

# **An Efficient Buchwald-Hartwig/Reductive Cyclization for the Scaffold Diversification of Halogenated Phenazines: Potent Antibacterial Targeting, Biofilm Eradication and Prodrug Exploration**

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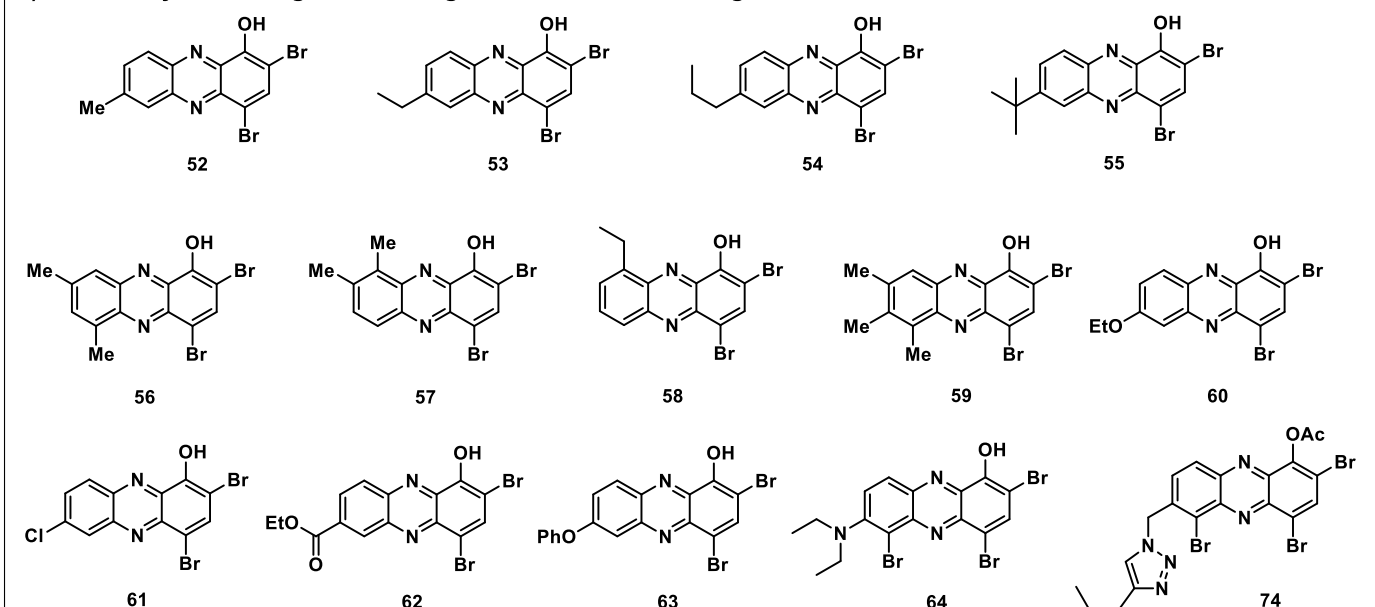
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## **Supporting Information**

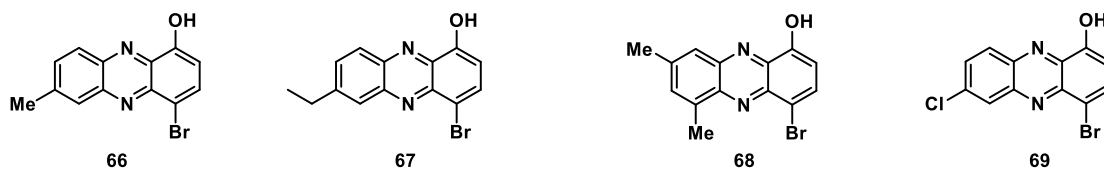
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## 1.) Supporting Figures:

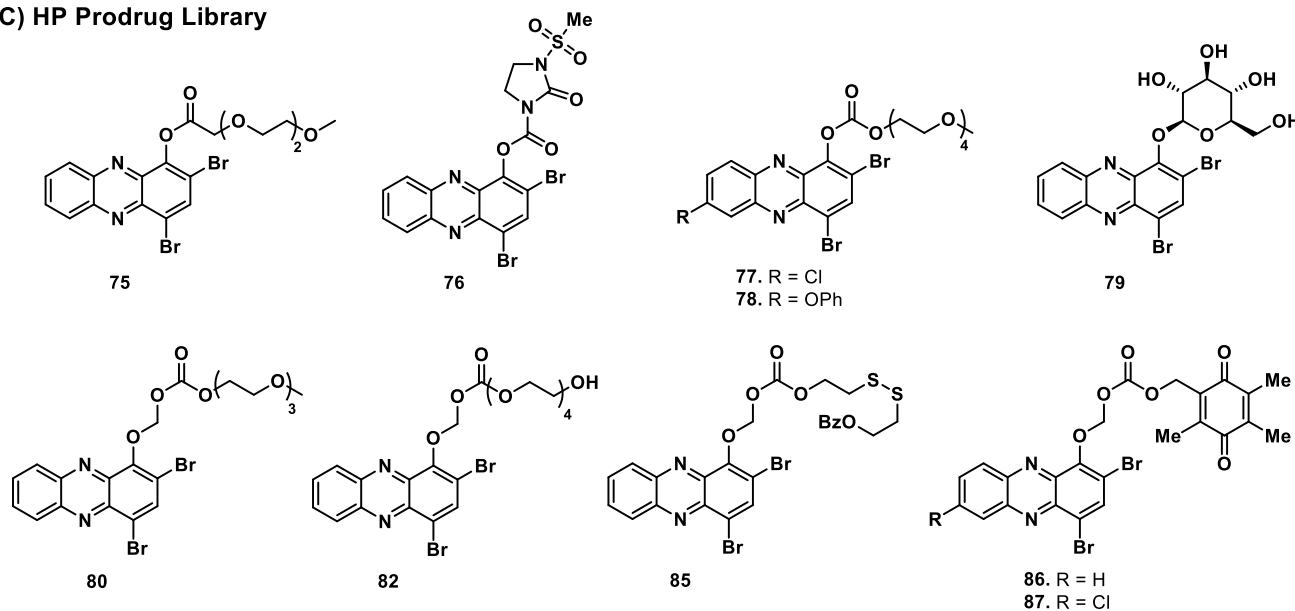
### A) HP Library Tested Against Pathogenic Bacteria, Including Biofilms



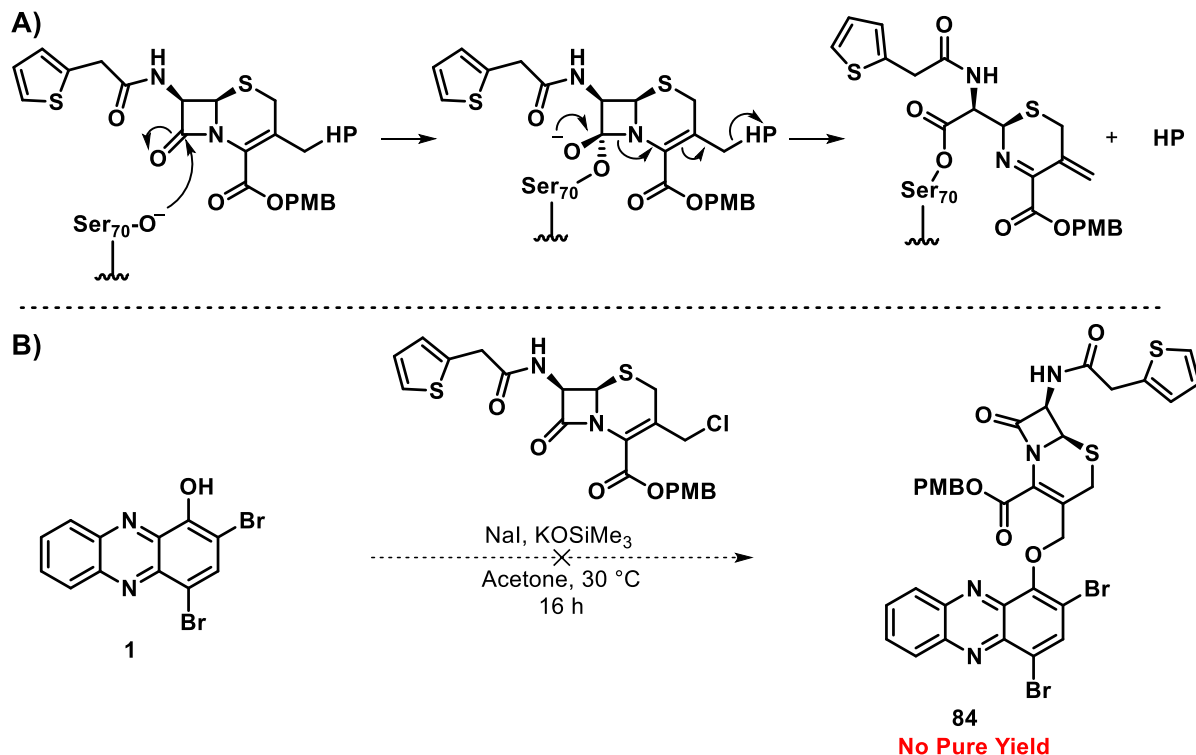
### B) HP Focused Library Synthesized for Testing Against *Mycobacterium tuberculosis*



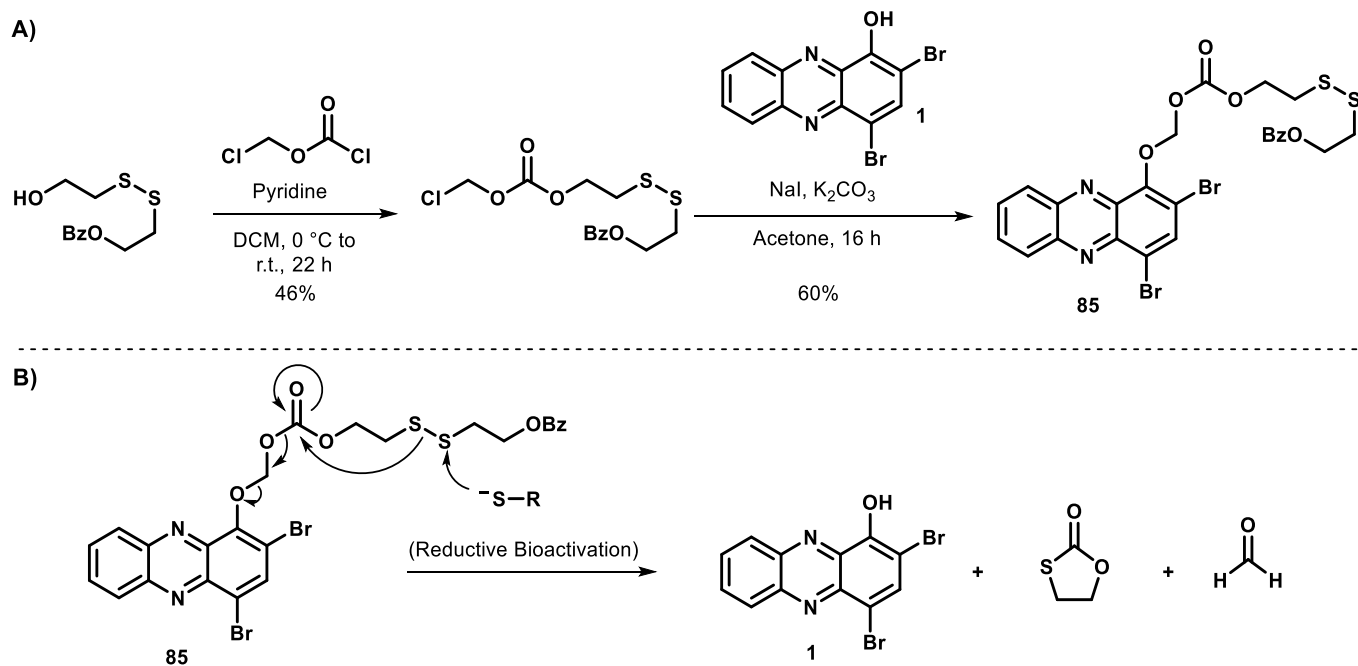
### C) HP Prodrug Library



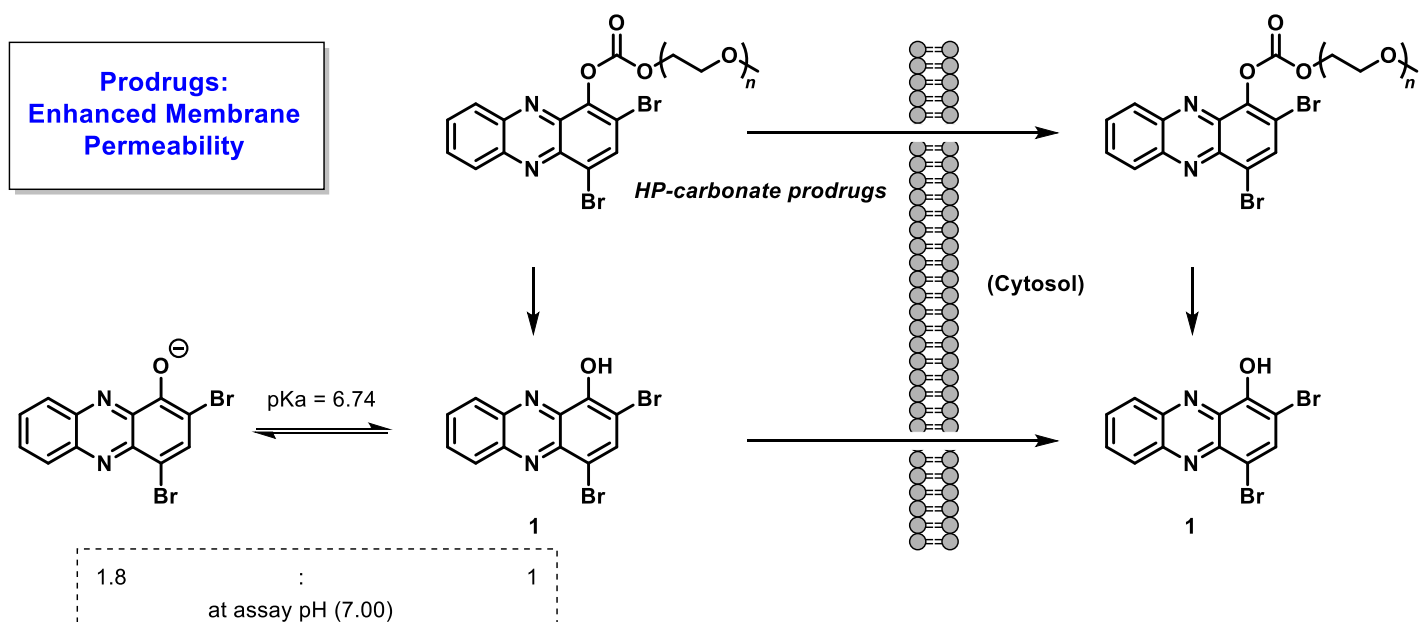
**Supporting Figure 1.** Library of halogenated phenazines tested for antibacterial and biofilm eradication activities. A) Dibrominated HPs used to target MRSA, MRSE, and VRE. B) Mono-halogenated anti-TB analogues. C) Library of evaluated HP prodrugs.



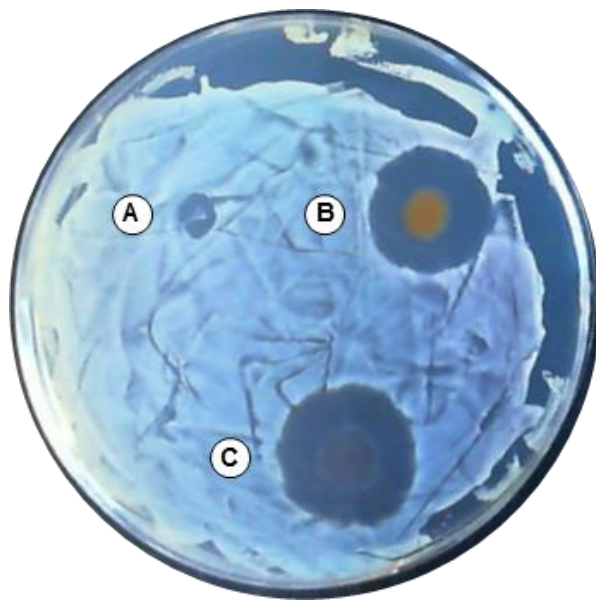
**Supporting Figure 2.** Proposed bioactivation and synthesis of general HP- $\beta$ -lactam prodrug **84**. A)  $\beta$ -Lactamase-mediated cleavage of  $\beta$ -lactam **84** and subsequent release of the active HP (halogenated phenazine). B) Attempted synthesis of HP- $\beta$ -lactam prodrug **84**.



**Supporting Figure 3.** Chemical synthesis of HP- disulfide AOCOM prodrug **85** and the mechanism of activation. A) Synthesis of HP **85** from HP **1**. B) Proposed mechanism of HP activation via reductive cytosolic environment.

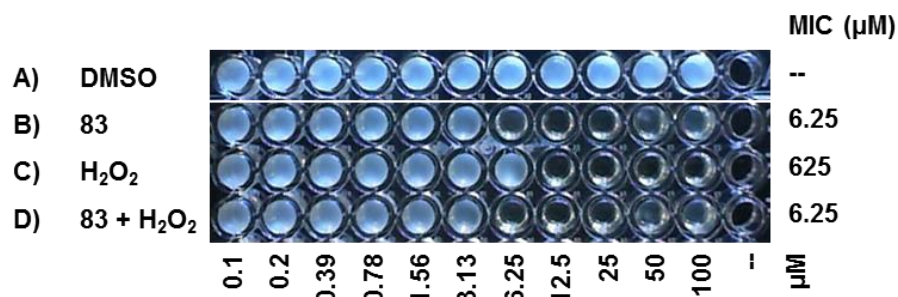


**Supporting Figure 4.** Proposed rationale behind improved activity for HP-carbonate prodrugs in MIC assays, disregarding the effect that 1% DMSO may have on HP  $\text{pK}_a$ .

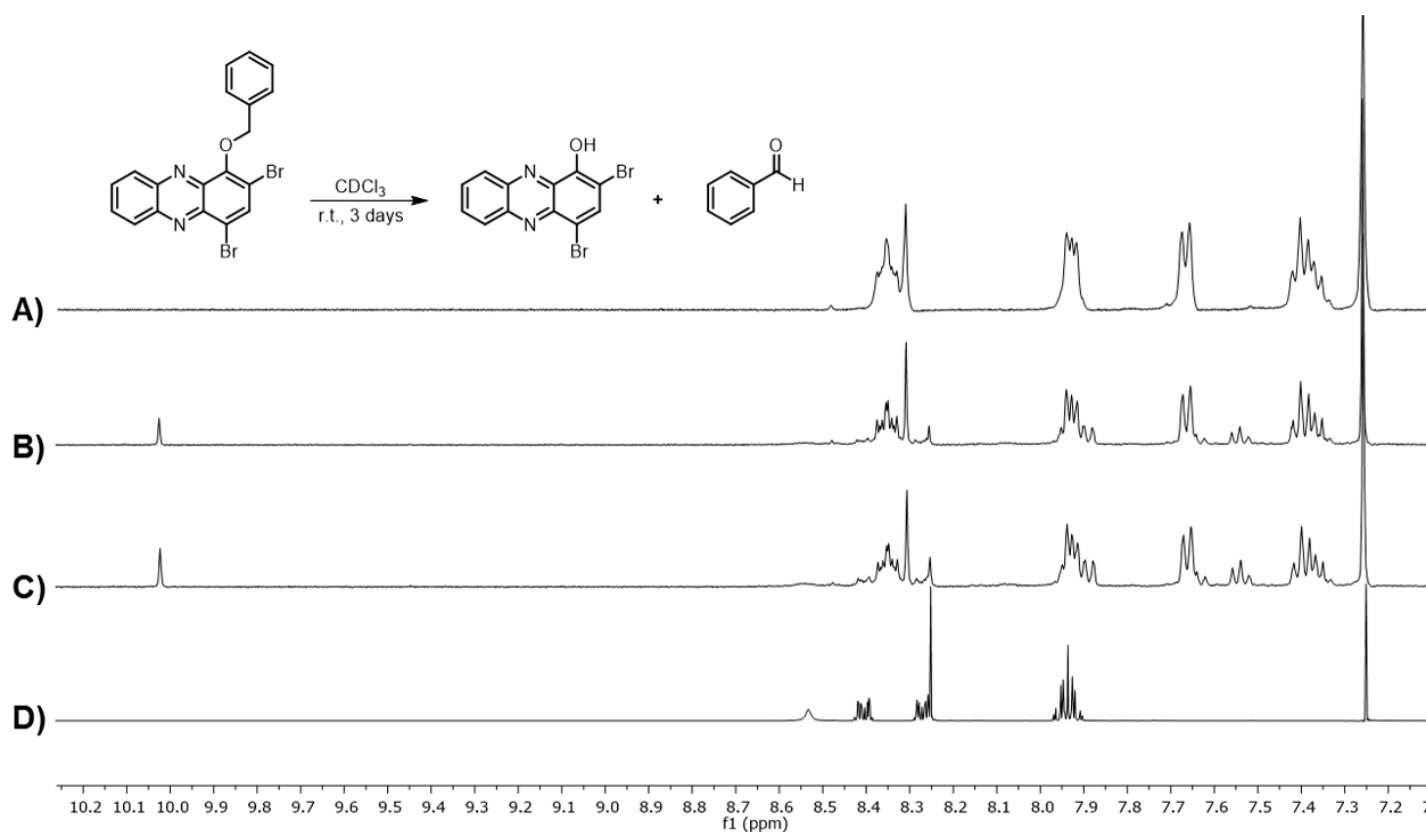


**Supporting Figure 5.** MRSA BAA-1707 agar diffusion assay to evaluate HP-carbonate **77** and HP **61**. A) DMSO. B) HP **61**. C). HP-carbonate **77**. It was reasoned that the semi-solid nature of the agar medium should reduce the susceptibility of LB-mediated carbonate cleavage.

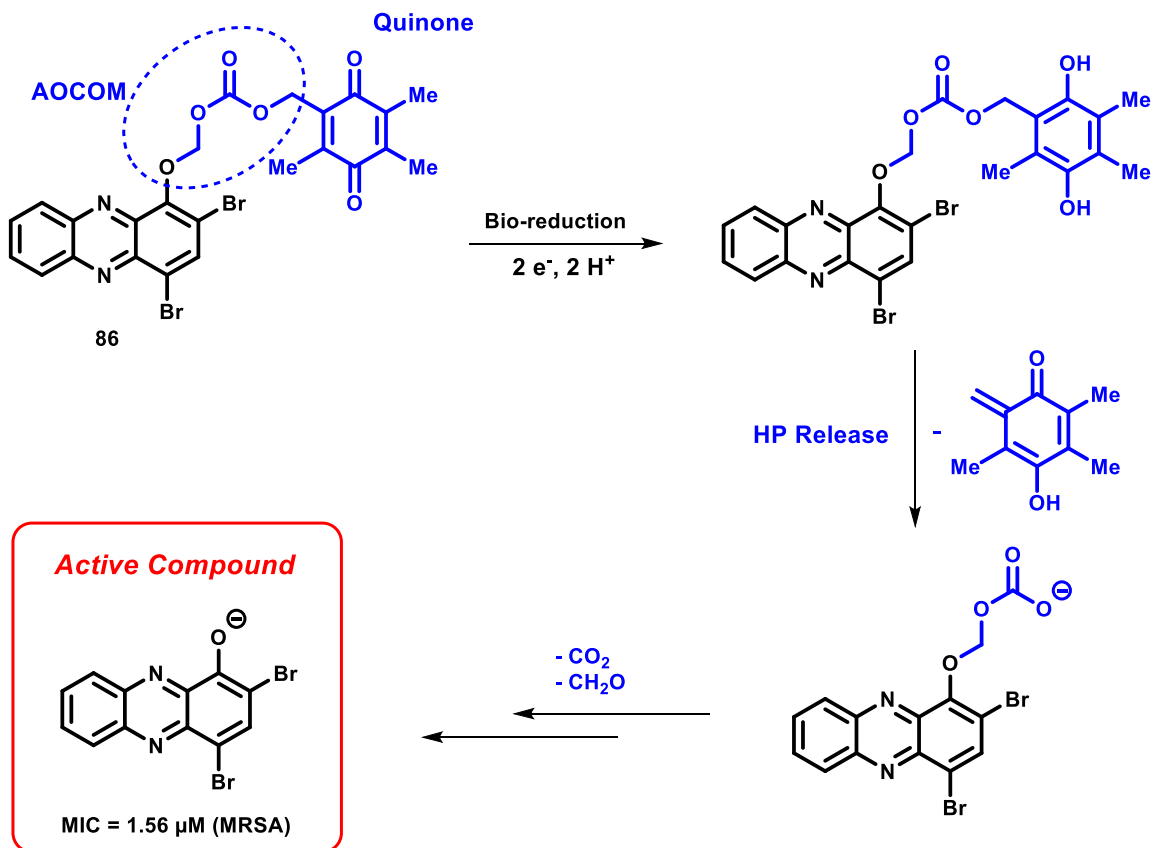




**Supporting Figure 6.** MRSA BAA-1707 MIC of HP-boronic ester prodrug **83** with and without equimolar supplementation of hydrogen peroxide ( $\text{H}_2\text{O}_2$ ). Activity is observed without co-treatment with activating oxidant  $\text{H}_2\text{O}_2$ , indicating prodrug instability (similar to NMR studies with benzyl-HP analogues; Supp. Fig. 7.).



**Supporting Figure 7.**  $^1\text{H}$  NMR spectra demonstrating time-dependent decomposition of a benzylated HP control in  $\text{CDCl}_3$  at room temperature. A) Time 0 h. B) Time 24 h. C) Time 48 h. D) HP **1** reference for comparison.



**Supporting Figure 8.** Reductive activation of QuAOCOM prodrug for release of active HP. The bacterial cytoplasm is known to be a reductive environment leading to the bioreduction of the quinone within mitomycin C.

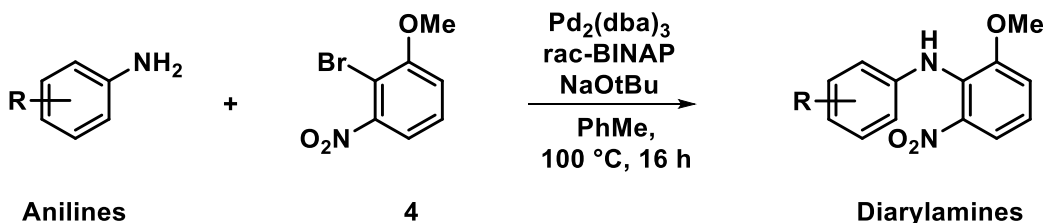
## **2.) General Information:**

All synthetic reactions were carried out under an inert atmosphere of argon unless otherwise specified. All reagents for chemical synthesis were purchased from commercial sources and used without further purification. Reagents were purchased at  $\geq 95\%$  purity and commercially available controls were used in our biological investigations without further purification. All microwave reactions were carried out in sealed tubes in an Anton Paar Monowave 300 Microwave Synthesis Reactor. A constant power was applied to ensure reproducibility. Temperature control was automated via IR sensor and all indicated temperatures correspond to the maximal temperature reached during each experiment. Analytical thin layer chromatography (TLC) was performed using 250  $\mu\text{m}$  Silica Gel 60 F254 pre-coated plates (EMD Chemicals Inc.). Flash column chromatography was performed using 230-400 Mesh 60Å Silica Gel from Sorbent Technologies. All melting points were obtained, uncorrected, using a Mel-Temp capillary melting point apparatus from Laboratory Services, Inc.

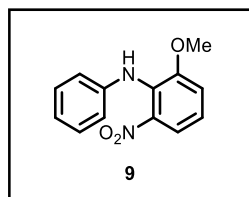
NMR experiments were recorded using broadband probes on a Varian Mercury-Plus-400 spectrometer via VNMR-J software (400 MHz for  $^1\text{H}$  and 100 MHz for  $^{13}\text{C}$ ) and a Bruker Avance II (600 MHz for  $^1\text{H}$  NMR; 150 MHz for  $^{13}\text{C}$  NMR). All spectra are presented using MestReNova 11.0 (Mnova) software and are displayed without the use of the signal suppression function. Spectra were obtained in the following solvents (reference peaks also included for  $^1\text{H}$  and  $^{13}\text{C}$  NMRs):  $\text{CDCl}_3$  ( $^1\text{H}$  NMR: 7.26 ppm;  $^{13}\text{C}$  NMR: 77.23 ppm) and  $d_6$ -DMSO ( $^1\text{H}$  NMR: 2.50 ppm;  $^{13}\text{C}$  NMR: 39.52 ppm). All NMR experiments were performed at room temperature. Chemical shift values ( $\delta$ ) are reported in parts per million (ppm) for all  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra.  $^1\text{H}$  NMR multiplicities are reported as: s = singlet, br. s = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Use of a temporary NMR probe presented an out-of-phase, spurious signal at 28.5 ppm (Chloroform-*d*) or 22.7 ppm (DMSO-*d*<sub>6</sub>) in select  $^{13}\text{C}$  NMR spectra (see HPs **19, 45, 56, 57, 61, 62, 63, 65, 69, 73**). The phantom signal is of unknown origin but is not a component of any samples herein as evidenced by its presence in “blank” Chloroform-*d*  $^{13}\text{C}$  NMR acquisitions. High-Resolution Mass Spectrometry (HRMS) were obtained for all new compounds from the Chemistry Department at the University of Florida.

All compounds evaluated in biological assays were determined to be  $\geq 95\%$  pure via LC-MS using a Shimadzu Prominence HPLC system, AB Sciex 3200 QTRAP spectrometer and a Kinetex C18 column (50 mm  $\times$  2.1 mm  $\times$  2.6  $\mu\text{m}$ ) with a 35-minute linear gradient from 10-65% acetonitrile in 0.5% formic acid at a flow rate of 0.25 mL/min. Bacterial strains used during these investigations include: methicillin-resistant *Staphylococcus aureus* (Clinical Isolate from Shands Hospital in Gainesville, FL: MRSA-2; ATCC strains: BAA-1707, BAA-44) methicillin-resistant *Staphylococcus epidermidis* (MRSE strain ATCC 35984), and vancomycin-resistant *Enterococcus faecium* (VRE strain ATCC 700221). All compounds were stored as DMSO stocks at room temperature in the absence of light for several months at a time without observing any loss in biological activity. To ensure compound integrity of our DMSO stock solutions, we did not subject DMSO stocks of our test compounds to freeze-thaw cycles.

### 3.) Synthetic Procedures and Characterization Data:



**General procedure for Buchwald-Hartwig amination.** To a stirring solution of **4** (436.2 mg, 1.88 mmol) and desired aniline (2.26 mmol) in toluene was added tris-(dibenzylideneacetone)dipalladium(0) (103.5 mg, 0.11 mmol), (±)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene (210.5 mg, 0.34 mmol), and sodium *tert*-butoxide (234.6 mg, 2.44 mmol). The reaction was allowed to stir for 16 hours at 100 °C. The mixture was then allowed to cool to room temperature and transferred to a separatory funnel containing ethyl acetate and saturated sodium bicarbonate. The organic layer was sequentially washed with sodium bicarbonate and brine before the organic layer was collected. The organic layer was then dried with anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude solid was purified via flash column chromatography using hexanes:ethyl acetate (95:5 to 80:20) to elute pure diarylamines.



**Yield:** 81%; 206.0 mg of **9** was isolated as a red oily residue.

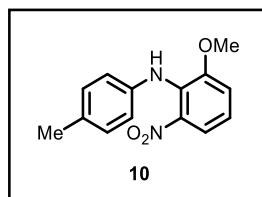
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.18 (br. s, 1H), 7.71 (dd, *J* = 8.5, 1.4 Hz, 1H), 7.28 – 7.17 (m, 2H), 7.09 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.01 (d, *J* = 8.3 Hz, 1H), 6.98 (tt, *J* = 7.2, 1.0 Hz, 1H), 6.85 – 6.79 (m, 2H), 3.75 (s, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 152.7, 142.3, 140.5, 129.6, 128.7, 122.4, 120.7, 118.6, 118.1, 116.3, 56.3.

**MP:** 55 – 57 °C.

**HRMS (ESI):** calc. for C<sub>13</sub>H<sub>13</sub>N<sub>2</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 245.0921, found: 245.0930.

**Note:** Compound has been previously reported (CAS: 7575-27-1), but no spectra were found for comparison.



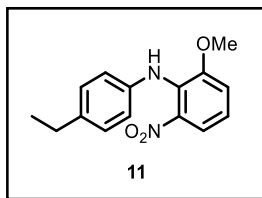
**Yield:** 94%; 460.8 mg of **10** was isolated as a red oily residue.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.18 (br. s, 1H), 7.71 (dd, *J* = 8.5, 1.4 Hz, 1H), 7.08 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.04 (d, *J* = 8.3 Hz, 2H), 6.97 (dd, *J* = 8.5, 8.0 Hz, 1H), 6.75 (d, *J* = 8.3 Hz, 2H), 3.75 (s, 3H), 2.31 (s, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 152.4, 139.9, 139.8, 132.1, 130.4, 129.3, 120.1, 118.9, 118.2, 116.3, 56.4, 20.9.

**HRMS (ESI):** calc. for C<sub>14</sub>H<sub>15</sub>N<sub>2</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 259.1077, found: 259.1085.

**MP:** 65 – 67 °C.

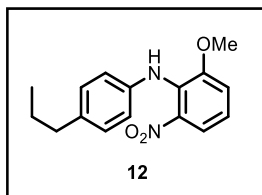


**Yield:** 71%; 83.3 mg of **11** was isolated as a red oily residue.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.21 (br. s, 1H), 7.72 (dd, *J* = 8.5, 1.4 Hz, 1H), 7.12 – 7.05 (m, 3H), 6.98 (dd, *J* = 8.5, 8.0 Hz, 1H), 6.85 – 6.68 (m, 2H), 3.76 (s, 3H), 2.62 (q, *J* = 7.6 Hz, 2H), 1.23 (t, *J* = 7.6 Hz, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 152.4, 139.9, 138.5, 130.3, 128.1, 120.1, 118.9, 118.1, 116.3, 56.3, 28.3, 15.8. Note: One <sup>13</sup>C signal missing in the aromatic region, likely due to signal overlap.

**HRMS (ESI):** calc. for C<sub>15</sub>H<sub>7</sub>N<sub>2</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 273.1234, found: 273.1243.

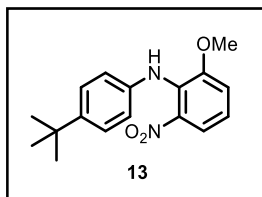


**Yield:** 71%; 453.3 mg of **12** was isolated as a red oily residue.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.24 (br. s, 1H), 7.72 (dd, *J* = 8.5, 1.4 Hz, 1H), 7.14 – 7.03 (m, 3H), 6.98 (dd, *J* = 8.5, 8.0 Hz, 1H), 6.84 – 6.73 (m, 2H), 3.75 (s, 3H), 2.57 (dd, *J* = 8.5, 6.7 Hz, 2H), 1.76 – 1.44 (m, 2H), 0.97 (t, *J* = 7.3 Hz, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 152.3, 139.9, 139.7, 136.8, 130.2, 128.6, 120.0, 118.7, 118.0, 116.2, 56.2, 37.4, 24.7, 13.9.

**HRMS (ESI):** calc. for C<sub>16</sub>H<sub>19</sub>N<sub>2</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 287.1390, found: 287.1398.

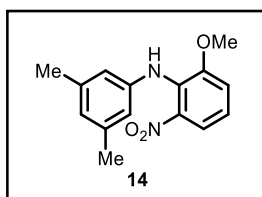


**Yield:** 63%; 477.0 mg of **13** was isolated as a red oily residue.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.22 (br. s, 1H), 7.73 (dd, *J* = 8.5, 1.4 Hz, 1H), 7.32 – 7.22 (m, 2H), 7.11 (dd, *J* = 8.1, 1.4 Hz, 1H), 6.99 (dd, *J* = 8.5, 8.0 Hz, 1H), 6.85 – 6.72 (m, 2H), 3.77 (s, 3H), 1.33 (s, 9H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 152.5, 145.3, 140.0, 139.7, 130.1, 125.4, 120.2, 118.3, 118.1, 116.3, 56.3, 34.3, 31.6.

**HRMS (ESI):** calc. for C<sub>17</sub>H<sub>21</sub>N<sub>2</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 301.1547, found: 301.1547.

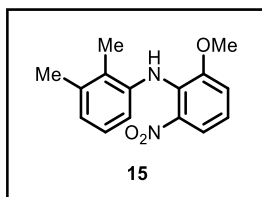


**Yield:** 67%; 366.1 mg of **14** was isolated as a red oily residue.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.02 (br. s, 1H), 7.70 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.11 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.01 (dd, *J* = 8.5, 8.1 Hz, 1H), 6.65 (m, 1H), 6.48 (m, 2H), 3.79 (s, 3H), 2.27 (q, *J* = 0.7 Hz, 6H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 152.7, 142.1, 140.4, 138.4, 129.6, 124.2, 120.4, 118.0, 116.3, 116.1, 56.3, 21.5.

**HRMS (ESI):** calc. for C<sub>15</sub>H<sub>17</sub>N<sub>2</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 273.1234, found: 273.1237.

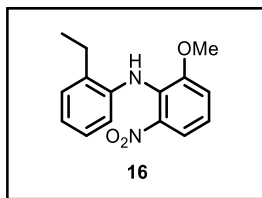


**Yield:** 65%; 315.8 mg of **15** was isolated as a red oily residue.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.10 (br. s, 1H), 7.74 (dd, *J* = 8.6, 1.4 Hz, 1H), 7.10 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.00 – 6.94 (m, 2H), 6.91 (m, 1H), 6.56 (m, 1H), 3.74 (s, 3H), 2.38 (s, 3H), 2.35 (s, 3H). Note: TMS used as reference (<sup>1</sup>H NMR spectrum; 0.00 ppm).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 152.1, 140.7, 139.3, 137.2, 131.4, 127.2, 125.0, 124.8, 119.5, 118.0, 116.7, 116.2, 56.3, 20.7, 13.7.

**HRMS (ESI):** calc. for C<sub>15</sub>H<sub>17</sub>N<sub>2</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 273.1234, found: 273.1233.

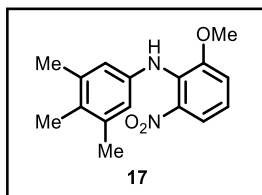


**Yield:** 60%; 260.2 mg of **16** was isolated as a red oily residue.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.17 (br. s, 1H), 7.68 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.19 (dd, *J* = 7.4, 1.8 Hz, 1H), 7.06 – 6.94 (m, 3H), 6.91 (dd, *J* = 8.5, 7.9 Hz, 1H), 6.60 (dd, *J* = 7.9, 1.5 Hz, 1H), 3.65 (s, 3H), 2.75 (q, *J* = 7.6 Hz, 2H), 1.31 (t, *J* = 7.6 Hz, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 152.2, 140.1, 139.5, 134.0, 131.1, 128.5, 125.8, 123.0, 119.8, 118.7, 118.0, 116.3, 56.2, 24.7, 13.8.

**HRMS (ESI):** calc. for C<sub>15</sub>H<sub>17</sub>N<sub>2</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 273.1234, found: 273.1233.

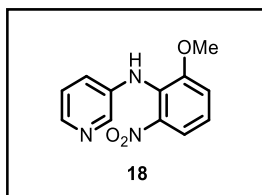


**Yield:** 61%; 427.6 mg of **17** was isolated as a red oily residue.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.00 (br. s, 1H), 7.69 (dd, *J* = 8.5, 1.4 Hz, 1H), 7.09 (dd, *J* = 8.0, 1.4 Hz, 1H), 6.97 (dd, *J* = 8.6, 8.0 Hz, 1H), 6.52 (pentet, *J* = 0.6 Hz, 2H), 3.78 (s, 3H), 2.22 (s, 3H), 2.22 (s, 3H), 2.12 (s, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 152.5, 139.9, 139.2, 136.9, 130.3, 129.4, 119.9, 118.2, 118.0, 116.1, 56.4, 20.9, 15.0.

**HRMS (ESI):** calc. for C<sub>16</sub>H<sub>19</sub>N<sub>2</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 287.1390, found: 287.1399.

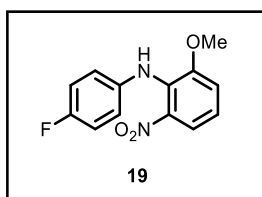


**Yield:** 76%; 249.1 mg of **18** was isolated as a yellow oily residue.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.25 (br. s, 1H), 8.18 – 8.10 (m, 2H), 7.67 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.15 – 7.05 (m, 2H), 7.05 – 6.94 (m, 2H), 3.70 (s, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 152.5, 142.9, 140.8, 140.7, 138.7, 128.2, 124.9, 123.0, 121.6, 117.9, 116.5, 56.2.

**HRMS (ESI):** calc. for C<sub>12</sub>H<sub>12</sub>N<sub>3</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 246.0873, found: 246.0884.

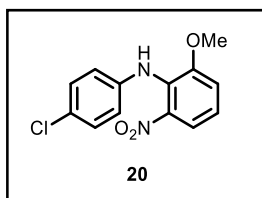


**Yield:** 81%; 401.8 mg of **19** was isolated as a red oily residue.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.22 (br. s, 1H), 7.71 (dd, *J* = 8.5, 1.4 Hz, 1H), 7.09 (dd, *J* = 8.1, 1.4 Hz, 1H), 6.99 (d, *J* = 8.3 Hz, 1H), 6.96 – 6.89 (m, 2H), 6.83 – 6.78 (m, 2H), 3.73 (s, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 158.6 (d, *J* = 240.8 Hz), 152.2, 139.8, 138.4 (d, *J* = 2.7 Hz), 130.2, 120.5 (d, *J* = 8.0 Hz), 120.3, 118.0, 116.4, 115.2 (d, *J* = 22.7 Hz), 56.2.

**HRMS (ESI):** calc. for C<sub>13</sub>H<sub>12</sub>FN<sub>2</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 263.0826, found: 263.0823.

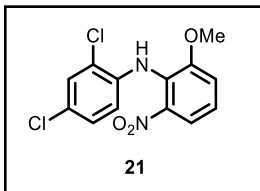


**Yield:** 83%; 515.0 mg of **20** was isolated as a red oily residue.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.14 (br. s, 1H), 7.70 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.21 – 7.13 (m, 2H), 7.11 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.03 (dd, *J* = 8.3, 8.3 Hz, 1H), 6.79 – 6.67 (m, 2H), 3.76 (s, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 152.5, 141.0, 140.5, 129.0, 128.6, 127.0, 121.2, 119.7, 118.0, 116.4, 56.2.

**HRMS (ESI):** calc. for C<sub>13</sub>H<sub>12</sub>ClN<sub>2</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 279.0531, found: 279.0538.



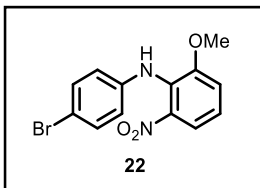
**Yield:** 60%; 354.7 mg of **21** was isolated as an orange solid.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.12 (br. s, 1H), 7.71 (dd, *J* = 7.6, 2.3 Hz, 1H), 7.36 (d, *J* = 2.3 Hz, 1H), 7.18 – 7.10 (m, 2H), 7.03 (ddd, *J* = 8.7, 2.3, 0.5 Hz, 1H), 6.46 (d, *J* = 8.7 Hz, 1H), 3.79 (s, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 153.0, 141.9, 137.9, 129.0, 127.2, 126.8, 126.2, 123.5, 122.6, 118.4, 118.0, 116.6, 56.4.

**HRMS (ESI):** calc. for C<sub>13</sub>H<sub>11</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 313.0141, found: 313.0146.

**MP:** 120 – 122 °C.

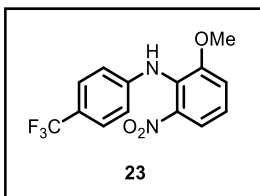


**Yield:** 52%; 289.5 mg of **22** was isolated as a red oily residue.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.11 (br. s, 1H), 7.70 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.34 – 7.27 (m, 2H), 7.11 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.04 (dd, *J* = 8.2, 8.2 Hz, 1H), 6.72 – 6.59 (m, 2H), 3.76 (s, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 152.6, 141.5, 140.7, 131.5, 128.8, 121.3, 120.1, 118.0, 116.5, 114.4, 56.3.

**HRMS (ESI):** calc. for C<sub>13</sub>H<sub>12</sub>BrN<sub>2</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 323.0026, found: 323.0037.

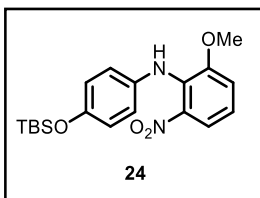


**Yield:** 21%; 124.5 mg of **23** was isolated as a red oily residue.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.10 (br. s, 1H), 7.73 (dd, *J* = 7.7, 2.1 Hz, 1H), 7.52 – 7.40 (m, 2H), 7.21 – 7.06 (m, 2H), 6.83 – 6.74 (m, 2H), 3.81 (s, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 153.3, 145.5 (d, *J* = 1.4 Hz), 142.0, 127.4, 126.1 (q, *J* = 3.8 Hz), 123.5 (q, *J* = 123.2 Hz), 123.3, 122.6, 118.0, 117.4, 116.6, 56.4.

**HRMS (ESI):** calc. for C<sub>14</sub>H<sub>12</sub>F<sub>3</sub>N<sub>2</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 313.0795, found: 313.0788.

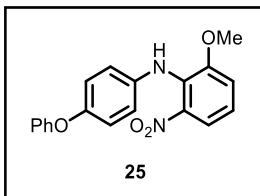


**Yield:** 53%; 474.2 mg of **24** was isolated as a red oily residue.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.36 (br. s, 1H), 7.71 (dd, *J* = 8.6, 1.4 Hz, 1H), 7.04 (dd, *J* = 8.0, 1.4 Hz, 1H), 6.91 (dd, *J* = 8.6, 7.9 Hz, 1H), 6.79 – 6.68 (m, 4H), 3.69 (s, 3H), 0.99 (s, 9H), 0.19 (s, 6H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 152.0, 151.5, 139.1, 136.2, 131.6, 121.1, 120.1, 119.3, 118.2, 116.4, 56.2, 25.9, 18.4, -4.3.

**HRMS (ESI):** calc. for C<sub>19</sub>H<sub>27</sub>N<sub>2</sub>O<sub>4</sub>Si [M+H]<sup>+</sup>: 375.1735, found: 375.1744.

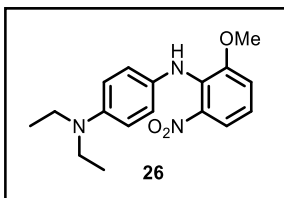


**Yield:** 76%; 646.9 mg of **25** was isolated as a red oily residue.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.29 (br. s, 1H), 7.73 (dd, *J* = 8.5, 1.4 Hz, 1H), 7.36 – 7.29 (m, 2H), 7.14 – 7.05 (m, 2H), 7.03 – 6.98 (m, 3H), 6.97 – 6.91 (m, 2H), 6.89 – 6.83 (m, 2H), 3.76 (s, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 158.1, 152.2, 152.0, 139.7, 138.1, 130.3, 129.8, 122.8, 120.4, 120.2, 119.7, 118.1, 116.4, 56.2. Note: One <sup>13</sup>C signal missing (aromatic region), likely due to overlap.

**HRMS (ESI):** calc. for C<sub>19</sub>H<sub>17</sub>N<sub>2</sub>O<sub>4</sub> [M+H]<sup>+</sup>: 337.1183, found: 337.1193.

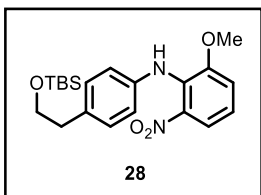


**Yield:** 50%; 298.7 mg of **26** was isolated as a dark purple oily residue.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.38 (br. s, 1H), 7.71 (dd, *J* = 8.7, 1.4 Hz, 1H), 7.02 (dd, *J* = 8.0, 1.4 Hz, 1H), 6.89 – 6.75 (m, 3H), 6.67 – 6.54 (m, 2H), 3.71 (s, 3H), 3.32 (q, *J* = 7.1 Hz, 4H), 1.15 (t, *J* = 7.1 Hz, 6H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 151.8, 144.7, 138.2, 132.4, 131.5, 121.6, 118.3, 118.3, 116.2, 112.7, 56.4, 44.8, 12.7.

**HRMS (ESI):** calc. for C<sub>17</sub>H<sub>22</sub>N<sub>3</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 316.1656, found: 316.1641.

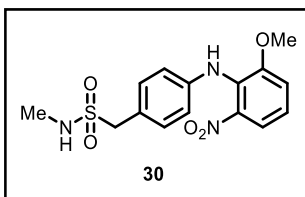


**Yield:** 83%; 695.1 mg of **28** was isolated as a red oily residue.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.21 (br. s, 1H), 7.70 (dd, *J* = 8.5, 1.4 Hz, 1H), 7.13 – 7.05 (m, 3H), 6.97 (m, 1H), 6.78 (d, *J* = 8.5 Hz, 2H), 3.81 (t, *J* = 7.0 Hz, 2H), 3.74 (s, 3H), 2.79 (t, *J* = 7.0 Hz, 2H), 0.91 (s, 9H), 0.02 (s, 6H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 152.4, 140.4, 139.9, 133.2, 129.9, 129.3, 120.2, 118.6, 117.9, 116.2, 64.7, 56.2, 39.0, 26.0, 18.4, -5.3.

**HRMS (ESI):** calc. for C<sub>21</sub>H<sub>31</sub>N<sub>2</sub>O<sub>4</sub>Si [M+H]<sup>+</sup>: 403.2048, found: 403.2061.



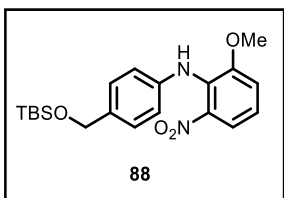
**Yield:** 46%; 228.1 mg of **30** was isolated as a red solid.

**<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):** δ 8.08 (s, 1H), 7.52 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.38 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.24 (dd, *J* = 8.3, 8.3 Hz, 1H), 7.11 (d, *J* = 8.5 Hz, 2H), 6.84 (q, *J* = 4.9 Hz, 1H), 6.63 (d, *J* = 8.5 Hz, 2H), 4.16 (s, 2H), 3.80 (s, 3H), 2.51 (d, *J* = 4.9 Hz, 3H).

**<sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):** δ 154.2, 144.0, 143.8, 131.1, 125.3, 123.5, 120.9, 116.5, 116.1, 114.9, 56.4, 55.5, 28.9.

**HRMS (ESI):** calc. for C<sub>15</sub>H<sub>17</sub>N<sub>3</sub>O<sub>5</sub>SNa [M+Na]<sup>+</sup>: 374.0781, found: 374.0791.

**MP:** 156 – 158 °C.

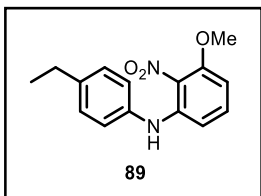


**Yield:** 82%; 601.9 mg of **88** was isolated as a red oily residue.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.23 (br. s, 1H), 7.72 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.09 (dd, *J* = 8.1, 1.4 Hz, 1H), 6.99 (t, *J* = 8.4 Hz, 1H), 6.81 (d, *J* = 8.4 Hz, 2H), 4.70 (s, 2H), 3.75 (s, 3H), 0.94 (s, 9H), 0.10 (s, 6H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 152.6, 141.2, 140.2, 135.5, 130.0, 126.7, 120.4, 118.6, 118.1, 116.3, 65.0, 56.3, 26.1, 18.6, -5.0.

**HRMS (ESI):** calc. for C<sub>20</sub>H<sub>27</sub>N<sub>2</sub>O<sub>4</sub>Si [M-H]<sup>-</sup>: 387.1746, found: 387.1744.



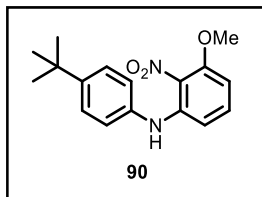
**Yield:** 60%; 397.1 mg of **89** was isolated as a red oily residue.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.58 (br. s, 1H), 7.22 – 7.13 (m, 3H), 7.11 – 7.05 (m, 2H), 6.79 (dd, *J* = 8.6, 1.1 Hz, 1H), 6.42 (dd, *J* = 8.3, 1.1 Hz, 1H), 3.89 (s, 3H), 2.65 (q, *J* = 7.6 Hz, 2H), 1.26 (t, *J* = 7.6 Hz, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 154.4, 141.0, 140.4, 137.5, 132.8, 129.5, 128.9, 122.5, 108.5, 102.0, 56.5, 28.3, 15.7.



**HRMS (ESI):** calc. for C<sub>15</sub>H<sub>17</sub>N<sub>2</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 273.1234, found: 273.1236.

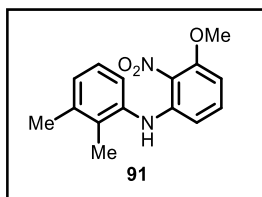


**Yield:** 84%; 502.3 mg of **90** was isolated as a red oily residue.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.57 (br. s, 1H), 7.42 – 7.31 (m, 2H), 7.19 (dd, *J* = 8.7, 8.5 Hz, 1H), 7.13 – 7.05 (m, 2H), 6.82 (dd, *J* = 8.7, 1.1 Hz, 1H), 6.42 (dd, *J* = 8.5, 1.1 Hz, 1H), 3.91 (s, 3H), 1.33 (s, 9H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 154.6, 147.4, 141.1, 137.4, 132.9, 129.7, 126.5, 122.2, 108.8, 102.2, 56.7, 34.6, 31.6.

**HRMS (ESI):** calc. for C<sub>17</sub>H<sub>21</sub>N<sub>2</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 301.1547, found: 301.1549.

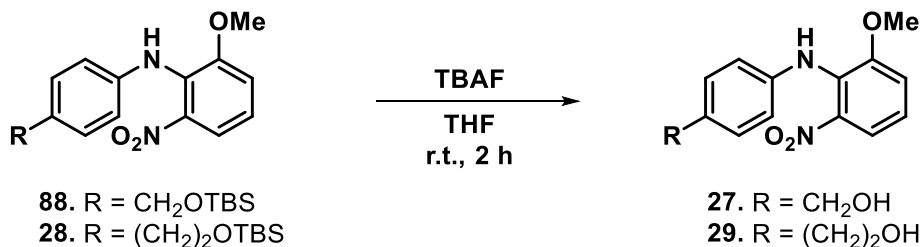


**Yield:** 49%; 295.3 mg of **91** was isolated as a red oily residue.

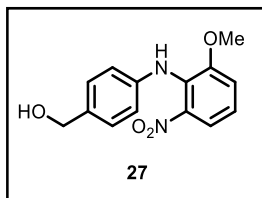
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.57 (br. s, 1H), 7.19 – 7.01 (m, 4H), 6.42 – 6.30 (m, 2H), 3.92 (s, 3H), 2.33 (s, 3H), 2.15 (s, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 154.9, 142.4, 138.6, 137.9, 133.2, 132.2, 128.7, 127.5, 126.3, 123.0, 108.2, 101.4, 56.7, 20.7, 14.0.

**HRMS (ESI):** calc. for C<sub>15</sub>H<sub>17</sub>N<sub>2</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 273.1234, found: 273.1236.



**General procedure for the deprotection of TBS ethers **28** and **88**.** To a stirring solution of *tert*-butyl-dimethyl silyl ethers (561.7 mg, 1.45 mmol) in anhydrous tetrahydrofuran (15 mL) was added 2.17 mL (2.17 mmol) of a 1 M solution of tetrabutylammonium fluoride in tetrahydrofuran. The reaction mixture was allowed to stir for 2 hours at room temperature. The reaction was then quenched with water and transferred to a separatory funnel containing ethyl acetate and brine. The organic layer was sequentially washed with brine before the organic layer was collected. The organic layer was dried with anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude solid was purified via flash column chromatography using hexanes:ethyl acetate (99:1 to 85:15) to elute pure alcohols as red oily residues.

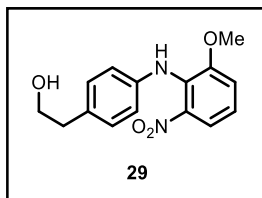


**Yield:** 99%; 422.1 mg of **27** was isolated as a red oily residue.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.12 (br. s, 1H), 7.69 (d, *J* = 8.2 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.10 (d, *J* = 8.2 Hz, 1H), 7.01 (dd, *J* = 8.2, 8.2 Hz, 1H), 6.79 (d, *J* = 8.3 Hz, 2H), 4.59 (s, 2H), 3.75 (s, 3H), 1.97 (br. s, 1H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 152.7, 141.8, 140.5, 134.8, 129.4, 127.8, 120.8, 118.5, 118.1, 116.3, 65.2, 56.3.

**HRMS (ESI):** calc. for C<sub>14</sub>H<sub>15</sub>N<sub>2</sub>O<sub>4</sub> [M+H]<sup>+</sup>: 275.1026, found: 275.1024.

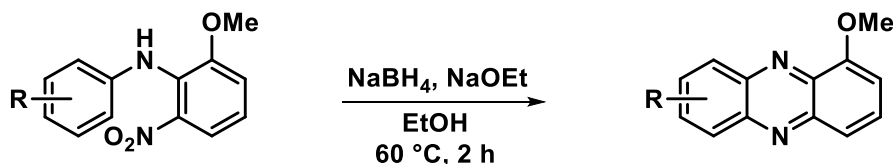


**Yield:** 97%; 297.4 mg of **29** was isolated as a red oily residue.

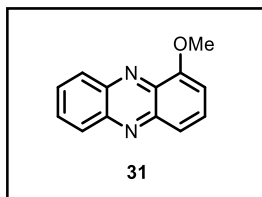
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.10 (br. s, 1H), 7.68 (dd, *J* = 8.5, 1.4 Hz, 1H), 7.13 – 7.03 (m, 3H), 6.98 (t, *J* = 8.3 Hz, 1H), 6.76 (d, *J* = 8.4 Hz, 2H), 3.79 (t, *J* = 6.6 Hz, 2H), 3.75 (s, 3H), 2.79 (t, *J* = 6.6 Hz, 2H), 1.94 (br. s, 1H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 152.5, 140.7, 140.1, 132.4, 129.7, 129.3, 120.5, 118.7, 118.0, 116.2, 63.8, 56.3, 38.6.

**HRMS (ESI):** calc. for C<sub>15</sub>H<sub>15</sub>N<sub>2</sub>O<sub>4</sub> [M-H]<sup>-</sup>: 287.1037, found: 287.1024.

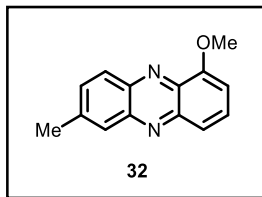


**General procedure for reductive cyclization.** To a stirring solution of diarylamine (1.27 mmol) in 2 N sodium ethoxide in ethanol (35 mL) was added sodium borohydride (290 mg, 7.66 mmol). The reaction was allowed to stir for 2 hours at 60 °C. The reaction was cooled to room temperature, quenched with water and then transferred to a separatory funnel containing ethyl acetate and brine. The organic layer was sequentially washed with brine before the organic layer was collected. The organic layer was dried with anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude solid was purified via flash column chromatography using hexanes:ethyl acetate (99:1 to 85:15) to elute pure 1-methoxyphenazine analogues.



**Yield:** 80%; 39.7 mg of **31** was isolated as a yellow solid.

**Note:** <sup>1</sup>H NMR and <sup>13</sup>C NMR spectral data match those previously reported.<sup>1</sup>



**Yield:** 83%; 265.9 mg of **32** was isolated as a yellow solid.

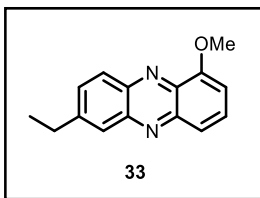
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.15 (m, 1H), 7.82 (m, 1H), 7.66 (dd, *J* = 8.9, 1.1 Hz, 1H), 7.56 (dd, *J* = 8.9, 7.5 Hz, 1H), 7.51 (dd, *J* = 8.9, 1.9 Hz, 1H), 6.86 (dd, *J* = 7.6, 1.1 Hz, 1H), 4.02 (s, 3H), 2.48 (d, *J* = 1.2 Hz, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 155.1, 144.1, 143.5, 141.5, 140.9, 136.2, 133.1, 130.2, 129.6, 127.3, 121.3, 105.9, 56.4, 22.2.

**HRMS (ESI):** calc. for C<sub>14</sub>H<sub>13</sub>N<sub>2</sub>O [M+H]<sup>+</sup>: 225.1022, found: 225.1026.

**MP:** 124 – 126 °C.

**Note:** Compound **32** is known (CAS: 13860-49-6), but no spectra were found for comparison.



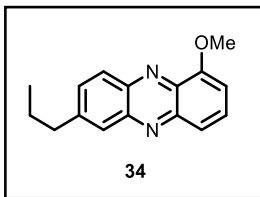
**Yield:** 97%; 294.4 mg of **33** was isolated as a yellow solid.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.05 (d, *J* = 8.9 Hz, 1H), 7.70 (m, 1H), 7.52 (dd, *J* = 8.9, 1.1 Hz, 1H), 7.41 – 7.33 (m, 2H), 6.68 (dd, *J* = 7.6, 1.1 Hz, 1H), 3.86 (s, 3H), 2.64 (qd, *J* = 7.5, 1.1 Hz, 2H), 1.12 (t, *J* = 7.6 Hz, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 155.3, 147.7, 144.3, 143.9, 141.4, 136.4, 132.5, 130.5, 129.9, 126.0, 121.4, 106.2, 56.6, 29.4, 14.6.

**HRMS (ESI):** calc. for C<sub>15</sub>H<sub>15</sub>N<sub>2</sub>O [M+H]<sup>+</sup>: 239.1179, found: 239.1182.

**MP:** 106 – 108 °C.



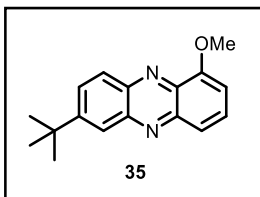
**Yield:** 70%; 277.3 mg of **34** was isolated as a yellow solid.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.24 (dd, *J* = 9.0, 0.6 Hz, 1H), 7.91 (dq, *J* = 1.8, 0.9 Hz, 1H), 7.74 (dd, *J* = 9.0, 1.1 Hz, 1H), 7.67 – 7.56 (m, 2H), 6.96 (dd, *J* = 7.8, 1.1 Hz, 1H), 4.10 (s, 3H), 2.81 (td, *J* = 7.5, 0.9 Hz, 2H), 1.92 – 1.52 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 155.2, 146.1, 144.3, 143.7, 141.3, 136.4, 132.6, 130.4, 129.8, 126.8, 121.4, 106.1, 56.5, 38.4, 23.6, 13.9.

**HRMS (ESI):** calc. for C<sub>16</sub>H<sub>17</sub>N<sub>2</sub>O [M+H]<sup>+</sup>: 253.1335, found: 253.1335.

**MP:** 70 – 72 °C.

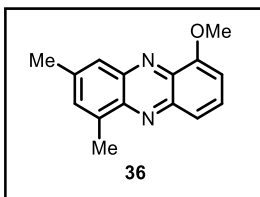


**Yield:** 94%; 363.8 mg of **35** was isolated as a yellow oily residue.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** 8.10 (dd, *J* = 9.2, 0.6 Hz, 1H), 7.89 (dd, *J* = 2.2, 0.6 Hz, 1H), 7.69 (dd, *J* = 9.2, 2.1 Hz, 1H), 7.53 (dd, *J* = 8.8, 1.1 Hz, 1H), 7.43 – 7.32 (m, 1H), 6.68 (dd, *J* = 7.6, 1.1 Hz, 1H), 3.86 (s, 3H), 1.22 (s, 9H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 154.8, 153.8, 143.9, 143.3, 140.7, 136.1, 129.9, 129.6, 129.2, 123.4, 120.9, 105.7, 56.1, 35.2, 30.5.

**HRMS (ESI):** calc. for C<sub>17</sub>H<sub>19</sub>N<sub>2</sub>O [M+H]<sup>+</sup>: 267.1492, found: 267.1502.



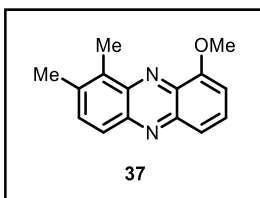
**Yield:** 86%; 233.1 mg of **36** was isolated as a yellow solid.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.91 (m, 1H), 7.75 (dd, *J* = 8.8, 1.1 Hz, 1H), 7.57 (dd, *J* = 8.8, 7.6 Hz, 1H), 7.37 (m, 1H), 6.93 (dd, *J* = 7.6, 1.1 Hz, 1H), 4.08 (s, 3H), 2.78 (dd, *J* = 1.0, 1.0 Hz, 3H), 2.49 (d, *J* = 1.0 Hz, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 154.9, 143.0, 142.5, 142.0, 140.6, 136.8, 136.3, 132.9, 129.2, 126.2, 121.9, 106.2, 56.4, 22.3, 17.6.

**HRMS (ESI):** calc. for C<sub>15</sub>H<sub>15</sub>N<sub>2</sub>O [M+H]<sup>+</sup>: 239.1179, found: 239.1177.

**MP:** 117 – 119 °C.



**Yield:** 44%; 121.3 mg of **37** was isolated as a yellow solid.

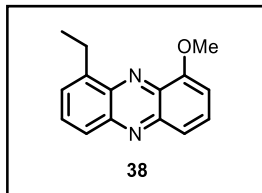
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.92 (d, *J* = 8.9 Hz, 1H), 7.75 (dd, *J* = 8.8, 1.1 Hz, 1H), 7.63 (dd, *J* = 8.8, 7.5 Hz, 1H), 7.58 (d, *J* = 8.9 Hz, 1H), 6.95 (dd, *J* = 7.5, 1.1 Hz, 1H), 4.10 (s, 3H), 2.86 (s, 3H), 2.49 (s, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 155.4, 143.2, 142.4, 141.7, 137.6, 136.0, 134.8, 134.7, 129.9, 126.1, 121.2, 106.3, 56.5, 20.8, 13.4.

**HRMS (ESI):** calc. for C<sub>15</sub>H<sub>15</sub>N<sub>2</sub>O [M+H]<sup>+</sup>: 239.1179, found: 239.1179.

**MP:** 157 – 159 °C, lit. 165 – 168 °C.<sup>2</sup>

**Note:** <sup>1</sup>H NMR tabulation and melting point match previously reported values.<sup>2</sup>



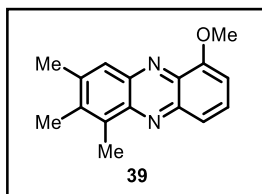
**Yield:** 46%; 104.5 mg of **38** was isolated as a yellow solid.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.03 (m, 1H), 7.78 (dd, *J* = 8.9, 1.2 Hz, 1H), 7.74 (dd, *J* = 8.7, 6.9 Hz, 1H), 7.68 (dd, *J* = 8.8, 7.5 Hz, 1H), 7.61 (dq, *J* = 6.9, 1.2 Hz, 1H), 6.99 (dd, *J* = 7.6, 1.1 Hz, 1H), 4.11 (s, 3H), 3.49 (q, *J* = 7.5 Hz, 2H), 1.45 (t, *J* = 7.5 Hz, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 155.6, 144.1, 143.9, 143.7, 141.4, 136.2, 131.0, 130.4, 127.5, 127.2, 121.3, 106.6, 56.7, 23.8, 14.5.

**HRMS (ESI):** calc. for C<sub>15</sub>H<sub>15</sub>N<sub>2</sub>O [M+H]<sup>+</sup>: 239.1179, found: 239.1184.

**MP:** 124 – 126 °C.



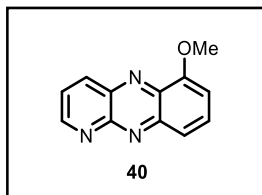
**Yield:** 60%; 213.2 mg of **39** was isolated as a yellow solid.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.93 (s, 1H), 7.74 (dd, *J* = 8.8, 1.1 Hz, 1H), 7.55 (dd, *J* = 8.8, 7.6 Hz, 1H), 6.89 (dd, *J* = 7.6, 1.1 Hz, 1H), 4.07 (s, 3H), 2.77 (s, 3H), 2.44 (d, *J* = 1.1 Hz, 3H), 2.32 (s, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 154.9, 143.1, 142.2, 141.3, 141.2, 138.5, 135.7, 133.4, 129.0, 126.3, 121.9, 105.8, 56.3, 21.9, 16.8, 13.4.

**HRMS (ESI):** calc. for C<sub>16</sub>H<sub>17</sub>N<sub>2</sub>O [M+H]<sup>+</sup>: 253.1335, found: 253.1339.

**MP:** 196 – 198 °C.



**Yield:** 42%; 49.4 mg of **40** was isolated as a yellow solid.

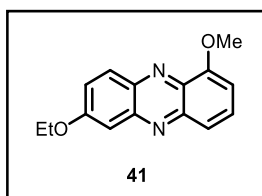
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 9.37 (dd, *J* = 3.9, 2.0 Hz, 1H), 8.76 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.97 (dd, *J* = 8.9, 1.1 Hz, 1H), 7.84 (dd, *J* = 8.9, 7.6 Hz, 1H), 7.78 (dd, *J* = 8.7, 3.9 Hz, 1H), 7.14 (dd, *J* = 7.6, 1.1 Hz, 1H), 4.20 (s, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 156.9, 155.1, 149.8, 145.9, 139.1, 137.9, 137.7, 132.2, 125.4, 122.1, 107.3, 56.7.

**HRMS (ESI):** calc. for C<sub>12</sub>H<sub>10</sub>N<sub>3</sub>O [M+H]<sup>+</sup>: 212.0818, found: 212.0822.

**MP:** 141 – 143 °C.

**Note:** Compound 40 is known (CAS: 54696-72-9), but no characterization data was reported.<sup>3</sup>



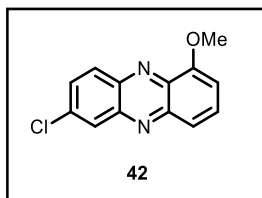
**Yield:** 79%; 110.0 mg of **41** was isolated as a yellow solid.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.12 (d, *J* = 9.5 Hz, 1H), 7.61 (dd, *J* = 8.8, 1.4 Hz, 1H), 7.56 (dd, *J* = 8.8, 7.3 Hz, 1H), 7.35 (dd, *J* = 9.5, 2.7 Hz, 1H), 7.21 (d, *J* = 2.7 Hz, 1H), 6.84 (dd, *J* = 7.4, 1.4 Hz, 1H), 4.10 (q, *J* = 7.0 Hz, 2H), 4.02 (s, 3H), 1.40 (t, *J* = 7.0 Hz, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 161.0, 155.5, 145.4, 144.2, 139.5, 135.1, 131.3, 130.6, 126.4, 120.9, 105.6, 104.9, 64.4, 56.6, 14.7.

**MP:** 149 – 151 °C, lit. 148 – 149 °C.<sup>4</sup>

**Note:** Compound **41** is known (CAS: 58476-65-6), but only melting point was found for comparison.



**Yield:** 71%; 380.0 mg of **42** was isolated as a yellow solid.

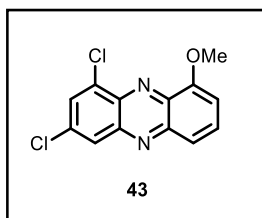
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.14 (dd, *J* = 9.2, 0.6 Hz, 1H), 8.00 (dd, *J* = 2.4, 0.6 Hz, 1H), 7.64 – 7.47 (m, 3H), 6.87 (dd, *J* = 6.2, 2.4 Hz, 1H), 4.02 (s, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 155.0, 144.3, 143.2, 140.3, 136.7, 136.5, 131.4, 131.3, 131.1, 127.6, 121.2, 106.6, 56.4.

**HRMS (ESI):** calc. for C<sub>13</sub>H<sub>10</sub>ClN<sub>2</sub>O [M+H]<sup>+</sup>: 245.0476, found: 245.0479.

**MP:** 162 – 164 °C, lit. 164 – 165 °C.<sup>5</sup>

**Note:** Compound **42** is known (CAS: 13554-02-4), but only melting point data was found for comparison.



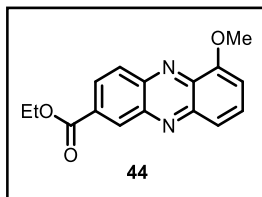
**Yield:** 15%; 10.2 mg of **43** was isolated as a yellow solid.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.17 (d, *J* = 2.2 Hz, 1H), 7.92 (d, *J* = 2.2 Hz, 1H), 7.86 – 7.75 (m, 2H), 7.11 (dd, *J* = 6.5, 2.3 Hz, 1H), 4.18 (s, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 155.6, 145.1, 143.7, 137.6, 136.8, 136.1, 135.0, 132.5, 130.9, 127.3, 121.1, 107.6, 56.9.

**HRMS (ESI):** calc. for C<sub>13</sub>H<sub>9</sub>Cl<sub>2</sub>N<sub>2</sub>O [M+H]<sup>+</sup>: 279.0086, found: 279.0082.

**MP:** 186 – 188 °C.



**Yield:** 84%; 77.5 mg of **44** was isolated as a yellow solid.

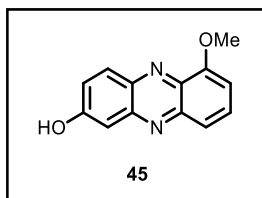
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.97 (dd, *J* = 1.8, 0.8 Hz, 1H), 8.43 (dd, *J* = 9.1, 0.7 Hz, 1H), 8.37 (dd, *J* = 9.1, 1.8 Hz, 1H), 7.84 (dd, *J* = 8.9, 1.2 Hz, 1H), 7.77 (dd, *J* = 8.9, 7.4 Hz, 1H), 7.10 (dd, *J* = 7.4, 1.2 Hz, 1H), 4.48 (q, *J* = 7.1 Hz, 2H), 4.18 (s, 3H), 1.46 (t, *J* = 7.1 Hz, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 165.9, 155.3, 145.0, 143.6, 142.8, 137.9, 132.7, 132.5, 131.3, 130.6, 129.3, 121.9, 107.6, 61.9, 56.8, 14.5.

**HRMS (ESI):** calc. for C<sub>16</sub>H<sub>15</sub>N<sub>2</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 305.0897, found: 305.0908.

**MP:** 139 – 141 °C.

**Note:** Product obtained from an acidic workup following reductive cyclization of diarylamine intermediate **23**.



**Yield:** 64%; 183.0 mg of **45** was isolated as a yellow solid.

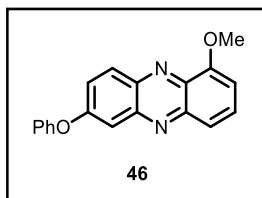
**<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):** δ 10.86 (s, 1H), 8.13 (d, *J* = 9.4 Hz, 1H), 7.77 (dd, *J* = 8.8, 7.6 Hz, 1H), 7.64 (dd, *J* = 8.8, 1.1 Hz, 1H), 7.55 (dd, *J* = 9.4, 2.6 Hz, 1H), 7.31 (d, *J* = 2.6 Hz, 1H), 7.14 (dd, *J* = 7.6, 1.1 Hz, 1H), 4.04 (s, 3H).

**<sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):** δ 159.8, 155.2, 144.6, 143.7, 138.1, 134.1, 131.1, 130.9, 125.8, 119.9, 106.9, 105.8, 55.9.

**HRMS (ESI):** calc. for C<sub>13</sub>H<sub>11</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 249.0634, found: 249.0636.

**MP:** 210 °C (decomp), lit. 200 °C (decomp).<sup>6</sup>

**Note:** Product obtained from reductive cyclization of TBS-protected diarylamine **24**. Compound **45** has been previously reported (CAS: 1071603-13-8), but no spectra were found for comparison.



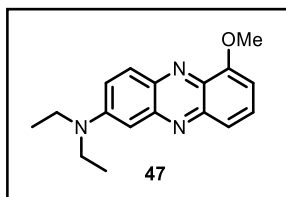
**Yield:** 71%; 388.2 mg of **46** was isolated as a yellow solid.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.35 (dd, *J* = 9.5, 0.5 Hz, 1H), 7.74 – 7.61 (m, 3H), 7.49 – 7.39 (m, 2H), 7.34 (dd, *J* = 2.7, 0.5 Hz, 1H), 7.29 – 7.16 (m, 3H), 6.96 (dd, *J* = 6.2, 2.5 Hz, 1H), 4.13 (s, 3H). Note: TMS used for reference of <sup>1</sup>H NMR spectrum (0.00 ppm).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 160.5, 155.2, 154.7, 144.5, 144.2, 139.5, 135.5, 131.8, 130.7, 130.3, 125.4, 125.3, 121.0, 120.8, 109.9, 105.8, 56.4.

**HRMS (ESI):** calc. for C<sub>19</sub>H<sub>15</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 303.1128, found: 303.1140.

**MP:** 163 – 165 °C.

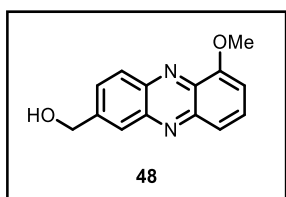


**Yield:** 89%; 88.3 mg of **47** was isolated as a red oily residue.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.15 (d, *J* = 9.7 Hz, 1H), 7.67 – 7.57 (m, 2H), 7.49 (dd, *J* = 9.7, 2.8 Hz, 1H), 7.00 (d, *J* = 2.8 Hz, 1H), 6.87 (dd, *J* = 6.2, 2.6 Hz, 1H), 4.12 (s, 3H), 3.54 (q, *J* = 7.1 Hz, 4H), 1.28 (t, *J* = 7.1 Hz, 6H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 155.6, 149.2, 146.2, 144.9, 138.2, 133.8, 131.2, 130.2, 122.3, 120.5, 104.2, 101.3, 56.4, 45.1, 13.0.

**HRMS (ESI):** calc. for C<sub>17</sub>H<sub>20</sub>N<sub>3</sub>O [M+H]<sup>+</sup>: 282.1601, found: 282.1607.



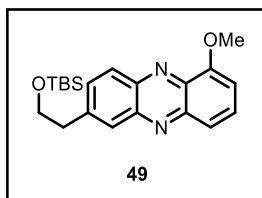
**Yield:** 68%; 148.5 mg of **48** was isolated as a yellow solid.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.35 (d, *J* = 9.0 Hz, 1H), 8.20 (d, *J* = 1.5 Hz, 1H), 7.85 – 7.72 (m, 3H), 7.07 (dd, *J* = 7.5, 1.2 Hz, 1H), 5.00 (d, *J* = 6.1 Hz, 2H), 4.18 (s, 3H), 2.57 (t, *J* = 6.1 Hz, 1H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 155.3, 144.5, 144.4, 143.6, 142.0, 136.9, 130.8, 130.6, 129.7, 125.7, 121.5, 106.6, 65.0, 56.7.

**HRMS (ESI):** calc. for C<sub>14</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub>Na [M+Na]<sup>+</sup>: 263.0791, found: 263.0802.

**MP:** 209 – 211 °C.

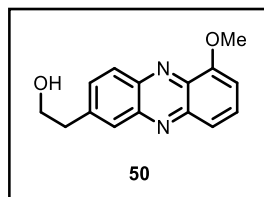


**Yield:** 31%; 161.6 mg of **49** was isolated as a yellow oily residue.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.25 (dd, *J* = 9.0, 0.8 Hz, 1H), 7.96 (dt, *J* = 1.9, 0.8 Hz, 1H), 7.75 (dd, *J* = 9.0, 1.2 Hz, 1H), 7.67 (dd, *J* = 8.9, 1.9 Hz, 1H), 7.65 (dd, *J* = 8.9, 7.5 Hz, 1H), 6.96 (dd, *J* = 7.7, 1.1 Hz, 1H), 4.10 (s, 3H), 3.93 (t, *J* = 6.7 Hz, 2H), 3.04 (td, *J* = 6.7, 0.8 Hz, 2H), 0.79 (s, 9H), -0.09 (s, 6H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 155.2, 144.3, 143.6, 143.1, 141.4, 136.5, 133.1, 130.4, 129.7, 128.0, 121.4, 106.2, 63.8, 56.5, 39.9, 26.0, 18.4, -5.3.

**HRMS (ESI):** calc. for C<sub>21</sub>H<sub>29</sub>N<sub>2</sub>O<sub>2</sub>Si [M+H]<sup>+</sup>: 369.1993, found: 369.2009.



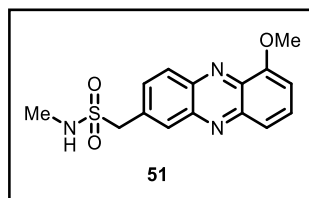
**Yield:** 64%; 116.1 mg of **50** was isolated as a yellow solid.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.28 (d, *J* = 8.9 Hz, 1H), 8.03 (m, 1H), 7.78 (dd, *J* = 8.9, 1.4 Hz, 1H), 7.76 – 7.67 (m, 2H), 7.05 (dd, *J* = 7.3, 1.4 Hz, 1H), 4.17 (s, 3H), 4.08 (t, *J* = 6.4 Hz, 2H), 3.16 (t, *J* = 6.4 Hz, 2H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 155.3, 144.4, 143.5, 142.5, 141.5, 136.7, 132.6, 130.8, 130.3, 128.2, 121.5, 106.5, 63.0, 56.7, 39.7.

**HRMS (ESI):** calc. for C<sub>15</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>Na [M+Na]<sup>+</sup>: 277.0947, found: 277.0946.

**MP:** 148 – 150 °C.



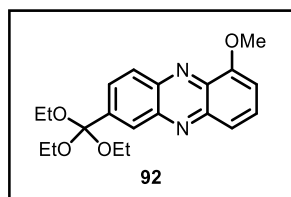
**Yield:** 73%; 71.4 mg of **51** was isolated as a yellow solid.

**<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):** δ 8.29 (d, *J* = 8.9 Hz, 1H), 8.24 (d, *J* = 1.6 Hz, 1H), 7.93 (dd, *J* = 9.0, 1.9 Hz, 1H), 7.88 (dd, *J* = 8.9, 7.5 Hz, 1H), 7.79 (dd, *J* = 8.9, 1.2 Hz, 1H), 7.29 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.09 (q, *J* = 4.8 Hz, 1H), 4.73 (s, 2H), 4.08 (s, 3H), 2.66 (d, *J* = 4.8 Hz, 3H).

**<sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):** δ 155.0, 143.7, 142.4, 141.1, 136.3, 134.0, 133.2, 131.5, 130.8, 129.4, 120.6, 107.4, 56.0, 55.4, 28.9.

**HRMS (ESI):** calc. for C<sub>15</sub>H<sub>16</sub>N<sub>3</sub>O<sub>3</sub>S [M+H]<sup>+</sup>: 318.0907, found: 318.0917.

**MP:** 171 – 173 °C.



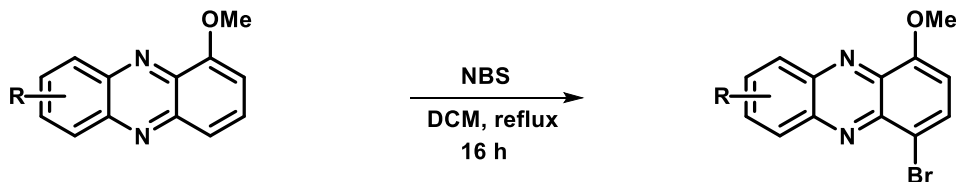
**Yield:** 77%; 109.1 mg of **92** was isolated as a yellow oily residue.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.46 (m, 1H), 8.30 (dd, *J* = 9.1, 1.6 Hz, 1H), 7.92 (dt, *J* = 9.1, 1.6 Hz, 1H), 7.72 (m, 1H), 7.64 (m, 1H), 6.95 (m, 1H), 4.06 (s, 3H), 3.35 (q, *J* = 7.2 Hz, 6H), 1.12 (t, *J* = 7.2 Hz, 9H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 155.1, 144.4, 142.9, 142.2, 141.0, 137.0, 130.6, 130.2, 129.2, 128.6, 121.4, 113.2, 106.7, 57.9, 56.5, 14.9.

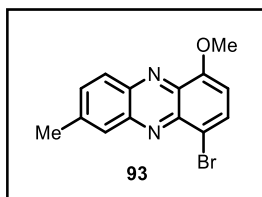
**HRMS (ESI):** calc. for C<sub>20</sub>H<sub>25</sub>N<sub>2</sub>O<sub>4</sub> [M+H]<sup>+</sup>: 357.1809, found: 357.1806.

**Note:** Unstable product obtained from a basic workup following reductive cyclization of diarylamine intermediate **23**.



**General procedure for mono-bromination of the 4-position of 1-methoxyphenazines (93 – 96):** 1-Methoxyphenazines (0.49 mmol) was dissolved in dichloromethane (15 mL) before *N*-bromosuccinimide (140.9 mg, 0.79 mmol) was added and the reaction was brought to reflux. The mixture was left to stir overnight until complete (monitored by TLC with dichloromethane). At this time, the reaction was concentrated and

adsorbed onto silica gel (via dissolving the crude reaction contents and silica gel in dichloromethane, then concentrating via rotavap) and purified via column chromatography using dichloromethane to elute pure 4-bromo-1-methoxyphenazines as yellow solids.



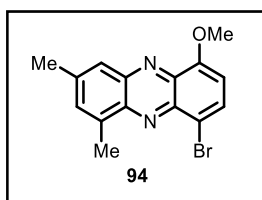
**Yield:** 88%; 172.5 mg of **93** was isolated as a yellow solid.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.27 (dt, *J* = 8.9, 0.5 Hz, 1H), 8.12 (ddd, *J* = 1.9, 1.2, 0.7 Hz, 1H), 8.03 (d, *J* = 8.2 Hz, 1H), 7.69 (dd, *J* = 8.9, 1.9 Hz, 1H), 6.91 (d, *J* = 8.3 Hz, 1H), 4.14 (s, 3H), 2.63 (d, *J* = 1.1 Hz, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 155.3, 143.9, 142.5, 141.3, 141.2, 136.7, 134.3, 133.1, 129.4, 128.1, 114.3, 106.6, 56.8, 22.4.

**HRMS (ESI):** calc. for C<sub>14</sub>H<sub>12</sub>BrN<sub>2</sub>O [M+H]<sup>+</sup>: 303.0128, found: 303.0140.

**MP:** 148 – 150 °C.



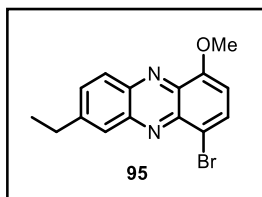
**Yield:** 55%; 71.6 mg of **94** was isolated as a yellow solid.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.00 (d, *J* = 8.2 Hz, 1H), 7.98 (m, 1H), 7.55 (m, 1H), 6.92 (d, *J* = 8.2 Hz, 1H), 4.15 (s, 3H), 2.93 (t, *J* = 0.8 Hz, 3H), 2.59 (d, *J* = 1.1 Hz, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 155.1, 142.9, 142.2, 142.0, 139.8, 137.7, 136.9, 133.7, 132.1, 125.9, 115.2, 106.9, 56.7, 22.6, 17.4.

**HRMS (ESI):** calc. for C<sub>15</sub>H<sub>14</sub>BrN<sub>2</sub>O [M+H]<sup>+</sup>: 317.0284, found: 317.0300.

**MP:** 170 – 172 °C.



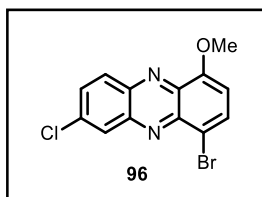
**Yield:** 83%; 154.7 mg of **95** was isolated as a yellow solid.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.21 (dd, *J* = 8.9, 0.6 Hz, 1H), 8.04 (m, 1H), 7.92 (d, *J* = 8.3 Hz, 1H), 7.64 (dd, *J* = 9.0, 1.9 Hz, 1H), 6.79 (d, *J* = 8.3 Hz, 1H), 4.05 (s, 3H), 2.86 (qd, *J* = 7.6, 1.1 Hz, 2H), 1.32 (t, *J* = 7.6 Hz, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 155.1, 148.2, 143.8, 141.3, 140.9, 136.5, 133.2, 132.9, 129.3, 126.3, 114.0, 106.4, 56.6, 29.3, 14.5.

**HRMS (ESI):** calc. for C<sub>15</sub>H<sub>14</sub>BrN<sub>2</sub>O [M+H]<sup>+</sup>: 317.0284, found: 317.0295.

**MP:** 137 – 139 °C.



**Yield:** 96%; 151.7 mg of **96** was isolated as a yellow solid.

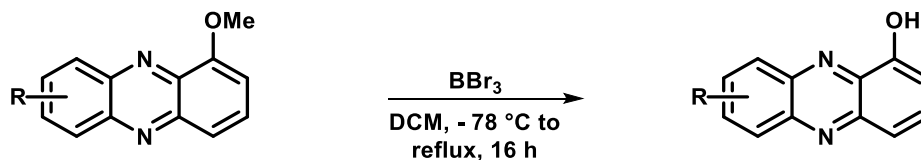
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.37 (dd, *J* = 2.3, 0.6 Hz, 1H), 8.33 (dd, *J* = 9.3, 0.6 Hz, 1H), 8.08 (d, *J* = 8.3 Hz, 1H), 7.78 (dd, *J* = 9.3, 2.3 Hz, 1H), 6.95 (d, *J* = 8.3 Hz, 1H), 4.16 (s, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 155.3, 143.6, 141.5, 140.9, 137.8, 137.2, 134.1, 132.7, 131.2, 128.4, 114.3, 107.3, 56.9.

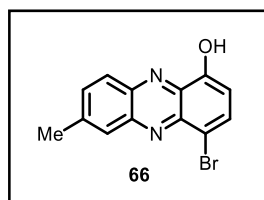
**HRMS (ESI):** calc. for C<sub>13</sub>H<sub>8</sub>BrClN<sub>2</sub>ONa [M+Na]<sup>+</sup>: 346.9379, found: 346.9392.

**MP:** 189 – 191 °C.





**General boron tribromide demethylation procedure.** To a round bottom flask was added the desired 1-methoxyphenazine (1.07 mmol) dissolved in anhydrous dichloromethane (18 mL). The mixture was brought to  $-78\text{ }^{\circ}\text{C}$  in a dry ice bath before dropwise addition of 1M boron tribromide solution in dichloromethane (6.4 mL, 6.41 mmol). The reaction was left to stir at  $-78\text{ }^{\circ}\text{C}$  for 1 hour, and then allowed to reach ambient temperature for reaction overnight. The reaction was heated to reflux for 8 hours until complete (monitored by TLC). The solution was transferred to a separatory funnel containing an aqueous solution of saturated sodium bicarbonate, and then extracted with dichloromethane. Organic solvents were dried with sodium sulfate, filtered through cotton, and removed *in vacuo*. The resulting solid was purified via column chromatography using dichloromethane to elute pure 1-hydroxyphenazines as yellow solids. **Note:** Analogous procedures were used for all demethylation reactions using  $\text{BBr}_3$ .



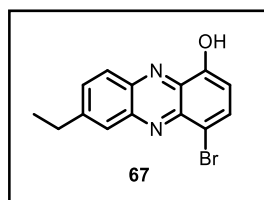
**Yield:** 96%; 122.6 mg of **66** was isolated as a yellow solid.

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta$  8.19 (s, 1H), 8.17 (ddd,  $J = 1.9, 1.2, 0.7$  Hz, 1H), 8.12 (dt,  $J = 8.9, 0.5$  Hz, 1H), 8.05 (d,  $J = 8.1$  Hz, 1H), 7.72 (dd,  $J = 8.9, 1.9$  Hz, 1H), 7.10 (d,  $J = 8.1$  Hz, 1H), 2.67 (d,  $J = 1.2$  Hz, 3H).

**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):**  $\delta$  151.9, 144.7, 142.5, 141.0, 140.3, 134.6, 134.4, 128.5, 128.5, 112.2, 109.2, 22.5. Note: One  $^{13}\text{C}$  NMR signal missing in the aromatic region, likely due to overlap.

**HRMS (ESI):** calc. for  $\text{C}_{13}\text{H}_{10}\text{BrN}_2\text{O}$   $[\text{M}+\text{H}]^+$ : 288.9971, found: 288.9978.

**MP:** 179 – 181  $^{\circ}\text{C}$ .



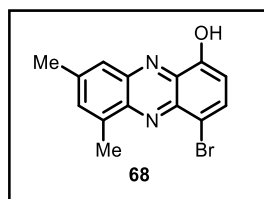
**Yield:** 92%; 136.1 mg of **67** was isolated as a yellow solid.

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta$  8.17 (br. s, 1H), 8.11 (m, 1H), 8.04 (dd,  $J = 8.9, 0.6$  Hz, 1H), 8.01 (d,  $J = 8.1$  Hz, 1H), 7.68 (m, 1H), 7.06 (d,  $J = 8.1$  Hz, 1H), 2.93 (qd,  $J = 7.5, 1.1$  Hz, 2H), 1.40 (t,  $J = 7.5$  Hz, 3H).

**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):**  $\delta$  151.8, 148.3, 144.7, 140.8, 140.3, 134.5, 134.3, 133.7, 128.4, 126.8, 112.1, 109.1, 29.5, 14.6.

**HRMS (ESI):** calc. for  $\text{C}_{14}\text{H}_{12}\text{BrN}_2\text{O}$   $[\text{M}+\text{H}]^+$ : 303.0128, found: 303.0126.

**MP:** 96 – 98  $^{\circ}\text{C}$ .



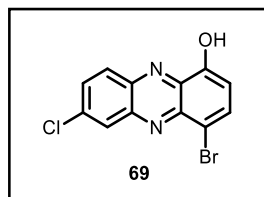
**Yield:** 82%; 56.3 mg of **68** was isolated as a yellow solid.

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta$  8.15 (br. s, 1H), 7.99 (d,  $J = 8.1$  Hz, 1H), 7.75 (m, 1H), 7.53 (dd,  $J = 2.0, 1.1$  Hz, 1H), 7.08 (d,  $J = 8.1$  Hz, 1H), 2.91 (s, 3H), 2.60 (d,  $J = 1.1$  Hz, 3H).

**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):**  $\delta$  151.6, 142.9, 142.4, 141.8, 139.5, 138.1, 134.6, 133.6, 133.3, 124.8, 113.0, 109.3, 22.6, 17.6.

**HRMS (ESI):** calc. for  $\text{C}_{14}\text{H}_{12}\text{BrN}_2\text{O}$   $[\text{M}+\text{H}]^+$ : 303.0128, found: 303.0130.

**MP:** 180 – 182 °C.



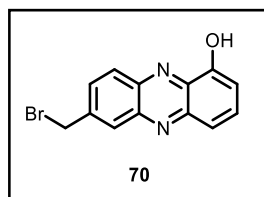
**Yield:** 90%; 120.2 mg of **69** was isolated as a yellow solid.

**<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):** δ 10.98 (br. s, 1H), 8.33 (d, *J* = 2.3 Hz, 1H), 8.30 (d, *J* = 9.3 Hz, 1H), 8.16 (d, *J* = 8.2 Hz, 1H), 7.95 (dd, *J* = 9.3, 2.3 Hz, 1H), 7.13 (d, *J* = 8.2 Hz, 1H).

**<sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):** δ 153.9, 142.7, 140.6, 139.9, 136.5, 136.4, 135.6, 132.1, 131.2, 127.5, 111.4, 110.3.

**HRMS (ESI):** calc. for C<sub>12</sub>H<sub>5</sub>BrClN<sub>2</sub>O [M-H]<sup>-</sup>: 308.9257, found: 308.9258.

**MP:** 199 – 201 °C.



**Yield:** 87%; 93.9 mg of **70** was isolated as a yellow solid.

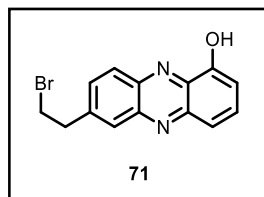
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.24 – 8.18 (m, 2H), 8.14 (s, 1H), 7.85 (dd, *J* = 9.0, 2.1 Hz, 1H), 7.79 – 7.75 (m, 2H), 7.24 (m, 1H), 4.73 (s, 2H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 152.0, 144.4, 144.0, 141.0, 140.6, 135.1, 132.3, 131.7, 130.2, 129.2, 120.2, 109.5, 32.8.

**HRMS (DART):** calc. for C<sub>13</sub>H<sub>10</sub>BrN<sub>2</sub>O [M+H]<sup>+</sup>: 288.9971, found: 288.9985.

**MP:** 160 – 162 °C.

**Note:** Product obtained from BBr<sub>3</sub> demethylation of HP **48**. NMR spectra acquired at 40 °C.



**Yield:** 53%; 70.3 mg of **71** was isolated as a yellow solid.

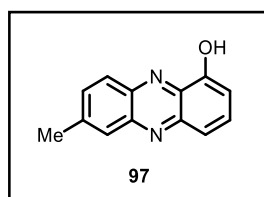
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.21 (br. s, 1H), 8.15 (dd, *J* = 8.9, 0.6 Hz, 1H), 8.07 (dt, *J* = 1.9, 0.8 Hz, 1H), 7.78 – 7.74 (m, 2H), 7.68 (dd, *J* = 8.9, 2.0 Hz, 1H), 7.22 (dd, *J* = 4.6, 3.9 Hz, 1H), 3.75 (t, *J* = 7.3 Hz, 2H), 3.46 (t, *J* = 7.3 Hz, 2H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 151.9, 144.2, 144.1, 142.0, 140.5, 134.7, 132.1, 132.1, 129.5, 128.6, 120.1, 109.0, 39.4, 31.8.

**HRMS (ESI):** calc. for C<sub>14</sub>H<sub>12</sub>BrN<sub>2</sub>O [M+H]<sup>+</sup>: 303.0128, found: 303.0128.

**MP:** 155 – 157 °C.

**Note:** Product obtained from BBr<sub>3</sub> demethylation of HP **50**.



**Yield:** 97%; 224.4 mg of **97** was isolated as a yellow solid.

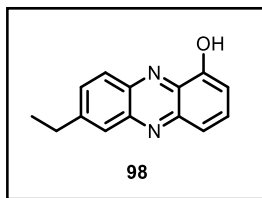
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.30 (br. s, 1H), 7.96 (d, *J* = 8.9 Hz, 1H), 7.91 (ddd, *J* = 1.9, 1.1, 0.7 Hz, 1H), 7.74 – 7.64 (m, 2H), 7.55 (dd, *J* = 8.9, 1.9 Hz, 1H), 7.16 (dd, *J* = 5.8, 2.7 Hz, 1H), 2.58 (d, *J* = 1.1 Hz, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 151.9, 144.2, 143.8, 141.6, 140.0, 134.2, 133.5, 131.7, 128.6, 127.8, 119.9, 108.6, 22.4.

**HRMS (ESI):** calc. for C<sub>13</sub>H<sub>11</sub>N<sub>2</sub>O [M+H]<sup>+</sup>: 211.0866, found: 211.0872.

**MP:** 151 – 153 °C.

**Note:** Compound **97** is known (CAS: 1393525-06-8), but no characterization data were found for comparison.



**Yield:** 93%; 245.8 mg of **98** was isolated as a yellow solid.

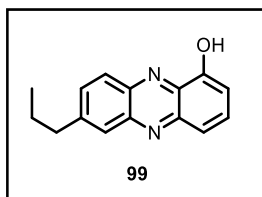
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.31 (s, 1H), 8.00 (d, *J* = 9.0 Hz, 1H), 7.95 (m, 1H), 7.73 – 7.65 (m, 2H), 7.60 (dd, *J* = 9.0, 2.0 Hz, 1H), 7.17 (dd, *J* = 6.2, 2.3 Hz, 1H), 2.89 (qd, *J* = 7.5, 1.0 Hz, 2H), 1.37 (t, *J* = 7.5 Hz, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 151.9, 147.5, 144.4, 143.8, 140.3, 134.3, 132.7, 131.7, 128.8, 126.3, 119.9, 108.7, 29.4, 14.6.

**HRMS (ESI):** calc. for C<sub>14</sub>H<sub>13</sub>N<sub>2</sub>O [M+H]<sup>+</sup>: 225.1022, found: 225.1023.

**MP:** 99 – 101 °C.

**Note:** Compound **98** is known (CAS: 21233-58-9), but no characterization data were found for comparison.



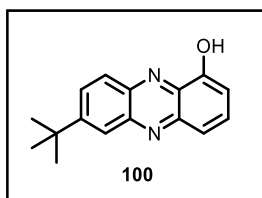
**Yield:** 88%; 227.8 mg of **99** was isolated as a yellow solid.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.30 (br. s, 1H), 8.03 (dd, *J* = 8.9, 0.6 Hz, 1H), 7.96 (dd, *J* = 1.9, 0.9 Hz, 1H), 7.76 – 7.64 (m, 2H), 7.61 (dd, *J* = 8.9, 1.9 Hz, 1H), 7.17 (dd, *J* = 6.4, 2.1 Hz, 1H), 2.84 (td, *J* = 7.5, 0.9 Hz, 2H), 1.85 – 1.73 (m, 2H), 1.00 (t, *J* = 7.3 Hz, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 151.9, 146.1, 144.4, 143.9, 140.3, 134.3, 132.9, 131.7, 128.8, 127.2, 119.9, 108.7, 38.5, 23.7, 14.0.

**HRMS (ESI):** calc. for C<sub>15</sub>H<sub>15</sub>N<sub>2</sub>O [M+H]<sup>+</sup>: 239.1179, found: 239.1184.

**MP:** 100 – 102 °C.

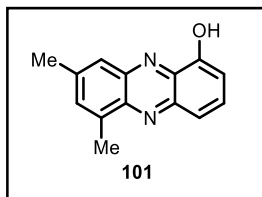


**Yield:** 80%; 286.1 mg of **100** was isolated as a yellow oily residue.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.42 (s, 1H), 8.09 (dd, *J* = 2.1, 0.6 Hz, 1H), 7.97 (dd, *J* = 9.2, 0.6 Hz, 1H), 7.81 (dd, *J* = 9.2, 2.2 Hz, 1H), 7.69 (dd, *J* = 8.9, 1.5 Hz, 1H), 7.65 (dd, *J* = 8.9, 7.1 Hz, 1H), 7.14 (dd, *J* = 7.0, 1.5 Hz, 1H), 1.41 (s, 9H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 154.2, 151.9, 144.2, 143.8, 140.0, 134.4, 131.5, 130.3, 128.5, 124.0, 119.8, 108.8, 35.6, 30.8.

**HRMS (ESI):** calc. for C<sub>16</sub>H<sub>17</sub>N<sub>2</sub>O [M+H]<sup>+</sup>: 253.1335, found: 253.1341.



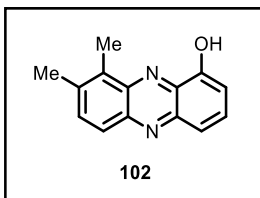
**Yield:** 89%; 187.2 mg of **101** was isolated as a yellow solid.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.20 (br. s, 1H), 7.77 (dd, *J* = 8.9, 1.1 Hz, 1H), 7.75 (ddq, *J* = 1.9, 1.3, 0.8 Hz, 1H), 7.68 (dd, *J* = 8.9, 7.3 Hz, 1H), 7.47 (m, 1H), 7.19 (dd, *J* = 7.4, 1.1 Hz, 1H), 2.86 (t, *J* = 0.8 Hz, 3H), 2.57 (d, *J* = 1.1 Hz, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 151.6, 142.9, 142.7, 141.7, 141.2, 137.5, 134.3, 133.0, 130.7, 125.3, 120.5, 108.7, 22.4, 17.9.

**HRMS (ESI):** calc. for C<sub>14</sub>H<sub>13</sub>N<sub>2</sub>O [M+H]<sup>+</sup>: 225.1022, found: 225.1025.

**MP:** 154 – 156 °C.



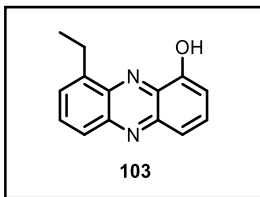
**Yield:** 83%; 89.1 mg of **102** was isolated as a yellow solid.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.15 (s, 1H), 7.87 (d, *J* = 8.9 Hz, 1H), 7.70 – 7.62 (m, 2H), 7.51 (d, *J* = 8.9 Hz, 1H), 7.14 (dd, *J* = 5.8, 2.7 Hz, 1H), 2.66 (s, 3H), 2.45 (s, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 151.8, 143.1, 142.7, 140.4, 138.0, 134.7, 133.4, 131.0, 126.5, 119.7, 108.5, 20.7, 13.2. Note: One <sup>13</sup>C NMR signal missing in the aromatic region, likely due to signal overlap.

**HRMS (ESI):** calc. for C<sub>14</sub>H<sub>13</sub>N<sub>2</sub>O [M+H]<sup>+</sup>: 225.1022, found: 225.1021.

**MP:** 164 – 166 °C.



**Yield:** 90%; 88.1 mg of **103** was isolated as a yellow solid.

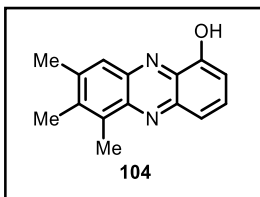
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.20 (s, 1H), 8.01 (ddd, *J* = 8.8, 1.2, 0.7 Hz, 1H), 7.72 – 7.64 (m, 3H), 7.54 (dq, *J* = 6.8, 1.2 Hz, 1H), 7.16 (dd, *J* = 5.8, 2.8 Hz, 1H), 3.29 (q, *J* = 7.5 Hz, 2H), 1.38 (t, *J* = 7.5 Hz, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 151.8, 144.5, 143.4, 142.8, 139.9, 133.5, 131.6, 130.9,

128.1, 127.6, 119.8, 108.7, 24.2, 14.7.

**HRMS (ESI):** calc. for C<sub>14</sub>H<sub>13</sub>N<sub>2</sub>O [M+H]<sup>+</sup>: 225.1022, found: 225.1019.

**MP:** 102 – 104 °C.



**Yield:** 89%; 175.2 mg of **104** was isolated as a yellow solid.

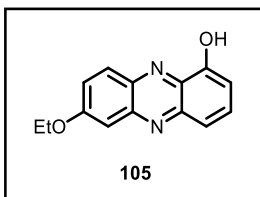
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.17 (br. s, 1H), 7.79 (m, 1H), 7.76 (dd, *J* = 8.9, 1.2 Hz, 1H), 7.67 (dd, *J* = 8.9, 7.4 Hz, 1H), 7.17 (dd, *J* = 7.4, 1.2 Hz, 1H), 2.88 (s, 3H), 2.55 (d, *J* = 1.2 Hz, 3H), 2.47 (s, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 151.6, 143.2, 142.8, 142.0, 140.4, 138.7, 134.1, 133.8,

130.5, 125.4, 120.5, 108.3, 22.1, 17.1, 13.8.

**HRMS (ESI):** calc. for C<sub>15</sub>H<sub>15</sub>N<sub>2</sub>O [M+H]<sup>+</sup>: 239.1179, found: 239.1185.

**MP:** 167 – 169 °C.



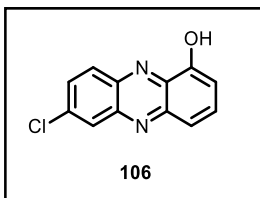
**Yield:** 88%; 89.2 mg of **105** was isolated as a yellow solid.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.18 (br. s, 1H), 8.00 (dd, *J* = 9.4, 0.5 Hz, 1H), 7.70 (dd, *J* = 8.9, 7.1 Hz, 1H), 7.66 (dd, *J* = 8.8, 1.5 Hz, 1H), 7.45 (dd, *J* = 9.4, 2.7 Hz, 1H), 7.35 (dd, *J* = 2.7, 0.5 Hz, 1H), 7.14 (dd, *J* = 7.0, 1.5 Hz, 1H), 4.22 (q, *J* = 7.0 Hz, 2H), 1.53 (t, *J* = 7.0 Hz, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 160.9, 152.1, 145.9, 143.8, 138.4, 133.0, 131.9, 130.2, 126.8, 119.3, 108.1, 105.2, 64.5, 14.7.

**HRMS (ESI):** calc. for C<sub>14</sub>H<sub>13</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 241.0972, found: 241.0973.

**MP:** 137 – 139 °C.



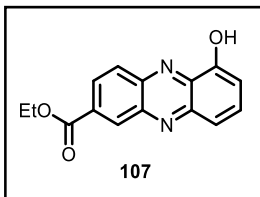
**Yield:** 92%; 226.1 mg of **106** was isolated as a yellow solid.

**<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):** δ 10.71 (s, 1H), 8.30 (m, 1H), 8.28 (dd, *J* = 5.0, 0.5 Hz, 1H), 7.92 (dd, *J* = 9.3, 2.3 Hz, 1H), 7.82 (dd, *J* = 8.8, 7.5 Hz, 1H), 7.66 (dd, *J* = 8.8, 1.2 Hz, 1H), 7.21 (dd, *J* = 7.5, 1.2 Hz, 1H).

**<sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):** δ 153.7, 144.0, 142.8, 139.7, 135.8, 135.6, 132.8, 131.4, 131.3, 127.4, 118.9, 110.9.

**MP:** 180 – 182 °C, lit. 203 – 204 °C.<sup>7</sup>

**Note:** Compound **106** is known (CAS: 105908-75-6), but no spectra were found for comparison.



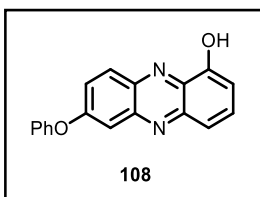
**Yield:** 85%; 49.5 mg of **107** was isolated as a yellow solid.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.99 (dd, *J* = 1.9, 0.7 Hz, 1H), 8.38 (dd, *J* = 9.1, 1.9 Hz, 1H), 8.23 (dd, *J* = 9.1, 0.7 Hz, 1H), 8.17 (s, 1H), 7.82 – 7.75 (m, 2H), 7.27 (m, 1H), 4.50 (q, *J* = 7.1 Hz, 2H), 1.49 (t, *J* = 7.1 Hz, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 165.8, 151.8, 144.6, 143.4, 142.5, 135.6, 132.9, 132.6, 132.4, 129.6, 129.5, 120.4, 110.2, 62.0, 14.5.

**HRMS (ESI):** calc. for C<sub>15</sub>H<sub>13</sub>N<sub>2</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 269.0921, found: 269.0930.

**MP:** 161 – 163 °C.



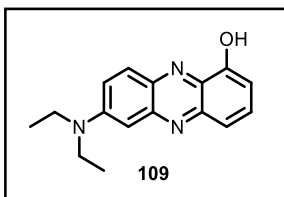
**Yield:** 88%; 333.6 mg of **108** was isolated as a yellow solid.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.18 (dd, *J* = 9.5, 0.5 Hz, 1H), 8.14 (br. s, 1H), 7.76 – 7.68 (m, 2H), 7.64 (dd, *J* = 8.9, 1.2 Hz, 1H), 7.52 – 7.41 (m, 2H), 7.38 (dd, *J* = 2.7, 0.5 Hz, 1H), 7.28 (m, 1H), 7.25 – 7.20 (m, 2H), 7.18 (dd, *J* = 7.4, 1.2 Hz, 1H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 160.7, 154.9, 152.1, 145.4, 144.0, 138.7, 133.6, 132.3, 130.9, 130.5, 126.0, 125.6, 121.2, 119.5, 110.5, 108.5.

**HRMS (ESI):** calc. for C<sub>18</sub>H<sub>13</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 289.0972, found: 289.0979.

**MP:** 148 – 150 °C.

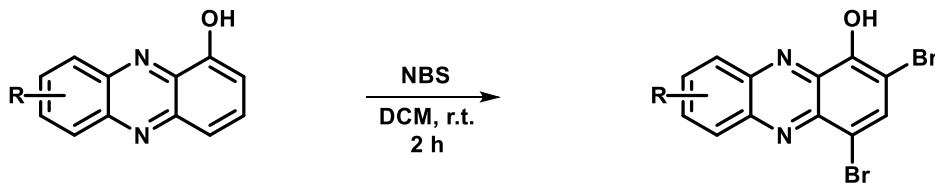


**Yield:** 94%; 79.4 mg of **109** was isolated as a red oily residue.

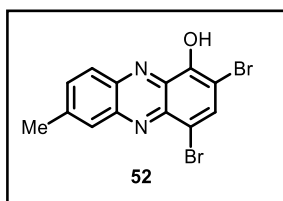
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.15 (br. s, 1H), 7.95 (d, *J* = 9.6 Hz, 1H), 7.62 (dd, *J* = 8.8, 7.2 Hz, 1H), 7.56 (dd, *J* = 8.8, 1.4 Hz, 1H), 7.48 (dd, *J* = 9.6, 2.8 Hz, 1H), 7.04 (d, *J* = 2.8 Hz, 1H), 7.02 (dd, *J* = 7.2, 1.3 Hz, 1H), 3.55 (q, *J* = 7.1 Hz, 4H), 1.29 (t, *J* = 7.1 Hz, 6H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 152.2, 149.1, 146.7, 144.4, 137.2, 131.8, 131.5, 130.1, 122.7, 118.8, 106.6, 101.6, 45.2, 13.0.

**HRMS (DART):** calc. for C<sub>16</sub>H<sub>18</sub>N<sub>3</sub>O [M+H]<sup>+</sup>: 268.1444, found: 268.1444.



**General di-bromination procedure:** Desired 1-hydroxyphenazines (0.24 mmol) and *N*-bromosuccinimide, (86.2 mg, 0.48 mmol) were dissolved in dichloromethane (15 mL) and allowed to stir at room temperature for 2 hours. The reaction was diluted with dichloromethane and quenched with brine (3 x 20 mL). The organic layer was dried with sodium sulfate, filtered and concentrated. The reaction contents were then concentrated, adsorbed onto silica gel and purified via column chromatography using dichloromethane to elute pure 2,4-dibromohydroxyphenazine analogues as yellow solids.



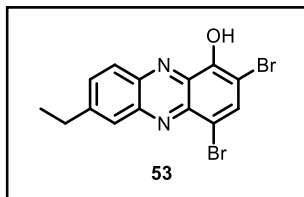
**Yield:** 52%; 51.2 mg of **52** was isolated as a yellow solid.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.50 (br. s, 1H), 8.21 (s, 1H), 8.17 – 8.15 (m, 1H), 8.14 (d, *J* = 9.0 Hz, 1H), 7.75 (dd, *J* = 8.9, 1.9 Hz, 1H), 2.67 (d, *J* = 1.1 Hz, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 149.3, 144.4, 142.9, 140.4, 140.1, 137.1, 135.3, 133.9, 128.5, 128.4, 113.0, 102.6, 22.5.

**HRMS (ESI):** calc. for C<sub>13</sub>H<sub>9</sub>Br<sub>2</sub>N<sub>2</sub>O [M+H]<sup>+</sup>: 368.9056, found: 368.9071.

**MP:** 200 – 202 °C.



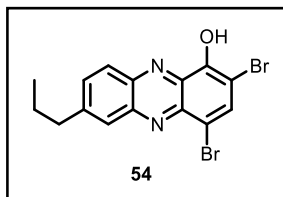
**Yield:** 74%; 117.9 mg of **53** was isolated as a yellow solid.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.48 (br. s, 1H), 8.19 (s, 1H), 8.15 – 8.10 (m, 2H), 7.76 (dd, *J* = 8.9, 2.0 Hz, 1H), 2.96 (qd, *J* = 7.5, 1.1 Hz, 2H), 1.42 (t, *J* = 7.5 Hz, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 149.0, 148.6, 144.3, 140.4, 139.8, 136.8, 134.3, 133.6, 128.2, 126.7, 112.7, 102.4, 29.3, 14.4.

**HRMS (ESI):** calc. for C<sub>14</sub>H<sub>11</sub>Br<sub>2</sub>N<sub>2</sub>O [M+H]<sup>+</sup>: 382.9213, found: 382.9302.

**MP:** 160 – 162 °C.



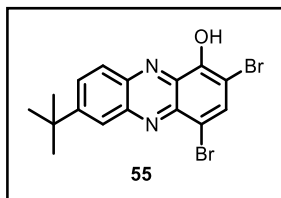
**Yield:** 76%; 89.6 mg of **54** was isolated as a yellow solid.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.50 (br. s, 1H), 8.20 (s, 1H), 8.17 – 8.10 (m, 2H), 7.76 (dd, *J* = 9.0, 1.9 Hz, 1H), 2.90 (td, *J* = 7.4, 0.9 Hz, 2H), 1.93 – 1.70 (m, 2H), 1.03 (t, *J* = 7.4 Hz, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 149.3, 147.4, 144.5, 140.6, 140.0, 137.0, 134.7, 133.9, 128.4, 127.9, 113.0, 102.6, 38.6, 23.8, 14.0.

**HRMS (ESI):** calc. for C<sub>15</sub>H<sub>13</sub>Br<sub>2</sub>N<sub>2</sub>O [M+H]<sup>+</sup>: 396.9369, found: 396.9389.

**MP:** 139 – 141 °C.



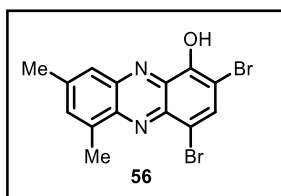
**Yield:** 61%; 139.1 mg of **55** was isolated as a yellow solid.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.50 (br. s, 1H), 8.26 (dd, *J* = 2.1, 0.6 Hz, 1H), 8.17 (s, 1H), 8.14 (dd, *J* = 9.2, 0.6 Hz, 1H), 8.01 (dd, *J* = 9.2, 2.1 Hz, 1H), 1.49 (s, 9H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 155.5, 149.3, 144.4, 140.4, 140.0, 136.9, 134.0, 132.2, 128.2, 124.8, 112.9, 102.6, 36.0, 30.9.

**HRMS (ESI):** calc. for C<sub>16</sub>H<sub>15</sub>Br<sub>2</sub>N<sub>2</sub>O [M+H]<sup>+</sup>: 410.9526, found: 410.9529.

**MP:** 176 – 178 °C.



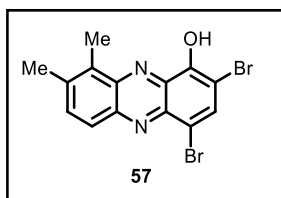
**Yield:** 73%; 87.4 mg of **56** was isolated as a yellow solid.

**<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):** δ 11.33 (br. s, 1H), 8.32 (s, 1H), 7.85 (dt, *J* = 2.0, 1.1 Hz, 1H), 7.68 (m, 1H), 2.80 (s, 3H), 2.59 (d, *J* = 1.1 Hz, 3H).

**<sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):** δ 150.6, 142.5, 141.6, 141.0, 137.9, 136.7, 135.7, 134.9, 133.8, 124.5, 111.9, 104.2, 21.9, 16.8.

**HRMS (ESI):** calc. for C<sub>14</sub>H<sub>11</sub>Br<sub>2</sub>N<sub>2</sub>O [M+H]<sup>+</sup>: 382.9213, found: 382.9208.

**MP:** 216 – 218 °C.



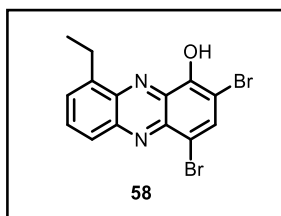
**Yield:** 66%; 70.7 mg of **57** was isolated as a yellow solid.

**<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):** δ 11.10 (s, 1H), 8.37 (s, 1H), 8.04 (d, *J* = 8.9 Hz, 1H), 7.89 (d, *J* = 8.9 Hz, 1H), 2.90 (s, 3H), 2.58 (s, 3H).

**<sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):** δ 150.7, 141.9, 140.7, 139.5, 138.4, 136.0, 135.9, 134.3, 125.9, 111.5, 103.8, 20.3, 13.3. Note: One <sup>13</sup>C NMR signal missing in the aromatic region, likely due to signal overlap.

**HRMS (ESI):** calc. for C<sub>14</sub>H<sub>9</sub>Br<sub>2</sub>N<sub>2</sub>O [M-H]<sup>-</sup>: 380.9067, found: 380.9067.

**MP:** 232 – 234 °C.



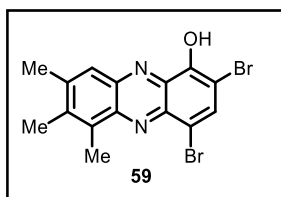
**Yield:** 76%; 113.5 mg of **58** was isolated as a yellow solid.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.50 (s, 1H), 8.22 – 8.19 (m, 1H), 8.21 (s, 1H), 7.85 (dd, *J* = 8.8, 6.9 Hz, 1H), 7.73 (dq, *J* = 6.9, 1.1 Hz, 1H), 3.38 (q, *J* = 7.5 Hz, 2H), 1.45 (t, *J* = 7.5 Hz, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 149.2, 144.7, 142.7, 140.4, 139.7, 137.1, 133.2, 131.9, 129.9, 128.2, 113.0, 102.9, 24.4, 14.7.

**HRMS (ESI):** calc. for C<sub>14</sub>H<sub>9</sub>Br<sub>2</sub>N<sub>2</sub>O [M-H]<sup>-</sup>: 380.9067, found: 380.9078.

**MP:** 161 – 163 °C.



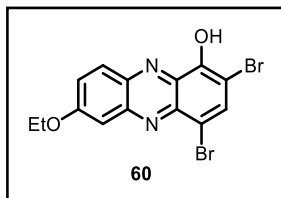
**Yield:** 84%; 83.8 mg of **59** was isolated as a yellow solid.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.14 (s, 1H), 7.82 (m, 1H), 2.93 (s, 3H), 2.59 (d, *J* = 1.1 Hz, 3H), 2.50 (s, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 149.0, 144.1, 142.8, 140.6, 140.1, 138.5, 135.8, 134.9, 133.4, 124.9, 113.8, 102.2, 22.3, 17.3, 13.8.

**HRMS (ESI):** calc. for C<sub>15</sub>H<sub>13</sub>Br<sub>2</sub>N<sub>2</sub>O [M+H]<sup>+</sup>: 396.9369, found: 396.9389.

**MP:** 226 – 228 °C.



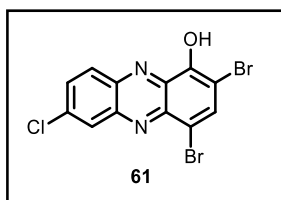
**Yield:** 88%; 48.0 mg of **60** was isolated as a yellow solid.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.45 (br. s, 1H), 8.20 (s, 1H), 8.09 (dd, *J* = 9.4, 0.5 Hz, 1H), 7.57 (dd, *J* = 9.4, 2.7 Hz, 1H), 7.52 (dd, *J* = 2.7, 0.5 Hz, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 1.56 (t, *J* = 7.1 Hz, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 161.8, 149.5, 146.3, 140.0, 138.8, 137.1, 132.6, 129.9, 128.6, 112.3, 105.8, 101.8, 64.9, 14.8.

**HRMS (ESI):** calc. for C<sub>14</sub>H<sub>11</sub>Br<sub>2</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 396.9182, found: 396.9168.

**MP:** 205 – 207 °C.



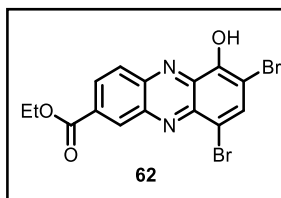
**Yield:** 90%; 184.0 mg of **61** was isolated as a yellow solid.

**<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):** δ 11.62 (s, 1H), 8.43 (s, 1H), 8.36 (d, *J* = 2.3 Hz, 1H), 8.32 (d, *J* = 9.3 Hz, 1H), 8.01 (dd, *J* = 9.3, 2.3 Hz, 1H).

**<sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):** δ 151.0, 142.7, 139.9, 139.8, 137.6, 136.8, 135.5, 132.9, 130.8, 127.7, 111.3, 104.9.

**HRMS (ESI):** calc. for C<sub>12</sub>H<sub>4</sub>Br<sub>2</sub>ClN<sub>2</sub>O [M-H]<sup>-</sup>: 386.8363, found: 386.8356.

**MP:** 234 – 236 °C.



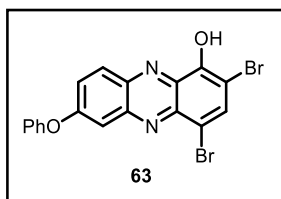
**Yield:** 35%; 23.2 mg of **62** was isolated as a yellow solid.

**<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):** δ 11.71 (s, 1H), 8.83 (d, *J* = 1.7 Hz, 1H), 8.50 (s, 1H), 8.46 (d, *J* = 9.1 Hz, 1H), 8.41 (dd, *J* = 9.1, 1.8 Hz, 1H), 4.46 (q, *J* = 7.1 Hz, 2H), 1.43 (t, *J* = 7.1 Hz, 3H).

**<sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):** δ 164.8, 151.0, 142.6, 141.8, 140.2, 137.6, 136.5, 132.4, 131.7, 130.0, 129.8, 111.7, 105.8, 61.7, 14.1.

**HRMS (ESI):** calc. for C<sub>15</sub>H<sub>11</sub>Br<sub>2</sub>N<sub>2</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 426.9111, found: 426.9128.

**MP:** 240 – 242 °C.



**Yield:** 55%; 37.1 mg of **63** was isolated as a yellow solid.

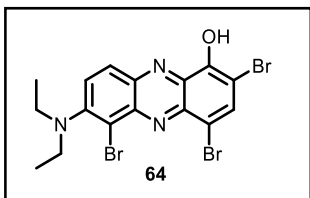
**<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):** δ 11.54 (s, 1H), 8.41 – 8.34 (m, 2H), 7.93 (dd, *J* = 9.4, 2.7 Hz, 1H), 7.59 (t, *J* = 7.7 Hz, 2H), 7.44 – 7.32 (m, 3H), 7.20 (d, *J* = 2.7 Hz, 1H).

**<sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):** δ 160.7, 154.1, 151.1, 143.9, 139.6, 138.7, 137.0, 134.3, 131.1, 130.7, 126.9, 125.8, 120.9, 110.9, 109.5, 103.7.

**HRMS (ESI):** calc. for C<sub>18</sub>H<sub>11</sub>Br<sub>2</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 446.9162, found: 446.9169.

**MP:** 240 °C (decomp).



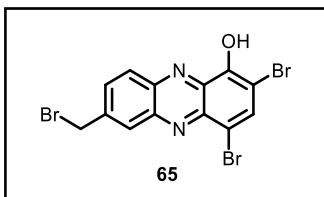


**Yield:** 53%; 51.1 mg of **64** was isolated as a red oily residue.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.30 (br. s, 1H), 8.20 (s, 1H), 8.05 (d, *J* = 9.5 Hz, 1H), 7.76 (d, *J* = 9.5 Hz, 1H), 3.53 (q, *J* = 7.1 Hz, 4H), 1.21 (t, *J* = 7.1 Hz, 6H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 152.7, 149.0, 143.6, 140.2, 139.4, 137.3, 132.8, 129.5, 127.6, 114.4, 113.3, 102.5, 46.7, 13.5.

**HRMS (DART):** calc. for C<sub>16</sub>H<sub>15</sub>Br<sub>2</sub>N<sub>3</sub>O [M+H]<sup>+</sup>: 503.8740, found: 503.8758.



**Yield:** 73%; 78.6 mg of **65** was isolated as a yellow solid.

**<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):** δ 11.58 (br. s, 1H), 8.43 (s, 1H), 8.41 (d, *J* = 1.9 Hz, 1H), 8.34 (d, *J* = 9.0 Hz, 1H), 8.05 (dd, *J* = 9.0, 1.9 Hz, 1H), 5.05 (s, 2H).

**<sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):** δ 151.0, 142.4, 142.1, 140.9, 139.7, 137.0, 135.6, 133.4, 129.5, 128.7, 111.4, 104.7, 33.4.

**HRMS (ESI):** calc. for C<sub>13</sub>H<sub>6</sub>Br<sub>3</sub>N<sub>2</sub>O [M-H]<sup>-</sup>: 444.8016, found: 444.8013.

**MP:** 214 – 216 °C.

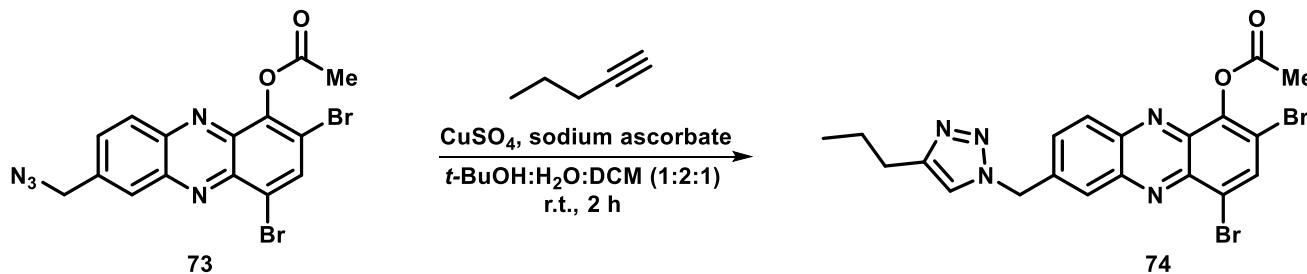


**Synthesis of 7-(azidomethyl)-2,4-dibromophenazin-1-yl acetate (73):** HP **65** (33.6 mg, 0.08mmol) was added to a round-bottom flask and dissolved in *N,N*-dimethylformamide (4 mL). Sodium azide (12.2 mg, 0.188 mmol) was added and the reaction was stirred at room temperature for 2 hours. Following completion by TLC, the reaction was diluted with ethyl acetate and quenched with brine (3 x 50 mL). The organic layer was dried with sodium sulfate, filtered and concentrated. The crude solid was then dissolved in dichloromethane (10 mL). Triethylamine (6 μL, 0.04 mmol), a catalytic amount of 4-dimethylaminopyridine, then acetyl chloride (3 μL, 0.03 mmol) were added at room temperature. The reaction was allowed to stir for one hour before being quenched with an aqueous solution of saturated sodium bicarbonate. The resulting mixture was then transferred to a separatory funnel and extracted with dichloromethane. The organic layer was then dried with anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude solid was purified via flash column chromatography using dichloromethane as the eluent to afford **73** as a yellow oily residue (20.1 mg, 59% over two steps).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.35 (s, 1H), 8.30 (m, 1H), 8.25 (d, *J* = 9.0 Hz, 1H), 7.83 (dd, *J* = 9.0, 1.9 Hz, 1H), 4.66 (s, 2H), 2.61 (s, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 168.3, 145.2, 143.4, 143.1, 140.6, 139.9, 137.9, 136.1, 132.1, 130.7, 128.4, 122.3, 117.5, 54.7, 20.9.

**HRMS (ESI):** calc. for C<sub>15</sub>H<sub>10</sub>Br<sub>2</sub>N<sub>5</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 451.9176, found: 451.9176.



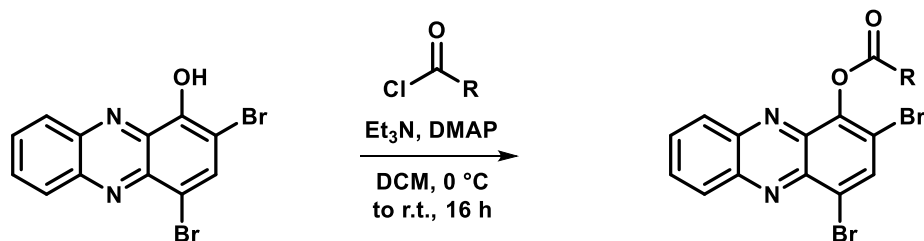
**Synthesis of 2,4-dibromo-7-((4-propyl-1H-1,2,3-triazol-1-yl)methyl)phenazin-1-yl acetate (74):** Anhydrous copper sulfate (2.2 mg, 0.01 mmol) and sodium ascorbate (8.0 mg, 0.04 mmol) were dissolved in a solution of *tert*-butanol:H<sub>2</sub>O (1:2, 300  $\mu$ L) and was added to a round-bottom flask containing **73** (12.2 mg, 0.06 mmol). 1-Pentyne (16.0  $\mu$ L, 0.16 mmol) was added, followed by dichloromethane (3.0 mL). The biphasic mixture was vigorously stirred at room temperature for 16 hours until starting material was fully consumed as determined by TLC analysis. The mixture was quenched with brine (2 x 50 mL) and the product was extracted with dichloromethane. The organics were collected, dried with sodium sulfate, filtered and concentrated to afford pure **74** (96%, 13.5 mg) as a yellow solid.

**<sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>):**  $\delta$  8.68 (s, 1H), 8.28 (d,  $J$  = 9.0 Hz, 1H), 8.08 – 8.06 (m, 2H), 7.93 (dd,  $J$  = 9.0, 1.9 Hz, 1H), 5.93 (s, 2H), 2.62 (t,  $J$  = 7.5 Hz, 2H), 2.57 (s, 3H), 1.62 (sextet,  $J$  = 7.4 Hz, 2H), 0.91 (t,  $J$  = 7.4 Hz, 3H).

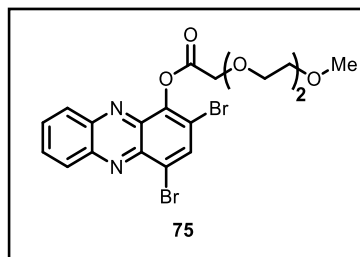
**<sup>13</sup>C NMR (150 MHz, DMSO-*d*<sub>6</sub>):**  $\delta$  168.0, 147.3, 144.5, 142.5, 142.1, 141.2, 139.7, 137.1, 135.8, 132.6, 129.9, 127.3, 122.7, 121.6, 117.2, 52.2, 27.1, 22.2, 20.4, 13.6.

**HRMS (ESI):** calc. for C<sub>20</sub>H<sub>18</sub>Br<sub>2</sub>N<sub>5</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 519.9803, found: 519.9793.

**MP:** 203 – 205 °C.



**General procedure for the synthesis of HP esters/carbamates from commercially available acid chlorides or carbamoyl chlorides.** To a stirring solution HP **1** (62.0 mg, 0.18 mmol), triethylamine (48  $\mu$ L, 0.35 mmol), and a catalytic amount of 4-dimethylaminopyridine in dichloromethane (20 mL) was added the acid chloride or carbamoyl chloride reagent (0.35 mmol) at room temperature. The reaction was allowed to stir for two hours before being quenched with an aqueous solution of saturated sodium bicarbonate. The resulting mixture was then transferred to a separatory funnel and ethyl acetate was added to extract the product. The organic layer was sequentially washed with water and brine before being collected. The organic layer was then dried with anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The respective ester or carbamate derivative was purified via flash column chromatography using hexanes:ethyl acetate (99:1 to 80:20) to elute, yielding pure products as yellow solids.



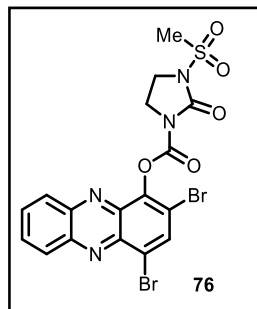
**Yield:** 63%; 53.3 mg of **75** was isolated as a yellow solid.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.33, (m, 1H), 8.32 (s, 1H), 8.18 (m, 1H), 7.94 – 7.84 (m, 2H), 4.78 (s, 2H), 4.01 – 3.96 (m, 2H), 3.82 – 3.76 (m, 2H), 3.72 – 3.68 (m, 2H), 3.60 – 3.54 (m, 2H), 3.38 (s, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 168.2, 144.6, 143.7, 143.4, 140.2, 137.4, 135.7, 132.4, 132.1, 130.1, 129.8, 122.5, 117.0, 72.1, 71.4, 70.8, 68.6, 59.2. Note: One <sup>13</sup>C NMR signal missing in the aliphatic region, likely due to signal overlap.

**HRMS (ESI):** calc. for C<sub>19</sub>H<sub>19</sub>Br<sub>2</sub>N<sub>2</sub>O<sub>5</sub> [M+H]<sup>+</sup>: 514.9636, found: 514.9630.

**MP:** 184 – 186 °C.



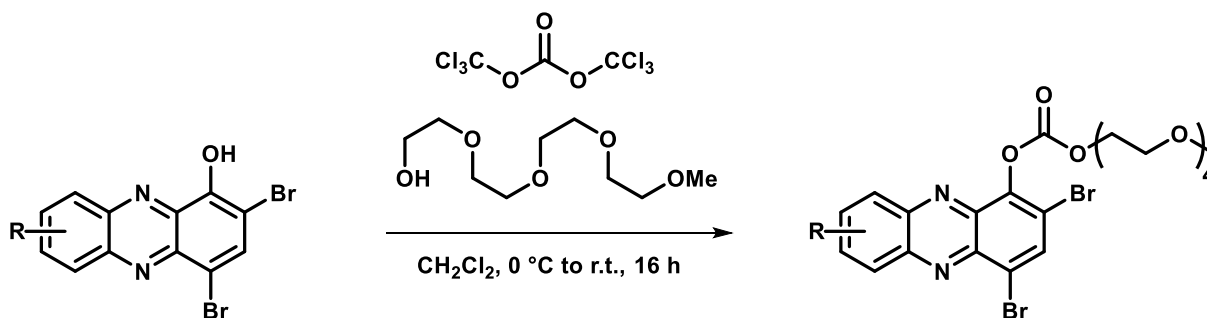
**Yield:** >99%; 95.7 mg of **76** was isolated as a pale yellow solid.

**<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):** δ 8.38 – 8.35 (m, 1H), 8.36 (s, 1H), 8.27 (m, 1H), 7.97 – 7.90 (m, 2H), 4.37 – 4.28 (m, 2H), 4.11 (t, *J* = 7.9 Hz, 2H), 3.45 (s, 3H).

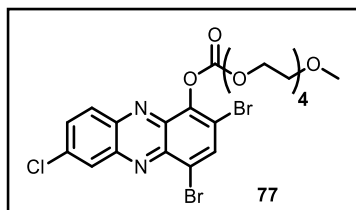
**<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):** δ 149.9, 147.9, 143.9, 143.8, 143.6, 140.3, 137.5, 135.6, 132.6, 132.3, 130.3, 130.0, 123.3, 117.3, 41.6, 41.0, 40.3.

**HRMS (ESI):** calc. for C<sub>17</sub>H<sub>13</sub>Br<sub>2</sub>N<sub>4</sub>O<sub>5</sub>S [M+H]<sup>+</sup>: 544.8948, found: 544.8949.

**MP:** > 250 °C.



**General Procedure for the Synthesis of HP-Carbonates (**77**, **78**):** Tetraethyleneglycol monomethyl ether (101.4 μL, 0.48 mmol) was placed in an oven-dried round-bottomed flask and dissolved in anhydrous dichloromethane (2 mL) and cooled to 0 °C. Pyridine (46.4 μL, 0.58 mmol) and triethylamine (16.8 μL 0.12 mmol) was then added via syringe, followed by triphosgene (71.2 mg, 0.24 mmol) dissolved in dichloromethane (2 mL). The resulting mixture was stirred from 0 °C to room temperature and continued to stir at room temperature for 5 hours. The reaction was then cooled to 0 °C before the addition of solution of **61** (118.2 mg, 0.30 mmol) and triethylamine (63 μL 0.45 mmol) in anhydrous dichloromethane was added to the reaction dropwise. The reaction was allowed to reach ambient temperature for reaction overnight. After the reaction was complete by TLC, the reaction mixture was poured into a separatory funnel containing brine (20 mL). The organic layer was drawn and the extracts were collected, dried over sodium sulfate, filtered, and concentrated under vacuum. The resulting crude material was purified using flash column chromatography with 3:1 hexanes:ethyl acetate to 100% ethyl acetate as eluent to yield **77** (183.1 mg, 99% yield) as a yellow solid.



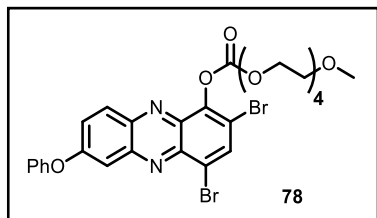
**Yield:** 99%; 183.1 mg of **77** was isolated as a yellow solid.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.35 (d, *J* = 2.3 Hz, 1H), 8.34 (s, 1H), 8.22 (d, *J* = 9.3 Hz, 1H), 7.83 (dd, *J* = 9.3, 2.3 Hz, 1H), 4.57 – 4.47 (m, 2H), 3.91 – 3.80 (m, 2H), 3.76 – 3.71 (m, 2H), 3.70 – 3.60 (m, 8H), 3.58 – 3.50 (m, 2H), 3.36 (s, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 152.3, 144.5, 143.5, 141.9, 140.5, 138.4, 137.5, 136.5, 133.9, 131.2, 128.5, 122.5, 117.3, 72.1, 71.0, 70.8, 70.8, 70.8, 70.7, 69.0, 68.9, 59.2.

**HRMS (ESI):** calc. for C<sub>22</sub>H<sub>23</sub>Br<sub>2</sub>ClN<sub>2</sub>O<sub>7</sub>Na [M+Na]<sup>+</sup>: 644.9433, found: 644.9433.

**MP:** 66 – 68 °C.



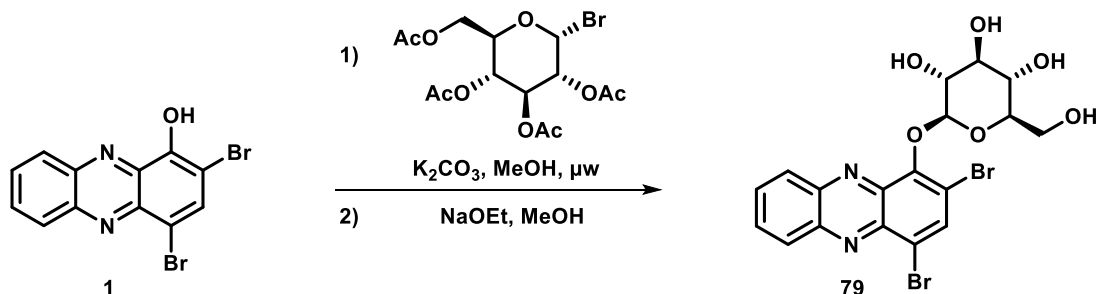
**Yield:** 71%; 47.9 mg of **78** was isolated as a yellow solid.

**<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):** δ 8.29 (s, 1H), 8.25 (d, *J* = 9.4 Hz, 1H), 7.78 (dd, *J* = 9.4, 2.7 Hz, 1H), 7.49 (t, *J* = 8.0 Hz, 2H), 7.42 (d, *J* = 2.7 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.23 – 7.20 (m, 2H), 4.56 – 4.51 (m, 2H), 3.91 – 3.87 (m, 2H), 3.74 (dd, *J* = 5.9, 3.5 Hz, 2H), 3.72 – 3.62 (m, 8H), 3.57 – 3.54 (m, 2H), 3.37 (s, 3H).

**<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):** δ 161.8, 154.5, 152.4, 145.1, 144.7, 141.0, 140.4, 136.4, 135.9, 131.6, 130.6, 128.1, 126.0, 121.9, 121.3, 115.5, 110.0, 72.1, 71.0, 70.9, 70.8, 70.8, 70.7, 69.0, 68.9, 59.2.

**HRMS (ESI):** calc. for C<sub>28</sub>H<sub>29</sub>Br<sub>2</sub>N<sub>2</sub>O<sub>8</sub> [M+H]<sup>+</sup>: 681.0267, found: 681.0275.

**MP:** 49 – 51 °C.



**Synthesis of HP-glucoconjugate prodrug 79 ((2*S*,3*R*,4*S*,5*S*,6*R*)-2-((2,4-dibromophenazin-1-yl)oxy)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol):** To a sealed microwave vial was added HP **1** (50.0 mg, 0.14 mmol), potassium carbonate (39.0 mg, 0.28 mmol) in methanol (5 mL). The resulting mixture was heated to 80 °C in the microwave reactor for a single 5 minute cycle. After that time, acetobromo-α-D-glucose (145 mg, 0.35 mmol) was added to the reaction vial. The reaction was cooled to room temperature and the solvent was removed *in vacuo*. The crude residue was taken up in ethyl acetate, transferred to a separatory funnel and then washed with water and extracted with ethyl acetate three times. The organic layers were combined, dried with anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude solid was dissolved in methanol (6 mL) and sodium ethoxide (40.8 mg, 0.60 mmol) was added. The reaction was allowed to stir for 16 hours, then was diluted with dichloromethane and transferred to a separatory funnel. The organic layer was drawn and the extracts were collected, dried over sodium sulfate, filtered, and concentrated under vacuum. The crude solid

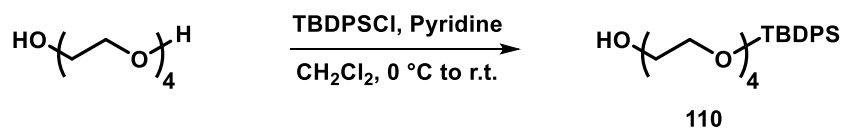
was rinsed with ice-cold water and methanol, then dried *in vacuo* to afford pure desired product as a pale yellow solid (17.7 mg, 24% over 2 steps).

**<sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>):** δ 8.56 (s, 1H), 8.38 – 8.26 (m, 2H), 8.14 – 8.02 (m, 2H), 6.03 (d, *J* = 7.7 Hz, 1H), 5.57 (d, *J* = 4.9 Hz, 1H), 5.11 (d, *J* = 5.2 Hz, 1H), 4.98 (d, *J* = 5.2 Hz, 1H), 4.20 (t, *J* = 5.7 Hz, 1H), 3.59 – 3.40 (m, 2H), 3.38 – 3.25 (m, 2H, partially buried under water signal), 3.14 (m, 2H).

**<sup>13</sup>C NMR (150 MHz, DMSO-*d*<sub>6</sub>):** δ 148.9, 142.3, 141.4, 139.8, 137.8, 136.4, 132.6, 132.5, 129.3, 118.0, 115.8, 104.0, 77.8, 76.9, 74.8, 69.9, 60.8. Note: Missing one <sup>13</sup>C signal in the aromatic region, likely due to signal overlap.

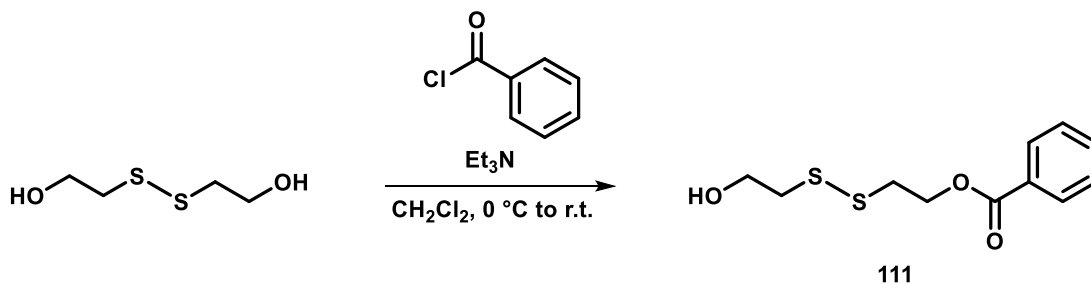
**HRMS (DART):** calc. for C<sub>18</sub>H<sub>17</sub>Br<sub>2</sub>N<sub>2</sub>O<sub>6</sub> [M+H]<sup>+</sup>: 516.9429, found: 516.9435.

**MP:** 199 – 201 °C.



**Procedure for the synthesis of tetraethylene glycol mono(*tert*-butyldiphenylsilyl) ether 110:** To a stirring solution of tetraethylene glycol (2.10 g, 10.8 mmol) and pyridine (95.4 μL, 0.188 mmol, 0.11 equivalents,) in dichloromethane (10 mL) was added *tert*-butyl(chloro)diphenylsilane (280 μL, 1.08 mmol, 0.1 equivalents) at 0 °C. The reaction was allowed to stir for one hour, slowly reaching ambient temperature, before being quenched with an aqueous solution of saturated sodium bicarbonate. The resulting mixture was then transferred to a separatory funnel and ethyl acetate was added to extract the product. The organic layer was sequentially washed with sodium bicarbonate and brine before being collected. The organic layer was then dried with anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The resulting crude oil was purified using flash column chromatography with 99:1 to 80:20 hexanes:ethyl acetate to separate mono-silylated (*R*<sub>f</sub> = 0.3 in 3:1 hexanes:ethyl acetate) and bis-silylated (*R*<sub>f</sub> = 0.8) products, affording **110** as a colorless oil (53%, 244.6 mg).

**Note:** <sup>1</sup>H NMR and <sup>13</sup>C NMR tabulation match those previously reported.<sup>8</sup>



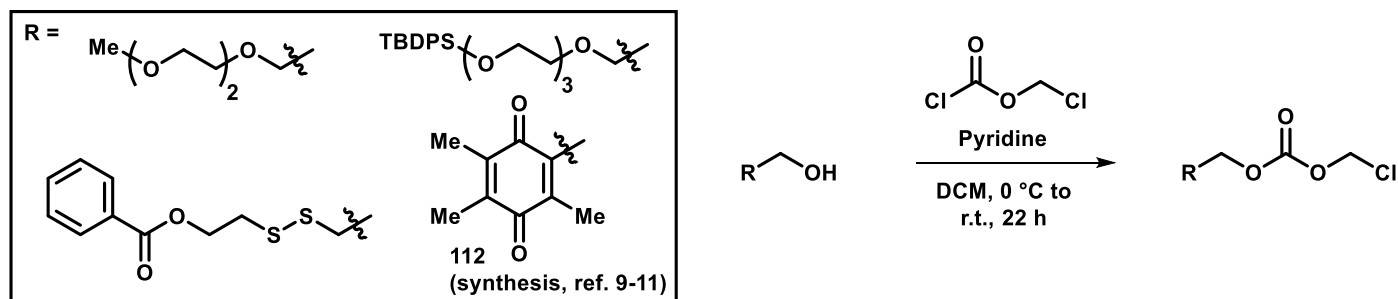
**Procedure for the synthesis of 2-((2-hydroxyethyl)disulfaneyl)ethyl benzoate (111):** To a stirring solution of 2,2'-disulfanediyldis(ethan-1-ol) (735 μL, 6.00 mmol) and triethylamine (835 μL, 6.00 mmol) in dichloromethane (15 mL) was added benzoyl chloride (349 μL, 3.00 mmol) at 0 °C. The reaction was allowed to stir for two hours, slowly reaching ambient temperature, before being quenched with an aqueous solution of saturated sodium bicarbonate. The resulting mixture was then transferred to a separatory funnel and ethyl acetate was added to extract the product. The organic layer was sequentially washed with sodium bicarbonate and brine before being collected. The organic layer was then dried with anhydrous sodium sulfate, filtered, and

concentrated *in vacuo*. The resulting crude oil was purified using flash column chromatography with 99:1 to 80:20 hexanes:ethyl acetate to separate mono-benzoyl ( $R_f = 0.3$  in 3:1 hexanes:ethyl acetate) and bis-benzoyl ( $R_f = 0.7$ ) products, affording **111** as a colorless oil (46%, 358.4 mg).

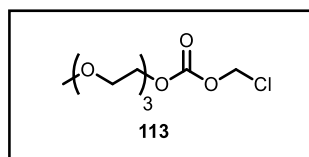
**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta$  8.05 – 8.00 (m, 2H), 7.54 (m, 1H), 7.45 – 7.38 (m, 2H), 4.57 (t,  $J = 6.7$  Hz, 2H), 3.86 (t,  $J = 5.9$  Hz, 2H), 3.03 (t,  $J = 6.7$  Hz, 2H), 2.87 (t,  $J = 5.9$  Hz, 2H), 2.76 (br. s, 1H).

**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):**  $\delta$  166.6, 133.3, 129.8, 129.7, 128.5, 63.0, 60.3, 41.6, 37.1.

**HRMS (ESI):** calc. for  $\text{C}_{11}\text{H}_{16}\text{O}_3\text{S}_2\text{Na}$   $[\text{M}+\text{Na}]^+$ : 281.0277, found: 281.0286.



**General procedure for the synthesis of alkyloxy chloromethyl carbonates (**113** - **116**):** To a stirring solution of desired alcohol (3.00 mmol) and pyridine (290  $\mu\text{L}$ , 3.60 mmol) in dichloromethane (10 mL) at 0  $^\circ\text{C}$  was added chloromethyl chloroformate (320  $\mu\text{L}$ , 3.60 mmol). The reaction was allowed to stir for 22 hours, slowly reaching ambient temperature overnight. The reaction was then quenched with an aqueous solution of saturated sodium bicarbonate. The resulting mixture was then transferred to a separatory funnel and ethyl acetate was added to extract the product. The organic layer was sequentially washed with sodium bicarbonate and brine before being collected. The organic layer was then dried with anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. Products were obtained as relatively pure oils and were taken on to subsequent reactions without further purification.

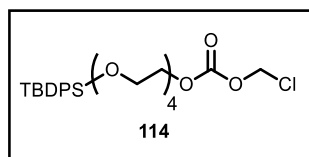


**Yield:** >99%; 919.0 mg of **113** was isolated as a pale yellow oil.

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta$  5.53 (s, 2H), 4.16 – 4.11 (m, 2H), 3.55 – 3.49 (m, 2H), 3.46 – 3.38 (m, 6H), 3.33 – 3.29 (m, 2H), 3.13 (s, 3H).

**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):**  $\delta$  152.9, 72.0, 71.4, 70.2, 70.1, 70.0, 68.1, 67.6, 58.4.

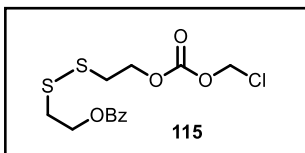
**Note:** Compound has been previously reported (CAS: 209551-63-3), but no spectra were found for comparison.



**Yield:** 88%; 259.4 mg of **114** was isolated as a colorless oil.

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.70 – 7.65 (m, 4H), 7.43 – 7.33 (m, 6H), 5.70 (s, 2H), 4.36 – 4.31 (m, 2H), 3.80 (dd,  $J = 5.9, 4.8$  Hz, 2H), 3.74 – 3.70 (m, 2H), 3.66 – 3.57 (m, 10H), 1.04 (s, 9H).

**HRMS (ESI):** calc. for  $\text{C}_{26}\text{H}_{37}\text{ClO}_7\text{SiNa}$   $[\text{M}+\text{Na}]^+$ : 547.1889, found: 547.1915.

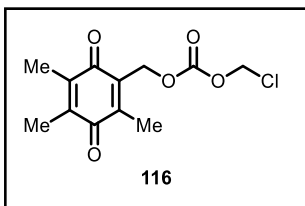


**Yield:** 46%; 358.4 mg of **115** was isolated as a colorless oil.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.06 – 8.01 (m, 2H), 7.56 (ddt, *J* = 7.9, 6.9, 1.4 Hz, 1H), 7.47 – 7.39 (m, 2H), 5.71 (s, 2H), 4.57 (t, *J* = 6.5 Hz, 2H), 4.47 (t, *J* = 6.6 Hz, 2H), 3.07 (t, *J* = 6.5 Hz, 2H), 2.99 (t, *J* = 6.6 Hz, 2H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 166.4, 153.3, 133.3, 129.9, 129.8, 128.5, 72.4, 66.7, 62.8, 37.4, 36.9.

**HRMS (ESI):** calc. for C<sub>13</sub>H<sub>15</sub>ClO<sub>5</sub>S<sub>2</sub>Na [M+Na]<sup>+</sup>: 372.9942, found: 372.9952.



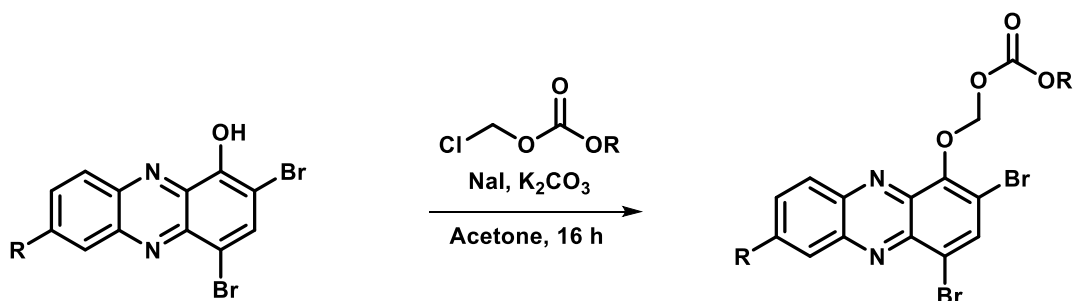
**Yield:** 13%; 18.5 mg of **116** was isolated as a yellow oily residue.

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 5.69 (s, 2H), 5.15 (s, 2H), 2.12 (s, 3H), 2.01 (m, 6H).

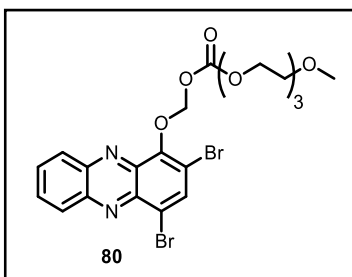
**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 187.3, 185.5, 153.3, 145.8, 141.5, 141.0, 135.4, 72.6, 61.6, 12.7, 12.7, 12.6.

**HRMS (ESI):** calc. for C<sub>12</sub>H<sub>14</sub>ClO<sub>5</sub> [M+H]<sup>+</sup>: 273.0527, found: 273.0527.

**Note:** Synthesized from **112**.<sup>9-11</sup> Compound is unstable and requires rapid advancement to subsequent reactions.



**Synthesis of alkyloxycarbonyloxymethyl (AOCOM) carbonate prodrugs (**80**, **81**, **85**, **86**, **87**):** To a stirring solution of the desired alkyloxy chloromethyl carbonate (0.08 mmol) in acetone (2 mL) was added sodium iodide (10.5 mg, 0.07 mmol). The reaction was allowed to stir for two hours at room temperature. Then, this mixture was added to a stirring solution of **1** (23.5 mg, 0.07 mmol) and potassium carbonate (11.0 mg, 0.08 mmol) in acetone (2 mL). After stirring for 14 additional hours, the reaction was quenched by addition of deionized water. The resulting mixture was then transferred to a separatory funnel and ethyl acetate was added to extract the product. The organic layer was sequentially washed with sodium bicarbonate and brine before being collected. The organic layer was then dried with anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The resulting crude material was purified using flash column chromatography with 3:1 hexanes:ethyl acetate to 100% ethyl acetate as eluent to yield AOCOM prodrugs as yellow solids.



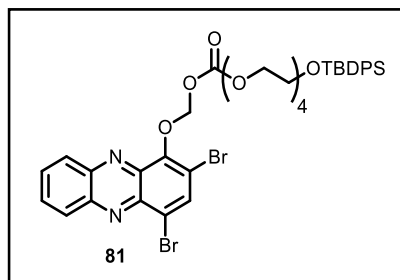
**Yield:** 54%; 43.4 mg of **80** was isolated as a yellow solid.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.37 (m, 1H), 8.32 (s, 1H), 8.28 (m, 1H), 7.97 – 7.89 (m, 2H), 6.26 (s, 2H), 4.34 – 4.29 (m, 2H), 3.73 – 3.68 (m, 2H), 3.62 (d, *J* = 5.5 Hz, 6H), 3.56 – 3.51 (m, 2H), 3.37 (s, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 154.7, 149.7, 143.5, 143.0, 140.7, 138.4, 136.5, 132.3, 132.0, 130.2, 129.8, 120.5, 116.8, 92.4, 72.1, 70.9, 70.8, 70.8, 68.9, 67.8, 59.3.

**HRMS (ESI):** calc. for C<sub>21</sub>H<sub>23</sub>Br<sub>2</sub>N<sub>2</sub>O<sub>7</sub> [M+H]<sup>+</sup>: 574.9848, found: 574.9821.

**MP:** 116 – 118 °C.



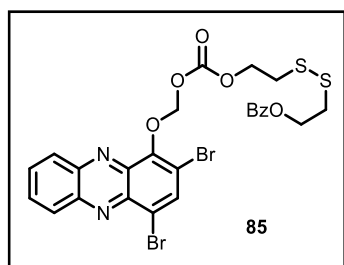
**Yield:** 69%; 38.2 mg of **81** was isolated as a yellow oily residue.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.36 (m, 1H), 8.30 (s, 1H), 8.27 (m, 1H), 7.96 – 7.88 (m, 2H), 7.68 (dt, *J* = 6.5, 1.7 Hz, 4H), 7.44 – 7.33 (m, 6H), 6.25 (s, 2H), 4.33 – 4.28 (m, 2H), 3.80 (t, *J* = 5.4 Hz, 2H), 3.71 – 3.66 (m, 2H), 3.66 – 3.56 (m, 10H), 1.04 (s, 9H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 154.7, 149.7, 143.5, 143.0, 140.7, 138.4, 136.4, 135.8, 133.9, 132.3, 132.0, 130.2, 129.8, 127.8, 120.5, 116.7, 92.3,

72.6, 70.9, 70.9, 70.9, 70.8, 68.9, 67.8, 63.6, 27.0, 19.4. **Note:** One <sup>13</sup>C signal missing in the aromatic region, likely due to signal overlap.

**HRMS (ESI):** calc. for C<sub>38</sub>H<sub>43</sub>Br<sub>2</sub>N<sub>2</sub>O<sub>8</sub>Si [M+H]<sup>+</sup>: 843.1134, found: 843.1147.



**Yield:** 60%; 69.8 mg of **85** was isolated as a yellow solid.

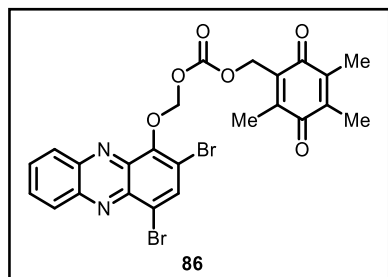
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.35 (m, 1H), 8.30 (s, 1H), 8.27 (m, 1H), 8.03 (m, 2H), 7.93 (ddd, *J* = 5.6, 4.7, 3.1 Hz, 2H), 7.54 (m, 1H), 7.42 (t, *J* = 7.7 Hz, 2H), 6.26 (s, 2H), 4.56 (t, *J* = 6.5 Hz, 2H), 4.43 (t, *J* = 6.6 Hz, 2H), 3.05 (t, *J* = 6.5 Hz, 2H), 2.95 (t, *J* = 6.6 Hz, 2H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 166.5, 154.5, 149.6, 143.5, 142.9, 140.7, 138.3, 136.4, 133.3, 132.4, 132.0, 130.2, 130.0, 129.9, 129.7, 128.6, 120.5, 116.7, 92.4,

66.3, 62.9, 37.5, 37.1.

**HRMS (ESI):** calc. for C<sub>25</sub>H<sub>20</sub>Br<sub>2</sub>N<sub>2</sub>O<sub>6</sub>S<sub>2</sub>Na [M+Na]<sup>+</sup>: 690.9002, found: 690.8986.

**MP:** 123 – 125 °C.



**Yield:** 13%; 9.1 mg of **86** was isolated as a yellow solid.

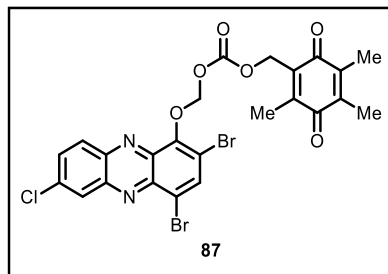
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 8.36 (m, 1H), 8.28 (s, 1H), 8.28 (m, 1H), 7.95 – 7.89 (m, 2H), 6.27 (s, 2H), 5.12 (s, 2H), 2.10 (s, 3H), 2.04 (m, 3H), 2.02 (m, 3H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 187.3, 185.5, 154.4, 149.6, 145.6, 143.5, 143.0, 141.3, 141.0, 140.7, 138.3, 136.4, 135.7, 132.4, 132.0, 130.2, 129.8, 120.5, 116.7, 92.5, 61.1, 12.8, 12.7, 12.6.

**HRMS (ESI):** calc. for C<sub>24</sub>H<sub>19</sub>Br<sub>2</sub>N<sub>2</sub>O<sub>6</sub> [M+H]<sup>+</sup>: 590.9586, found: 590.9577.

**MP:** 181 – 183 °C.





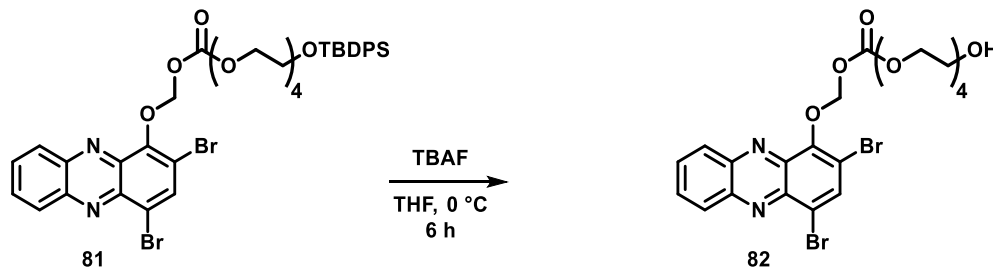
**Yield:** 8%; 15.0 mg of **87** was isolated as a yellow solid.

**$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):**  $\delta$  8.38 (d,  $J = 2.3$  Hz, 1H), 8.30 (s, 1H), 8.23 (d,  $J = 9.2$  Hz, 1H), 7.85 (dd,  $J = 9.2, 2.3$  Hz, 1H), 6.23 (s, 2H), 5.11 (s, 2H), 2.11 (s, 3H), 2.04 (m, 3H), 2.03 (m, 3H).

**$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):**  $\delta$  187.3, 185.5, 154.4, 149.7, 145.6, 143.3, 141.4, 141.4, 141.0, 141.0, 138.4, 138.2, 137.1, 135.6, 133.8, 131.0, 128.6, 120.5, 117.1, 92.5, 61.1, 12.8, 12.7, 12.6.

**HRMS (ESI):** calc. for  $\text{C}_{24}\text{H}_{18}\text{Br}_2\text{ClN}_2\text{O}_6$   $[\text{M}+\text{H}]^+$ : 624.9195, found: 624.9190.

**MP:** 179 – 181 °C.



**Procedure for the deprotection of AOCOM-TBDPS ether **81**:** To a stirring solution of **81** (25.8 mg, 0.03 mmol) at 0 °C in 6 mL of anhydrous tetrahydrofuran was added 34  $\mu\text{L}$  of a 1 M solution of tetrabutylammonium fluoride (0.03 mmol). The reaction mixture was allowed to stir for 6 hours, slowly reaching ambient temperature. The reaction was then quenched with water and transferred to a separatory funnel containing ethyl acetate and brine. The organic layer was sequentially washed with brine before the organic layer was collected. The organic layer was dried with anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude solid was purified via flash column chromatography using ethyl acetate to elute pure **82** as a yellow oily residue (60% yield, 11.0 mg).

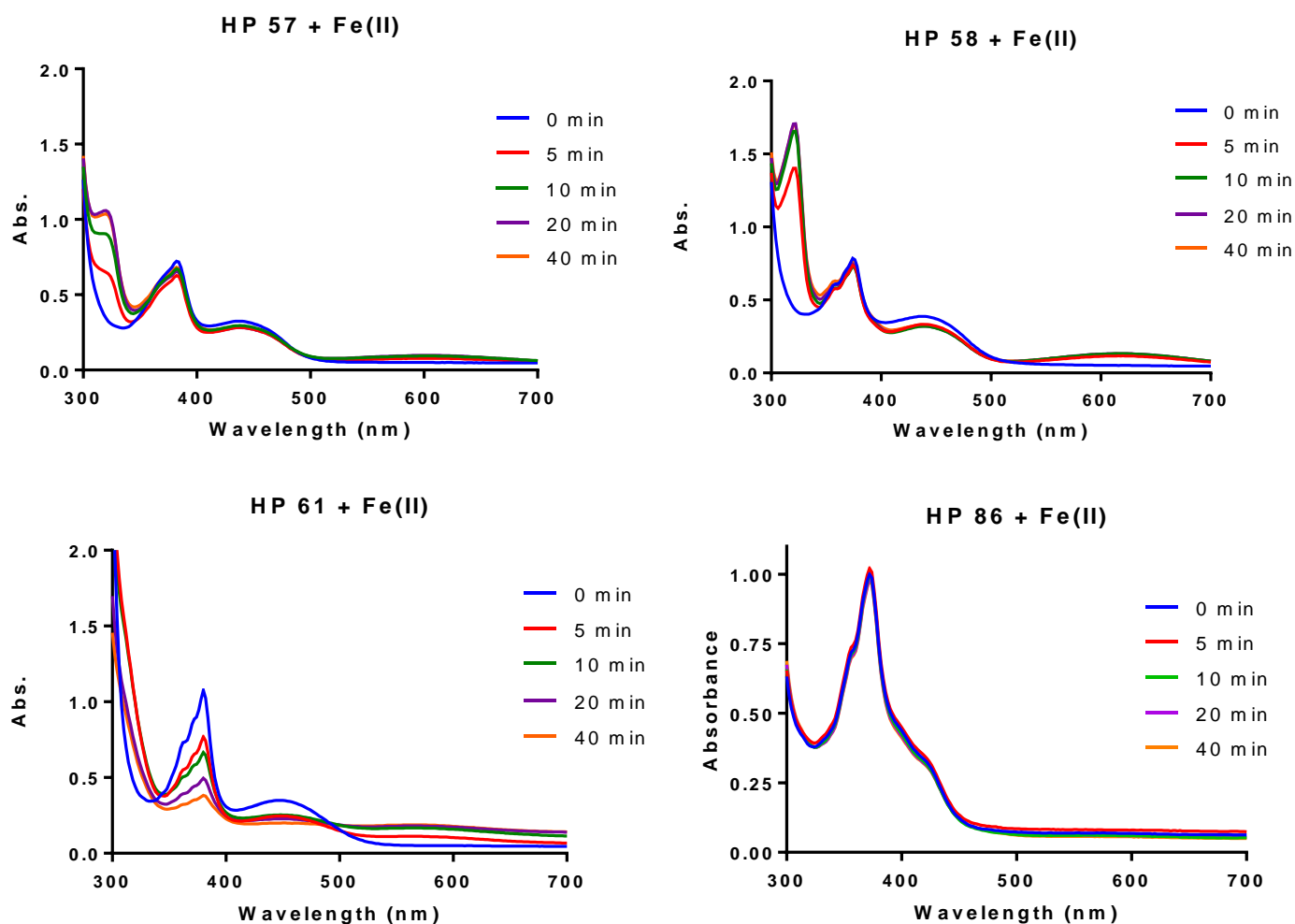
**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta$  8.37 (m, 1H), 8.32 (s, 1H), 8.28 (m, 1H), 7.97 – 7.89 (m, 2H), 6.26 (s, 2H), 4.39 – 4.23 (m, 2H), 3.73 – 3.68 (m, 4H), 3.68 – 3.54 (m, 10H).

**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):**  $\delta$  154.7, 149.7, 143.5, 143.0, 140.7, 138.4, 136.5, 132.3, 132.0, 130.2, 129.8, 120.5, 116.7, 92.4, 72.7, 70.9, 70.9, 70.7, 70.5, 69.0, 67.7, 62.0.

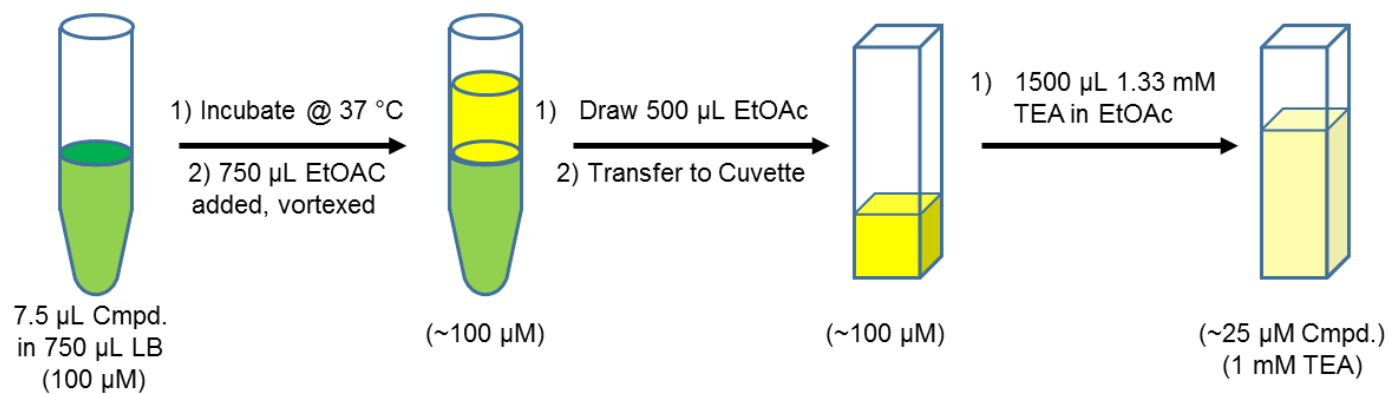
**HRMS (ESI):** calc. for  $\text{C}_{22}\text{H}_{25}\text{Br}_2\text{N}_2\text{O}_8$   $[\text{M}+\text{H}]^+$ : 604.9954, found: 604.9951.

#### 4.) UV-Vis Spectroscopy:

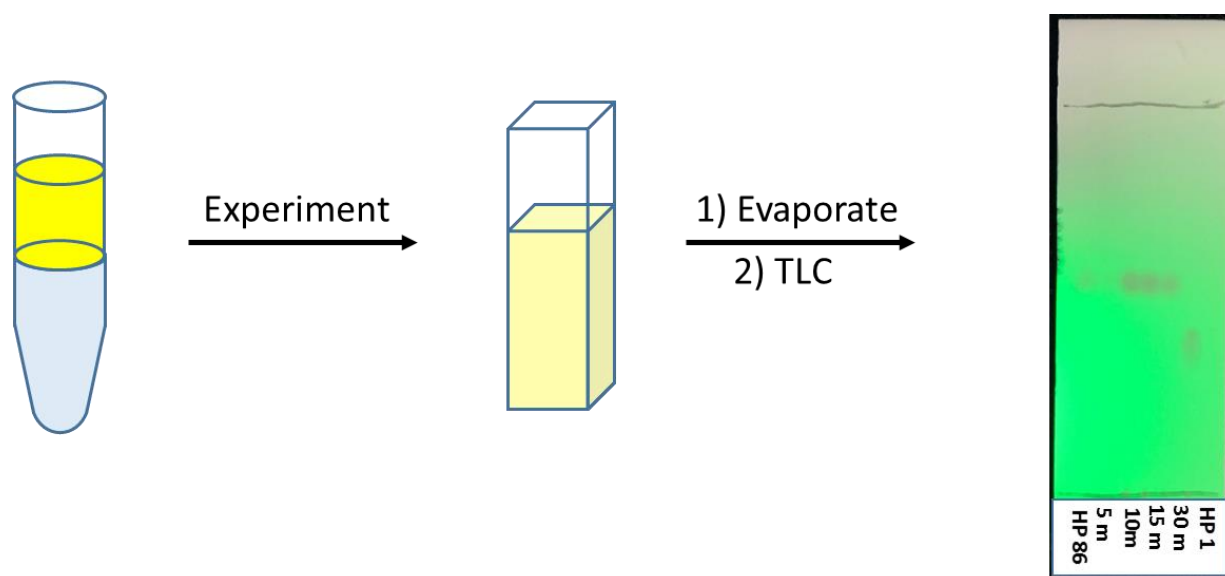
**A.) HP Complex Formation with Fe(II):** The rates of phenazine-iron(II) complex formation were independently evaluated via UV-vis spectrometry following addition of 0.5 equivalents ammonium iron(II) sulfate hexahydrate to stirring solutions of HP **57**, **58**, **61**, or **86** (5 mM, 5 mL) in dimethyl sulfoxide. Aliquots (20  $\mu$ L) were removed from each stirring solution and added to 980  $\mu$ L dimethyl sulfoxide in a cuvette. Spectral scanning was performed from 300 to 700 nm in 2 nm increments. The  $\lambda_{\text{max}}$  value was determined to be 374 nm for all HP analogues tested herein. A loss of absorbance at 374 nm corresponds to a loss of free hydroxyphenazine and apparent formation of a phenazine-iron(II) complex.



**B.) Spectrophotometric Determination of Prodrug Stability in LB Media:** Into 1.5 mL Eppendorf tubes was added 750  $\mu$ L of LB at 37  $^{\circ}$ C. To this solution was added 7.5  $\mu$ L of test compound (10 mM DMSO stock). Tubes were briefly vortexed, then incubated for up to 48 hours. At the indicated time points, 750  $\mu$ L ethyl acetate was added to the LB solution and the tubes were vigorously vortexed. From the organic layer was drawn 500  $\mu$ L, which was added to 1.5 mL of 1.33 mM triethylamine in ethyl acetate in a quartz cuvette (due to overlapping absorbance spectra for prodrugs and the respective HP, triethylamine was added as a reporter to generate the HP anions, which fortunately presented spectra distinct from those of the prodrugs). Spectral scans were taken from 200 to 700 nm at 2 nm increments. Results were plotted using GraphPad Prism.



**Figure S9.** General workflow for UV-vis prodrug stability assays.



**Figure S10.** TLC validation of UV-Vis stability assay (TLC eluent: 3:1 hexanes:ethyl acetate).

## **5.) Biological Methods:**

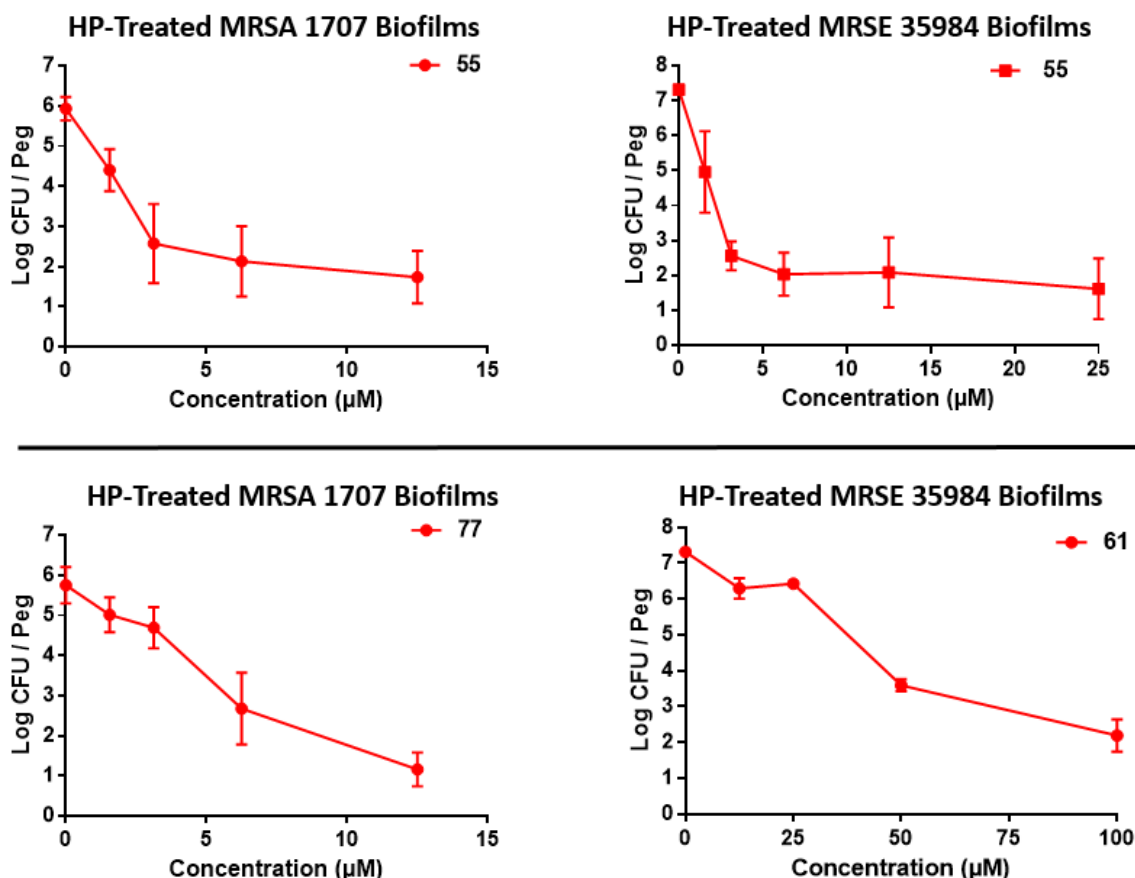
**A.) Minimum Inhibitory Concentration (MIC) Susceptibility Assay (in 96-well plate):** The minimum inhibitory concentration (MIC) for each phenazine analogue was determined by the broth microdilution method as recommended by the Clinical and Laboratory Standards Institute (CLSI).<sup>12</sup> In a 96-well plate, eleven two-fold serial dilutions of each compound were made in a final volume of 100  $\mu$ L Lysogeny Broth. Each well was inoculated with  $\sim 10^5$  bacterial cells at the initial time of incubation, prepared from a fresh log phase culture ( $OD_{600}$  of 0.5 to 1.0 depending on bacterial strain). The MIC was defined as the lowest concentration of compound that prevented bacterial growth after incubating 16 to 18 hours at 37 °C (MIC values were supported by spectrophotometric readings at  $OD_{600}$ ). The concentration range tested for each phenazine analogue/antibacterial during this study was 0.10 to 100  $\mu$ M. DMSO served as our vehicle and negative control in each microdilution MIC assay. DMSO was serially diluted with a top concentration of 1% v/v. All compounds were tested in two independent experiments, active compounds were tested in a third independent experiment (lead compounds were tested in more assays as positive controls during these studies).

**B.) MIC Assay for *Mycobacterium tuberculosis*:** *M. tuberculosis* H37Ra (ATCC 25177) was inoculated in 10 mL Middlebrook 7H9 medium and allowed to grow for two weeks. The culture was then diluted with fresh medium until an  $OD_{600}$  of 0.01 was reached. Aliquots of 200  $\mu$ L were then added to each well of a 96-well plate starting from the second column. Test compounds were dissolved in DMSO at final concentration of 10 mM. 7.5  $\mu$ L of each compound along with DMSO (negative control) and streptomycin (positive control-40mg/ml stock solution) were added to 1.5 mL of the *Mycobacterium* diluted cultures, resulting in 50  $\mu$ M final concentration of each halogenated phenazine analogues and 340  $\mu$ M for streptomycin. The final DMSO concentration was maintained at 0.5%. Aliquots of 400  $\mu$ L were added to wells of the first column of the 96-well plate and serially diluted two-fold (200  $\mu$ L) per well across the plate to obtain final concentrations that ranges from 0.024 to 50  $\mu$ M for the test compounds and 0.16 to 340  $\mu$ M for streptomycin. Three rows were reserved for each compound. The plates were then incubated at 37°C for seven days. Minimum inhibitory concentrations are reported as the lowest concentration at which no bacterial growth was observed.  $OD_{600}$  absorbance was recorded using SpectraMax M5 (Molecular Devices). Data obtained from three independent experiments were analyzed using Excel.

**C.) Calgary Biofilm Device (CBD) Experiments:** Biofilm eradication experiments were performed using the Calgary Biofilm Device to determine MBC/MBEC values for various compounds of interest (Innovotech, product code: 19111). The Calgary device (96-well plate with lid containing pegs to establish biofilms on) was inoculated with 125  $\mu$ L of a mid-log phase culture diluted 1,000-fold in tryptic soy broth with 0.5% glucose (TSBG) to establish bacterial biofilms after incubation at 37 °C for 24 hours. The lid of the Calgary device was then removed, washed and transferred to another 96-well plate containing 2-fold serial dilutions of the test compounds (the “challenge plate”). The total volume of media with compound in each well in the challenge plate is 150  $\mu$ L. The Calgary device was then incubated at 37 °C for 24 hours. The lid was then removed from the challenge plate and MBC/MBEC values were determined using different final assays. To determine MBC values, 20  $\mu$ L of the challenge plate was transferred into a fresh 96-well plate containing 180  $\mu$ L TSBG and incubated overnight at 37 °C. The MBC values were determined as the concentration giving a lack of visible bacterial growth (i.e., turbidity). For determination of MBEC values, the Calgary device lid (with attached pegs/treated biofilms) was transferred to a new 96-well plate containing 150  $\mu$ L of fresh TSBG media in each well and incubated for 24 hours at 37 °C to allow viable biofilms to grow and disperse resulting in turbidity after the incubation period. MBEC values were determined as the lowest test concentration that resulted in

eradicated biofilm (i.e., wells that had no turbidity after final incubation period). All compounds were tested in a minimum of three independent experiments. In select experiments, both treated and untreated pegs from the Calgary Biofilm Device were removed from active HP biofilm eradicators after final incubation, sonicated for 30 minutes in PBS and plated out to determine biofilm cell killing (see dose-response curve data below).

Also see (MBEC reference): <http://www.innovotech.ca/documents/MBEC-Procedural-Manual-v1.1.pdf>



Biofilm cell killing results from select HPs in CBD experiments against MRSA and MRSE biofilms.

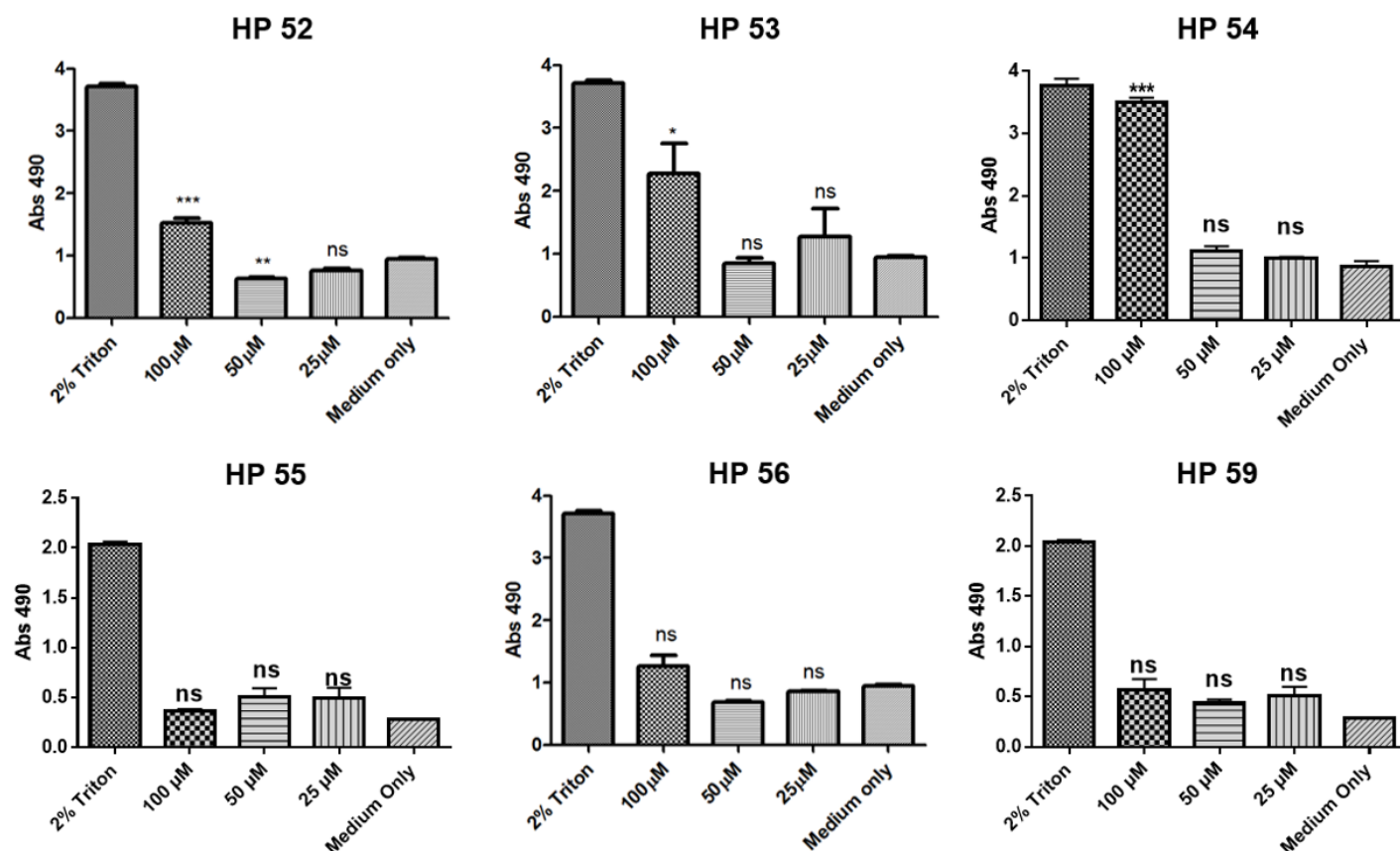
**D.) Live / Dead staining (Fluorescence Microscopy) of MRSE 35984 biofilms:** A mid-log culture of MRSE 35984 was diluted 1:1,000-fold and 500 µL was transferred to each compartment of a 4 compartment CELLview dish (Greiner Bio-One 627871). The dish was then incubated for 24 hours at 37 °C. After this time, the cultures were removed and the plate was washed with 0.9% saline. The dish was then treated with the compounds in fresh media at various concentrations. DMSO was used as our negative control in this assay. The dish was incubated with the compound for 24 hours at 37 °C. After this time, the cultures were removed and the dish was washed with 0.9% saline for 2 minutes. Saline was then removed and 500 µL of the stain (Live/Dead BacLight Viability Kit, Invitrogen) were added for 15 minutes and left in the dark. After this time, the stain was removed and the dish was washed twice with 0.9% saline. Then the dish was fixed with 500 µL 4% paraformaldehyde in PBS for 30 minutes. Images of remaining MRSE biofilms were then taken with a fluorescence microscope. All data were analyzed using Image J software from three independent experiments.

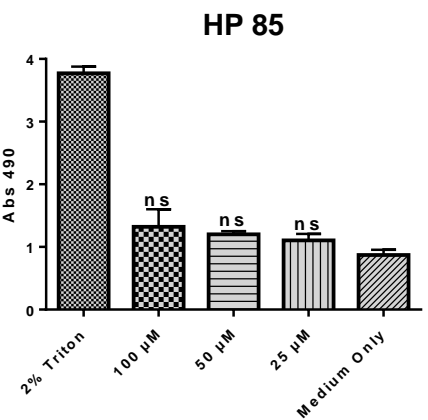
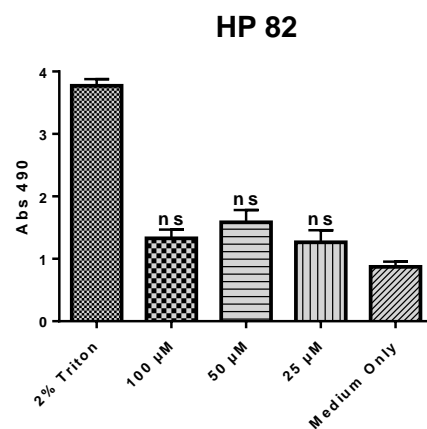
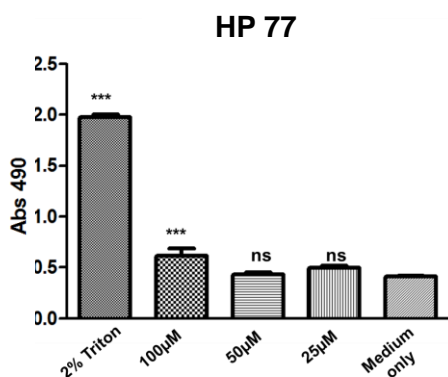
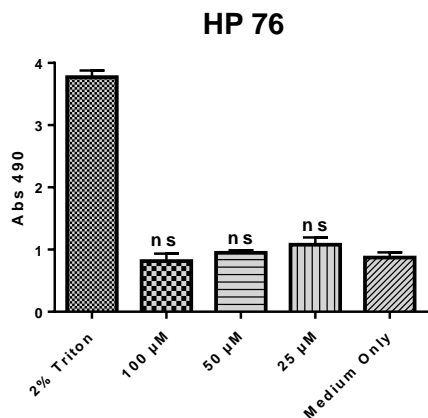
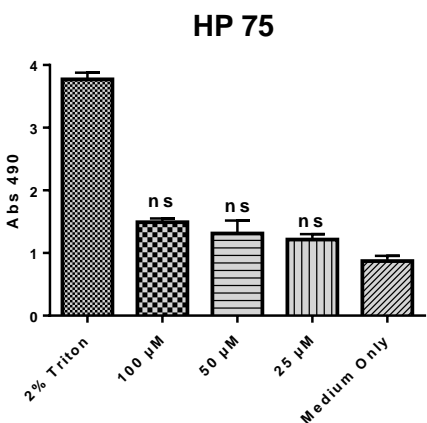
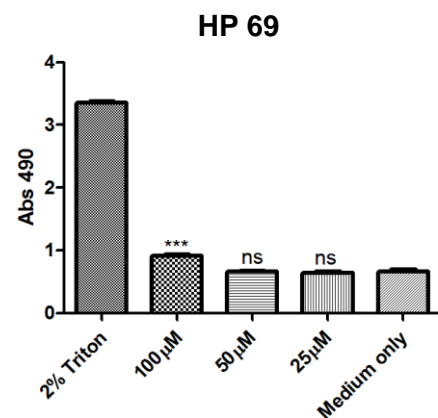
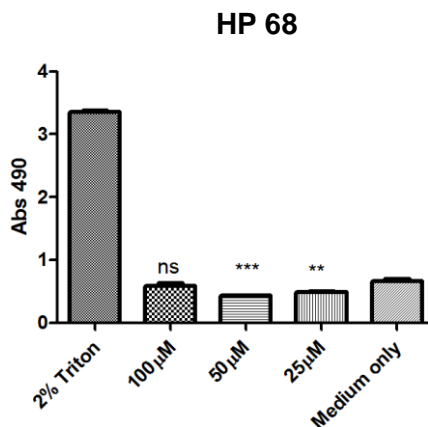
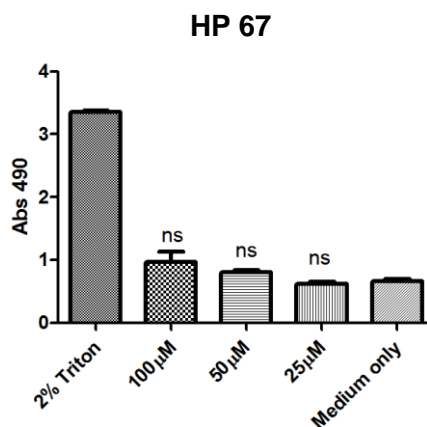
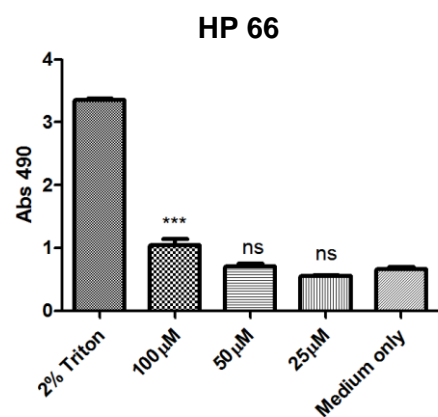
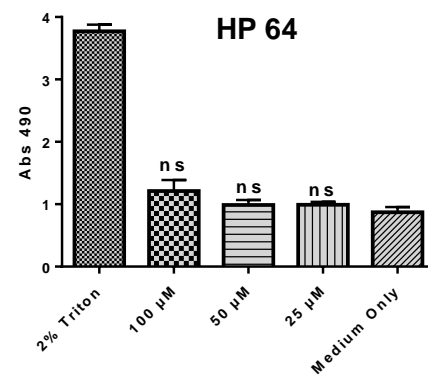
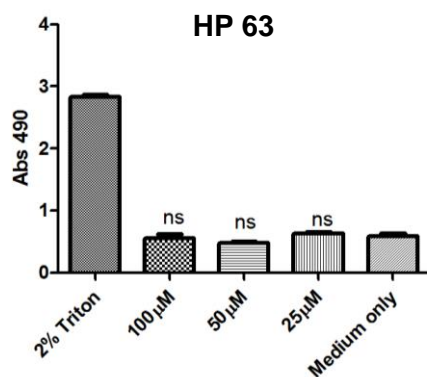
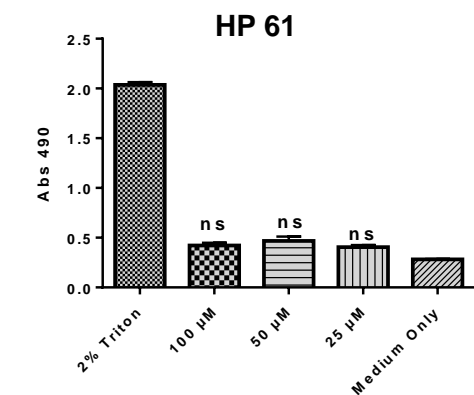
**E.) Hemolysis Assay with Red Blood Cells:** Freshly drawn human red blood cells (hRBC with ethylenediaminetetraacetic acid (EDTA) as an anticoagulant) were washed with Tris-buffered saline (0.01M

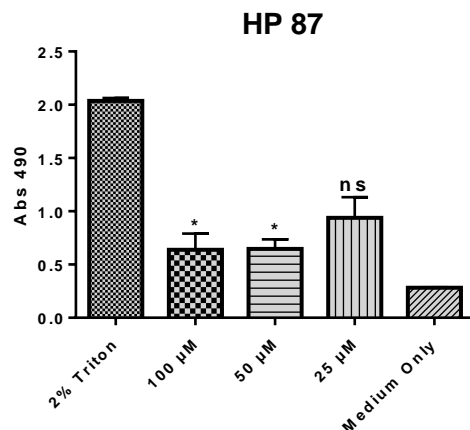
Tris-base, 0.155 M sodium chloride (NaCl), pH 7.2) and centrifuged for 5 minutes at 3,500 rpm. The washing was repeated three times with the buffer. In 96-well plate, test compounds were added to the buffer from DMSO stocks. Then 2% hRBCs (50  $\mu$ L) in buffer were added to test compounds to give a final concentration of 200  $\mu$ M. The plate was then incubated for 1 hour at 37 °C. After incubation, the plate was centrifuged for 5 minutes at 3,500 rpm. Then 80  $\mu$ L of the supernatant was transferred to another 96-well plate and the optical density (OD) was read at 405 nm. DMSO served as our negative control (0% hemolysis) while Triton X served as our positive control (100% hemolysis). The percent of hemolysis was calculated as (OD<sub>405</sub> of the compound- OD<sub>405</sub> DMSO) / (OD<sub>405</sub> Triton X- OD<sub>405</sub> buffer) from three independent experiments.

**F.) LDH Release Assay for HeLa Cytotoxicity Assessment:** HeLa cytotoxicity was assessed using the LDH release assay described by CytoTox96 (Promega G1780). HeLa cells were grown in Dulbecco's Modified Eagle Medium (DMEM; Gibco) supplemented with 10% Fetal Bovine Serum (FBS) at 37°C with 5% CO<sub>2</sub>. When the HeLa cultures exhibited 70-80% confluence, halogenated phenazines were then diluted by DMEM (10% FBS) at concentrations of 25, 50 and 100  $\mu$ M and added to HeLa cells. Triton X-100 (at 2% v/v) was used as the positive control for maximum lactate dehydrogenate (LDH) activity in this assay (i.e., complete cell death) while "medium only" lanes served as negative control lanes (i.e., no cell death). DMSO was used as our vehicle control. HeLa cells were treated with compounds for 24 hours and then 50  $\mu$ L of the supernatant was transferred into a fresh 96-well plate where 50  $\mu$ L of the reaction mixture was added to the 96-well plate and incubated at room temperature for 30 minutes. Finally, Stop Solution (50  $\mu$ L) was added to the incubating plates and the absorbance was measured at 490 nm. Results are on the next page and are from three independent experiments.

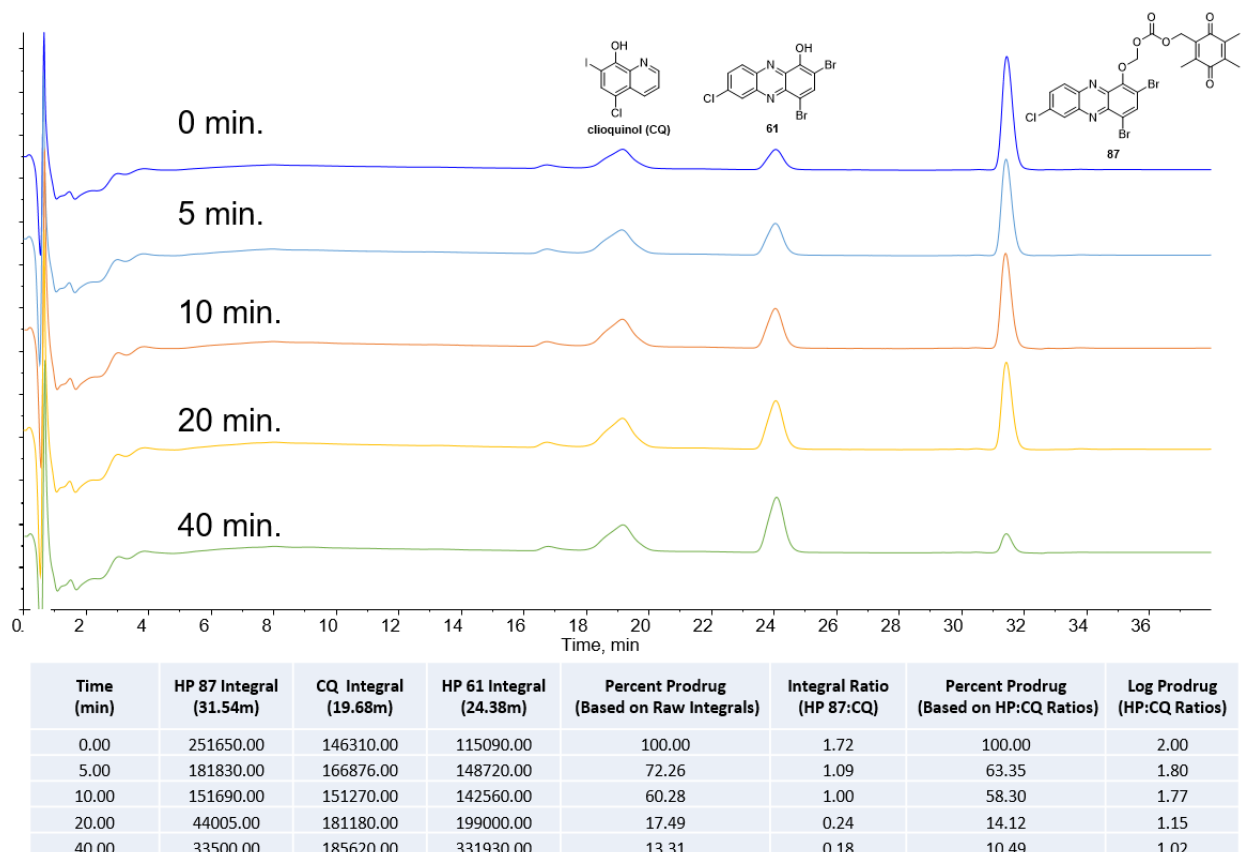
**Halogenated Phenazine cytotoxicity results (Triton-X = 100% cell death; Medium Only: 0% cell death):**







**G.) Prodrug Serum Stability Assay:** *In vitro* serum stability assays were performed according to previously reported procedures with minor modifications.<sup>13</sup> First, human serum was temperature-equilibrated at 37 °C and then 200  $\mu$ L of the serum solution was allocated into 1.5 mL Eppendorf tubes. To each tube was added 7.5  $\mu$ L of the prodrug analyte (from 10 mM DMSO stocks) and 7.5  $\mu$ L of internal standard. The serum analyte solutions were vortex-mixed for 5 seconds and then incubated for 1 minute to 60 minutes. At the end of each incubation interval, 400  $\mu$ L of acetonitrile (0.5% formic acid) was added to precipitate serum proteins. The tubes were then centrifuged for 5 minutes at 1500 rcf and the supernatant was removed and evaporated to dryness under reduced pressure. Samples were reconstituted in 400  $\mu$ L acetonitrile (0.5% formic acid) and analyzed via LC-MS using a Shimadzu Prominence HPLC system, AB Sciex 3200 QTRAP spectrometer and a Kinetex C18 column (50 mm  $\times$  2.1 mm  $\times$  2.6  $\mu$ m) with a 35-minute linear gradient from 10-65% acetonitrile in 0.5% formic acid at a flow rate of 0.25 mL/min. Formation of active HPs from prodrugs was quantified by comparison of observed ratios of HPs to internal standard with previously generated standard curves.





**H.) Agar Diffusion Assay:** Agar diffusion assays for prodrug evaluation were performed according to the standard Kirby-Bauer disk diffusion susceptibility test protocol with some minor modifications.<sup>14</sup> First, 100  $\mu\text{L}$  of MRSA BAA-1707 ( $\text{OD}_{600} = 0.7$ ,  $\sim 10^8$  CFU) was spread on lysogeny broth (LB) agar plates. The plates were dried for 10 min, and 20  $\mu\text{L}$  of test compound from 10 mM DMSO stocks was gently pipetted onto the plate. The plates were incubated at 37°C for 16 h, images were taken, and zones of bacterial clearance (area) were measured using ImageJ software (NIH).<sup>15</sup>

## **6.) Literature References:**

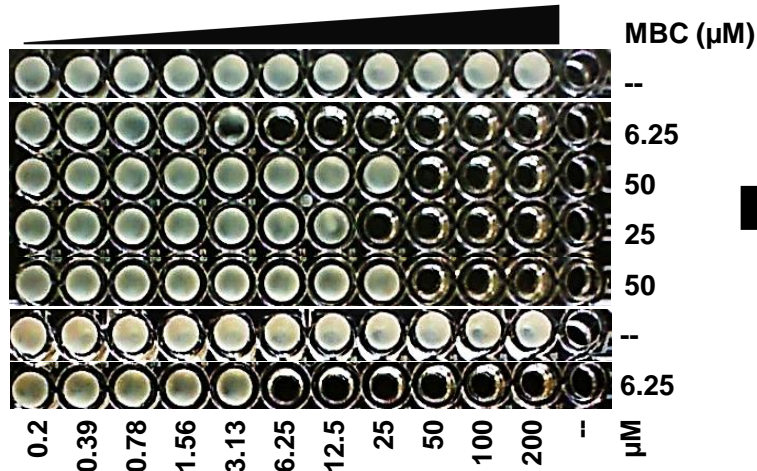
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## **7.) Supporting Images for MIC and MBEC (CBD) Assays:**

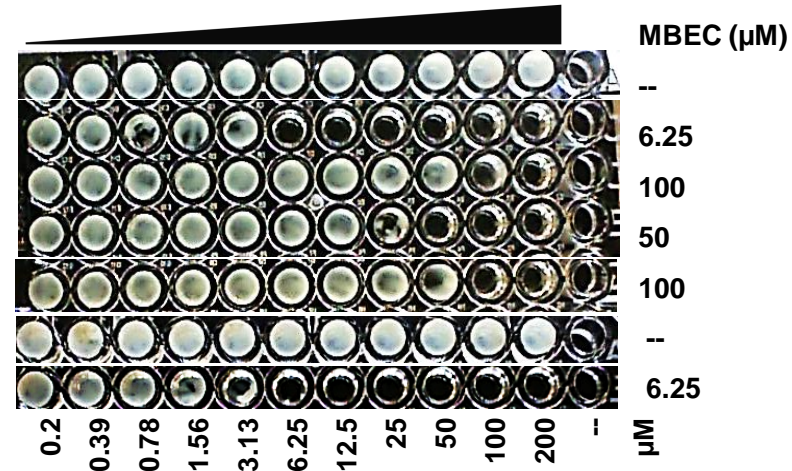
# CBD Assay for MRSA BAA-1707 Biofilms

## Planktonic Eradication

- A) DMSO
- B) 56
- C) 53
- D) 52
- E) 54
- F) DMSO
- G) 55

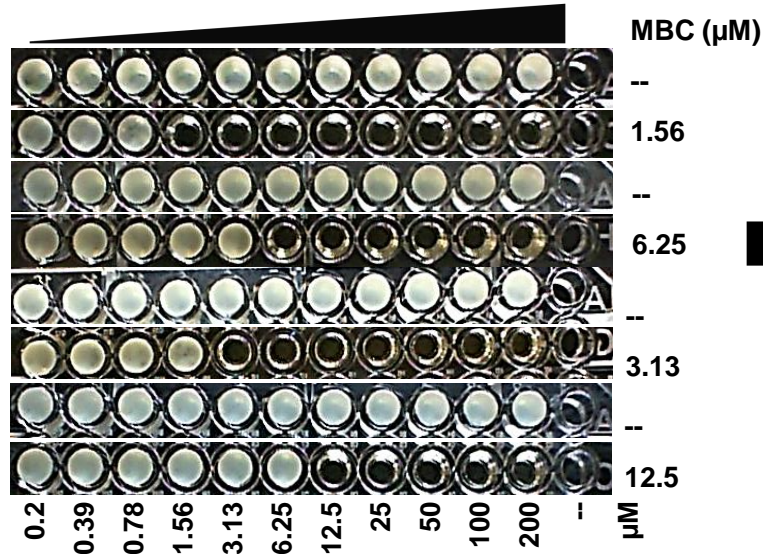


## Biofilm Eradication

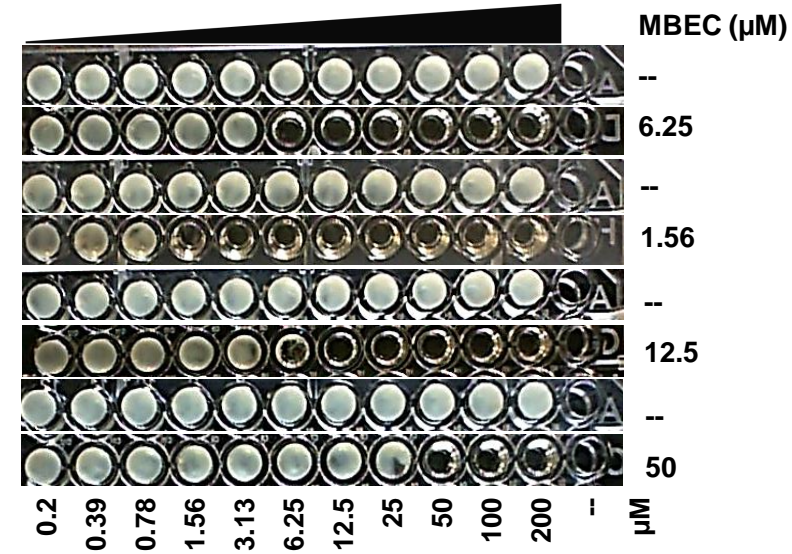


## Planktonic Eradication

- A) DMSO
- B) 61
- C) DMSO
- D) 63
- E) DMSO
- F) 77
- G) DMSO
- H) 75



## Biofilm Eradication

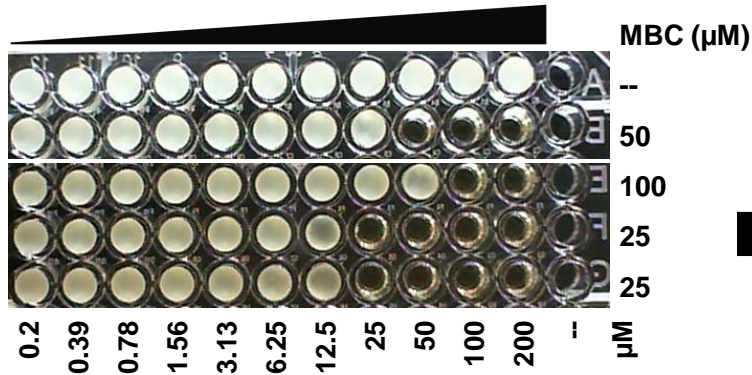




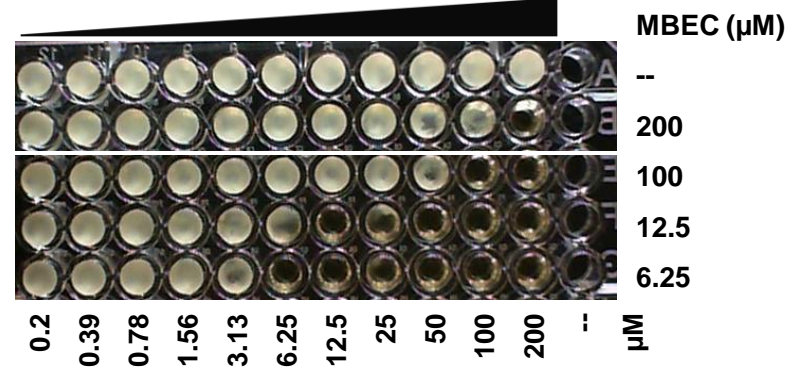
# CBD Assay for MRSA BAA-44 Biofilms

## Planktonic Eradication

- A) DMSO
- B) 1
- C) 53
- D) 63
- E) 55



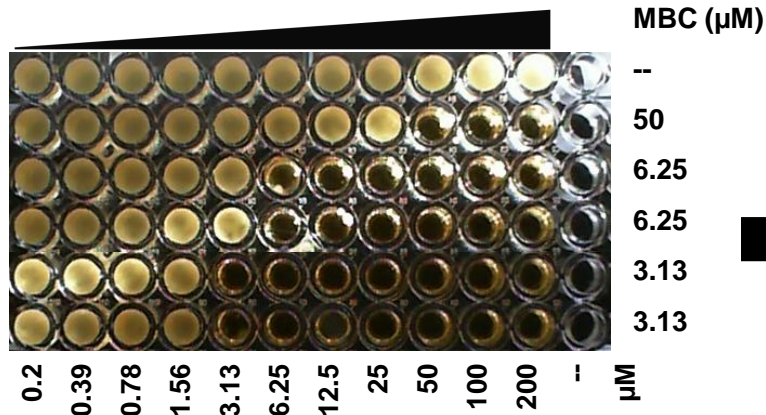
## Biofilm Eradication



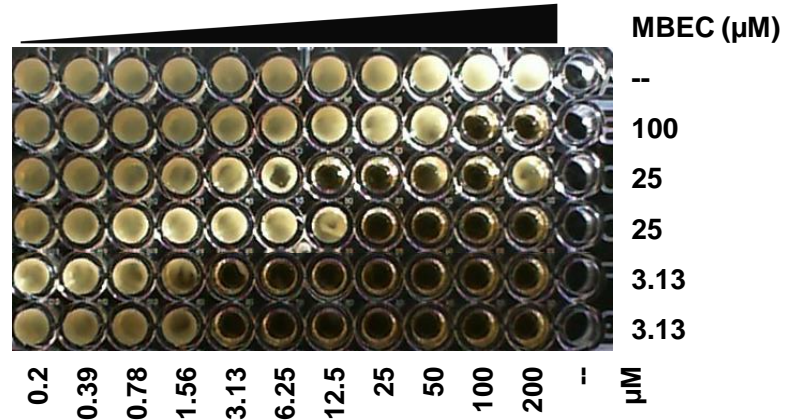
# CBD Assay for MRSA-2 Biofilms

## Planktonic Eradication

- A) DMSO
- B) 1
- C) 56
- D) 61
- E) 63
- F) 55

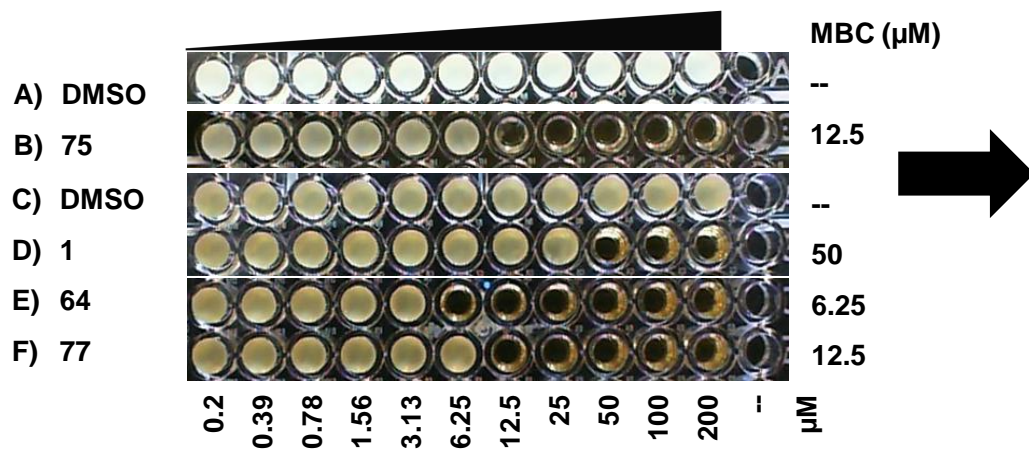


## Biofilm Eradication

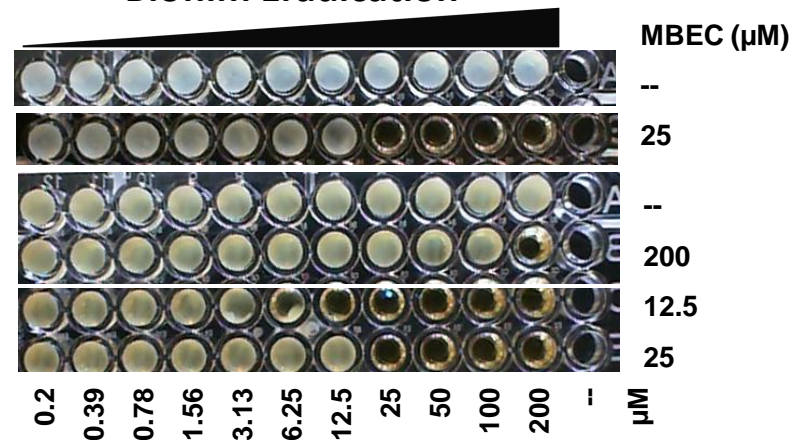


# CBD Assay for MRSE 35984 Biofilms

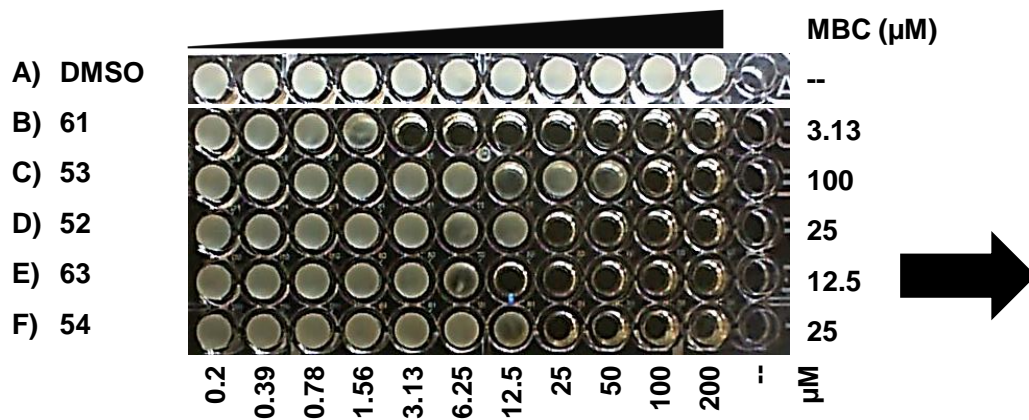
## Planktonic Eradication



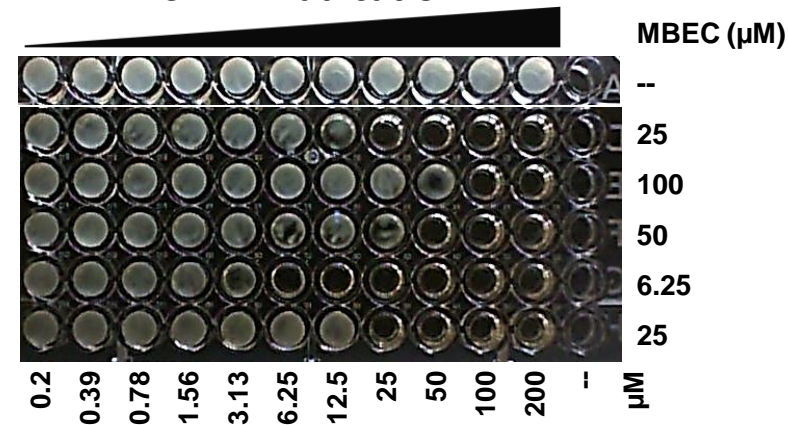
## Biofilm Eradication



## Planktonic Eradication



## Biofilm Eradication

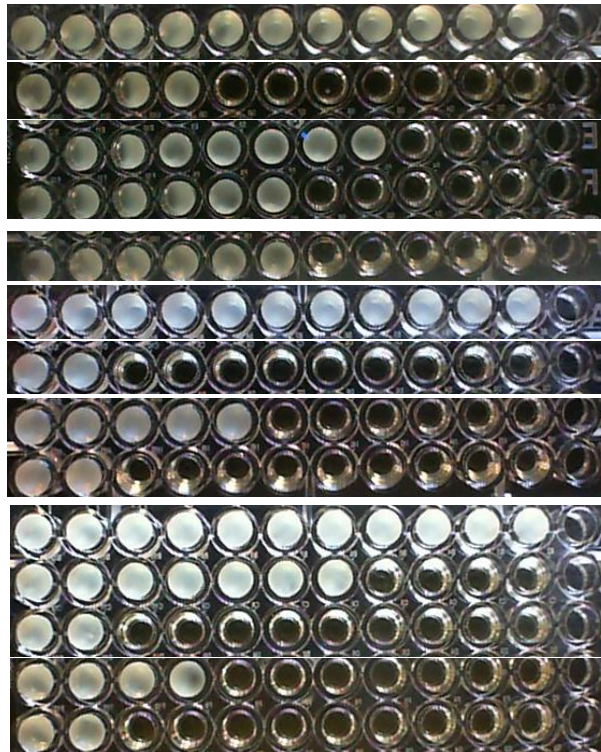




# CBD Assay for VRE 700221 Biofilms

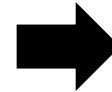
## Planktonic Eradication

A) DMSO  
B) 59  
C) 53  
D) 52  
E) 54  
F) DMSO  
G) 55  
H) 75  
I) 56  
J) DMSO  
K) 1  
L) 61  
M) 64  
N) 77

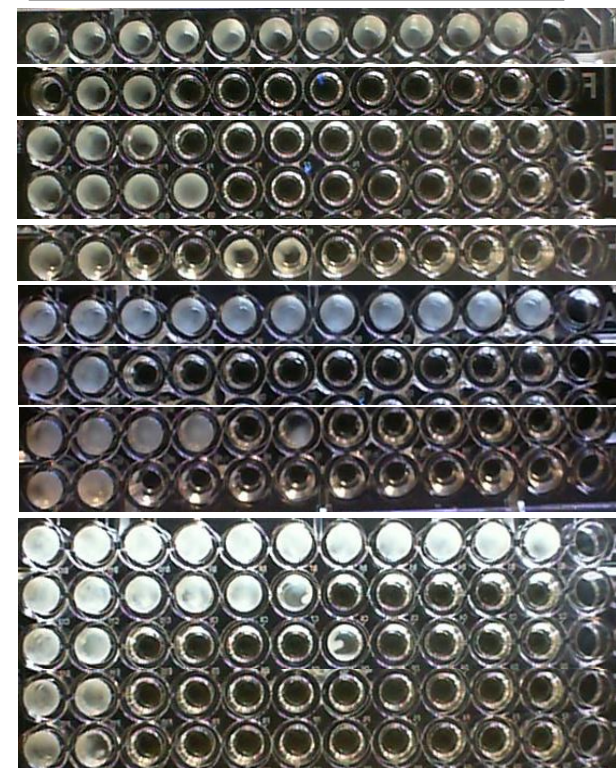


MBC (μM)

--  
3.13  
50  
12.5  
12.5  
--  
0.78  
6.25  
0.78  
--  
25  
0.78  
3.13  
0.78



## Biofilm Eradication

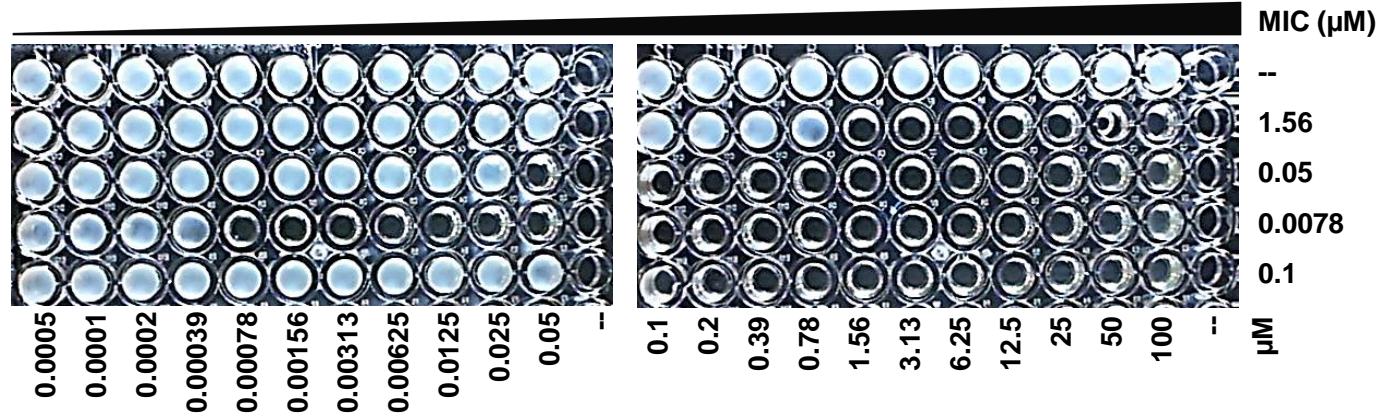


MBEC (μM)

--  
1.56  
1.56  
3.13  
12.5  
--  
0.78  
3.13  
0.78  
--  
12.5  
0.78  
0.78  
0.78

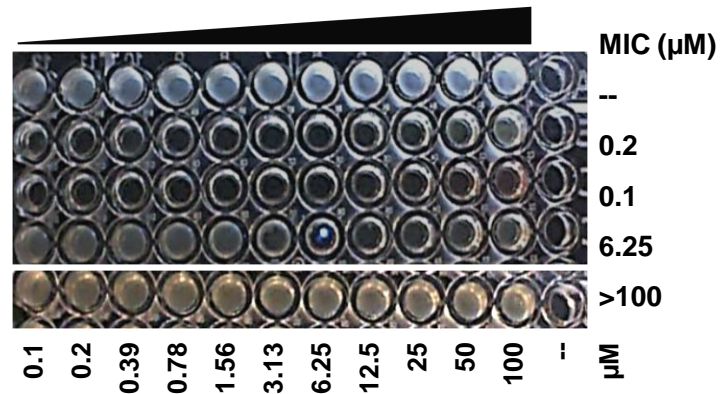
# MIC Assay against MRSA BAA-1707

- A) DMSO
- B) 1
- C) 61
- D) 77
- E) 56



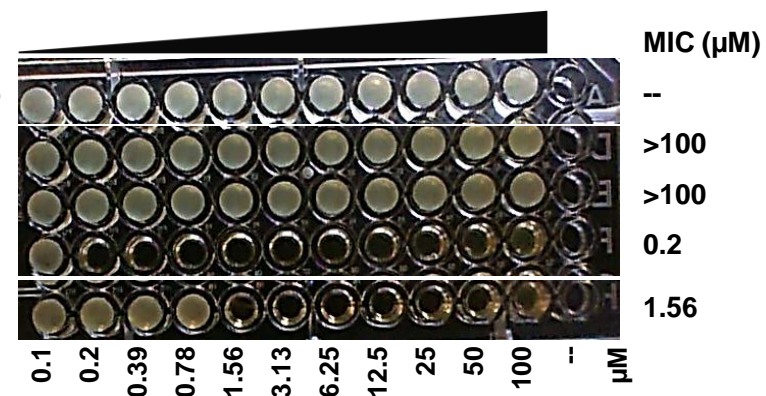
## MIC Assay against MRSE 35984

- A) DMSO
- B) 54
- C) 64
- D) 62
- E) 80



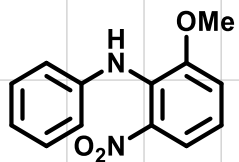
## MIC Assay against VRE 700221

- A) DMSO
- B) 57
- C) 58
- D) 63
- E) 52

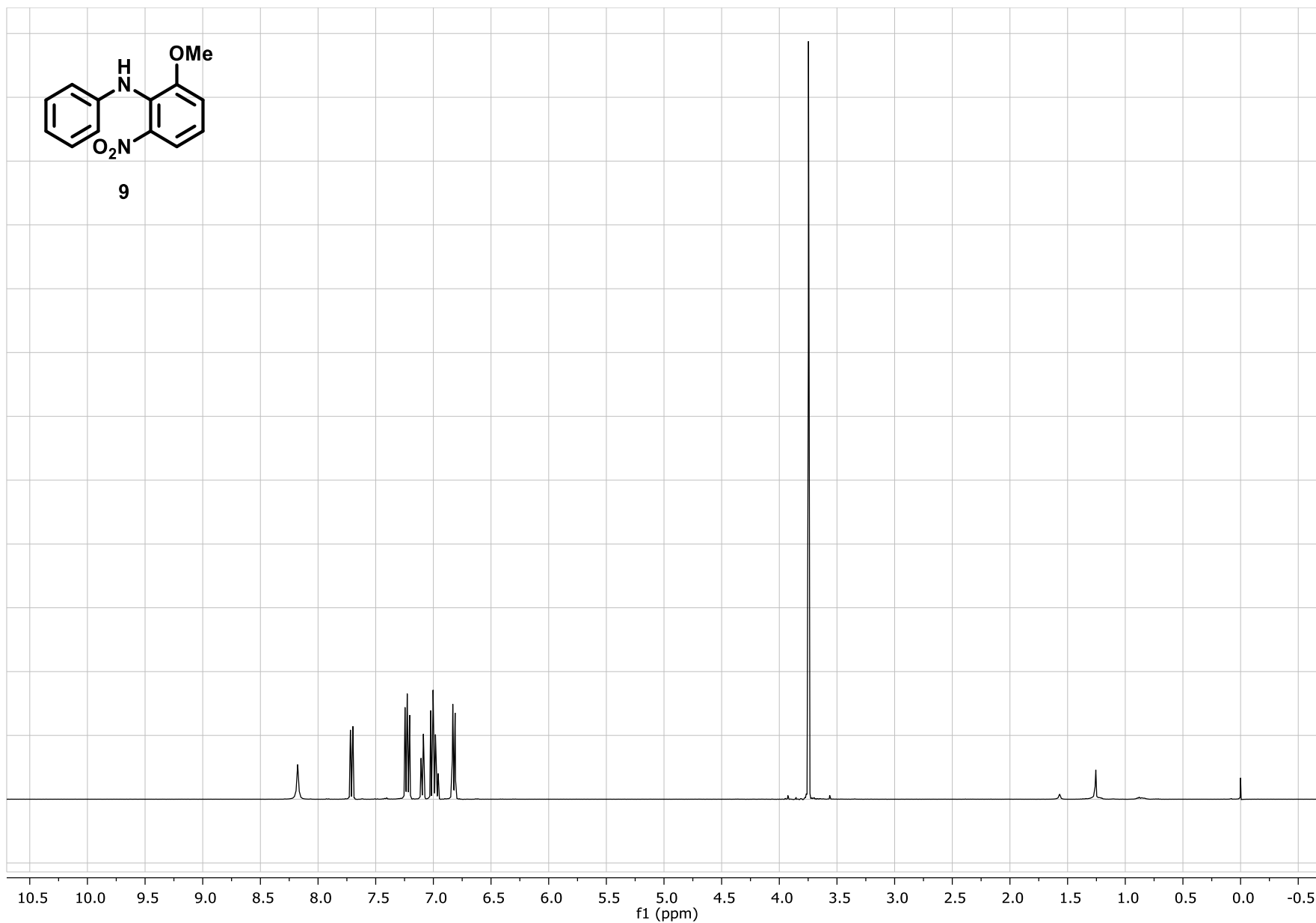




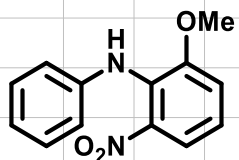
## **8.) $^1\text{H}$ NMR & $^{13}\text{C}$ NMR Spectra for New Compounds**



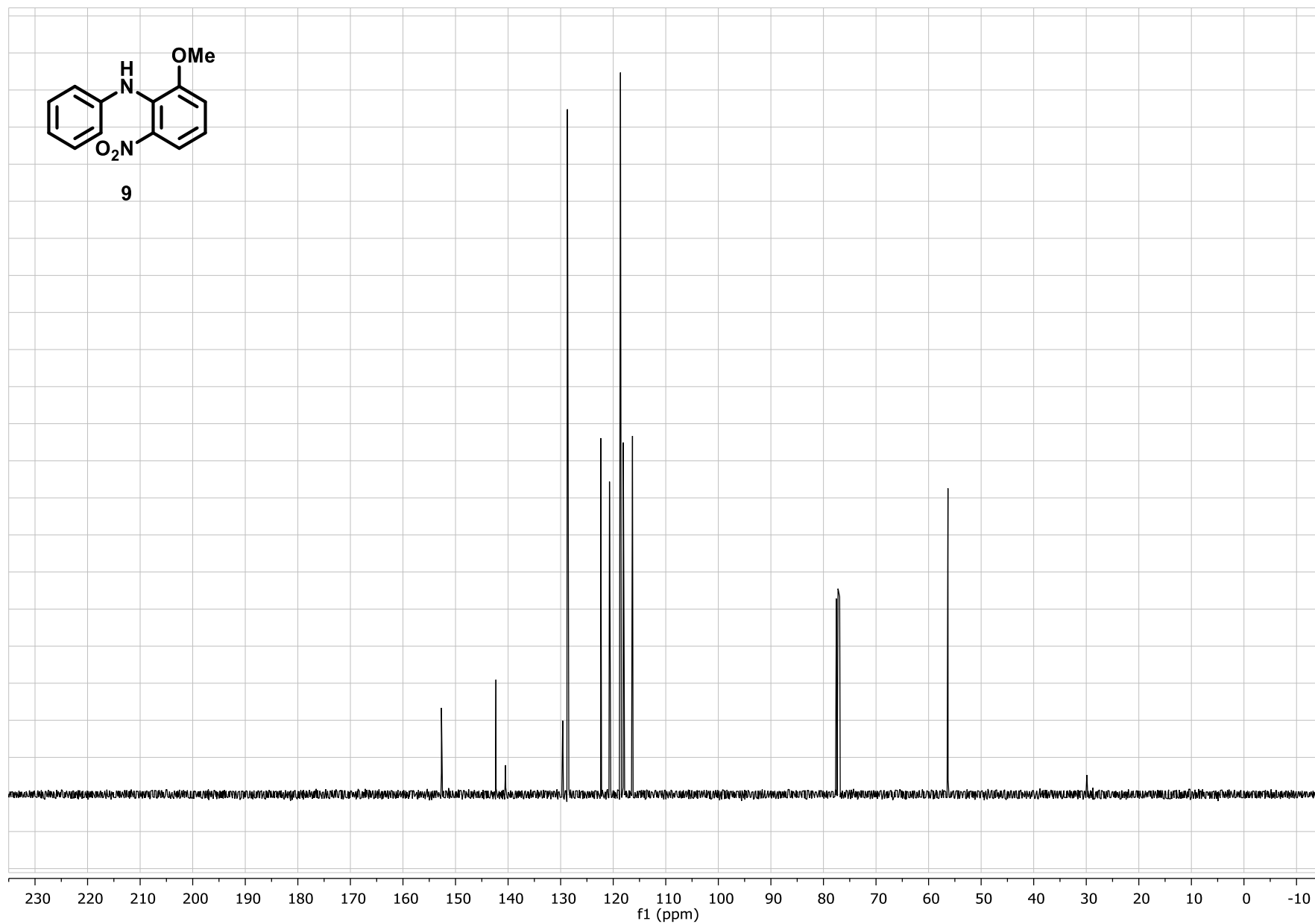
9



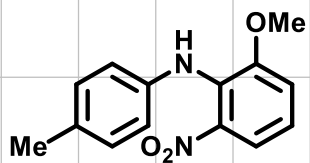
S54



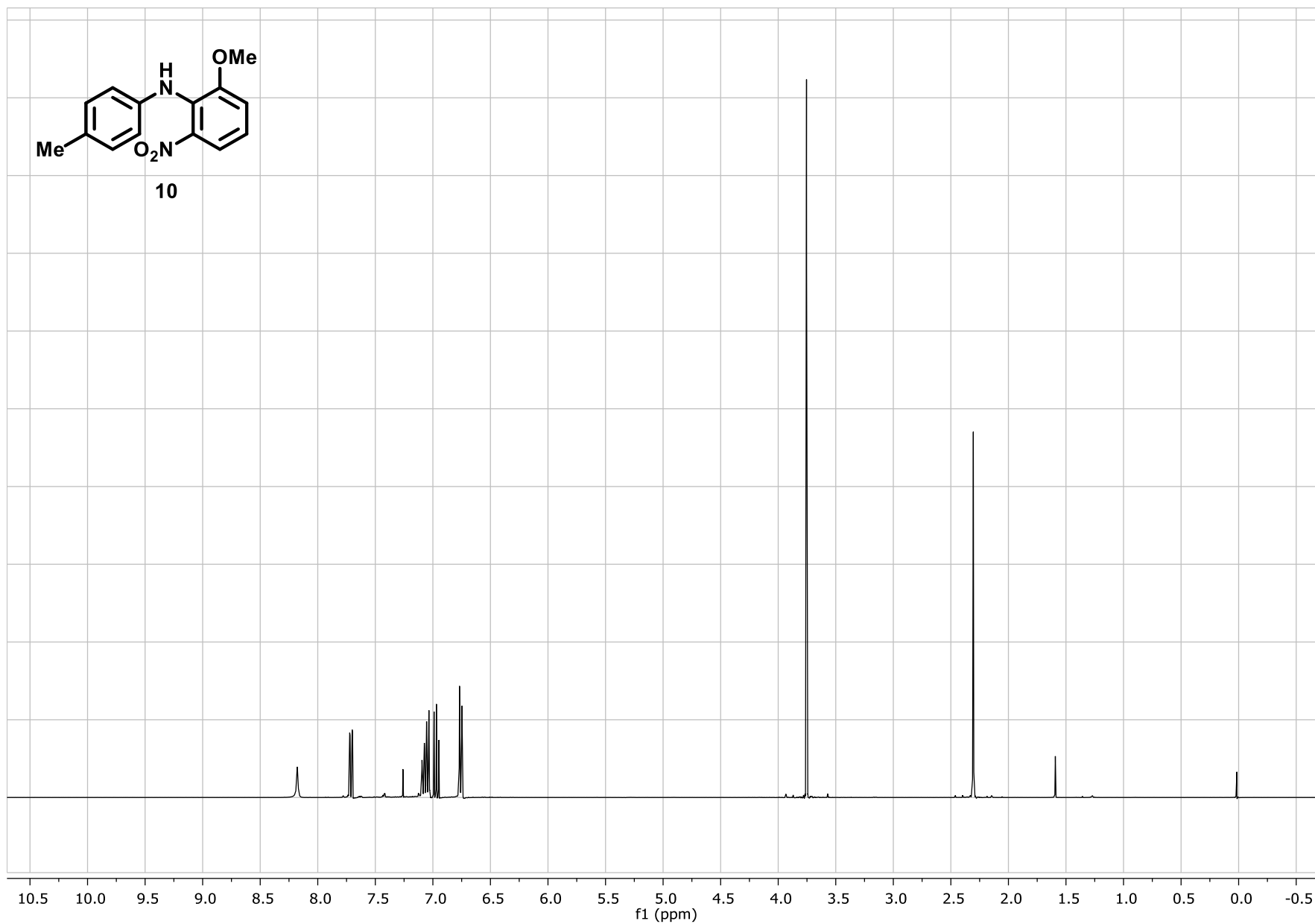
9



S55

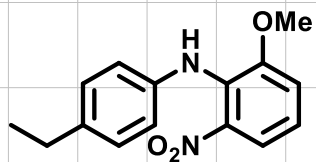


10

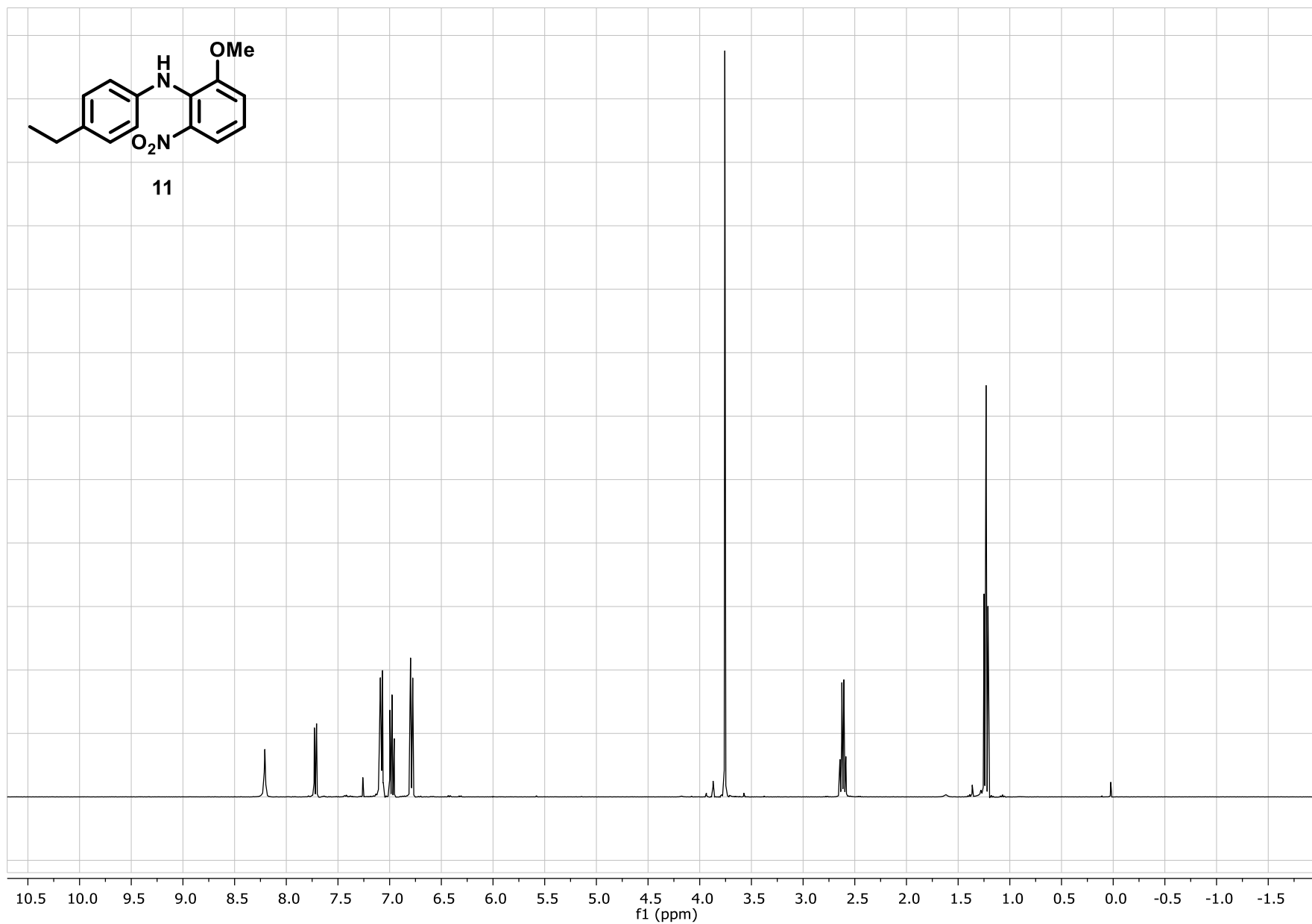


S56

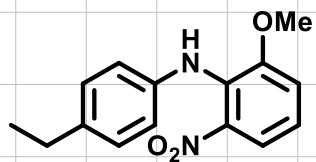




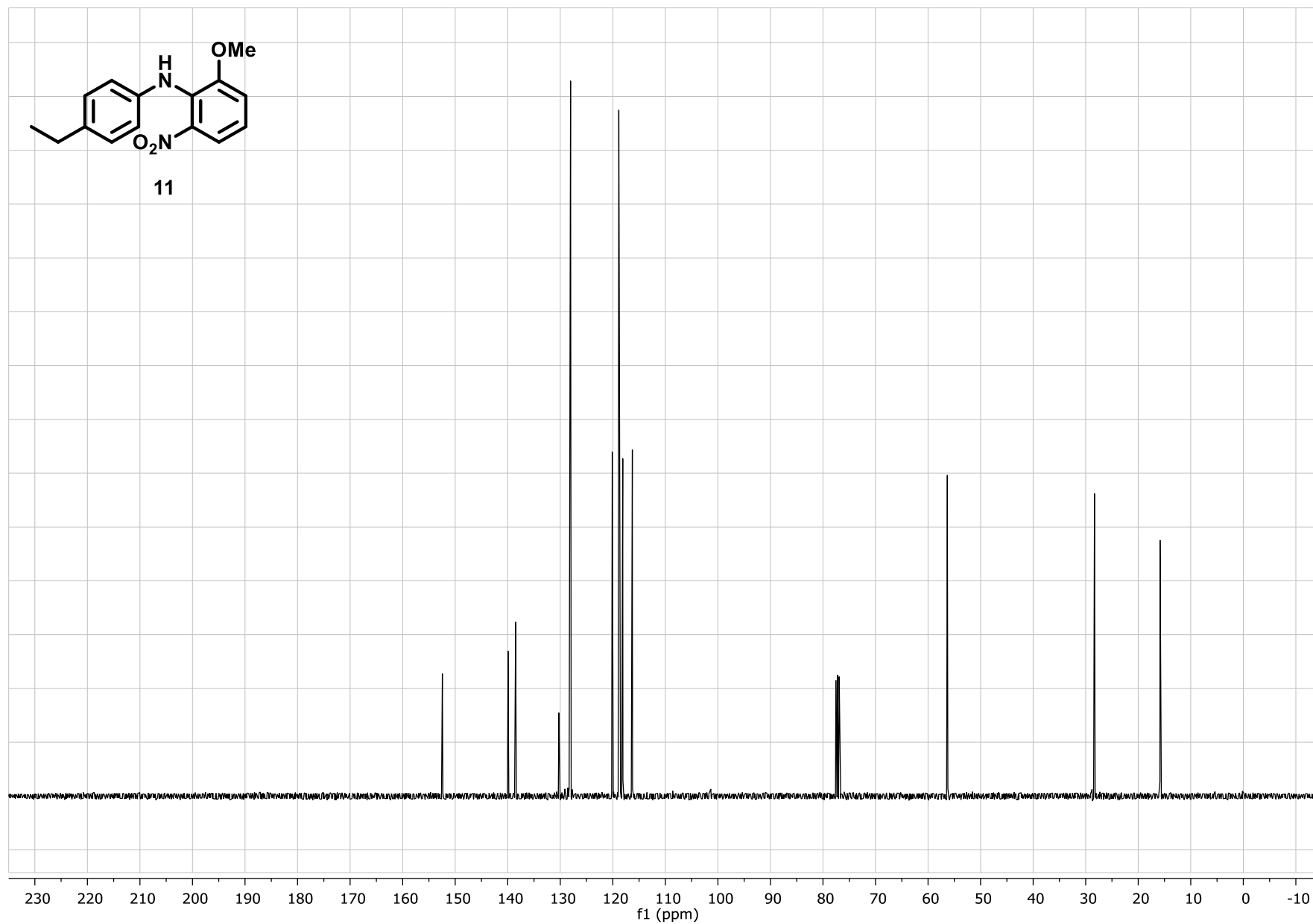
11

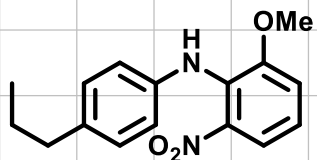


S58

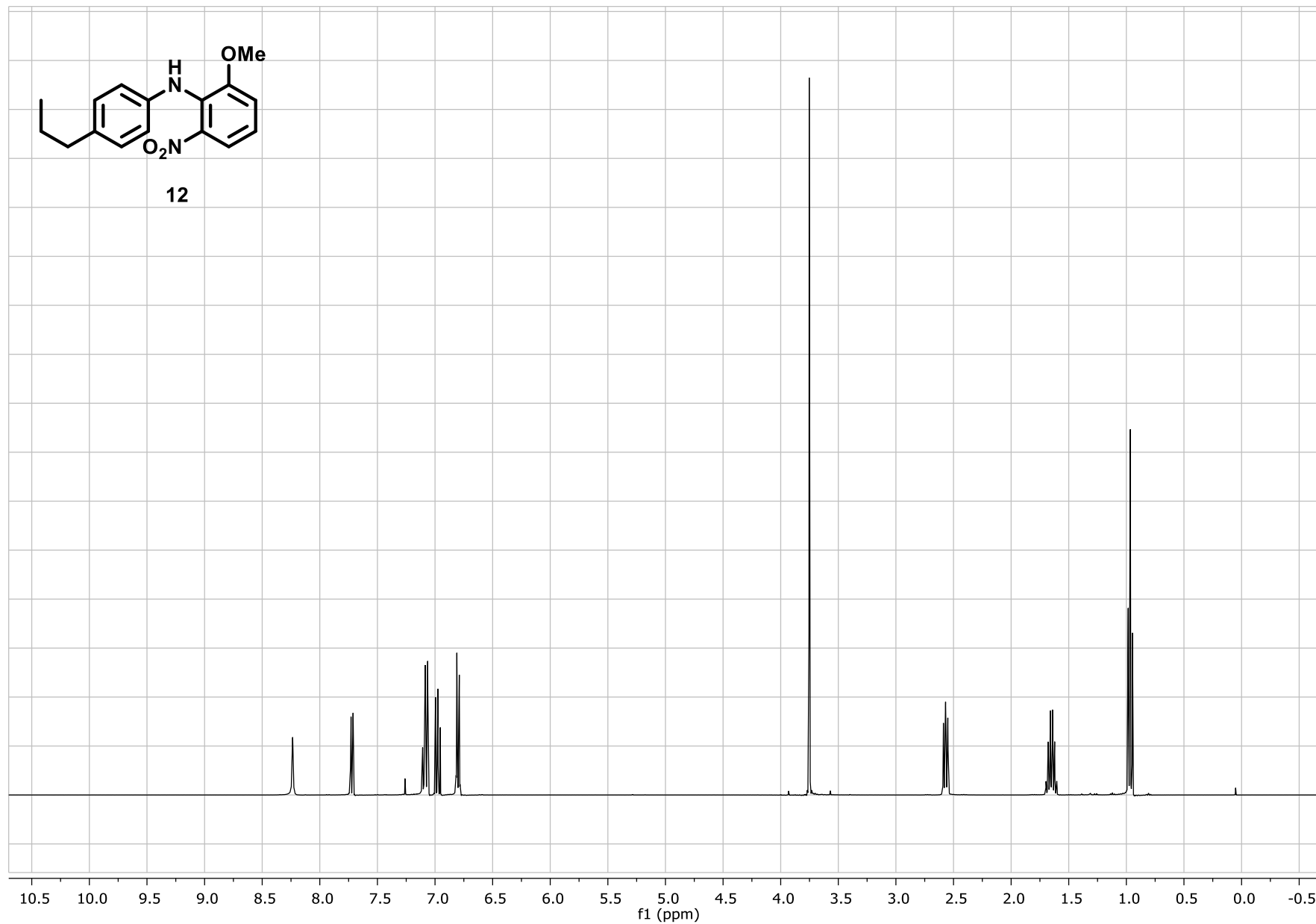


11



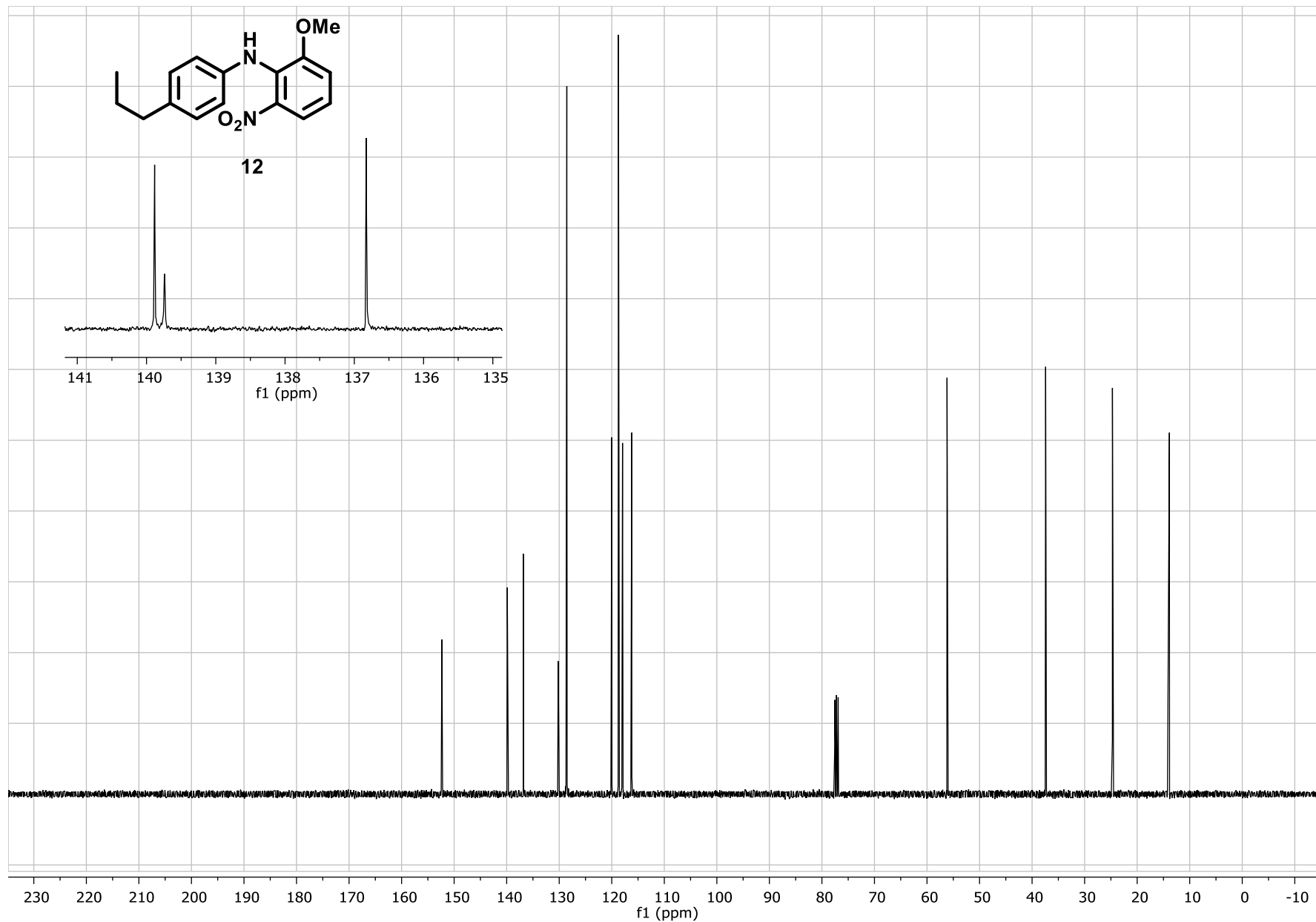


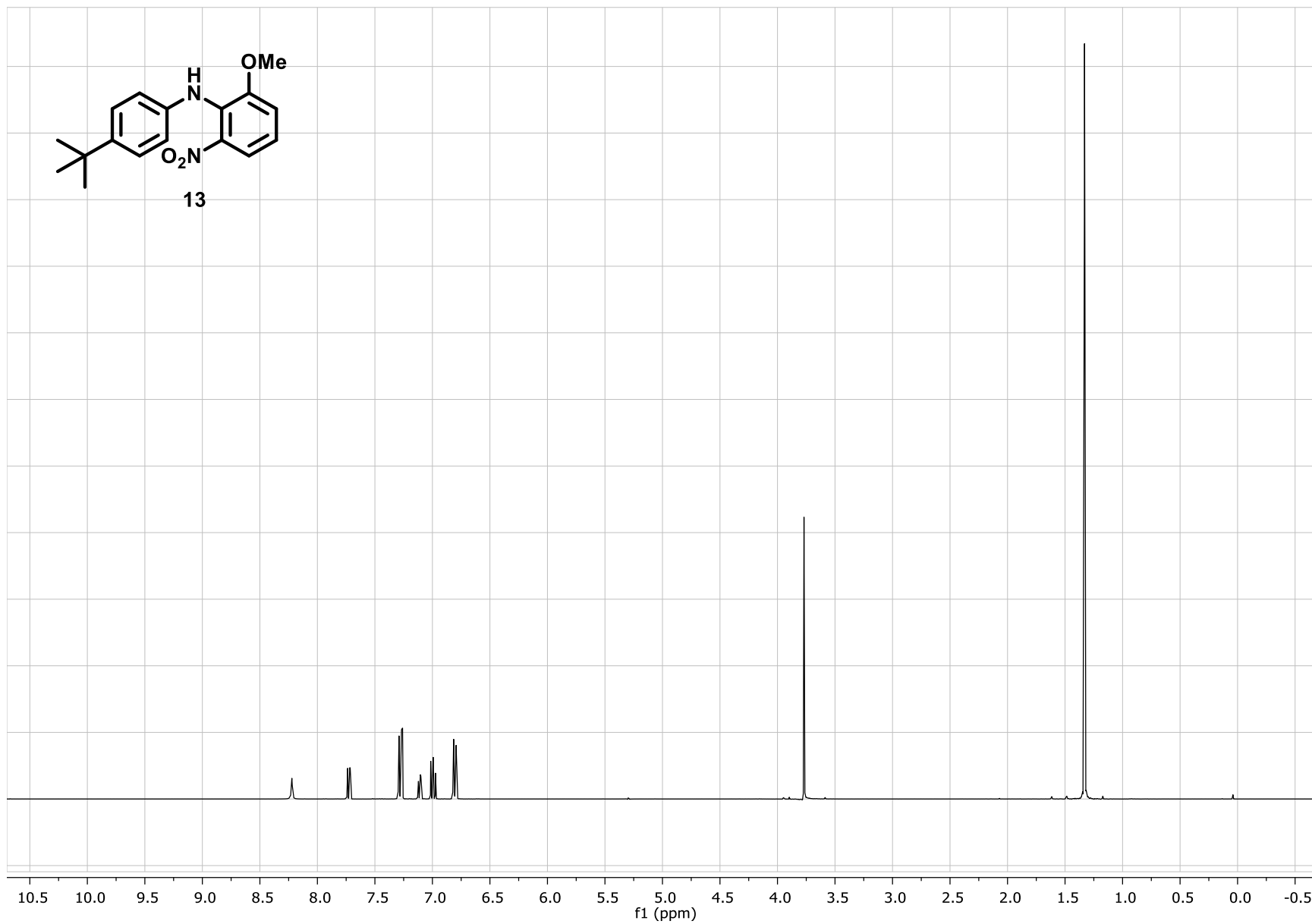
12

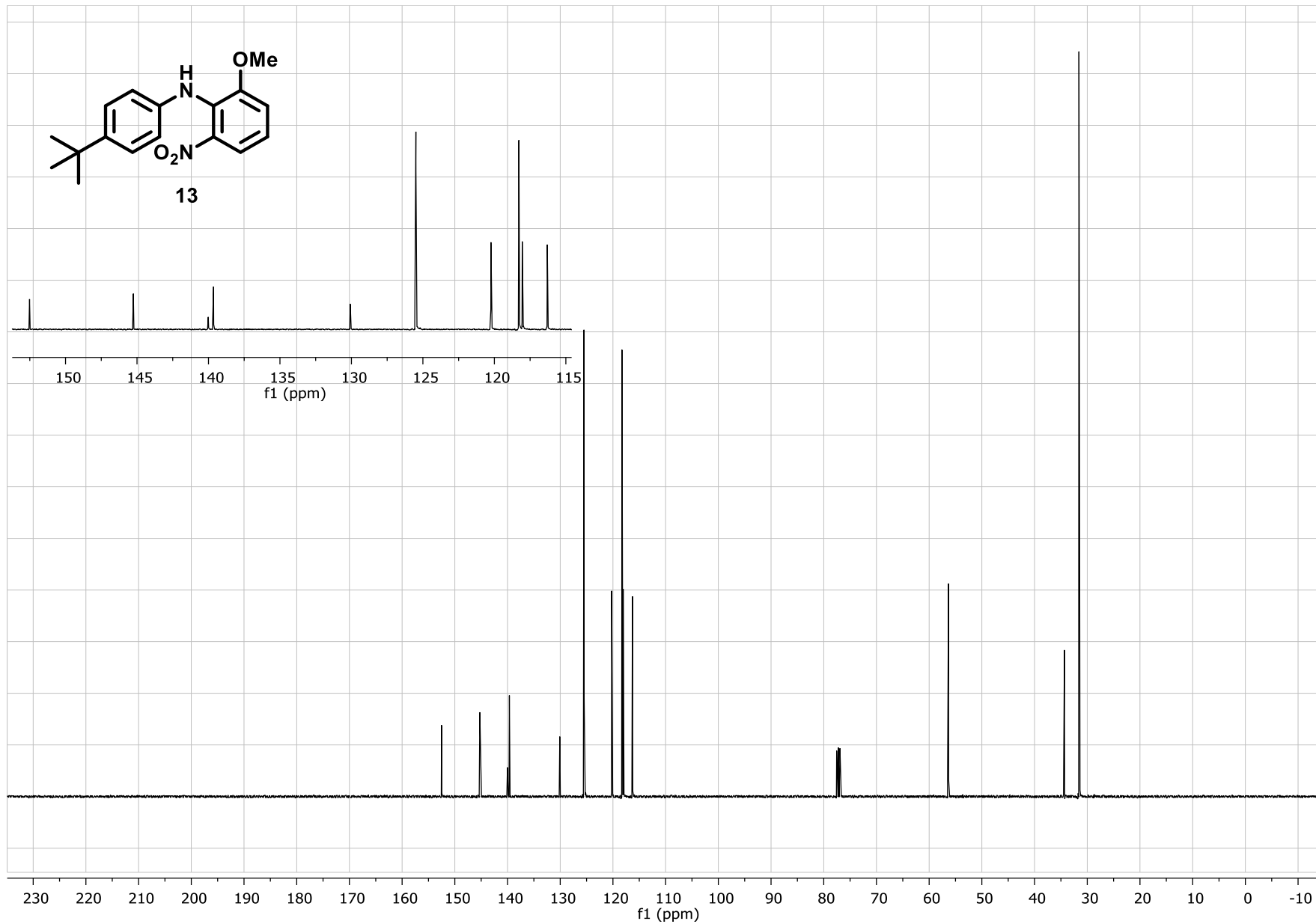
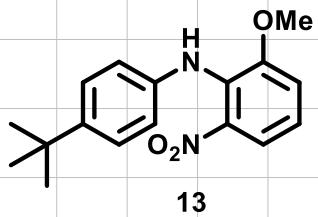


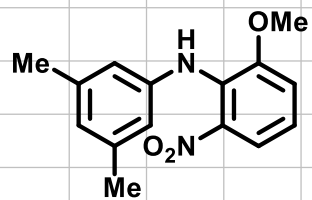
S60



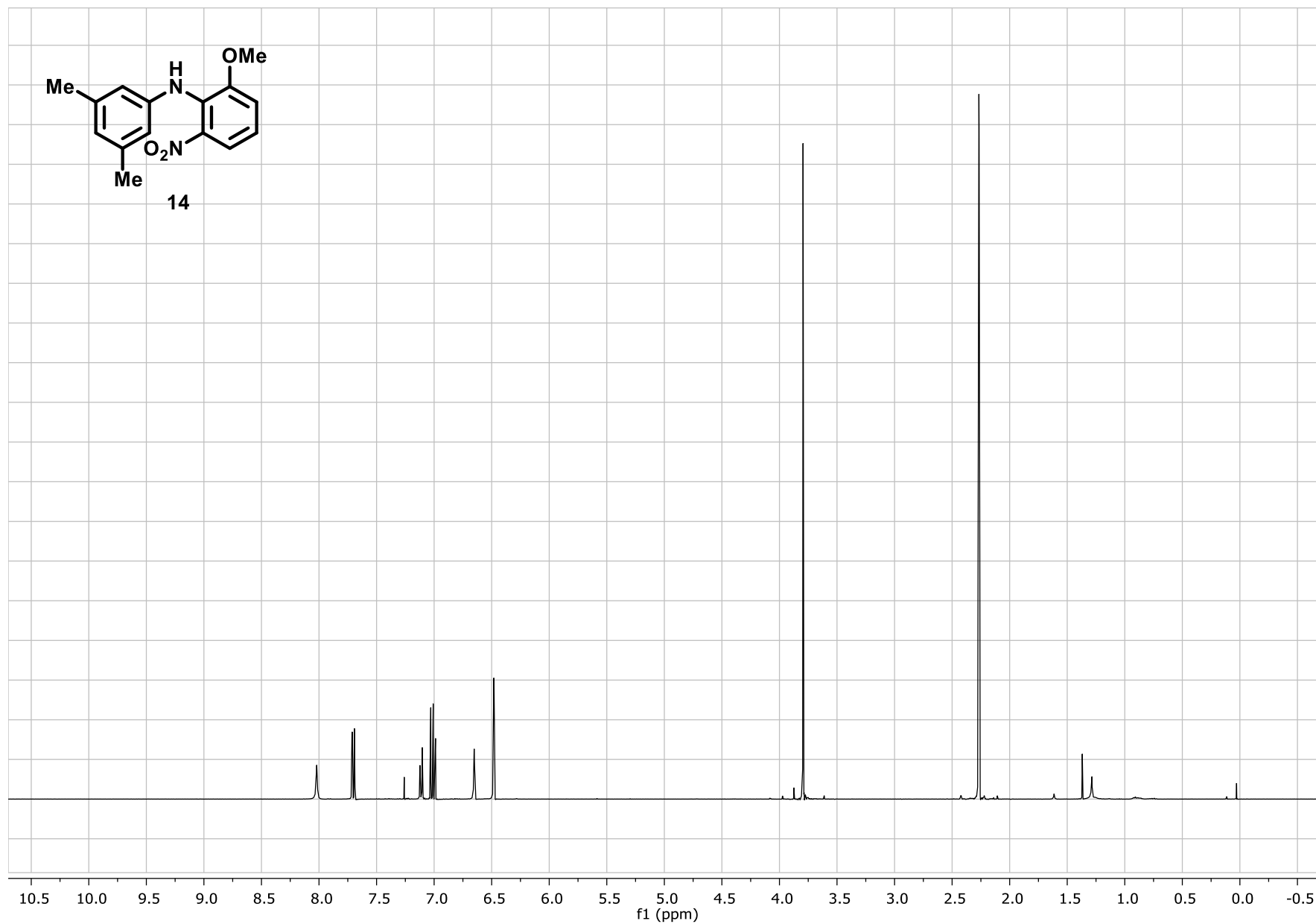




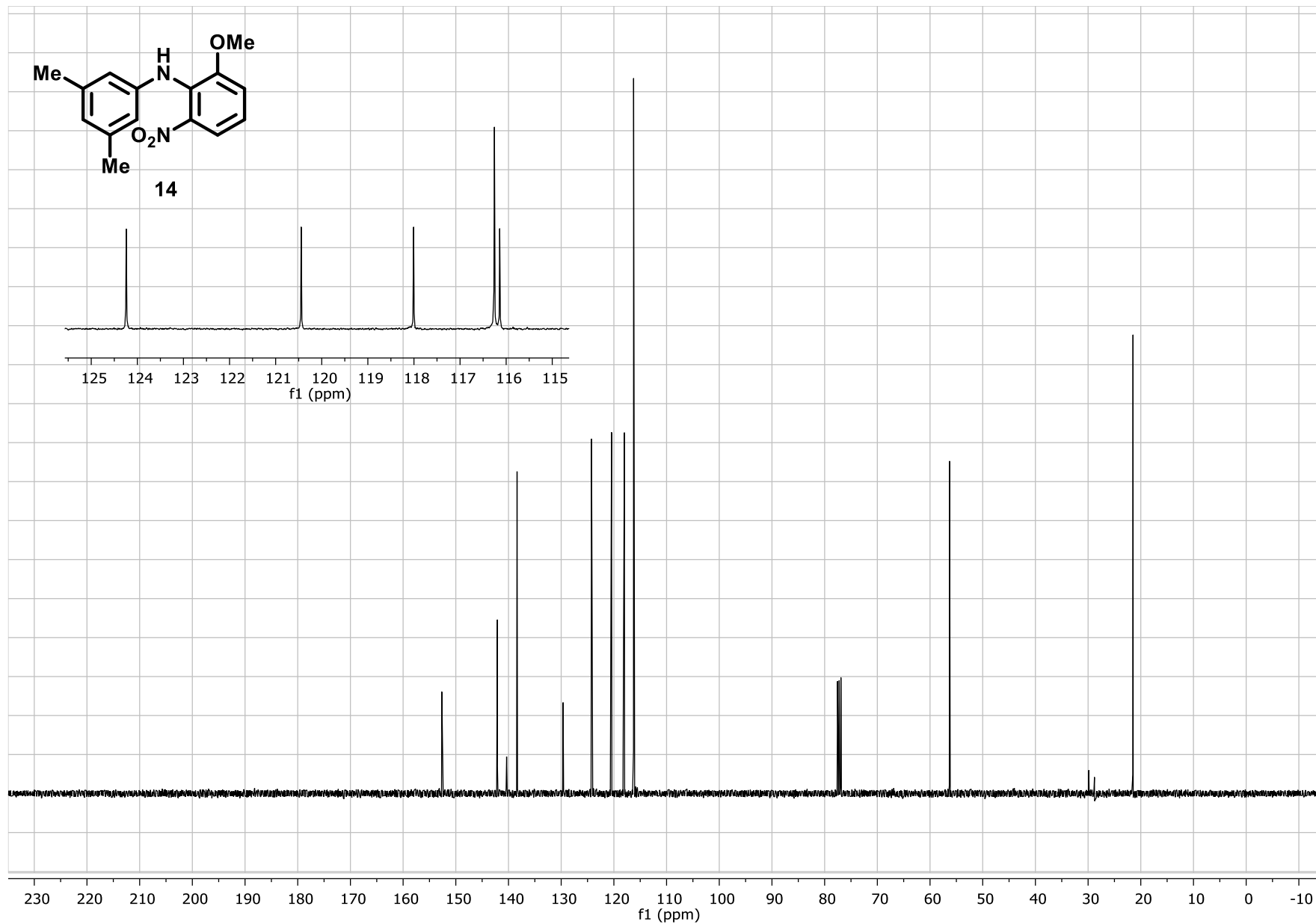


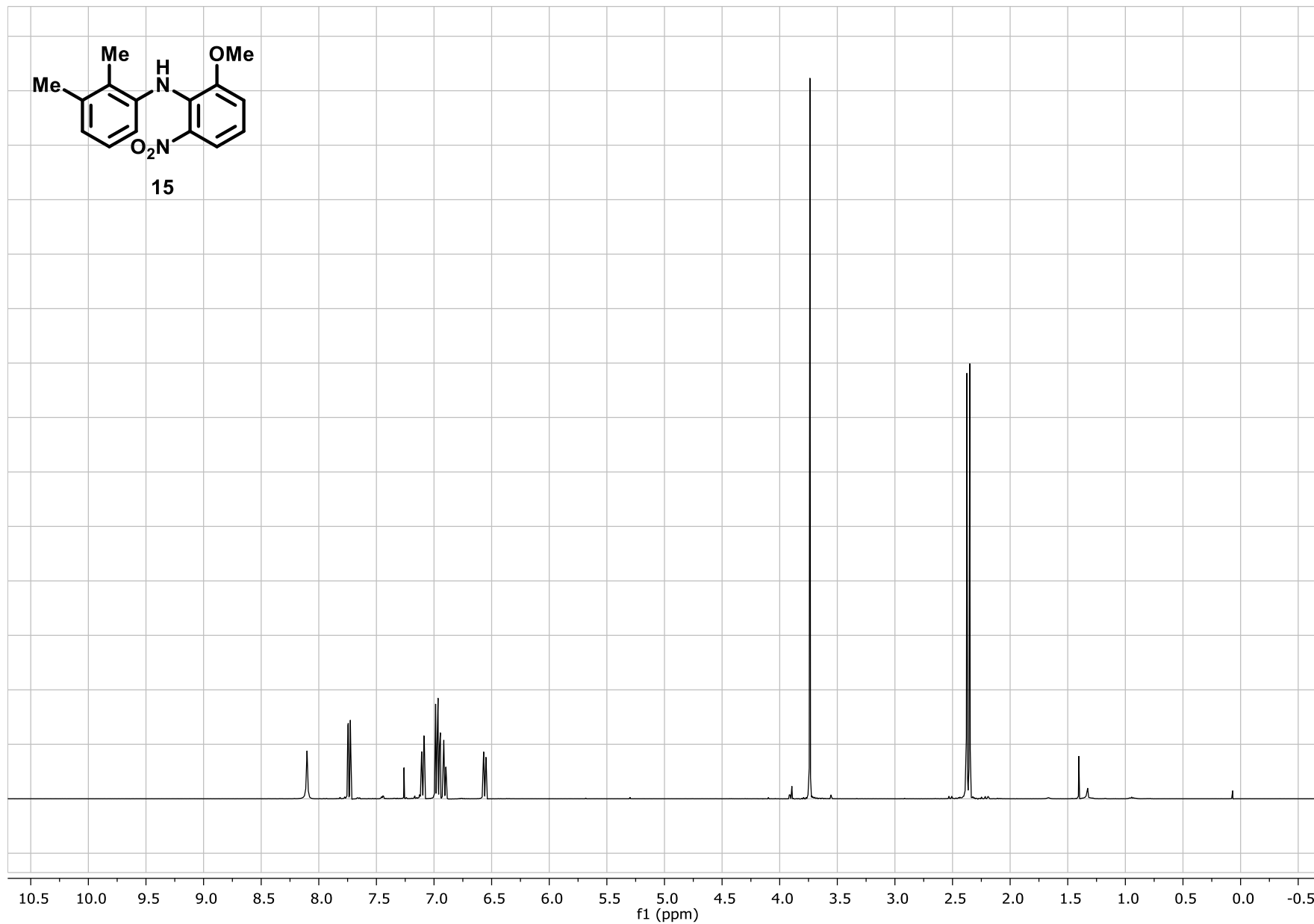
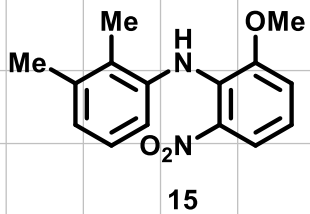


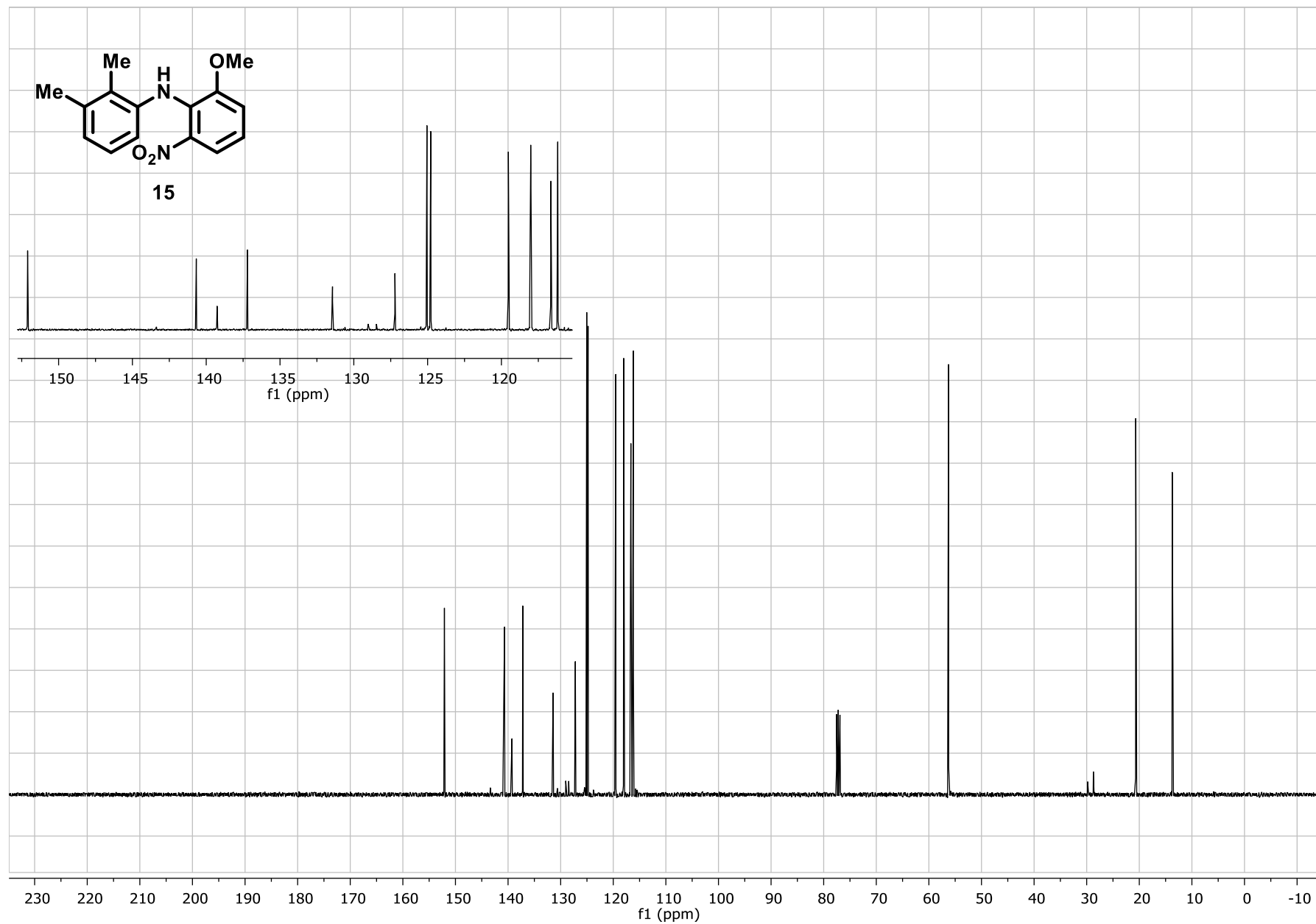
14

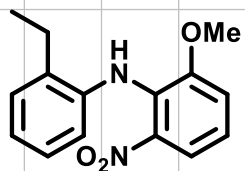


S64

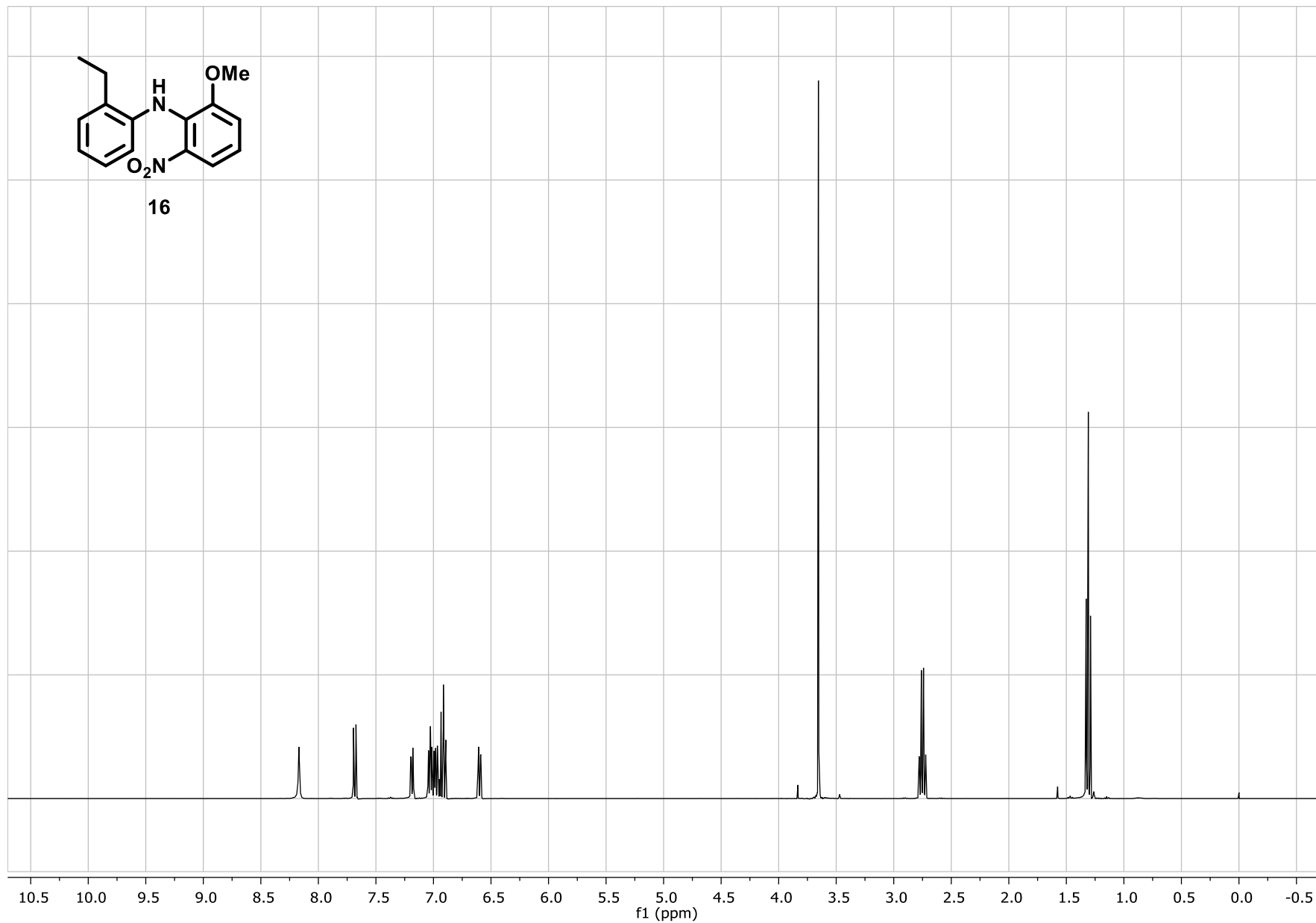






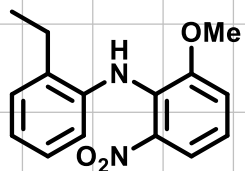


16

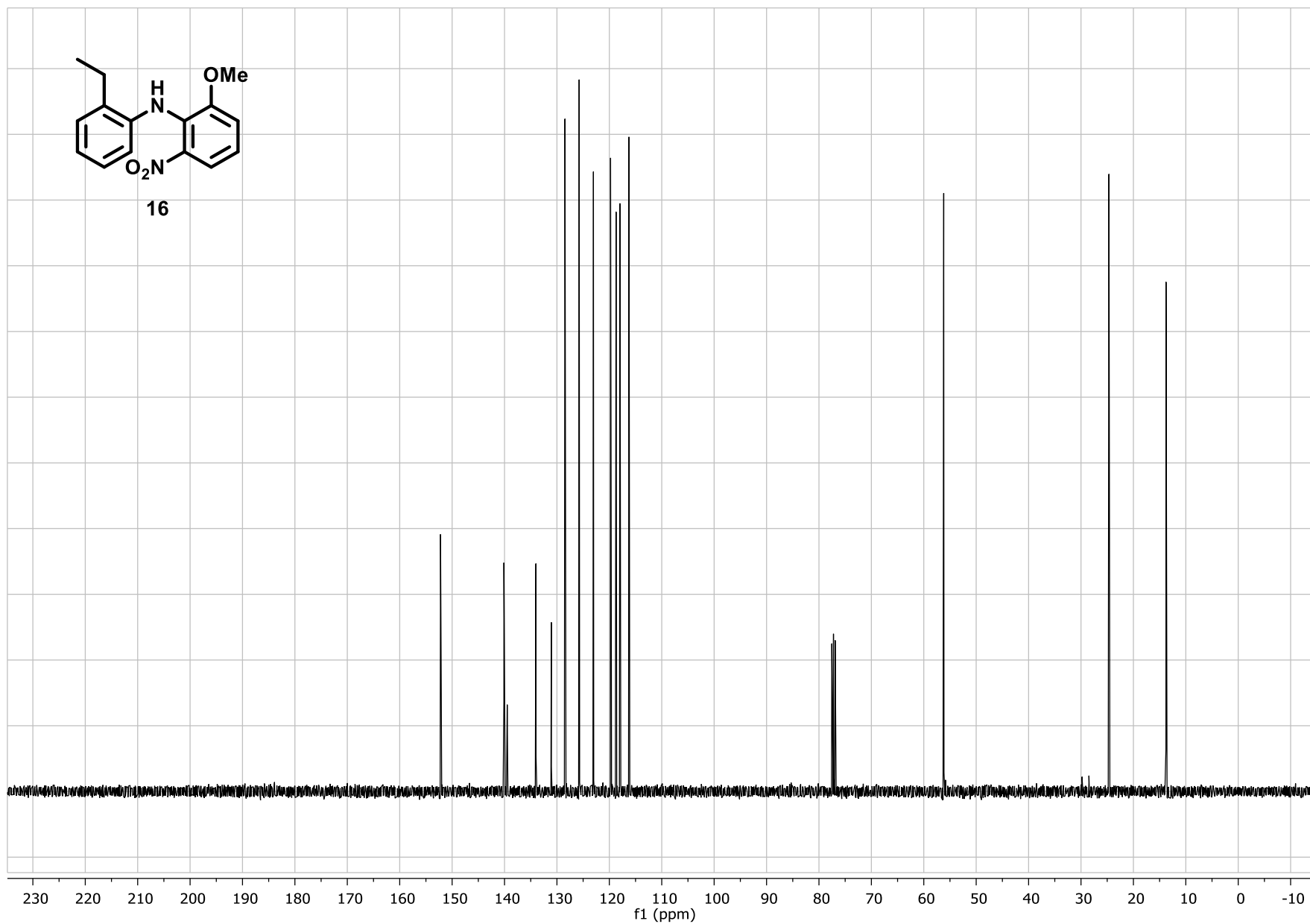


S68

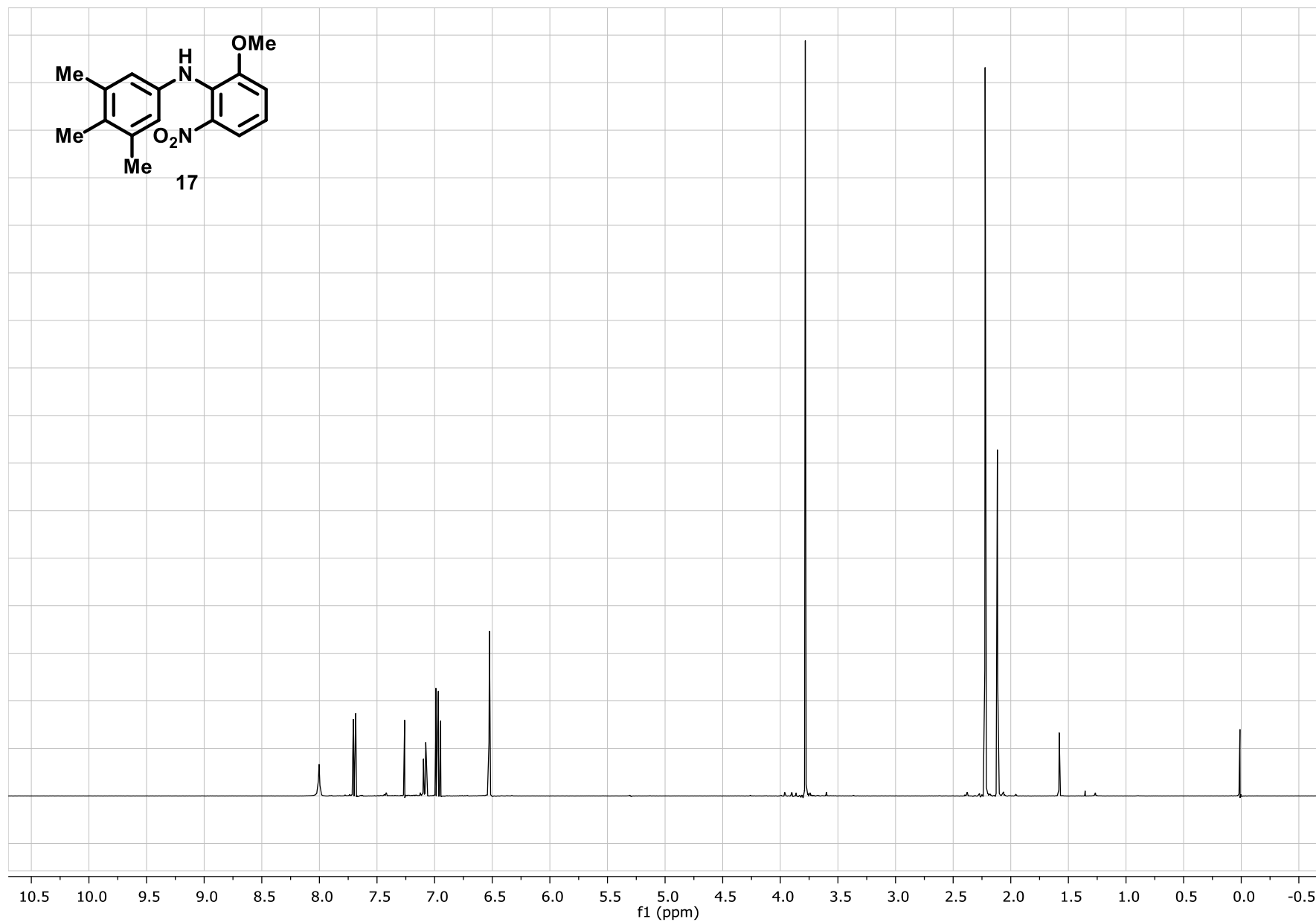
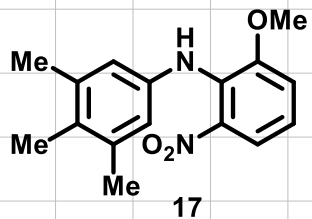


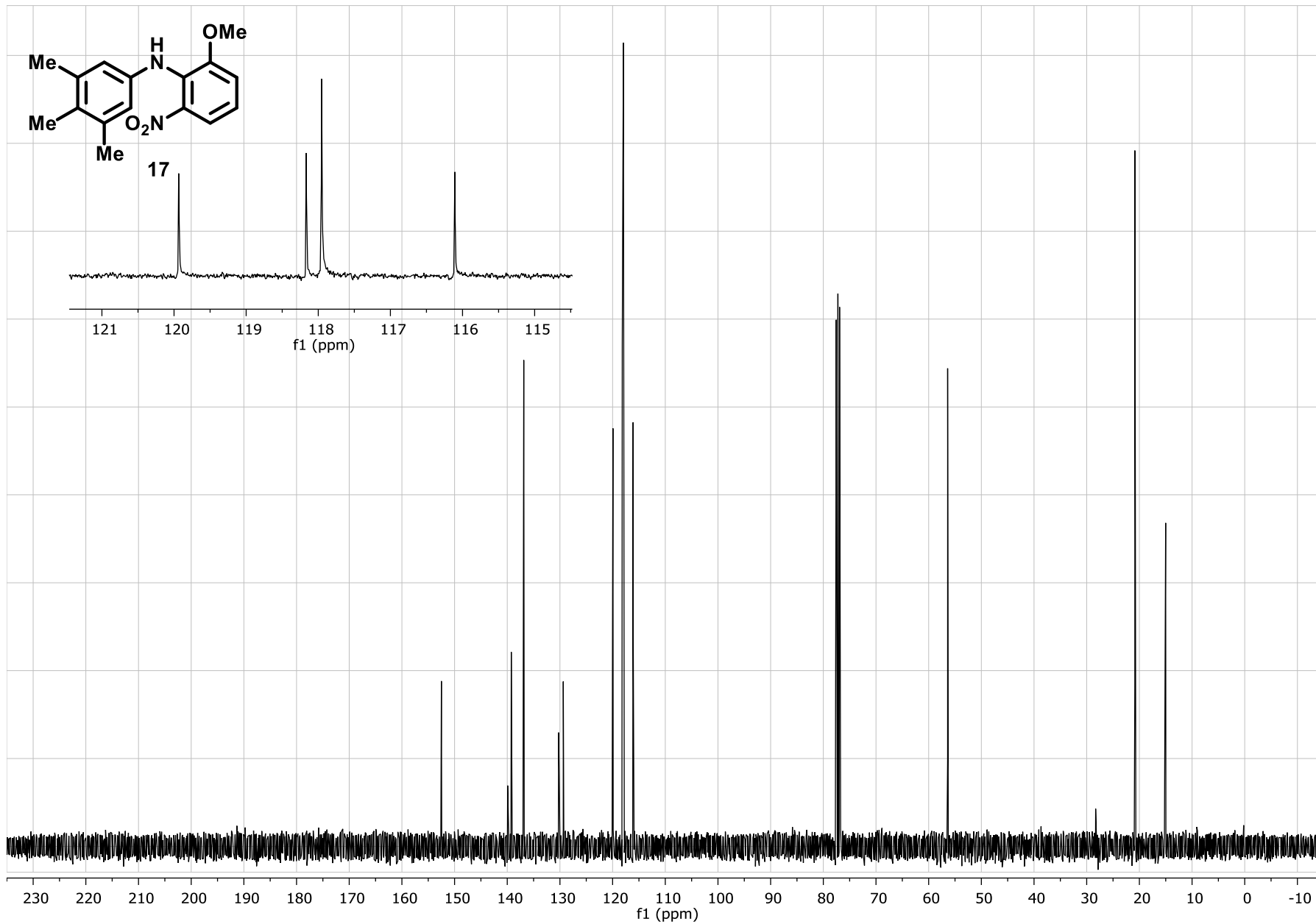


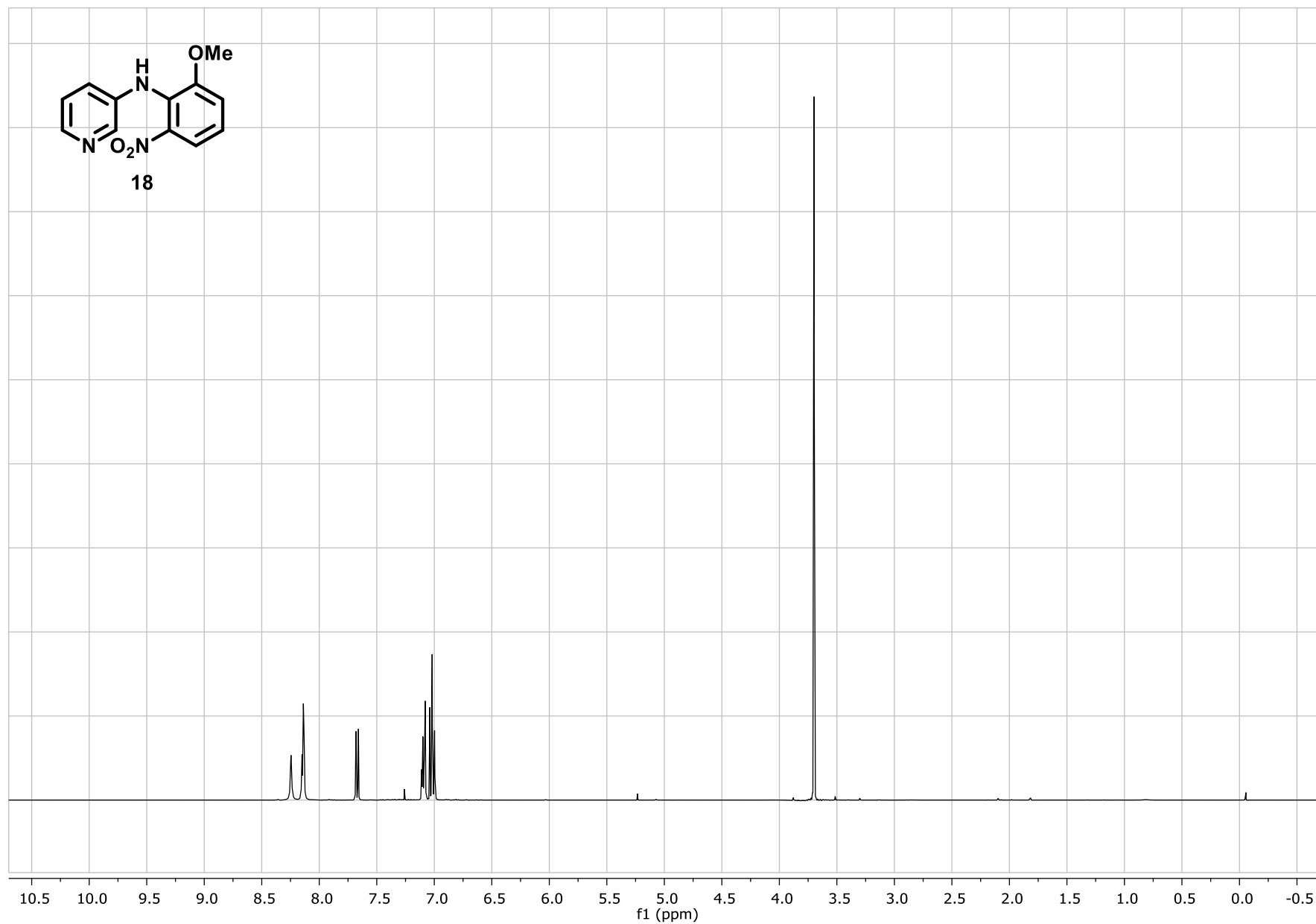
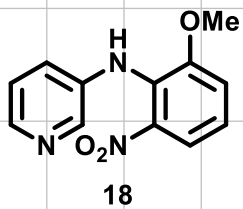
16

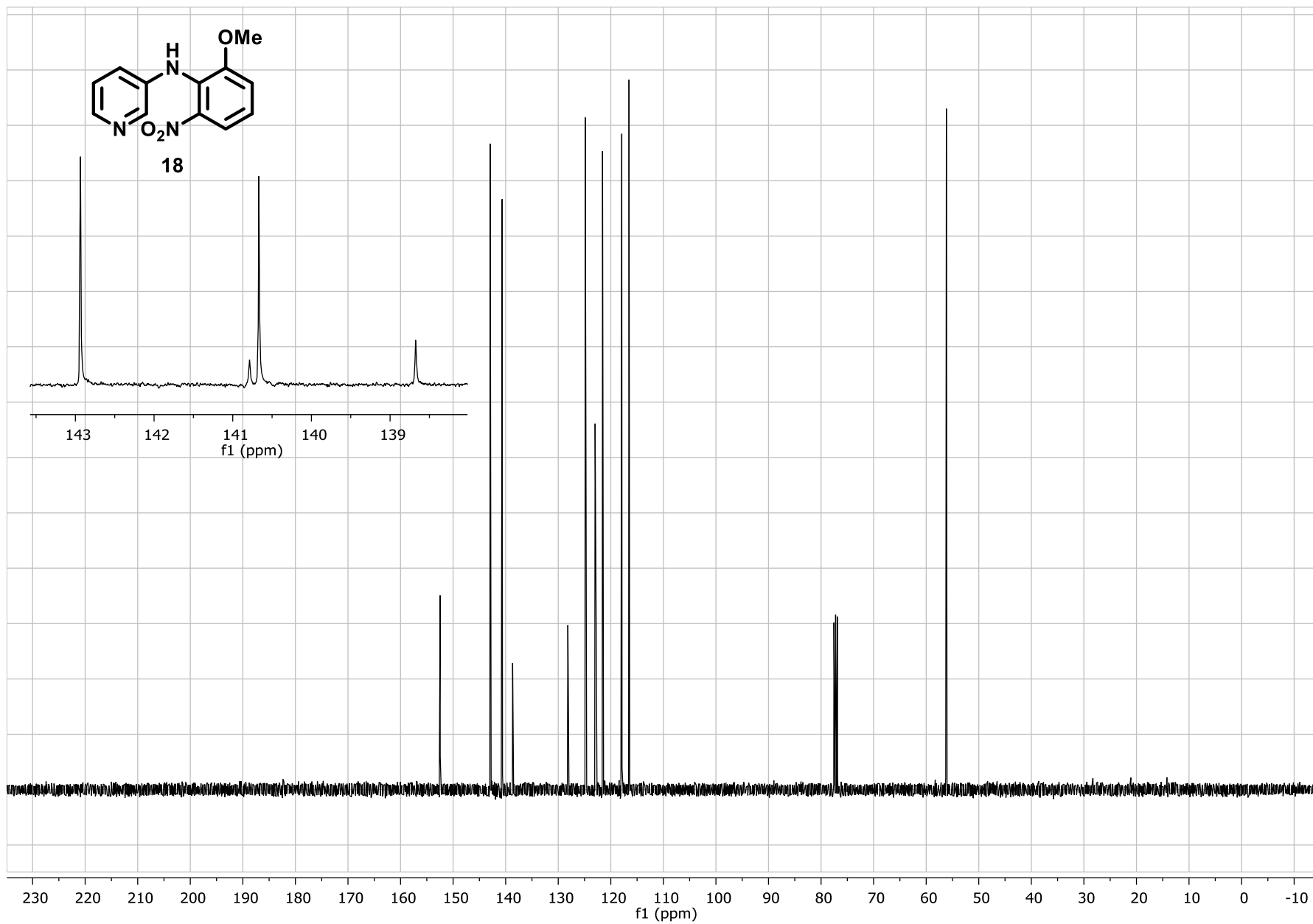


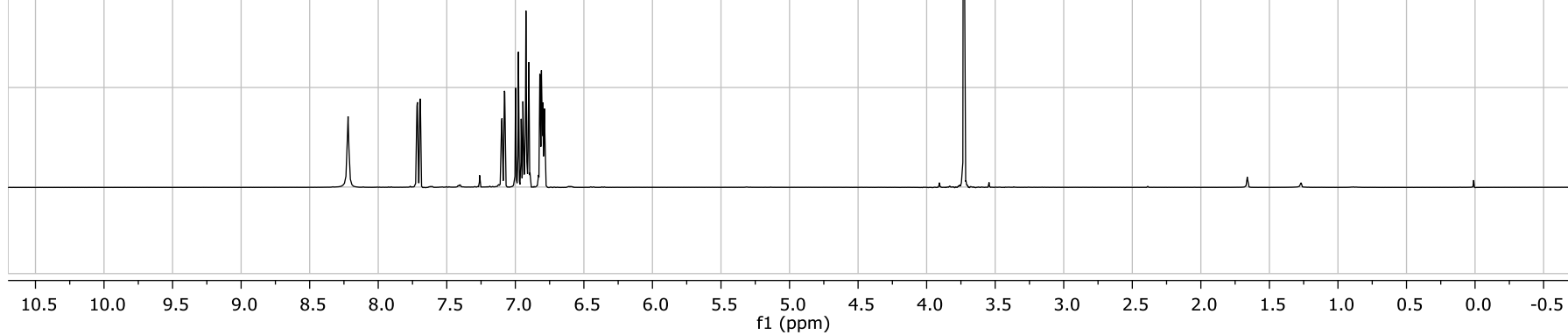
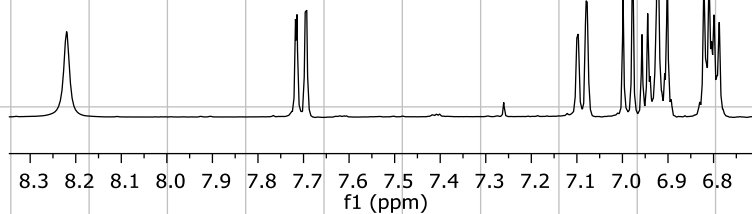
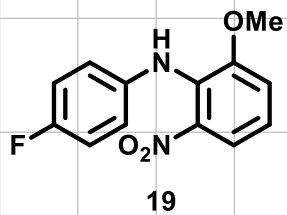
S69

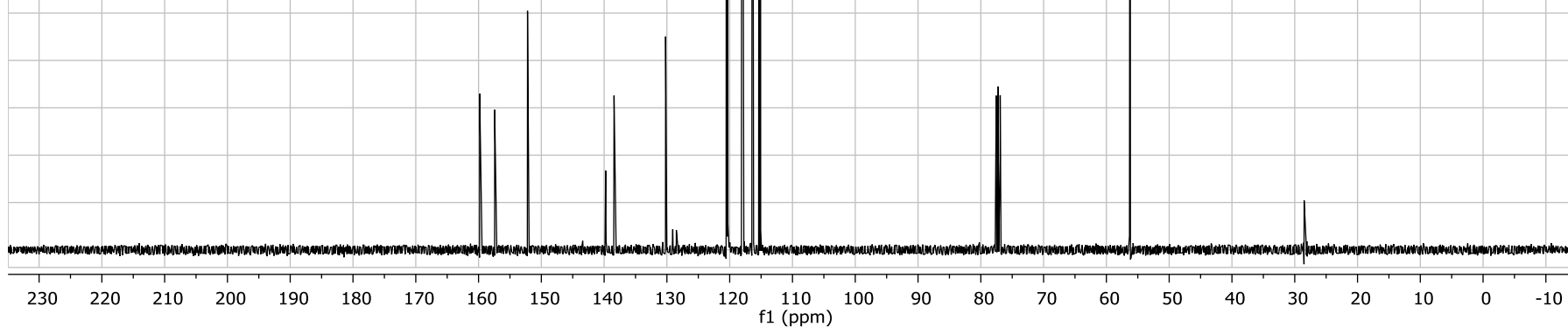
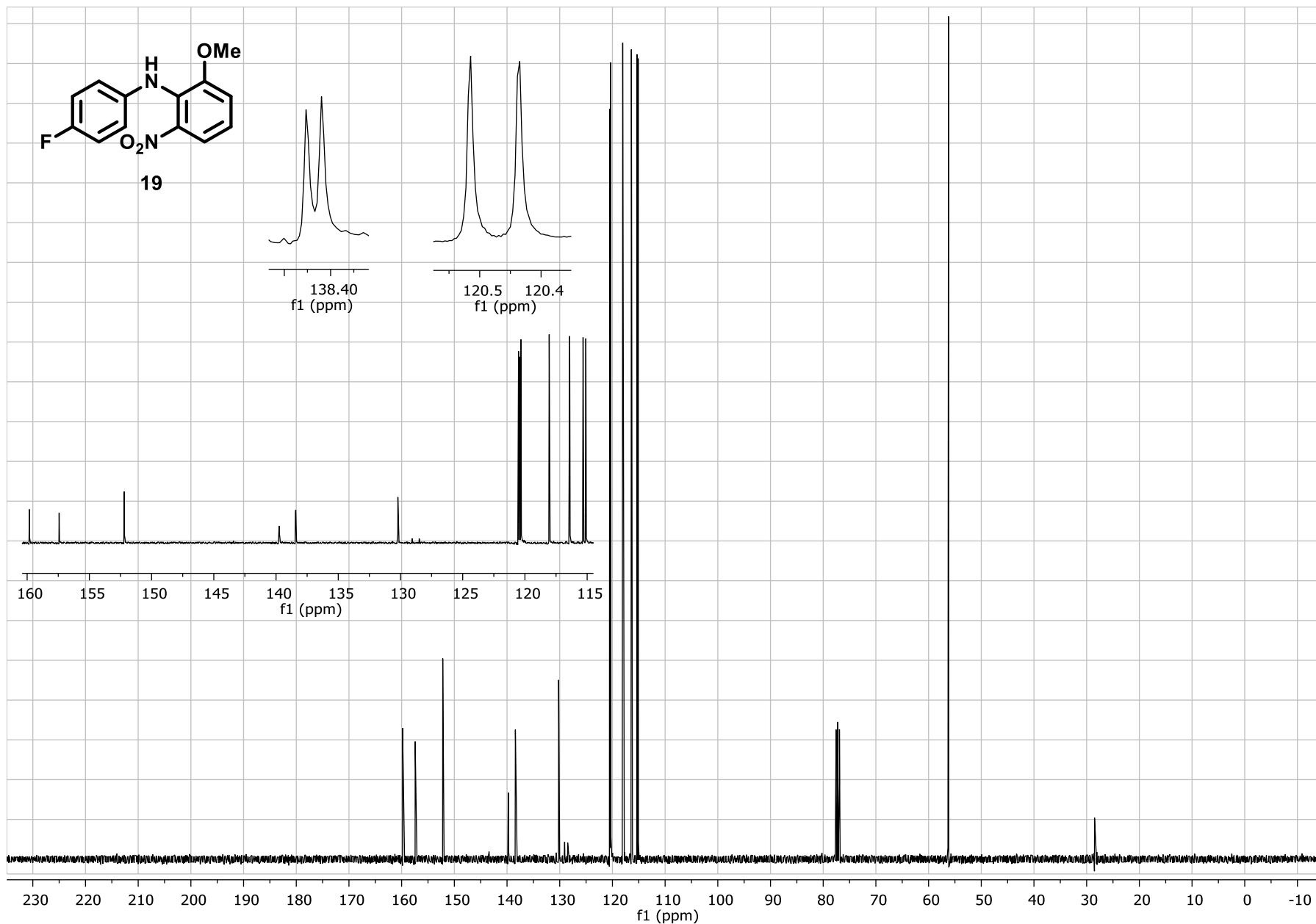
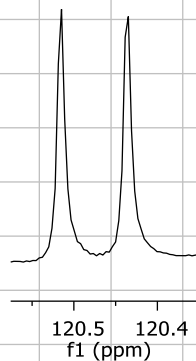
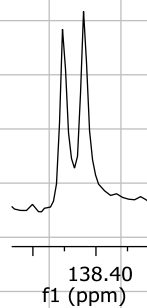
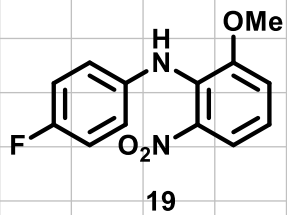


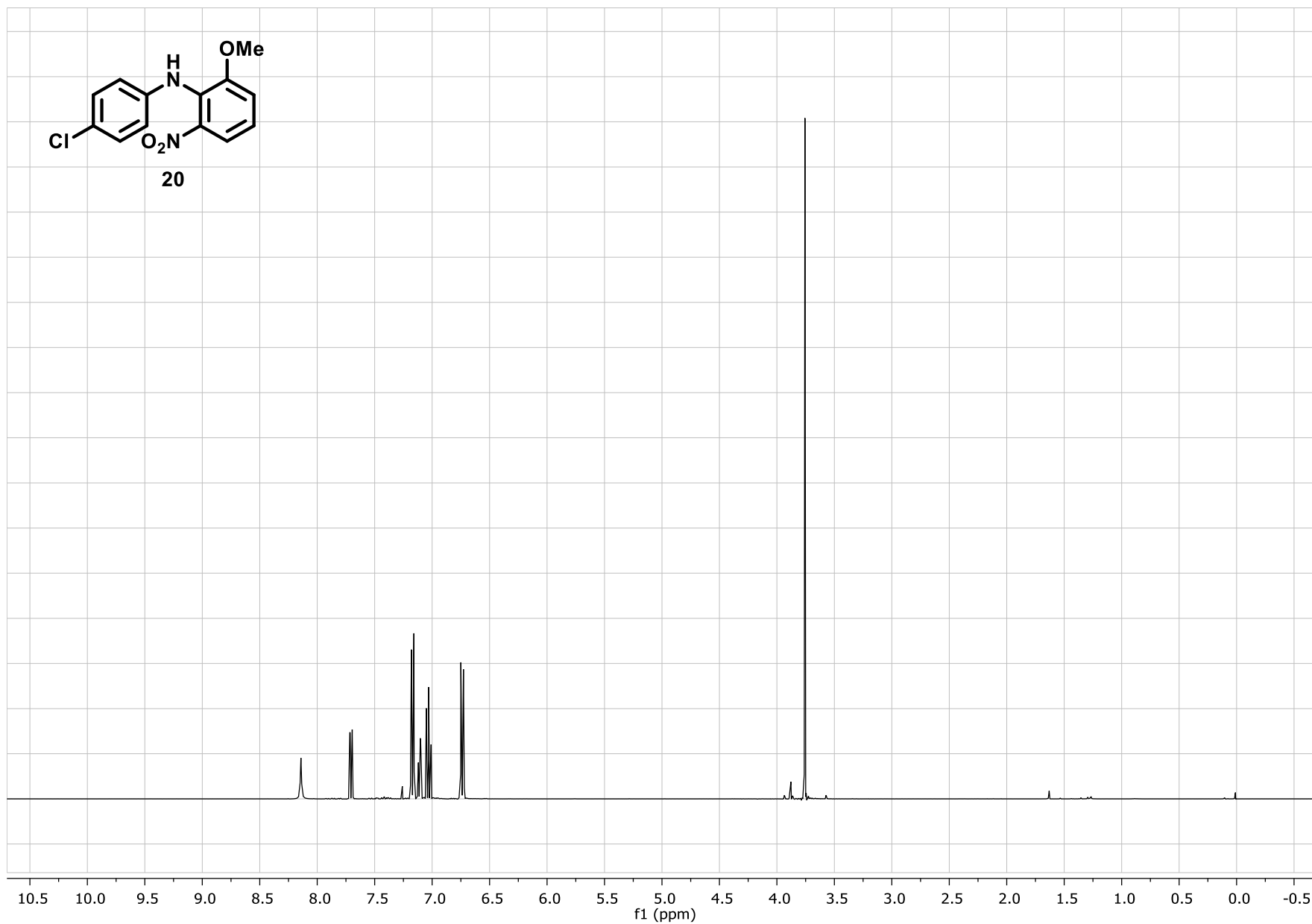
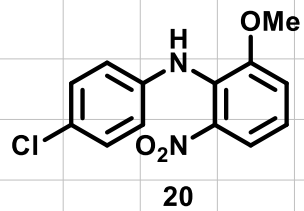




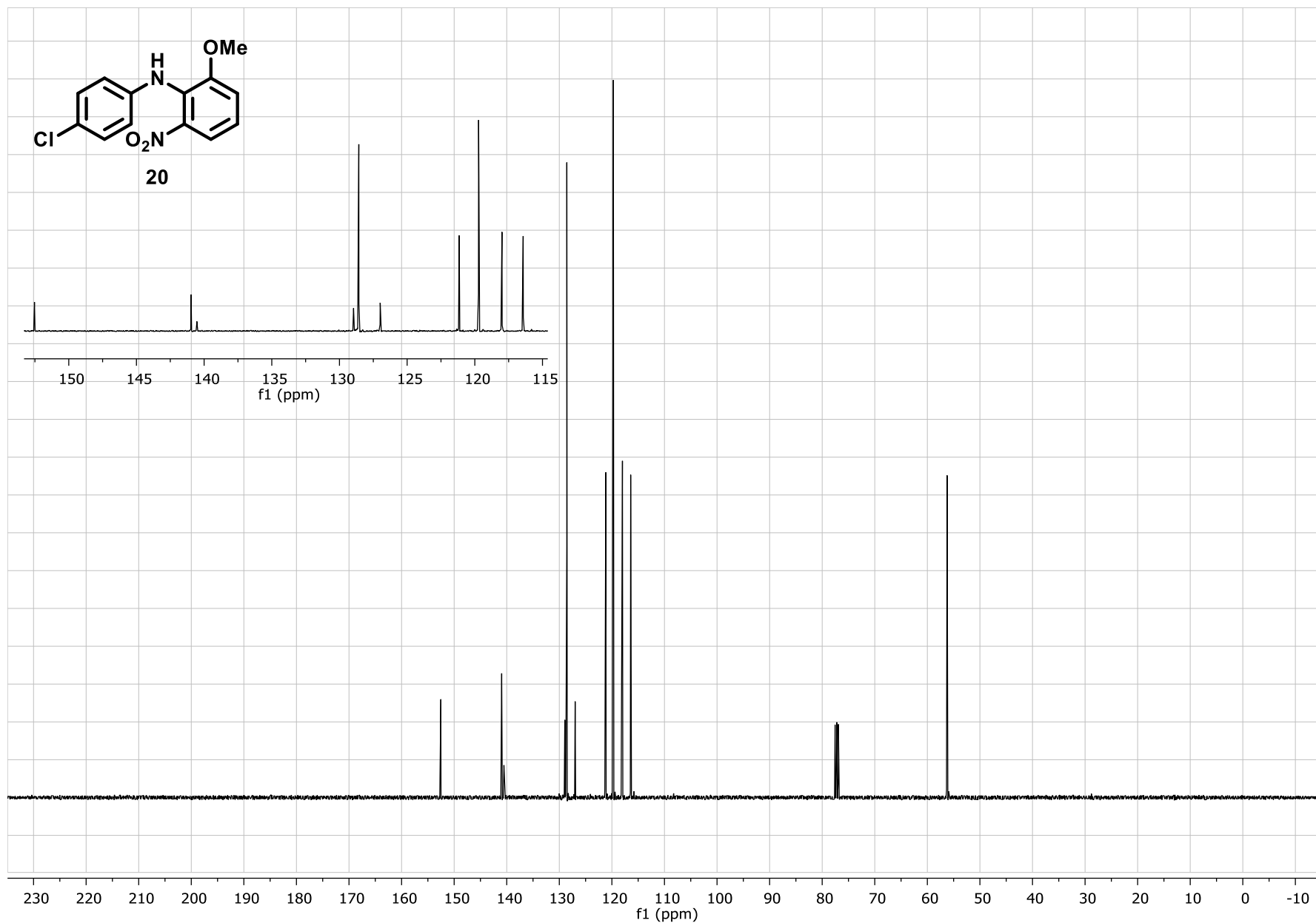
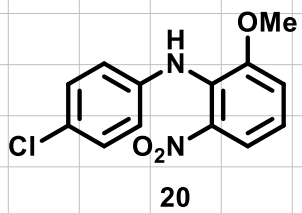


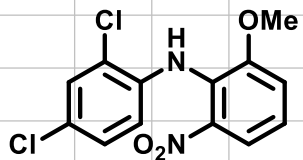




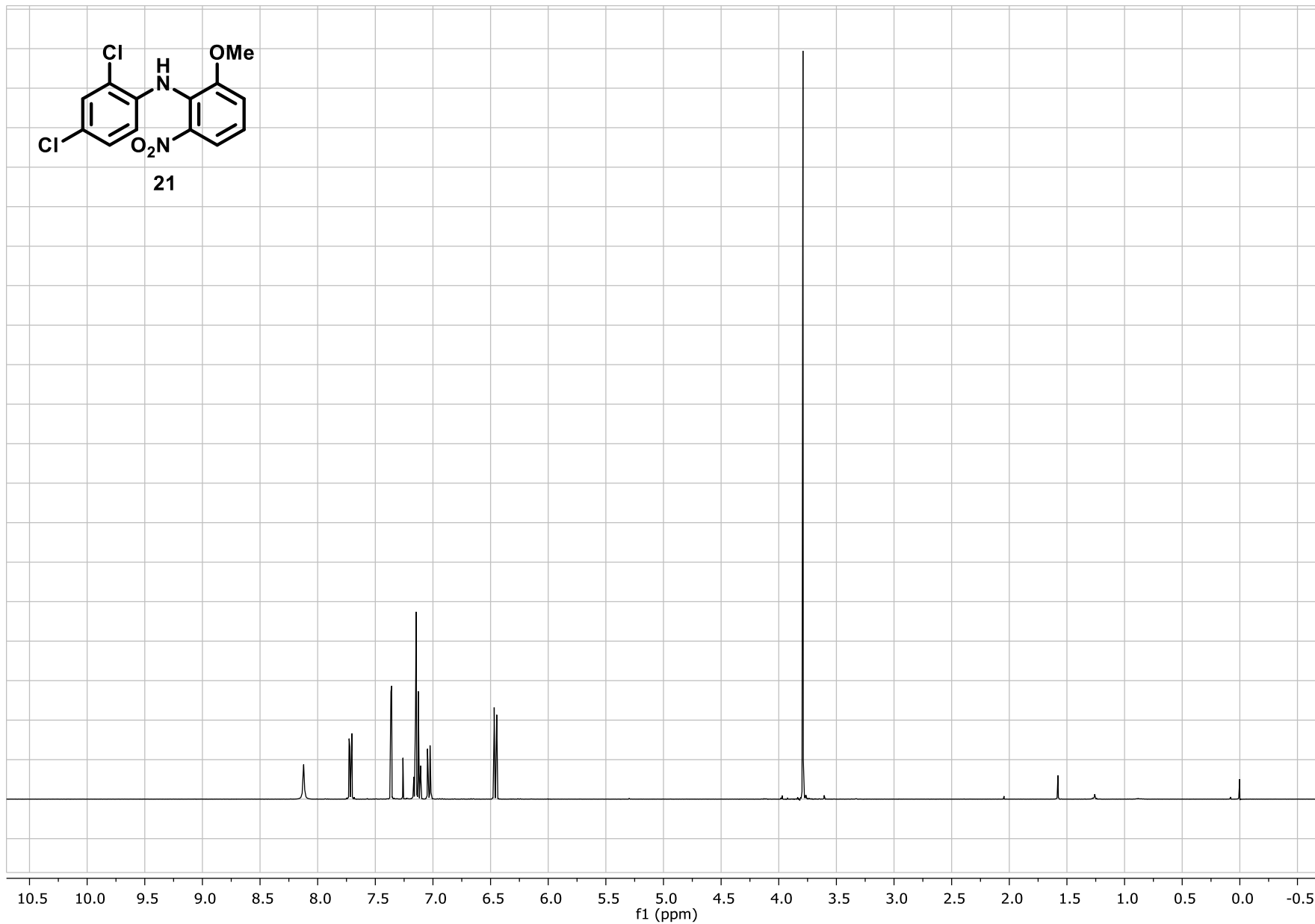




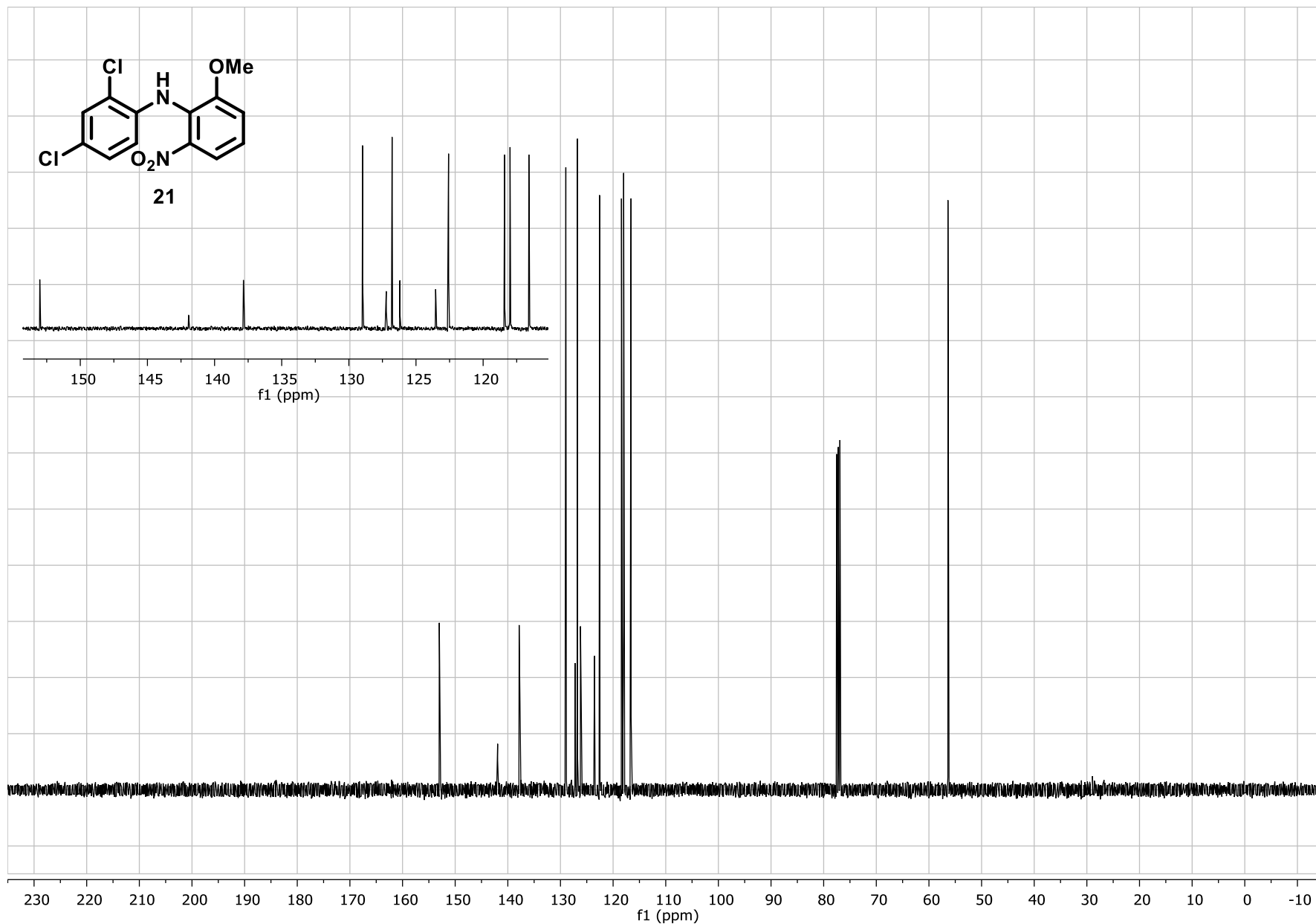


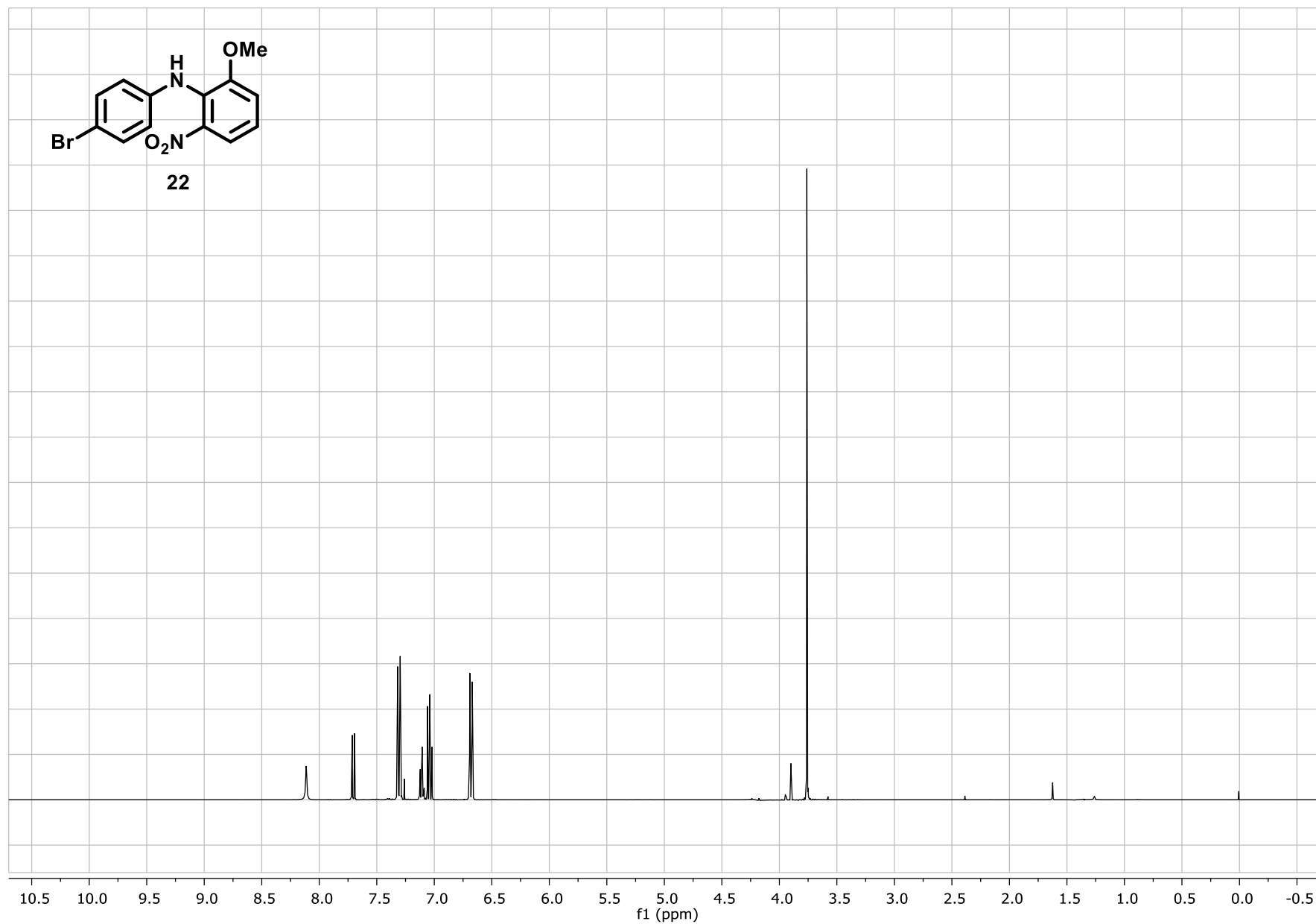
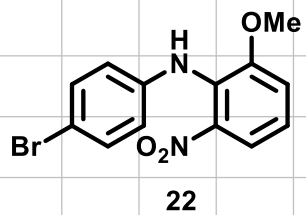


21

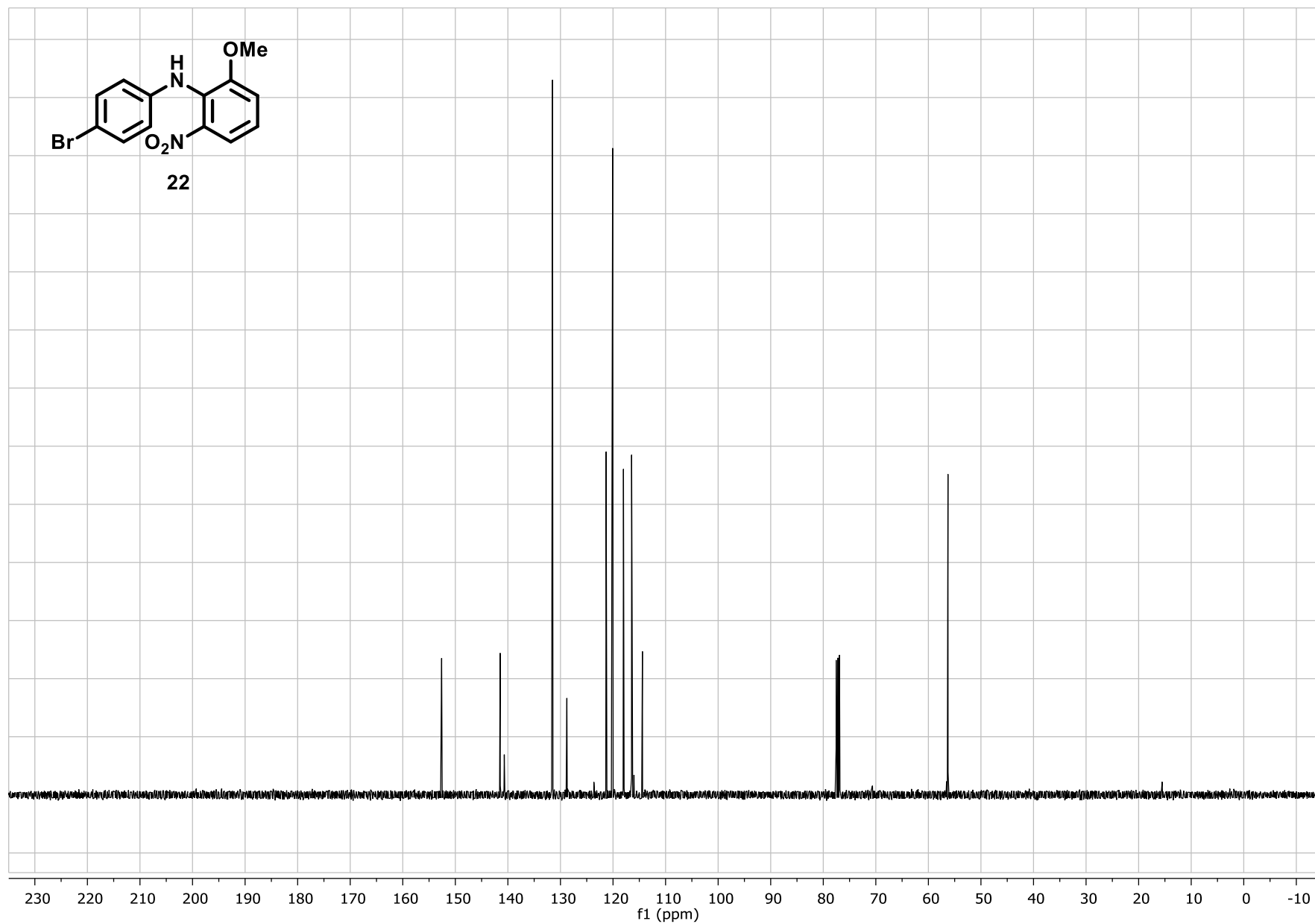
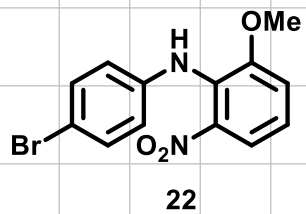


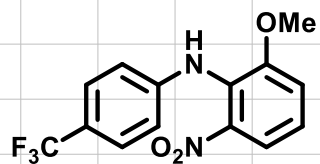
S78



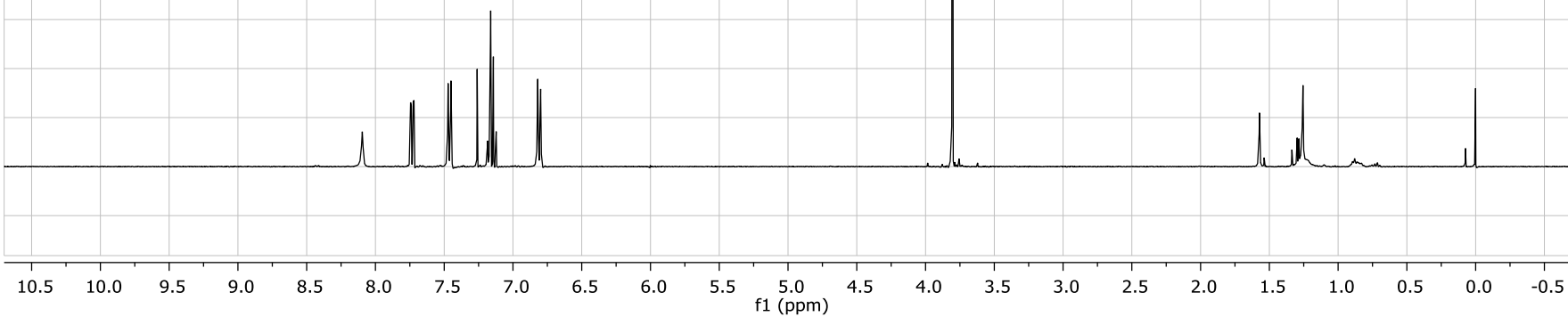
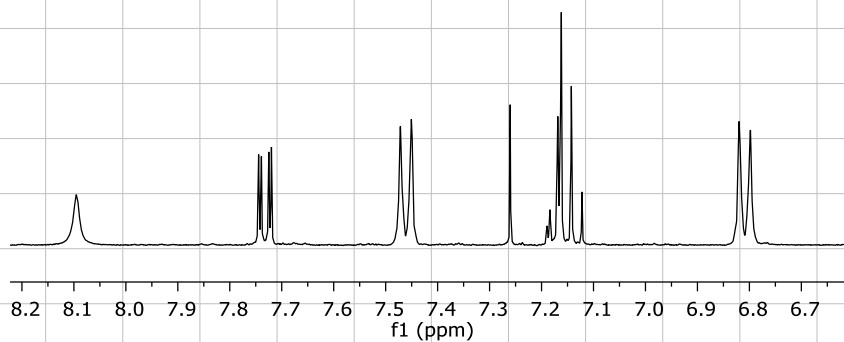


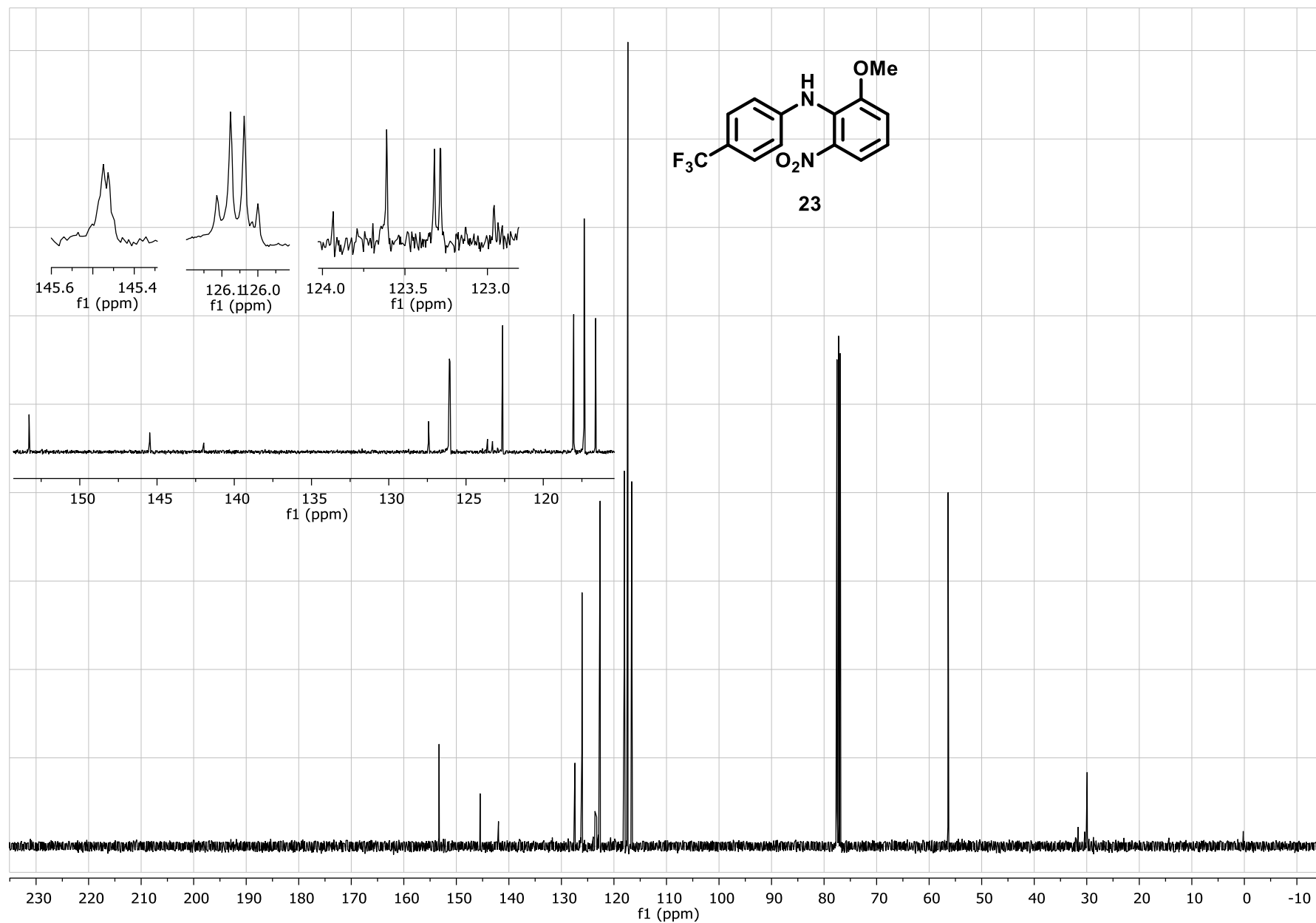
S80

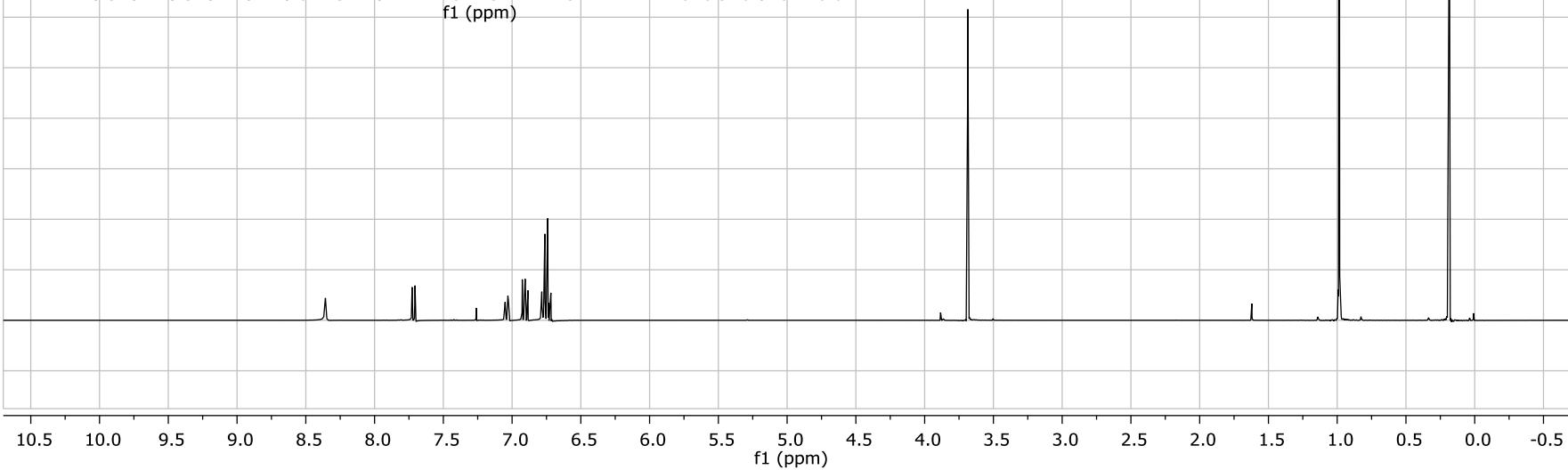
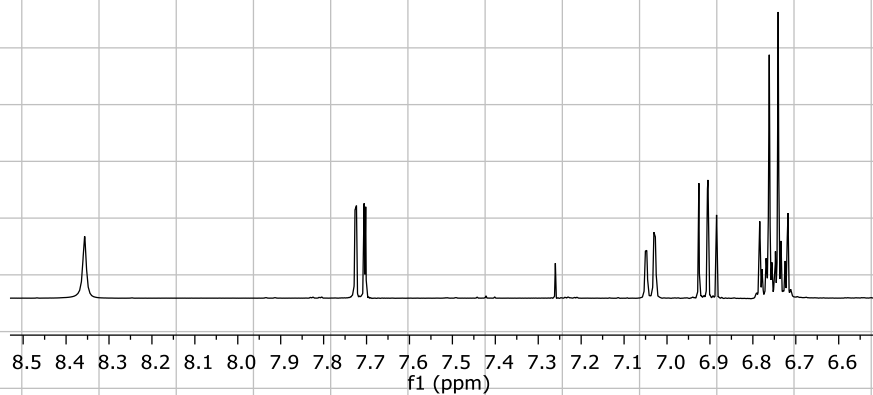
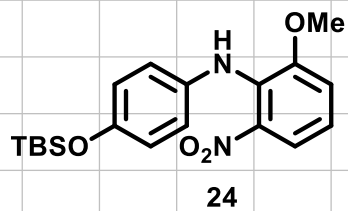




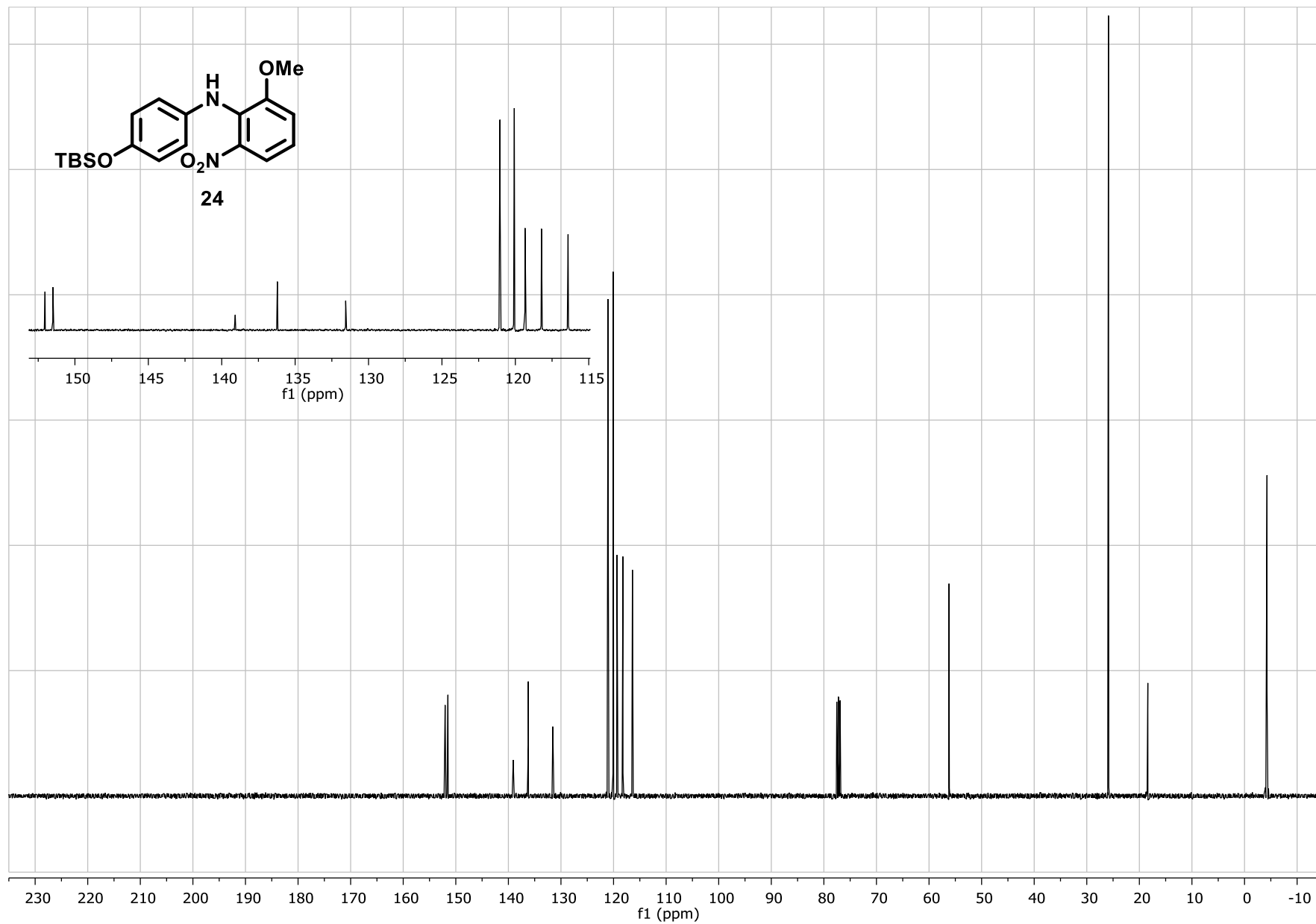
23

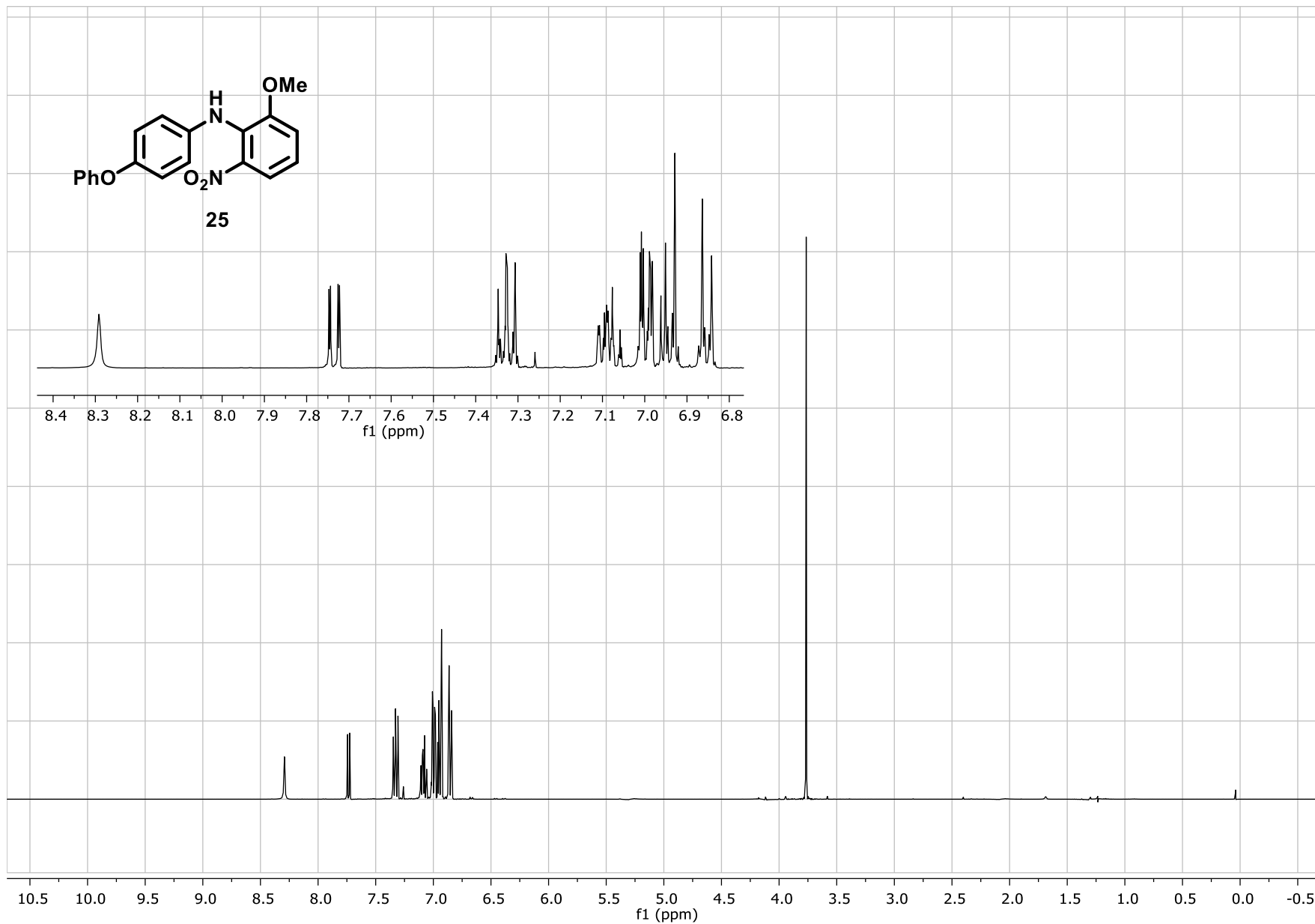
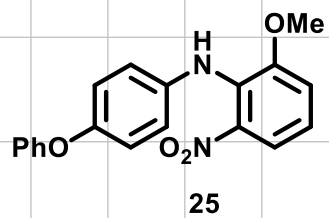


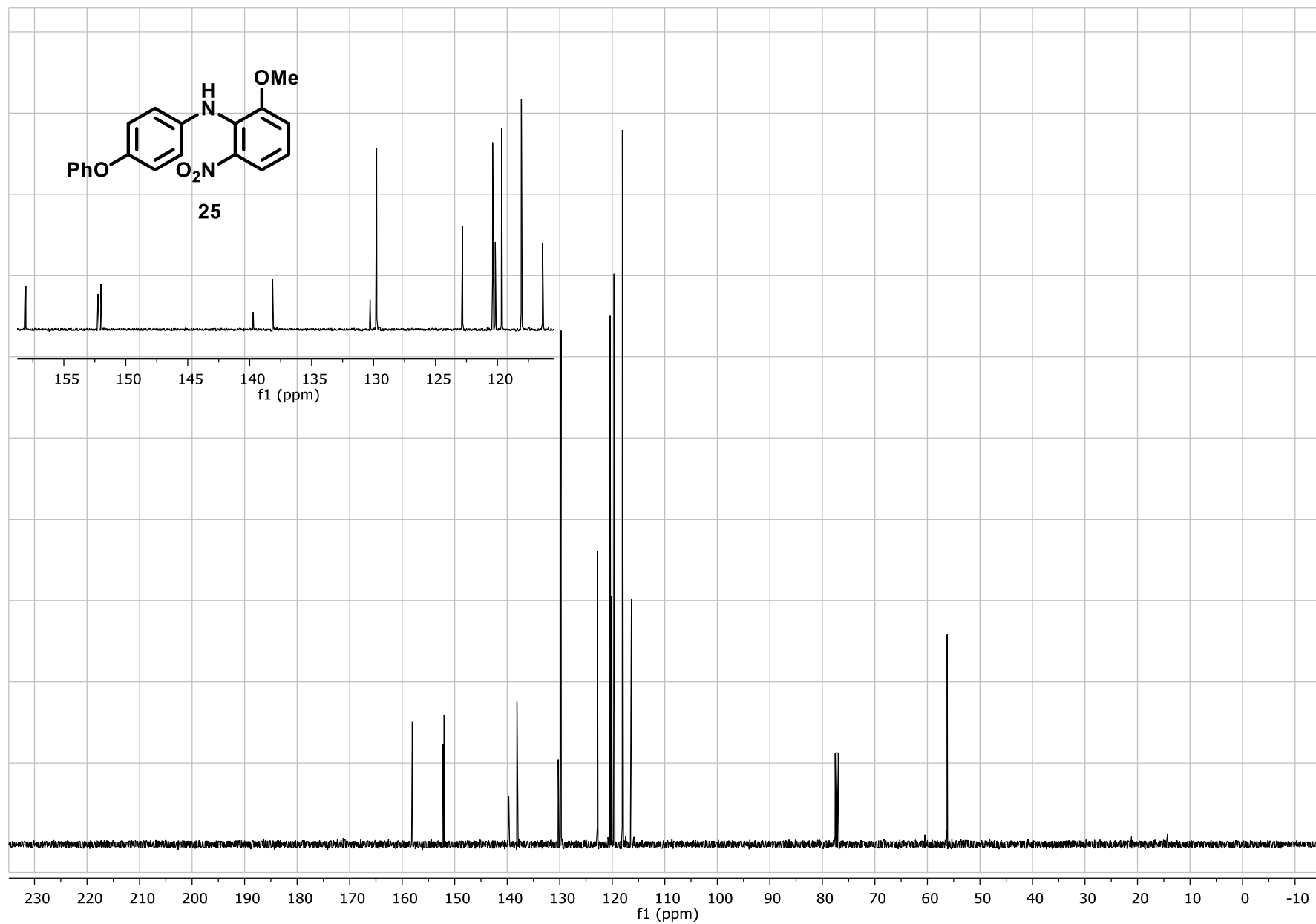


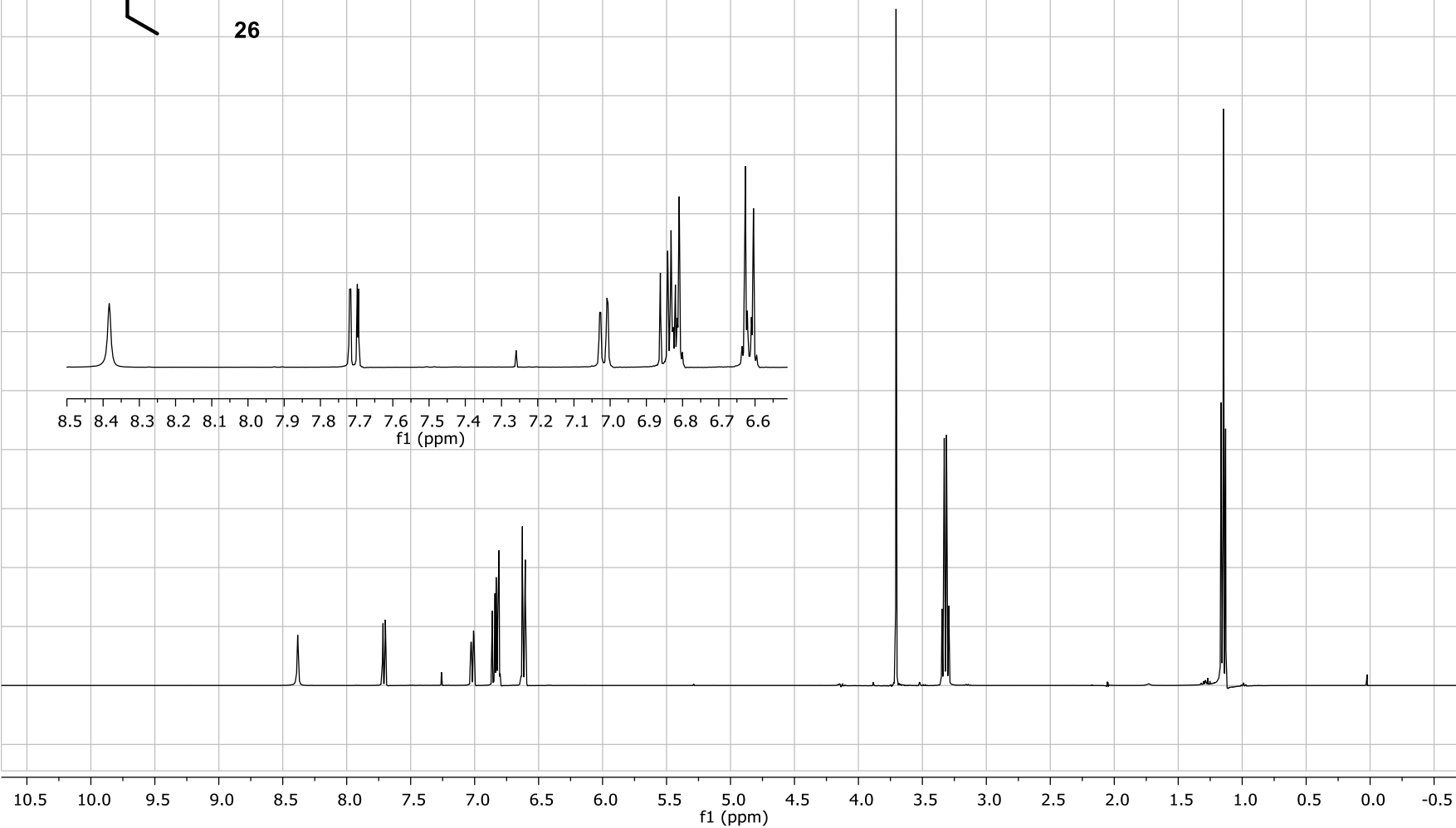
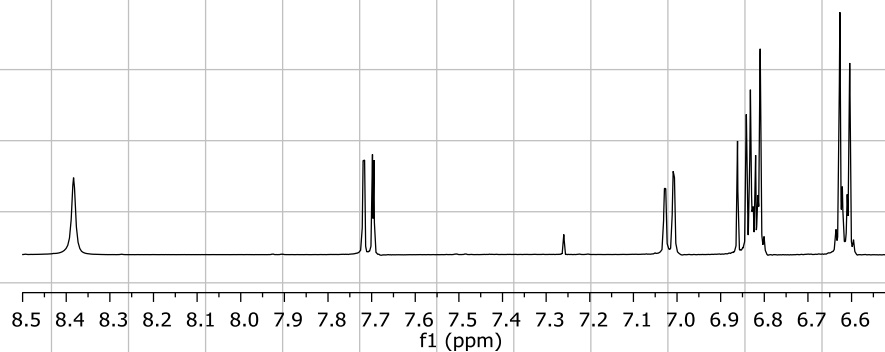
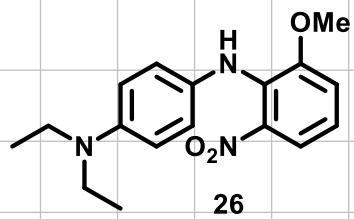


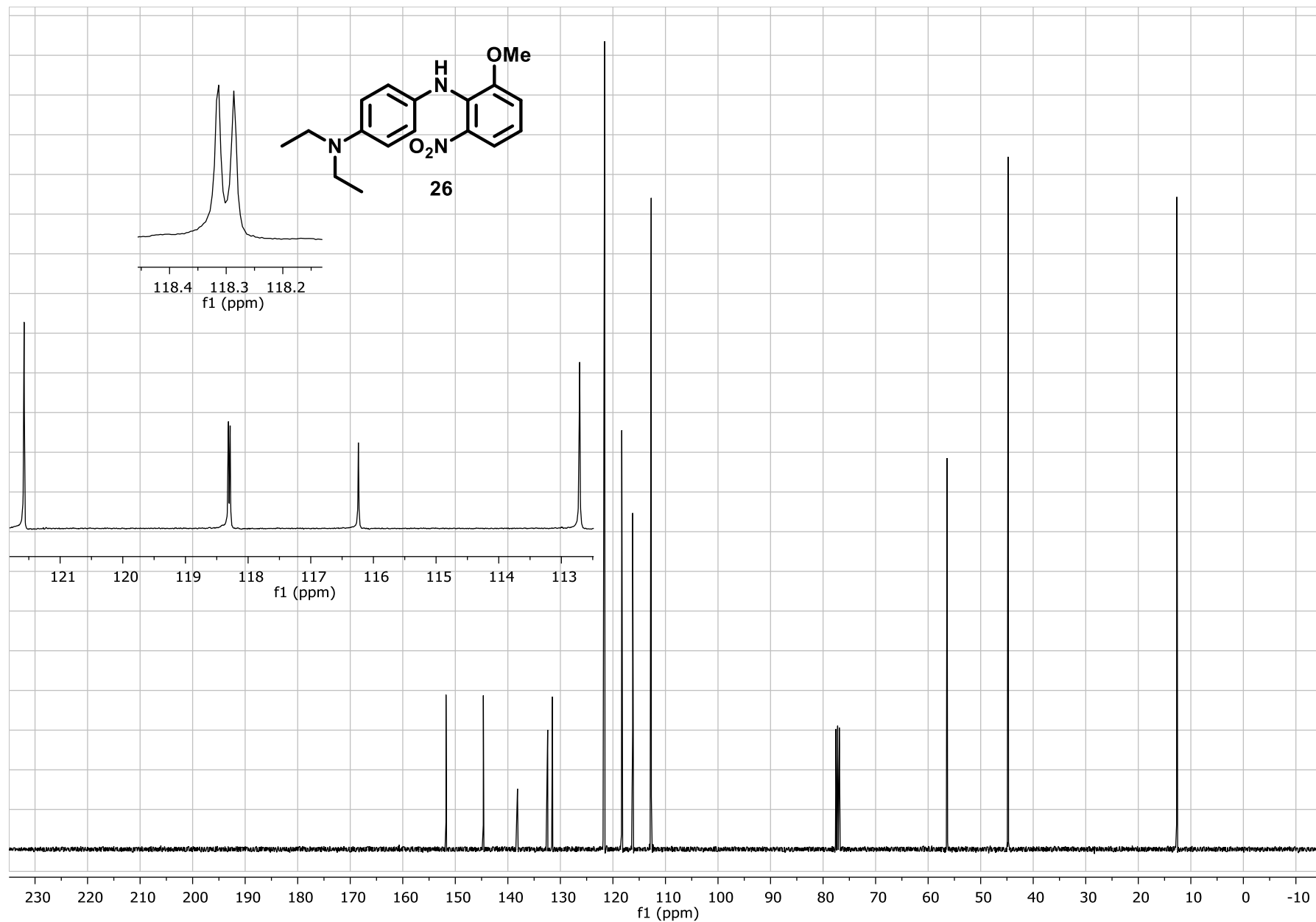


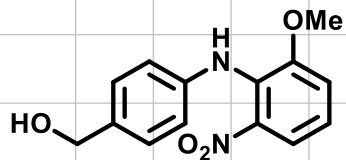




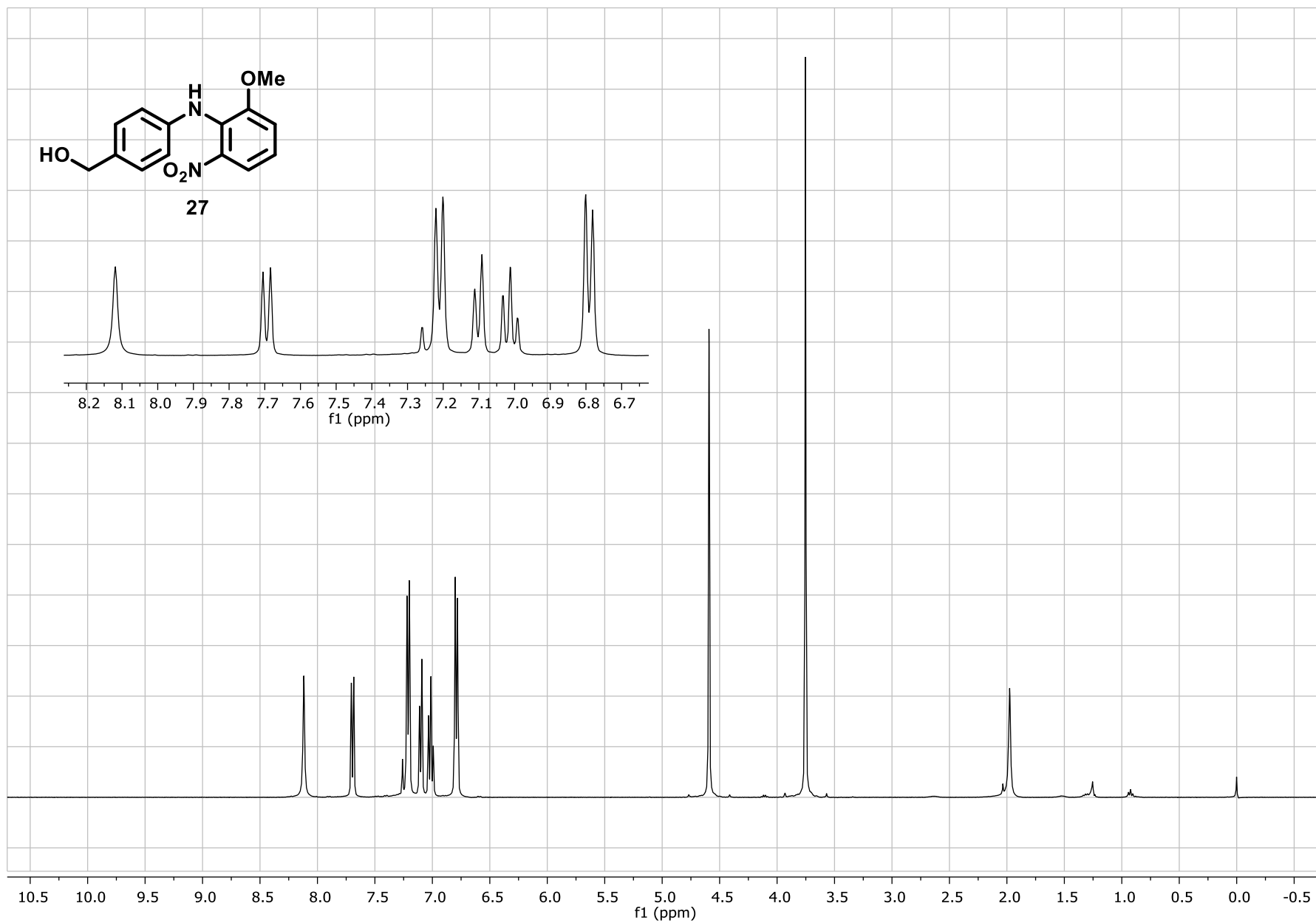
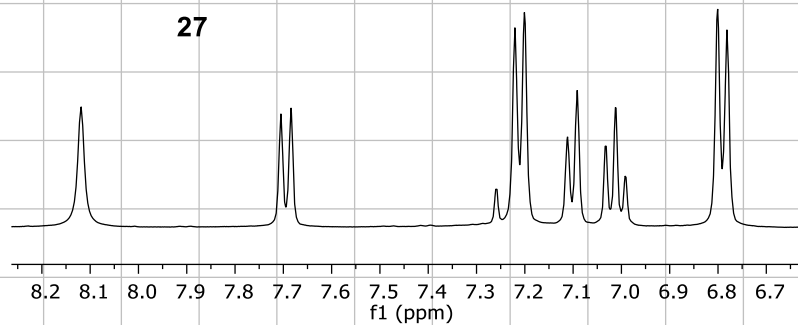


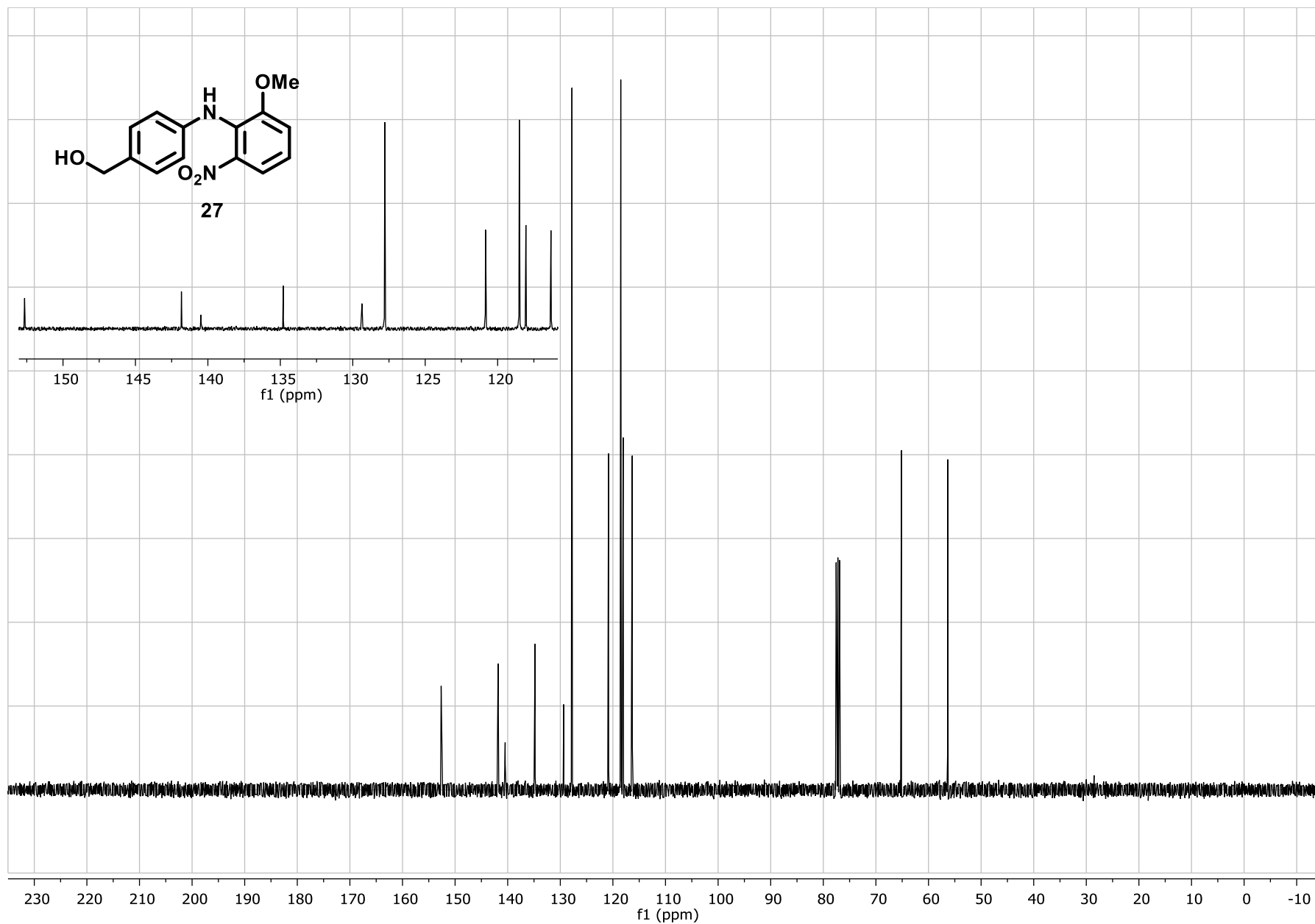


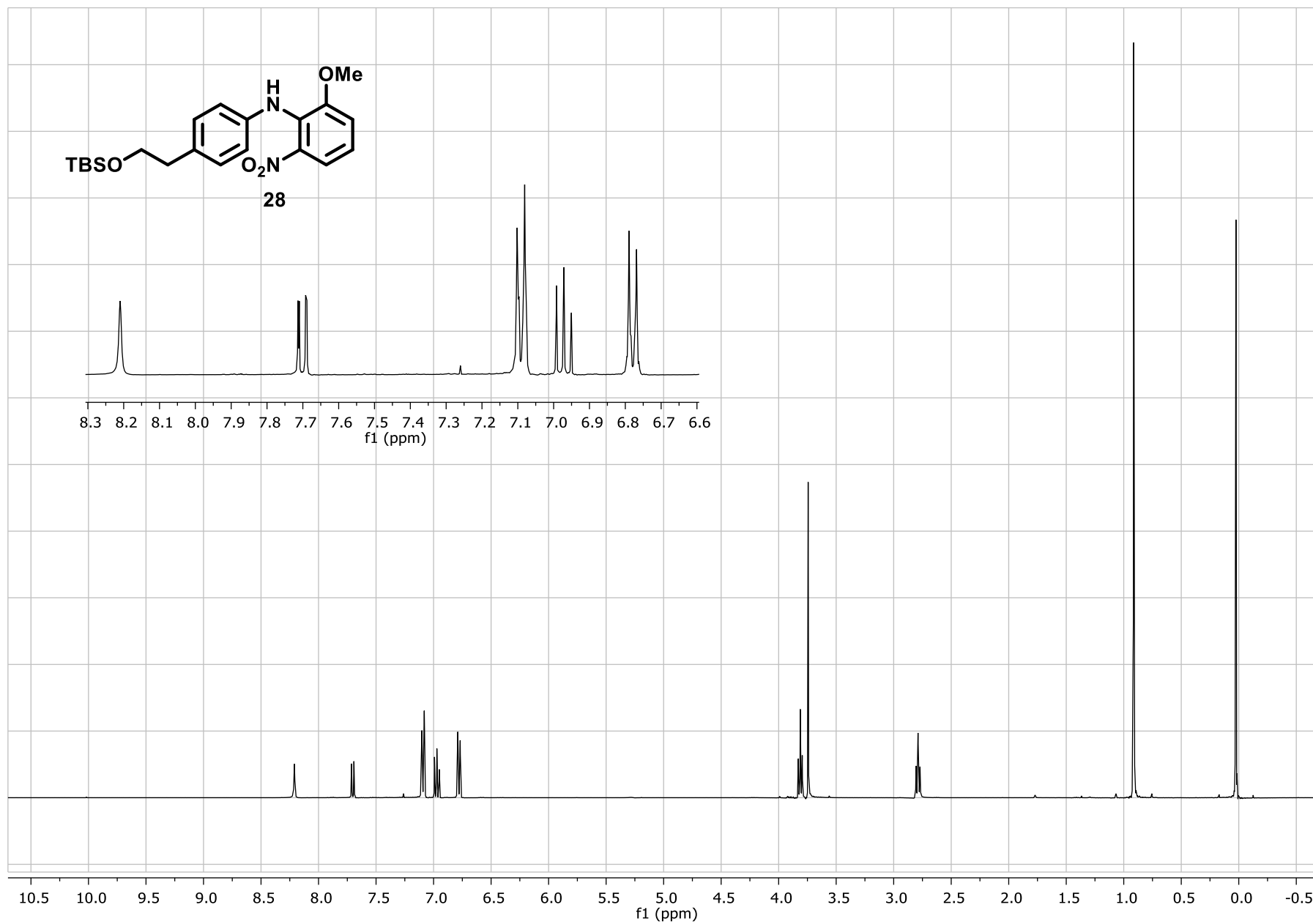




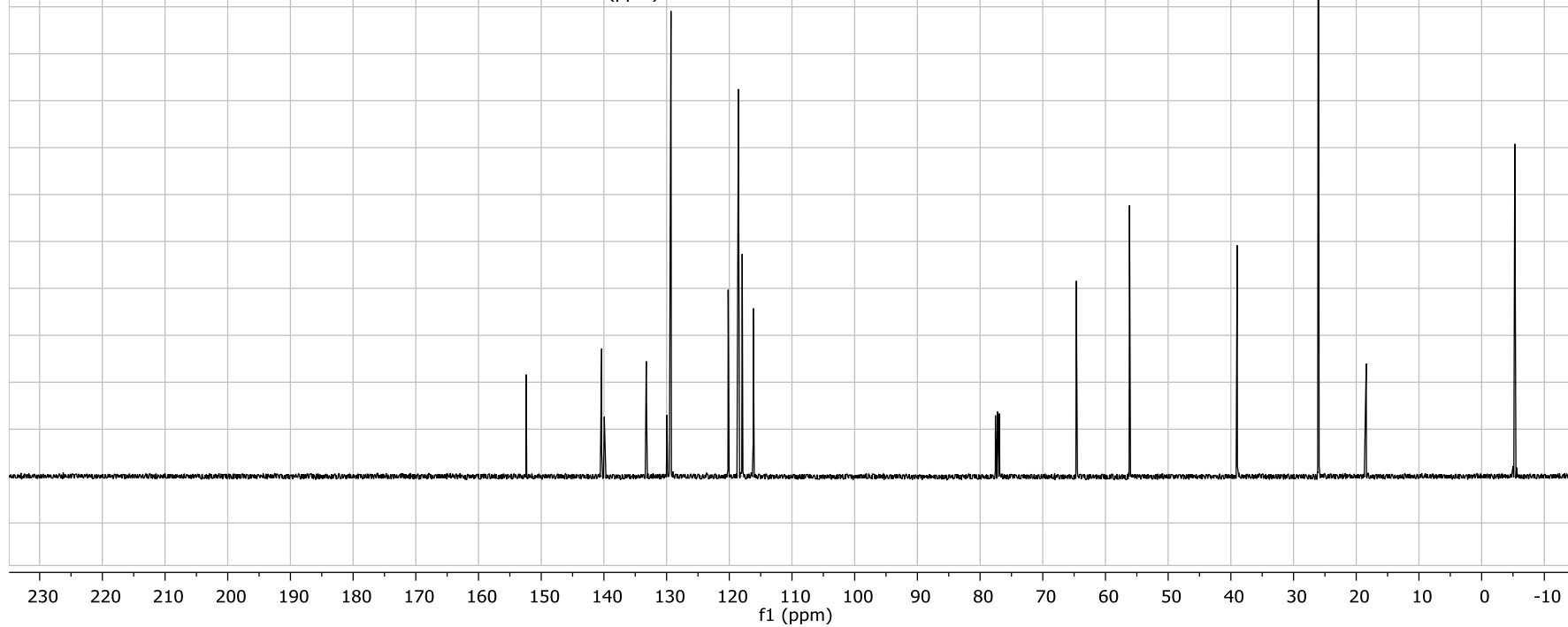
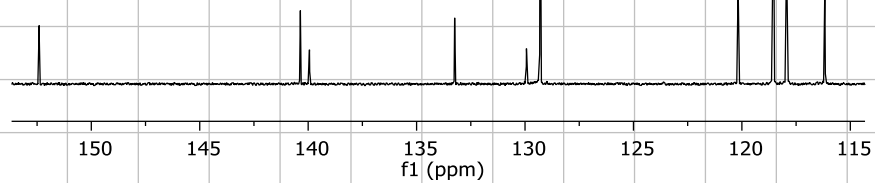
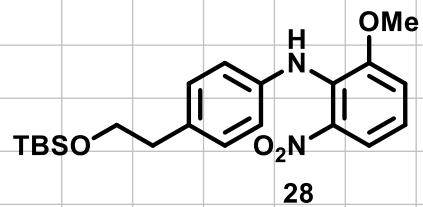
27

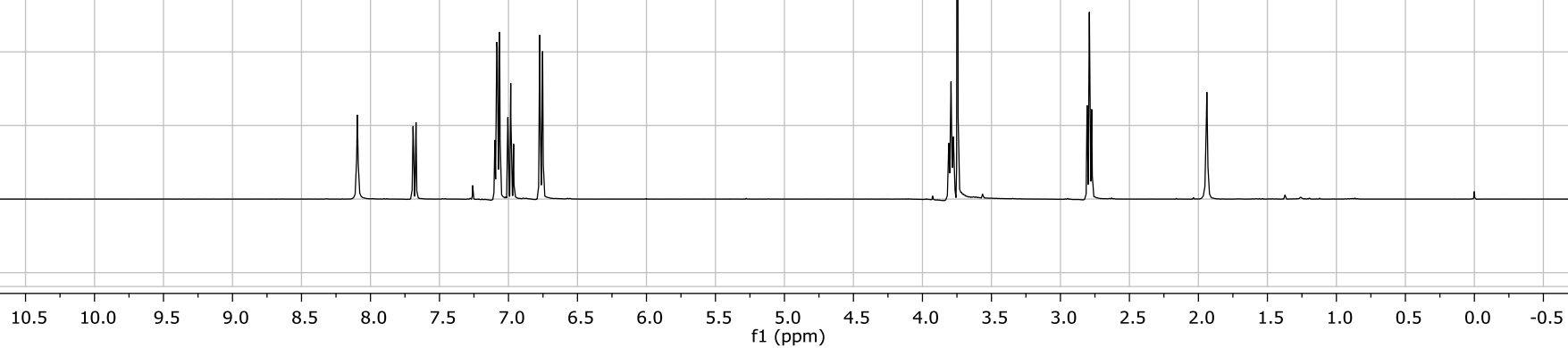
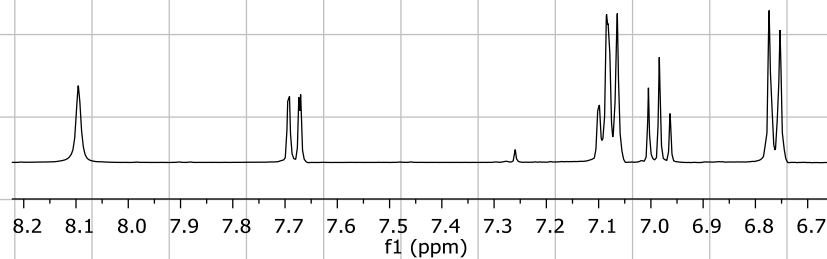
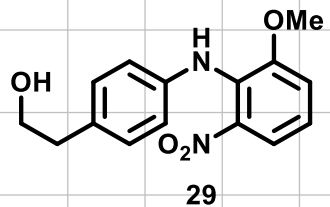


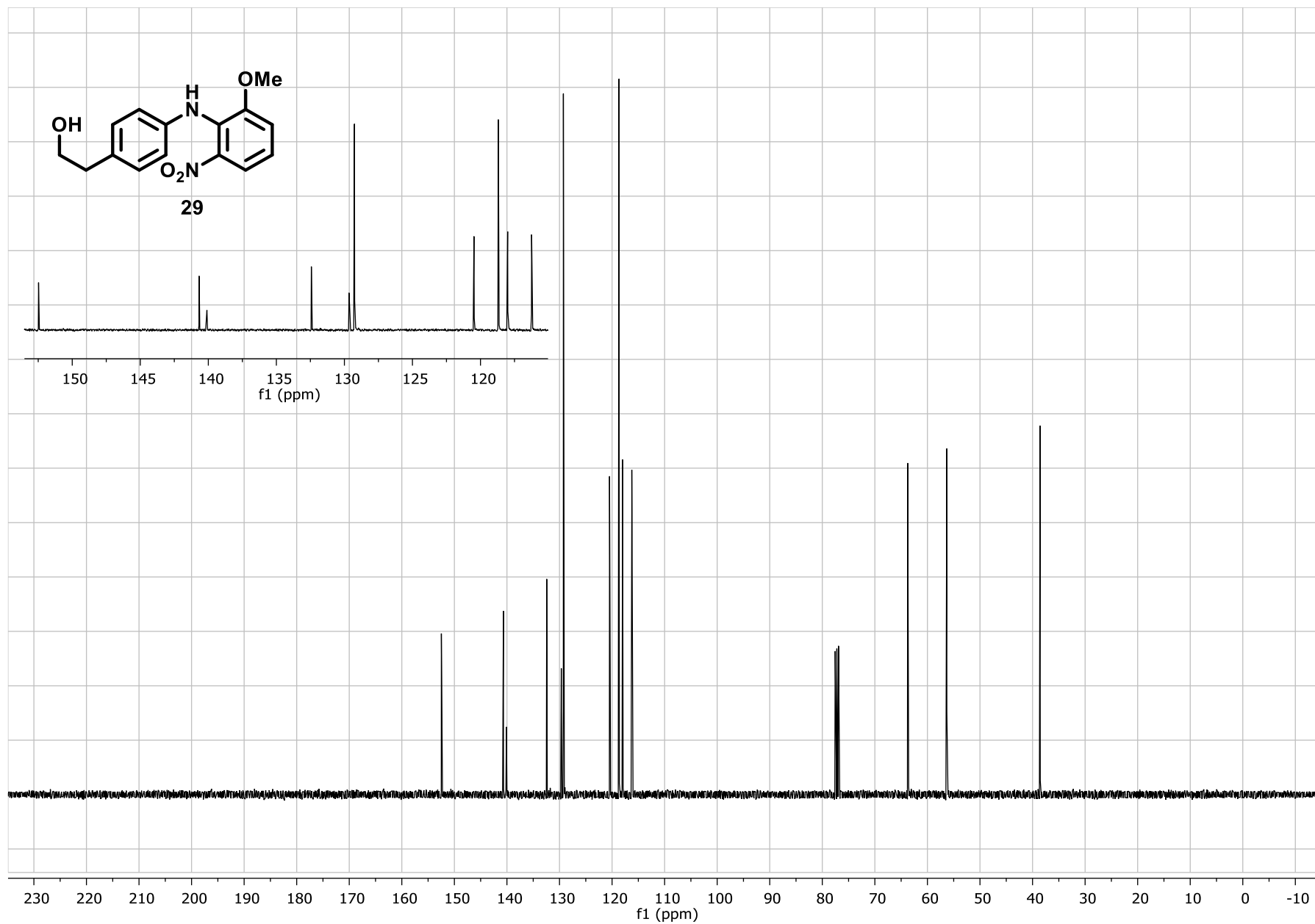


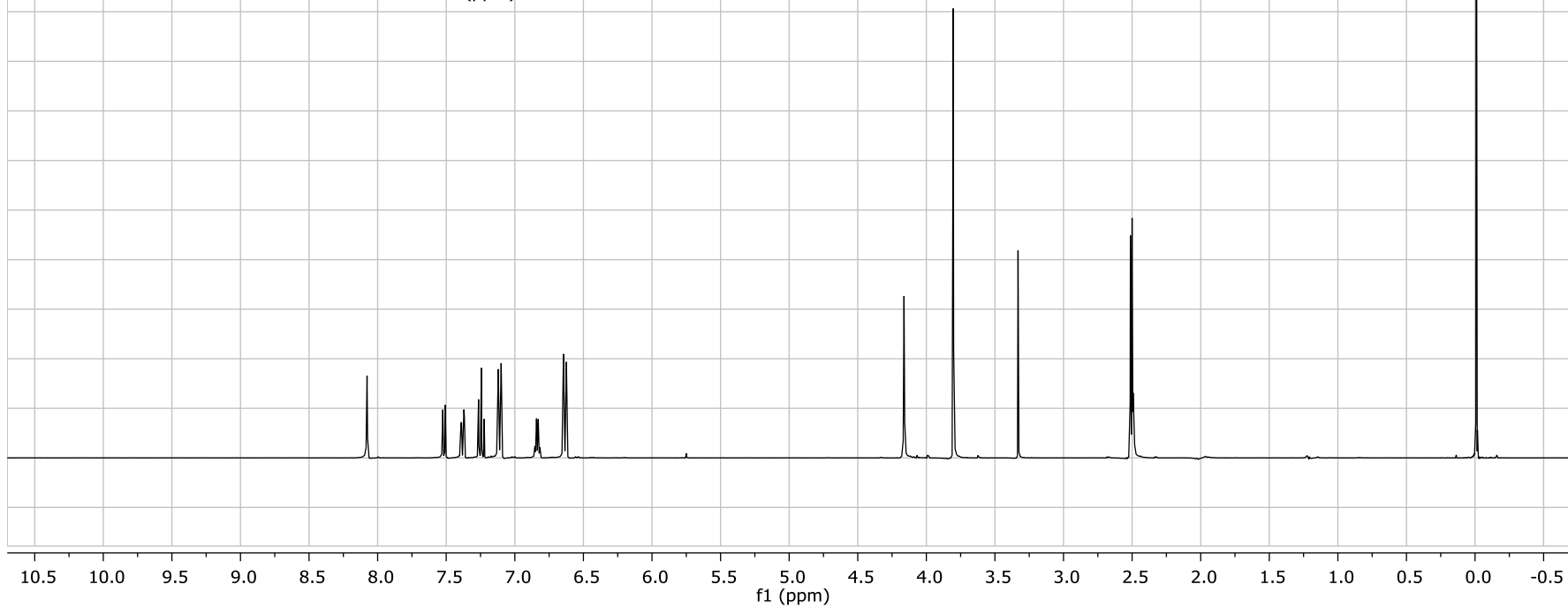
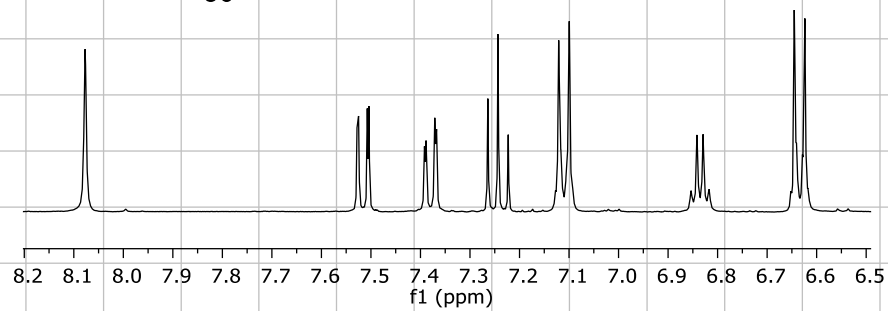
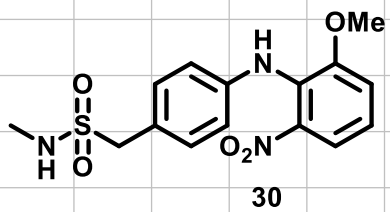


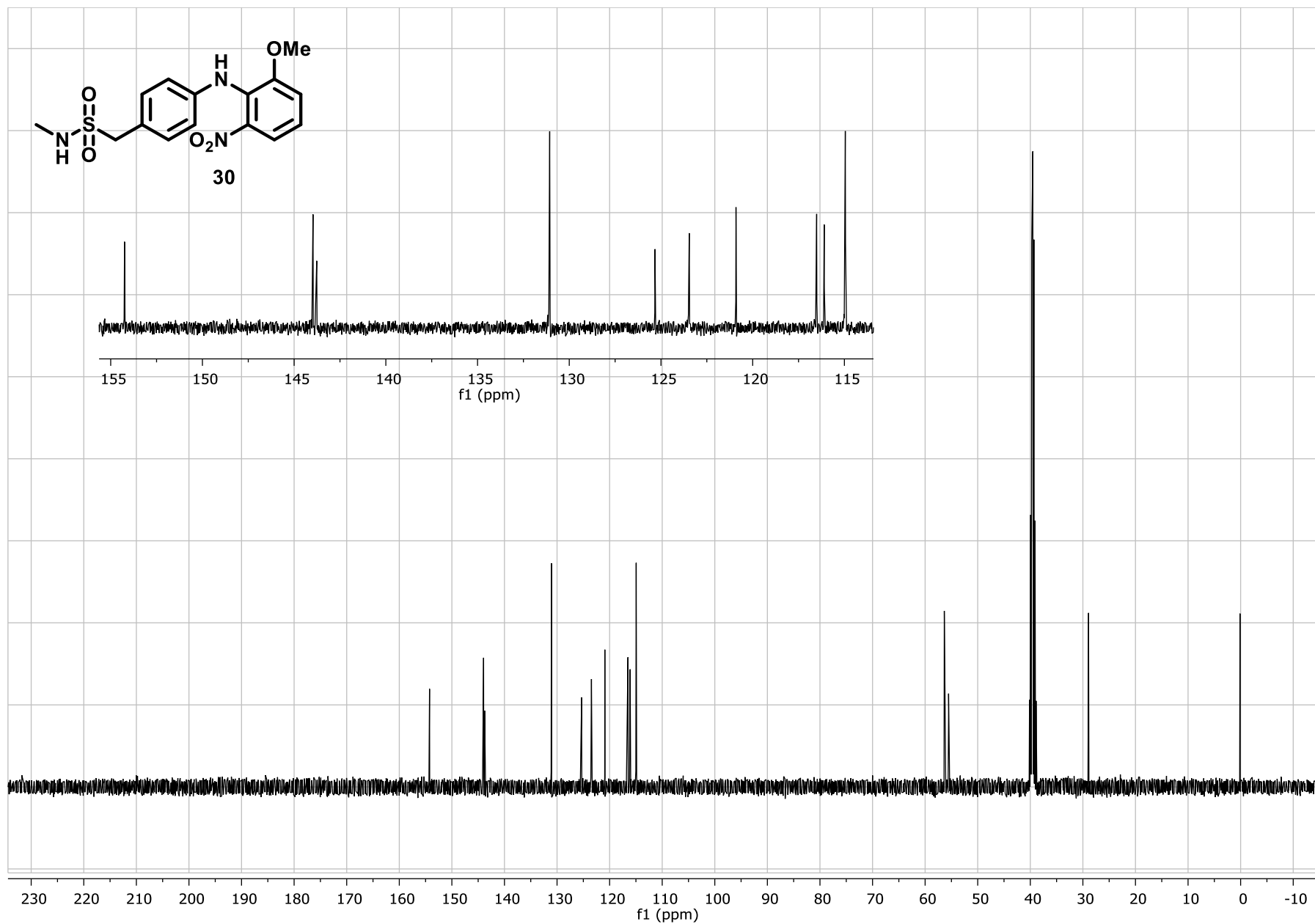


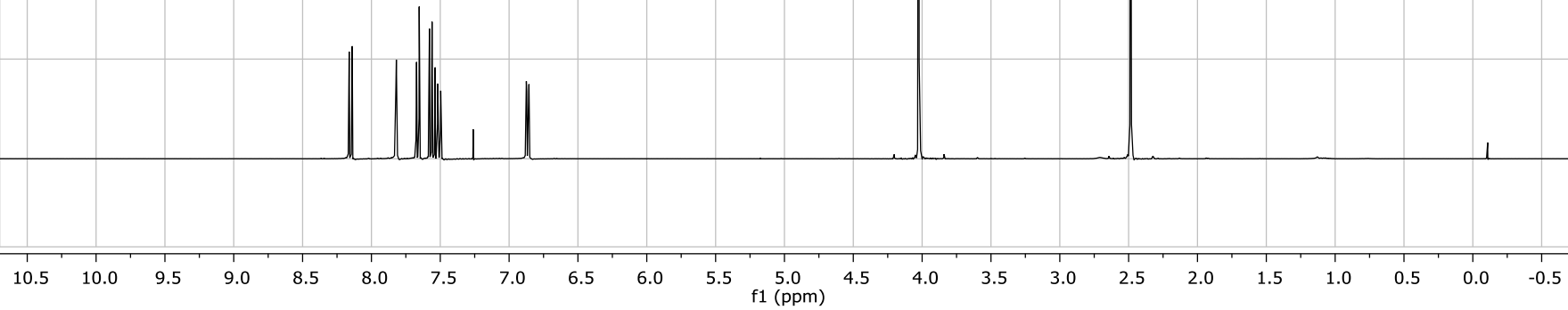
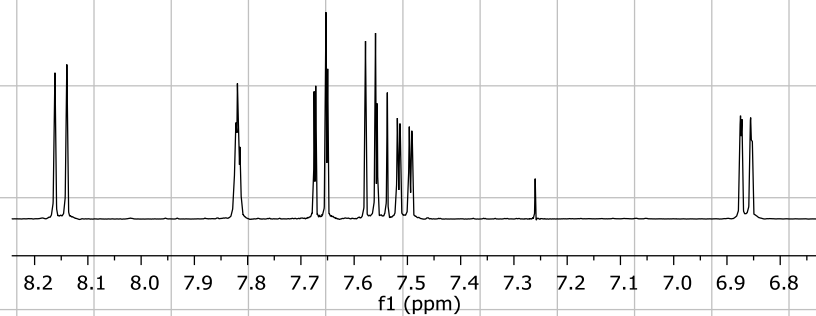
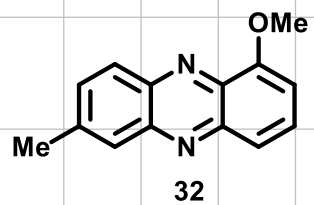


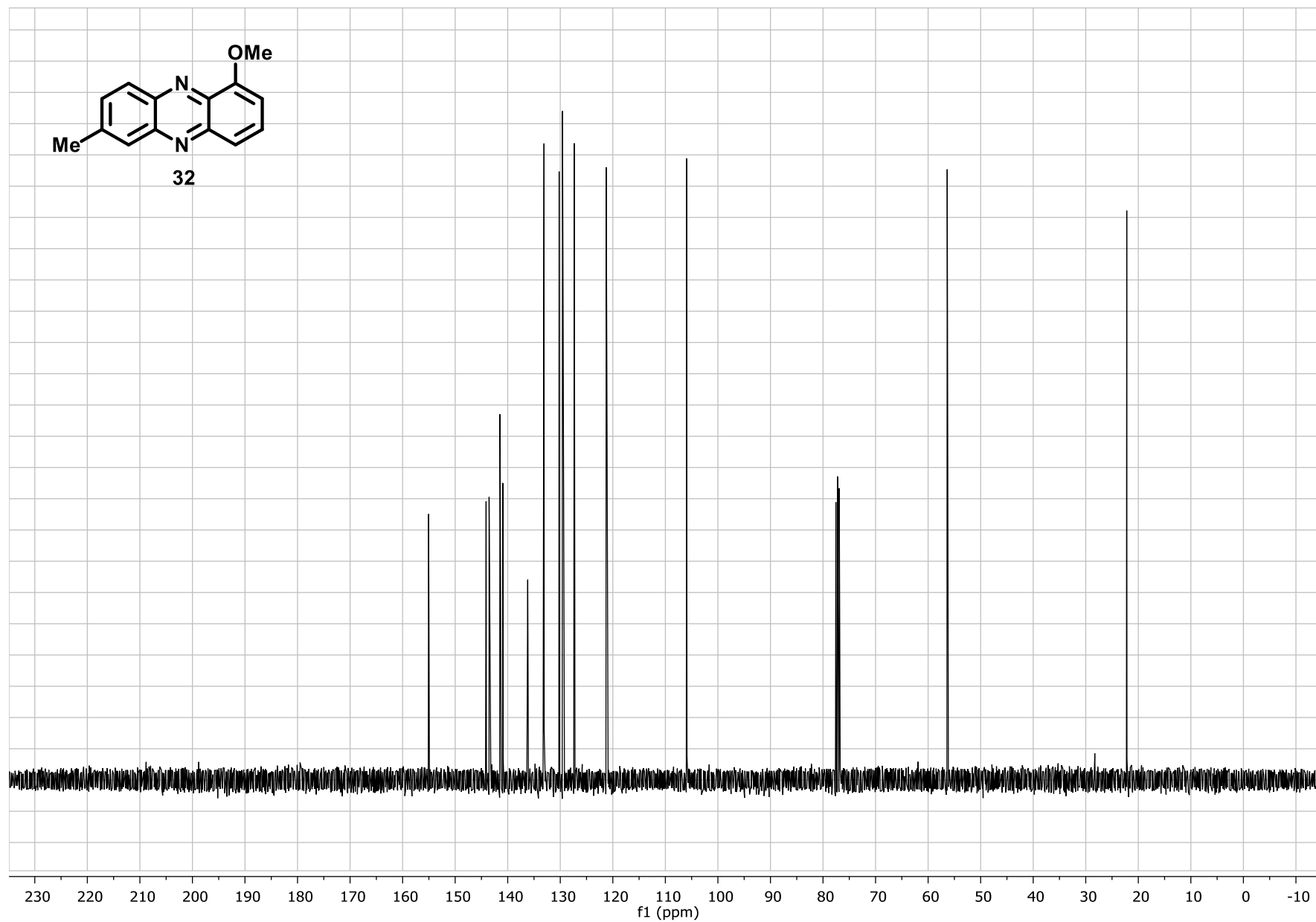
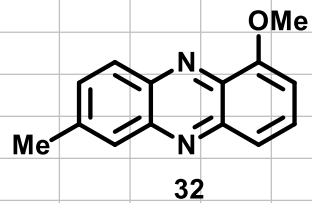




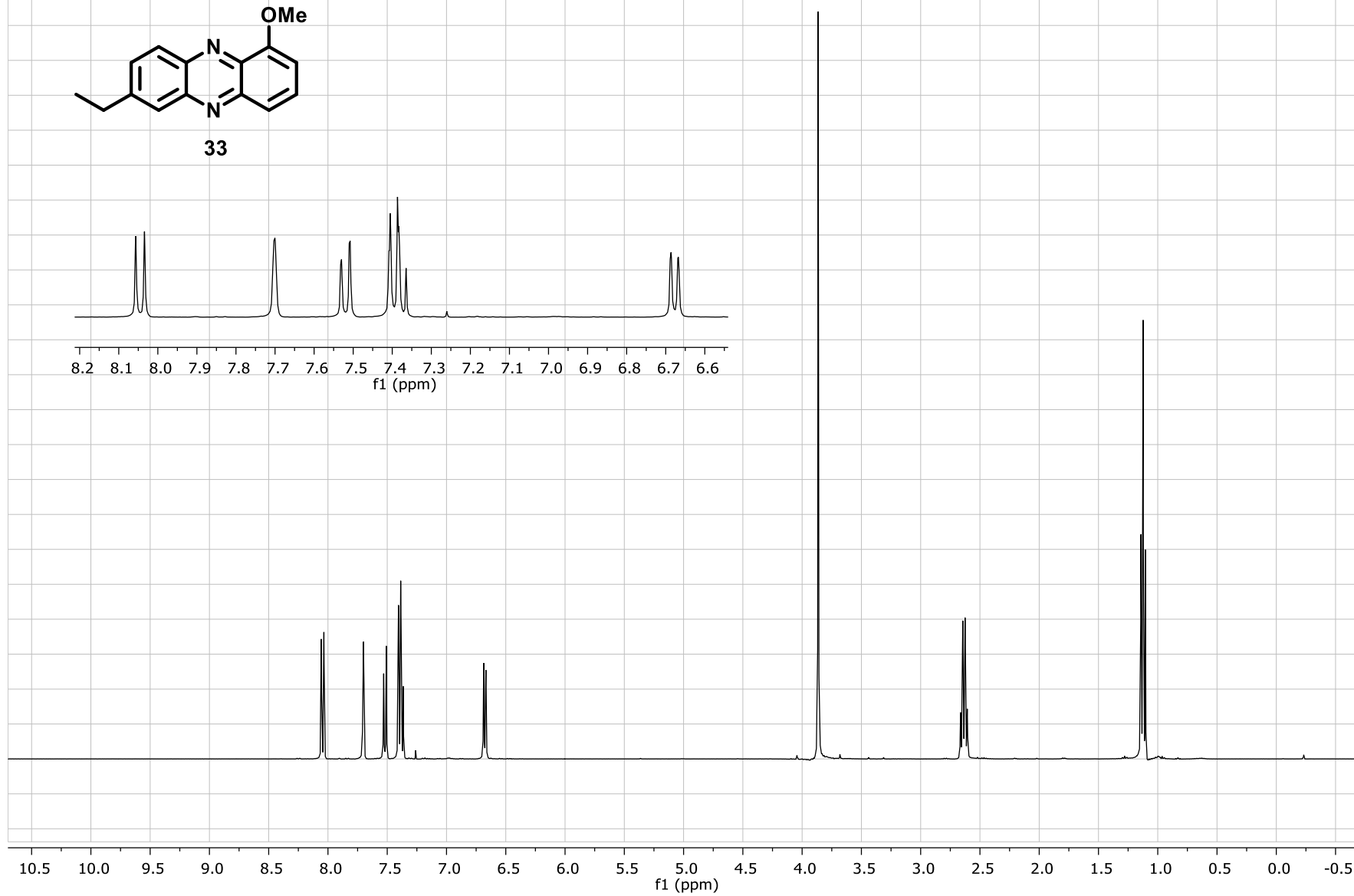
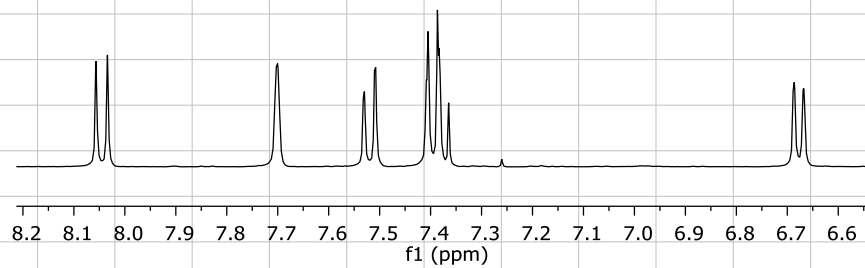
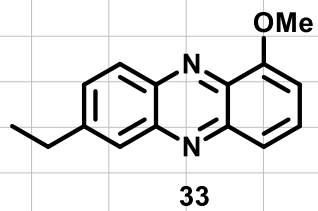




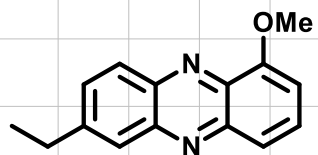




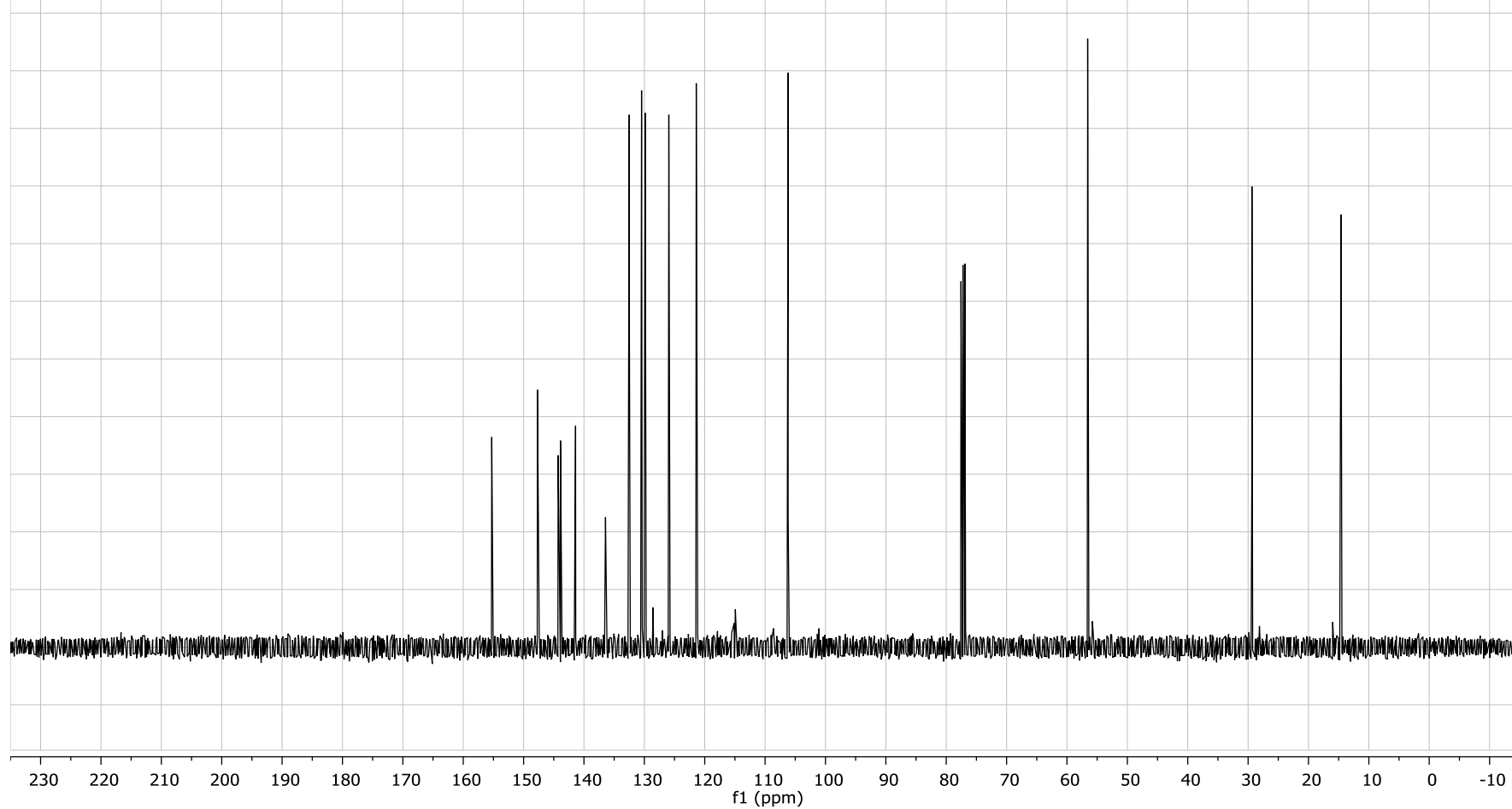
S99



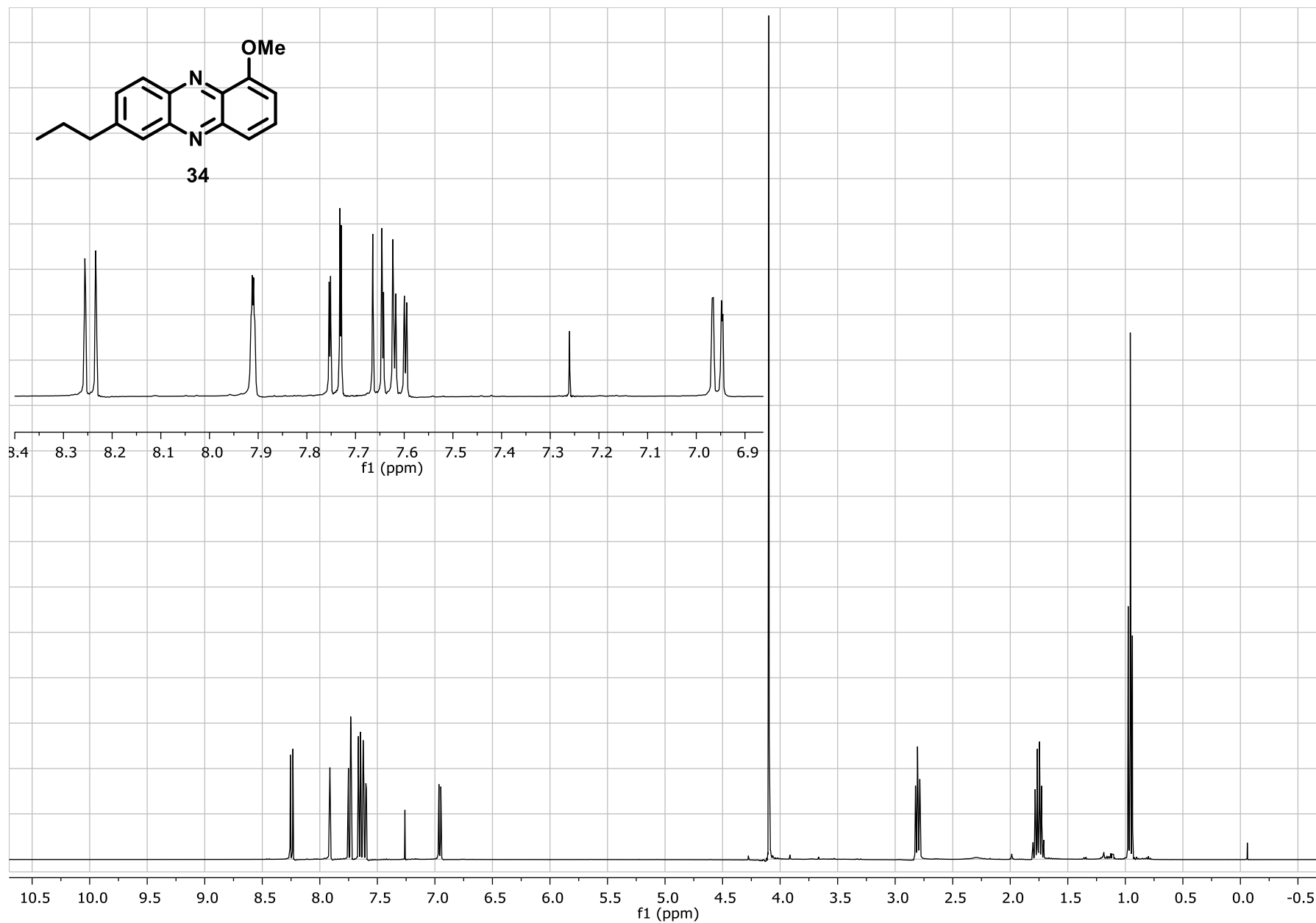


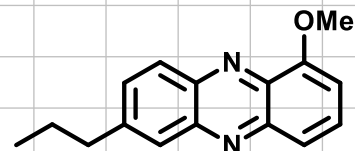


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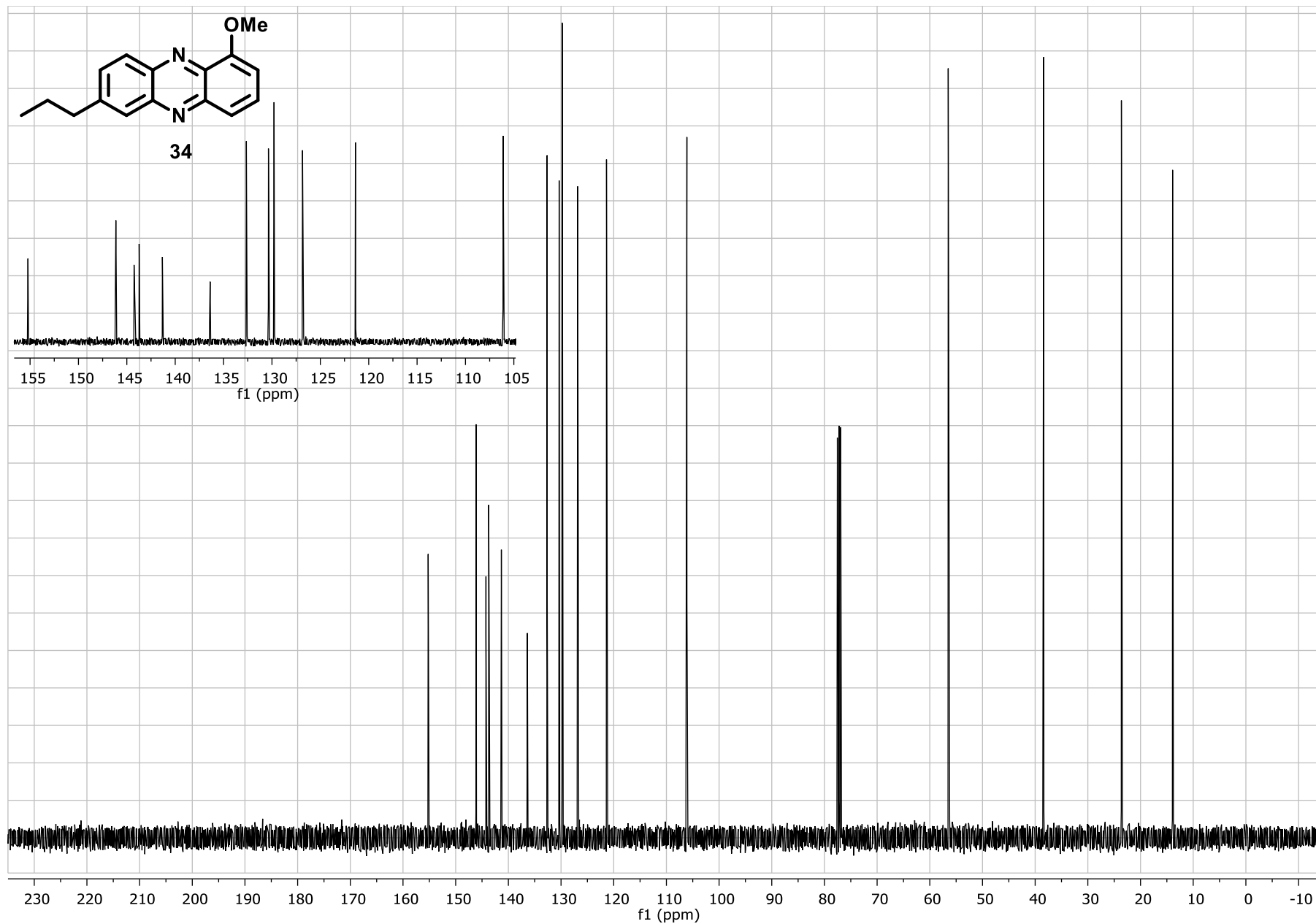


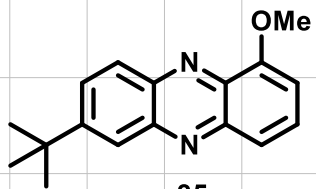
S101



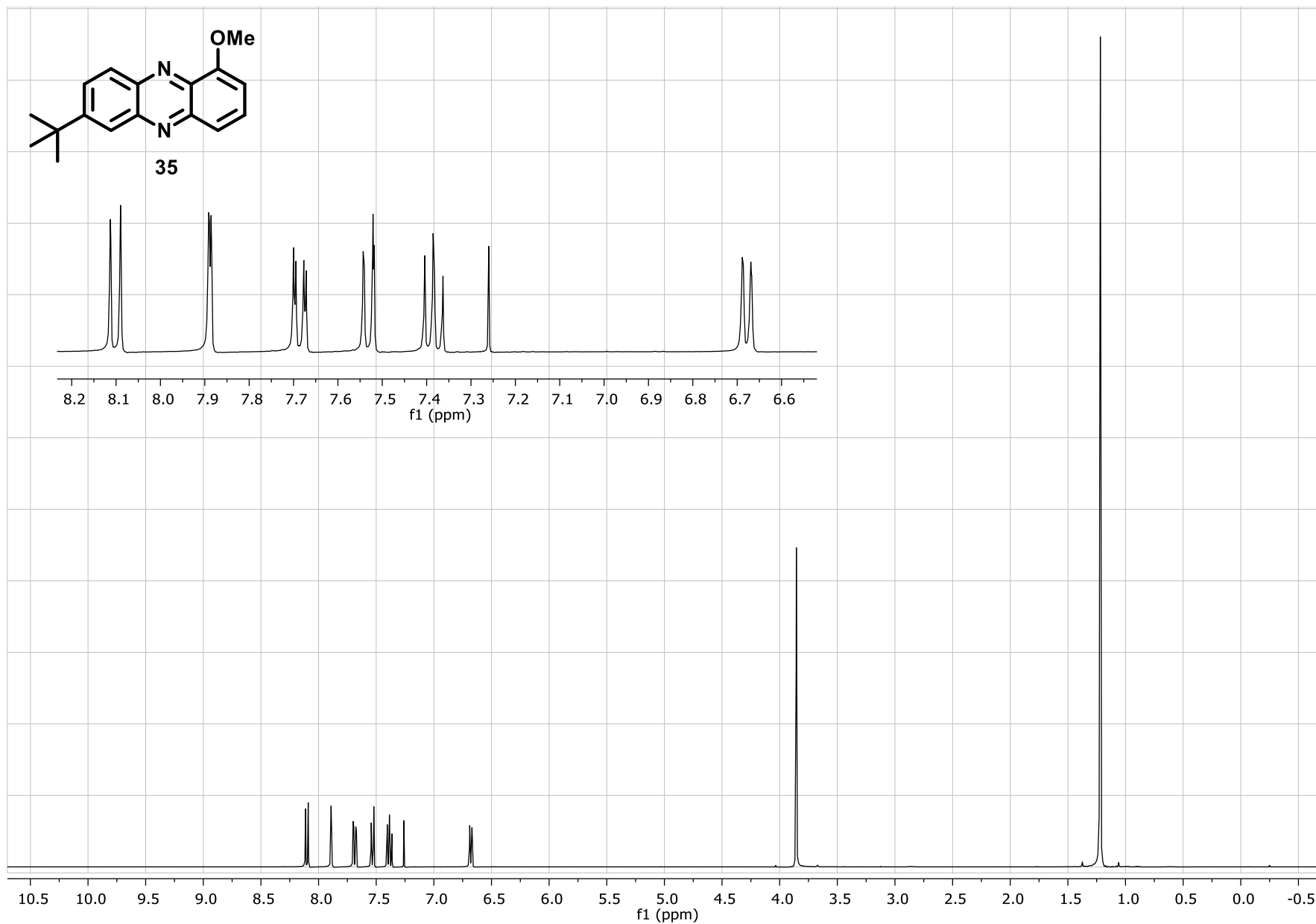


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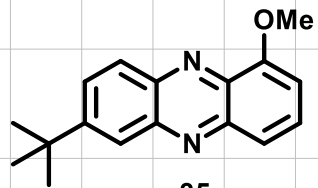




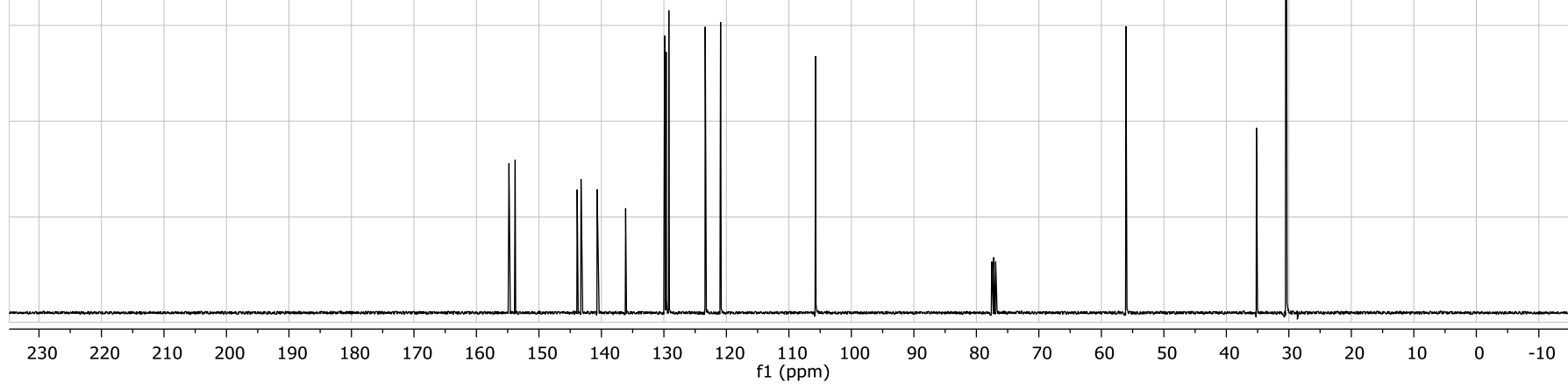
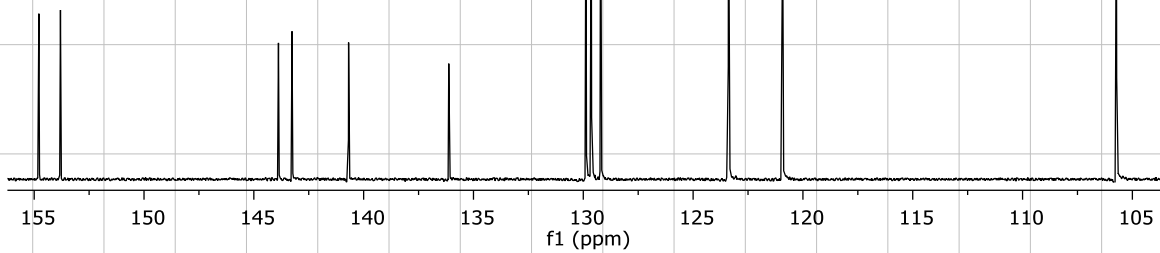
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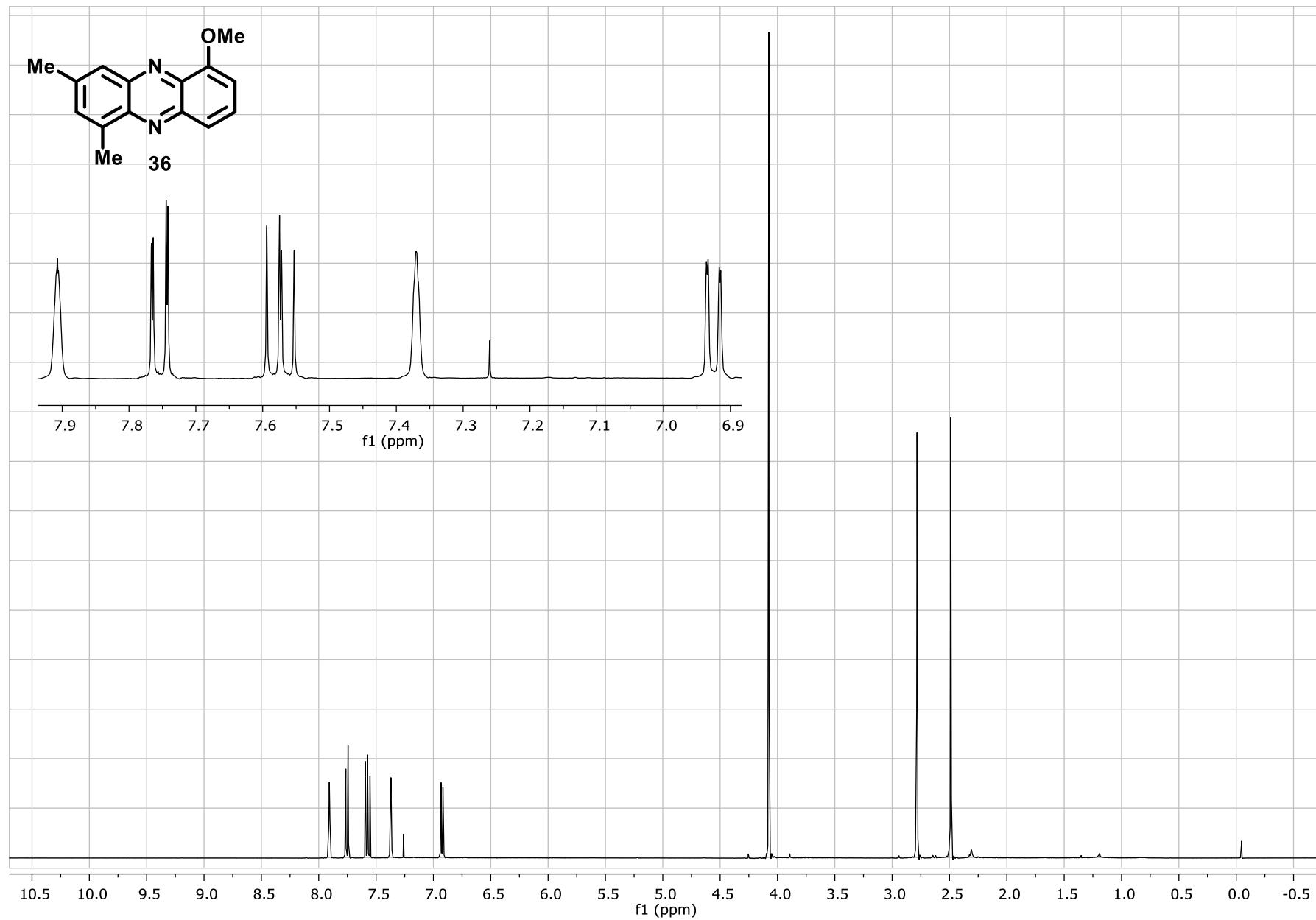


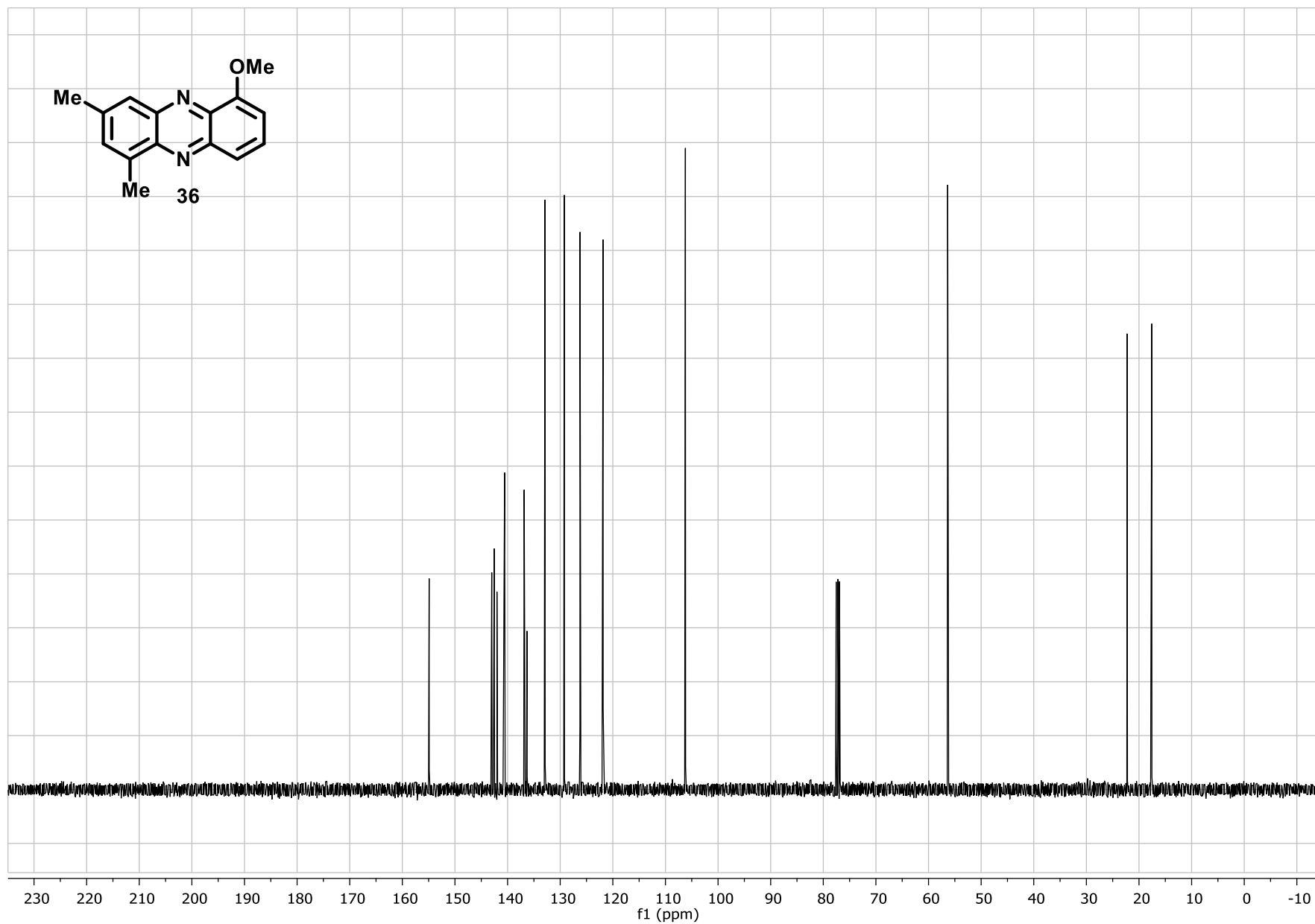
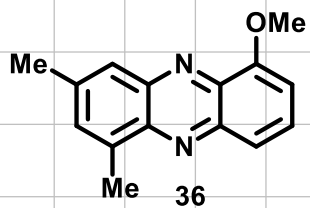
S104



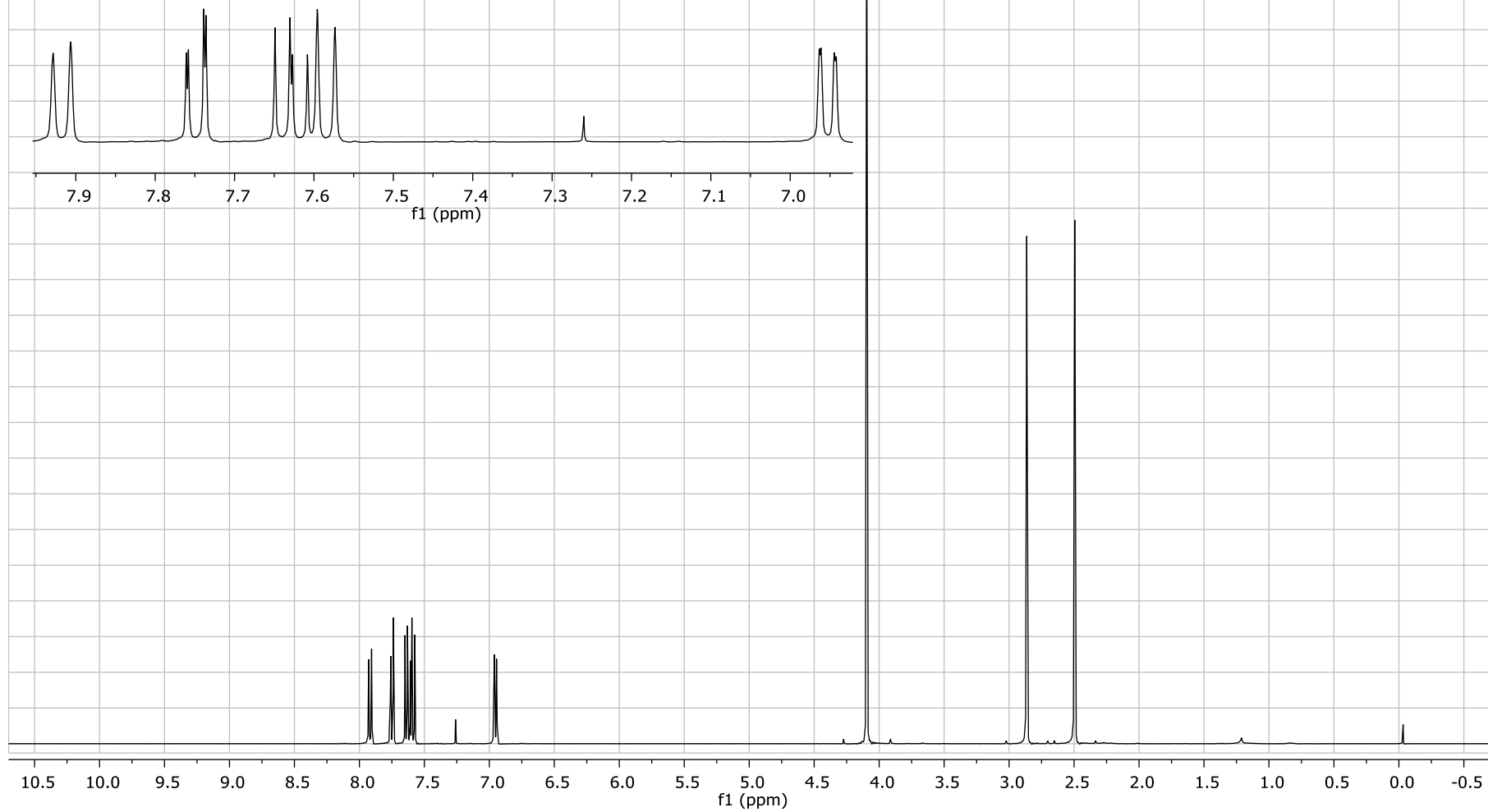
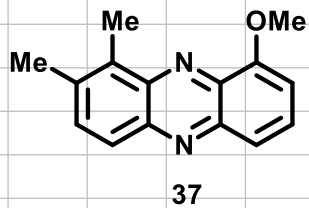
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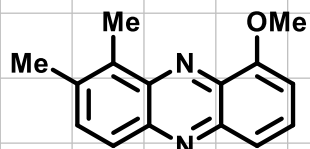




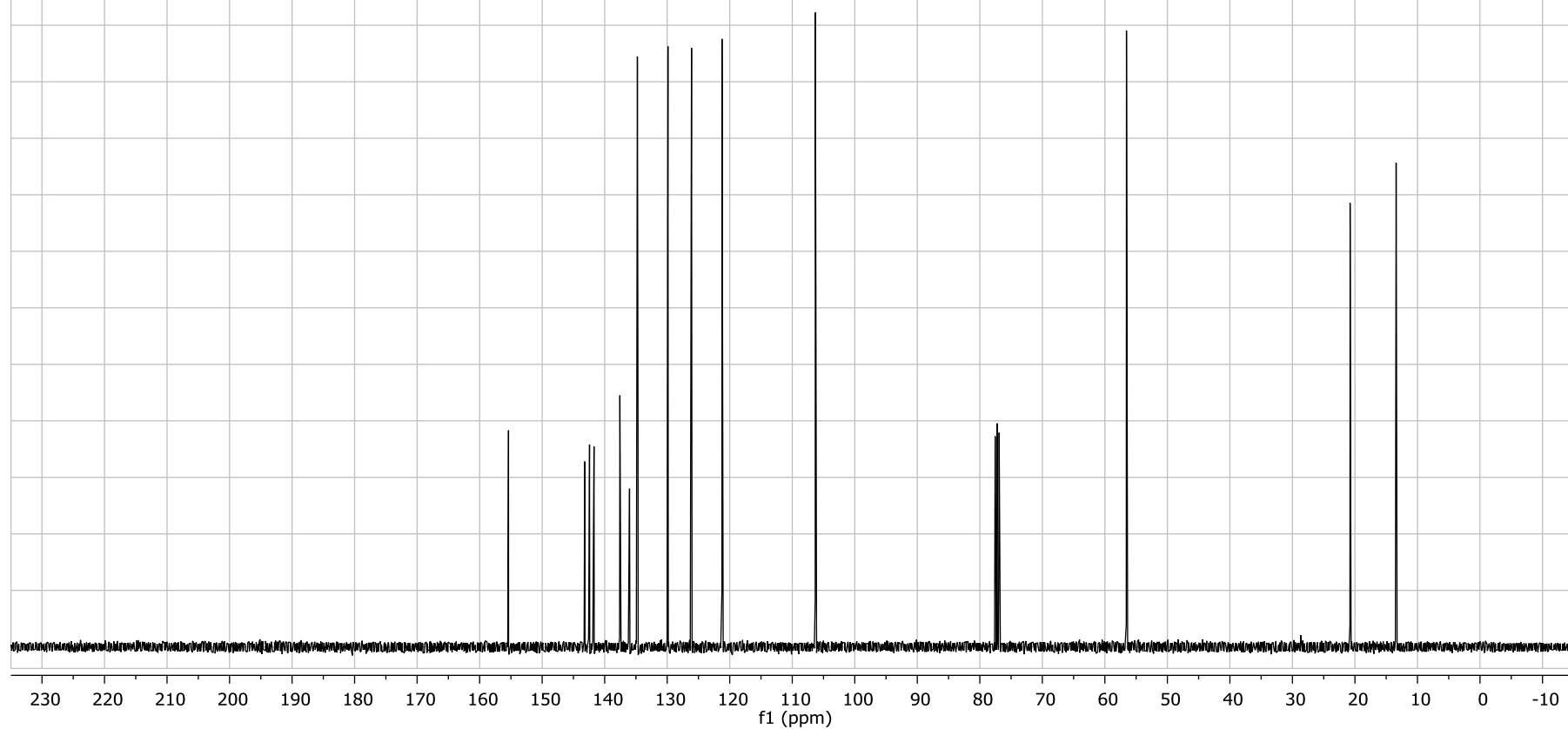
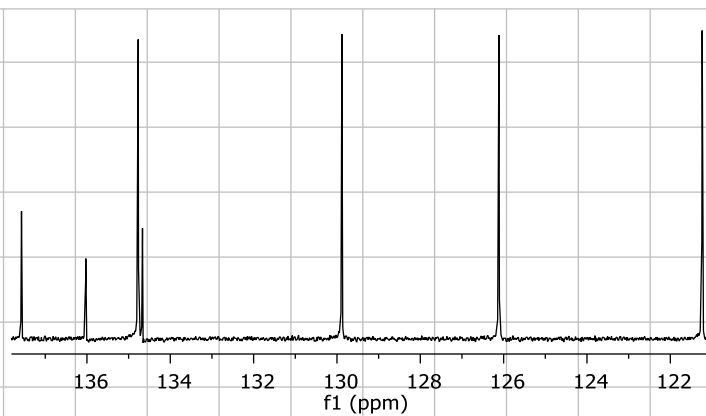
S107

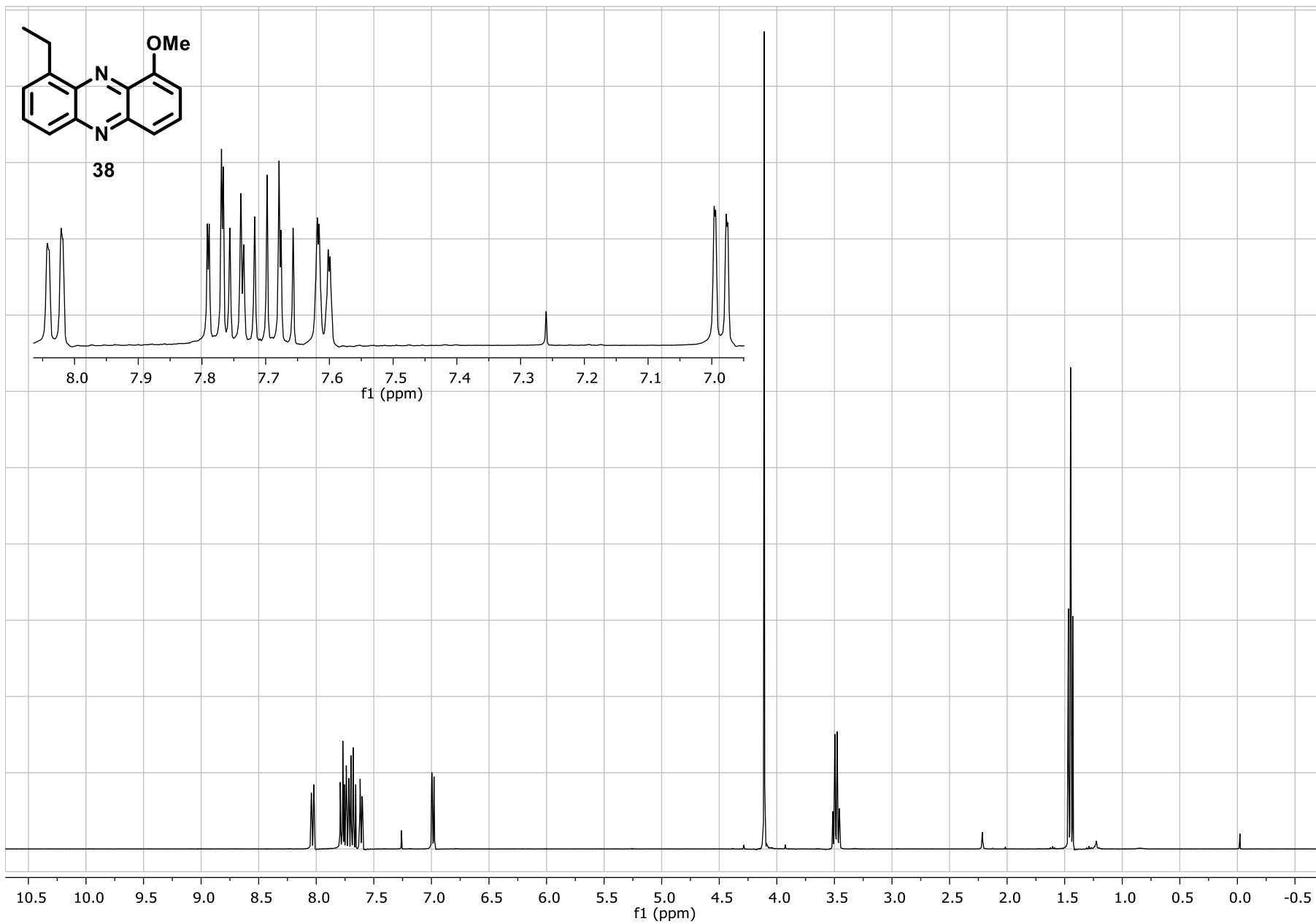




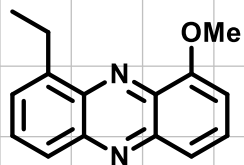


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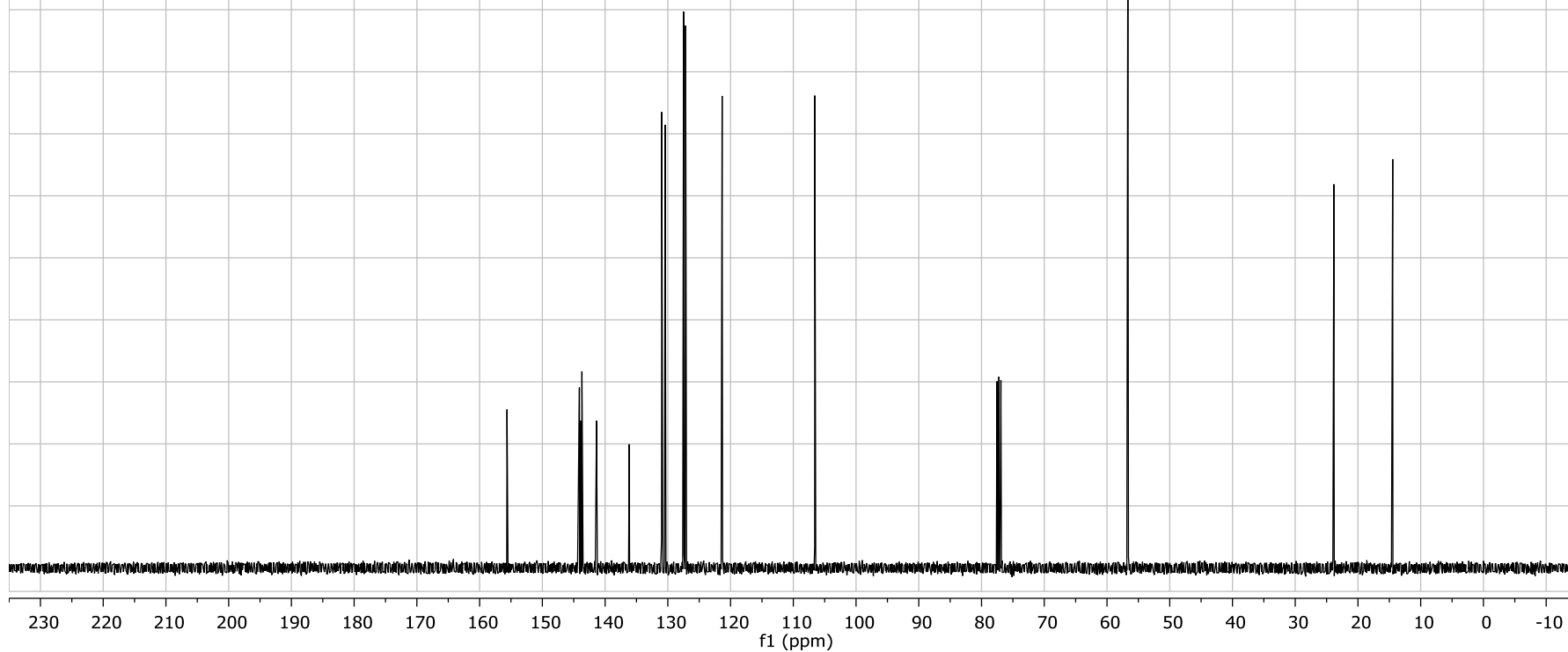
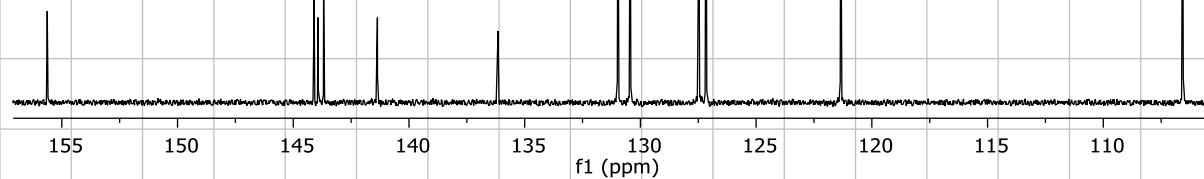


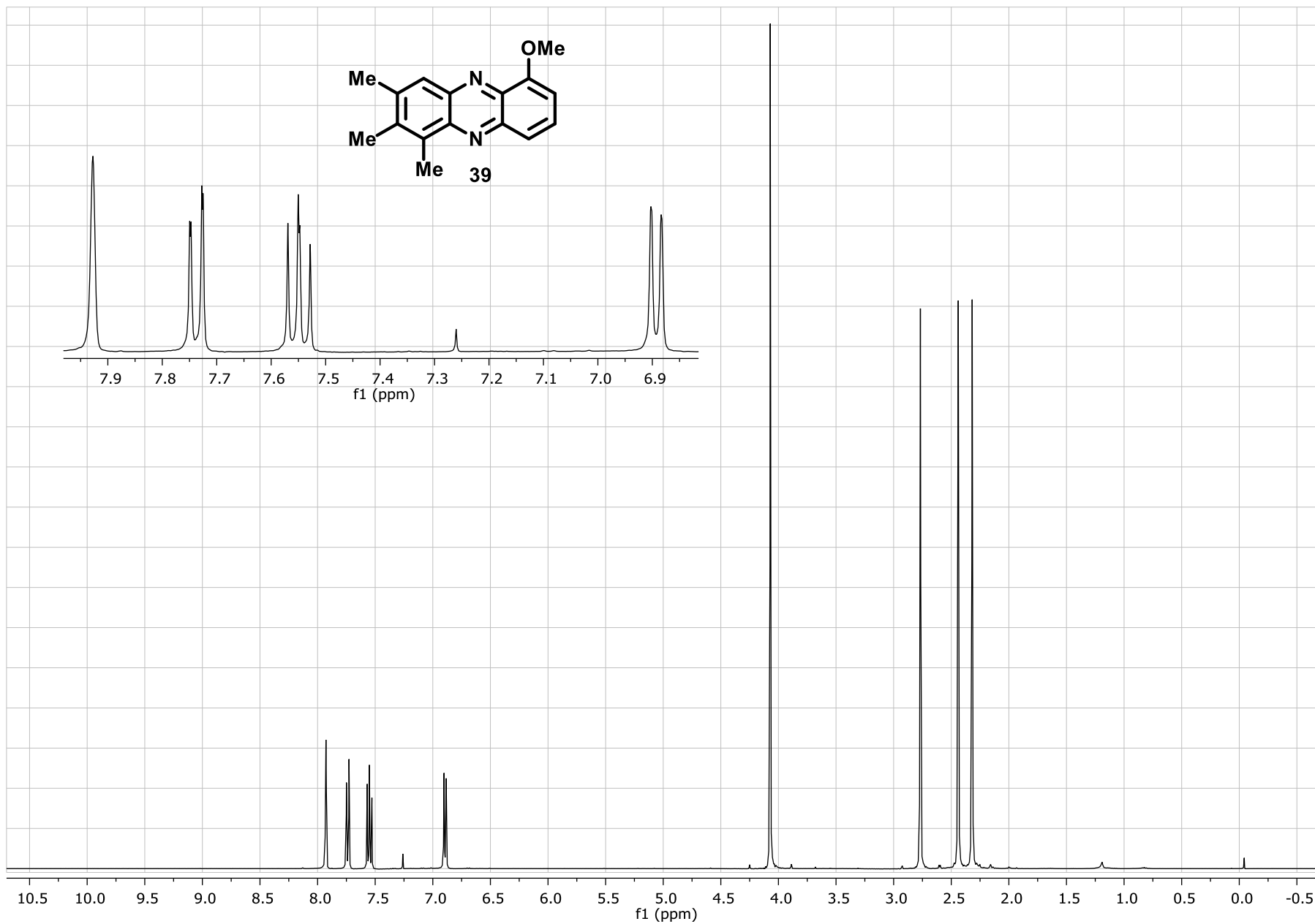


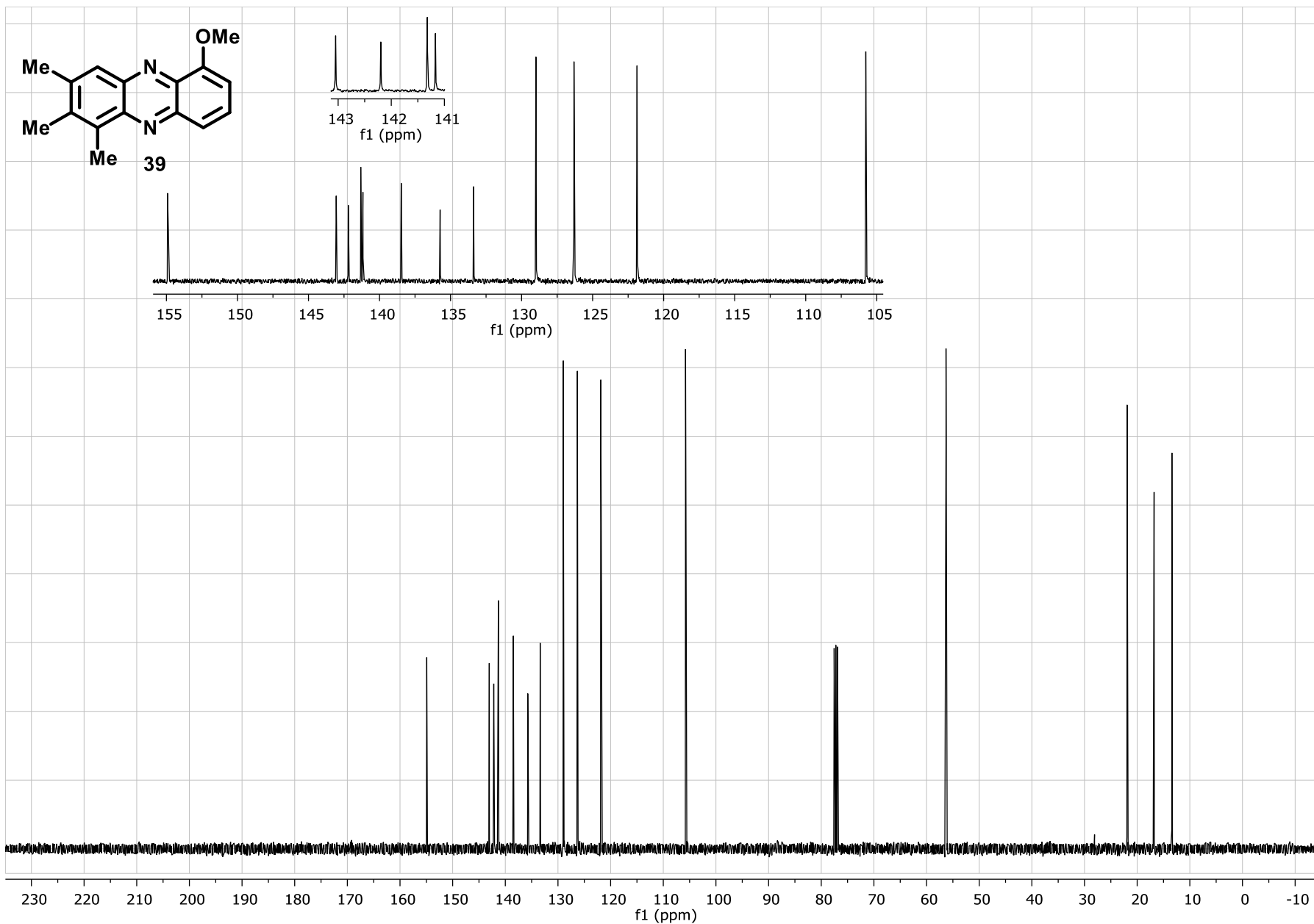
S110

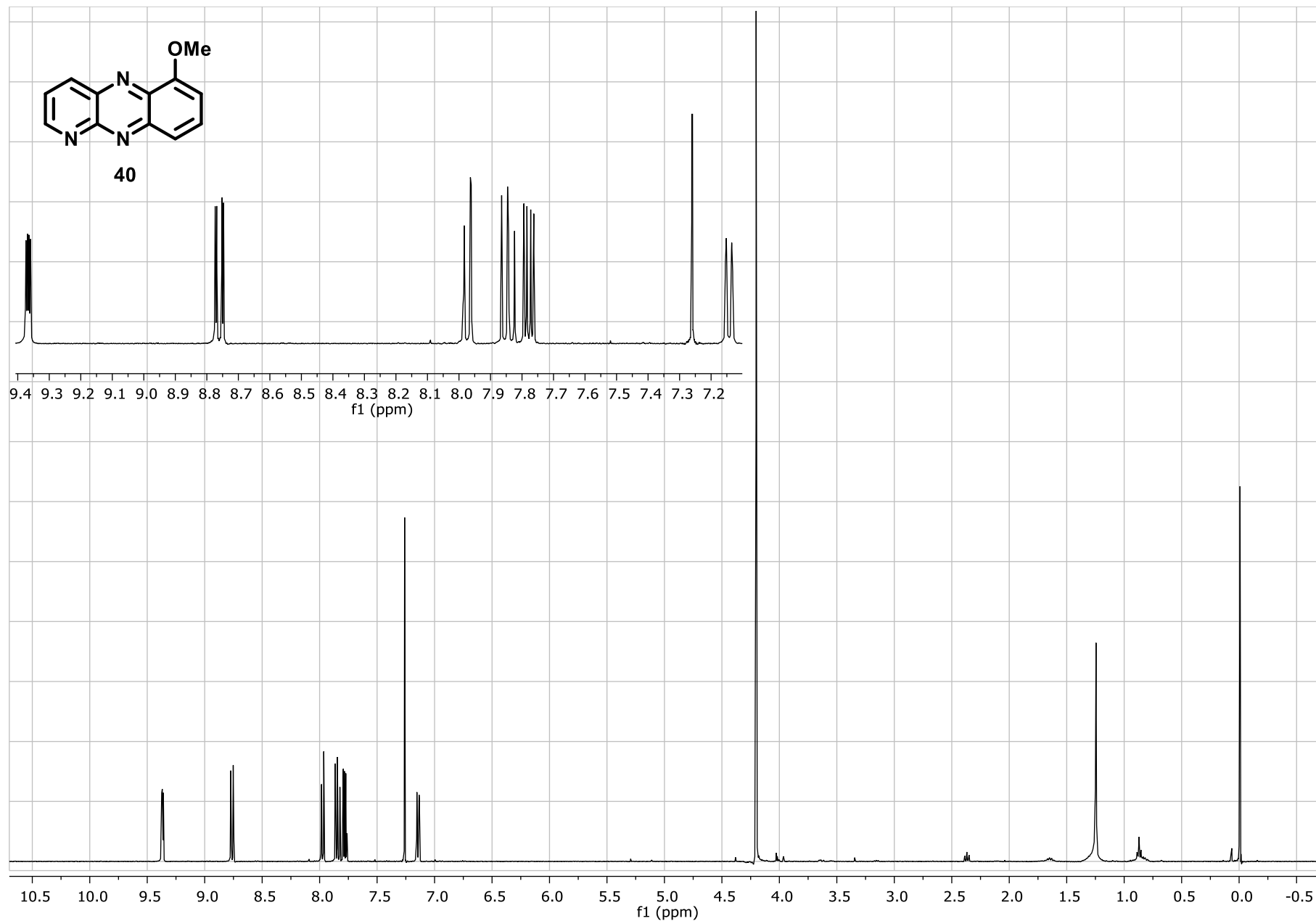


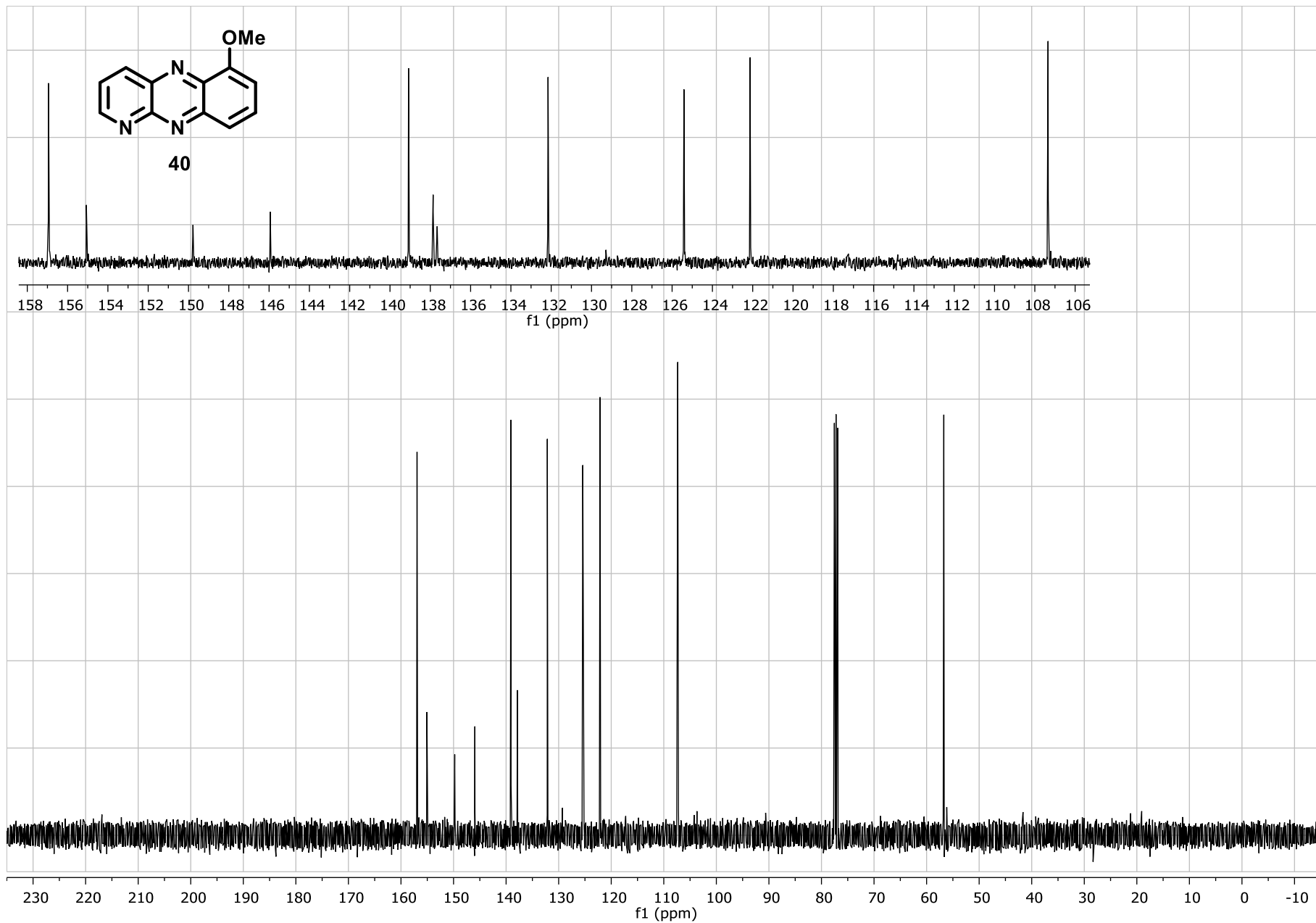
38

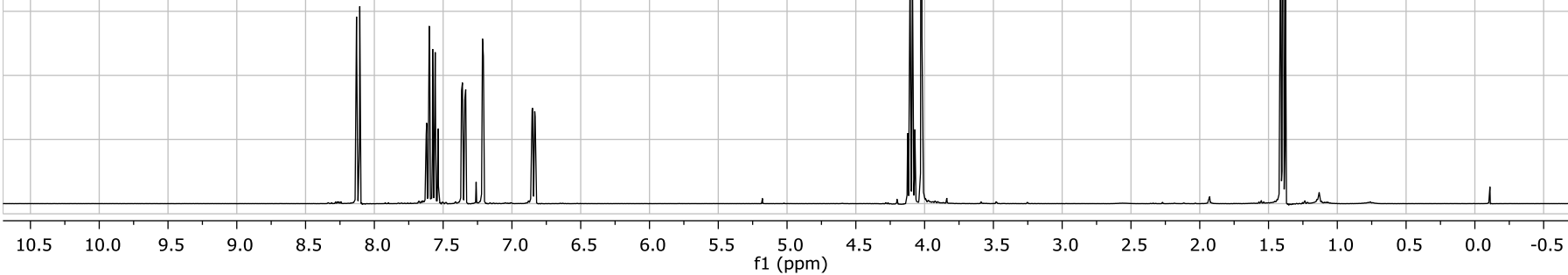
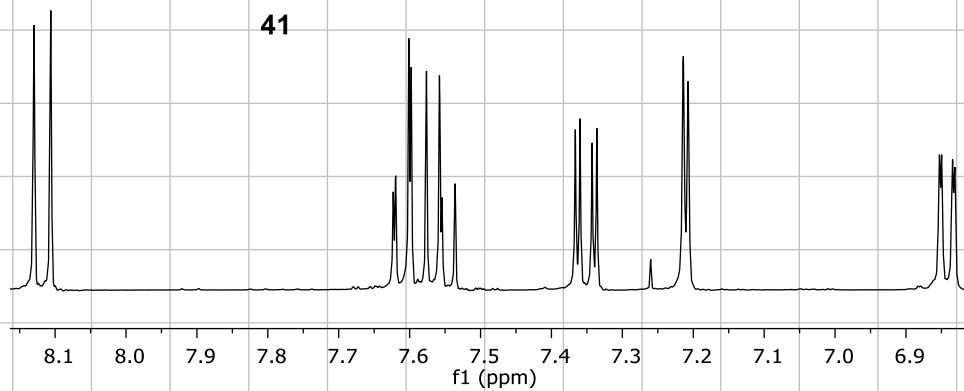
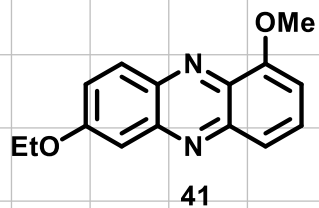




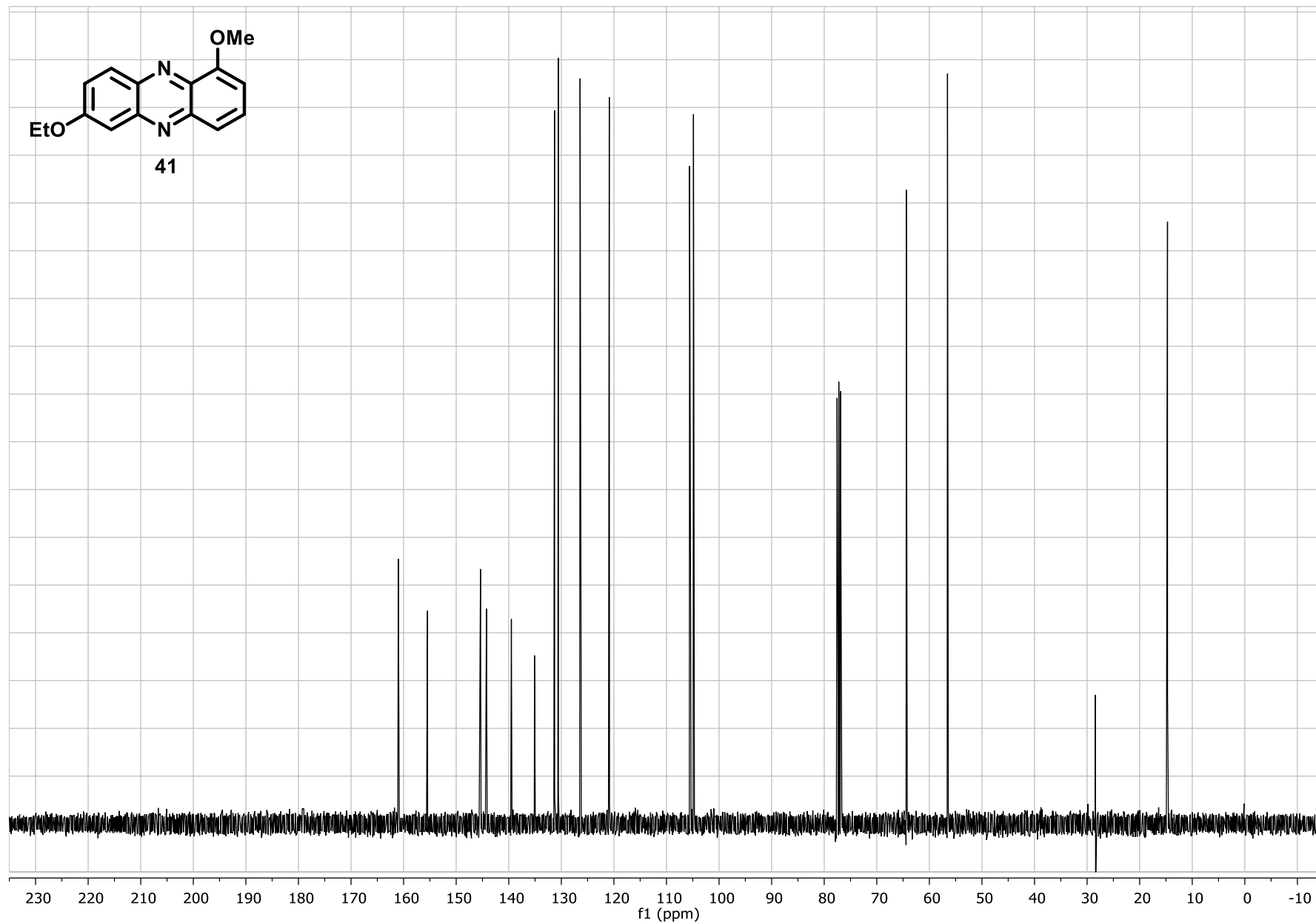
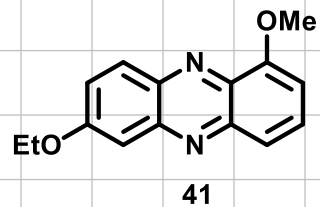


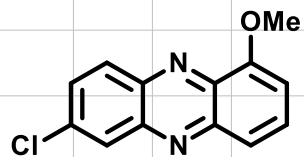




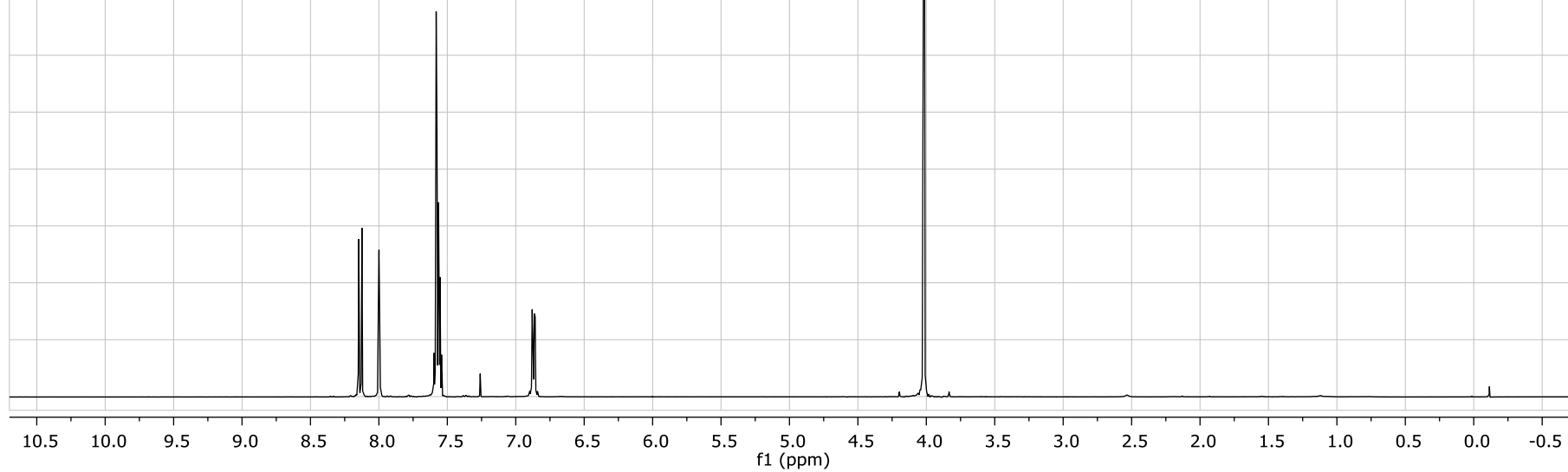
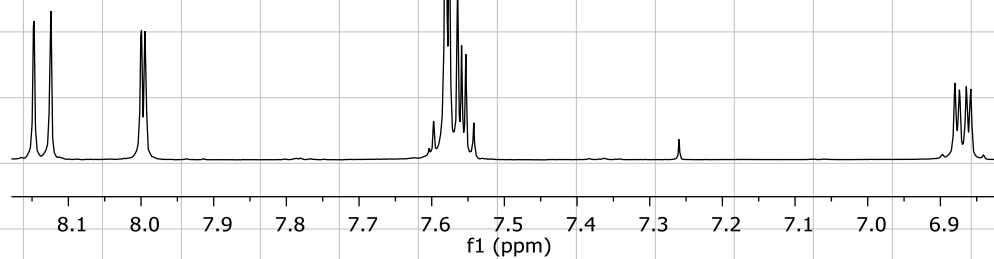




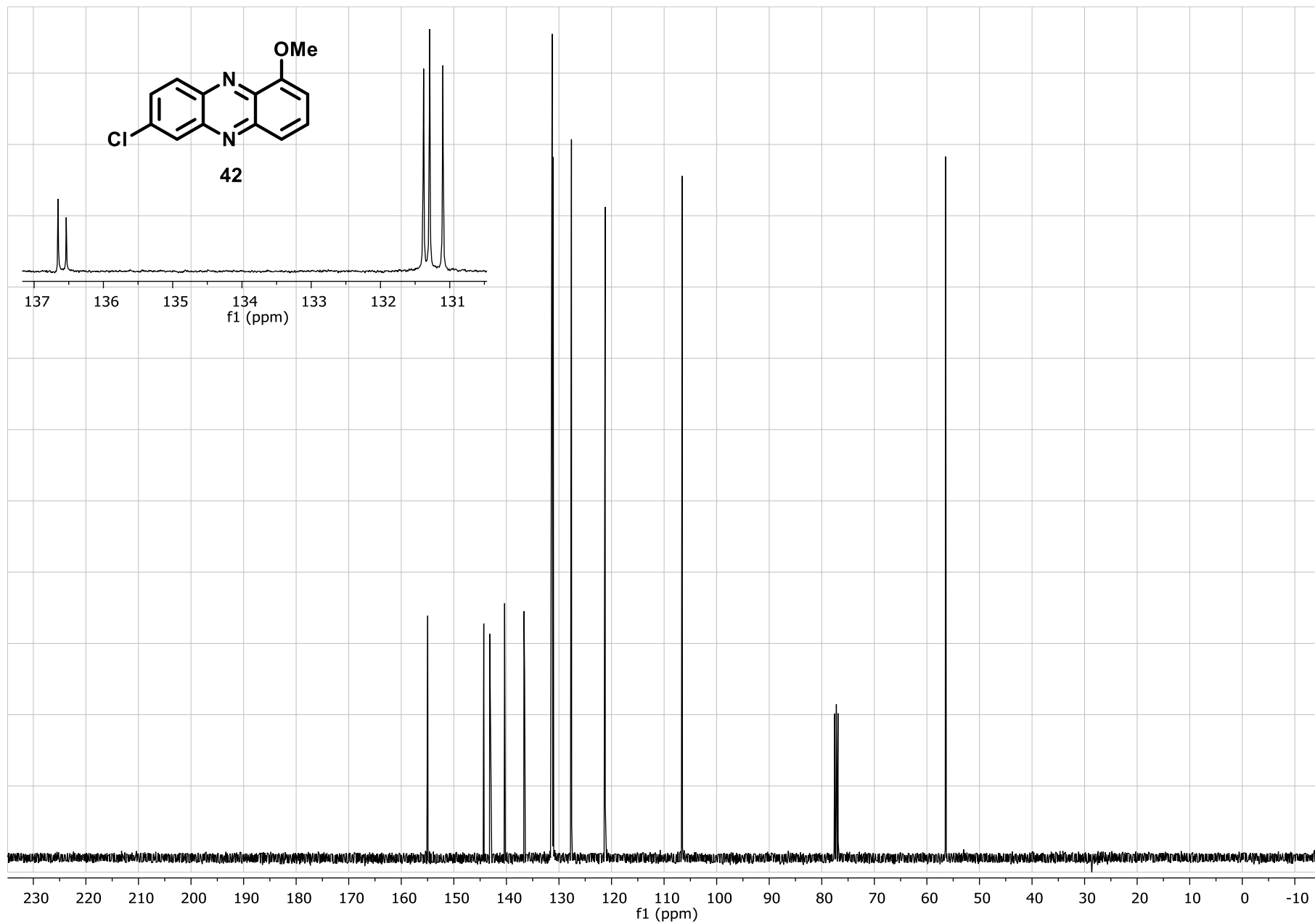


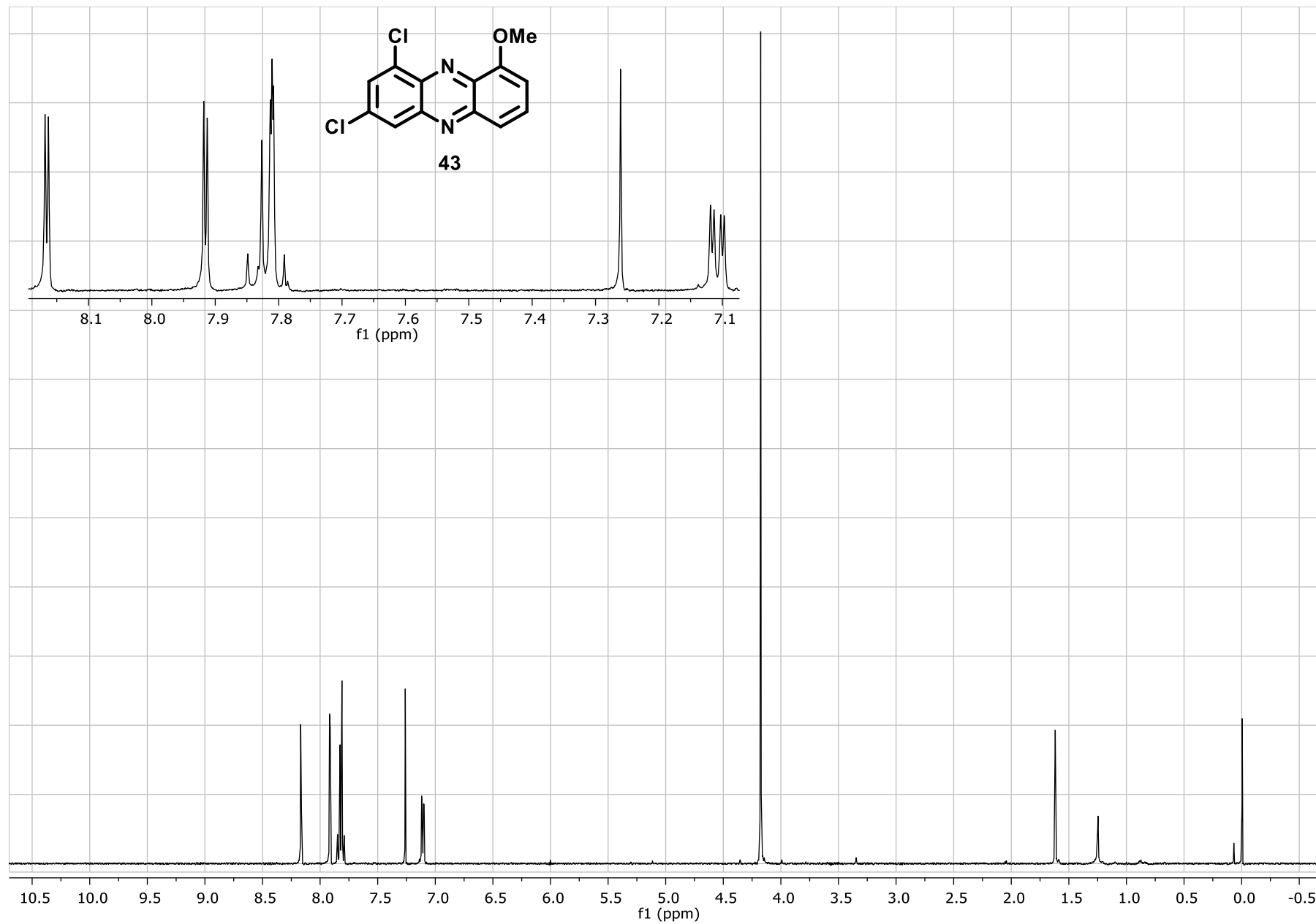
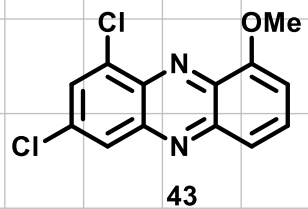


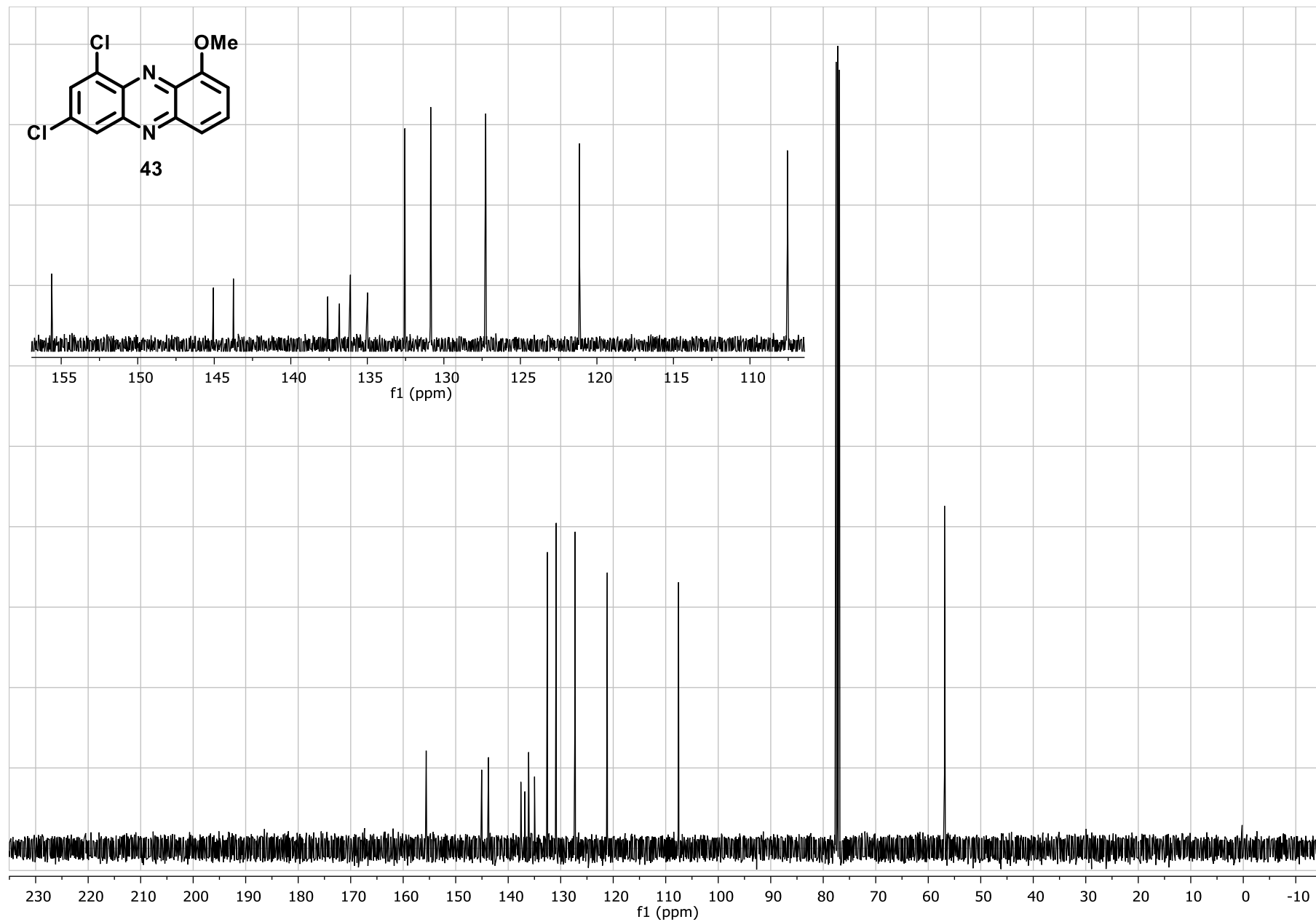
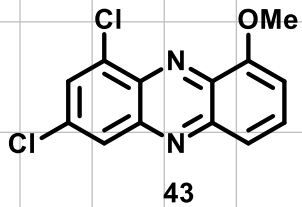
42

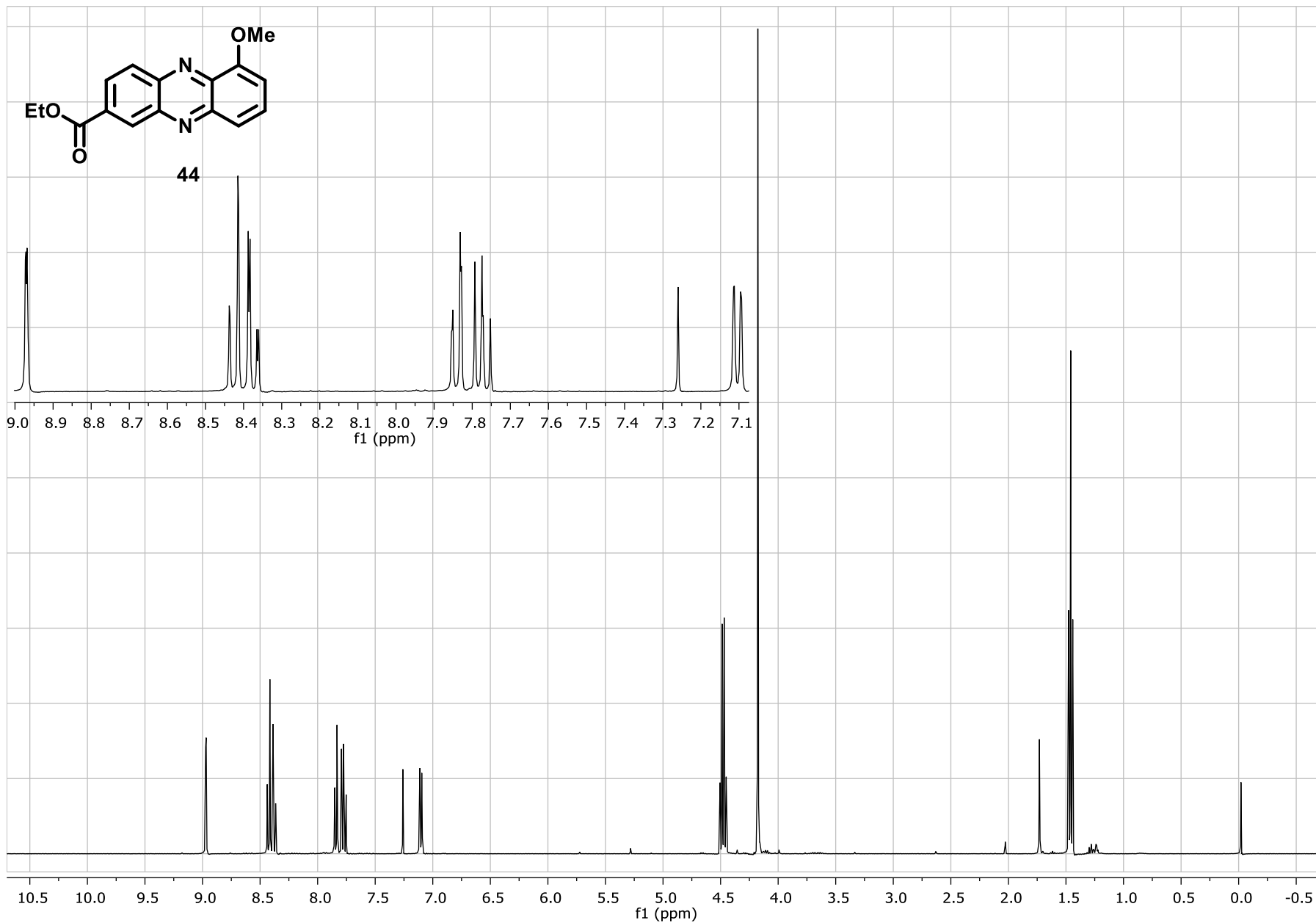


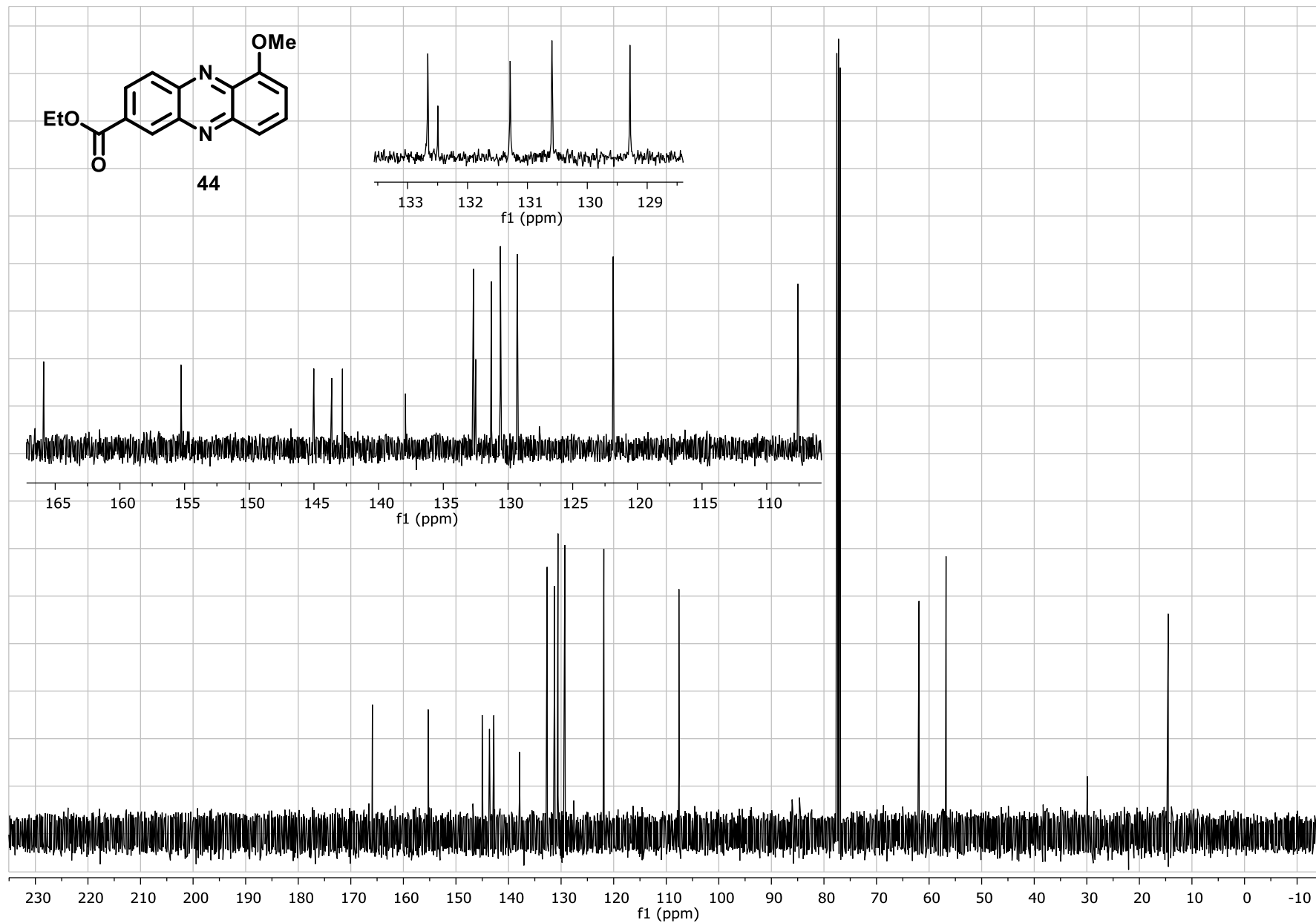
S118

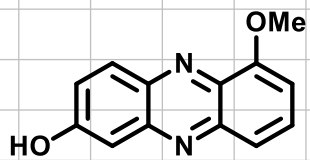




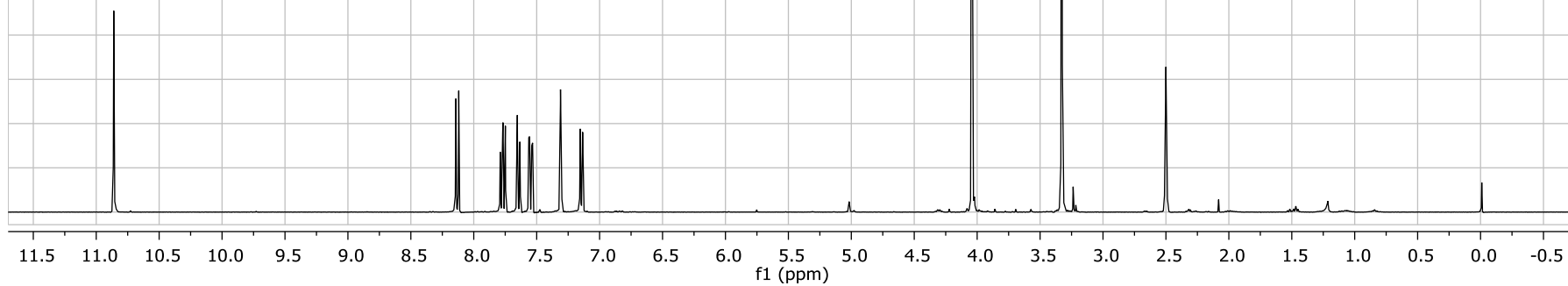
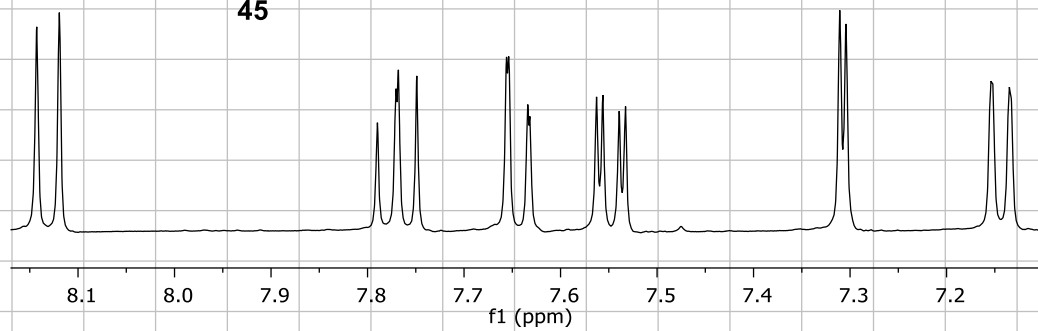




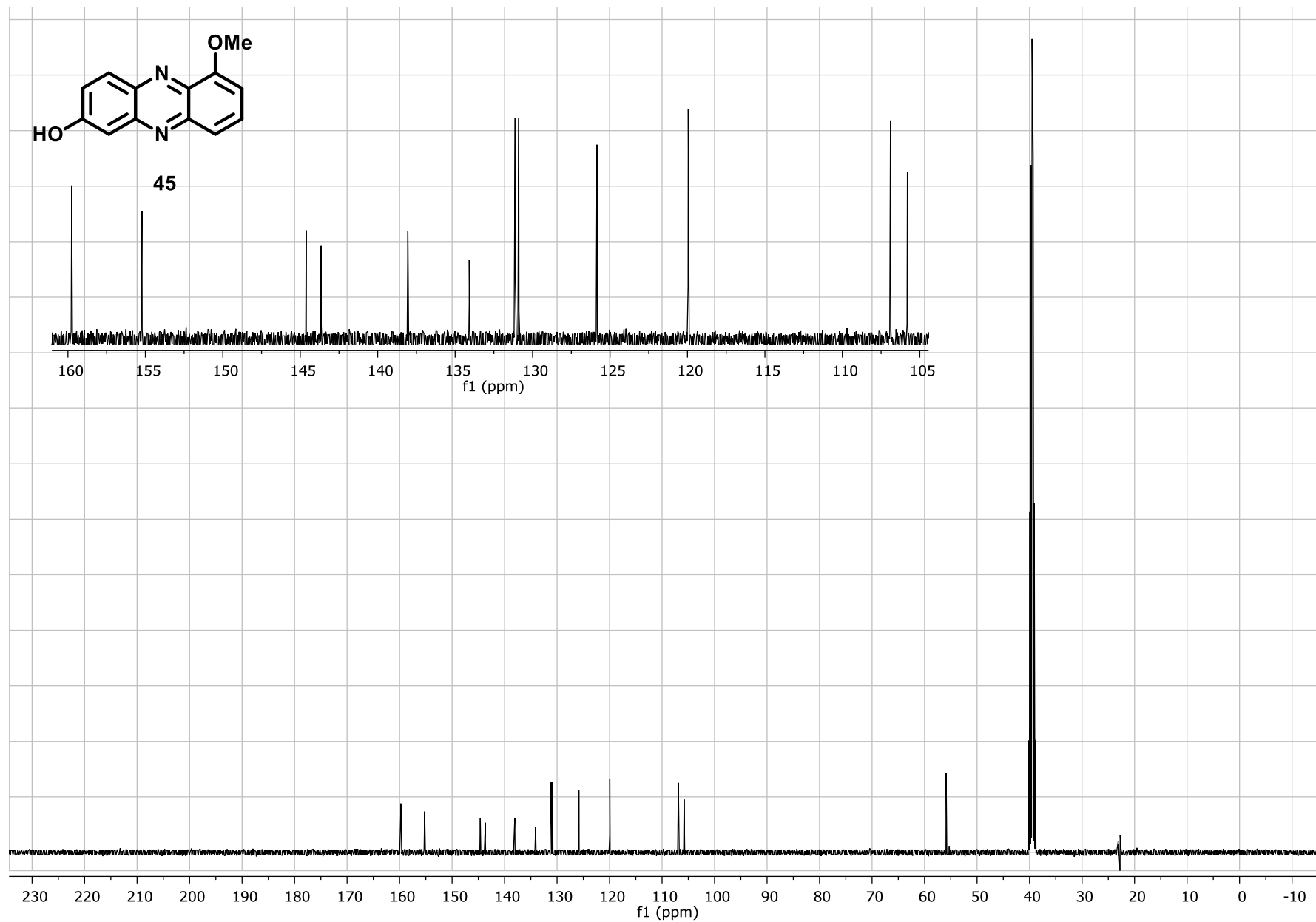


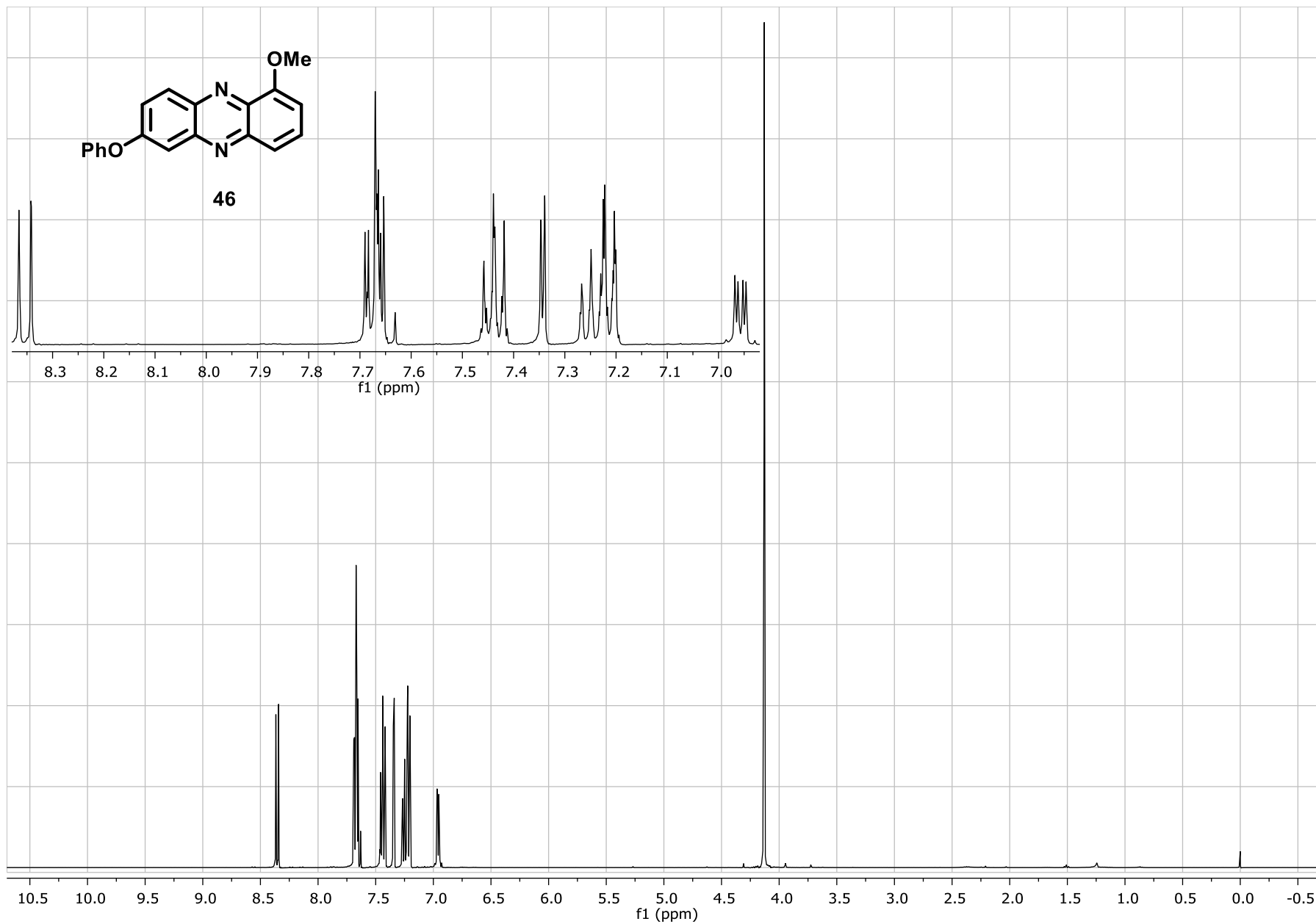


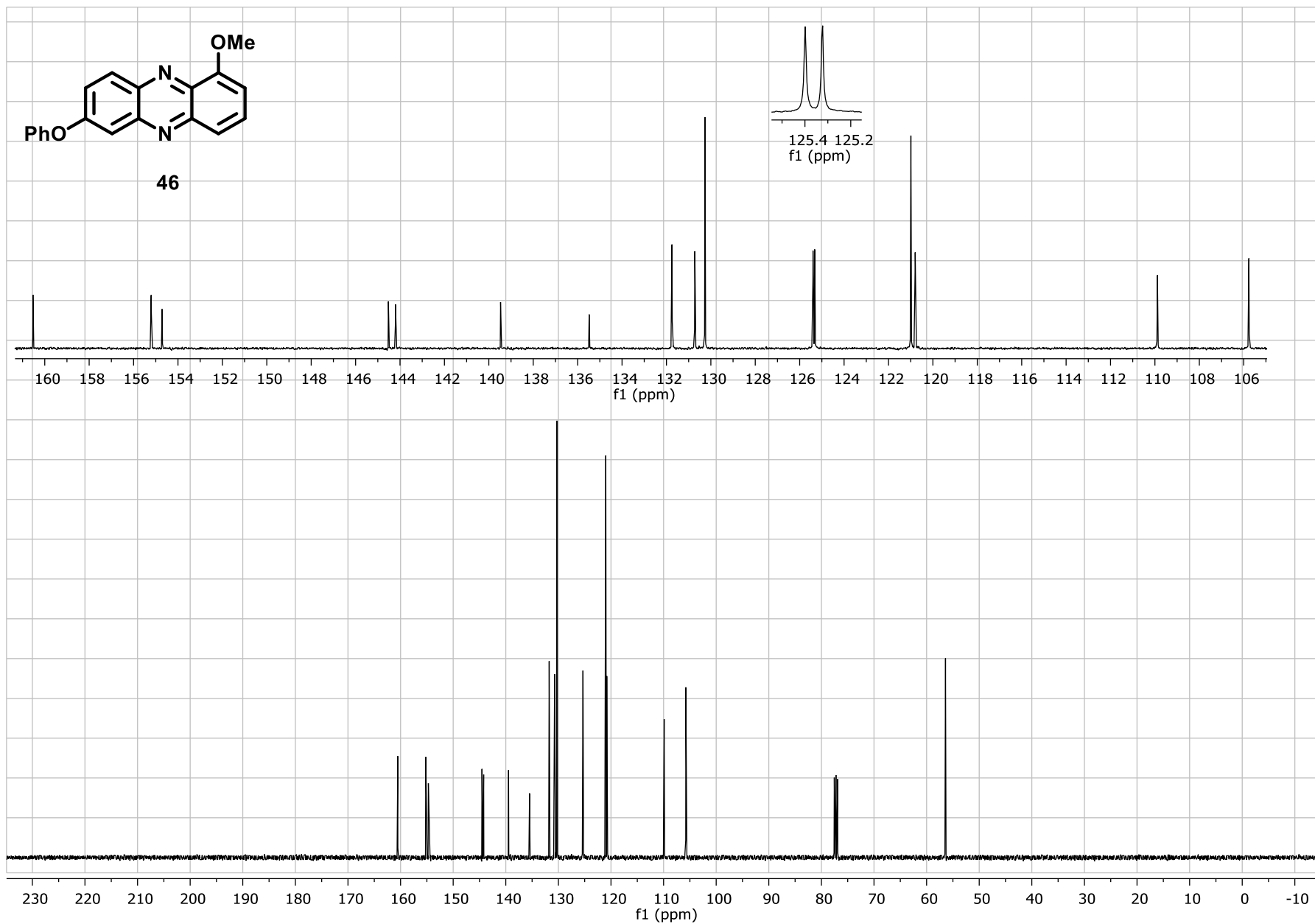
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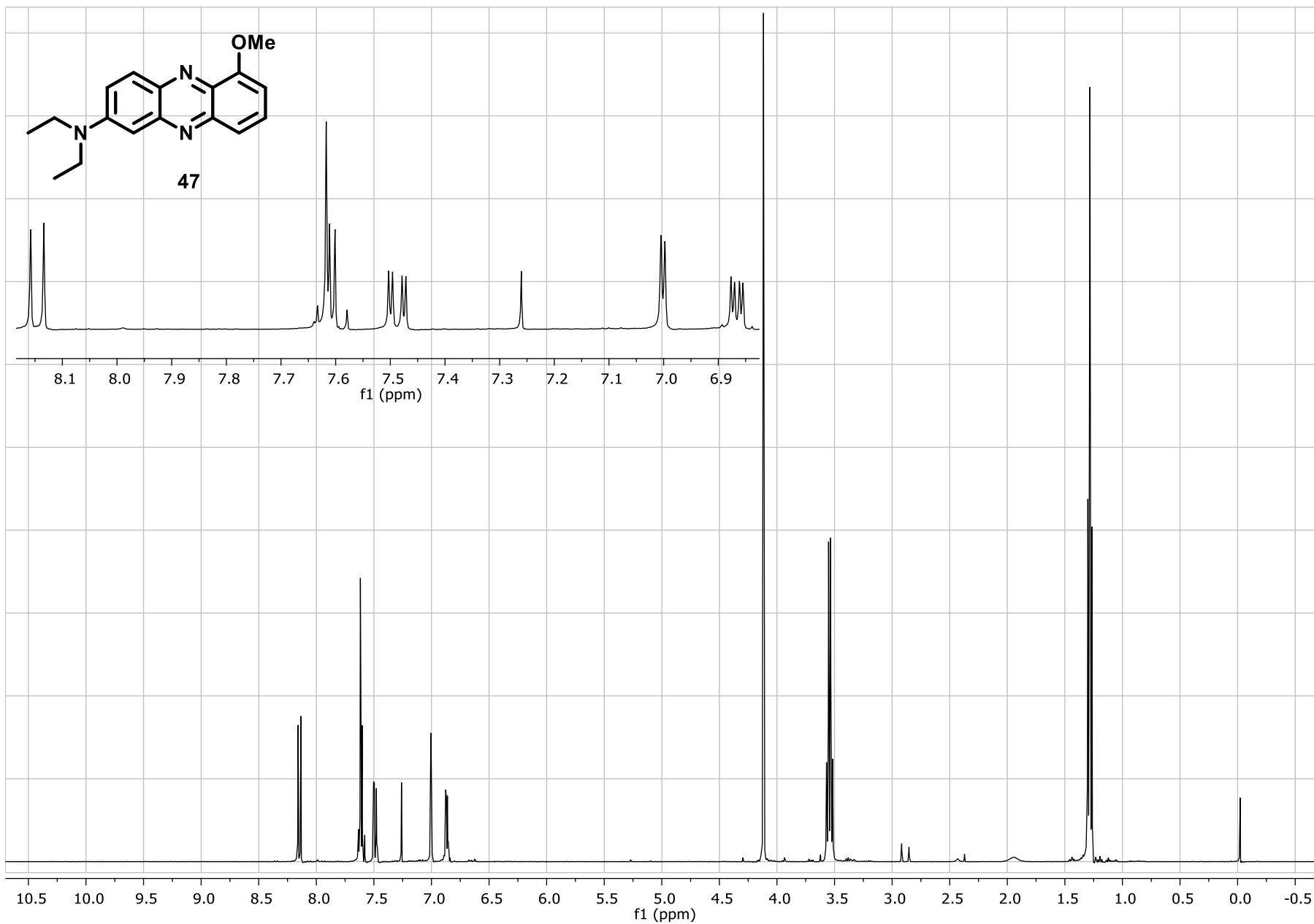


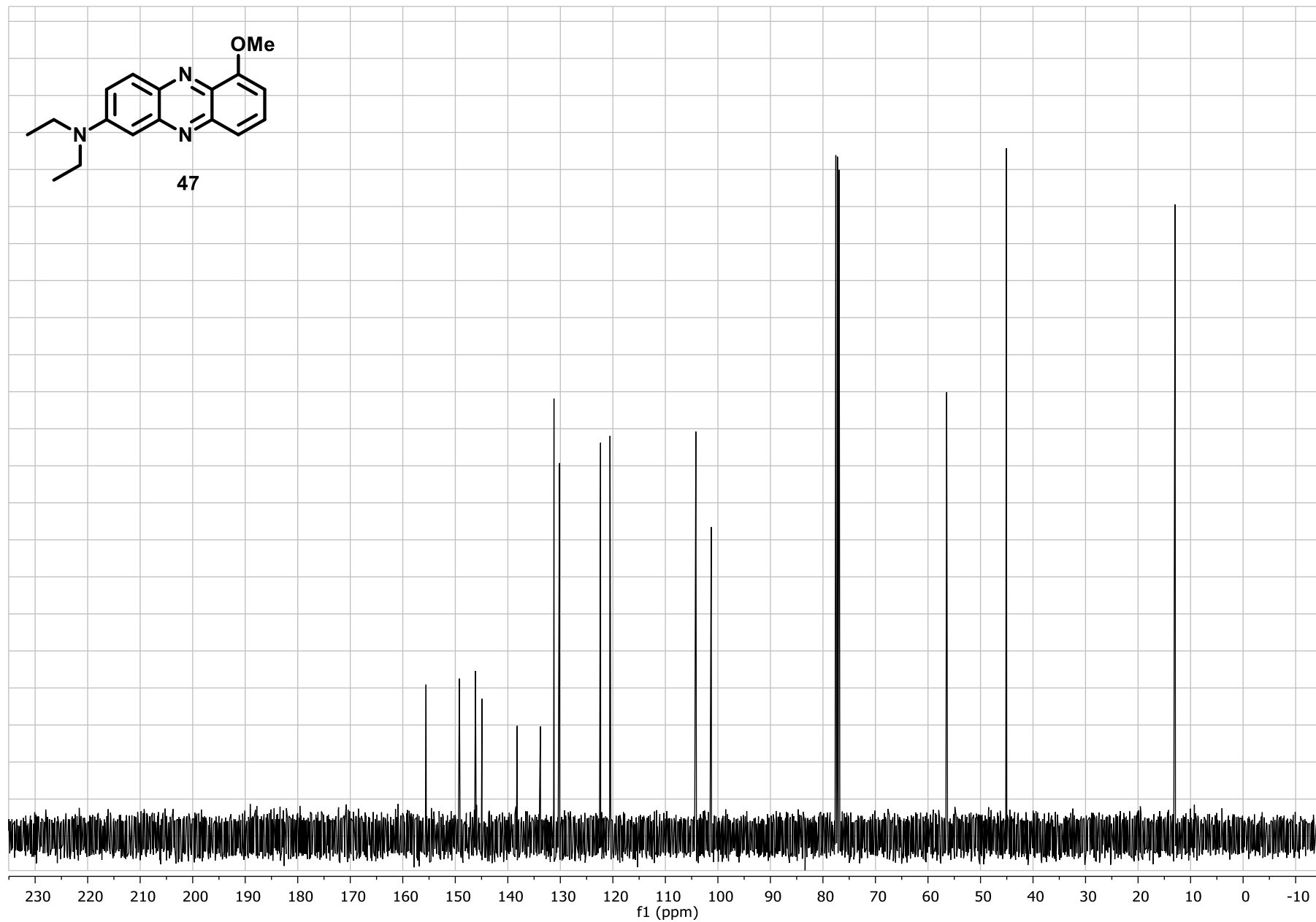
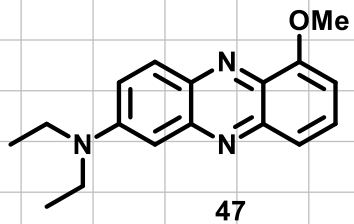


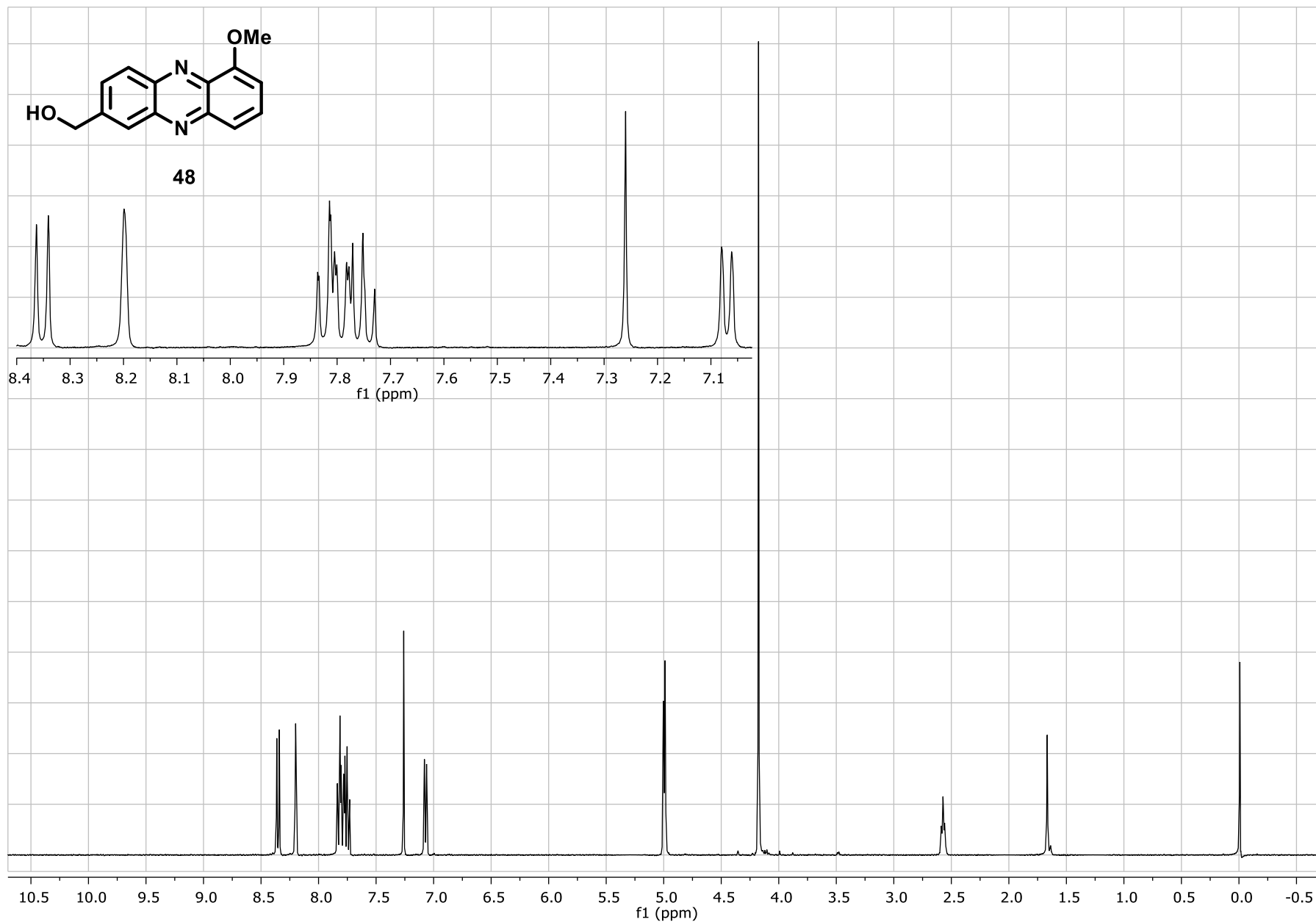


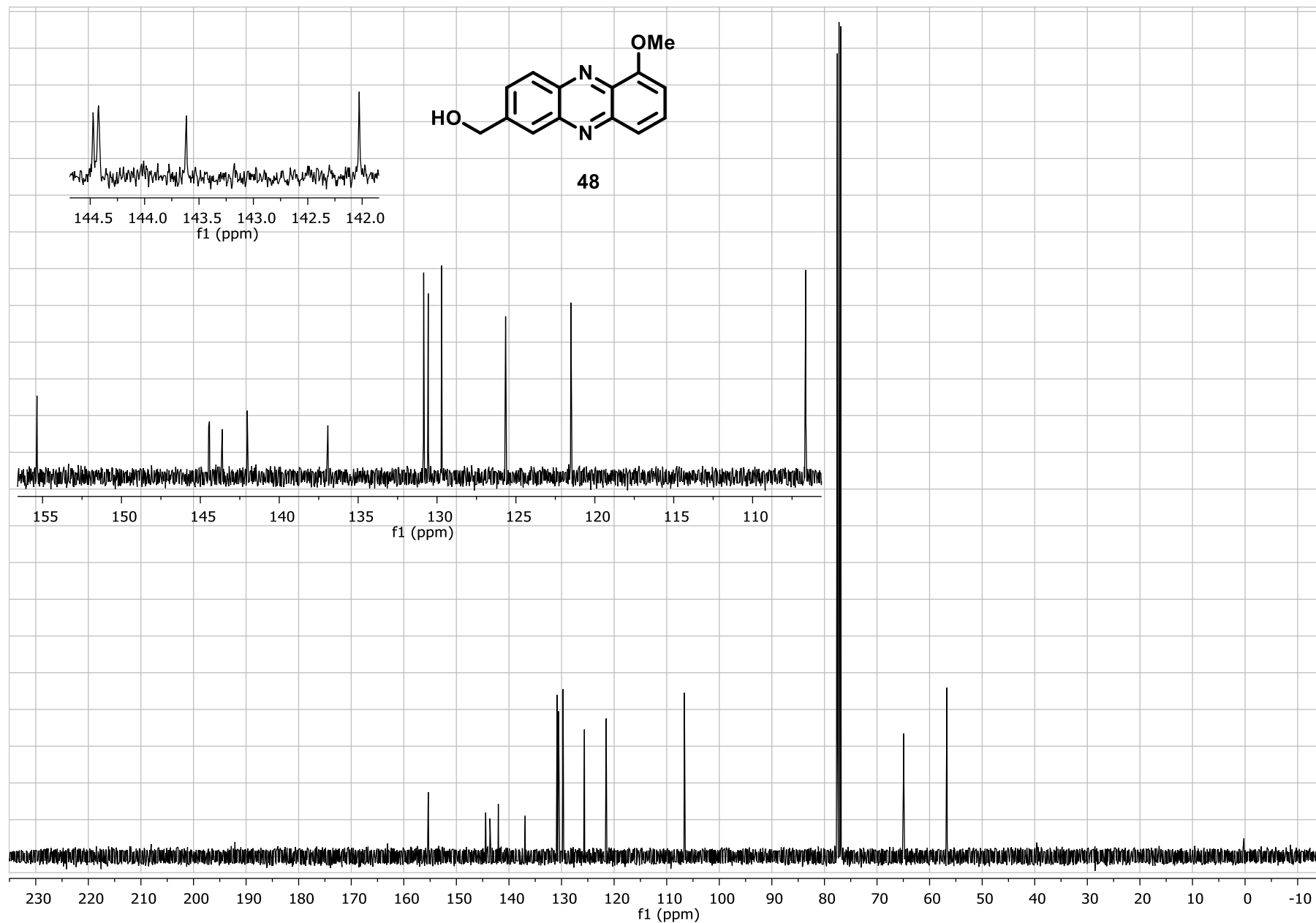


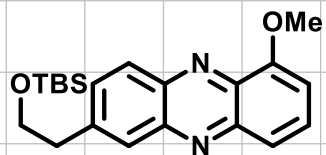




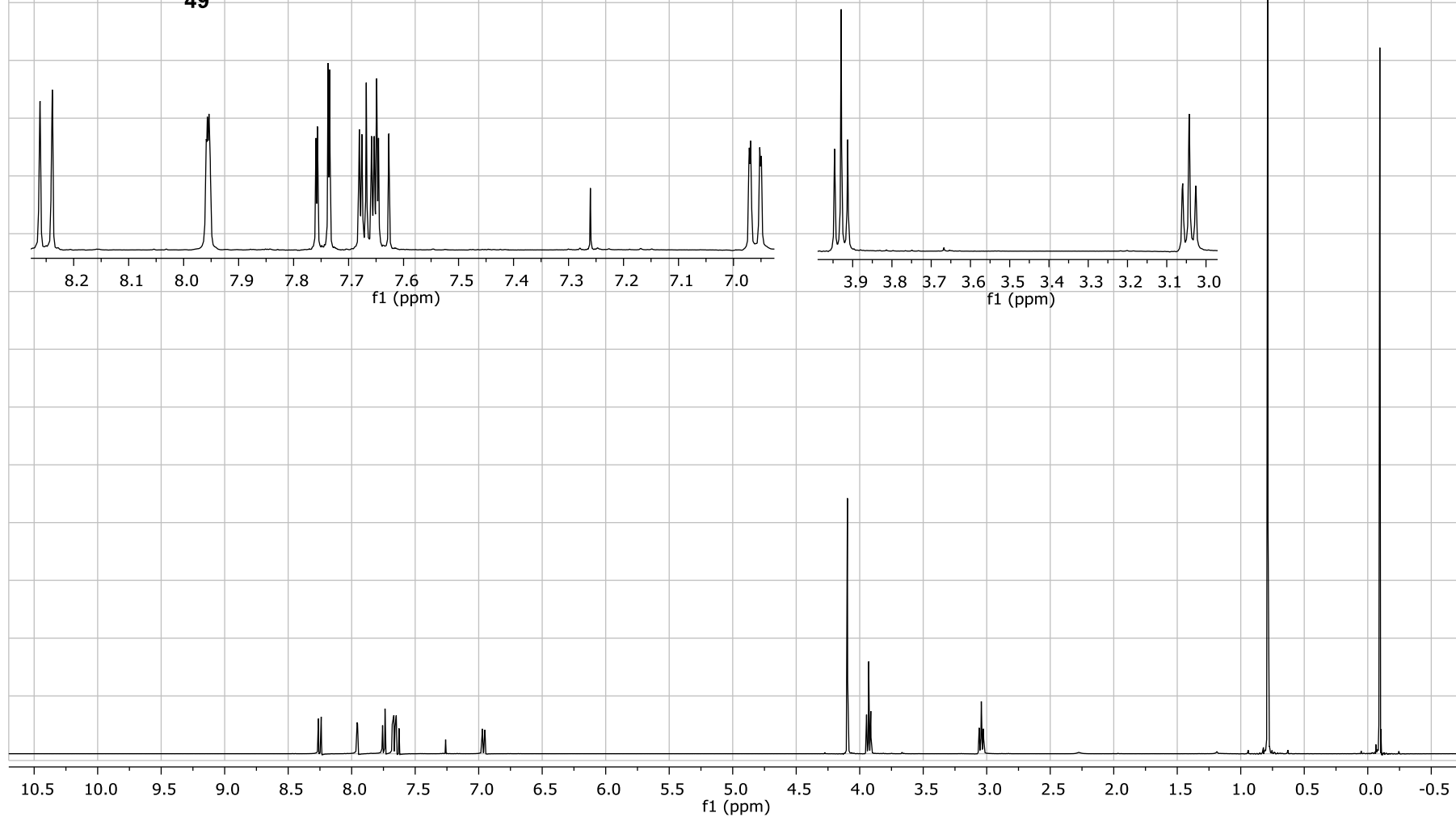




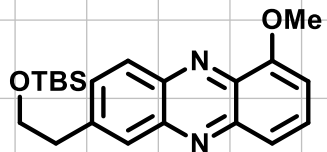




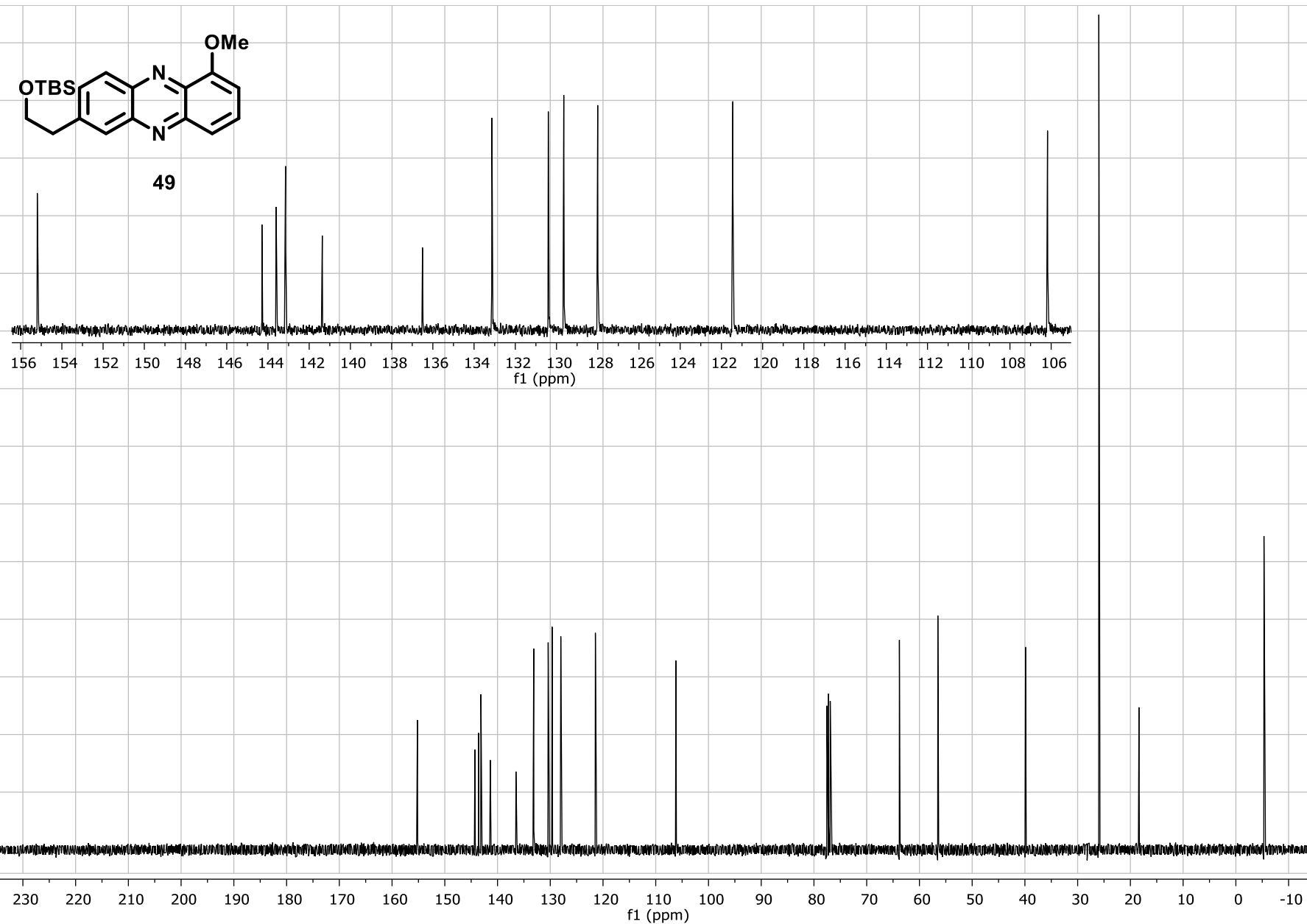
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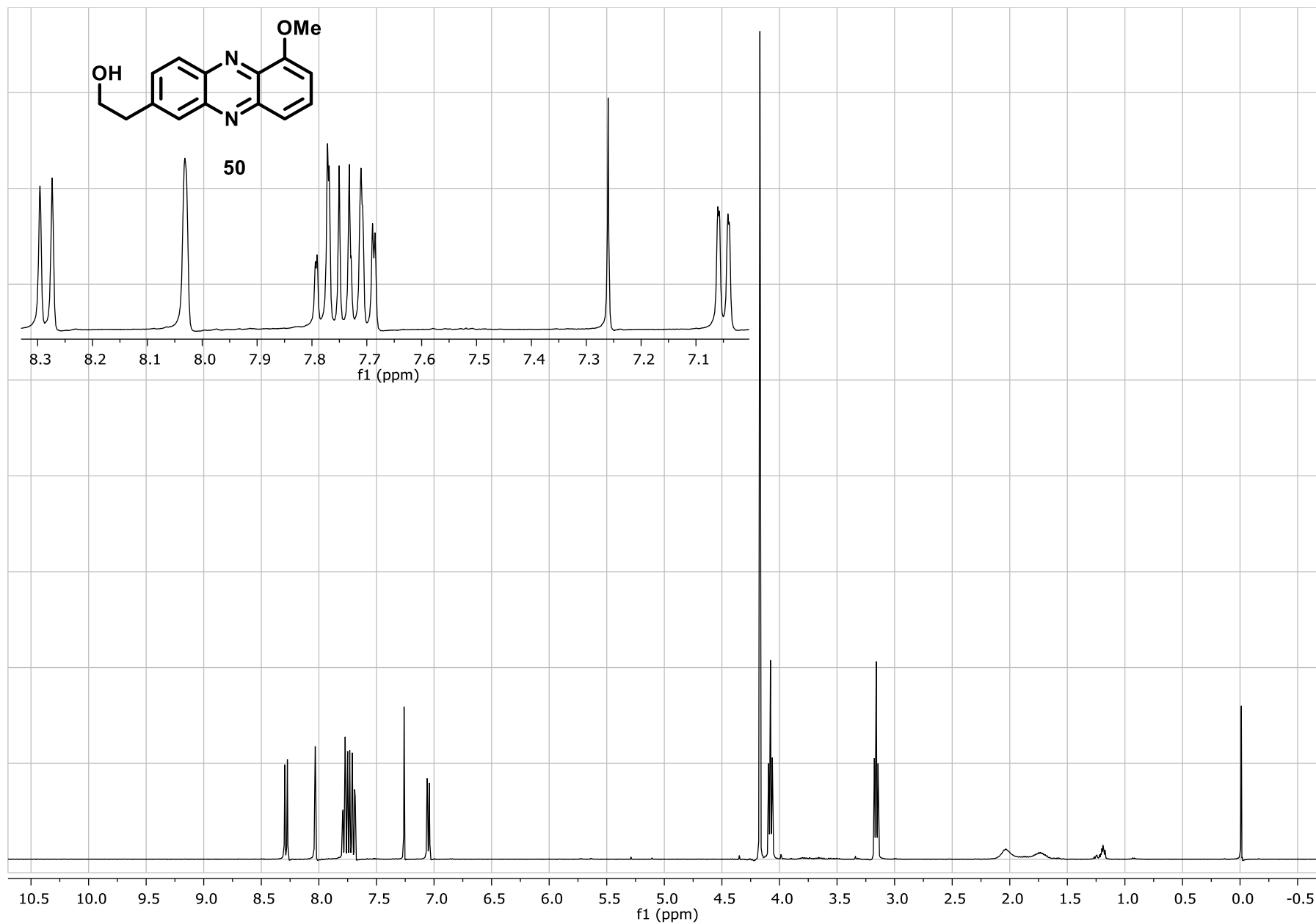




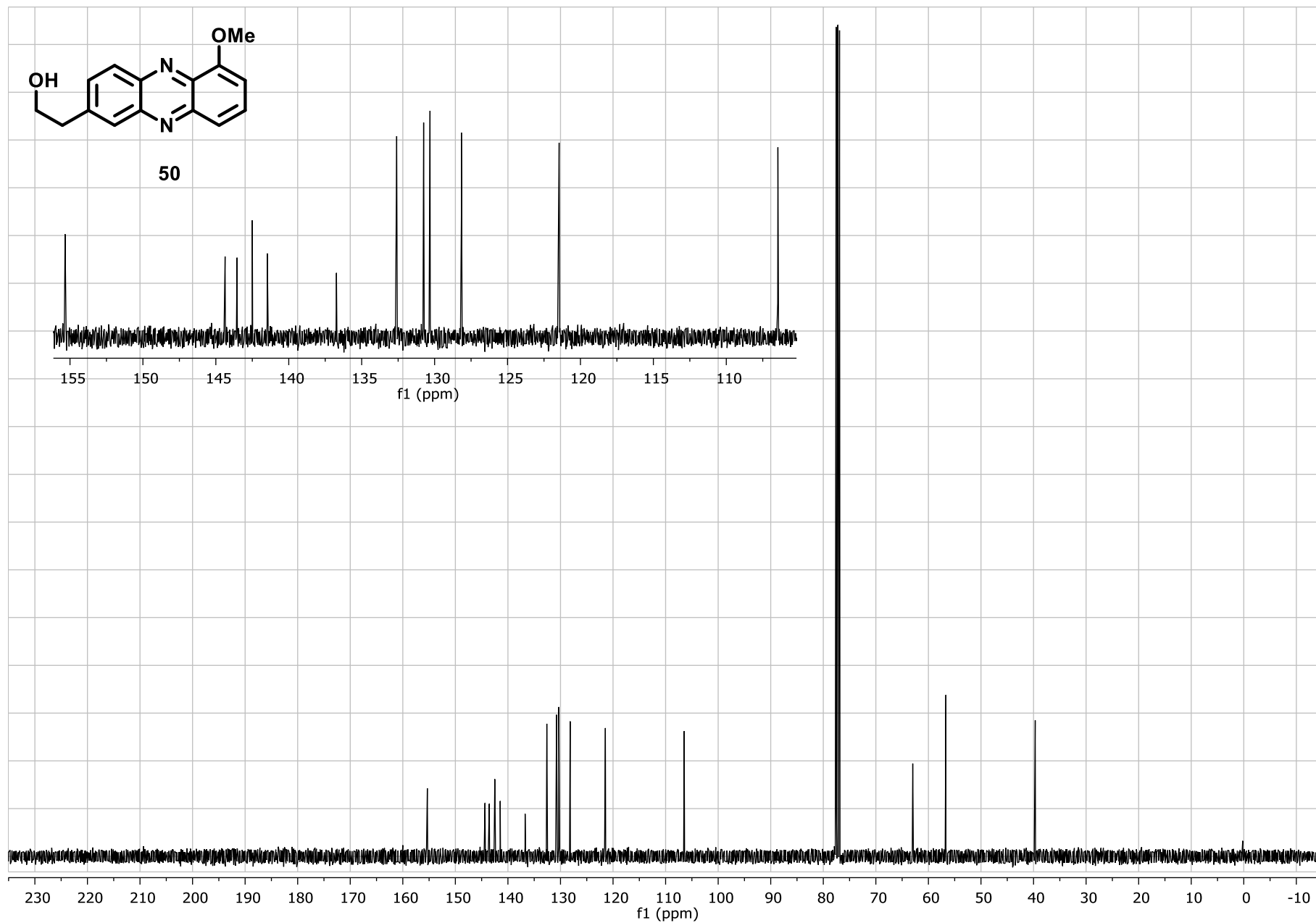


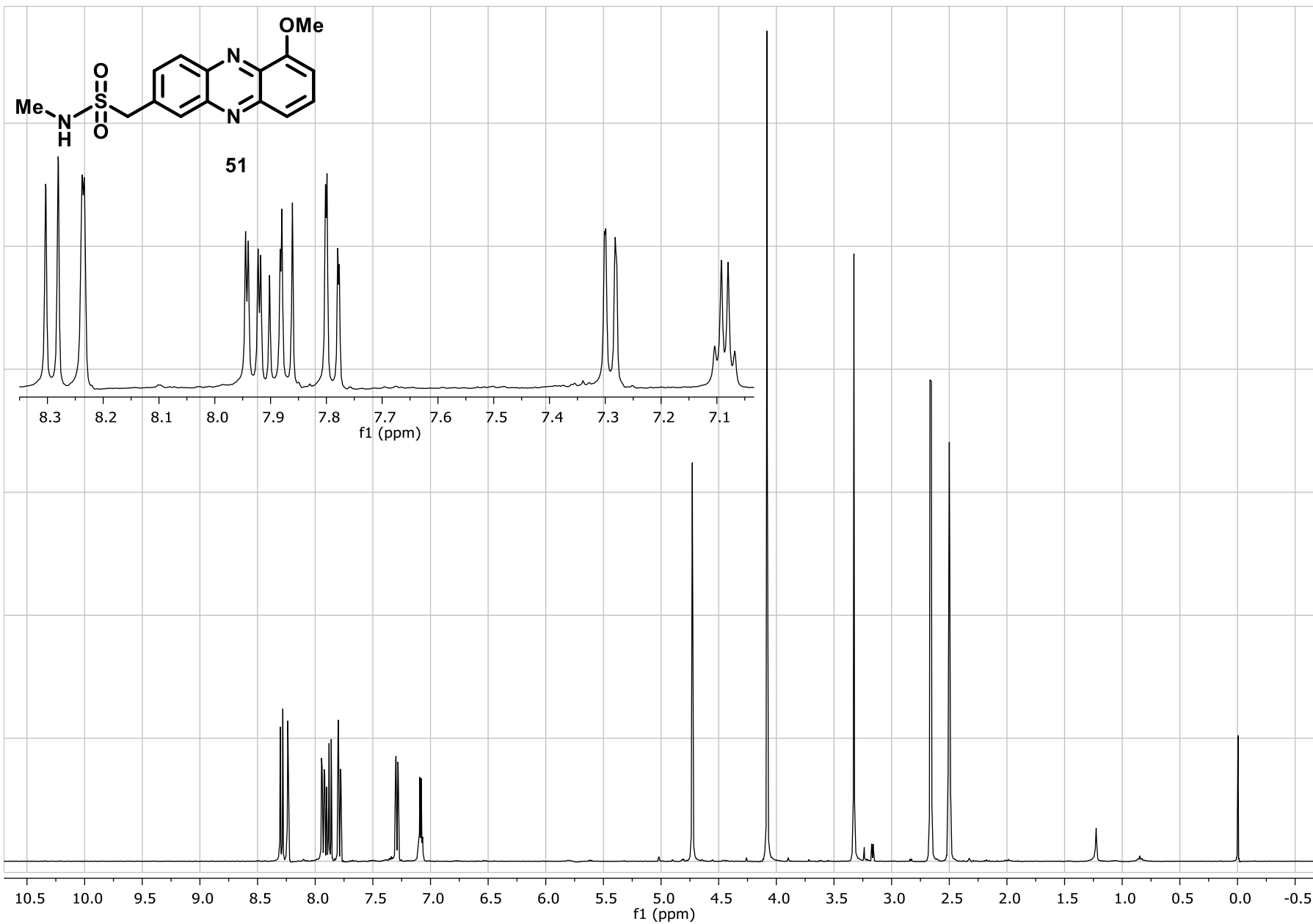
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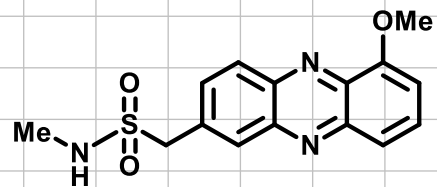




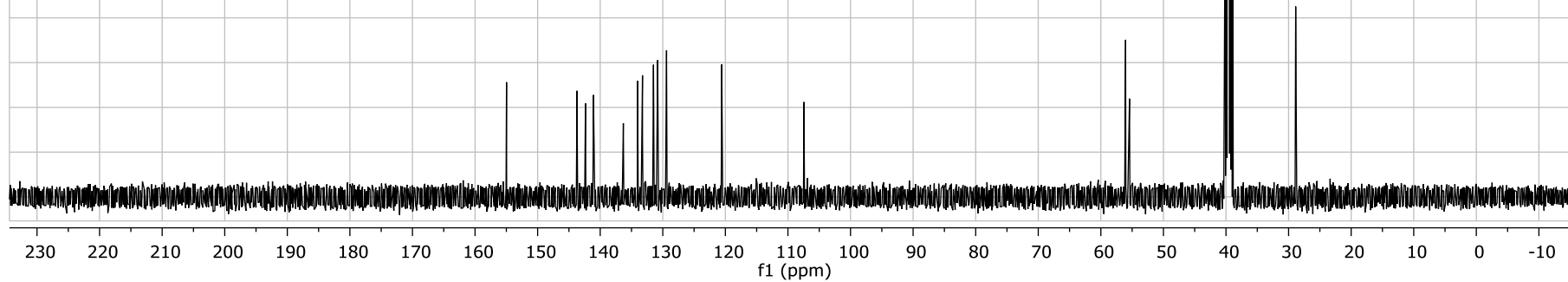
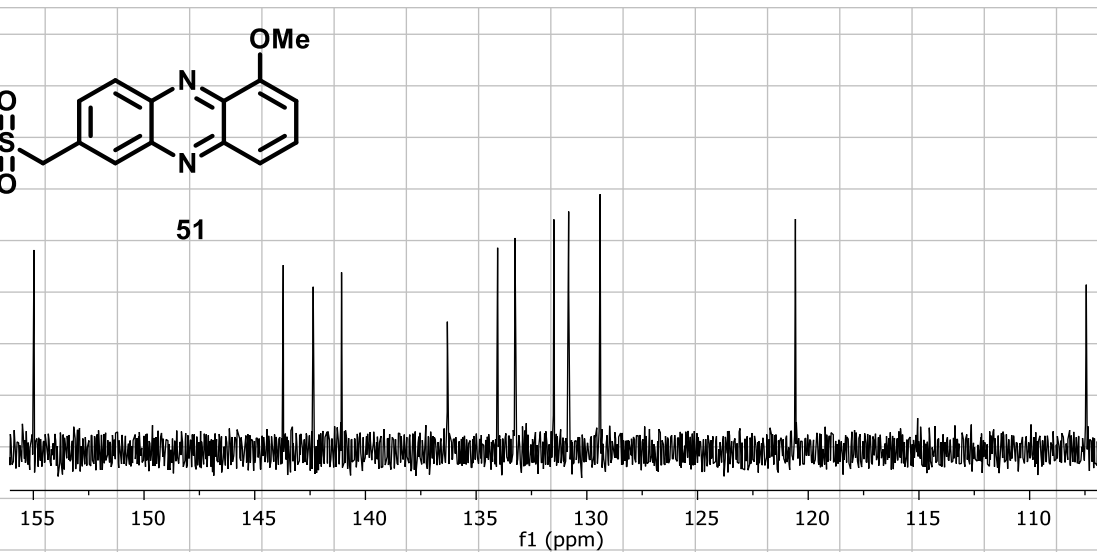
S134

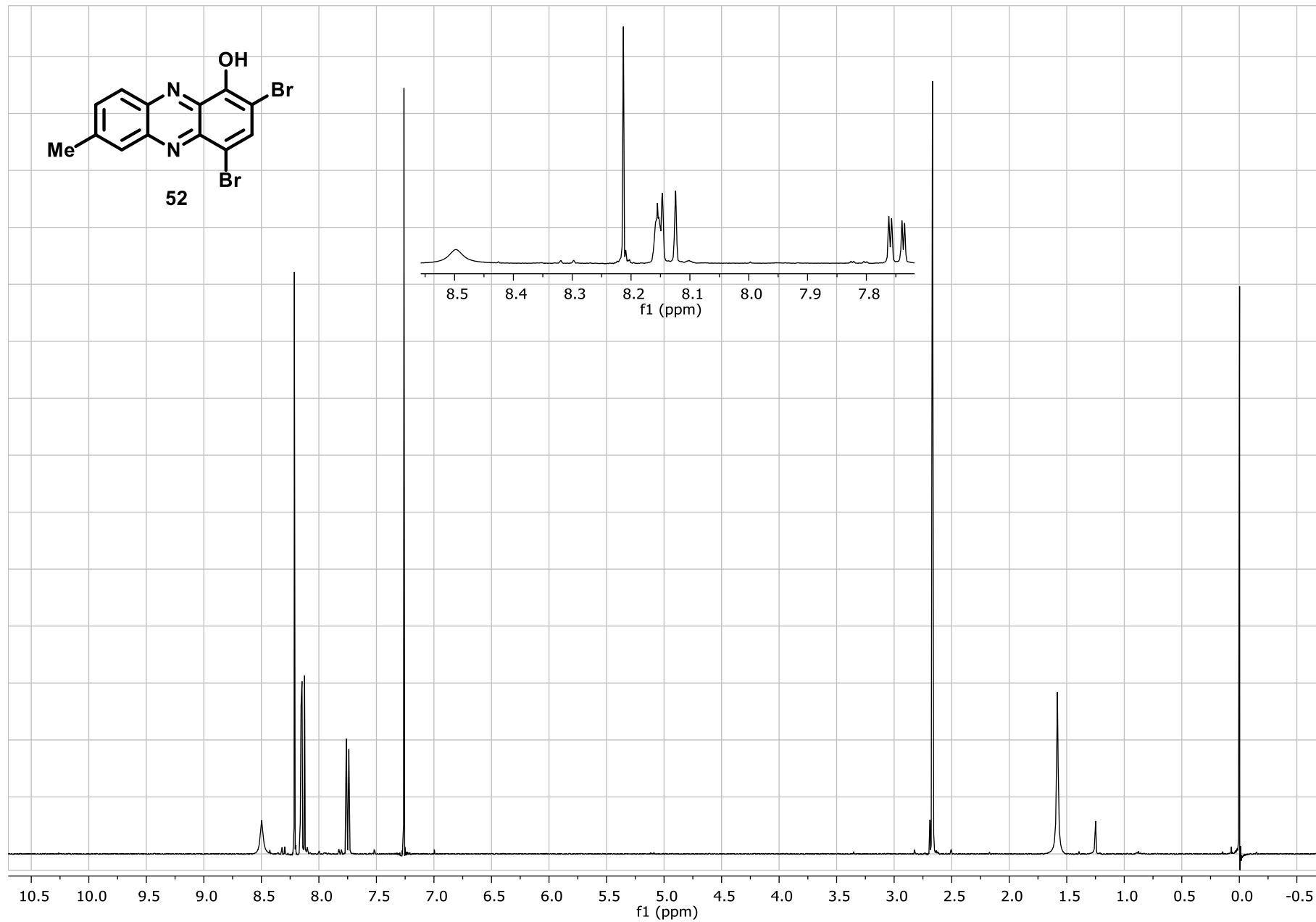
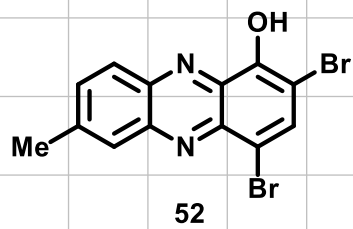




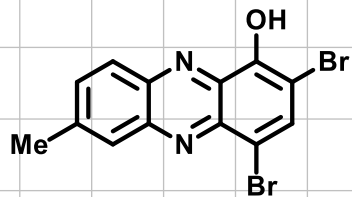


51

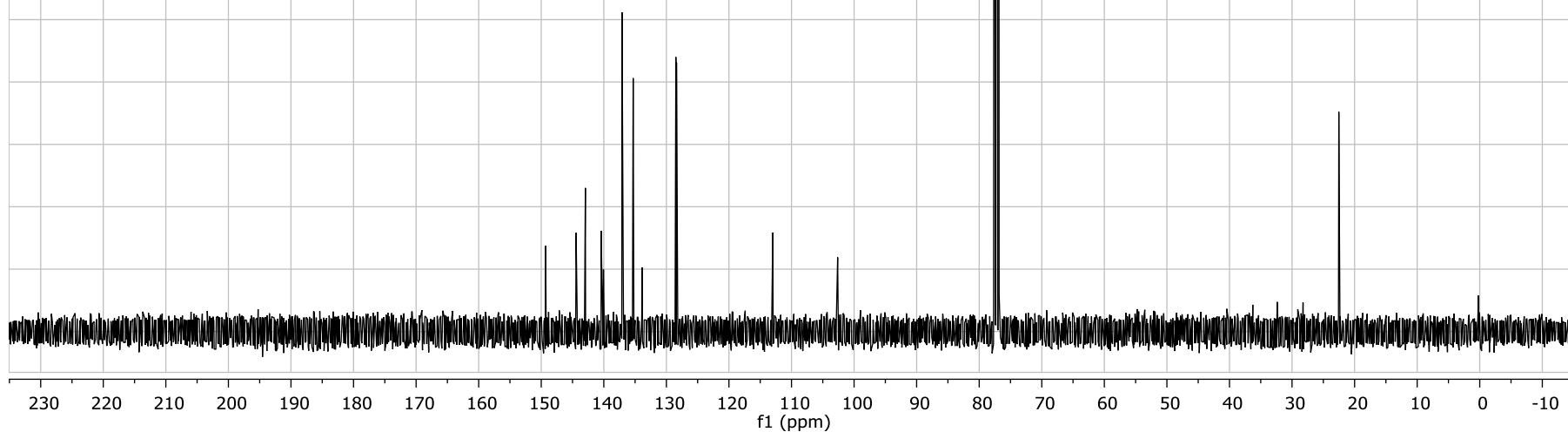
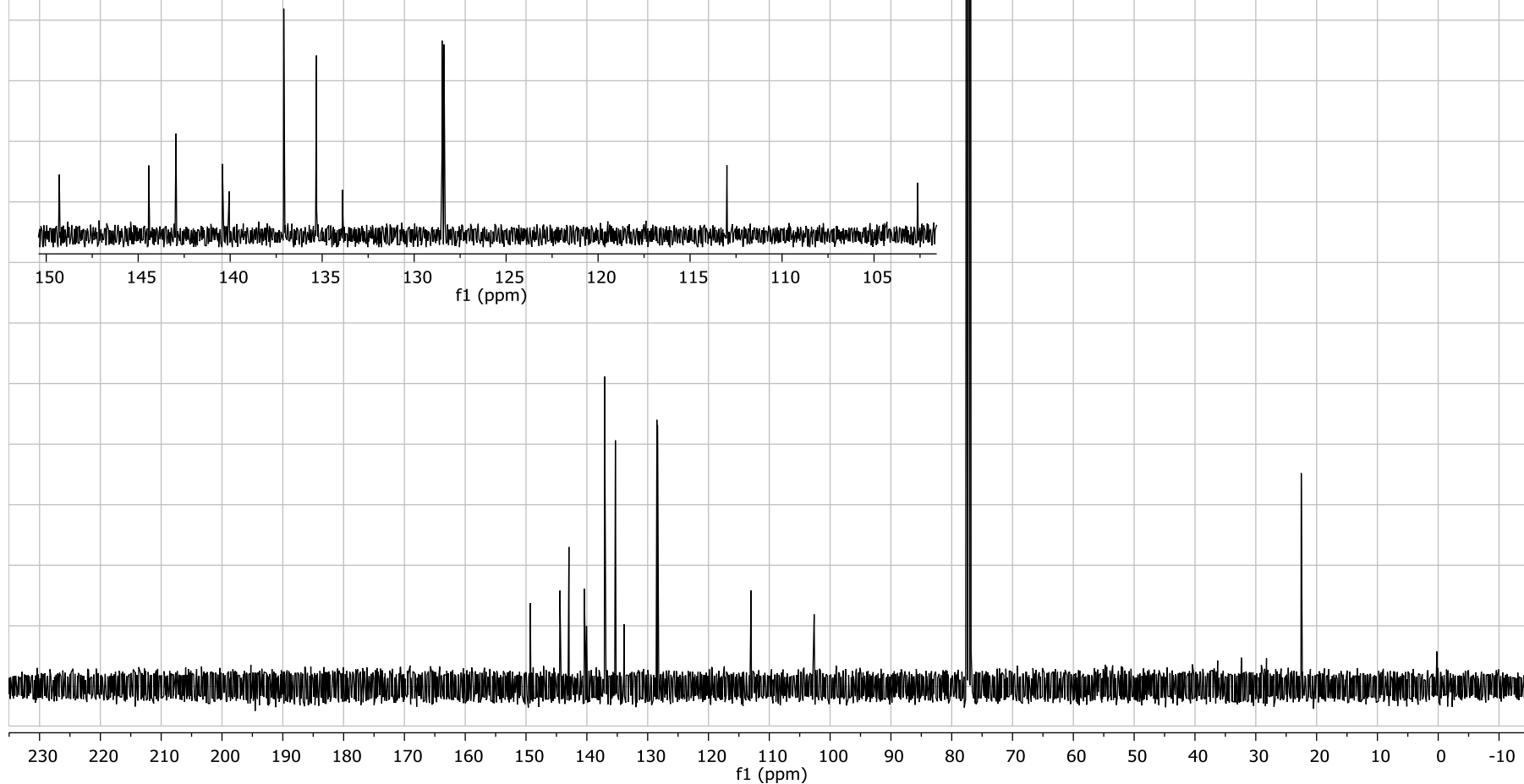
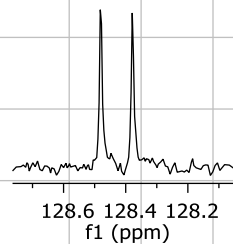


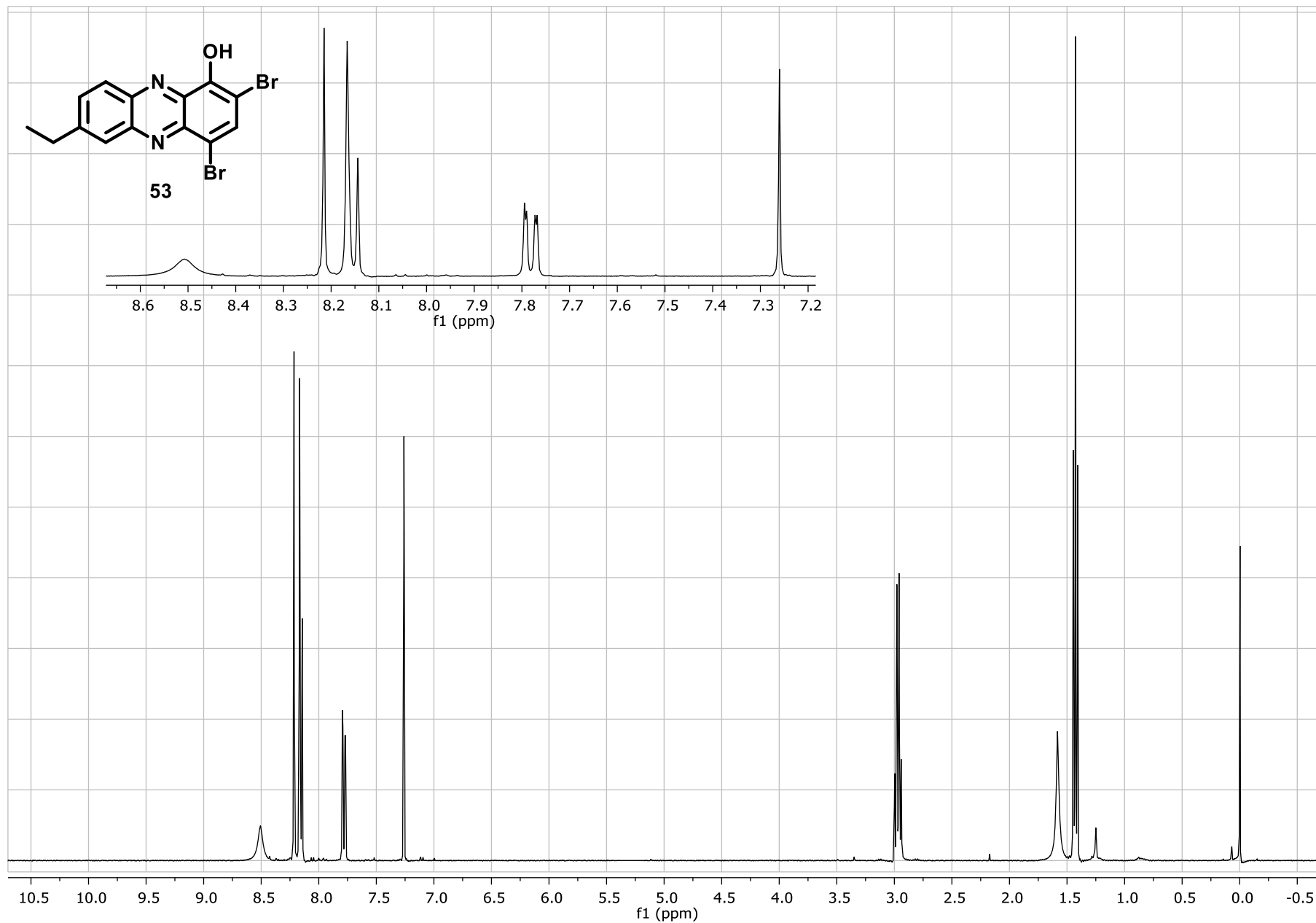


S138



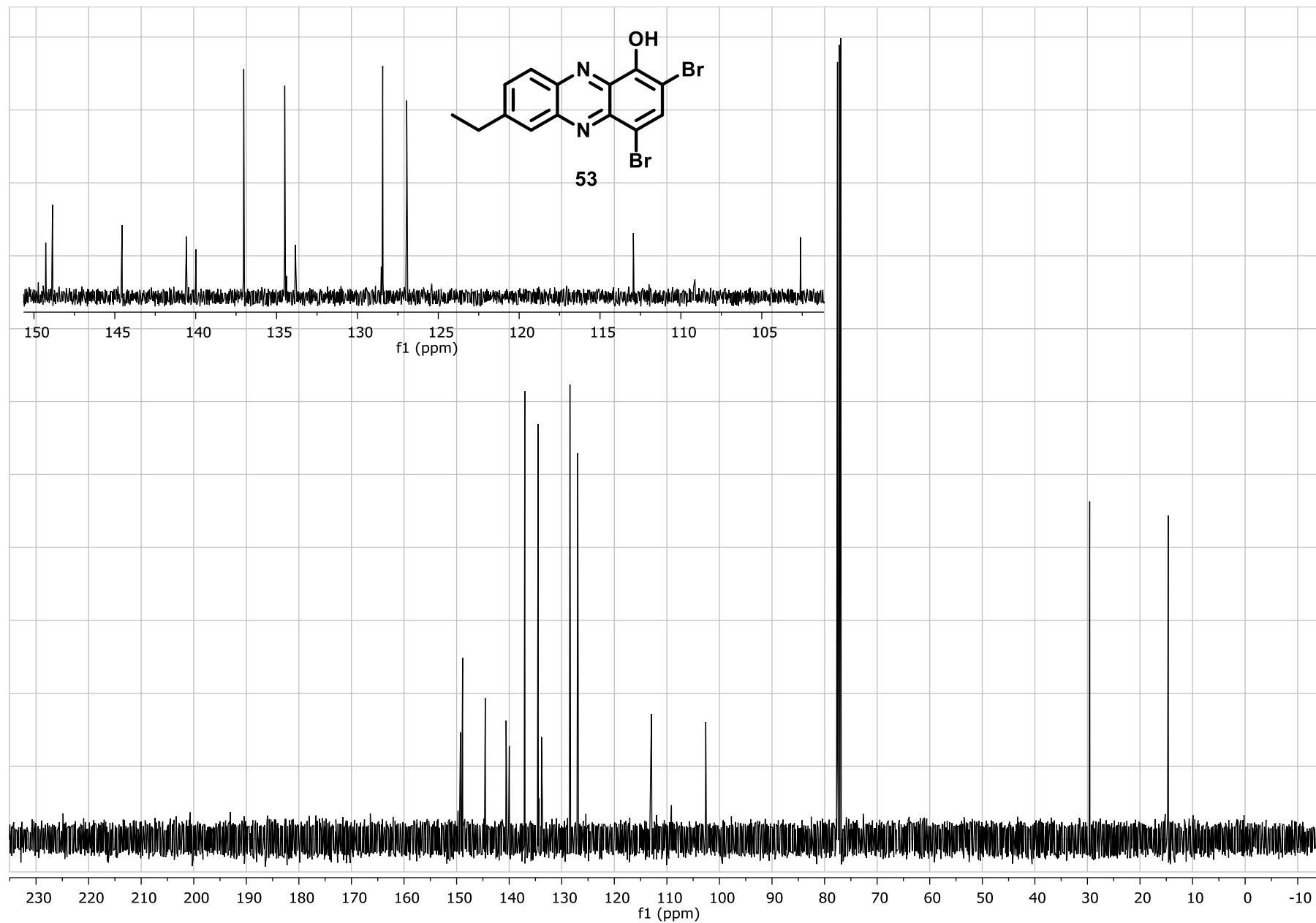
52

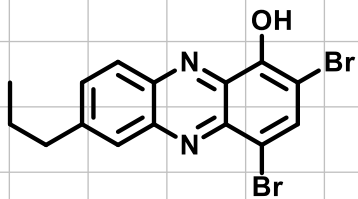




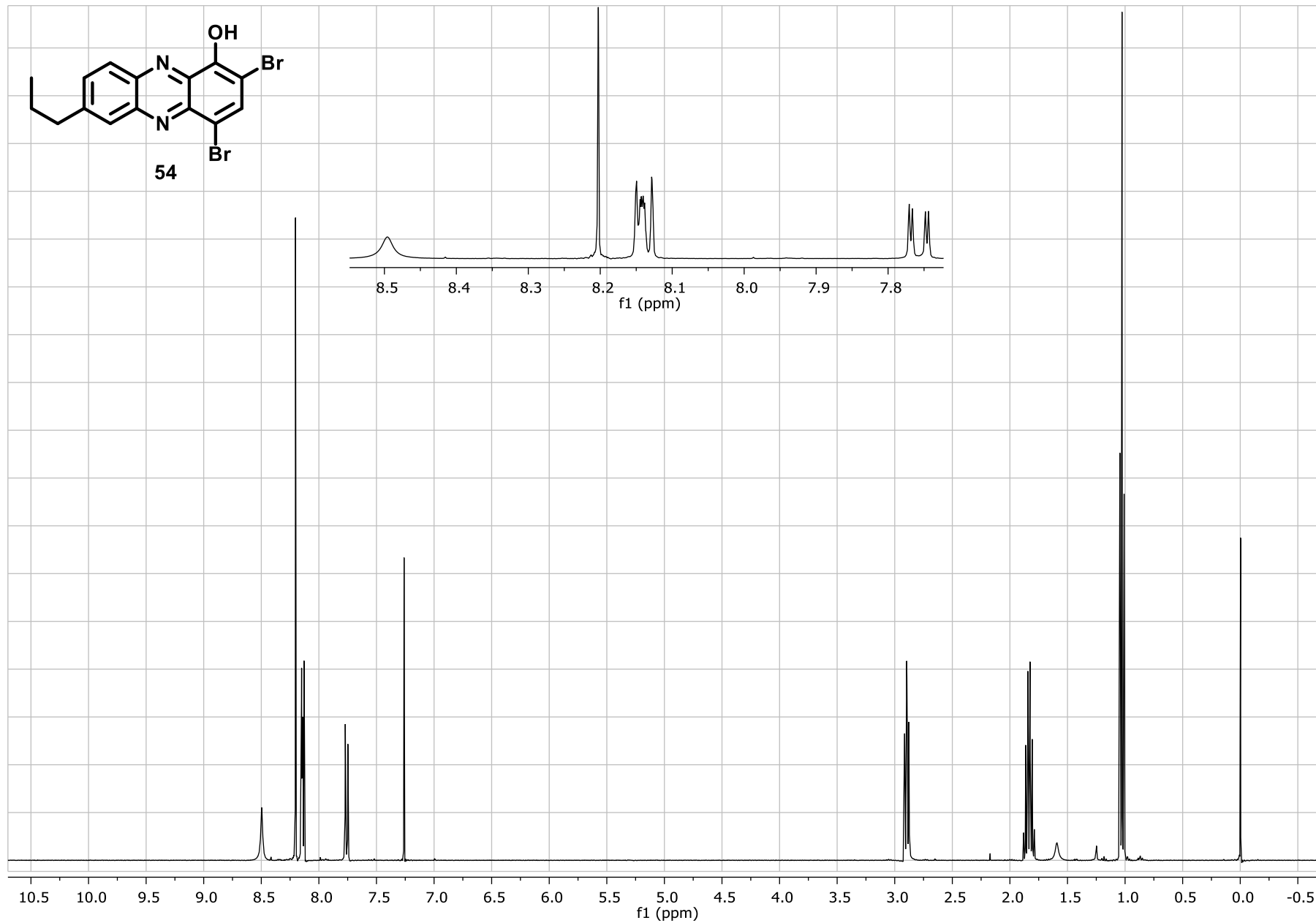
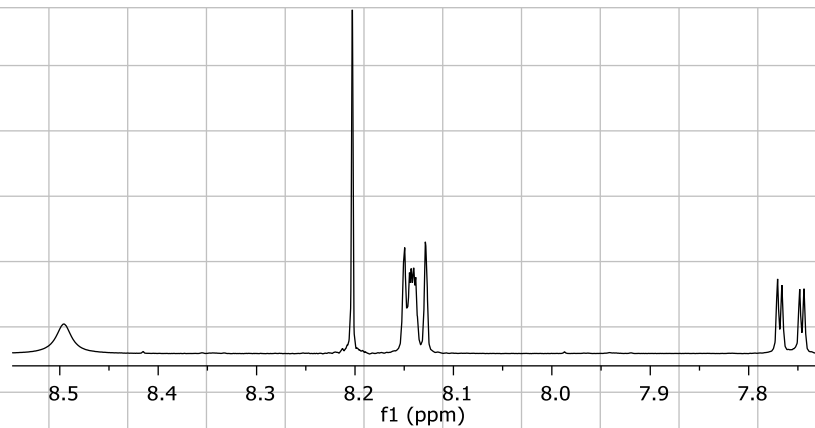
S140



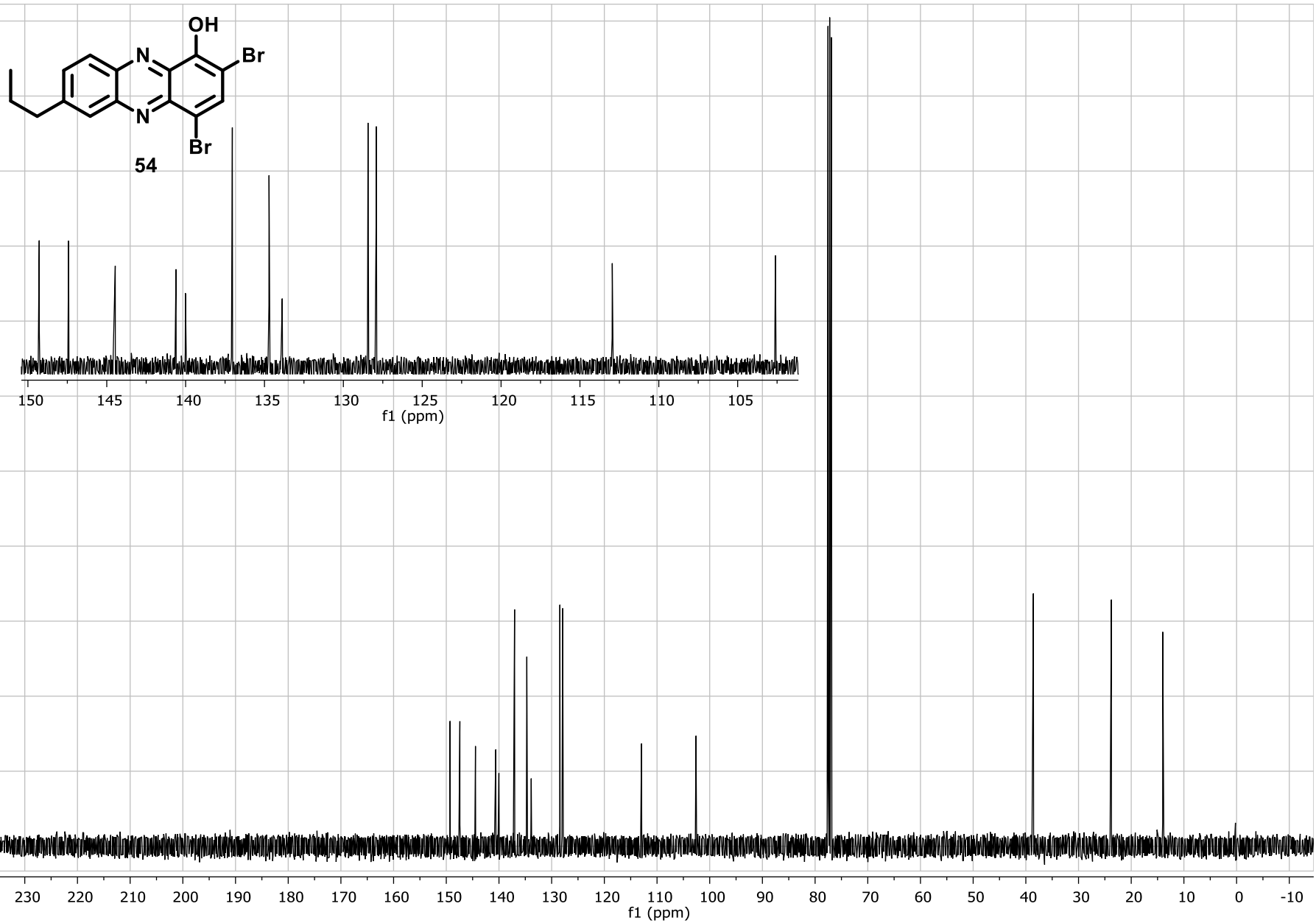


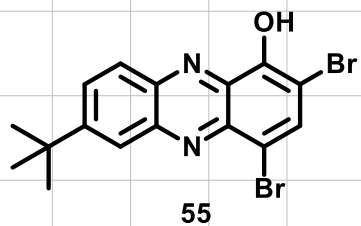


54



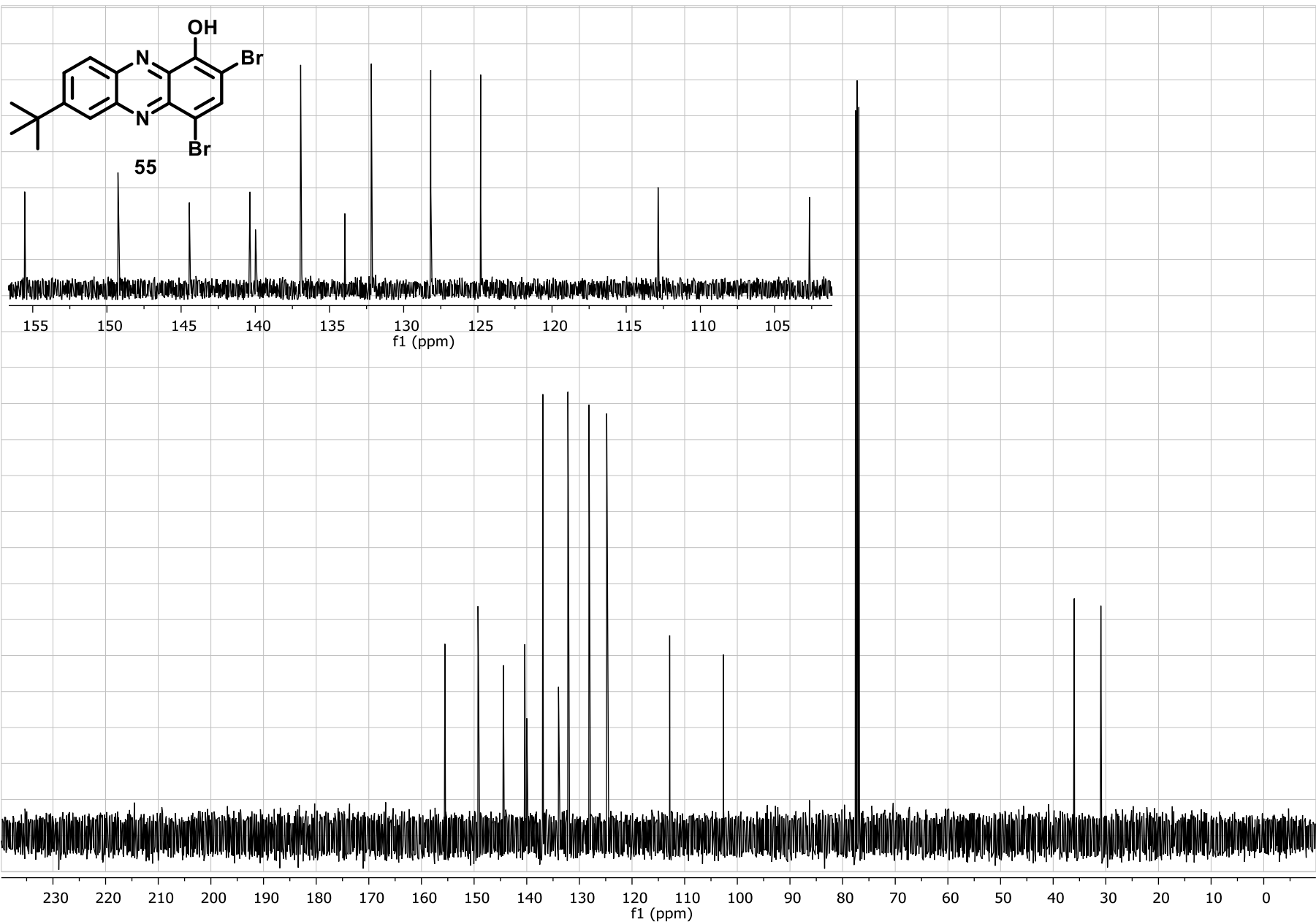
S142



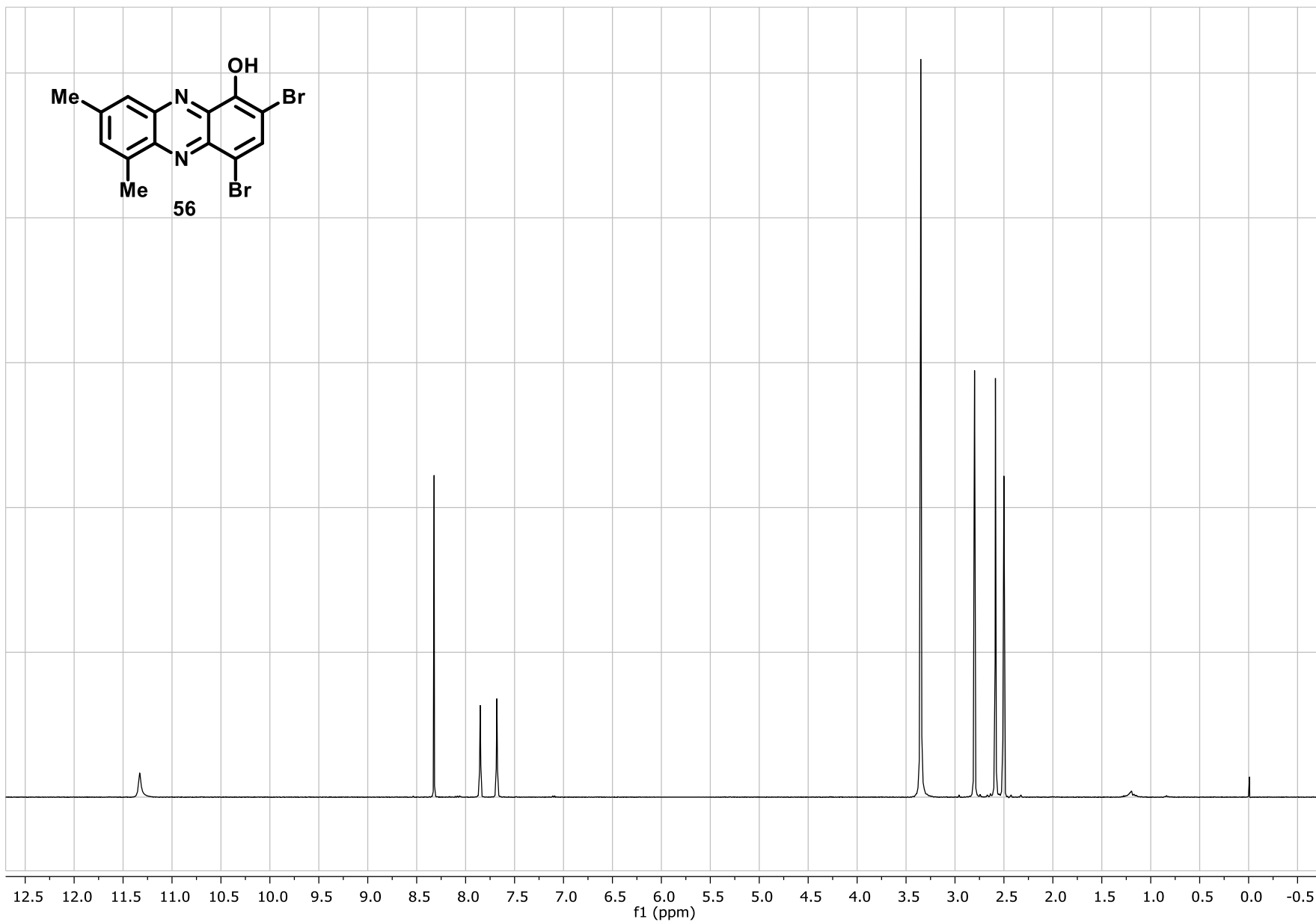
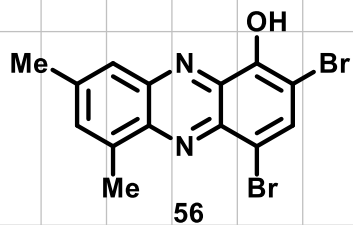


8.55 8.50 8.45 8.40 8.35 8.30 8.25 8.20 8.15 8.10 8.05 8.00  
f1 (ppm)

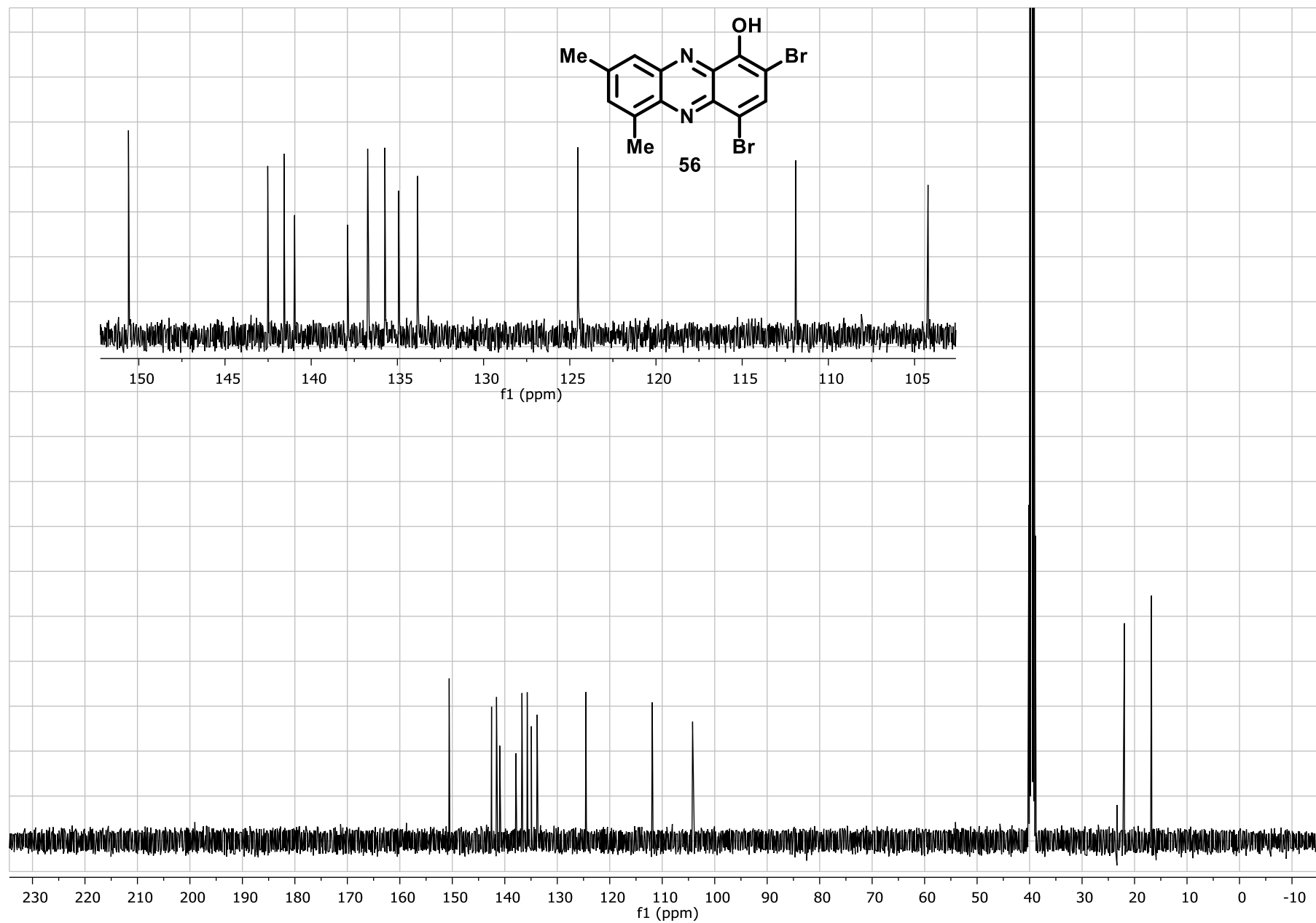
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5  
f1 (ppm)

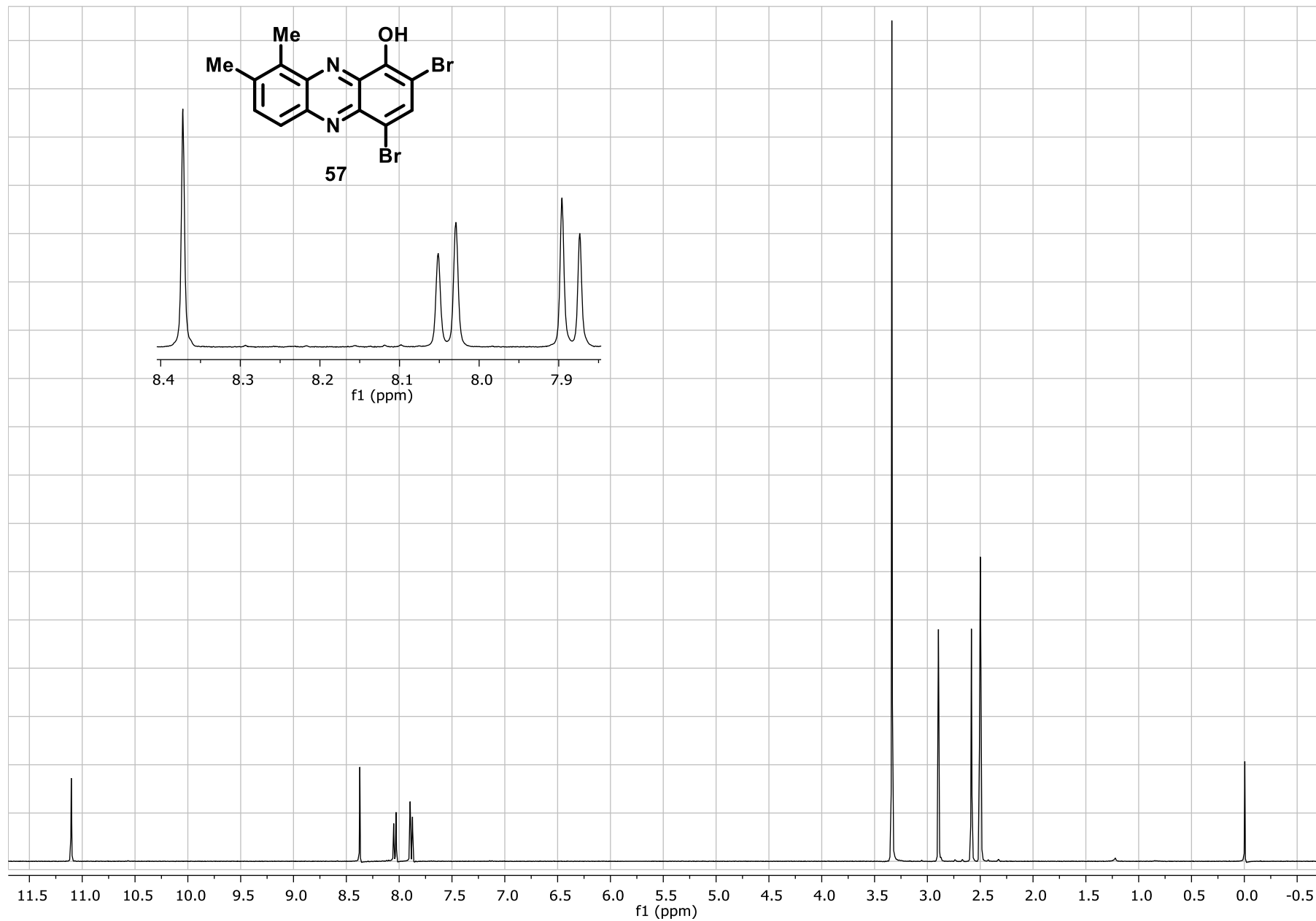


S145



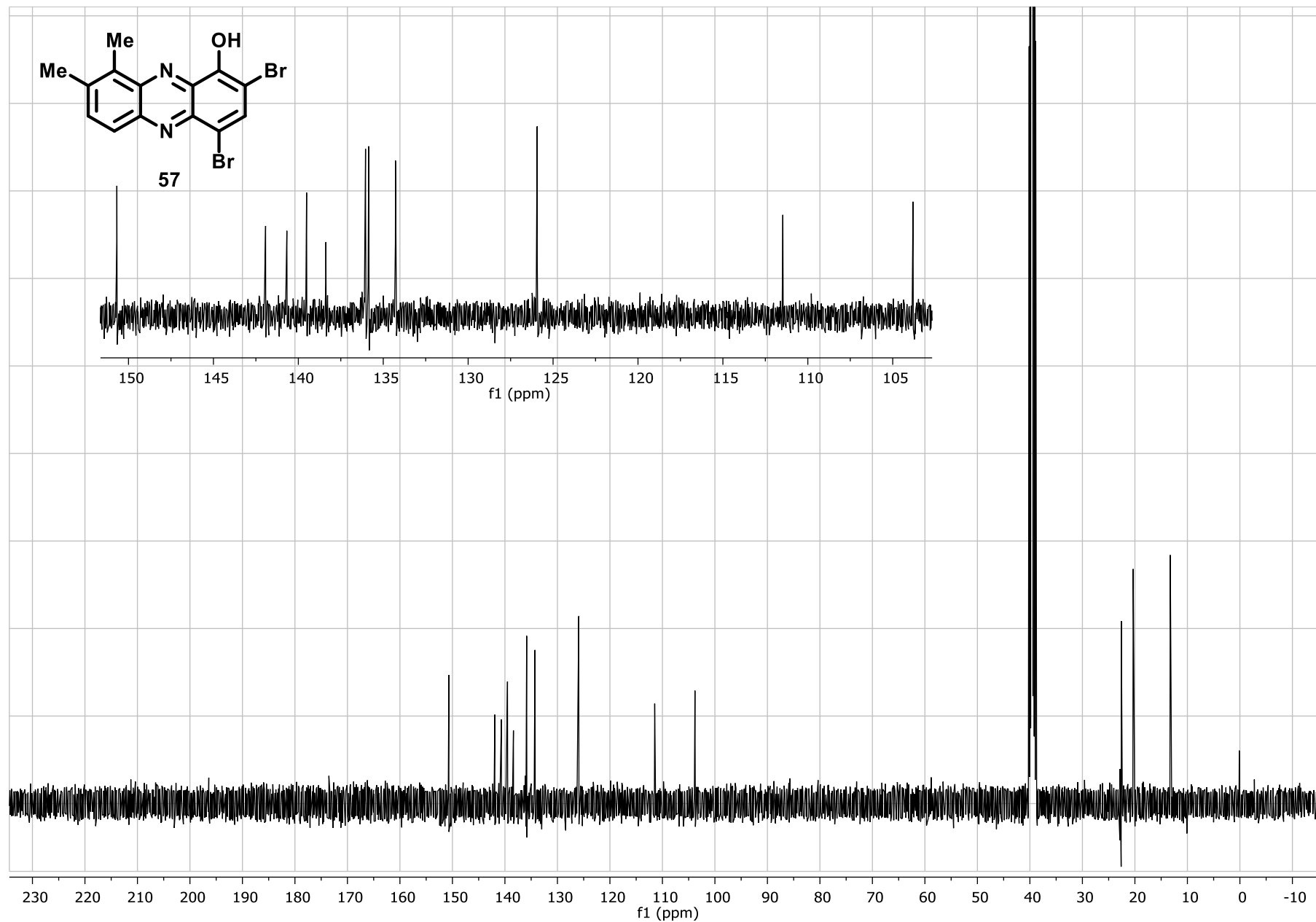
S146

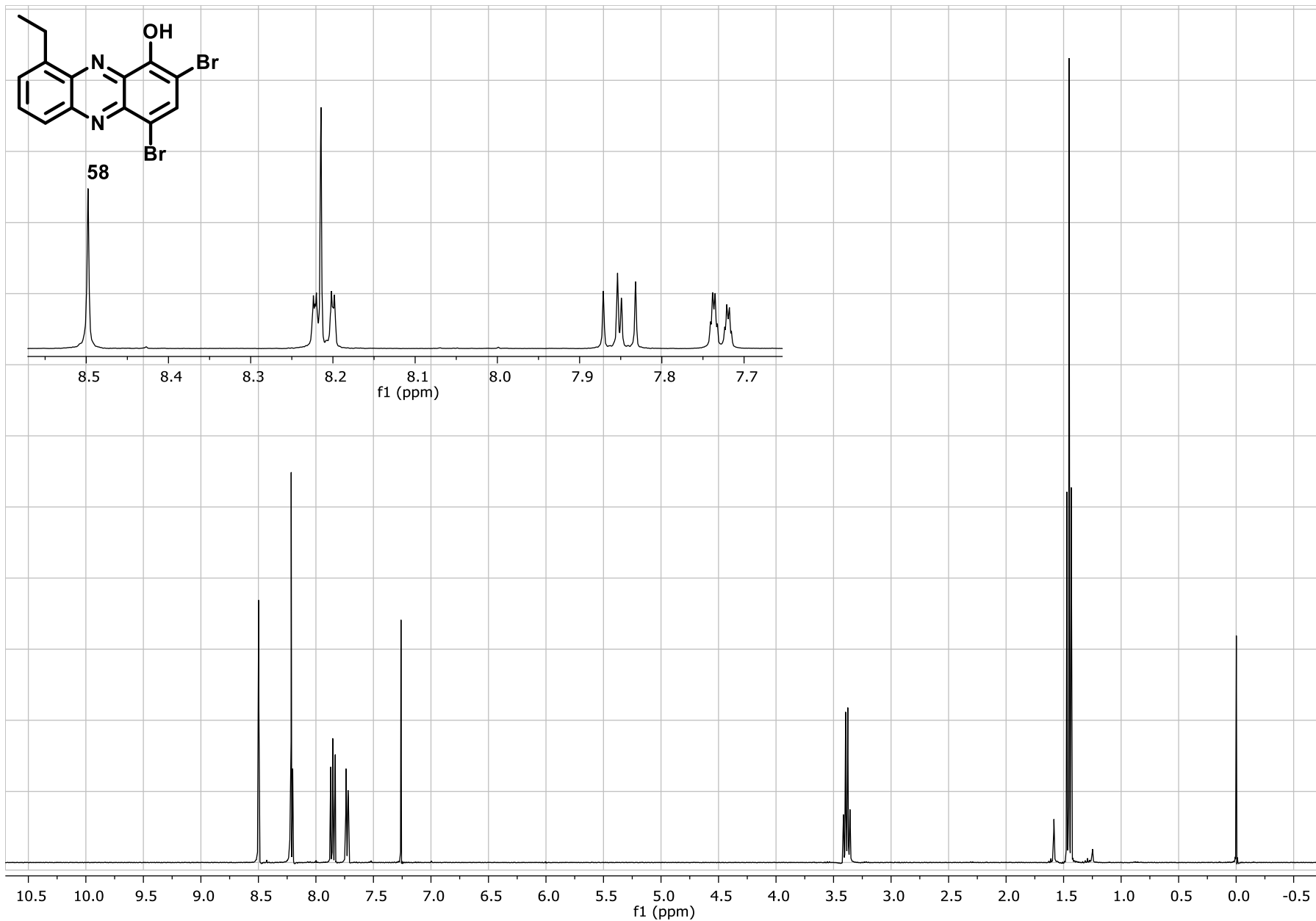




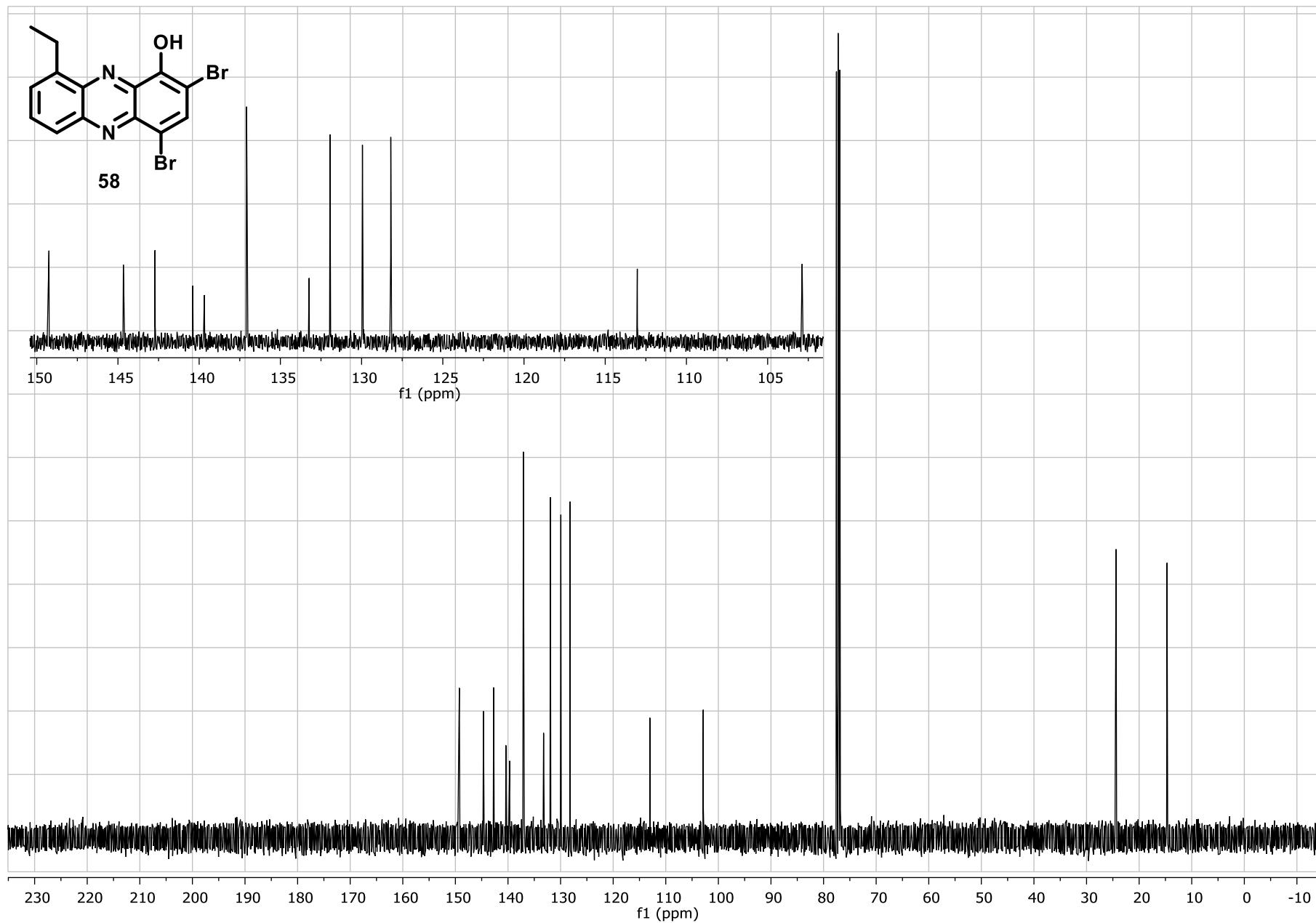
S148

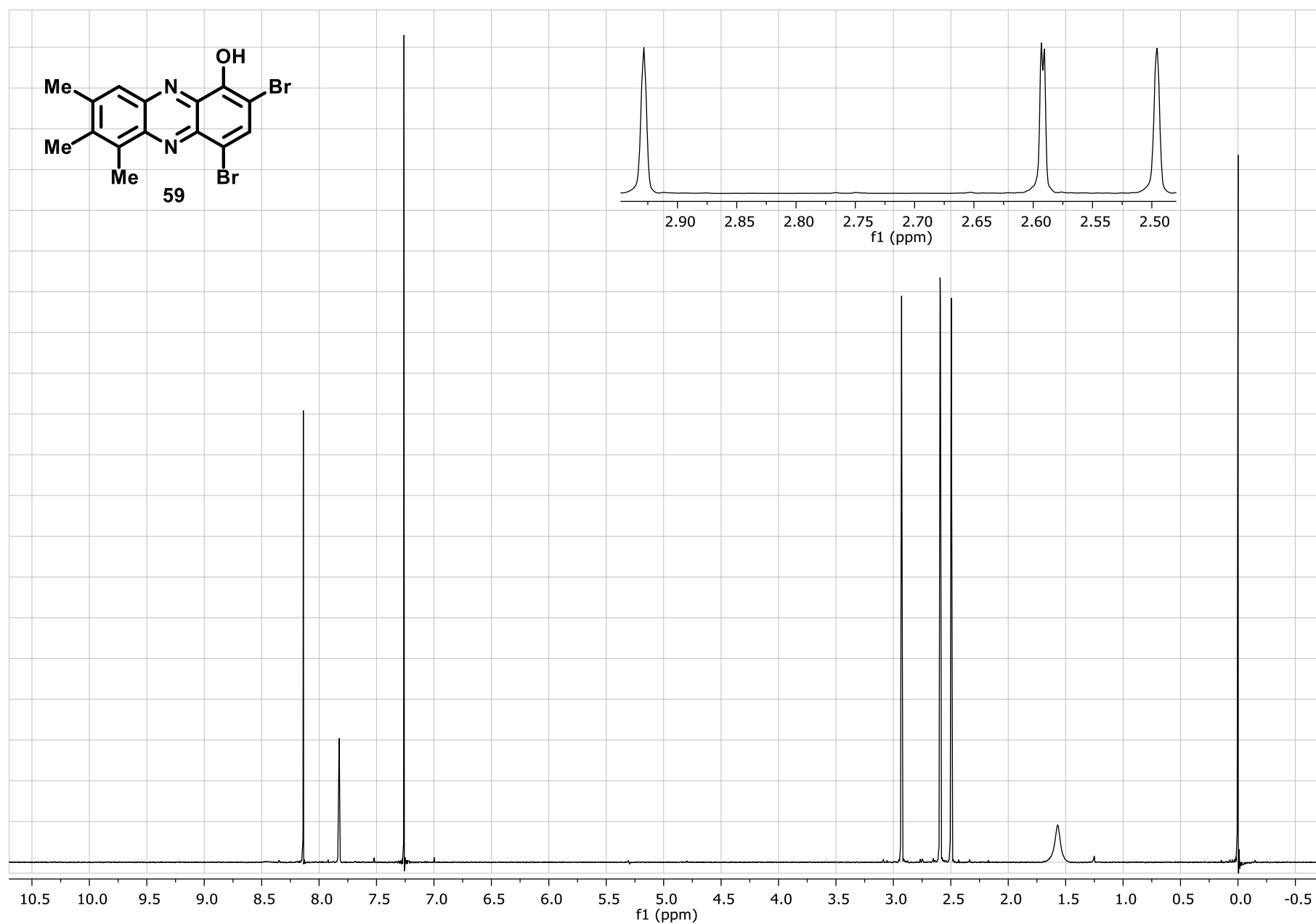
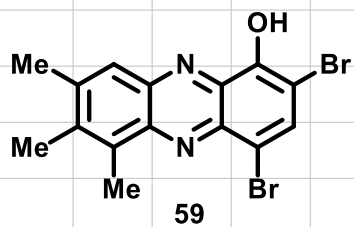




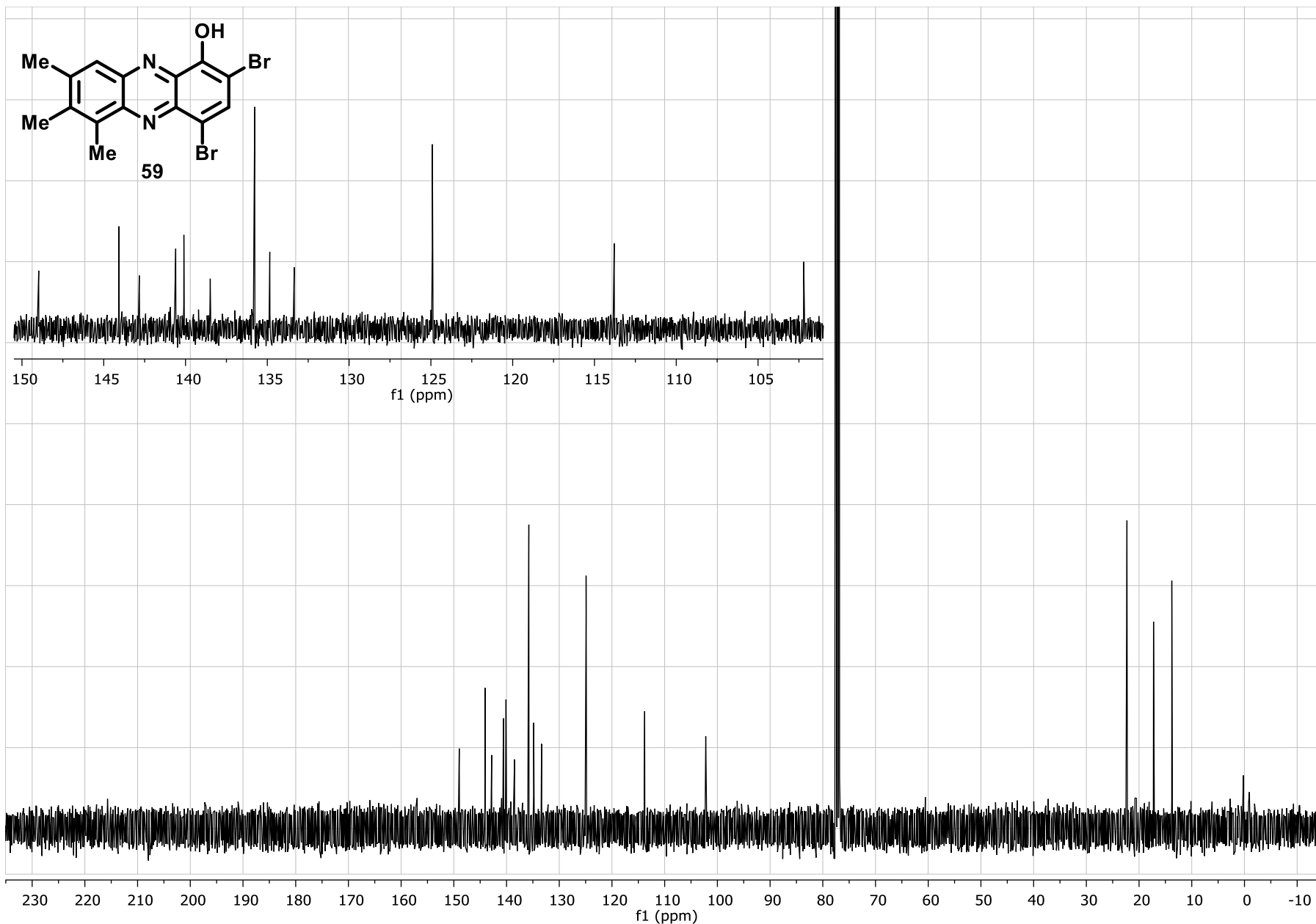


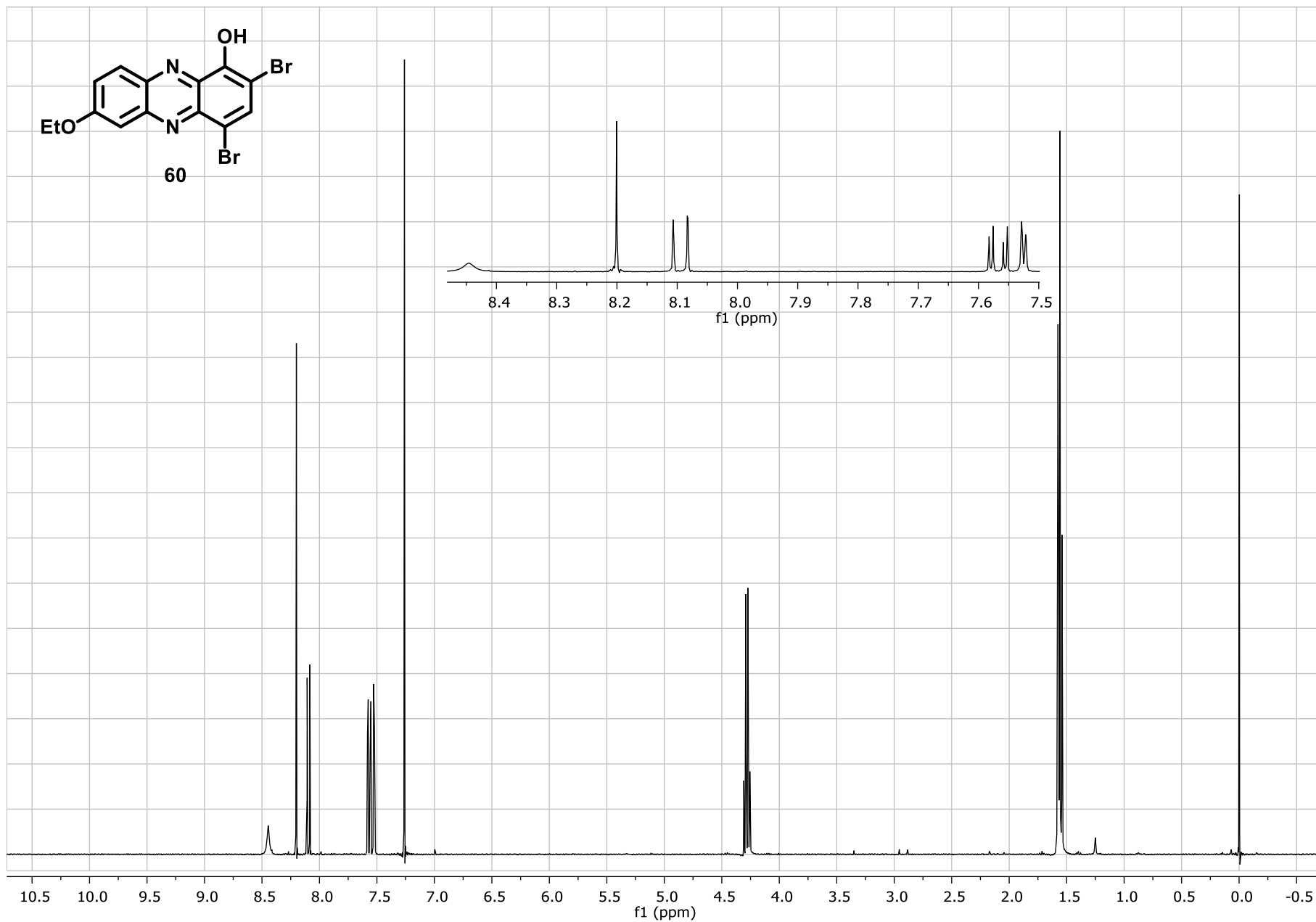
S150



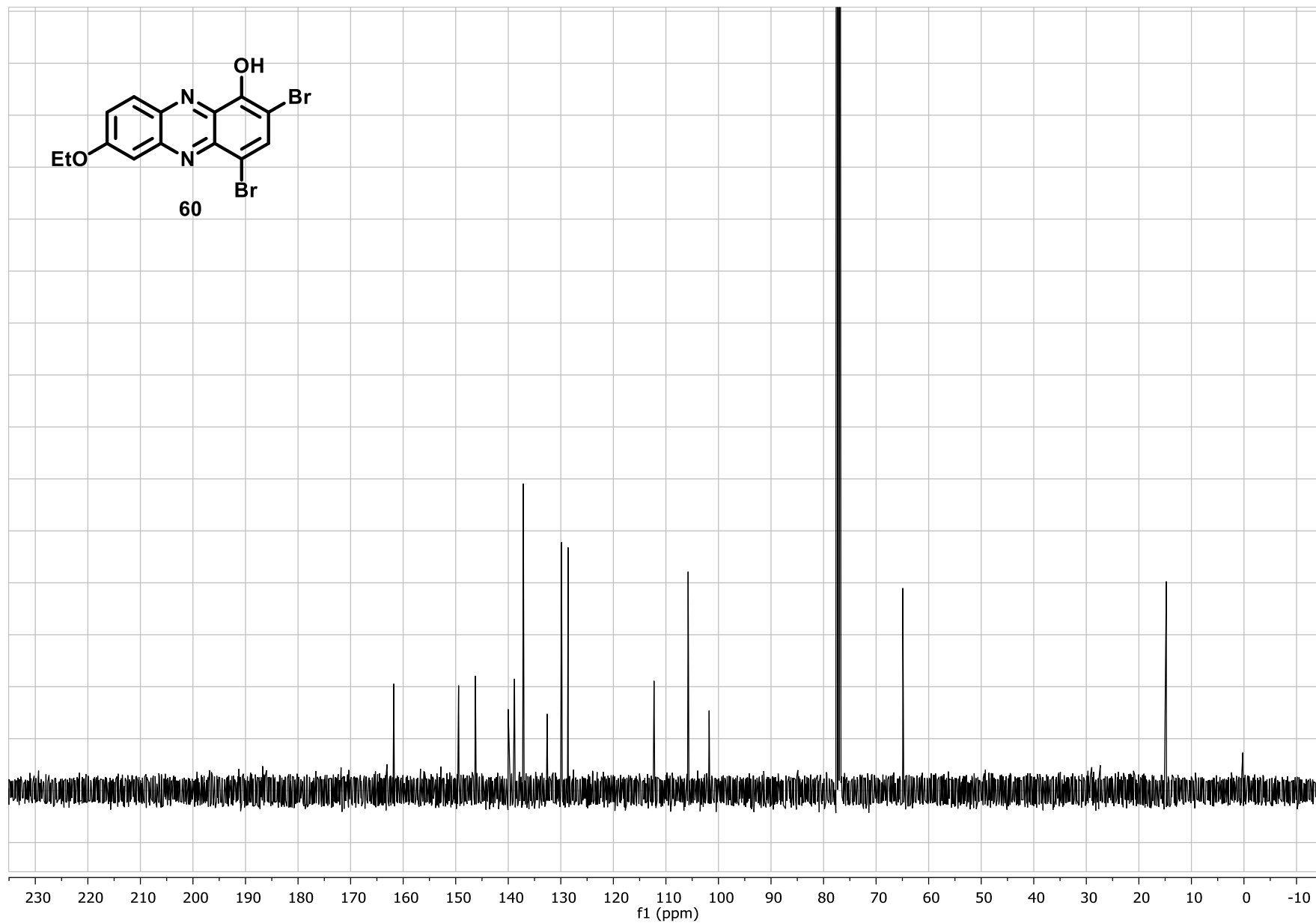
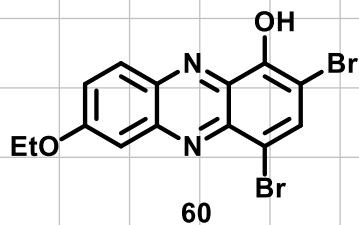


S152

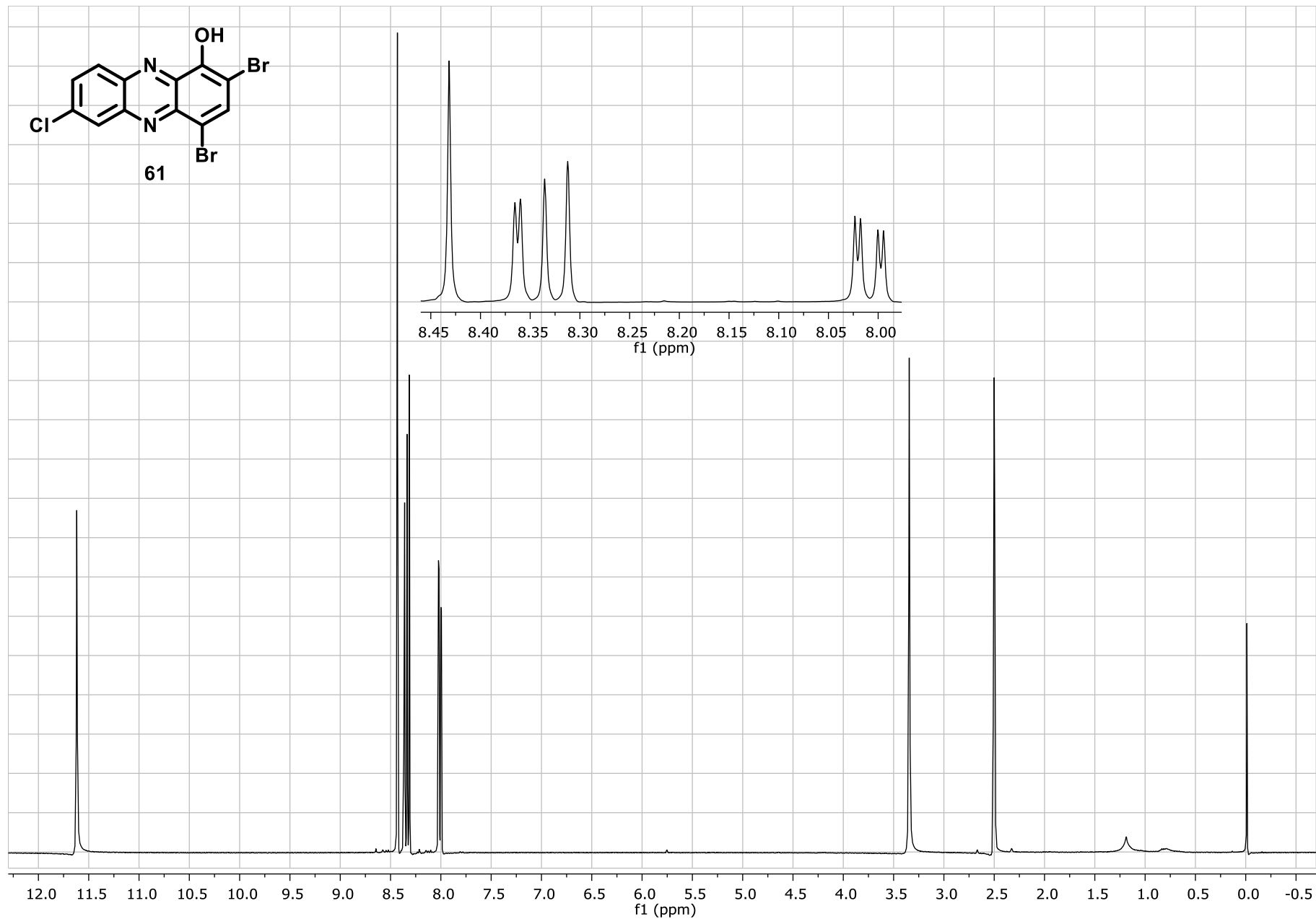
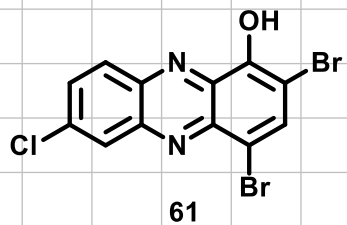




S154

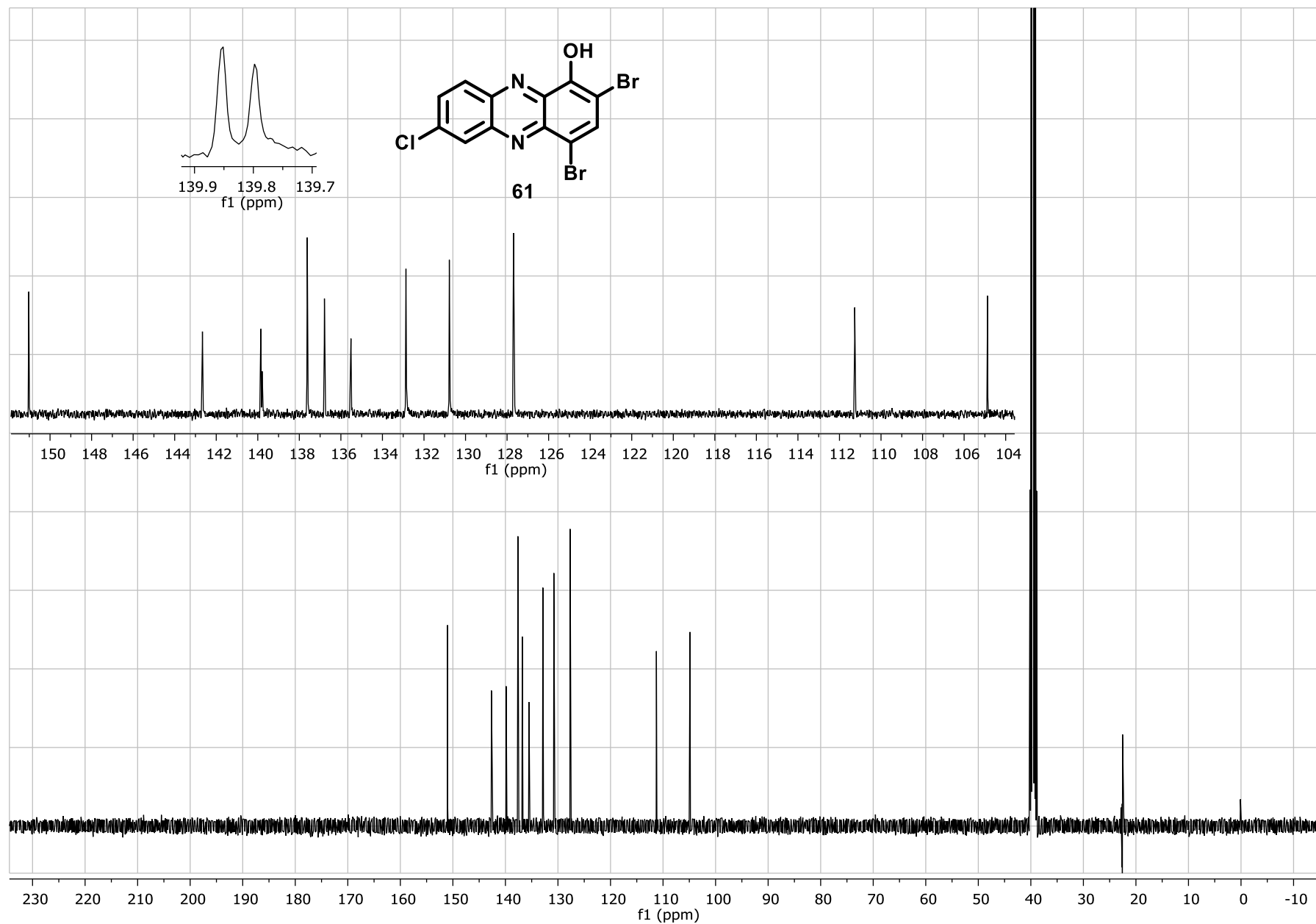


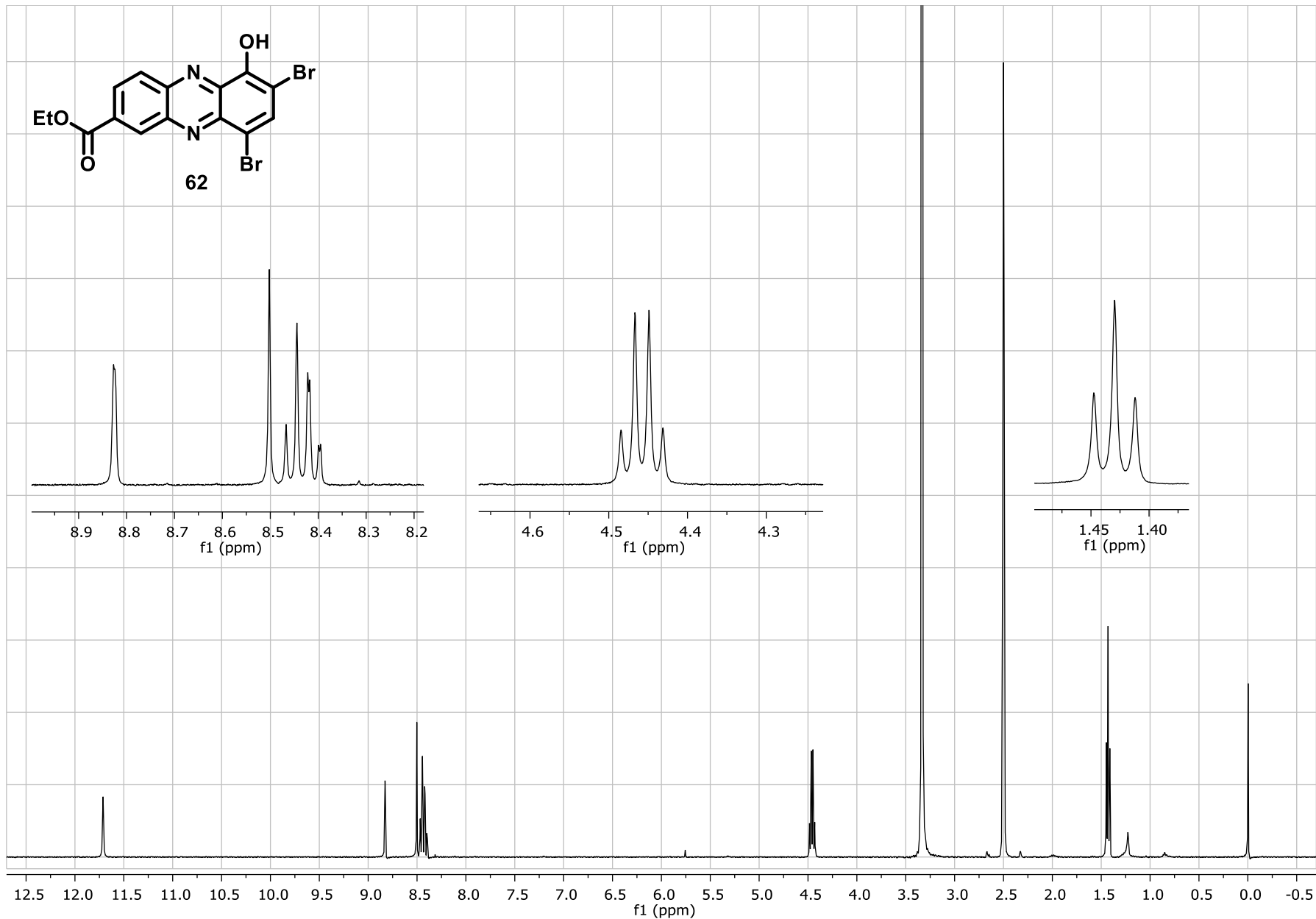
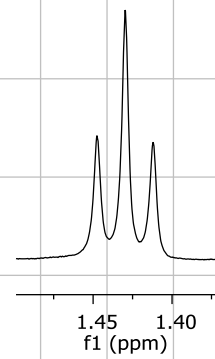
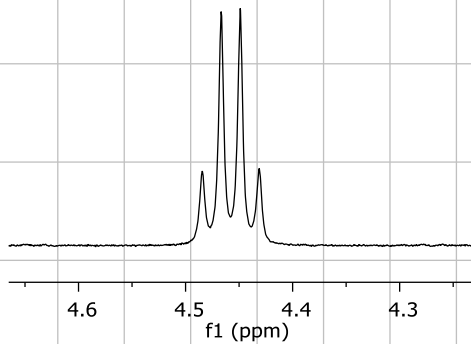
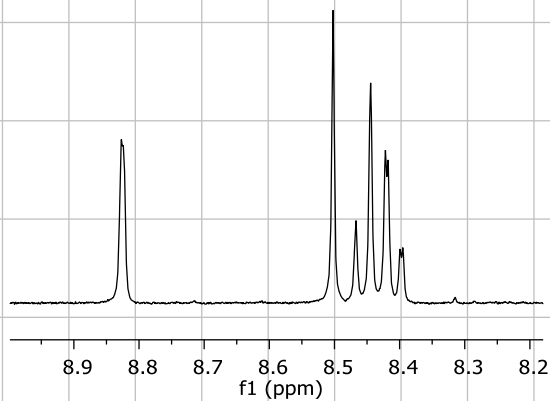
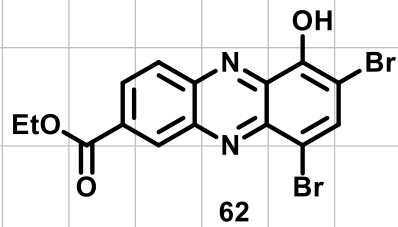
S155

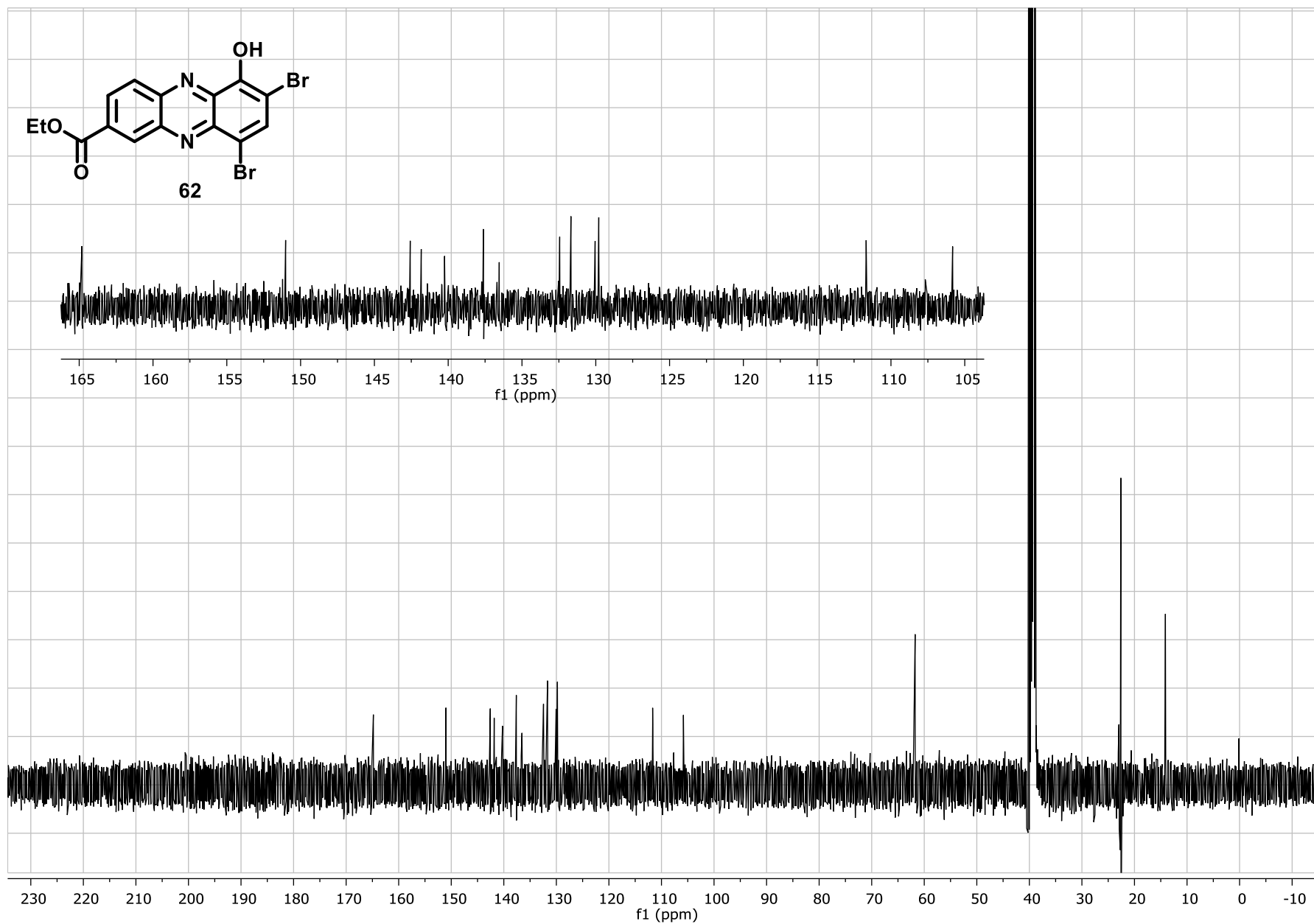
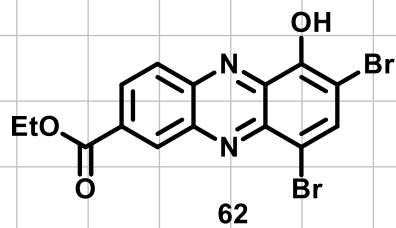


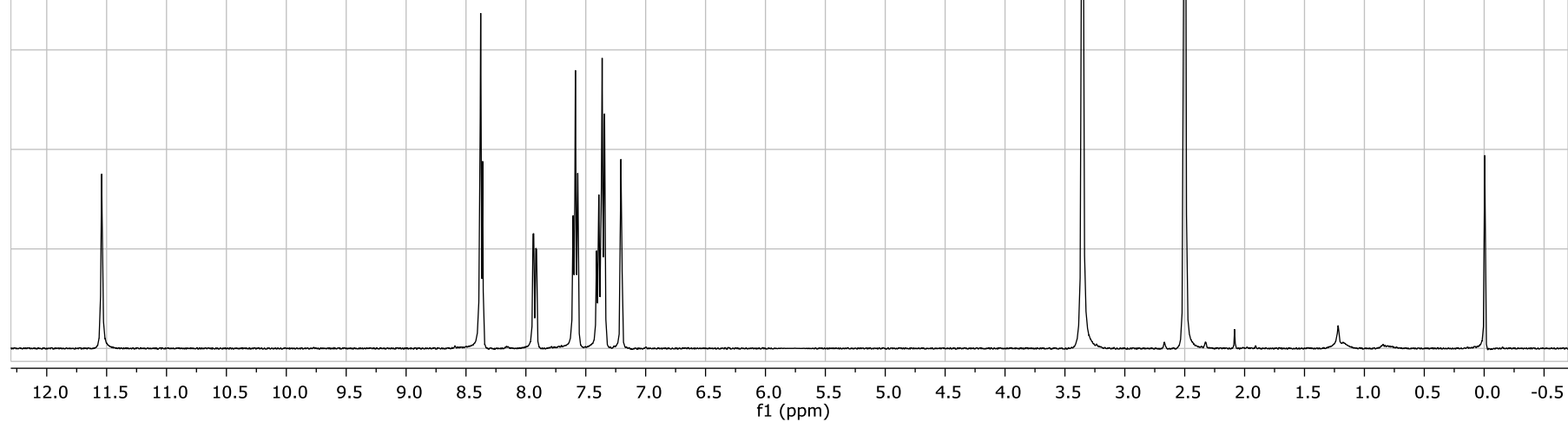
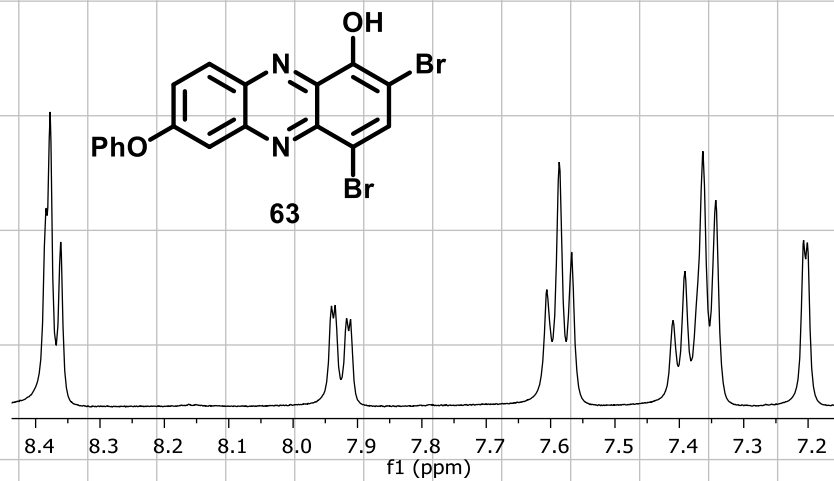
S156

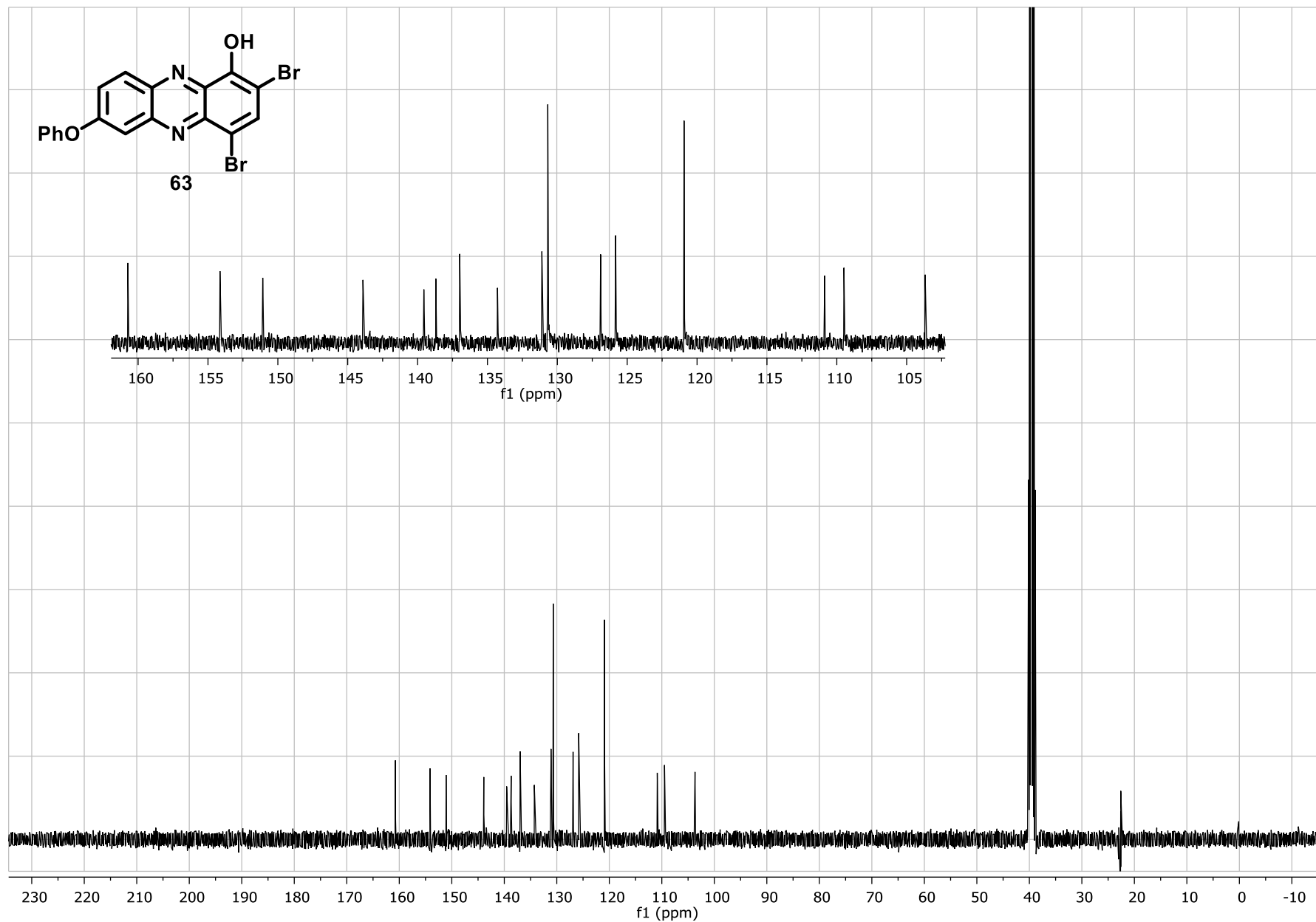
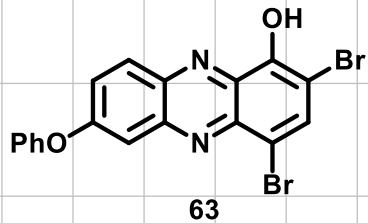


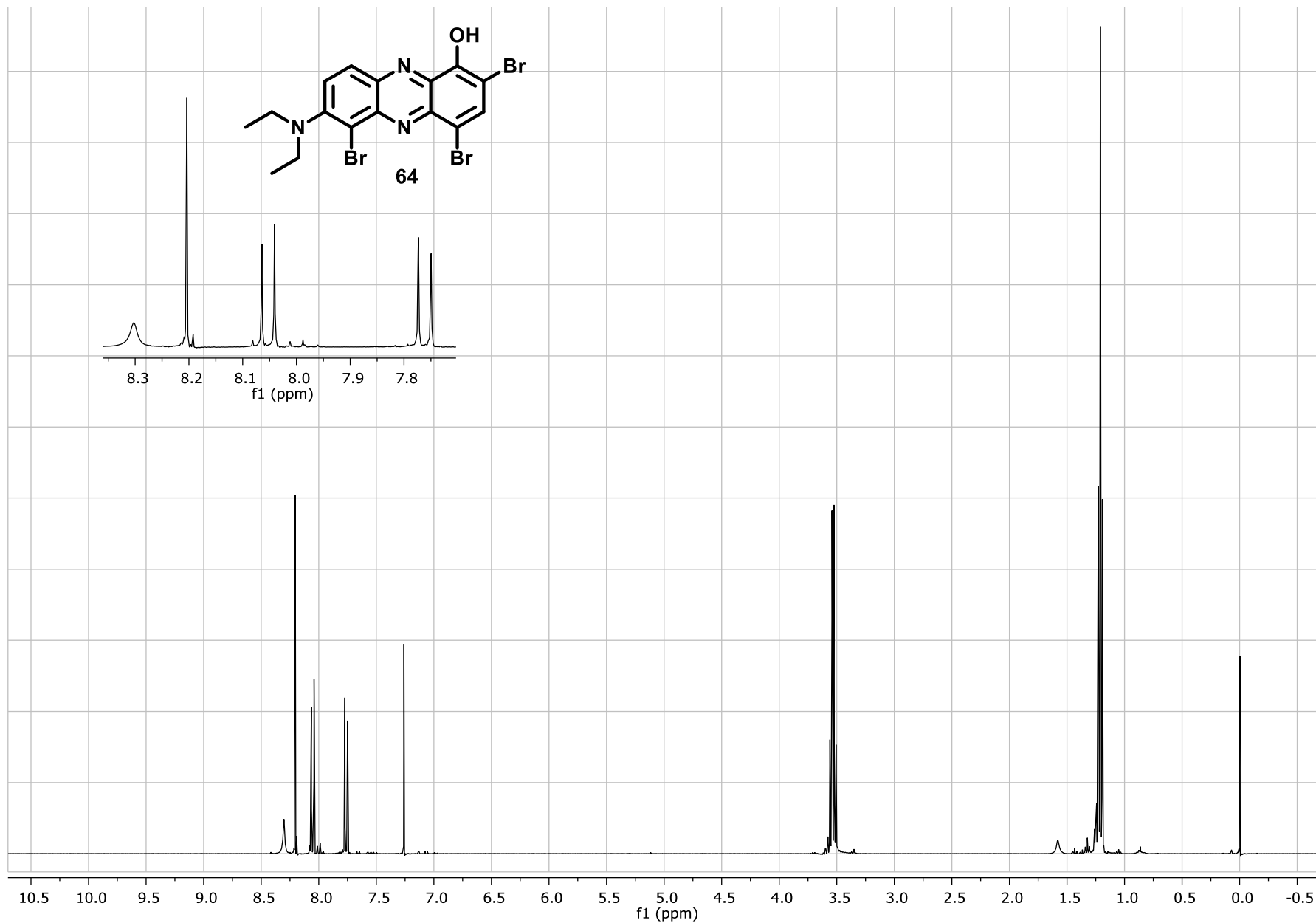


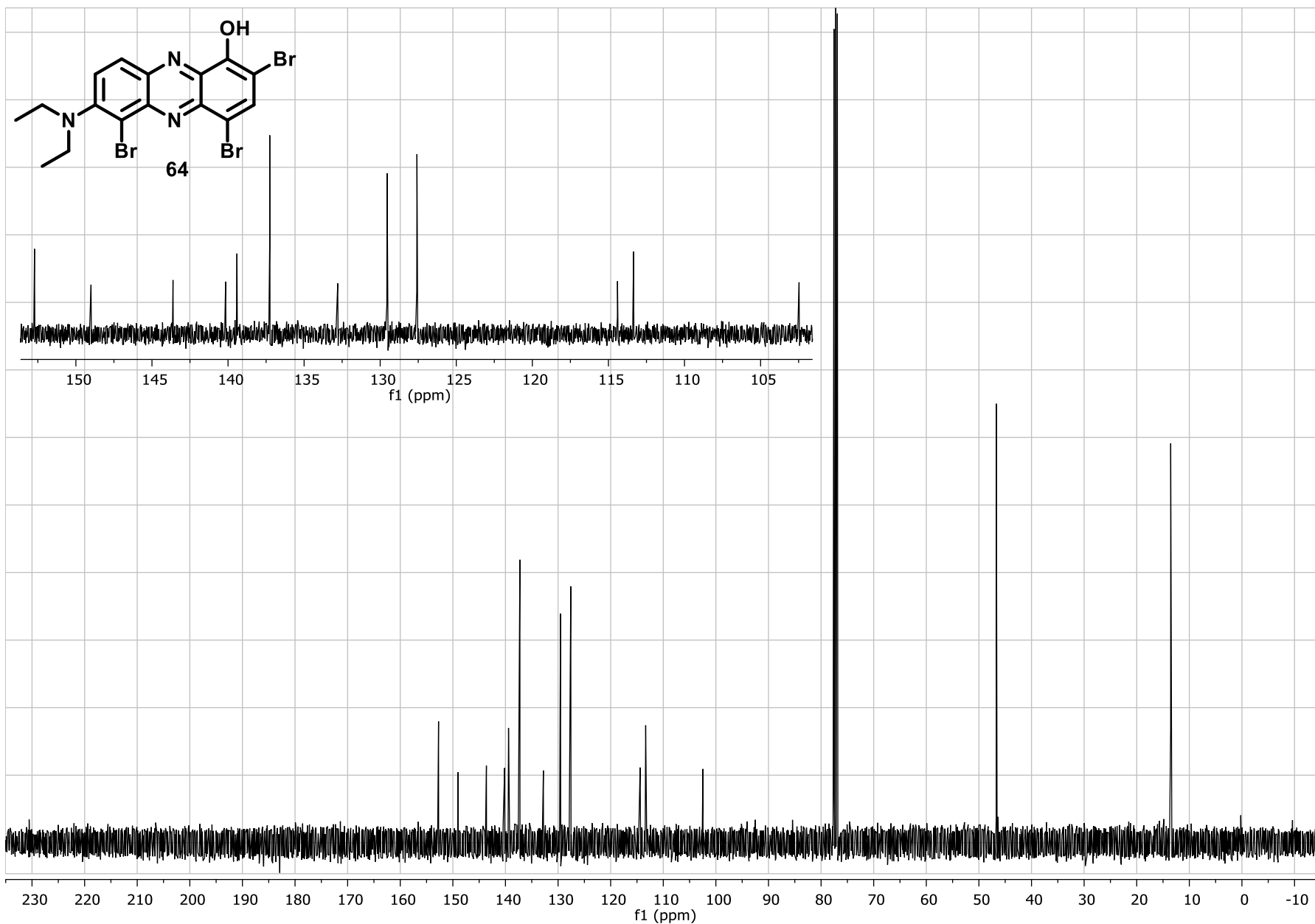


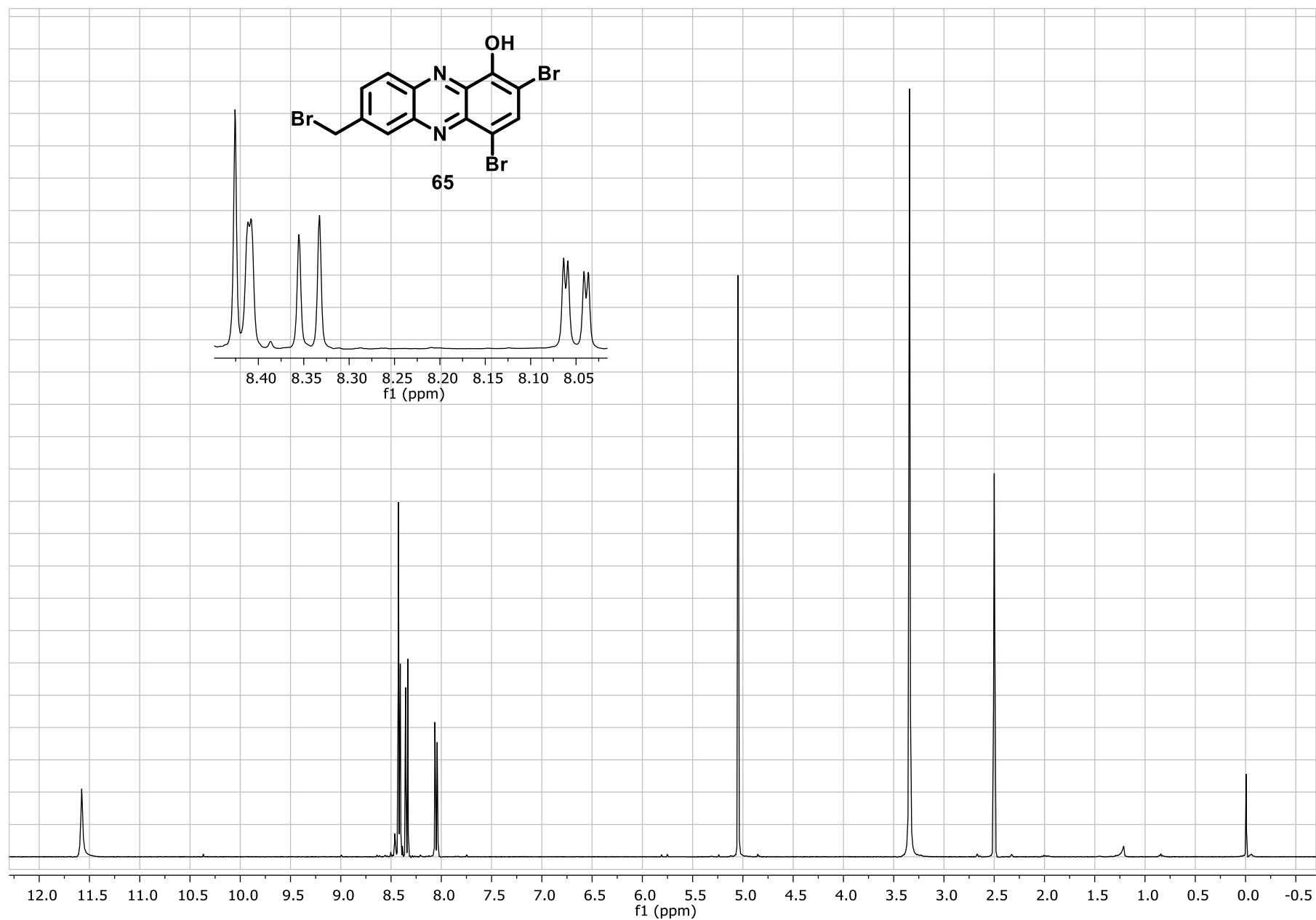
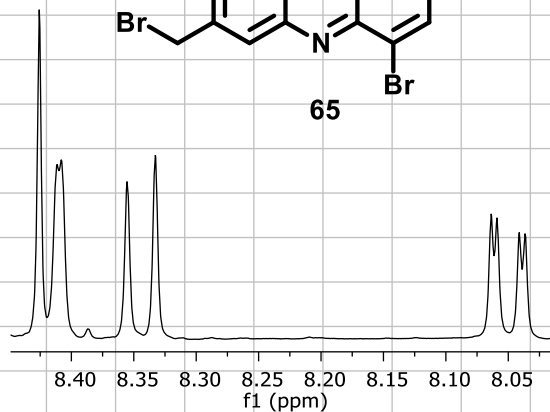
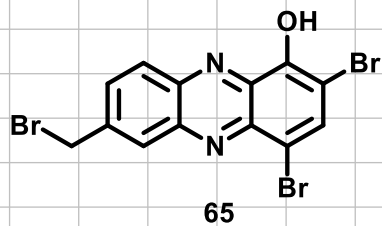




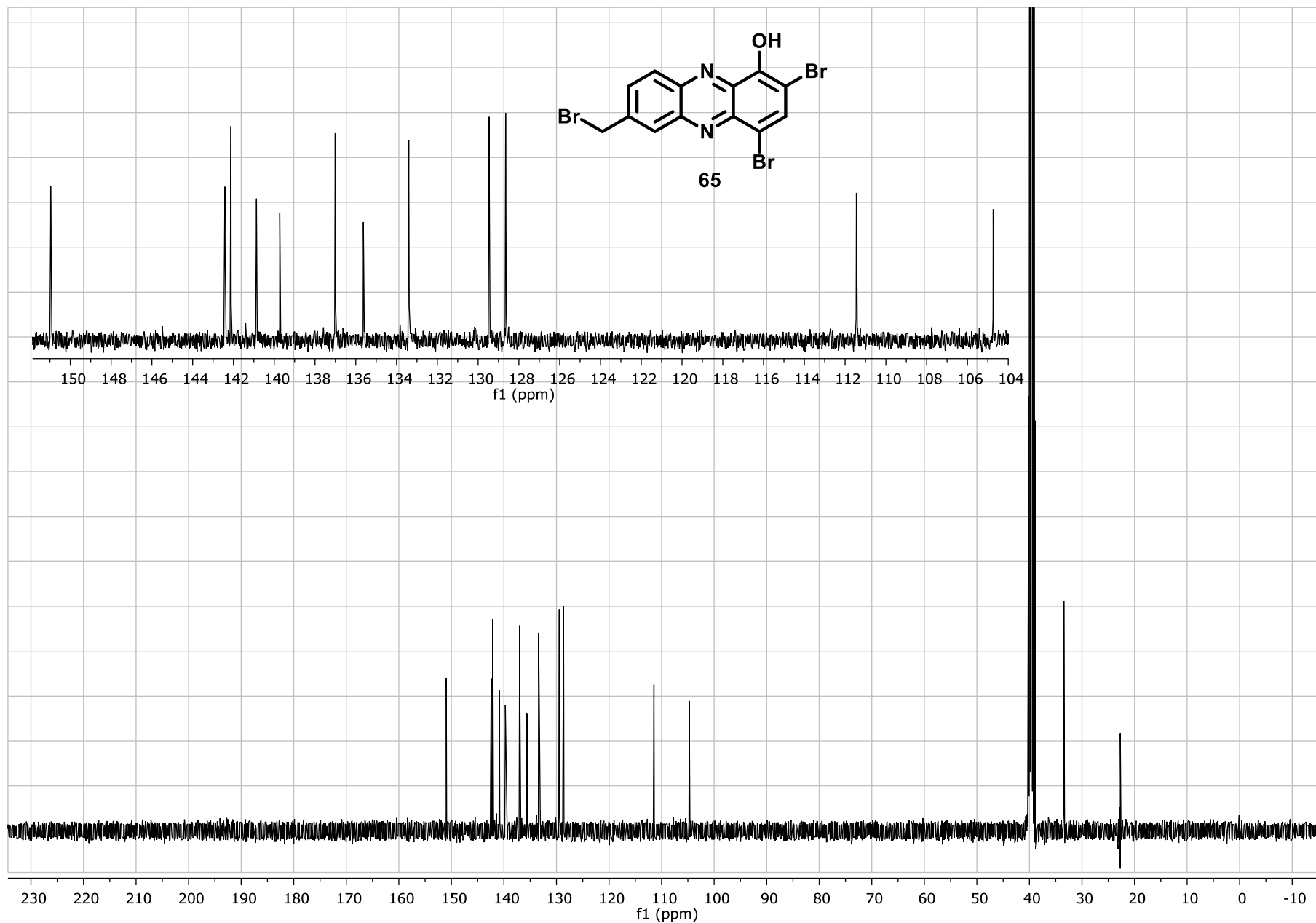


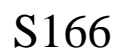
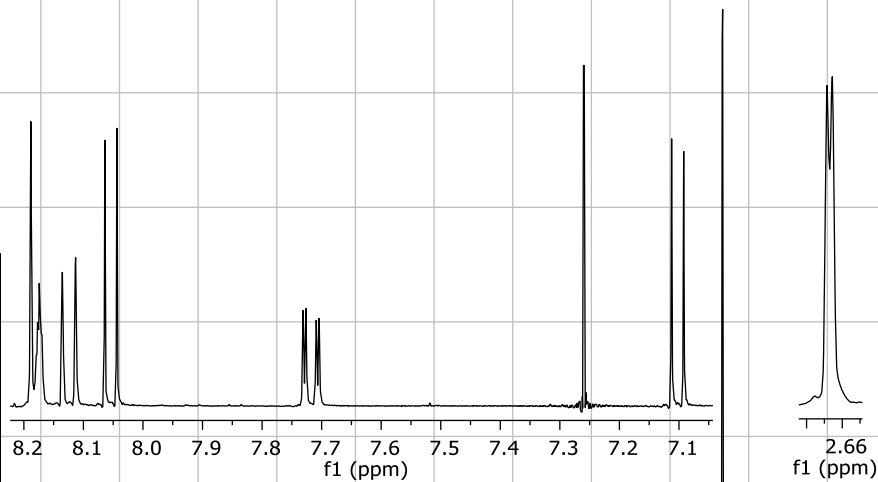


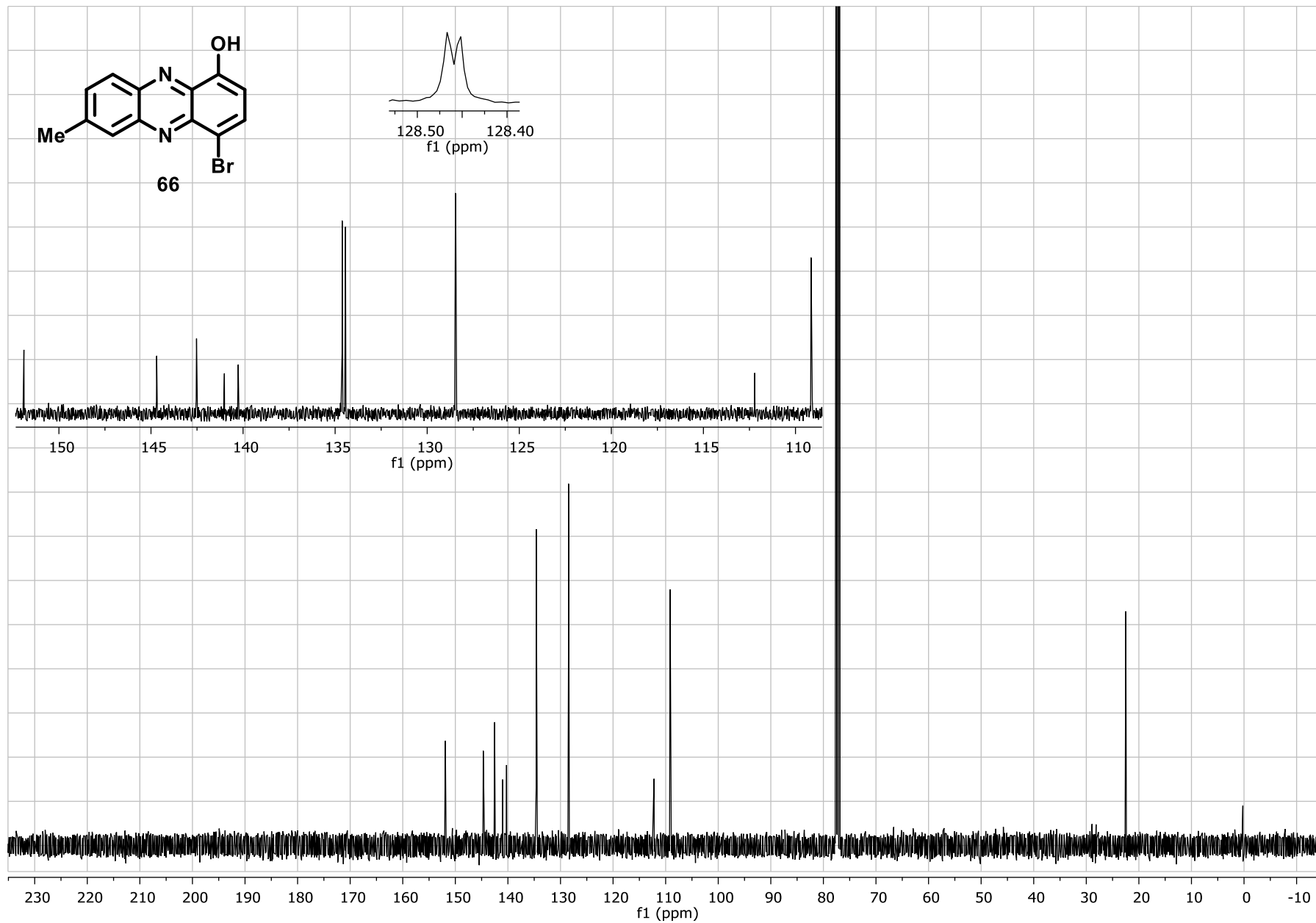


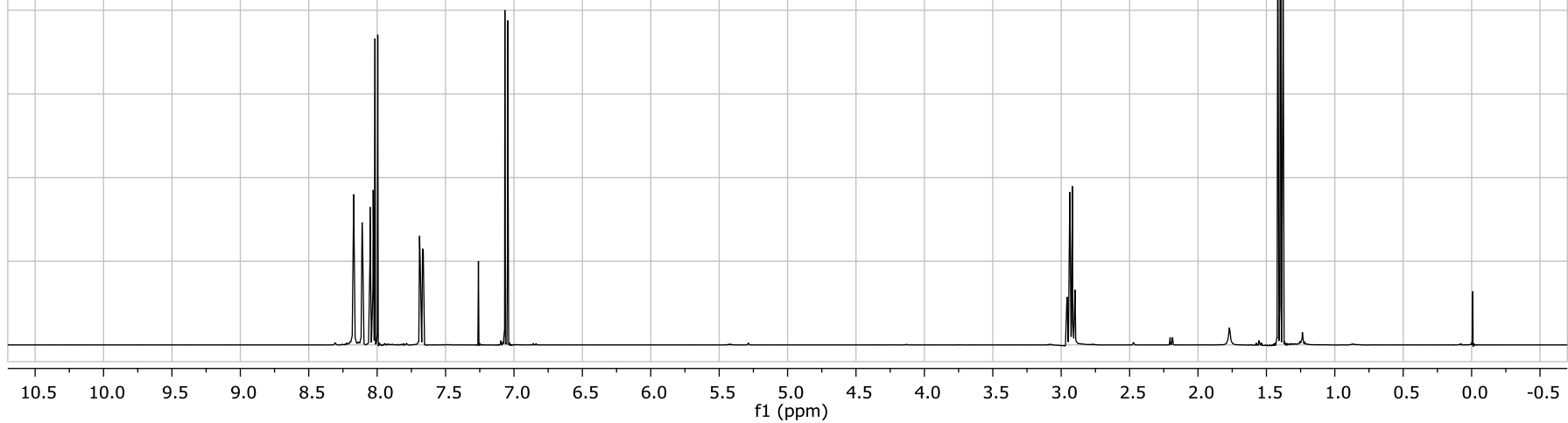
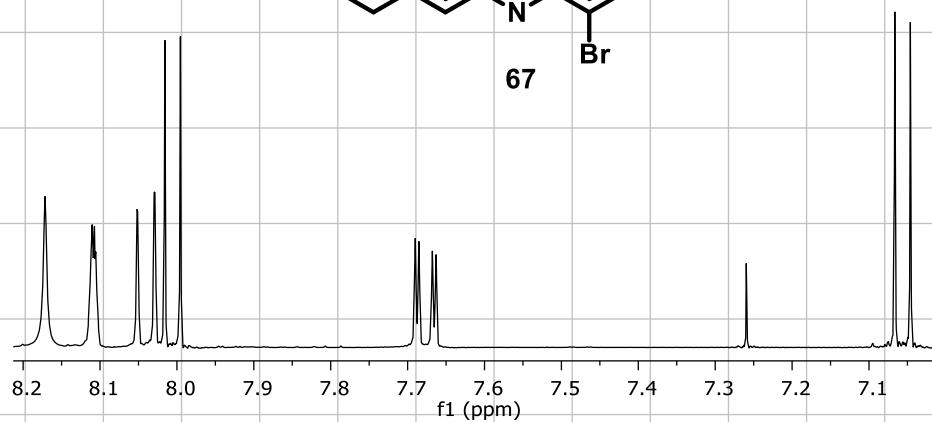
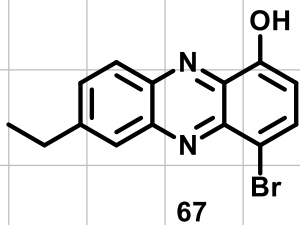


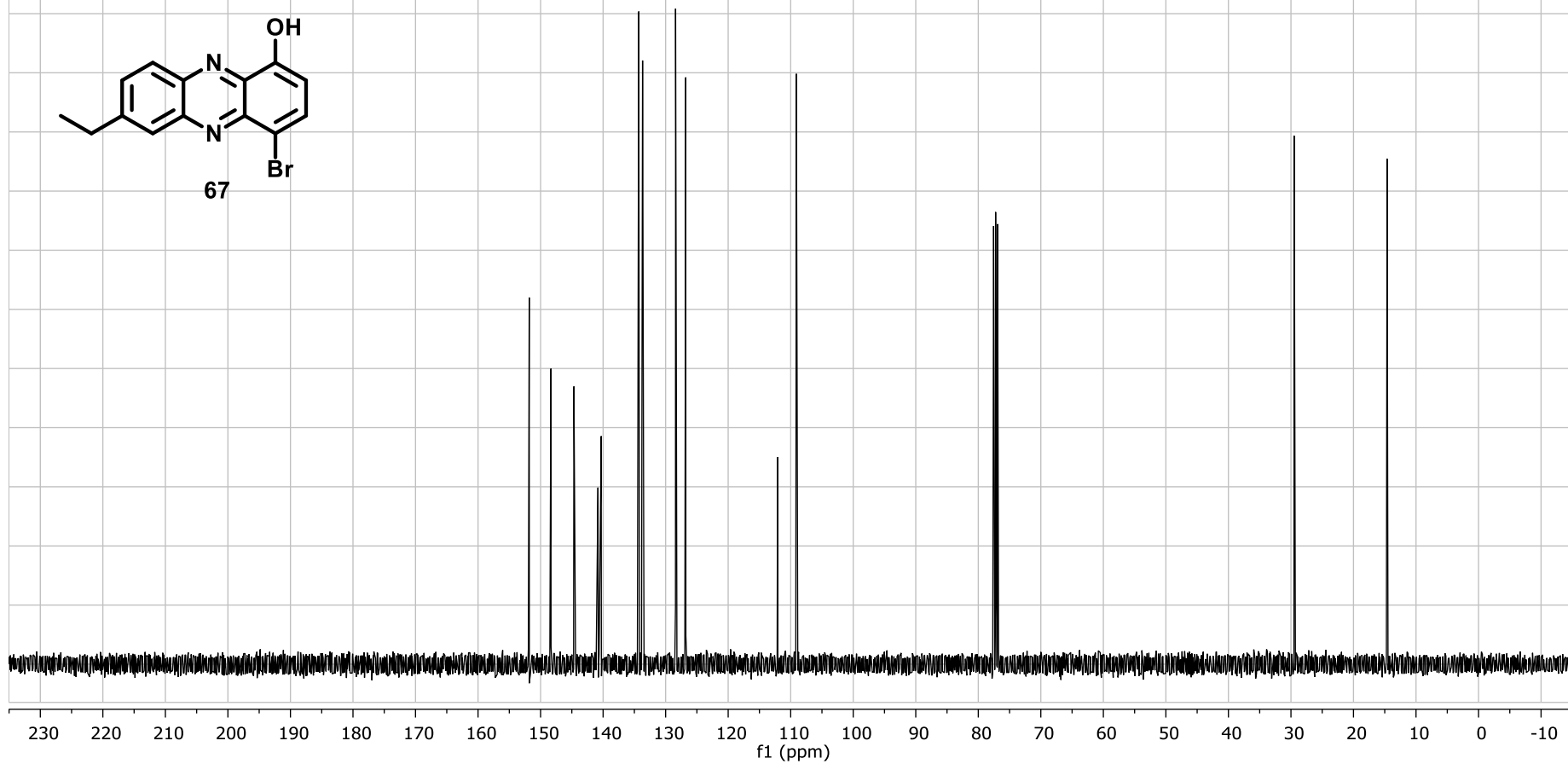
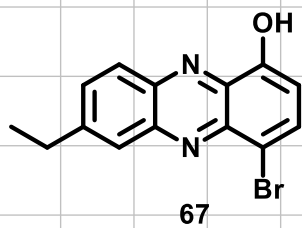
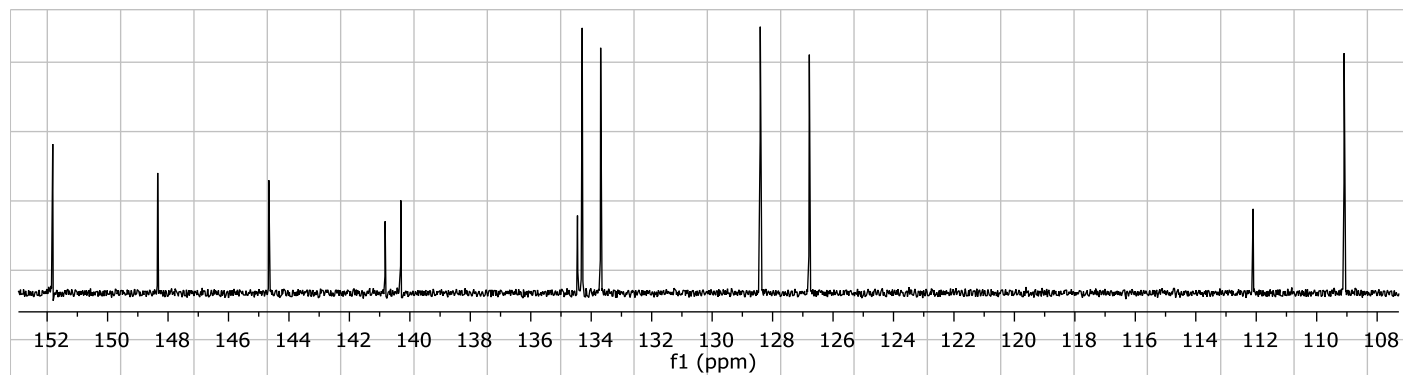




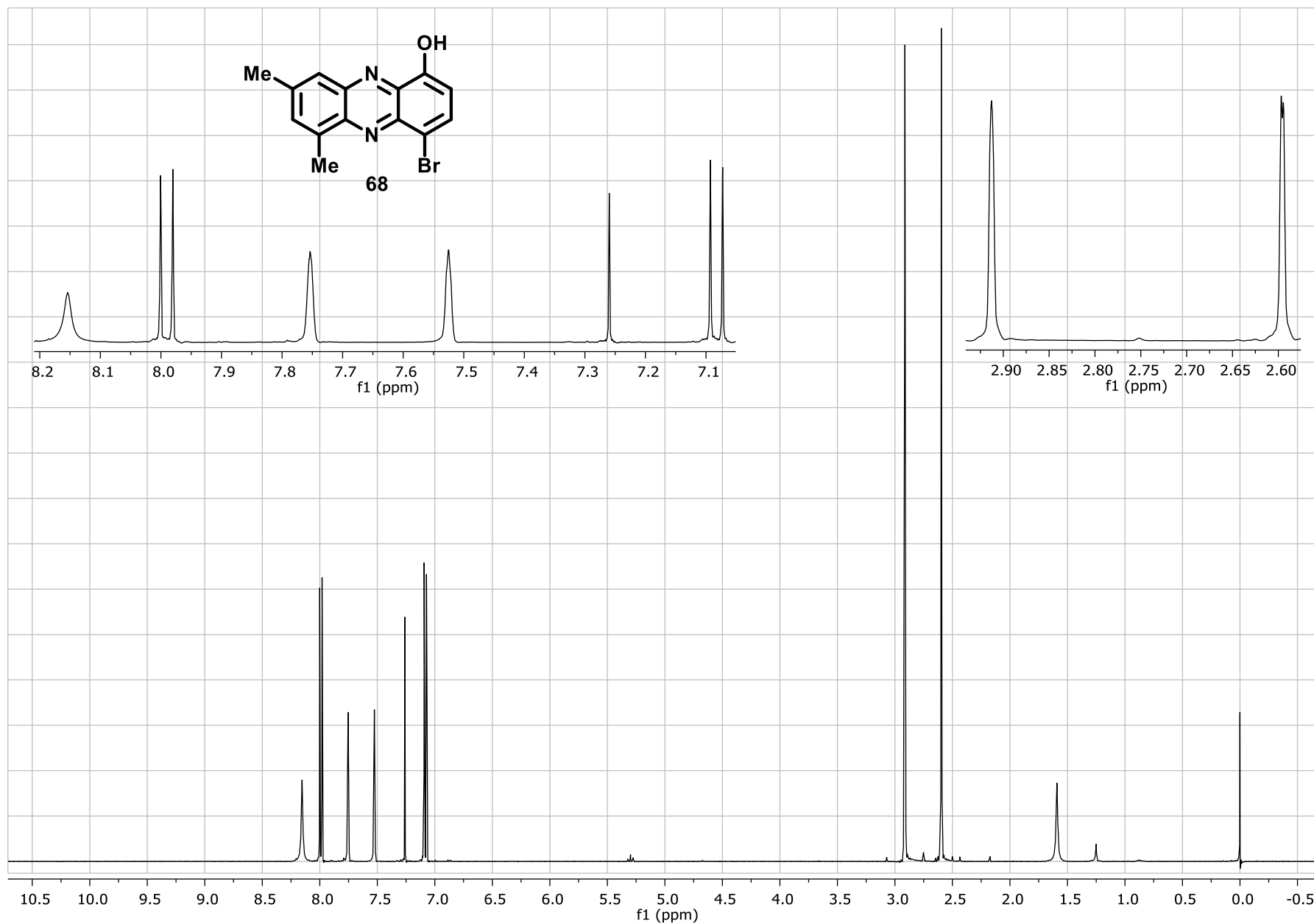




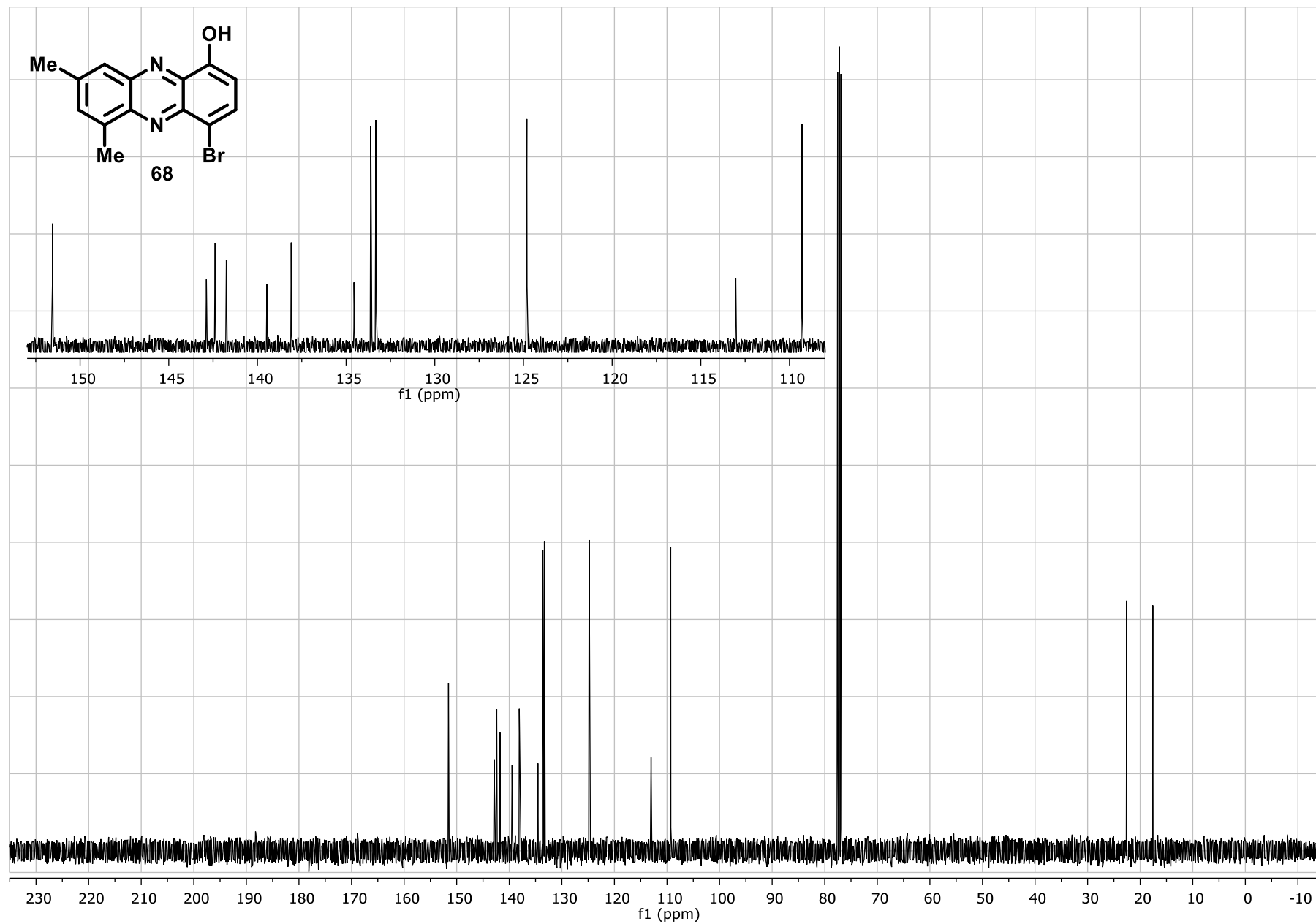


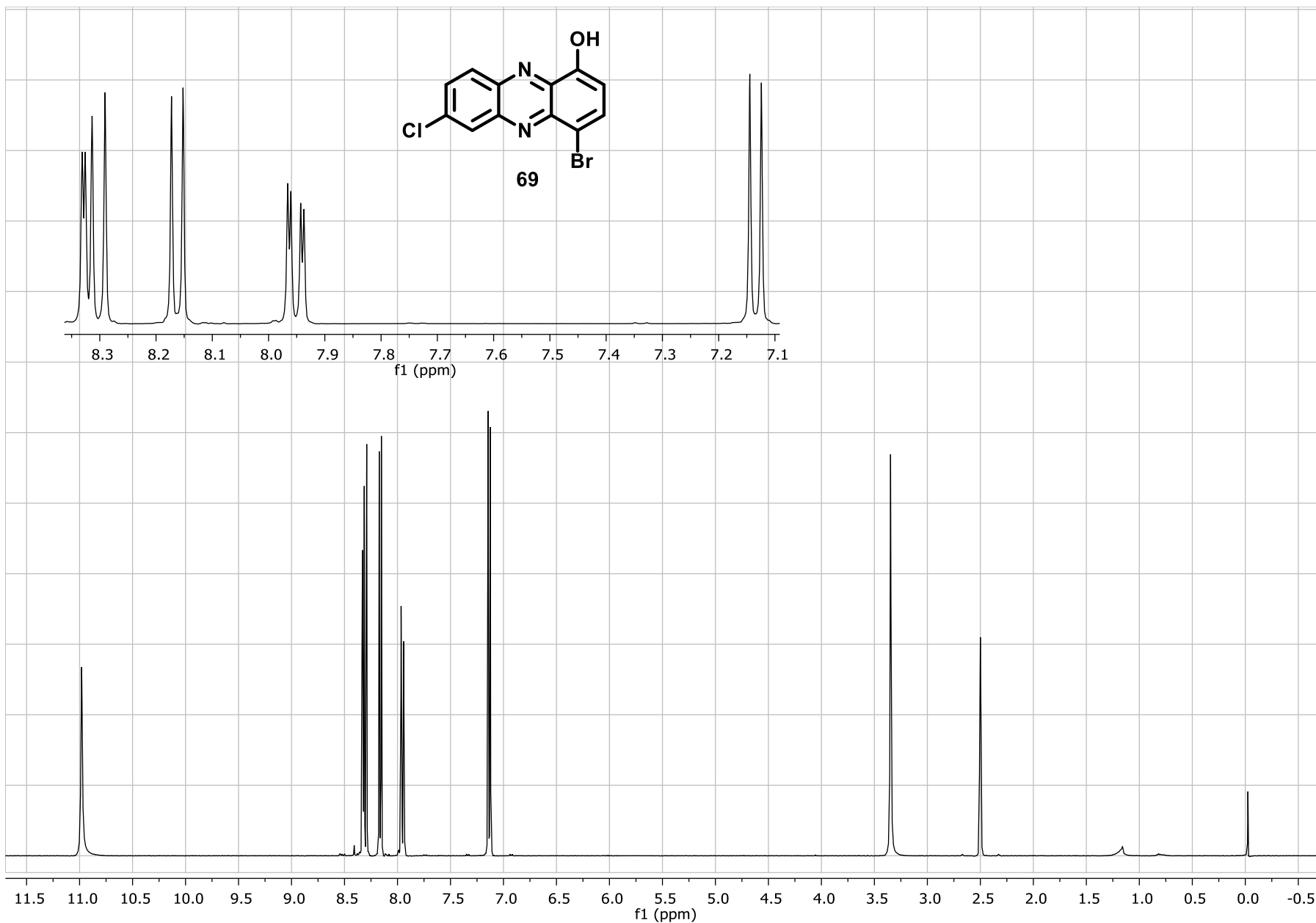


S169

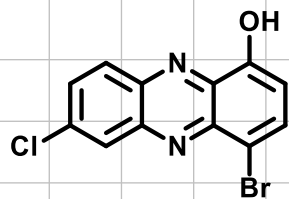


S170

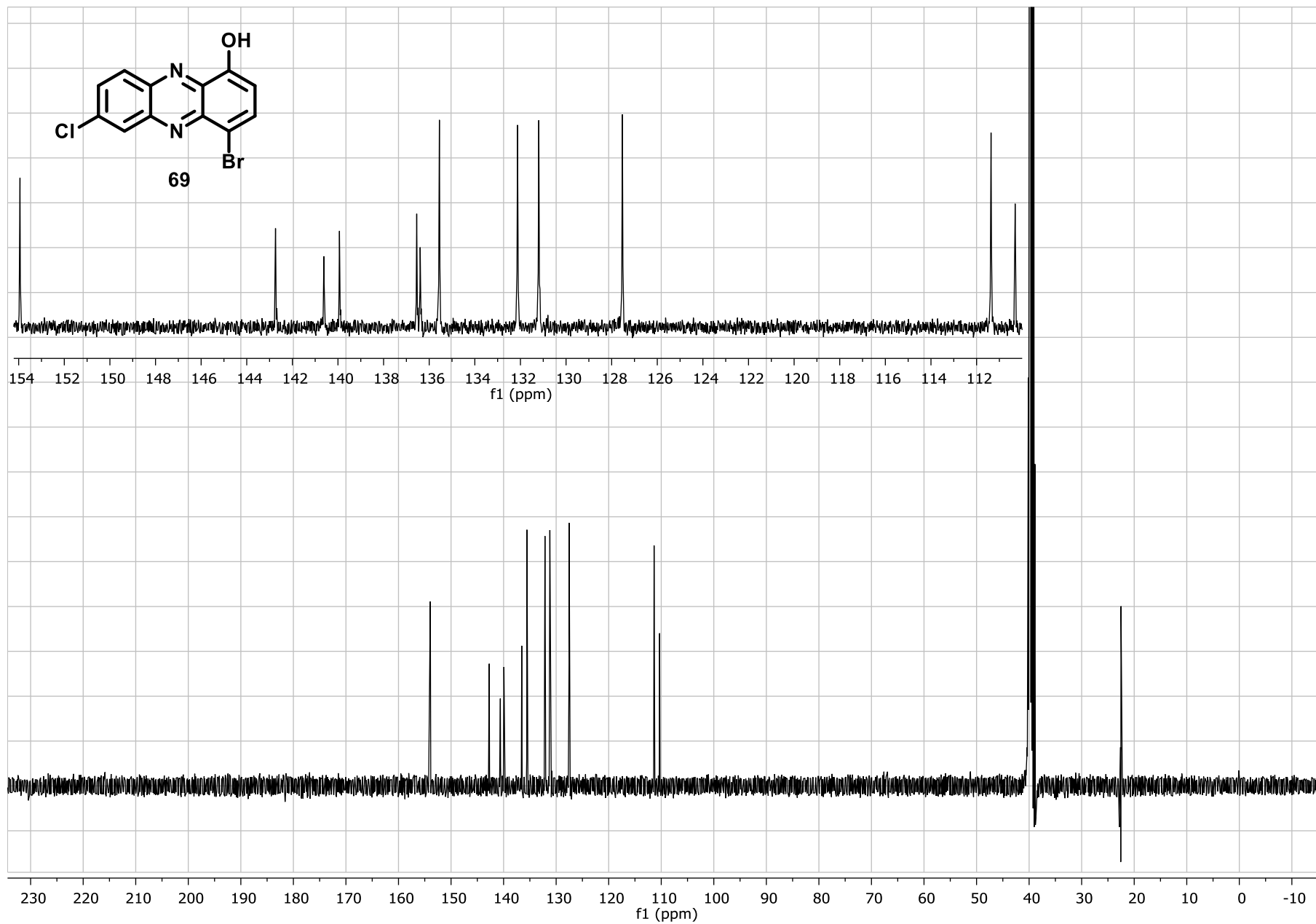


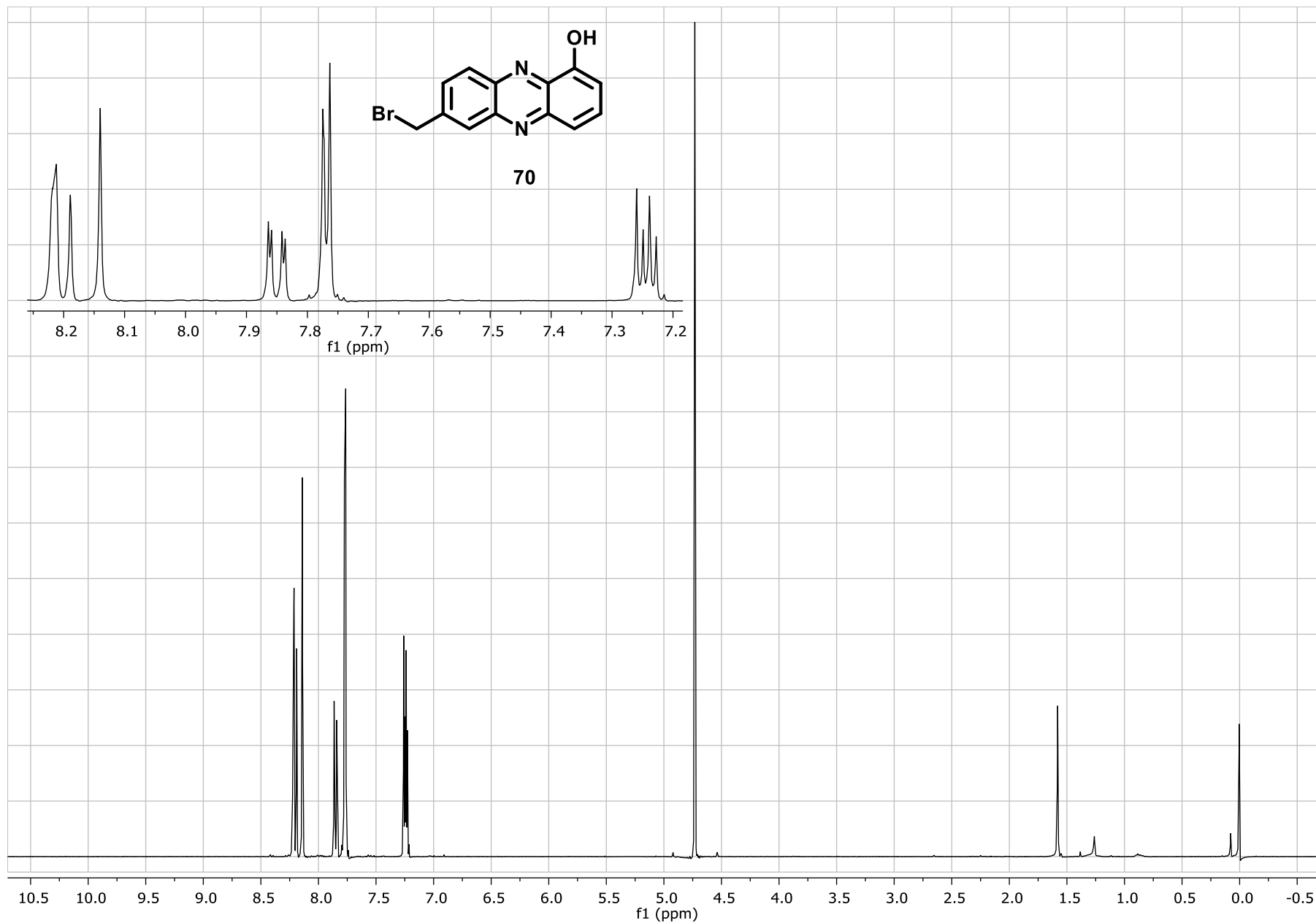


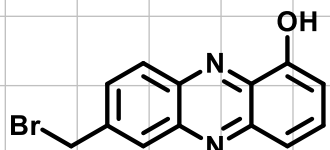




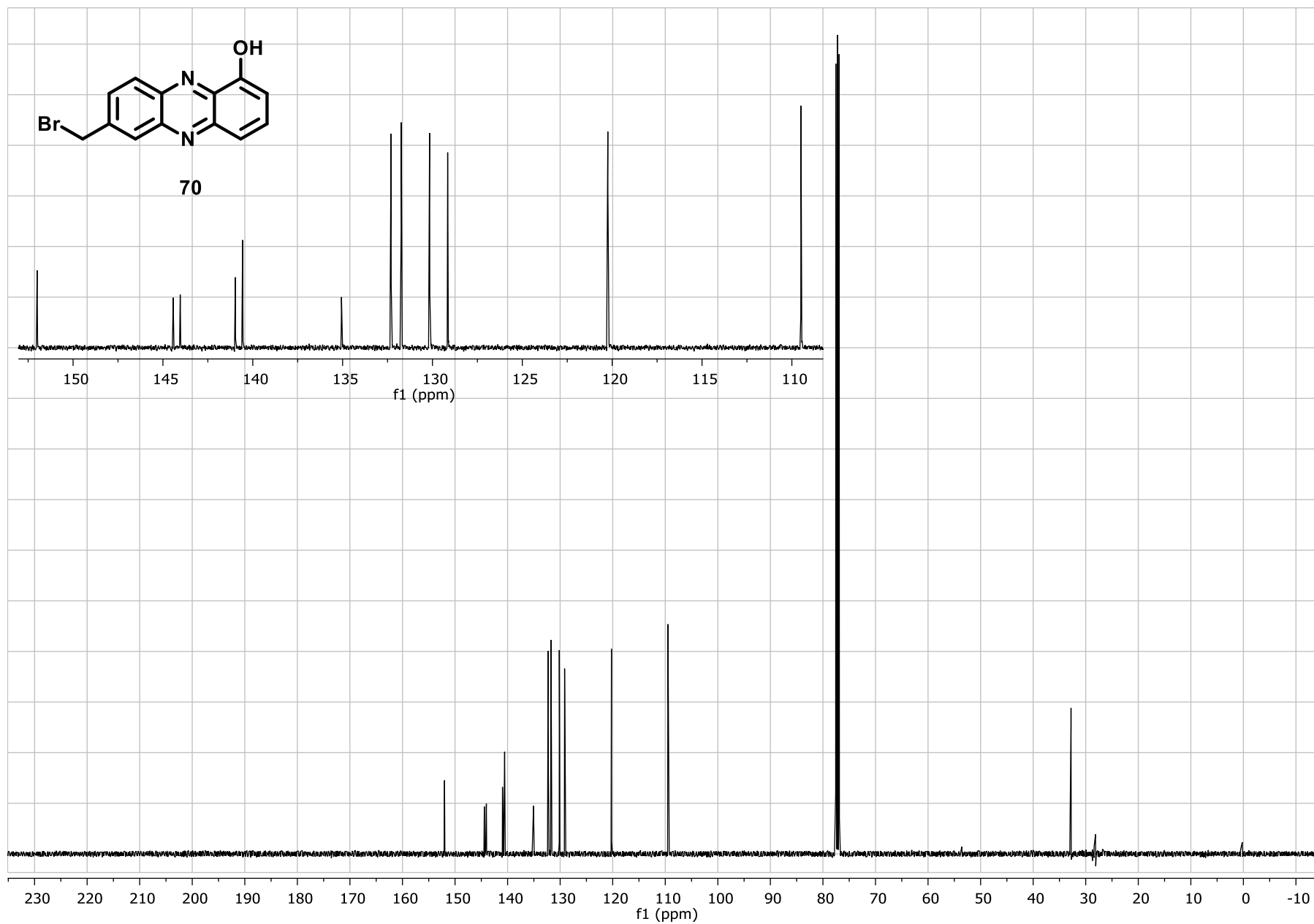
69

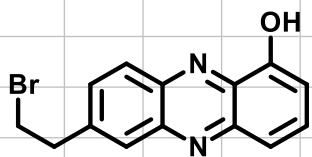




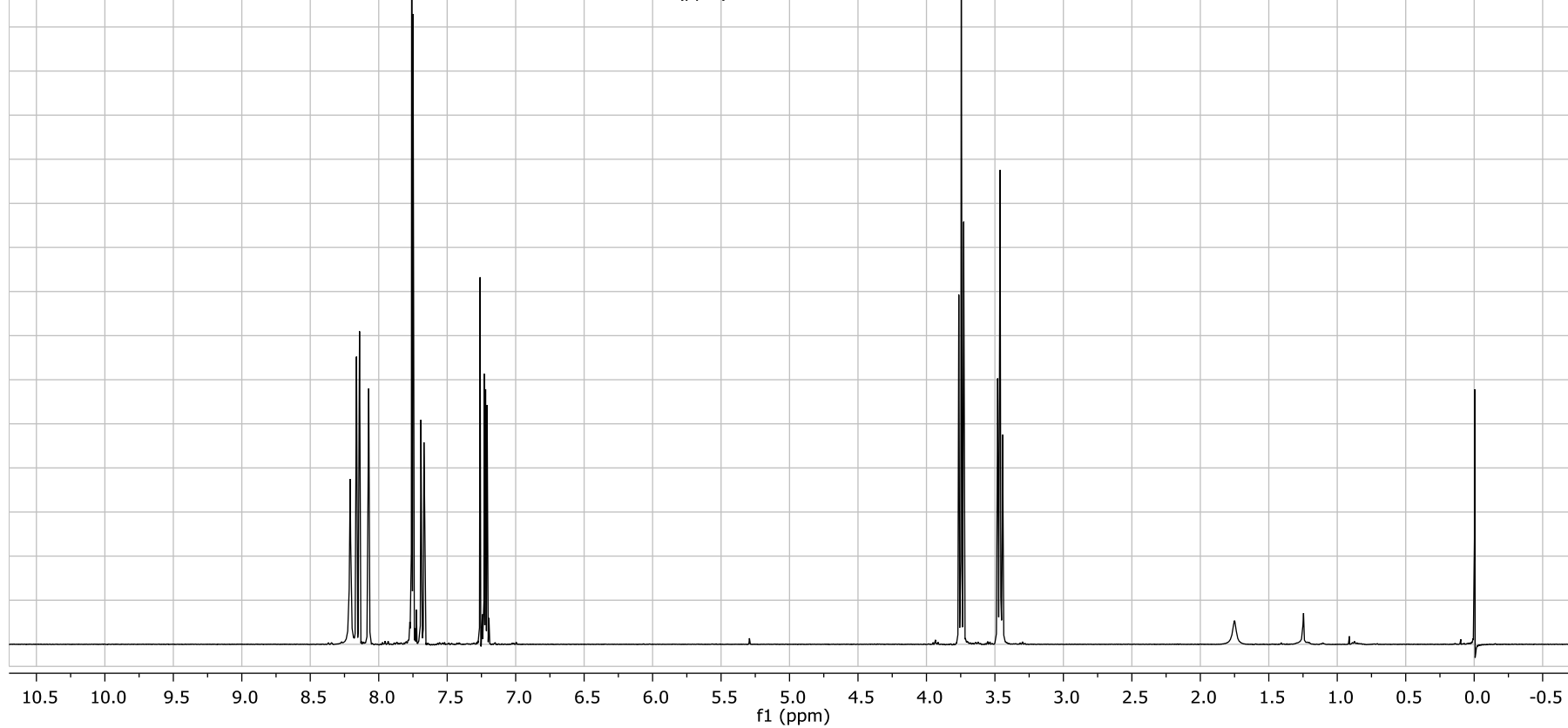
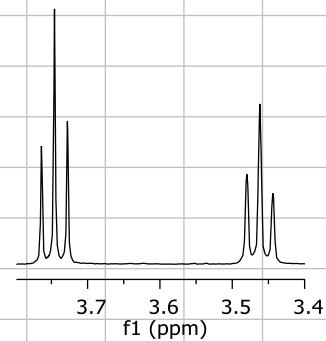
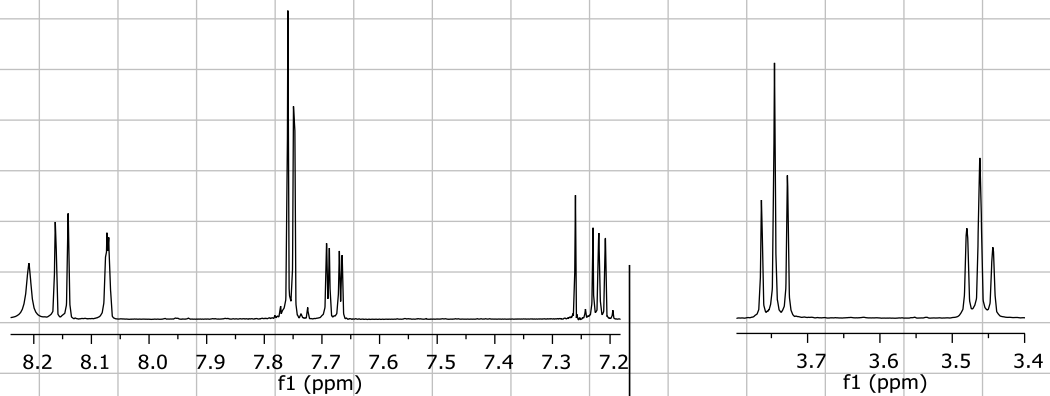


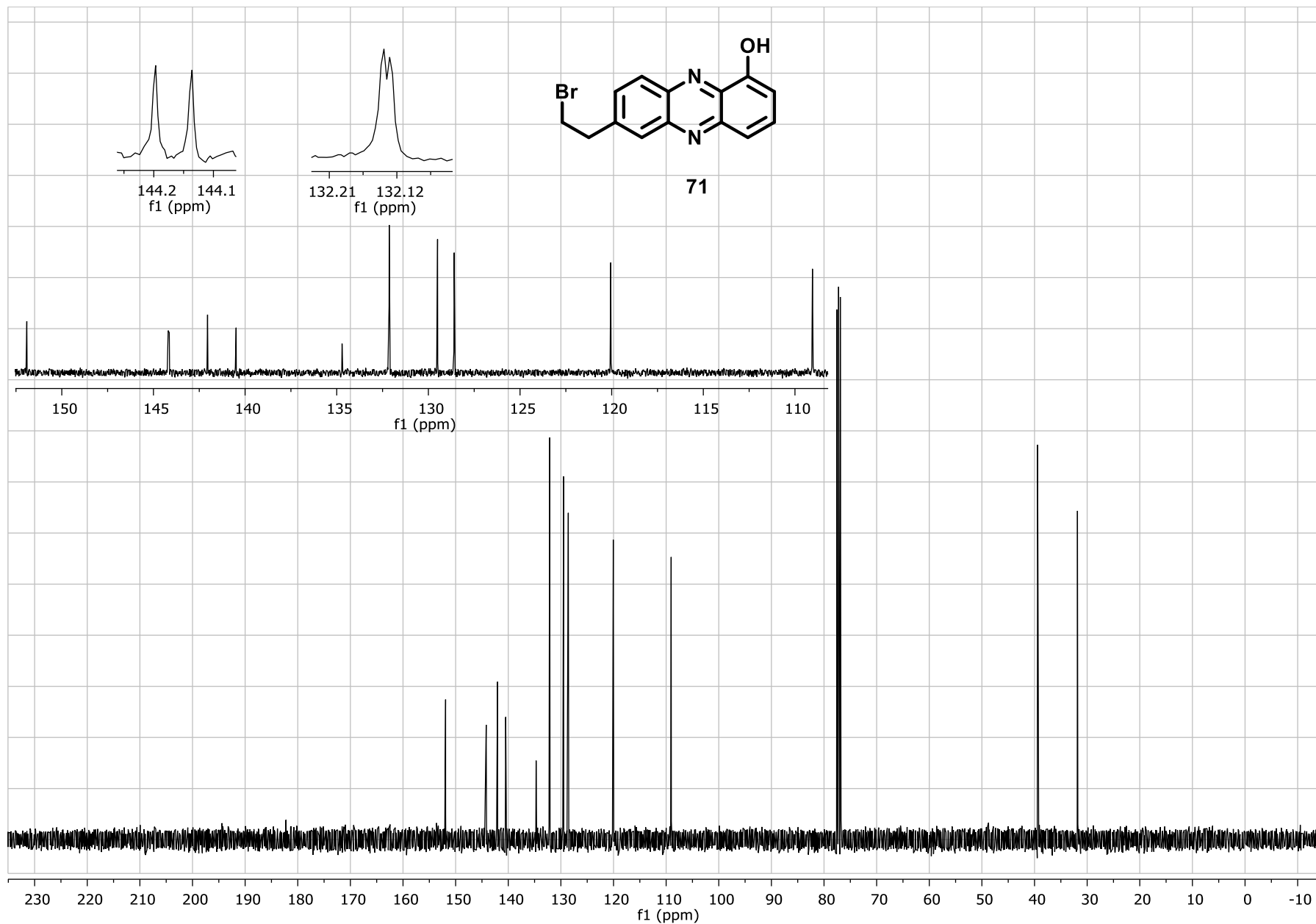
70

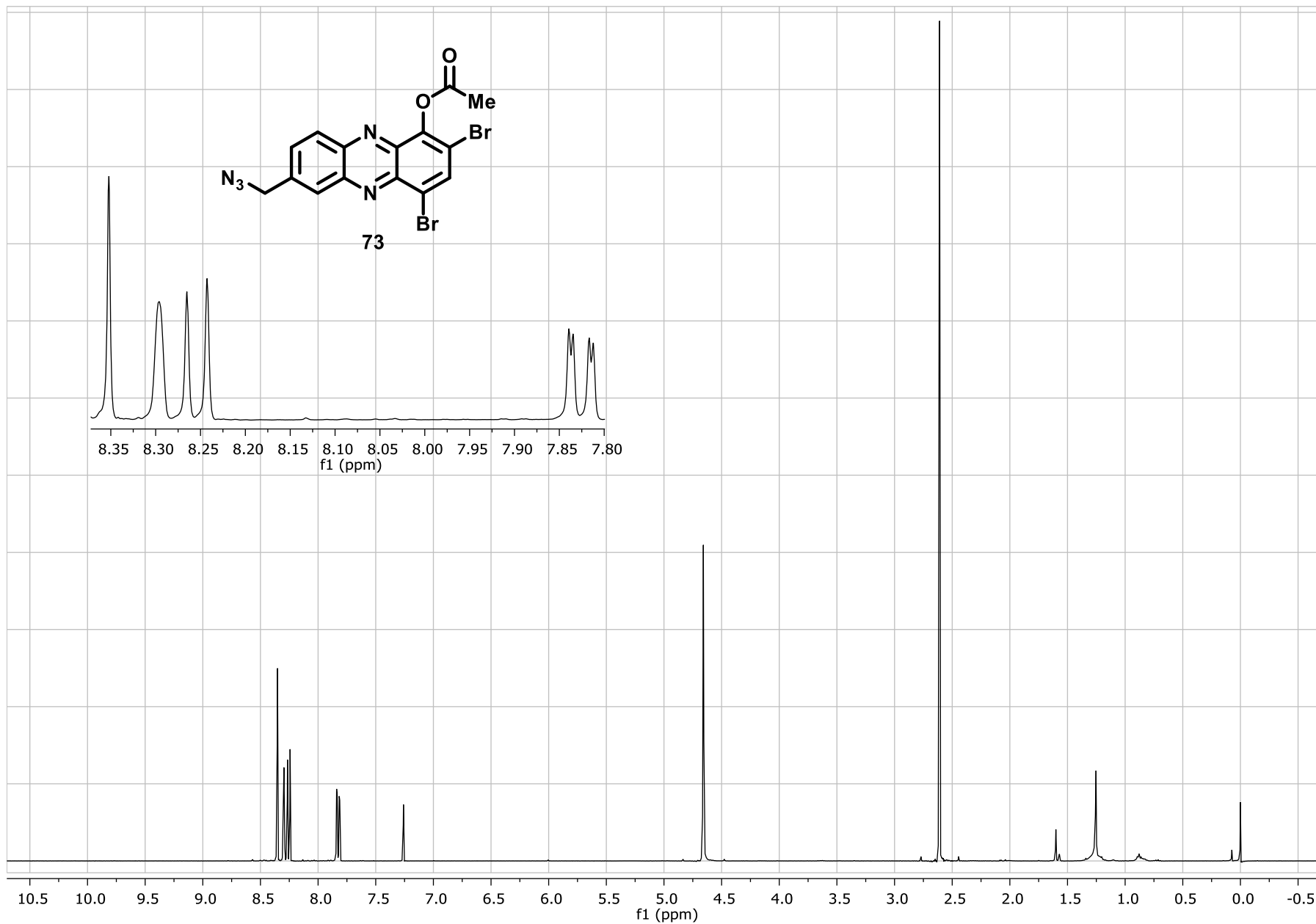




71

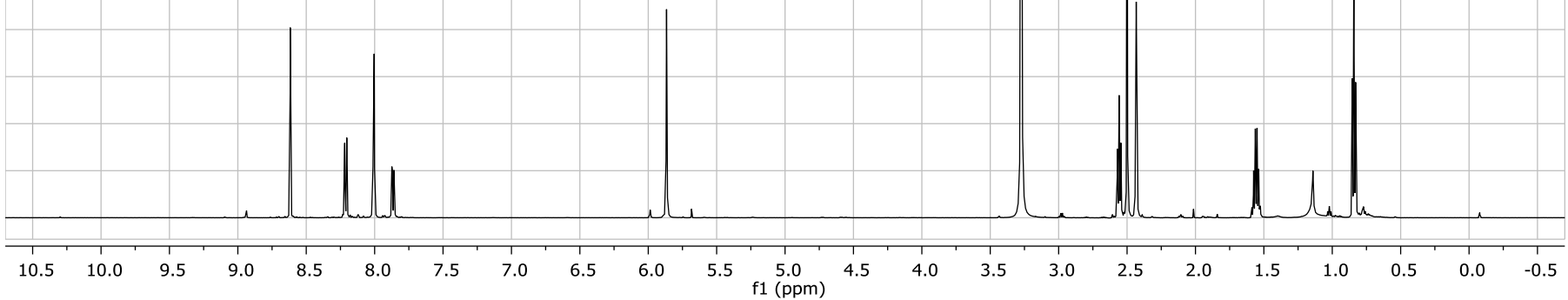
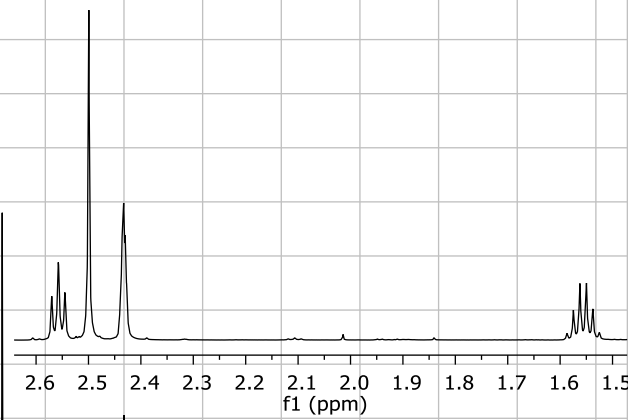
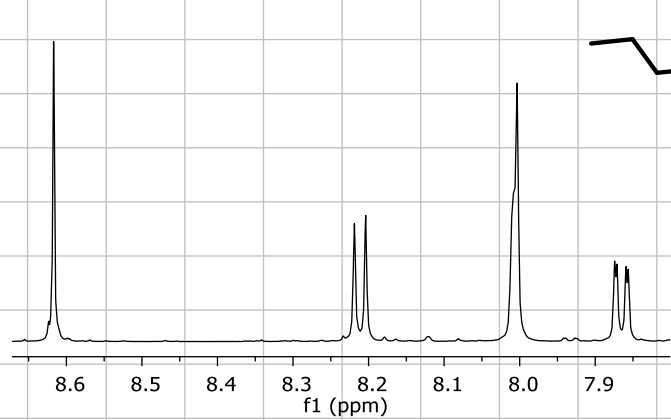
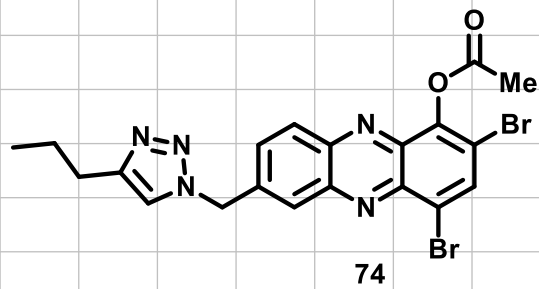




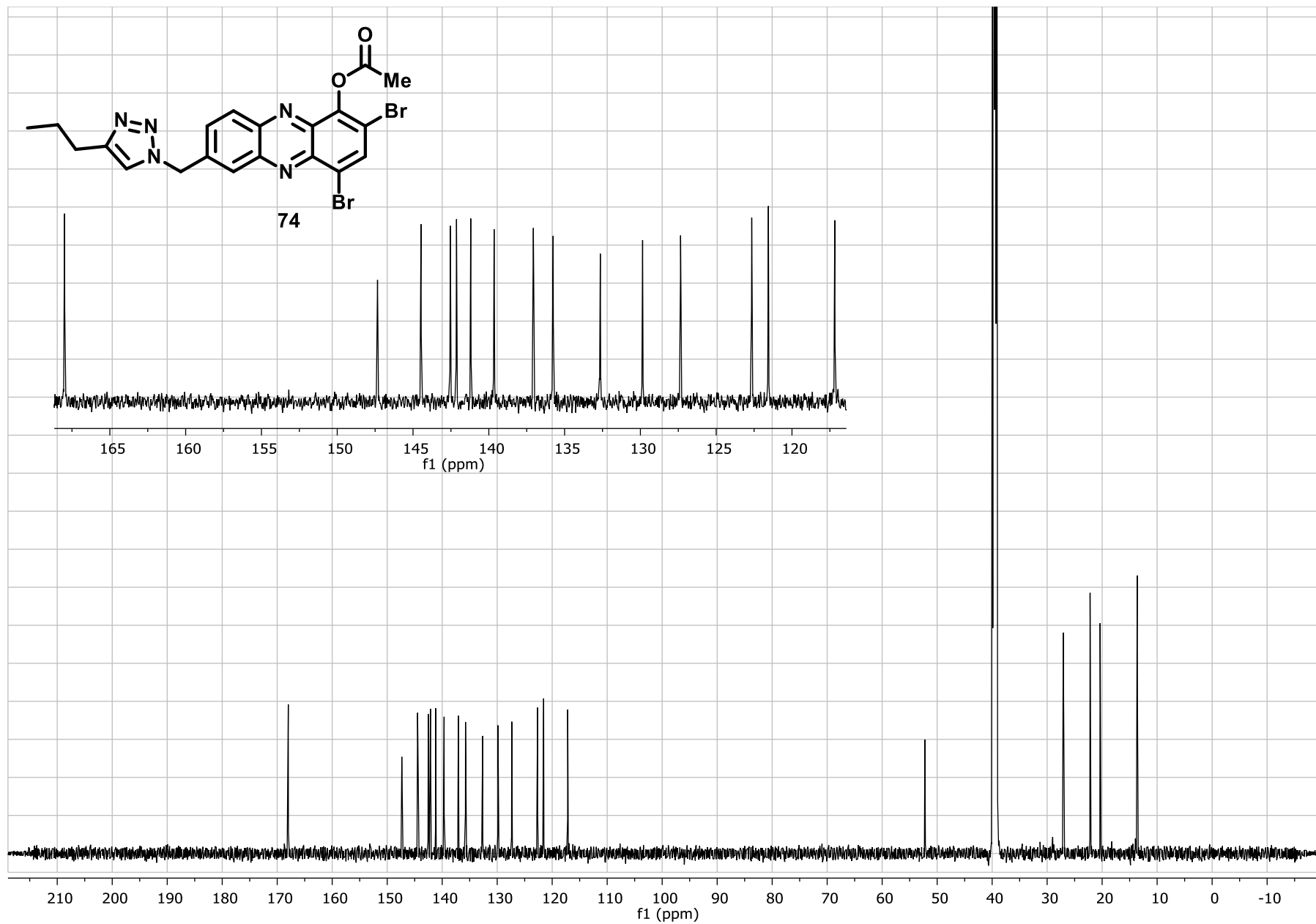


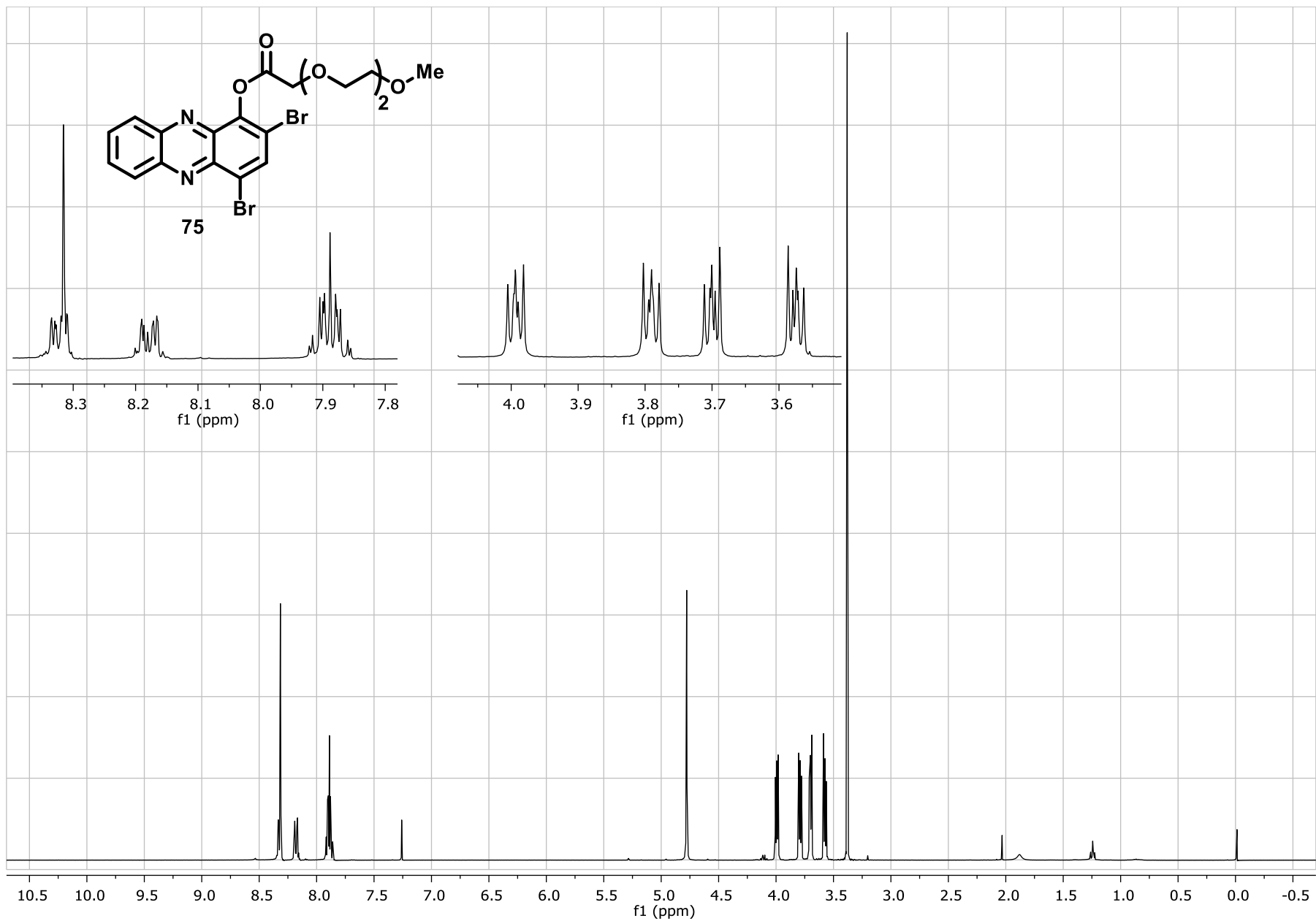
S178

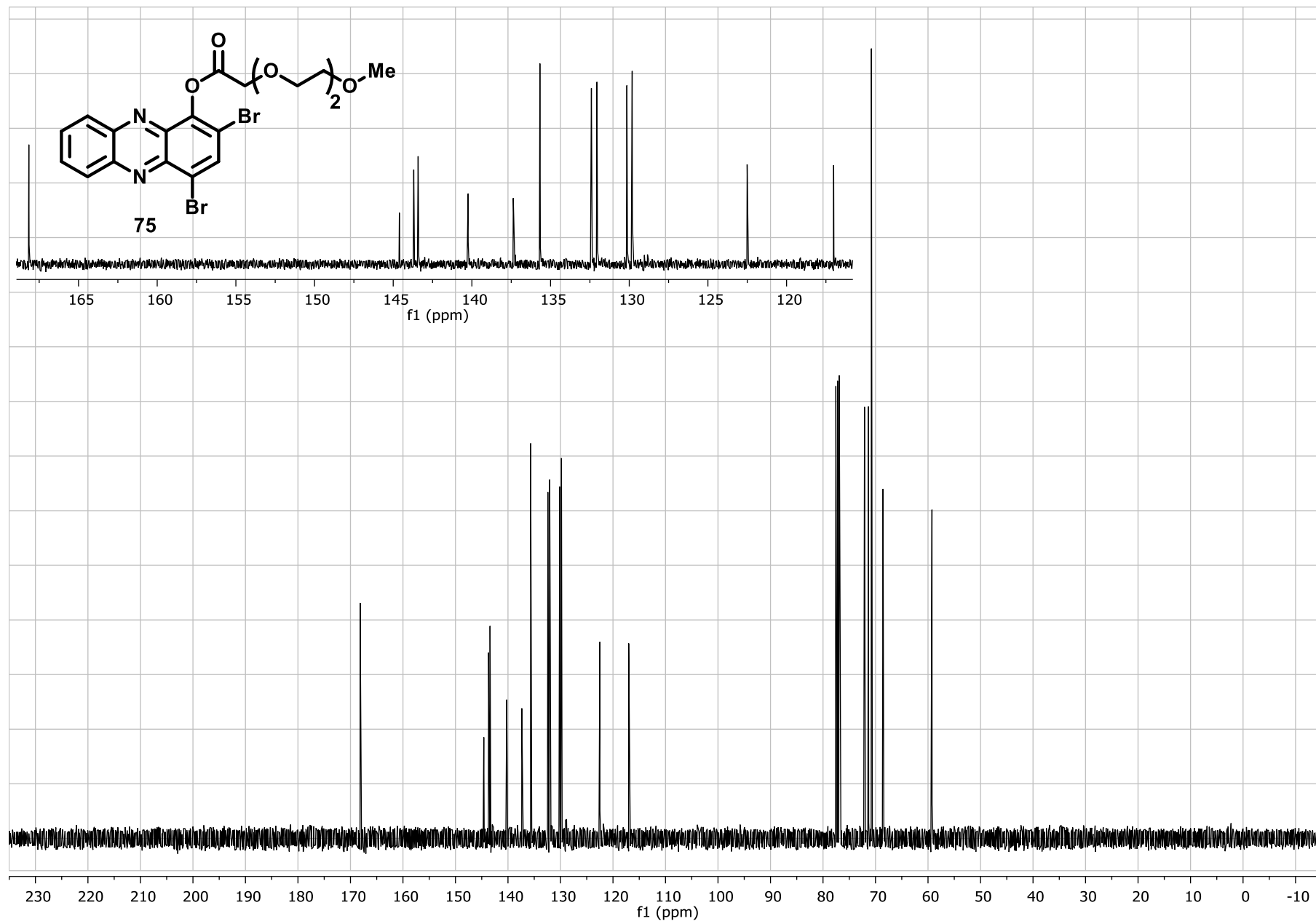


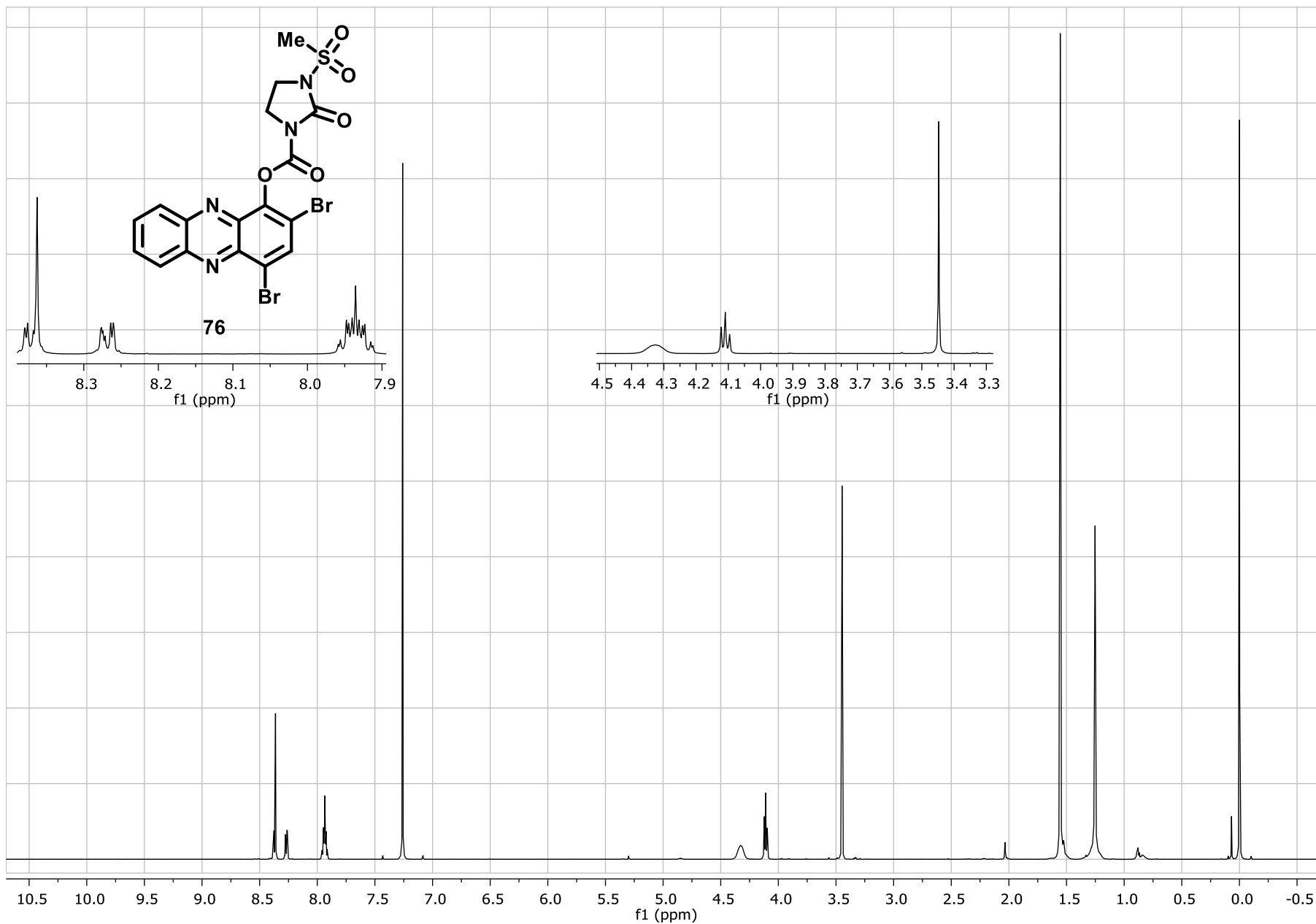


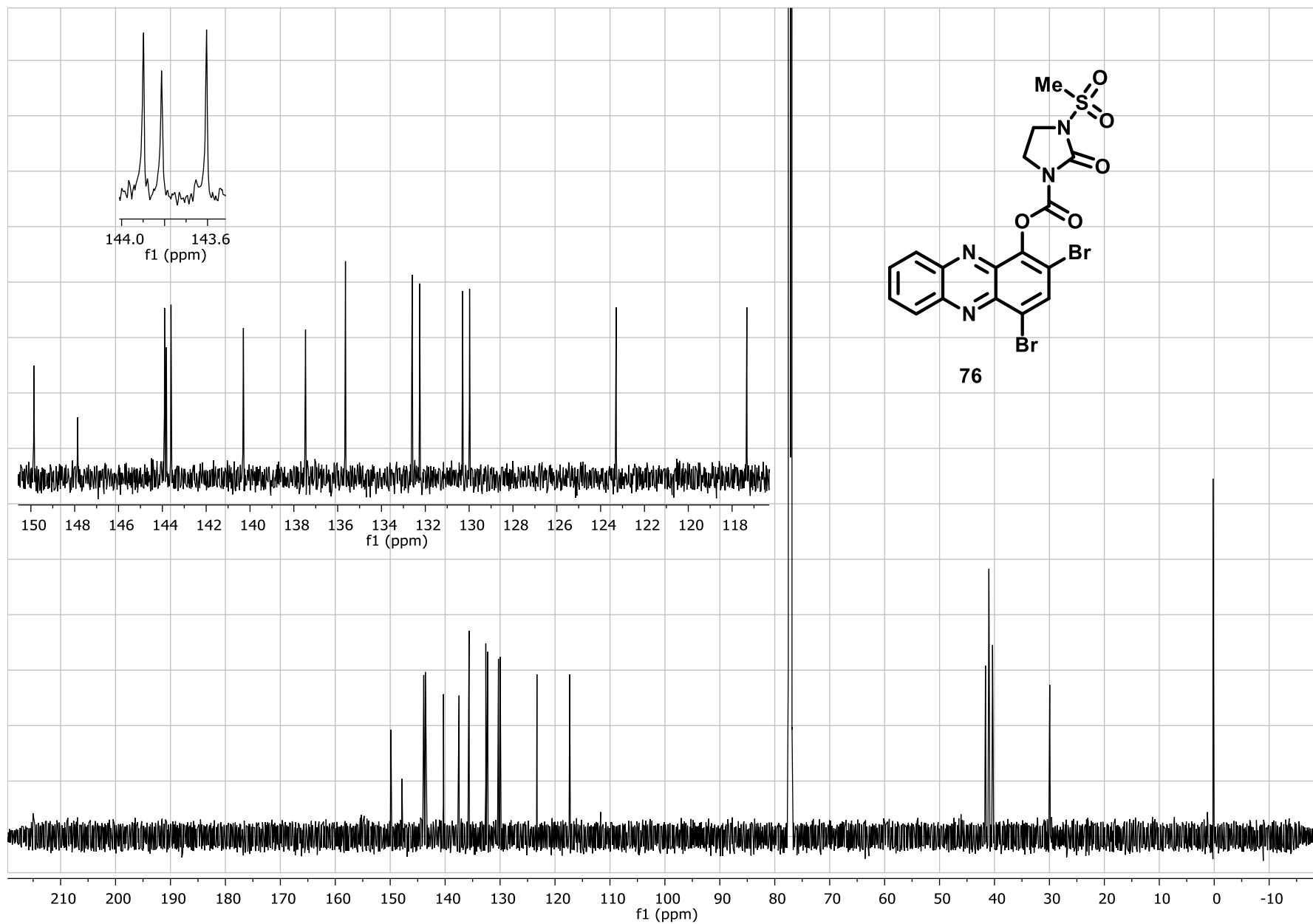


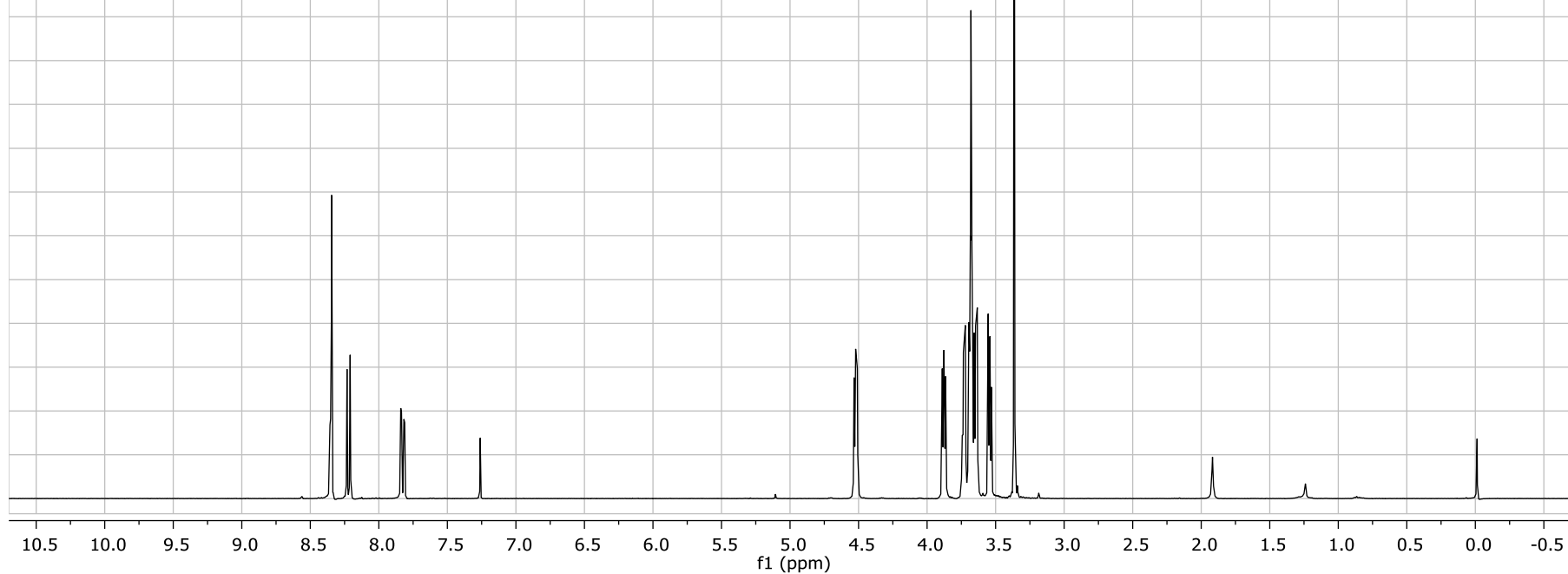
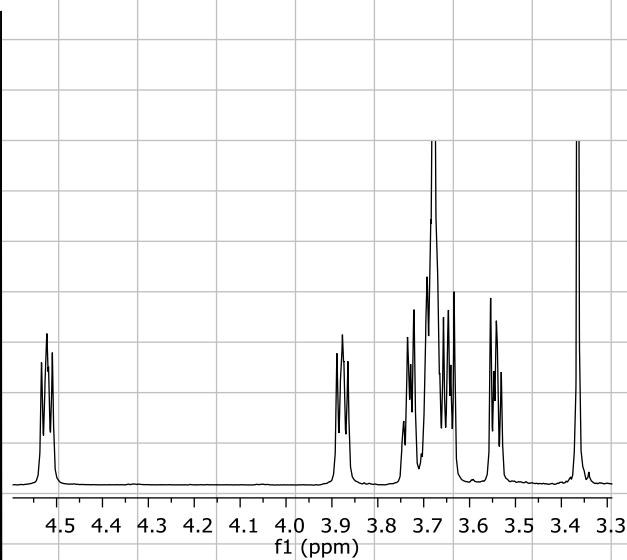
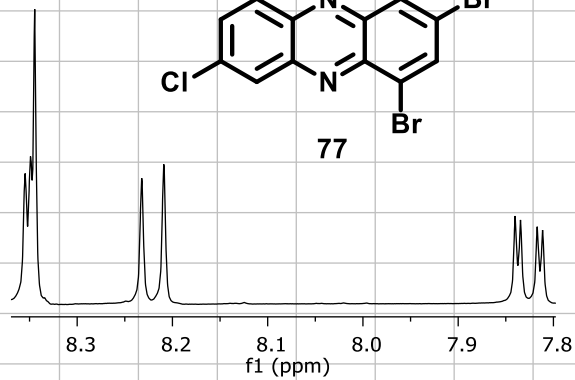
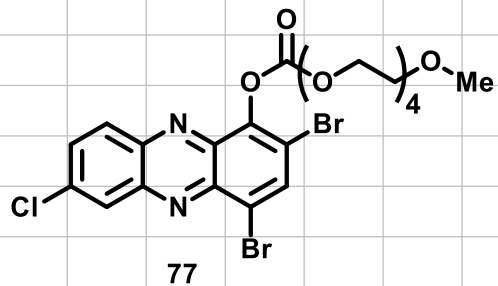


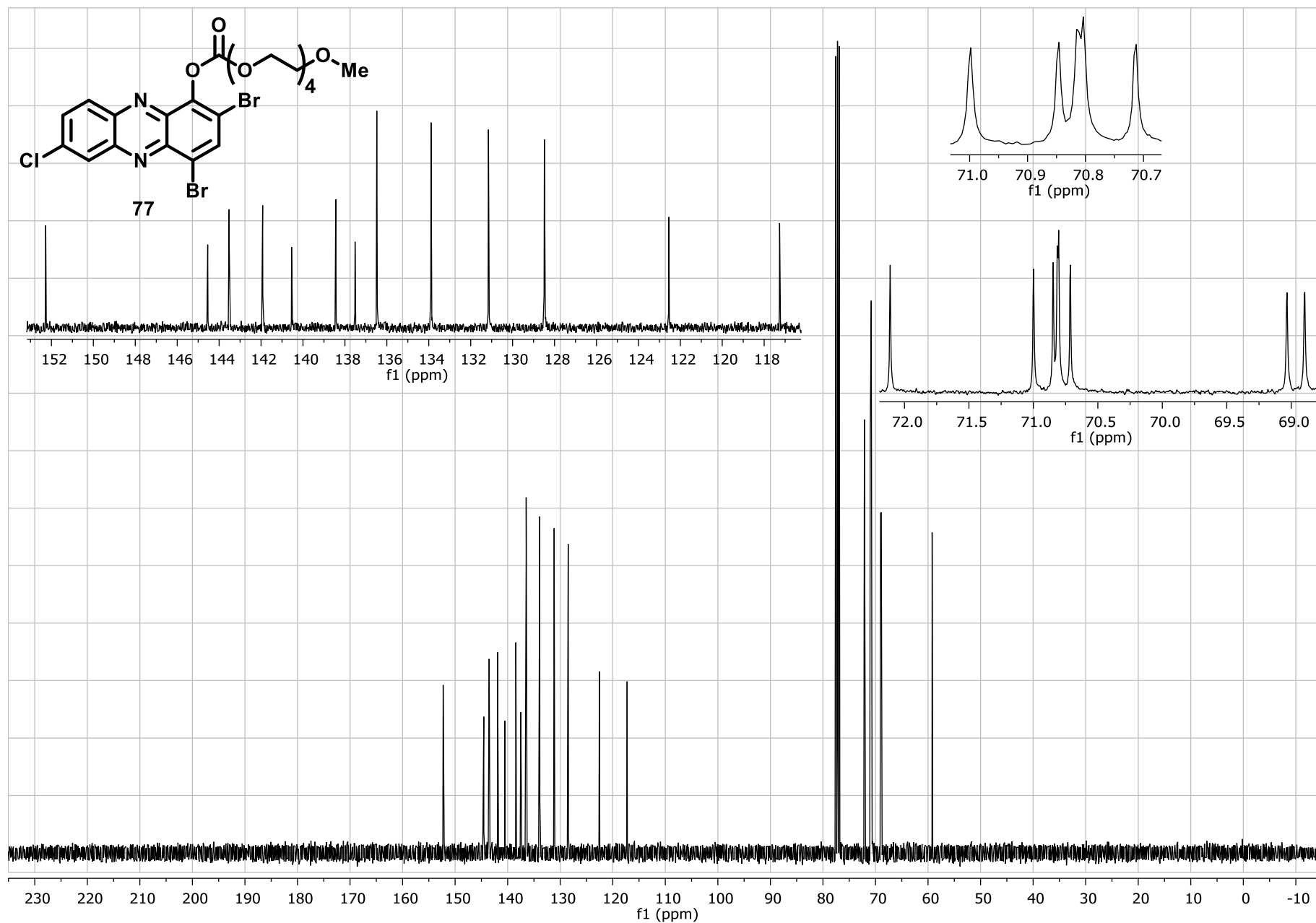


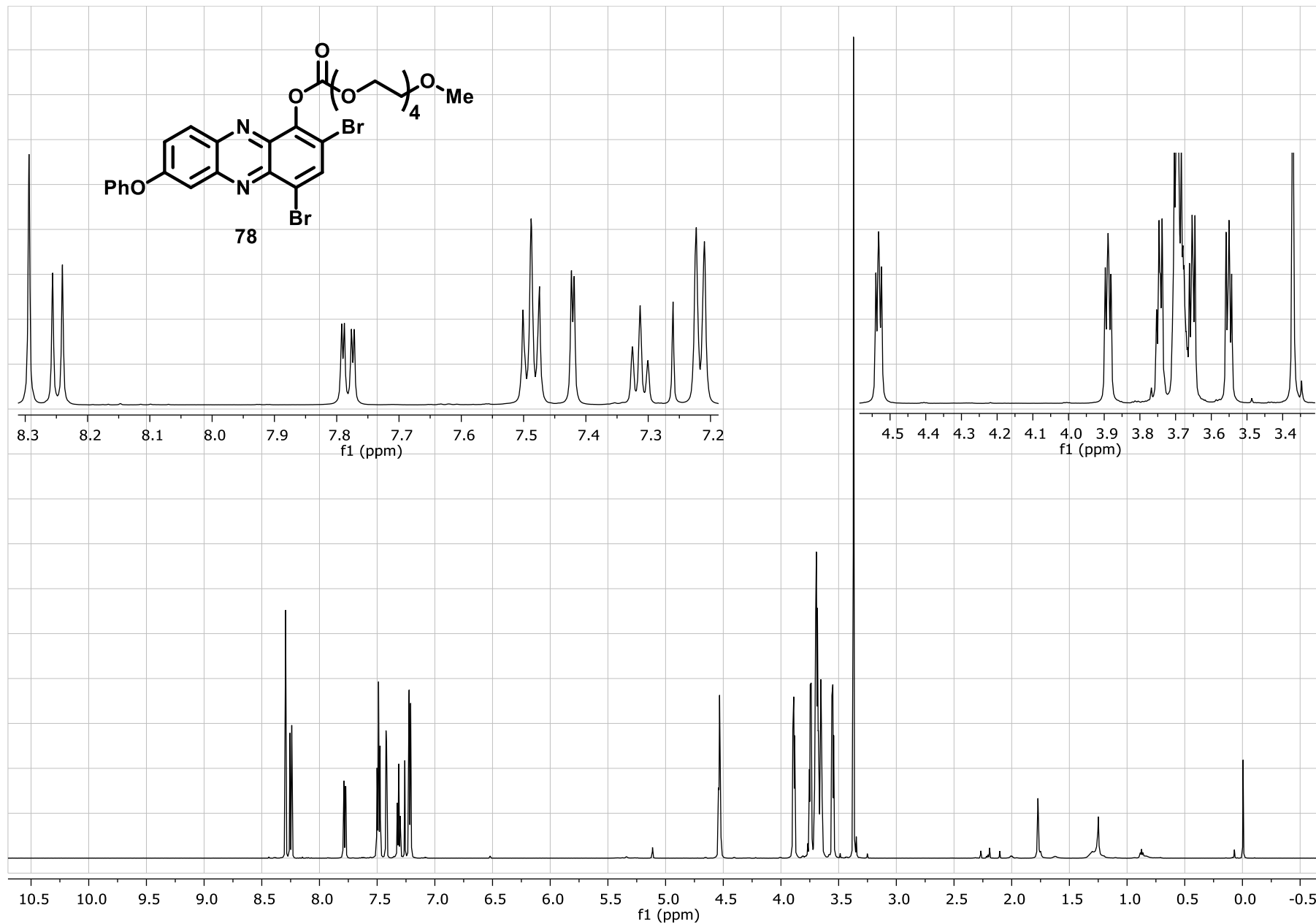




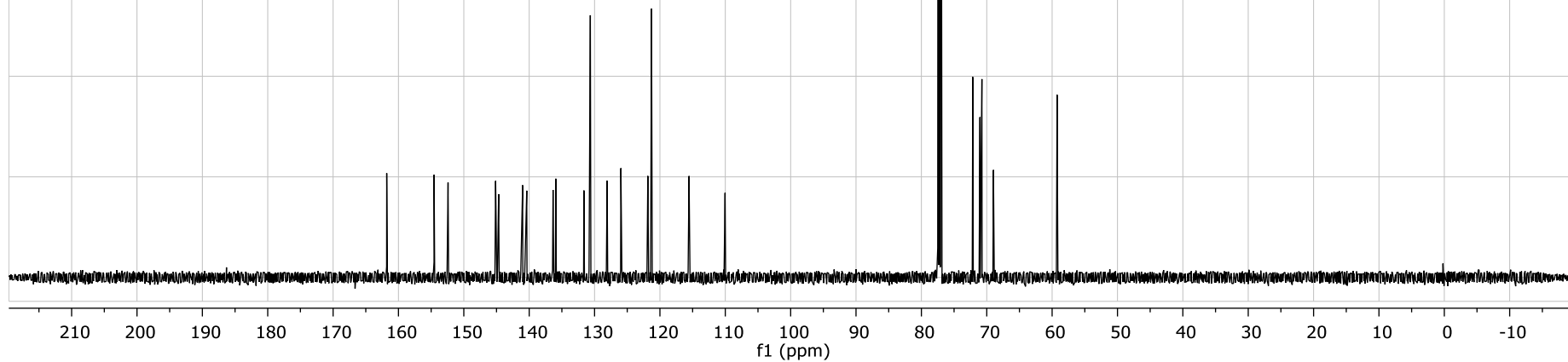
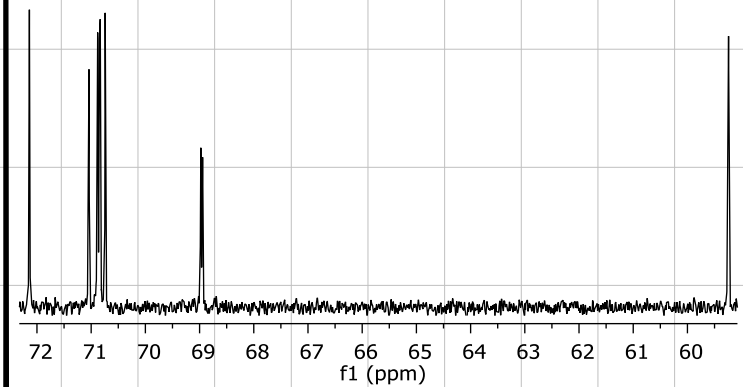
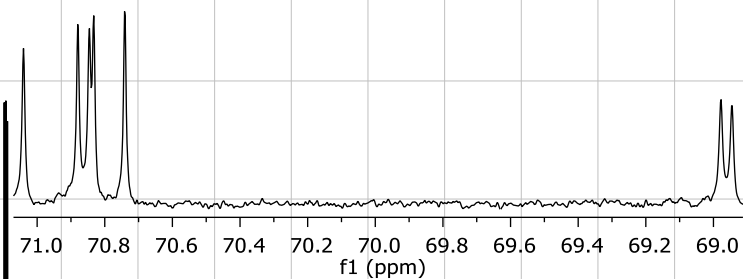
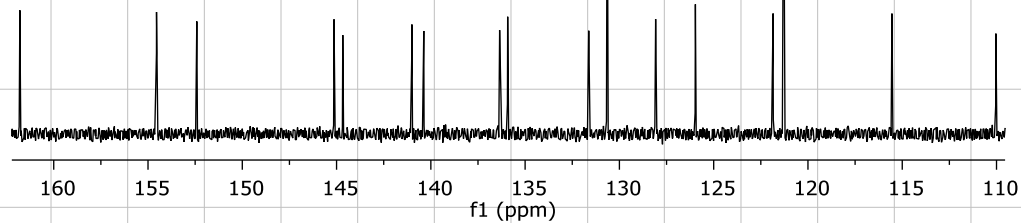
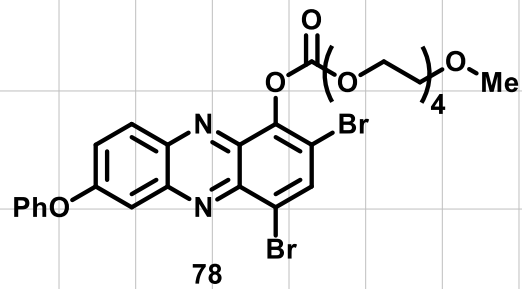


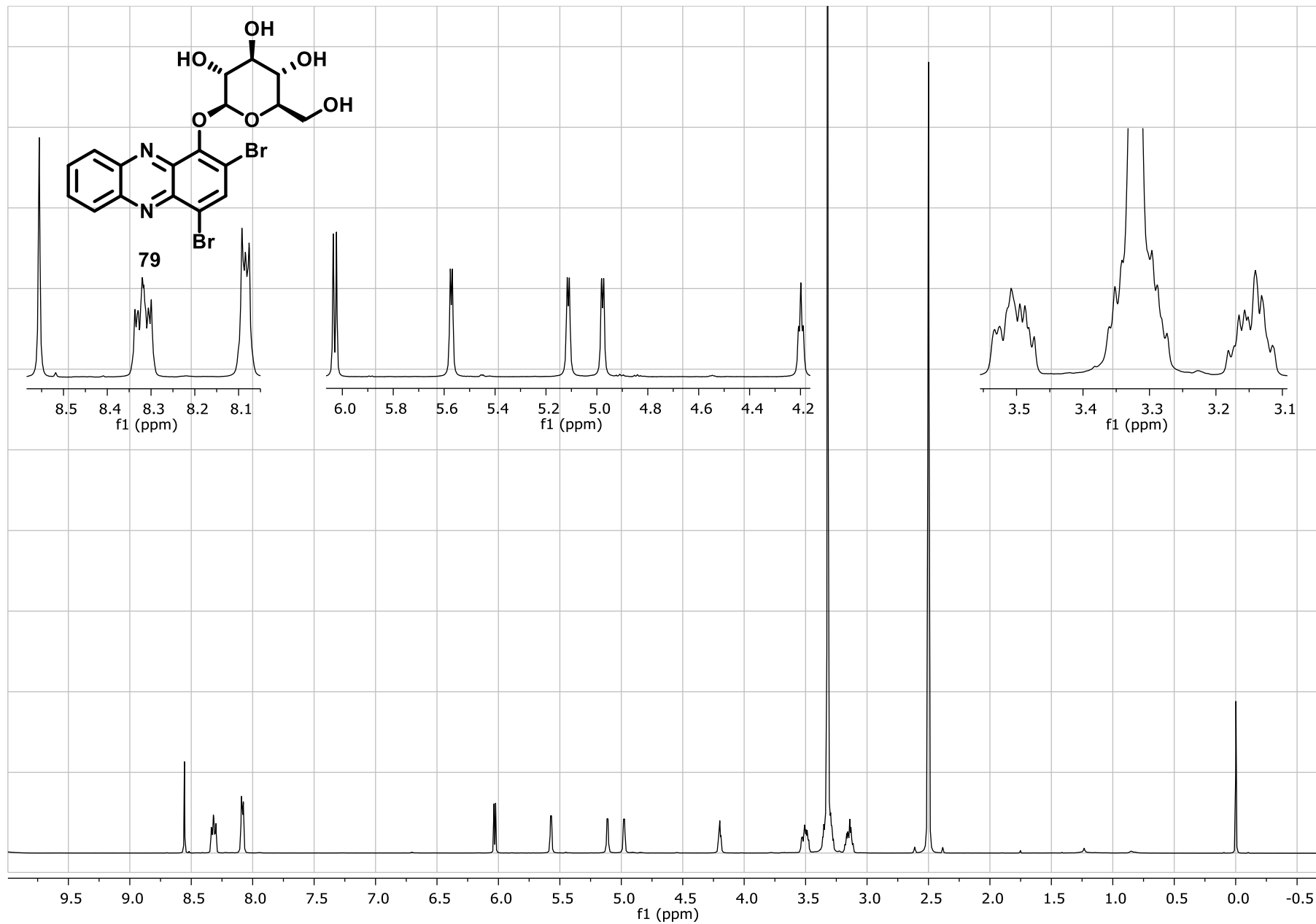


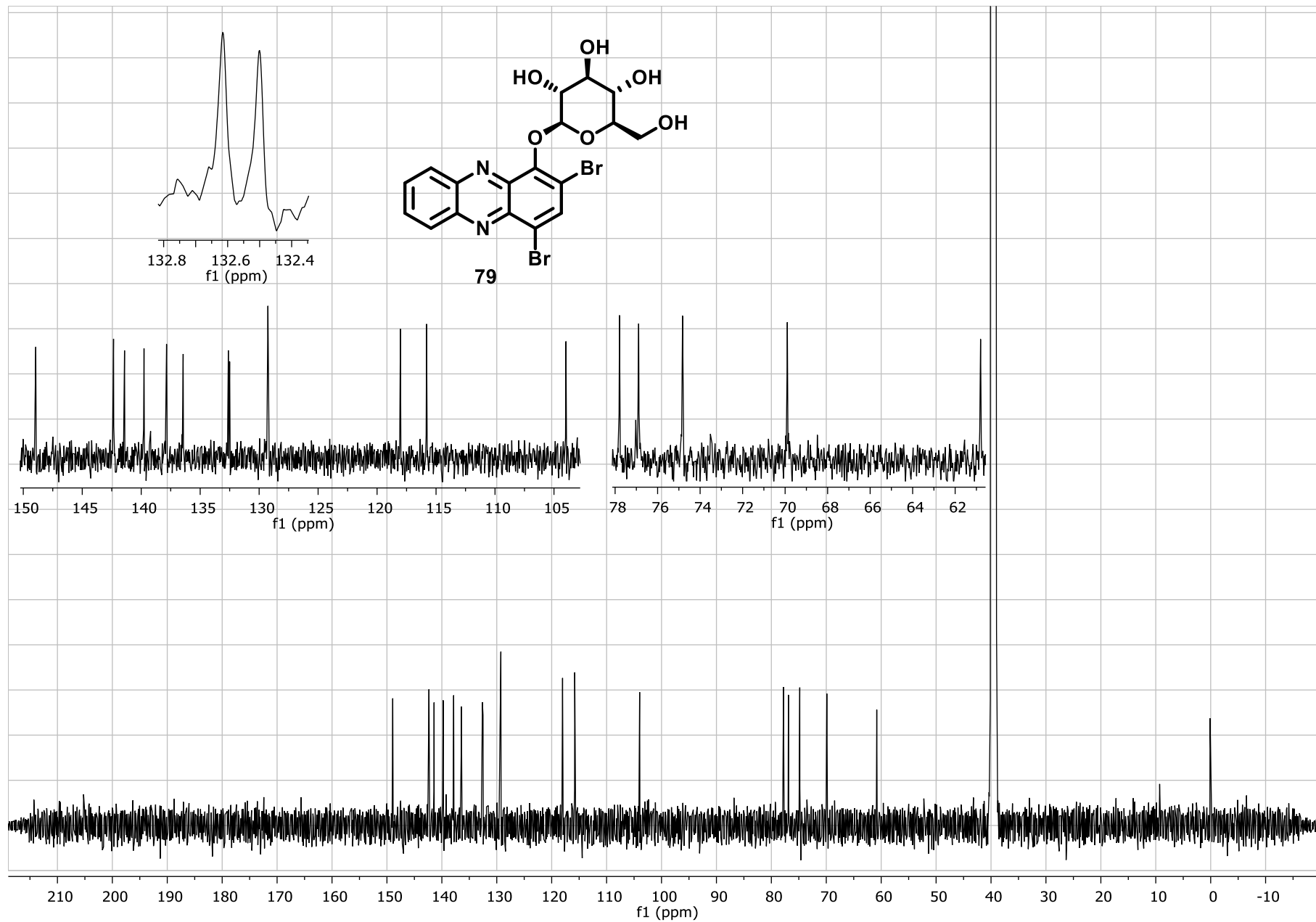


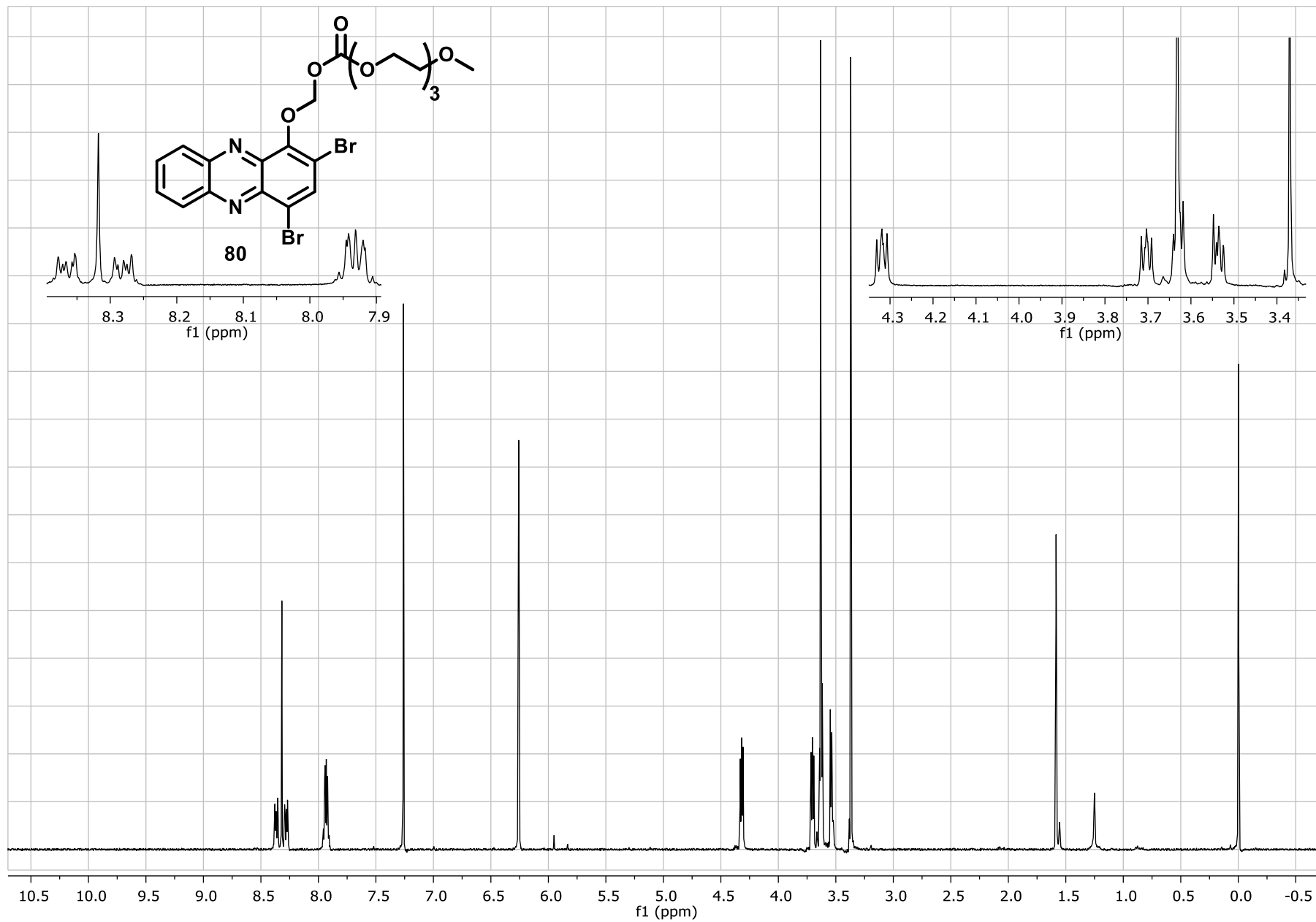




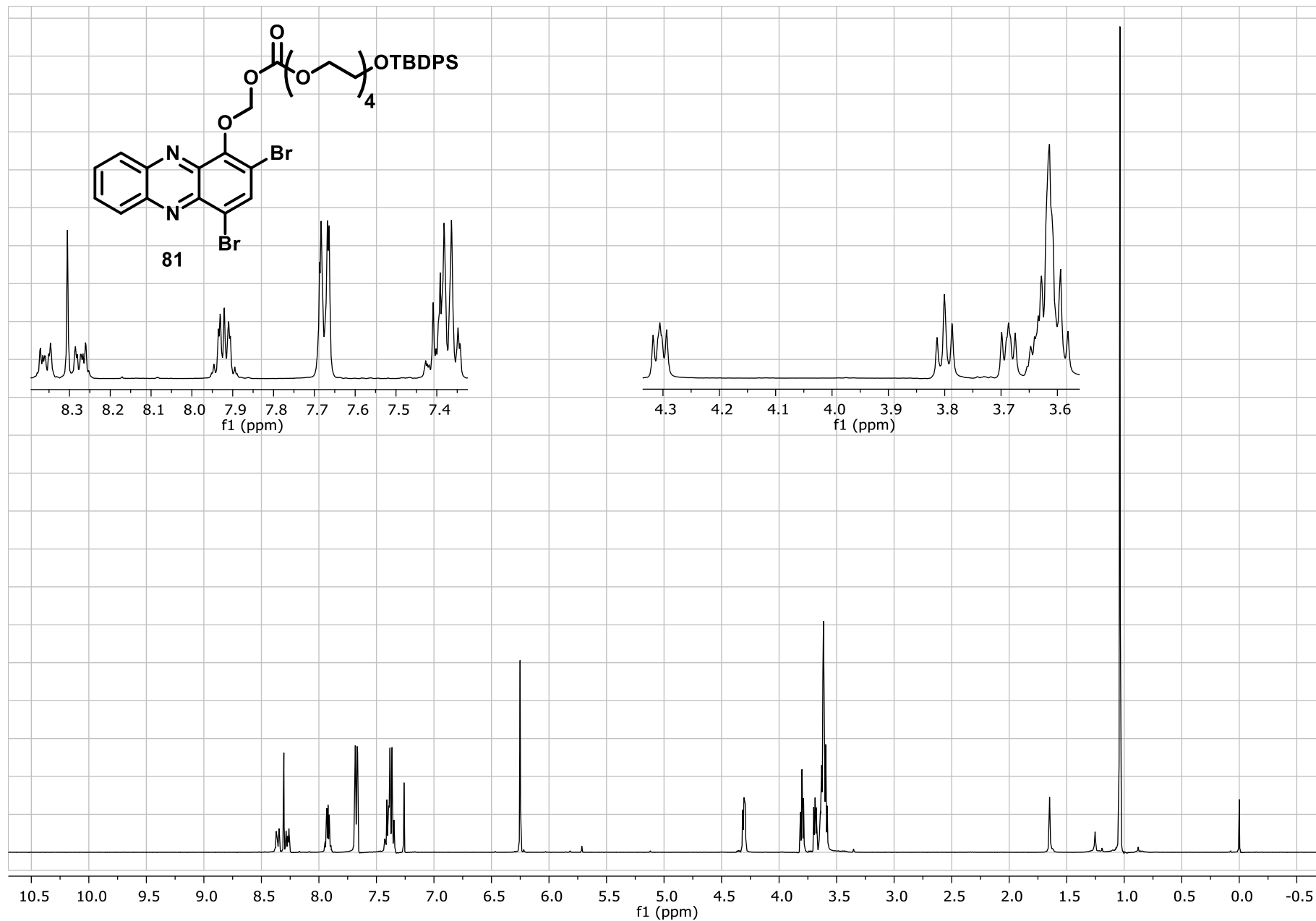


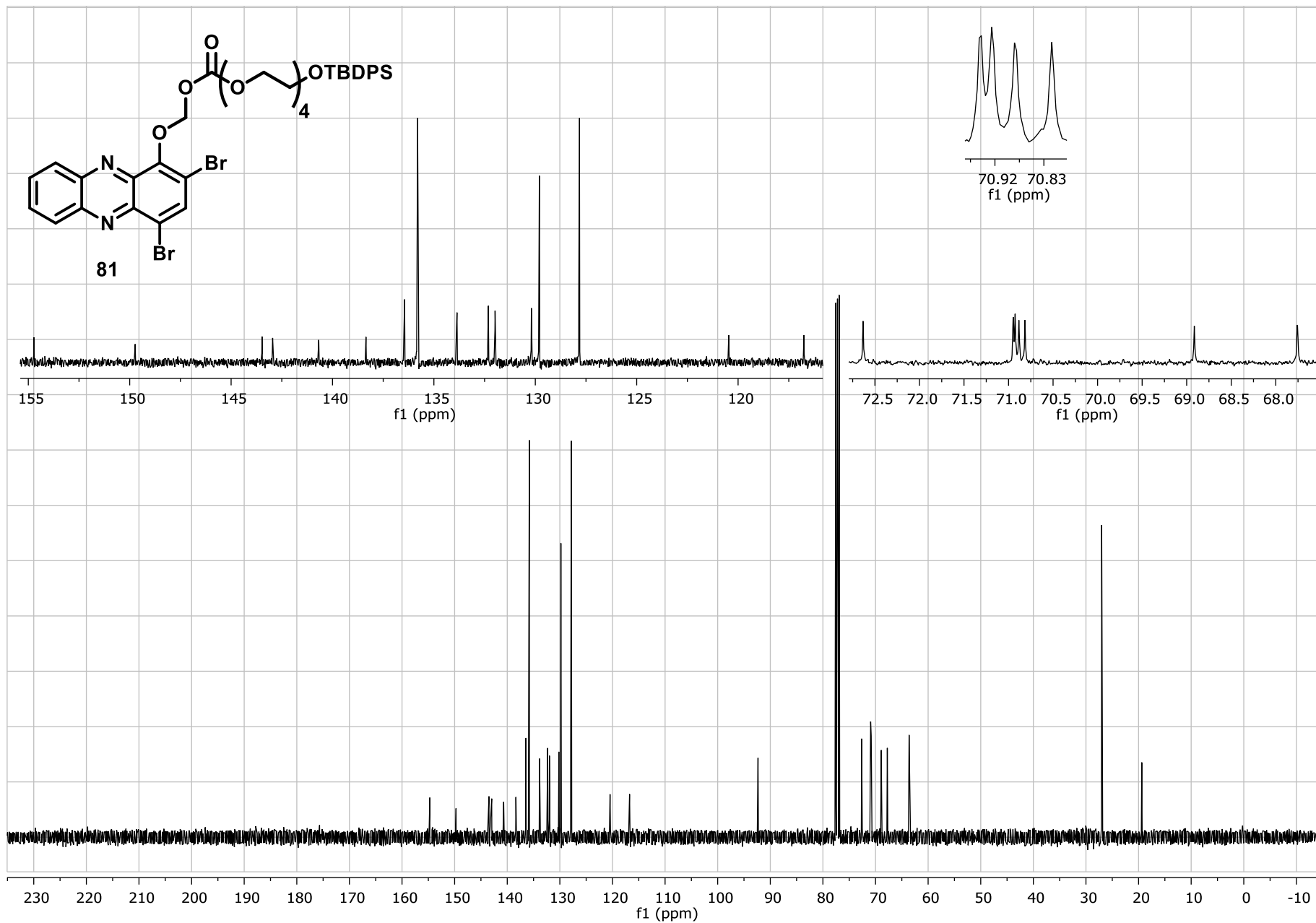


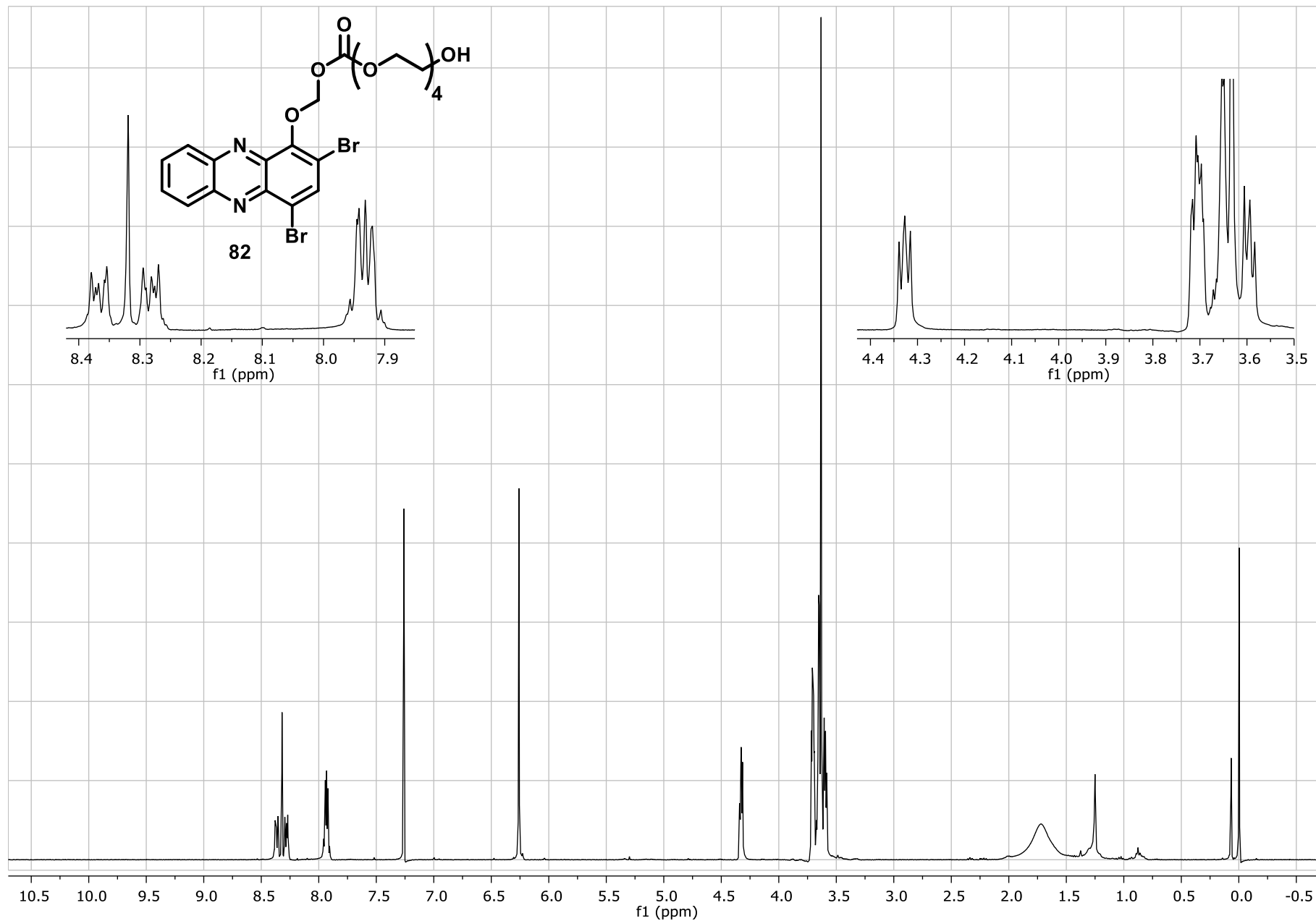




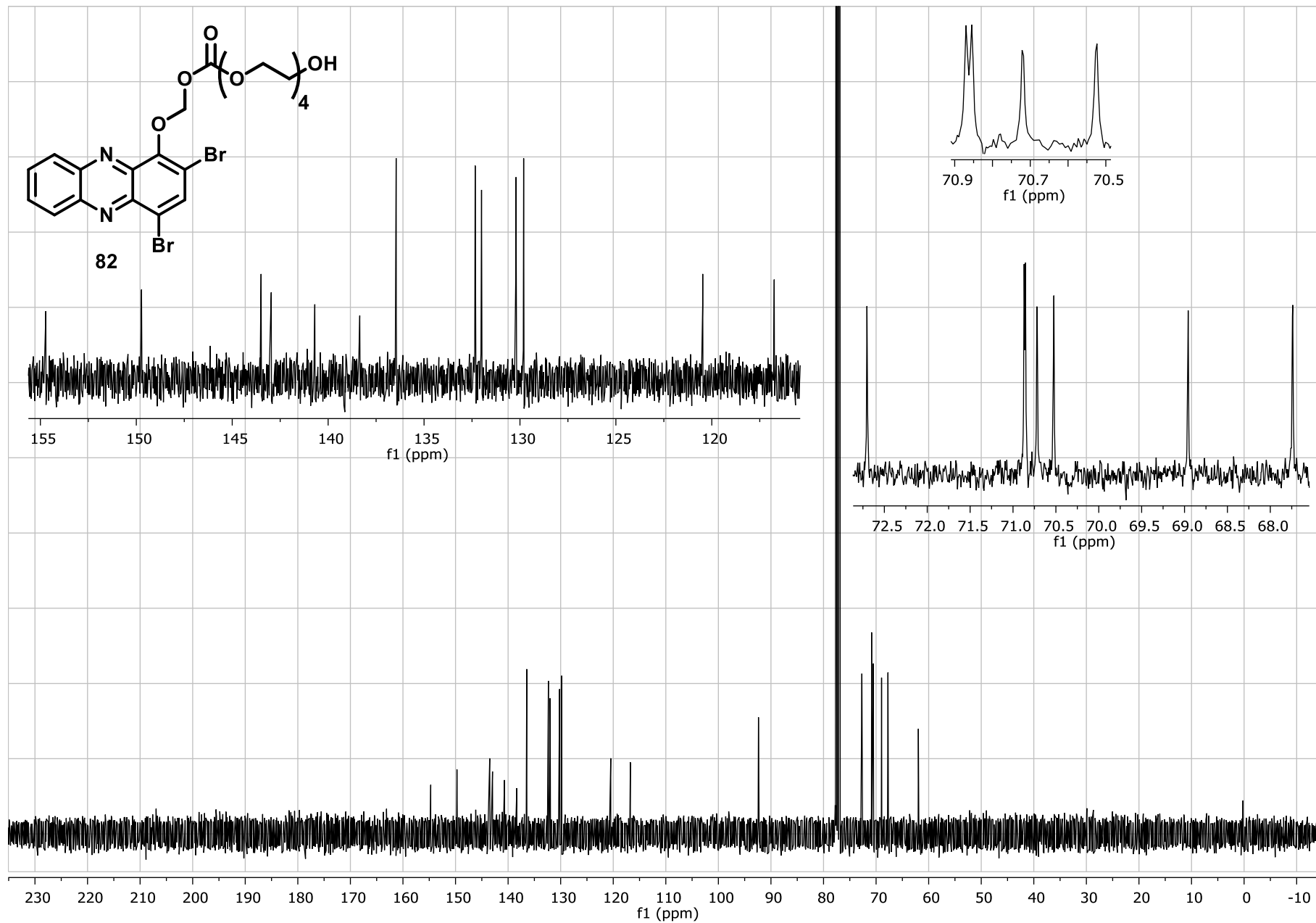


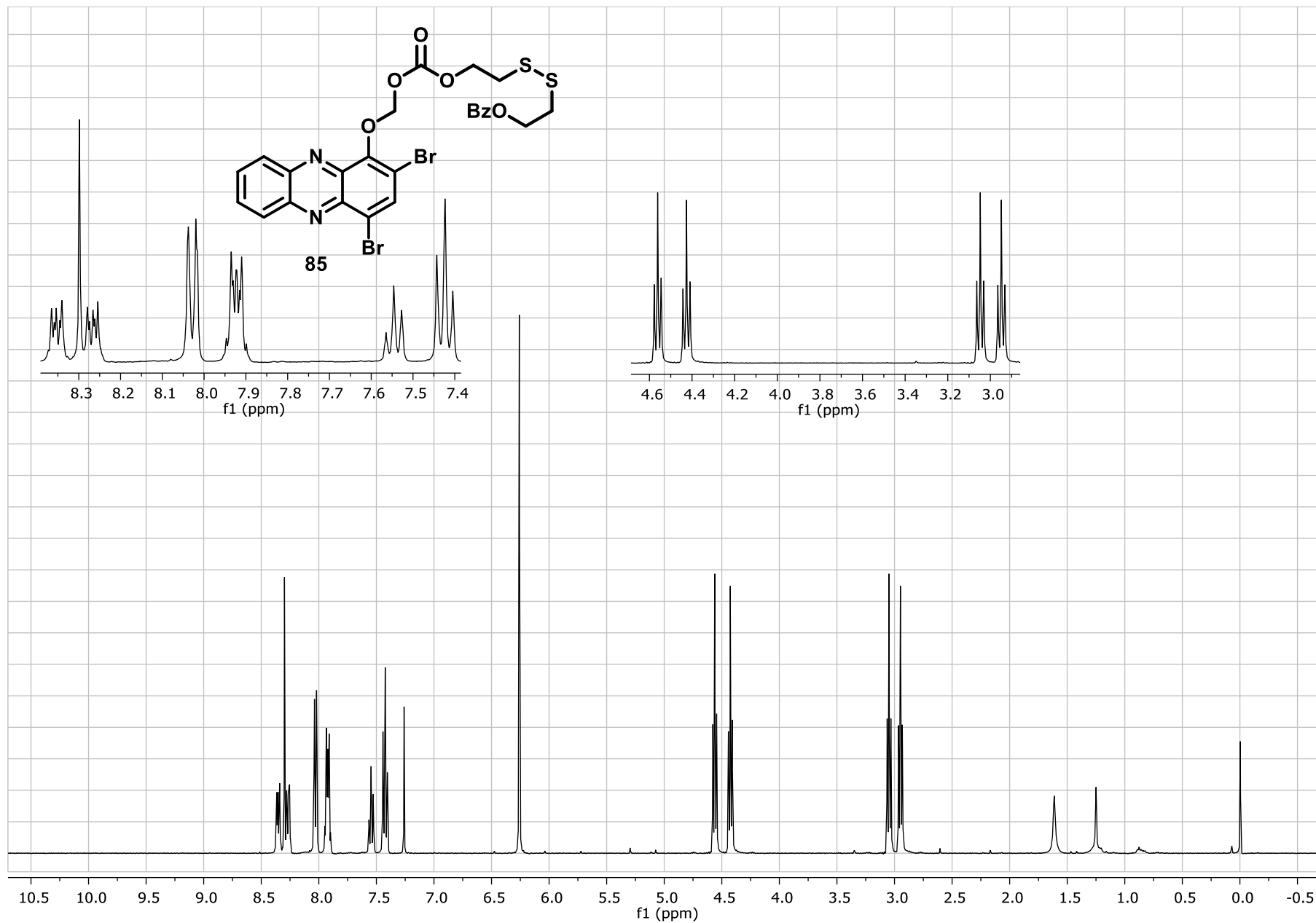


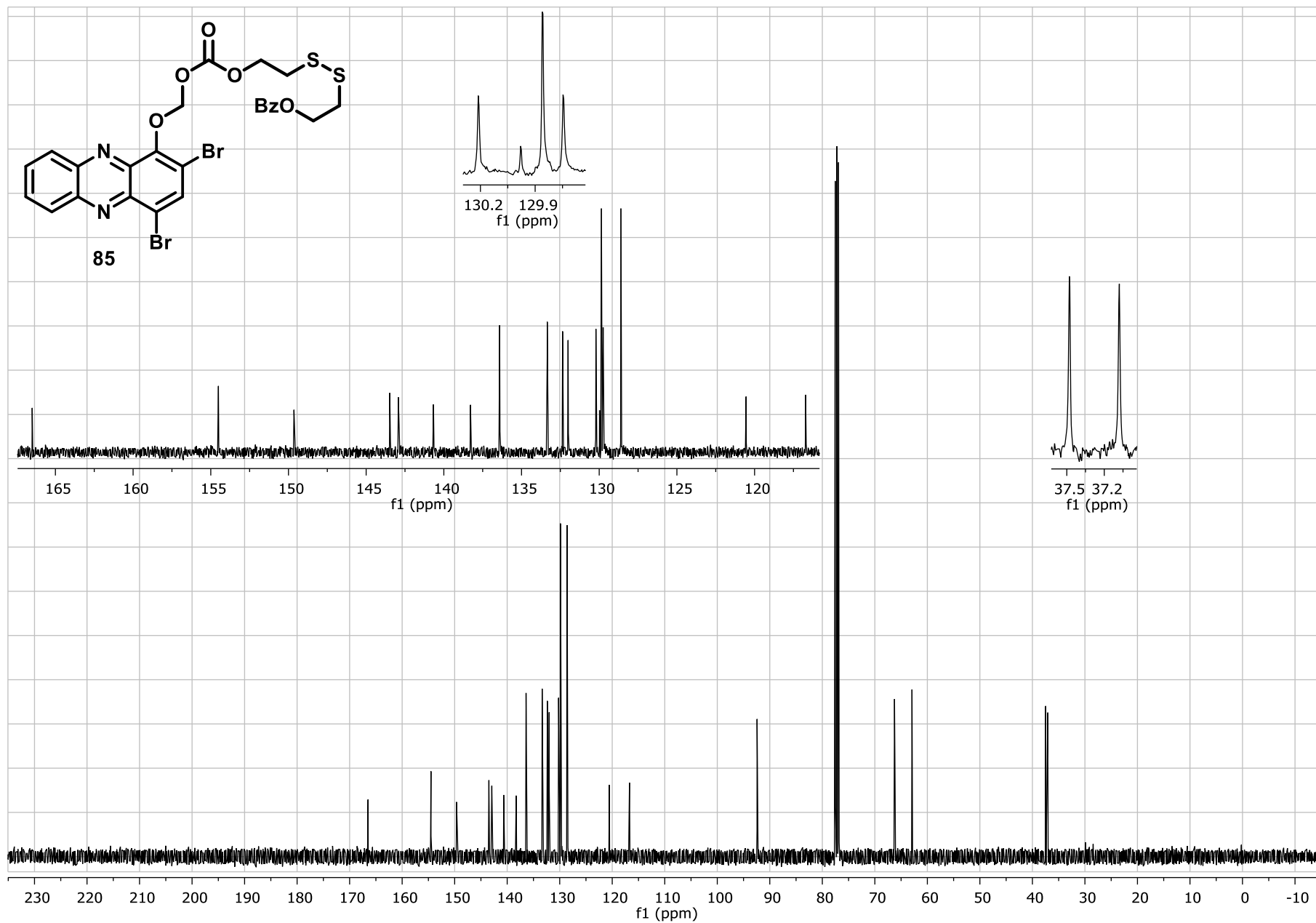


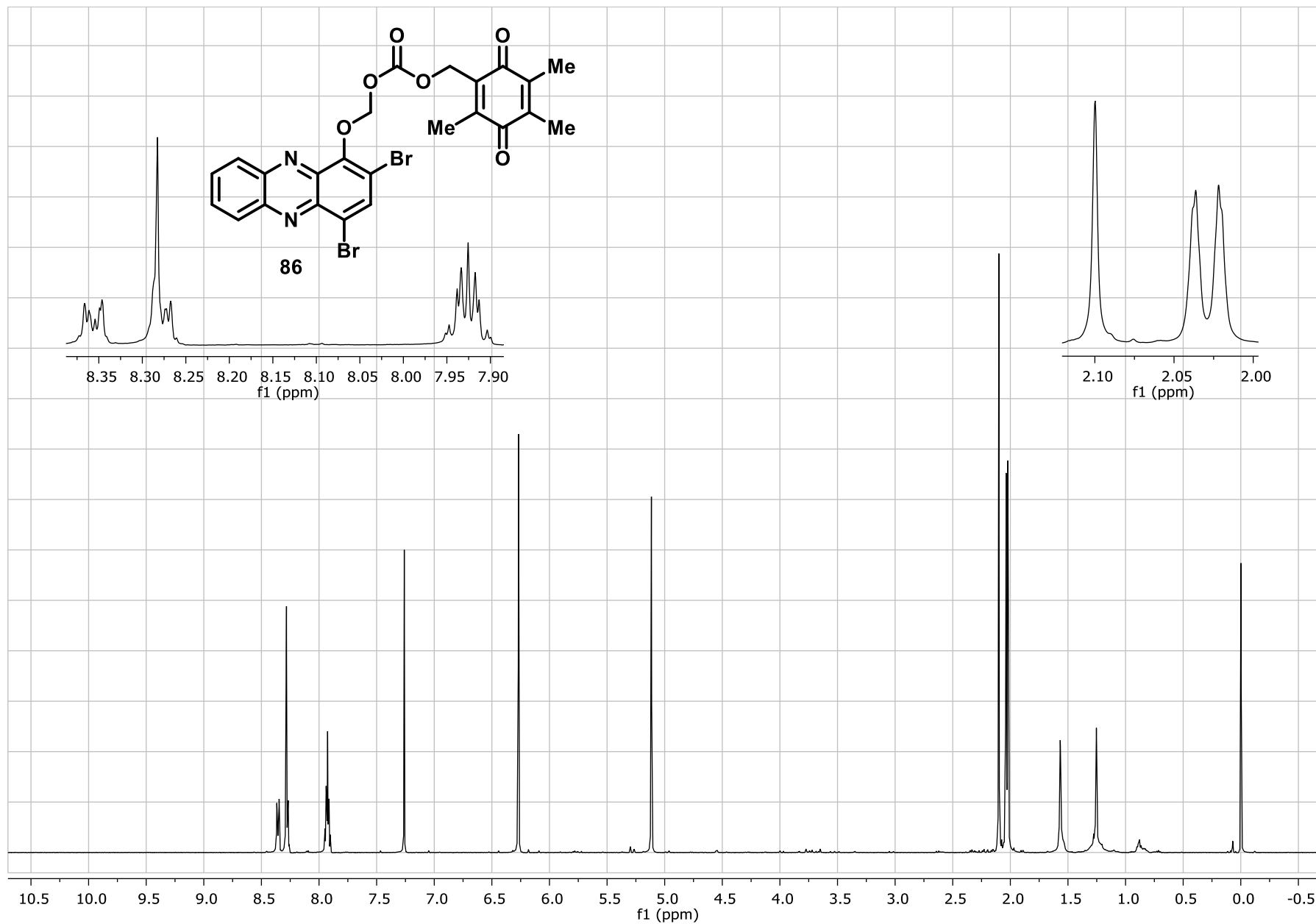




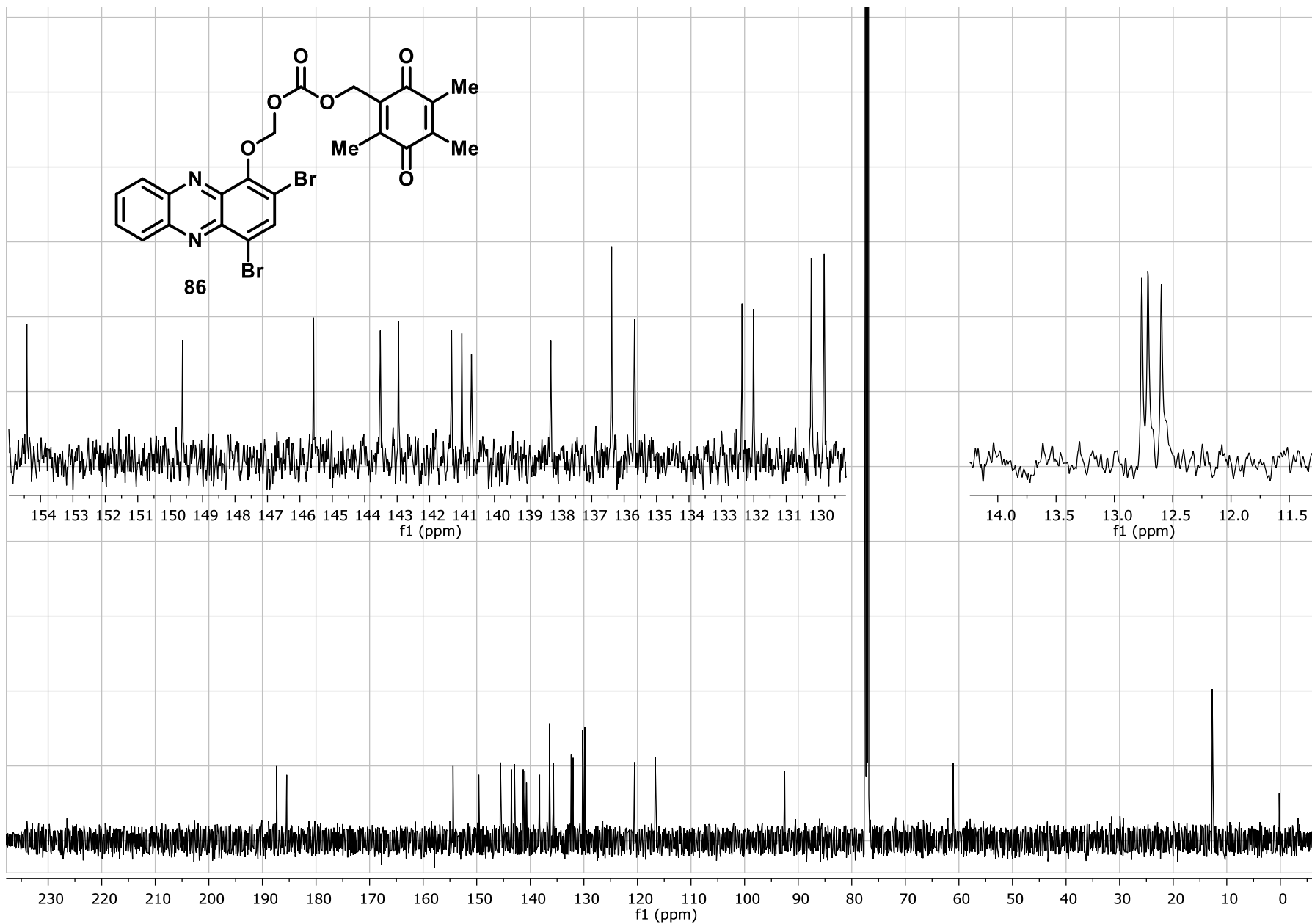
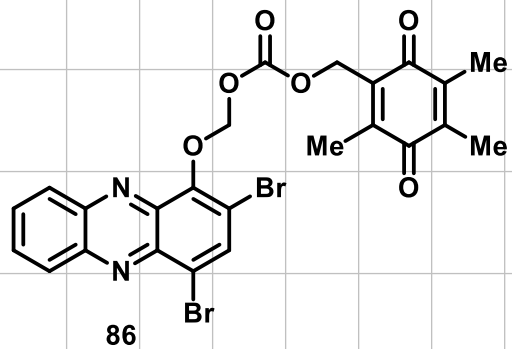




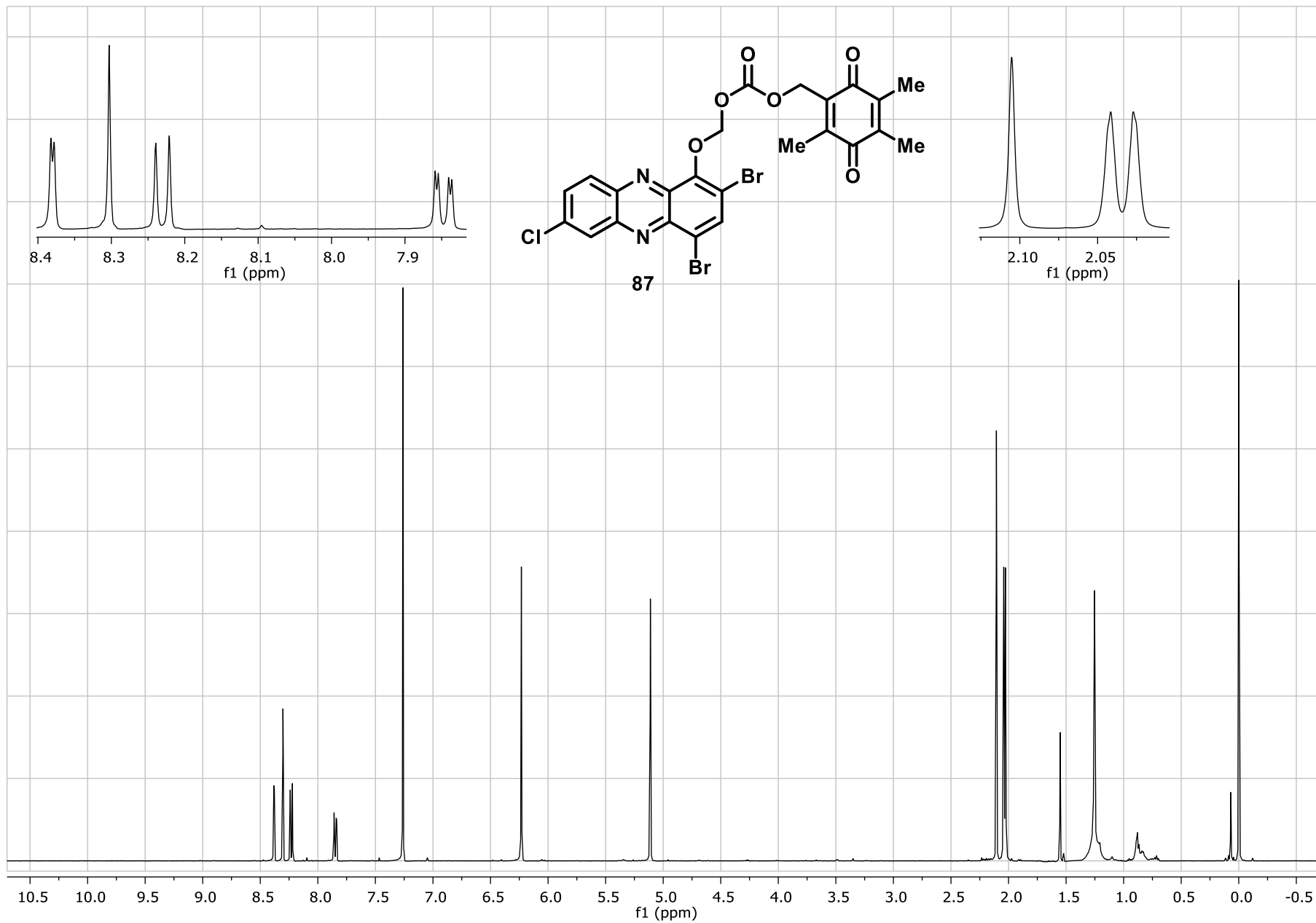




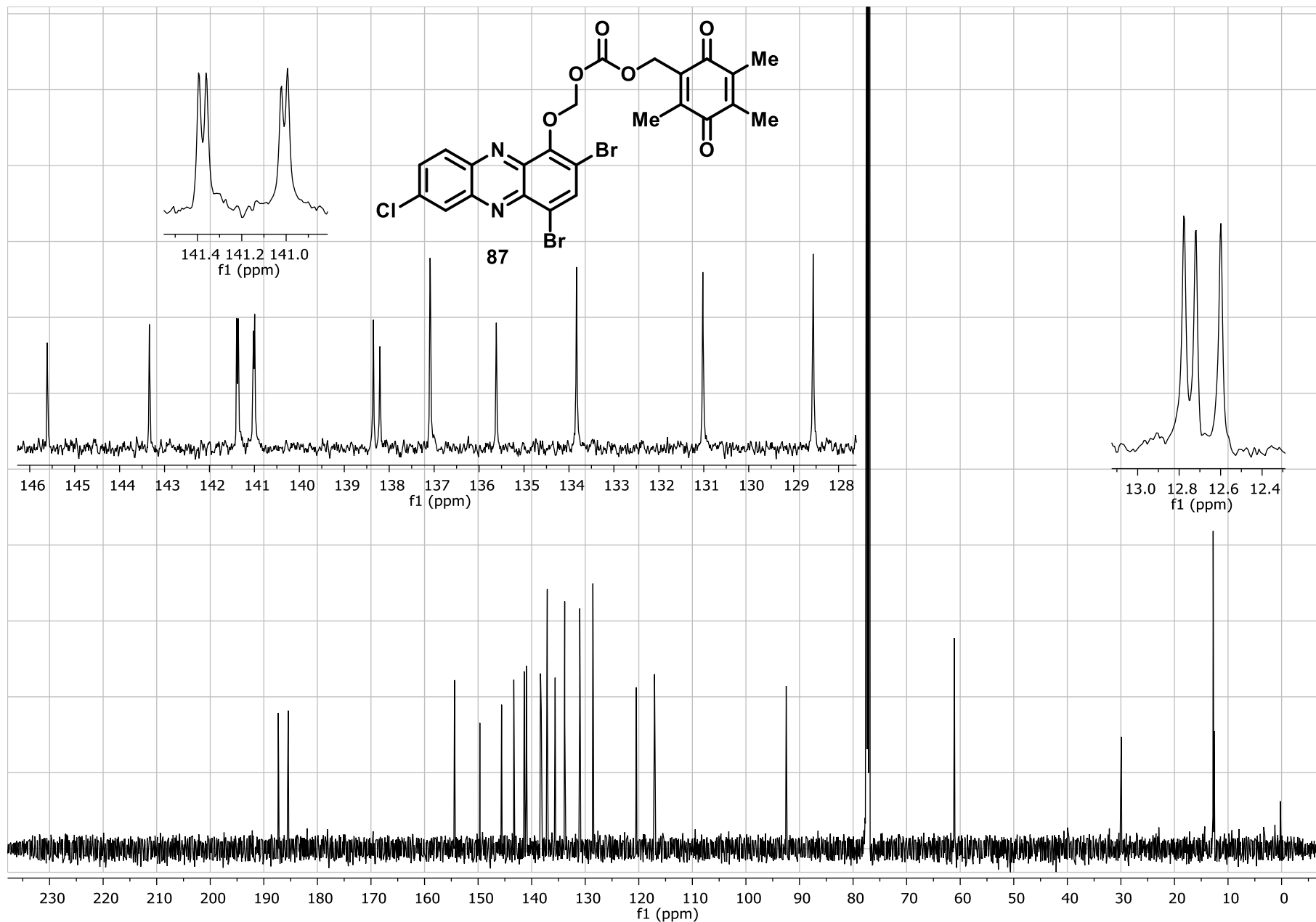
S200



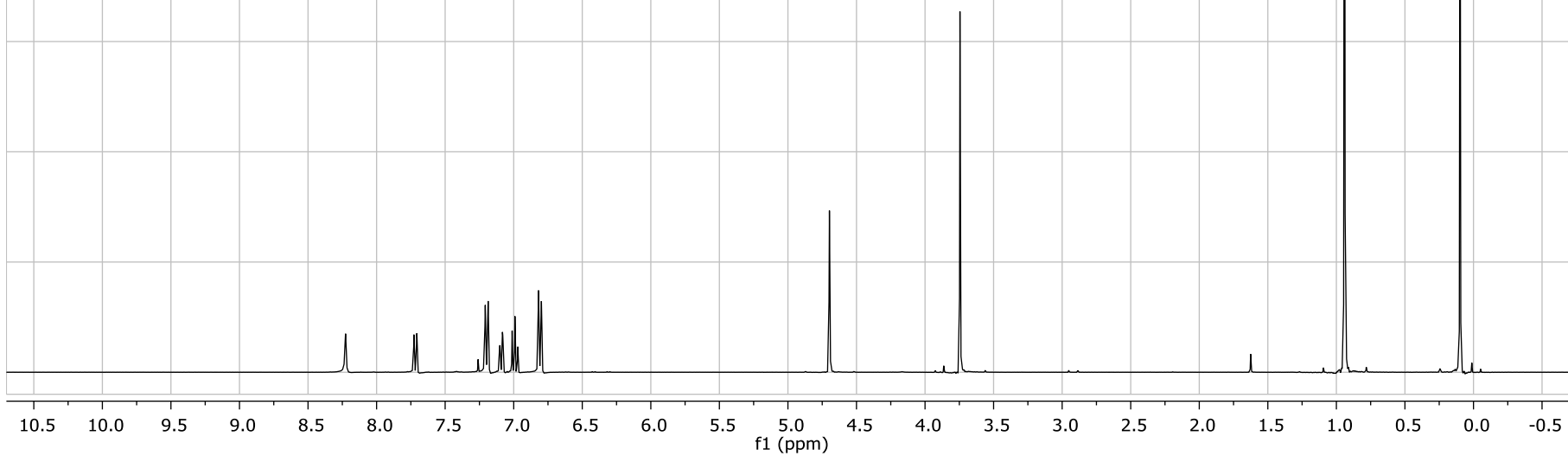
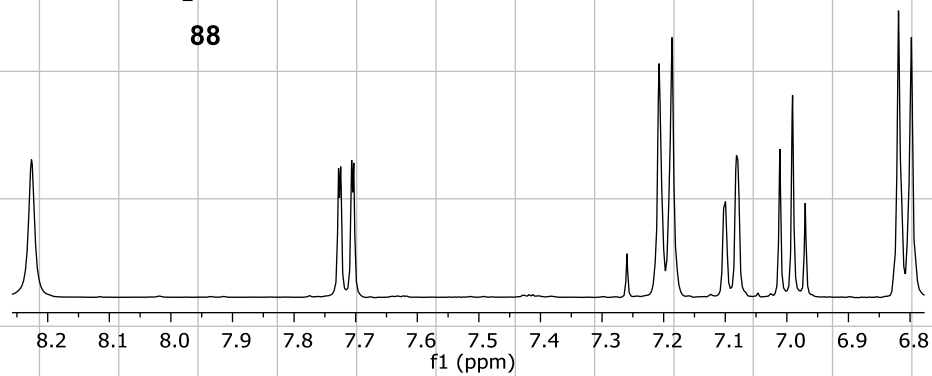
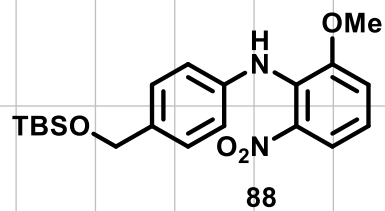
S201



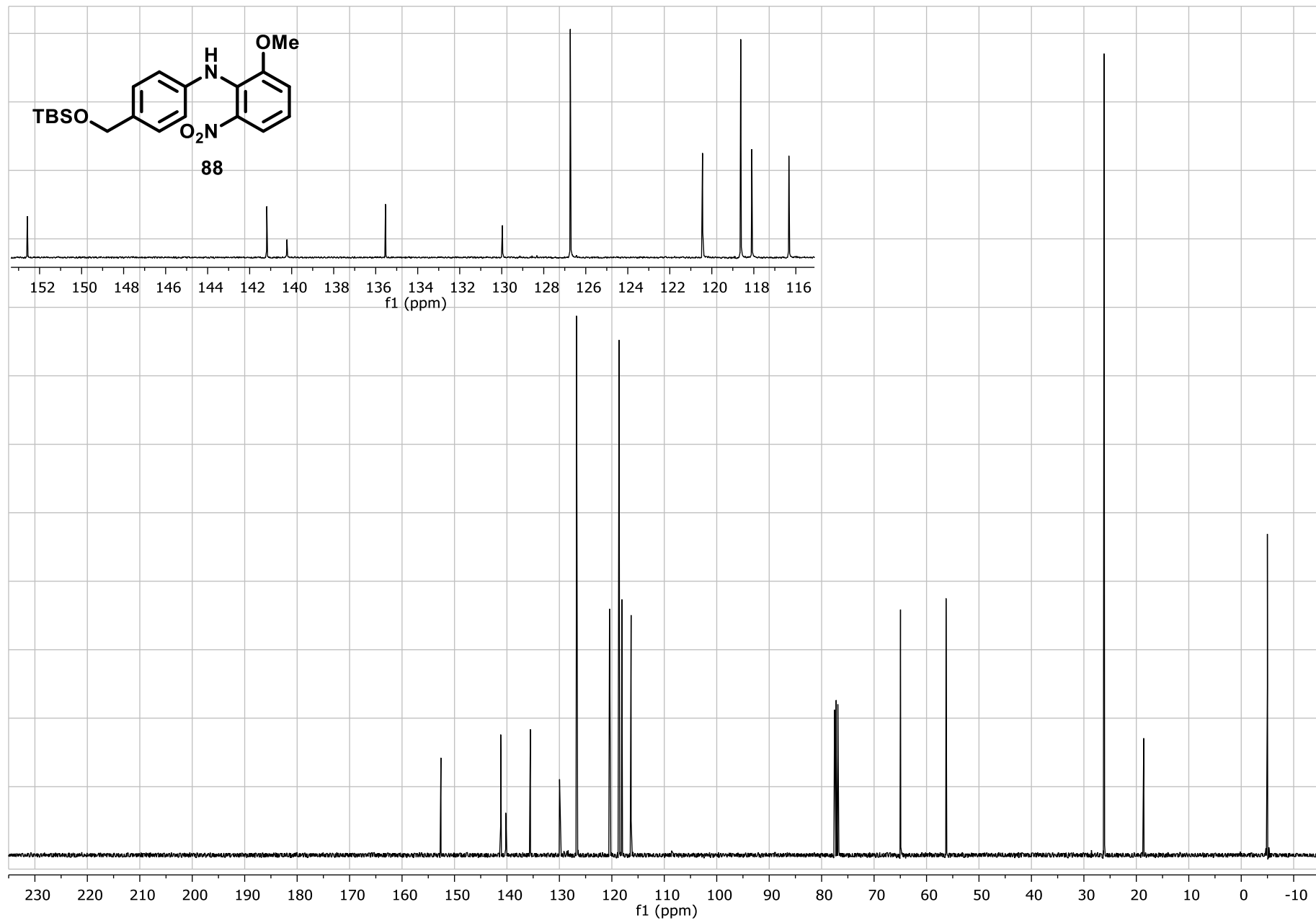
S202

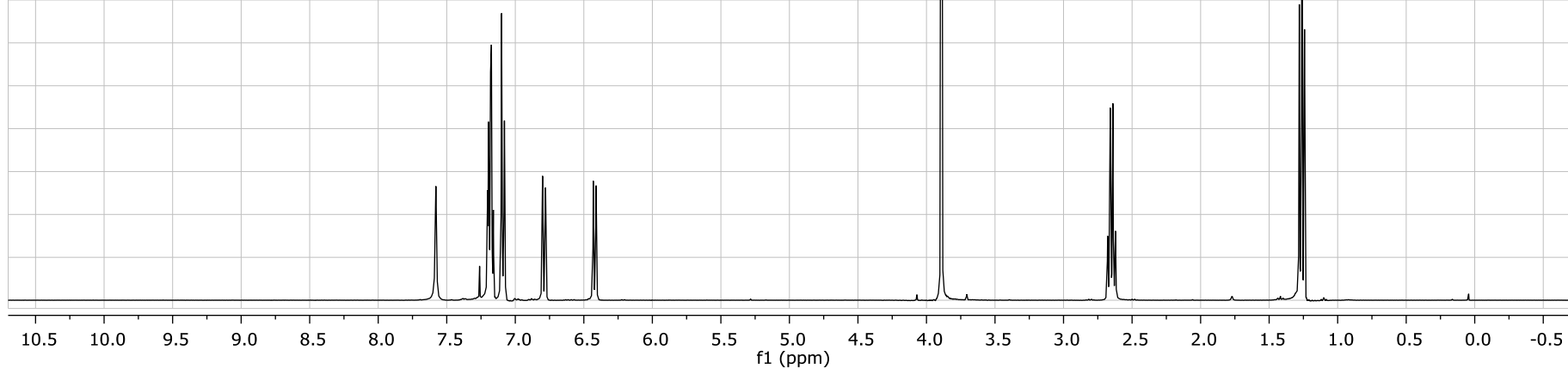
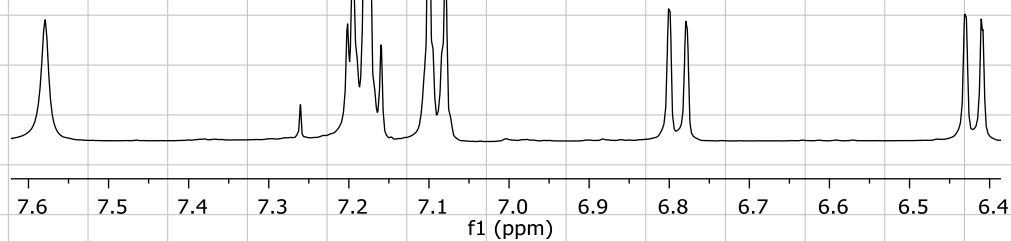
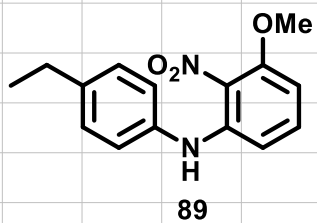


S203

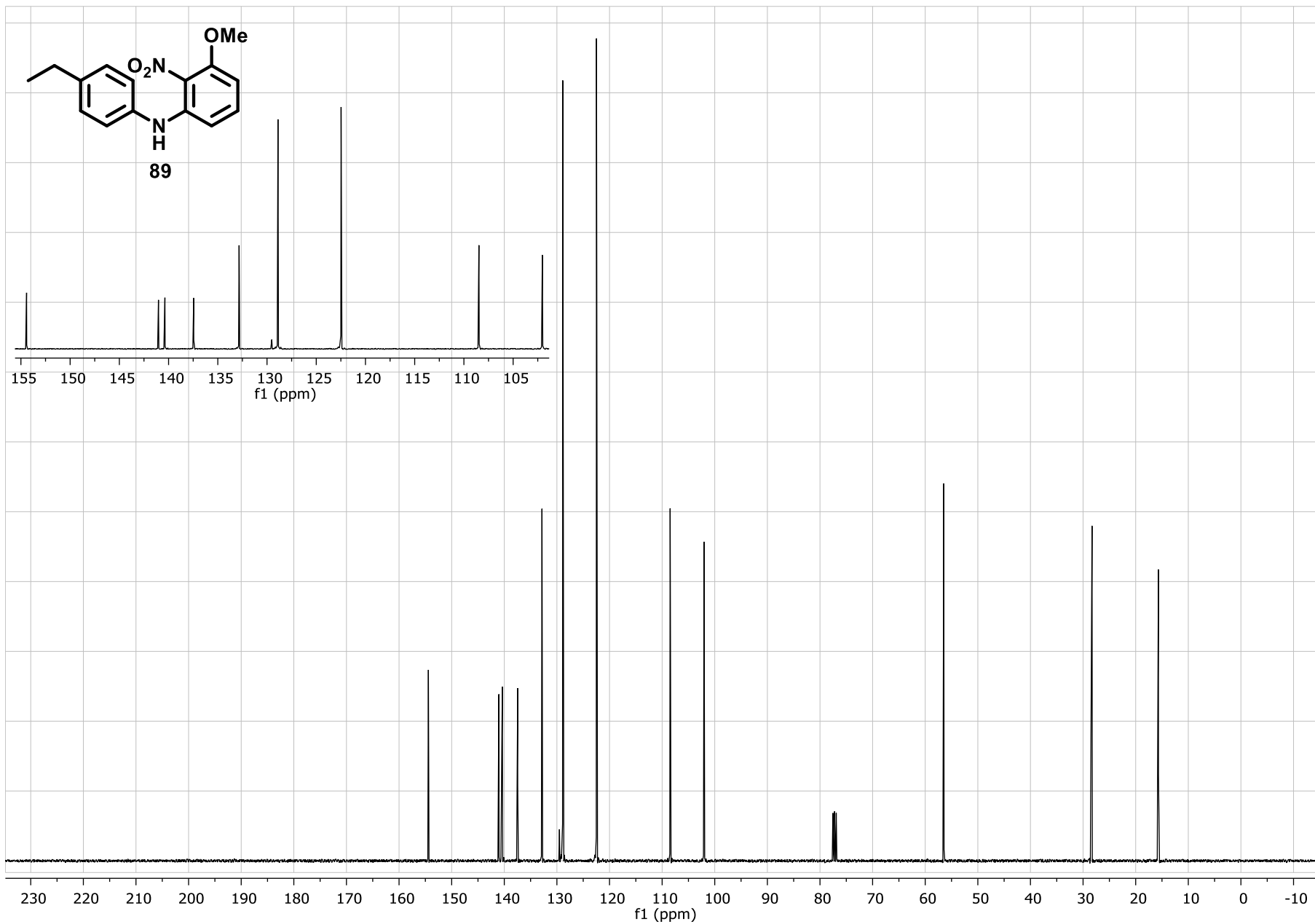


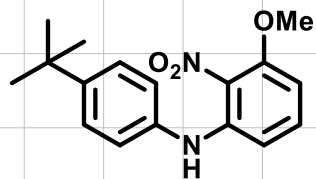




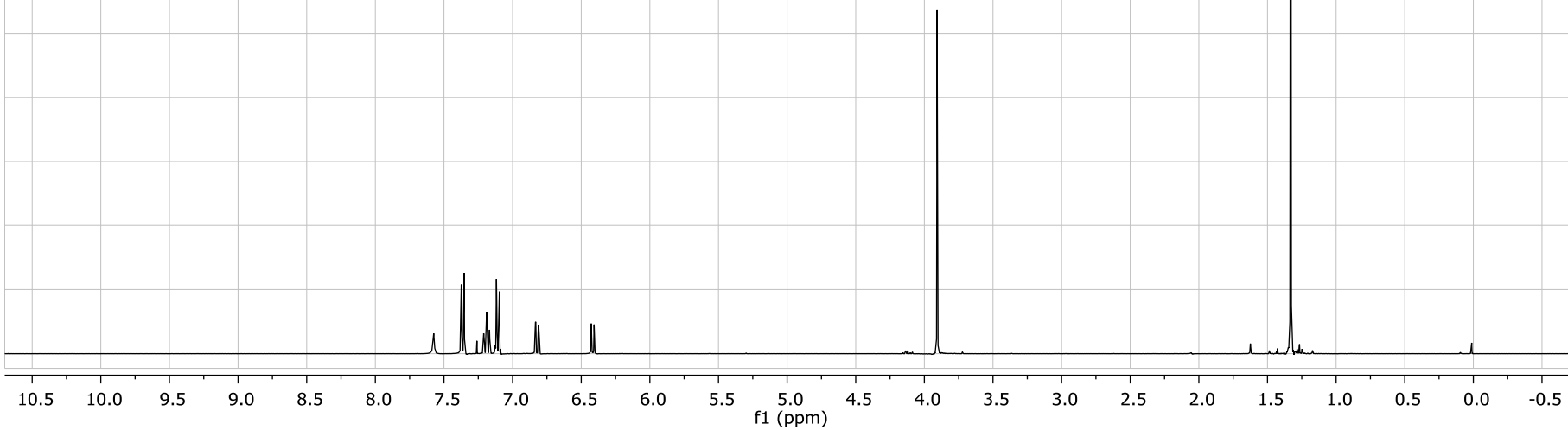
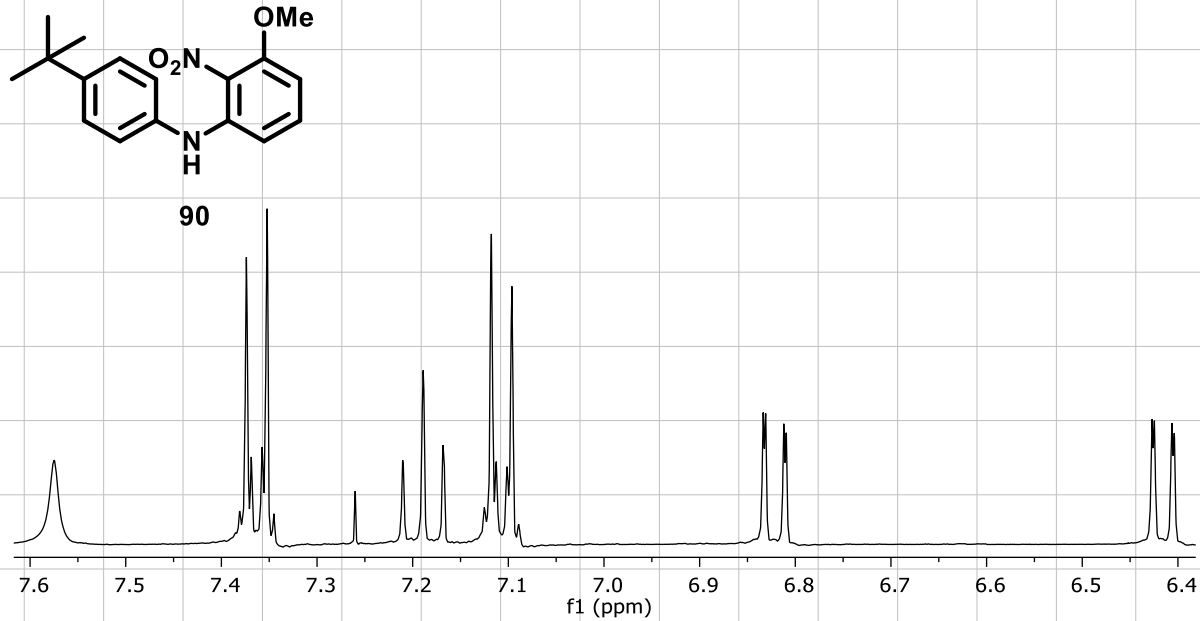


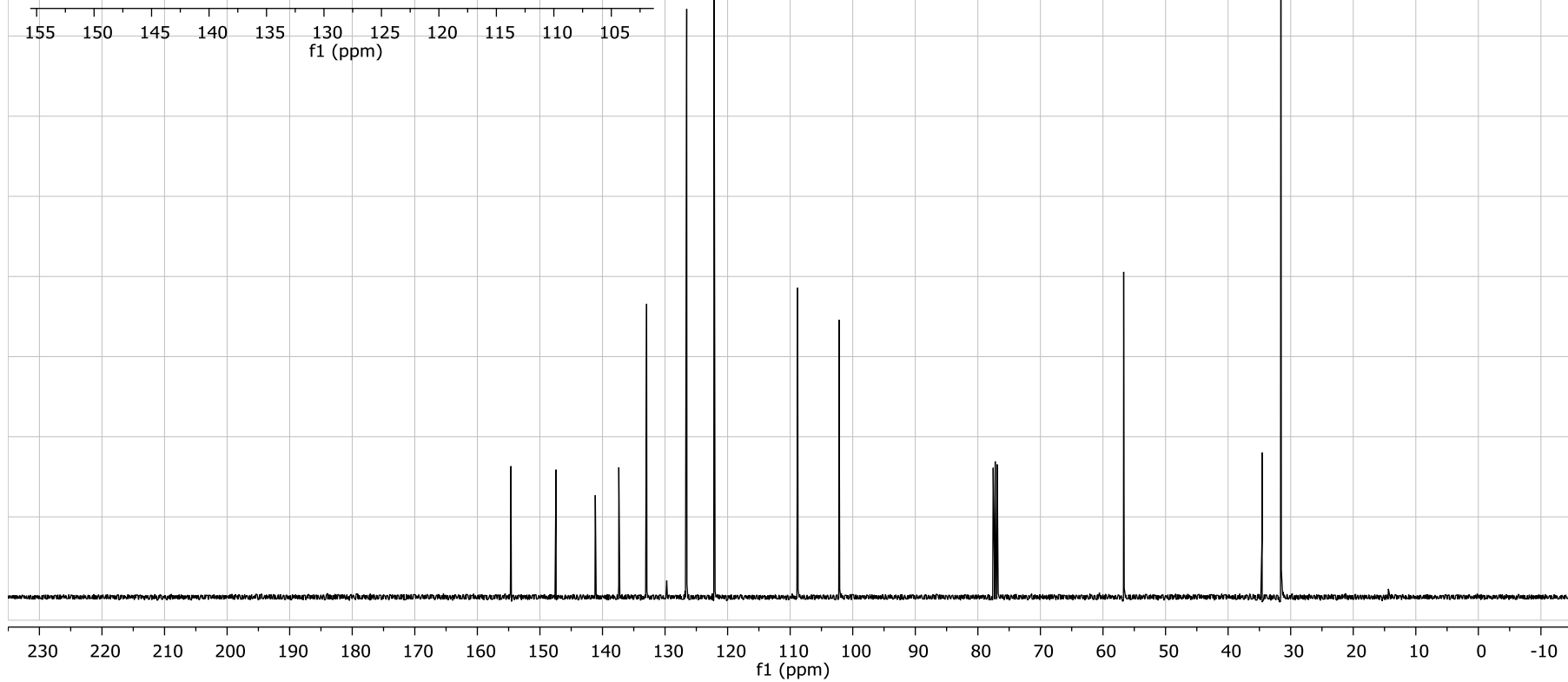
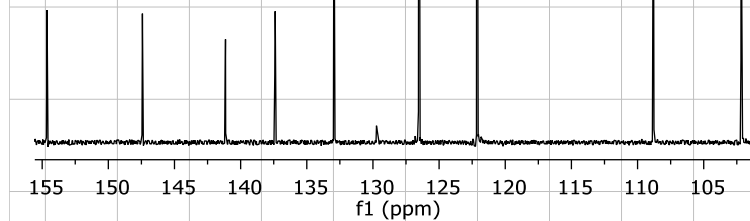
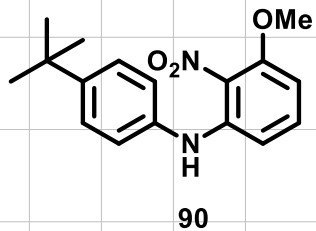
S206

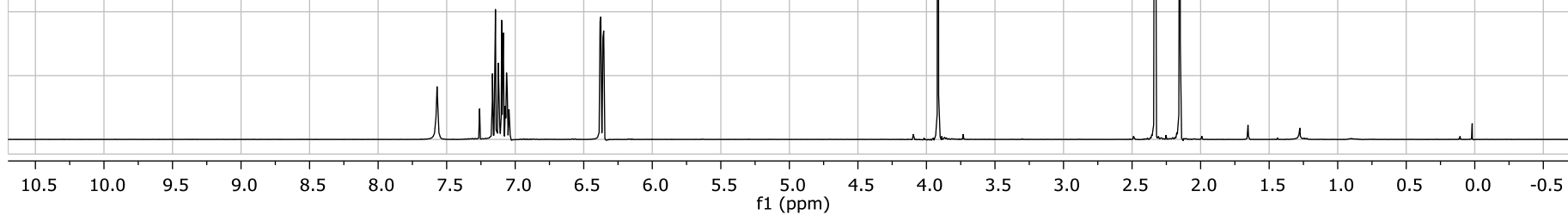
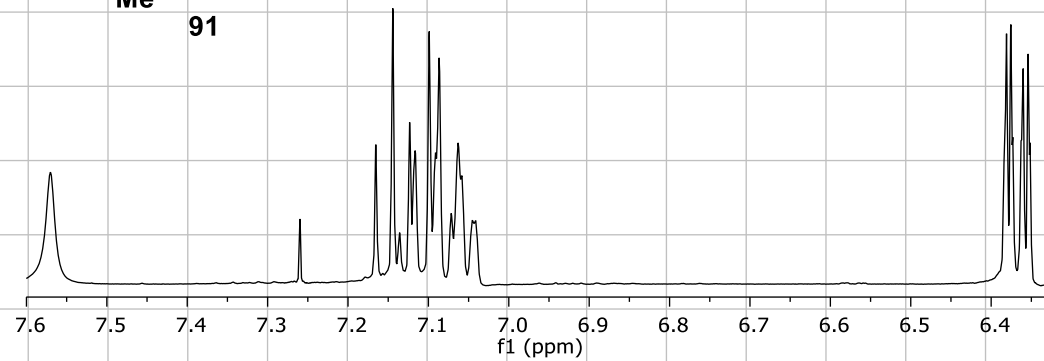
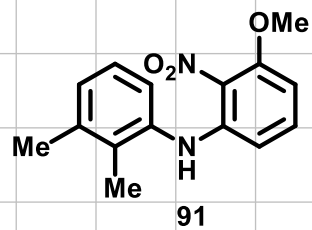


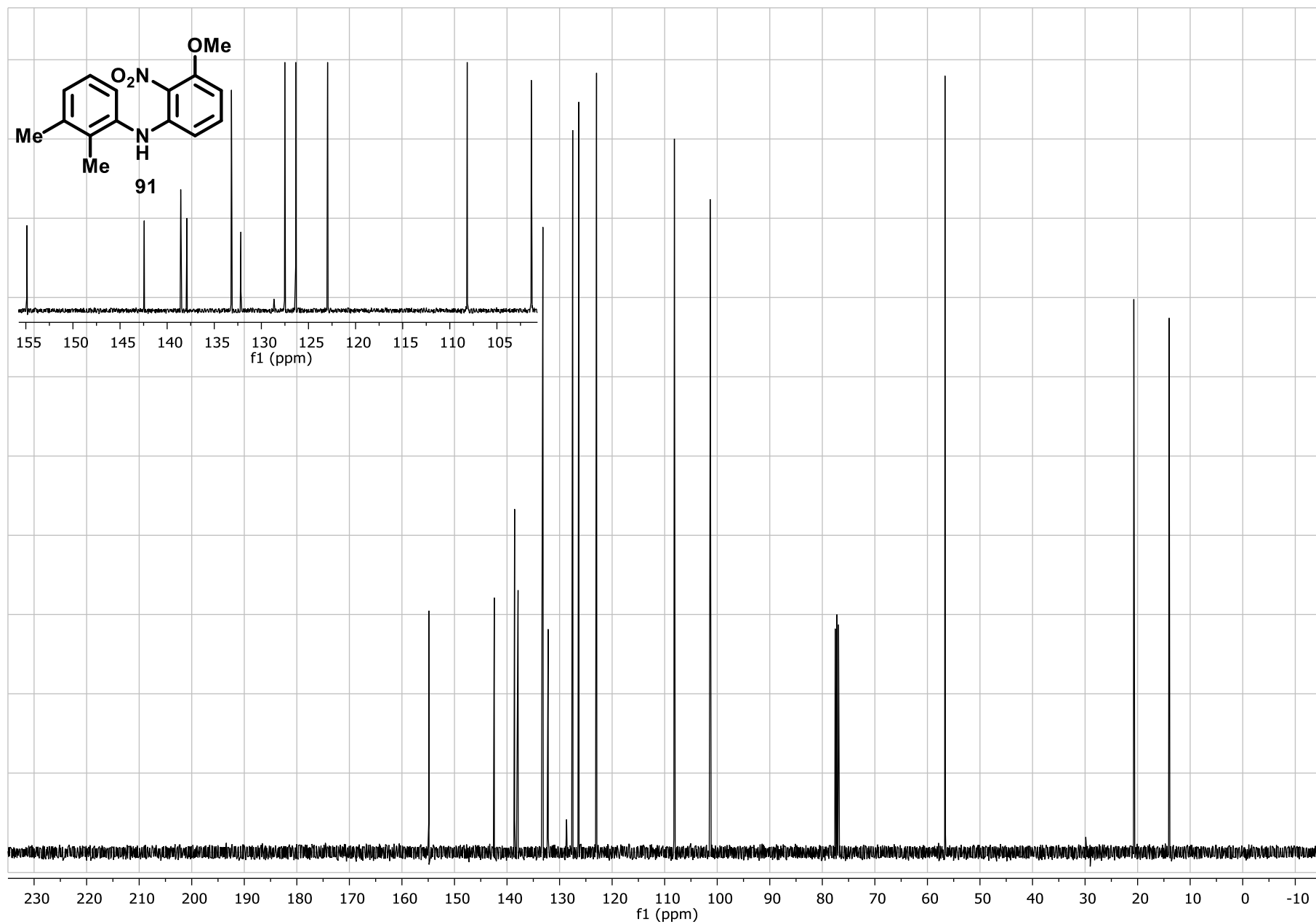


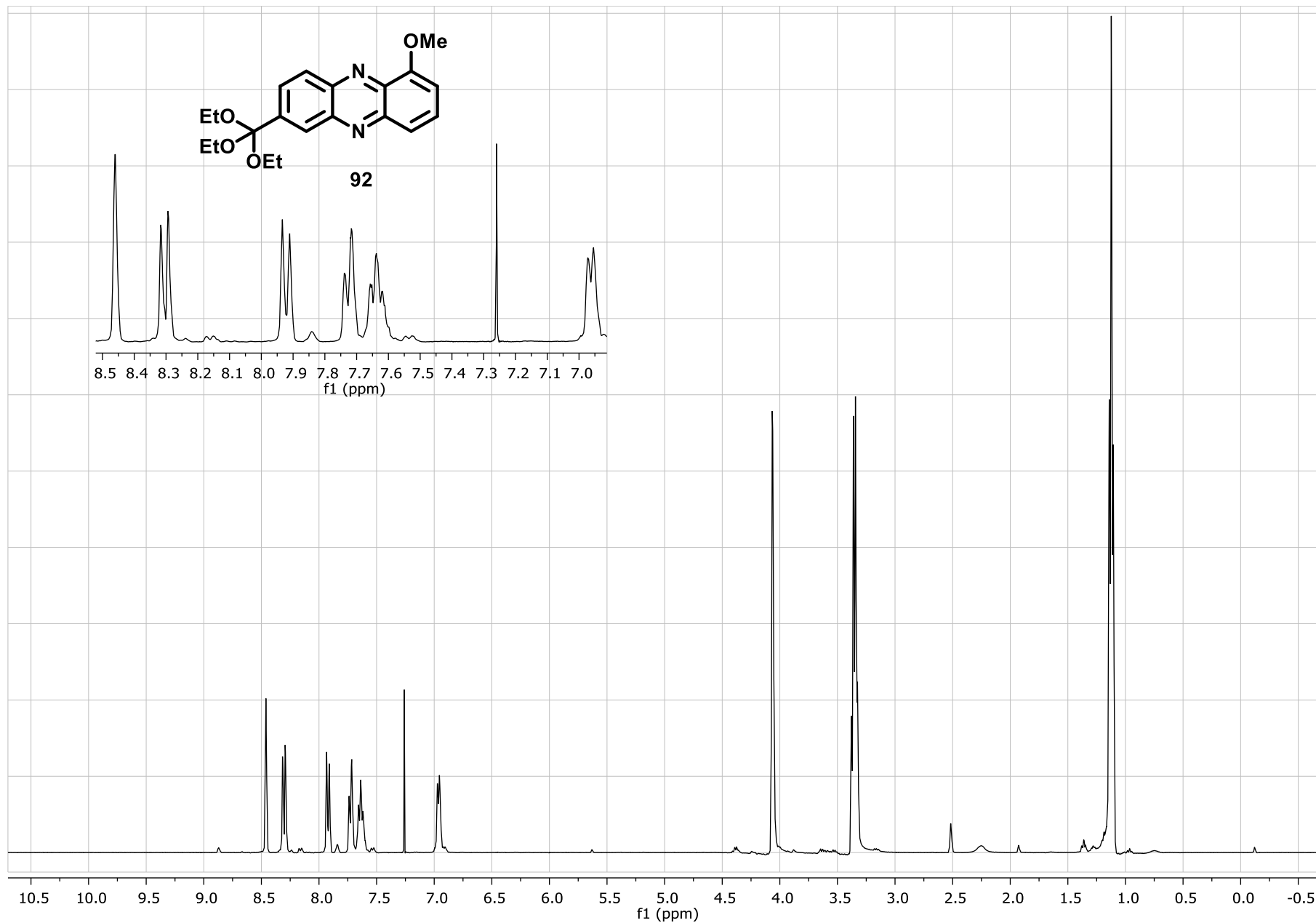
90





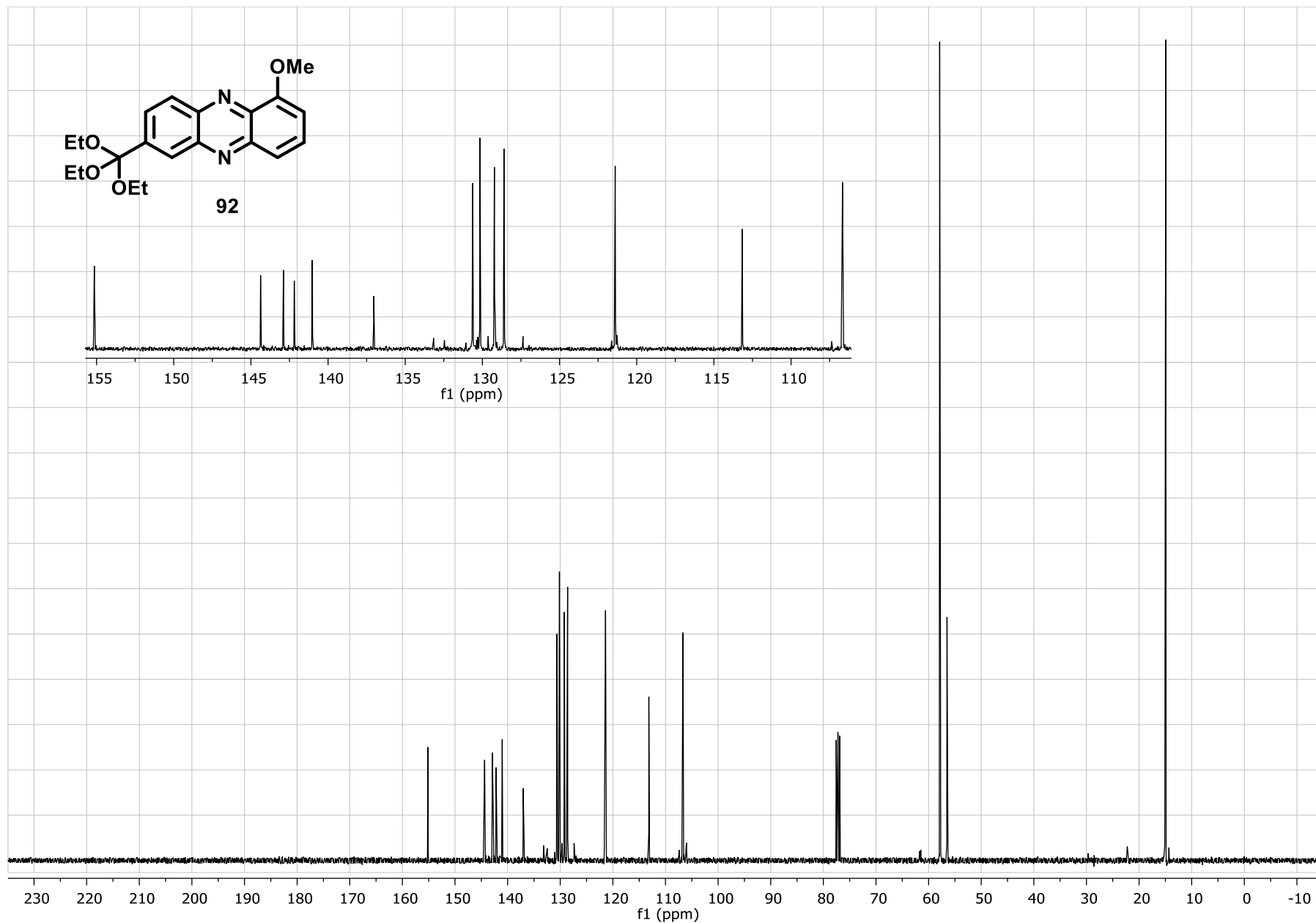
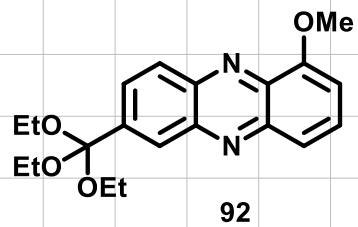




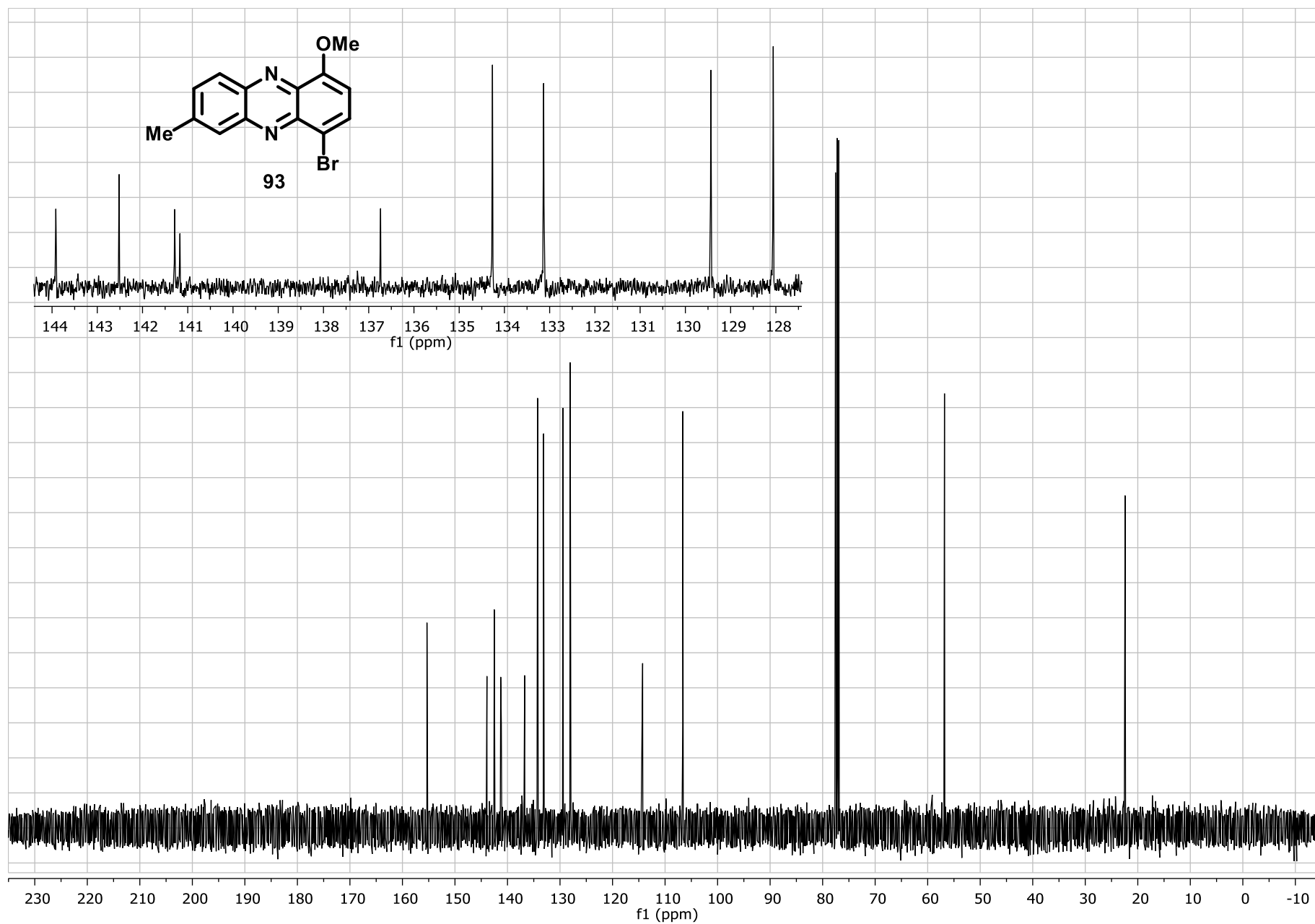
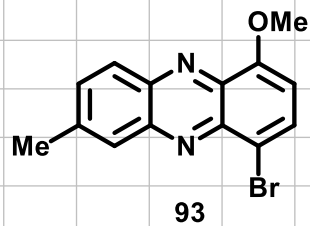


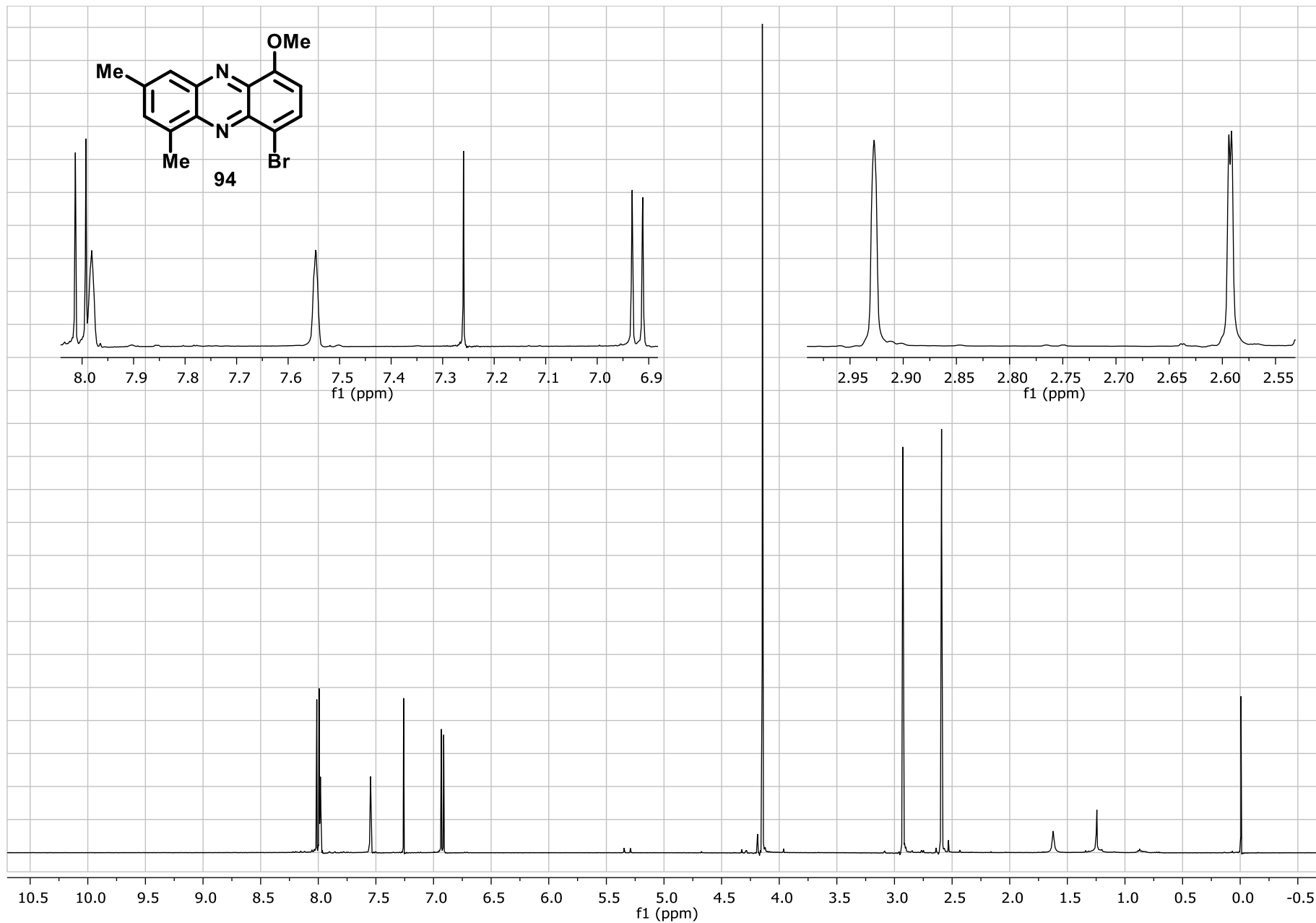
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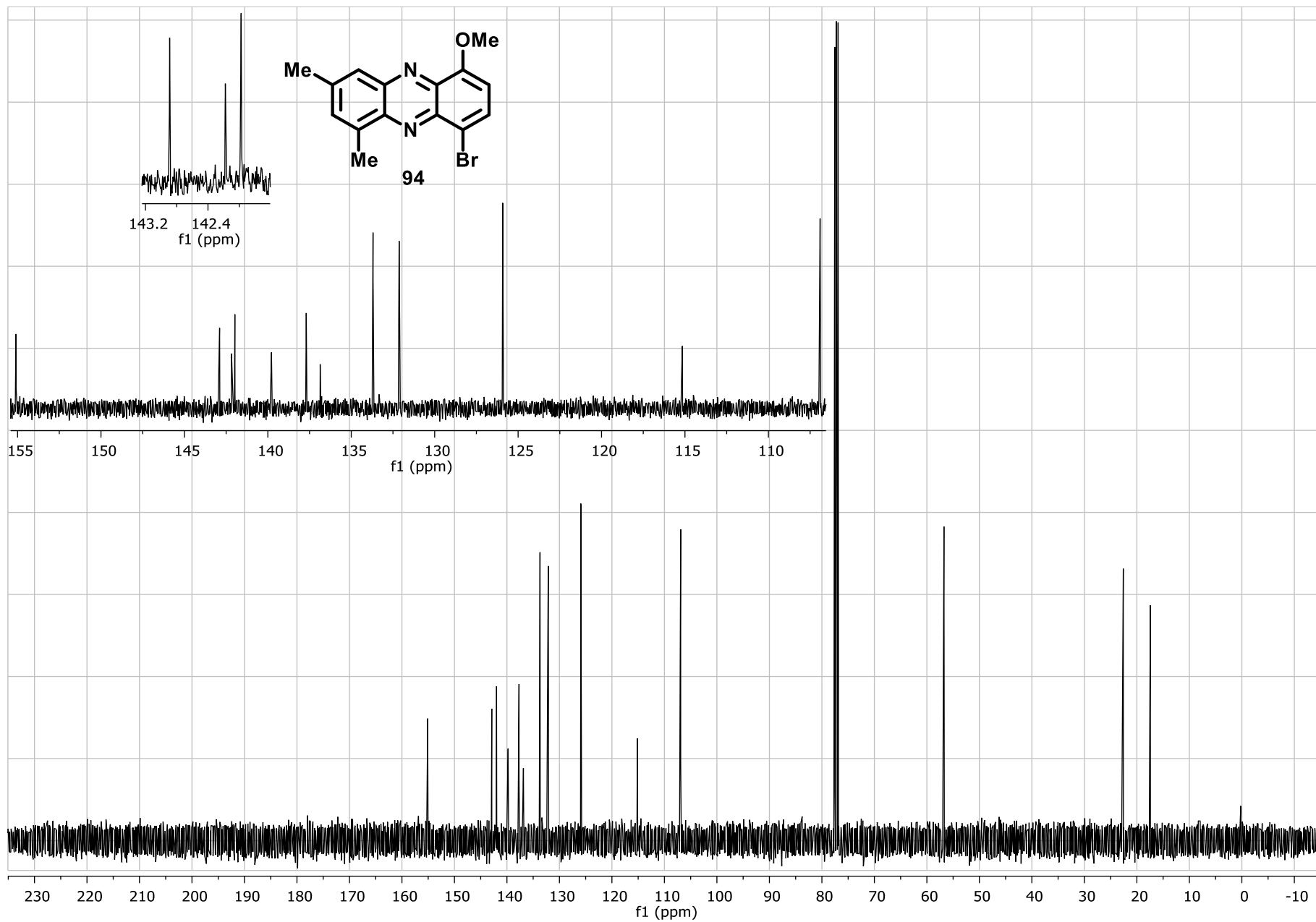


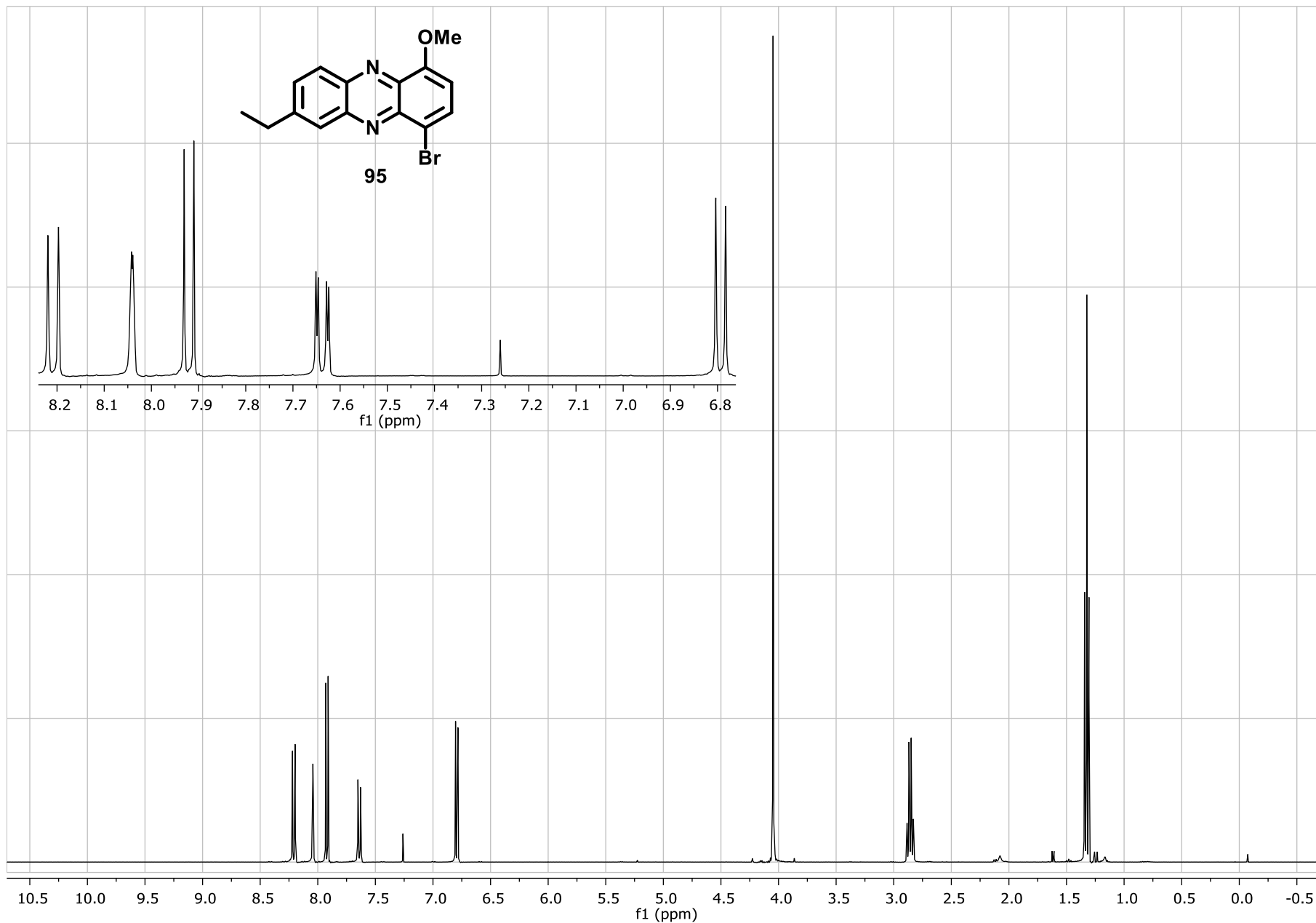




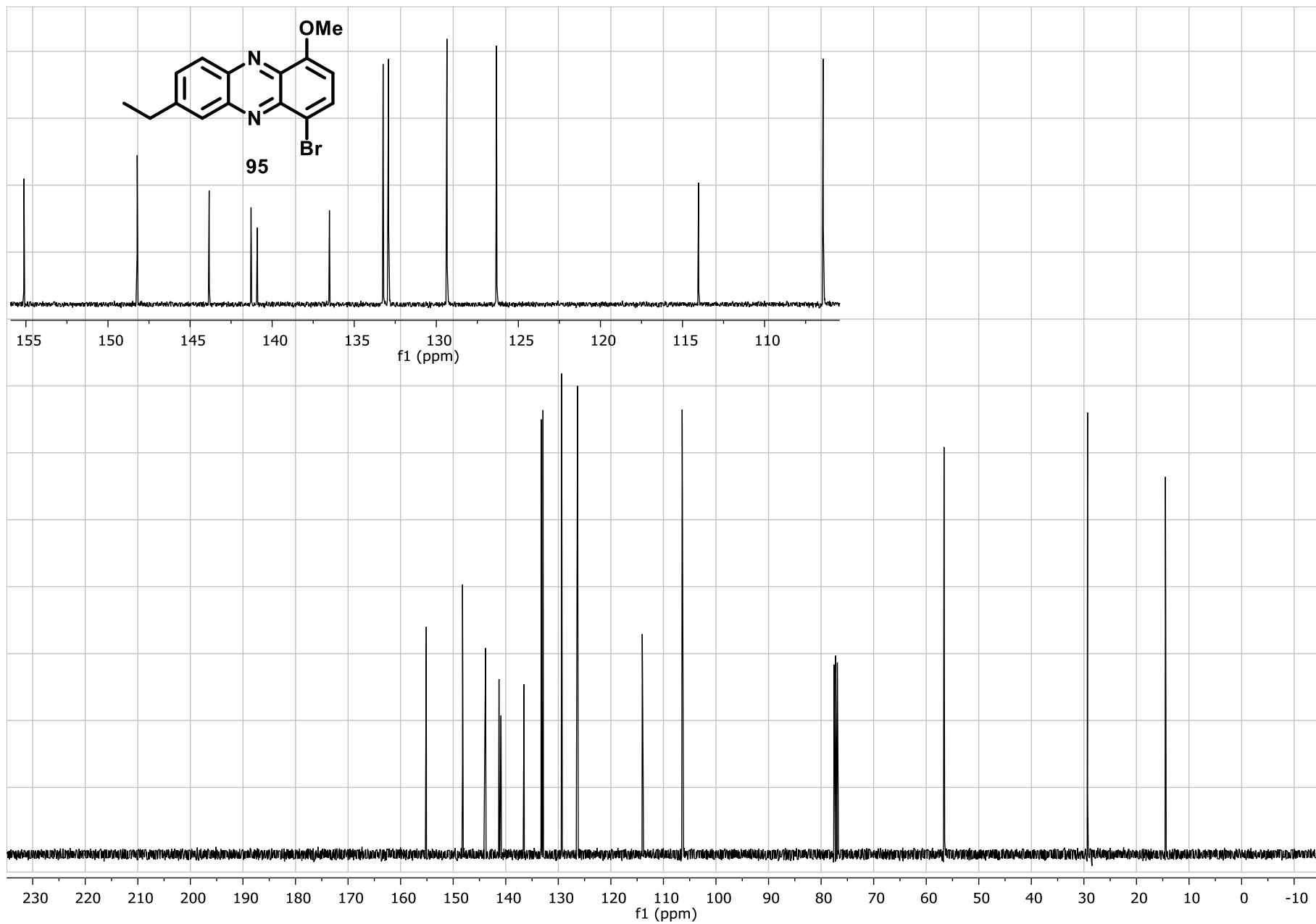


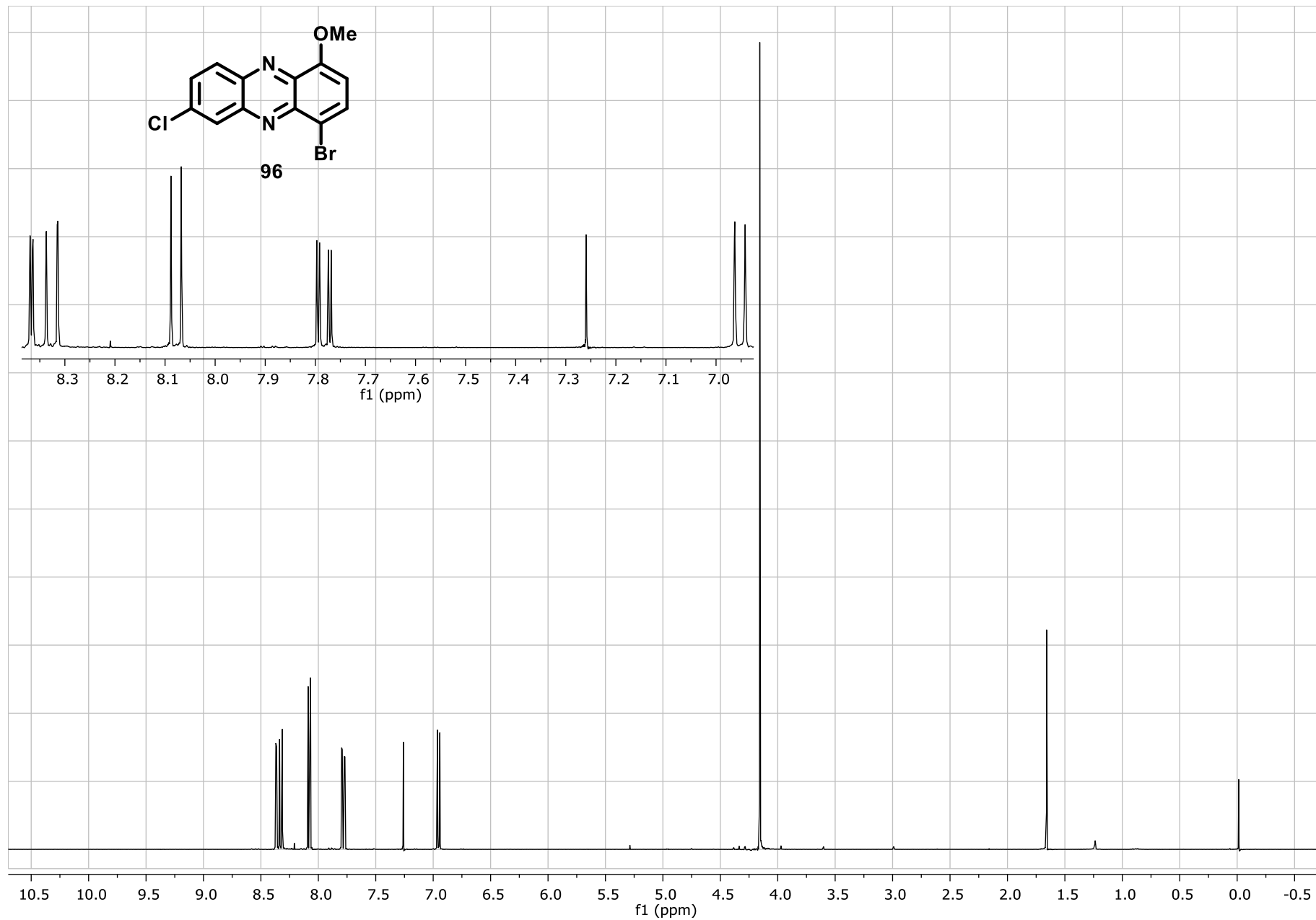
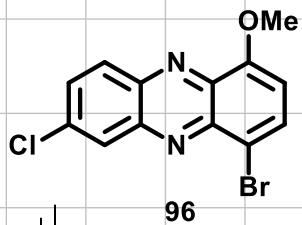






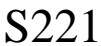
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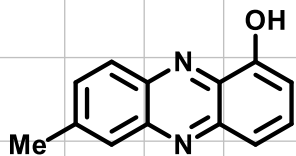




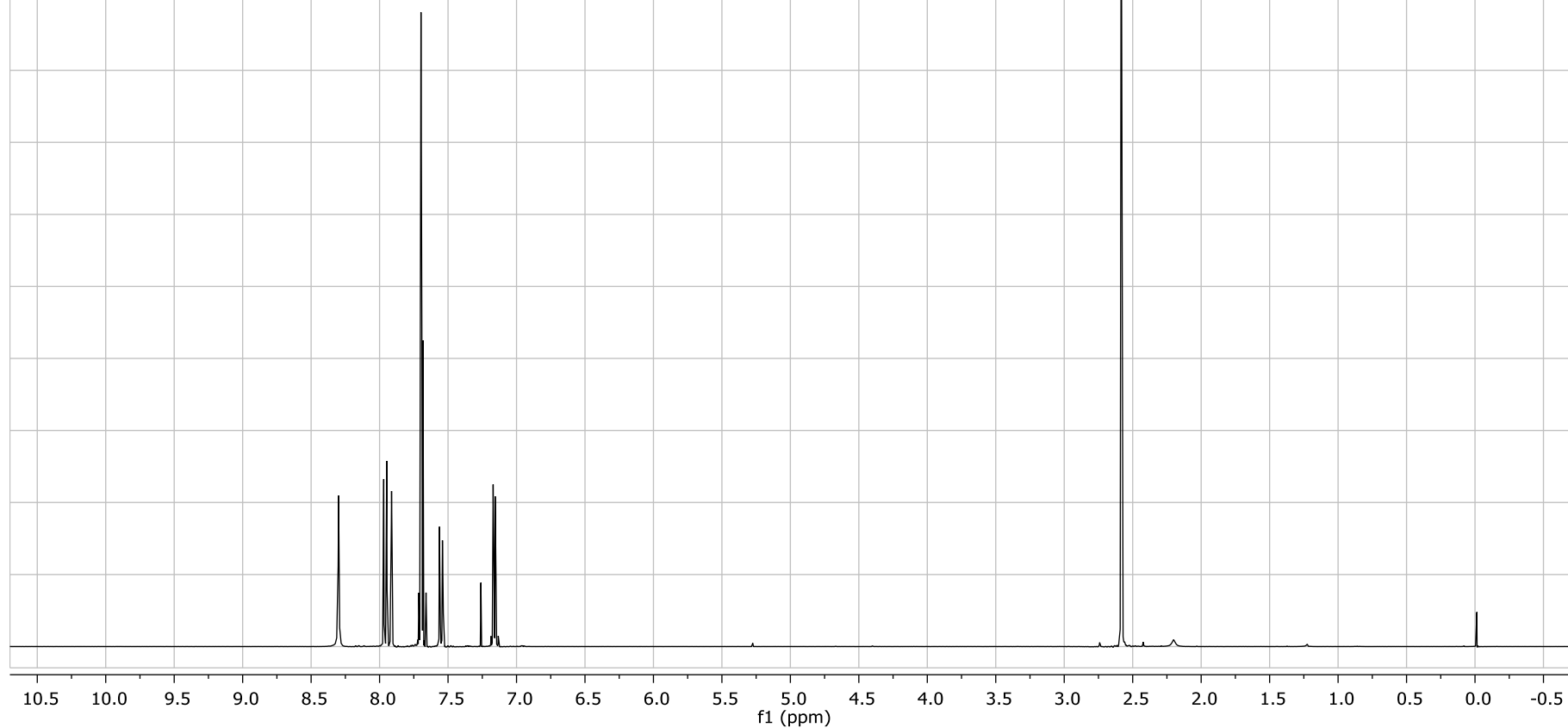
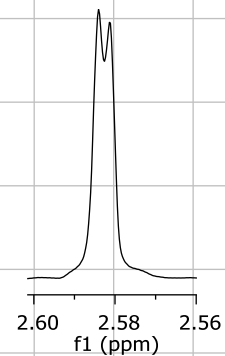
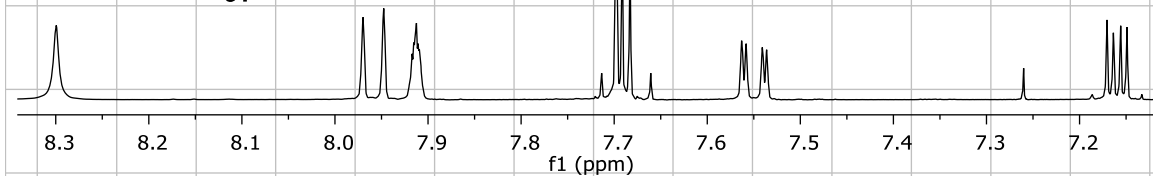
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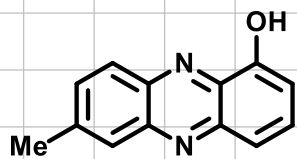




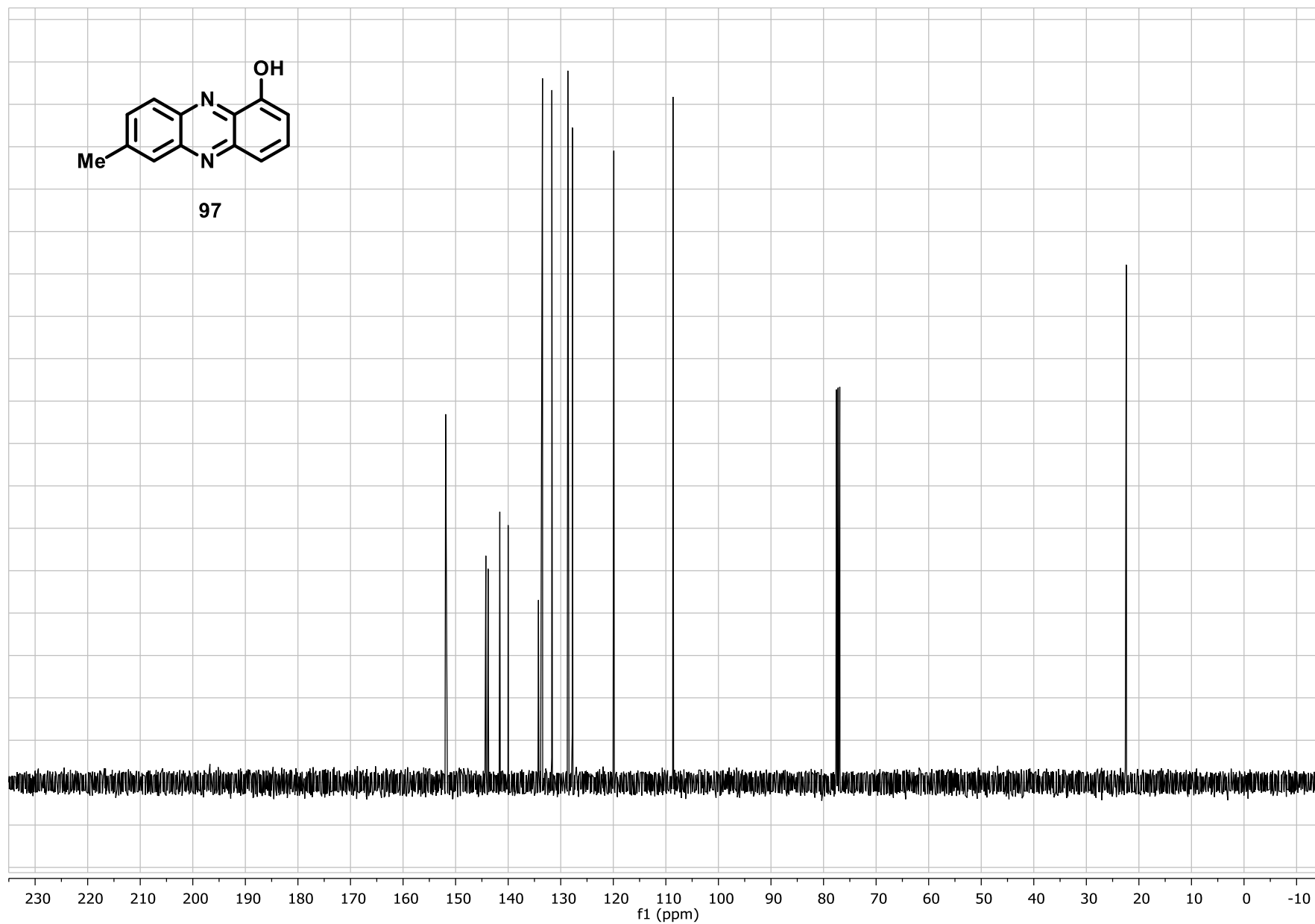
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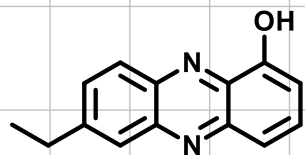
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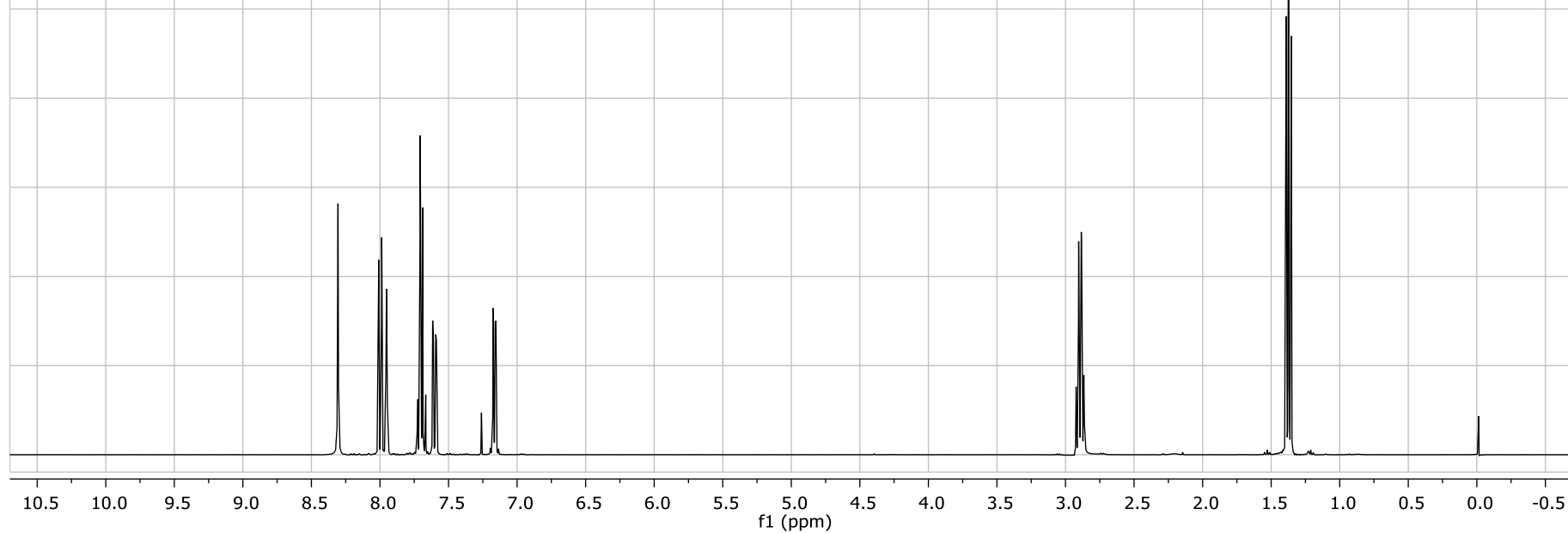
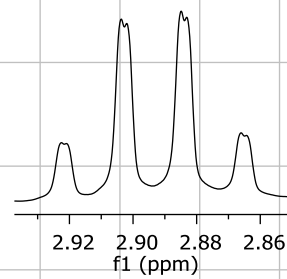
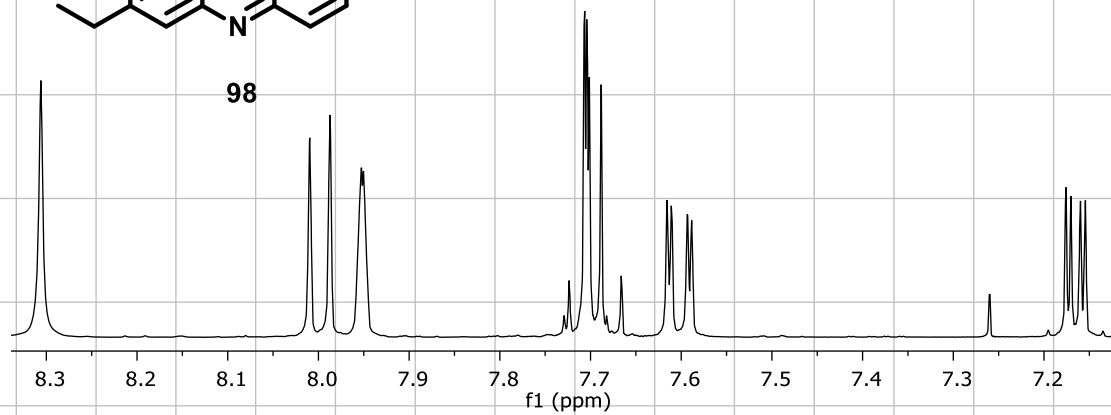
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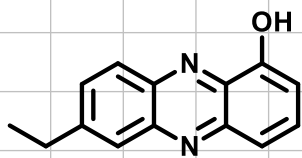
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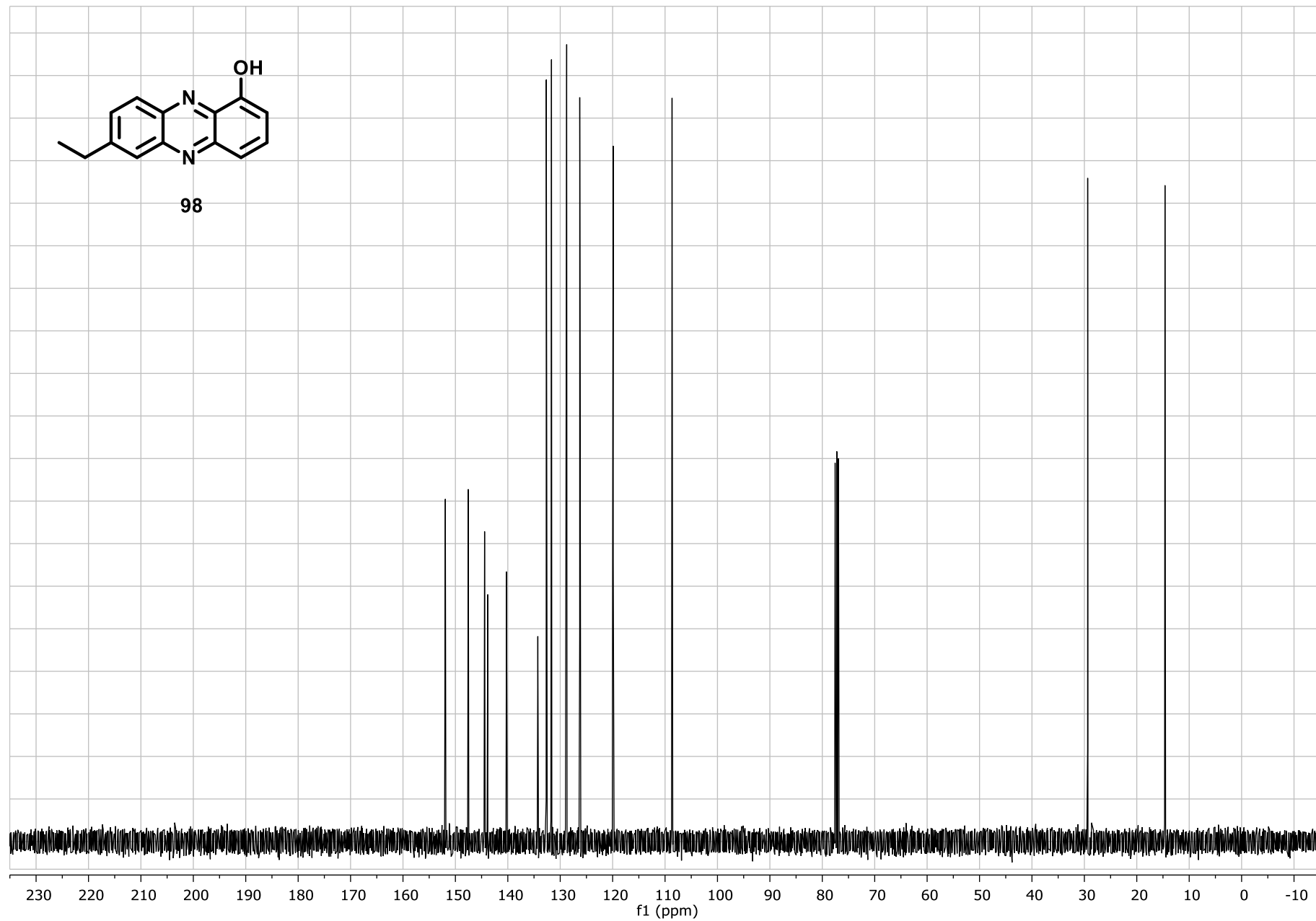
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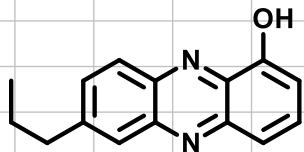
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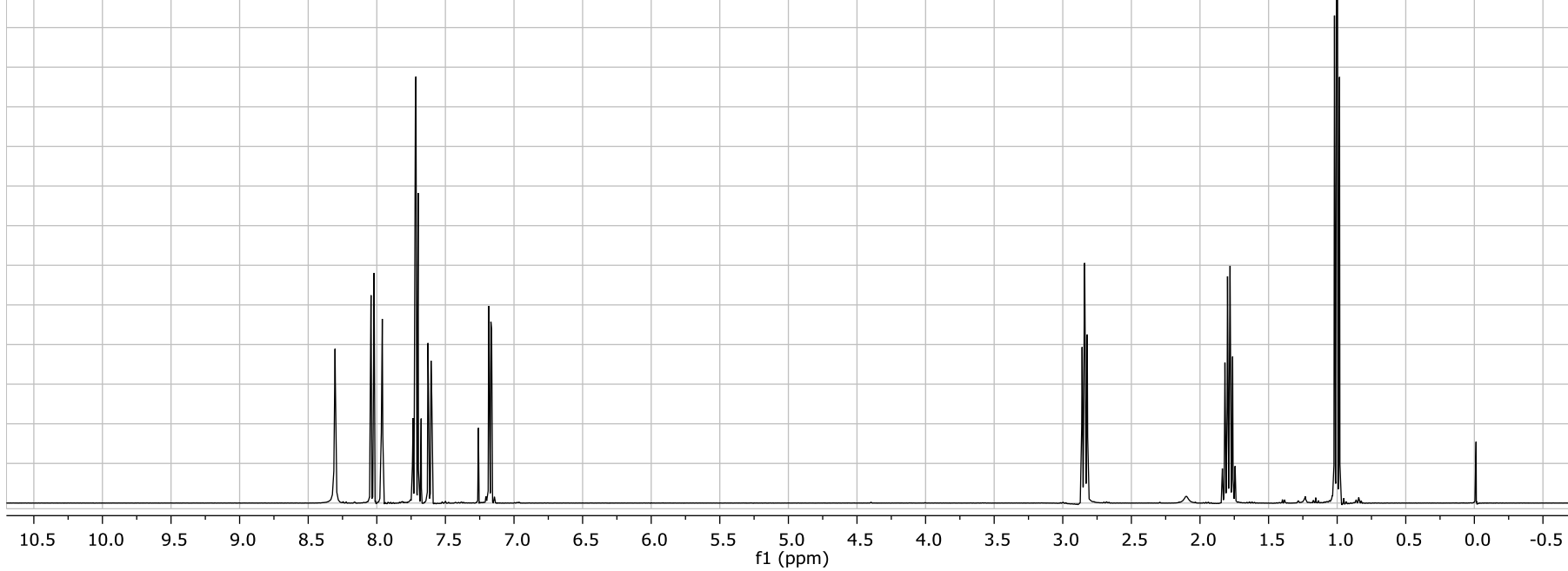
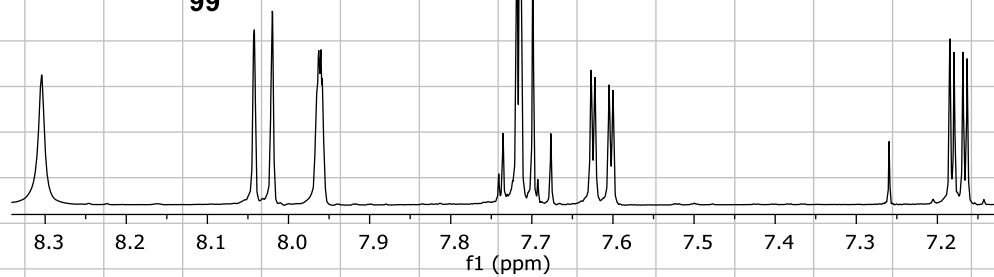
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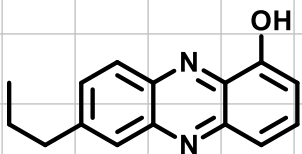
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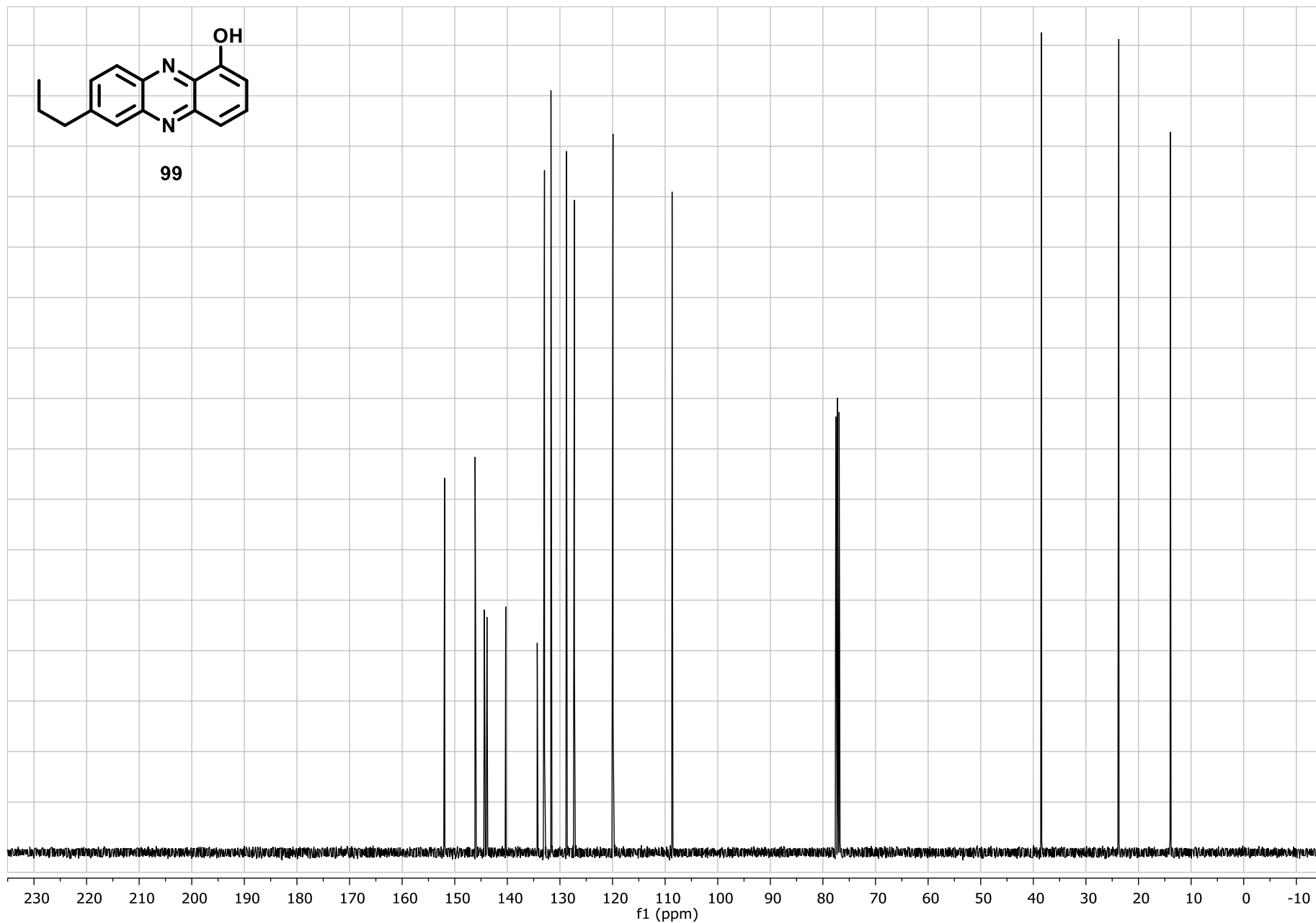
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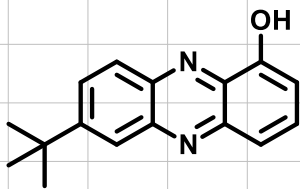


S226

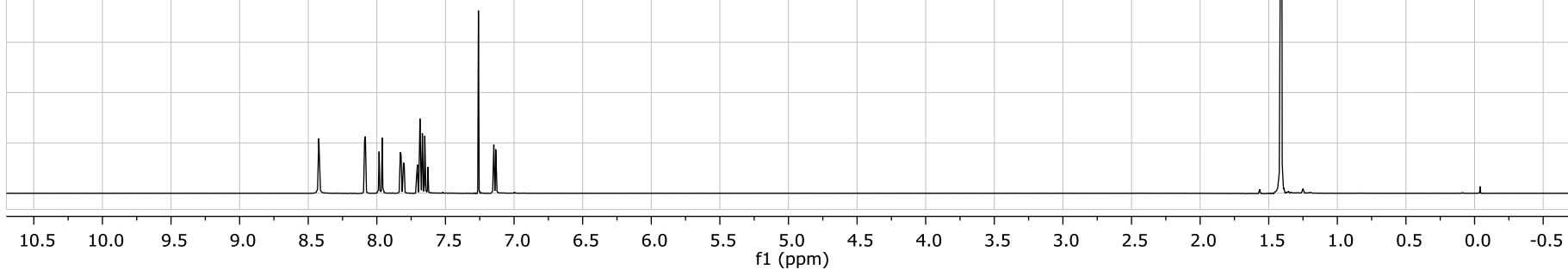
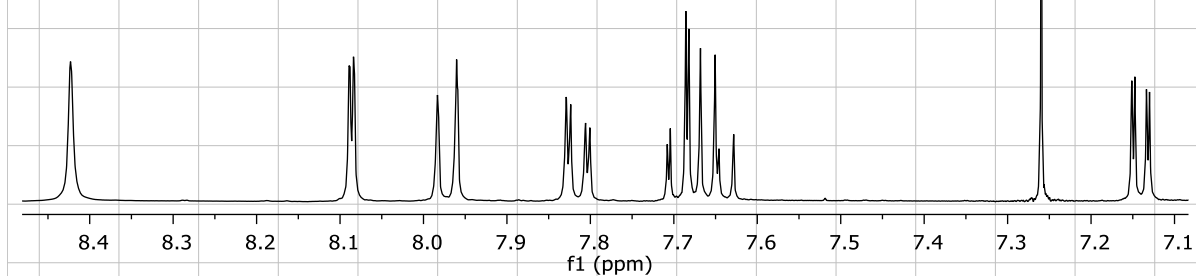


99



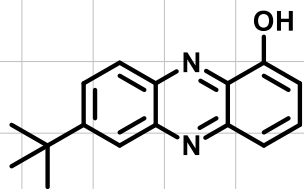


100



S228

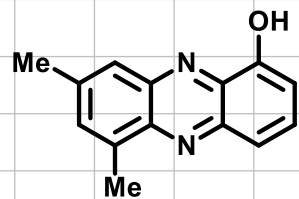




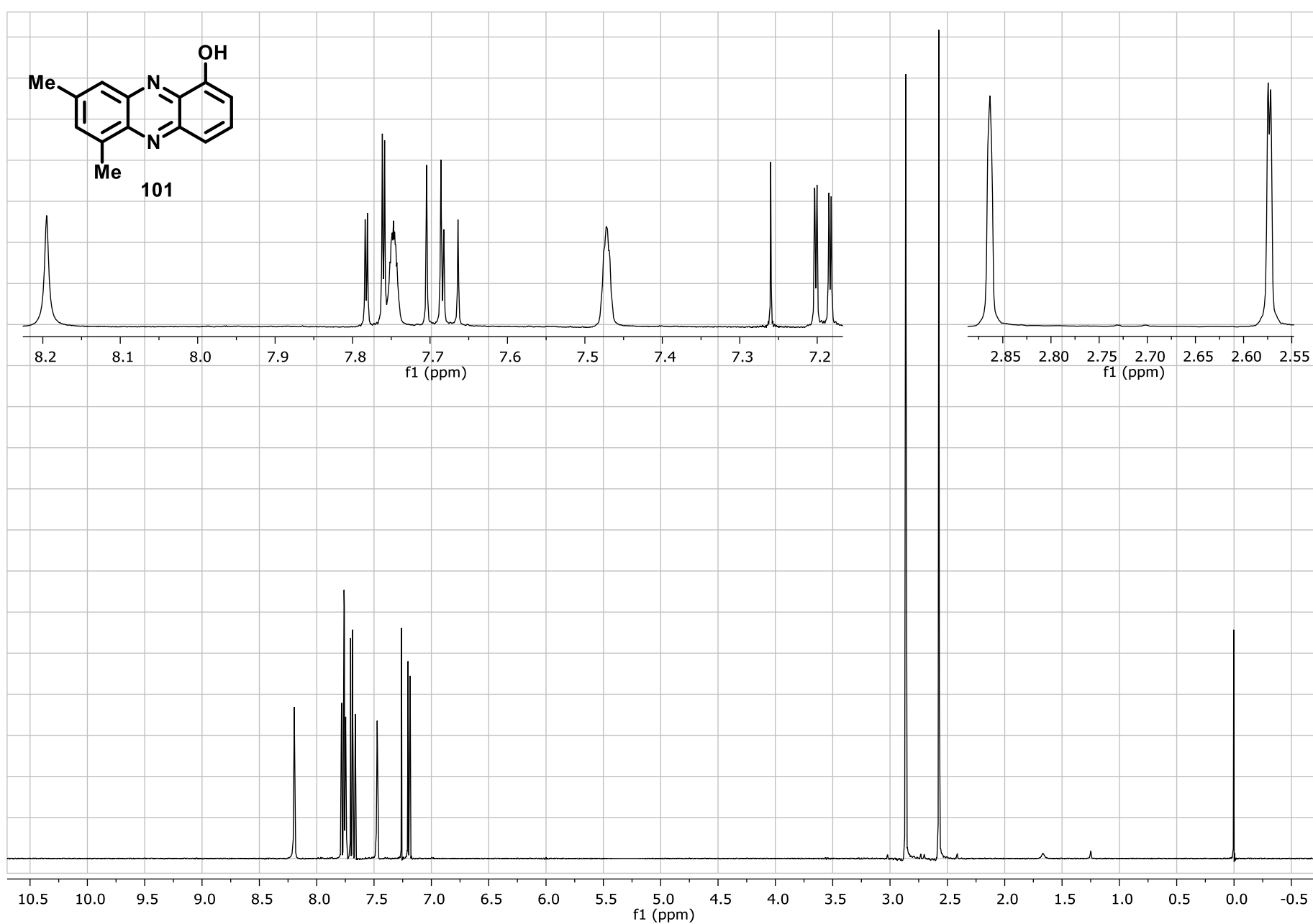
100

155 150 145 140 135 130 125 120 115 110  
f1 (ppm)

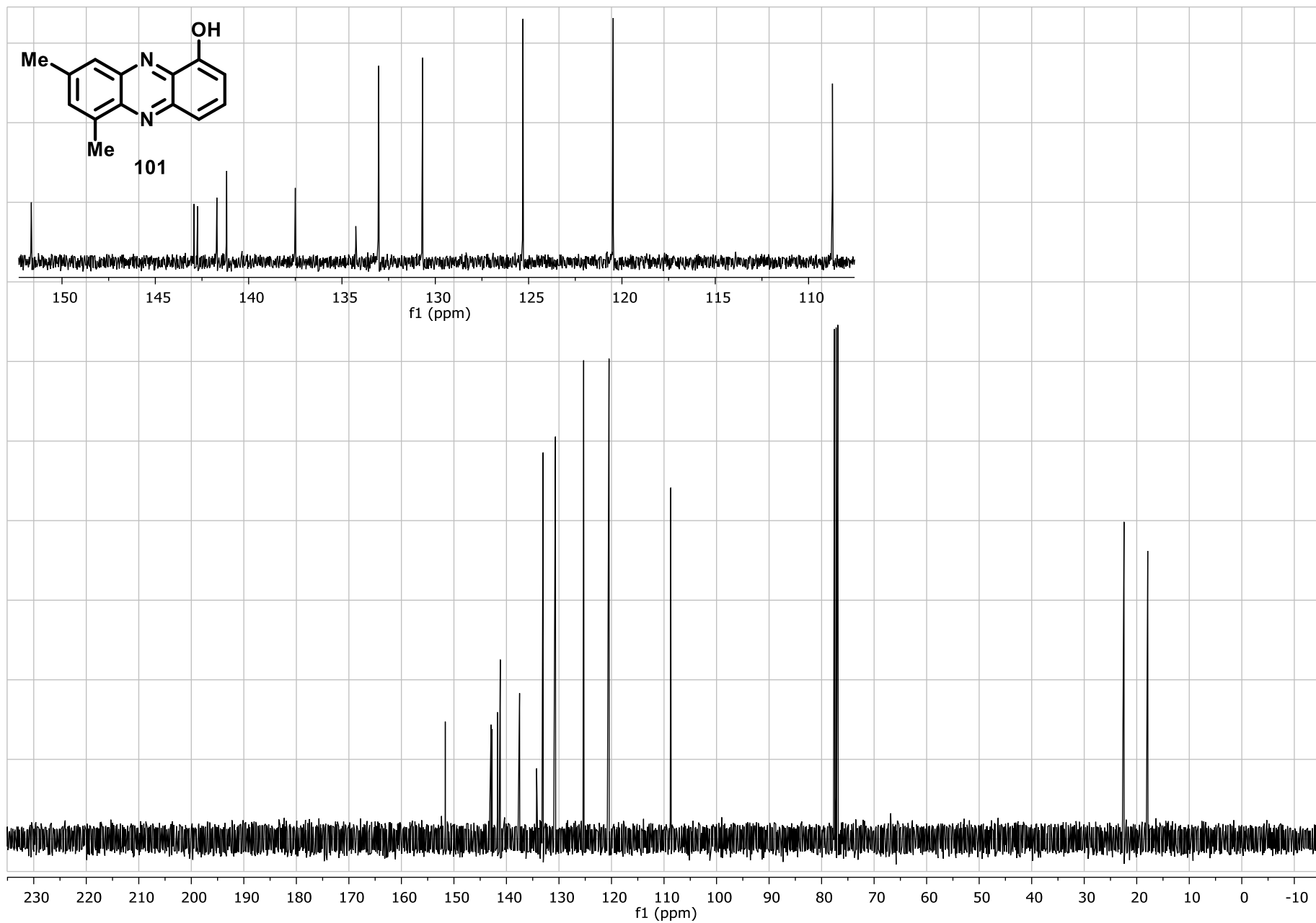
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10  
f1 (ppm)



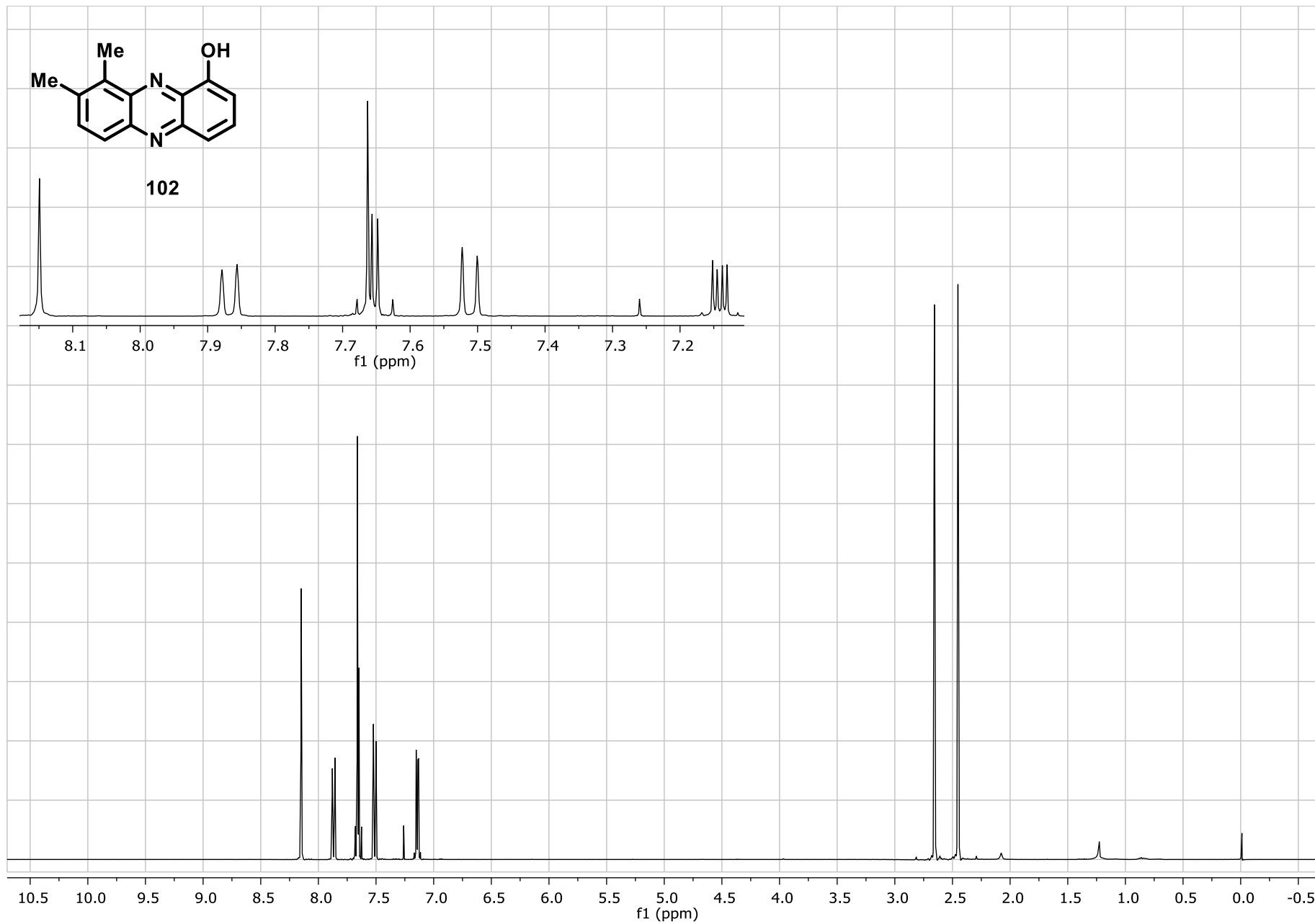
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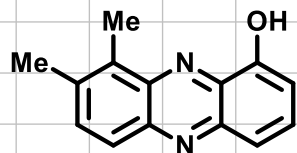
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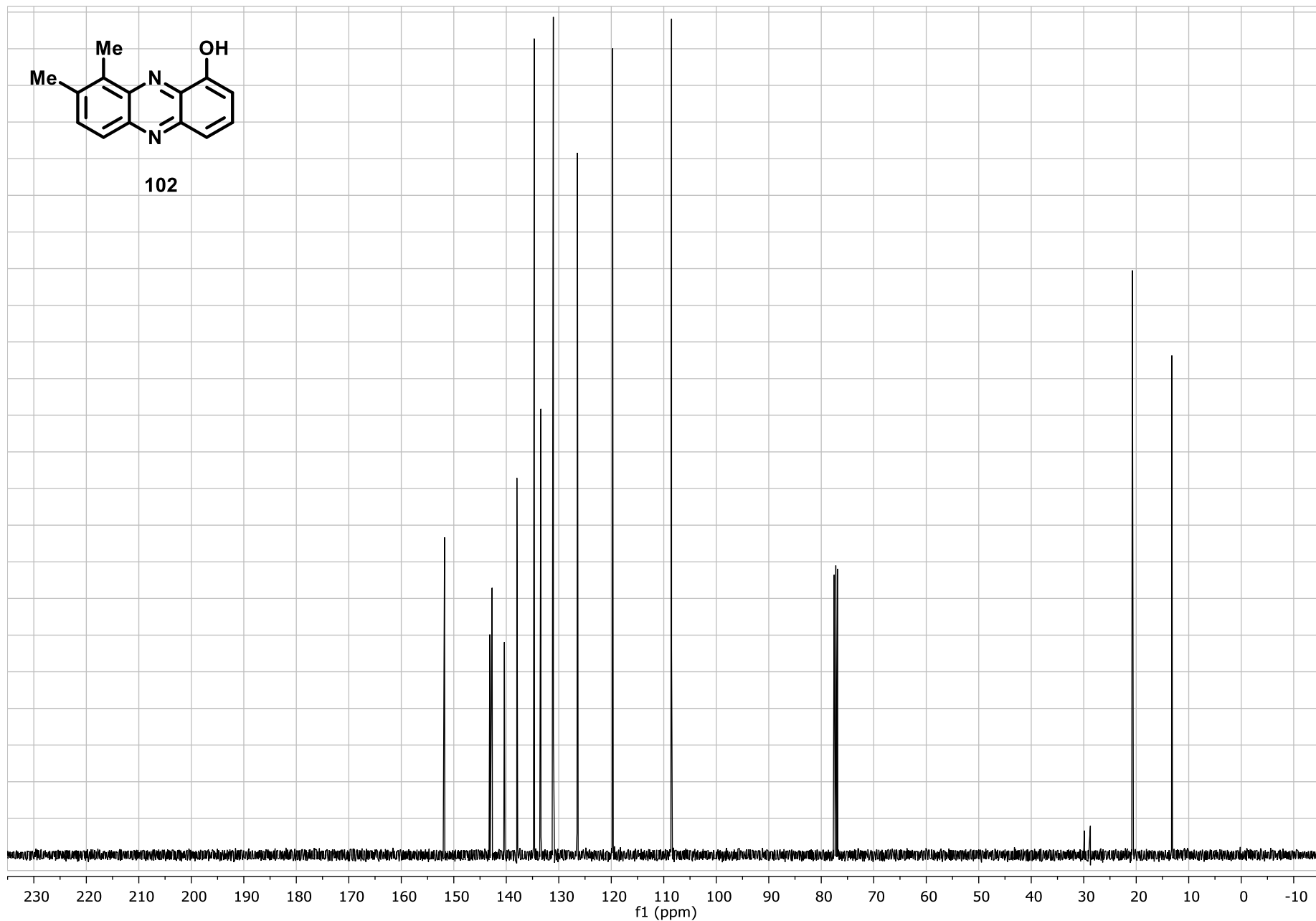
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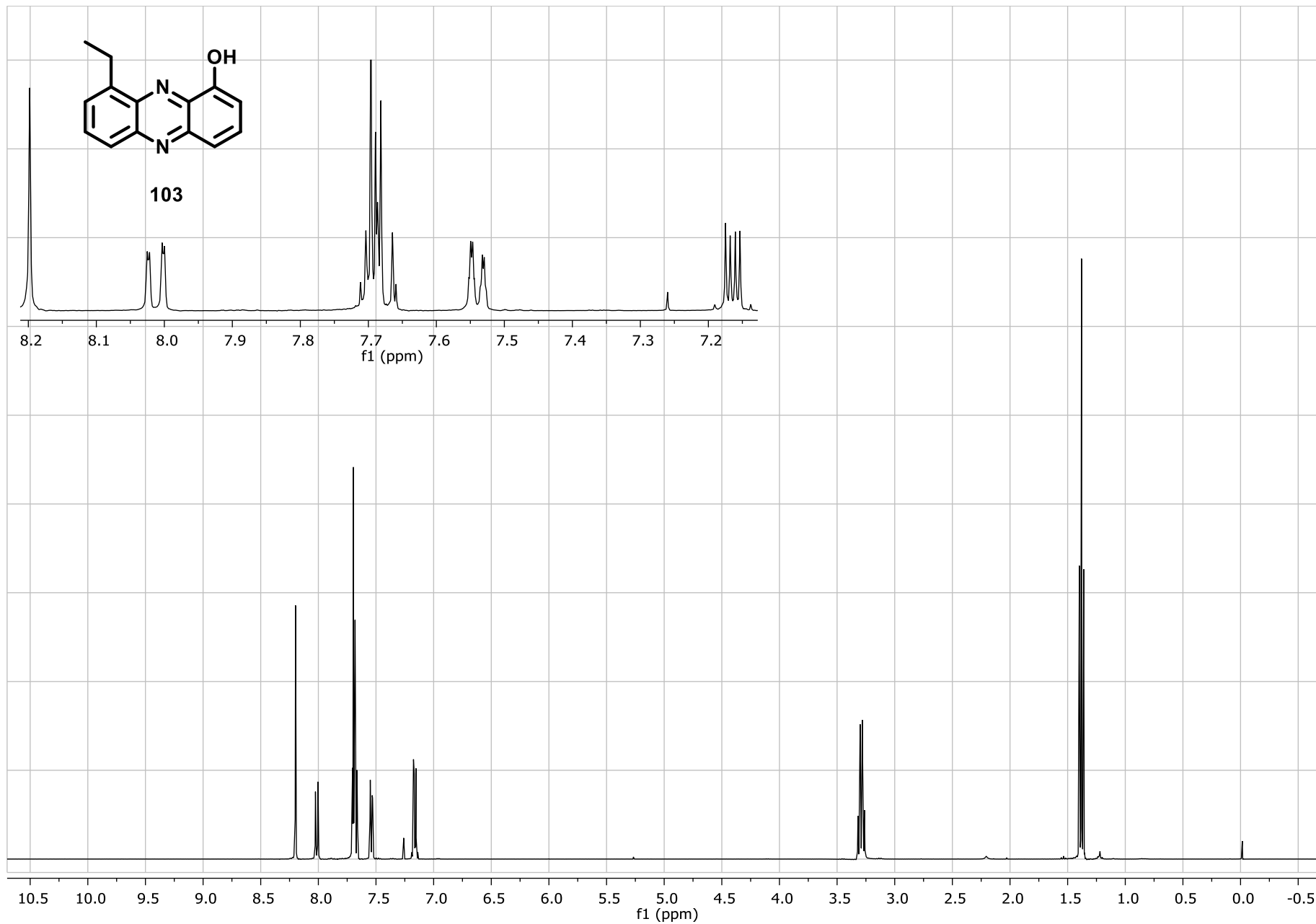


S232

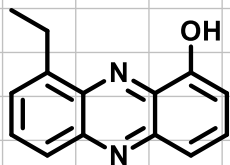


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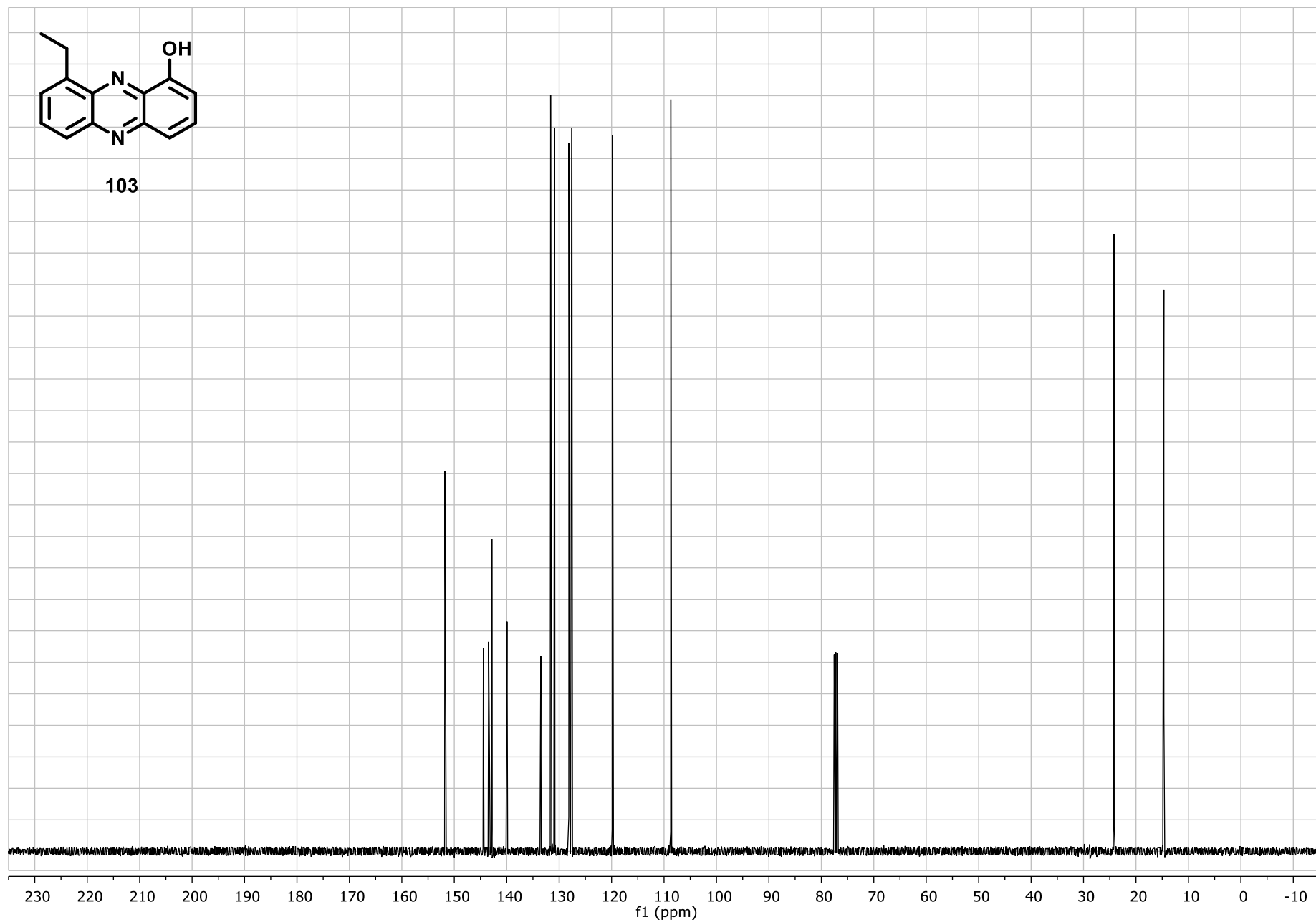




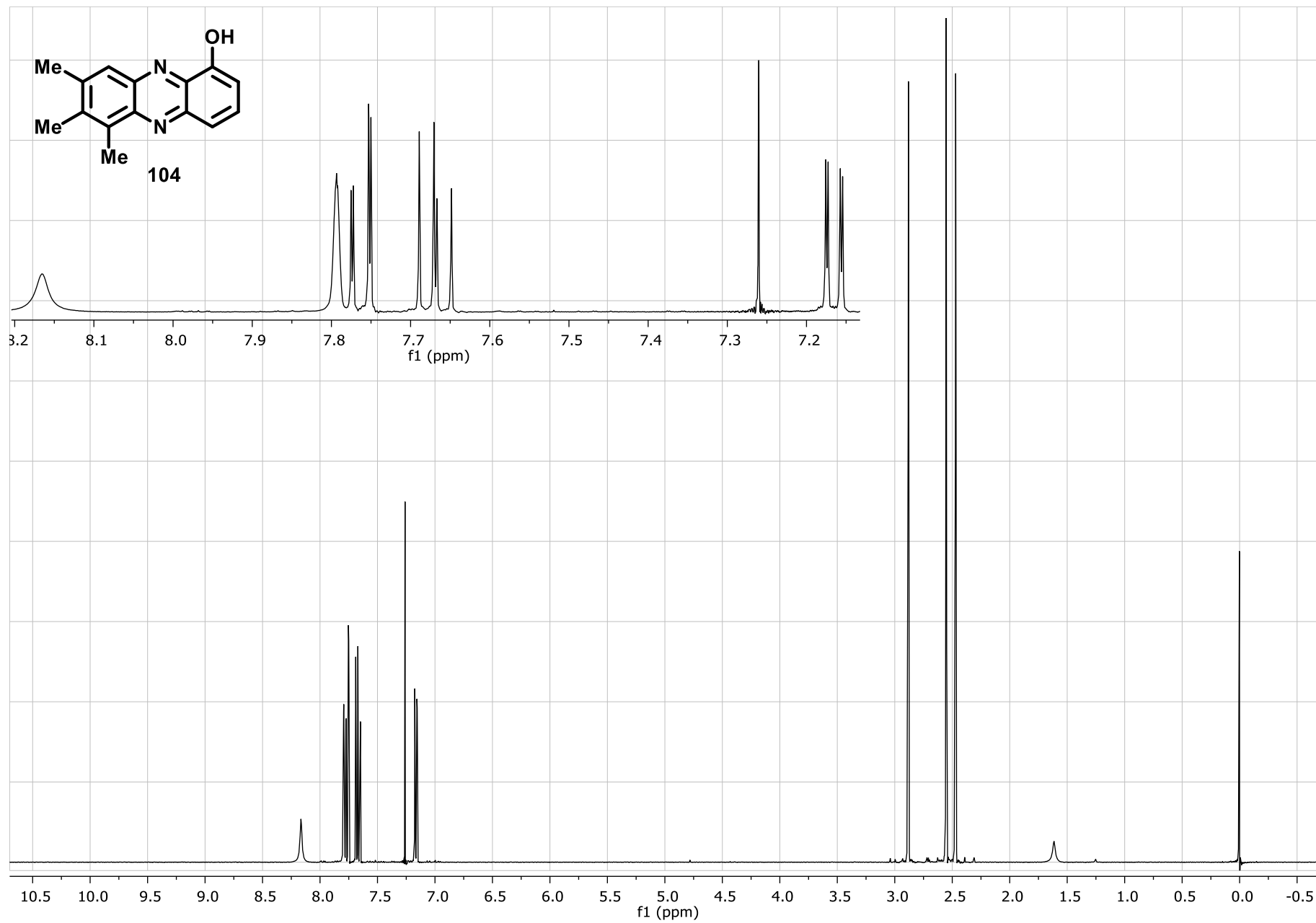
S234



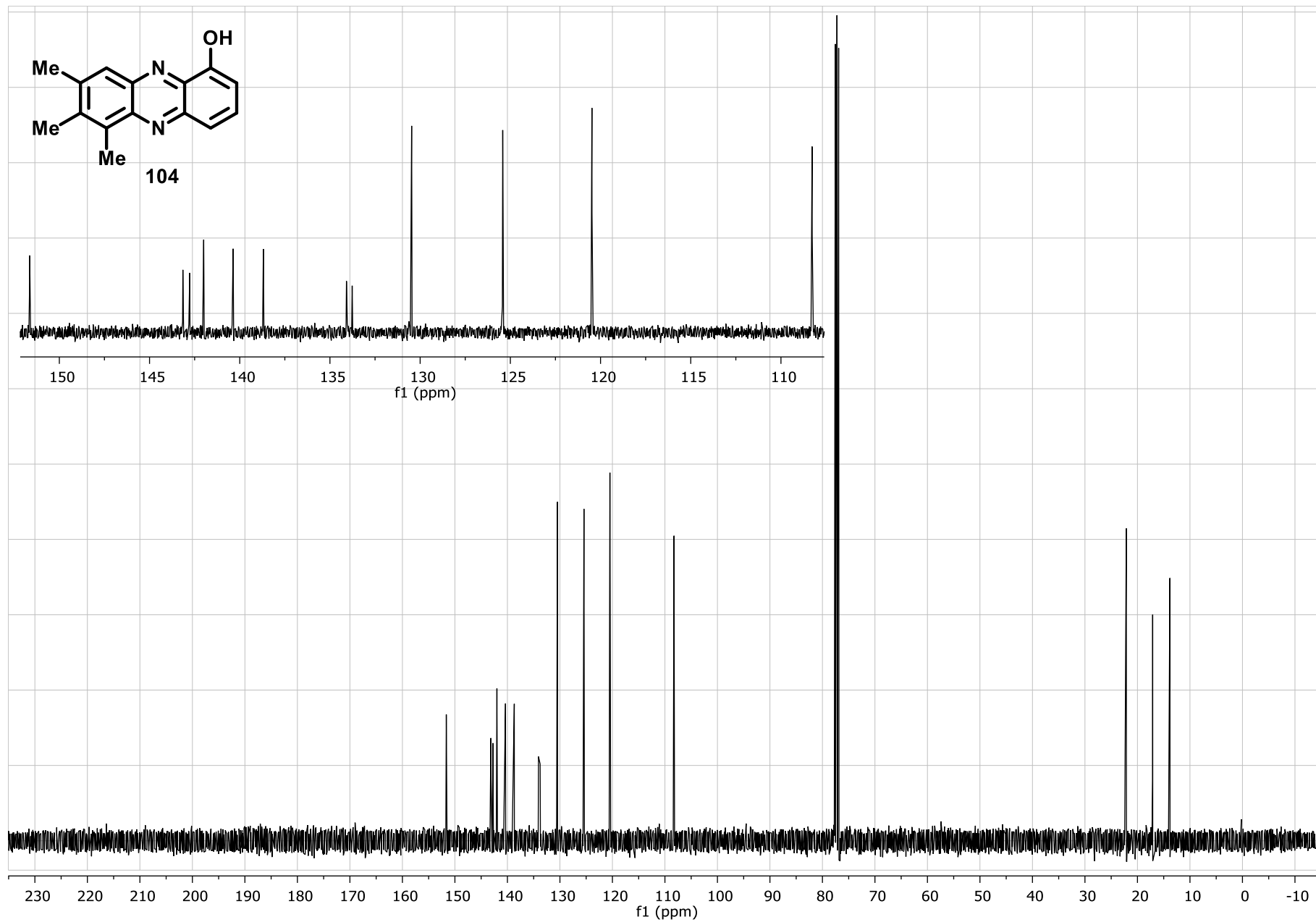
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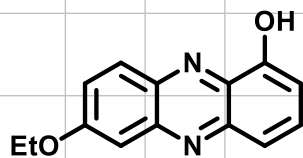


S235

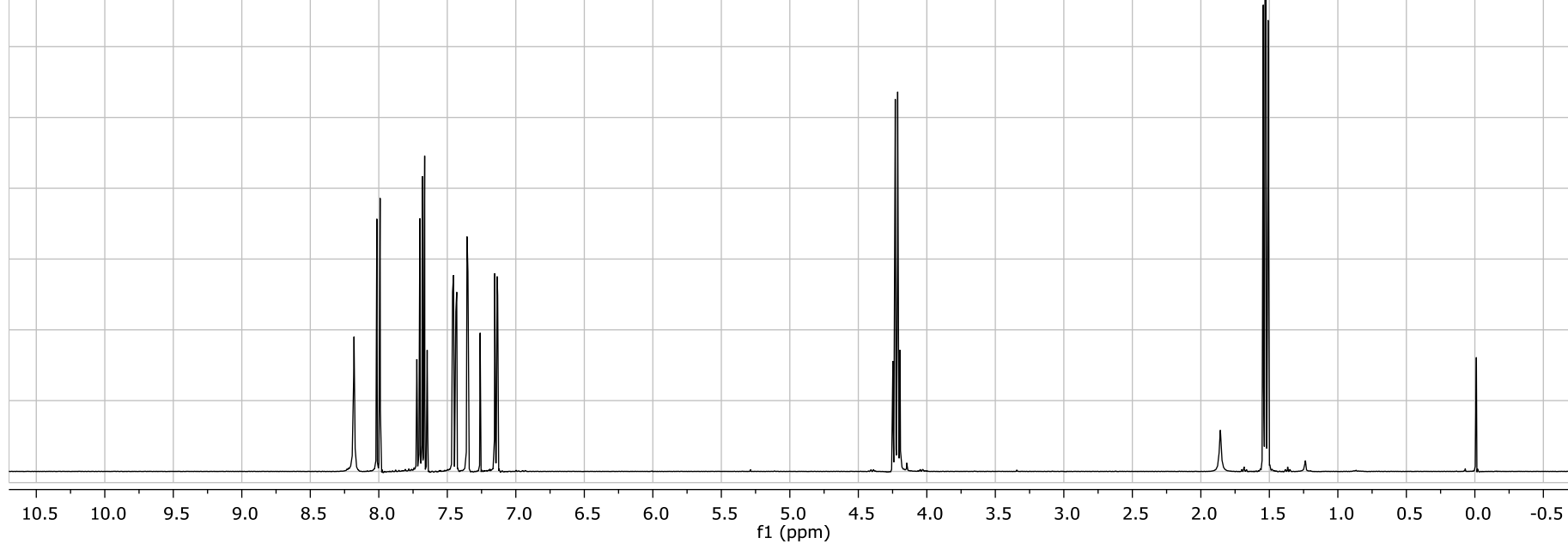
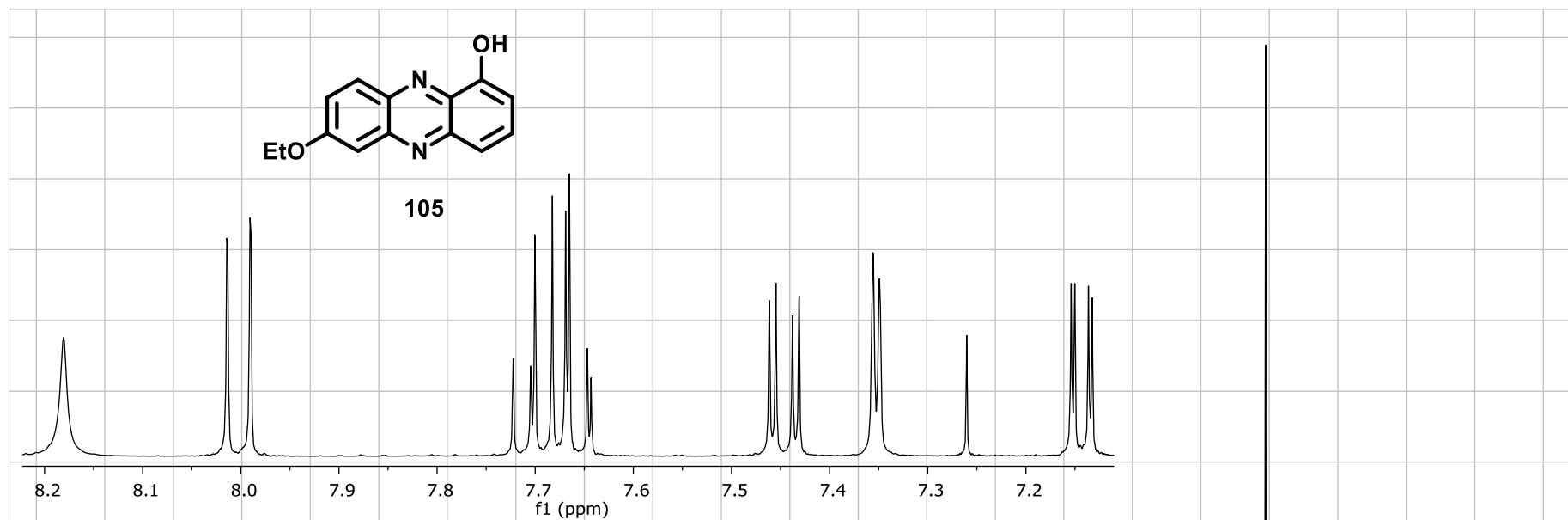




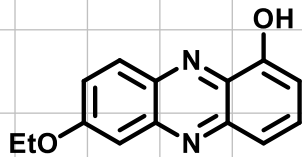




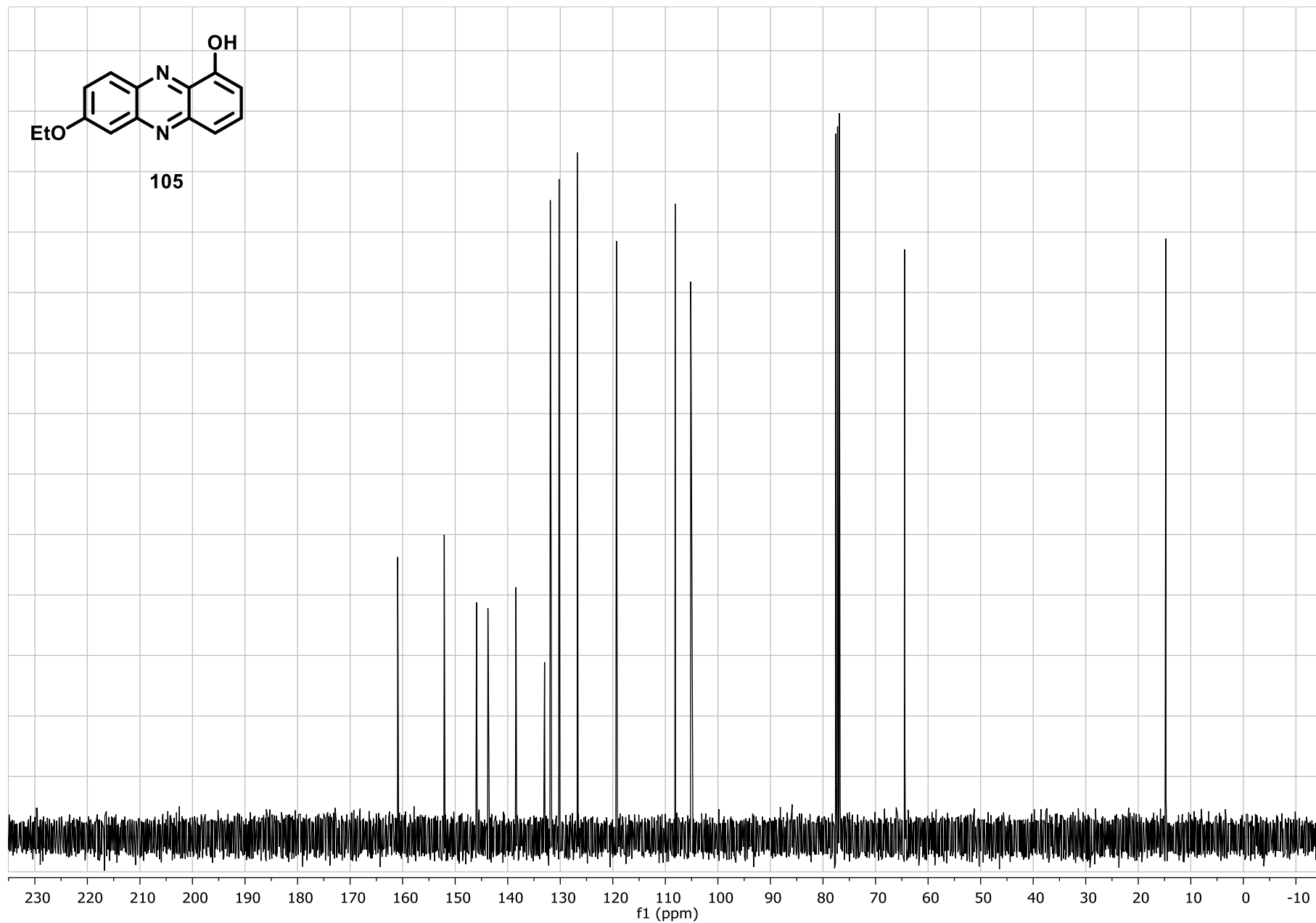
105



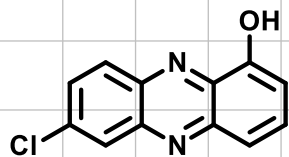
S238



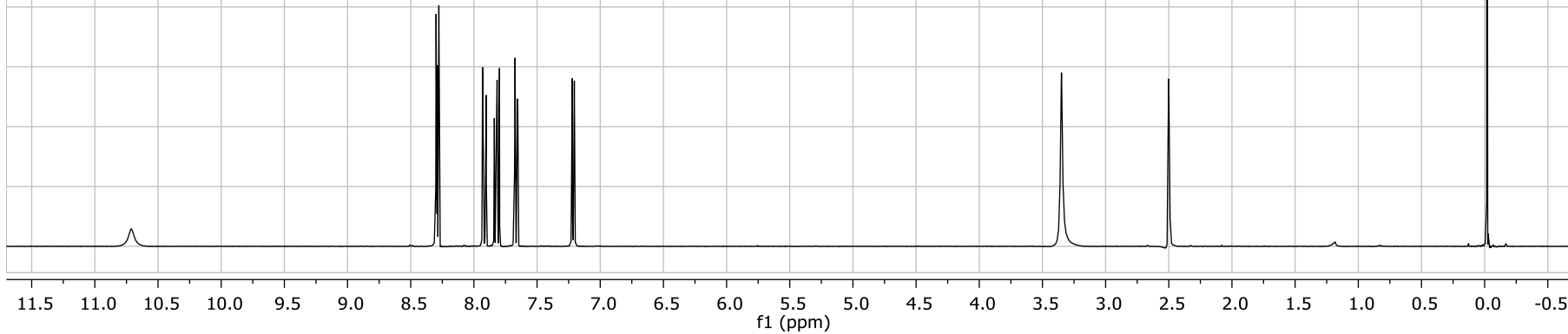
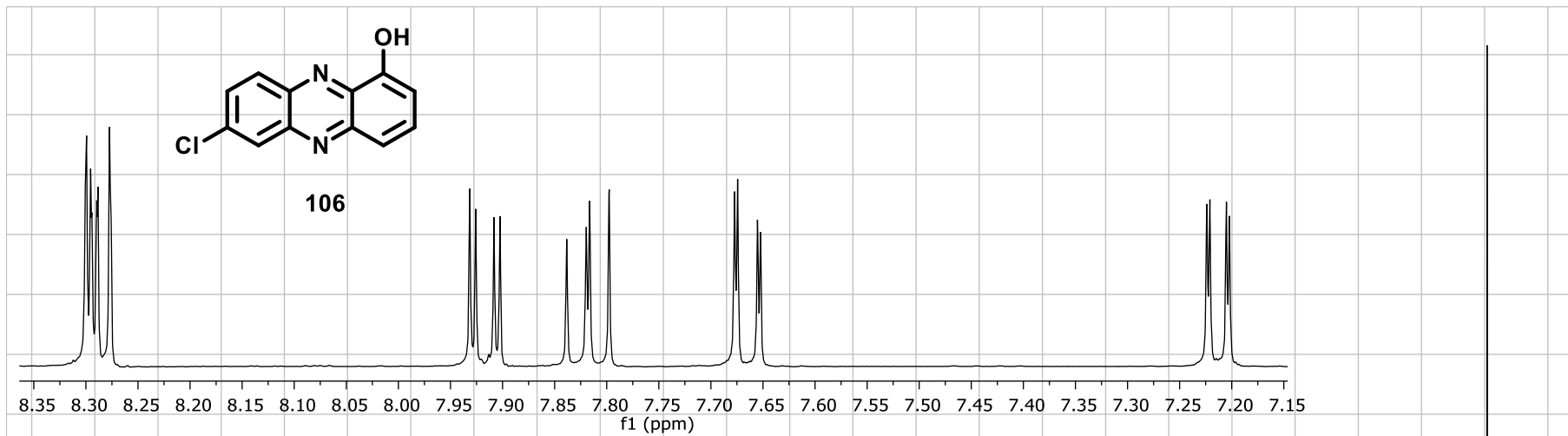
105



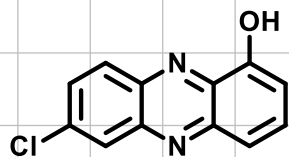
S239



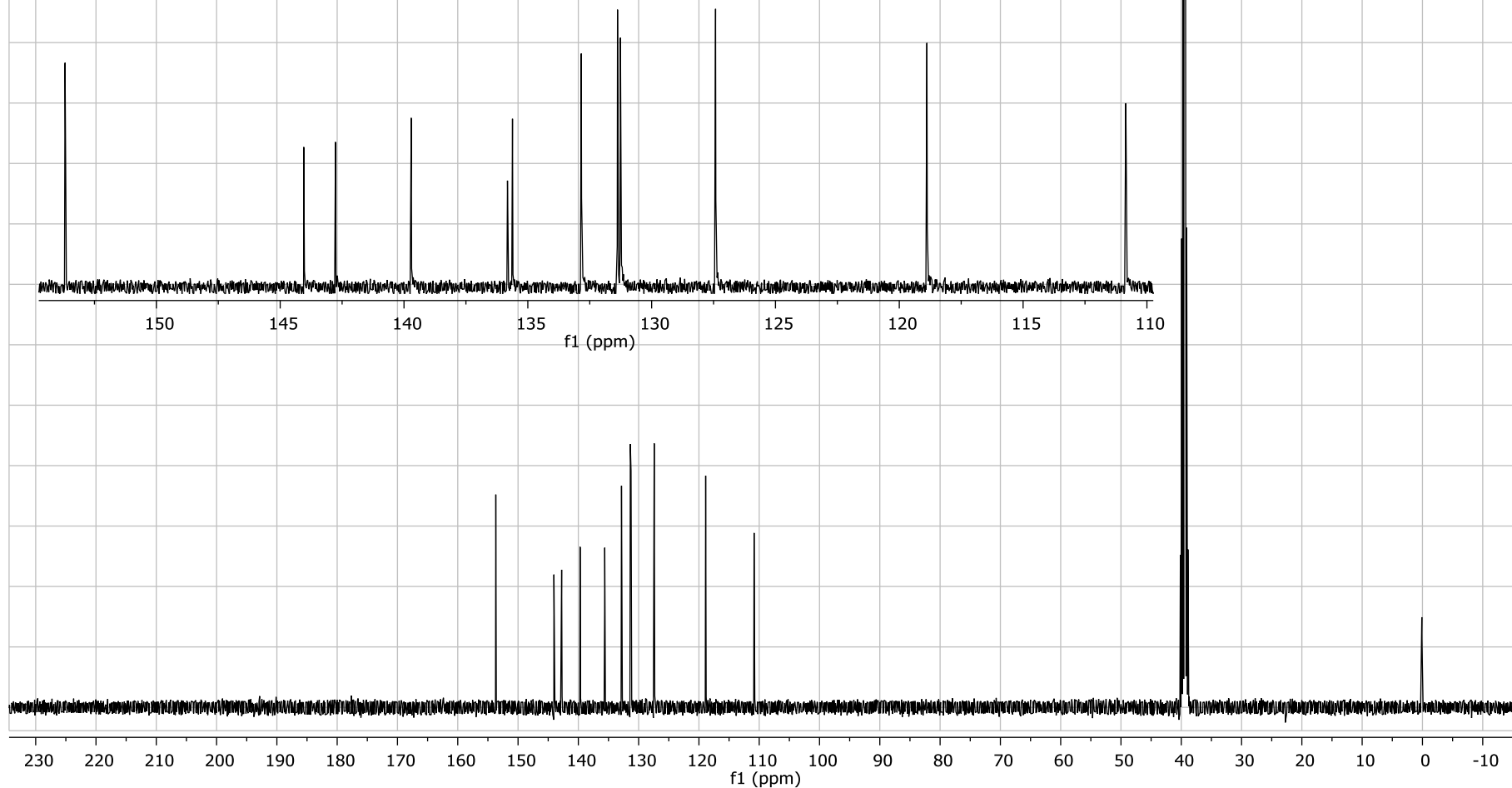
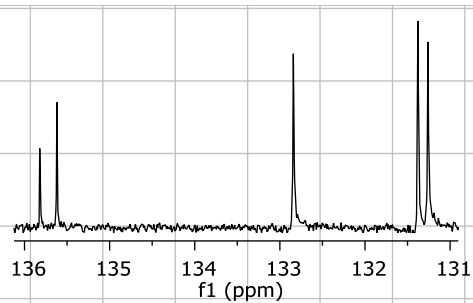
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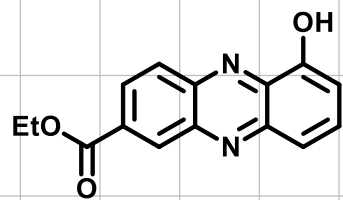


S240

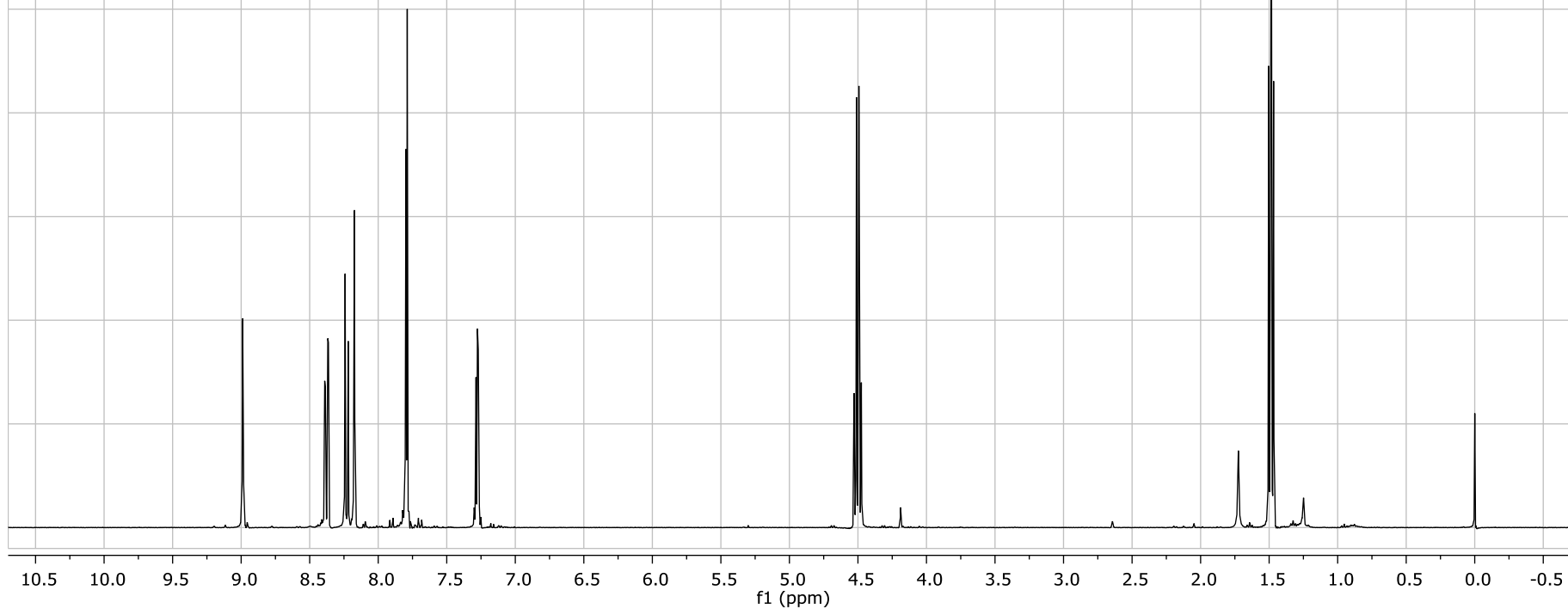
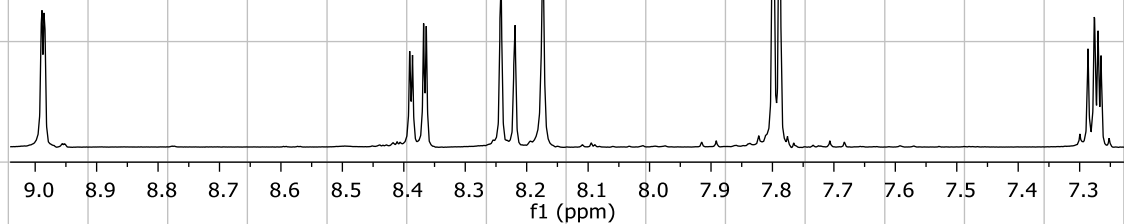


106

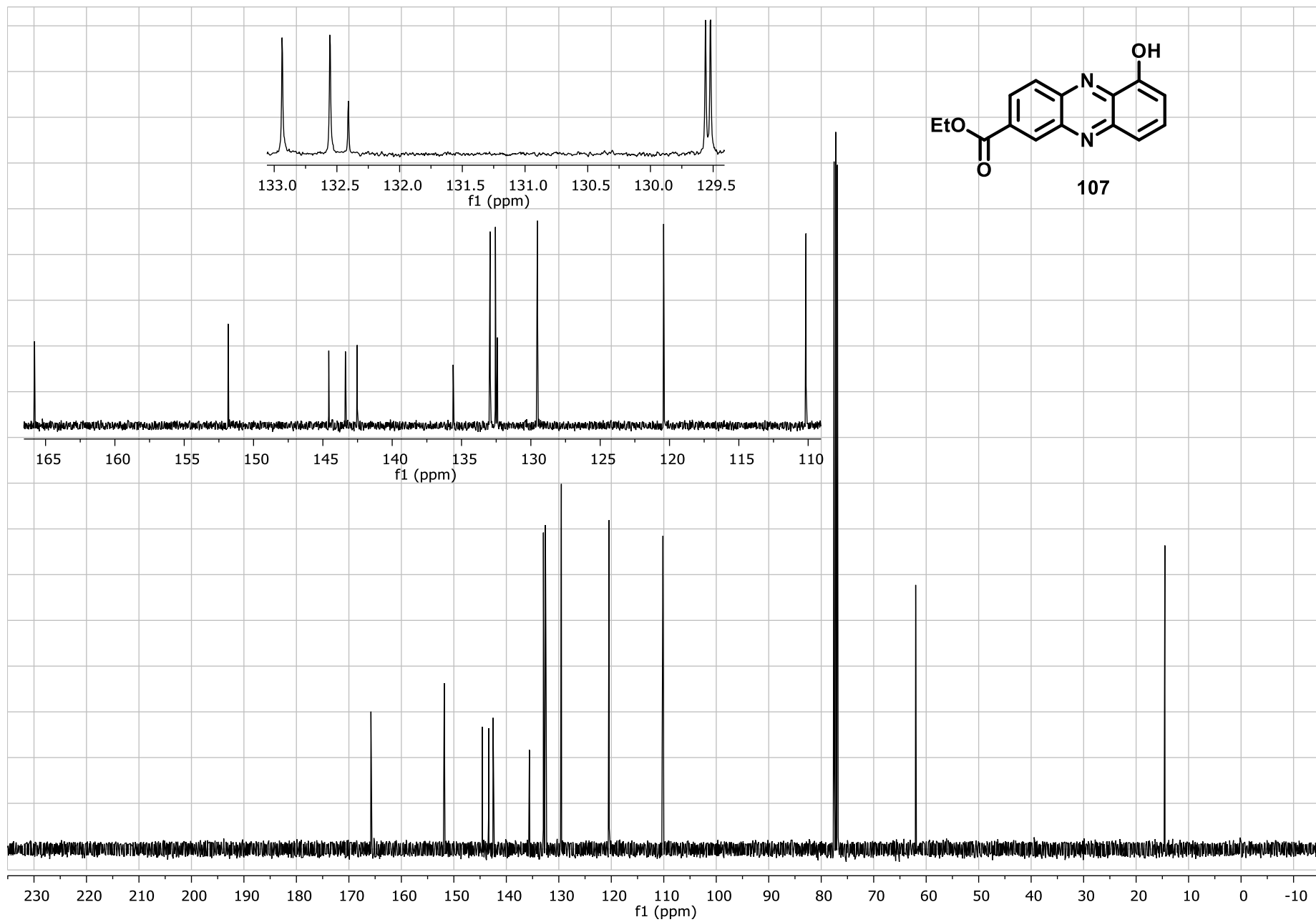




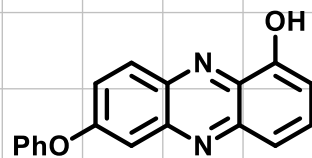
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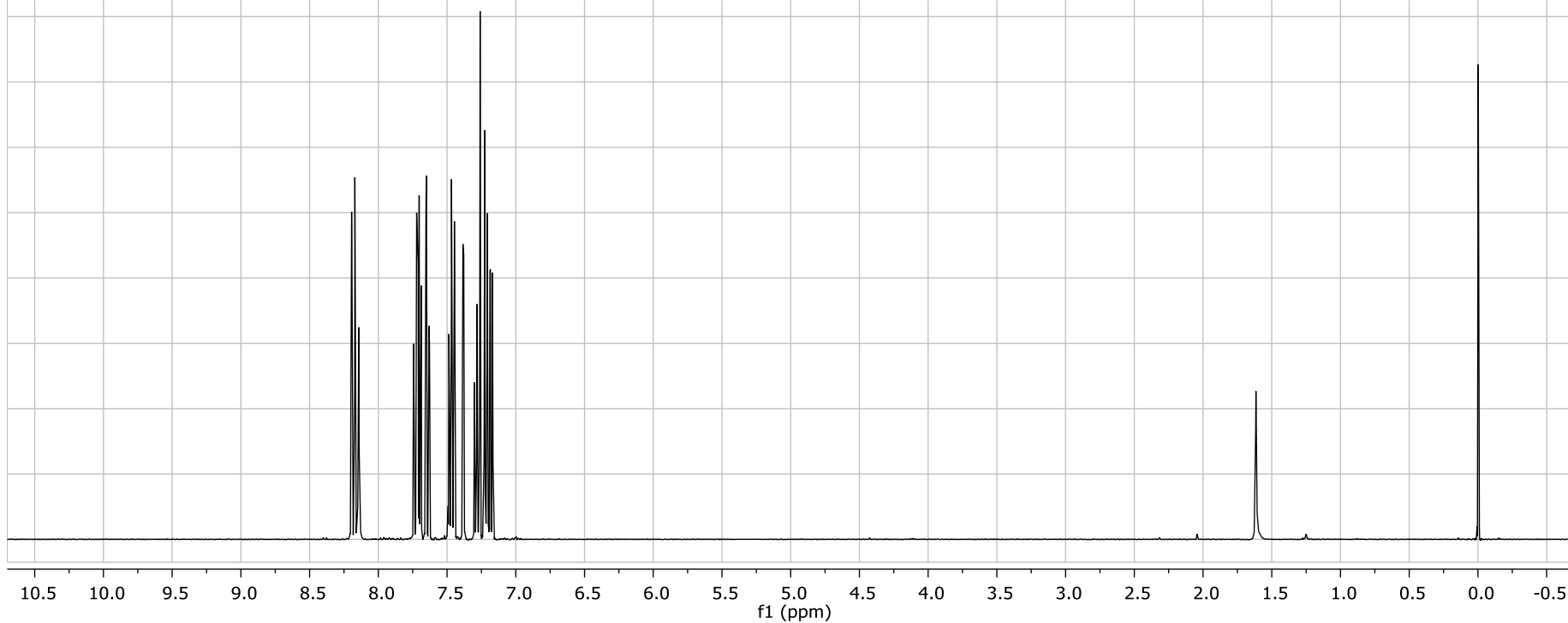
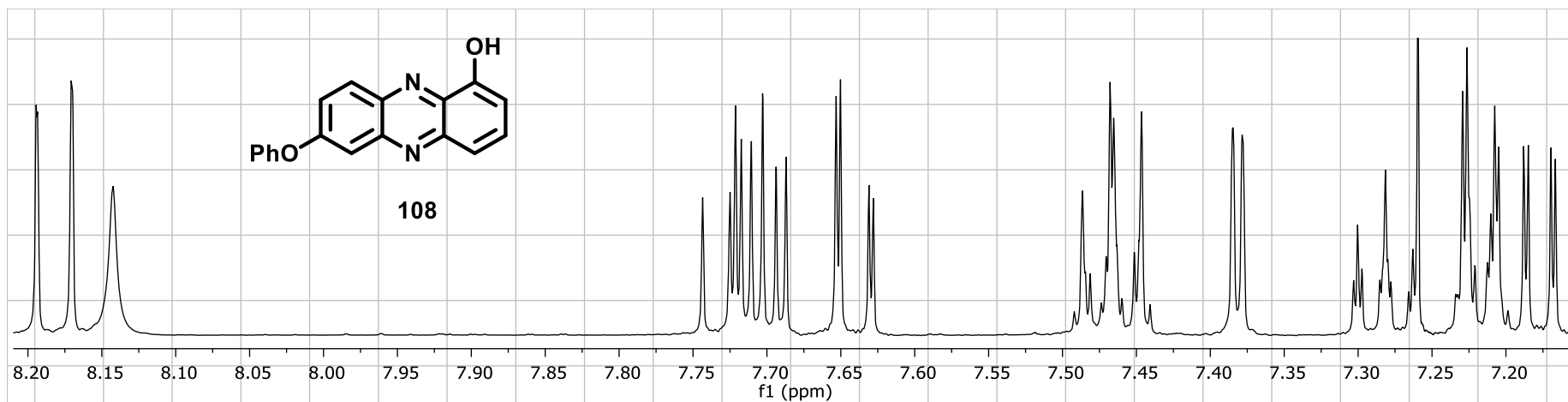
S242



S243

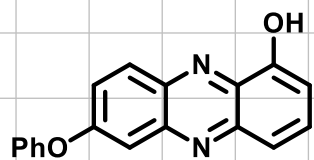


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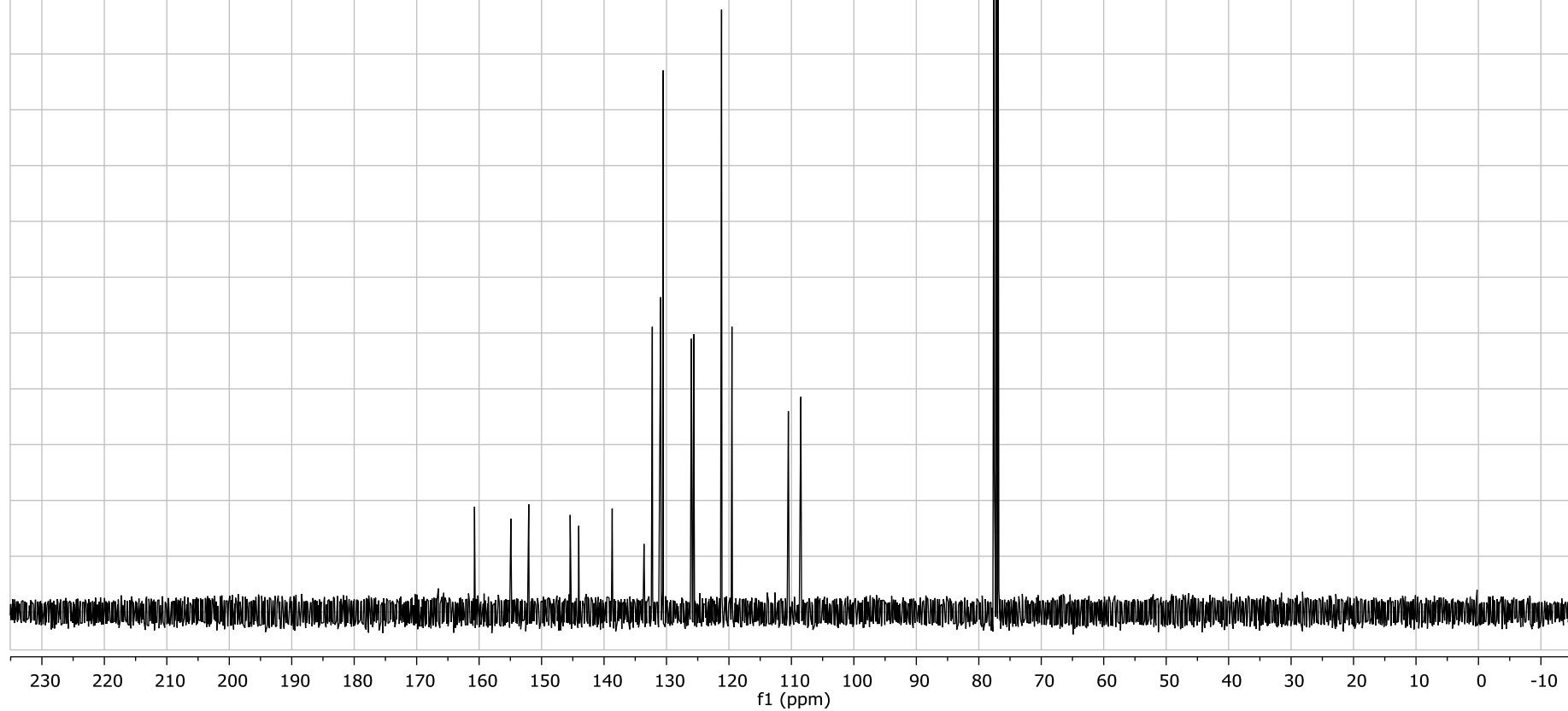
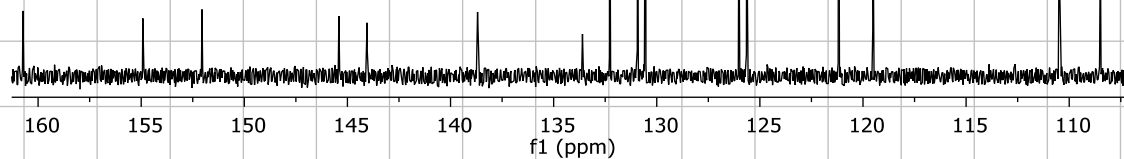


S244

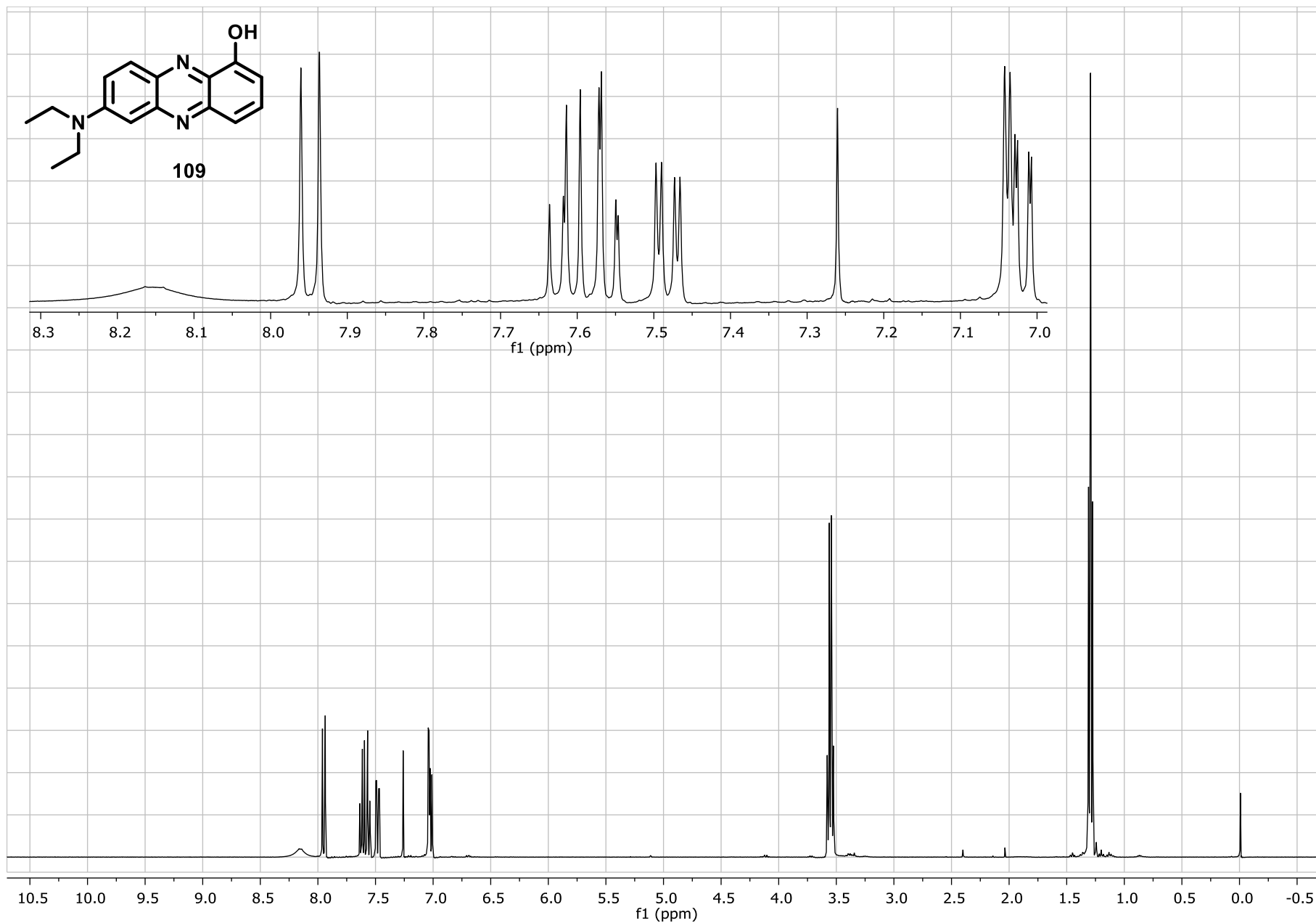




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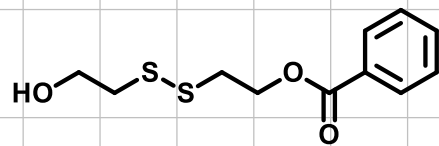


S245

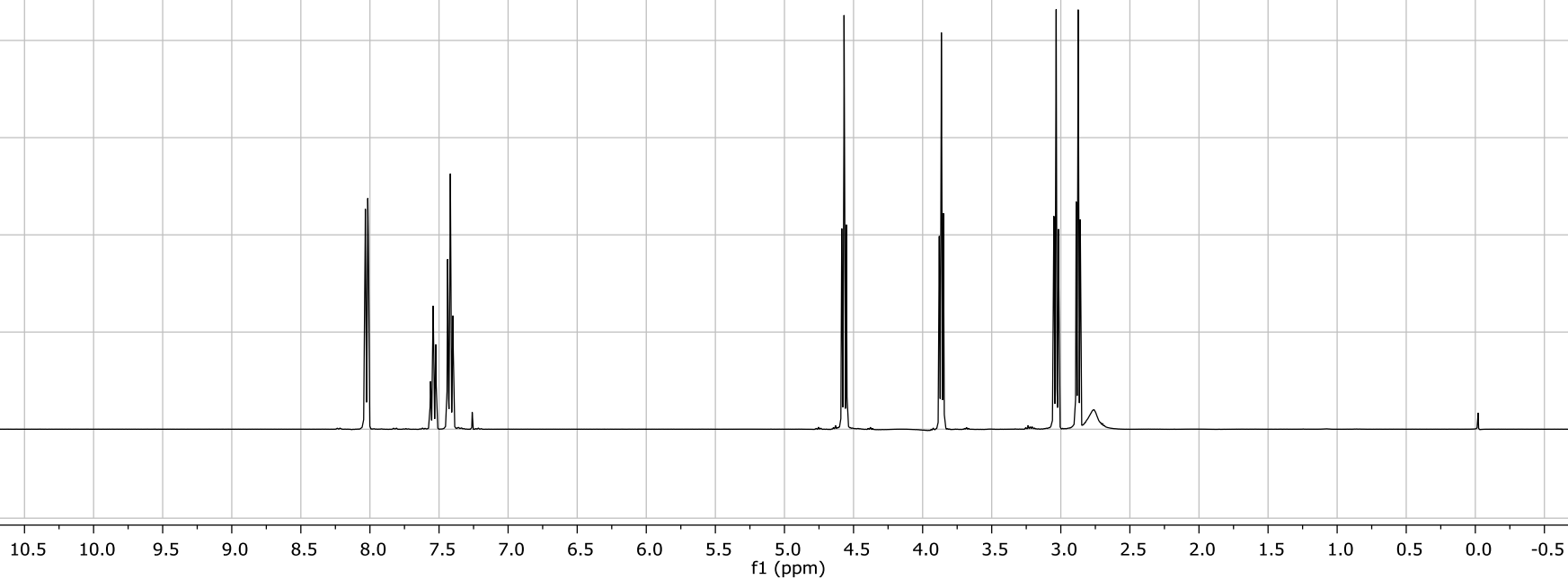
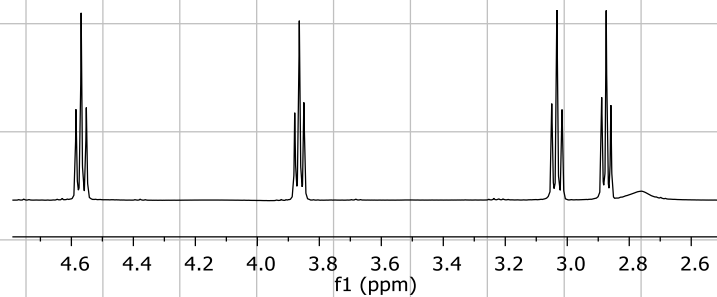
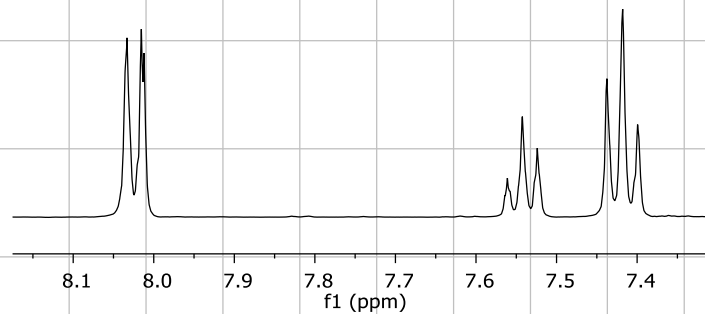


S246

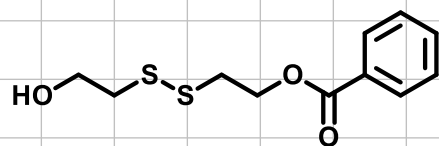




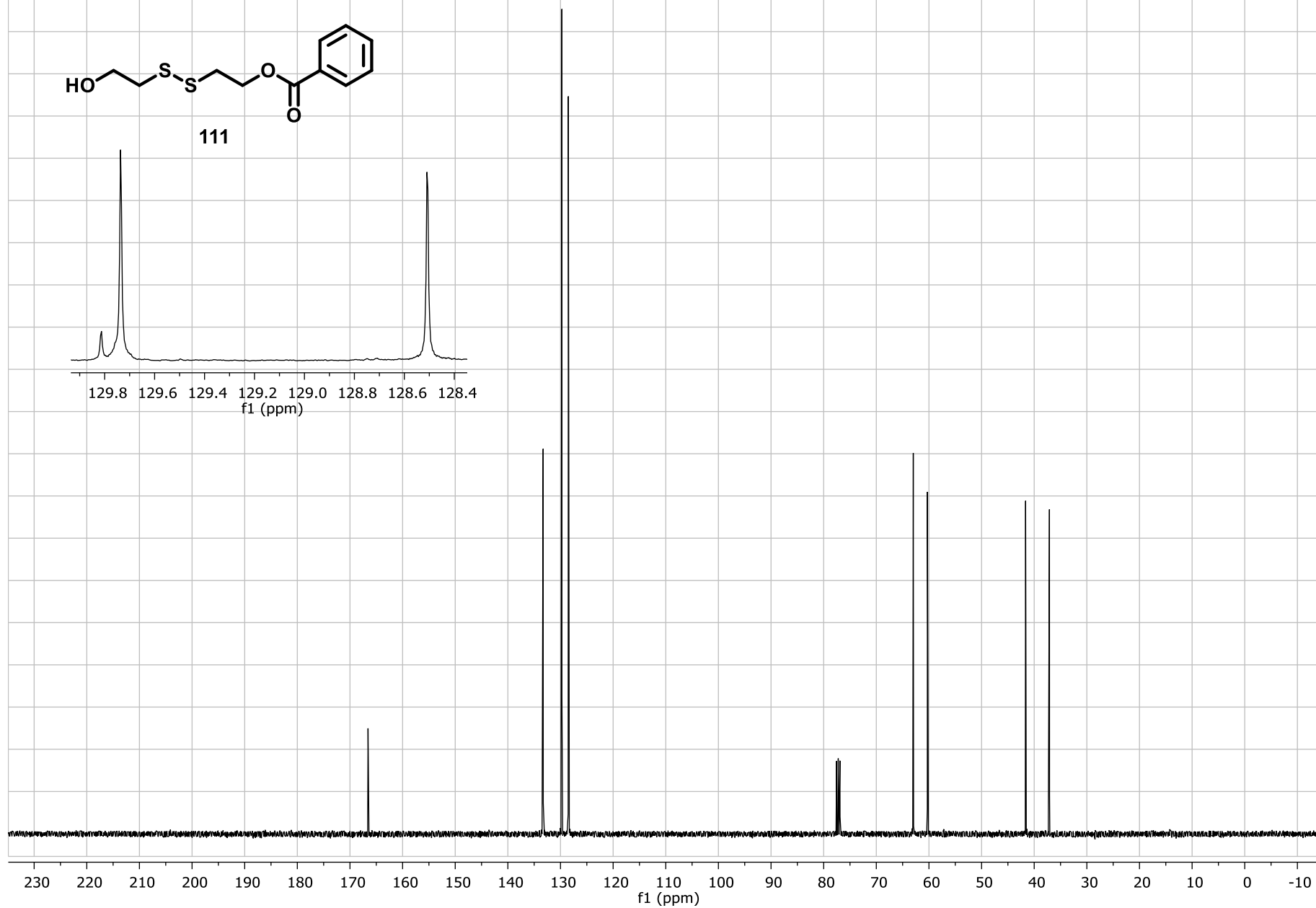
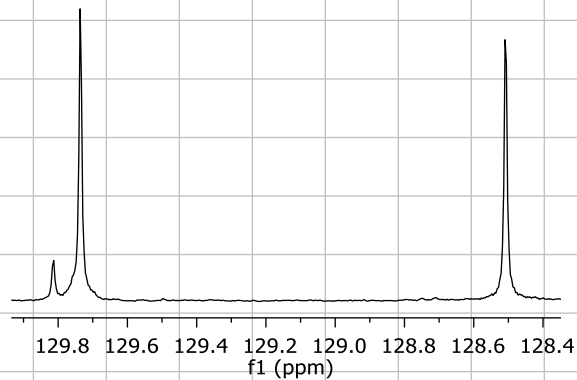
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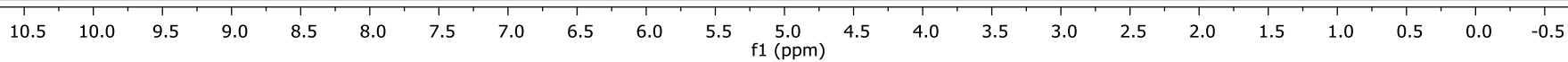


S248

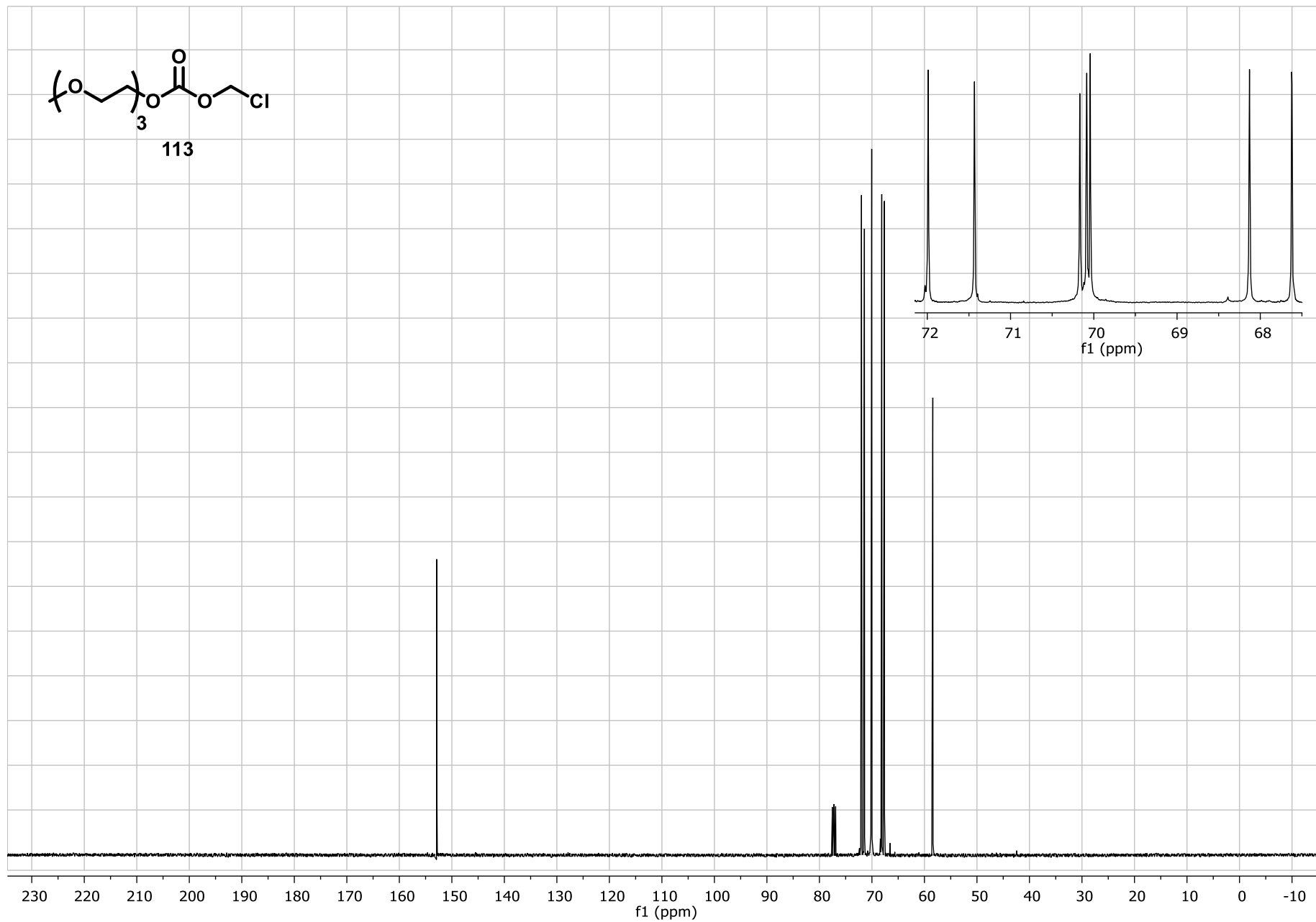


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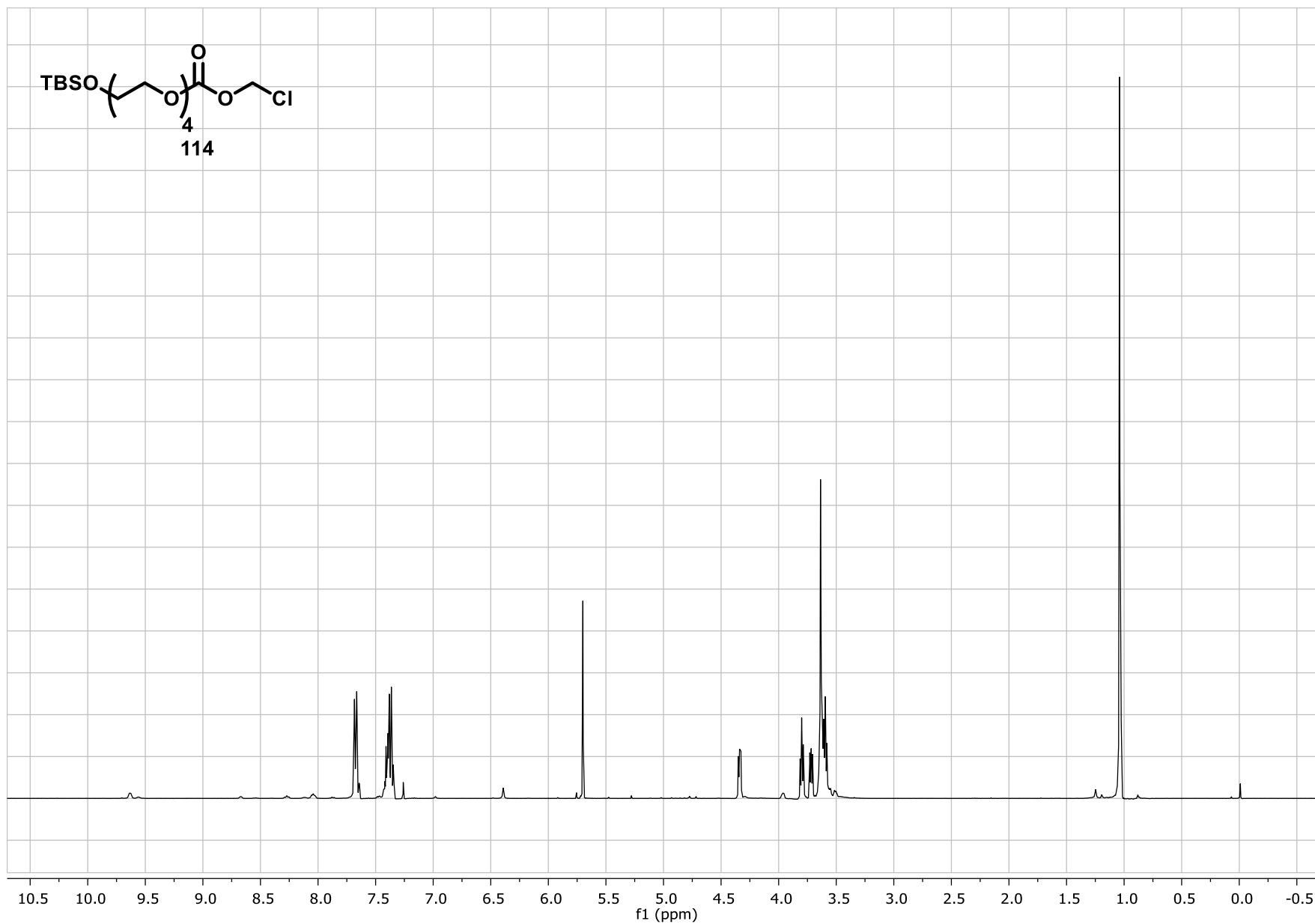
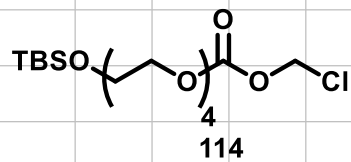




S250

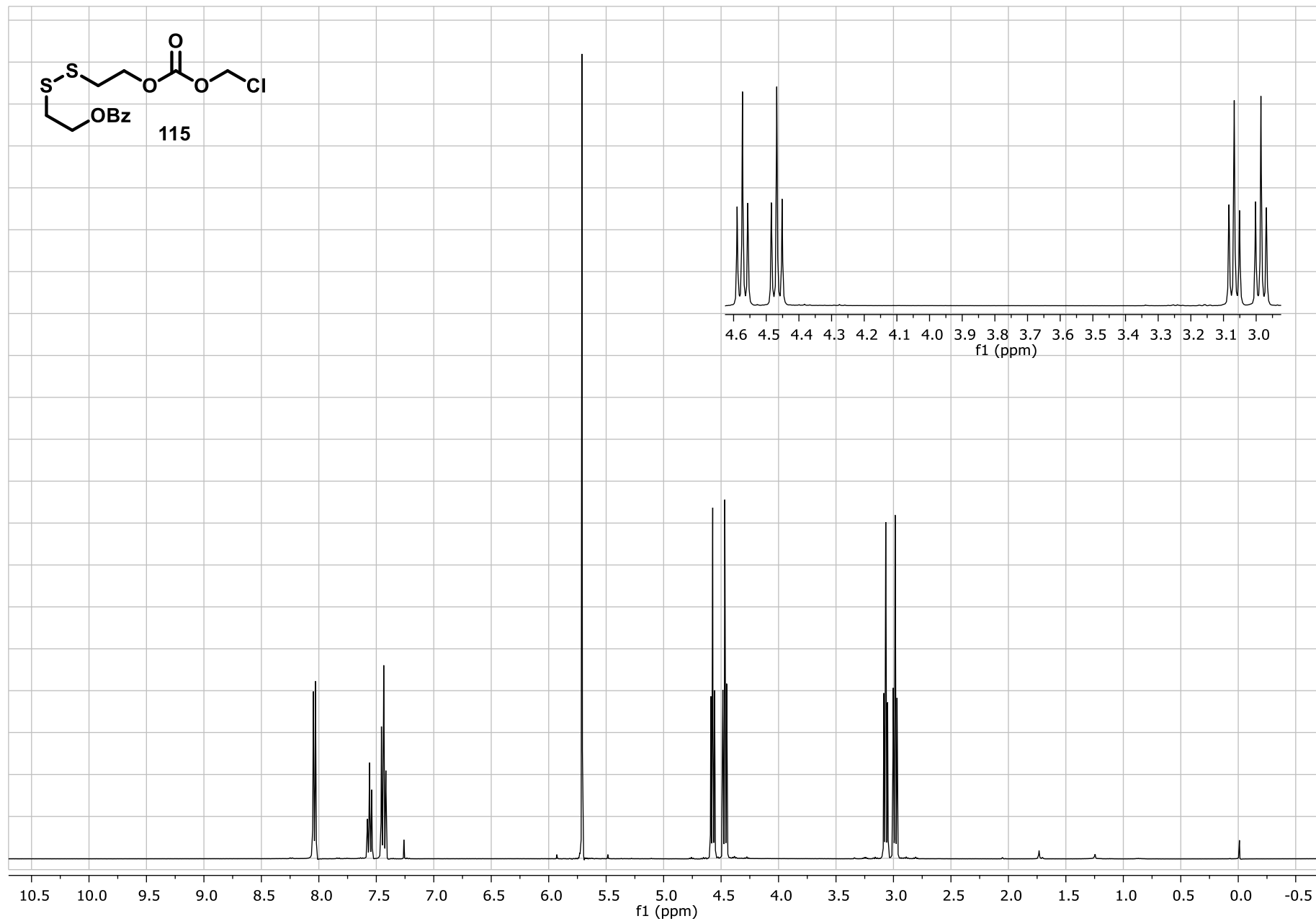
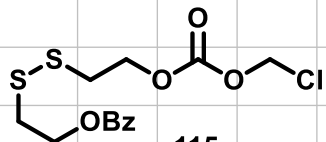


S251

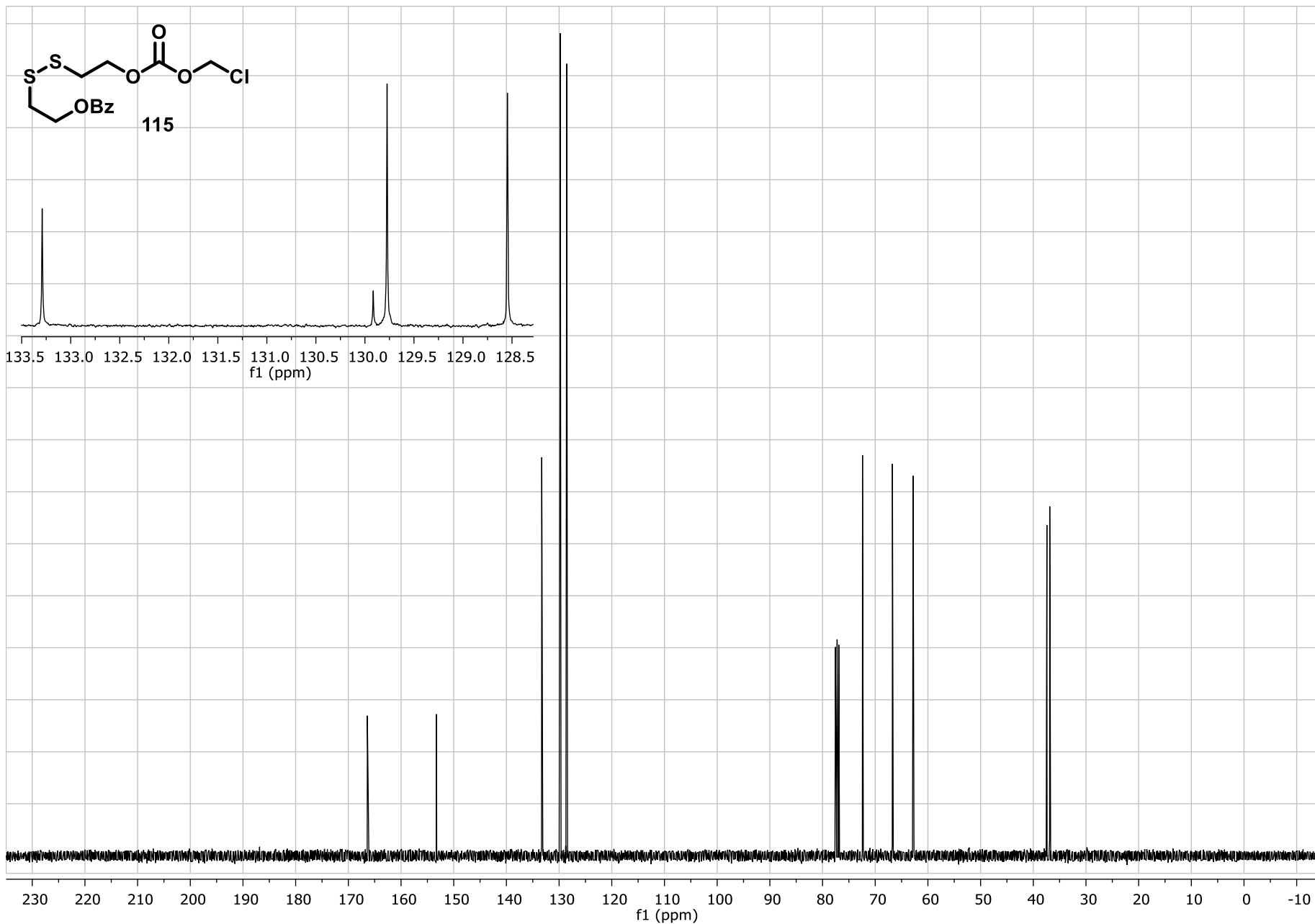


S252

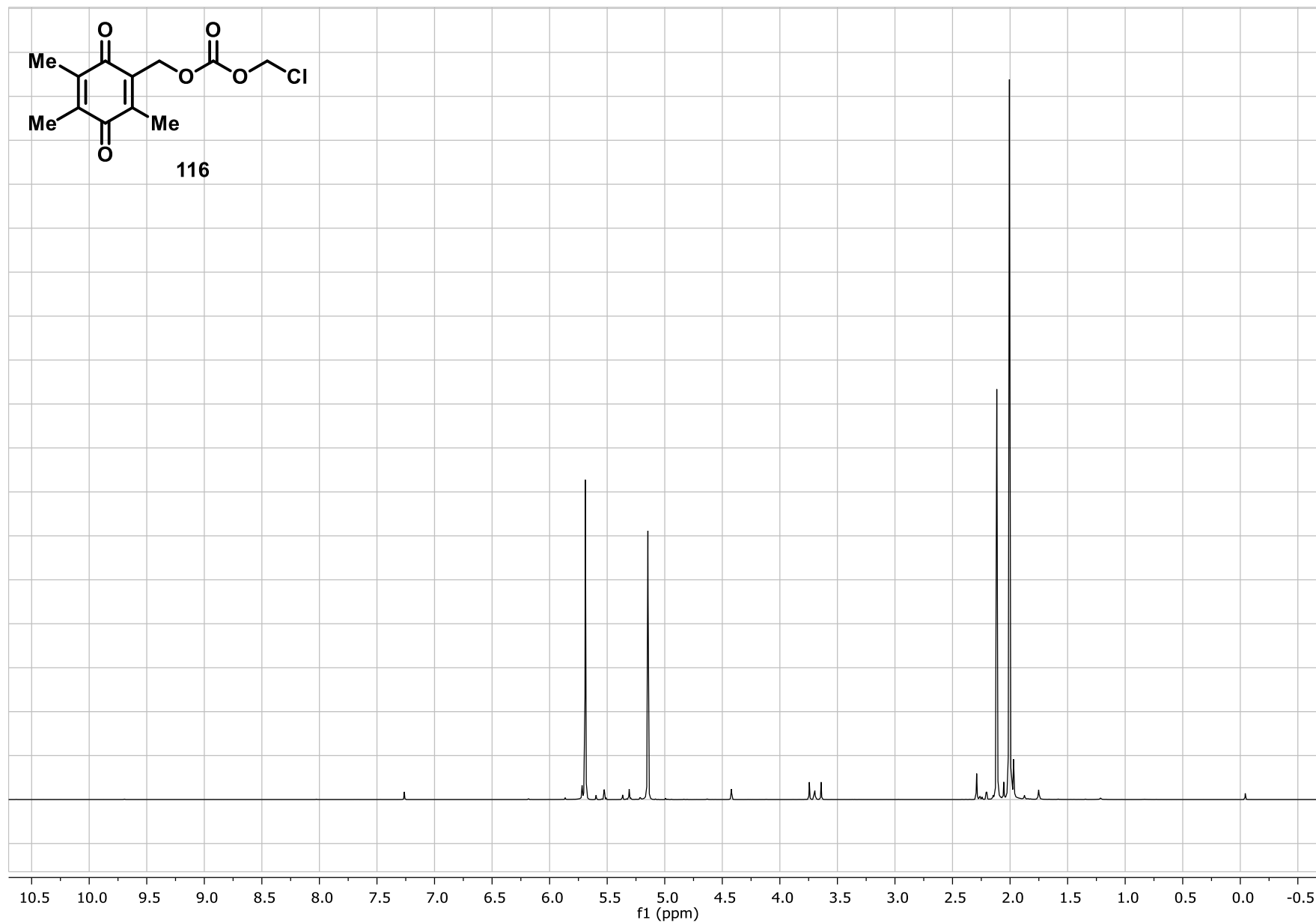
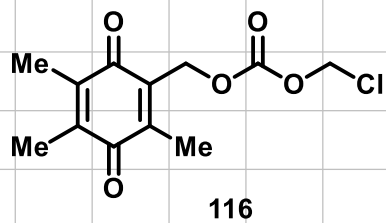




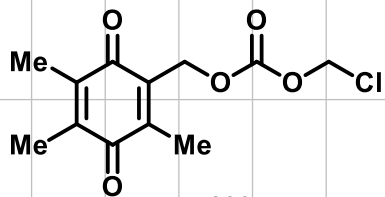
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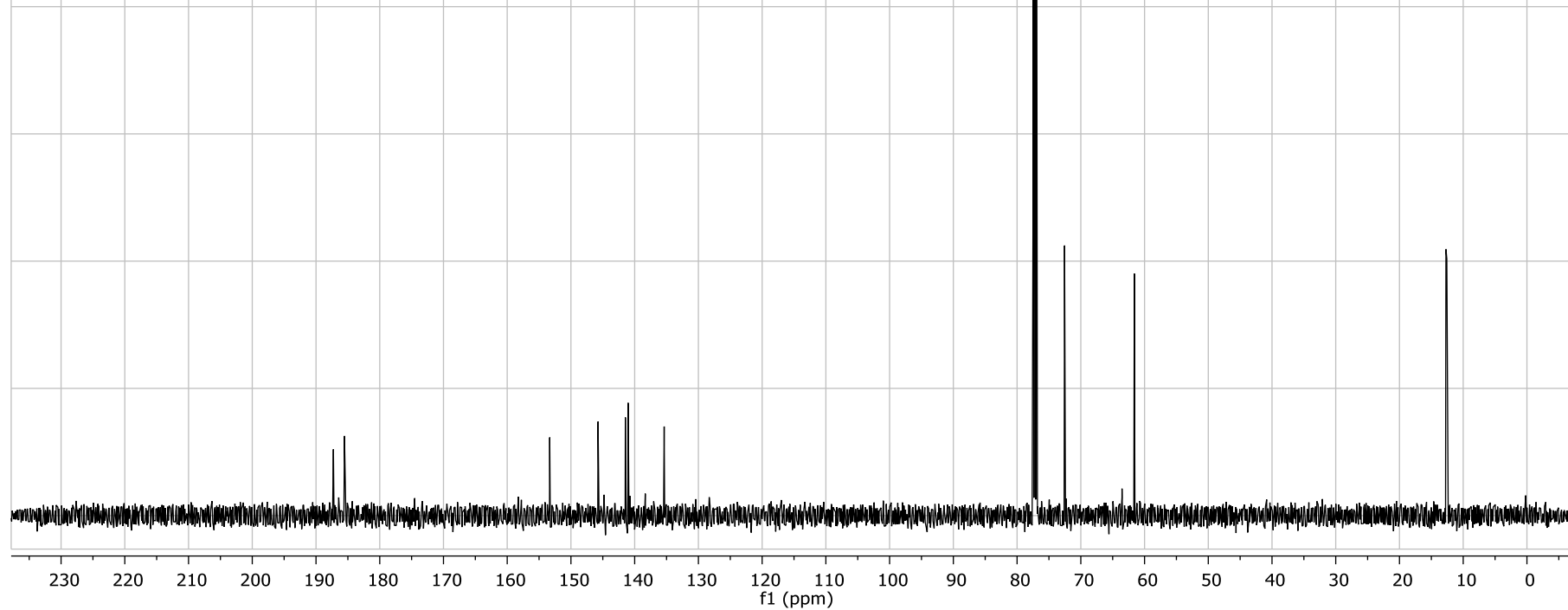
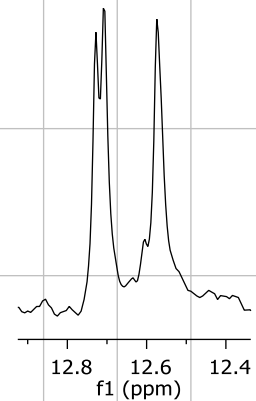
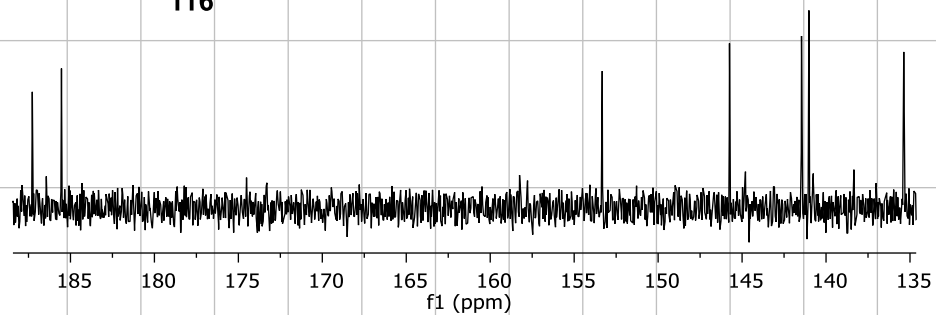
S254



S255



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S256