

## **Synthesis, Resolution, and Biological Evaluation of Atropisomeric (aR)- and (aS)-16-Methylamellarins N: Unique Effects of the Axial Chirality on the Selectivity of Protein Kinases Inhibition**

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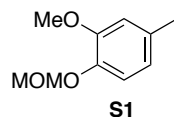
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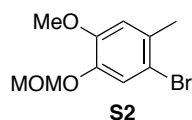
### **List of Contents**

Experimental data for <b>11</b>	S2-S3
<sup>1</sup> H NMR and <sup>13</sup> C NMR spectra	S4-S21

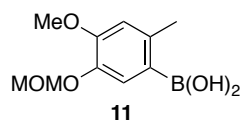
## Synthesis of boronic acid 11.



**2-Methoxy-1-methoxymethoxy-4-methylbenzene (S1).** Under an argon atmosphere, chloromethyl methyl ether (18.0 mL, 237 mmol) was added dropwise to a solution of 2-methoxy-4-methylphenol (21.8 g, 158 mmol) and *N,N*-diisopropylethylamine (55.1 mL, 316 mmol) in DCM (600 mL) at 0 °C. After being stirred for 1 h, the reaction mixture was allowed to warm to rt and stirred for an additional 10 h. The mixture was quenched with saturated aqueous ammonia and the products were extracted with DCM. The extract was washed with water, 10% aqueous NaOH, and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated. The residue was purified by bulb-to-bulb distillation (80 °C / 0.5 mmHg) to give **S1** as colorless oil (19.1 g, 66%). IR (KBr) 1511, 1267, 1156, 1078, 1004 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.30 (s, 3H), 3.51 (s, 3H), 3.86 (s, 3H), 5.18 (s, 2H), 6.68 (dd, *J* = 1.6 and 8.4 Hz, 1H), 6.72 (d, *J* = 1.6 Hz, 1H), 7.03 (d, *J* = 8.4 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 21.1, 55.8, 56.1, 95.8, 112.9, 116.8, 121.0, 132.4, 144.2, 149.6. Anal. Calcd for C<sub>10</sub>H<sub>14</sub>O<sub>3</sub>: C, 65.91; H, 7.74. Found: C, 65.67; H, 7.83.

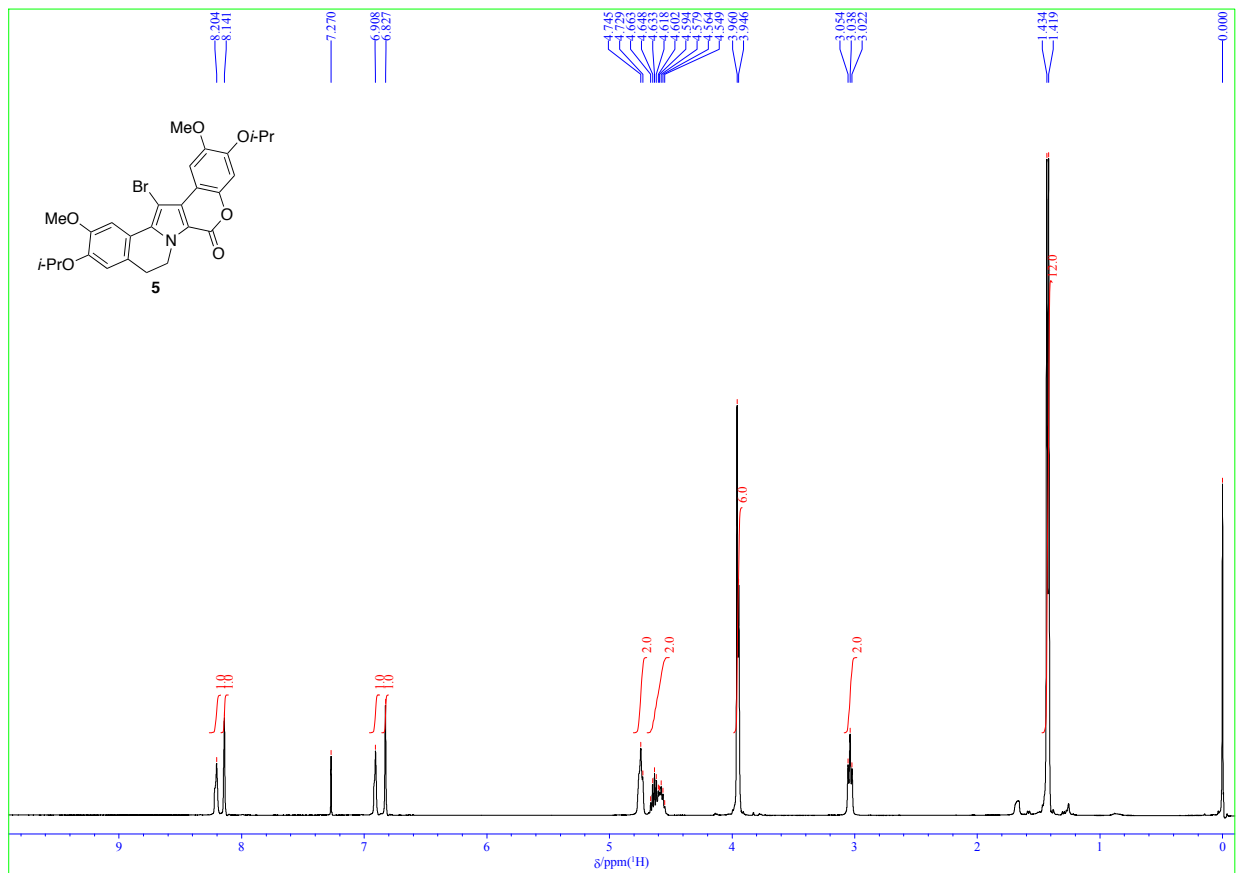


**1-Bromo-4-methoxy-5-methoxymethoxy-2-methylbenzene (S2).** A solution of NBS (17.6 g, 98.0 mmol) in DMF (50 mL) was added dropwise to a solution of **S1** (17.8 g, 97.9 mmol) in DMF (100 mL) at 0 °C. After being stirred for 5 h, the reaction mixture was quenched with water at the same temperature and allowed to warm to rt. The products were extracted with diethyl ether and the extract was washed with water and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated. The residue was purified by bulb-to-bulb distillation (100 °C / 0.1 mmHg) to give **S2** as colorless oil (24.9 g, 97%). IR (KBr) 1501, 1256, 1152, 1081, 994 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.33 (s, 3H), 3.51 (s, 3H), 3.85 (s, 3H), 5.18 (s, 2H), 6.76 (s, 1H), 7.31 (s, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 22.5, 56.0, 56.3, 95.8, 113.9, 114.5, 120.4, 131.5, 145.0, 149.0; HRFABMS *m/z* calcd for C<sub>10</sub>H<sub>13</sub>BrO<sub>3</sub> (M<sup>+</sup>) 260.0048, found 260.0024.

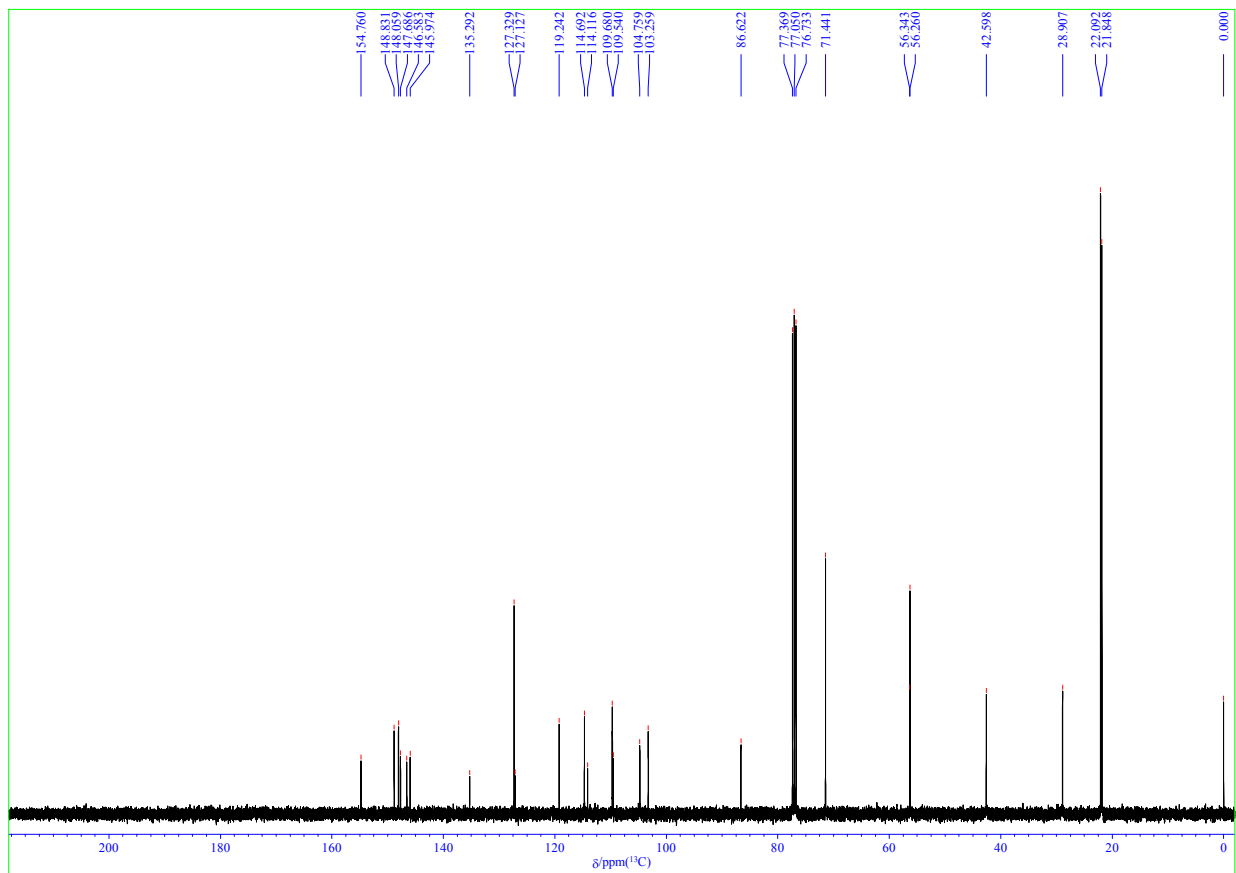


**4-Methoxy-5-methoxymethoxy-2-methylphenyl boronic acid (11).** Under an argon atmosphere, a pentane solution of *t*-butyllithium (1.43 M, 100 mL, 143 mmol) was added dropwise to a solution of **S2** (17.8 g, 68.1 mmol) in THF (400 mL) at -78 °C. After being stirred for 1 h, trimethyl borate (11.4 mL, 102 mmol) was added as a neat liquid and the mixture was stirred for 1 h at -78 °C. The reaction mixture was

allowed to warm to rt and stirred for an additional 1 h. The mixture was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  and concentrated. The products were adjusted to pH 3 with acetic acid and the mixture was extract with DCM. The extract was washed successively with water, saturated aqueous  $\text{NaHCO}_3$ , and brine, dried over  $\text{Na}_2\text{SO}_4$ , and evaporated. The residue was washed with hexane and dried under reduced pressure to give **11** as pale brown powder (11.9 g, 77%). This compound was used for the next reaction without further purification. IR (KBr) 1600, 1517, 1324, 1151, 1081  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.79 (s, 3H), 3.54 (s, 3H), 3.93 (s, 3H), 5.26 (s, 2H), 6.79 (s, 1H), 8.01 (s, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  22.7, 55.7, 56.1, 95.7, 114.1, 125.1, 142.5, 143.7, 152.7.



**Figure S1.**  $^1\text{H}$  NMR spectrum of compound **5** (400 MHz,  $\text{CDCl}_3$ ).



**Figure S2.**  $^{13}\text{C}$  NMR spectrum of compound **5** (100 MHz,  $\text{CDCl}_3$ ).

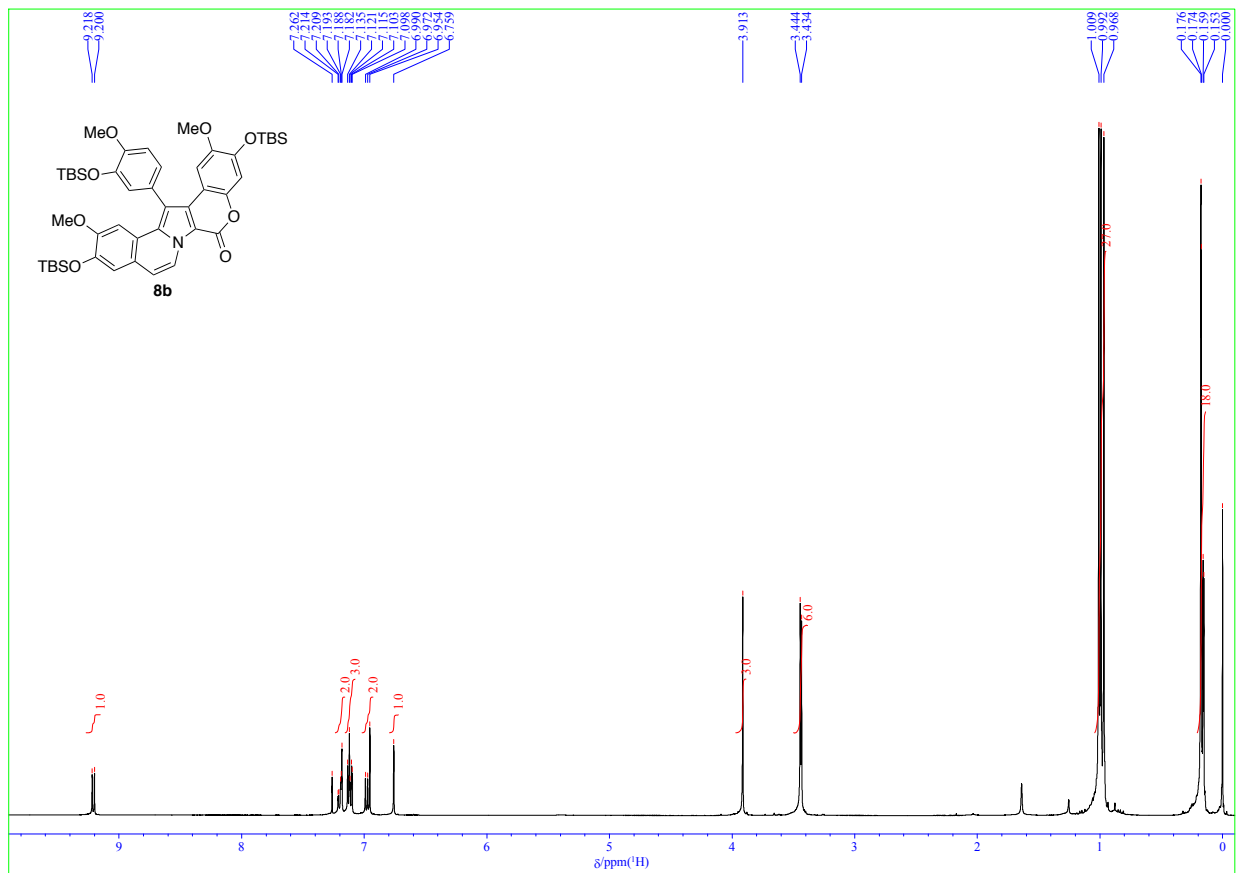


Figure S3.  $^1\text{H}$  NMR spectrum of compound **8b** (400 MHz,  $\text{CDCl}_3$ ).

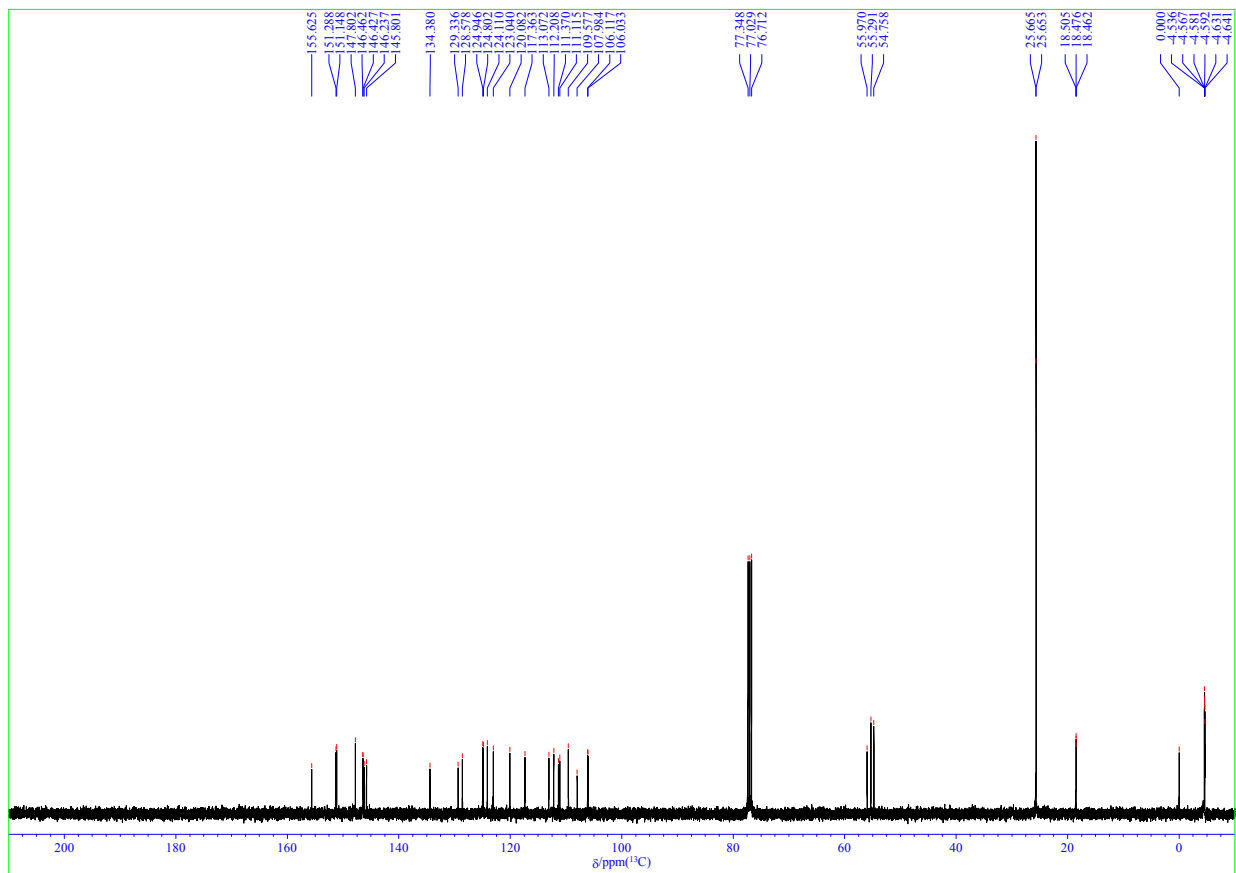


Figure S4.  $^{13}\text{C}$  NMR spectrum of compound **8b** (100 MHz,  $\text{CDCl}_3$ ).

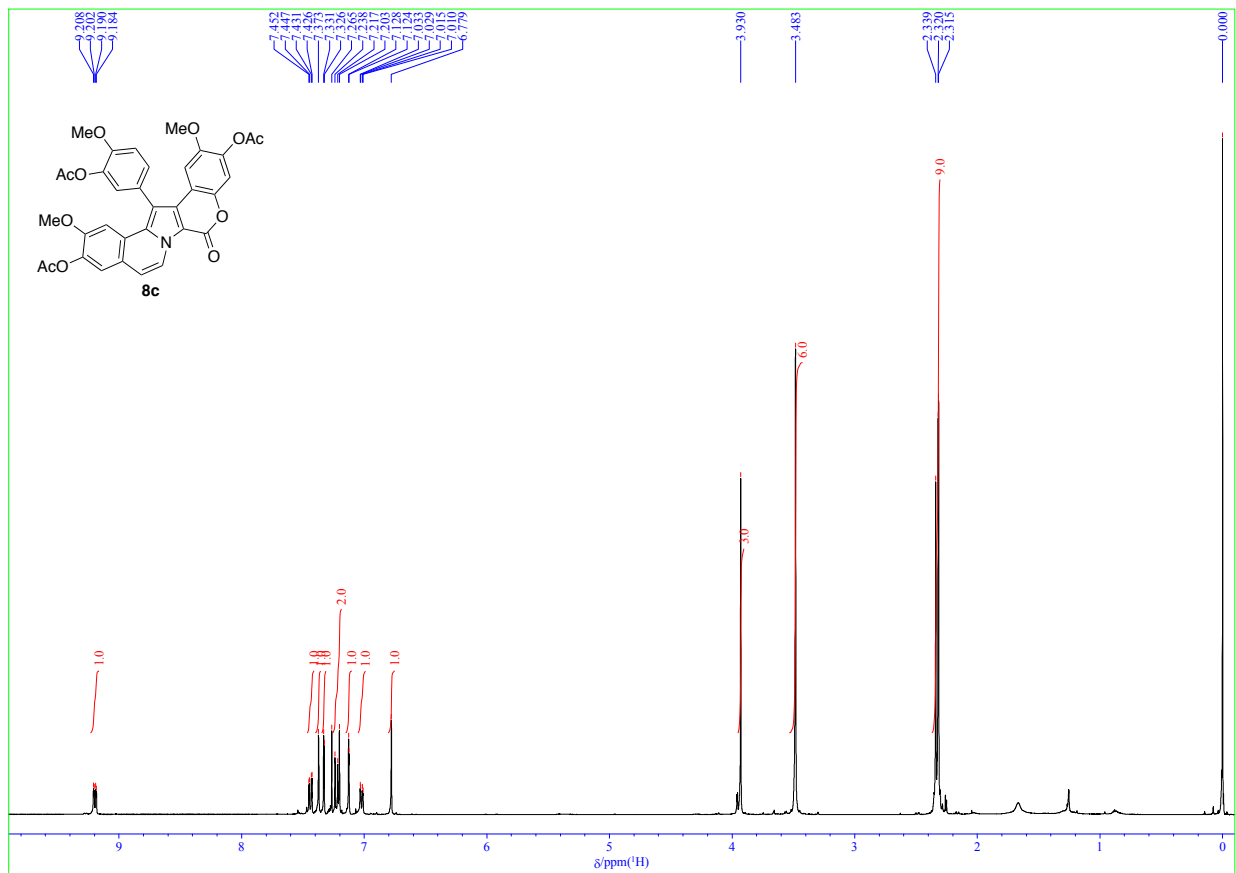


Figure S5.  $^1\text{H NMR}$  spectrum of compound **8c** (400 MHz,  $\text{CDCl}_3$ ).

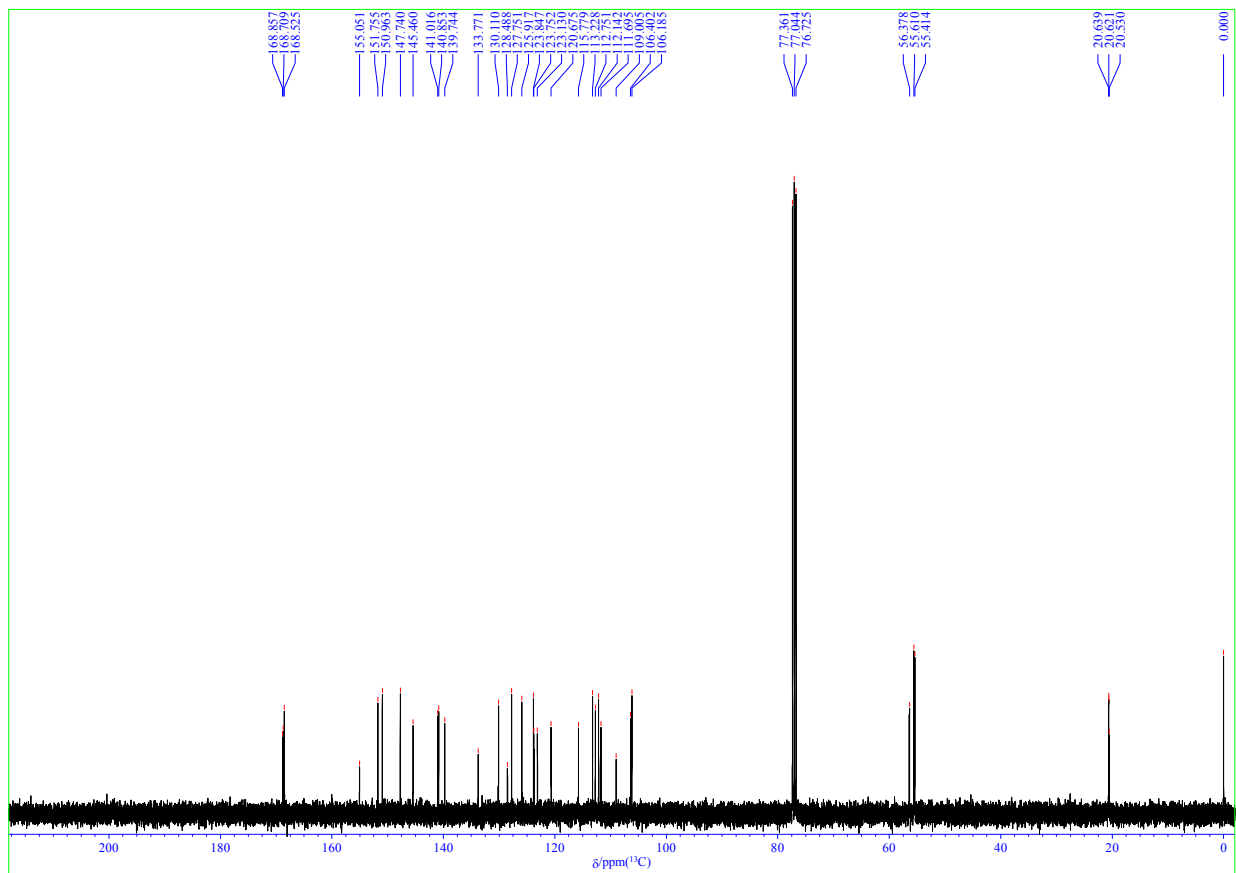
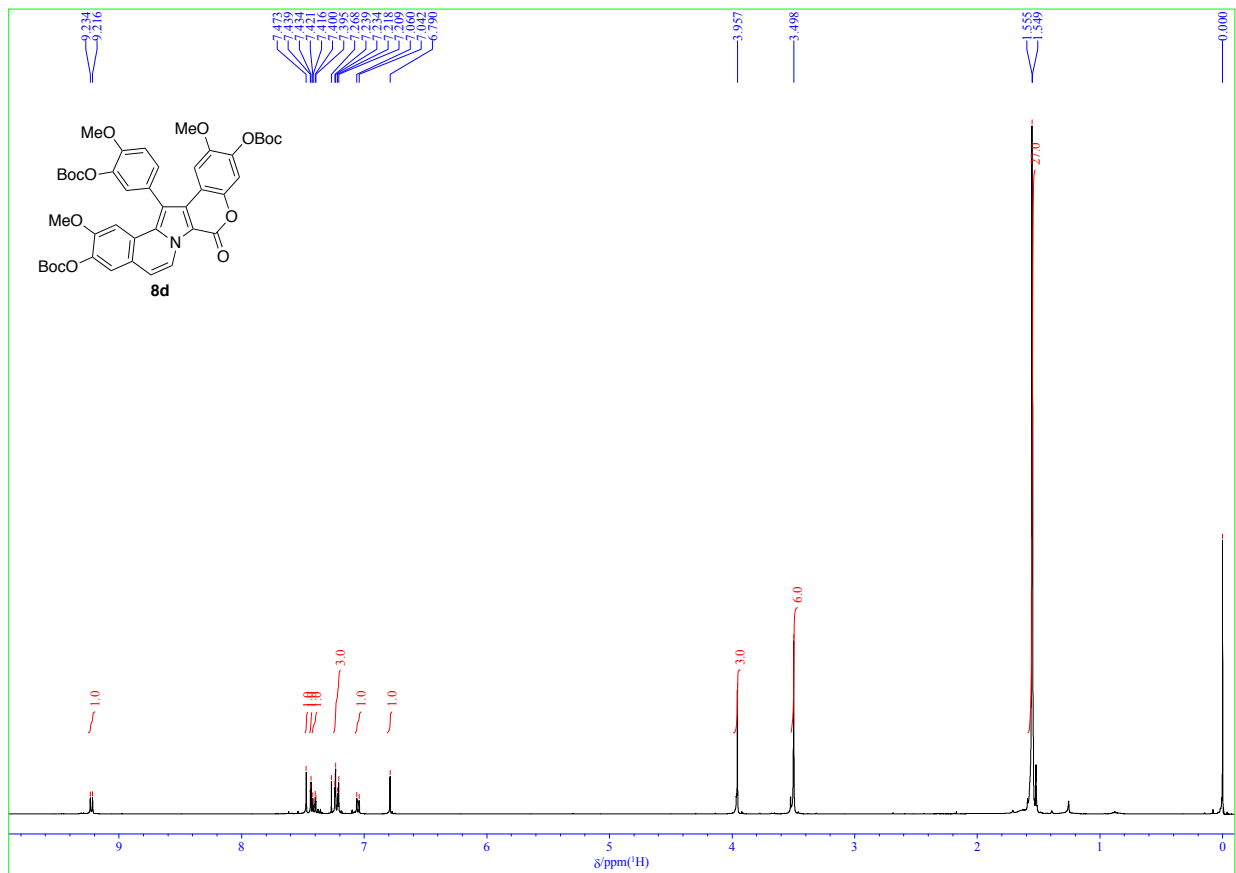
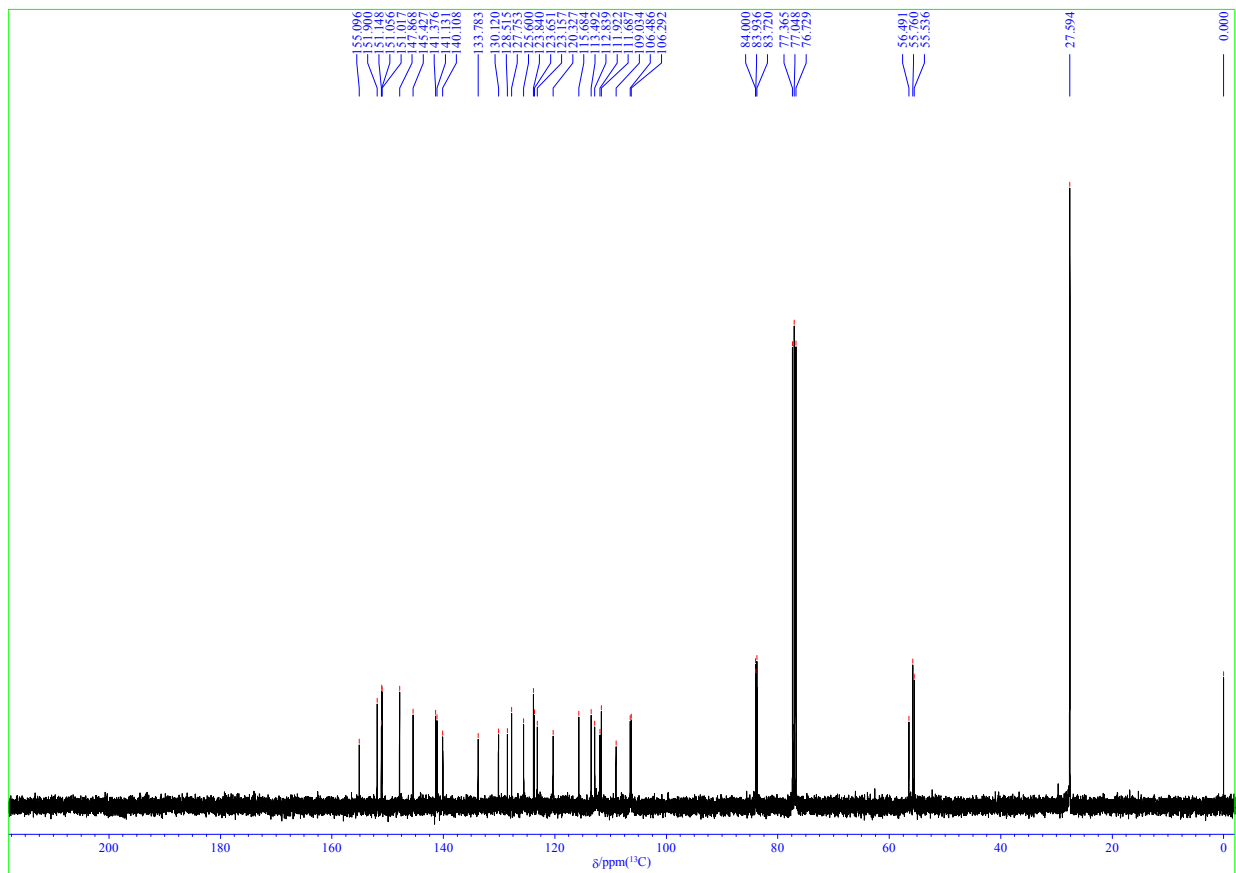


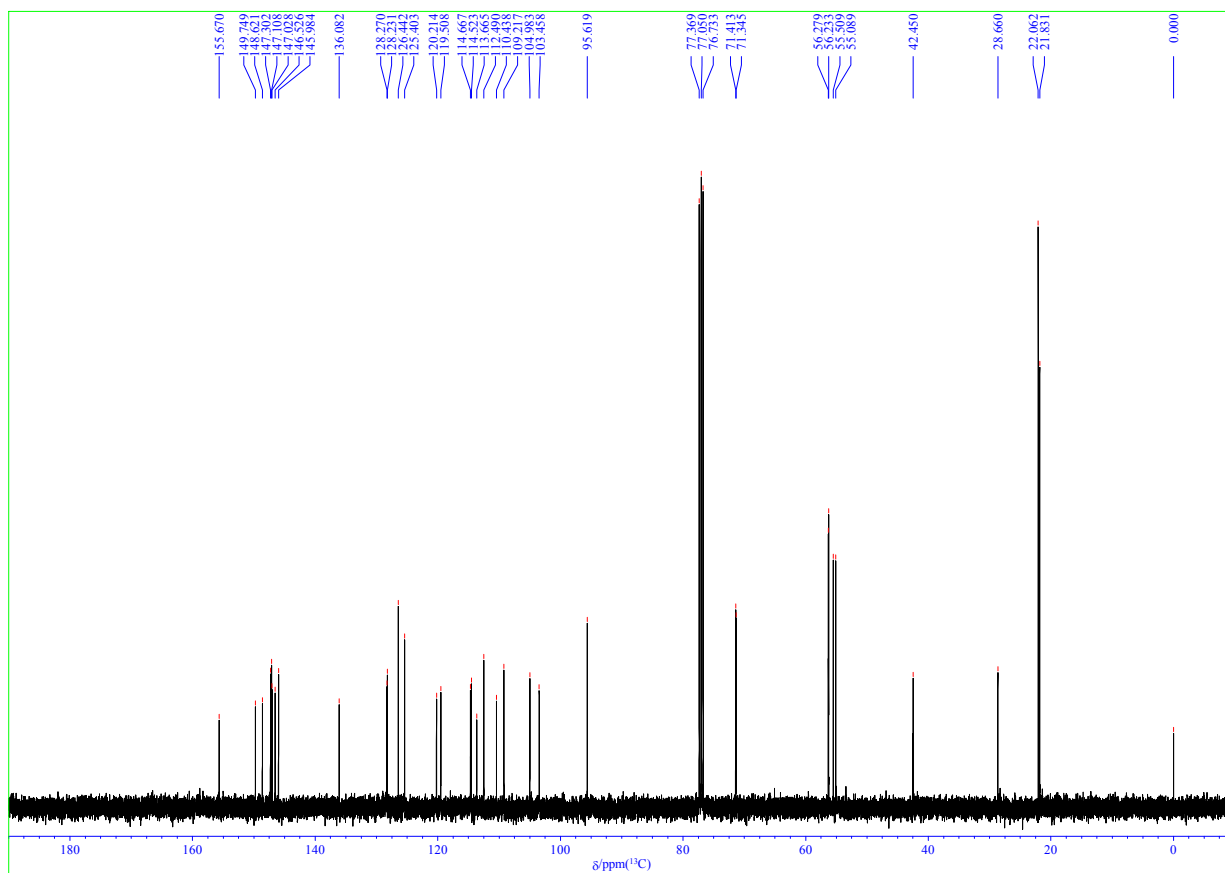
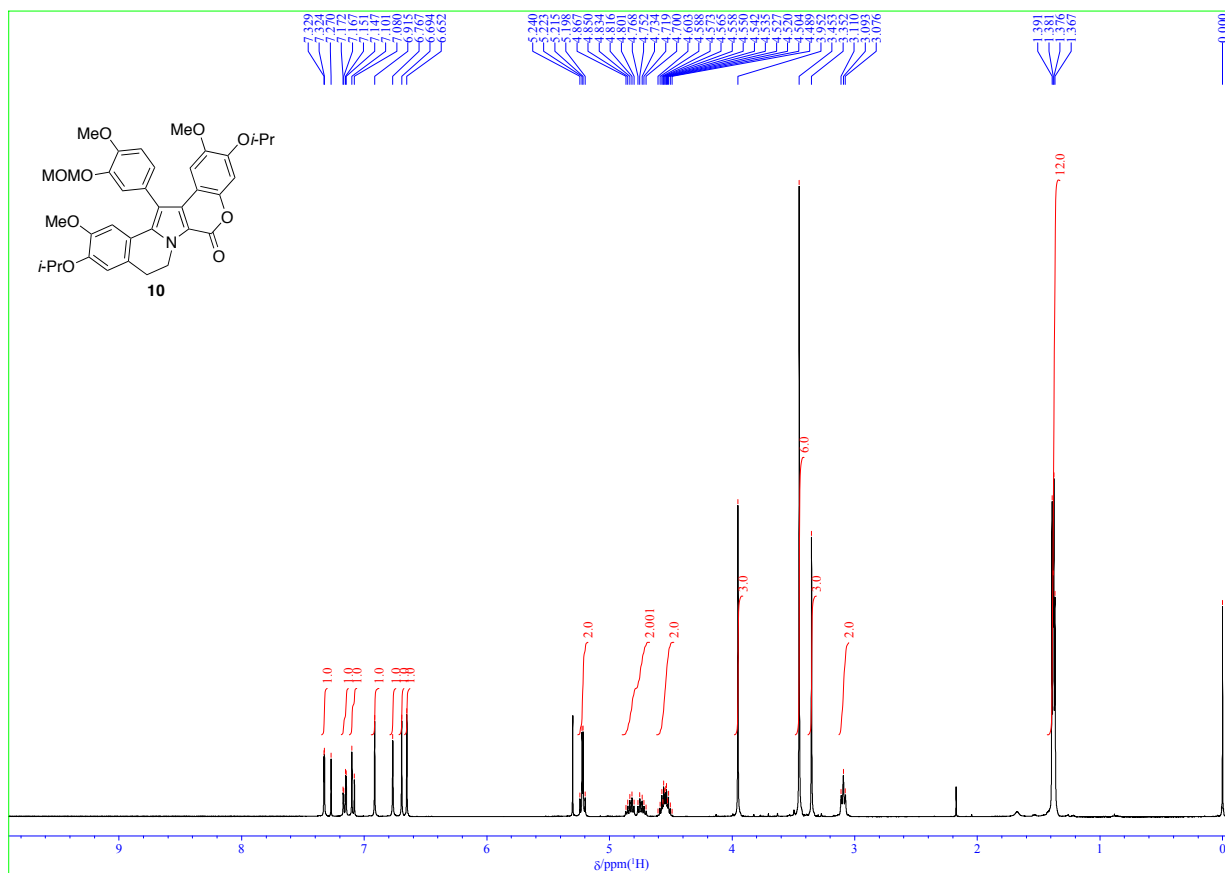
Figure S6.  $^{13}\text{C NMR}$  spectrum of compound **8c** (100 MHz,  $\text{CDCl}_3$ ).

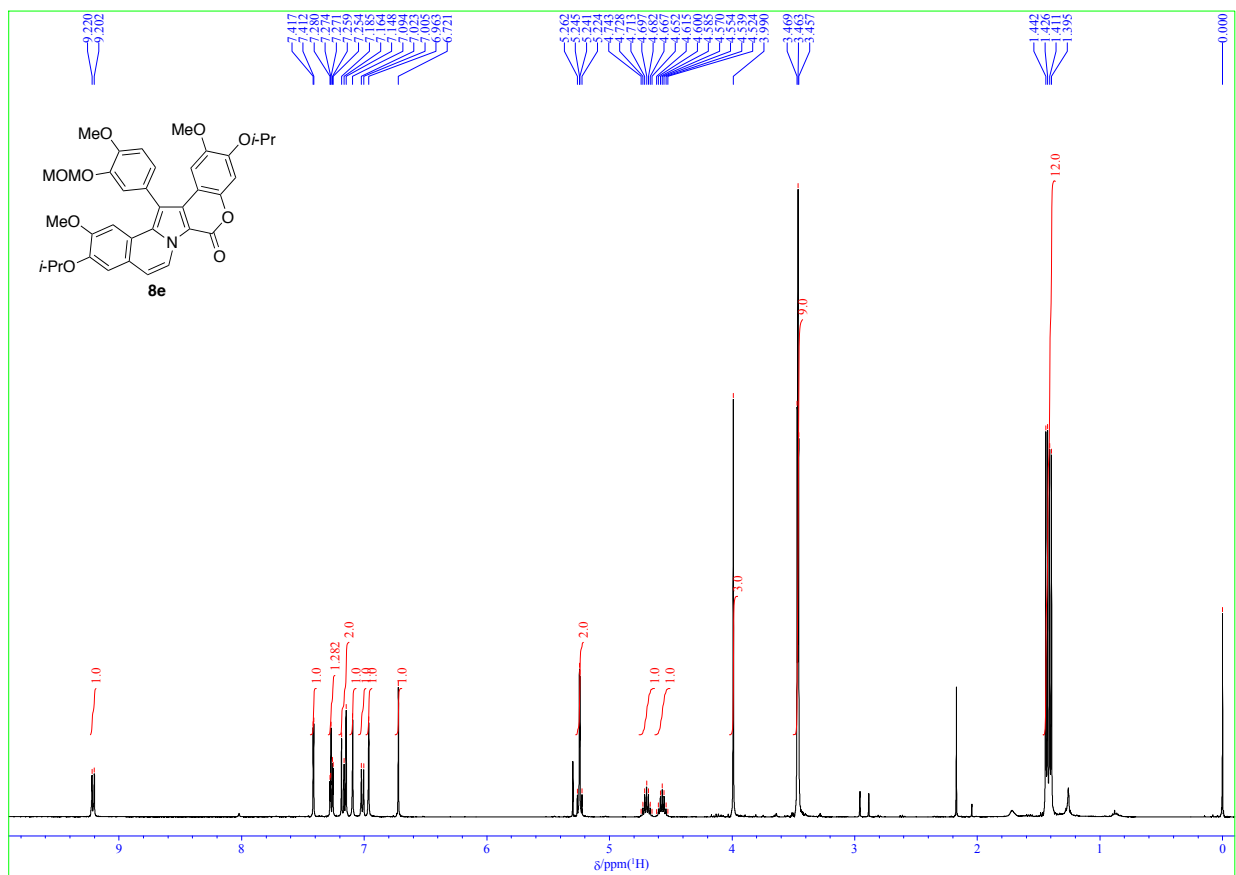


**Figure S7.** <sup>1</sup>H NMR spectrum of compound **8d** (400 MHz, CDCl<sub>3</sub>).

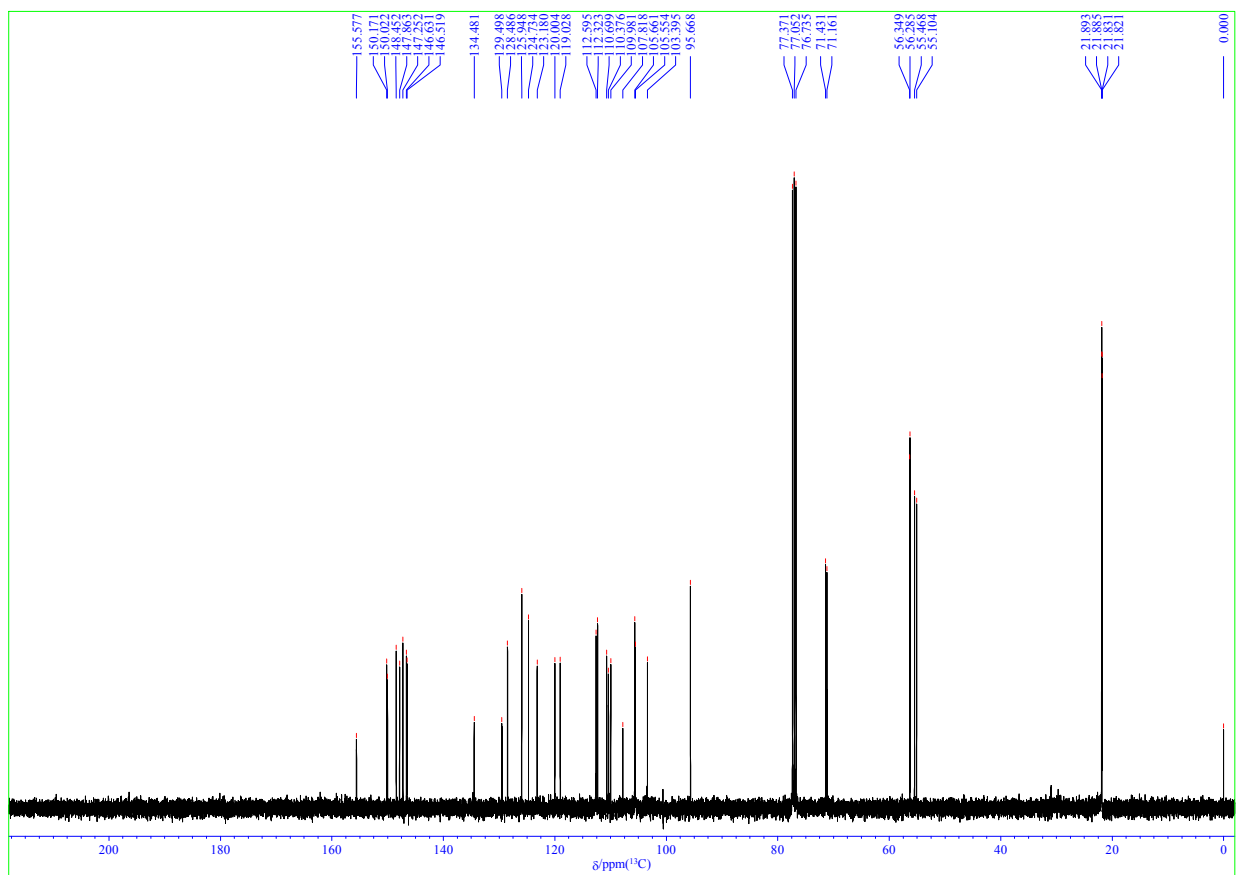


**Figure S8.** <sup>13</sup>C NMR spectrum of compound **8d** (100 MHz, CDCl<sub>3</sub>).

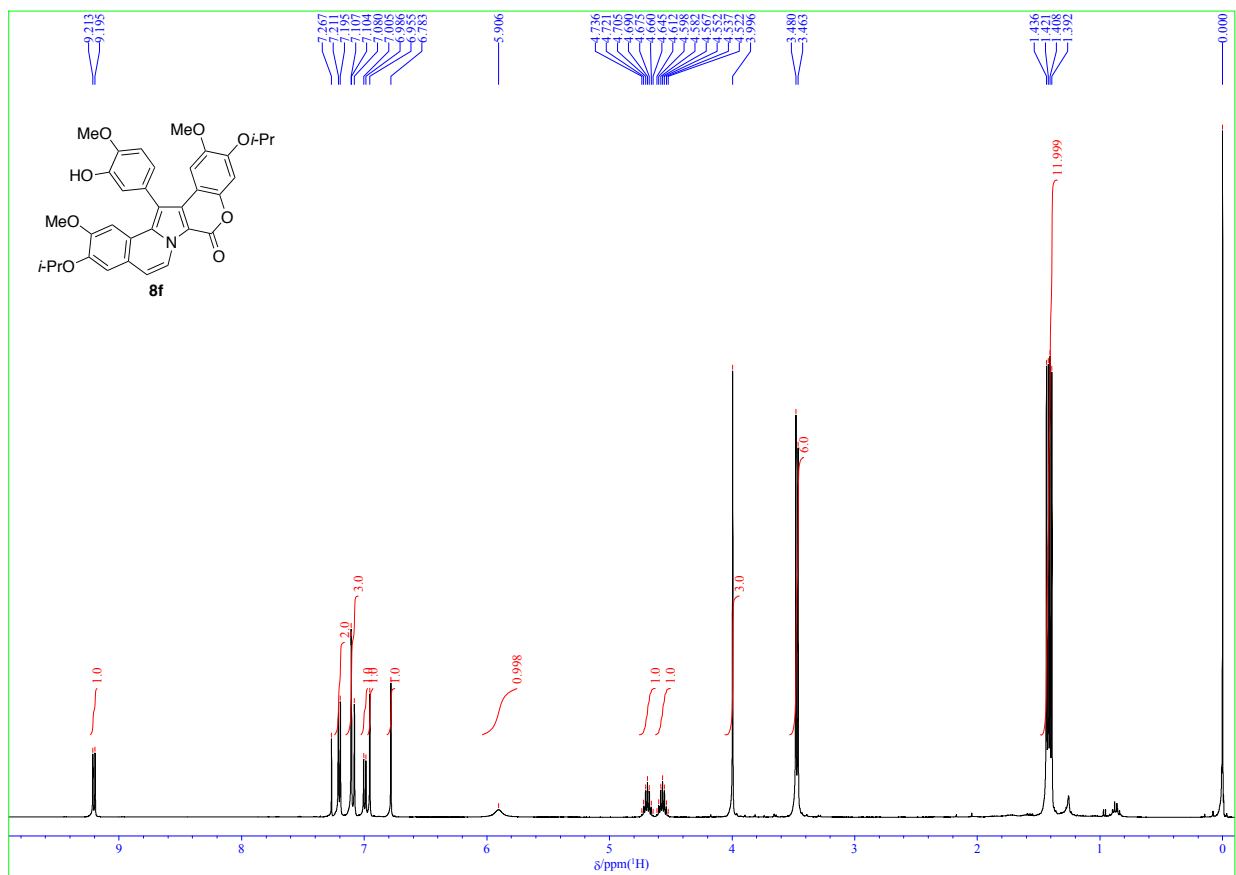




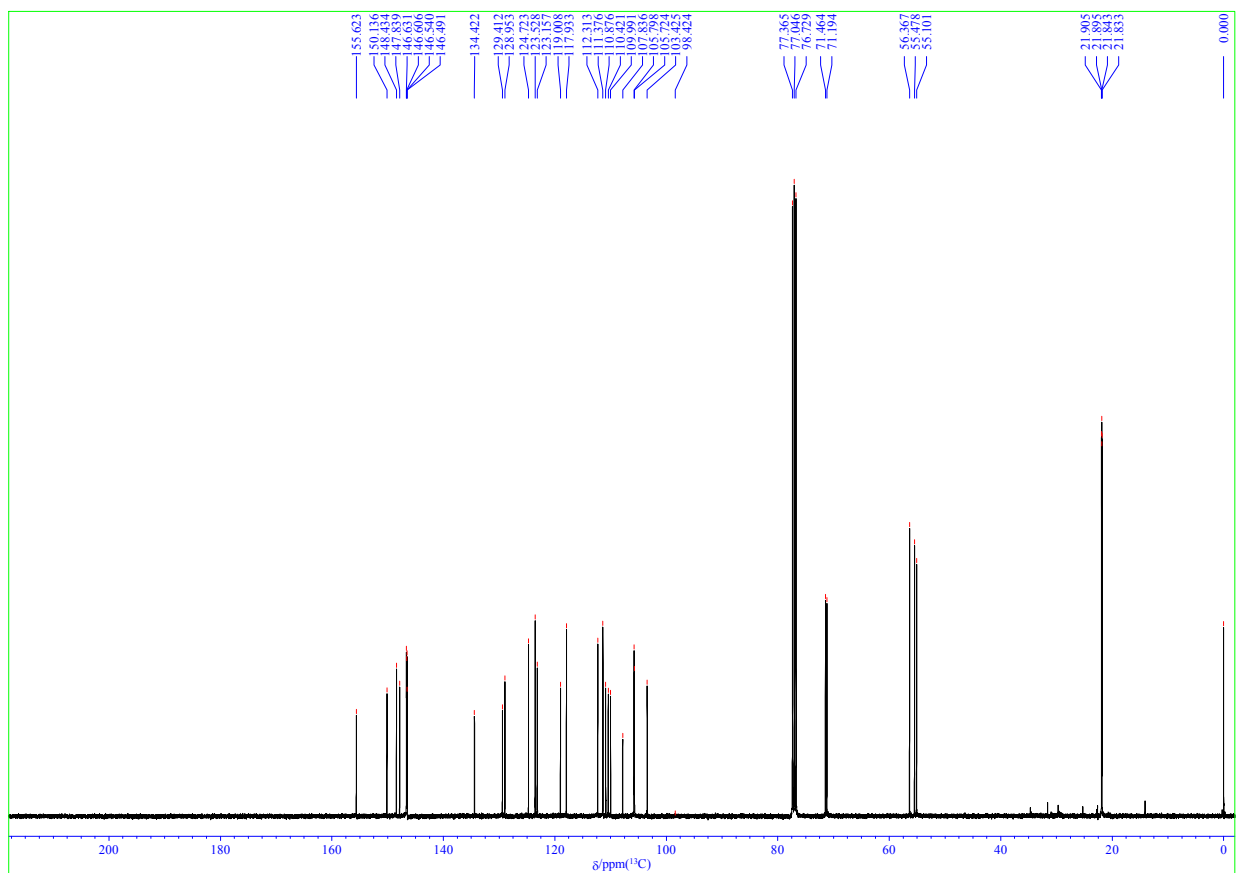
**Figure S11.**  $^1\text{H}$  NMR spectrum of compound **8e** (400 MHz,  $\text{CDCl}_3$ ).



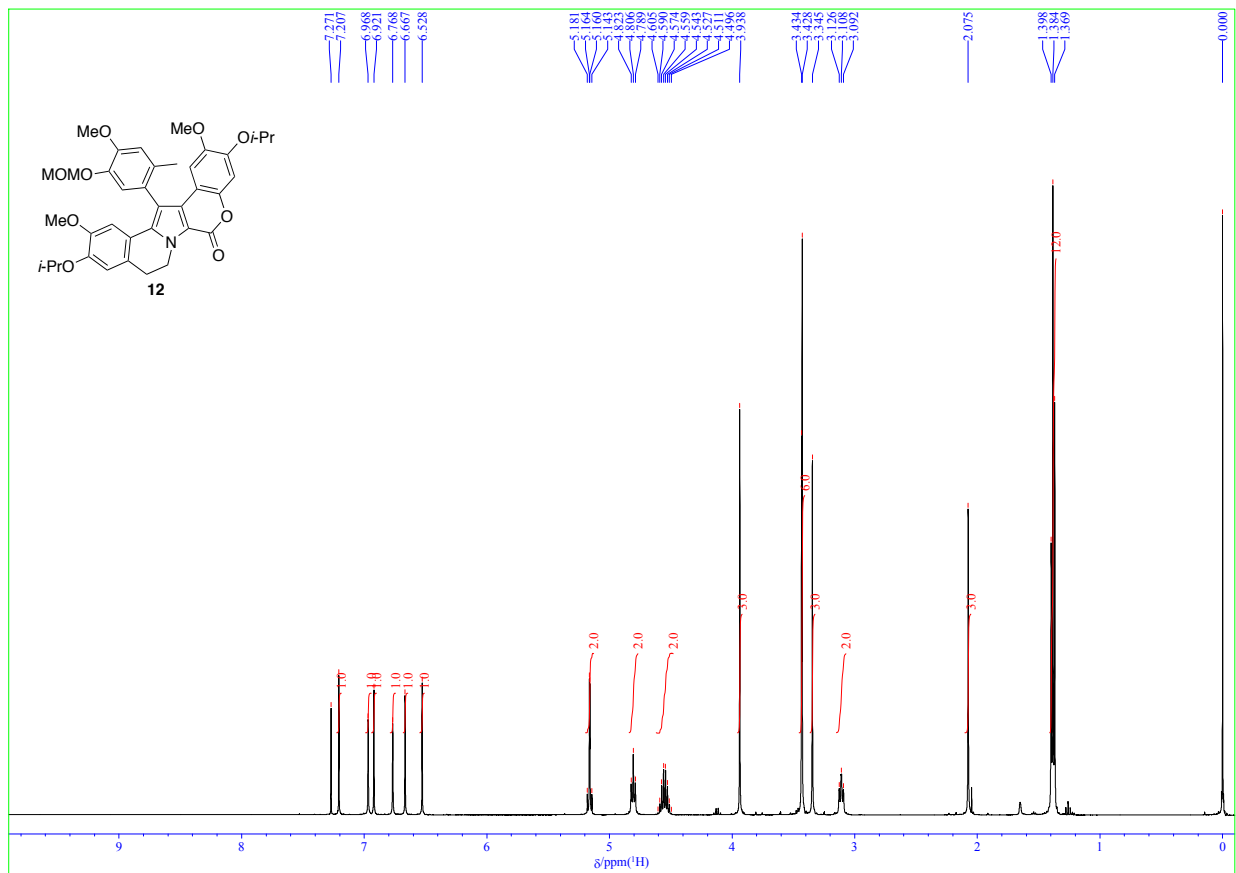
**Figure S12.**  $^{13}\text{C}$  NMR spectrum of compound **8e** (100 MHz,  $\text{CDCl}_3$ ).

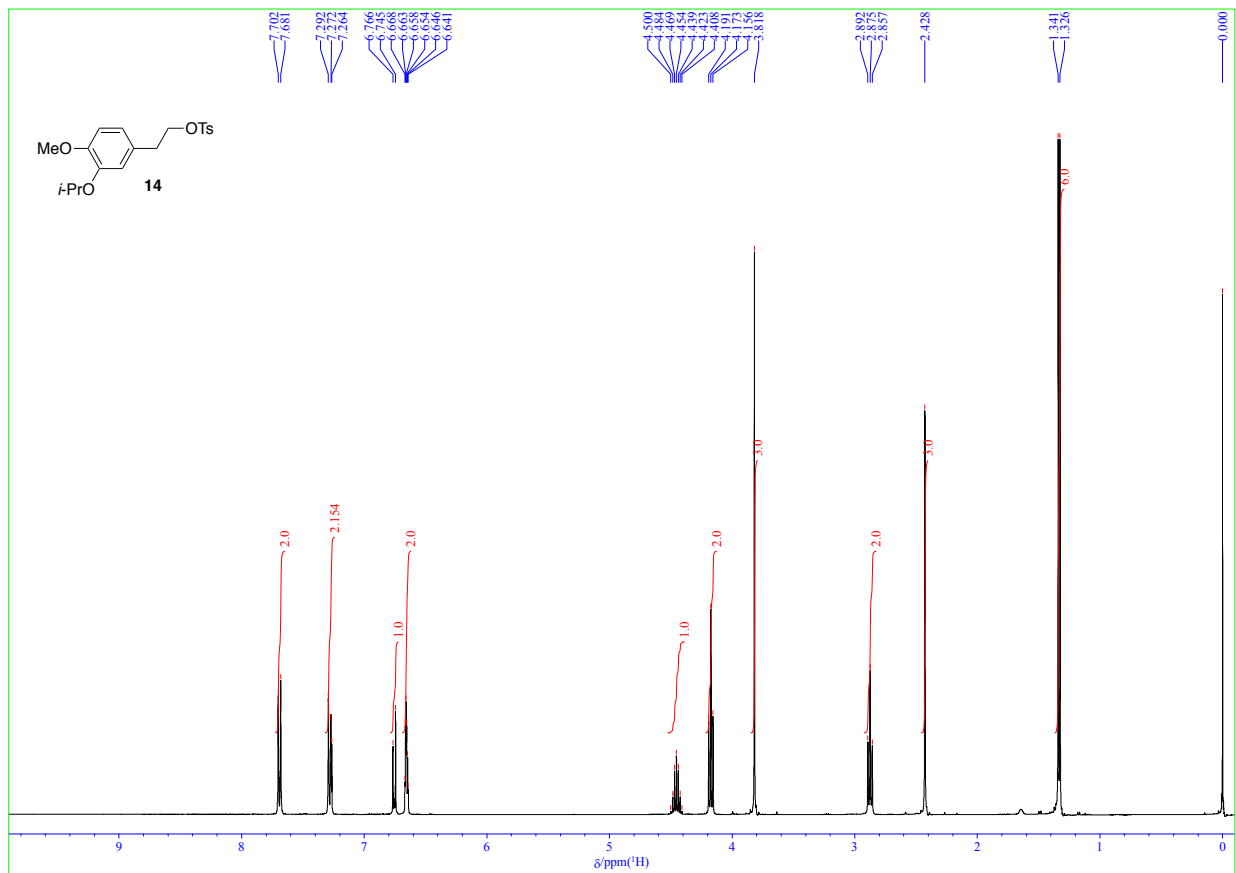


**Figure S13.** <sup>1</sup>H NMR spectrum of compound **8f** (400 MHz, CDCl<sub>3</sub>).

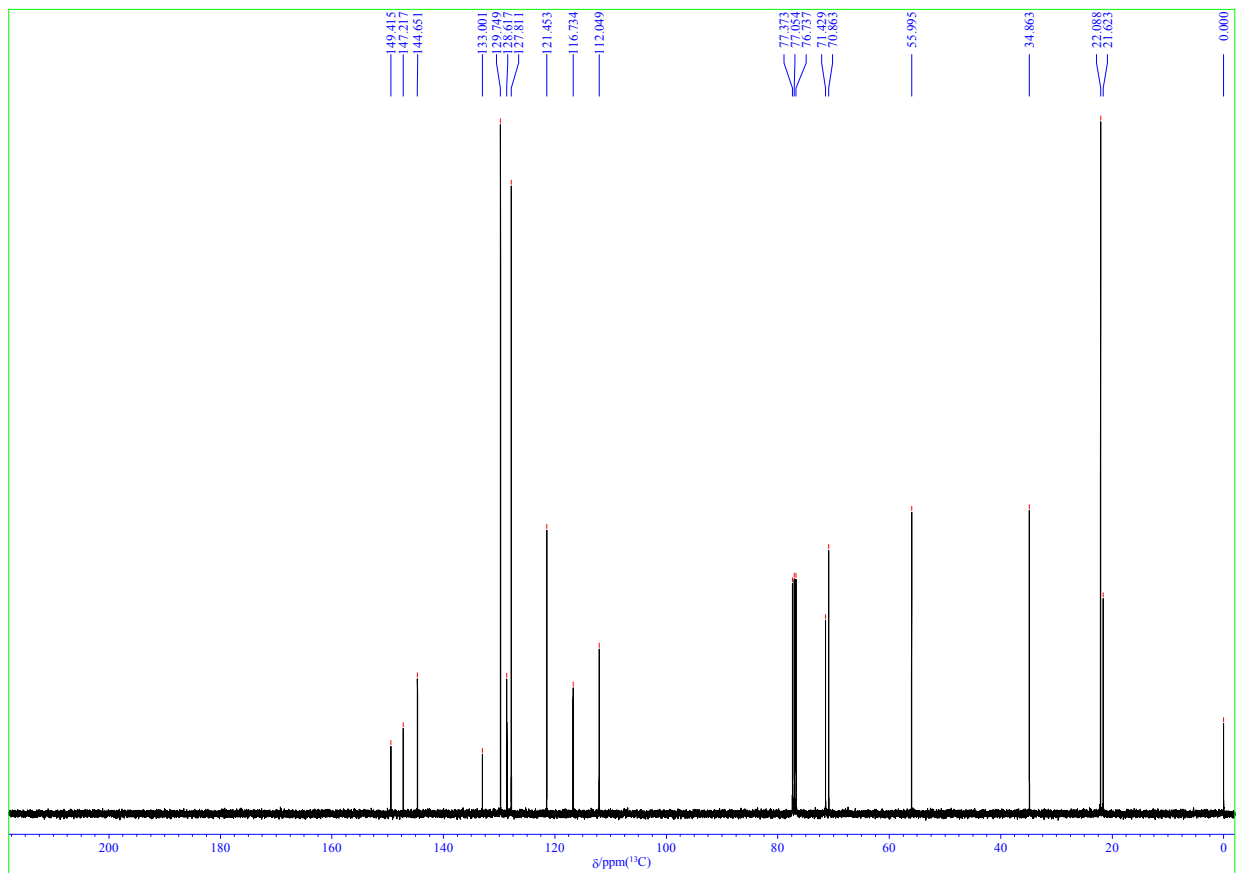


**Figure S14.** <sup>13</sup>C NMR spectrum of compound **8f** (100 MHz, CDCl<sub>3</sub>).

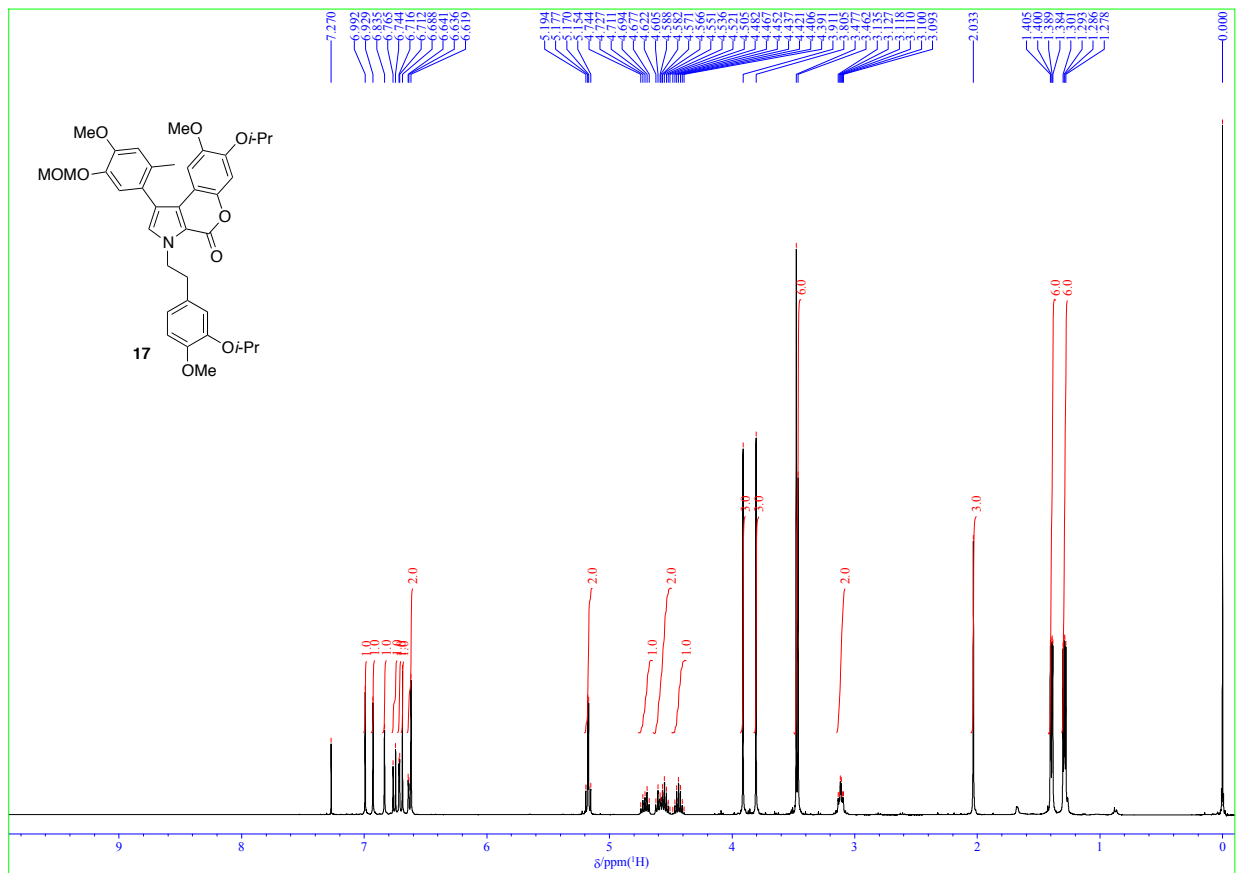




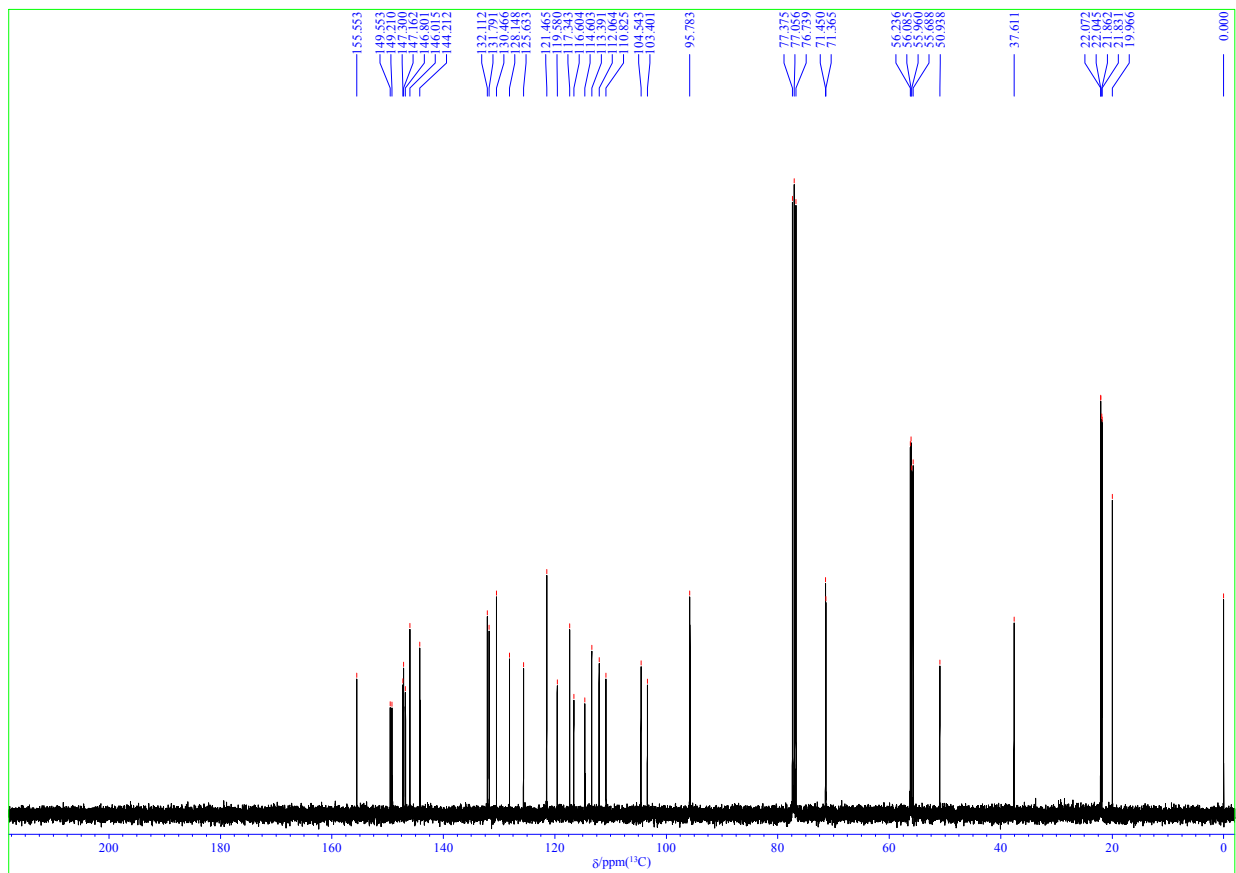
**Figure S17.** <sup>1</sup>H NMR spectrum of compound **14** (400 MHz, CDCl<sub>3</sub>).



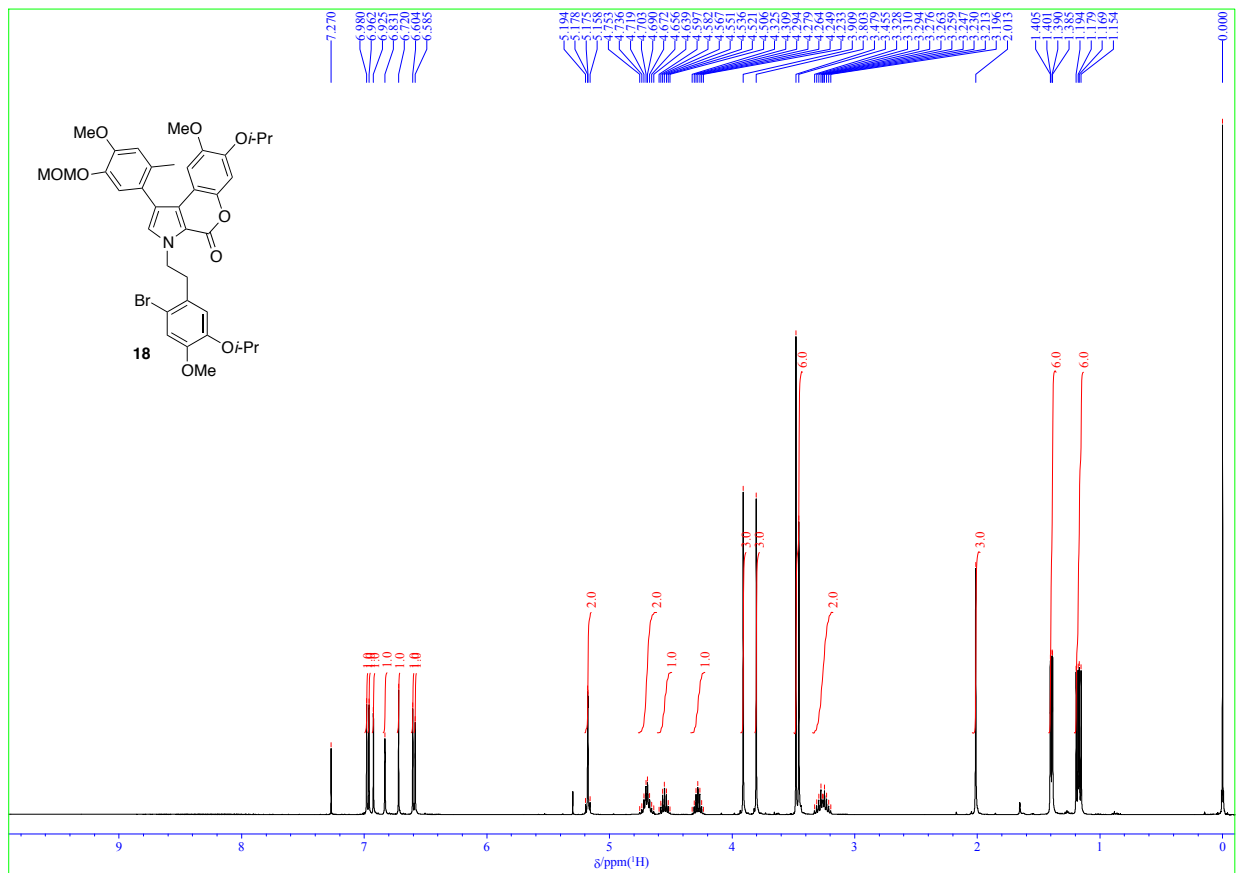
**Figure S18.** <sup>13</sup>C NMR spectrum of compound **14** (100 MHz, CDCl<sub>3</sub>).



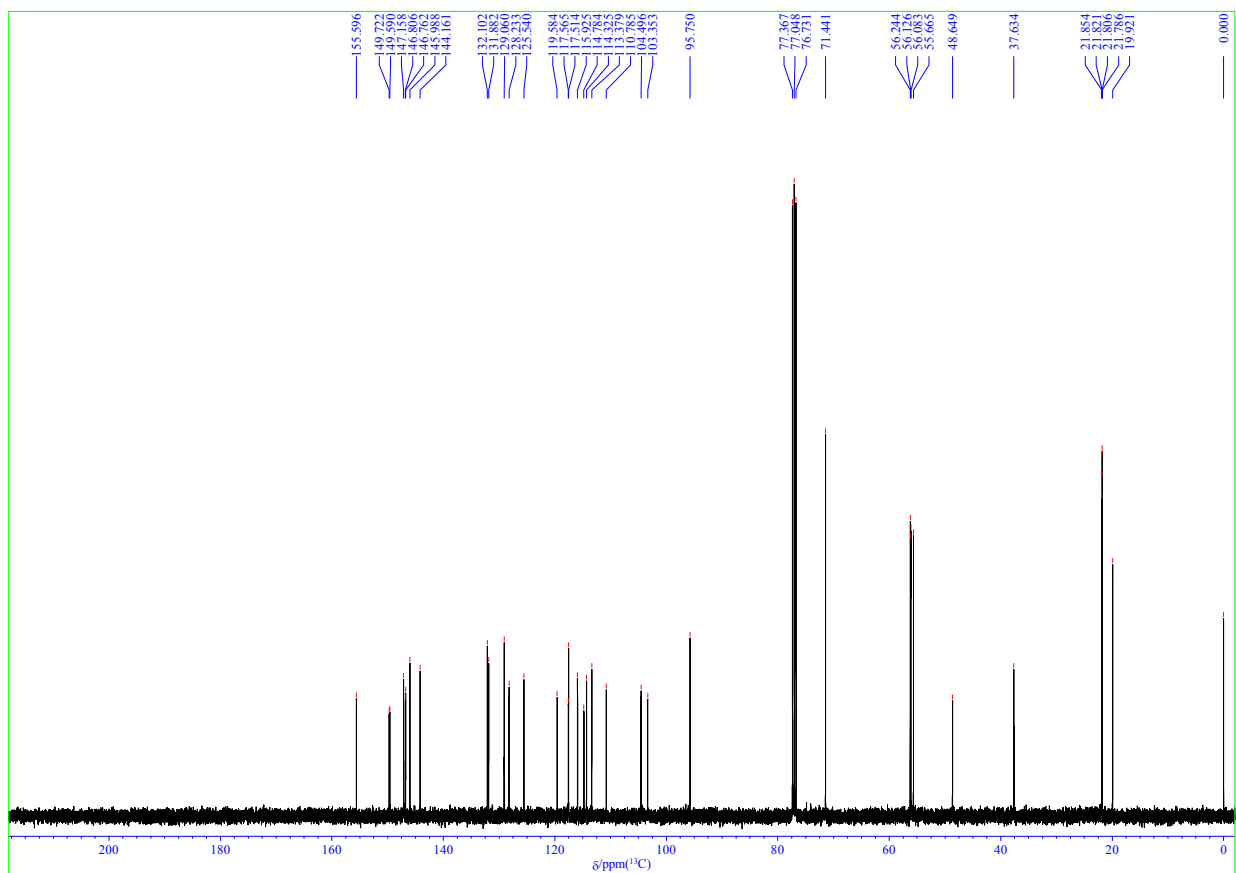
**Figure S19.**  $^1\text{H}$  NMR spectrum of compound **17** (400 MHz,  $\text{CDCl}_3$ ).



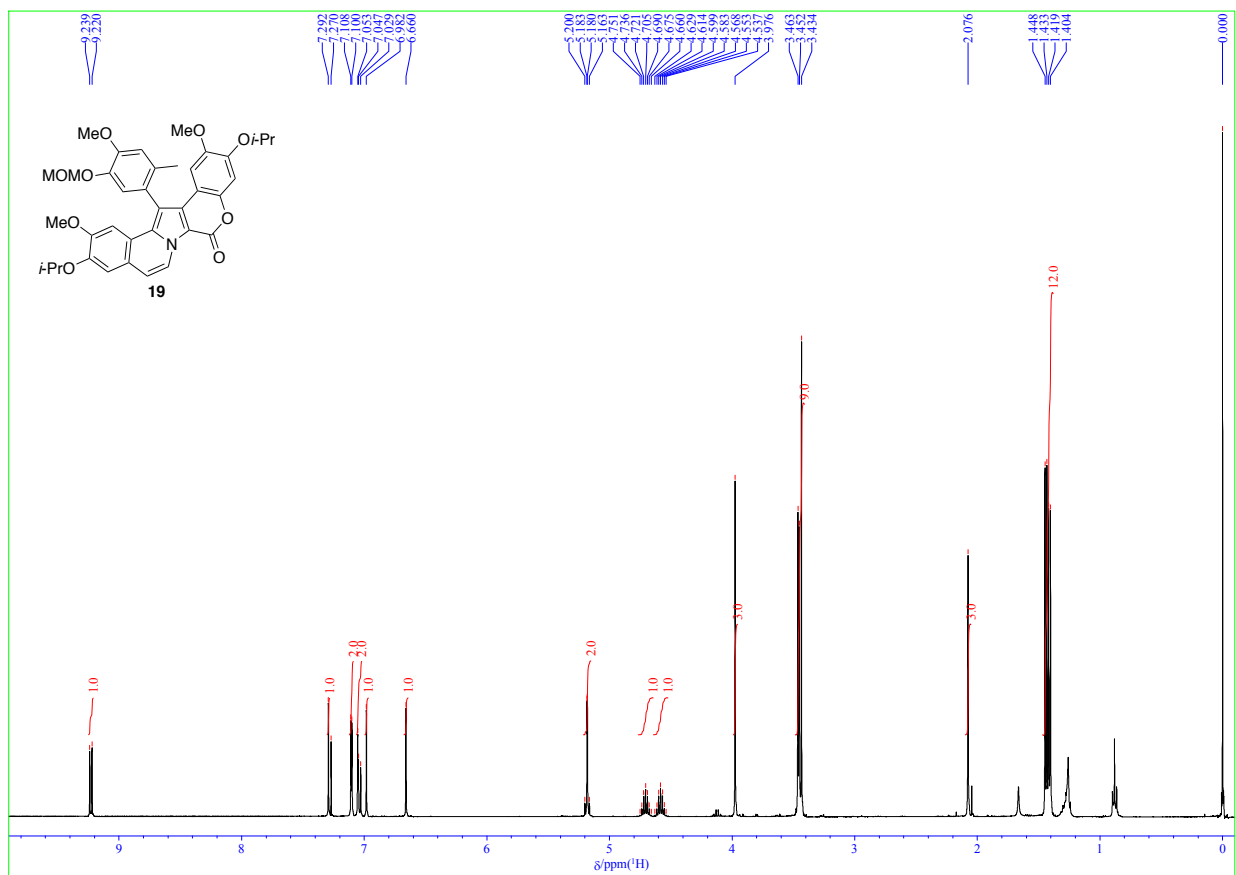
**Figure S20.**  $^{13}\text{C}$  NMR spectrum of compound **17** (100 MHz,  $\text{CDCl}_3$ ).



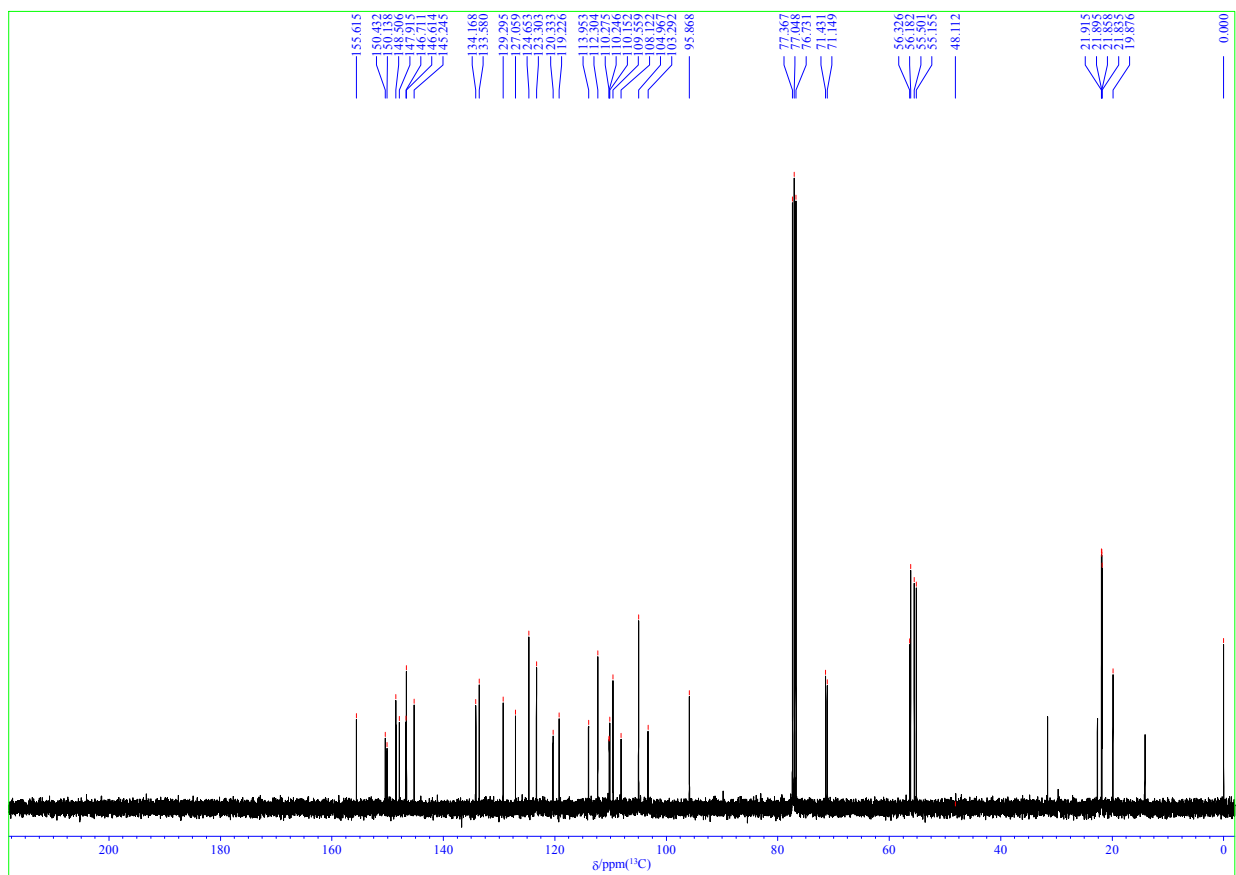
**Figure S21.** <sup>1</sup>H NMR spectrum of compound **18** (400 MHz, CDCl<sub>3</sub>).



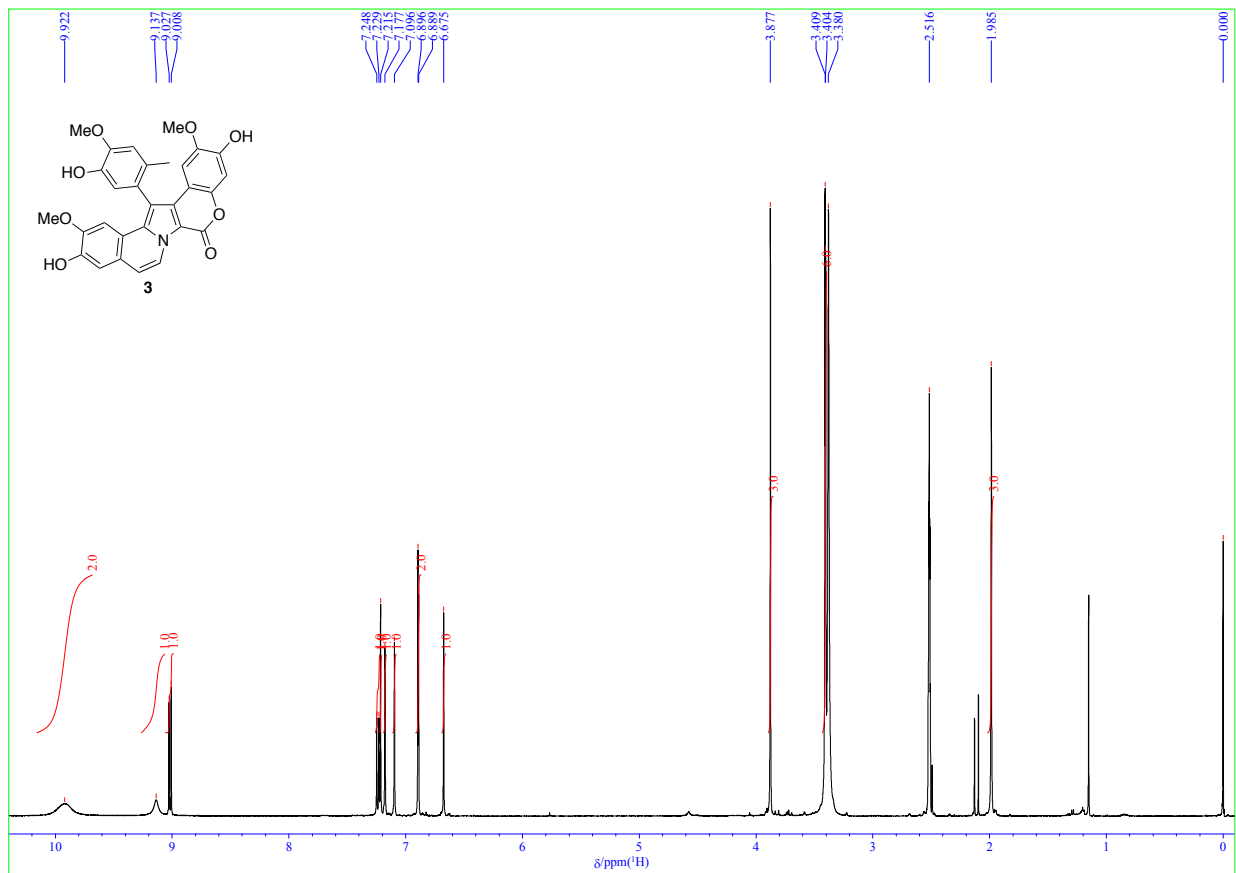
**Figure S22.** <sup>13</sup>C NMR spectrum of compound **18** (100 MHz, CDCl<sub>3</sub>).



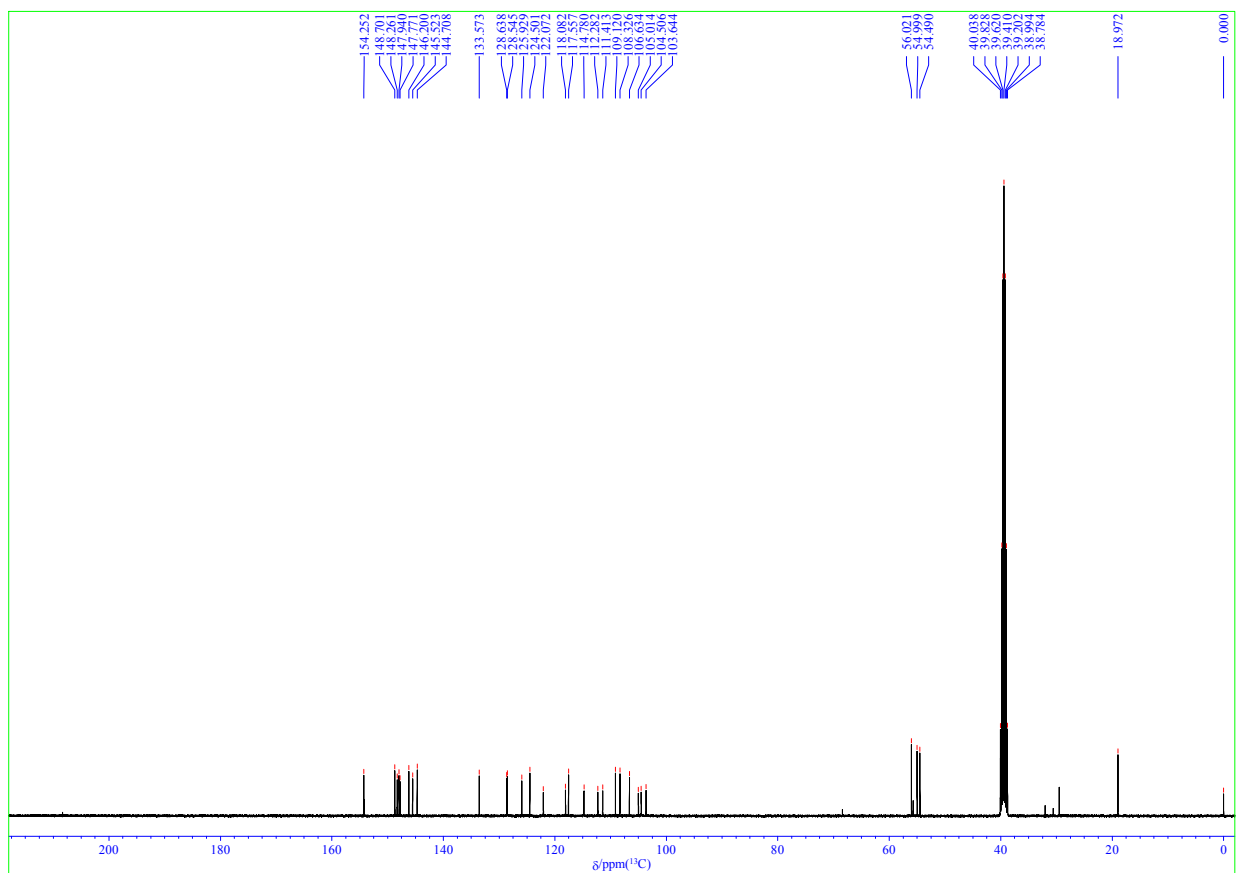
**Figure S23.**  $^1\text{H}$  NMR spectrum of compound **19** (400 MHz,  $\text{CDCl}_3$ ).



**Figure S24.**  $^{13}\text{C}$  NMR spectrum of compound **19** (100 MHz,  $\text{CDCl}_3$ ).



**Figure S25.** <sup>1</sup>H NMR spectrum of compound **3** (400 MHz, DMSO-*d*<sub>6</sub>).



**Figure S26.** <sup>13</sup>C NMR spectrum of compound **3** (100 MHz, DMSO-*d*<sub>6</sub>).

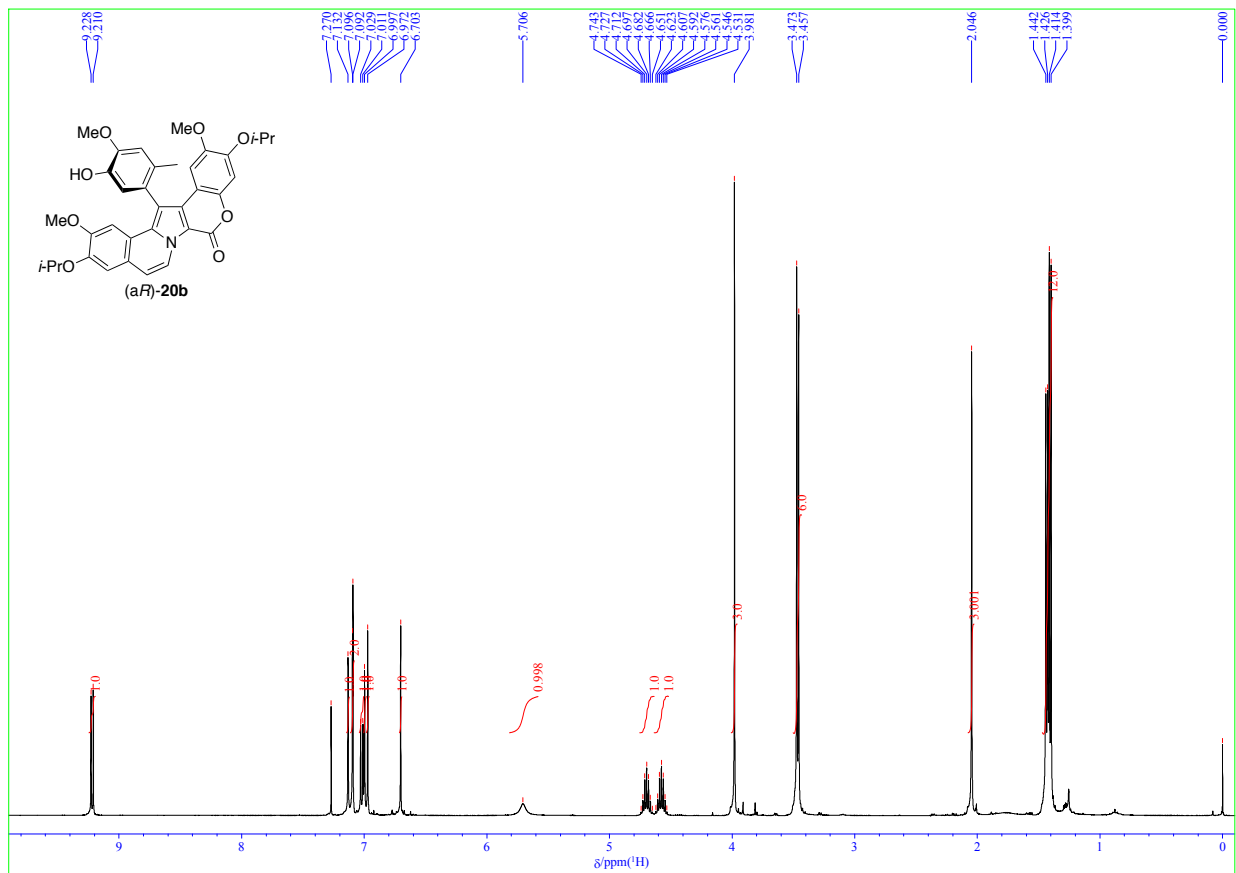


Figure S27. <sup>1</sup>H NMR spectrum of compound (aR)-20b (400 MHz, CDCl<sub>3</sub>).

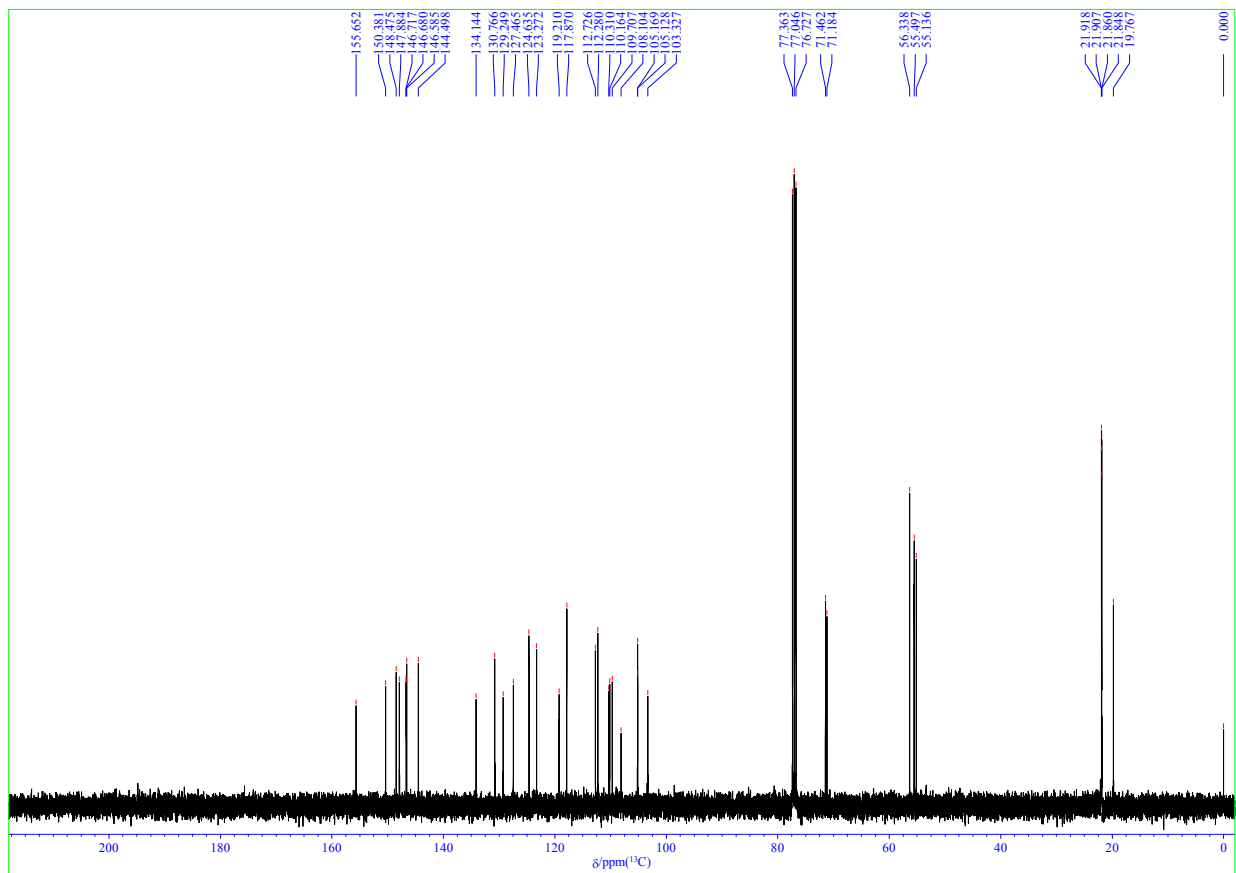


Figure S28. <sup>13</sup>C NMR spectrum of compound (aR)-20b (100 MHz, CDCl<sub>3</sub>).

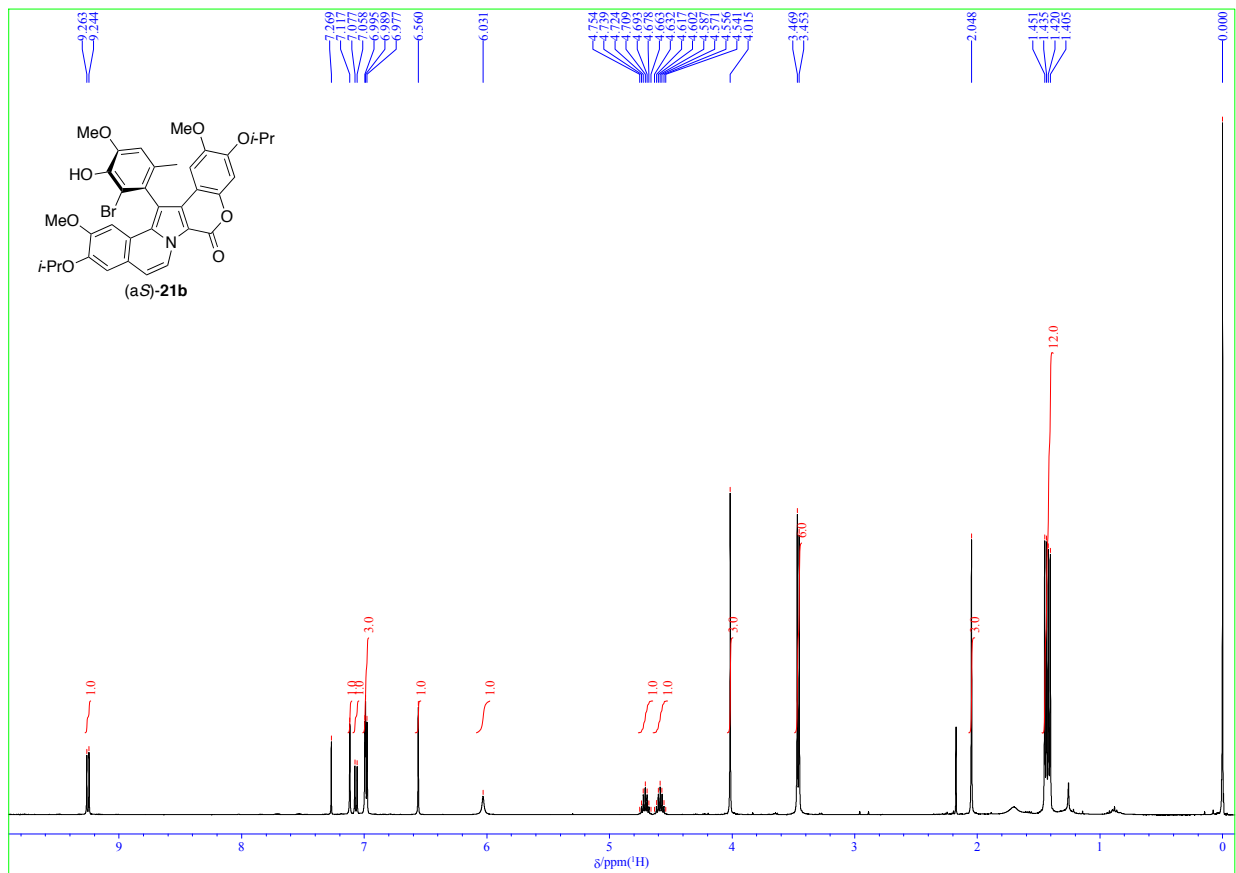


Figure S29. <sup>1</sup>H NMR spectrum of compound (aS)-21b (400 MHz, CDCl<sub>3</sub>).

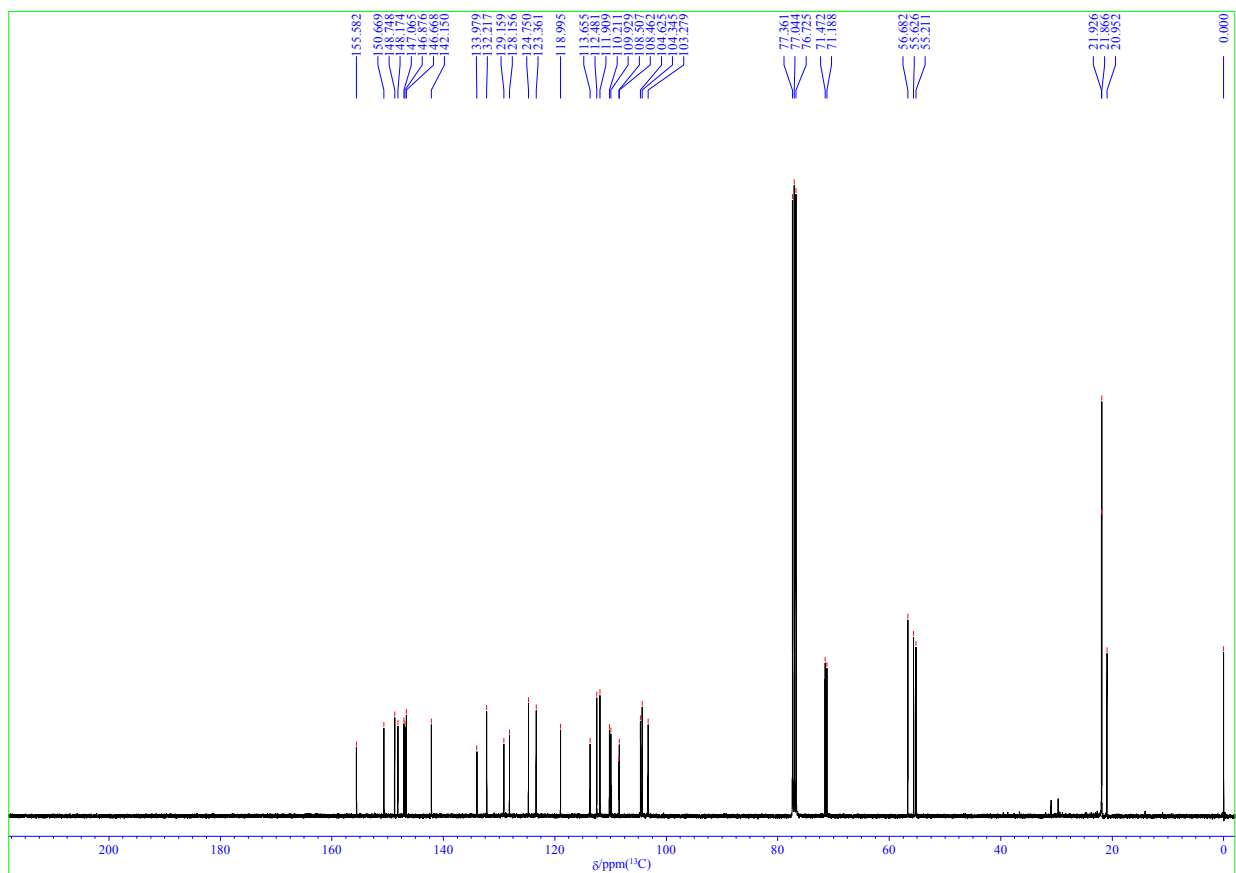
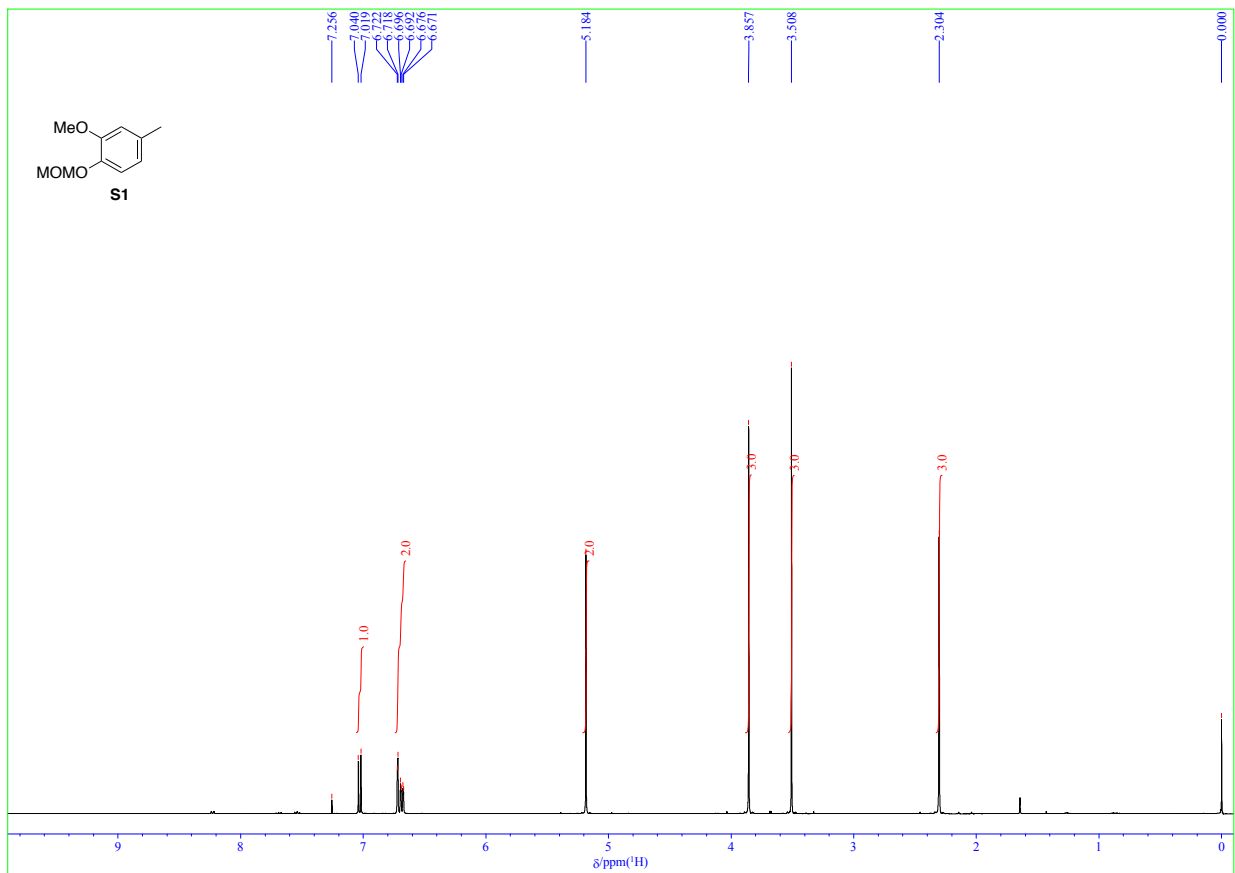
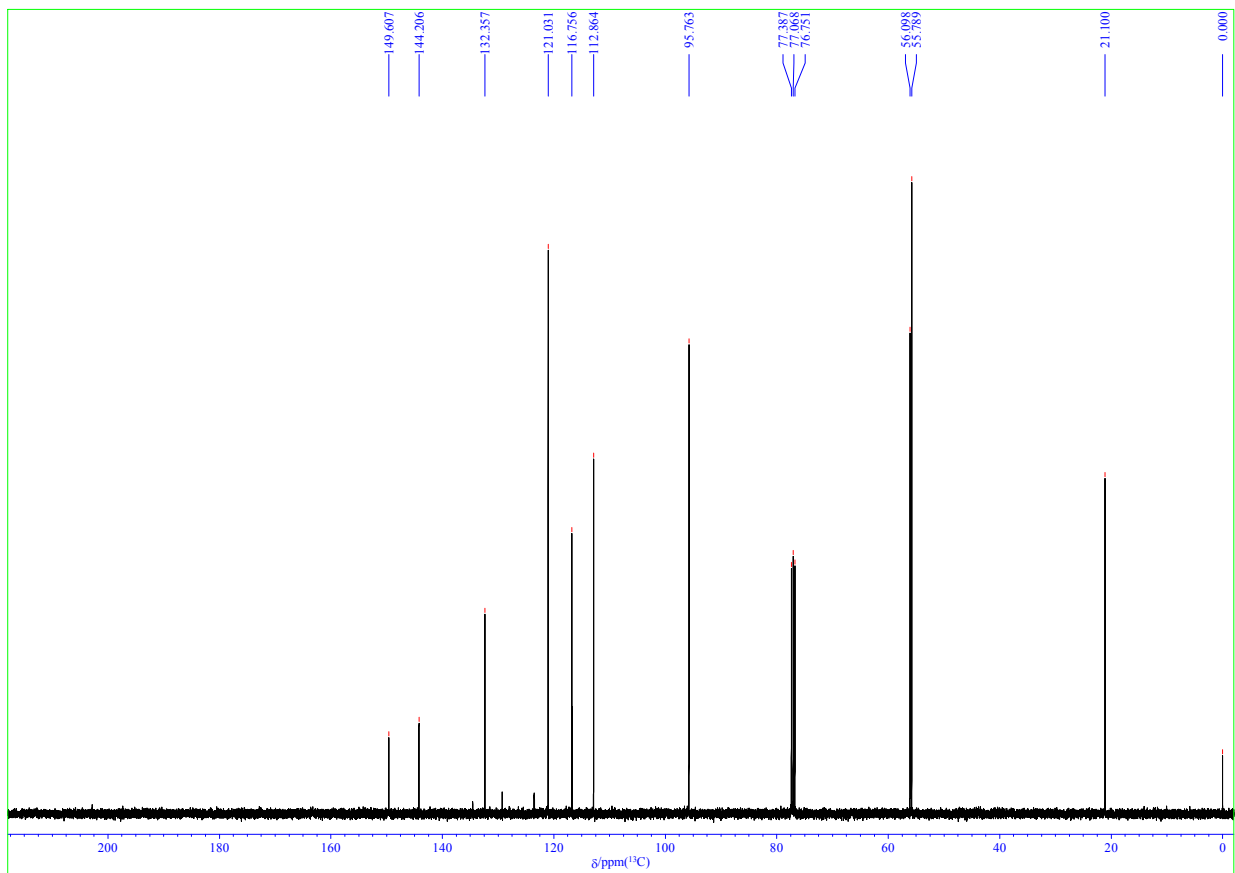


Figure S30. <sup>13</sup>C NMR spectrum of compound (aS)-21b (100 MHz, CDCl<sub>3</sub>).



**Figure S31.** <sup>1</sup>H NMR spectrum of compound **S1** (400 MHz, CDCl<sub>3</sub>).



**Figure S32.** <sup>13</sup>C NMR spectrum of compound **S1** (100 MHz, CDCl<sub>3</sub>).

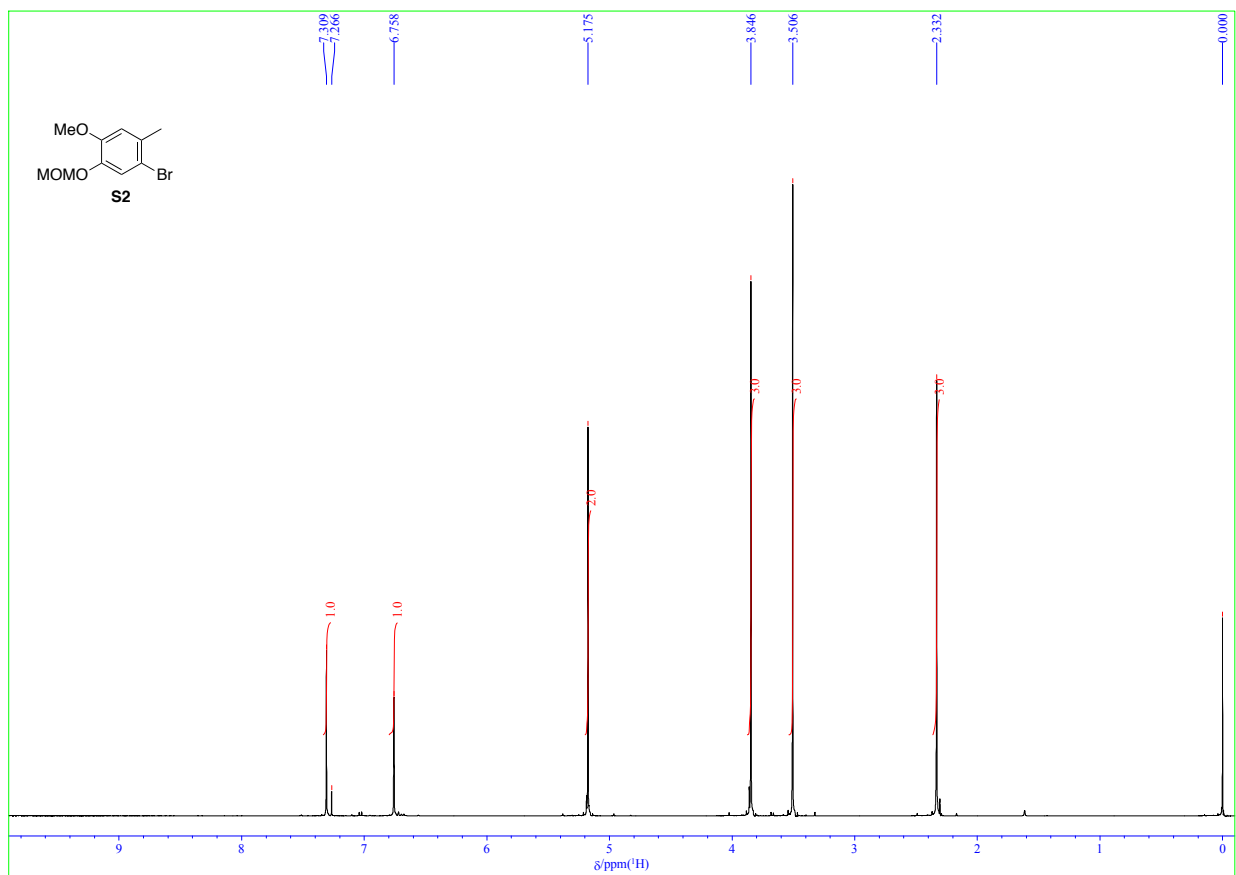


Figure S33. <sup>1</sup>H NMR spectrum of compound S2 (400 MHz, CDCl<sub>3</sub>).

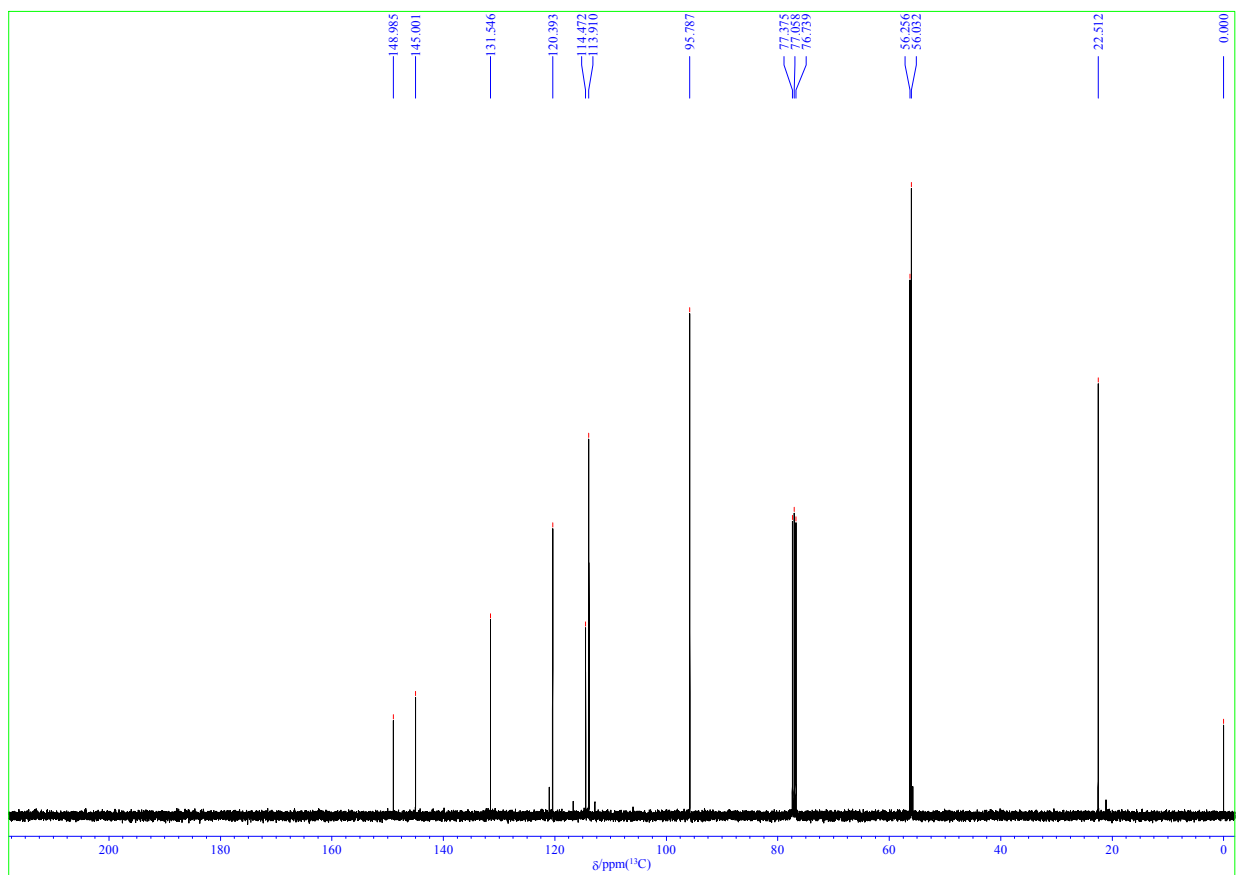
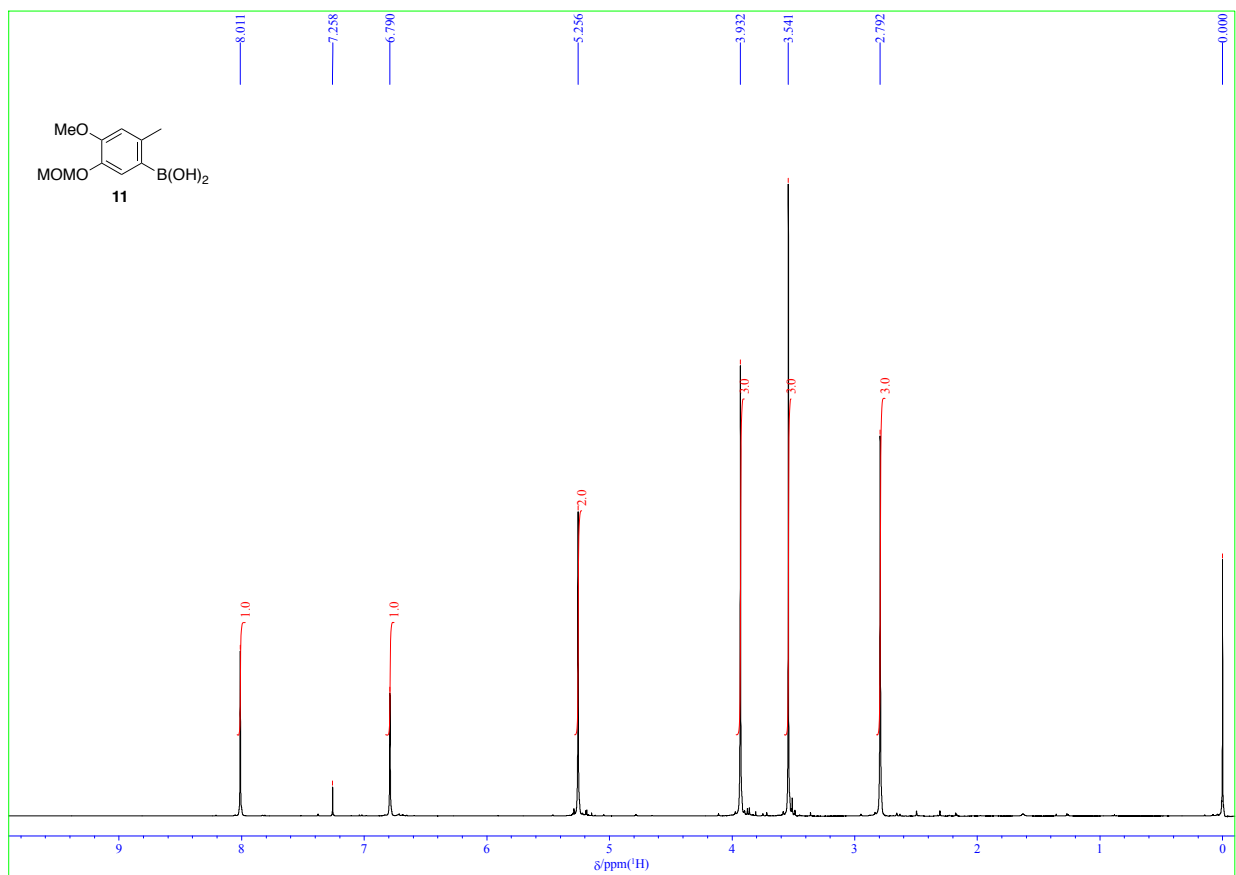
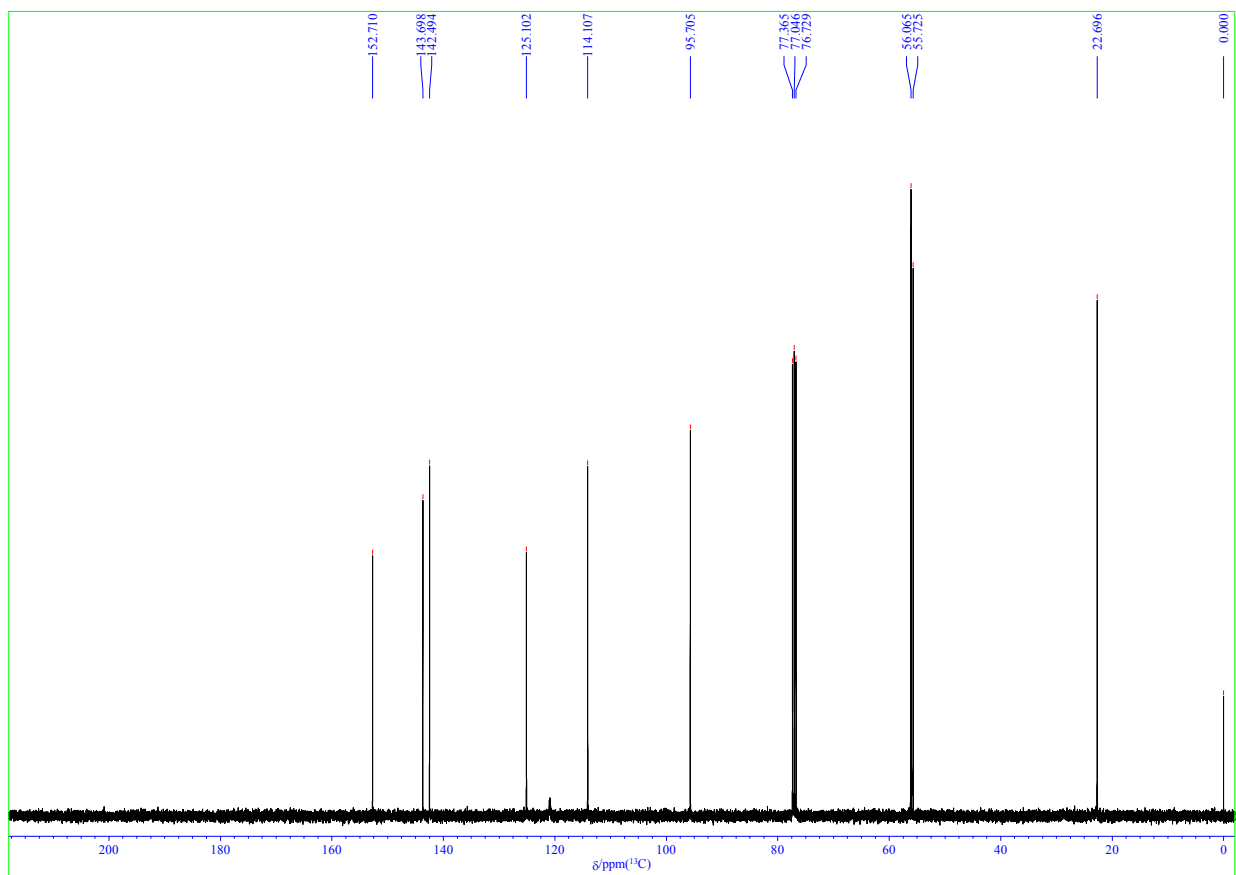


Figure S34. <sup>13</sup>C NMR spectrum of compound S2 (100 MHz, CDCl<sub>3</sub>).



**Figure S35.**  $^1\text{H}$  NMR spectrum of compound **11** (400 MHz,  $\text{CDCl}_3$ ).



**Figure S36.**  $^{13}\text{C}$  NMR spectrum of compound **11** (100 MHz,  $\text{CDCl}_3$ ).