

## One-Pot Synthesis of Luotonin A and Its Analogues

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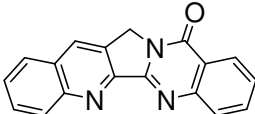
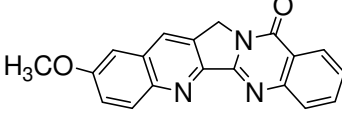
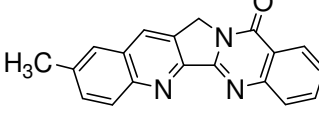
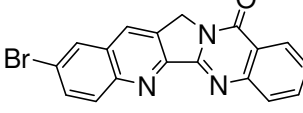
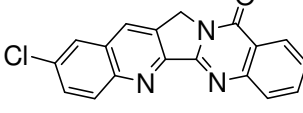
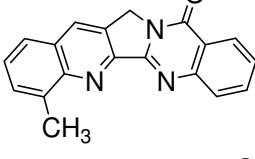
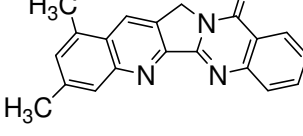
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**Table S1.** Screening of Lewis acids

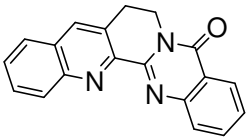
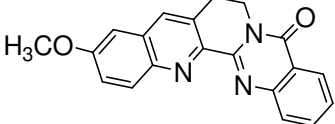
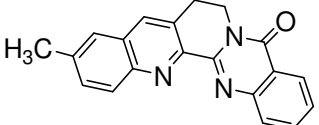
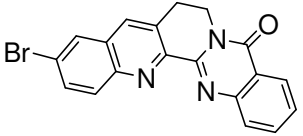
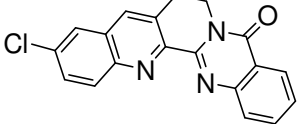
| Entry | Lewis acid           | Isolated yield (%) of luotonin A ( <b>1</b> ) |            |            |
|-------|----------------------|-----------------------------------------------|------------|------------|
|       |                      | 0.2 equiv.                                    | 0.5 equiv. | 1.0 equiv. |
| 1     | AgOTf                | 17                                            |            |            |
| 2     | Al(OTf) <sub>3</sub> | 19                                            |            |            |
| 3     | Cu(OTf) <sub>2</sub> | 14                                            |            |            |
| 4     | Dy(OTf) <sub>3</sub> | 26                                            | 26         | 27         |
| 5     | In(OTf) <sub>3</sub> | 24                                            |            |            |
| 6     | La(OTf) <sub>3</sub> | 24                                            |            |            |
| 7     | Mg(OTf) <sub>2</sub> | 19                                            |            |            |
| 8     | Sc(OTf) <sub>3</sub> | 24                                            | 25         | 28         |
| 9     | Sn(OTf) <sub>2</sub> | 15                                            |            |            |
| 10    | Yb(OTf) <sub>3</sub> | 35                                            | 31         | 34         |
| 11    | Zn(OTf) <sub>2</sub> | 23                                            |            |            |

**Table S2.** Synthesis of luotonin A (**1**) and its analogues (**2a-f**)

| Entry | Product                                                                             | Yield (%) <sup>a</sup> |
|-------|-------------------------------------------------------------------------------------|------------------------|
| 1     |    | <b>1</b> 35            |
| 2     |    | <b>2a</b> 33           |
| 3     |    | <b>2b</b> 26           |
| 4     |    | <b>2c</b> 37           |
| 5     |   | <b>2d</b> 40           |
| 6     |  | <b>2e</b> 35           |
| 7     |  | <b>2f</b> 18           |

<sup>a</sup> Isolated yield.

**Table S3.** Synthesis of C ring-expanded luotonin A analogues (**3a-e**)

| Entry | Product                                                                            | Yield (%) <sup>a</sup> |
|-------|------------------------------------------------------------------------------------|------------------------|
| 1     |   | <b>3a</b> 36           |
| 2     |   | <b>3b</b> 17           |
| 3     |   | <b>3c</b> 20           |
| 4     |   | <b>3d</b> 19           |
| 5     |  | <b>3e</b> 20           |

<sup>a</sup> Isolated yield.

## General Procedure

To a solution of isatoic anhydride (20 mg, 0.123 mmol) in DMF (0.1 mL) was added progargylamine or 3-butyne-1-amine<sup>1</sup> (0.172 mmol). The resulting solution was stirred at ambient temperature and monitored by TLC. After the reaction was completed, DMF and excess alkynylamine were removed under reduced pressure. The residue was added *o*-xylene (20 mL), aniline (1.15 mmol), Yb(OTf)<sub>3</sub> (15 mg, 0.023 mol), and 40% glyoxal (198  $\mu$ L, 1.725 mmol). After being heated to 150 °C for 12 h, the reaction mixture was allowed to cool and concentrated under reduced pressure. The residue was then purified by column chromatography (50% ethyl acetate in hexane, followed by 100% dichloromethane) to give desired products **1**, **2a-2f** and **3a-3e** (18%-40%).

Luotonin A (**1**). White solid (12.3 mg, 35% yield);  $R_f$  = 0.19 (ethyl acetate : hexane = 1 : 1); mp 269-270 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  5.34 (s, 2 H, CH<sub>2</sub>), 7.59 (t,  $J$  = 8.0 Hz, 1 H, ArH), 7.69 (t,  $J$  = 8.0 Hz, 1 H, ArH), 7.86 (m, 2 H, ArH), 7.94 (d,  $J$  = 8.0 Hz, 1 H, ArH), 8.12 (d,  $J$  = 8.2 Hz, 1 H, ArH), 8.41-8.48 (m, 3 H, ArH); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  47.5, 121.6, 126.7, 127.7, 128.2, 128.8, 129.0, 129.7, 130.9, 131.0, 131.8, 134.8, 149.6, 149.7, 151.4, 152.8, 160.9; FAB-HRMS  $m/z$  [M+H]<sup>+</sup> calcd for C<sub>18</sub>H<sub>12</sub>N<sub>3</sub>O 286.0980, found 286.0978.

Compound **2a**. White solid (12.8 mg, 33% yield);  $R_f$  = 0.13 (ethyl acetate : hexane = 1 : 1); mp 307-308 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub> /TFA, 20/1 (v/v))  $\delta$  4.05 (s, 3 H, OCH<sub>3</sub>), 5.60 (s, 2 H, CH<sub>2</sub>), 7.35 (s, 1 H, ArH), 7.71 (dd,  $J$  = 2.6, 9.6 Hz, 1 H, ArH), 7.81-7.84 (m, 1 H, ArH), 8.27 (d,  $J$  = 9.4 Hz, 1 H, ArH), 8.47 (d,  $J$  = 7.9 Hz, 1 H, ArH), 8.72 (s, 1 H, ArH); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub> /TFA, 20/1 (v/v))  $\delta$  50.1, 56.2, 105.5, 116.1 (q,  $J_{CF}$  = 283 Hz, CF<sub>3</sub>), 119.2, 122.3, 128.0, 128.5, 129.0, 130.4, 131.2, 132.9, 133.5, 137.4, 139.6, 140.0, 143.2, 153.0,

158.0, 160.1 (q,  $J_{\text{CF}} = 43$  Hz, CO), 162.0; FAB-HRMS  $m/z$   $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{19}\text{H}_{14}\text{N}_3\text{O}_2$  316.1086, found 316.1080.

Compound **2b**. White solid (9.6 mg, 26% yield);  $R_f = 0.19$  (ethyl acetate : hexane = 1 : 1); mp 321-322 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.60 (s, 3 H,  $\text{CH}_3$ ), 5.31 (s, 2 H,  $\text{CH}_2$ ), 7.44 (t,  $J = 8.8$  Hz, 1 H, ArH), 7.52-7.58 (m, 2 H, ArH), 7.69 (d,  $J = 8.8$  Hz, 1 H, ArH), 8.11 (d,  $J = 8.4$  Hz, 1 H, ArH), 8.35 (s, 1 H, ArH), 8.36 (d,  $J = 9.2$  Hz, 1 H, ArH), 8.43 (d,  $J = 8.0$  Hz, 1 H, ArH);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  21.7, 47.2, 121.2, 126.3, 126.6, 127.2, 128.8, 129.4, 140.2, 130.6, 133.0, 134.5, 138.9, 148.1, 149.3, 150.2, 152.6, 160.6; FAB-HRMS  $m/z$   $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{19}\text{H}_{14}\text{N}_3\text{O}$  300.1137, found 300.1135.

Compound **2c**. White solid (16.6 mg, 37% yield);  $R_f = 0.26$  (ethyl acetate : hexane = 1 : 1); mp 329-330 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.37 (s, 2 H,  $\text{CH}_2$ ), 7.61 (t,  $J = 7.2$  Hz, 1 H, ArH), 7.88 (t,  $J = 7.2$  Hz, 1 H, ArH), 7.91 (dd,  $J = 2.0, 6.8$  Hz, 1 H, ArH), 8.11 (s, 1 H, ArH), 8.13 (d,  $J = 2.4$  Hz, 1 H, ArH), 8.34 (d,  $J = 9.2$  Hz, 1 H, ArH), 8.37 (s, 1 H, ArH), 8.44 (d,  $J = 7.2$  Hz, 1 H, ArH);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  47.6, 121.6, 123.2, 126.8, 127.9, 129.1, 130.0, 130.3, 130.6, 130.8, 132.5, 134.6, 135.0, 148.3, 149.5, 151.9, 152.5, 160.8; FAB-HRMS  $m/z$   $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{18}\text{H}_{11}\text{BrN}_3\text{O}$  364.0085, found 364.0085.

Compound **2d**. White solid (15.7 mg, 40% yield);  $R_f = 0.26$  (ethyl acetate : hexane = 1 : 1); mp 341-343 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3/\text{TFA}$ , 20/1 (v/v))  $\delta$  5.71 (s, 2 H,  $\text{CH}_2$ ), 7.93 (t,  $J = 7.2$  Hz, 1 H, ArH), 8.05-8.11 (m, 2 H, ArH), 8.17-8.20 (m, 2 H, ArH), 8.34 (d,  $J = 8.0$  Hz, 1 H, ArH), 8.54 (d,  $J = 8.54$  Hz, 1 H, ArH), 8.62 (s, 1 H, ArH);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3/\text{TFA}$ , 20/1 (v/v))  $\delta$  49.9, 112.0 (q,  $J_{\text{CF}} = 286$  Hz,  $\text{CF}_3$ ), 119.1, 119.3, 122.2, 126.9, 127.9, 129.2, 130.2, 131.1, 131.5, 132.0, 133.7, 137.3, 137.5, 147.4, 154.2, 157.9, 159.9 (q,  $J_{\text{CF}} = 40$  Hz, CO); FAB-HRMS  $m/z$   $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{18}\text{H}_{11}\text{ClN}_3\text{O}$  320.0591, found 320.0595.

Compound **2e**. White solid (12.9 mg, 35% yield);  $R_f$  = 0.29 (ethyl acetate : hexane = 1 : 1); mp 294-295 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  2.86 (s, 3H,  $\text{CH}_3$ ), 5.29 (s, 2 H,  $\text{CH}_2$ ), 7.60-7.74 (m, 2 H, ArH), 7.74 (d,  $J$  = 6.4 Hz, 1 H, ArH), 7.90-8.00 (m, 3 H, ArH), 8.28 (d,  $J$  = 8.0 Hz, 1 H, ArH), 8.71 (s, 1 H, ArH);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-}d_6$ )  $\delta$  18.4, 47.7, 121.3, 126.2, 126.8, 127.5, 128.3, 128.4, 130.7, 131.2, 132.4, 134.8, 137.8, 147.9, 149.4, 150.8, 153.6, 160.1; FAB-HRMS  $m/z$   $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{19}\text{H}_{14}\text{N}_3\text{O}$  300.1137, found 300.1130.

Compound **2f**. White solid (6.9 mg, 18% yield);  $R_f$  = 0.29 (ethyl acetate : hexane = 1 : 1); mp 306-308 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3/\text{TFA}$ , 20/1 (v/v))  $\delta$  2.73 (s, 3 H,  $\text{CH}_3$ ), 2.93 (s, 3 H,  $\text{CH}_3$ ), 5.39 (s, 2 H,  $\text{CH}_2$ ), 7.73 (s, 1 H, ArH), 7.82-7.86 (m, 1 H, ArH), 8.01-8.10 (m, 3 H, ArH), 8.49 (d,  $J$  = 8.0 Hz, 1 H, ArH), 9.32 (s, 1 H, ArH);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3/\text{TFA}$ , 20/1 (v/v))  $\delta$  18.6, 22.6, 49.7, 114.6 (q,  $J_{\text{CF}}$  = 284 Hz,  $\text{CF}_3$ ), 120.0, 120.1, 125.7, 127.5, 129.2, 130.7, 130.9, 135.1, 137.1, 137.2, 142.1, 142.8, 144.0, 148.9, 149.9, 159.6, 160.3 (q,  $J_{\text{CF}}$  = 42 Hz, CO); FAB-HRMS  $m/z$   $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{20}\text{H}_{16}\text{N}_3\text{O}$  314.1293, found 314.1285.

Compound **3a**. Light yellow solid (13.3 mg, 36% yield);  $R_f$  = 0.11 (ethyl acetate : hexane = 1 : 1); mp 245-247 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.36 (t,  $J$  = 6.0 Hz, 2 H,  $\text{CH}_2$ ), 4.56 (t,  $J$  = 6.0 Hz, 2 H,  $\text{CH}_2$ ), 7.55 (t,  $J$  = 8.0 Hz, 1 H, ArH), 7.65 (t,  $J$  = 7.6 Hz, 1H, ArH), 7.78-7.87 (m, 3 H, ArH), 8.1 (d,  $J$  = 8.4 Hz, 1 H, ArH), 8.14 (s, 1 H, ArH), 8.37 (d,  $J$  = 6.8 Hz, 1 H, ArH), 8.44 (d,  $J$  = 8.4 Hz, 1 H, ArH);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  27.4, 39.5, 121.1, 126.7, 126.9, 127.6, 128.6, 128.8, 129.1, 129.9, 131.1, 134.4, 134.9, 147.0, 147.6, 148.2, 148.3, 161.5; FAB-HRMS  $m/z$   $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{19}\text{H}_{14}\text{N}_3\text{O}$  300.1137, found 300.1143.

Compound **3b**. Yellow solid (6.9 mg, 17% yield);  $R_f$  = 0.11 (ethyl acetate : hexane = 1 : 1); mp 222-224 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.31 (t,  $J$  = 6.0 Hz, 2 H,  $\text{CH}_2$ ), 4.01 (s, 3 H,  $\text{OCH}_3$ ), 4.53 (t,  $J$  = 6.0 Hz, 2 H,  $\text{CH}_2$ ), 7.06 (s, 1 H, ArH), 7.41 (d,  $J$  = 8.8 Hz, 1 H, ArH), 7.52 (t,  $J$  = 7.2 Hz, 1 H, ArH), 7.80 (t,  $J$  = 7.2 Hz, 1 H, ArH), 8.06 (d,  $J$  = 8.4 Hz, 1 H, ArH),

8.32 (t,  $J = 8.8$  Hz, 1 H, ArH).;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  27.3, 39.4, 55.6, 104.0, 121.0, 123.2, 126.7, 127.3, 129.0, 130.0, 132.6, 133.3, 134.3, 144.4, 144.5, 147.6, 148.5, 159.4, 161.5; FAB-HRMS  $m/z$   $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{20}\text{H}_{16}\text{N}_3\text{O}_2$  330.1243 found 330.1239 .

Compound **3c**. Light yellow solid (7.7 mg, 20% yield);  $R_f = 0.13$  (ethyl acetate : hexane = 1 : 1); mp 281-284 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.58 (s, 3 H,  $\text{CH}_3$ ), 3.33 (t,  $J = 6.1$  Hz, 2 H,  $\text{CH}_2$ ), 4.55 (t,  $J = 6.4$  Hz, 2 H,  $\text{CH}_2$ ), 7.52 (t,  $J = 6.9$  Hz, 1 H, ArH), 7.60 (s, 1 H, ArH), 7.61 (d,  $J = 7.0$  Hz, 1 H, ArH), 7.81 (t,  $J = 7.3$  Hz, 1 H, ArH), 8.03 (s, 1H, ArH), 8.09 (d,  $J = 8.2$  Hz, 1 H, ArH), 8.31-8.37 ( m, 2 H, ArH). ;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  21.9, 27.4, 39.5, 121.1, 125.7, 126.7, 129.5, 128.9, 129.1, 129.7, 130.7, 132.4, 134.1, 134.3, 139.0, 146.1, 146.9, 147.7, 148.5, 161.5; FAB-HRMS  $m/z$   $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{20}\text{H}_{16}\text{N}_3\text{O}$  314.1293, found 314.1292.

Compound **3d**. White solid (8.8 mg, 19% yield);  $R_f = 0.19$  (ethyl acetate : hexane = 1 : 1); mp 292-295 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.36 ( t,  $J = 6.0$  Hz, 2 H,  $\text{CH}_2$ ), 4.56 (t,  $J = 6.0$  Hz, 2 H,  $\text{CH}_2$ ), 7.56 (t,  $J = 8.0$  Hz, 1 H, ArH), 7.83-7.86 (m, 2 H), ArH, 8.02 (s, 1 H, ArH), 8.02 (s, 1 H, ArH), 8.07 (d,  $J = 8.4$  Hz, 1 H, ArH), 8.30 (d,  $J = 9.2$  Hz, 1 H, ArH), 8.35 (d,  $J = 8.0$  Hz, 1 H, ArH) ;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  27.4, 39.3, 121.1, 123.0, 126.8, 127.8, 129.0, 129.1, 129.7, 130.6, 132.6, 133.6, 133.8, 134.4, 146.7, 147.5, 148.0, 161.3; FAB-HRMS  $m/z$   $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{19}\text{H}_{13}\text{BrN}_3\text{O}$  378.0242, found 378.0242.

Compound **3e**: Light yellow solid (8.2 mg, 20% yield);  $R_f = 0.19$  (ethyl acetate : hexane = 1 : 1); mp 284-285 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.36 ( t,  $J = 6.0$  Hz, 2 H,  $\text{CH}_2$ ), 4.56 (t,  $J = 6.0$  Hz, 2 H,  $\text{CH}_2$ ), 7.56 (t,  $J = 8.0$  Hz, 1 H, ArH), 7.71 (dd,  $J = 2.0, 8.8$  Hz, 1 H, ArH), 7.80-7.84 (m, 1 H, ArH), 8.05-8.09 (m, 2 H, ArH), 8.35-8.39 (m, 2 H, ArH), 8.35 (d,  $J = 8.0$  Hz, 1 H, ArH) ;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  27.3, 39.2, 121.1, 125.5, 126.7, 127.7, 129.0, 129.2,

130.6, 131.0, 132.5, 133.9, 134.3, 146.4, 147.2, 147.4, 147.9, 161.3; FAB-HRMS  $m/z$   $[M+H]^+$  calcd for  $C_{19}H_{13}ClN_3O$  334.0747, found 334.0746.

### **Recombinant human Top1 (hTop1) protein expression and purification<sup>2</sup>**

Complementary (c)DNAs encoding full-length hTop1 were subcloned into the baculoviral expression vectors, pFastBac HTa and pFastBac HTc. The bacmid constructs were prepared using a Bac-to-Bac baculovirus expression system protocol (Invitrogen, Carlsbad, CA, USA). To express and purify the recombinant hTop1, a recombinant baculoviral stock was used to infect  $2 \times 10^7$  Sf-9 insect cells per 140-mm plate. Infected cells were cultured at 27 °C for 3 days. A Ni-NTA column/imidazole was used for hTop1 fractionation. Aliquots were stored at -70 °C until use in relaxation assays.

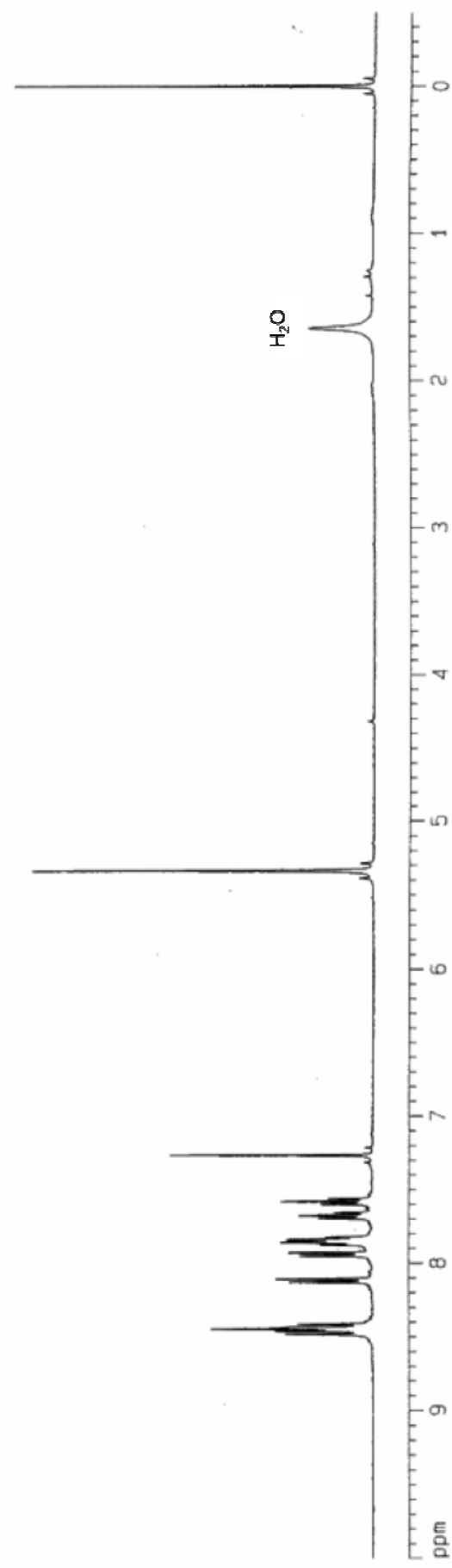
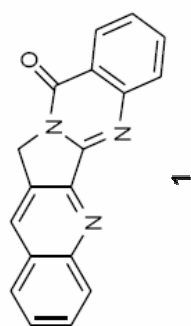
### **DNA relaxation assay<sup>2</sup>**

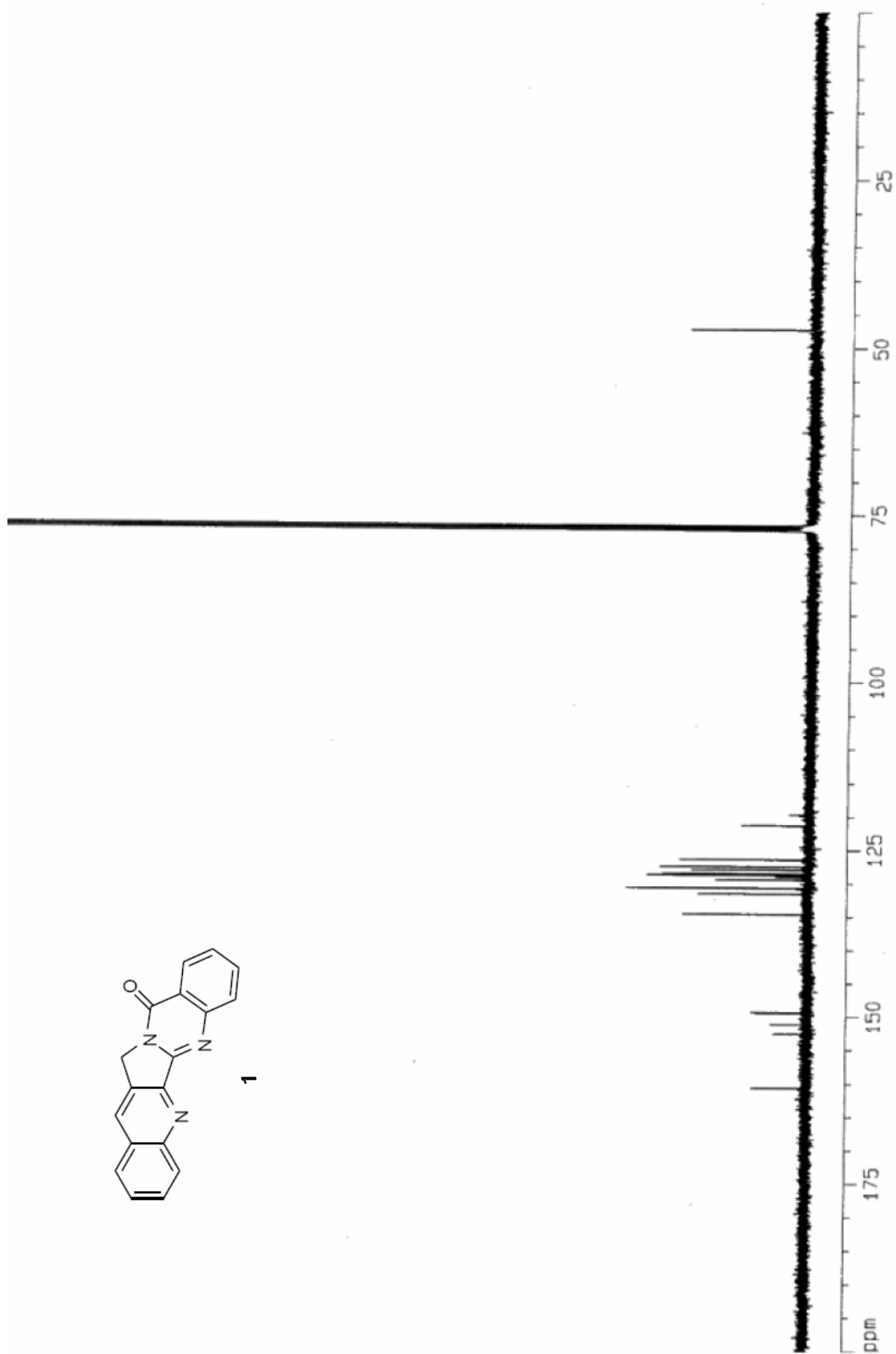
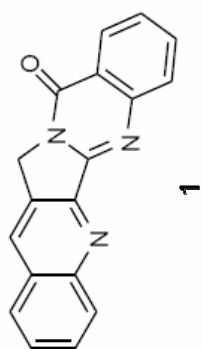
The inhibitory effect of **1**, **2a-2f** and **3a-3e** on supercoiled DNA strand breakage caused by hTop1 was evaluated. pBlueScript SK+ DNA (200 ng) was incubated at 37 °C for 30 min in a reaction solution (40 mM Tris-acetate, 100 mM NaCl, 2.5 mM  $MgCl_2$ , and 0.1 mM EDTA; pH 7.5) in the presence or absence of 5  $\mu$ M of inhibitor in a final volume of 20  $\mu$ L. The conversion of the covalently closed circular double-stranded supercoiled DNA to a relaxed form was used to evaluate DNA strand breakage induced by hTop 1. Samples were loaded onto a 1% agarose gel, and electrophoresis was performed in TAE buffer (40 mM Tris-acetate and 1 mM EDTA). The gel was stained with ethidium bromide (0.5  $\mu$ g/mL) for 5 min then photographed under transmitted ultraviolet light.

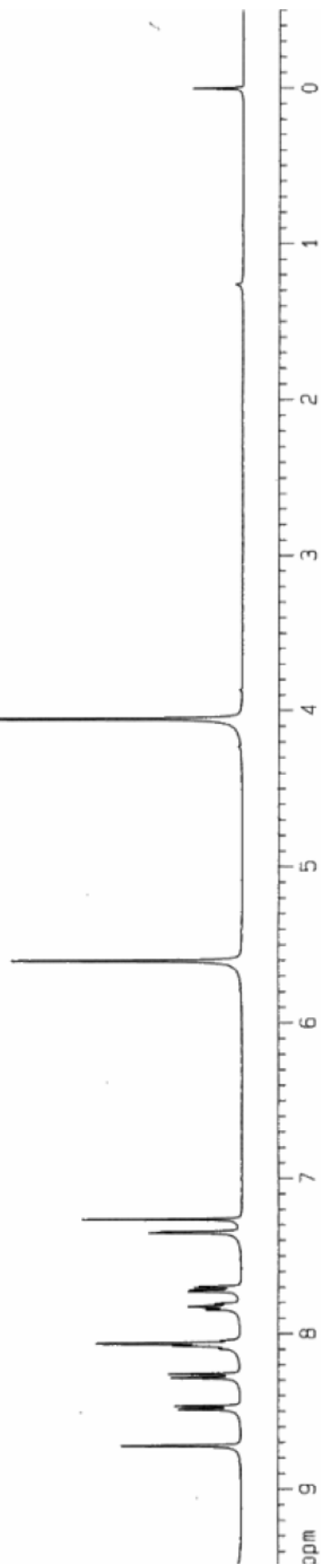
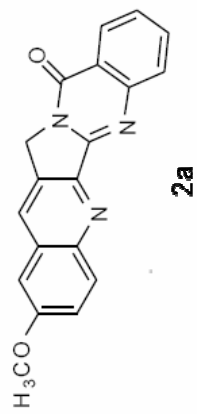
### **References**

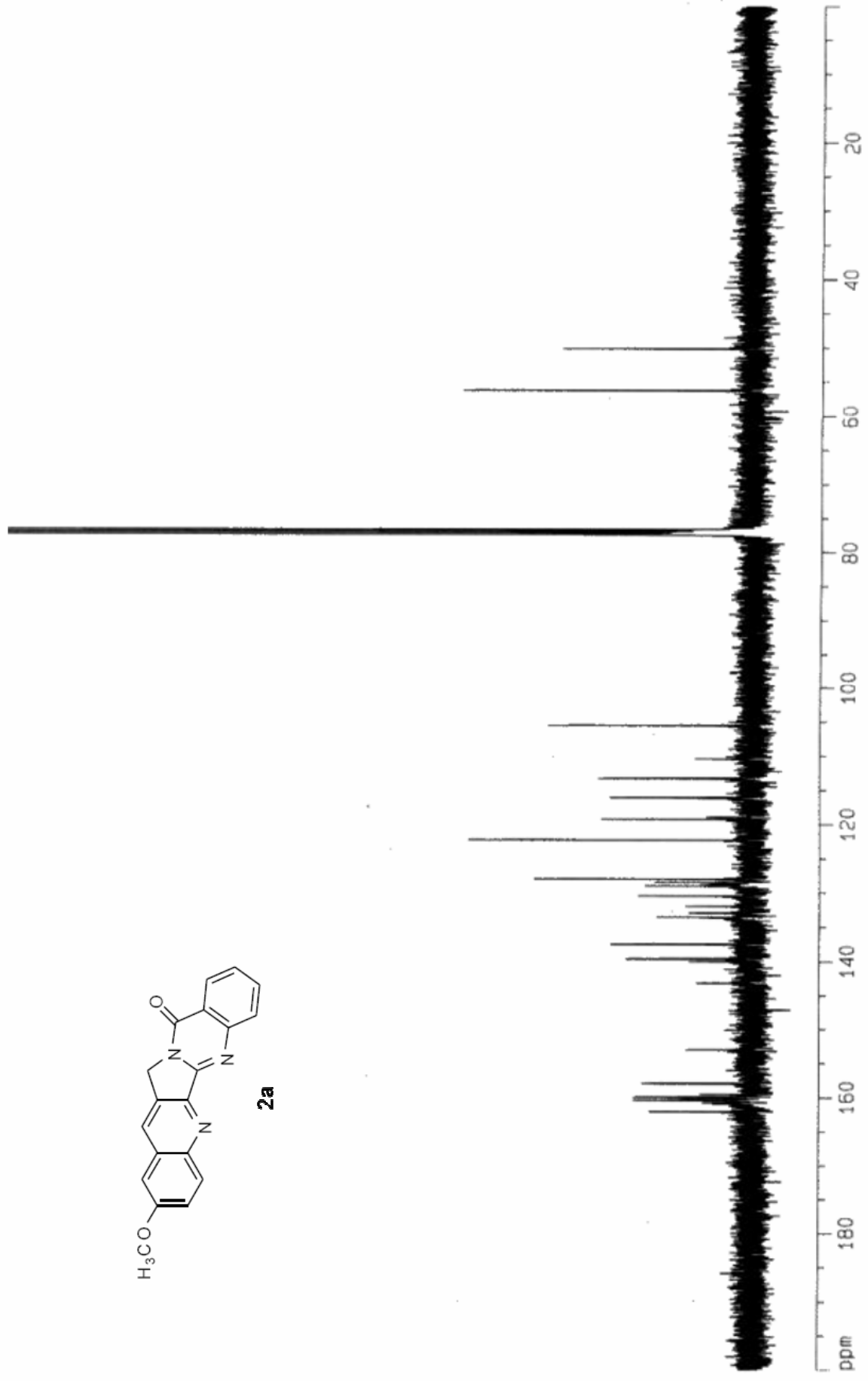
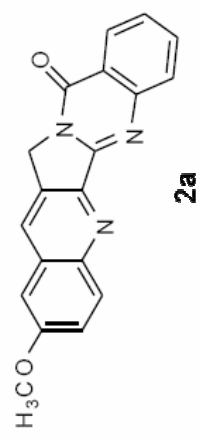
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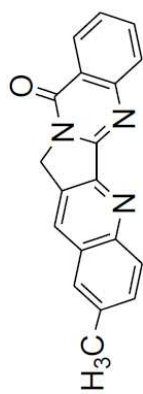
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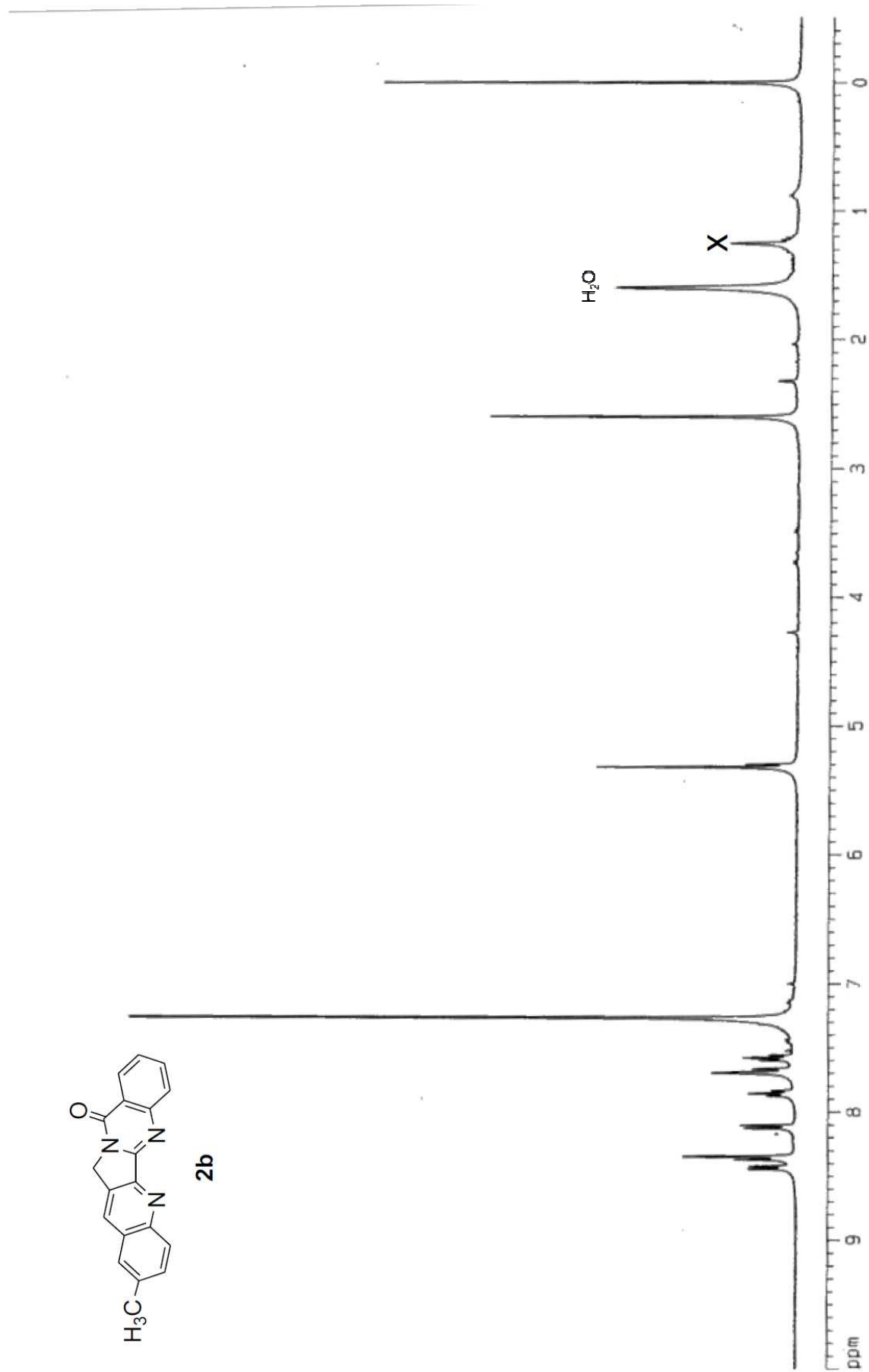


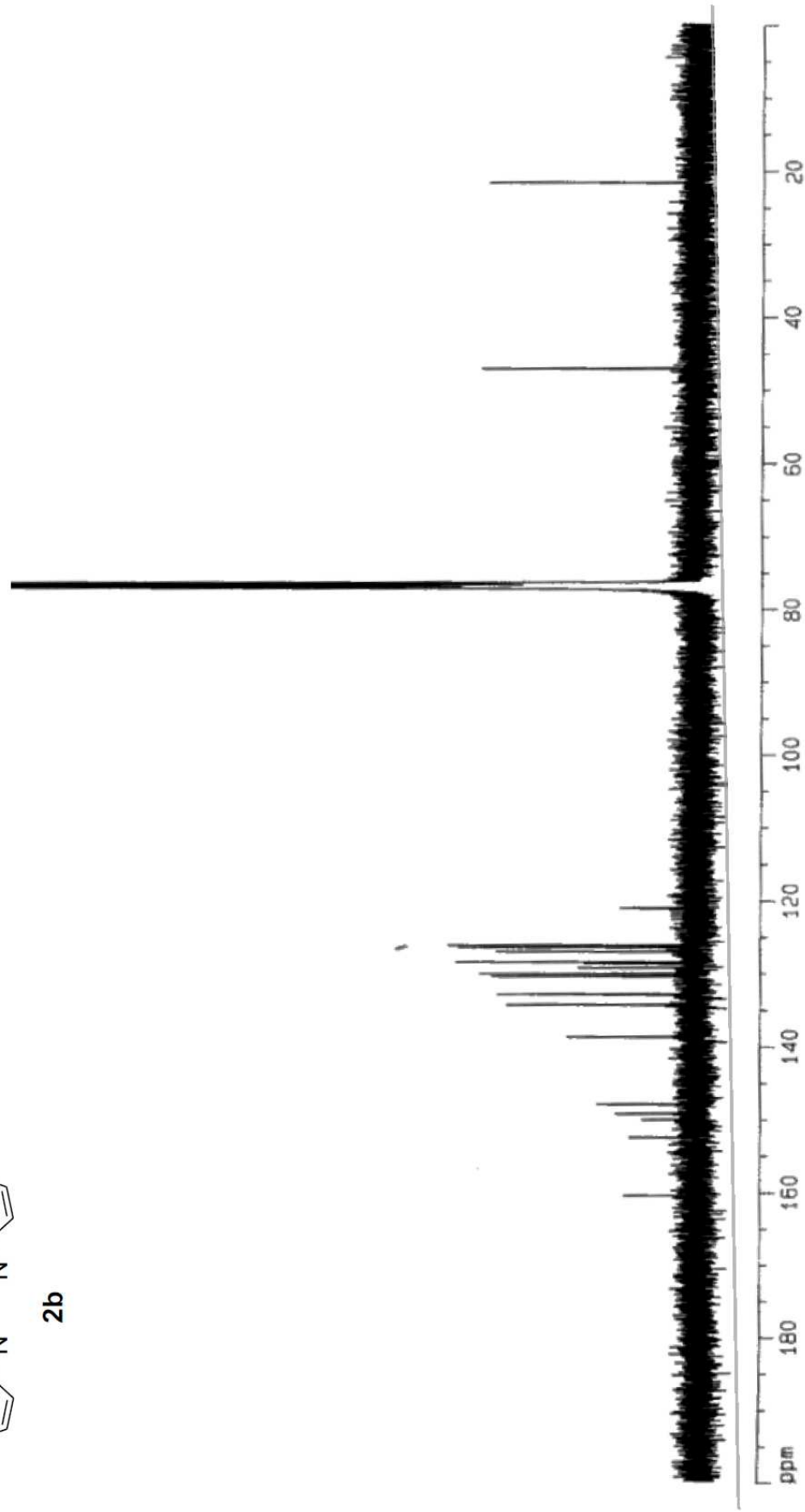
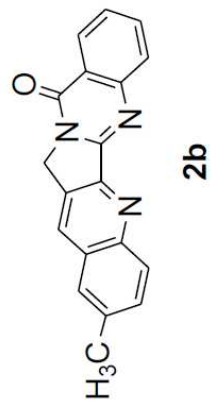


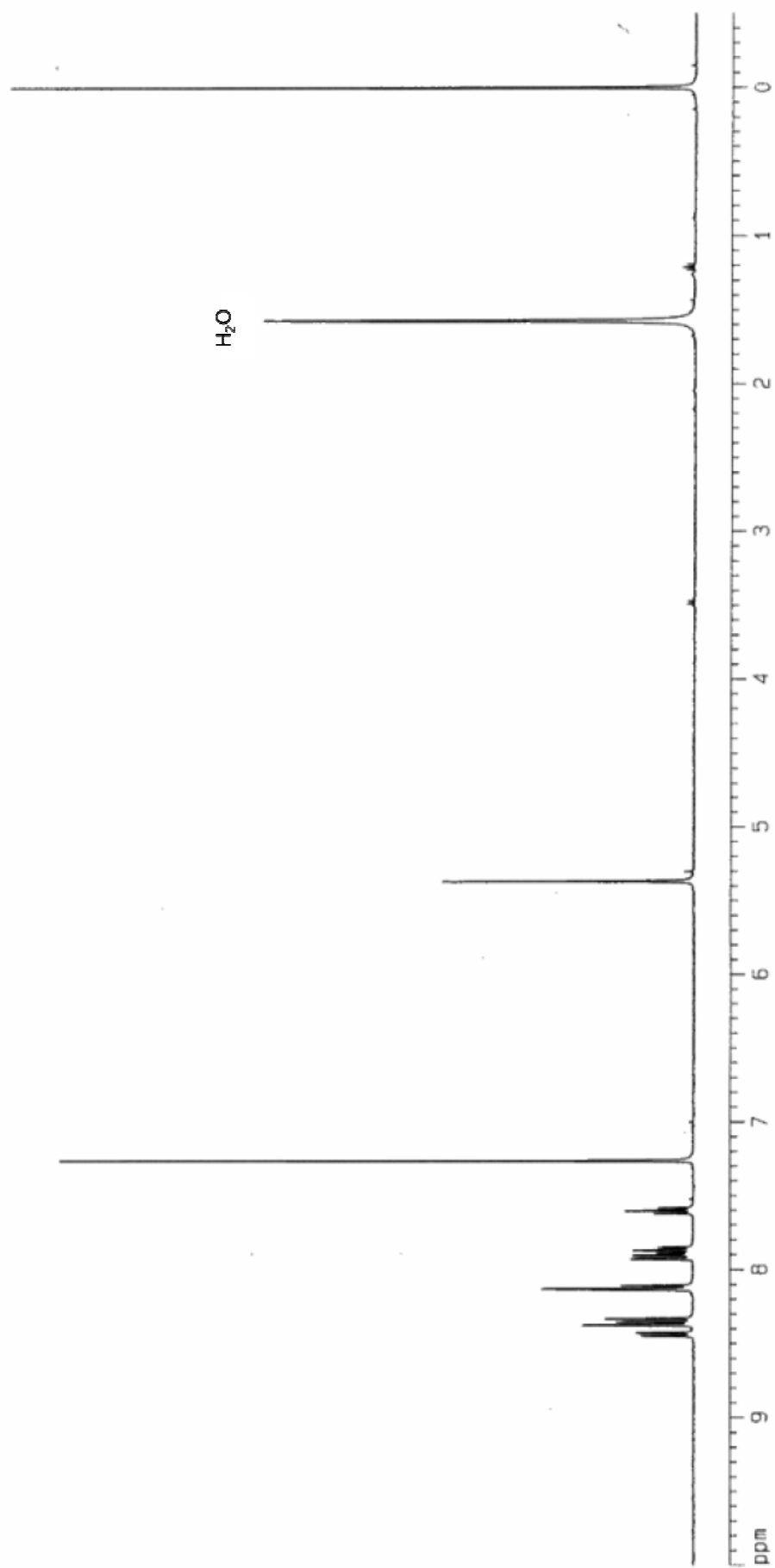
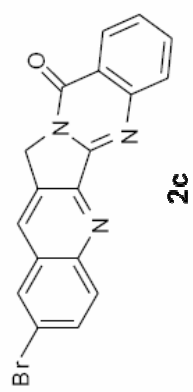


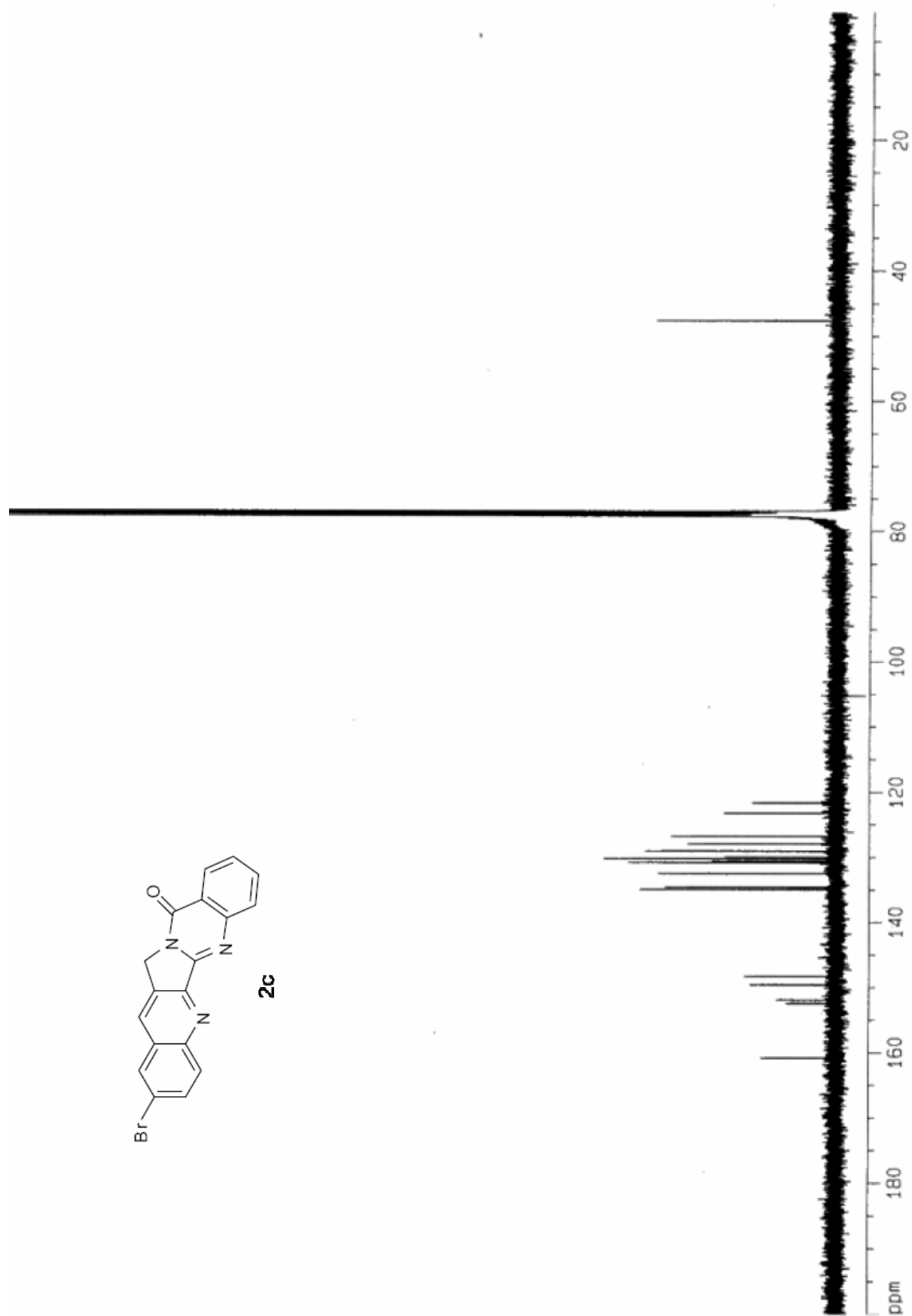


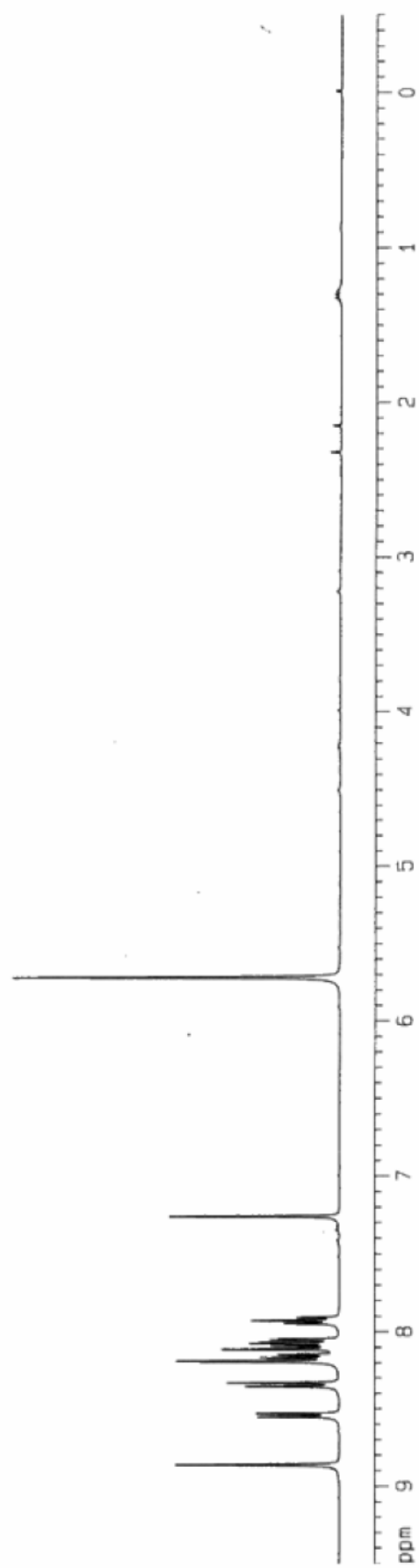
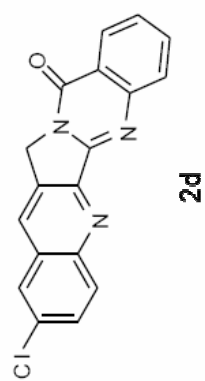
2b

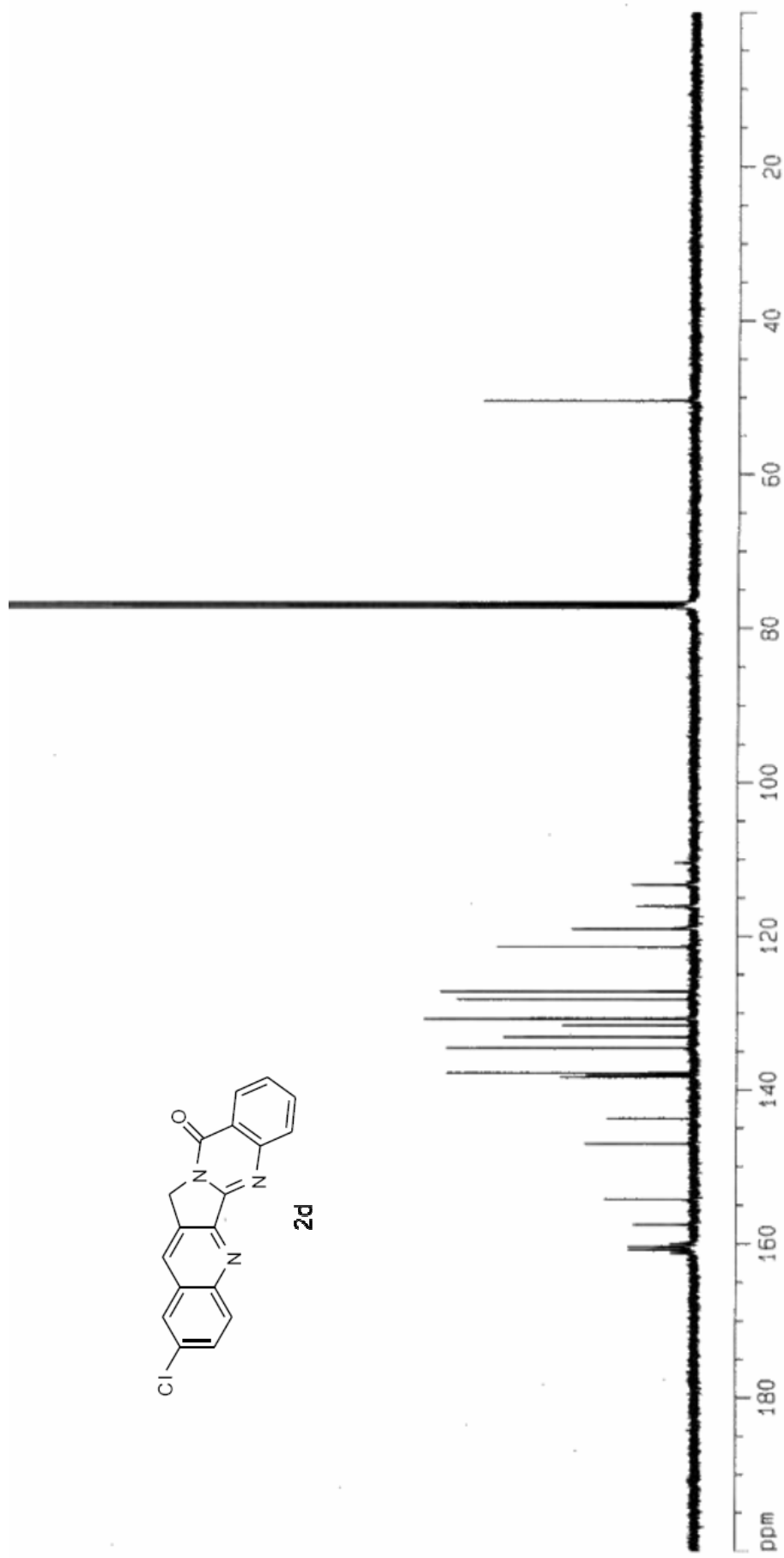
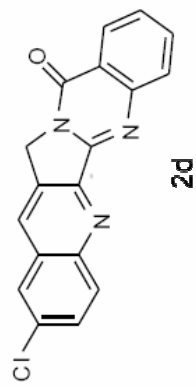


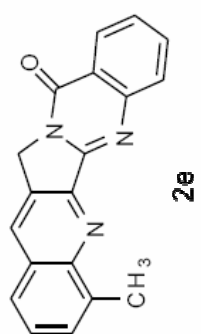




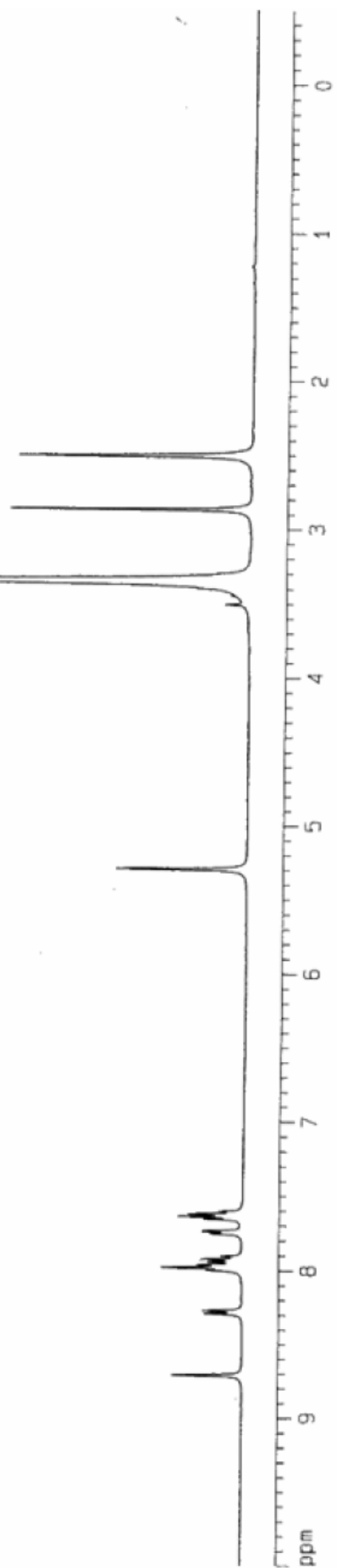


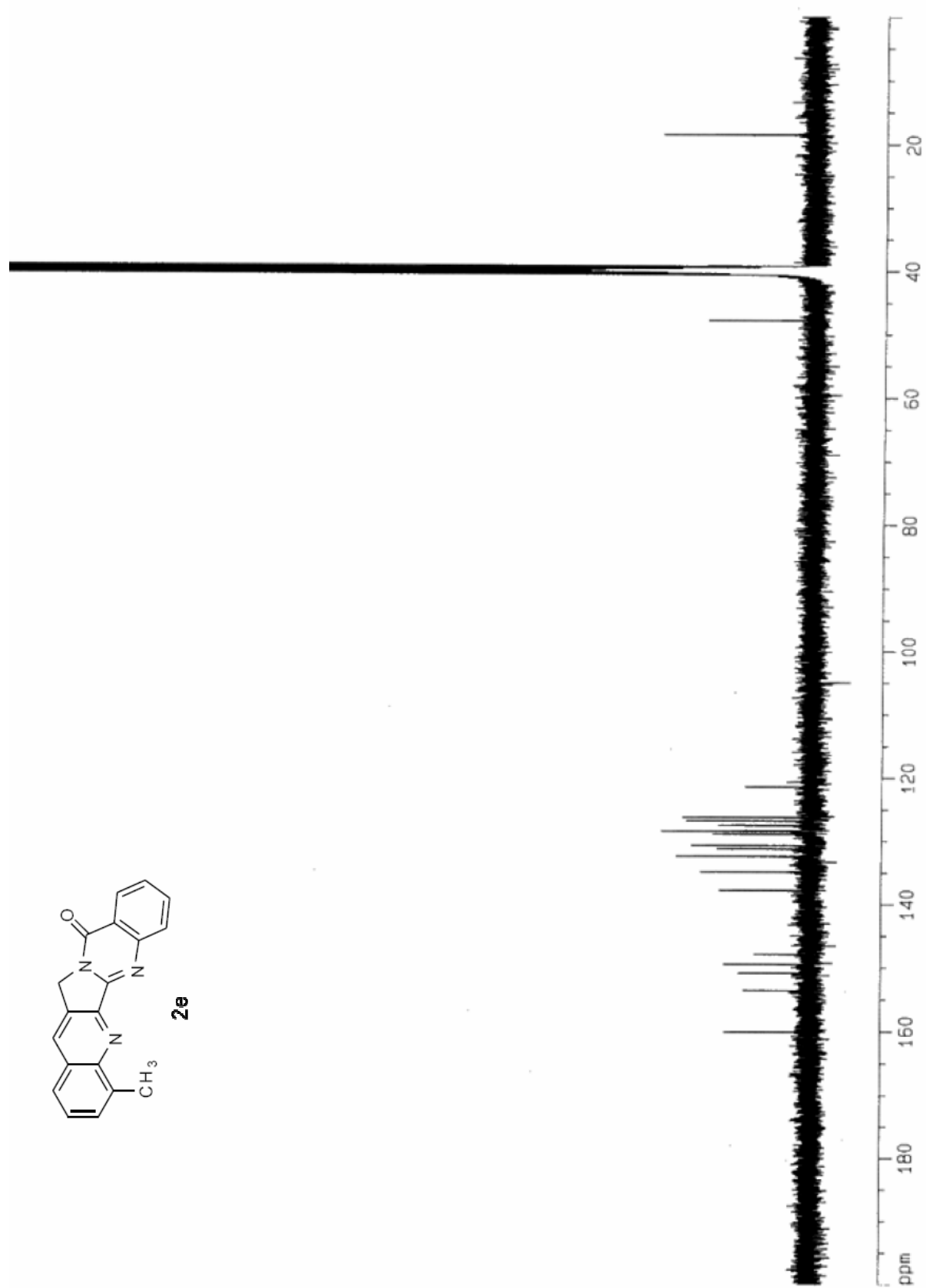
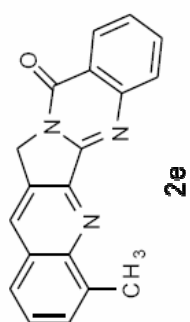






H<sub>2</sub>O





CF<sub>3</sub>CO<sub>2</sub>H

