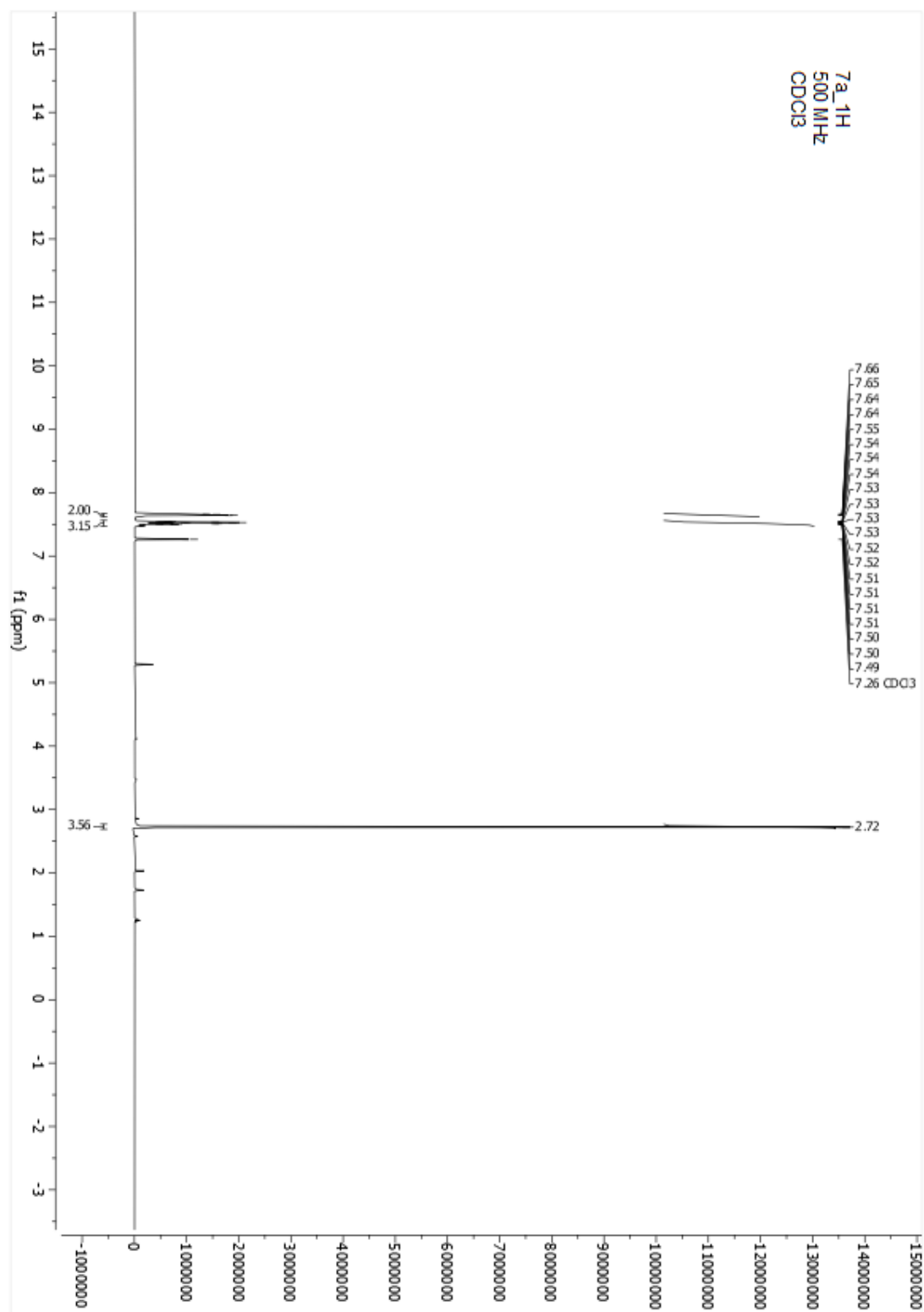


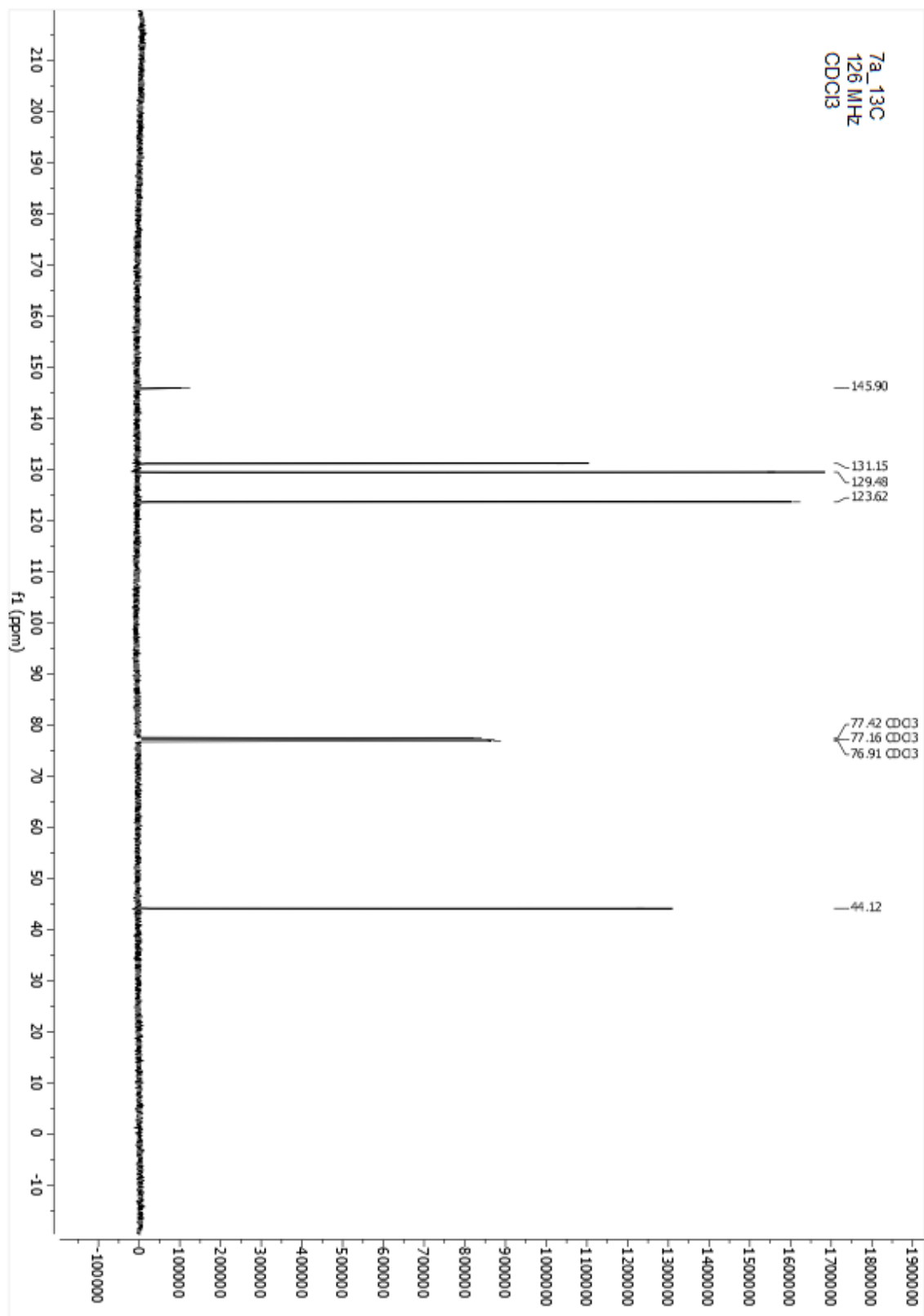
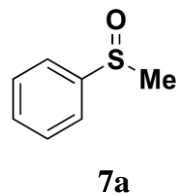
S20. ^{13}C NMR Spectrum of **5g**.



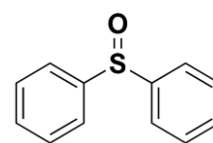
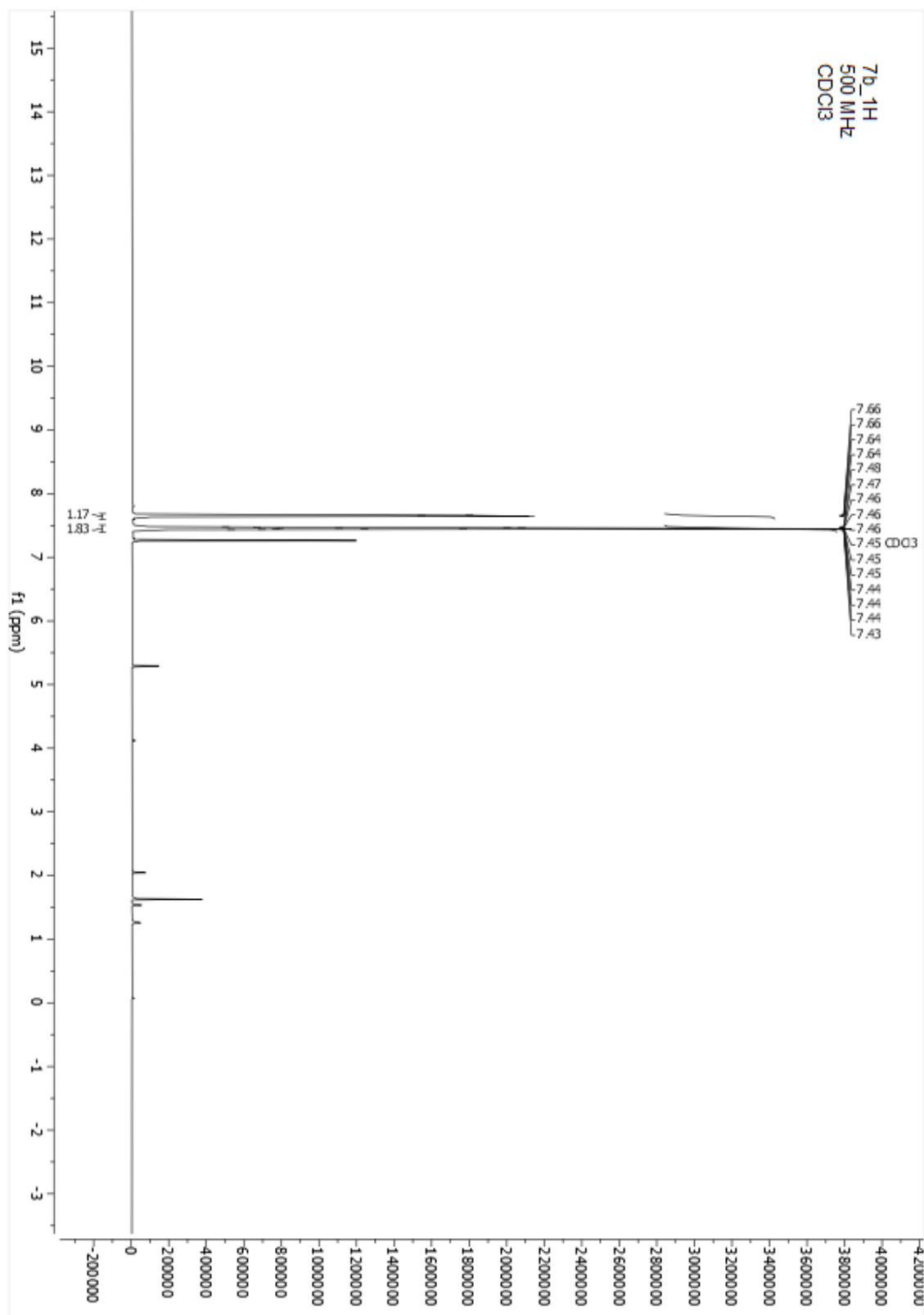


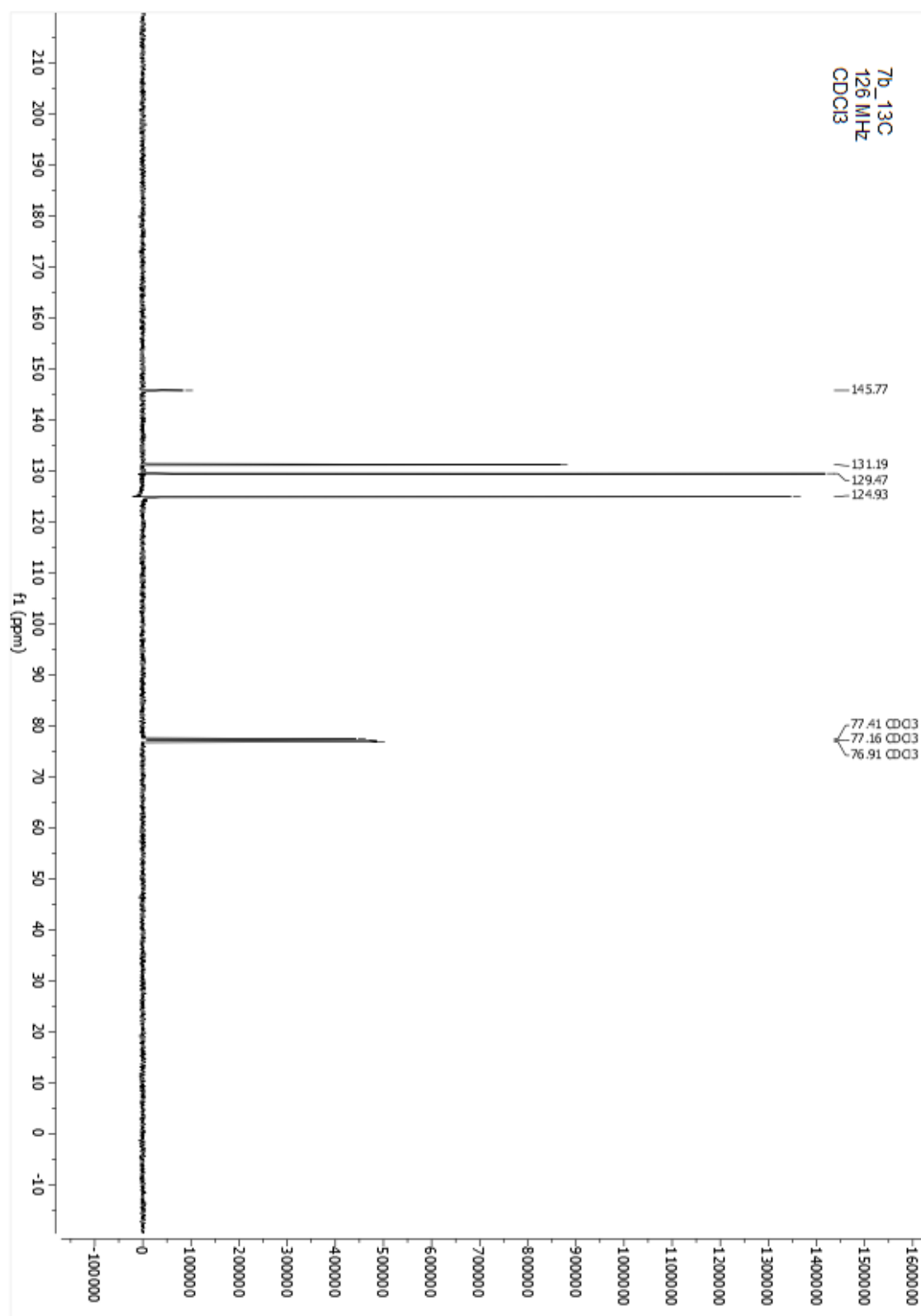
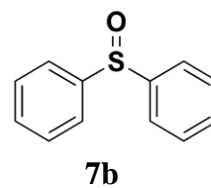
S22. ^{13}C NMR Spectrum of 5h.

**7a****S23.** ¹H NMR Spectrum of **7a**.

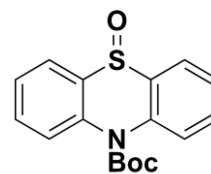
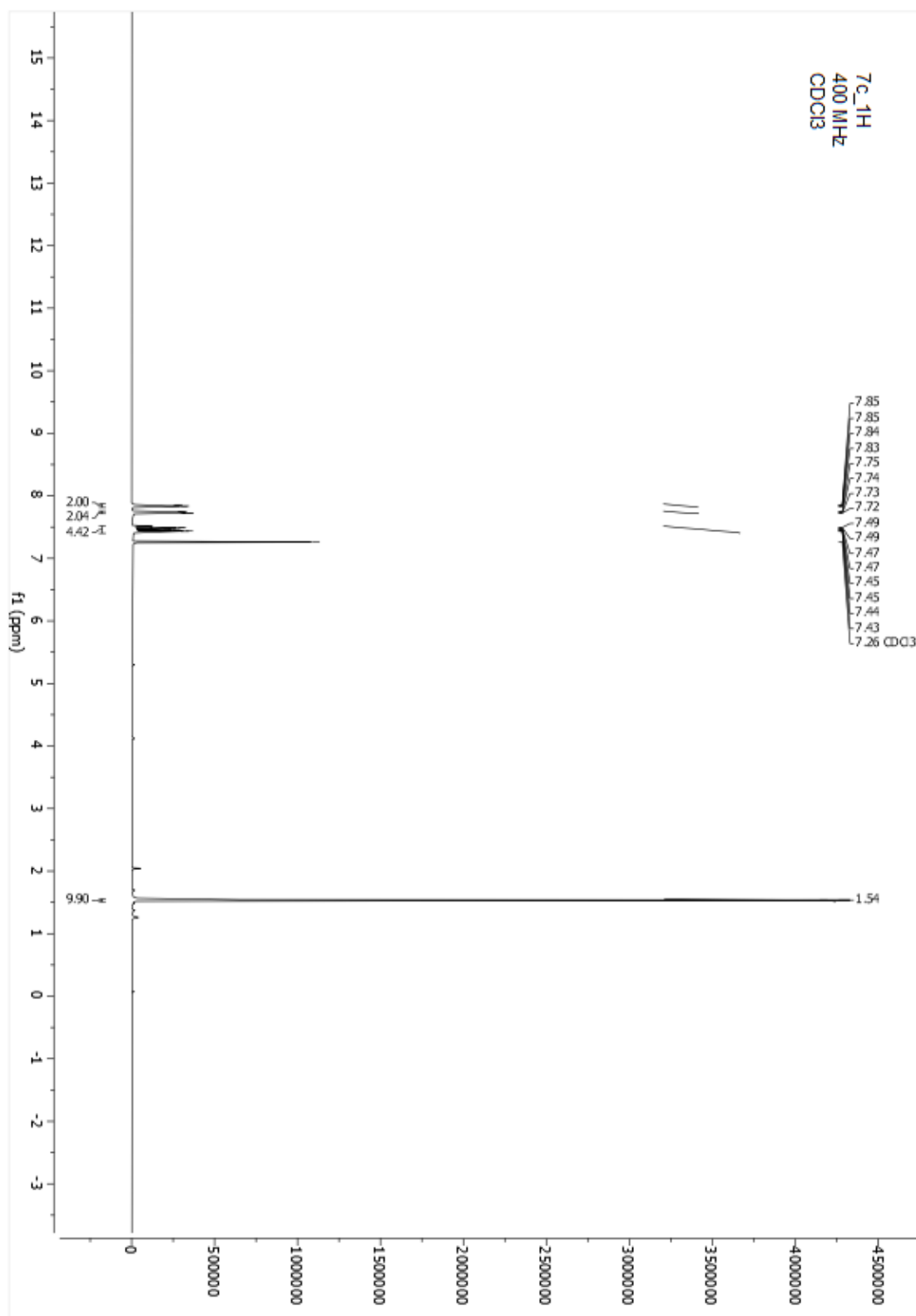


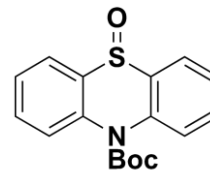
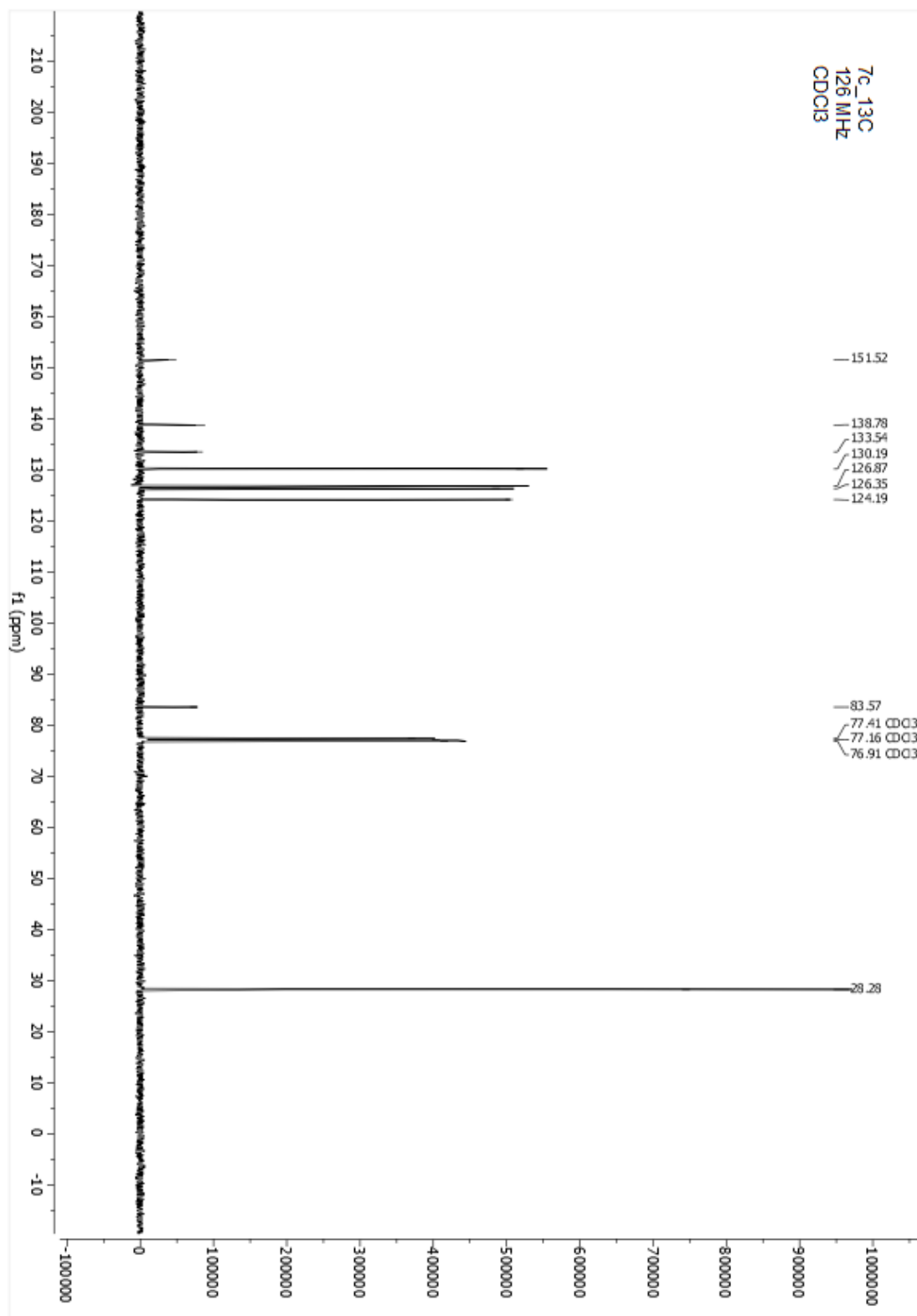
S24. ¹³C NMR Spectrum of **7a**.

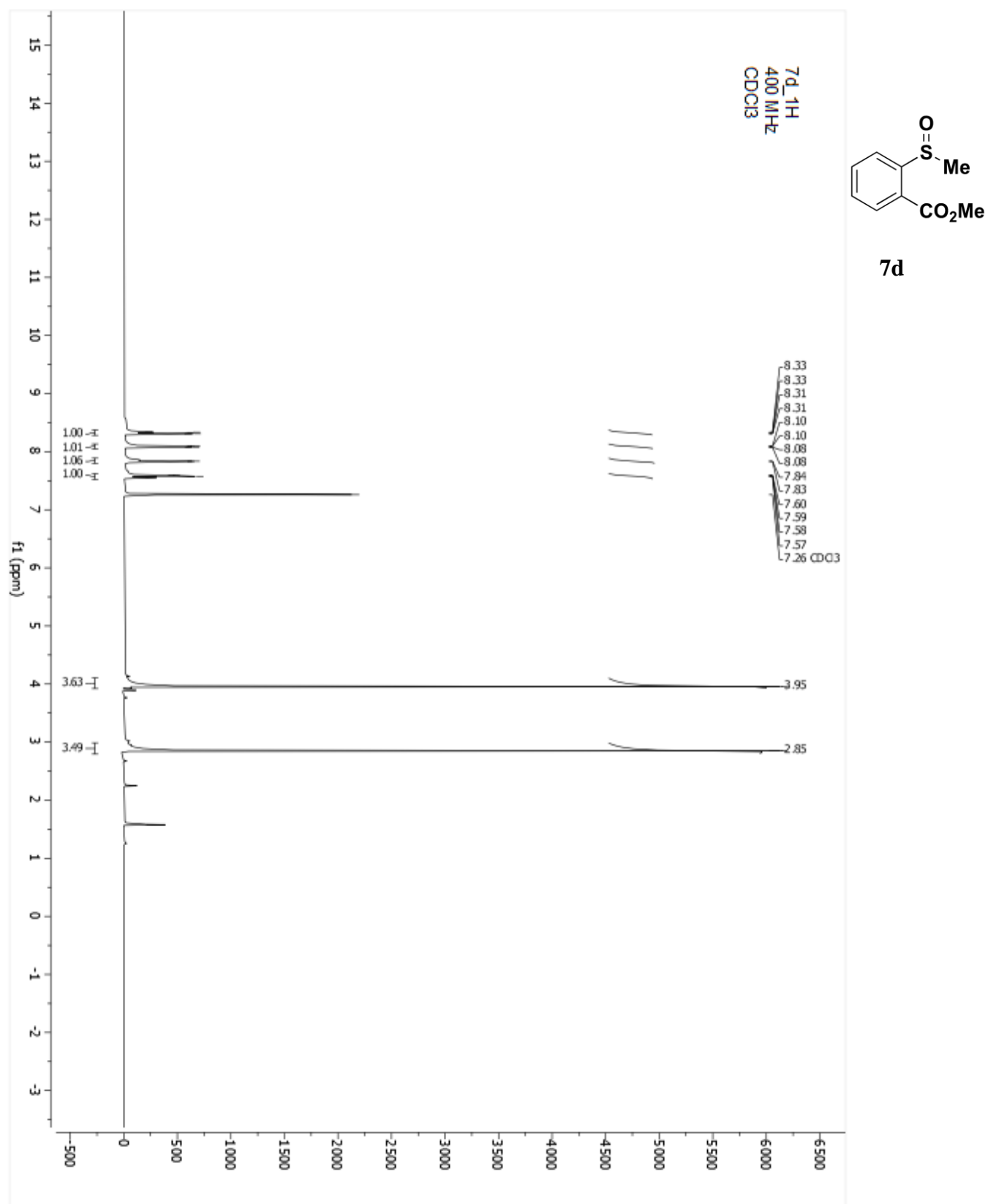
**7b****S25.** ¹H NMR Spectrum of **7b**.

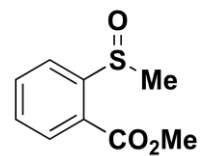
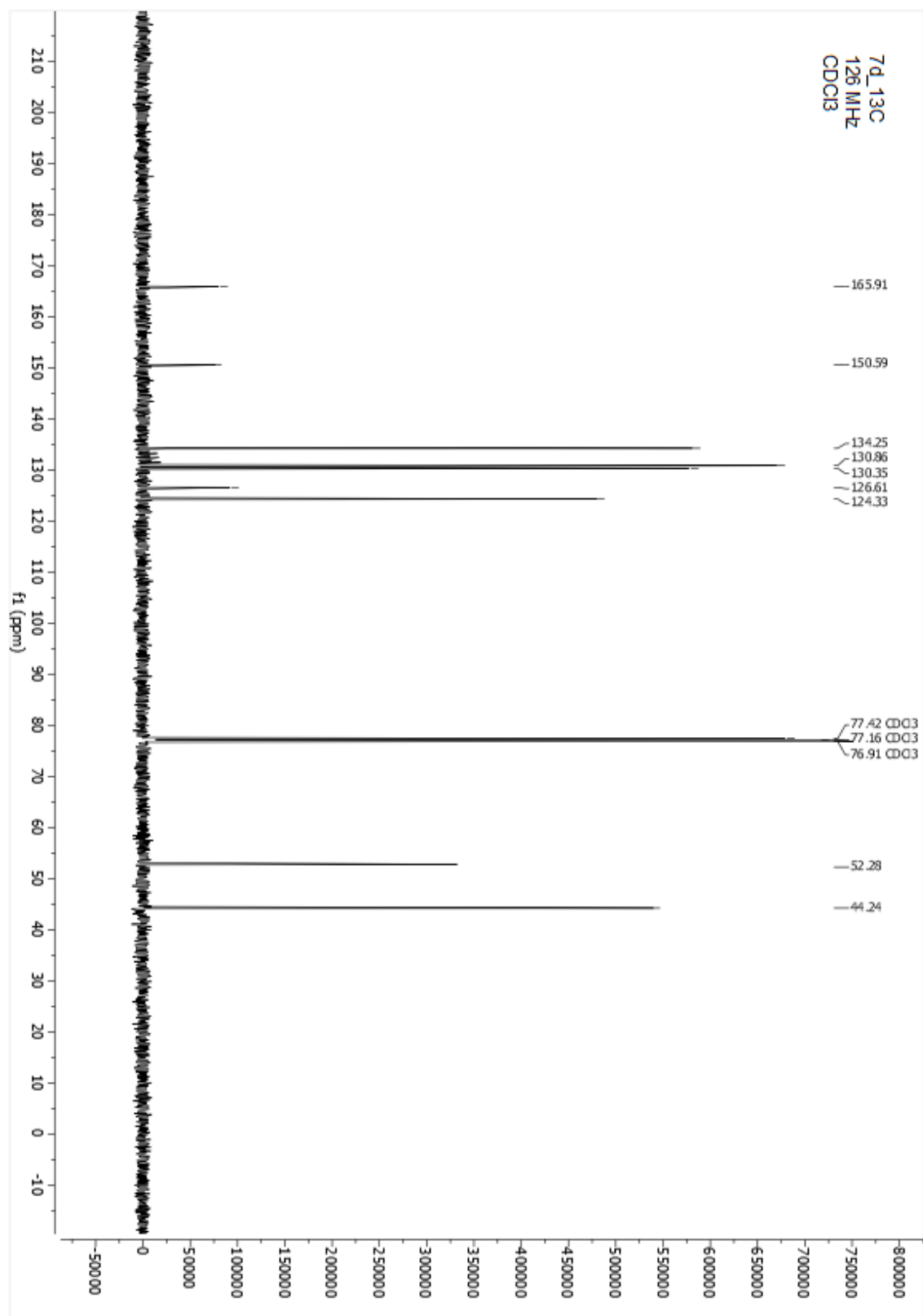


S26. ^{13}C NMR Spectrum of **7b**

**7c****S27.** ¹H NMR Spectrum of **7c**.

**7c****S28.** ¹³C NMR Spectrum of **7c**.

**S29.** ¹H NMR Spectrum of **7d**.

**7d****S30.** ¹³C NMR Spectrum of **7d**.