

## Novel conjugates of 4-amino-2,3-polymethylenequinolines and vanillin as potential multitarget agents for AD treatment

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### *General procedure of the synthesis of conjugates of 4-amino-2,3-polymethylenequinolines and vanillin.*

To a solution of aminoquinoline **2a-c** (1.0 mM) in toluene (5 ml), vanillin (1.0 mM) was added, and the mixture was refluxed for 3 h. Toluene was evaporated *in vacuo*, the residue was recrystallized from chloroform-diethyl ether mixture (2:1) to obtain imines **3a-c**.

Imines **3a-c** (0.5 mM) were dissolved methanol (5 ml), NaBH<sub>4</sub> (30 mg) was added, and the mixture was stirred for 1 h at room temperature. The solvent was evaporated *in vacuo*, the residue was diluted with water and extracted with chloroform (2×5 ml). The combined extract was washed with water, brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, evaporated *in vacuo*. The residue was recrystallized from chloroform-diethyl ether mixture (2:1) to obtain amines **4a-c**.

*2-Methoxy-4-[[3-(7,8,9,10-tetrahydro-6H-cyclohepta[b]quinolin-11-ylamino)-propylimino]methyl]phenol 3a.* Yield 71%, mp 79–81 °C, cream powder. <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>), δ: 1.57-1.95 (m, 6H, 3×CH<sub>2</sub>), 2.04 (q, 2H, *J* = 5.9 Hz, CH<sub>2</sub>), 2.82-3.01 (m, 2H, CH<sub>2</sub>), 3.06-3.26 (m, 2H, CH<sub>2</sub>), 3.50 (t, 2H, *J* = 5.9 Hz, CH<sub>2</sub>), 3.78 (t, 2H, *J* = 5.7 Hz, CH<sub>2</sub>), 3.83 (s, 3H, OCH<sub>3</sub>), 6.84-7.13 (m, 2H, 2×H<sub>ar</sub>), 7.15-7.33 (m, 2H, 2×H<sub>ar</sub>), 7.53 (t, 1H, *J* = 7.4 Hz, H<sub>ar</sub>), 7.88-8.05 (m, 2H, 2×H<sub>ar</sub>), 8.15 (s, 1H, =CH). <sup>13</sup>C-NMR (50 MHz, CDCl<sub>3</sub>), δ: 25.14, 25.92, 26.44, 29.69, 31.00, 36.17, 49.13, 55.83, 59.54, 108.59, 114.42, 119.90, 121.05, 123.62, 123.77, 123.96, 128.17, 128.41, 128.98, 147.13, 147.50, 149.21, 150.95, 161.62, 162.58. Anal. calcd for C<sub>25</sub>H<sub>29</sub>N<sub>3</sub>O<sub>2</sub>: C, 74.41; H, 7.24; N, 10.41. Found: C, 74.68; H, 7.39; N, 10.21.

*2-Methoxy-4-[[3-(6,7,8,9,10,11-hexahydrocycloocta[b]quinolin-12-ylamino)-propylimino]methyl]phenol 3b*. Yield 67%, mp 90–93 °C, yellow powder. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>), δ: 1.19-1.41 (m, 2H, CH<sub>2</sub>), 1.41-1.56 (m, 2H, CH<sub>2</sub>), 1.57-1.76 (m, 2H, CH<sub>2</sub>), 1.76-1.96 (m, 2H, CH<sub>2</sub>), 2.09 (q, 2H, *J* = 6.3 Hz, CH<sub>2</sub>), 2.94 (t, 2H, *J* = 5.7 Hz, CH<sub>2</sub>), 3.13 (t, 2H, *J* = 5.7 Hz, CH<sub>2</sub>), 3.62 (t, 2H, *J* = 6.1 Hz, CH<sub>2</sub>), 3.75 (t, 2H, *J* = 5.9 Hz, CH<sub>2</sub>), 3.87 (s, 3H, OCH<sub>3</sub>), 6.84-6.98 (m, 1H, H<sub>ar</sub>), 7.00-7.12 (m, 1H, H<sub>ar</sub>), 7.13-7.46 (m, 2H, 2×H<sub>ar</sub>), 7.53 (t, 1H, *J* = 7.4 Hz, H<sub>ar</sub>), 7.90-8.08 (m, 2H, 2×H<sub>ar</sub>), 8.17 (s, 1H, =CH). <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>), δ: 25.22, 25.95, 26.50, 29.80, 30.06, 32.57, 36.54, 49.15, 55.94, 59.56, 108.42, 114.23, 120.23, 121.30, 123.60, 123.80, 123.93, 128.26, 128.49, 128.67, 147.20, 147.57, 148.73, 150.75, 161.48, 162.89. Anal. calcd for C<sub>26</sub>H<sub>31</sub>N<sub>3</sub>O<sub>2</sub>: C, 74.79; H, 7.48; N, 10.06. Found: C, 74.32; H, 7.29; N, 10.28.

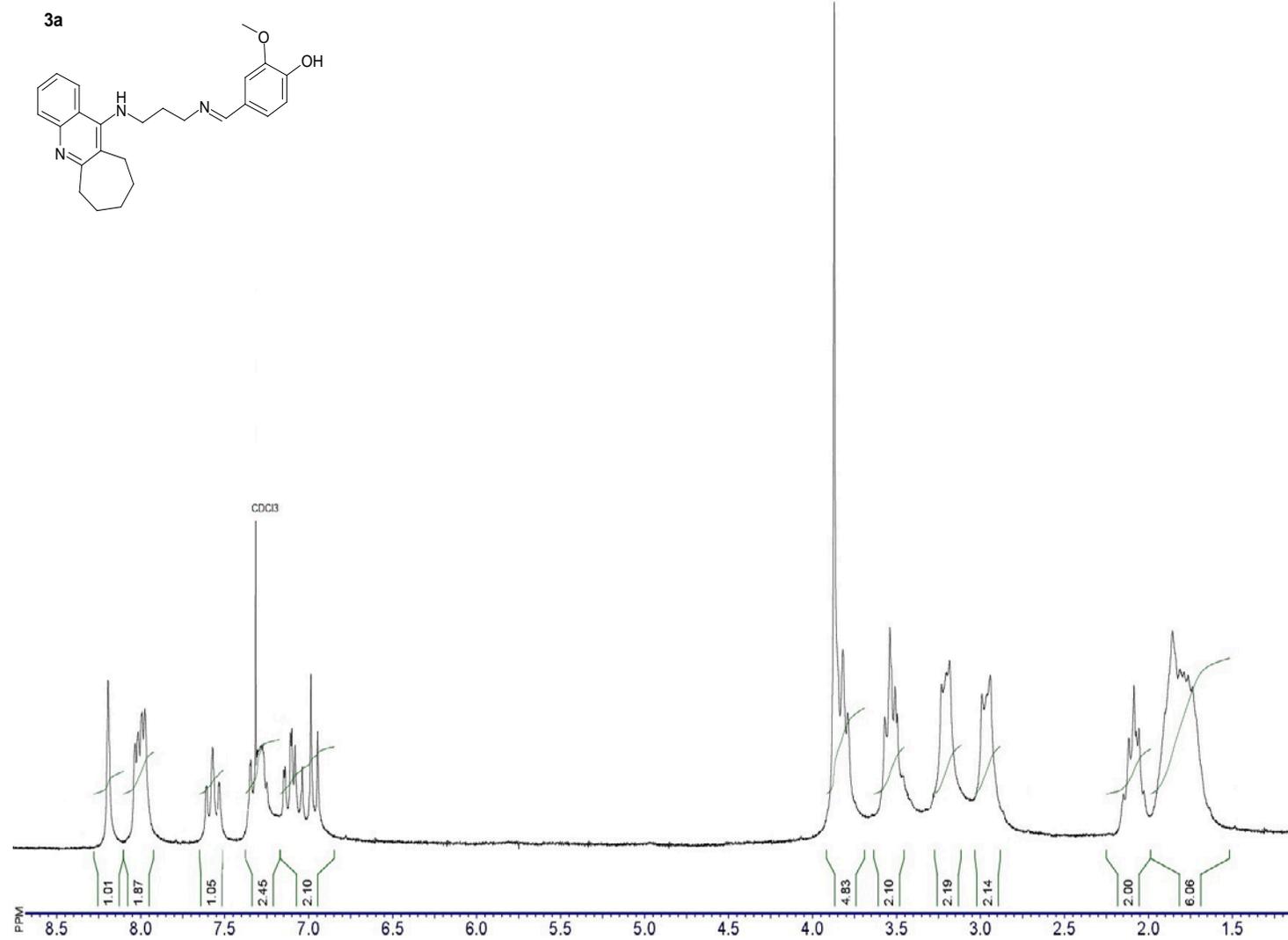
*2-Methoxy-4-[[4-(6,7,8,9,10,11-hexahydrocycloocta[b]quinolin-12-ylamino)butylimino]methyl]phenol 3c*. Yield 76%, mp 110–112 °C, brown powder. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>), δ: 1.05-1.48 (m, 4H, 2×CH<sub>2</sub>), 1.48-2.05 (m, 8H, 4×CH<sub>2</sub>), 2.67-2.98 (m, 2H, CH<sub>2</sub>), 2.98-3.17 (m, 2H, CH<sub>2</sub>), 3.32-3.73 (m, 4H, 2×CH<sub>2</sub>), 3.87 (s, 3H, OCH<sub>3</sub>), 6.74-6.81 (m, 1H, H<sub>ar</sub>), 7.92 (t, 1H, *J* = 6.8 Hz, H<sub>ar</sub>), 6.98-7.27 (m, 2H, 2×H<sub>ar</sub>), 7.51 (t, 1H, *J* = 7.4 Hz, H<sub>ar</sub>), 7.87-8.17 (m, 3H, 2×H<sub>ar</sub>, =CH). <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>), δ: 24.43, 24.87, 25.91, 26.42, 28.41, 29.39, 30.91, 35.48, 50.05, 55.94, 60.83, 108.26, 114.23, 123.63, 123.81, 124.30, 125.26, 127.52, 128.19, 129.00, 139.57, 147.16, 147.49, 148.46, 150.59, 161.12, 162.39. Anal. calcd for C<sub>27</sub>H<sub>33</sub>N<sub>3</sub>O<sub>2</sub>: C, 75.14; H, 7.71; N, 9.74. Found: C, 75.37; H, 7.85; N, 9.55.

*2-Methoxy-4-[[3-(7,8,9,10-tetrahydro-6H-cyclohepta[b]quinolin-11-ylamino)-propylamino]methyl]phenol 4a*. Yield 74%, mp 62–63 °C, cream powder. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>), δ: 1.27-1.56 (m, 2H, CH<sub>2</sub>), 1.57-1.74 (m, 2H, CH<sub>2</sub>), 1.76-2.07 (m, 4H, 2×CH<sub>2</sub>), 2.73-3.03 (m, 4H, 2×CH<sub>2</sub>), 3.17 (t, 2H, *J* = 6.4 Hz, CH<sub>2</sub>), 3.58 (t, 2H, *J* = 6.3 Hz, CH<sub>2</sub>), 3.76 (s, 2H, CH<sub>2</sub>), 3.83 (s, 3H, OCH<sub>3</sub>), 6.65-6.96 (m, 3H, 3×H<sub>ar</sub>), 7.25-7.45 (t, 1H, *J* = 7.3 Hz, H<sub>ar</sub>), 7.56 (t, 1H, *J* = 7.2 Hz, H<sub>ar</sub>), 7.94-8.16 (m, 2H, 2×H<sub>ar</sub>). <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>), δ: 25.09, 25.86, 26.42, 29.58, 30.98, 36.22, 47.79, 49.61, 54.07, 55.65, 111.04, 114.58, 119.70, 120.81, 120.97, 123.53, 123.79, 128.26 (2), 131.20, 145.32, 147.11, 147.22, 150.79, 162.55. Anal. calcd for C<sub>25</sub>H<sub>31</sub>N<sub>3</sub>O<sub>2</sub>: C, 74.04; H, 7.70; N, 10.36. Found: C, 74.38; H, 7.55; N, 10.11.

*2-Methoxy-4-[[3-(6,7,8,9,10,11-hexahydrocycloocta[b]quinolin-12-ylamino)-propylamino]methyl]phenol 4b*. Yield 72%, mp 65–67 °C, white powder. <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>), δ: 1.08-1.56 (m, 4H, 2×CH<sub>2</sub>), 1.57-1.74 (m, 2H, CH<sub>2</sub>), 1.74-2.06 (m, 4H, 2×CH<sub>2</sub>), 2.65-3.03 (m, 4H, 2×CH<sub>2</sub>), 3.04-3.27 (m, 2H, CH<sub>2</sub>), 3.54 (t, 2H, *J* = 6.2 Hz, CH<sub>2</sub>), 3.73 (s, 2H, CH<sub>2</sub>), 3.77 (s, 3H, OCH<sub>3</sub>), 6.58-7.00 (m, 3H, 3×H<sub>ar</sub>), 7.31 (t, 1H, *J* = 7.4 Hz, H<sub>ar</sub>), 7.53 (t, 1H, *J* = 7.5 Hz, H<sub>ar</sub>), 7.82-8.09 (m, 2H, 2×H<sub>ar</sub>). <sup>13</sup>C-NMR (50 MHz, CDCl<sub>3</sub>), δ: 24.82, 25.87, 26.35, 29.17, 30.01, 30.85, 34.49, 47.76, 49.57, 53.97, 55.83, 111.13, 114.42, 117.54, 119.29, 121.18, 123.90, 124.21, 125.76, 129.58, 130.56, 144.38, 145.19, 146.84, 152.17, 159.98. Anal. calcd for C<sub>26</sub>H<sub>33</sub>N<sub>3</sub>O<sub>2</sub>: C, 74.43; H, 7.93; N, 10.01. Found: C, 74.69; H, 8.12; N, 9.85.

*2-Methoxy-4-[[4-(6,7,8,9,10,11-hexahydrocycloocta[b]quinolin-12-ylamino)butylamino]methyl]phenol 4c*. Yield 67%, mp 81–82 °C, yellow powder. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>), δ: 1.16-1.62 (m, 4H, 2×CH<sub>2</sub>), 1.55-2.03 (m, 8H, 4×CH<sub>2</sub>), 2.84-3.06 (m, 2H, CH<sub>2</sub>), 3.14 (t, 2H, *J* = 5.6 Hz, CH<sub>2</sub>), 3.28-3.62 (m, 4H, 2×CH<sub>2</sub>), 3.71 (s, 2H, CH<sub>2</sub>), 3.84 (s, 3H, OCH<sub>3</sub>), 6.64-7.07 (m, 3H, 3×H<sub>ar</sub>), 7.26-7.49 (m, 1H, H<sub>ar</sub>), 7.56 (t, 1H, *J* = 7.5 Hz, H<sub>ar</sub>), 7.80-8.14 (m, 2H, 2×H<sub>ar</sub>). <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>), δ: 24.94, 25.80, 26.33, 27.13, 29.26, 29.46, 30.90, 36.25, 48.64, 50.18, 53.68, 55.55, 111.17, 114.64, 119.91, 120.78, 121.02, 123.38, 123.87, 128.22, 128.35, 130.87, 145.37, 147.19, 147.25, 150.44, 162.60. Anal. calcd for C<sub>27</sub>H<sub>35</sub>N<sub>3</sub>O<sub>2</sub>: C, 74.79; H, 8.14; N, 9.69. Found: C, 74.99; H, 8.28; N, 9.45.

**<sup>1</sup>H NMR spectra**  
**Figure S1**



**Figure S2**  
**3b**

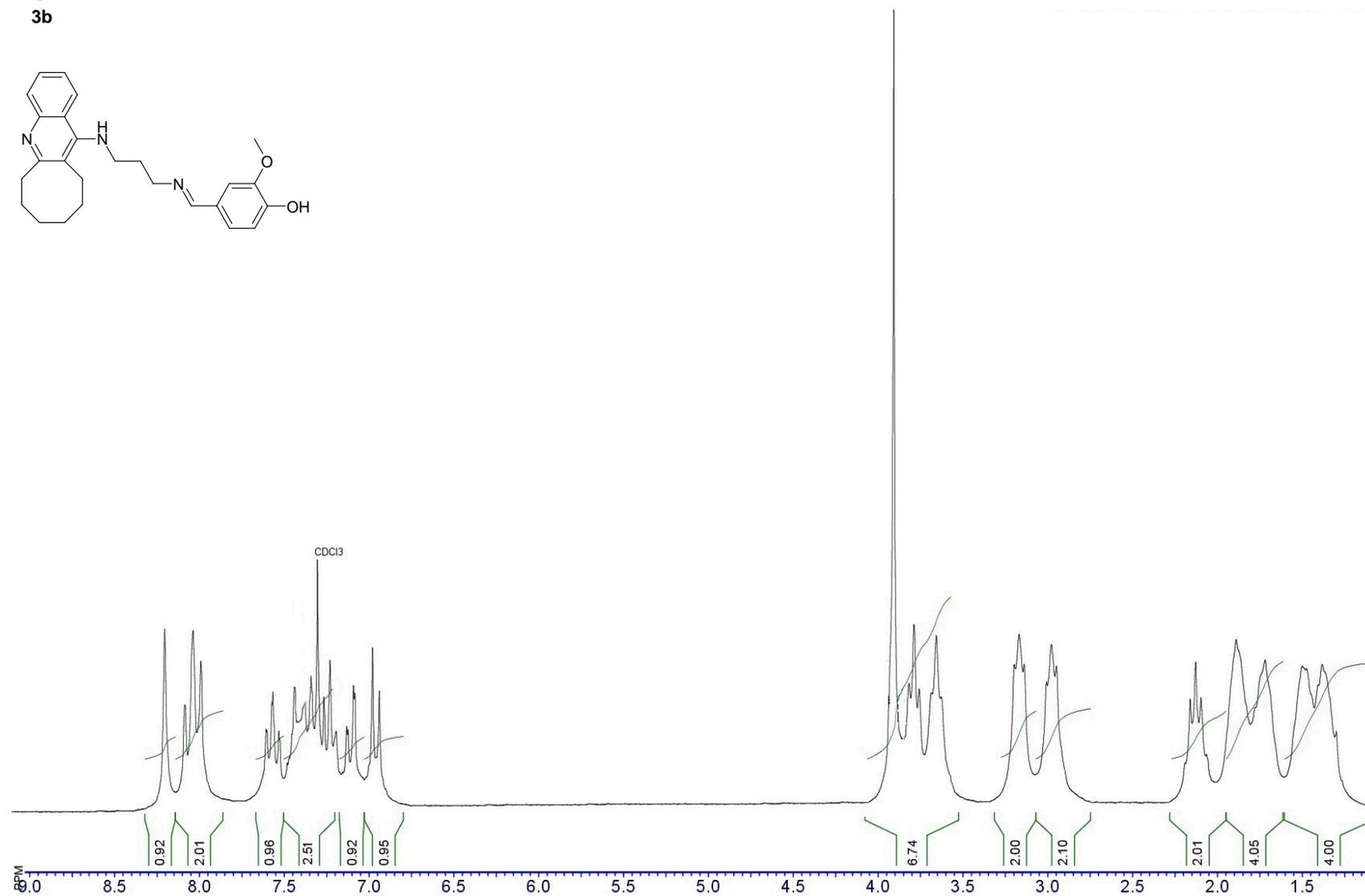
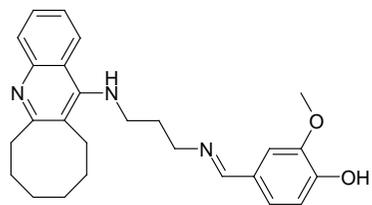


Figure S3

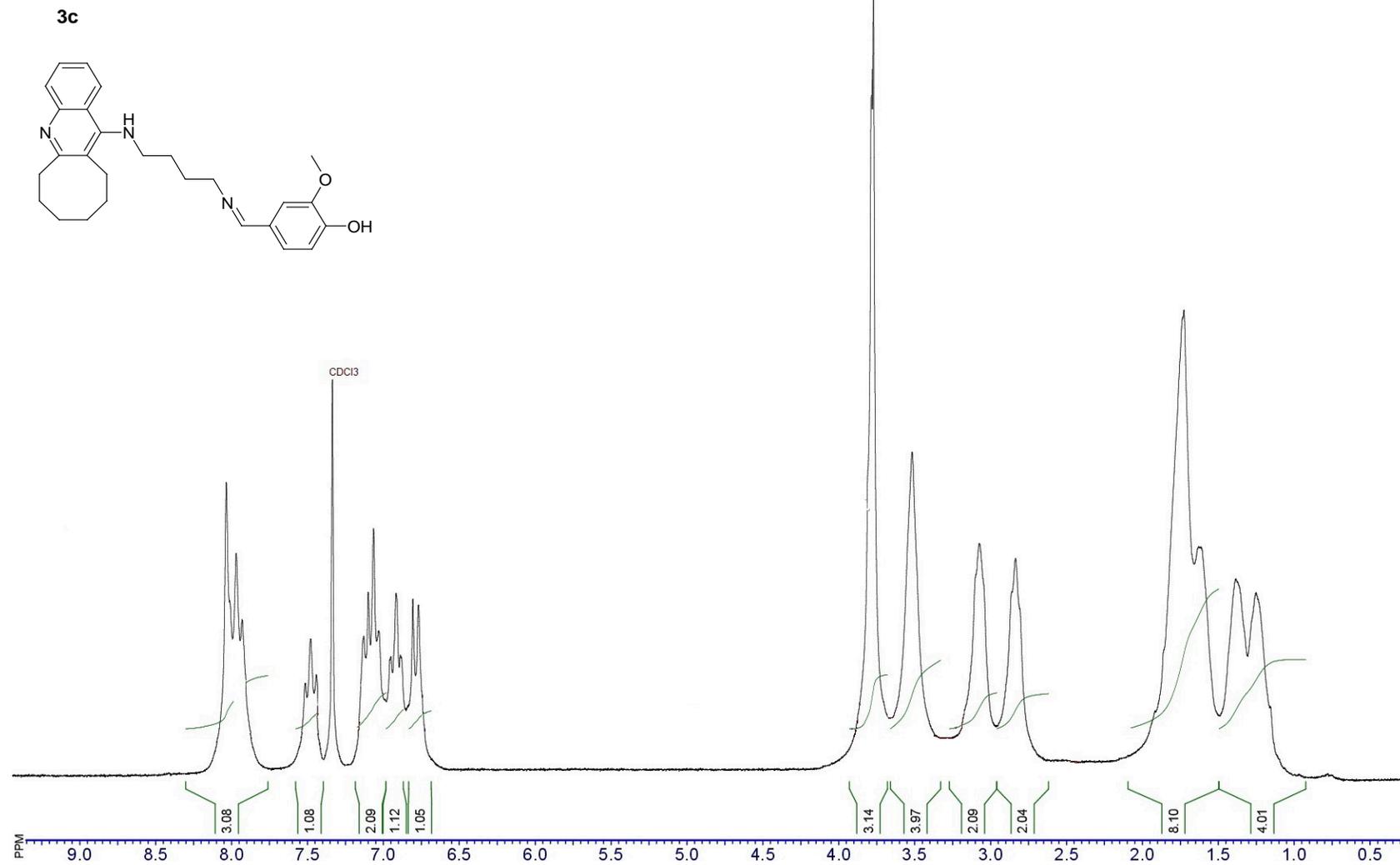


Figure S4

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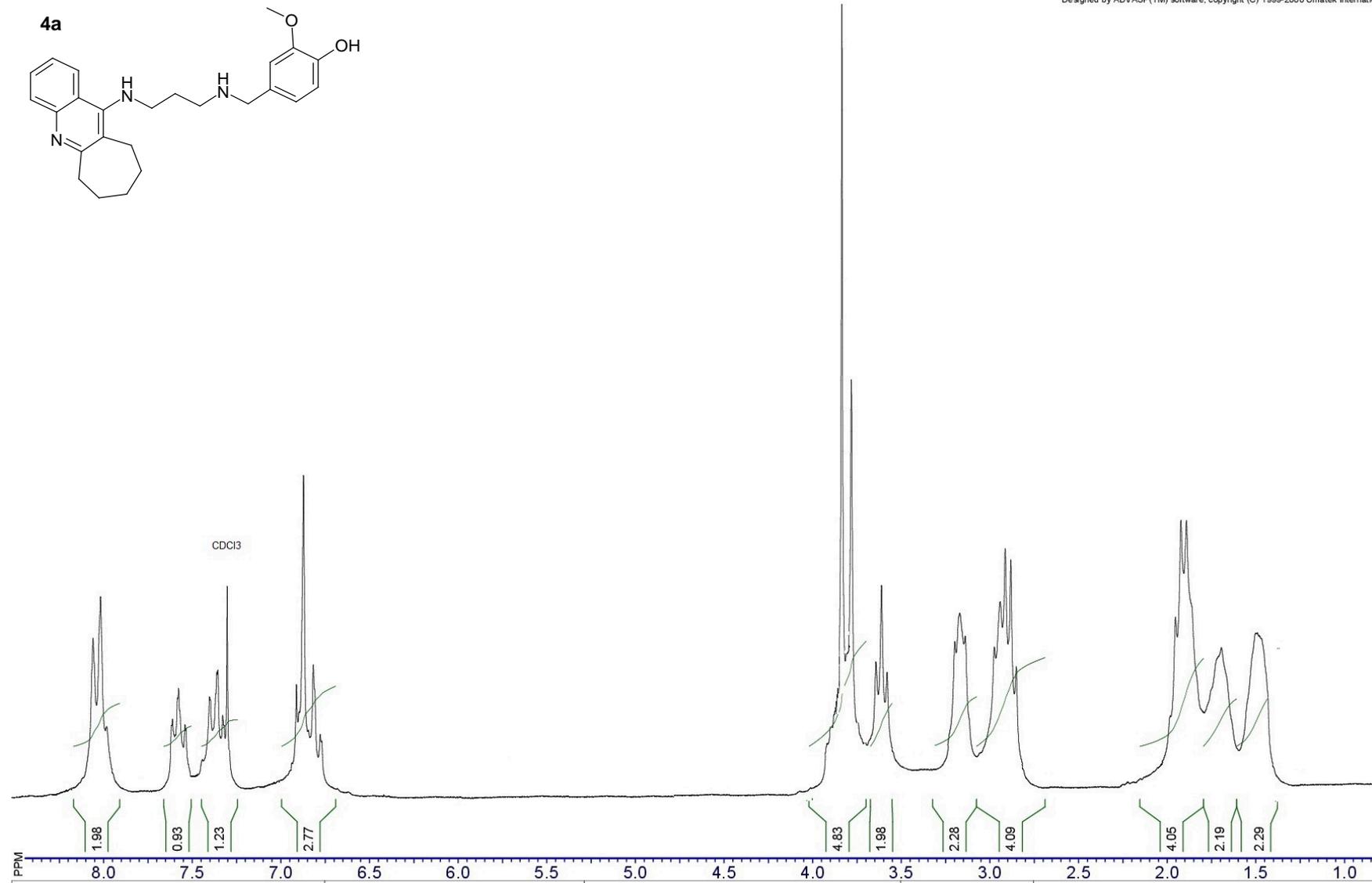


Figure S5

4b

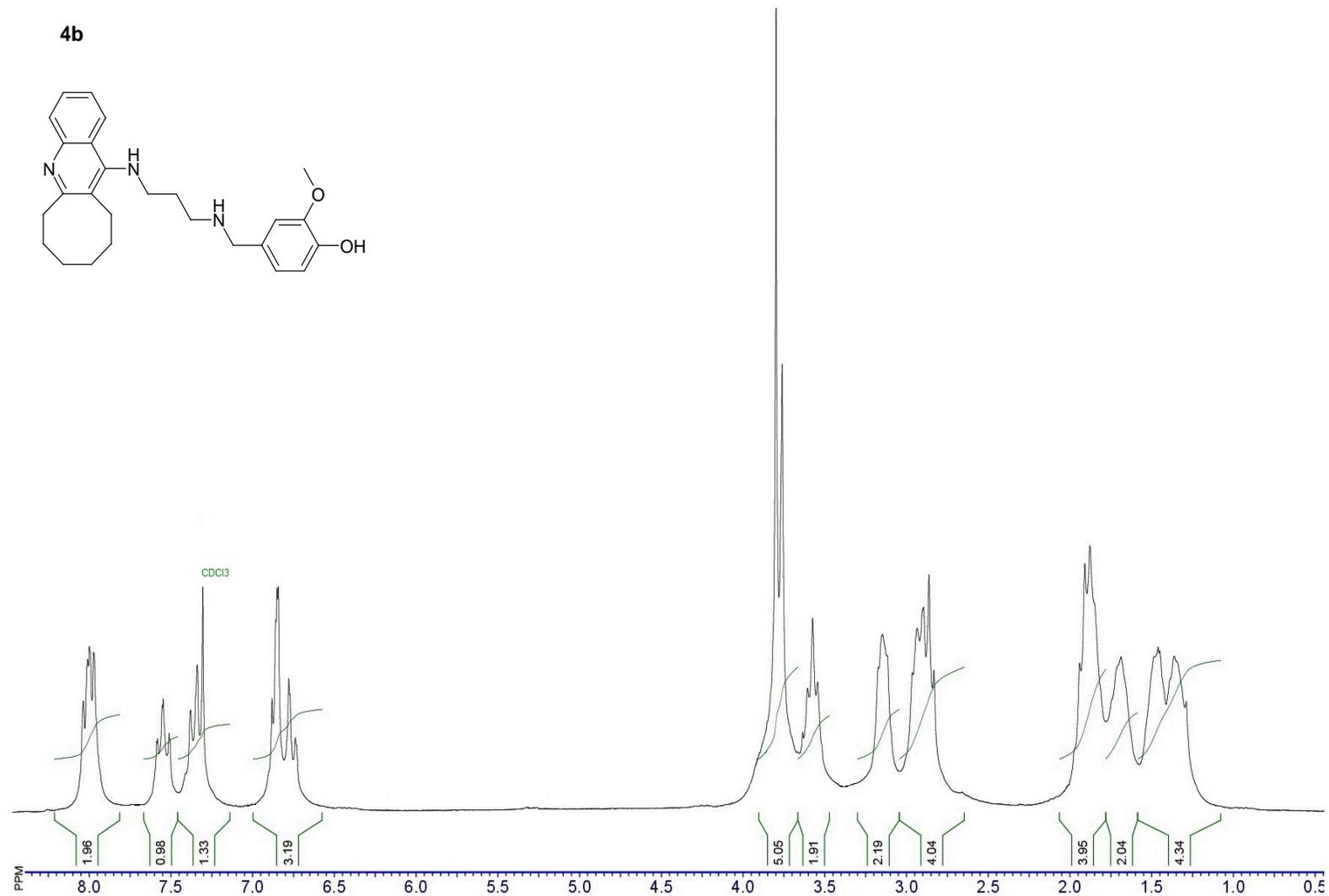
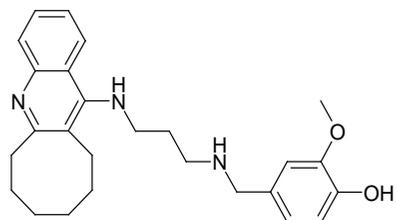
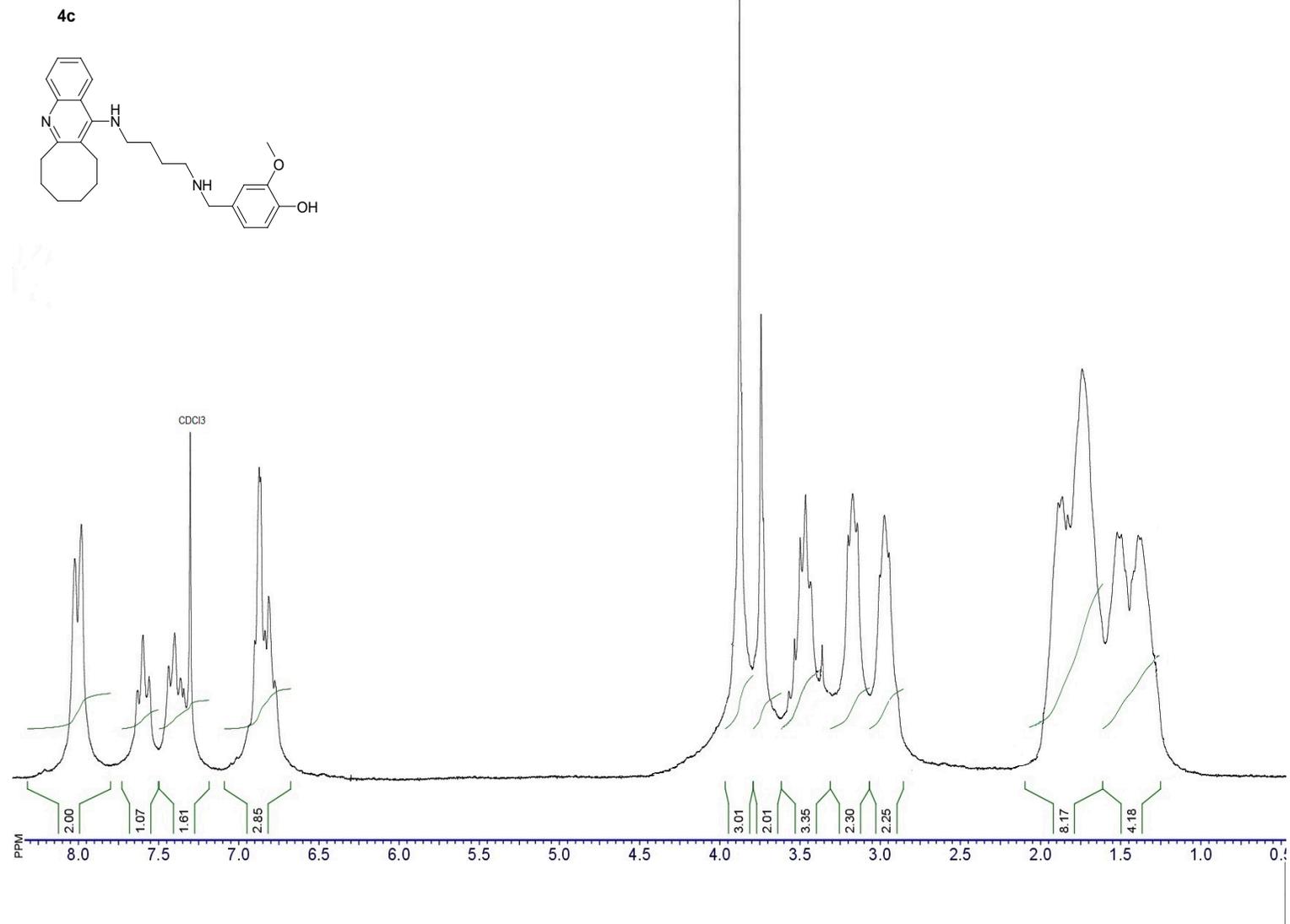


Figure S6



**<sup>13</sup>C NMR spectra**  
**Figure S7**

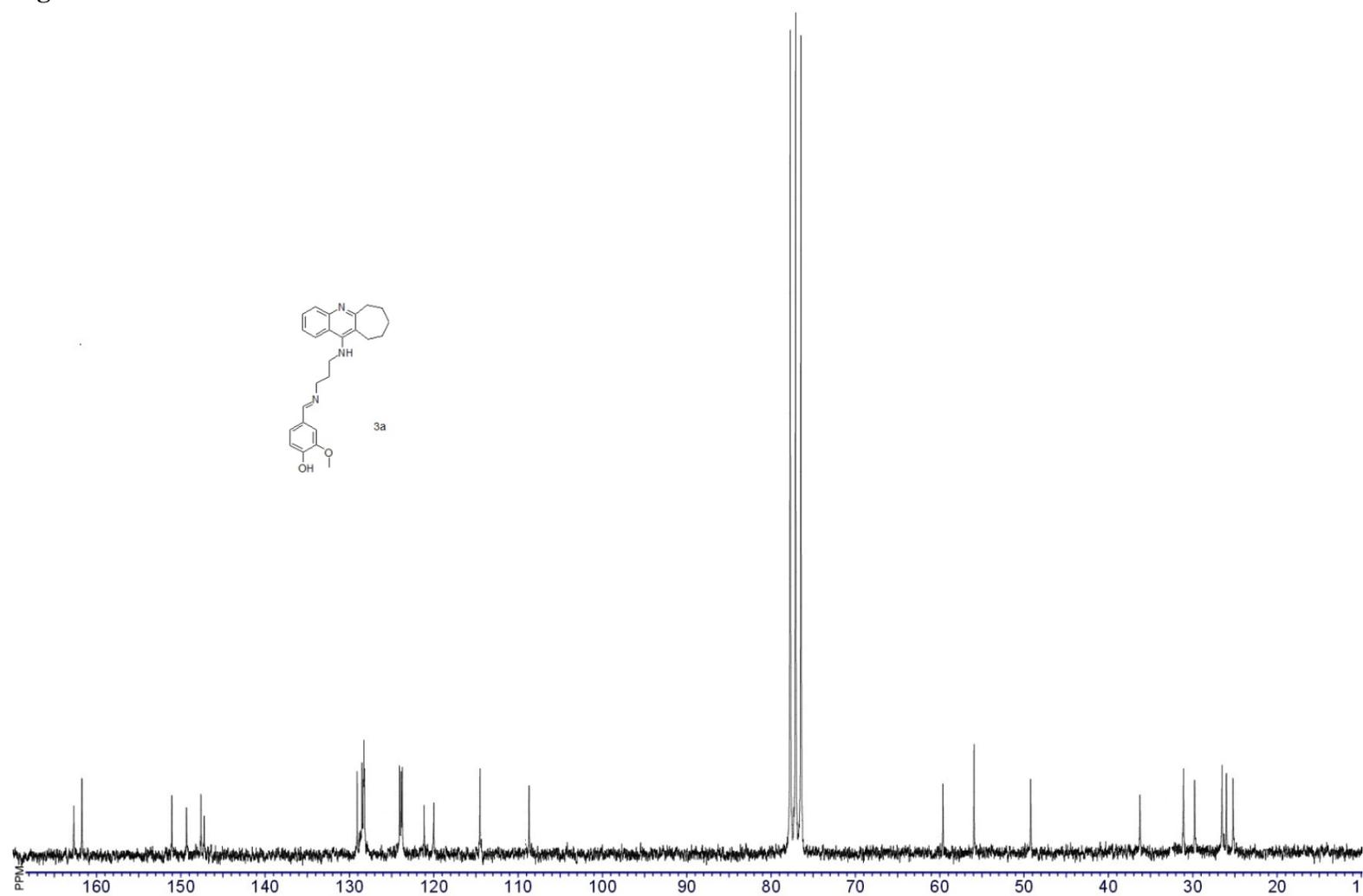


Figure S8

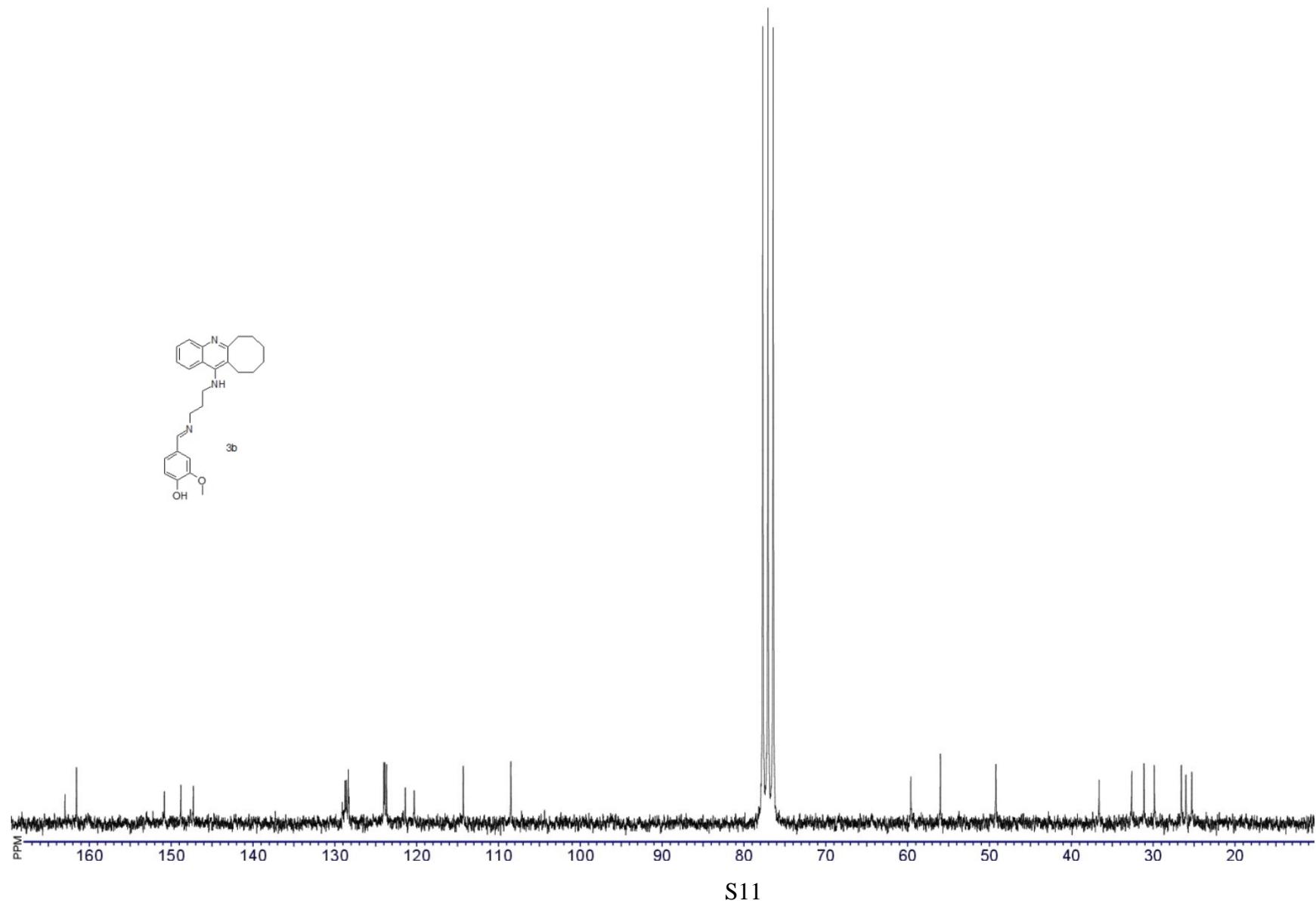


Figure S9

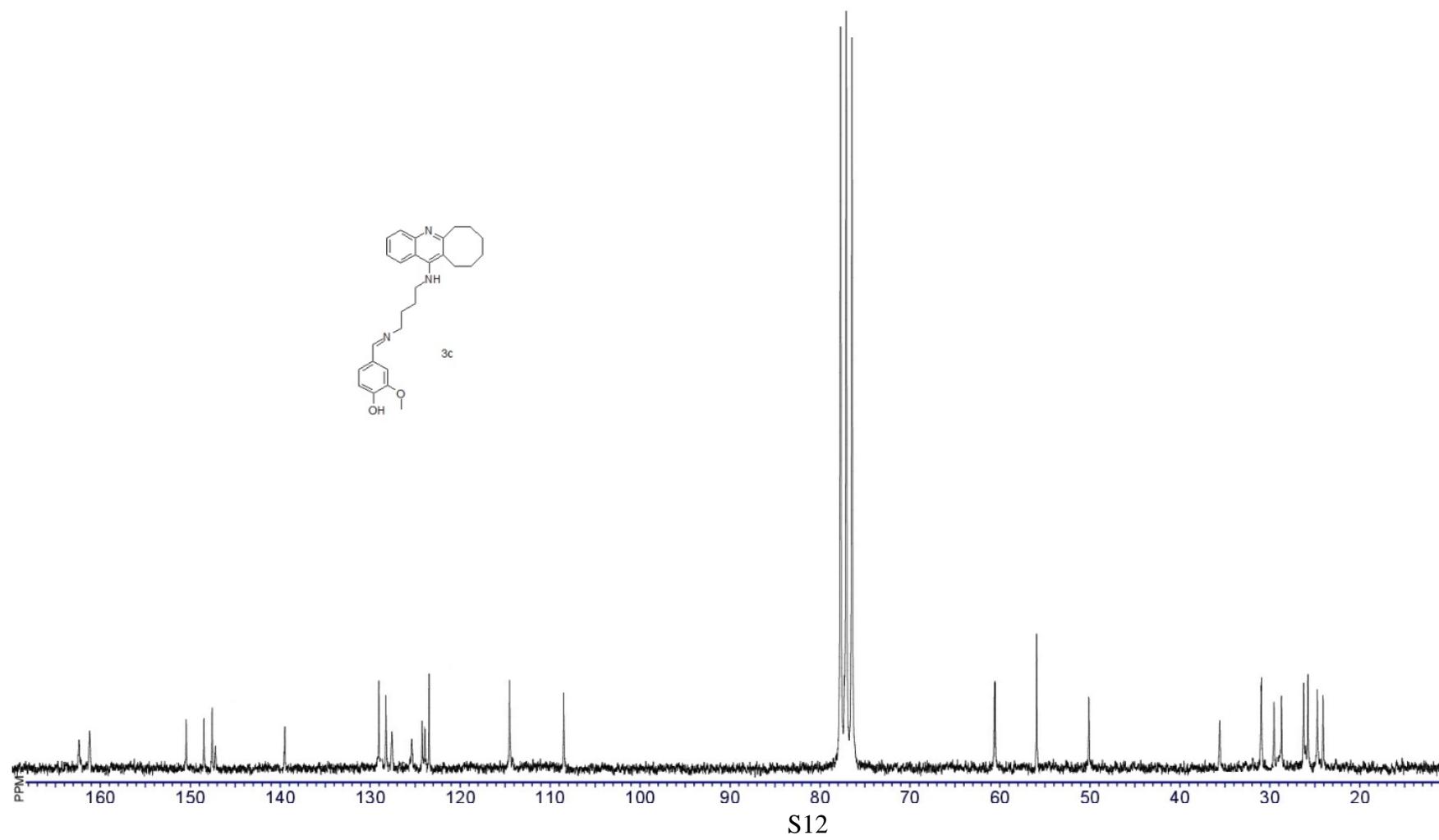


Figure S10

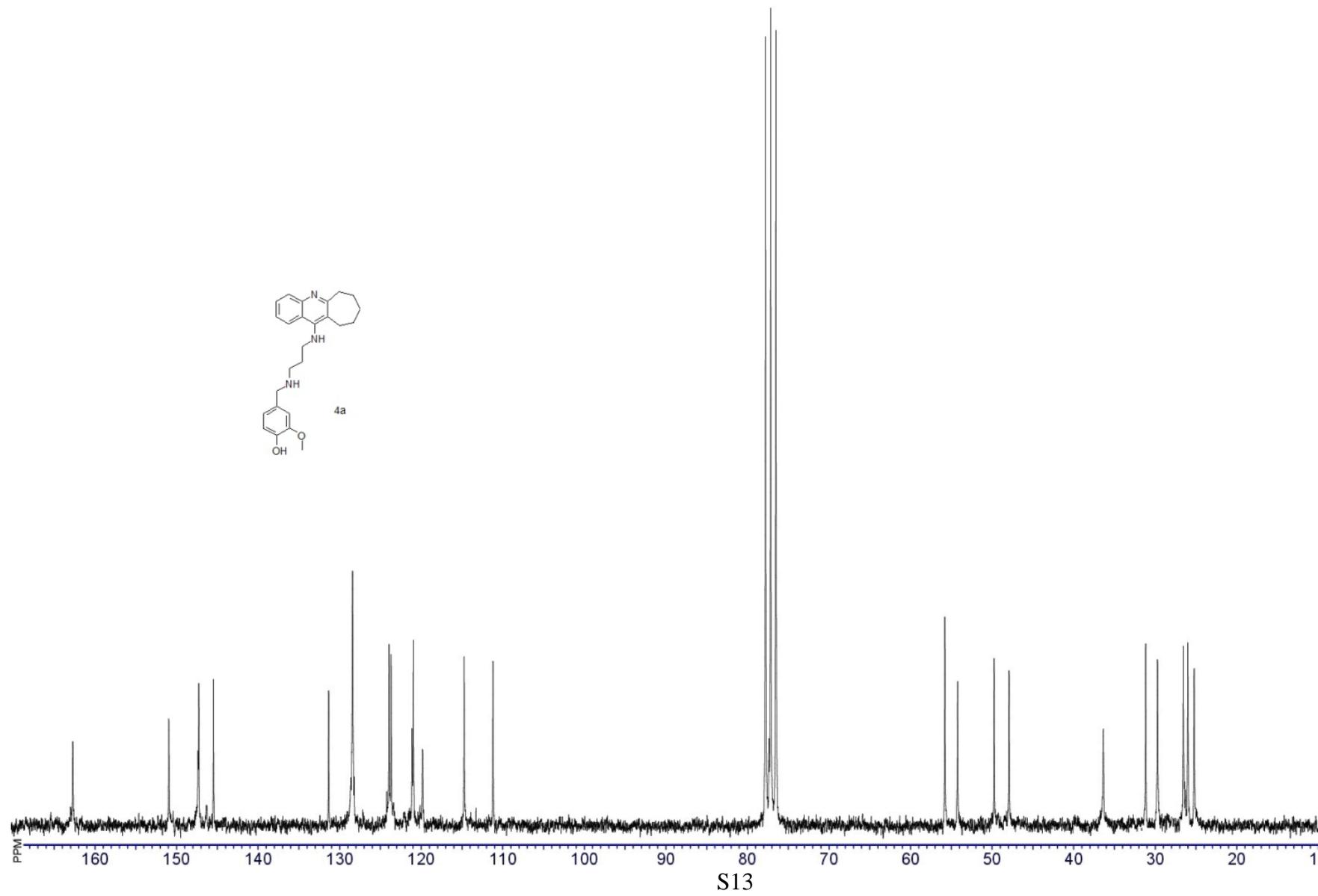


Figure S11

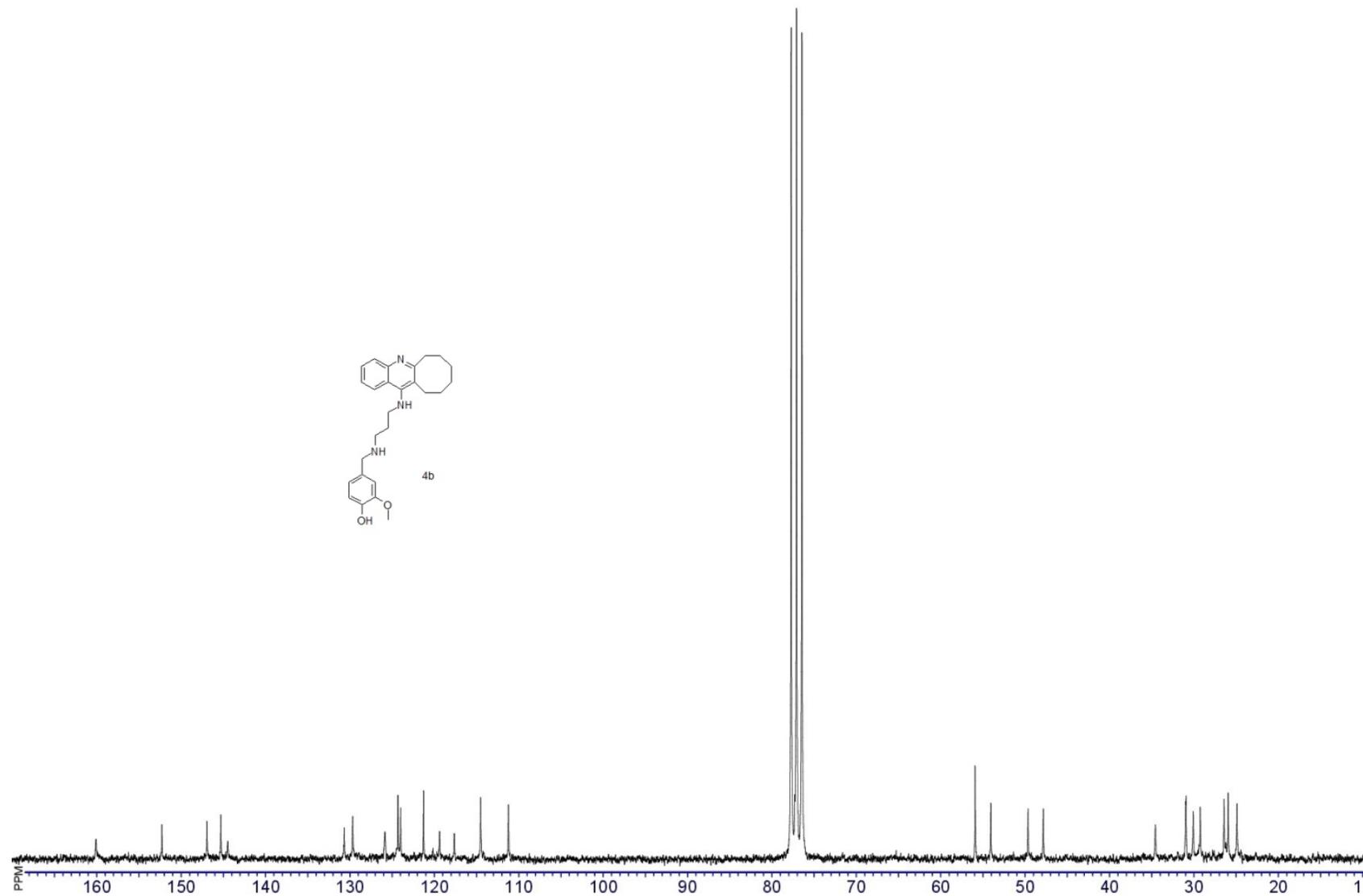


Figure S12

