The Redox-Mannich Reaction

Weijie Chen and Daniel Seidel*

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

Supporting Information

General Information: Starting materials, reagents, and solvents were purchased from commercial sources and used as received unless stated otherwise. Pyrrolidine, 1,2,3,4-tetrahydroisoquinoline, acetophenone, nitroalkanes and 2-ethylhexanoic acid (2-EHA) were distilled prior to use. Benzoic acid, 4-methoxybenzoic acid and 4-(dimethylamino)benzoic acid were recrystallized from toluene/ethanol. All aldehydes were purified by distillation or recrystallization. Purification of reaction products was carried out by flash column 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 or Dragendorff-Munier stains, 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 or Varian VNMRS-400 MHz and chemical shifts are reported in ppm using the solvent as an internal standard ($CDCl_3$ at 7.26 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 or Varian VNMRS-400 MHz and chemical shifts are reported in ppm using the solvent as an internal standard ($CDCl_3$ at 77.0 ppm). Mass spectra were recorded on a Finnigan LCQ-DUO mass spectrometer. Ratios of diastereomeric products were determined by ^{1}H-NMR analysis of the crude reaction mixture. NMR yields were determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as the internal standard.

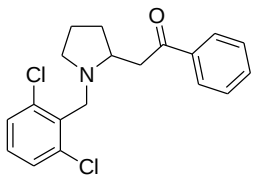
General Procedure for the Redox-Mannich Reaction with Pyrrolidine:

To a solution of benzoic acid (0.25 mmol, 0.5 equiv) in toluene (2 mL) was added pyrrolidine (2.5 mmol, 5 equiv). The resulting mixture was heated under reflux and a solution of 2,6-dichlorobenzaldehyde (0.5 mmol, 1 equiv) and ketone (0.75 mmol, 1.5 equiv) in 0.5 mL of toluene was delivered through the top of the reflux condenser over 5 hours via syringe pump. Reflux was continued until the aldehyde was consumed as judged by TLC analysis (0–30 min). Subsequently, the reaction mixture was allowed to cool to room temperature, diluted with EtOAc (10 mL) and washed with saturated aqueous $NaHCO_3$ (3 x 10 mL). The combined aqueous layers were extracted with EtOAc (3 x 10 mL) and the combined organic layers washed with water (40 mL), brine (40 mL), and dried over anhydrous Na_2SO_4. Solvent was then removed under reduced pressure and the residue purified by silica gel chromatography.

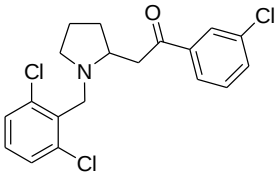
General Procedure for the Redox-Mannich Reaction with 1,2,3,4-Tetrahydroisoquinoline:

A 10 mL round-bottom flask was charged with 4Å molecular sieves (112 mg, 200 weight%), benzoic acid (0.1 mmol, 0.2 equiv), toluene (2 mL), the aldehyde (0.5 mmol, 1 equiv), acetophenone (0.75 mmol, 1.5 equiv) or acetone (1.5 mmol, 3 equiv) and tetrahydroisoquinoline (0.75 mmol, 1.5 equiv). The mixture was stirred at 50 °C for 12 hours at which time the aldehyde was consumed as judged by TLC analysis. The reaction mixture was allowed to cool to room temperature and filtered through a short pad of celite that was then rinsed with EtOAc (30 mL). The filtrate was washed with saturated aqueous $NaHCO_3$ (3 x 10 mL). The combined aqueous layers were extracted with EtOAc (3 x 10 mL), and the combined organic layers were washed with water (40 mL), brine (40 mL), and dried over anhydrous Na_2SO_4. Solvent was then removed under reduced pressure and the residue purified by silica gel chromatography.

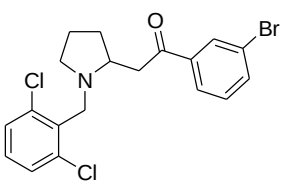
2-(1-(2,6-dichlorobenzyl)pyrrolidin-2-yl)-1-phenylethanone (1a): Following the general procedure compound **1a** was obtained from acetophenone, pyrrolidine and 2,6-dichlorobenzaldehyde as a light yellow solid in 56% yield (R_f = 0.40 in hexanes/EtOAc 80:20 v/v); mp: 116–118 ºC; IR (KBr) 3054, 2979, 2935, 2911, 2870, 2850, 2822, 2802, 1679, 1596, 1581, 1561, 1461, 1436, 1375, 1366, 1339, 1297, 1240, 1210, 1194, 1144, 1116, 1085, 998, 975, 898, 789, 762, 751, 689 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 8.00–7.93 (comp, 2H), 7.59–7.52 (m, 1H), 7.50–7.42 (comp, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 1H), 4.08 (d, *J* = 12.4 Hz, 1H), 3.51 (d, *J* = 12.4 Hz, 1H), 3.55 (dd, *J* = 16.6, 2.9 Hz, 1H), 3.31–3.18 (m, 1H), 3.05 (dd, *J* = 16.6, 9.1 Hz, 1H), 2.96–2.81 (m, 1H), 2.54 (app q, *J* = 8.6 Hz, 1H), 2.15 (app dq, *J* = 12.8, 8.2 Hz, 1H), 1.78–1.63 (comp, 2H), 1.55–1.43 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.6, 137.2, 136.5, 135.0, 132.9, 128.7, 128.5(1), 128.4(5), 128.0, 60.8, 53.6, 52.5, 44.0, 31.2, 22.5; *m/z* (ESI–MS) 348.0 ($^{35}Cl/^{35}Cl$) $[M + H]^+$, 350.0 ($^{35}Cl/^{37}Cl$) $[M + H]^+$.



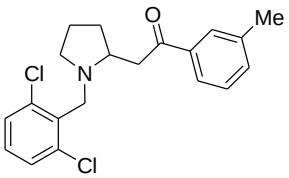
2-(1-(2,6-dichlorobenzyl)pyrrolidin-2-yl)-1-(3-chlorophenyl)ethanone (1b): Following the general procedure compound **1b** was obtained from 3'-chloroacetophenone, pyrrolidine and 2,6-dichlorobenzaldehyde as a yellow oil in 59% yield (R_f = 0.45 in hexanes/EtOAc 80:20 v/v); IR (KBr) 3066, 2961, 2874, 2845, 2804, 1687, 1562, 1435, 1366, 1335, 1298, 1264, 1242, 1204, 1154, 1113, 1087, 998, 971, 899, 778, 765, 737, 706, 681 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.91 (app t, *J* = 1.9 Hz, 1H), 7.83–7.78 (m, 1H), 7.52 (ddd, *J* = 7.9, 2.1, 1.0 Hz, 1H), 7.39 (t, *J* = 7.9 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.15–7.09 (m, 1H), 4.05 (d, *J* = 12.4 Hz, 1H), 3.80 (d, *J* = 12.4 Hz, 1H), 3.47 (dd, *J* = 16.7, 3.8 Hz, 1H), 3.29–3.19 (m, 1H), 3.00 (dd, *J* = 16.7, 8.9 Hz, 1H), 2.94–2.84 (m, 1H), 2.54 (app q, *J* = 8.8 Hz, 1H), 2.14 (app dq, *J* = 12.7, 8.3 Hz, 1H), 1.78–1.64 (comp, 2H), 1.53–1.43 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.3, 138.7, 136.5, 134.9, 132.8, 129.8, 128.7, 128.5, 128.1, 126.1, 60.6, 53.6, 52.5, 44.2, 31.3, 22.5; *m/z* (ESI–MS) 382.0 ($^{35}Cl/^{35}Cl/^{35}Cl$) $[M + H]^+$, 384.0 ($^{35}Cl/^{35}Cl/^{37}Cl$) $[M + H]^+$.



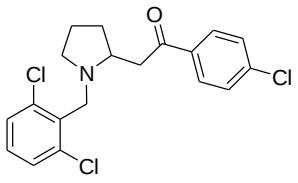
2-(1-(2,6-dichlorobenzyl)pyrrolidin-2-yl)-1-(3-bromophenyl)ethanone (1c): Following the general procedure compound **1c** was obtained from 3'-bromoacetophenone, pyrrolidine and 2,6-dichlorobenzaldehyde as a yellow oil in 52% yield (R_f = 0.46 in hexanes/EtOAc 80:20 v/v); IR (KBr) 3063, 2961, 2873, 2845, 2807, 2360, 1687, 1581, 1562, 1435, 1366, 1333, 1297, 1264, 1243, 1203, 1154, 1112, 1088, 1068, 996, 777, 765, 736, 680 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 8.09–8.05 (m, 1H), 7.88–7.83 (m, 1H), 7.70–7.64 (m, 1H), 7.33 (t, *J* = 7.9 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.14–7.10 (m, 1H), 4.05 (d, *J* = 12.4 Hz, 1H), 3.81 (d, *J* = 12.4 Hz, 1H), 3.47 (dd, *J* = 16.8, 3.9 Hz, 1H), 3.28–3.20 (m, 1H), 3.00 (dd, *J* = 16.8, 8.9 Hz, 1H), 2.94–2.85 (m, 1H), 2.54 (app q, *J* = 8.8 Hz, 1H), 2.13 (app dq, *J* = 12.7, 8.3 Hz, 1H), 1.78–1.64 (comp, 2H), 1.53–1.43 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.2, 138.9, 136.5, 135.8, 134.8, 131.1, 130.1, 128.7, 128.5, 126.6, 122.9, 60.6, 53.7, 52.5, 44.2, 31.3, 22.5; *m/z* (ESI–MS) 425.9 ($^{35}Cl/^{35}Cl/^{79}Br$) $[M + H]^+$, 427.9 ($^{35}Cl/^{35}Cl/^{81}Br$) or ($^{35}Cl/^{37}Cl/^{79}Br$) $[M + H]^+$, 429.9 ($^{35}Cl/^{37}Cl/^{81}Br$) $[M + H]^+$.



2-(1-(2,6-dichlorobenzyl)pyrrolidin-2-yl)-1-*m*-tolylethanone (1d): Following the general procedure compound **1d** was obtained from 3'-methylacetophenone, pyrrolidine and 2,6-dichlorobenzaldehyde as a yellow oil in 54% yield (R_f = 0.46 in hexanes/EtOAc 80:20 v/v); IR (KBr) 3064, 2958, 2871, 2844, 2804, 1682, 1604, 1583, 1562, 1435, 1365, 1335, 1299, 1240, 1194, 1153, 1112, 1088, 1041, 1000, 898, 778, 765, 690 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.82–7.73 (comp, 2H), 7.41–7.32 (comp, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.12 (t, *J* = 8.0, 1H), 4.08 (d, *J* = 12.4 Hz, 1H), 3.81 (d, *J* = 12.4 Hz, 1H), 3.52 (dd, *J* = 16.6, 3.7 Hz, 1H), 3.29–3.19 (m, 1H), 3.04 (dd, *J* = 16.6, 9.0 Hz, 1H), 2.96–2.82 (m, 1H), 2.54 (app q, *J* = 8.8 Hz, 1H), 2.41 (s, 3H), 2.14 (app dq, *J* = 12.7, 8.1 Hz, 1H), 1.80–1.61 (comp, 2H), 1.55–1.44 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.9, 138.3, 137.3, 136.5, 135.0, 133.7, 128.7, 128.5(2), 128.4(6), 128.3(9), 125.3, 60.9, 53.6, 52.5, 44.1, 31.2, 22.5, 21.3; *m/z* (ESI–MS) 362.0 ($^{35}Cl/^{35}Cl$) $[M + H]^+$, 364.0 ($^{35}Cl/^{37}Cl$) $[M + H]^+$.

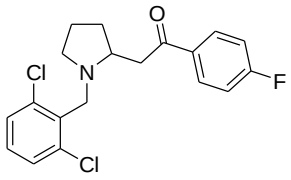


2-(1-(2,6-dichlorobenzyl)pyrrolidin-2-yl)-1-(4-chlorophenyl)ethanone (1e): Following



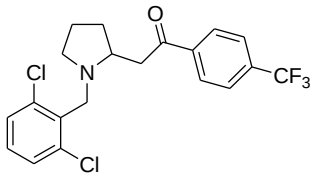
the general procedure compound **1e** was obtained from 4'-chloroacetophenone, pyrrolidine and 2,6-dichlorobenzaldehyde as a yellow oil in 47% yield (R_f = 0.45 in hexanes/EtOAc 80:20 v/v); IR (KBr) 3056, 2960, 2871, 2848, 2802, 1683, 1588, 1562, 1435, 1400, 1367, 1334, 1282, 1207, 1175, 1153, 1092, 1013, 995, 815, 777, 765, 735 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.92–7.85 (comp, 2H), 7.45–7.40 (comp, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.12 (t, *J* = 8.0 Hz, 1H), 4.05 (d, *J* = 12.4 Hz, 1H), 3.80 (d, *J* = 12.4 Hz, 1H), 3.48 (dd, *J* = 16.7, 3.7 Hz, 1H), 3.28–3.19 (m, 1H), 3.00 (dd, *J* = 16.7, 9.0 Hz, 1H), 2.95–2.84 (m, 1H), 2.54 (app q, *J* = 8.8 Hz, 1H), 2.13 (app dq, *J* = 12.8, 8.3 Hz, 1H), 1.87–1.65 (comp, 2H), 1.53–1.43 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.4, 139.4, 136.5, 135.5, 134.9, 129.4, 128.8, 128.7, 128.5, 60.7, 53.7, 52.5, 44.1, 31.2, 22.5; *m/z* (ESI–MS) 382.0 ($^{35}Cl/^{35}Cl/^{35}Cl$) $[M + H]^+$, 384.0 ($^{35}Cl/^{35}Cl/^{37}Cl$) $[M + H]^+$.

2-(1-(2,6-dichlorobenzyl)pyrrolidin-2-yl)-1-(4-fluorophenyl)ethanone (1f): Following



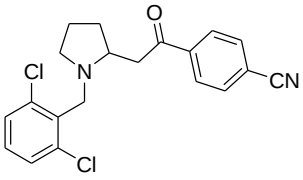
the general procedure compound **1f** was obtained from 4'-fluoroacetophenone, pyrrolidine and 2,6-dichlorobenzaldehyde as a yellow oil in 47% yield (R_f = 0.40 in hexanes/EtOAc 80:20 v/v); IR (KBr) 3066, 2962, 2873, 2844, 2804, 1683, 1597, 1562, 1506, 1436, 1410, 1365, 1332, 1298, 1279, 1232, 1208, 1156, 1098, 995, 834, 779, 765, 736, 587 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 8.01–7.94 (comp, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.16–7.07 (comp, 3H), 4.06 (d, *J* = 12.4 Hz, 1H), 3.80 (d, *J* = 12.4 Hz, 1H), 3.49 (dd, *J* = 16.7, 3.8 Hz, 1H), 3.28–3.19 (m, 1H), 3.01 (dd, *J* = 16.7, 9.0 Hz, 1H), 2.94–2.84 (m, 1H), 2.54 (app q, *J* = 8.8 Hz, 1H), 2.14 (app dq, *J* = 12.7, 8.3 Hz, 1H), 1.77–1.62 (comp, 2H), 1.53–1.43 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.0, 165.7 (d, J_{C-F} = 254.7 Hz), 136.5, 134.9, 133.7 (d, J_{C-F} = 3.0 Hz), 130.6 (d, J_{C-F} = 9.3 Hz), 128.7, 128.5, 115.6 (d, J_{C-F} = 11.1 Hz), 60.8, 53.7, 52.6, 44.0, 31.3, 22.5; *m/z* (ESI–MS) 366.0 ($^{35}Cl/^{35}Cl$) $[M + H]^+$, 368.0 ($^{35}Cl/^{37}Cl$) $[M + H]^+$.

2-(1-(2,6-dichlorobenzyl)pyrrolidin-2-yl)-1-(4-(trifluoromethyl)phenyl)ethanone (1g):

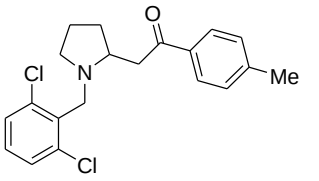


Following the general procedure compound **1g** was obtained from 4'-trifluoromethylacetophenone, pyrrolidine and 2,6-dichlorobenzaldehyde as a yellow oil in 35% yield (R_f = 0.35 in hexanes/EtOAc 80:20 v/v); IR (KBr) 3058, 2979, 2936, 2910, 2878, 2848, 2819, 2799, 2361, 2340, 1694, 1582, 1561, 1510, 1461, 1437, 1410, 1379, 1332, 1207, 1170, 1131, 1106, 1069, 998, 899, 829, 787, 764, 725, 605 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 8.04 (app d, *J* = 8.1 Hz, 2H), 7.73 (app d, *J* = 8.1 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.13 (t, *J* = 8.0 Hz, 1H), 4.06 (d, *J* = 12.4 Hz, 1H), 3.82 (d, *J* = 12.4 Hz, 1H), 3.53 (dd, *J* = 16.9, 3.8 Hz, 1H), 3.31–3.22 (m, 1H), 3.06 (dd, *J* = 16.9, 8.8 Hz, 1H), 2.95–2.87 (m, 1H), 2.56 (app q, *J* = 8.9 Hz, 1H), 2.16 (app dq, *J* = 12.7, 8.2 Hz, 1H), 1.79–1.67 (comp, 2H), 1.54–1.44 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.6, 139.8, 136.5, 134.8, 134.3 (q, J_{C-F} = 32.5 Hz), 128.8, 128.5, 128.4, 125.6 (q, J_{C-F} = 3.8 Hz), 123.6 (q, J_{C-F} = 272.3 Hz), 60.6, 53.7, 52.6, 44.5, 31.3, 22.6; *m/z* (ESI–MS) 416.0 ($^{35}Cl/^{35}Cl$) $[M + H]^+$, 418.0 ($^{35}Cl/^{37}Cl$) $[M + H]^+$.

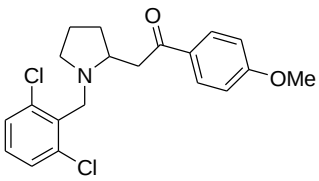
4-(2-(1-(2,6-dichlorobenzyl)pyrrolidin-2-yl)acetyl)benzonitrile (1h): Following the general procedure compound **1h** was obtained from 4'-cyanoacetophenone, pyrrolidine and 2,6-dichlorobenzaldehyde as a yellow oil in 50% yield (R_f = 0.27 in hexanes/EtOAc 80:20 v/v); IR (KBr) 2960, 2872, 2864, 2807, 2362, 2335, 2231, 1690, 1581, 1562, 1436, 1404, 1366, 1293, 1207, 1154, 1109, 997, 825, 779, 765 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 8.06–7.99 (comp, 2H), 7.80–7.74 (comp, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.14 (t, *J* = 8.0 Hz, 1H), 4.18–3.97 (m, 1H), 3.94–3.76 (m, 1H), 3.62–3.44 (m, 1H), 3.39–3.19 (m, 1H), 3.17–2.82 (comp, 2H), 2.68–2.49 (m, 1H), 2.25–2.10 (m, 1H), 1.86–1.64 (comp, 2H), 1.59–1.41 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.2, 140.0, 136.6, 132.5, 128.9, 128.6, 128.5, 117.9, 116.3, 60.6, 53.7, 52.5, 44.4, 31.3, 22.6; *m/z* (ESI–MS) 372.9 ($^{35}Cl/^{35}Cl$) $[M + H]^+$, 374.9 ($^{35}Cl/^{37}Cl$) $[M + H]^+$.



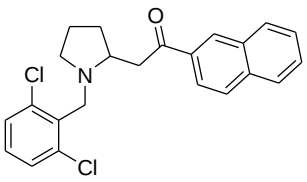
2-(1-(2,6-dichlorobenzyl)pyrrolidin-2-yl)-1-*p*-tolylethanone (1i): Following the general procedure compound **1i** was obtained from 4'-methylacetophenone, pyrrolidine and 2,6-dichlorobenzaldehyde as a yellow oil in 49% yield (R_f = 0.40 in hexanes/EtOAc 80:20 v/v); IR (KBr) 3056, 3030, 2979, 2913, 2851, 2827, 2797, 1679, 1606, 1582, 1561, 1461, 1437, 1416, 1378, 1369, 1338, 1298, 1240, 1223, 1208, 1181, 1166, 1146, 1117, 1085, 1000, 973, 898, 806, 788, 760, 720, 570 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.91–7.83 (comp, 2H), 7.34–7.22 (comp, 4H), 7.12 (t, *J* = 8.0, 1H), 4.08 (d, *J* = 12.4 Hz, 1H), 3.80 (d, *J* = 12.4 Hz, 1H), 3.52 (dd, *J* = 16.5, 3.5 Hz, 1H), 3.29–3.18 (m, 1H), 3.03 (dd, *J* = 16.5, 9.1 Hz, 1H), 2.95–2.82 (m, 1H), 2.53 (app q, *J* = 8.7 Hz, 1H), 2.41 (s, 3H), 2.13 (app dq, *J* = 12.7, 8.2 Hz, 1H), 1.80–1.61 (comp, 2H), 1.55–1.44 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.3, 143.7, 136.5, 135.0, 134.8, 129.2, 128.7, 128.5, 128.2, 60.9, 53.6, 52.5, 43.9, 31.2, 22.5, 21.6; *m/z* (ESI–MS) 362.0 ($^{35}Cl/^{35}Cl$) $[M + H]^+$, 364.0 ($^{35}Cl/^{37}Cl$) $[M + H]^+$.



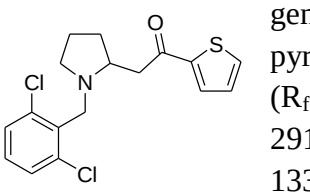
2-(1-(2,6-dichlorobenzyl)pyrrolidin-2-yl)-1-(4-methoxyphenyl)ethanone (1j): Following the general procedure compound **1j** was obtained from 4'-methoxyacetophenone, pyrrolidine and 2,6-dichlorobenzaldehyde as a yellow oil in 52% yield (R_f = 0.24 in hexanes/EtOAc 80:20 v/v); IR (KBr) 3055, 2976, 2936, 2850, 2803, 1671, 1607, 1576, 1560, 1504, 1455, 1423, 1376, 1368, 1339, 1303, 1263, 1212, 1181, 1108, 1029, 992, 898, 832, 805, 788, 758, 721, 593, 573 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.98–7.91 (comp, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.11 (t, *J* = 8.0 Hz, 1H), 6.97–6.89 (comp, 2H), 4.08 (d, *J* = 12.3 Hz, 1H), 3.86 (s, 3H), 3.79 (d, *J* = 12.3 Hz, 1H), 3.49 (dd, *J* = 16.4, 3.8 Hz, 1H), 3.27–3.17 (m, 1H), 3.00 (dd, *J* = 16.4, 9.1 Hz, 1H), 2.93–2.82 (m, 1H), 2.59–2.48 (m, 1H), 2.12 (app dq, *J* = 12.7, 8.2 Hz, 1H), 1.77–1.61 (comp, 2H), 1.54–1.43 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.2, 163.4, 136.5, 135.0, 130.4, 130.3, 128.7, 128.5, 113.6, 61.0, 55.4, 53.6, 52.5, 43.6, 31.2, 22.5; *m/z* (ESI–MS) 377.9 ($^{35}Cl/^{35}Cl$) $[M + H]^+$, 379.9 ($^{35}Cl/^{37}Cl$) $[M + H]^+$.



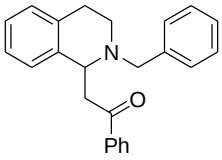
2-(1-(2,6-dichlorobenzyl)pyrrolidin-2-yl)-1-(naphthalen-2-yl)ethanone (1k): Following the general procedure compound **1k** was obtained from 2-acetonaphthone, pyrrolidine and 2,6-dichlorobenzaldehyde as a yellow oil in 56% yield (R_f = 0.36 in hexanes/EtOAc 80:20 v/v); IR (KBr) 3056, 2961, 2871, 2845, 2809, 1679, 1628, 1581, 1562, 1469, 1435, 1367, 1297, 1275, 1186, 1154, 1124, 1088, 862, 821, 778, 765, 739 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 8.51–8.46 (m, 1H), 8.04 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.92–7.84 (comp, 2H), 7.63–7.51 (comp, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.11 (t, *J* = 8.0 Hz, 1H), 4.13 (d, *J* = 12.4 Hz, 1H), 3.85 (d, *J* = 12.4 Hz, 1H), 3.65 (dd, *J* = 16.3, 3.7 Hz, 1H), 3.37–3.27 (m, 1H), 3.20 (dd, *J* = 12.4, 9.0 Hz, 1H), 2.99–2.87 (m, 1H), 2.57 (app q, *J* = 8.7 Hz, 1H), 2.17 (app dq, *J* = 12.8, 8.1 Hz, 1H), 1.81–1.65 (comp, 2H), 1.61–1.50 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.6, 136.5, 135.5, 135.0, 134.6, 132.5, 129.7, 129.6, 128.7, 128.5, 128.4, 128.3, 127.7, 126.7, 123.8, 61.0, 53.7, 52.6, 44.1, 31.3, 22.5; *m/z* (ESI–MS) 398.0 ($^{35}Cl/^{35}Cl$) $[M + H]^+$, 400.0 ($^{35}Cl/^{37}Cl$) $[M + H]^+$.



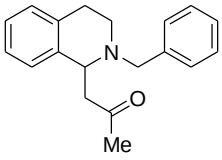
2-(1-(2,6-dichlorobenzyl)pyrrolidin-2-yl)-1-(thiophen-2-yl)ethanone (1l): Following the general procedure compound **1l** was obtained from 2-acetylthiophene, pyrrolidine and 2,6-dichlorobenzaldehyde as a yellow oil in 40% yield (R_f = 0.32 in hexanes/EtOAc 80:20 v/v); IR (KBr) 3054, 2979, 2934, 2916, 2850, 2825, 2796, 1655, 1581, 1560, 1520, 1437, 1422, 1366, 1336, 1301, 1223, 1214, 1117, 1086, 1057, 974, 897, 787, 765, 725 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.71 (dd, *J* = 3.8, 1.1 Hz, 1H), 7.63 (dd, *J* = 4.9, 1.1 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.16–7.10 (comp, 2H), 4.08 (d, *J* = 12.4 Hz, 1H), 3.82 (d, *J* = 12.4 Hz, 1H), 3.45 (dd, *J* = 15.7, 3.2 Hz, 1H), 3.30–3.15 (m, 1H), 2.98 (dd, *J* = 15.7, 9.0 Hz, 1H), 2.93–2.79 (m, 1H), 2.54 (app q, *J* = 8.6 Hz, 1H), 2.11 (app dq, *J* = 12.7, 8.1 Hz, 1H), 1.79–1.64 (comp, 2H), 1.60–1.48 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.4, 144.8, 136.5, 135.0, 133.6, 131.9, 128.7, 128.5, 128.1, 61.0, 53.6, 52.5, 44.8, 31.1, 22.5; *m/z* (ESI–MS) 353.9 ($^{35}Cl/^{35}Cl$) $[M + H]^+$, 355.9 ($^{35}Cl/^{37}Cl$) $[M + H]^+$.



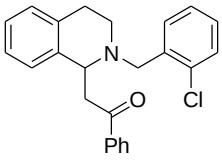
2-(2-benzyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-phenylethanone (2a): Following the general procedure compound **2a** was obtained from acetophenone, tetrahydroisoquinoline and benzaldehyde as a yellow oil in 46% yield (R_f = 0.49 in hexanes/EtOAc 80:20 v/v); IR (KBr) 3061, 3026, 2923, 2829, 2807, 2362, 2332, 1679, 1597, 1580, 1493, 1449, 1355, 1283, 1265, 1200, 1103, 1075, 1022, 749, 691 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.99–7.94 (comp, 2H), 7.59–7.54 (m, 1H), 7.50–7.43 (comp, 2H), 7.30–7.10 (comp, 9H), 4.69–4.60 (m, 1H), 3.82–3.58 (comp, 3H), 3.27–3.16 (comp, 2H), 3.01 (ddd, *J* = 16.8, 10.8, 6.0 Hz, 1H), 2.88–2.78 (m, 1H), 2.67–2.56 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.9, 139.0, 138.1, 137.4, 134.2, 132.8, 129.1, 128.8, 128.5, 128.2, 128.1, 127.6, 126.9, 126.3, 126.0, 58.2, 57.8, 45.6, 42.2, 24.2; m/z (ESI–MS) 342.1 $[M + H]^+$.



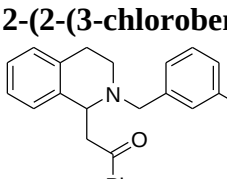
1-(2-benzyl-1,2,3,4-tetrahydroisoquinolin-1-yl)propan-2-one (2b): Following the general procedure compound **2b** was obtained from acetone, tetrahydroisoquinoline and benzaldehyde as a yellow oil in 45% yield (R_f = 0.42 in hexanes/EtOAc 80:20 v/v); IR (KBr) 3061, 3026, 2920, 2831, 2362, 2332, 1709, 1647, 1493, 1453, 1429, 1358, 1277, 1229, 1162, 1102, 1076, 1035, 756, 739, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.37–7.30 (comp, 4H), 7.30–7.24 (m, 1H), 7.20–7.15 (comp, 2H), 7.15–7.10 (m, 1H), 7.10–7.05 (m, 1H), 4.38–4.30 (m, 1H), 3.78–3.69 (comp, 2H), 3.22–3.13 (m, 1H), 3.08–2.93 (comp, 2H), 2.89–2.80 (m, 1H), 2.70 (dd, *J* = 15.3, 5.2 Hz, 1H), 2.62–2.51 (m, 1H), 2.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.4, 138.9, 137.3, 134.1, 129.2, 129.0, 128.2, 127.4, 127.1, 126.4, 126.1, 57.9, 57.6, 50.6, 42.1, 30.3, 23.6; *m/z* (ESI–MS) 280.1 $[M + H]^+$.



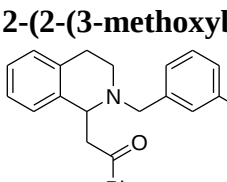
2-(2-(2-chlorobenzyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-phenylethanone (2c): Following the general procedure compound **2c** was obtained from acetophenone, tetrahydroisoquinoline and 2-chlorobenzaldehyde as a yellow oil in 42% yield (R_f = 0.53 in hexanes/EtOAc 80:20 v/v); IR (KBr) 3061, 2924, 2839, 2359, 2332, 1682, 1597, 1580, 1447, 1354, 1282, 1121, 1037, 750, 690 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.96–7.90 (comp, 2H), 7.57–7.51 (m, 1H), 7.47–7.40 (comp, 2H), 7.39–7.31 (m, 1H), 7.31–7.29 (m, 1H), 7.23–7.05 (comp, 6H), 4.68–4.57 (m, 1H), 3.92 (d, *J* = 14.2 Hz, 1H), 3.73 (d, *J* = 14.2 Hz, 1H), 3.62 (dd, *J* = 15.5, 7.6 Hz, 1H), 3.30–3.14 (comp, 2H), 3.13–2.99 (m, 1H), 2.90–2.77 (m, 1H), 2.69–2.55 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.9, 138.2, 137.4, 136.6, 134.2, 134.0, 132.8, 130.6, 129.2, 128.5, 128.2, 128.0, 127.6, 126.5, 126.4, 126.0, 58.6, 54.6, 45.7, 42.7, 24.5; *m/z* (ESI–MS) 375.9 $[M + H]^+$.



2-(2-(3-chlorobenzyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-phenylethanone (2d): Following the general procedure compound **2d** was obtained from acetophenone, tetrahydroisoquinoline and 3-chlorobenzaldehyde as a yellow oil in 46% yield (R_f = 0.51 in hexanes/EtOAc 80:20 v/v); IR (KBr) 3060, 3019, 2923, 2833, 1683, 1597, 1578, 1448, 1429, 1354, 1280, 1200, 1105, 1075, 1020, 776, 750, 690 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 8.00–7.93 (comp, 2H), 7.60–7.54 (m, 1H), 7.50–7.44 (comp, 2H), 7.25–7.04 (comp, 8H), 4.66–4.55 (m, 1H), 3.80–3.57 (comp, 3H), 3.27–3.13 (comp, 2H), 3.00 (ddd, *J* = 16.8, 11.1, 6.1 Hz, 1H), 2.86–2.75 (m, 1H), 2.67–2.55 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.8, 141.3, 137.8, 137.3, 134.1, 134.0, 132.9, 129.3, 129.2, 128.7, 128.5, 128.1, 127.6, 127.1, 126.8, 126.4, 126.1, 58.4, 57.3, 45.6, 42.2, 24.0; *m/z* (ESI–MS) 375.9 $[M + H]^+$.

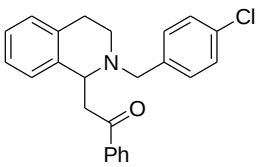


2-(2-(3-methoxybenzyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-phenylethanone (2e): Following the general procedure compound **2e** was obtained from acetophenone, tetrahydroisoquinoline and *m*-anisaldehyde as a yellow oil in 50% yield (R_f = 0.32 in hexanes/EtOAc 80:20 v/v); IR (KBr) 3059, 3022, 2937, 2834, 2360, 1682, 1598, 1585, 1488, 1449, 1354, 1263, 1199, 1153, 1043, 1022, 778, 749, 692 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 8.00–7.94 (comp, 2H), 7.59–7.53 (m, 1H), 7.49–7.42 (comp, 2H), 7.22–7.11 (comp, 5H),



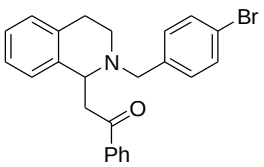
6.90–6.80 (comp, 2H), 6.77 (app dd, *J* = 8.1, 2.0 Hz, 1H), 4.69–4.60 (m, 1H), 3.80–3.61 (comp, 6H), 3.27–3.14 (comp, 2H), 3.01 (ddd, *J* = 16.9, 10.8, 5.9 Hz, 1H), 2.90–2.79 (m, 1H), 2.67–2.55 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.8, 159.5, 140.7, 138.0, 137.4, 134.2, 132.8, 129.1, 129.0, 128.5, 128.1, 127.6, 126.3, 126.0, 121.0, 113.8, 112.8, 58.4, 57.8, 55.0, 45.6, 42.2, 24.2; (ESI–MS) 372.0 $[M + H]^+$.

2-(2-(4-chlorobenzyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-phenylethanone (2f):



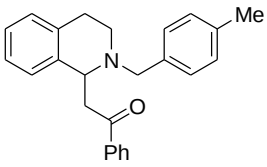
Following the general procedure compound **2f** was obtained from acetophenone, tetrahydroisoquinoline and 4-chlorobenzaldehyde as a yellow oil in 45% yield (R_f = 0.44 in hexanes/EtOAc 80:20 v/v); IR (KBr) 3061, 3022, 2924, 2831, 1682, 1597, 1490, 1448, 1407, 1355, 1284, 1201, 1089, 1015, 749, 690 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.96–7.89 (comp, 2H), 7.60–7.54 (m, 1H), 7.49–7.41 (comp, 2H), 7.22–7.04 (comp, 8H), 4.63–4.50 (m, 1H), 3.78–3.51 (comp, 3H), 3.30–3.13 (comp, 2H), 2.99 (ddd, *J* = 16.9, 11.2, 6.0 Hz, 1H), 2.88–2.74 (m, 1H), 2.69–2.52 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.7, 137.8, 137.5, 137.2, 134.1, 132.9, 132.5, 130.1, 129.2, 128.5, 128.1(9), 128.1(6), 127.6, 126.5, 126.1, 58.1, 57.0, 45.7, 42.3, 23.9; *m/z* (ESI–MS) 375.9 $[M + H]^+$.

2-(2-(4-bromobenzyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-phenylethanone (2g):



Following the general procedure compound **2g** was obtained from acetophenone, tetrahydroisoquinoline and 4-bromobenzaldehyde as a yellow oil in 45% yield (R_f = 0.46 in hexanes/EtOAc 80:20 v/v); IR (KBr) 3060, 3019, 2924, 2833, 2360, 1682, 1597, 1580, 1487, 1448, 1404, 1355, 1284, 1264, 1200, 1096, 1069, 1011, 750, 691 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.96–7.90 (comp, 2H), 7.60–7.54 (m, 1H), 7.50–7.42 (comp, 2H), 7.36–7.29 (comp, 2H), 7.22–7.10 (comp, 4H), 7.10–7.02 (comp, 2H), 4.60–4.52 (m, 1H), 3.70 (d, *J* = 13.4 Hz, 1H), 3.66–3.52 (comp, 2H), 3.28–3.15 (comp, 2H), 2.99 (ddd, *J* = 16.9, 11.2, 6.2 Hz, 1H), 2.87–2.75 (m, 1H), 2.66–2.53 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.7, 138.0, 137.7, 137.2, 134.0, 132.9, 131.1, 130.4, 129.2, 128.5, 128.1, 127.6, 126.5, 126.1, 120.7, 58.1, 57.0, 45.7, 42.3, 23.9; *m/z* (ESI–MS) 419.9 (^{79}Br) $[M + H]^+$, 421.9 (^{81}Br) $[M + H]^+$.

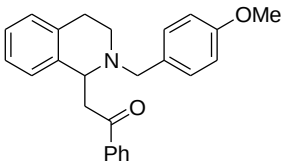
2-(2-(4-methylbenzyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-phenylethanone (2h):



Following the general procedure compound **2h** was obtained from acetophenone, tetrahydroisoquinoline and *p*-tolualdehyde as a yellow oil in 46% yield (R_f = 0.35 in hexanes/EtOAc 80:20 v/v); IR (KBr) 3055, 3013, 2936, 2903, 2887, 2802, 2360, 2342, 1683, 1595, 1578, 1512, 1488, 1447, 1431, 1408, 1359, 1315, 1295, 1264, 1239, 1210, 1119, 1102, 976, 963, 805, 753, 686, 650 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.98–7.93 (comp, 2H), 7.60–7.54 (m, 1H), 7.49–7.42 (comp, 2H), 7.22–7.10 (comp, 6H), 7.09–7.03 (comp, 2H), 4.69–4.59 (m, 1H), 3.79–3.57 (comp, 3H), 3.28–3.15 (comp, 2H), 3.01 (ddd, *J* = 16.9, 10.8, 5.9 Hz, 1H), 2.90–2.79 (m, 1H), 2.68–2.55 (m, 1H), 2.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.9, 138.1, 137.4, 136.4, 135.8, 134.2, 132.7, 129.1, 128.8, 128.7, 128.4,

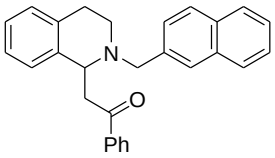
128.2, 127.6, 126.3, 126.0, 58.1, 57.5, 45.6, 42.2, 24.2, 21.0; *m/z* (ESI–MS) 356.1 $[M + H]^+$.

2-(2-(4-methoxybenzyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-phenylethanone (2i):



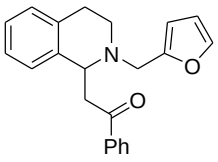
Following the general procedure compound **2i** was obtained from acetophenone, tetrahydroisoquinoline and *p*-anisaldehyde as a yellow oil in 44% yield (R_f = 0.24 in hexanes/EtOAc 80:20 v/v); IR (KBr) 3061, 2932, 2834, 1682, 1611, 1581, 1511, 1449, 1355, 1301, 1284, 1246, 1179, 1101, 1035, 833, 750, 691 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.96–7.91 (comp, 2H), 7.57–7.52 (m, 1H), 7.47–7.41 (comp, 2H), 7.20–7.07 (comp, 6H), 6.80–6.73 (comp, 2H), 4.67–4.56 (m, 1H), 3.78 (s, 3H), 3.73–3.56 (comp, 3H), 3.25–3.14 (comp, 2H), 2.99 (ddd, *J* = 16.9, 10.9, 5.9 Hz, 1H), 2.88–2.77 (m, 1H), 2.66–2.54 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.8, 158.6, 138.0, 137.4, 134.2, 132.8, 130.9, 129.9, 129.1, 128.5, 128.2, 127.6, 126.3, 126.0, 113.5, 58.0, 57.1, 55.1, 45.7, 42.1, 24.1; *m/z* (ESI–MS) 372.0 $[M + H]^+$.

2-(2-(naphthalen-2-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-phenylethanone (2j):



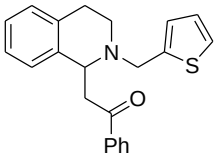
Following the general procedure compound **2j** was obtained from acetophenone, tetrahydroisoquinoline and 2-naphthaldehyde as a yellow oil in 46% yield (R_f = 0.40 in hexanes/EtOAc 80:20 v/v); IR (KBr) 3057, 3019, 2923, 2834, 1683, 1598, 1580, 1508, 1492, 1448, 1353, 1266, 1199, 1123, 1103, 1021, 855, 822, 748, 691 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.98–7.93 (comp, 2H), 7.83–7.78 (m, 1H), 7.77–7.69 (comp, 2H), 7.65 (br s, 1H), 7.55–7.49 (m, 1H), 7.48–7.34 (comp, 5H), 7.24–7.11 (comp, 4H), 4.75–4.66 (m, 1H), 3.94 (d, *J* = 13.3 Hz, 1H), 3.87 (d, *J* = 13.3 Hz, 1H), 3.77–3.62 (m, 1H), 3.31–3.17 (comp, 2H), 3.05 (ddd, *J* = 16.8, 10.9, 6.0 Hz, 1H), 2.93–2.82 (m, 1H), 2.69–2.55 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.9, 138.0, 137.3, 136.6, 134.2, 133.2, 133.0, 132.8(0), 132.7(6), 129.2, 128.5, 128.2, 127.8, 127.6(4), 127.6(2), 127.6, 127.2, 126.4, 126.1, 125.7, 125.4, 58.4, 58.0, 45.7, 42.2, 24.1; *m/z* (ESI–MS) 392.0 $[M + H]^+$.

2-(2-(furan-2-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-phenylethanone (2k):



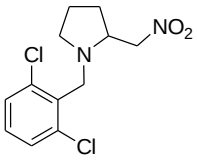
Following the general procedure compound **2k** was obtained from acetophenone, tetrahydroisoquinoline and 2-furaldehyde as a yellow oil in 33% yield (R_f = 0.28 in hexanes/EtOAc 80:20 v/v); IR (KBr) 3061, 3022, 2923, 2834, 1682, 1645, 1597, 1580, 1491, 1448, 1353, 1282, 1201, 1149, 1103, 1077, 1014, 918, 748, 691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.97–7.87 (comp, 2H), 7.58–7.49 (m, 1H), 7.48–7.40 (comp, 2H), 7.33–7.30 (m, 1H), 7.19–7.07 (comp, 4H), 6.31–6.25 (m, 1H), 6.22–6.14 (m, 1H), 4.74–4.59 (m, 1H), 3.86–3.71 (comp, 2H), 3.69–3.57 (m, 1H), 3.34–3.19 (comp, 2H), 3.07–2.88 (comp, 2H), 2.78–2.62 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.4, 152.0, 142.1, 137.7, 137.2, 133.8, 132.9, 129.0, 128.5, 128.2, 128.1, 127.6, 126.3, 110.0, 108.6, 56.7, 50.4, 46.0, 43.7, 24.6; *m/z* (ESI–MS) 332.0 $[M + H]^+$.

1-phenyl-2-(2-(thiophen-2-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)ethanone (2l):



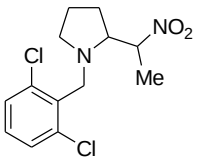
Following the general procedure compound **2l** was obtained from acetophenone, tetrahydroisoquinoline and 2-thiophenecarboxaldehyde as a yellow oil in 38% yield (R_f = 0.45 in hexanes/EtOAc 80:20 v/v); IR (KBr) 3061, 3019, 2923, 2833, 1682, 1597, 1580, 1490, 1448, 1351, 1280, 1200, 1104, 1020, 750, 691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.99–7.93 (comp, 2H), 7.60–7.52 (m, 1H), 7.50–7.42 (comp, 2H), 7.21–7.09 (comp, 5H), 6.92–6.81 (comp, 2H), 4.74–4.66 (m, 1H), 3.99 (d, *J* = 14.0 Hz, 1H), 3.89 (d, *J* = 14.0 Hz, 1H), 3.71–3.56 (m, 1H), 3.30–3.16 (comp, 2H), 3.05–2.88 (comp, 2H), 2.71–2.57 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.7, 143.2, 137.8, 137.3, 134.0, 132.8, 129.1, 128.5, 128.2, 127.6, 127.0, 126.8, 126.2, 125.4, 124.9, 57.7, 52.5, 45.9, 42.6, 24.4; *m/z* (ESI–MS) 348.0 $[M + H]^+$.

1-(2,6-dichlorobenzyl)-2-(nitromethyl)pyrrolidine (3a): To a solution of benzoic acid



(0.25 mmol, 0.5 equiv) in toluene (2 mL) were added nitromethane (1.5 mmol, 3 equiv) and pyrrolidine (0.75 mmol, 1.5 equiv). The resulting mixture was heated under reflux and solution of 2,6-dichlorobenzaldehyde (0.5 mmol, 1 equiv) in 0.5 mL of toluene was delivered through the top of the reflux condenser over 5 hours via syringe pump. Subsequently, the reaction mixture was allowed to cool to room temperature, diluted with EtOAc (10 mL) and washed with saturated aqueous $NaHCO_3$ (3 x 10 mL). The combined aqueous layers were extracted with EtOAc (3 x 10 mL) and the combined organic layers washed with water (40 mL), brine (40 mL), and dried over anhydrous Na_2SO_4. Solvent was then removed under reduced pressure and the residue purified by eluting through a short silica gel plug with hexanes/EtOAc (80:20 v/v). Compound **3a** was obtained as a yellow oil in 59% yield (R_f = 0.45 in hexanes/EtOAc 90:10 v/v); IR (KBr) 3078, 2966, 2918, 2852, 2815, 1582, 1548, 1436, 1385, 1359, 1245, 1206, 1123, 1089, 968, 916, 869, 779, 766, 745, 710, 642 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.31 (d, *J* = 8.0 Hz, 2H), 7.15 (t, *J* = 8.0 Hz, 1H), 4.53 (dd, *J* = 11.8, 3.6 Hz, 1H), 4.24–4.14 (m, 1H), 4.06 (d, *J* = 12.5 Hz, 1H), 3.99 (d, *J* = 12.5 Hz, 1H), 3.53–3.44 (m, 1H), 2.95–2.85 (m, 1H), 2.68–2.59 (m, 1H), 2.13–2.01 (m, 1H), 1.84–1.66 (comp, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.4, 134.2, 129.1, 128.5, 79.1, 61.7, 53.7, 52.6, 29.4, 23.1; *m/z* (ESI–MS) 289.0 ($^{35}Cl/^{35}Cl$) $[M + H]^+$, 291.0 ($^{35}Cl/^{37}Cl$) $[M + H]^+$.

1-(2,6-dichlorobenzyl)-2-(1-nitroethyl)pyrrolidine (3b): The synthetic procedure



followed was the same as for **3a**. Compound **3b** was obtained from nitroethane, pyrrolidine and 2,6-dichlorobenzaldehyde in 91% NMR yield (2:1 mixture of diastereomers) (R_f = 0.55 in hexanes/EtOAc 90:10 v/v) (Note: The product isolated by silica gel chromatography contained some impurities that could not be removed); IR (KBr) 3081, 2968, 2871, 2849, 2814, 1579, 1544, 1529, 1436, 1389, 1339, 1326, 1301, 1206, 1097, 984, 886, 871, 781, 766, 744 cm^{-1}; ^1H NMR (Note: due to overlapping peaks, integration values of the diastereomers and the impurities are reported together) (500 MHz, $CDCl_3$) 7.39 (d, *J* = 8.0 Hz, 2.16H), 7.34–7.28 (comp, 4.68H), 7.18–7.11 (comp, 1.84H), 4.61 (app dq, *J* = 6.7, 4.6 Hz, 1.00H), 4.48–4.40 (m, 0.77H), 4.10 (d, *J* = 12.5 Hz, 0.88H), 4.05 (d, *J* = 12.4 Hz, 1.09H), 4.02–3.95 (comp, 1.83H), 3.46 (ddd, *J* = 4.6, 4.6, 4.2 Hz, 1.00H), 3.26 (ddd, *J* = 9.0, 5.7, 3.6 Hz, 0.79H), 2.93–2.81

(comp, 1.93H), 2.70–2.58 (comp, 1.98H), 2.03–1.49 (comp, 8.64H), 1.46 (d, *J* = 6.7 Hz, 2.98H), 1.43 (d, *J* = 6.8 Hz, 2.39H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.7, 136.5, 134.4, 134.3, 134.2, 130.5(8), 130.5(7), 129.0(2), 129.0(1), 128.5(0), 128.4(8), 128.3, 128.2, 85.3, 84.0, 67.0, 66.1, 53.8, 53.7, 53.6, 52.9, 27.1, 25.7, 24.4, 23.5, 16.4, 14.3, 12.4; *m/z* (ESI–MS) 303.0 (^{35}Cl/^{35}Cl) $[M + H]^+$, 305.0 (^{35}Cl/^{37}Cl) $[M + H]^+$.

1-(2,6-dichlorobenzyl)-2-(1-nitropropyl)pyrrolidine (3c): The synthetic procedure followed was the same as for **3a**. Compound **3c** was obtained from 1-nitropropane, pyrrolidine and 2,6-dichlorobenzaldehyde in 98% NMR yield (1.4:1 mixture of diastereomers) (R_f = 0.58 in hexanes/EtOAc 90:10 v/v) (Note: The product isolated by silica gel chromatography contained impurities that could not be removed); IR (KBr) 2972, 2879, 2851, 2809, 1581, 1545, 1459, 1436, 1376, 1356, 1339, 1205, 1088, 780, 766 cm^{-1}; ^{1}H NMR (Note: due to overlapping peaks, integration values of the diastereomers and the impurities are reported together) (500 MHz, $CDCl_3$) 7.40–7.37 (comp, 0.61H), 7.35–7.27 (comp, 3.64H), 7.18–7.10 (comp, 1.68H), 4.43–4.36 (m, 1.00H), 4.28 (ddd, *J* = 9.8, 6.4, 4.5 Hz, 0.63H), 4.12 (d, *J* = 12.5 Hz, 0.69H), 4.04 (d, *J* = 12.3 Hz, 1.07H), 4.01–3.93 (comp, 1.67H), 3.34 (app dt, *J* = 8.3, 4.9 Hz, 1.01H), 3.21 (ddd, *J* = 8.8, 6.4, 3.7 Hz, 0.64H), 2.93–2.80 (comp, 1.74H), 2.67–2.55 (comp, 1.96H), 2.48 (app q, *J* = 7.4 Hz, 0.62H), 2.01–1.52 (comp, 11.14H), 1.06 (t, *J* = 7.4 Hz, 0.84H), 0.92–0.83 (comp, 5.29H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.8, 136.5, 134.3, 134.2, 130.4, 129.0(4), 128.9(9), 128.4(8), 128.4(7), 127.5, 92.2, 91.9, 66.2(5), 66.2(1), 64.5, 53.6(2), 53.5(9), 53.4, 53.0, 50.0, 26.7, 26.2, 24.6, 24.3, 23.5, 23.0, 21.4, 20.3, 11.3, 10.8, 10.6, 10.2; *m/z* (ESI–MS) 317.0 (^{35}Cl/^{35}Cl) $[M + H]^+$, 319.0 (^{35}Cl/^{37}Cl) $[M + H]^+$.

2-benzyl-1-(nitromethyl)-1,2,3,4-tetrahydroisoquinoline (4): A 10 mL round-bottom flask was charged with 4 Å molecular sieves (112 mg, 200 weight%), benzoic acid (0.1 mmol, 0.2 equiv), toluene (2 mL), benzaldehyde (0.5 mmol, 1 equiv), nitromethane (1.5 mmol, 3 equiv) and tetrahydroisoquinoline (0.75 mmol, 1.5 equiv). The mixture was stirred at 50 °C for 12 hours at which time the aldehyde was consumed as judged by TLC analysis. The mixture was allowed to cool to room temperature and filtered through a short pad of celite that was then rinsed with EtOAc (30 mL). The filtrate was washed with saturated aqueous $NaHCO_3$ (3 x 10 mL). The combined aqueous layers were extracted with EtOAc (3 x 10 mL), and the combined organic layers were washed with water (40 mL), brine (40 mL), and dried over anhydrous Na_2SO_4. Solvent was then removed under reduced pressure and the residue was purified by eluting through a short silica gel plug with hexanes/EtOAc (80:20 v/v). Compound **4** was obtained as a yellow oil in 83% yield (R_f = 0.50 in hexanes/EtOAc 90:10 v/v); IR (KBr) 3062, 3025, 2922, 2834, 2809, 2740, 1553, 1494, 1454, 1428, 1381, 1319, 1264, 1209, 1123, 1027, 742, 700, 660 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.39–7.16 (comp, 8H), 7.13–7.08 (m, 1H), 4.75 (dd, *J* = 11.8, 10.2 Hz, 1H), 4.58 (dd, *J* = 10.2, 4.5 Hz, 1H), 4.49 (dd, *J* = 11.8, 4.5 Hz, 1H), 3.86 (d, *J* = 13.3 Hz, 1H), 3.77 (d, *J* = 13.3 Hz, 1H), 3.23 (ddd, *J* = 13.8, 11.5, 4.4 Hz, 1H), 3.06 (ddd, *J* = 17.0, 11.5, 5.7 Hz, 1H), 2.99–2.91 (m, 1H), 2.60–2.50 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.2, 135.2, 132.1, 129.6, 128.7,

128.3, 127.6, 127.5, 127.3, 126.5, 79.4, 59.6, 57.5, 41.7, 22.8; *m/z* (ESI–MS) 222.1 [M – CH_2NO_2]$^+$.

3-(3,4-dihydroisoquinolin-2(1H)-yl)-1,3-diphenylpropan-1-one (6): Compound **6** was synthesized according to a literature procedure[1]. To a suspension of chalcone (10 mmol, 1 equiv) in 95% ethanol (8 mL) was added tetrahydroisoquinoline (10.4 mmol, 1.04 equiv). The mixture was briefly heated to reflux and was then allowed to stir at room temperature for two days followed by standing in a –20 °C refrigerator for four days. The solid formed was filtered off and washed with cold 95% ethanol followed by recrystallization from 95% ethanol. Compound **6** was obtained as a white solid in 56% yield (R_f = 0.27 in hexanes/EtOAc 80:20 v/v); mp: 78–80 ºC; IR (KBr) 3058, 3027, 2968, 2920, 2793, 2755, 1672, 1596, 1580, 1497, 1464, 1449, 1377, 1341, 1304, 1284, 1225, 1185, 1092, 1001, 991, 935, 758, 738, 709, 683, 648, 561 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 8.00–7.91 (comp, 2H), 7.59–7.52 (m, 1H), 7.51–7.40 (comp, 4H), 7.39–7.32 (comp, 2H), 7.31–7.24 (m, 1H), 7.18–7.05 (comp, 3H), 7.02–6.93 (m, 1H), 4.47 (app t, *J* = 6.6 Hz, 1H), 3.81–3.66 (comp, 3H), 3.55 (dd, *J* = 16.5, 7.4 Hz, 1H), 2.97–2.79 (comp, 3H), 2.72–2.59 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.2, 139.9, 137.1, 134.8, 134.3, 132.9, 128.5(1), 128.4(9), 128.3, 128.2, 128.0, 127.3, 126.6, 125.9, 125.4, 64.8, 53.3, 47.6, 42.4, 29.5; m/z (ESI–MS) 342.3 [M + H]$^+$.

3-(2,6-dichlorophenyl)-1-phenyl-3-(pyrrolidin-1-yl)propan-1-one (8): Compound **8** was synthesized according to a literature procedure describing similar products.[2] A mixture of chalcone **7**[3] (0.5 mmol, 1 equiv), pyrrolidine (5 mmol, 10 equiv) and water (5 mmol, 10 equiv) was stirred at room temperature for two days. The mixture was then diluted with EtOAc (10 mL), washed with water (40 mL) and brine (40 mL), and dried over anhydrous Na_2SO_4. Solvent was then removed under reduced pressure and ^{1}H-NMR was taken for the crude product (Note: the crude product contained unreacted chalcone which was not removed). ^{1}H NMR of aliphatic protons (400 MHz, $CDCl_3$) 5.03 (dd, *J* = 7.1, 5.9 Hz, 1H), 3.89 (dd, *J* = 17.2, 7.1 Hz, 1H), 3.77 (dd, *J* = 17.2, 5.9 Hz, 1H), 2.70–2.57 (comp, 2H), 2.45–2.34 (comp, 2H), 1.83–1.64 (comp, 4H).

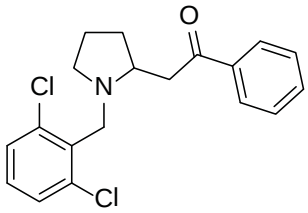
References:

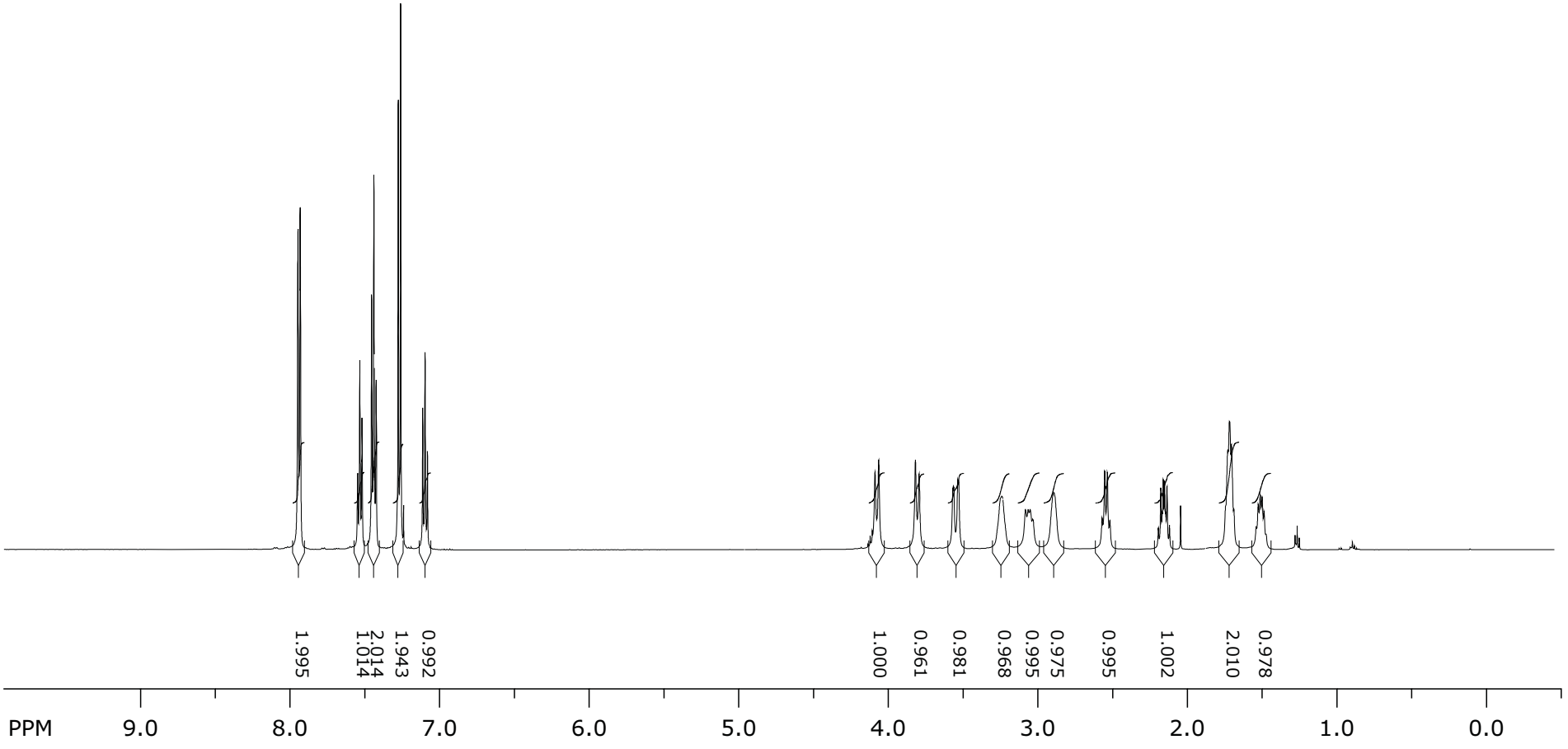
(1) Cromwell, N. H.; Burch, J. S. *J. Am. Chem. Soc.* **1944**, *66*, 872

(2) Moghaddam, F. M.; Mohammadi, M.; Hosseinnia, A. *Synth. Commun.* **2000**, *30*, 643.

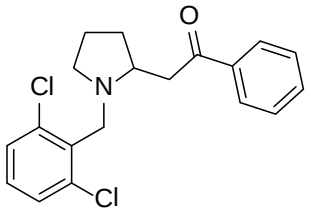
(3) Boumendjel, A.; Boccard, J.; Carrupt, P.-A.; Nicolle, E.; Blanc, M.; Geze, A.; Choisnard, L.; Wouessidjewe, D.; Matera, E.-L.; Dumontet, C. *J. Med. Chem.* **2008**, *51*, 2307.

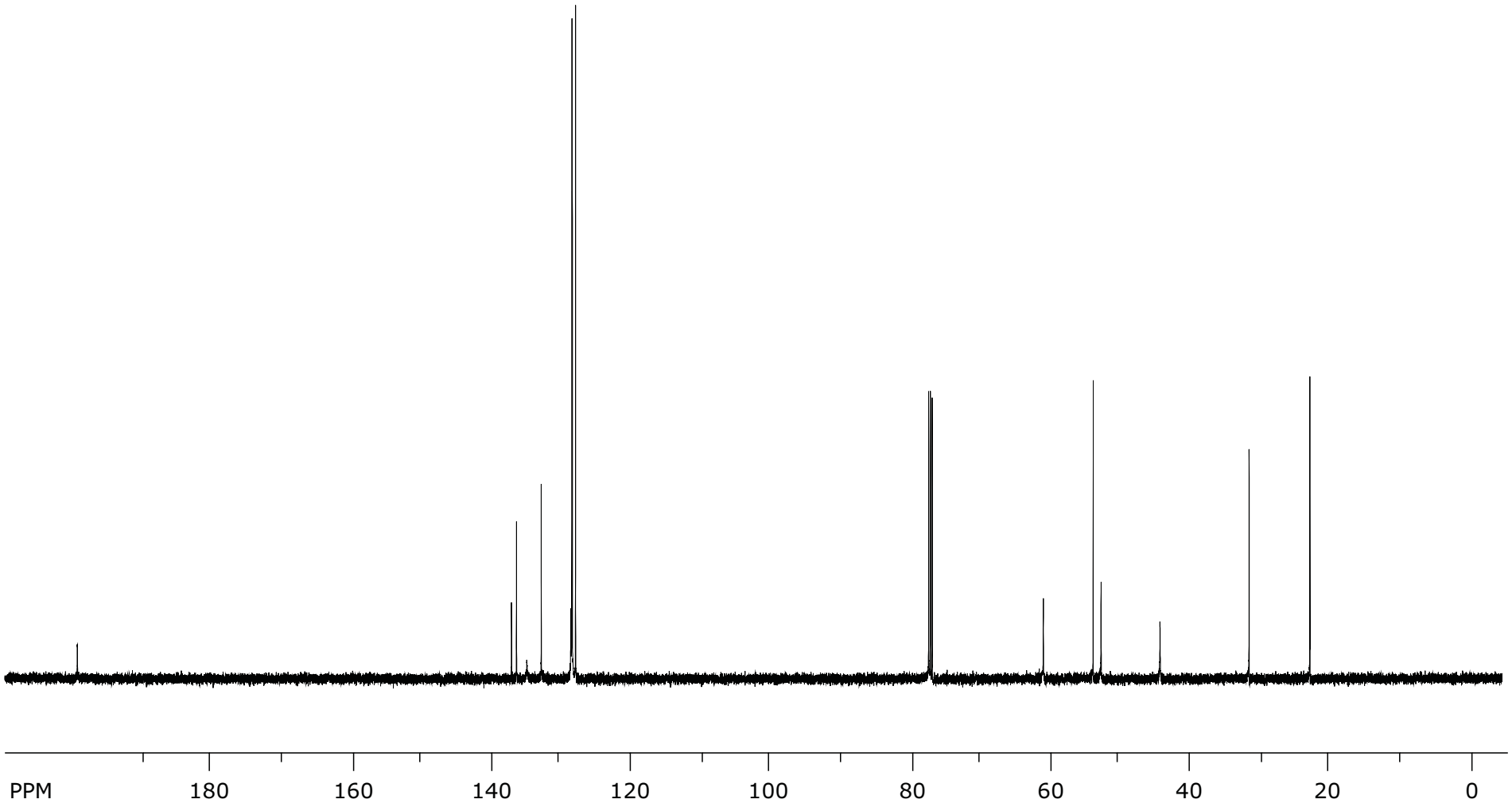
^{1}H NMR of **1a** in $CDCl_3$



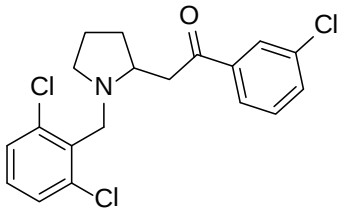


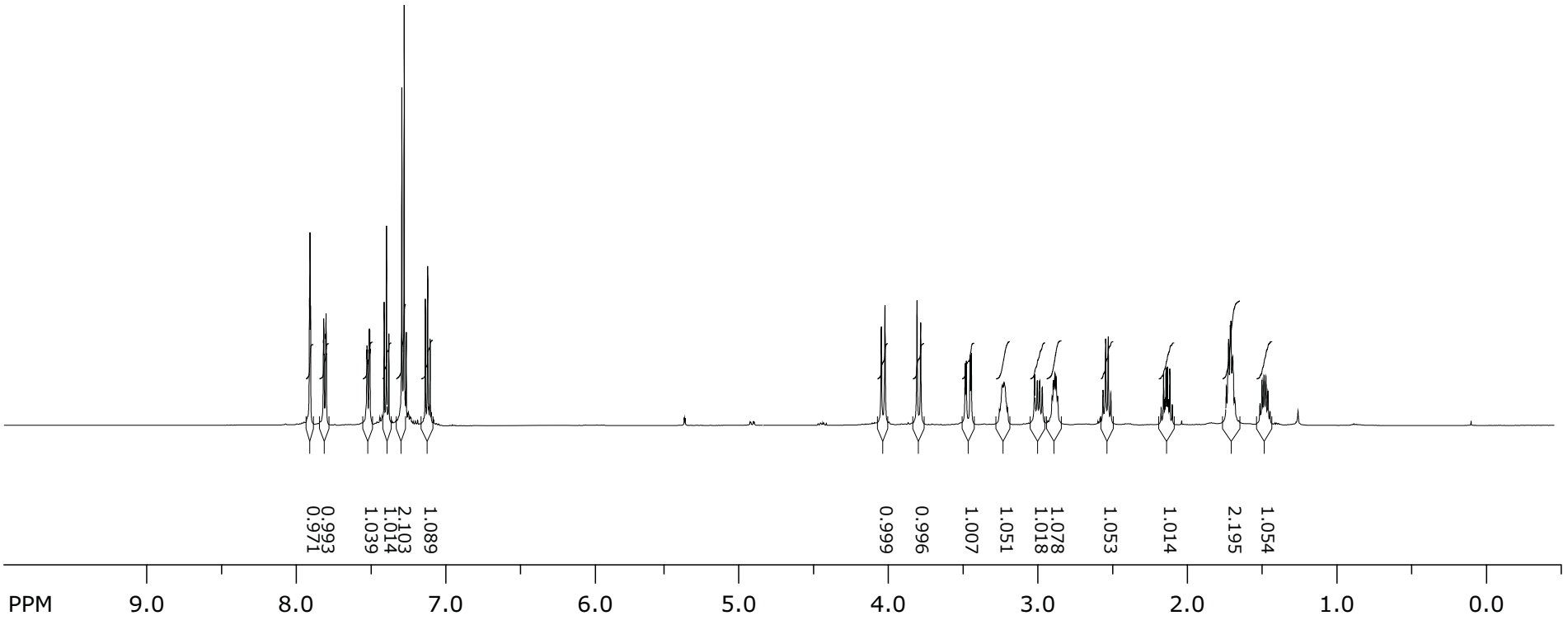
^{13}C NMR of **1a** in $CDCl_3$



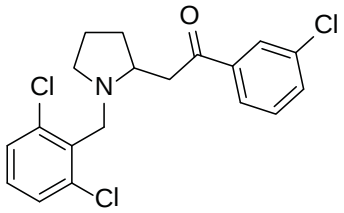


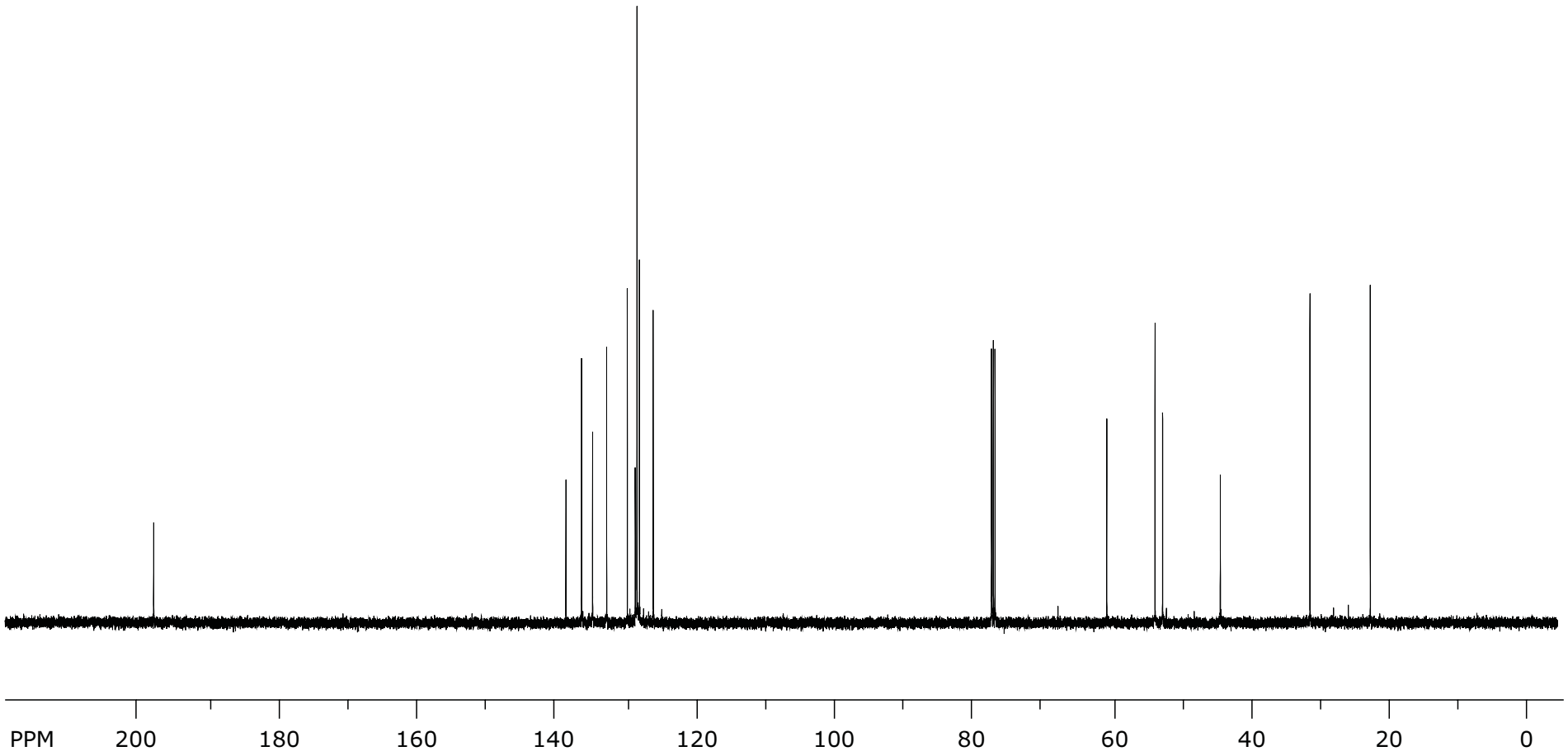
^{1}H NMR of **1b** in $CDCl_3$



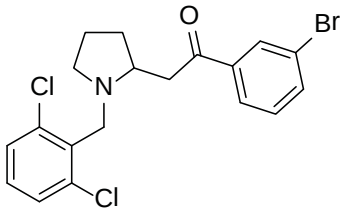


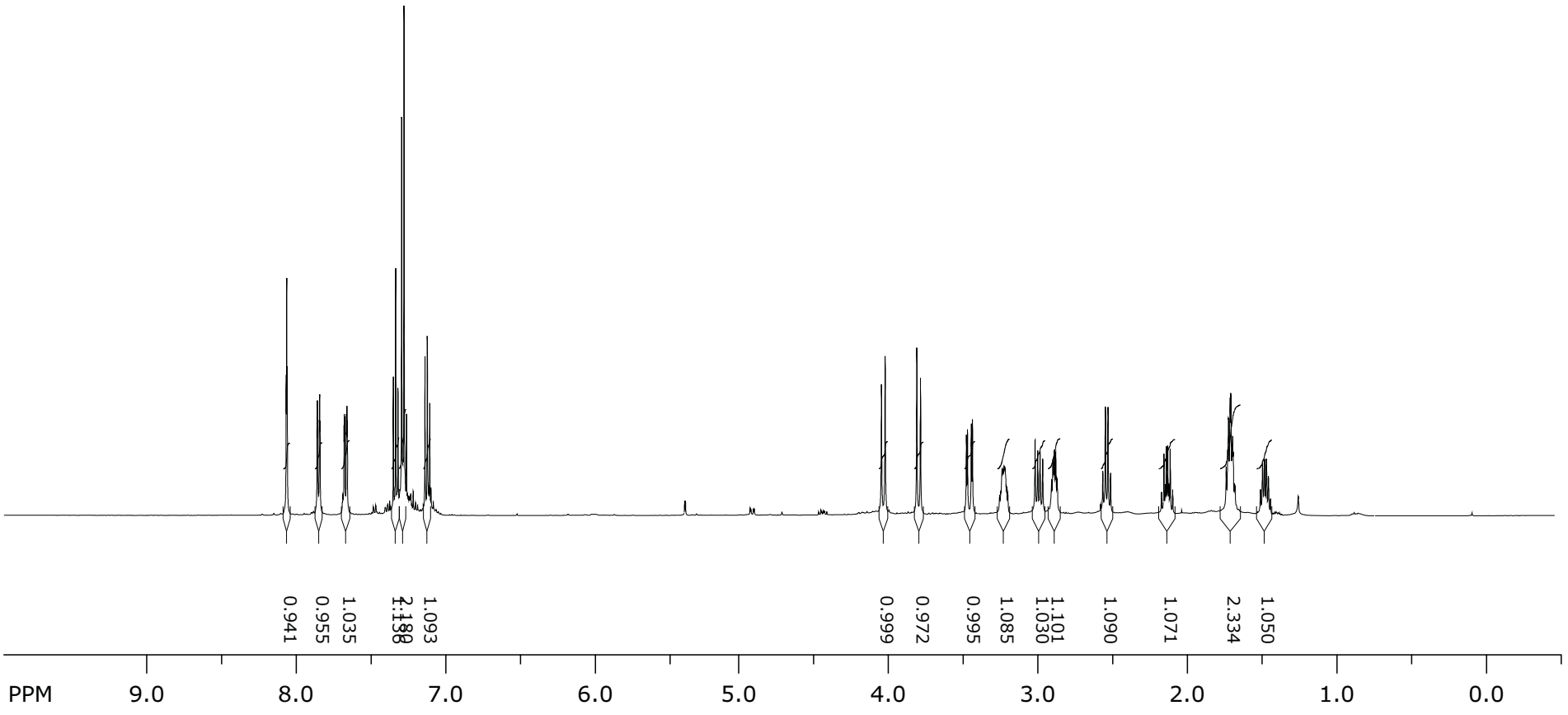
^{13}C NMR of **1b** in $CDCl_3$





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





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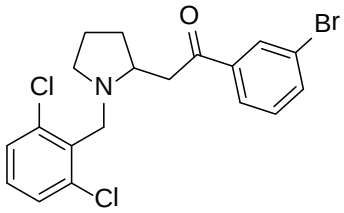
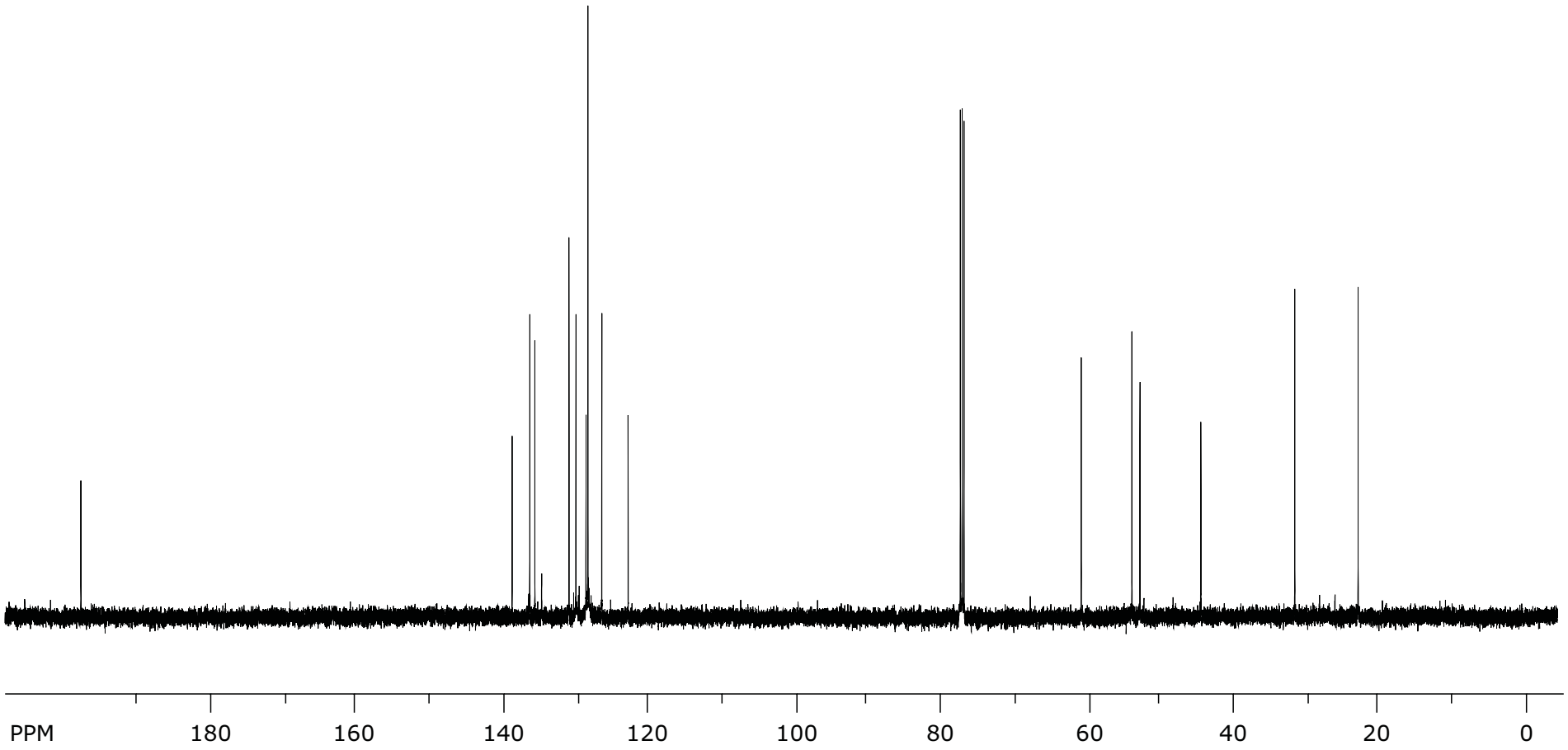
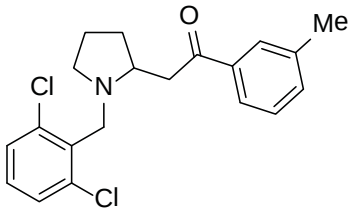
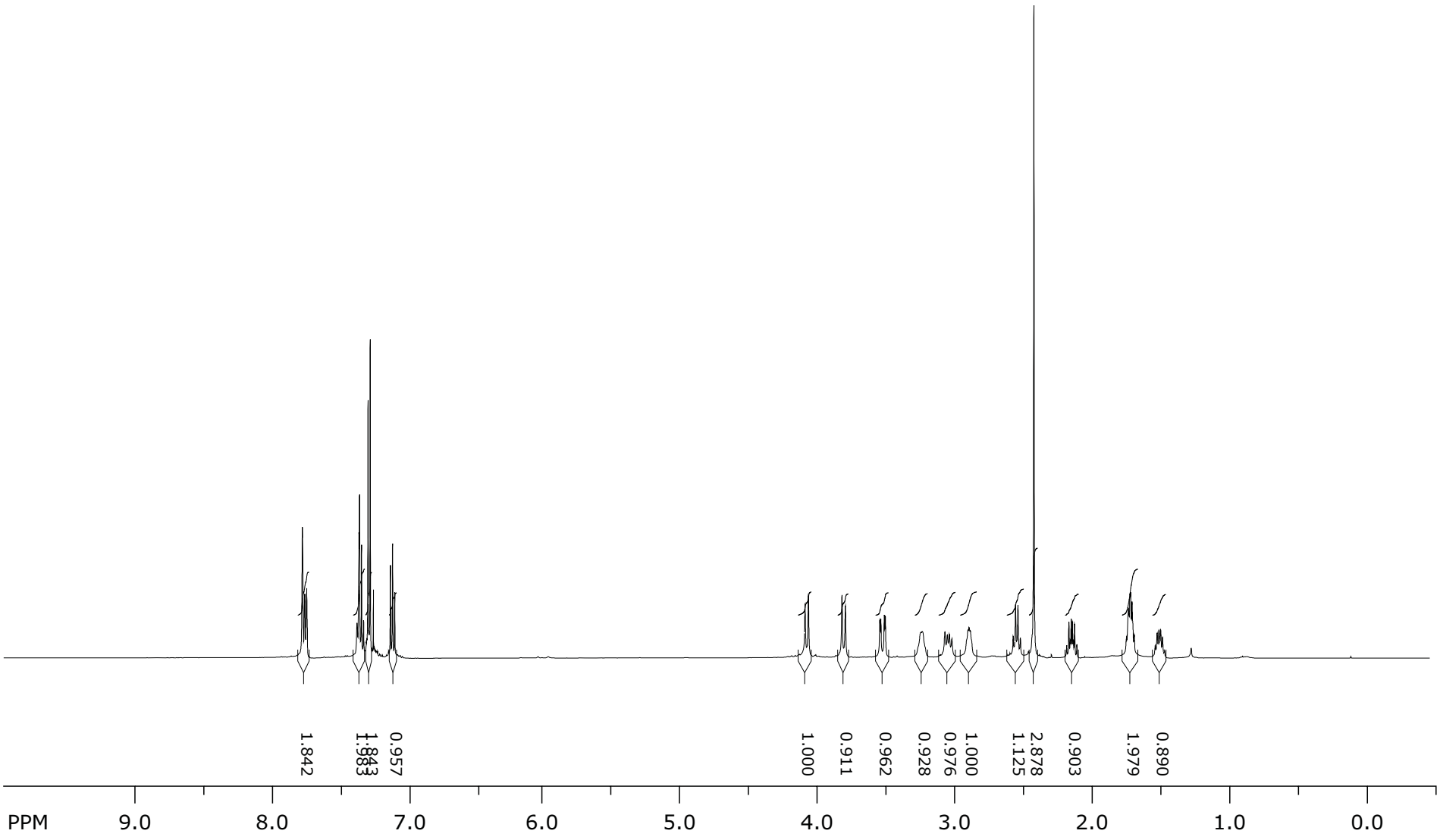


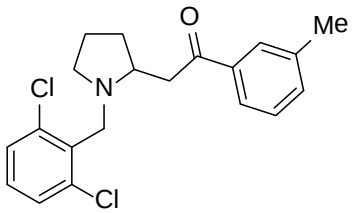


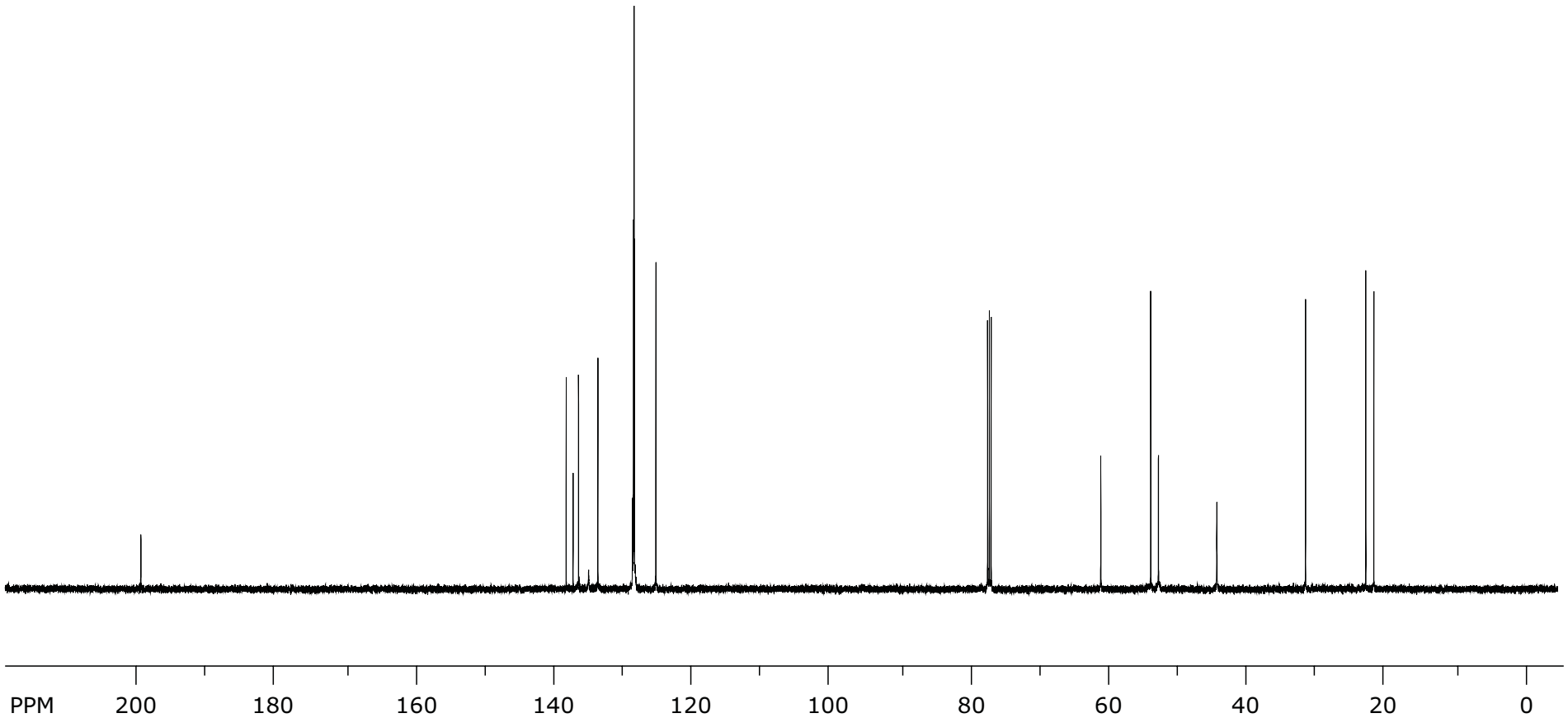
^{1}H NMR of **1d** in $CDCl_3$



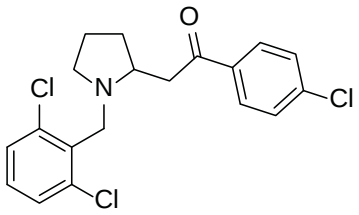


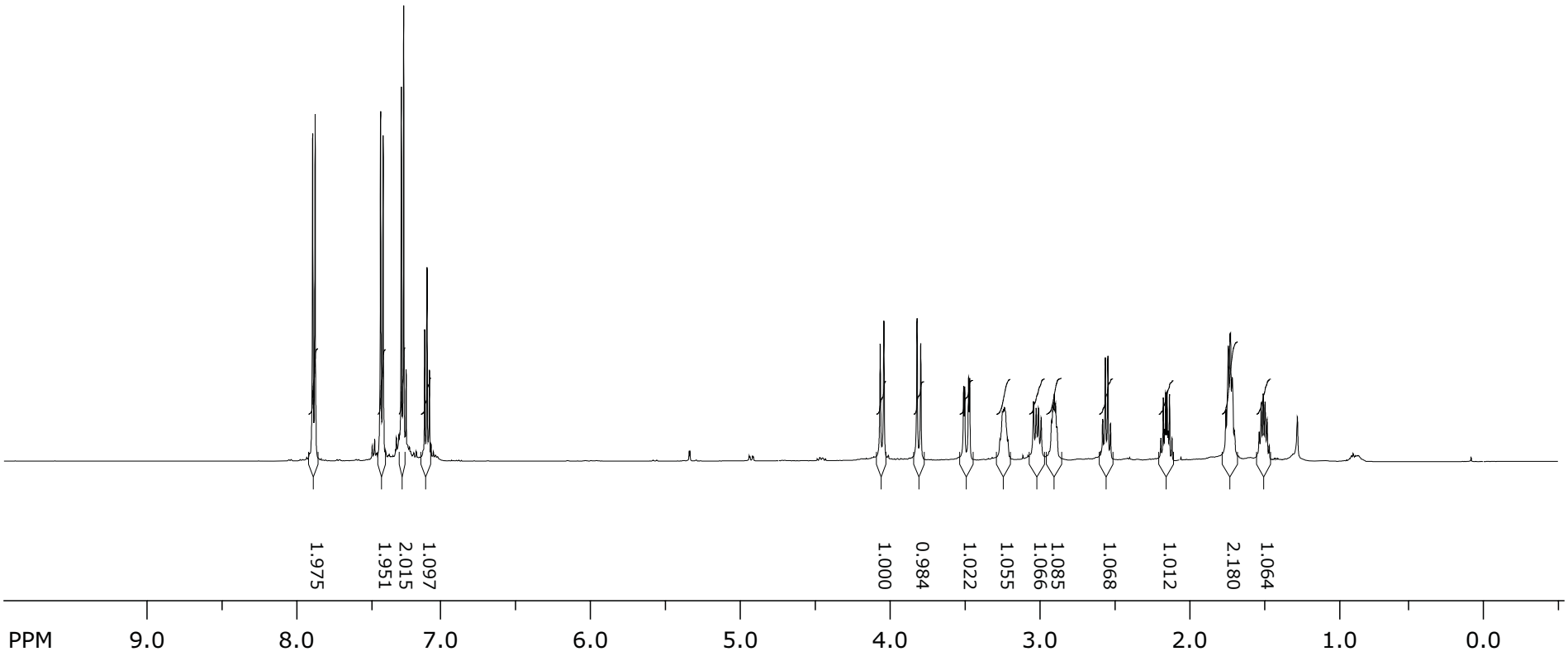
^{13}C NMR of **1d** in $CDCl_3$



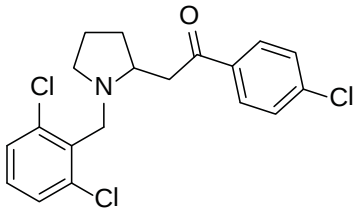


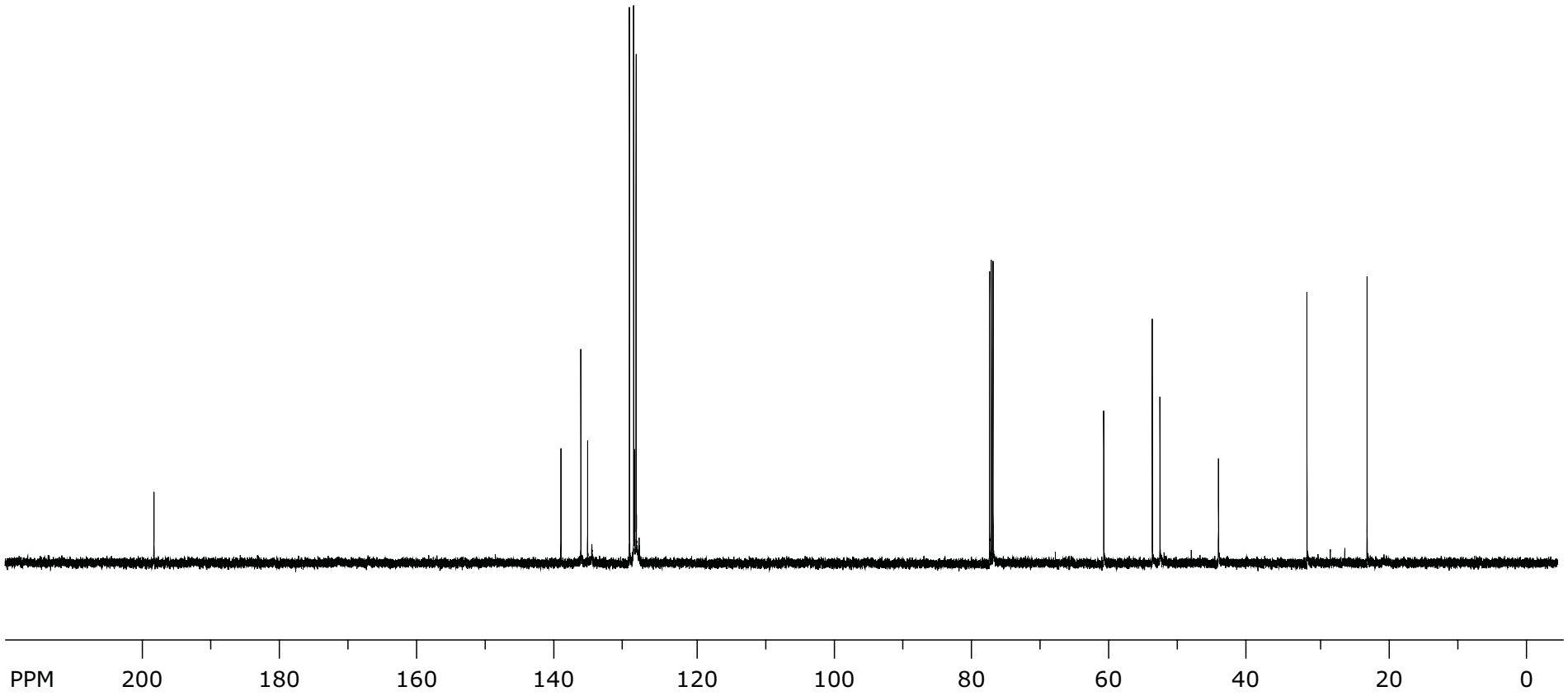
^{1}H NMR of **1e** in $CDCl_3$



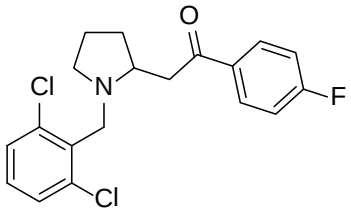


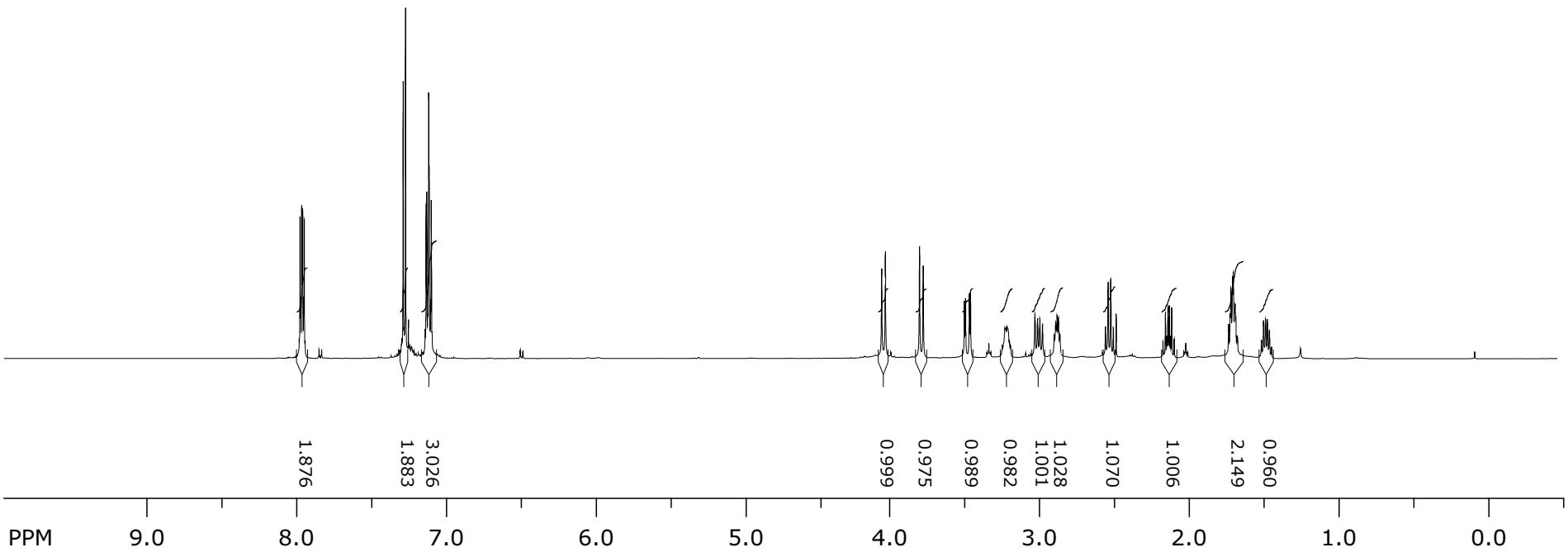
^{13}C NMR of **1e** in $CDCl_3$



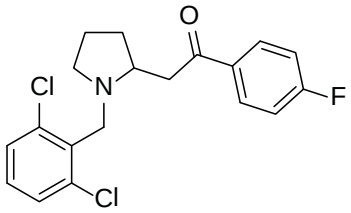


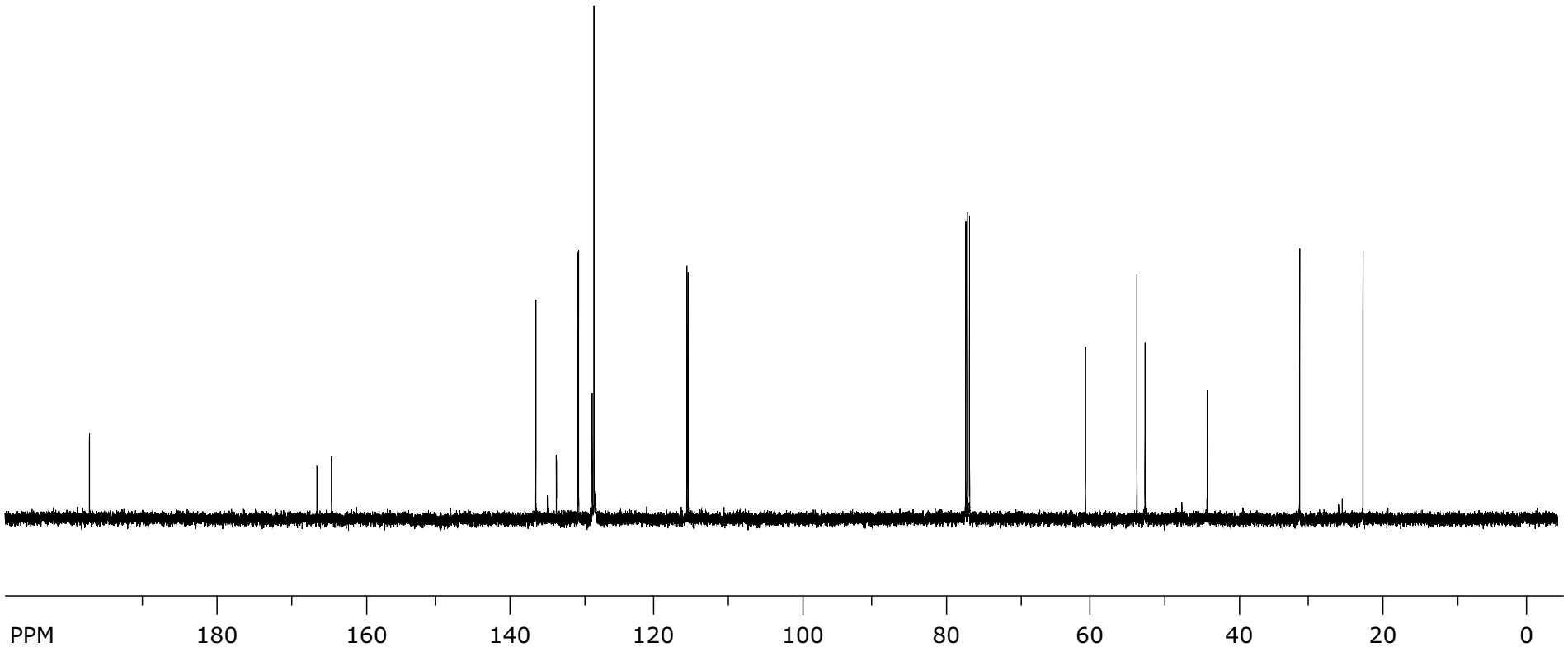
^{1}H NMR of **1f** in $CDCl_3$



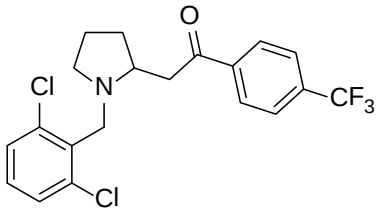


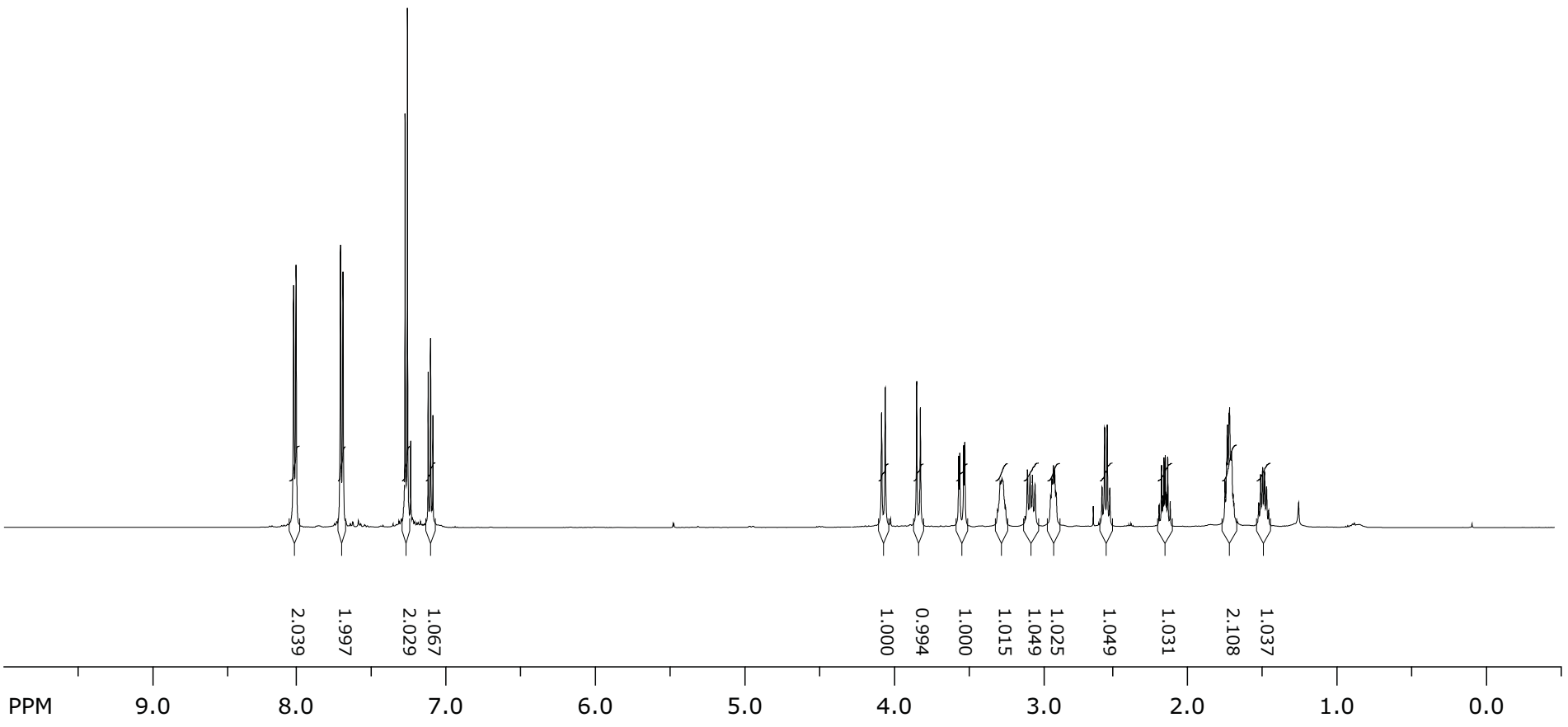
^{13}C NMR of **1f** in $CDCl_3$



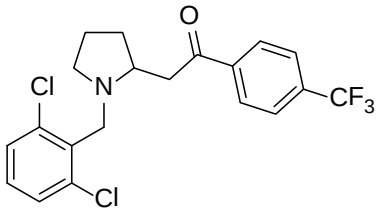


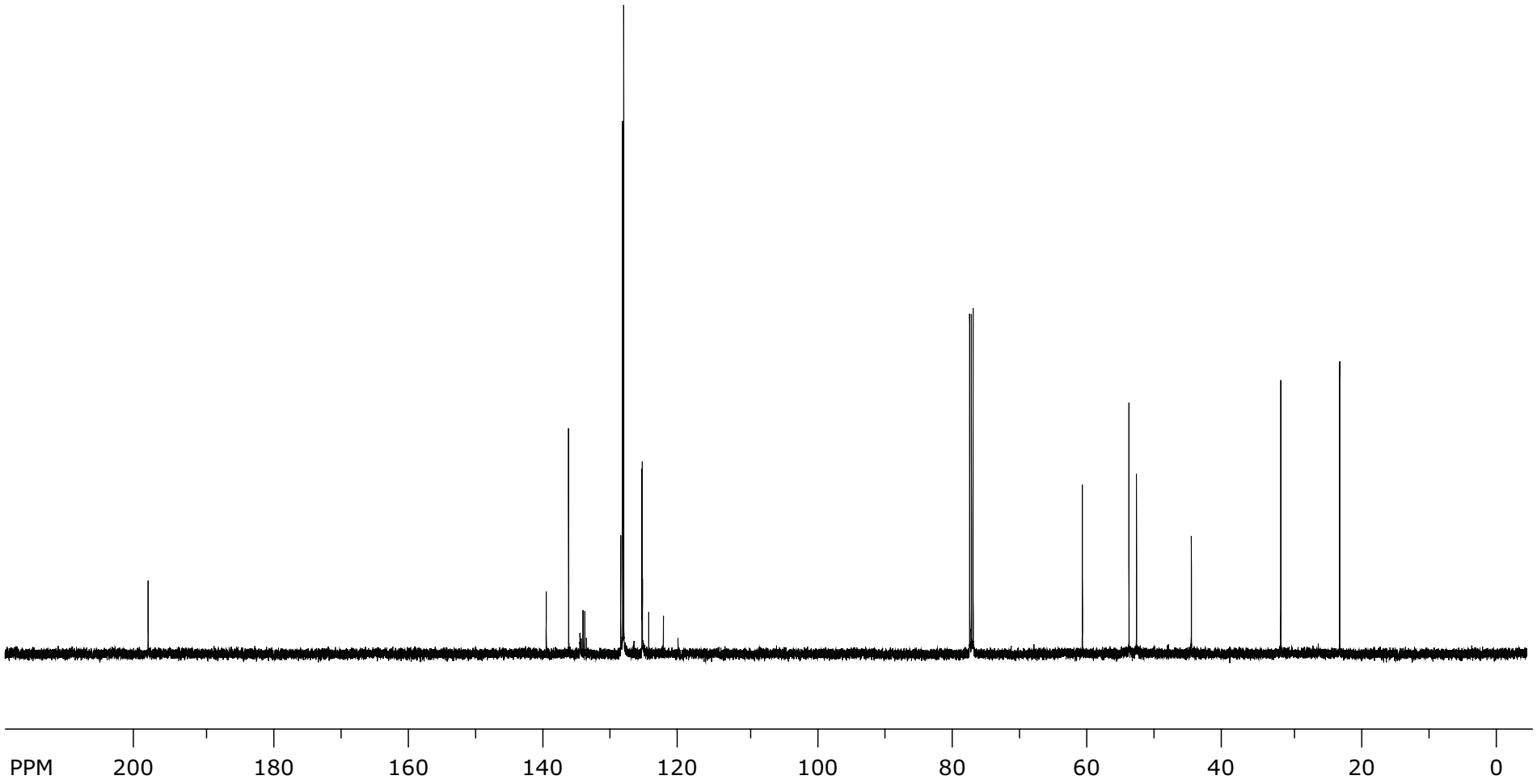
^{1}H NMR of **1g** in $CDCl_3$



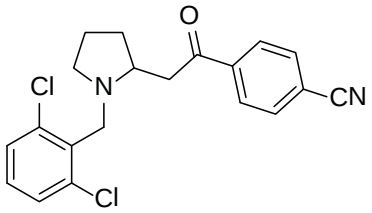


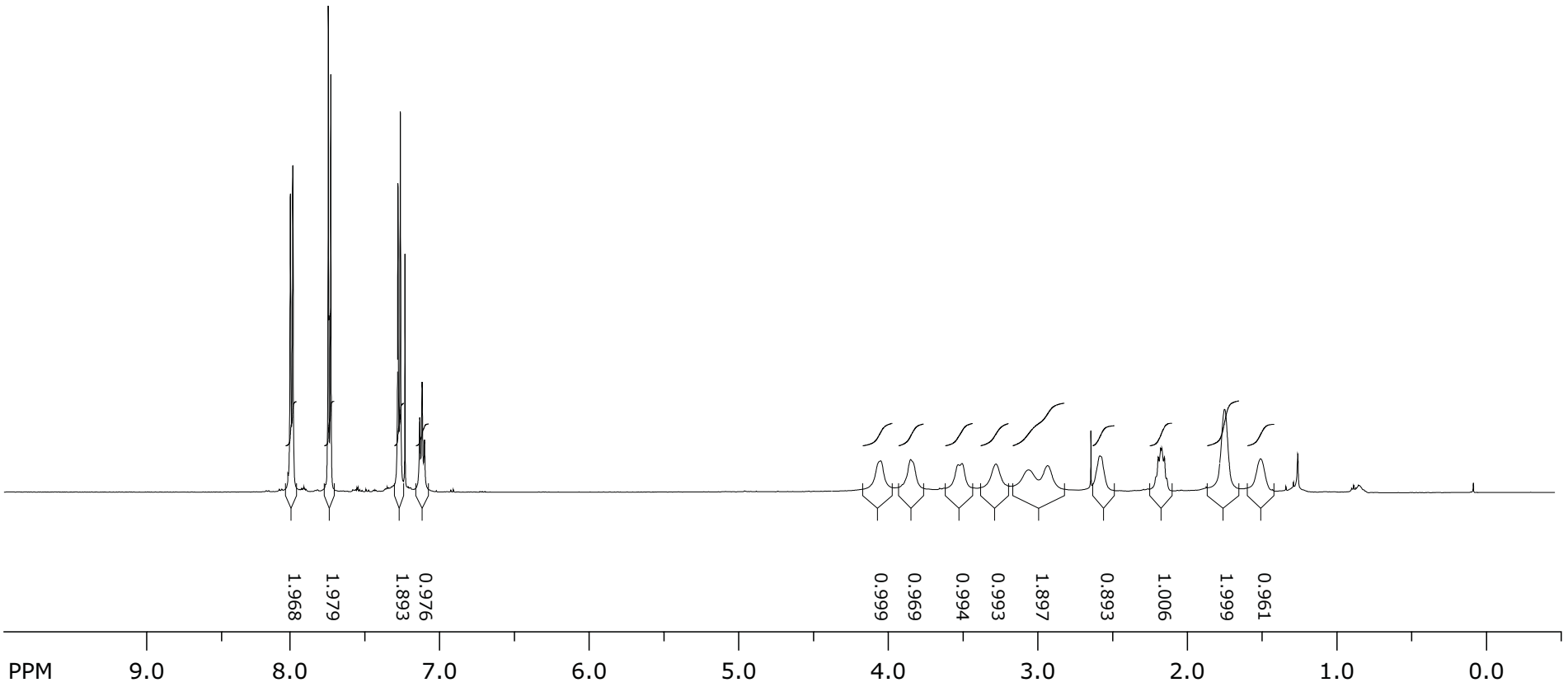
^{13}C NMR of **1g** in $CDCl_3$



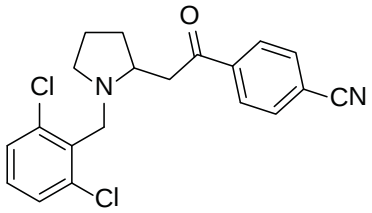


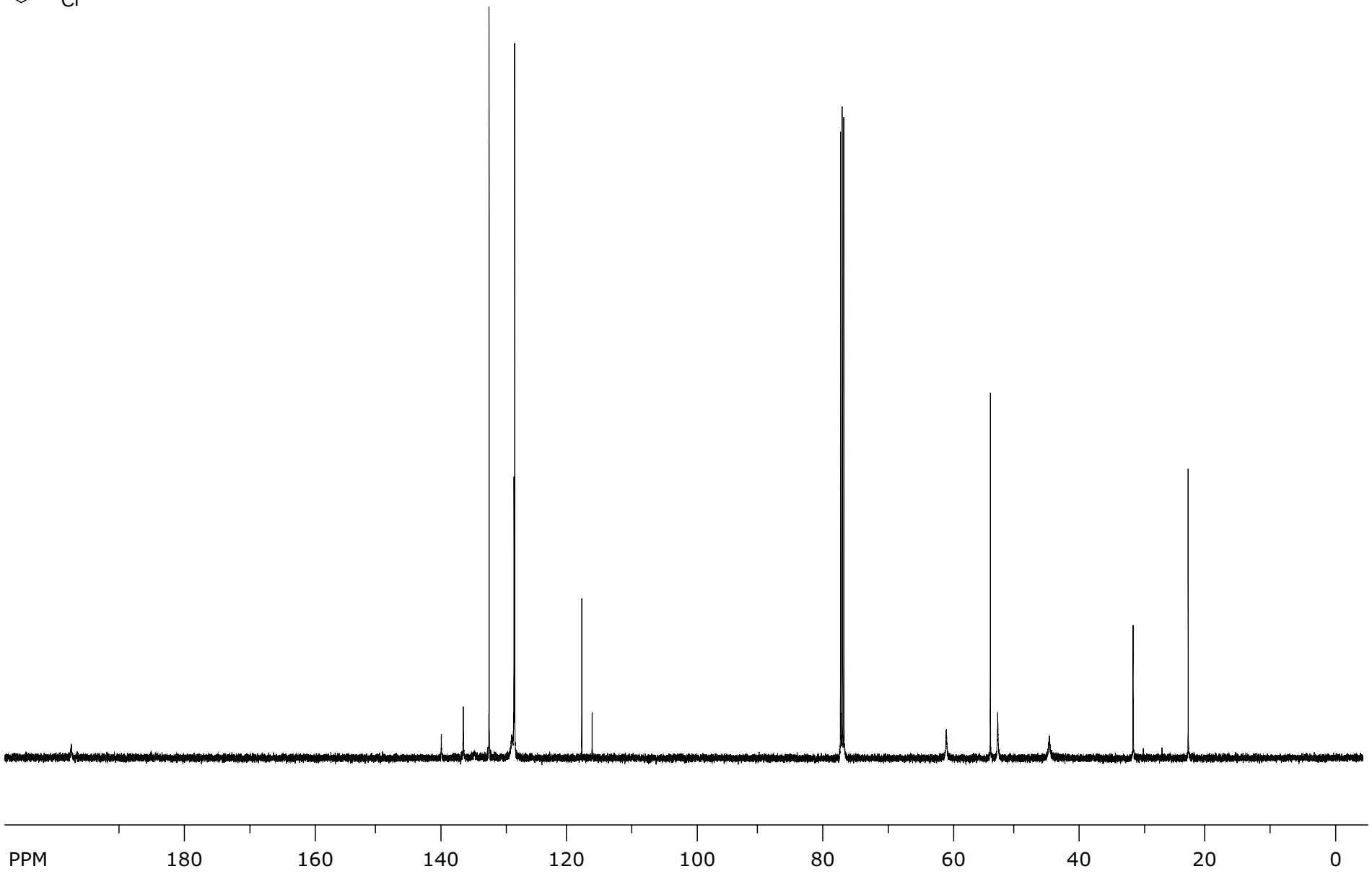
^{1}H NMR of **1h** in $CDCl_3$



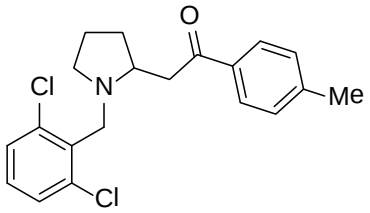


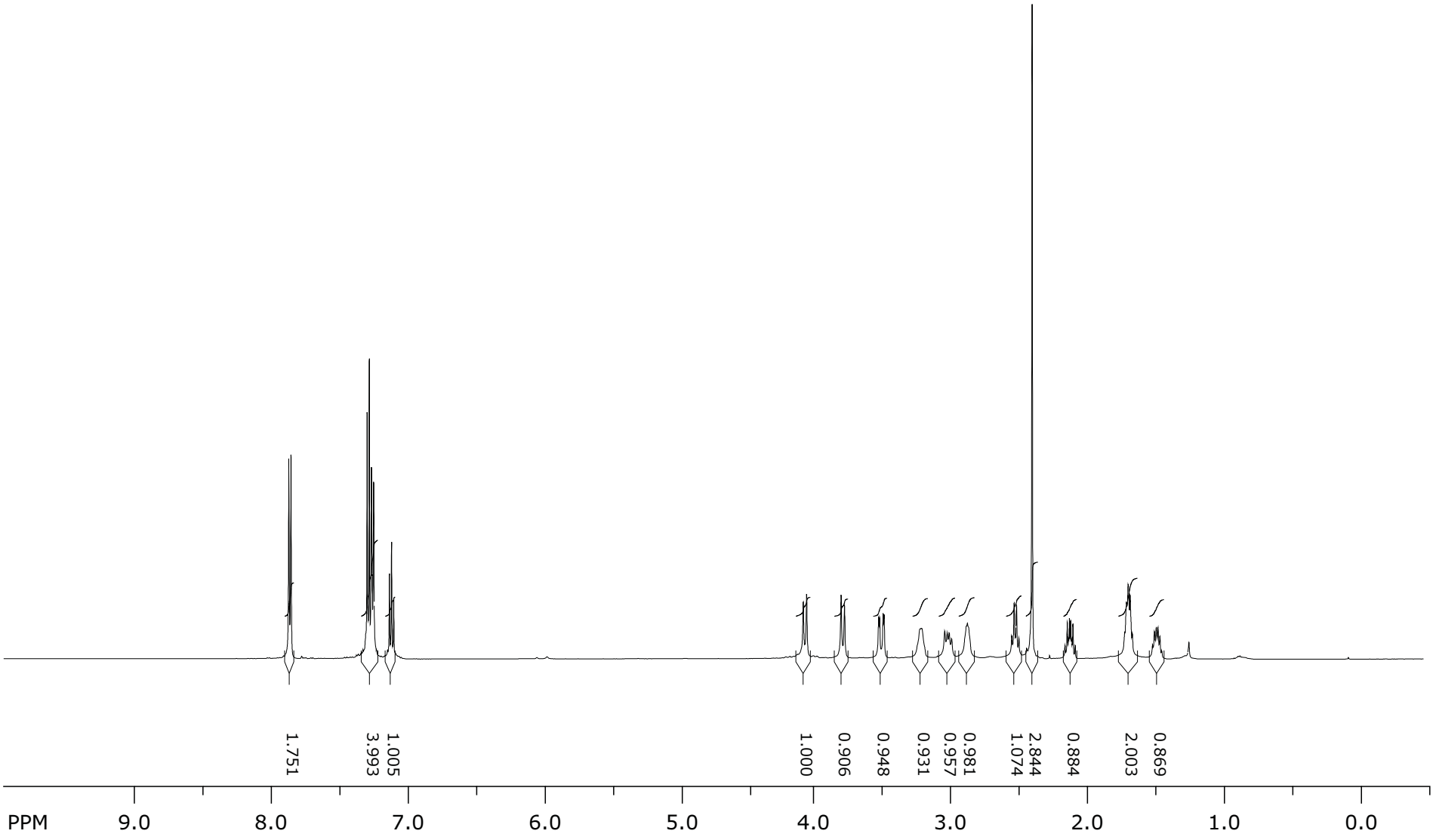
^{13}C NMR of **1h** in $CDCl_3$



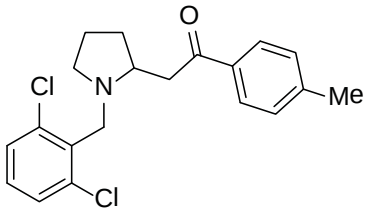


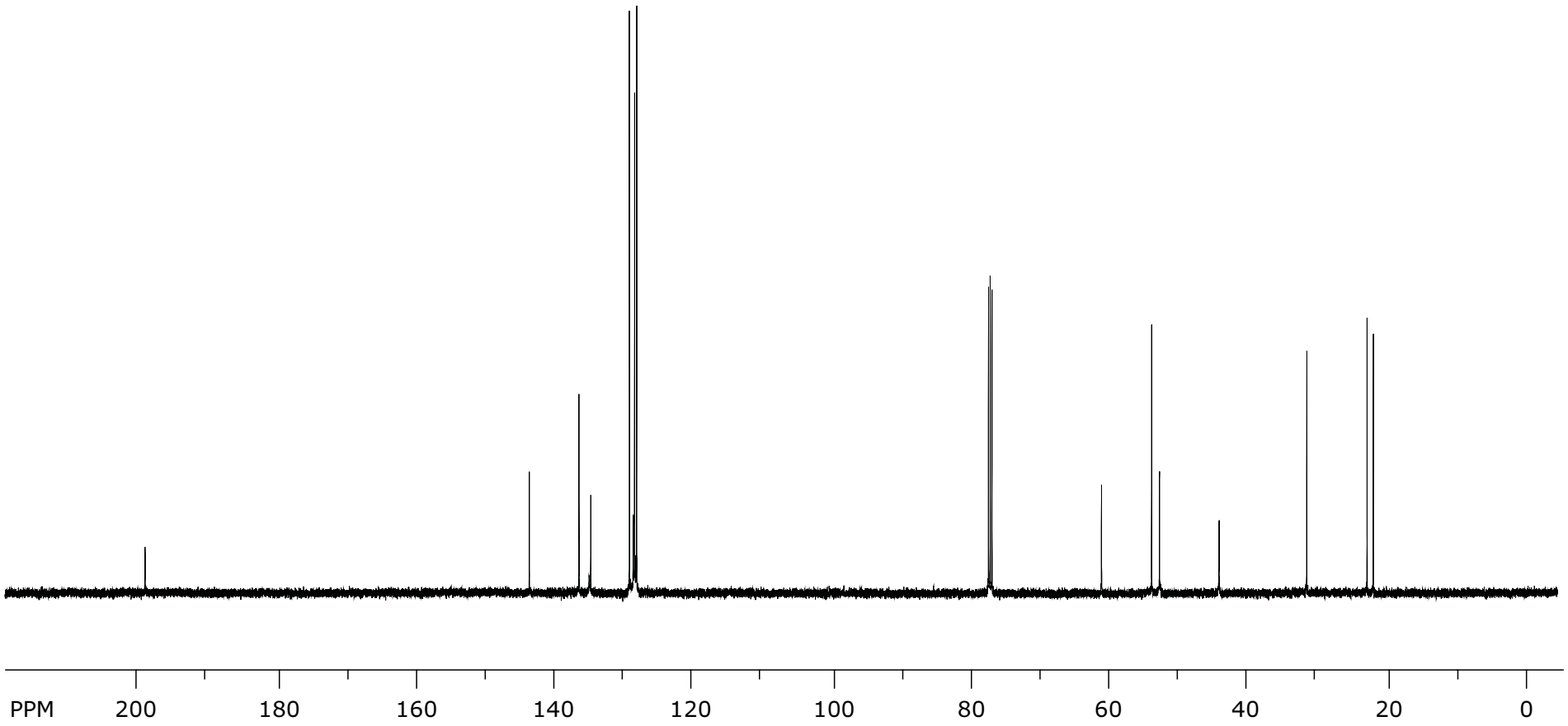
^{1}H NMR of **1i** in $CDCl_3$



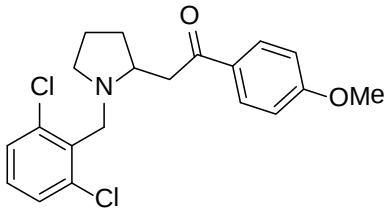


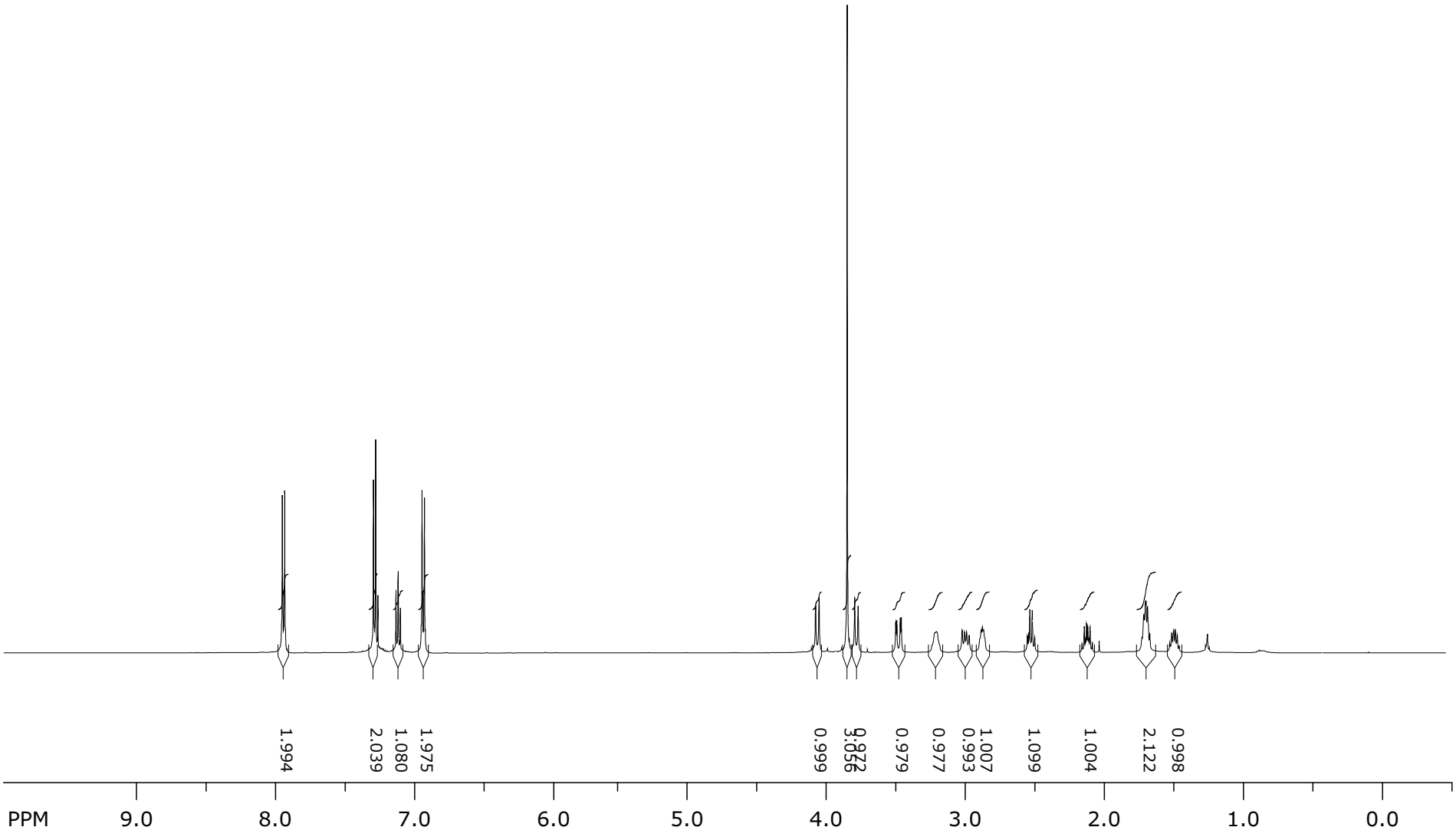
^{13}C NMR of **1i** in $CDCl_3$





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





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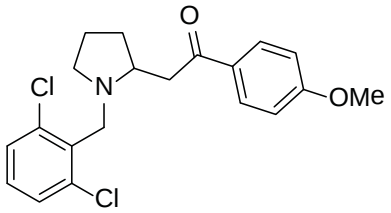
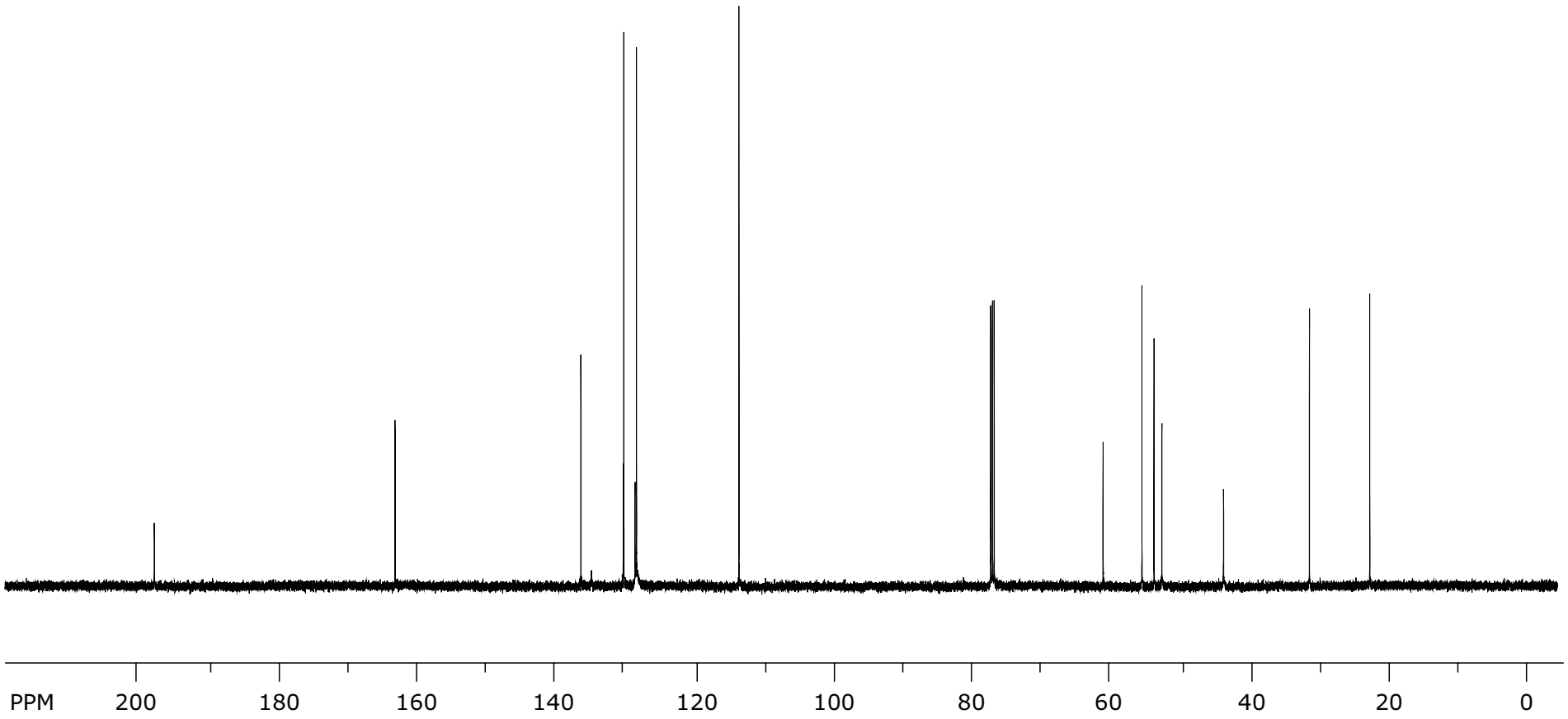
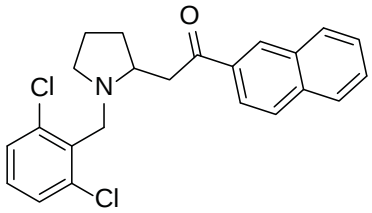
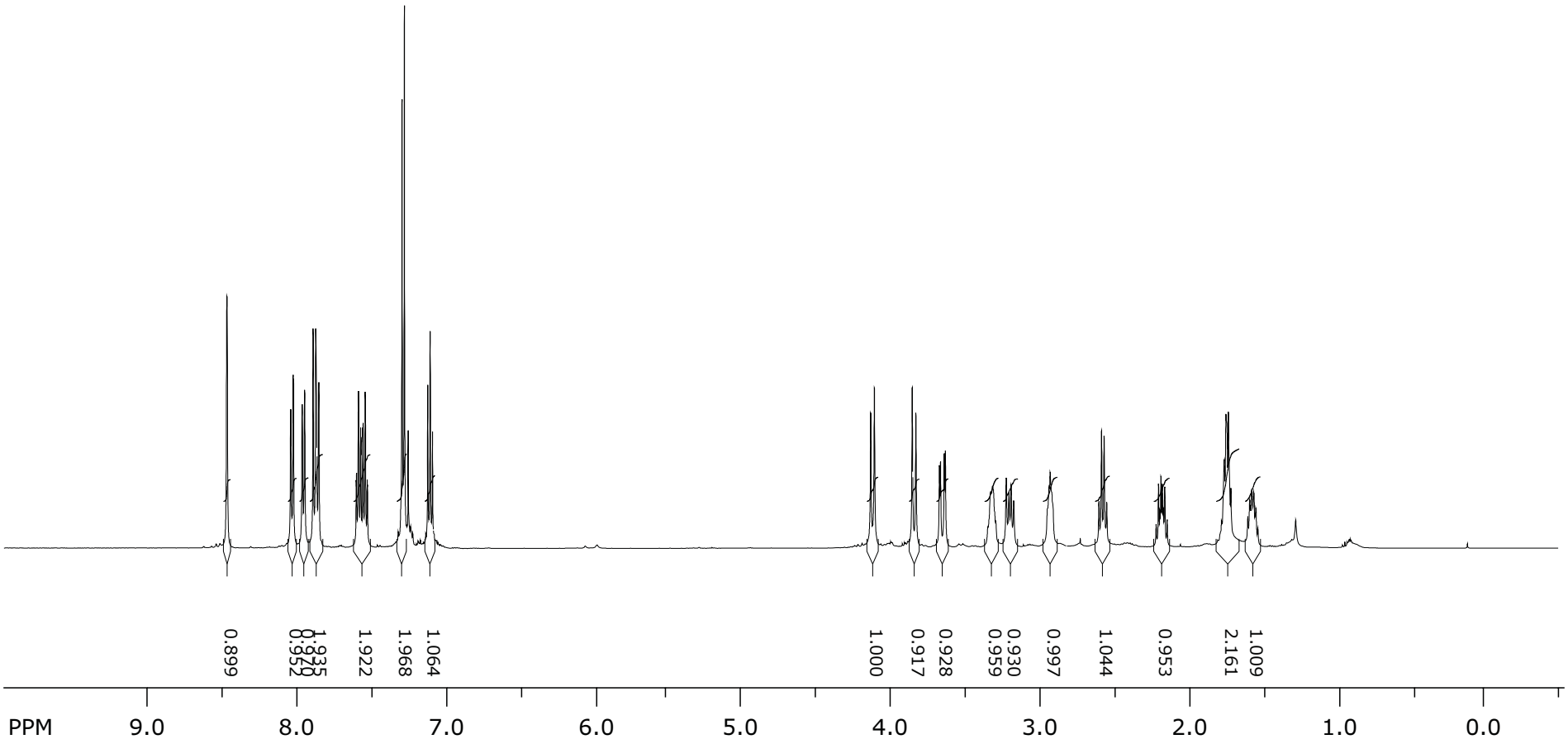




^{1}H NMR of **1k** in $CDCl_3$





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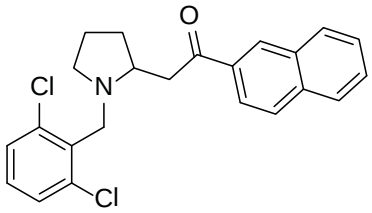

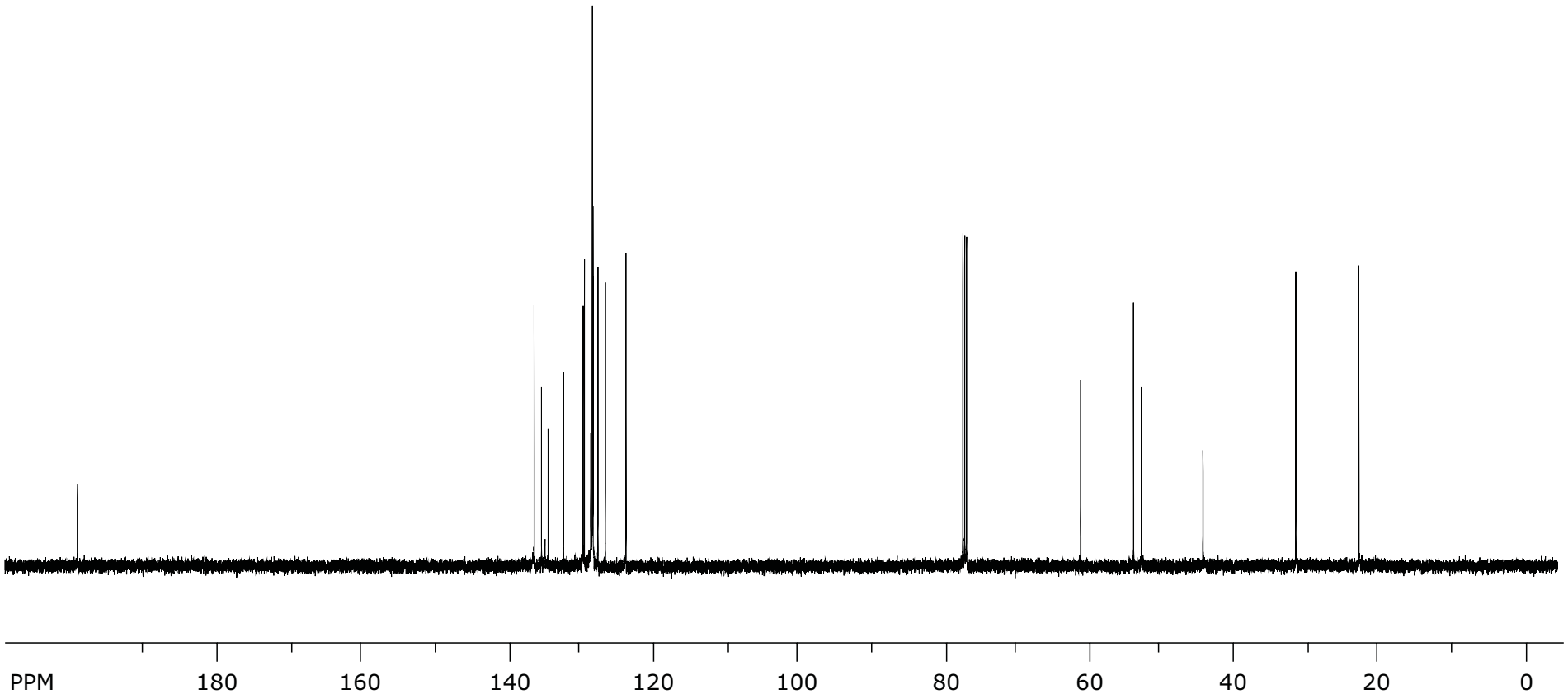

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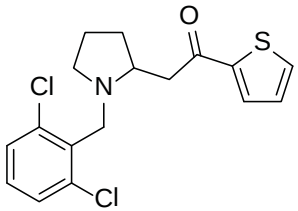

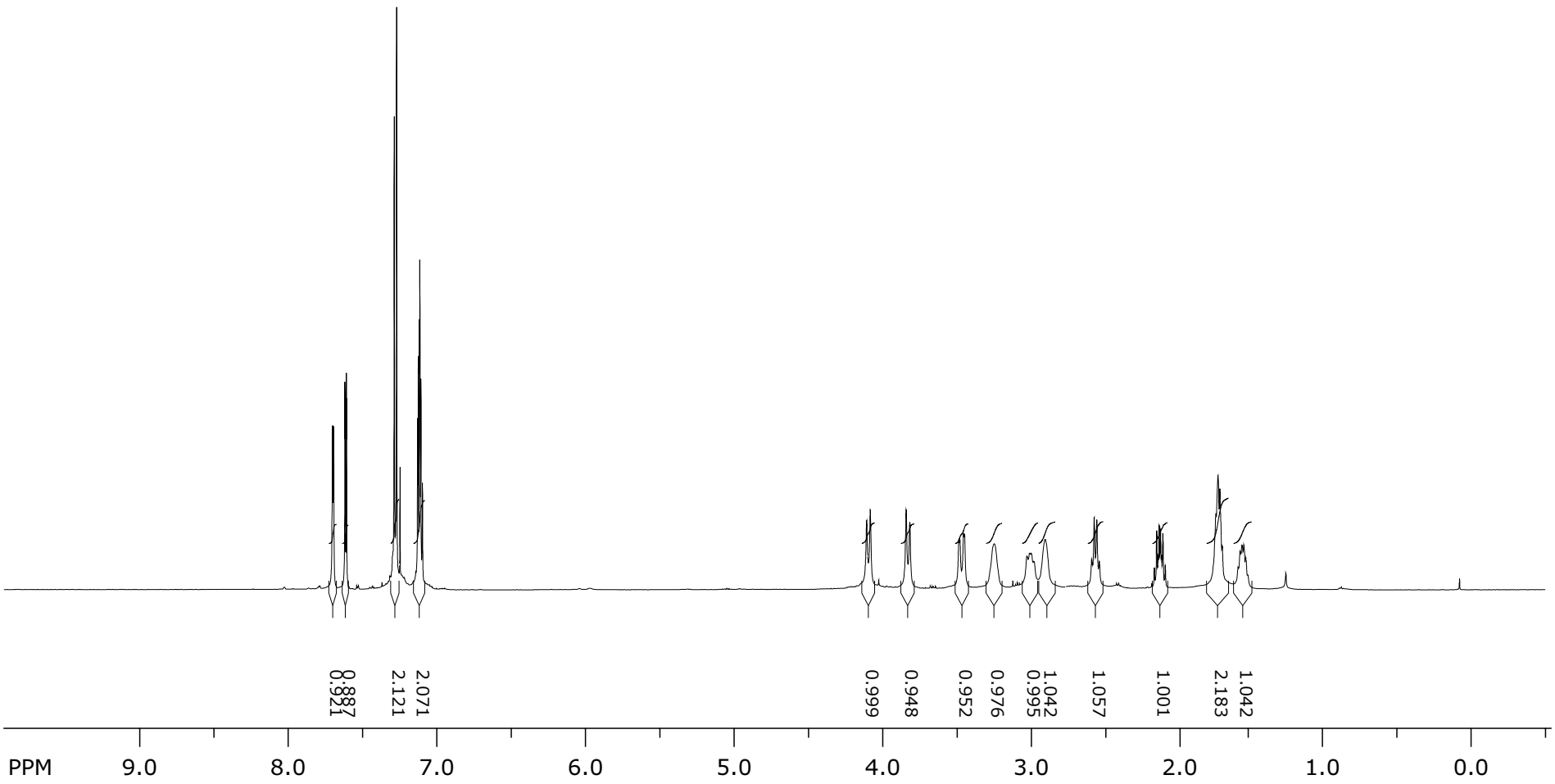

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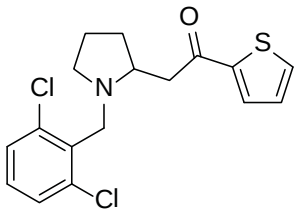
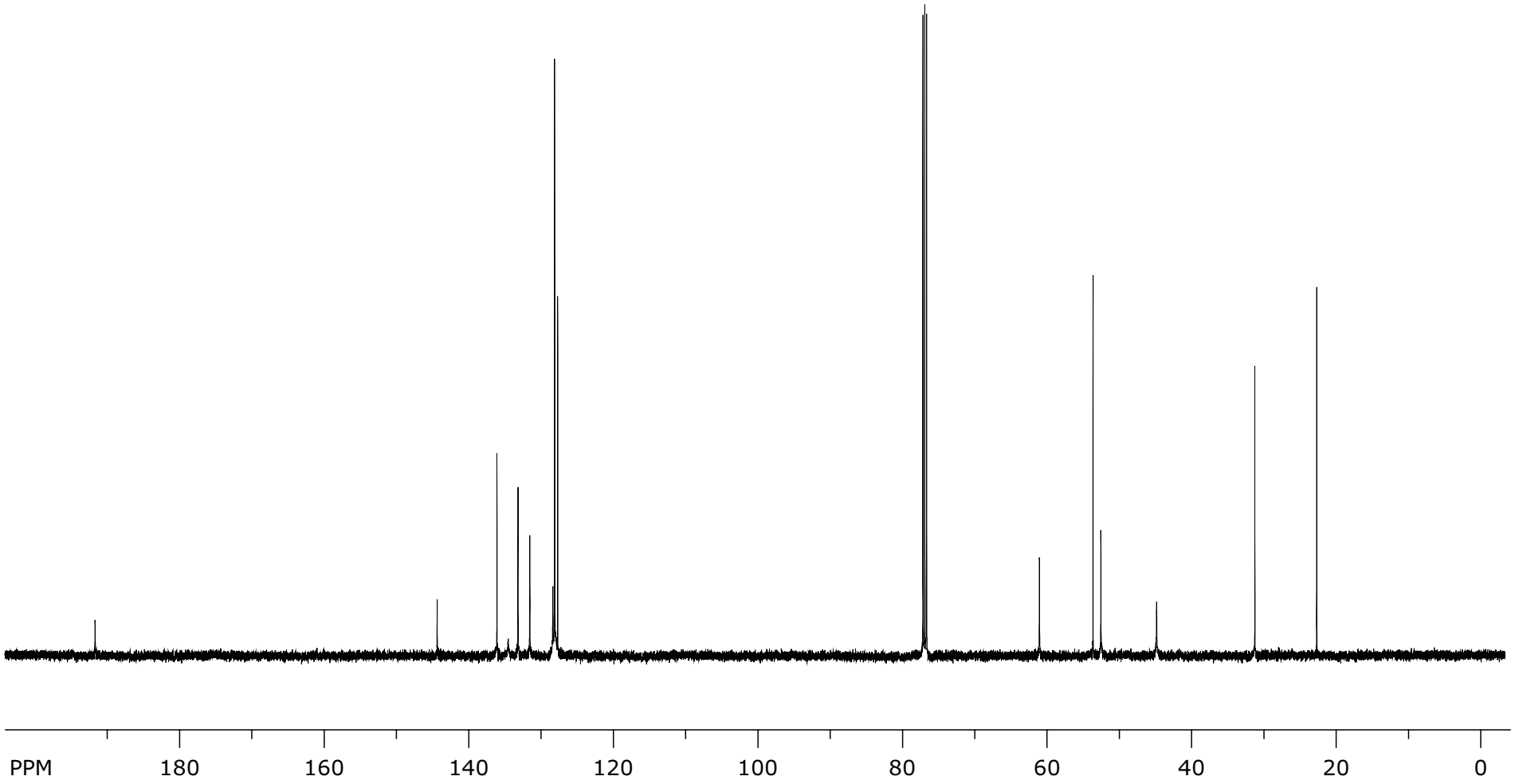
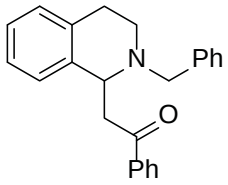
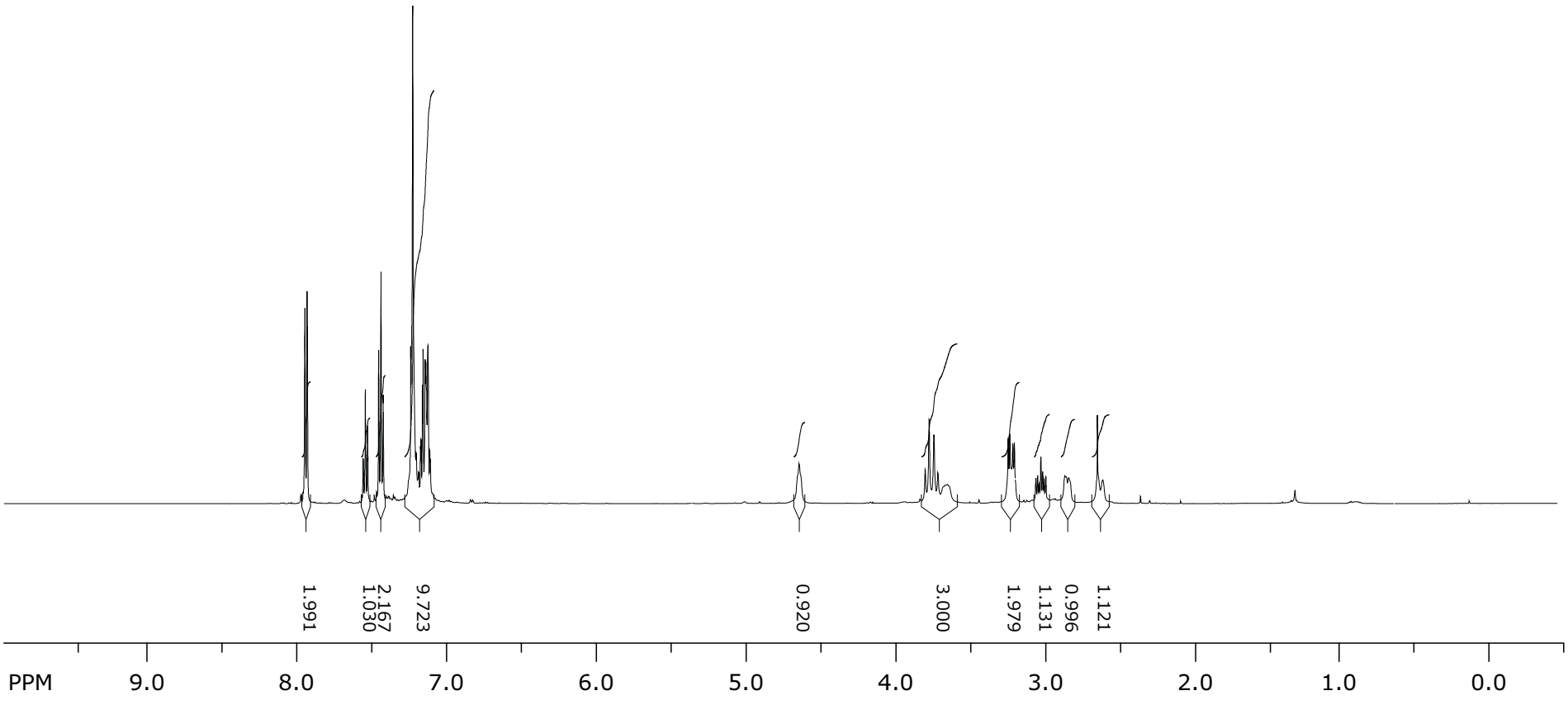


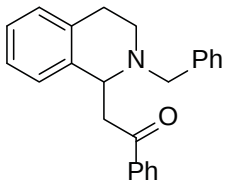


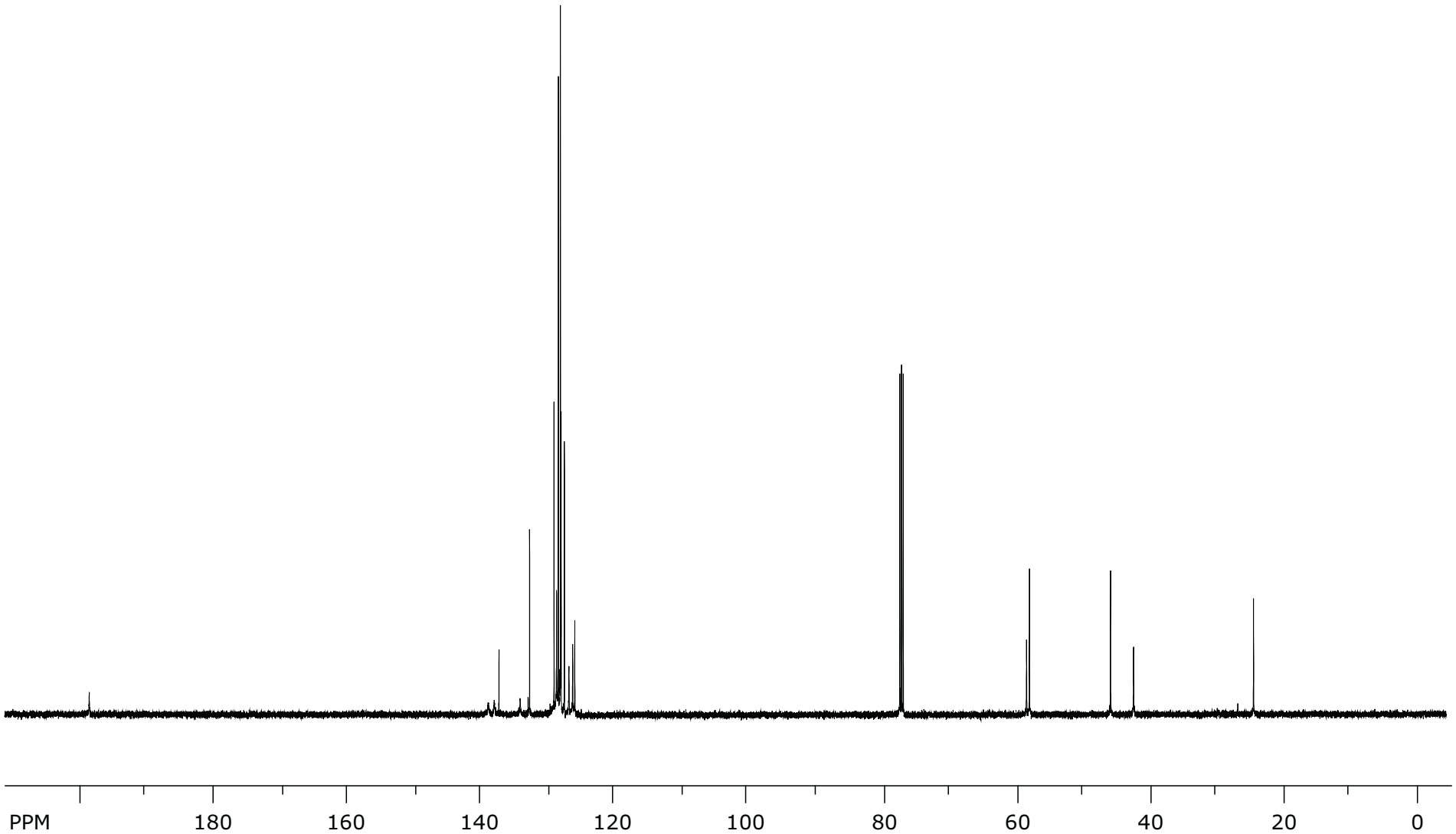
^{1}H NMR of **2a** in $CDCl_3$



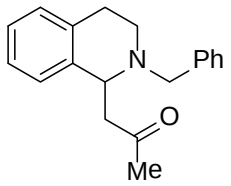


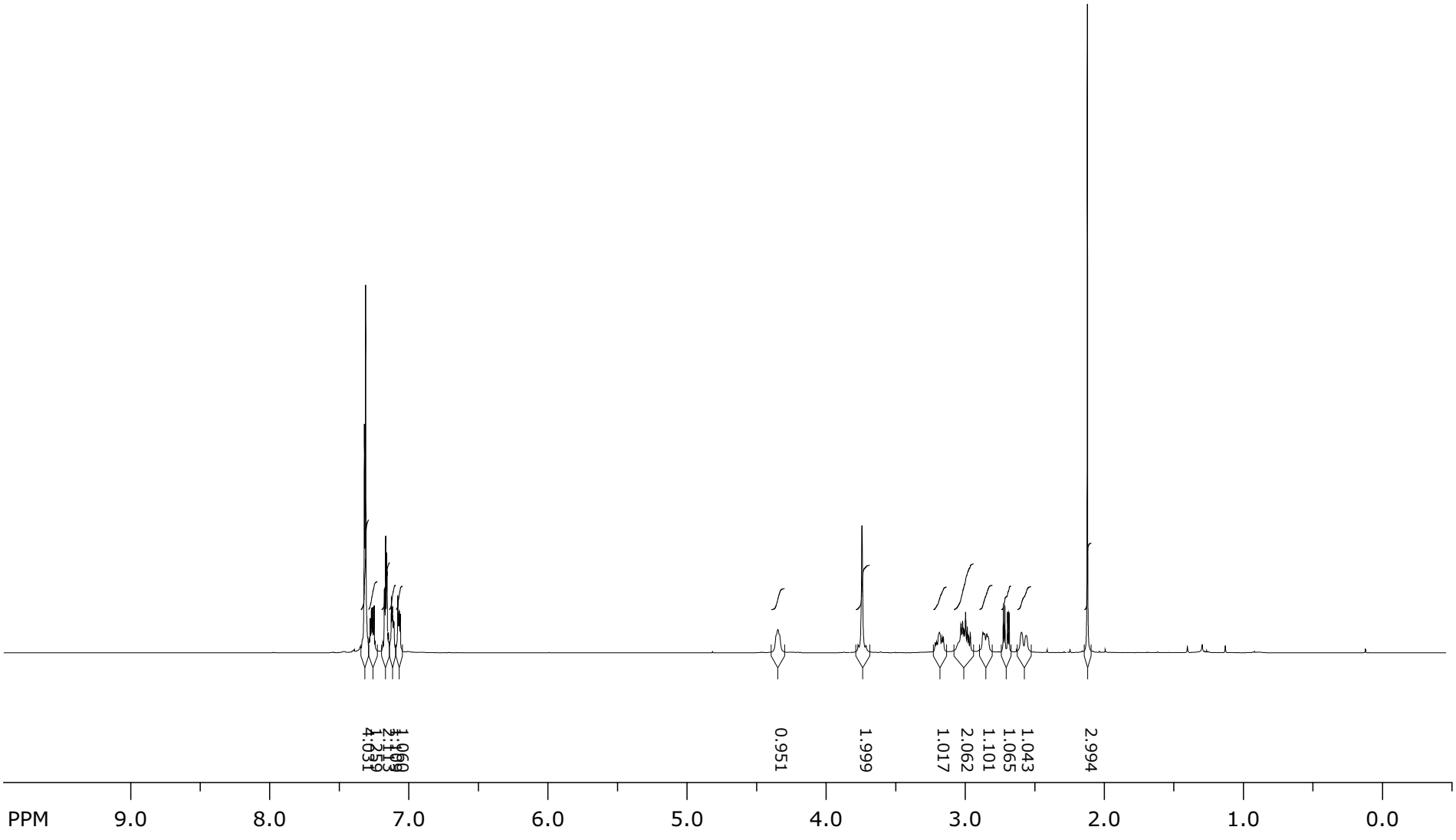
^{13}C NMR of **2a** in $CDCl_3$



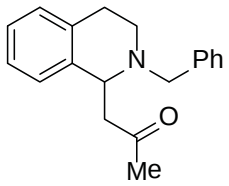


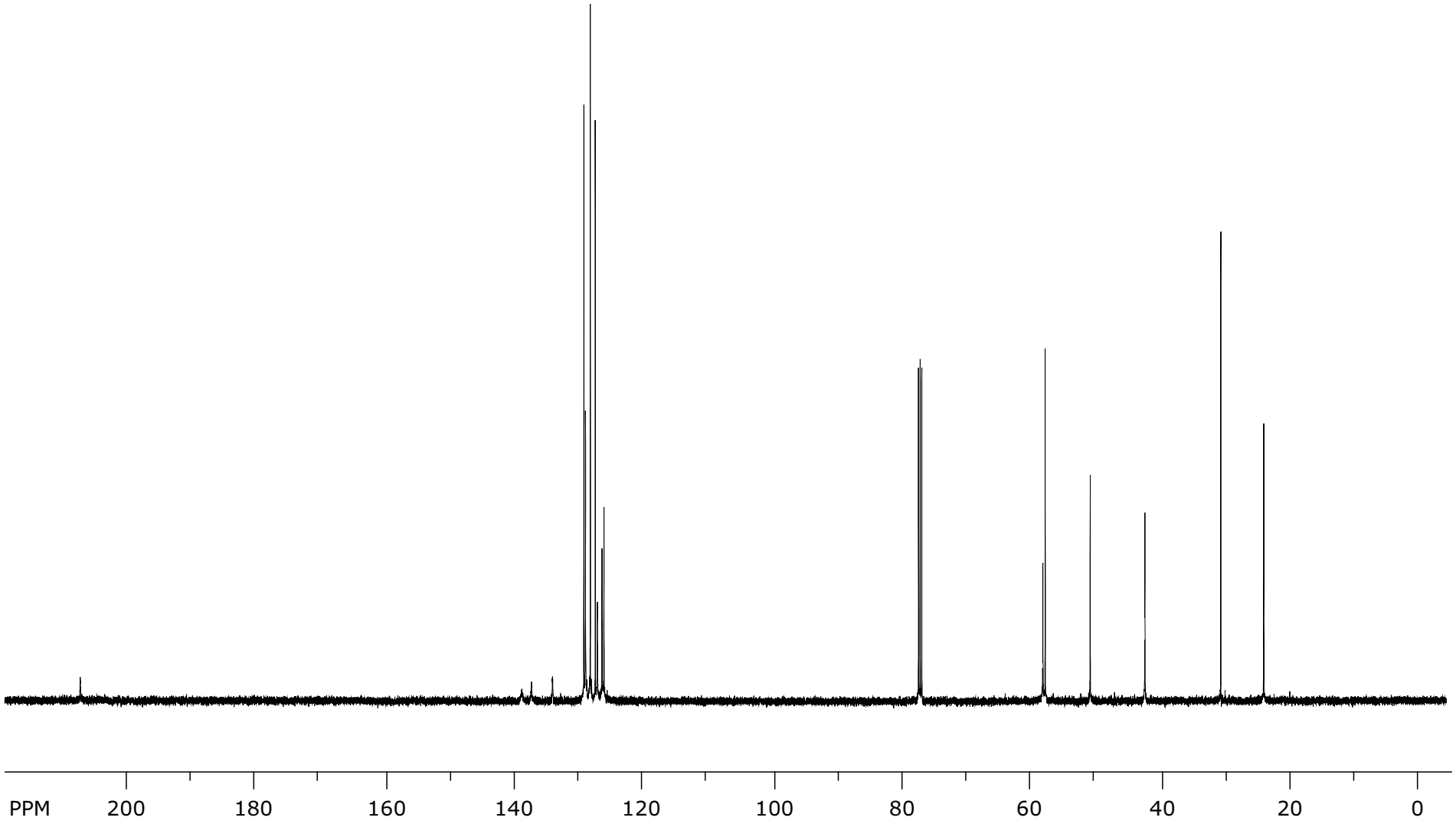
^{1}H NMR of **2b** in $CDCl_3$





^{13}C NMR of **2b** in $CDCl_3$





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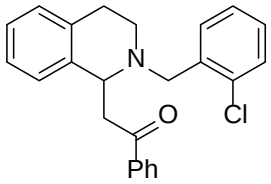
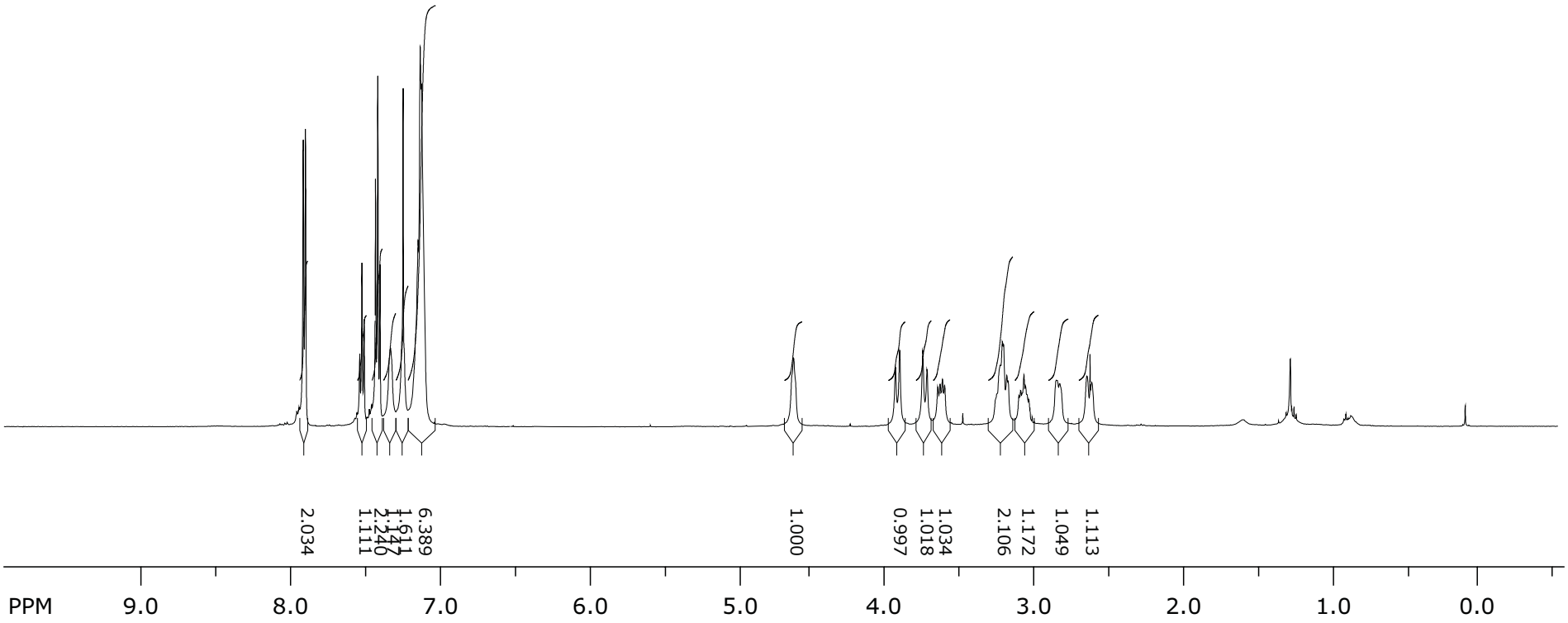
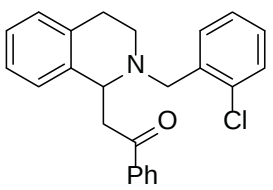
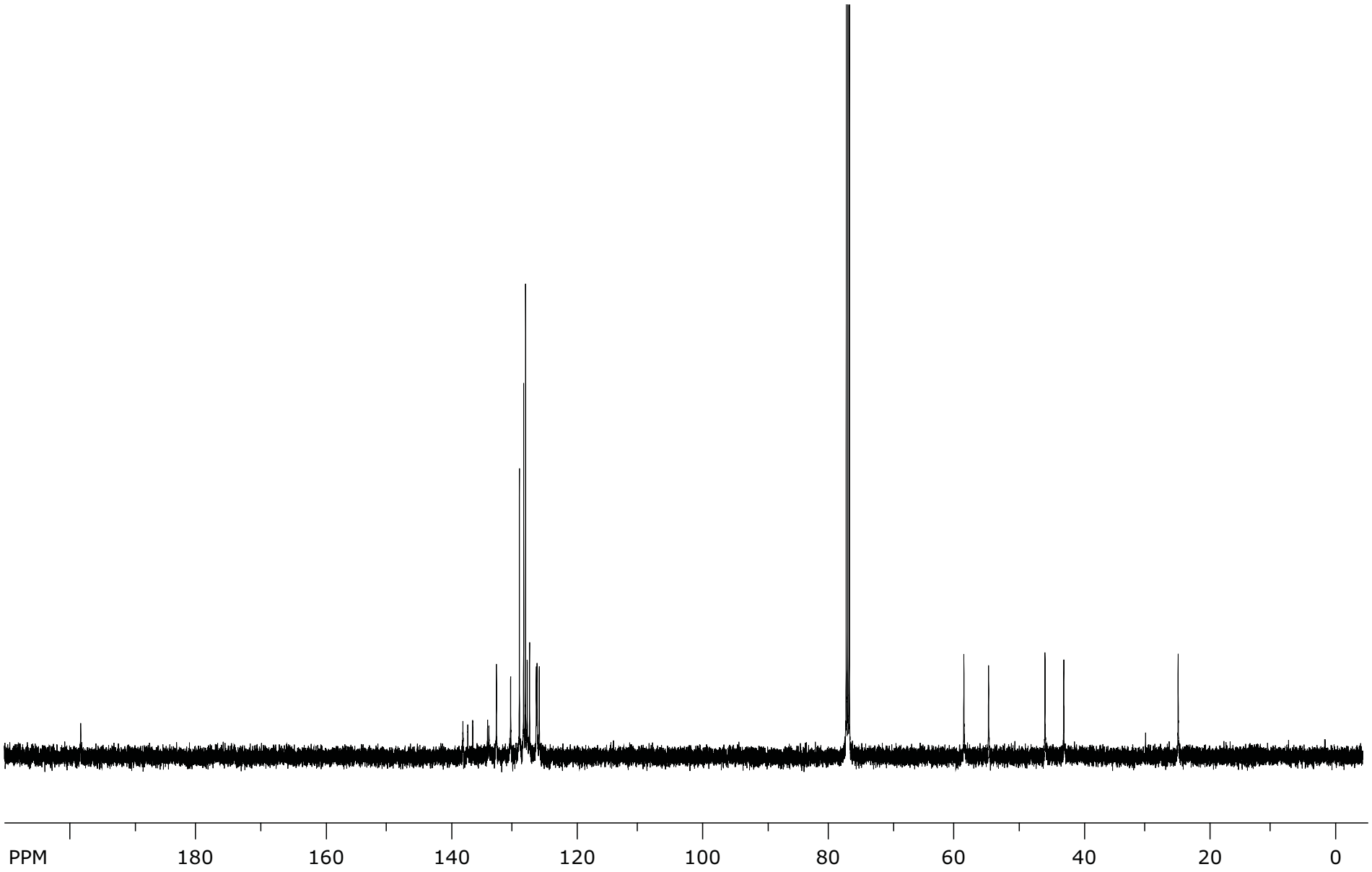




^{13}C NMR of **2c** in $CDCl_3$





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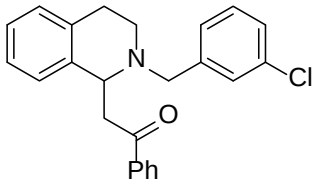
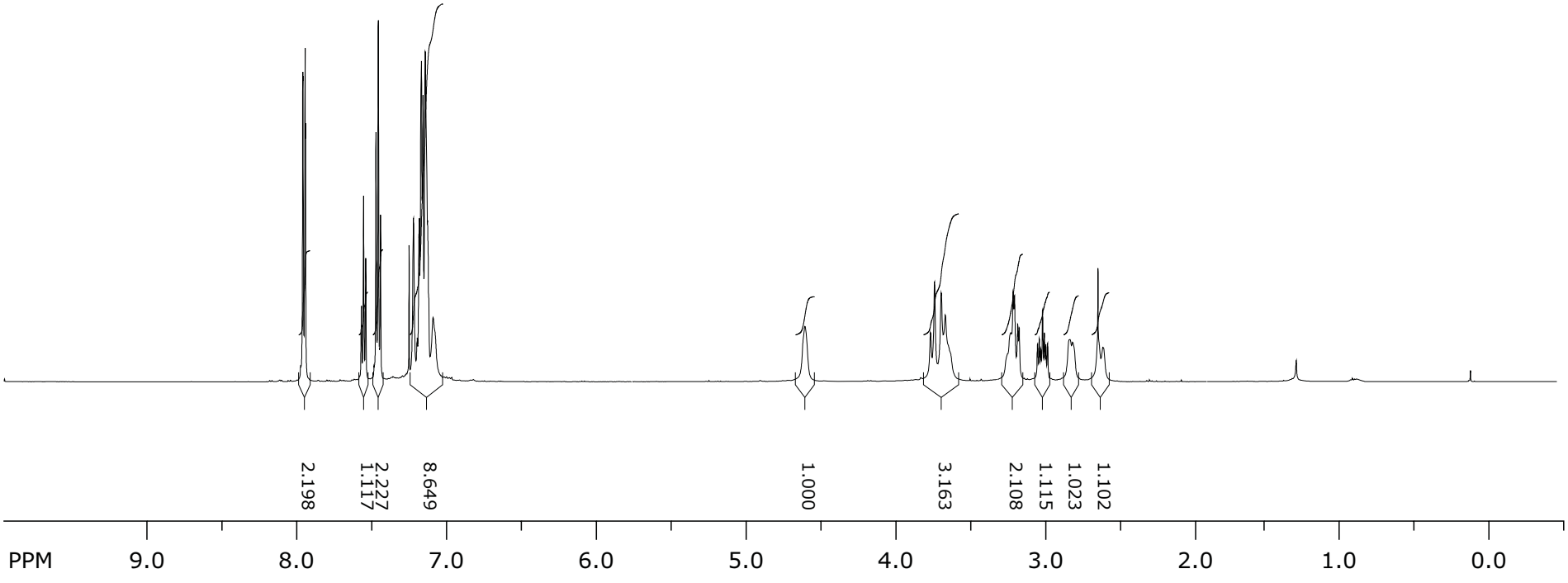
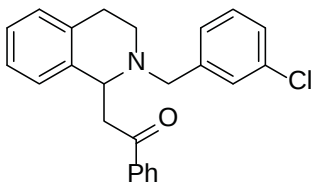
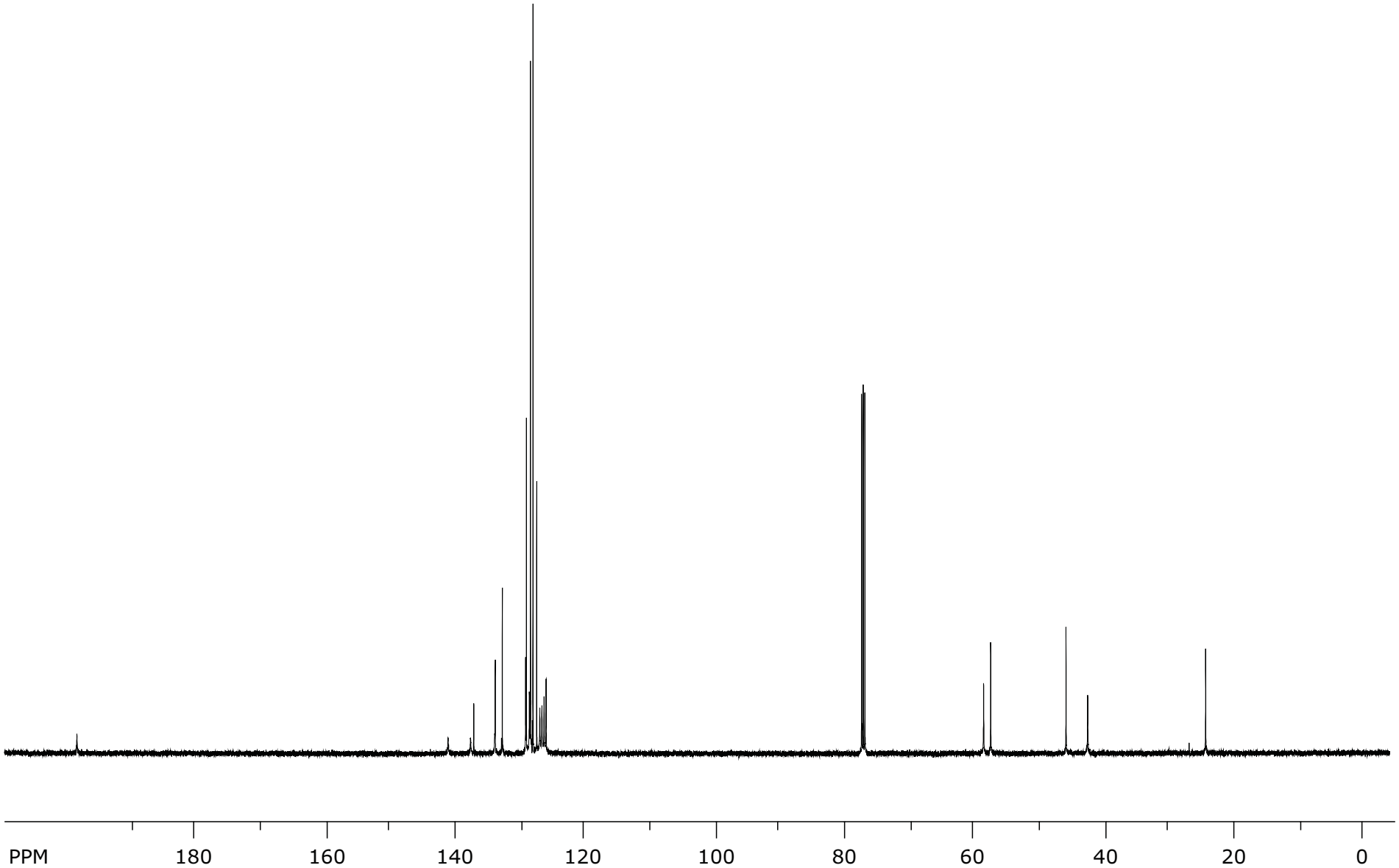


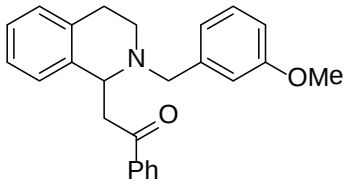


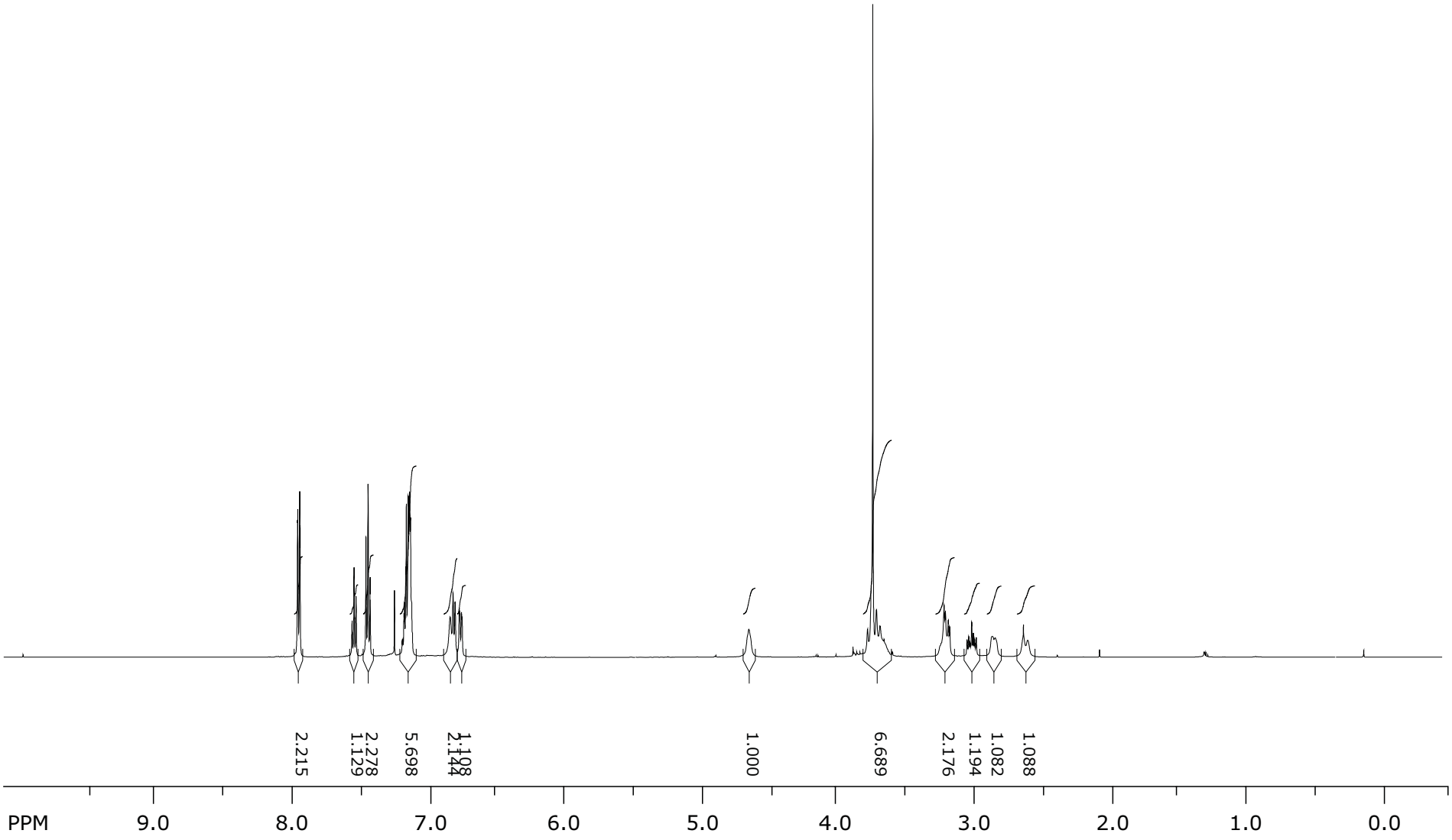
^{13}C NMR of **2d** in $CDCl_3$



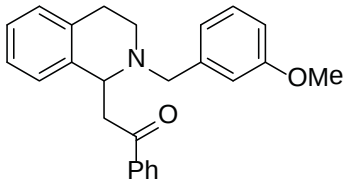


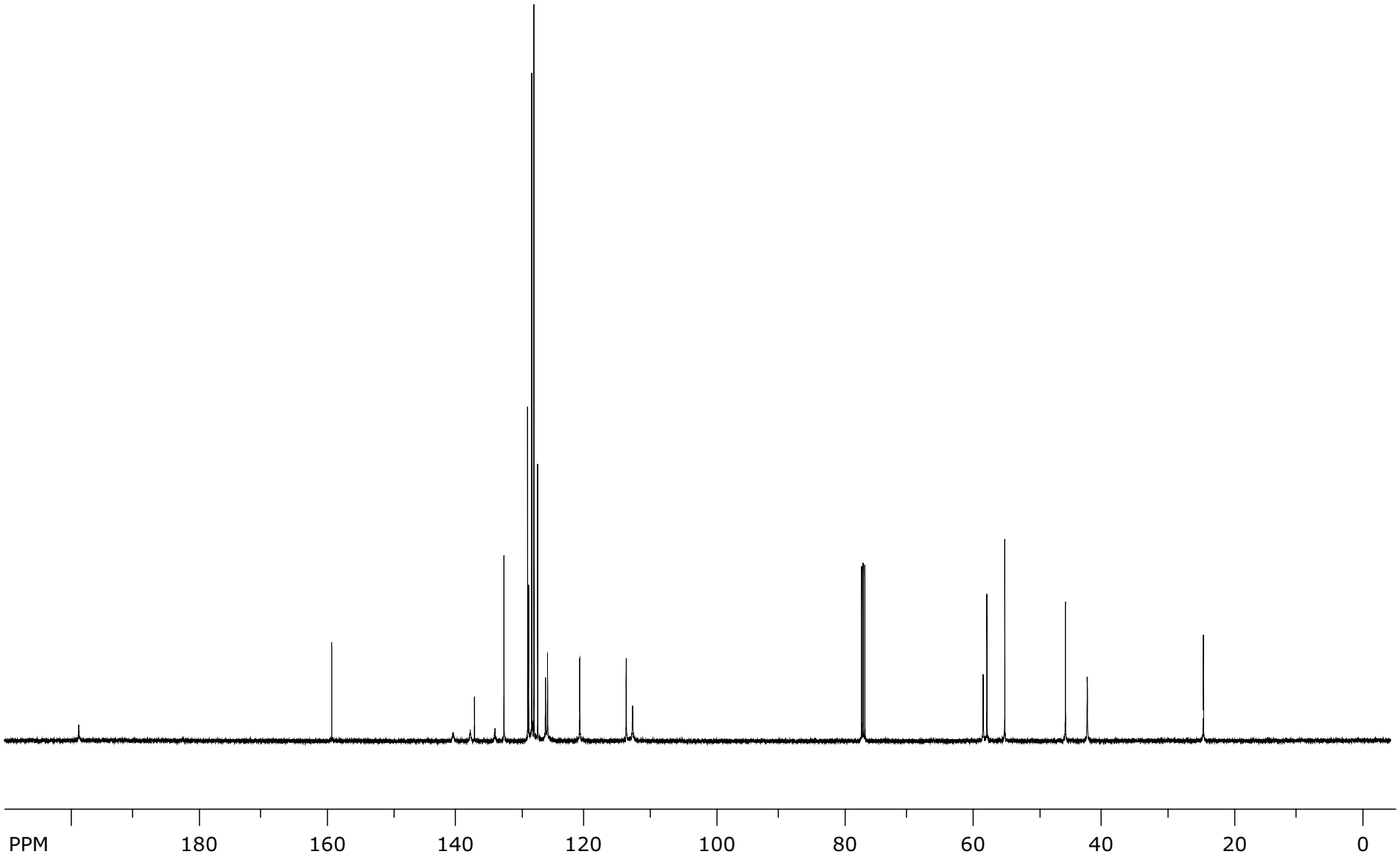
^{1}H NMR of **2e** in $CDCl_3$





^{13}C NMR of **2e** in $CDCl_3$





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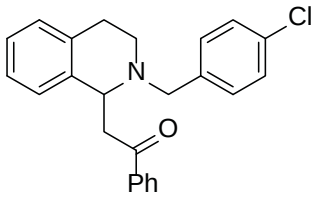
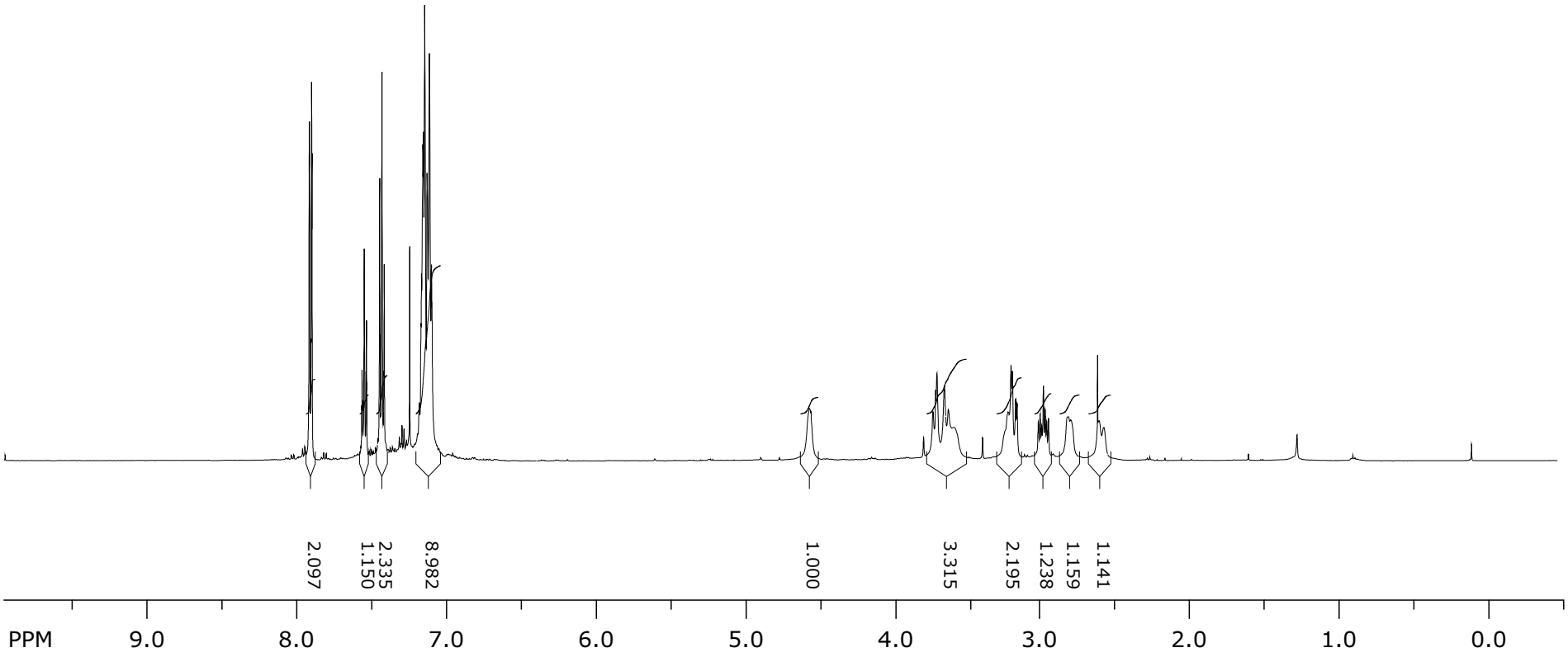
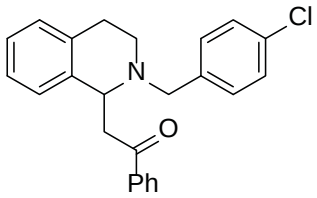
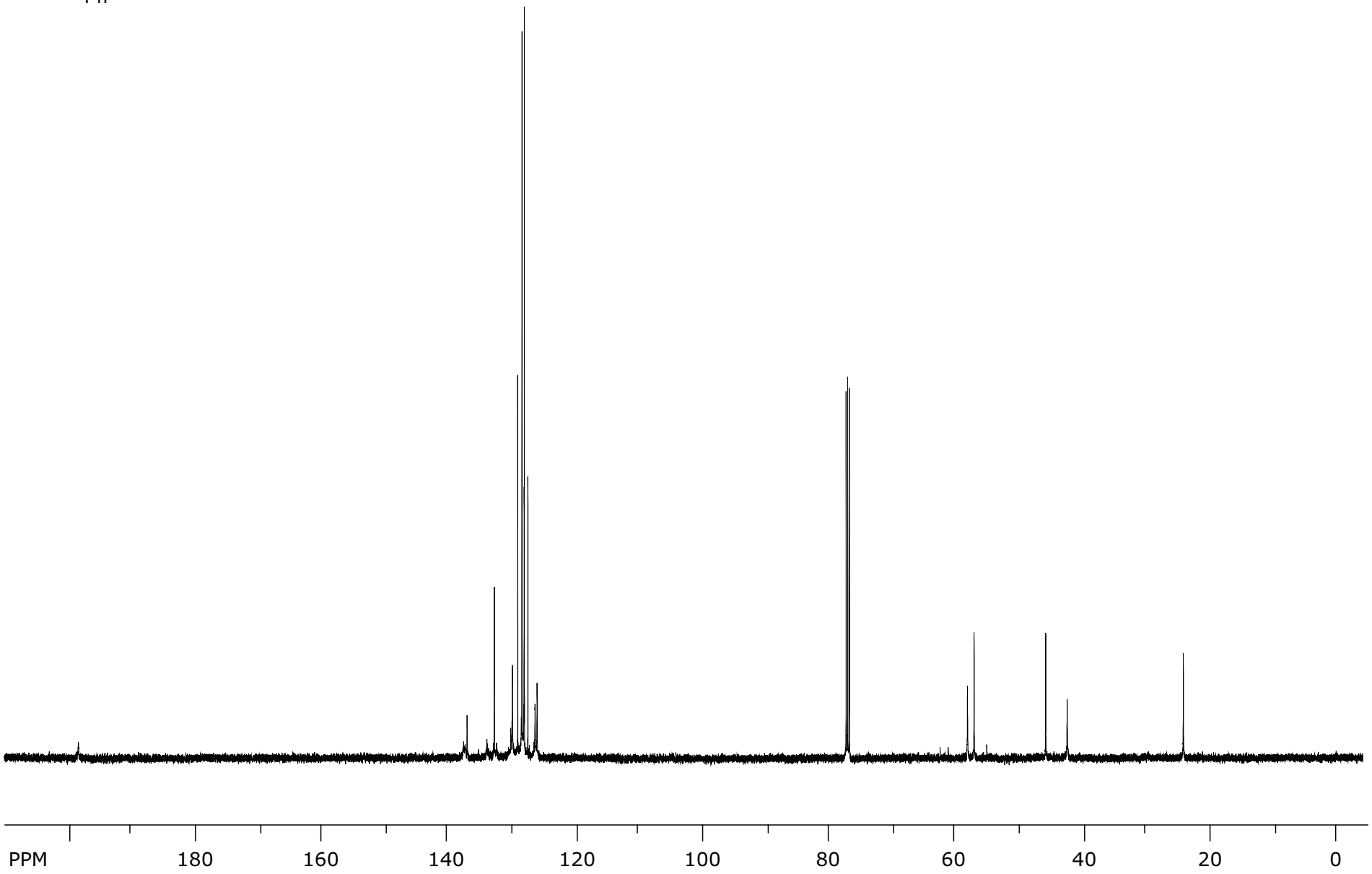


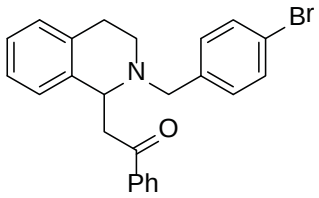


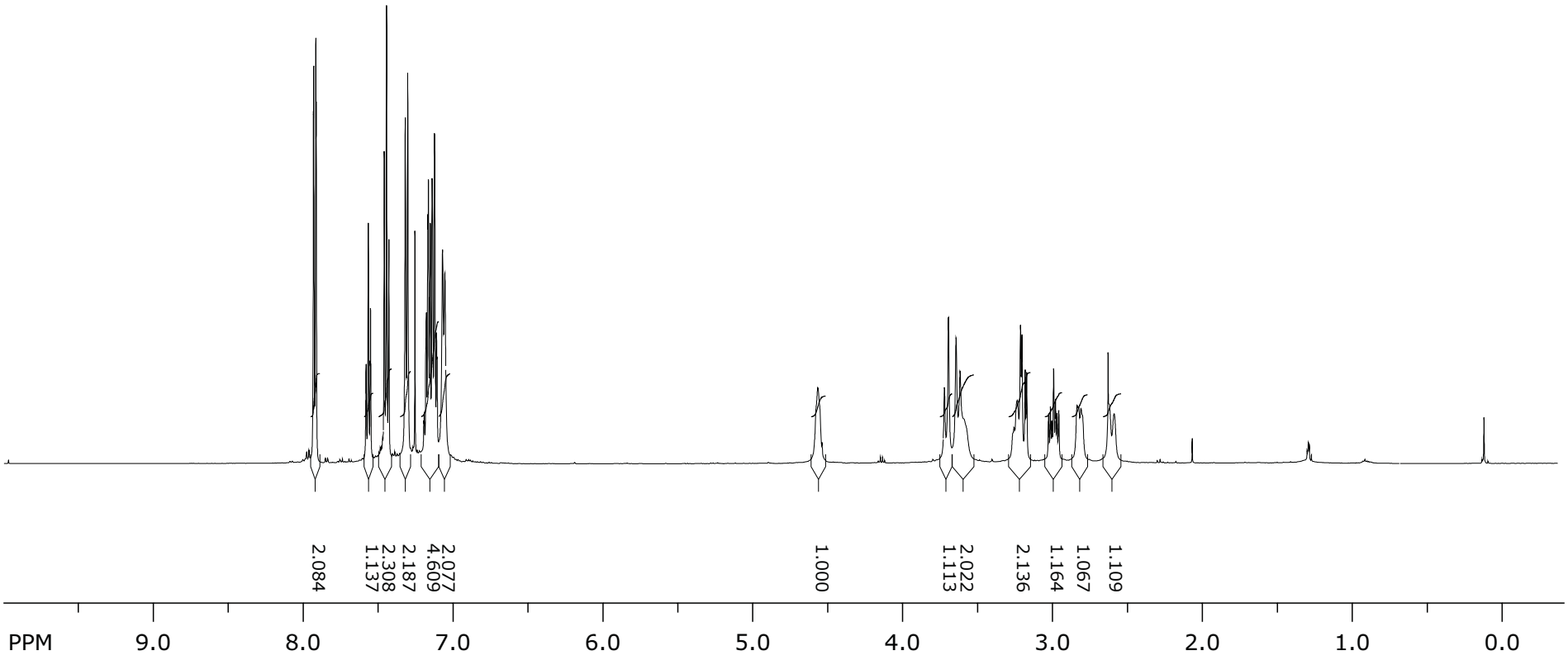
^{13}C NMR of **2f** in $CDCl_3$



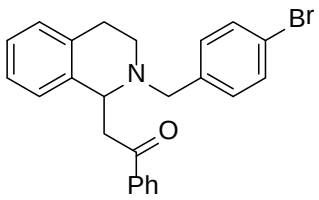


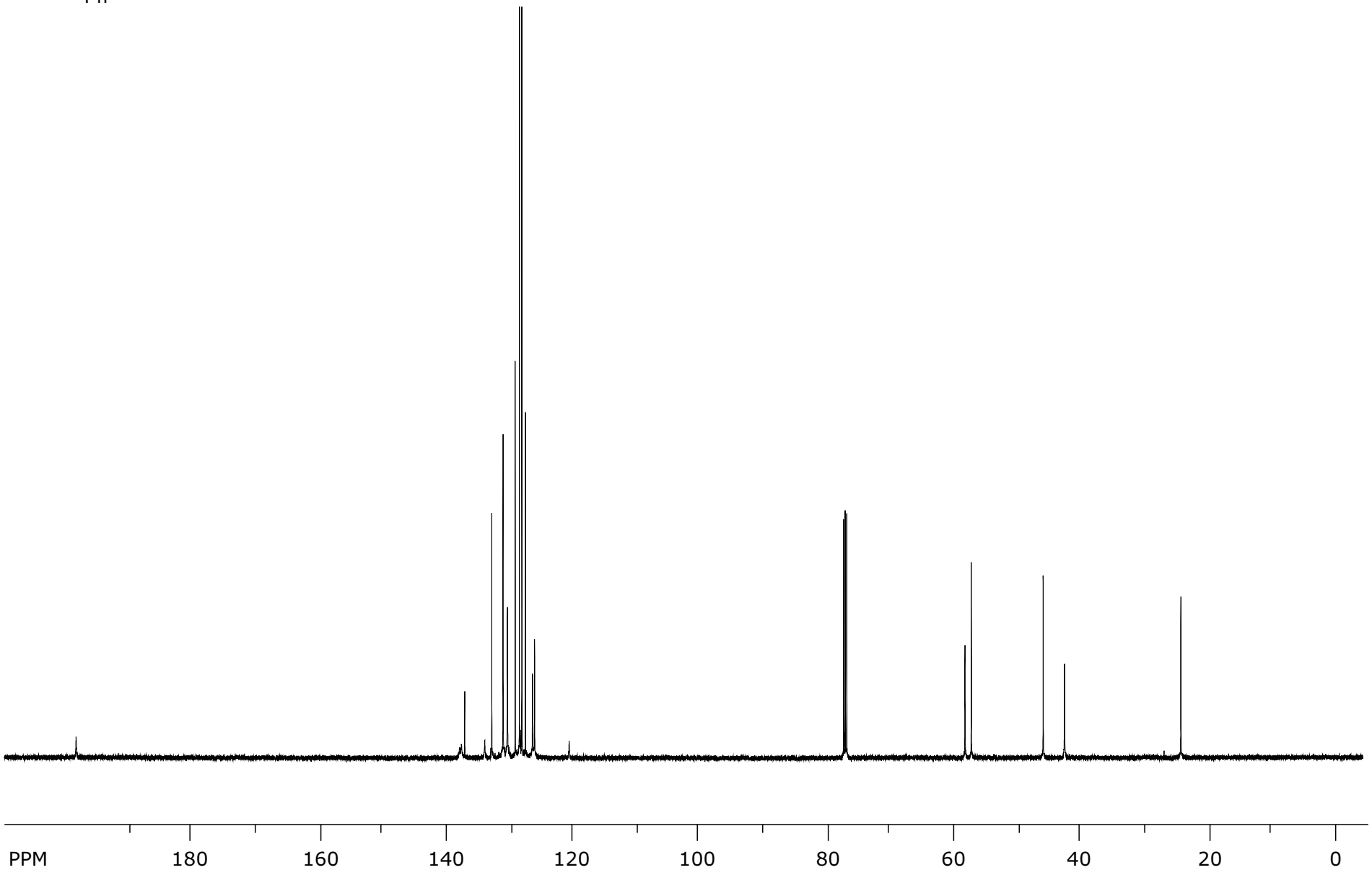
^{1}H NMR of **2g** in $CDCl_3$



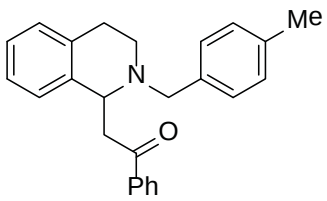


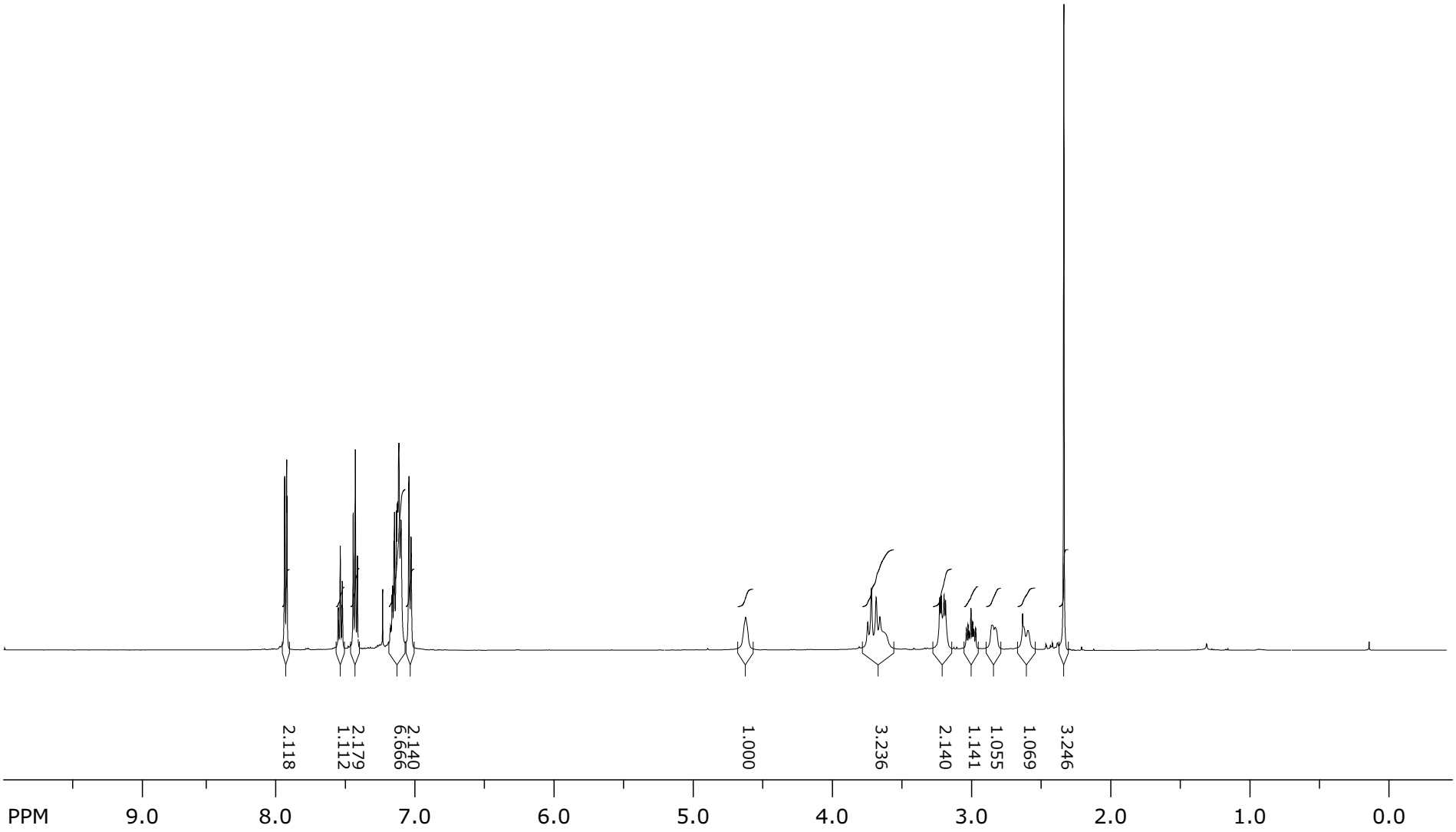
^{13}C NMR of **2g** in $CDCl_3$



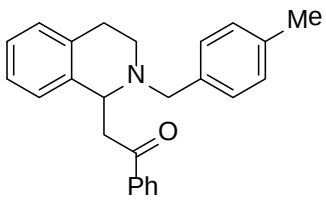


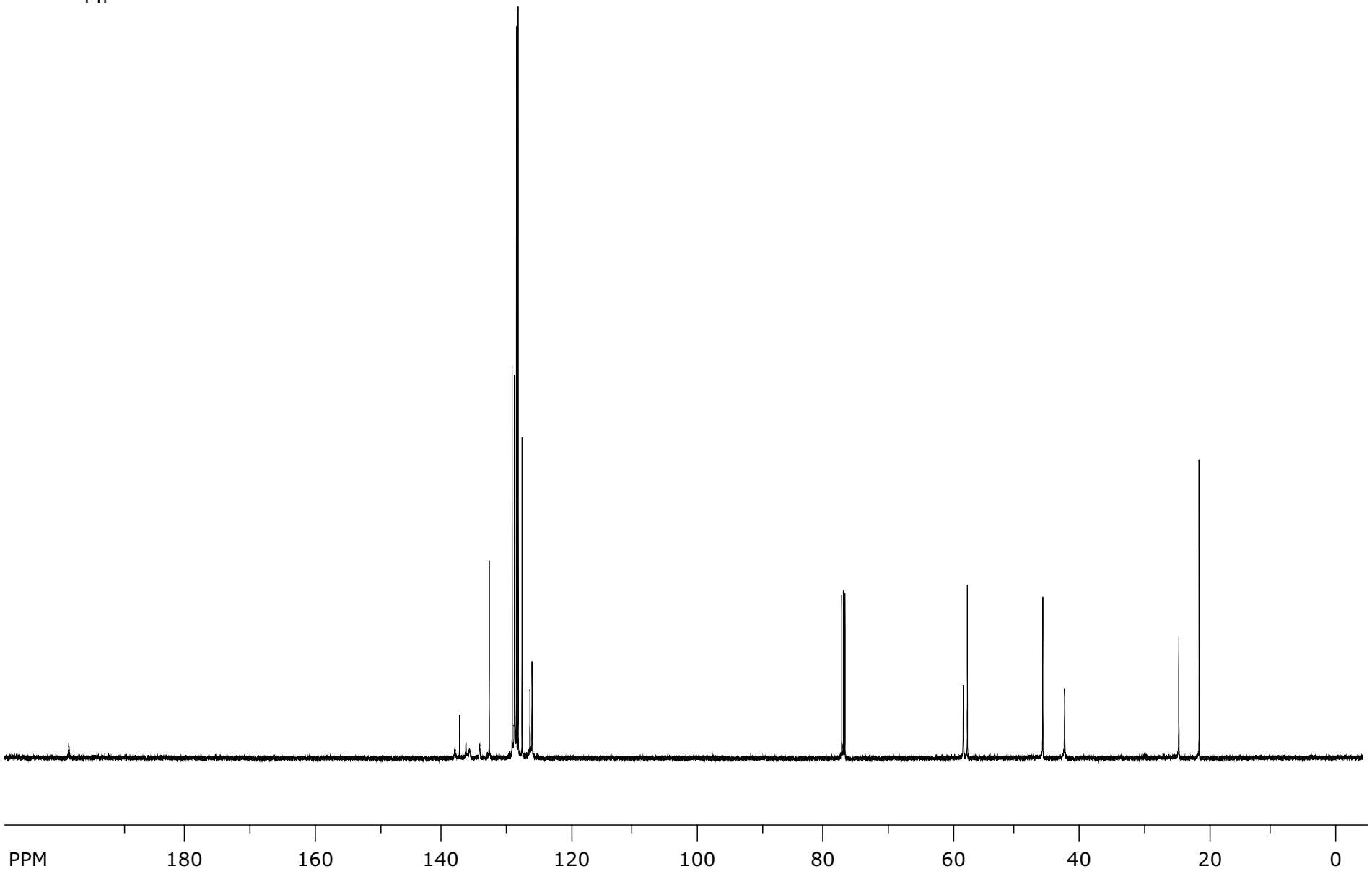
^{1}H NMR of **2h** in $CDCl_3$



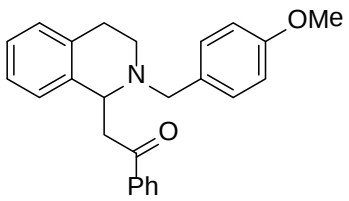


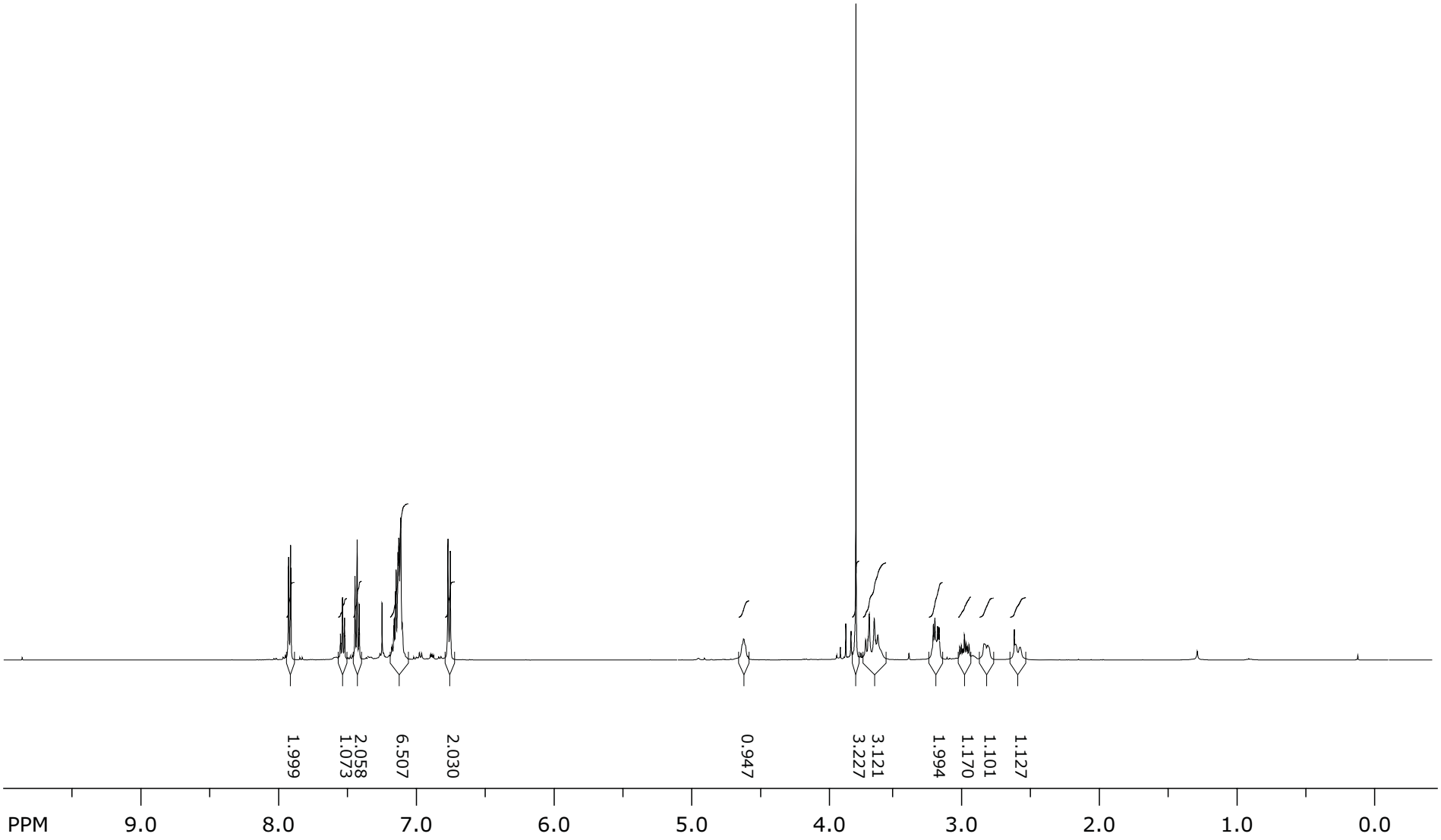
^{13}C NMR of **2h** in $CDCl_3$



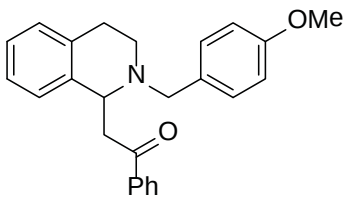


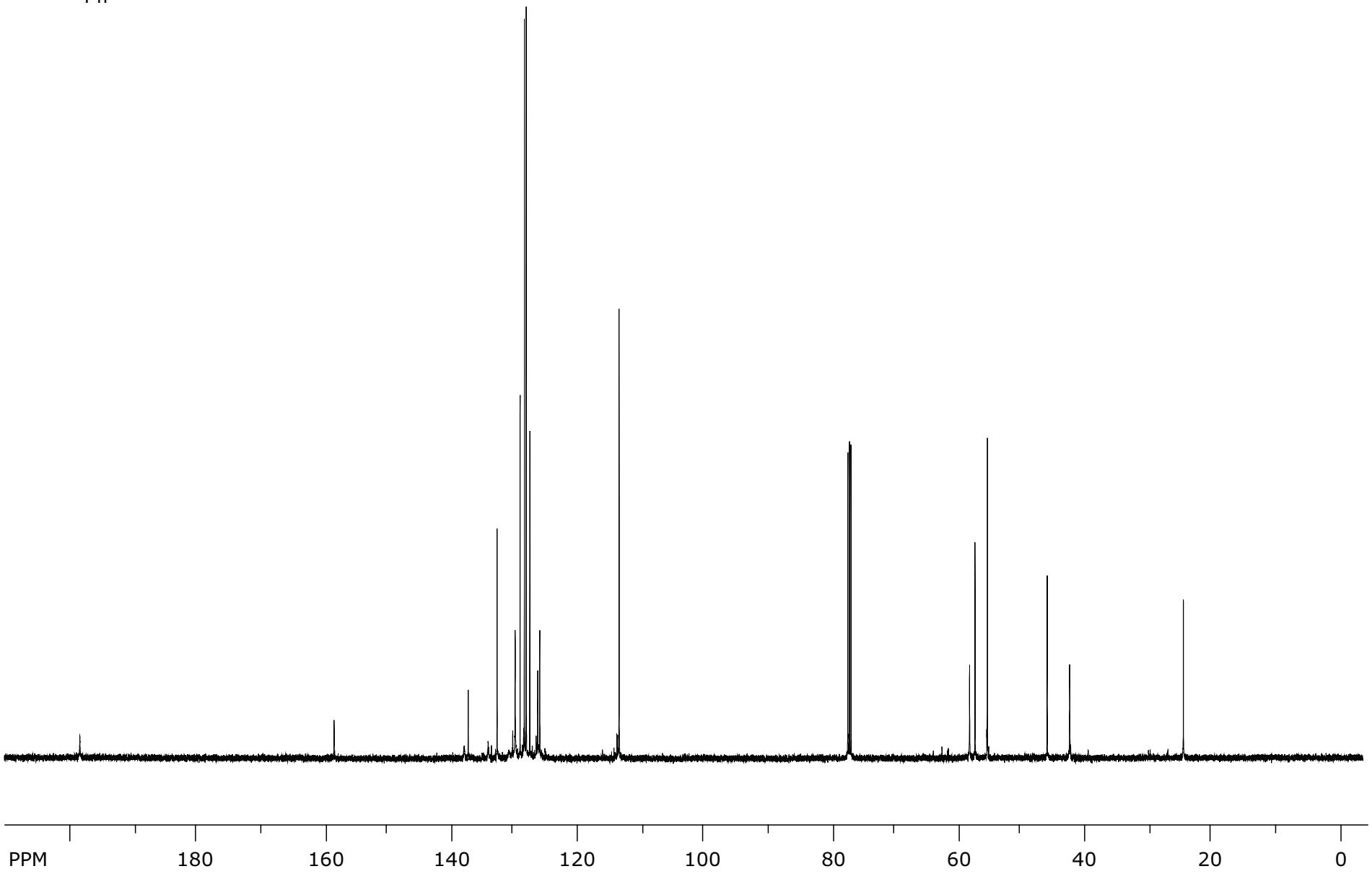
^{1}H NMR of **2i** in $CDCl_3$



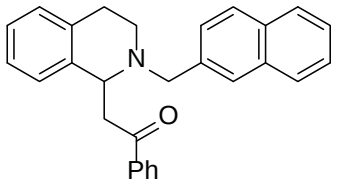


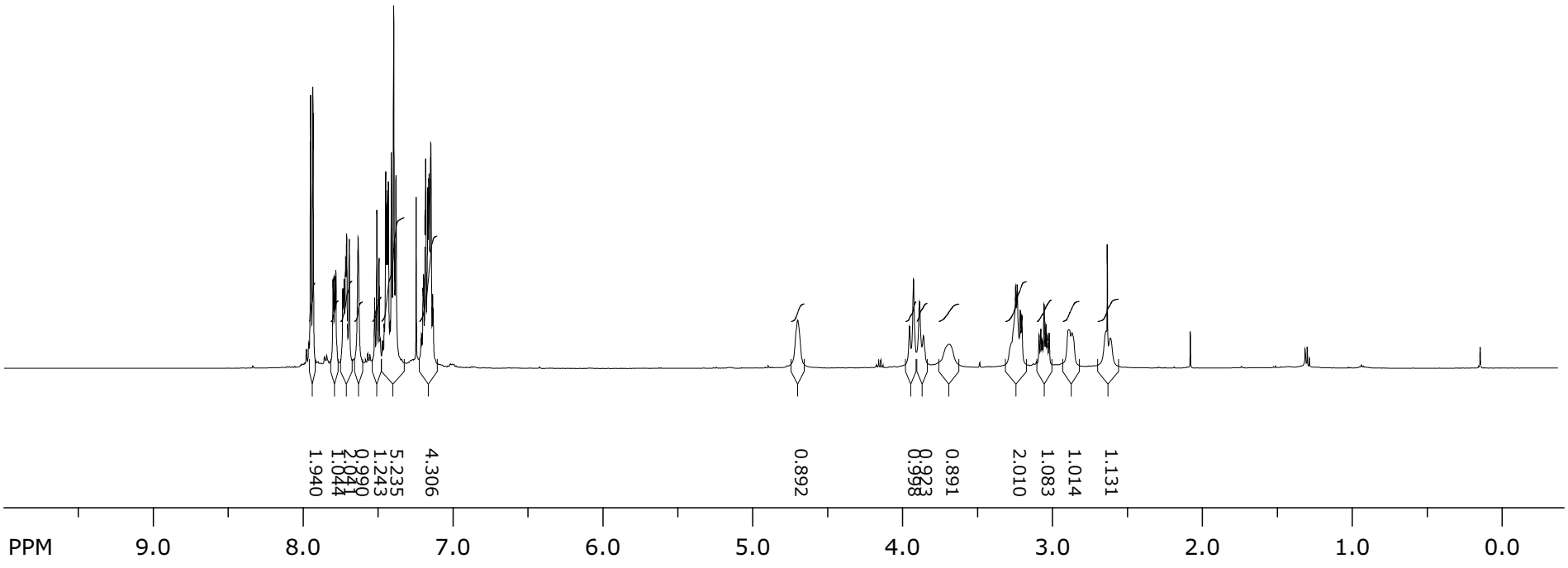
^{13}C NMR of **2i** in $CDCl_3$



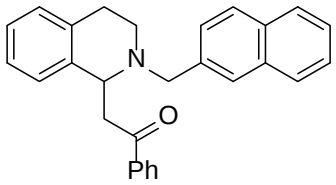


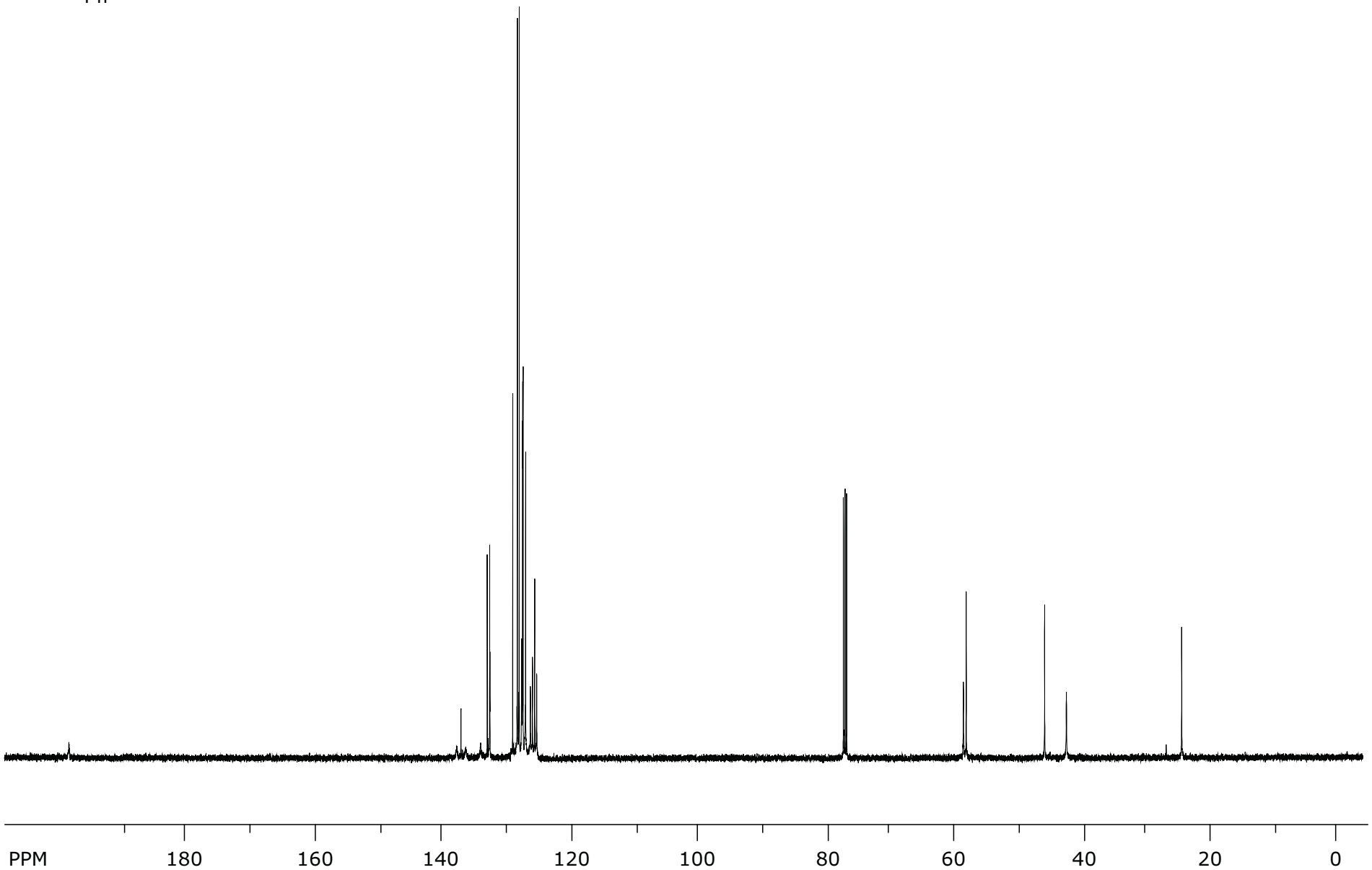
^{1}H NMR of **2$_j$** in $CDCl_3$



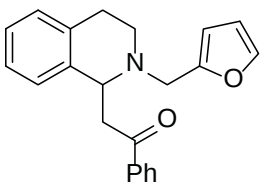


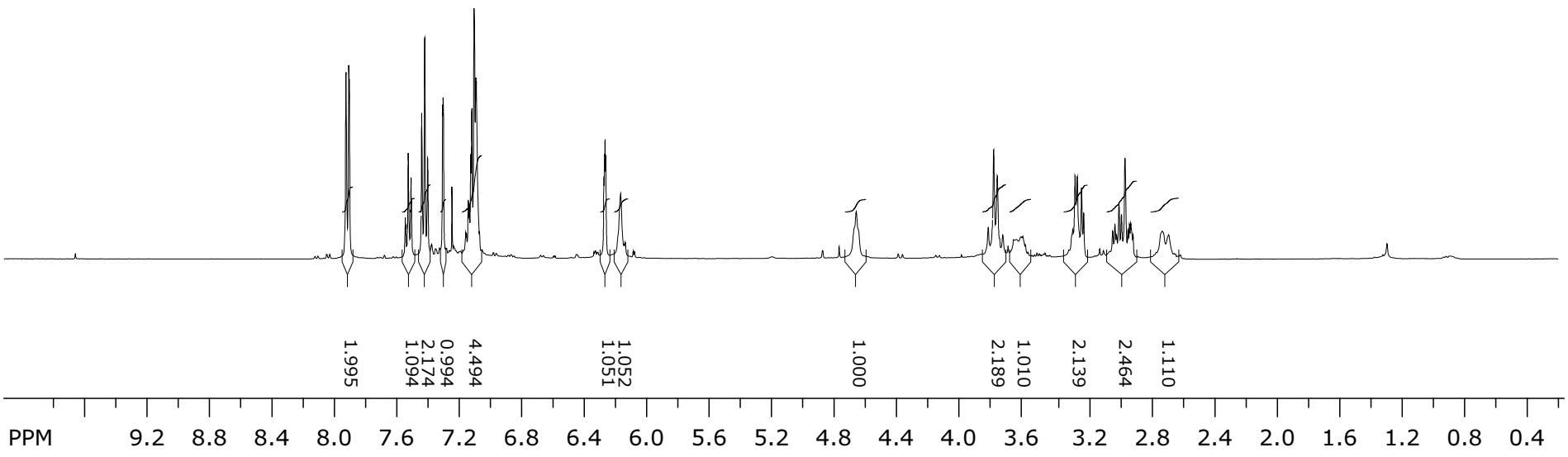
^{13}C NMR of **2j** in $CDCl_3$



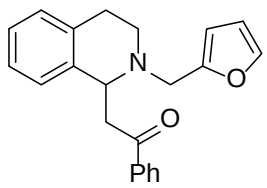


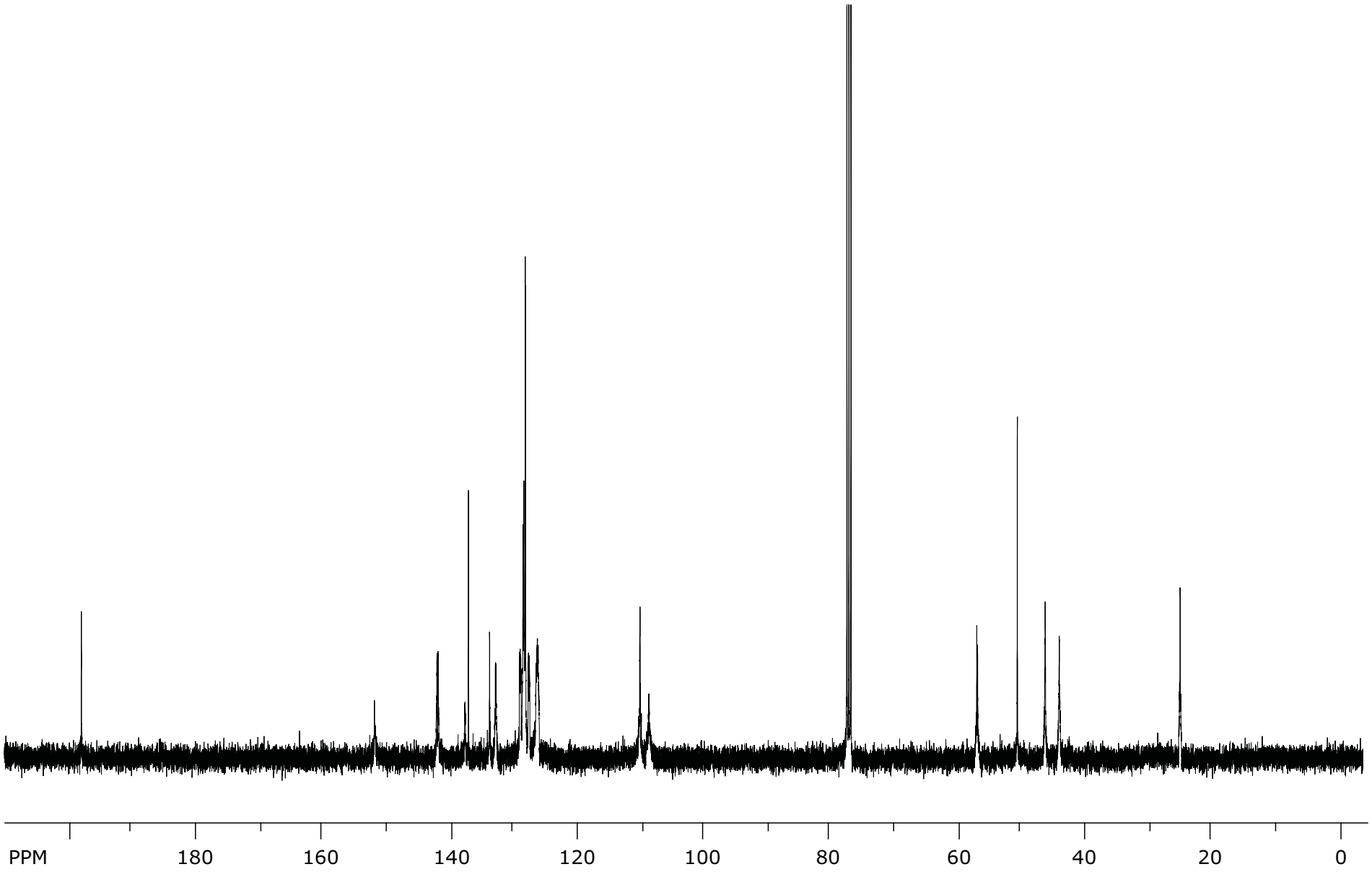
^{1}H NMR of **2k** in $CDCl_3$



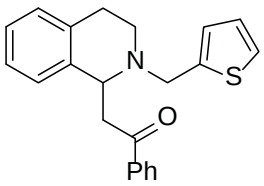


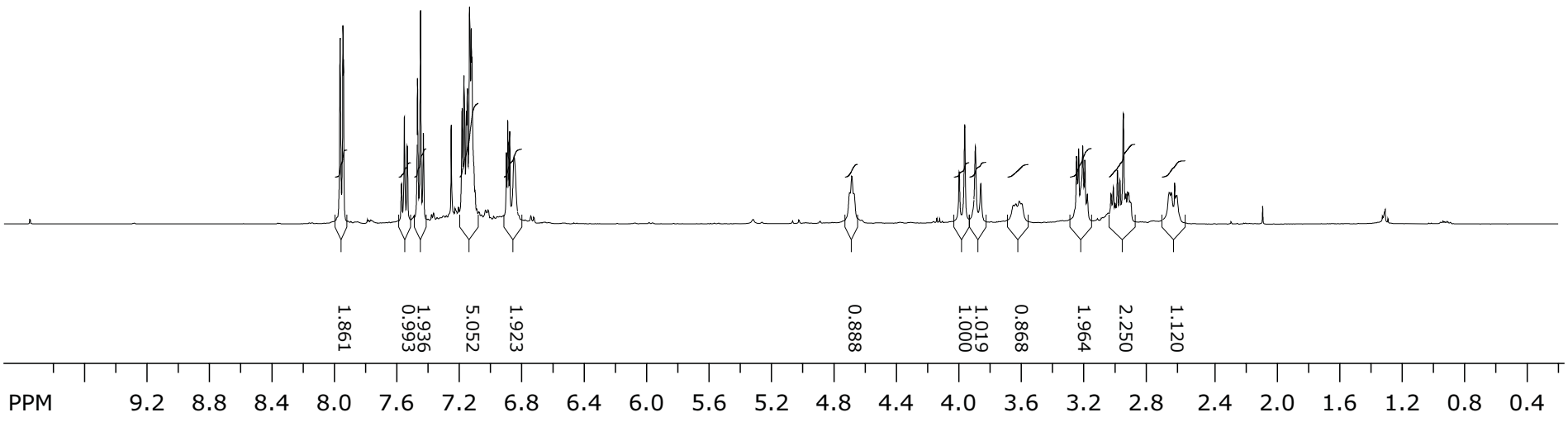
^{13}C NMR of **2k** in $CDCl_3$



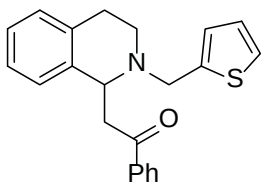


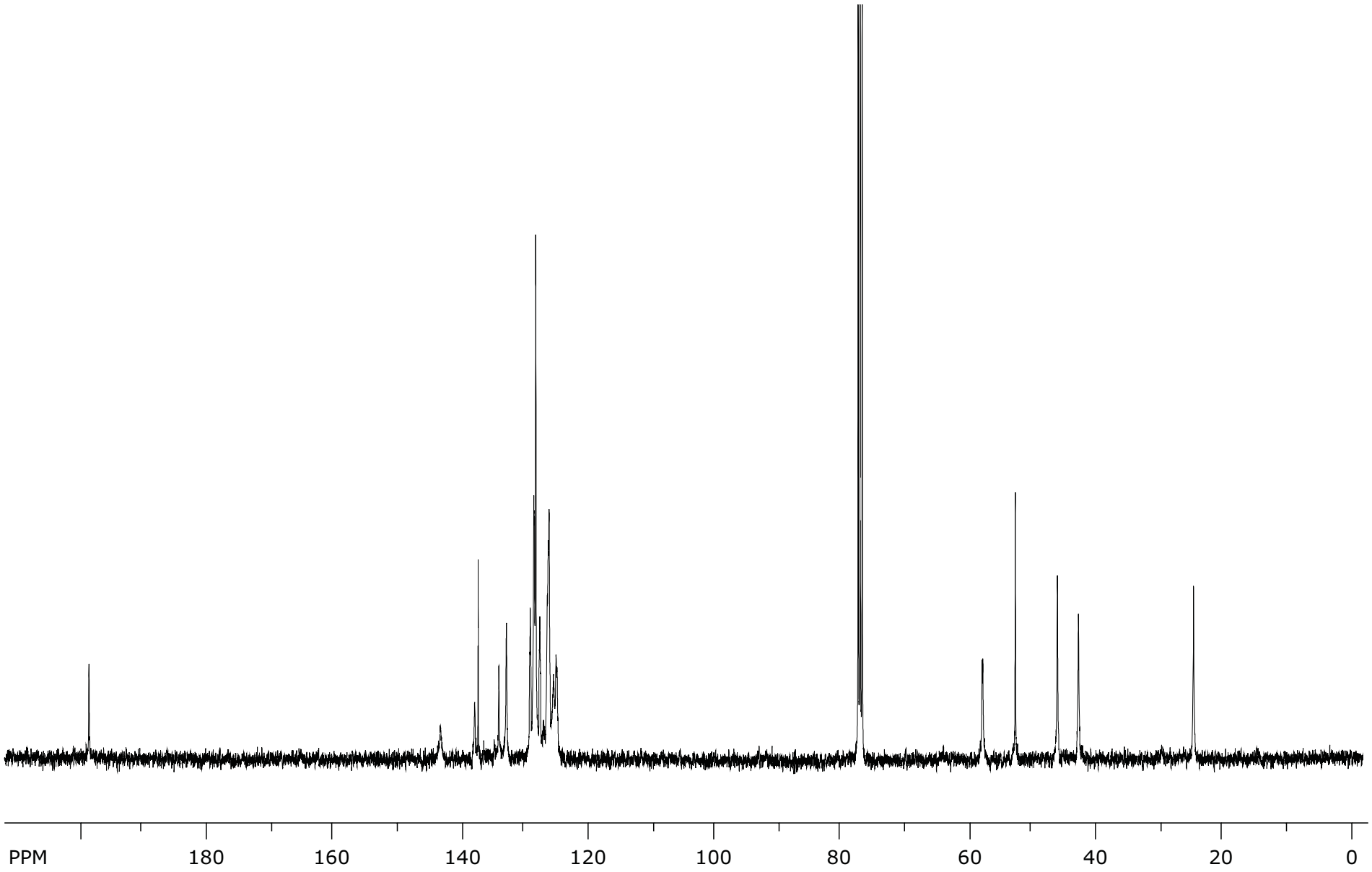
^{1}H NMR of **2l** in $CDCl_3$



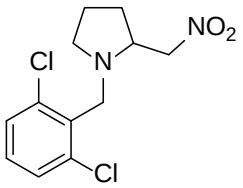


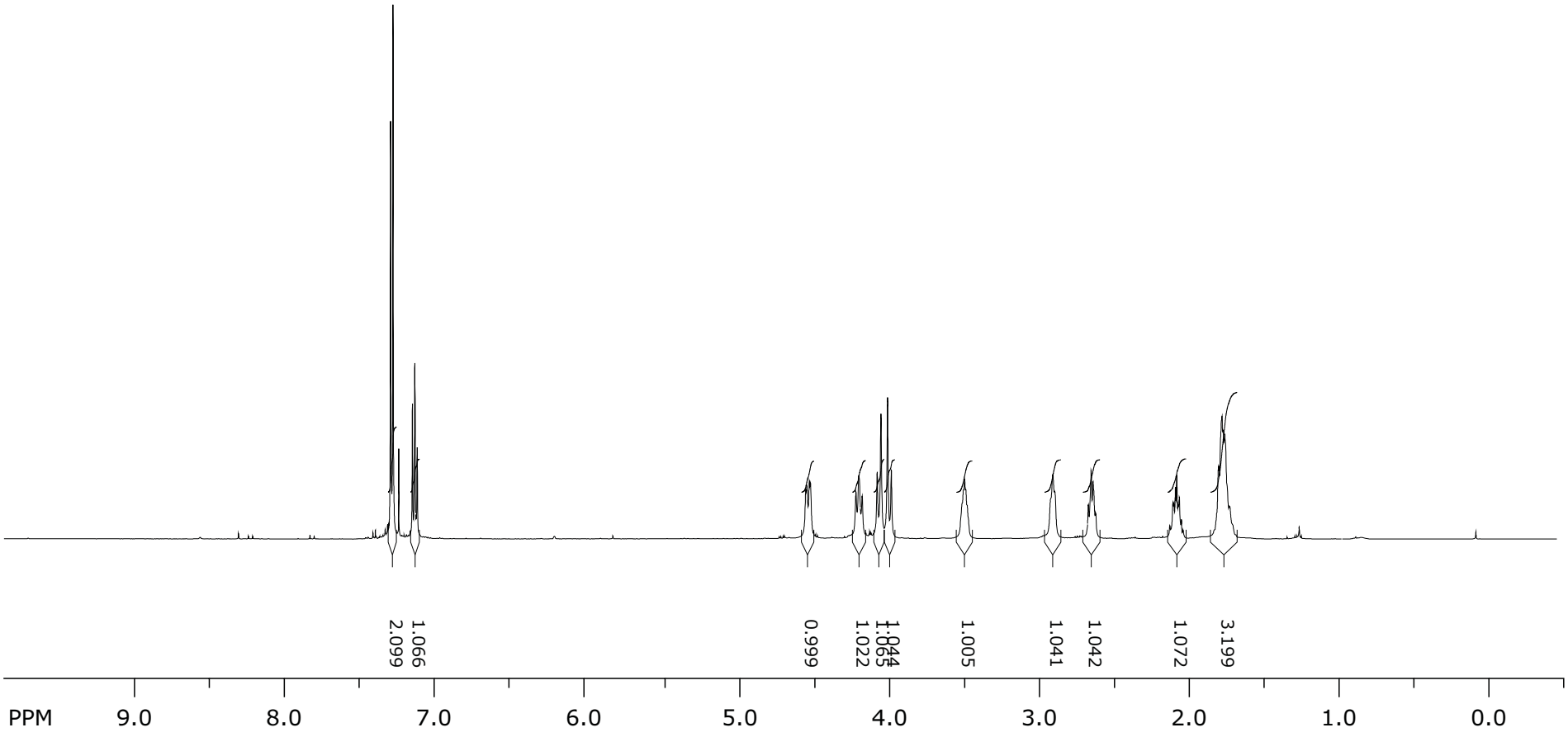
^{13}C NMR of **2l** in $CDCl_3$



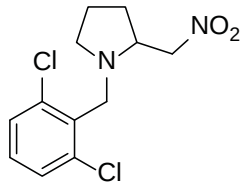


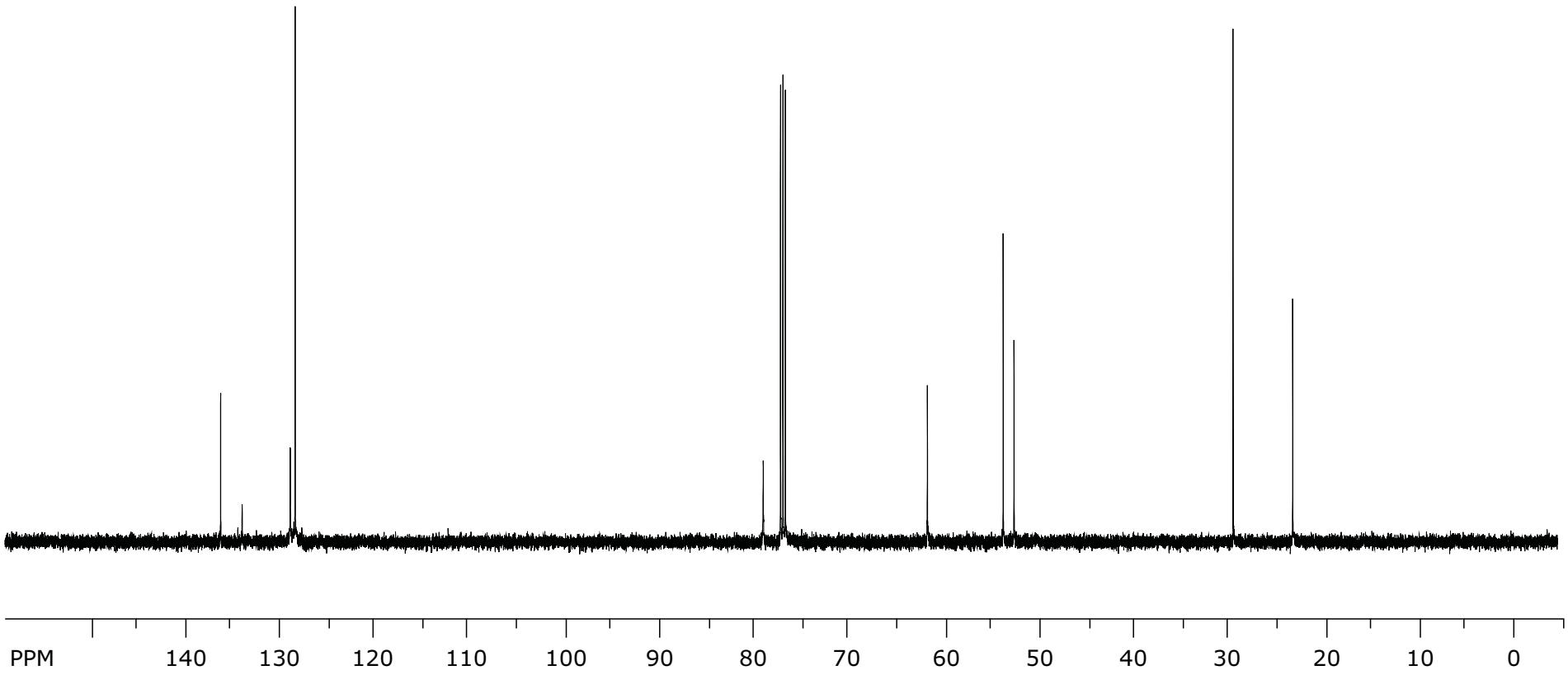
^{1}H NMR of **3a** in $CDCl_3$



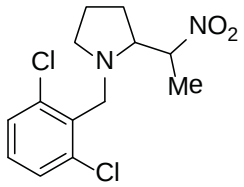


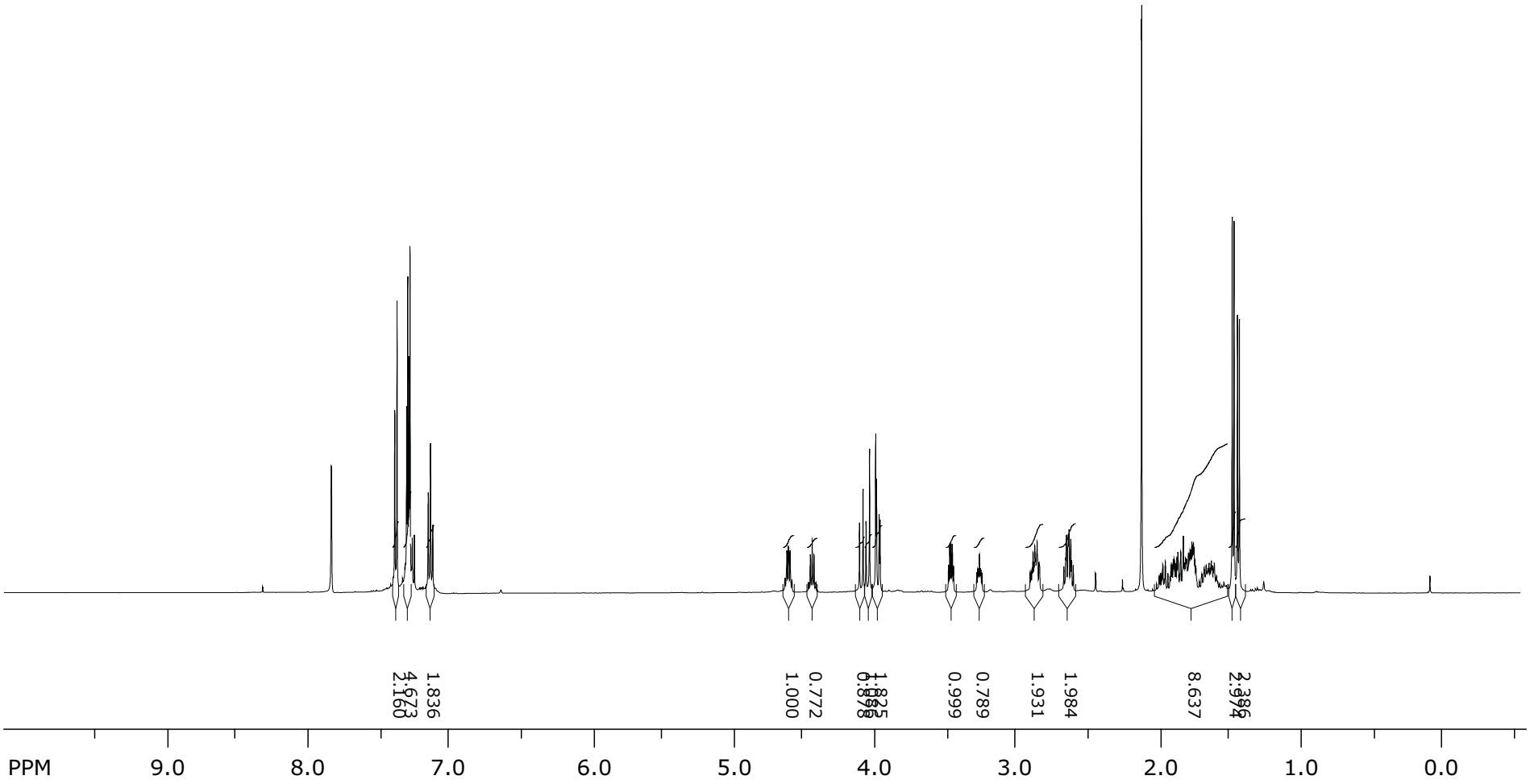
^{13}C NMR of **3a** in $CDCl_3$



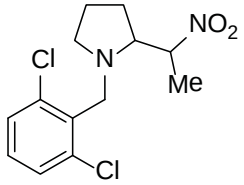


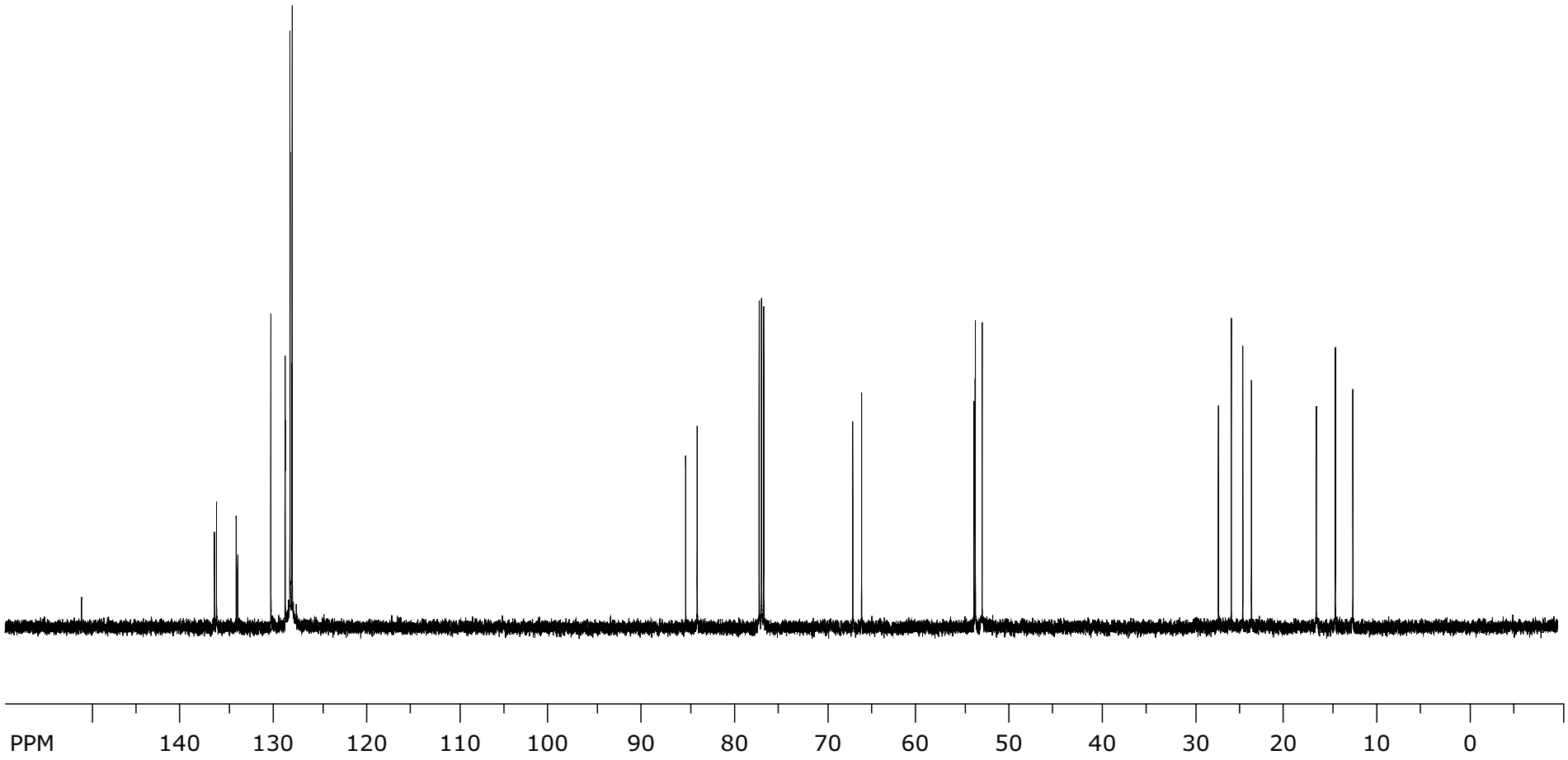
^{1}H NMR of **3b** in $CDCl_3$
(mixture of diastereomers
and impurities)



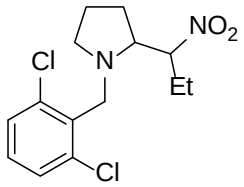


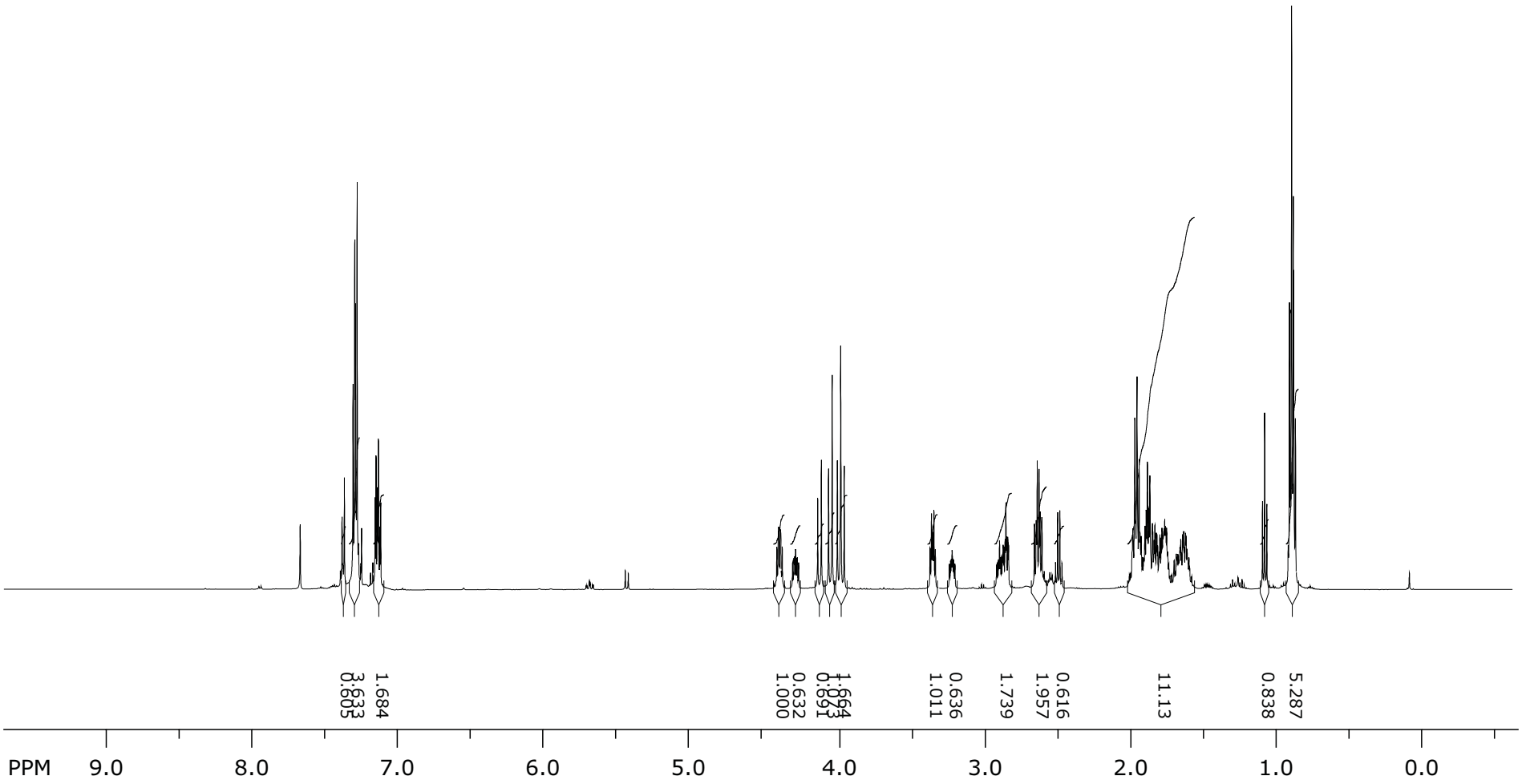
^{13}C NMR of **3b** in $CDCl_3$
(mixture of diastereomers
and impurities)



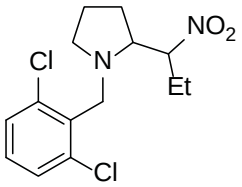


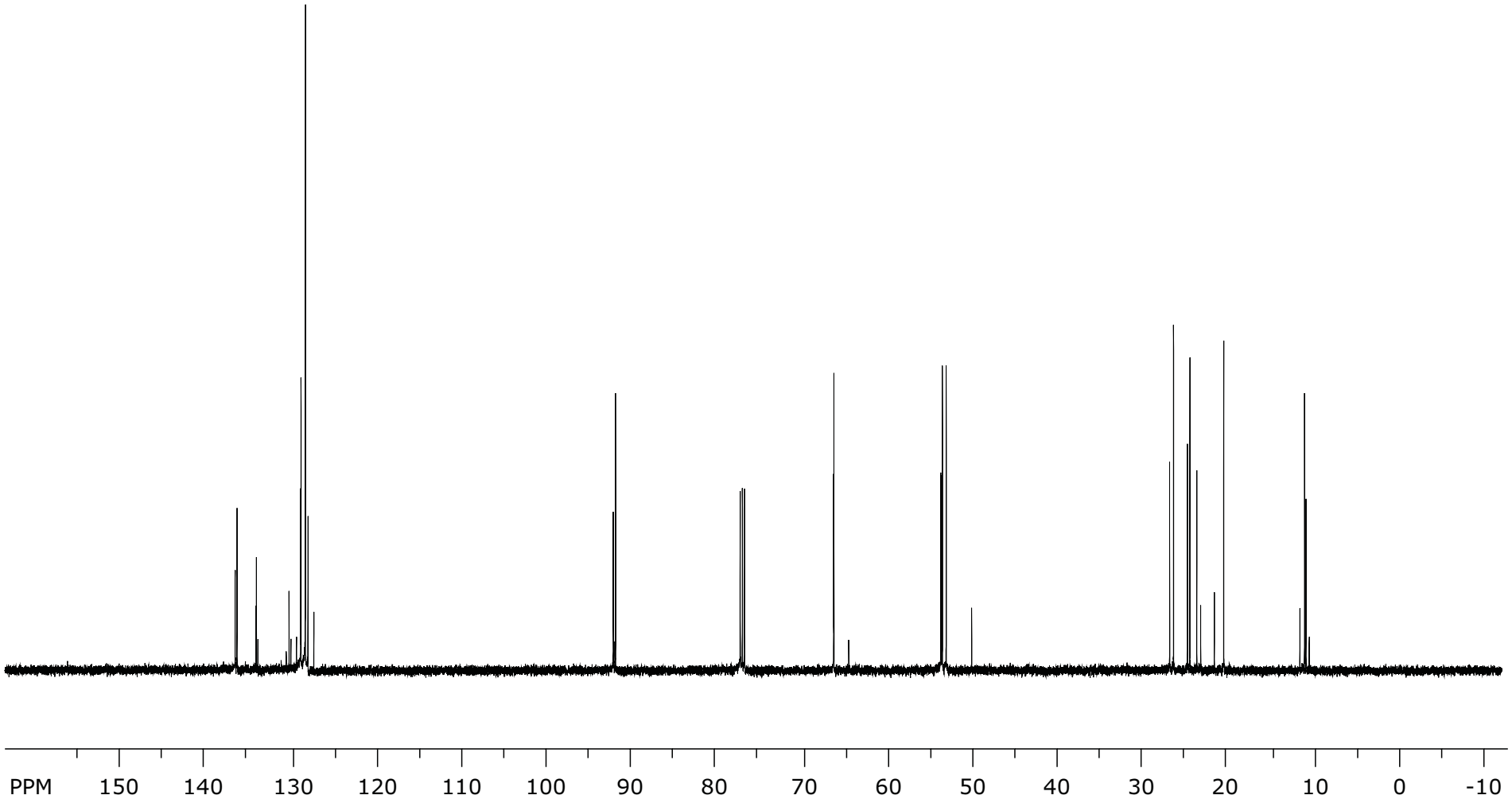
^{1}H NMR of **3c** in $CDCl_3$
(mixture of diastereomers
and impurities)



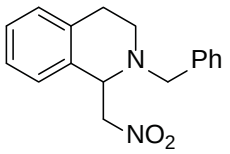


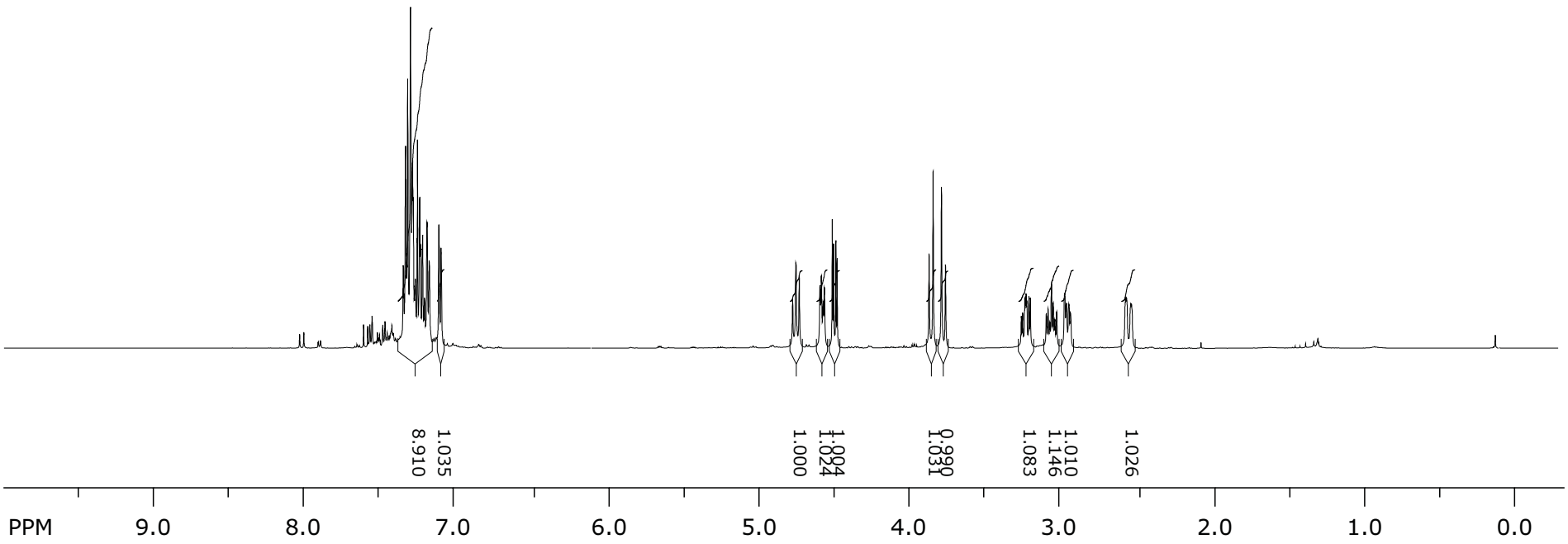
^{13}C NMR of **3c** in $CDCl_3$
(mixture of diastereomers
and impurities)



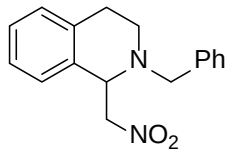


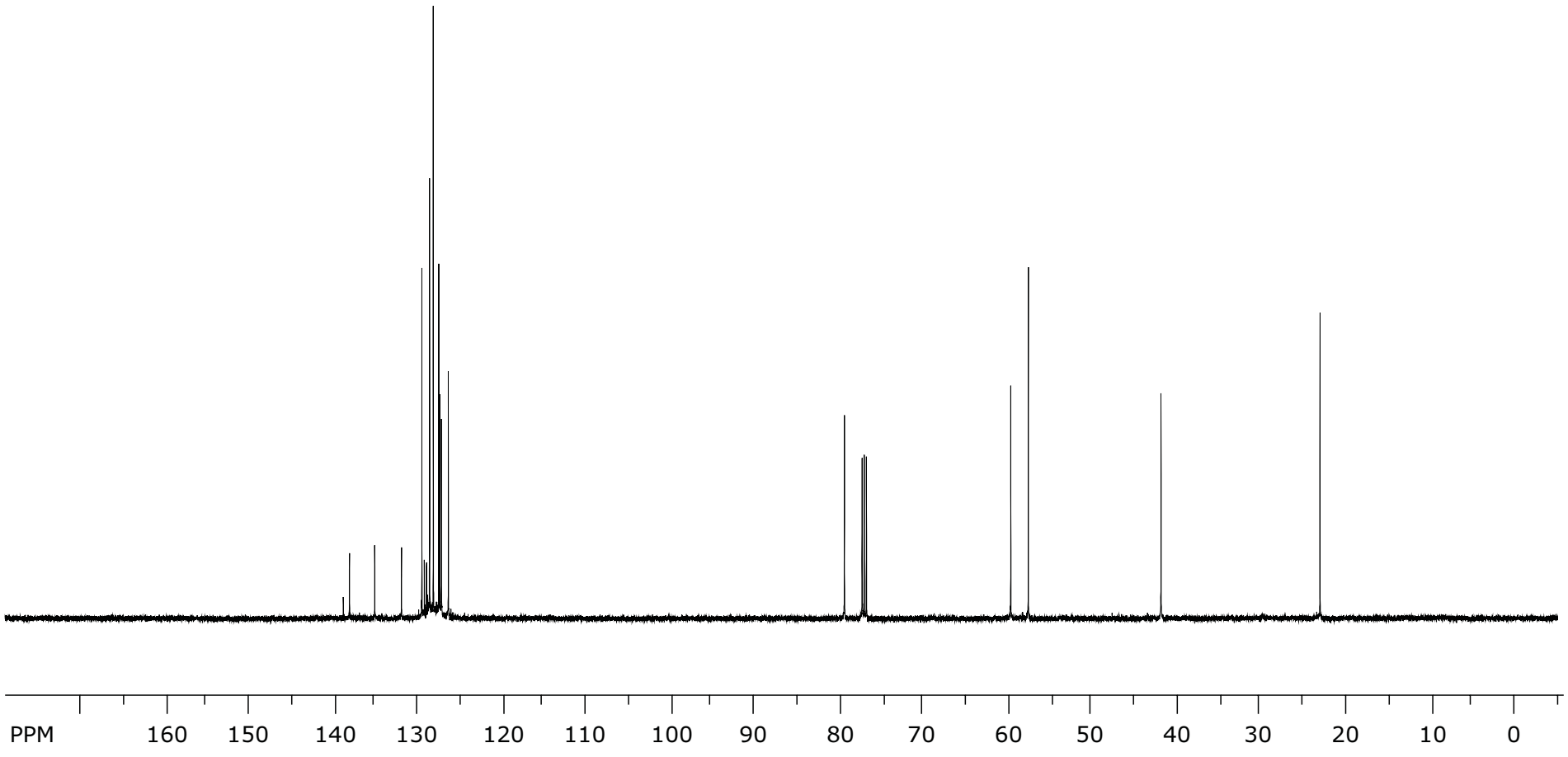
^{1}H NMR of **4** in $CDCl_3$



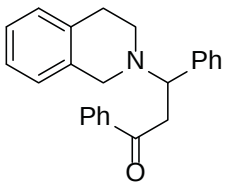


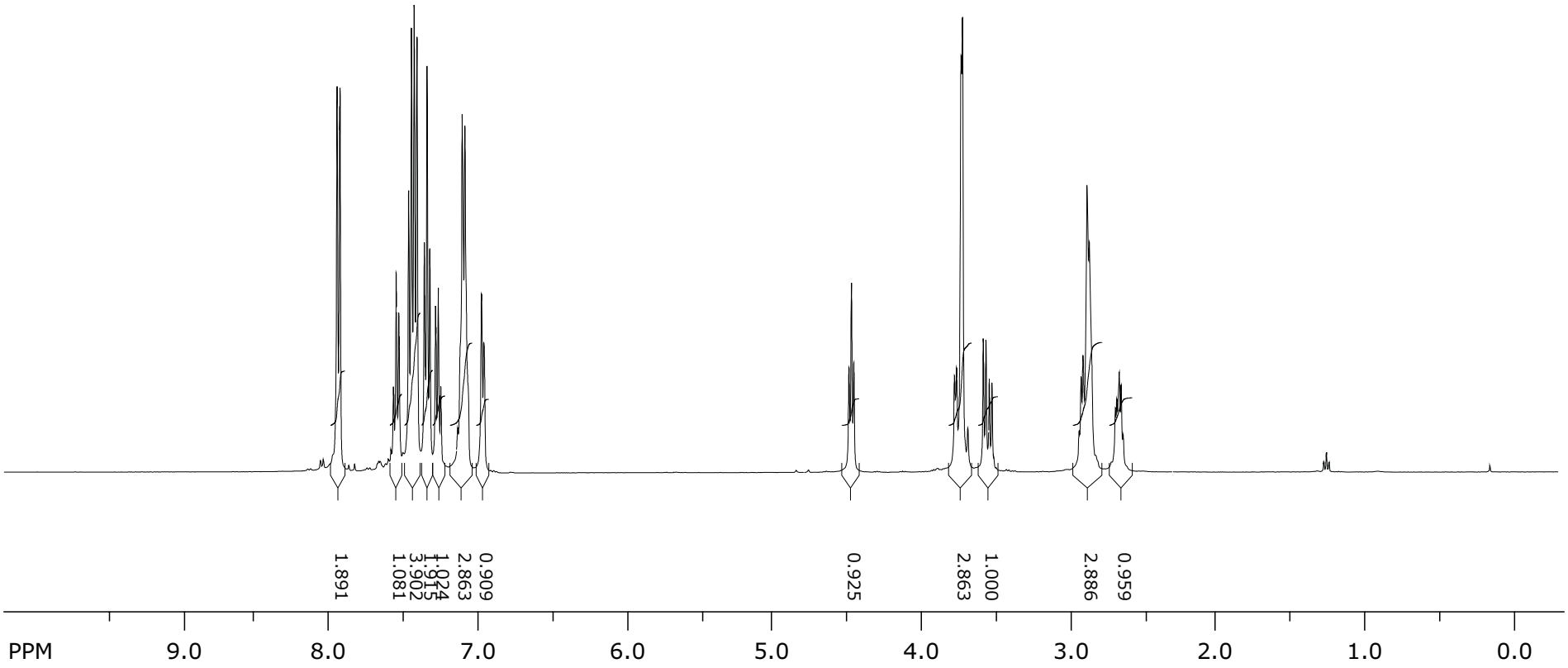
^{13}C NMR of **4** in $CDCl_3$



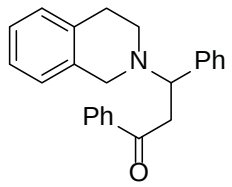


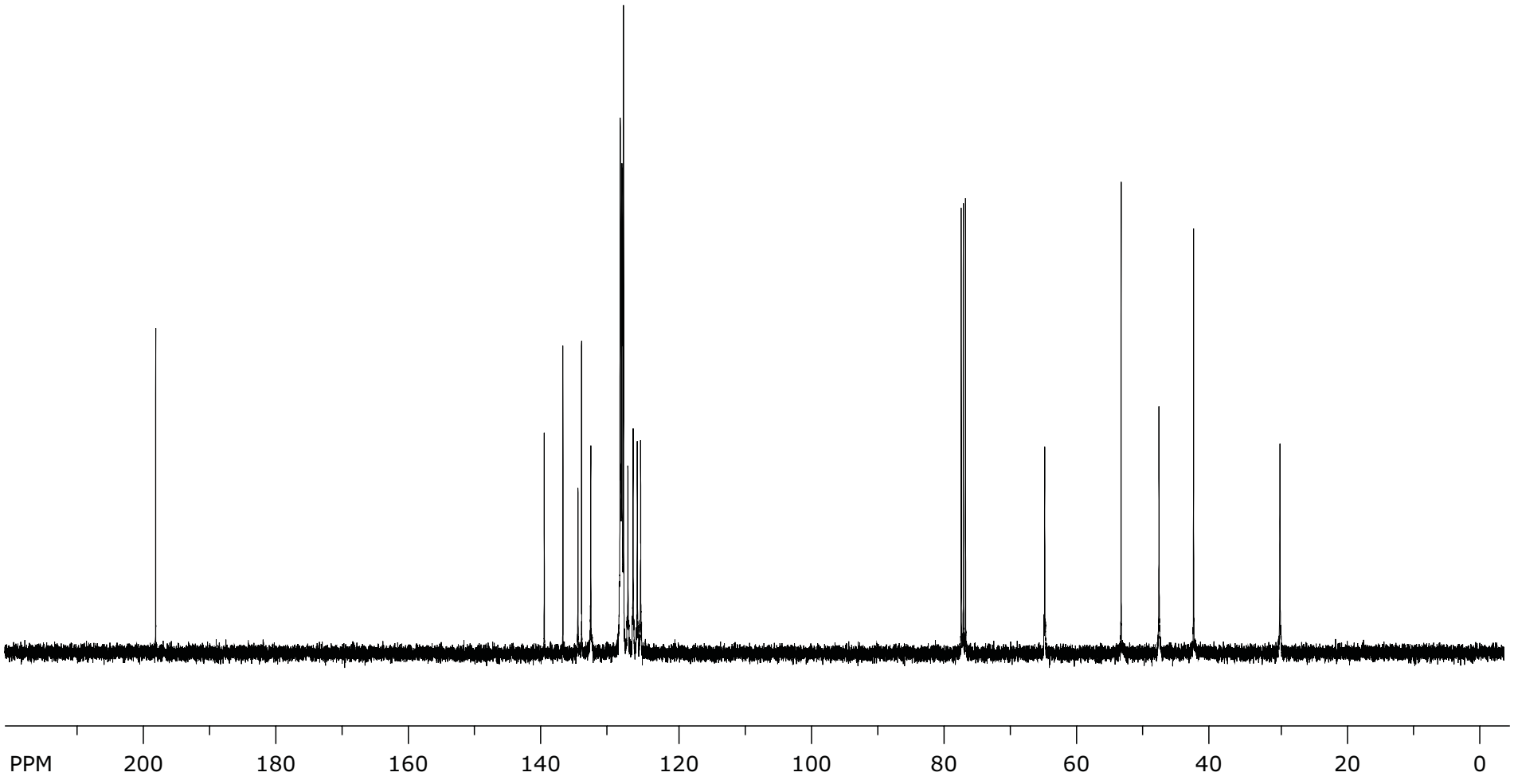
^{1}H NMR of **6** in $CDCl_3$





^{13}C NMR of **6** in $CDCl_3$





^{1}H NMR of crude **8** in $CDCl_3$
(with unreacted chalcone **7**)