Redox Neutral Indole Annulation Cascades

Michael C. Haibach, Indubhusan Deb, Chandra Kanta De, and Daniel Seidel*

Department of Chemistry and Chemical Biology, Rutgers, The State University of New Jersey, Piscataway, New Jersey 08854.

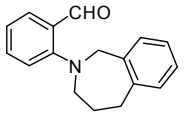
Supporting Information

Complete reference 13e:

Lundquist, J. T.; Harnish, D. C.; Kim, C. Y.; Mehlmann, J. F.; Unwalla, R. J.; Phipps, K. M.; Crawley, M. L.; Commons, T.; Green, D. M.; Xu, W. X.; Hum, W. T.; Eta, J. E.; Feingold, I.; Patel, V.; Evans, M. J.; Lai, K.; Borges-Marcucci, L.; Mahaney, P. E.; Wrobel, J. E. *J. Med. Chem.* **2010**, *53*, 1774

General Information: Reagents and solvents were purchased from commercial sources and were used as received. Microwave reactions were carried out in a CEM Discover reactor. Silicon carbide (SiC) passive heating elements were purchased from Anton Paar. Purification of reaction products was carried out by flash chromatography using Sorbent Technologies Standard Grade silica gel (60 Å, 230–400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60 F_{254} plates. Visualization was accomplished with UV light and PMA stain, followed by heating. Melting points were recorded on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on an ATI Mattson Genesis Series FT-Infrared spectrophotometer. Proton nuclear magnetic resonance spectra (^{1}H-NMR) were recorded on a Varian VNMRS-500 MHz and Varian VNMRS-400 MHz instrument and are reported in ppm using the solvent as an internal standard ($CDCl_3$ at 7.26 ppm, $(CD_3)_2SO$ at 2.50 ppm, $(CD_3)_2CO$ at 2.05 ppm). Data are reported as app = apparent, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, comp = complex, br = broad; coupling constant(s) in Hz. Proton-decoupled carbon nuclear magnetic resonance spectra (^{13}C-NMR) spectra were recorded on a Varian VNMRS-500 MHz and Varian VNMRS-400 MHz instrument and are reported in ppm using the solvent as an internal standard ($CDCl_3$ at 77.0 ppm, $(CD_3)_2SO$ at 39.5 ppm, $(CD_3)_2CO$ at 29.8 ppm). Mass spectra were recorded on a Finnigan LCQ-DUO mass spectrometer. The starting materials 2-(3,4-dihydroisoquinolin-2(1H)-yl)benzaldehyde[1] (**9a**), 2-(pyrrolidin-1-yl)benzaldehyde[2], 2-(piperidin-1-yl)benzaldehyde[2], 2-(azepan-1-yl)benzaldehyde[3], 2-(2-methylpiperidin-1-yl) benzaldehyde[2], 2-(2-methylpyrrolidin-1-yl) benzaldehyde[2], 2-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)benzaldehyde[1], 2-(9-methyl-3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)benzaldehyde[4], and 2,3,4,5-tetrahydro-1H-benzo[c]azepine[5] were prepared according to literature procedures.

2-(4,5-dihydro-1*H*-benzo[c]azepin-2(3*H*)-yl)benzaldehyde (13h): Starting from 2-fluorobenzaldehyde and 2,3,4,5-tetrahydro-1H-benzo[c]azepine, the title compound was prepared according to a literature procedure[1] and isolated as a yellow solid in 70 % yield, mp = 80–83 °C (R_f = 0.3 Hexanes/EtOAc 9:1 v/v); IR (KBr) 3061, 2926, 2741, 1677, 1590, 1481, 1444, 1385, 1349, 1269, 1191, 1086, 931, 888, 755 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.17 (s, 1H), 7.8 (app dd, *J* = 7.5, 1.5 Hz, 1H), 7.44 (ddd, *J* = 9.0, 7.2, 1.7 Hz, 1H), 7.15–7.23 (comp, 4H), 7.12 (app d, *J* = 6.2 Hz, 1H), 7.03 (app t. *J* = 7.4 Hz, 1H), 4.38 (s, 2H), 3.59 (t, *J* = 5.5 Hz, 2H), 3.01 (t, *J* = 5.5 Hz, 2H), 2.00 (app quintet, *J* = 5.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.1, 156.9, 142.1, 138.8, 134.5, 129.6, 129.4, 128.9, 128.3, 127.5, 126.4, 121.4, 119.6, 62.7, 59.1, 34.7, 28.7; *m/z* (ESI-MS) 252.3 $[M+H]^+$.



General Procedure A:

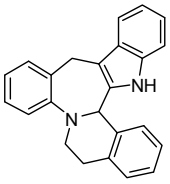
A 10 mL microwave reaction tube was charged with indole (0.275 mmol, 1.1 equiv.), aminobenzaldehyde (0.25 mmol, 1.0 equiv.), toluene (2.5 mL), diphenyl phosphate (0.05 mmol, 0.2 equiv.) and a Teflon stir bar. The reaction tube was sealed with a Teflon-lined snap cap, and heated in the microwave reactor at 150 °C (250 W, 25–50 psi) for the appropriate time under efficient stirring (setting = "HIGH"). After cooling with compressed air flow, the crude reaction mixture was diluted with EtOAc (5 mL) and washed with saturated aqueous $NaHCO_3$ (3 x 5 mL). The aqueous layers were extracted with EtOAc (3 x 5 mL) and the combined organic layers dried over anhydrous Na_2SO_4. The resulting solution was adsorbed on Celite, the solvent was removed in vacuo, and the Celite was loaded onto a column for purification.

General Procedure B:

A 10 mL microwave reaction tube was charged with indole (0.275 mmol, 1.1 equiv.), aminobenzaldehyde (0.25 mmol, 1.0 equiv.), toluene (2.5 mL), diphenyl phosphate (0.05 mmol, 0.2 equiv.) and a Teflon stir bar. The reaction mixture was stirred for 1 min at room temperature, and the stir bar was removed. A 10 x 8 mm SiC passive heating element was carefully added to the reaction tube. The reaction tube was sealed with a Teflon-lined snap cap, and heated in the microwave reactor at 200 °C, (250 W, 50–100 psi) for the appropriate time. (***Note: SiC passive heating elements must not be used in conjunction with stir bars; they may score glass and cause vessel failure***). The reaction was worked up as in general procedure A.

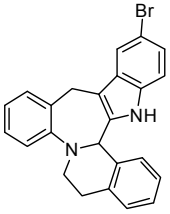
Characterization data:

6,12,17,17b-tetrahydro-5H-benzo[6,7]indolo[2',3':3,4]azepino[2,1-a]isoquinoline (12a):



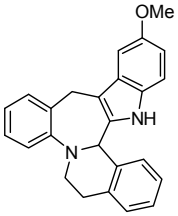
Following general procedure A, compound **12a** was obtained as an orange solid in 83% yield. mp = 164–167 ºC; R_f = 0.25 (Hexanes/EtOAc 95:5 v/v); IR (KBr) 3401, 3056, 2921, 1607, 1486, 1454, 1332, 1148, 1043, 942, 746 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.63–7.61 (m, 1H), 7.56 (br s, 1H), 7.33–7.27 (comp, 6H), 7.23–7.19 (comp, 2H), 7.13–7.08 (comp, 3H), 5.49 (s, 1H), 4.39 (d, *J* = 16.8 Hz, 1H), 4.12 (d, *J* = 16.8 Hz, 1H), 3.65 (ddd, *J* = 11.4, 7.4, 4.6 Hz, 1H), 3.42 (app dt, *J* = 11.4, 5.5 Hz, 1H), 3.10 (app dt, *J* = 15.9, 6.1 Hz, 1H), 2.97 (app dt, *J* = 15.9, 5.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.6, 138.3, 136.6, 136.1, 135.3, 130.2, 129.8, 129.8, 128.5, 127.6, 127.5, 126.7, 126.4, 126.1, 125.2, 121.7, 119.6, 118.2, 110.9, 109.3, 60.3, 47.0, 30.9, 30.3; *m/z* (ESI-MS) 335.3 $[M-H]^+$.

14-bromo-6,12,17,17b-tetrahydro-5H-benzo[6,7]indolo[2',3':3,4]azepino[2,1-a]isoquinoline (12e):



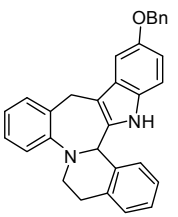
Following general procedure A using 2.0 equiv. of indole, compound **12e** was obtained as an orange solid in 54% yield. mp = 207–210 ºC; R_f = 0.54 (Hexanes/EtOAc 9:1 v/v); IR (KBr) 3443, 3021, 2914, 2826, 1586, 1456, 1372, 1290, 1224, 1145, 1045, 943, 861, 796, 752, 579, 431 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.74 (app d, *J* = 1.5 Hz, 1H), 7.68 (br s, 1H), 7.34–7.28 (comp, 7H), 7.23 (app td, *J* = 7.5, 1.1 Hz, 1H), 7.16 (app dd, *J* = 8.5, 1.5 Hz, 1H), 7.11 (app dt, *J* = 7.5, 1.1 Hz, 1H), 7.07 (app d, *J* = 8.5 Hz, 1H), 5.45 (s, 1H), 4.34 (d, *J* = 16.7 Hz, 1H), 4.02 (d, *J* = 16.7 Hz, 1H), 3.61 (ddd, *J* = 11.2, 6.9, 4.6 Hz, 1H), 3.42 (app dt, *J* = 11.2, 6.0 Hz, 1 H), 3.08 (ddd, *J* = 16.0, 6.9, 5.4 Hz, 1H), 2.99 (app dt, *J* = 16.0, 5.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.5, 140.0, 136.8, 136.7, 135.7, 133.8, 130.3, 130.3, 129.7, 127.7, 127.7, 126.7, 126.5, 125.9, 125.3, 124.4, 120.9, 112.9, 112.4, 109.1, 60.3, 40.1, 30.9, 30.2; *m/z* (ESI-MS) 413.4 $[M-H]^+$.

14-methoxy-6,12,17,17b-tetrahydro-5H-benzo[6,7]indolo[2',3':3,4]azepino[2,1-a]isoquinoline



(12b): Following general procedure A, compound **12b** was obtained as a light yellow solid in 54% yield. mp = 160–162 ºC; R_f = 0.30 (Hexanes/EtOAc 9:1 v/v); IR (KBr) 3449, 33.95, 2924, 2824, 1590, 1482, 1449, 1285, 1212, 103, 1031, 906, 824 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.50 (app d, *J* = 7.5 Hz, 1H), 7.46 (app dd, *J* = 5.5, 3.4 Hz, 2H), 7.41–7.45 (comp, 3H), 7.39 (app td, *J* = 7.1, 1.5 Hz, 1H), 7.28 (app dd, *J* = 7.4, 1.4 Hz, 1H), 7.24 (app d, *J* = 7.1 Hz, 2H), 6.95 (app dd, *J* = 8.6, 2.5 Hz, 1H), 5.61 (s, 1H), 4.53 (d, *J* = 16.6 Hz, 1H), 4.24 (d, *J* = 16.6 Hz, 1H), 4.06 (s, 3H), 3.79 (ddd, *J* = 11.3, 7.2, 4.6 Hz, 1H), 3.56 (app dt *J* = 11.3, 5.4 Hz, 1H), 3.24 (ddd, *J* = 15.7, 7.2, 5.5 Hz, 1H), 3.12 (app dt, *J* = 15.7, 5.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.0, 151.3, 137.8, 136.2, 135.9, 135.7, 130.1, 129.9, 129.5, 128.6, 127.2, 127.1, 126.4, 126.0, 125.6, 124.7, 111.4, 111.3, 108.9, 100.1, 60.0, 55.9, 46.9, 30.5, 30.1; *m/z* (ESI-MS) 365.2 $[M-H]^+$.

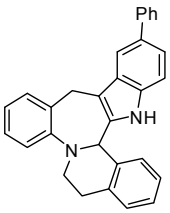
14-benzyloxy-6,12,17,17b-tetrahydro-5H-benzo[6,7]indolo[2',3':3,4]azepino[2,1-a]isoquinoline



(12c): Following general procedure A, compound **12c** was obtained as a yellow solid in 65% yield. mp = 101–103 ºC; Rf = 0.40 (Hexanes/EtOAc 7:3 v/v); IR (KBr)) 3446, 2919, 1626, 1482, 1454, 1376, 1285, 1195 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 10.67 (s, 1H), 7.48 (app d, *J* = 7.2 Hz, 2H), 7.39 (app t, *J* = 6.7 Hz, 2H), 7.32 (app td, *J* = 7.4, 1.3 Hz, 1H), 7.26–7.08 (comp, 9 H), 6.88 (app td, *J* = 6.9, 1.9 Hz, 1H), 6.75 (app dd, *J* = 8.0, 2.0 Hz, 1H), 5.37 (s, 1H), 5.12 (dd, *J* = 16.4, 11.9 Hz, 2H), 4.09 (d, *J* = 14.2

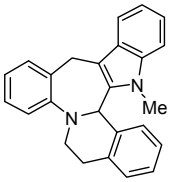
Hz, 1H), 3.77 (d, J = 14.1 Hz, 1H), 3.60 (ddd, J = 12.0, 6.2, 3.7 Hz, 1H), 3.50 (ddd, J = 14.1, 5.4, 8.9 Hz, 1H), 3.11 (app dt, J = 16.2, 7.4 Hz, 1H), 2.96 (app dt, J = 16.2, 3.7 Hz, 1H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 152.2, 149.9, 140.8, 137.8, 137.1, 134.9, 134.5, 130.3, 128.9, 128.3, 127.6, 127.5, 127.1, 126.8, 126.7, 126.6, 126.4, 125.6, 123.0, 122.7, 111.7, 111.2, 110.7, 101.4, 69.5, 61.4, 49.2, 29.6, 27.9; *m/z* (ESI-MS) 441.2 $[M-H]^+$.

14-phenyl-6,12,17,17b-tetrahydro-5H-benzo[6,7]indolo[2',3':3,4]azepino[2,1-a]isoquinoline (12d):

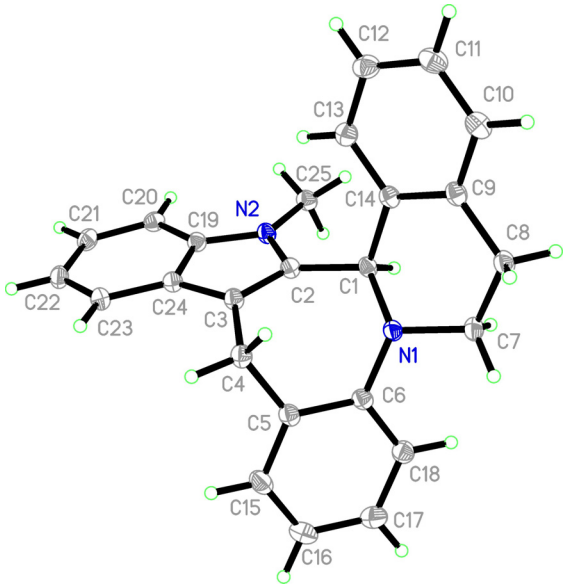


Following general procedure A, compound **12d** was obtained as a white solid in 54% yield. mp = 135–138 ºC; Rf = 0.25 (Hexanes/EtOAc 9:1 v/v); IR (KBr) 3449, 2919, 1597, 1488, 1469, 1453, 761, 750, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (app d, J = 1.5 Hz, 1H), 7.68 (app dt, J = 8.1, 1.5 Hz, 2H), 7.60 (br s, 1H), 7.45 (app t, J = 7.5 Hz, 2H), 7.40–7.27 (comp, 9H), 7.23 (app dt, J = 7.4, 1.4 Hz, 1H), 7.11 (app dt, J = 7.4, 1.4 Hz, 1H), 5.51 (s, 1H), 4.43 (d, J = 16.8 Hz, 1H), 4.22 (d, J = 16.8 Hz, 1H), 3.67 (ddd, J = 11.4, 7.3, 5.2 Hz, 1H), 3.44 (app dt, J = 11.4, 5.2 Hz, 1H), 3.11 (ddd, J = 15.9, 7.3, 5.2 Hz, 1H), 2.98 (app dt, J = 15.9, 5.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.3, 142.7, 137.9, 136.3, 135.8, 135.7, 134.4, 133.0, 130.0, 129.6, 128.8, 128.6, 127.4, 127.4, 127.3, 126.5, 126.2, 126.2, 125.9, 125.0, 121.3, 116.5, 110.9, 109.4, 60.06, 46.8, 30.6, 30.1; *m/z* (ESI-MS) 411.3 $[M-H]^+$.

17-methyl-6,12,17,17b-tetrahydro-5H-benzo[6,7]indolo[2',3':3,4]azepino[2,1-a]isoquinoline (12f):

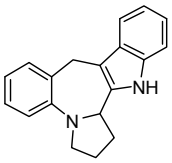


Following general procedure A using 0.5 equiv. diphenyl phosphate, compound **12f** was obtained as a yellow solid in 62% yield. mp = 164–167 ºC; Rf = 0.71 (Hexanes/EtOAc 9:1 v/v); IR (KBr) 3416, 3055, 2922, 2807, 1600, 1478, 1369, 1257, 1130, 1049, 933, 744, 653, 554 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (app dt, J = 9.8, 1.1 Hz, 1H), 7.32 (app d, J=10.0 Hz, 1H), 7.27–7.19 (comp, 3H) 7.16 (app tt, J = 10.0, 1.2 Hz, 2H), 7.05 (app td, J = 9.8, 2.0 Hz, 1H), 7.0 (app t, J = 7.3 Hz, 1H), 6.91 (app dd, J = 9.1, 0.9 Hz, 1 H), 6.57 (d, J = 9.7 Hz, 1H), 5.42 (s, 1H), 4.20 (d, 17.8 Hz, 1H) 3.93–3.85 (comp, 3H), 3.64 (s, 3H), 3.37 (app dt, J = 17.1, 8.4 Hz, 1H), 3.17 (ddd, J = 8.6, 5.5, 3.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.2, 141.1, 138.2, 135.2, 128.9, 127.5, 127.2, 126.7, 126.25, 125.7, 122.5, 121.6, 121.5, 119.4, 118.3, 113.4, 109.2, 61.64, 51.1, 30.4, 29.1, 28.7 ; *m/z* (ESI-MS) 349.5 $[M-H]^+$.

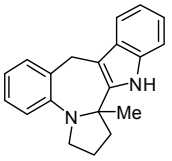


Compound **12f** was further characterized by X-ray crystallography. Suitable orange crystals were grown from the vapor phase of a CH_2Cl_2/ether solution of the compound over several days at room temperature. The requisite CIF has been submitted to the journal.

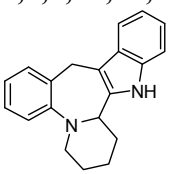
1,2,3,9,14,14b-hexahydrobenzo[6,7]pyrrolo[1',2':1,2]azepino[3,4-b]indole (14c): Following general procedure A using 0.5 equiv. diphenyl phosphate, compound **14c** was obtained as a white solid in 67% yield. mp = 121–124 ºC; R_f = 0.20 (Hexanes/EtOAc 9:1 v/v); IR (KBr) 3407, 2954, 1491, 1465, 1453, 1331, 1263, 1156, 741 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.69-7.63 (m, 1H), 7.61 (s, 1H), 7.31–7.19 (comp, 3H), 7.19–7.10 (comp, 3H), 6.98 (app t, *J* = 7.3 Hz, 1H), 4.31 (d, *J* = 15.0 Hz, 1H), 3.98 (app t, *J* = 8.2 Hz, 1H), 3.82 (d, *J* = 15.0 Hz, 1H), 3.42 (app dd, *J* = 17.4, 8.8 Hz, 1H), 3.32 (app dt, *J* = 6.5, 2.3 Hz, 1H), 2.53–2.39 (m, 1H), 2.18–2.00 (comp, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.0, 137.4, 135.8, 135.5, 128.6, 127.3, 126.9, 122.9, 121.3, 119.3, 118.3, 117.9, 110.3, 108.7, 61.6, 50.9, 32.4, 28.9, 21.8; *m/z* (ESI-MS) 275.5 $[M+H]^+$.



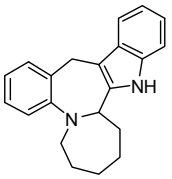
14b-methyl-1,2,3,9,14,14b-hexahydrobenzo[6,7]pyrrolo[1',2':1,2]azepino[3,4-b]indole (14e): Following general procedure A, compound **14e** was obtained as a white solid in 76% yield. mp = 87–92 ºC; R_f = 0.23 (Hexanes/EtOAc 9:1 v/v); IR (KBr) 3452, 3399, 2927, 2826, 1590,1484, 1451, 1215, 1095, 1031, 760, 731 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.71–7.63 (m, 1H), 7.57 (br s, 1H), 7.34–7.27 (comp, 2H), 7.24–7.19 (comp, 2H), 7.18–7.14 (comp, 2H), 7.00 (app td, *J* = 7.0, 1.8 Hz, 1H), 4.30 (d, *J* = 16.0 Hz, 1H), 3.83 (d, *J* = 16.0 Hz, 1H), 3.73 (app dd, *J* = 17.0, 9.0 Hz, 1H), 3.25 (ddd, *J* =10.0, 7.0, 3.0 Hz, 1H), 2.42 (ddd, *J* = 12.0 10.0, 6.0 Hz , 1H), 2.28–2.16 (m, 1H), 2.13–1.94 (comp, 2H), 1.19 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.3, 140.8, 137.9, 135.3, 128.8, 127.4, 126.4, 123.0, 121.5, 121.2, 119.2, 118.0, 110.3, 107.1, 62.9, 48.2, 40.0, 29.3, 23.1, 21.4; *m/z* (ESI-MS) 289.4 $[M+H]^+$.



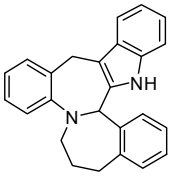
2,3,4,10,15,15b-hexahydro-1H-benzo[6,7]pyrido[1',2':1,2]azepino[3,4-b]indole (14d): Following general procedure B, compound **14d** was obtained as a light green solid in 58% yield. mp = 100–105 ºC; R_f = 0.52 (Hexanes/EtOAc 9:1 v/v); IR (KBr) 3405, 3055, 2931, 2853, 2356, 1608, 1454, 1339, 1242, 1111, 1054, 941, 835, 746, 613, 478 cm^{-1}. ^1H NMR (500 MHz) δ 7.61–7.60 (m, 1H), 7.56 (br s, 1H), 7.21–7.08 (comp, 6H), 6.88 (app td, *J* = 1.0, 7.1 Hz, 1H), 4.44 (d, *J* = 14.0 Hz, 1H), 3.91 (app d, *J* = 10.0 Hz, 1H), 3.60 (d, *J* = 14.0 Hz, 1H), 3.37 (app d, *J* = 11.4 Hz, 1H), 3.19 (app td, *J* = 1.5, 11.4 Hz, 1H), 2.08 (app d, *J* = 13.1 Hz 1H), 1.96–1.85 (comp, 3H), 1.82–1.74 (m, 1H), 1.62–1.58 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.8, 142.7, 136.1, 135.0, 127.4, 127.0, 126.7, 122.9, 121.4, 121.0, 119.5, 117.9, 111.7, 110.6, 62.6, 53.5, 36.4, 27.9, 26.8, 25.0; *m/z* (ESI-MS) 287.2 $[M-H]^+$



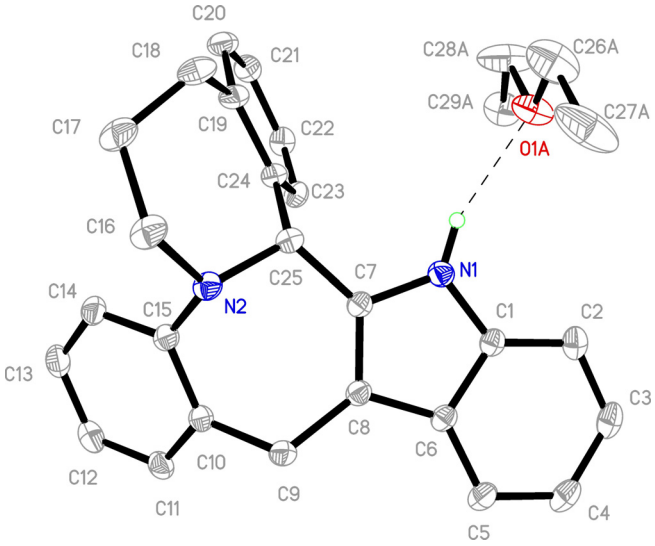
1,2,3,4,5,11,16,16b-octahydroazepino[1',2':1,2]benzo[6,7]azepino[3,4-b]indole (14g): Following general procedure A, compound **14g** was obtained as an orange solid in 57% yield. mp = 143–147 ºC; R_f = 0.70 (Hexanes/EtOAc 9:1 v/v); IR (KBr) 3394, 3059, 2926, 2864, 1611, 1455, 1330, 1250, 748; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.62–7.61 (comp, 2H), 7.27–7.17 (comp, 4H), 7.12–7.10 (comp, 2H), 6.98 (app t, *J* = 6.9 Hz, 1H), 4.43 (app t, *J* = 4.7 Hz, 1H), 4.34 (d, *J* = 14.9 Hz, 1H), 3.81 (d, *J* = 14.9 Hz, 1H), 3.46 (app t, *J* = 5.2 Hz, 1H), 2.31–2.27 (m, 1H) 2.09–2.05 (m, 1H), 1.86–1.62 (comp, 7H); ^{13}C (125 MHz, $CDCl_3$) δ 152.8, 141.9, 137.3, 136.4, 135.4, 132.5, 128.0, 125.7, 124.2, 121.4, 119.4, 117.9, 111.6, 110.5, 61.0, 52.5, 34.8, 33.0, 29.2, 29.0, 24.4; *m/z* (ESI-MS) 301.3 $[M-H]^+$.



5,6,7,13,18,18b-hexahydrobenzo[6,7]benzo[3',4']azepino[1',2':1,2]azepino[3,4-b]indole (14h):

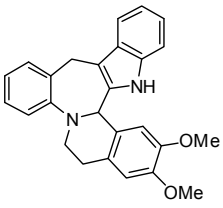


Following general procedure A, compound **14h** was obtained as a light yellow solid in 90% yield. mp = 115–121 ºC; R_f = 0.30 (Hexanes/EtOAc 9:1 v/v); IR (KBr) 3403, 3055, 3017, 2929, 1849, 1489, 1455, 1363, 1322, 1236, 1157, 1146, 1133, 741, 483 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 10.54 (s, 1H), 7.72–7.56 (m, 1H), 7.31–7.15 (comp, 3H), 7.12–6.97 (comp, 3H), 6.93–6.84 (m, 1H), 6.80 (app td, *J* = 7.2, 2.5 Hz, 1H) 6.73 (app t, *J* = 7.5 Hz, 1H), 6.26 (s, 1H), 5.98 (app d, *J* = 7.5 Hz, 1H), 4.08 (d, *J* = 4.5 Hz, 1H), 4.02–3.80 (comp, 2H), 3.75– 3.48 (comp, 2H), 2.96 (app dd, *J* = 12.8, 4.5 Hz, 1H), 2.25-2.12 (m, 1H), 1.86 (app d, *J* = 12.8 Hz, 1H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 149.0, 141.5, 141.3, 137.9, 135.5, 134.1, 128.3, 128.3, 126.9, 126.7, 126.6, 126.5, 125.4, 122.8, 122.0, 120.6, 118.1, 117.5, 110.7, 109.5, 61.0, 57.0, 40.0, 39.9, 39.8, 39.7, 39.5, 39.4, 39.2, 39.0, 33.3, 29.2, 28.6; *m/z* (ESI-MS) 351.2 $[M+H]^+$.

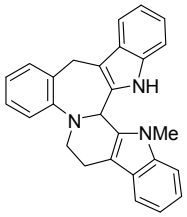


Compound **14h** was further characterized by X-ray crystallography. Suitable white crystals were grown from the vapor phase of an ether solution of the compound over one day at room temperature. The requisite CIF has been submitted to the journal.

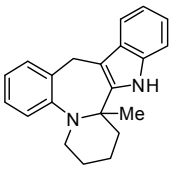
2,3-dimethoxy-6,12,17,17b-tetrahydro-5H-benzo[6,7]indolo[2',3':3,4]azepino[2,1-a]isoquinoline (14a):



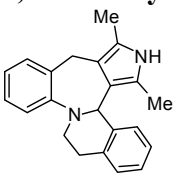
Following general procedure A, compound **14a** was obtained as a yellow solid in 43% yield. mp = 118–119 ºC; R_f = 0.40 (Hexanes/EtOAc 7:3 v/v); IR (KBr) 3371, 2921, 1605, 1514, 1454, 1365, 1338, 1256, 1113, 853, 743 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.63–7.61 (m, 1H), 7.56 (s, 1H), 7.31 (app d, *J* = 7.4 Hz, 1H), 7.25 (app d, *J* = 5.7 Hz, 1H), 7.23–7.19 (comp, 2H), 7.12 (app t, *J* =3.7 Hz, 2H), 7.08 (app t, *J* = 7.4 Hz, 1H), 6.80 (s, 1H), 6.77 (s, 1H), 5.49 (s, 1H), 4.36 (d, *J* = 17.1 Hz, 1H), 4.21 (d, *J* = 17.1 Hz, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 3.56 (ddd *J* = 11.5, 8.3, 4.5 Hz, 1H), 3.39 (app dt, *J* = 11.1, 3.3, Hz 1H), 3.05 (ddd, *J* = 15.7, 8.0, 5.6 Hz, 1H), 2.85 (app dt, *J* = 15.7, 4.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.3, 148.4, 147.4, 136.5, 135.8, 134.8, 129.9, 128.5, 128.2, 127.2, 127.1, 126.2, 124.5, 121.4, 119.4, 117.9, 112.6, 110.7, 110.0, 108.9, 59.0, 56.4, 55.9, 47.1, 30.2, 30.1; *m/z* (ESI-MS) 395.3$[M-H]^+$.

1-methyl-1,5c,6,9,15,16-hexahydrobenzo[6',7']indolo[2'',3'':3',4']azepino[1',2':1,2]pyrido[4,3-b] indole (14b): 

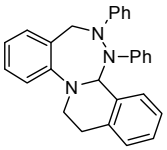
Following general procedure B, compound **14b** was obtained as a yellow solid in 52% yield. mp = 126–128 ºC; R_f = 0.40 (Hexanes/EtOAc 7:3 v/v); IR (KBr) 3436, 3051, 1606, 1460, 1368, 1339, 1273, 1230 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.62–7.66 (comp, 2H), 7.56 (s, 1H), 7.43 (app d, *J* = 8.2 Hz, 1H), 7.34–7.30 (comp, 2H), 7.23–7.20 (comp, 4H), 7.14 (ddd, *J* = 7.4, 3.8, 1.5 Hz, 2H), 7.05 (ddd, *J* = 8.0, 6.6, 2.0 Hz, 1H), 5.96 (s, 1H), 4.55 (d, *J* = 18.0 Hz, 1H), 4.34 (d, *J* = 18.0 Hz, 1H), 3.70 (s, 3H), 3.50 (app dd, *J* = 12.2, 5.6 Hz, 1H), 3.42 (app dt, *J* = 11.0, 3.8 Hz, 1H), 3.18 (ddd, *J* = 15.1, 3.8, 1.6 Hz, 1H), 2.83 (ddd, *J* = 12.1, 6.1, 1.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.1, 137.7, 135.0, 134.8, 133.4, 132.1, 131.3, 128.1, 128.0, 127.2 (x 2), 123.7, 121.8, 121.5, 119.7, 119.6, 118.6, 118.0, 111.0, 110.1, 109.3, 109.2, 52.4, 48.7, 30.3, 30.0, 23.2; *m/z* (ESI-MS) 388.3 $[M-H]^+$.

15b-methyl-2,3,4,10,15,15b-hexahydro-1H-benzo[6,7]pyrido[1',2':1,2]azepino[3,4-b]indole (14f): 

Following general procedure A, compound **14f** was obtained as a yellow liquid in 45% yield, as an inseparable mixture of regioisomers. ^1H NMR indicated a 20:3:2 ratio of the major regioisomer to the two diastereomers of the minor regioisomer. Data for the major regioisomer (pictured): R_f = 0.30 (Hexanes/EtOAc 9.5:0.5 v/v); IR (KBr) 3467, 3055, 2980, 2936, 1451, 1265, 1154, 1117, 896 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.61 (app dd, *J* = 5.9, 3.0 Hz, 1H), 7.58 (s, 1H), 7.26–7.24 (m, 1H), 7.20–7.18 (comp, 2H), 7.16–7.13 (comp, 2H), 7.11 (app dd, *J* = 5.9, 3.0 Hz, 1H), 7.00 (app td, *J* = 7.6, 1.5 Hz, 1H), 4.43 (d, *J* = 15.5 Hz, 1H), 3.78 (d, *J* = 15.5 Hz, 1H), 3.30 (ddd, *J* = 11.4, 8.1, 3.5 Hz, 1H), 3.20 (ddd, *J* = 11.5, 6.5, 3.5 Hz, 1H), 2.12–2.06 (m, 1H), 1.94–1.89 (m, 1H), 1.81–1.75 (comp, 2H), 1.72–1.65 (comp 2H), 1.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.4, 141.9, 140.3, 134.8, 128.1, 127.7, 127.3, 126.4, 124.3, 121.2, 119.2, 117.8, 110.3, 108.9, 58.1, 47.8, 40.3, 29.1, 26.9, 22.7, 21.5; *m/z* (ESI-MS) 303.2 $[M+H]^+$.

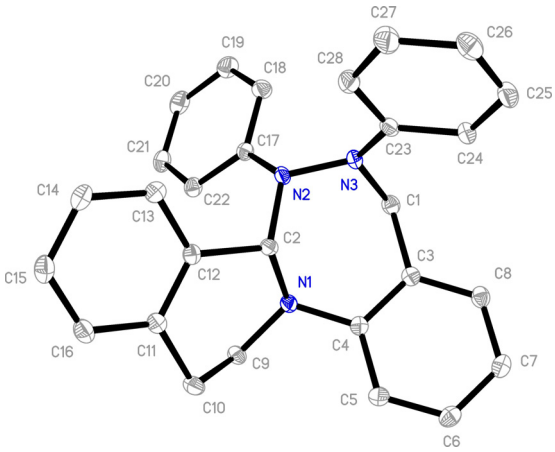
5,7-dimethyl-6,8,14,15-tetrahydro-4bH-benzo[6,7]pyrrolo[3',4':3,4]azepino[2,1-a]isoquinoline (15): 

Following general procedure A using 2.0 equiv. of 2,5-dimethylpyrrole, compound **15** was obtained as an orange solid in 59% yield. mp = 172–178 ºC; R_f = 0.23 (Hexanes/EtOAc 9:1 v/v); IR (KBr) 3427, 3410, 2909, 2852, 1487, 1448, 1257, 1220, 1219, 1134, 758, 740, 512 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25–7.15 (comp, 3H), 7.15–7.10 (comp, 2H), 7.07 (app dd, *J* = 7.4, 1.6 Hz, 1H), 7.03 (app dd, *J* = 8.0, 1.0 Hz, 1H), 6.97 (app d, *J* = 7.6 Hz, 1H), 6.81 (app td, *J* = 7.4, 1.0 Hz, 1H), 5.44 (s, 1H), 3.80 (d, *J* = 14.6 Hz, 1H), 3.76 (app dt, *J* = 11.6, 5.5 Hz, 1H), 3.68 (d, *J* = 14.6 Hz, 1H), 3.62 (ddd, *J* = 13.1, 7.6, 5.9 Hz, 1H), 3.20–3.04 (comp, 2H), 2.22 (s, 3H), 1.85 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.8, 139.1, 136.5, 135.3, 135.2, 128.7, 128.3, 126.6, 126.6, 126.2, 125.7, 122.9, 122.2, 121.0, 119.4, 117.4, 117.1, 59.5, 50.5, 30.6, 30.3, 11.4, 10.7; *m/z* (ESI-MS) 315.1 $[M+H]^+$.

1,2-diphenyl-1,2,3,9,10,14b-hexahydrobenzo[5,6][1,2,4]triazepino[3,4-a]isoquinoline (16) : 

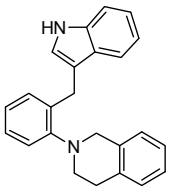
Following the general procedure A using 1.4 equiv. of 1,2-diphenylhydrazine and 0.05 equiv. of diphenyl phosphate, compound **16** was obtained as an off-white solid in 72% yield. mp = 205–206 ºC; R_f = 0.86 (Hexanes/EtOAc 9:1 v/v); IR (KBr) 3444, 3025, 2930, 2893, 1590, 1489, 1358, 1281, 1228, 1147, 1097, 1033, 999, 957, 922, 870, 819, 753, 681, 553, 510, 422 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.70–7.68 (m, 1H), 7.40 (app dd, *J* = 2.3, 1.4 Hz, 1H), 7.29–7.15 (comp, 7H), 7.12–7.05 (comp, 4H), 6.96, (app dd, *J* = 3.5, 0.9 Hz, 2H), 6.91 (app td, *J* = 7.4, 0.8 Hz 1H) 6.82–6.76 (comp, 2H), 5.46 (s, 1H), 4.66 (d, *J* = 18.5 Hz, 1H), 4.62 (d, *J* = 18.5 Hz, 1H), 4.04 (app dt, *J* = 14.0, 3.9 Hz, 1H), 3.69 (ddd, *J* =14.0, 11.5, 2.8 Hz,

1H), 3.14 (ddd, J = 15.3, 11.5, 4.2 Hz, 1H), 2.99 (app dt, J = 15.3, 2.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 148.8, 146.3, 136.1, 135.0, 131.7, 129.50 129.3, 128.9, 128.5, 127.5, 127.4, 127.3, 121.3, 120.3, 119.3, 117.7, 117.8, 114.5, 77.4, 52.9, 47.1, 30.6; *m/z* (ESI-MS) 402.4 $[M-H]^+$.

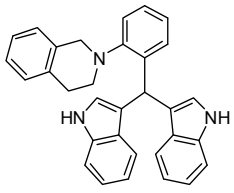


Compound **16** was further characterized by X-ray crystallography. Suitable white crystals were grown in solution by allowing ether to slowly evaporate from a 10% ether/hexanes solution of the compound over 5 hours at room temperature. The requisite CIF has been submitted to the journal.

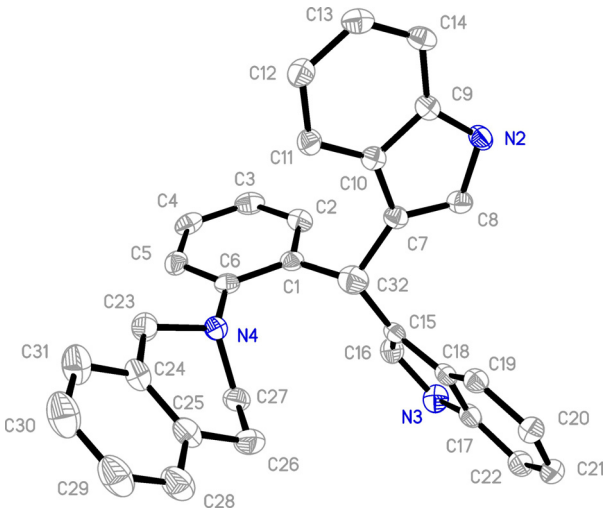
2-(2-((1H-indol-3-yl)methyl)phenyl)-1,2,3,4-tetrahydroisoquinoline (11a): A round bottom flask was charged with indole (0.250 mmol, 1.00 equiv), **9a** (0.275 mmol, 1.1 equiv), *n*BuOH (2.50 mL), 48% aqueous HBF_4 (0.300 mmol, 1.2 equiv), and a Teflon stir bar. The reaction mixture was heated under reflux for 24 h with efficient stirring, and worked up following the general procedures. Compound **11a** was obtained as a yellow oil in 54% yield. R_f = 0.3 (Hexanes/EtOAc 9:1 v/v); IR (KBr) 3417, 3054, 2919, 1591, 1489, 1453, 1376, 1218 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.52 (app d, J = 8.0 Hz, 1H), 7.35 (app d, J = 8.0 Hz, 1H), 7.24 (app d, J = 7.5 Hz, 1H), 7.22–7.21 (comp, 2H), 7.20–7.15 (comp, 4H), 7.06 (app td, J = 7.9, 1.0 Hz, 2H), 7.03–6.99 (m, 1H), 6.91 (app t, J = 1.0 Hz, 1H), 4.24 (s, 2H), 4.19 (s, 2H), 3.27 (t, J = 5.6 Hz, 2H), 3.016 (t, J = 5.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.2, 136.4, 136.2, 135.5, 134.6, 130.5, 128.9, 127.7, 126.7, 126.4, 126.1, 125.6, 123.7, 122.3, 121.9, 119.9, 119.3, 119.2, 116.2, 110.9, 54.9, 51.1, 29.7, 26.2; *m/z* (ESI-MS) 337.3 $[M-H]^+$.



2-(2-(di(1H-indol-3-yl)methyl)phenyl)-1,2,3,4-tetrahydroisoquinoline (10a): A round bottom flask was charged with indole (1.00 mmol, 2.0 equiv), **9a** (0.500 mmol, 1.0 equiv), 5.00 mL of absolute EtOH, 48% aqueous HBF_4 (0.600 mmol, 1.2 equiv), and a Teflon stir bar. The reaction mixture was stirred at room temperature. After 48 hours, a brilliant orange precipitate formed. EtOH was removed in vacuo, and the reaction was worked up following the general procedures. Compound **10a** was obtained in 62% yield as an off-white solid. R_f = 0.18 (Hexanes/CH_2Cl_2 1:1 v/v); mp = 154–158 ºC; IR (KBr) 3405, 3052, 2892, 2804, 1604, 1487, 1454, 1417, 1373, 1340, 1281, 1214, 1148, 1089, 1048, 1009, 936, 862, 744, 595, 465, 428 cm^{-1}; ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 9.97 (br s, 2H), 7.41 (app dd, J = 7.8, 0.8 Hz, 1H), 7.37 (app d, J = 8.1 Hz, 2H), 7.33 (app dd, J = 8.1, 0.8 Hz, 1H), 7.30 (app d, J = 7.6 Hz, 2H), 7.21 (app td, J = 7.6, 1.6 Hz, 1H), 7.12–6.99 (comp, 6H), 6.89 (app d, J = 7.8 Hz, 1H), 6.85–6.82 (comp, 4H), 6.60 (s, 1H) 4.20 (s, 2H), 3.19 (t, J = 5.7 Hz, 2H), 2.90 (t, J = 5.7 Hz, 2H). ^{13}C NMR (500 MHz, $(CD_3)_2CO$) δ 150.9, 140.3, 137.5, 135.9, 134.6, 130.6,



128.9, 127.6, 126.8, 126.6, 126.2, 125.7, 123.7, 123.6, 121.4, 120.3, 120.0, 119.6, 118.6, 111.4, 55.2, 51.7, 33.2, 30.0; *m/z* (ESI-MS) 454.1 $[M+H]^+$.



Compound **10a** was further characterized by X-Ray crystallography. Suitable colorless crystals were grown from the vapor phase of a CH_2Cl_2/ether solution of the compound at room temperature over one day. The requisite CIF has been submitted to the journal.

References:

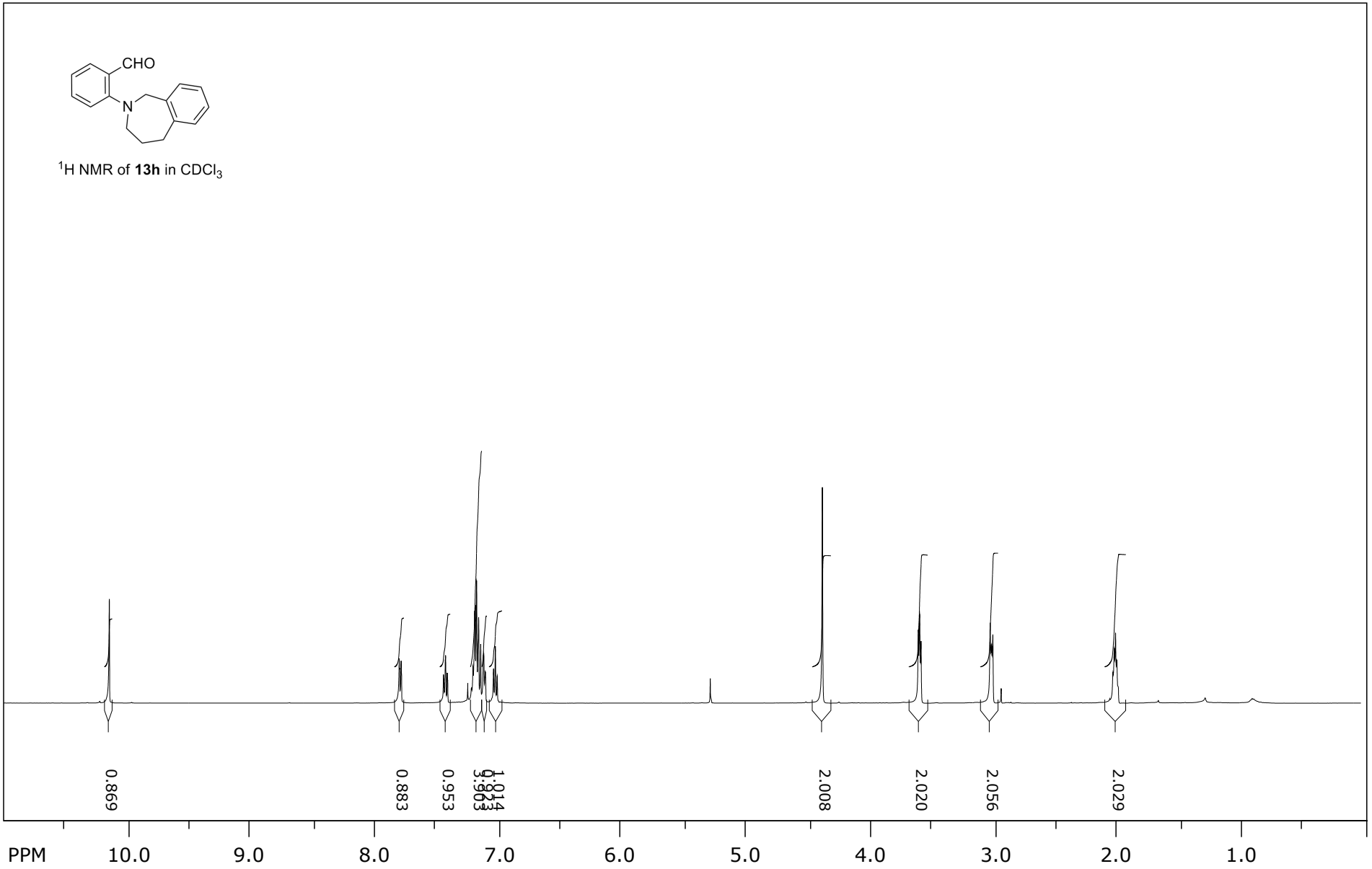
(1) Nijhuis, W. H. N.; Leus, G. R. B.; Egberink, R. J. M.; Verboom, W.; Reinhoudt, D. N. *Recl. Trav. Chim. Pays–Bas.* **1989**, *108*, 172–178.

(2) Nijhuis, W. H. N.; Verboom, W.; Abuelfadl, A.; Harkema, S.; Reinhoudt, D. N. *J. Org. Chem.* **1989**, *54*, 199–209.

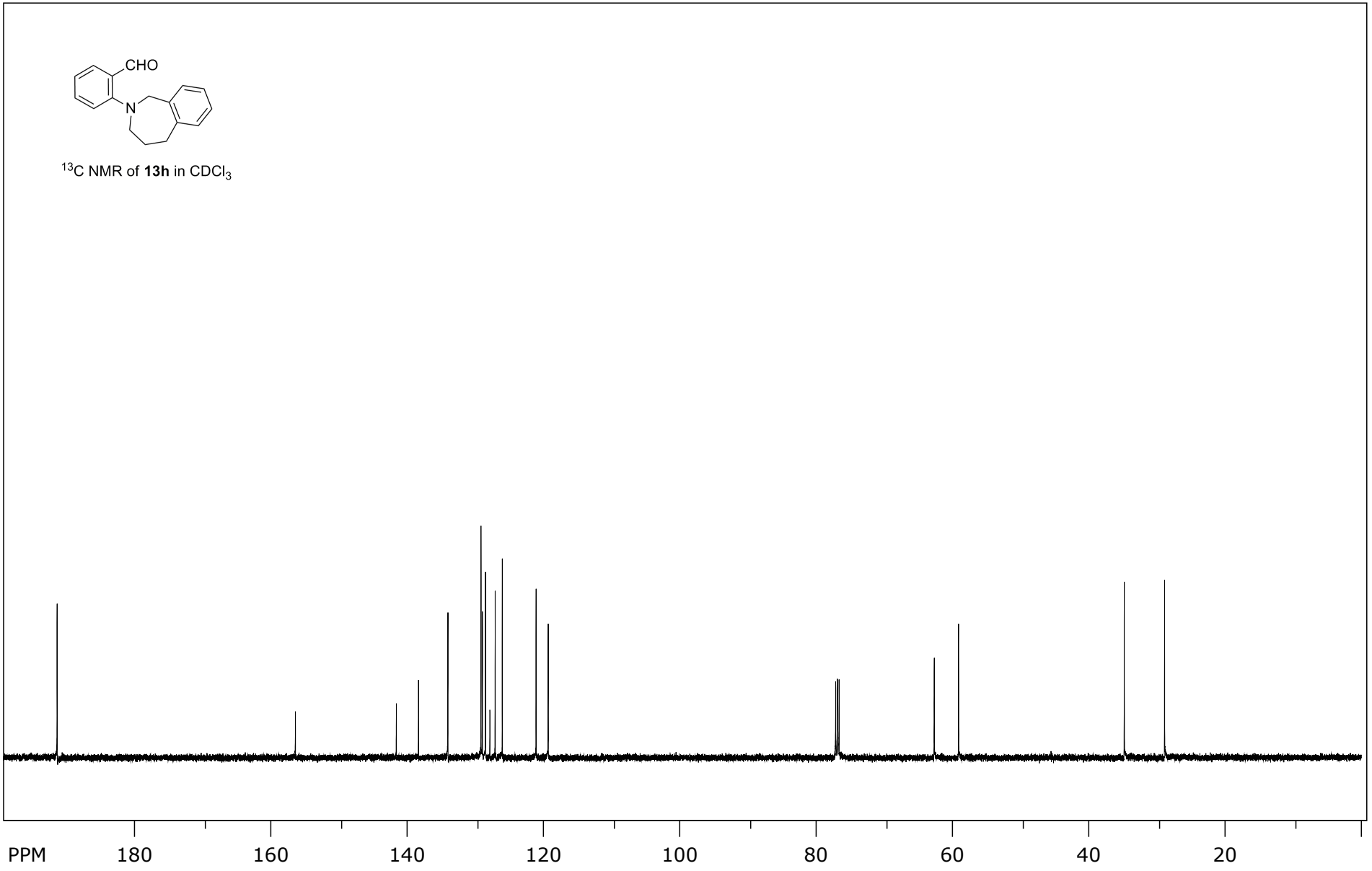
(3) D'yachenko, E. V.; Glukhareva, T. V.; Nikolaenko, E. F.; Tkachev, A. V.; Morzherin, Yu. Yu. *Russ. Chem. Bull.* **2004**, *53*, 1240–1247.

(4) Murarka, S.; Deb, I.; Zhang, C.; Seidel, D. *J. Am. Chem. Soc.* **2009**, *131*, 13226–13227.

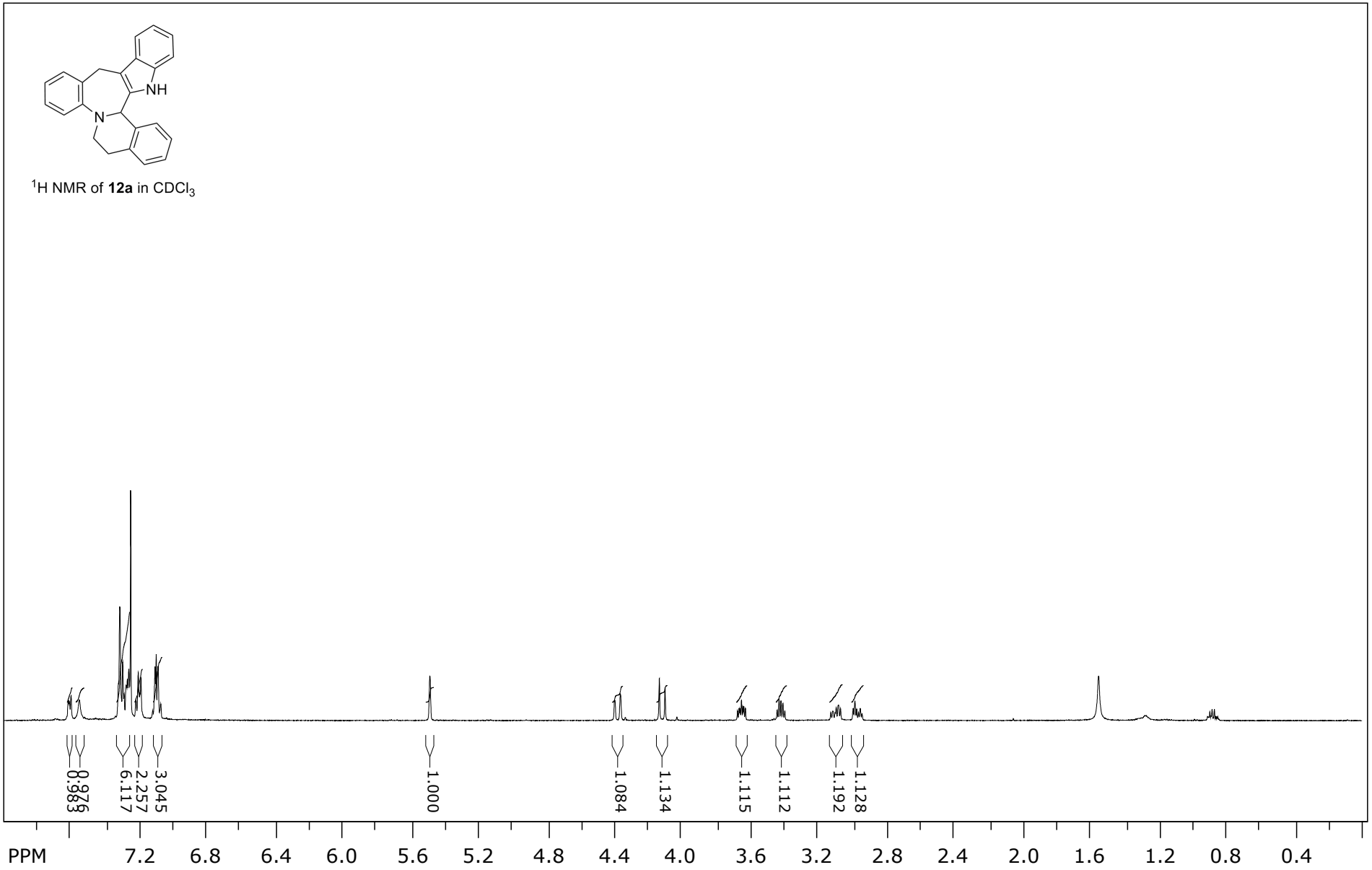
(5) Grunewald, G. L.; Dahunkar, V. H.; Ching, P.; Criscione, K. R. *J. Med. Chem.* **1996**, *39*, 3539–3546.

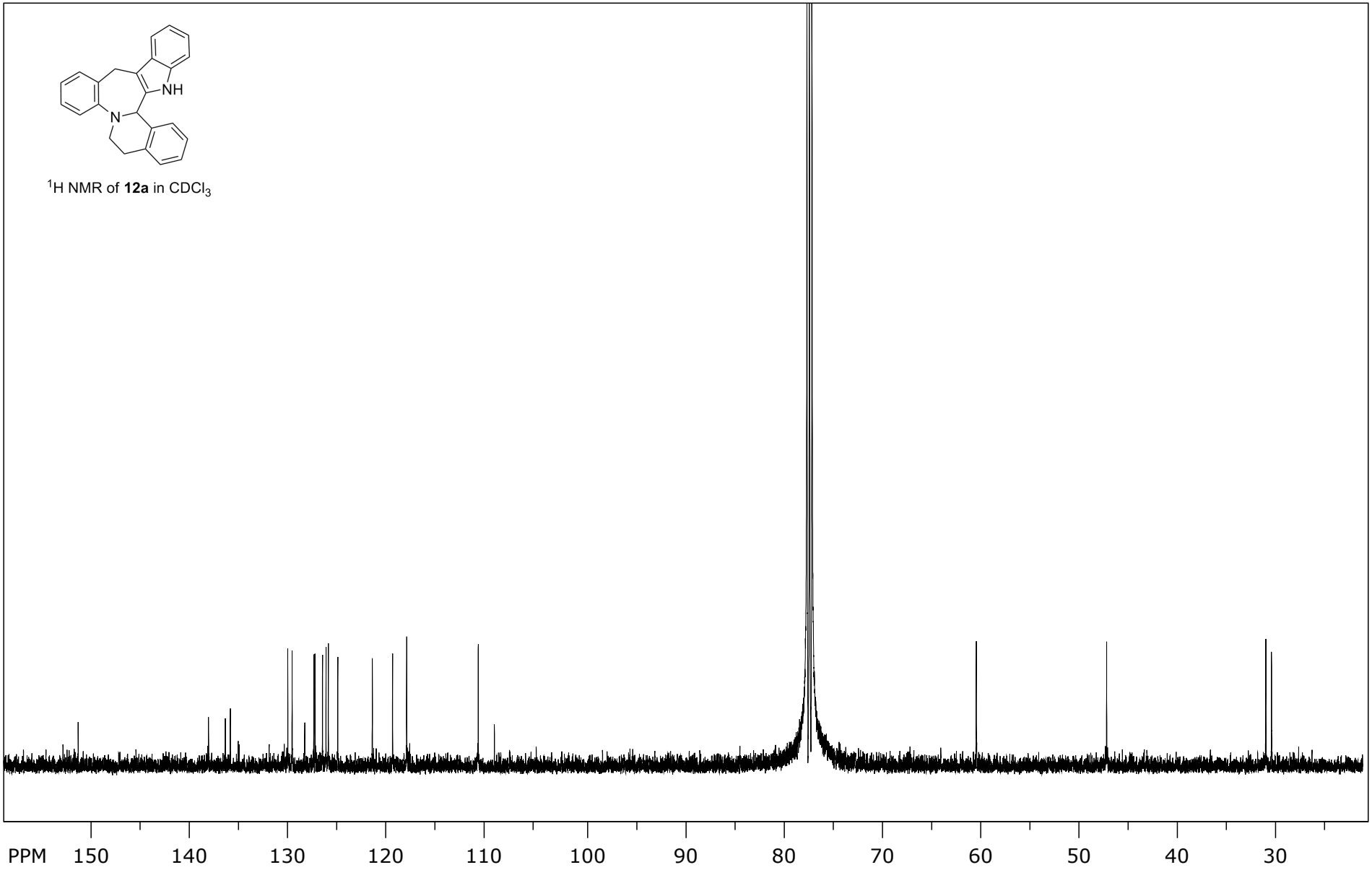


^{1}H NMR of **13h** in $CDCl_3$

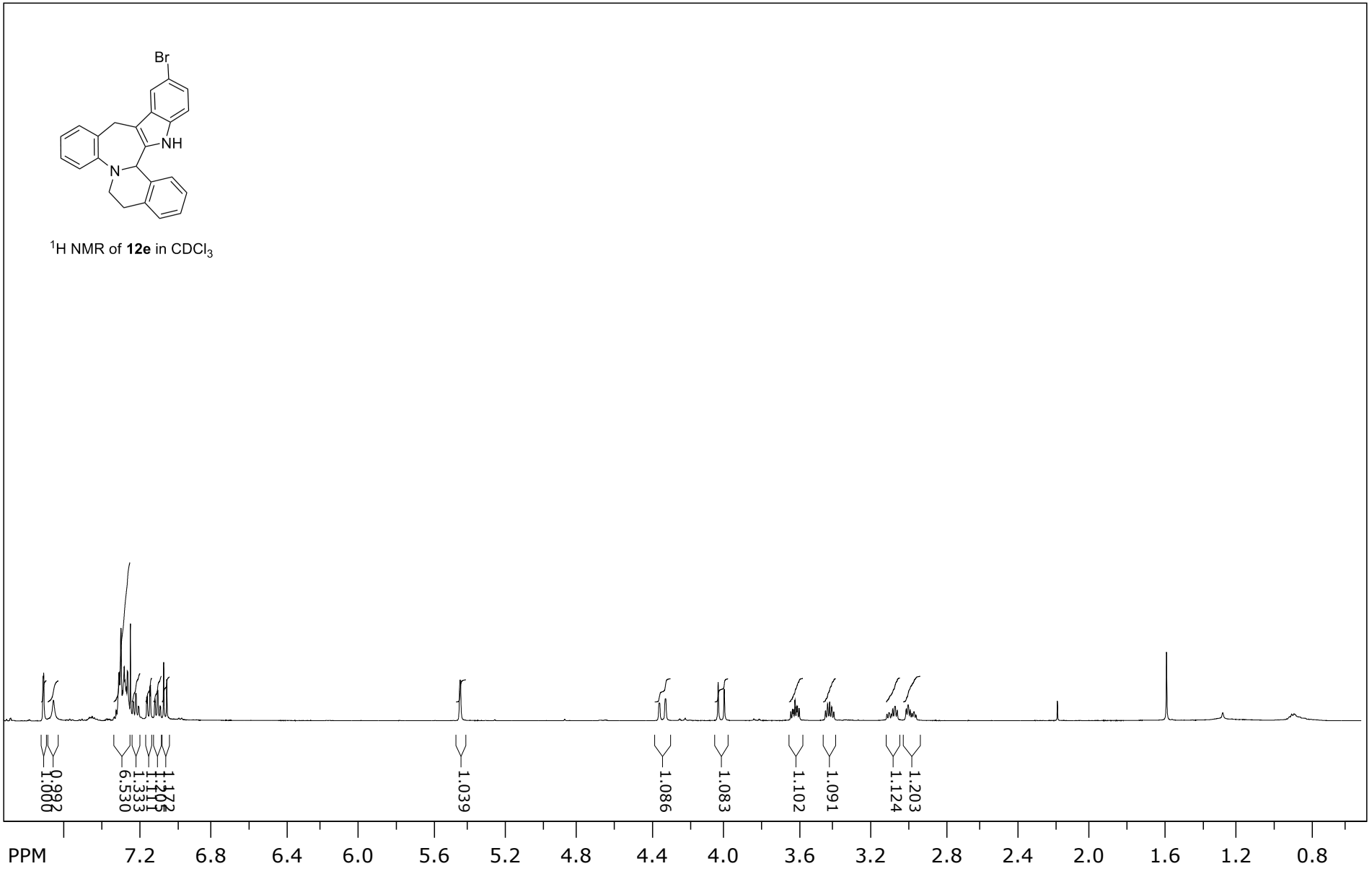


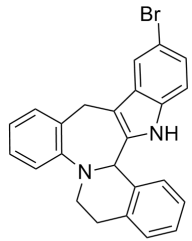
^{13}C NMR of **13h** in $CDCl_3$


NH
N
1H NMR of 12a in CDCl3
0.983
0.976
6.117
2.257
3.045
1.000
1.084
1.134
1.115
1.112
1.192
1.128
PPM
7.2
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
1.6
1.2
0.8
0.4

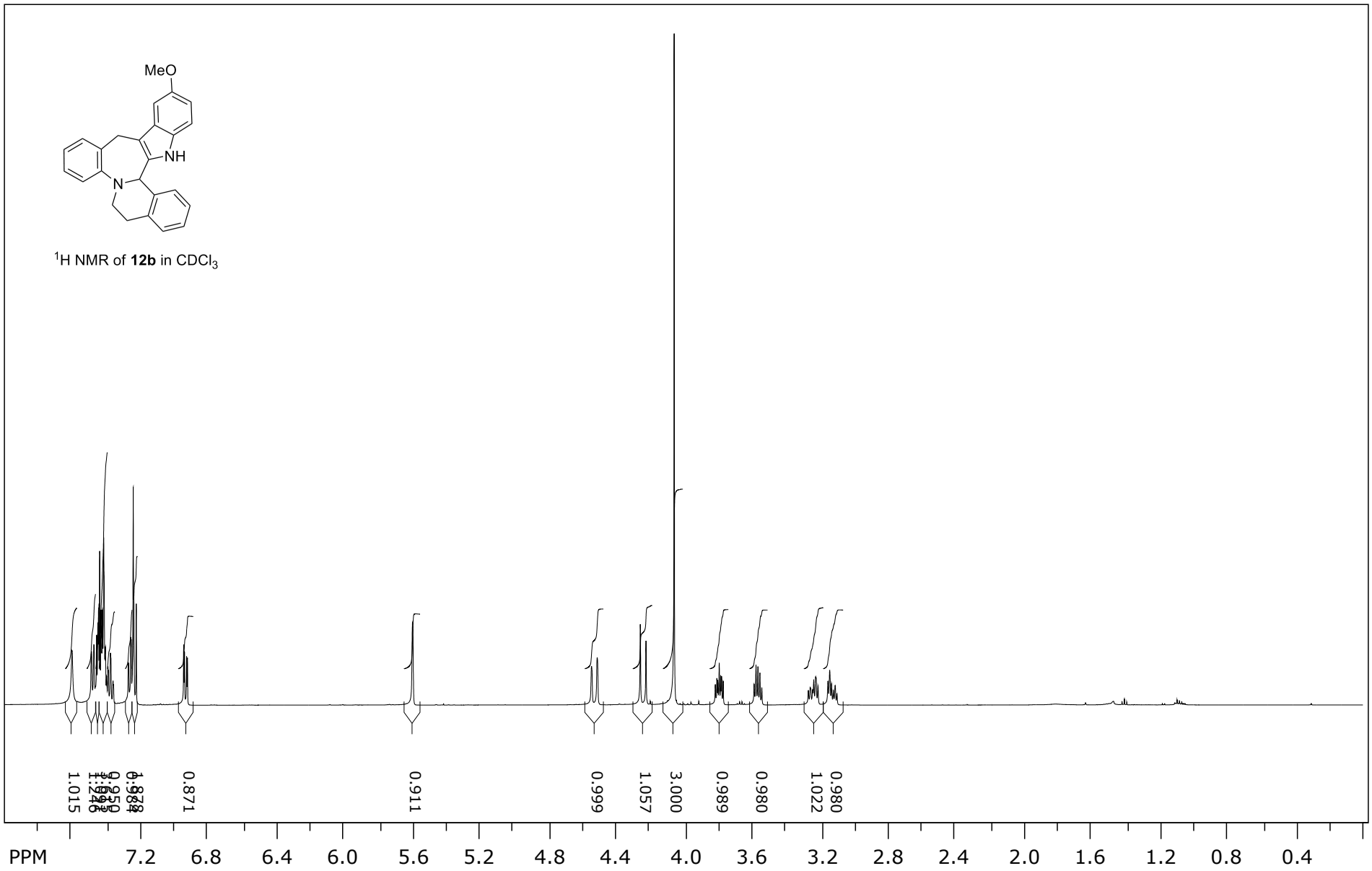


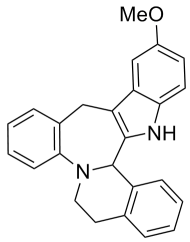
^{1}H NMR of **12a** in $CDCl_3$


Br
NH
N
1H NMR of 12e in CDCl3
1.000
0.886
6.530
1.333
1.039
1.086
1.083
1.102
1.091
1.124
1.203
PPM
7.2
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
1.6
1.2
0.8

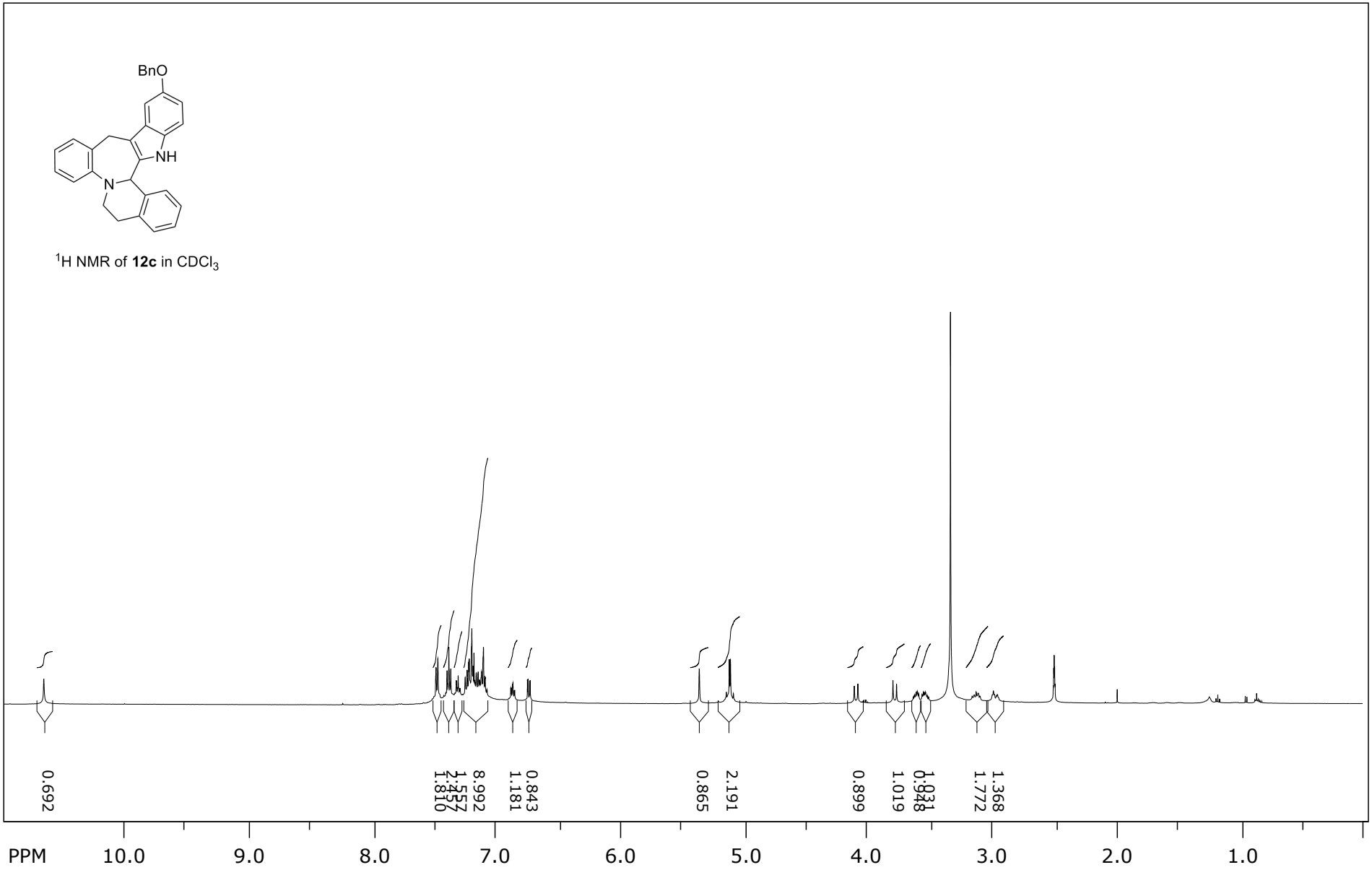


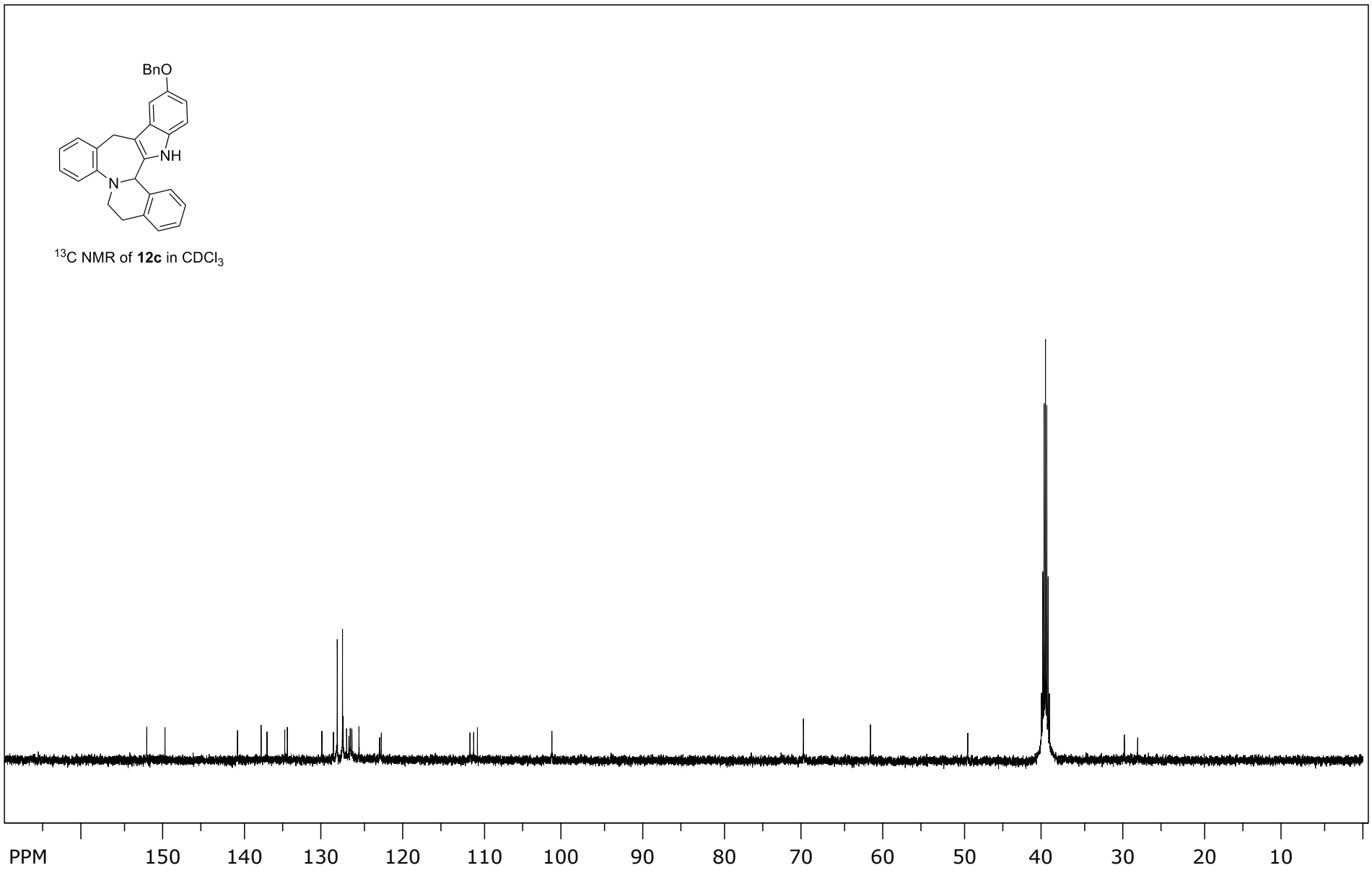
^{13}C NMR of **12e** in $CDCl_3$


MeO
NH
N
1H NMR of 12b in CDCl3
1.015
0.871
0.911
0.999
1.057
3.000
0.989
0.980
1.022
0.980
PPM
7.2
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
1.6
1.2
0.8
0.4

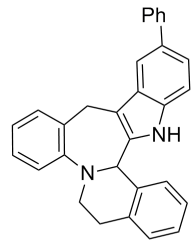


^{13}C NMR of **12b** in $CDCl_3$

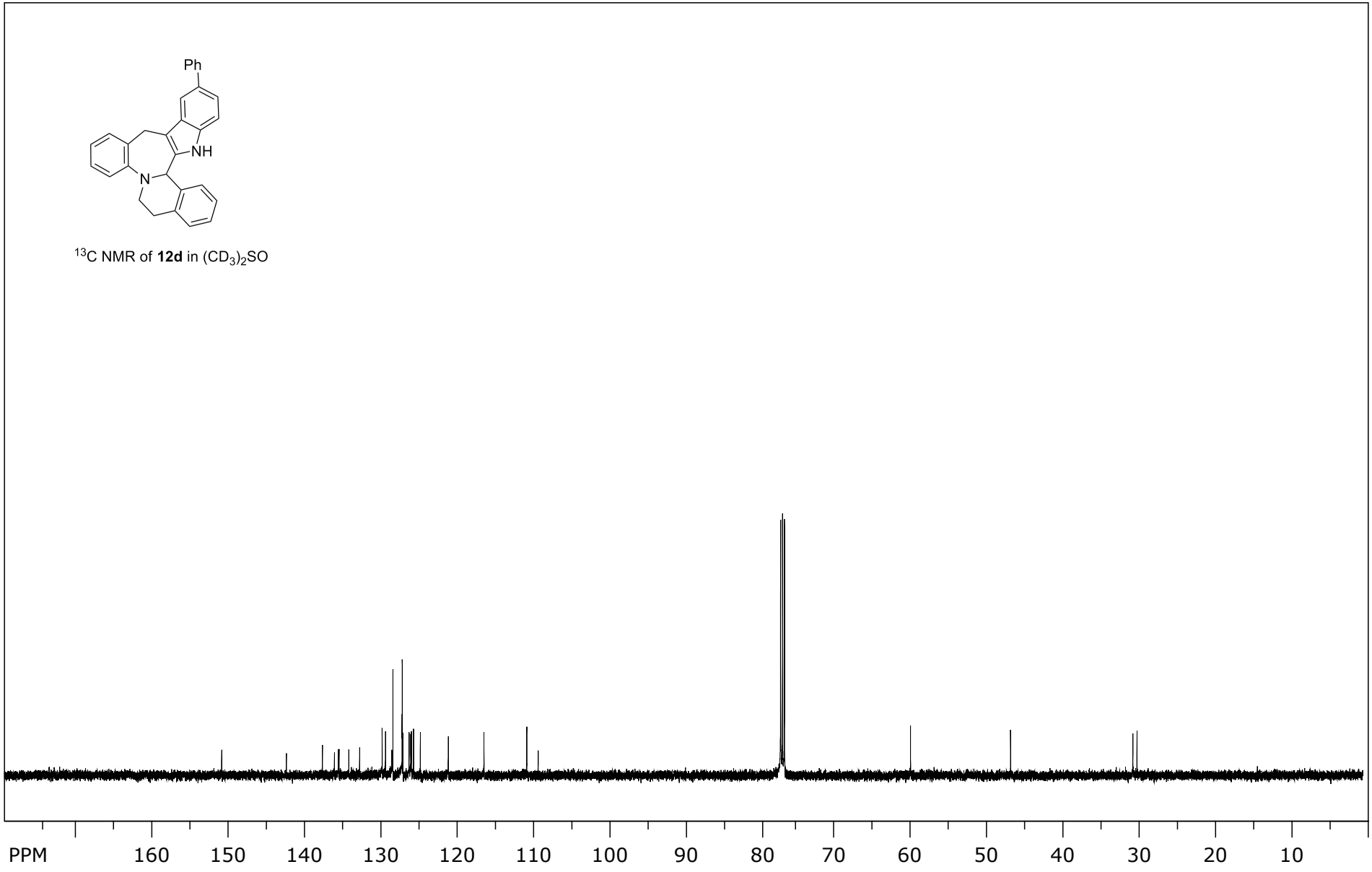

BnO
NH
N
^{1}H NMR of **12c** in $CDCl_3$
0.692
1.810
1.437
1.557
8.992
1.181
0.843
0.865
2.191
0.899
1.019
0.948
1.031
1.772
1.368
PPM
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0



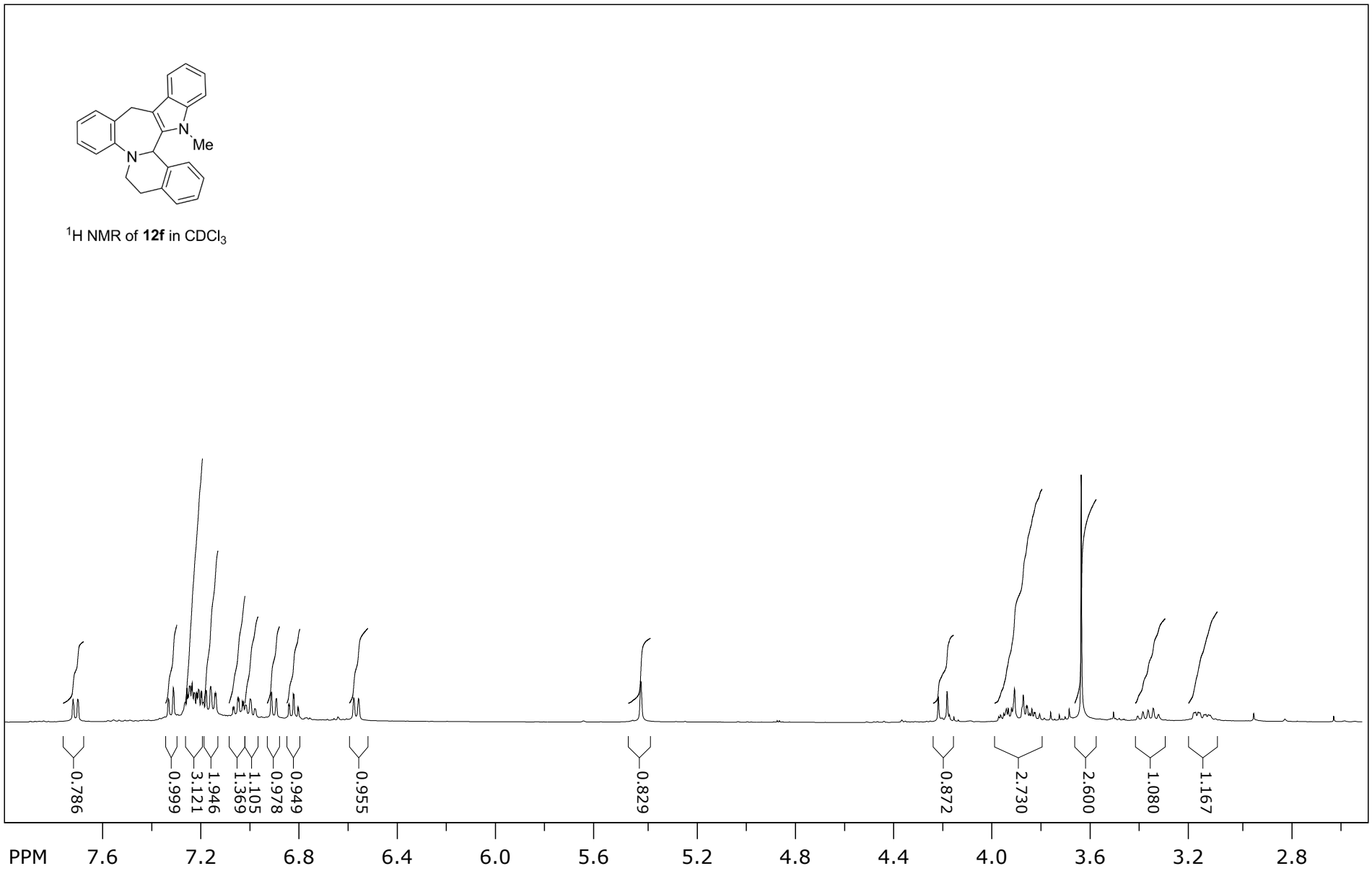
^{13}C NMR of **12c** in $CDCl_3$

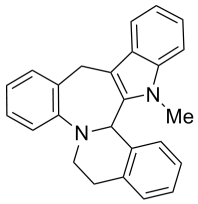


^{1}H NMR of **12d** in $(CD_3)_2SO$

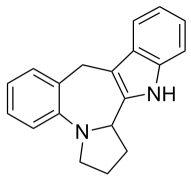


^{13}C NMR of **12d** in $(CD_3)_2SO$

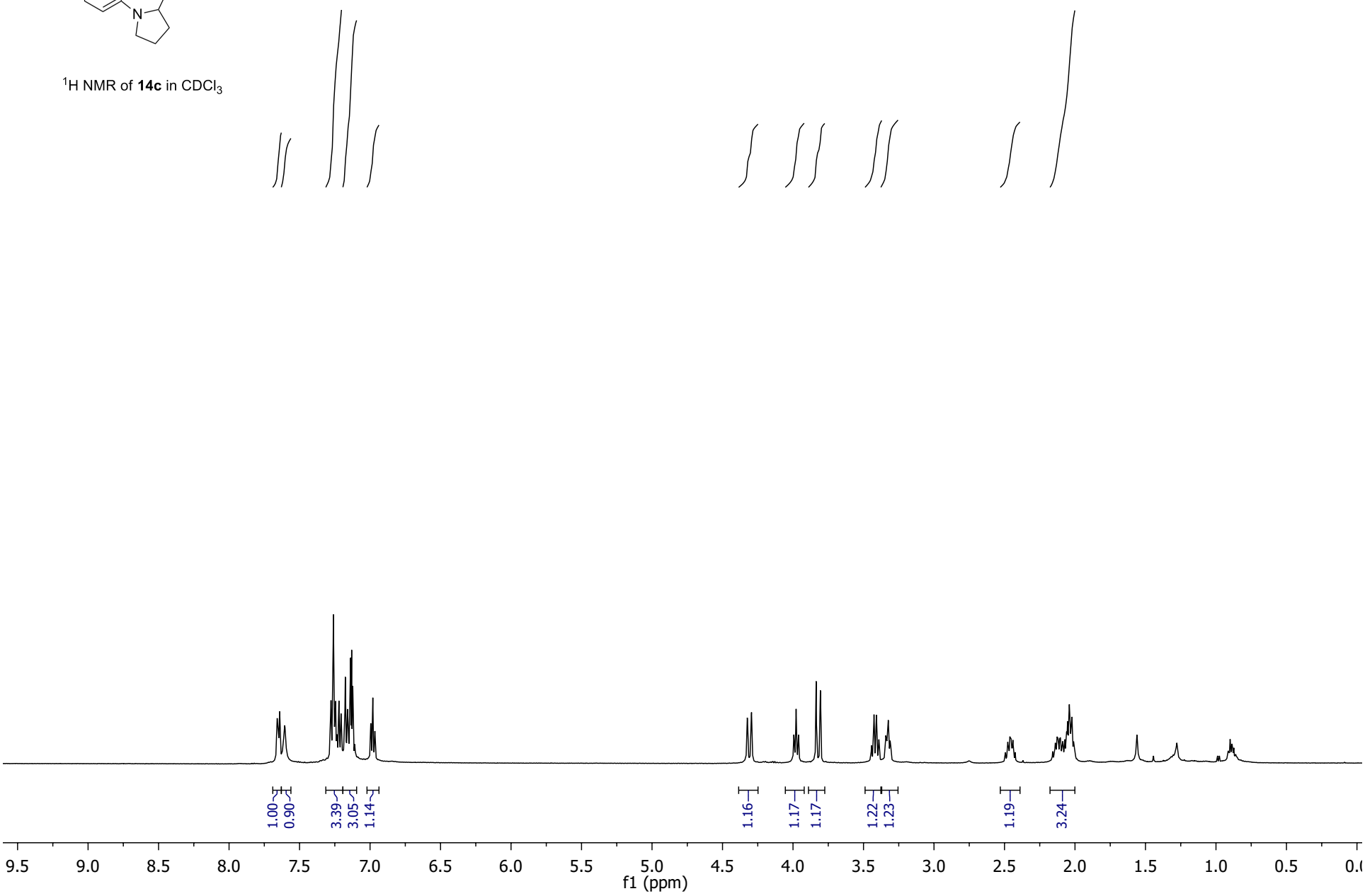

N
Me
N
^{1}H NMR of **12f** in $CDCl_3$
0.786
0.999
3.121
1.946
1.369
1.105
0.978
0.949
0.955
0.829
0.872
2.730
2.600
1.080
1.167
PPM
7.6
7.2
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8

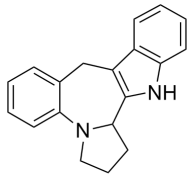


^{13}C NMR of **12f** in $CDCl_3$

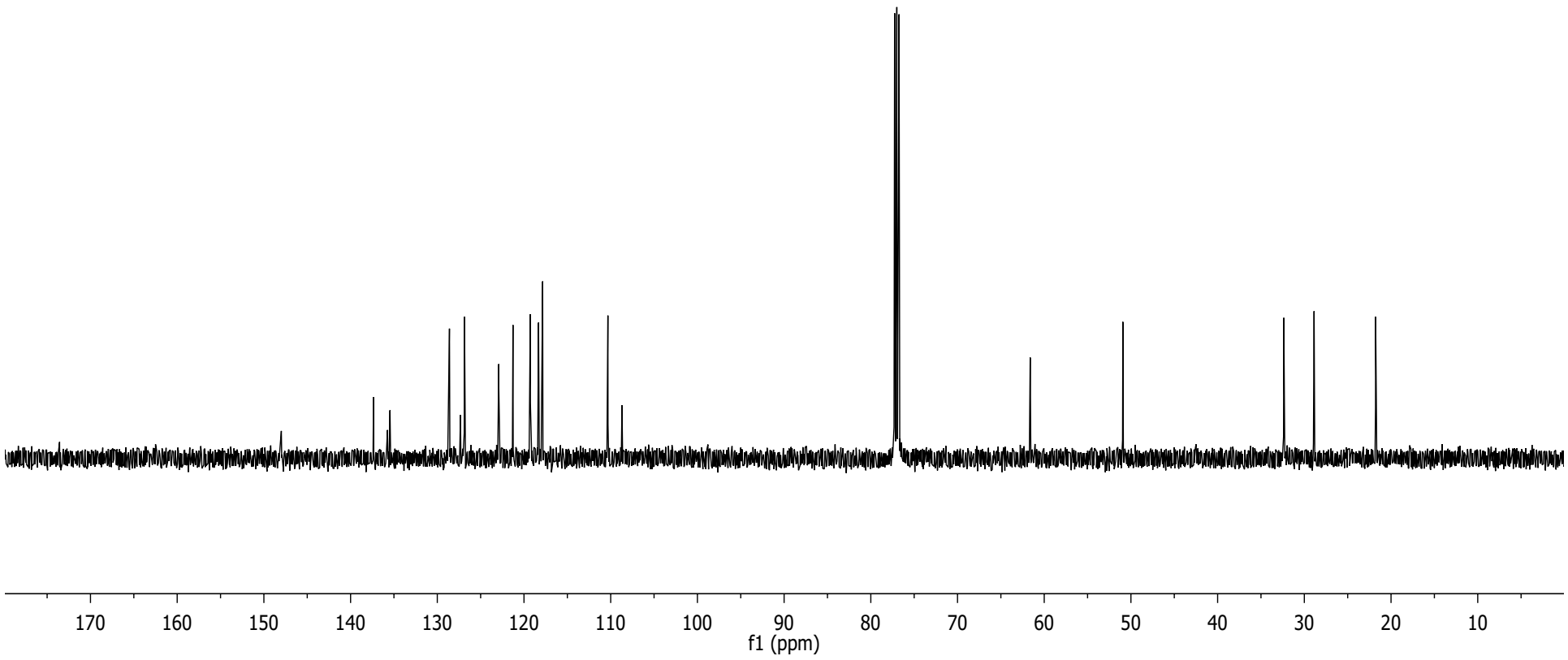


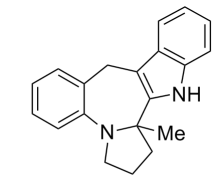
^{1}H NMR of **14c** in $CDCl_3$



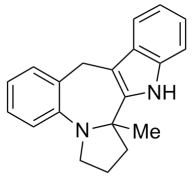


^{13}C NMR of **14c** in $CDCl_3$

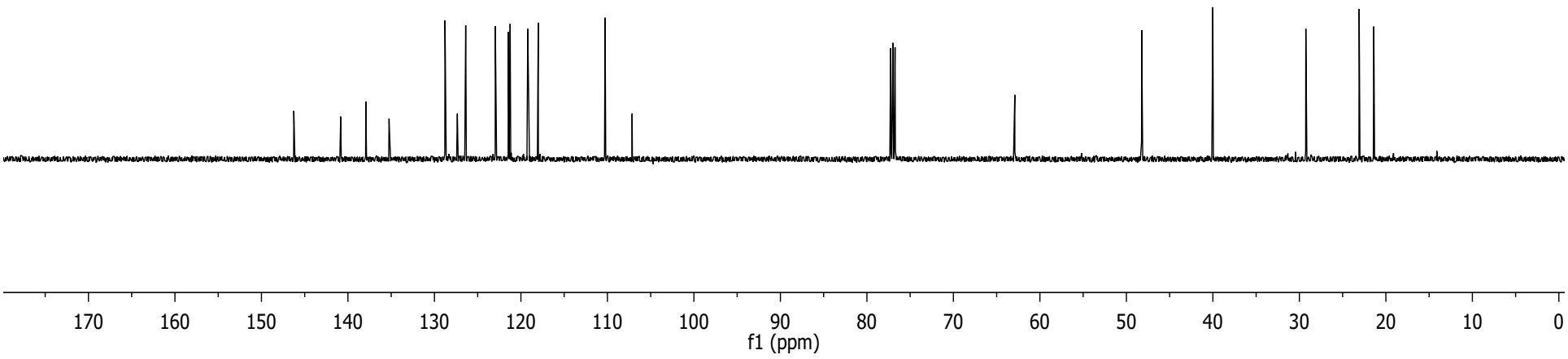


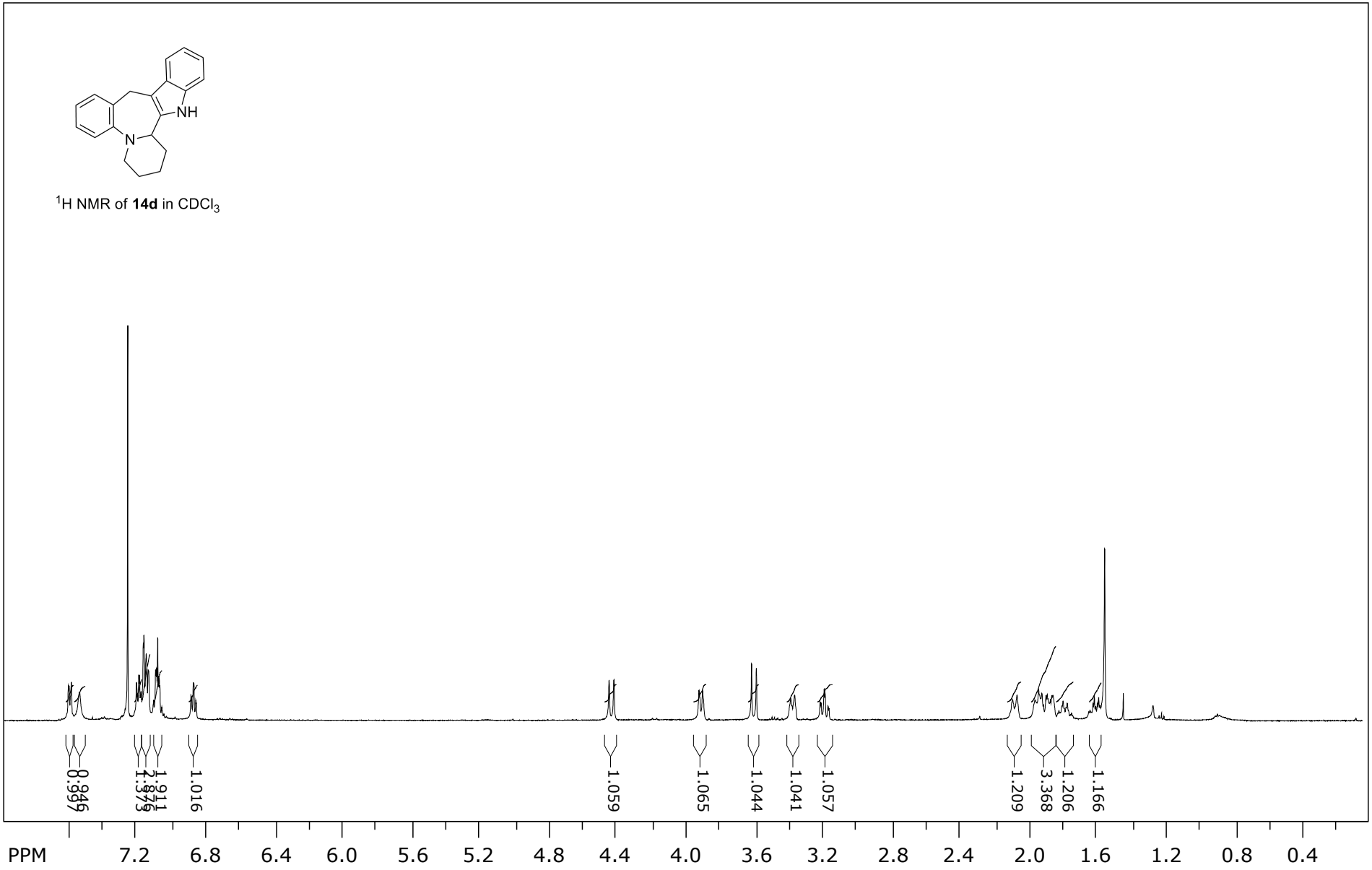


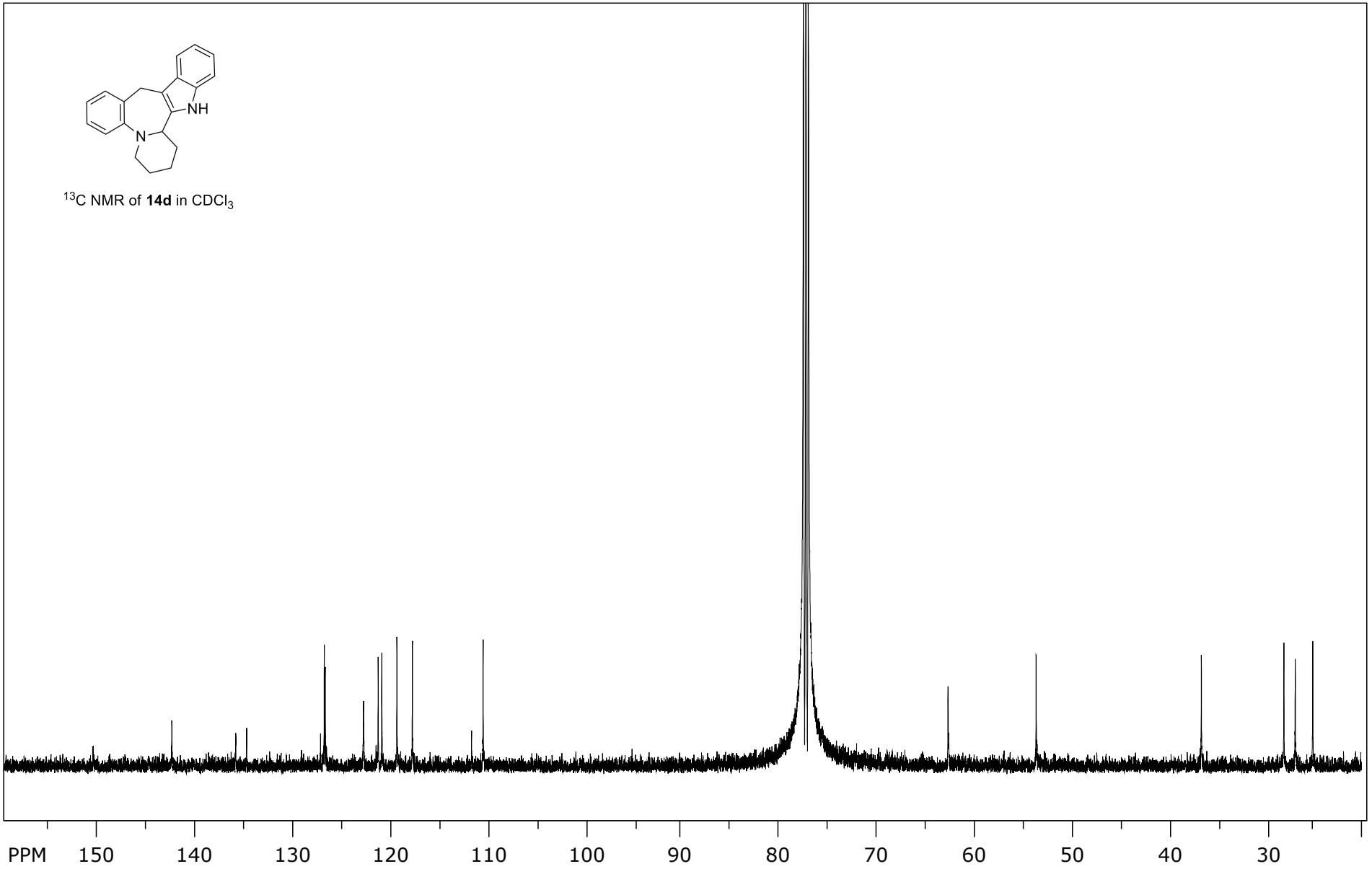
^{1}H NMR of **14e** in $CDCl_3$



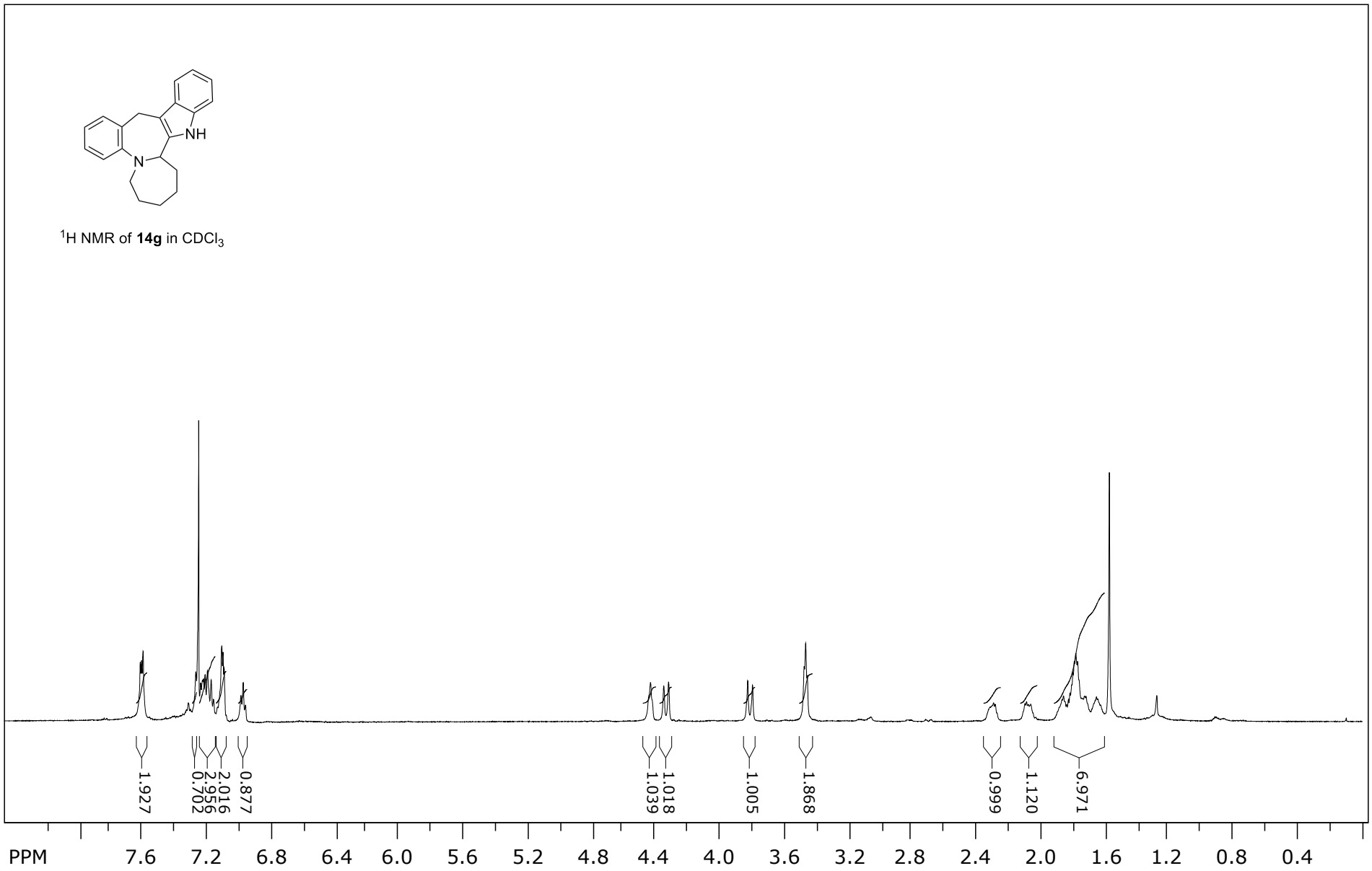
^{13}C NMR of **14e** in $CDCl_3$

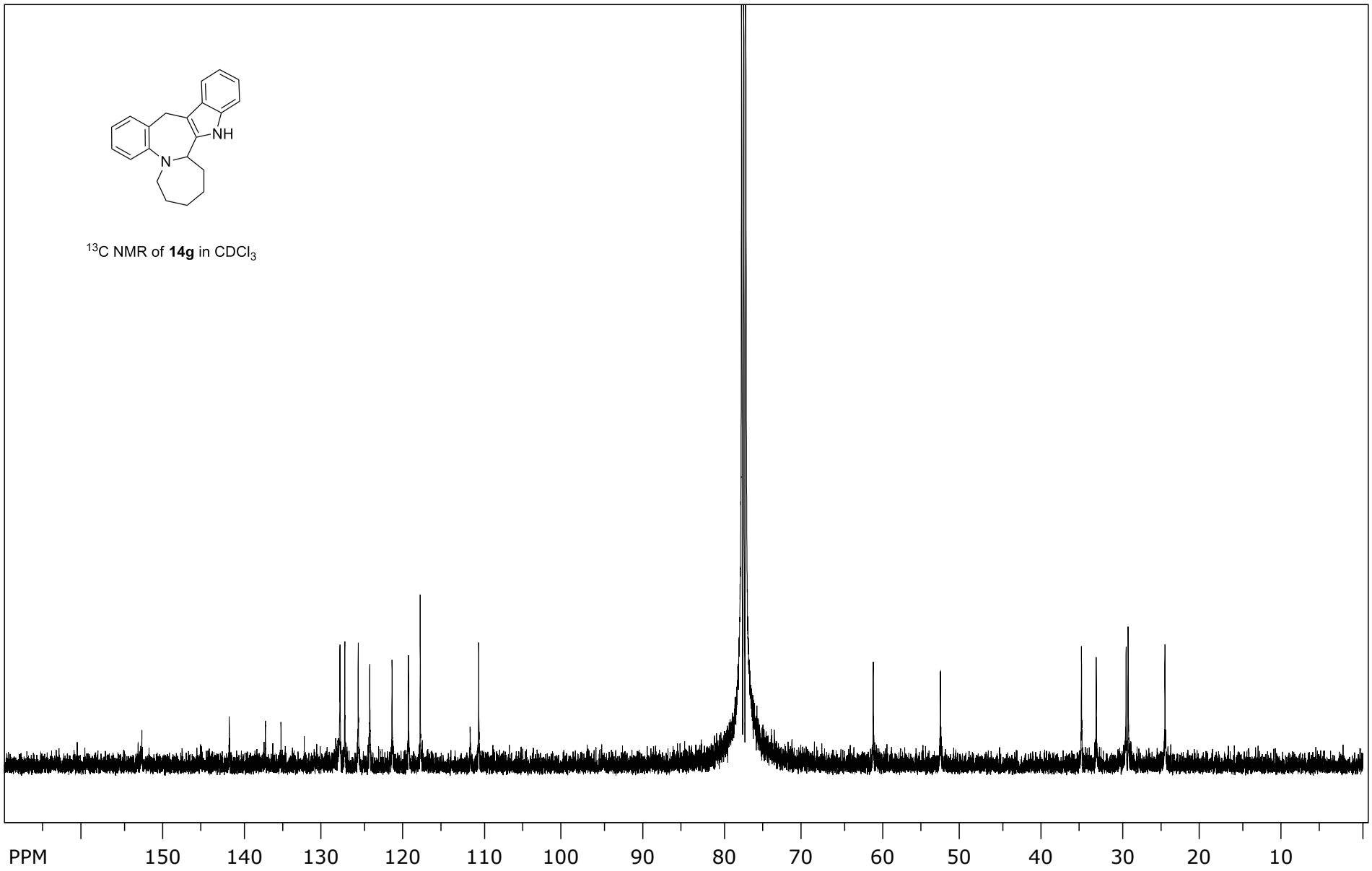



NH
N
^{1}H NMR of **14d** in $CDCl_3$
0.997
0.946
1.373
1.911
1.016
1.059
1.065
1.044
1.041
1.057
1.209
3.368
1.206
1.166
PPM
7.2
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
1.6
1.2
0.8
0.4

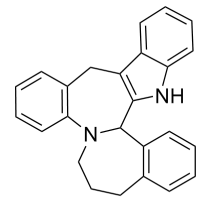


^{13}C NMR of **14d** in $CDCl_3$

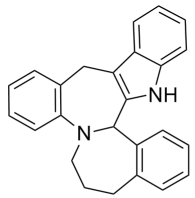

NH
N
1H NMR of 14g in CDCl3
1.927
0.702
2.956
2.016
0.877
1.039
1.018
1.005
1.868
0.999
1.120
6.971
PPM
7.6
7.2
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
1.6
1.2
0.8
0.4



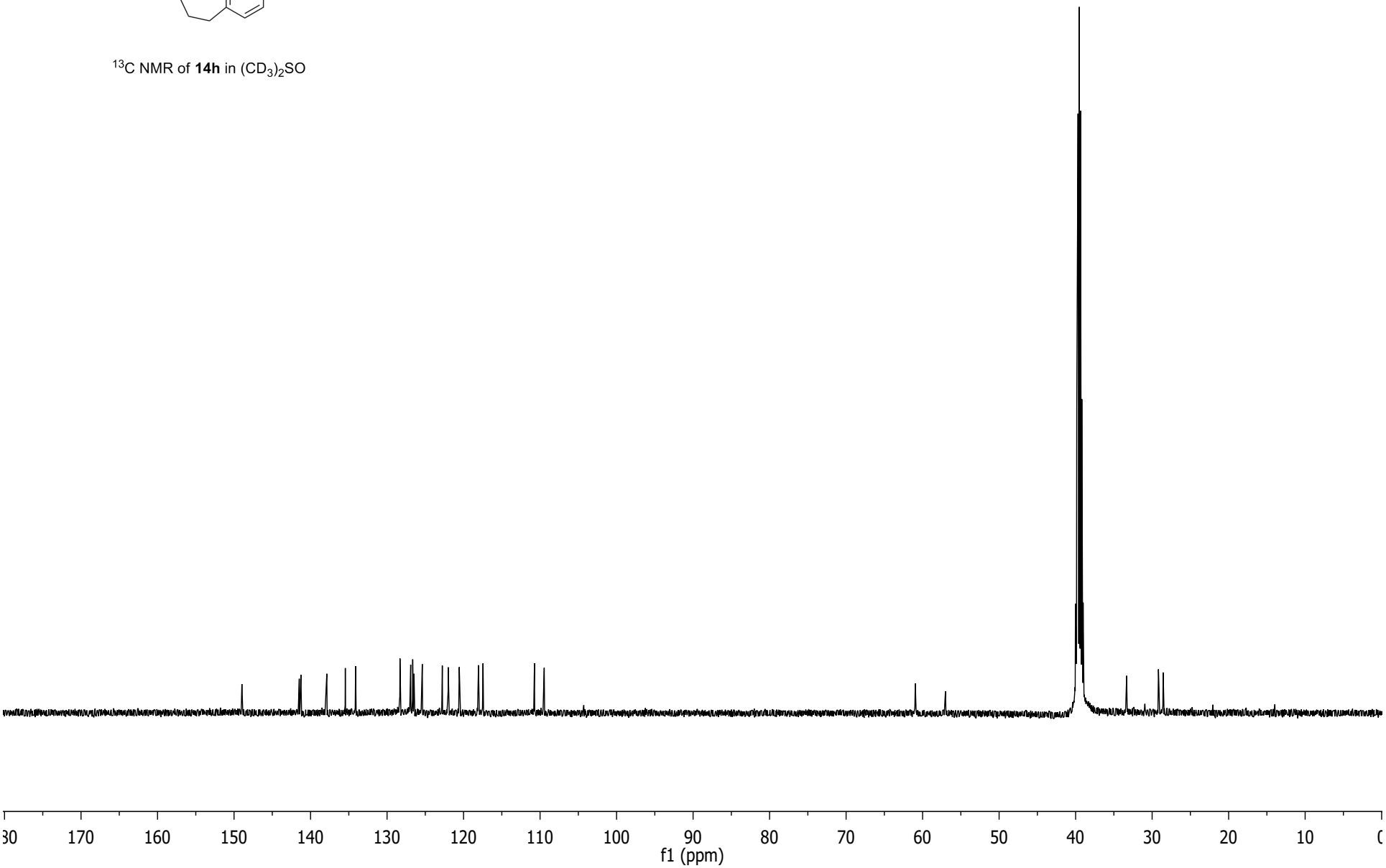
^{13}C NMR of **14g** in $CDCl_3$

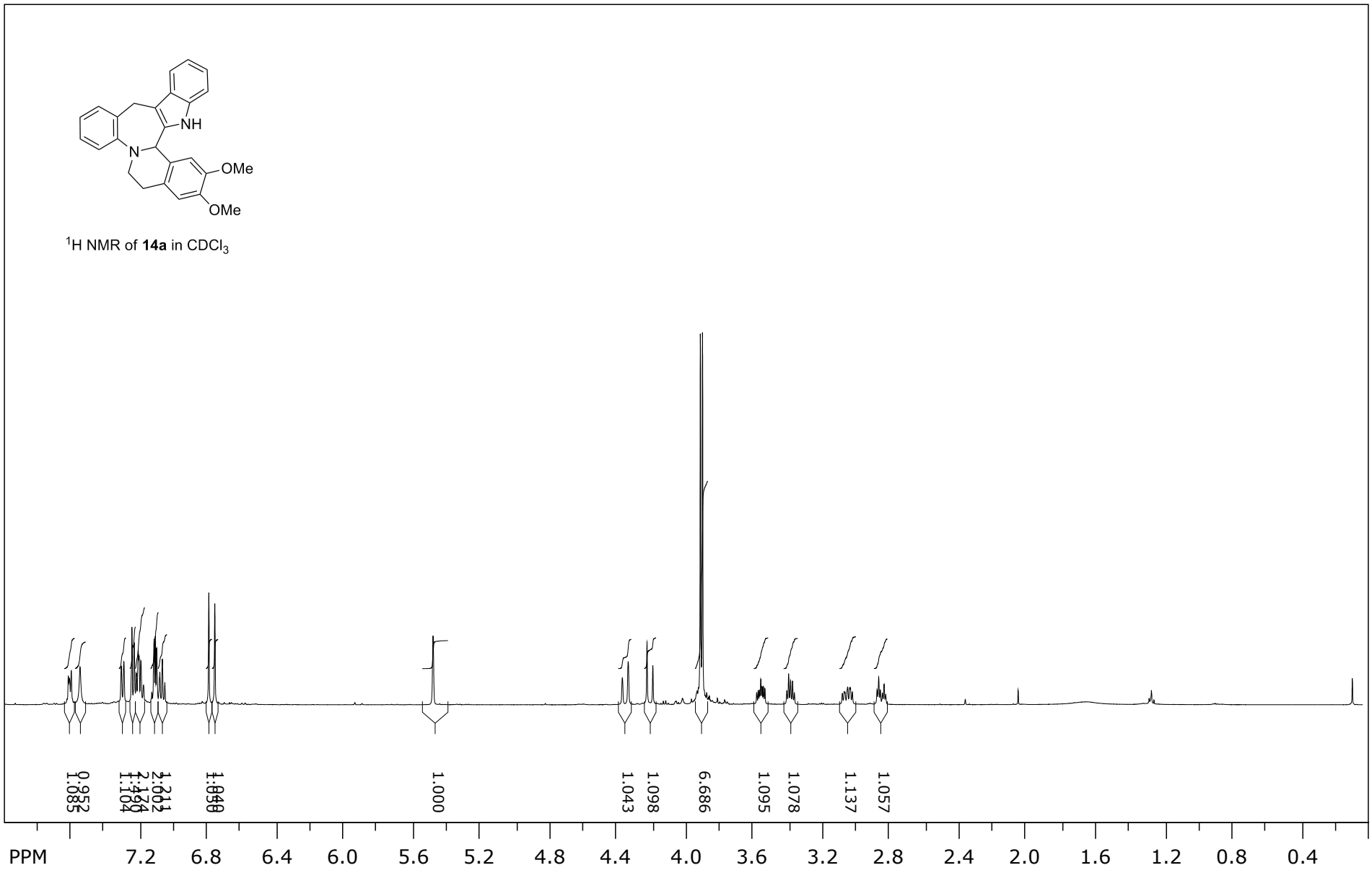


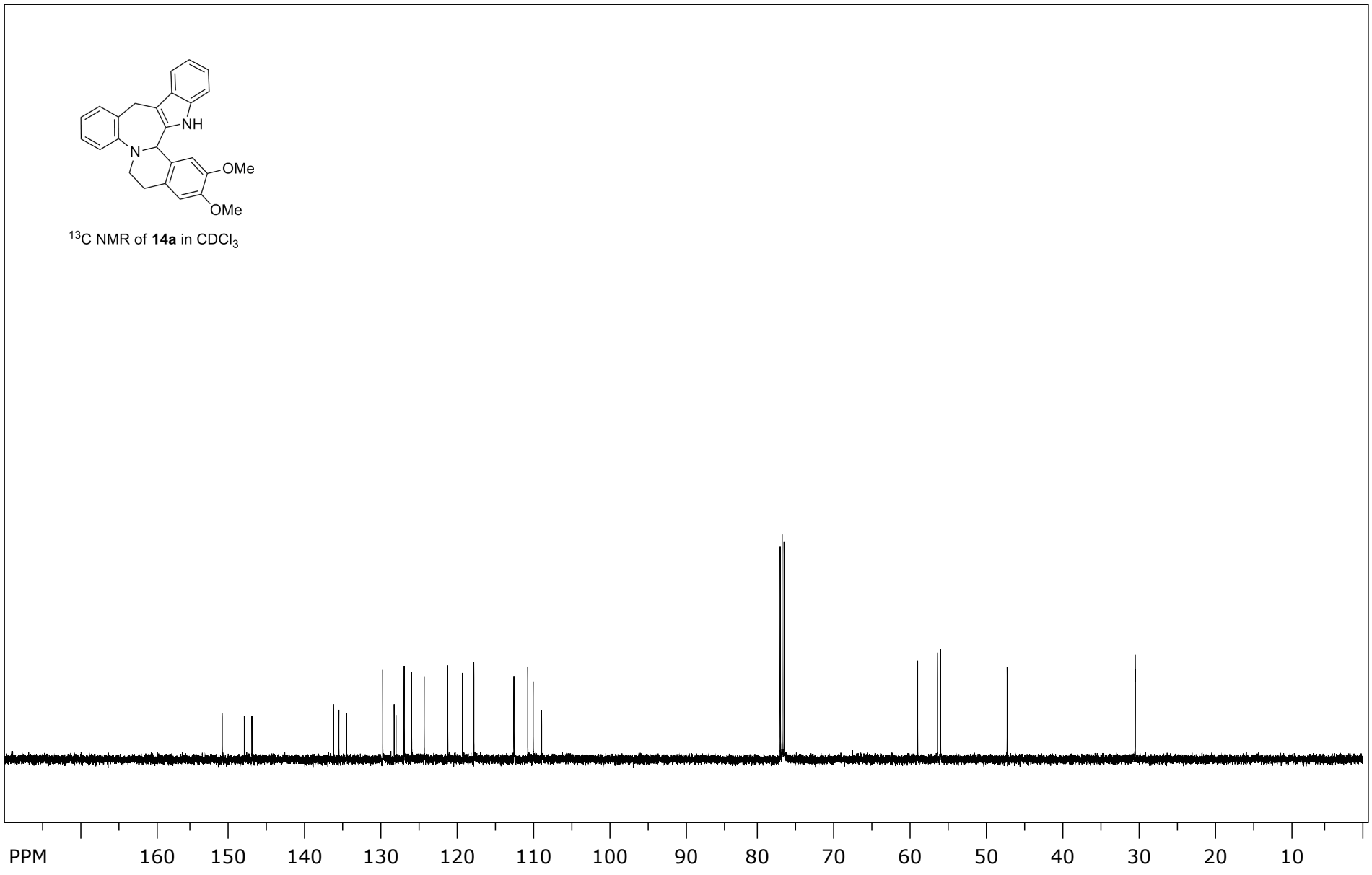
^{1}H NMR of **14h** in $(CD_3)_2SO$



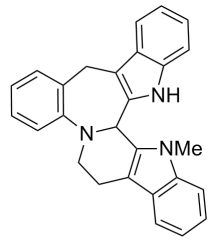
^{13}C NMR of **14h** in $(CD_3)_2SO$



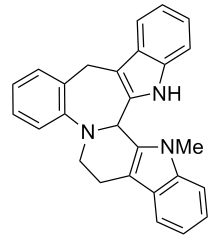

NH
N
OMe
OMe
1H NMR of 14a in CDCl3
0.952
1.085
1.211
1.000
1.043
1.098
6.686
1.095
1.078
1.137
1.057
PPM
7.2
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
1.6
1.2
0.8
0.4



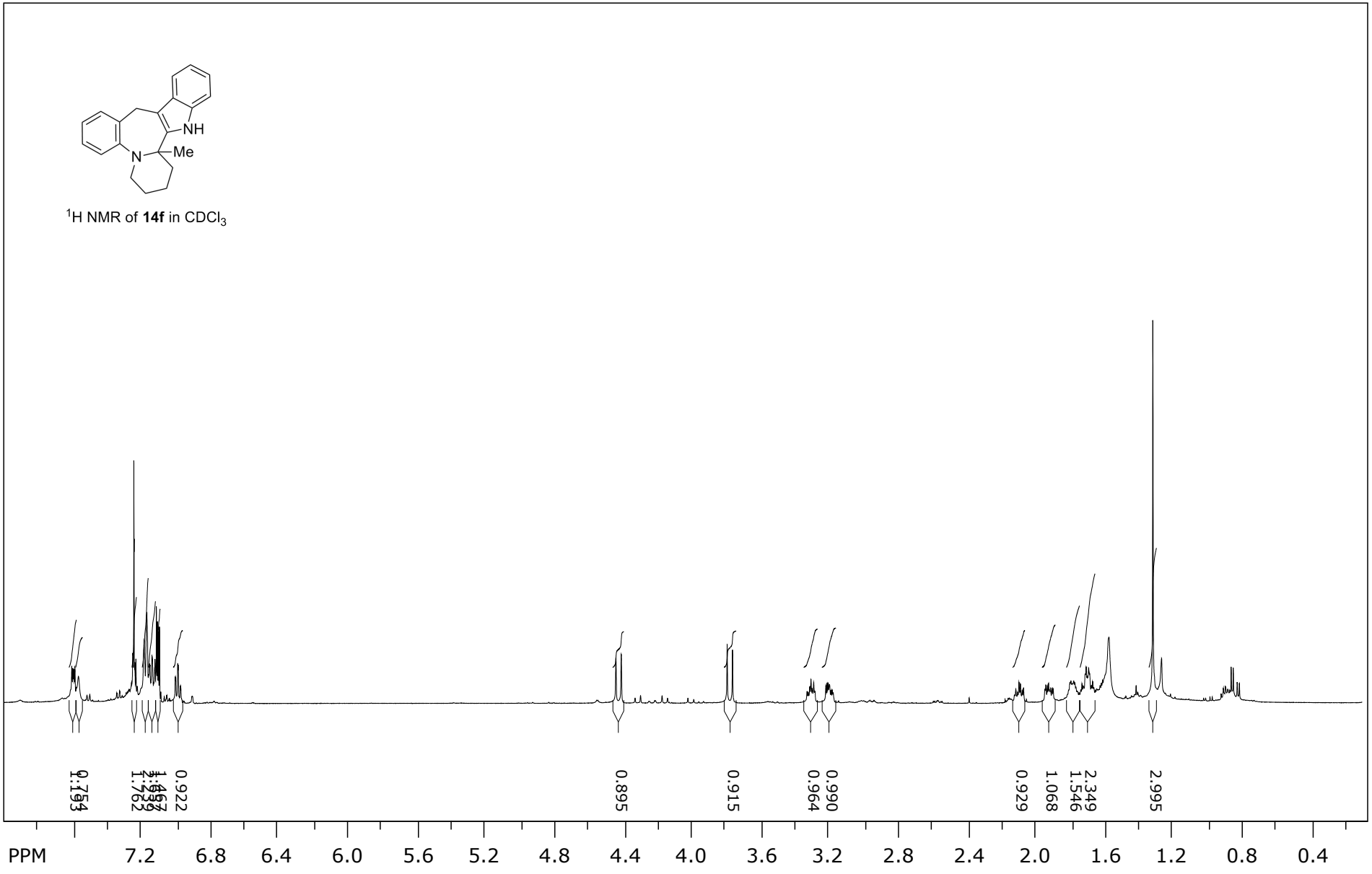
^{13}C NMR of **14a** in $CDCl_3$



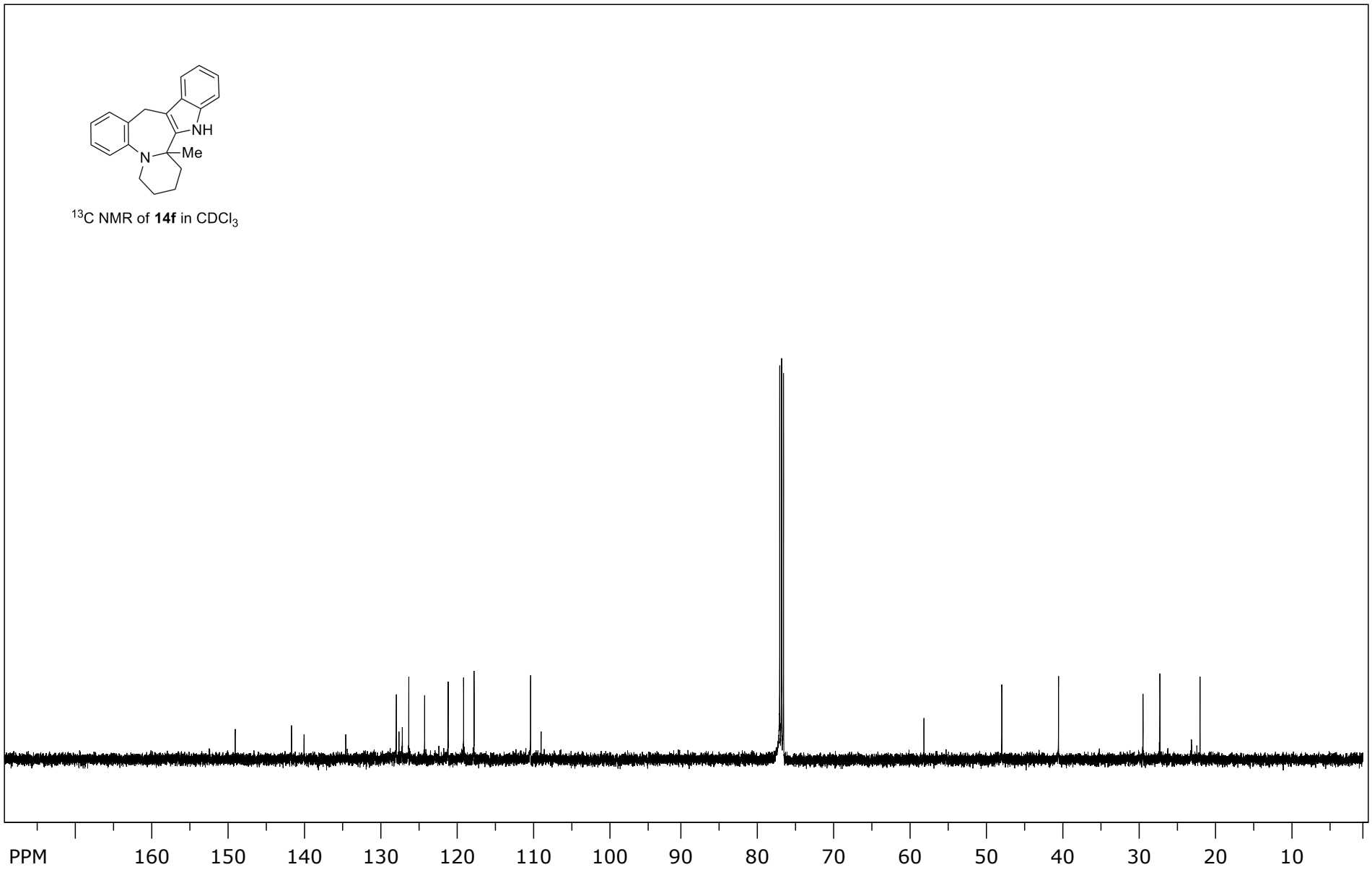
^{1}H NMR of **14b** in $CDCl_3$



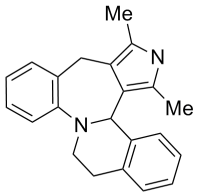
^{13}C NMR of **14b** in $CDCl_3$



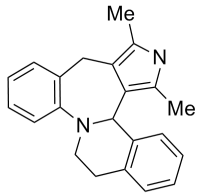
^{1}H NMR of **14f** in $CDCl_3$



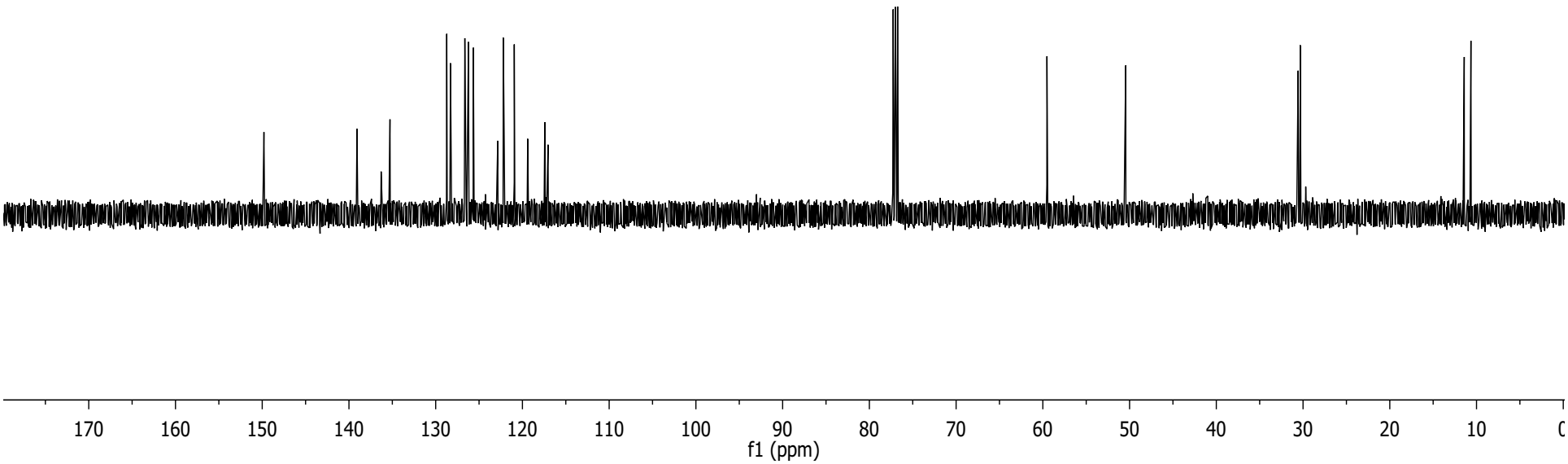
^{13}C NMR of **14f** in $CDCl_3$

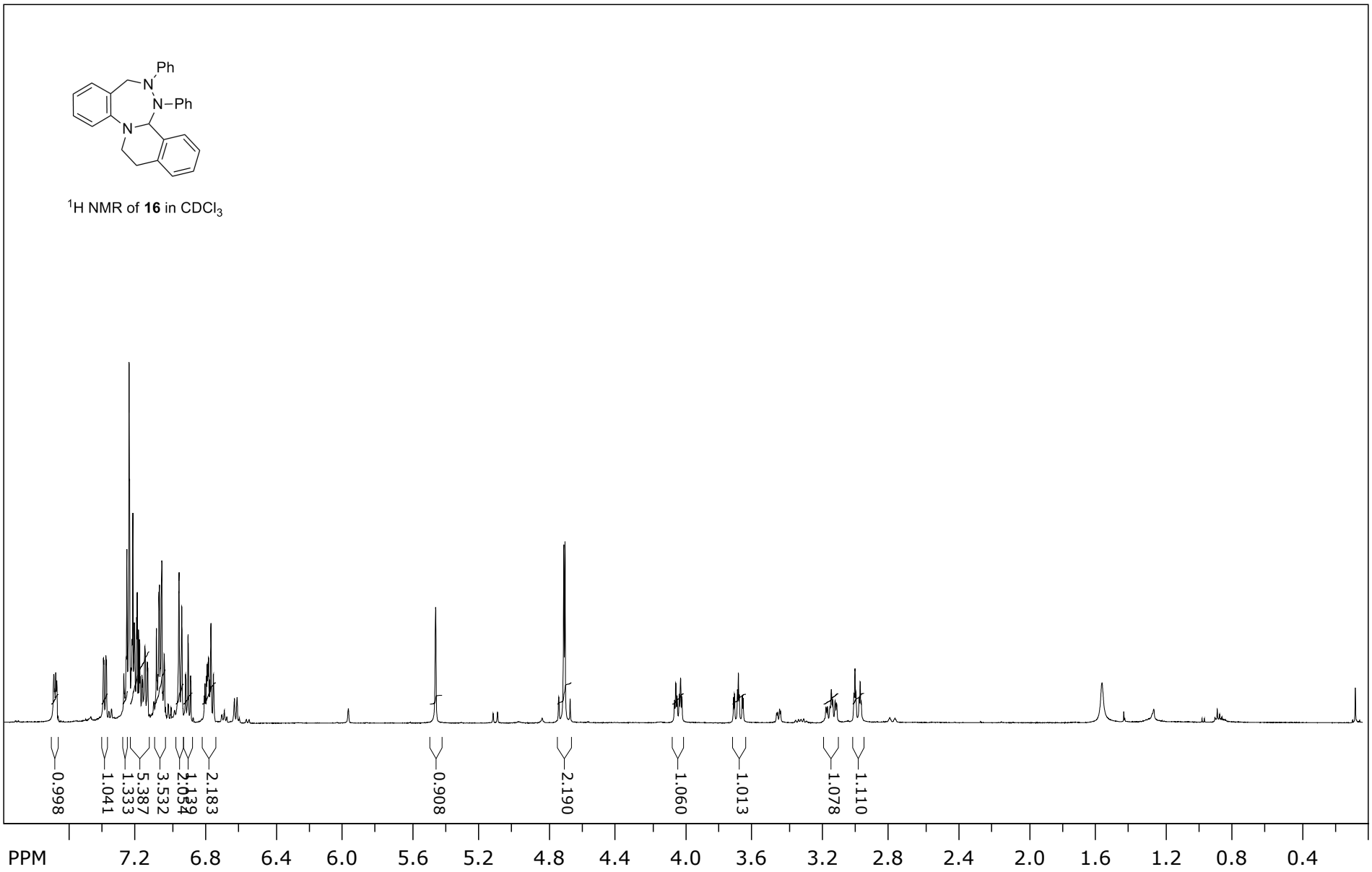


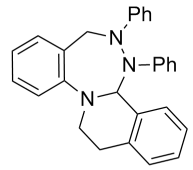
^{1}H NMR of **15** in $CDCl_3$



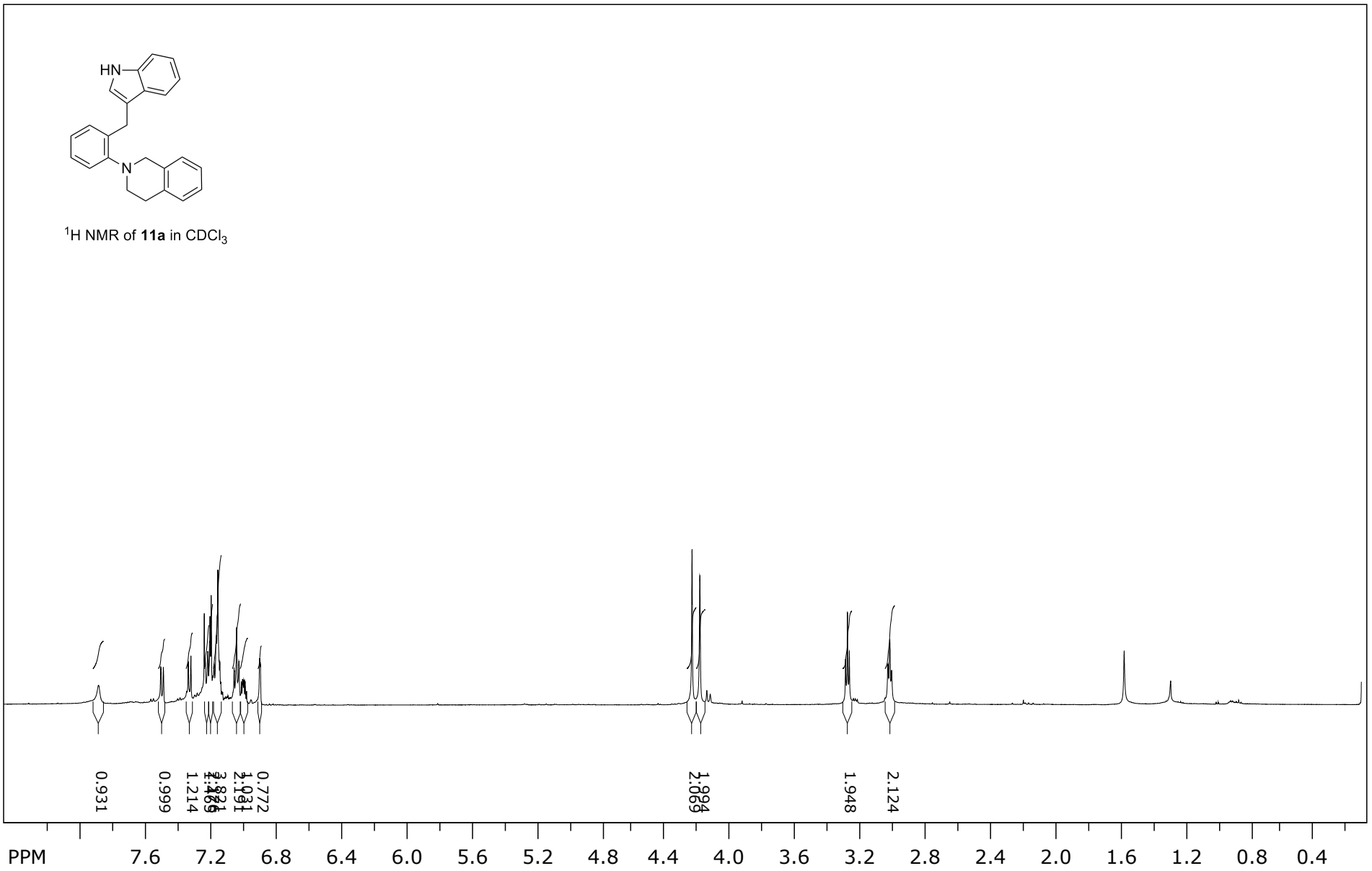
^{13}C NMR of **15** in $CDCl_3$

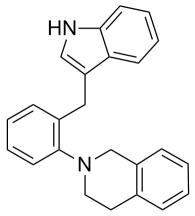



Ph
N
N–Ph
N
^{1}H NMR of **16** in $CDCl_3$
0.998
1.041
1.333
5.387
3.532
2.054
1.139
2.183
0.908
2.190
1.060
1.013
1.078
1.110
PPM
7.2
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
1.6
1.2
0.8
0.4

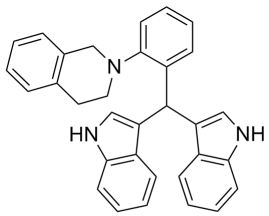


^{13}C NMR of **16** in $CDCl_3$

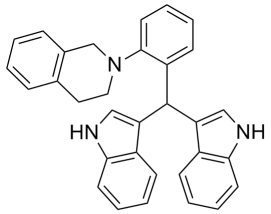

HN
N
^{1}H NMR of **11a** in $CDCl_3$
0.931
0.999
1.214
3.821
1.931
0.772
1.994
2.069
1.948
2.124
PPM
7.6
7.2
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
1.6
1.2
0.8
0.4



^{13}C NMR of **11a** in $CDCl_3$



^{1}H NMR of **10a** in $(CD_3)_2CO$



^{13}C NMR of **10a** in $(CD_3)_2CO$