

# Redox-Neutral $\alpha$ -Cyanation of Amines

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## Supporting Information

**General Information:** Starting materials, reagents, and solvents were purchased from commercial sources and used as received unless stated otherwise. Pyrrolidine, piperidine, azepane, 1,2,3,4-tetrahydroisoquinoline, 2-methylpyrrolidine, *N*-benzylmethylamine, and 2-ethylhexanoic acid were distilled prior to use. Benzoic acid was recrystallized from toluene/ethanol. Aldehydes were purified either by distillation or by recrystallization prior to use. 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 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<sub>254</sub> plates. Visualization was accomplished with UV light, potassium permanganate 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 (<sup>1</sup>H-NMR) were recorded on a Varian VNMRS-500 MHz and are reported in ppm using the solvent as an internal standard (CDCl<sub>3</sub> 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 (<sup>13</sup>C-NMR) spectra were recorded on a Varian VNMRS-500 MHz and are reported in ppm using the solvent as an internal standard (CDCl<sub>3</sub> at 77.0 ppm). Mass spectra were recorded on a Finnigan LCQ-DUO mass spectrometer. The starting materials **6a**,<sup>1</sup> **20**<sup>1</sup> and cyanohydrins<sup>2</sup> were prepared according to modified literature procedures. 2-hydroxy-2-(pyridin-3-yl)acetonitrile<sup>3</sup> and 2-hydroxy-2,2-diphenylacetonitrile<sup>4</sup> were prepared according to published procedures. Products **5a–5q**,<sup>5</sup> **6p**,<sup>6</sup> **14**,<sup>7</sup> **18**,<sup>5</sup> **22**<sup>8</sup> and **23**<sup>9</sup> were previously reported and their published characterization data matched our own in all respects. Ratios of regioisomeric products were determined by <sup>1</sup>H-NMR analysis of the crude reaction mixture.

**Caution: Due to the potential for HCN formation, all operations should be conducted inside a well ventilated fume hood. SiC passive heating elements must not be used in conjunction with stir bars; they may score glass and cause vessel failure.**

### General Procedure for the Isomerization of 2-Phenyl-2-(pyrrolidin-1-yl)acetonitrile (**6a**):

A 10 mL microwave reaction tube was charged with a 10 x 8 mm SiC passive heating element, **6a** (0.25 mmol, 1 equiv), solvent (2.5 mL) and catalyst (0.05 mmol, 0.2 equiv). The reaction tube was sealed with a Teflon-lined snap cap, and heated in a microwave reactor at stated temperatures for the designated time. After cooling with compressed air flow, the reaction

mixture was diluted with EtOAc (10 mL) and washed with saturated aqueous NaHCO<sub>3</sub> (3 x 5 mL). The combined aqueous layers were extracted with EtOAc (3 x 5 mL), the combined organic layer was washed with water (20 mL) and brine (20 mL), and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Solvent was then removed in vacuo and the reaction mixture was loaded onto a column for purification (silica gel, pre-basified with eluent containing 1% Et<sub>3</sub>N).

### **General Procedure for the Synthesis of Cyanohydrins (adopted from reference 2):**

In a 25 mL round bottom flask, aldehyde (5 mmol, 1 equiv) and Cu(OTf)<sub>2</sub> (0.25 mmol, 0.05 equiv) were added to dichloromethane (7.5 mL) at room temperature. The resulting mixture was stirred for 15 min, followed by slow addition of TMSCN (6.5 mmol, 1.3 equiv). The reaction mixture was stirred at room temperature for 18 hours. The solvent was then removed in vacuo, and acetonitrile (5 mL) and HCl (1M, 5 mL) were added to the residue. It was stirred at 0 °C for 10 min and then extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with water (10 mL), brine (10 mL), and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Solvent was then removed in vacuo and the reaction mixture was loaded onto a column for purification (silica gel) or recrystallized from EtOAc/Hexanes. **Due to the use of excess TMSCN and potential formation of HCN, all steps must be carried out inside a well ventilated fume hood.**

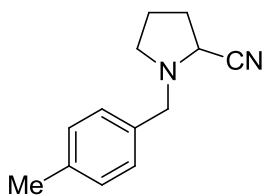
### **Procedure for the Synthesis of 1-Benzylpyrrolidine-2-carbonitrile (5a) via Three-Component Approach:**

A 10 mL microwave reaction tube was charged with a 10 x 8 mm SiC passive heating element, benzaldehyde (0.25 mmol, 1 equiv), toluene (2.5 mL), pyrrolidine (0.325 mmol, 1.3 equiv), TMSCN (0.325 mmol, 1.3 equiv) and benzoic acid (0.05 mmol, 0.2 equiv). The reaction tube was sealed with a Teflon-lined snap cap, and heated in a microwave reactor at 200 °C (200 W, 70–100 psi) for 30 minutes. After cooling with compressed air flow, the reaction mixture was diluted with EtOAc (10 mL) and washed with saturated aqueous NaHCO<sub>3</sub> (3 x 5 mL). The combined aqueous layers were extracted with EtOAc (3 x 5 mL), the combined organic layer was washed with water (20 mL), brine (20 mL), and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Solvent was then removed in vacuo and the reaction mixture was loaded onto a column for purification (silica gel, hexanes/EtOAc/Et<sub>3</sub>N 95/5/1 v/v/v). Product **5a** was obtained as a colorless oil in 62% yield as 9:1 mixture of regioisomers.

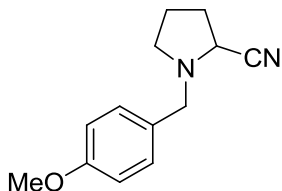
### **General Procedure for the Direct $\alpha$ -Cyanation of Pyrrolidine with Cyanohydrins:**

A 10 mL microwave reaction tube was charged with a 10 x 8 mm SiC passive heating element, cyanohydrin (0.25 mmol, 1 equiv), toluene (2.5 mL), pyrrolidine (0.325 mmol, 1.3 equiv) and 2-ethylhexanoic acid (0.05 mmol, 0.2 equiv). The reaction tube was sealed with a Teflon-lined snap cap, and heated in a microwave reactor at 200 °C (200 W, 70–100 psi) for the designated time. After cooling with compressed air flow, the reaction mixture was diluted with EtOAc (10 mL) and washed with saturated aqueous NaHCO<sub>3</sub> (3 x 5 mL). The combined aqueous layers were extracted with EtOAc (3 x 5 mL), the combined organic layer was washed with water (20 mL) and brine (20 mL), and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Solvent was then removed in vacuo and the reaction mixture was loaded onto a column for purification (silica gel, pre-basified with eluent containing 1% Et<sub>3</sub>N).

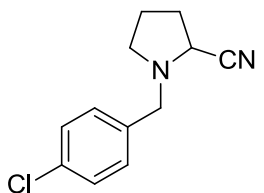
**1-(4-Methylbenzyl)pyrrolidine-2-carbonitrile (5b):** Following the general procedure compound **5b** was obtained from pyrrolidine and *p*-tolualdehyde cyanohydrin as a colorless liquid in 80% yield (16:1 mixture of regioisomers) ( $R_f = 0.14$  in 5% EtOAc in hexanes); Characterization data of the major regioisomer: IR (KBr) 2960, 2815, 2220, 1633, 1573, 1473, 1445, 1376, 1132, 1052, 1039, 755, 683  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) 7.25 (d,  $J = 7.9$  Hz, 2H), 7.14 (d,  $J = 7.9$  Hz, 2H), 3.89 (d,  $J = 12.9$  Hz, 1H), 3.69 (dd,  $J = 7.4, 2.7$  Hz, 1H), 3.63 (d,  $J = 12.9$  Hz, 1H), 2.93 (ddd,  $J = 9.4, 8.3, 4.2$  Hz, 1H), 2.62–2.54 (m, 1H), 2.35 (s, 3H), 2.20–2.07 (comp, 2H), 2.00–1.84 (comp, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  137.1, 134.5, 129.1, 128.8, 118.0, 56.2, 53.1, 51.1, 29.5, 21.8, 21.1;  $m/z$  (ESI-MS) 174.1  $[\text{M}-\text{CN}]^+$ .



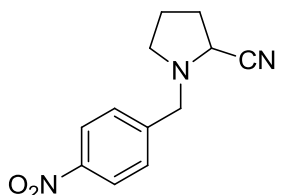
**1-(4-Methoxybenzyl)pyrrolidine-2-carbonitrile (5c):** Following the general procedure compound **5c** was obtained from pyrrolidine and *p*-anisaldehyde cyanohydrin as a colorless liquid in 67% yield (11:1 mixture of regioisomers) ( $R_f = 0.19$  in 10% EtOAc in hexanes); Characterization data of the major regioisomer: IR (KBr) 2958, 2816, 2222, 1612, 1513, 1462, 1377, 1301, 1245, 1174, 10393, 821  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) 7.27 (d,  $J = 8.6$  Hz, 2H), 6.86 (d,  $J = 8.7$  Hz, 2H), 3.86 (d,  $J = 12.8$  Hz, 1H), 3.80 (s, 3H), 3.67 (dd,  $J = 7.3, 2.8$  Hz, 1H), 3.60 (d,  $J = 12.8$  Hz, 1H), 2.92 (ddd,  $J = 9.4, 8.3, 4.2$  Hz, 1H), 2.60–2.52 (m, 1H), 2.20–2.06 (comp, 2H), 2.00–1.84 (comp, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  158.9, 129.9, 129.6, 117.9, 113.7, 55.7, 55.1, 52.9, 51.0, 29.4, 21.8;  $m/z$  (ESI-MS) 190.0  $[\text{M}-\text{CN}]^+$ .



**1-(4-Chlorobenzyl)pyrrolidine-2-carbonitrile (5d):** Following the general procedure compound **5d** was obtained from pyrrolidine and *p*-chlorobenzaldehyde cyanohydrin as a white sticky solid in 94% yield (>20:1 mixture of regioisomers) ( $R_f = 0.13$  in 5% EtOAc in hexanes); Characterization data of the major regioisomer: IR (KBr) 2960, 2819, 2222, 1644, 1491, 1447, 1409, 1376, 1334, 1124, 1084, 1016, 881, 840  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) 7.38–7.27 (comp, 4H), 3.87 (d,  $J = 13.1$  Hz, 1H), 3.68 (dd,  $J = 7.4, 2.6$  Hz, 1H), 3.64 (d,  $J = 13.1$  Hz, 1H), 2.91 (ddd,  $J = 9.4, 8.4, 4.2$  Hz, 1H), 2.63–2.53 (m, 1H), 2.25–2.07 (comp, 2H), 2.04–1.84 (comp, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  136.1, 133.1, 130.0, 128.6, 117.7, 55.7, 53.1, 51.1, 29.4, 21.8;  $m/z$  (ESI-MS) 194.1  $[\text{M}-\text{CN}]^+$ .

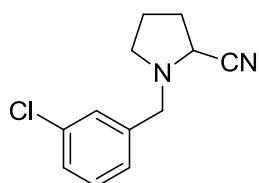


**1-(4-Nitrobenzyl)pyrrolidine-2-carbonitrile (5e):** Following the general procedure for the synthesis of  $\alpha$ -aminonitrile via three-component approach, compound **5e** was obtained from pyrrolidine, *p*-nitrobenzaldehyde and  $\text{TMSCN}$  as an off-white solid in 41% yield (1.4:1 mixture of regioisomers) ( $R_f = 0.24$  in 20% EtOAc in hexanes); Characterization data of the major regioisomer: mp: 80–83  $^\circ\text{C}$ ; IR (KBr) 2961, 2820, 2220, 1606, 1518, 1346, 1108,



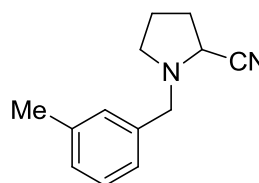
1015, 853, 806, 739  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) 8.20 (d,  $J = 8.7$  Hz, 2H), 7.54 (d,  $J = 8.8$  Hz, 2H), 4.00 (d,  $J = 13.8$  Hz, 1H), 3.81 (d,  $J = 13.8$  Hz, 1H), 3.72 (dd,  $J = 7.5, 2.7$  Hz, 1H), 2.92 (ddd,  $J = 9.4, 8.3, 4.3$  Hz, 1H), 2.63–2.56 (m, 1H), 2.26–2.11 (comp, 2H), 2.05–1.87 (comp, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  147.5, 145.2, 129.3, 123.8, 117.6, 55.9, 53.4, 51.3, 29.6, 22.0;  $m/z$  (ESI-MS) 205.2  $[\text{M}-\text{CN}]^+$ .

**1-(3-Chlorobenzyl)pyrrolidine-2-carbonitrile (5f):** Following the general procedure



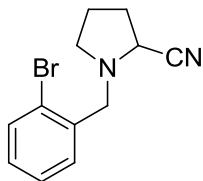
compound **5f** was obtained from pyrrolidine and *m*-chlorobenzaldehyde cyanohydrin as a colorless liquid in 87% yield (>20:1 mixture of regioisomers) ( $R_f = 0.14$  in 5% EtOAc in hexanes); Characterization data of the major regioisomer: IR (KBr) 3062, 2961, 2881, 2820, 2222, 1600, 1576, 1475, 1431, 1373, 1334, 1210, 1144, 1076, 995, 883, 786, 685;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) 7.37 (s, 1H), 7.29–7.21 (comp, 3H), 3.89 (d,  $J = 13.2$  Hz, 1H), 3.71 (dd,  $J = 7.5, 2.5$  Hz, 1H), 3.65 (d,  $J = 13.2$  Hz, 1H), 2.93 (ddd,  $J = 9.4, 8.2, 4.2$  Hz, 1H), 2.62–2.54 (m, 1H), 2.24–2.09 (comp, 2H), 2.02–1.86 (comp, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  139.7, 134.3, 129.7, 128.7, 127.7, 126.8, 117.8, 55.9, 53.2, 51.2, 29.5, 21.9;  $m/z$  (ESI-MS) 194.1  $[\text{M}-\text{CN}]^+$ .

**1-(3-Methylbenzyl)pyrrolidine-2-carbonitrile (5g):** Following the general procedure



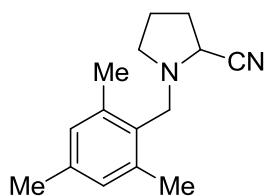
compound **5g** was obtained from pyrrolidine and *m*-tolualdehyde cyanohydrin as a colorless liquid in 79% yield (19:1 mixture of regioisomers) ( $R_f = 0.14$  in 5% EtOAc in hexanes); Characterization data of the major regioisomer: IR (KBr) 2959, 2922, 2881, 2814, 2221, 1610, 1487, 1460, 1378, 1334, 1160, 1124, 1089, 886, 789, 700  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) 7.25–7.20 (m, 1H), 7.19–7.14 (comp, 2H), 7.09 (app d,  $J = 7.5$  Hz, 1H), 3.89 (d,  $J = 12.9$  Hz, 1H), 3.70 (dd,  $J = 7.5, 2.6$  Hz, 1H), 3.63 (d,  $J = 12.9$  Hz, 1H), 2.94 (ddd,  $J = 12.6, 8.2, 4.3$  Hz, 1H), 2.63–2.54 (m, 1H), 2.35 (s, 3H), 2.23–2.08 (comp, 2H), 2.02–1.86 (comp, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  138.1, 137.5, 129.5, 128.3, 128.2, 125.9, 118.0, 56.5, 53.2, 51.2, 29.5, 21.8, 21.3;  $m/z$  (ESI-MS) 174.1  $[\text{M}-\text{CN}]^+$ .

**1-(2-Bromobenzyl)pyrrolidine-2-carbonitrile (5h):** Following the general procedure



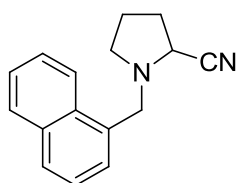
compound **5h** was obtained from pyrrolidine and *o*-bromobenzaldehyde cyanohydrin as a colorless liquid in 85% yield (>20:1 mixture of regioisomers) ( $R_f = 0.19$  in 3% EtOAc in hexanes); Characterization data of the major regioisomer: IR (KBr) 3059, 2959, 2814, 2221, 1567, 1468, 1439, 1375, 1335, 1246, 1134, 1028, 994, 882, 754, 660  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) 7.56 (app dd,  $J = 7.9, 1.2$  Hz, 1H), 7.42 (app dd,  $J = 7.6, 1.6$  Hz, 1H), 7.29 (app td,  $J = 7.5, 1.3$  Hz, 1H), 7.14 (app td,  $J = 7.9, 1.7$  Hz, 1H), 3.96 (d,  $J = 13.7$  Hz, 1H), 3.86 (d,  $J = 13.8$  Hz, 1H), 3.78 (dd,  $J = 7.6, 2.7$  Hz, 1H), 2.93 (ddd,  $J = 9.3, 8.5, 4.5$  Hz, 1H), 2.72–2.62 (m, 1H), 2.26–2.09 (comp, 2H), 2.04–1.84 (comp, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  136.9, 133.0, 130.6, 128.9, 127.4, 124.6, 118.3, 56.0, 53.5, 51.1, 29.7, 22.0;  $m/z$  (ESI-MS) 239.2  $[\text{M}-\text{CN}]^+$ .

**1-(2,4,6-Trimethylbenzyl)pyrrolidine-2-carbonitrile (5i):** Following the general procedure compound **5i** was obtained from pyrrolidine and mesitaldehyde



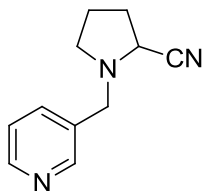
cyanohydrin as a colorless liquid in 89% yield (>20:1 mixture of regioisomers) ( $R_f = 0.16$  in 3% EtOAc in hexanes); Characterization data of the major regioisomer: IR (KBr) 2954, 2858, 2221, 1613, 1461, 1374, 1332, 1120, 1046, 851, 665  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) 6.84 (s, 2H), 3.85 (d,  $J = 12.8$  Hz, 1H), 3.74 (d,  $J = 12.8$  Hz, 1H), 3.70 (dd,  $J = 7.1, 3.3$  Hz, 1H), 2.77 (ddd,  $J = 9.0, 8.4, 4.5$  Hz, 1H), 2.66–2.57 (m, 1H), 2.37 (s, 6H), 2.26 (s, 3H), 2.16–2.06 (comp, 2H), 1.95–1.85 (m, 1H), 1.85–1.76 (m, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  137.7, 136.7, 131.2, 129.1, 118.8, 53.5, 50.2, 49.5, 29.7, 22.0, 20.8, 20.0;  $m/z$  (ESI-MS) 202.0  $[\text{M}-\text{CN}]^+$ .

**1-(Naphthalen-1-ylmethyl)pyrrolidine-2-carbonitrile (5j):** Following the general procedure



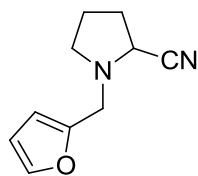
compound **5j** was obtained from pyrrolidine and 1-naphthaldehyde cyanohydrin as an off-white solid in 85% yield (18:1 mixture of regioisomers) ( $R_f = 0.27$  in 5% EtOAc in hexanes); Characterization data of the major regioisomer: mp: 42–44  $^\circ\text{C}$ ; IR (KBr) 2957, 2817, 2221, 1597, 1509, 1460, 1379, 1331, 1234, 1142, 1019, 880, 779  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) 8.24 (app d,  $J = 8.5$  Hz, 1H), 7.90–7.84 (m, 1H), 7.81 (app d,  $J = 8.2$  Hz, 1H), 7.57–7.47 (comp, 3H), 7.47–7.40 (m, 1H), 4.44 (d,  $J = 12.9$  Hz, 1H), 4.02 (d,  $J = 12.9$  Hz, 1H), 3.69–3.59 (m, 1H), 3.02 (app td,  $J = 8.9, 4.2$  Hz, 1H), 2.72–2.63 (m, 1H), 2.18–2.06 (comp, 2H), 2.03–1.85 (comp, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  133.8, 133.3, 132.1, 128.4(2), 128.4(0), 127.2, 125.9, 125.7, 125.2, 124.3, 118.1, 54.7, 53.2, 51.1, 29.5, 21.8;  $m/z$  (ESI-MS) 210.1  $[\text{M}-\text{CN}]^+$ .

**1-(Pyridin-3-ylmethyl)pyrrolidine-2-carbonitrile (5k):** Following the general procedure



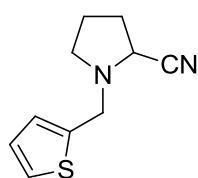
compound **5k** was obtained from pyrrolidine and 3-pyridinecarboxaldehyde cyanohydrin as a colorless liquid in 60% yield (>20:1 mixture of regioisomers) ( $R_f = 0.19$  in 50% EtOAc in hexanes); Characterization data of the major regioisomer: IR (KBr) 2962, 2822, 2222, 1656, 1579, 1479, 1427, 1378, 1330, 1187, 1124, 1029, 799, 714  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) 8.60 (s, 1H), 8.53 (app d,  $J = 4.2$  Hz, 1H), 7.68 (app dt,  $J = 7.8, 1.8$  Hz, 1H), 7.26 (app dd,  $J = 7.8, 4.8$  Hz, 1H), 3.90 (d,  $J = 13.3$  Hz, 1H), 3.70 (d,  $J = 13.3$  Hz, 1H), 3.71–3.69 (m, 1H), 2.90 (ddd,  $J = 9.2, 8.4, 4.3$  Hz, 1H), 2.63–2.53 (m, 1H), 2.23–2.08 (comp, 2H), 2.02–1.84 (comp, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  150.2, 149.0, 136.4, 133.1, 123.4, 117.7, 53.9, 53.3, 51.2, 29.5, 21.9;  $m/z$  (ESI-MS) 188.1  $[\text{M}+\text{H}]^+$ , 161.2  $[\text{M}-\text{CN}]^+$ .

**1-(Furan-2-ylmethyl)pyrrolidine-2-carbonitrile (5l):** Following the general procedure



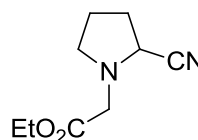
compound **5l** was obtained from pyrrolidine and furfural cyanohydrin as a colorless liquid in 64% yield (20:1 mixture of regioisomers) ( $R_f = 0.16$  in 10% EtOAc in hexanes); Characterization data of the major regioisomer: IR (KBr) 2962, 2882, 2818, 2222, 1601, 1505, 1445, 1372, 1335, 1224, 1149, 1014, 916, 739,  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) 7.40–7.37 (m, 1H), 6.35–6.31 (m, 1H), 6.31–6.26 (m, 1H), 3.88 (d,  $J = 14.0$  Hz, 1H), 3.76 (d,  $J = 14.0$  Hz, 1H), 3.73 (dd,  $J = 7.6, 2.7$  Hz, 1H), 2.96 (ddd,  $J = 9.3, 8.3, 4.4$  Hz, 1H), 2.68–2.58 (m, 1H), 2.25–2.09 (comp, 2H), 2.02–1.86 (comp, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  151.2, 142.8, 118.0, 110.5, 109.1, 53.2, 51.4, 48.7, 29.8, 22.2;  $m/z$  (ESI-MS) 150.1  $[\text{M}-\text{CN}]^+$ .

**1-(Thiophen-2-ylmethyl)pyrrolidine-2-carbonitrile (5m):** Following the general procedure



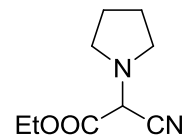
compound **5m** was obtained from pyrrolidine and 2-thiophenecarboxaldehyde cyanohydrin as a colorless liquid in 82% yield (>20:1 mixture of regioisomers) ( $R_f = 0.24$  in 10% EtOAc in hexanes); Characterization data of the major regioisomer: IR (KBr) 2959, 2808, 2222, 1645, 1444, 1377, 1329, 1223, 1117, 951, 851, 696  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) 7.25 (app dd,  $J = 5.0, 1.1$  Hz, 1H), 7.01 (d,  $J = 3.3$  Hz, 1H), 6.94 (dd,  $J = 5.1, 3.5$  Hz, 1H), 4.08 (d,  $J = 13.8$  Hz, 1H), 3.94 (d,  $J = 13.8$  Hz, 1H), 3.78 (dd,  $J = 7.3, 2.5$  Hz, 1H), 3.01 (ddd,  $J = 9.1, 7.9, 4.2$  Hz, 1H), 2.67–2.57 (m, 1H), 2.25–2.08 (comp, 2H), 2.04–1.86 (comp, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  140.7, 126.6, 126.34, 125.5, 117.7, 52.8, 51.0, 50.8, 29.5, 21.9;  $m/z$  (ESI-MS) 166.0  $[\text{M}-\text{CN}]^+$ .

**Ethyl 2-(2-cyanopyrrolidin-1-yl)acetate (5n) and ethyl 2-cyano-2-(pyrrolidin-1-yl)acetate**



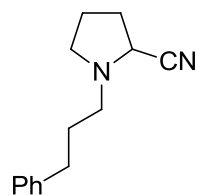
(**6n**): Following the general procedure compounds **5n** and **6n** were obtained from pyrrolidine and ethyl glyoxalate cyanohydrin as a colorless liquid in 62% yield (1:1.4 mixture of regioisomers). Characterization data of **5n**:  $R_f = 0.26$  in 20% EtOAc in hexanes; IR (KBr) 2982, 2822, 2220, 1743, 1464, 1428, 1384, 1200, 1160, 1028, 863  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) 4.14 (qd,  $J = 7.2, 1.0$  Hz, 2H), 4.10 (dd,  $J = 7.9, 2.8$  Hz, 1H), 3.53–3.40 (comp, 2H), 3.02 (ddd,  $J = 9.1, 7.7, 5.4$  Hz, 1H), 2.66–2.58 (m, 1H), 2.27–2.17 (m, 1H), 2.14–2.05 (m, 1H), 1.97–1.84 (comp, 2H), 1.23 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  169.7, 118.0, 60.7, 52.8, 52.4, 51.3, 29.8, 22.1, 14.0;  $m/z$  (ESI-MS) 156.1  $[\text{M}-\text{CN}]^+$ .

Characterization data of **6n**:  $R_f = 0.20$  in 20% EtOAc in hexanes; IR (KBr) 2976, 2879, 2821,



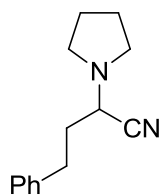
2359, 1746, 1463, 1445, 1370, 1201, 1154, 1117, 1024, 904, 851  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) 4.59 (s, 1H), 4.25 (q,  $J = 7.3$  Hz, 2H), 2.81–2.63 (comp, 4H), 1.91–1.75 (comp, 4H), 1.28 (t,  $J = 7.1$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  164.0, 112.6, 62.8, 57.8, 50.3, 23.4, 13.8;  $m/z$  (ESI-MS) 183.2  $[\text{M} + \text{H}]^+$ .

**1-(3-Phenylpropyl)pyrrolidine-2-carbonitrile (5o) and 4-phenyl-2-(pyrrolidin-1-yl)butanenitrile (6o):** Following the general procedure compounds **5o** and **6o**

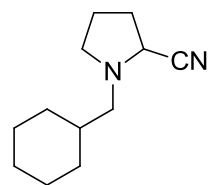


were obtained from pyrrolidine and hydrocinnamaldehyde cyanohydrin as colorless liquid in 74% yield (1:3 mixture of regioisomers). Characterization data of **5o**:  $R_f = 0.16$  in 10% EtOAc in hexanes; IR (KBr) 3026, 2942, 2813, 2220, 1602, 1496, 1454, 1386, 1318, 1182, 1145, 1123, 1079, 1030, 966, 882, 747, 700  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) 7.33–7.27 (comp, 2H), 7.23–7.18 (comp, 3H), 3.76 (dd,  $J = 7.6, 2.8$  Hz, 1H), 2.89 (ddd,  $J = 9.4, 8.4, 4.6$  Hz, 1H), 2.73 (m, 1H), 2.69 (t,  $J = 7.6$  Hz, 2H), 2.64–2.52 (comp, 2H), 2.23–2.08 (comp, 2H), 2.01–1.82 (comp, 4H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  141.7, 128.3, 128.2, 125.8, 118.1, 53.6, 51.8, 51.0, 33.3, 30.0, 29.5, 21.8;  $m/z$  (ESI-MS) 188.3  $[\text{M}-\text{CN}]^+$ .

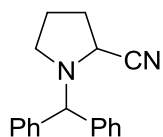
Characterization data of **6o**:  $R_f = 0.32$  in 10% EtOAc in Hexanes; IR (KBr) 3062, 3027, 2961, 2811, 2222, 1603, 1496, 1455, 1354, 1318, 1143, 1123, 1030, 903, 869, 752, 700  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) 7.35–2.28 (comp, 2H), 7.26–7.18 (comp, 3H), 3.69 (t,  $J = 7.9$  Hz, 1H), 2.91–2.77 (comp, 2H), 2.77–2.68 (comp, 2H), 2.68–2.56 (comp, 2H), 2.14–2.04 (comp, 2H), 1.90–1.79 (comp, 4H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  139.8, 128.3(2), 128.3(0), 126.1, 117.2, 53.9, 49.6, 33.8, 31.6, 23.2;  $m/z$  (ESI-MS) 188.1  $[\text{M}-\text{CN}]^+$ .



**1-(Cyclohexylmethyl)pyrrolidine-2-carbonitrile (5p):** Following the general procedure compound **5p** was obtained from pyrrolidine and cyclohexanecarboxaldehyde cyanohydrin as a colorless liquid in 78% yield (1:5 mixture of regioisomers) ( $R_f = 0.23$  in 5% EtOAc in hexanes); Characterization data of **5p**: IR (KBr) 2923, 2851, 2810, 2221, 1449, 1341, 1244, 1189, 1147, 1114, 1082, 879  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) 3.71 (dd,  $J = 7.5, 2.7$  Hz, 1H), 2.86–2.79 (m, 1H), 2.54–2.43 (comp, 2H), 2.40–2.33 (m, 1H), 2.19–2.04 (comp, 2H), 1.96–1.81 (comp, 2H), 1.81–1.73 (comp, 2H), 1.73–1.59 (comp, 3H), 1.48–1.37 (m, 1H), 1.29–1.08 (comp, 3H), 0.94–0.81 (comp, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  118.3, 59.4, 54.0, 51.4, 36.5, 31.6, 31.5, 29.6, 26.6, 25.8(9), 25.8(8), 21.9;  $m/z$  (ESI-MS) 166.2  $[\text{M}-\text{CN}]^+$ .

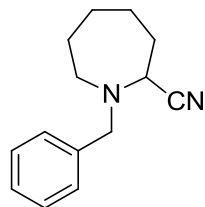


**1-Benzhydrylpyrrolidine-2-carbonitrile (5q):** Following the general procedure but using benzoic acid as a catalyst compound **5q** was obtained from pyrrolidine and benzophenone cyanohydrin as a white solid in 40% yield (>20:1 mixture of regioisomers) ( $R_f = 0.22$  in 3% EtOAc in hexanes); Characterization data of the major regioisomer: mp: 108–111  $^\circ\text{C}$ ; IR (KBr) 3061, 3028, 2958, 2821, 2222, 1598, 1491, 1453, 1306, 1186, 1130, 1076, 1028, 927, 887, 748, 706, 628  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) 7.55–7.46 (comp, 4H), 7.34–7.27 (comp, 4H), 7.24–7.17 (comp, 2H), 4.60 (s, 1H), 3.78 (app d,  $J = 7.3$  Hz, 1H), 3.03–2.93 (m, 1H), 2.46–2.34 (m, 1H), 2.25–2.13 (m, 1H), 2.13–2.04 (m, 1H), 2.02–1.86 (comp, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  142.5, 142.0, 128.8, 128.6, 127.5(9), 127.5(6), 127.3(3), 127.3(2), 117.7, 71.9, 53.1, 49.9, 29.4, 21.8;  $m/z$  (ESI-MS) 236.0



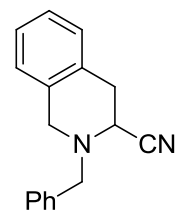
[M-CN]<sup>+</sup>.

**1-benzylazepane-2-carbonitrile (16):** Following the general procedure but conducting the



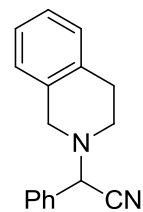
reaction at 220 °C, compound **16** was obtained from azepane and benzaldehyde cyanohydrin as colorless liquid in 79% yield (11:1 mixture of regioisomers) ( $R_f = 0.40$  in 10% EtOAc in Hexanes); Characterization data of the major regioisomer: IR (KBr) 2931, 2852, 2821, 2220, 1602, 1452, 1357, 1150, 1072, 957, 906, 747, 698  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) 7.38–7.33 (comp, 3H), 7.33–7.30 (m, 1H), 7.30–7.25 (m, 1H), 3.80 (d,  $J = 13.4$  Hz, 1H), 3.76 (dd,  $J = 7.5, 5.6$  Hz, 1H), 3.73 (d,  $J = 13.4$  Hz, 1H), 2.75 (app dd,  $J = 6.8, 4.6$  Hz, 2H), 2.08–2.00 (m, 1H), 1.90–1.82 (m, 1H), 1.81–1.71 (comp, 3H), 1.71–1.59 (comp, 2H), 1.59–1.50 (m, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  138.2, 128.7, 128.4, 127.5, 118.4, 61.1, 54.3, 51.2, 32.4, 28.5, 27.2, 23.4;  $m/z$  (ESI-MS) 188.3 [M - CN]<sup>+</sup>.

**2-Benzyl-1,2,3,4-tetrahydroisoquinoline-3-carbonitrile (18):** Following the general procedure



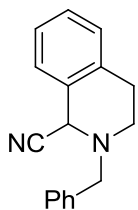
compound **18** was obtained from 1,2,3,4-tetrahydroisoquinoline and benzaldehyde cyanohydrin as an off-white solid in 63% yield (17:1:1 mixture of **18**, **19** and **20**) ( $R_f = 0.21$  in 3% EtOAc in hexanes); Characterization data of **18**: mp: 110–112 °C; IR (KBr) 2818, 2222, 1644, 1496, 1455, 1357, 1315, 1145, 1091, 1074, 1028, 989, 741, 701  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) 7.45–7.29 (comp, 5H), 7.21–7.15 (comp, 2H), 7.14–7.09 (m, 1H), 7.08–7.03 (m, 1H), 4.03 (d,  $J = 6.3$  Hz, 1H), 3.98 (d,  $J = 15.5$  Hz, 1H), 3.92 (d,  $J = 13.2$  Hz, 1H), 3.78 (d,  $J = 15.6$  Hz, 1H), 3.70 (d,  $J = 13.1$  Hz, 1H), 3.31 (dd,  $J = 16.4, 6.2$  Hz, 1H), 2.98 (d,  $J = 16.5$  Hz, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  136.4, 132.8, 129.8, 129.0, 128.7(2), 128.7(0), 127.9, 126.7, 126.6, 126.5, 116.3, 60.2, 51.6, 49.3, 32.6;  $m/z$  (ESI-MS) 222.2 [M-CN]<sup>+</sup>.

**2-(3,4-dihydroisoquinolin-2(1H)-yl)-2-phenylacetonitrile (19):** Following a literature procedure,<sup>1</sup> compound **19** was obtained from 1,2,3,4-tetrahydroisoquinoline,



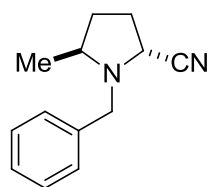
benzaldehyde and TMS-CN as an off-white solid in 38% yield ( $R_f = 0.29$  in 10% EtOAc in Hexanes); mp: 77–80 °C; IR (KBr) 3044, 2960, 2925, 2834, 2786, 2751, 2360, 2343, 2223, 1494, 1449, 1390, 1317, 1267, 1131, 1094, 1044, 934, 914, 872, 759, 741, 702  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) 7.65–7.58 (comp, 2H), 7.47–7.37 (comp, 3H), 7.18–7.10 (comp, 3H), 7.02–6.98 (m, 1H), 5.08 (s, 1H), 3.83–3.74 (comp, 2H), 3.02–2.81 (comp, 4H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  133.7, 133.6, 133.0, 129.0, 128.8, 128.7, 127.8, 126.6, 126.4, 125.8, 115.3, 62.2, 52.4, 47.5, 29.3;  $m/z$  (ESI-MS) 222.1 [M - CN]<sup>+</sup>.

**2-Benzyl-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (20):** Following literature procedures,<sup>10</sup> compound **20** was obtained as an off-white solid in 47% yield (three



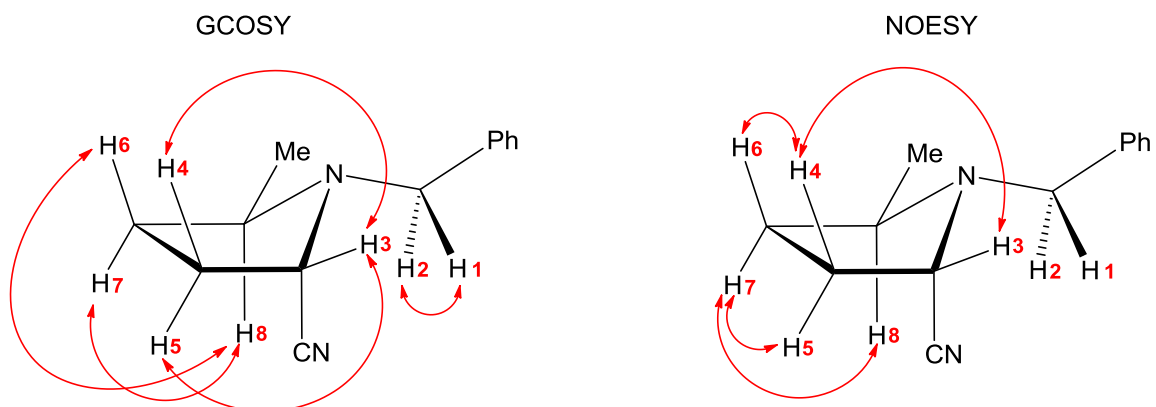
steps) ( $R_f = 0.32$  in 10% EtOAc in Hexanes); mp: 72–75 °C; IR (KBr) 3084, 3065, 3024, 2969, 2928, 2827, 2218, 1493, 1451, 1369, 1336, 1134, 1095, 1050, 936, 738, 698  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) 7.46–7.41 (comp, 2H), 7.40–7.35 (comp, 2H), 7.35–7.30 (m, 1H), 7.28–7.23 (m, 1H), 7.21–7.16 (comp, 2H), 7.16–7.12 (m, 1H), 4.69 (s, 1H), 3.94 (d,  $J = 13.2$  Hz, 1H), 3.84 (d,  $J = 13.2$  Hz, 1H), 3.14–3.02 (comp, 2H), 2.94–2.85 (m, 1H), 2.83–2.76 (m, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  136.6, 134.4, 129.6, 129.4, 129.1, 128.6, 128.4, 127.8, 127.3, 126.4, 116.6, 59.9, 54.4, 46.6, 28.5;  $m/z$  (ESI-MS) 222.2  $[\text{M} - \text{CN}]^+$ .

**trans-1-benzyl-5-methylpyrrolidine-2-carbonitrile (trans-21):** According to the general



procedure, 2-methylpyrrolidine and benzaldehyde cyanohydrin were allowed to react at 180 °C to give rise to a colorless liquid consisting of a mixture of 1-benzyl-2-methylpyrrolidine-2-carbonitrile (**22**, 11%),<sup>8</sup> and *trans-21*/*cis-21* (4.8:1, 52%). The relative configuration of the major diastereomer (*trans-21*) was determined by GCOSY and NOESY. ( $R_f = 0.27$  in 5% EtOAc in Hexanes). Characterization data of the major diastereomer *trans-21*: IR (KBr) 3029.5, 2963.9, 2812.7, 2221.0, 1495.4, 1454.3, 1324.7, 1153.6, 1136.9, 1075.7, 1028.7, 970.6, 848.3, 741.8, 699.5  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) 7.41–7.36 (comp, 2H), 7.36–7.30 (comp, 2H), 7.29–7.26 (m, 1H), 4.08 (d,  $J = 13.3$  Hz, 1H), 3.68 (app d,  $J = 7.5$  Hz, 1H), 3.44 (d,  $J = 13.3$  Hz, 1H) 2.89–2.79 (m, 1H), 2.25–2.14 (m, 1H), 2.11–2.02 (m, 1H), 2.01–1.93 (m, 1H), 1.59–1.50 (m, 1H), 1.23 (d,  $J = 6.0$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  138.0, 128.9, 128.5, 127.4, 117.9, 57.0, 53.6, 53.4, 30.9, 27.3, 19.4;  $m/z$  (ESI-MS) 174.1  $[\text{M} - \text{CN}]^+$ .

**2D-NMR Analysis for Compound *trans*-21, Selected Interactions:**



<sup>1</sup>H NMR shifts

Protons	Chemical shifts (ppm)
H1, H2	4.08, 3.44
H3	3.68
H4	2.11–2.02
H5	2.01–1.93
H6	1.59–1.50
H7	2.25–2.14
H8	2.89–2.79
Me	1.23

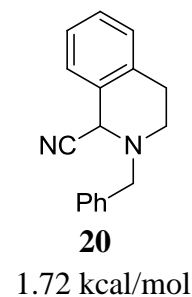
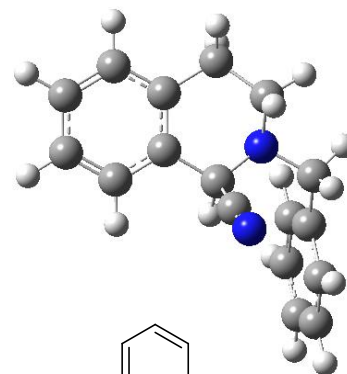
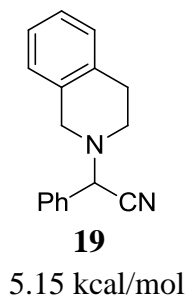
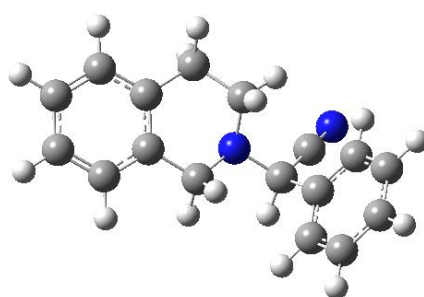
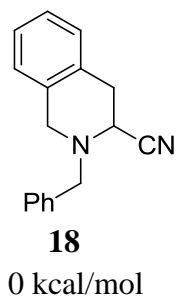
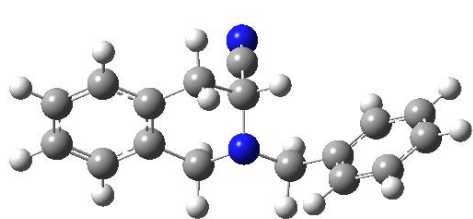
## Computational Study:

A preliminary computational investigation indicates that compound **18** is the thermodynamically most stable of the three regioisomers that are formed in a reaction of 1,2,3,4-tetrahydroisoquinoline with benzaldehyde cyanohydrin. The computed free energies for compounds **18**, **19** and **20** are in good qualitative agreement with our experimental findings and indicate that the reaction is under thermodynamic control.

**Computational Method:** All calculations were carried out with the *Gaussian 09* collection of computer programs.<sup>11</sup> Density functional theory was used as the computational method<sup>12</sup> and the M06 model<sup>13</sup> was employed with the 6-311G(d) basis set.<sup>14</sup>

Compound	E (kcal/mol)	H (kcal/mol)	S (kcal/(K·mol))	G (kcal/mol)	$\Delta G$ (kcal/mol)
<b>18</b>	-480988	-480796	127.853	-480834.5927	0
<b>19</b>	-480983	-480792	124.705	-480829.4408	5.15184889
<b>20</b>	-480987	-480795	125.663	-480832.8714	1.72125719

## 3D Models of Optimized Geometries and Cartesian Coordinates (Å)



**Compound 18**

Row	Symbol	X(Å)	Y(Å)	Z(Å)
1	N	-0.1008220	-0.2646650	0.5774080
2	C	3.5758840	-0.5269650	1.2573340
3	H	3.5721020	-0.6157170	2.3439380
4	C	-0.0154330	0.5480620	-0.6260010
5	H	-0.9794410	0.4737780	-1.1469830
6	C	4.7679640	-0.6149030	0.5612230
7	C	-2.5615220	-0.1987950	0.6415890
8	C	-2.8740470	-1.4666720	0.1547700
9	H	-2.1746060	-2.2843600	0.3237110
10	C	0.1878290	1.9750790	-0.3093600
11	N	0.3249170	3.0737470	0.0117100
12	C	-1.2787250	0.0245310	1.3863900
13	H	-1.2482580	1.0580020	1.7855310
14	C	1.1053380	-0.1896180	1.3862180
15	H	1.0517920	-0.9895870	2.1378520
16	H	1.1409590	0.7637410	1.9563690
17	C	1.0775830	0.0008740	-1.5323690
18	H	0.7159070	-0.9583300	-1.9273440
19	H	1.2211650	0.6672700	-2.3925670
20	C	-4.0522360	-1.6818780	-0.5410330
21	H	-4.2888340	-2.6765690	-0.9127050
22	C	2.3709600	-0.3221410	0.5902760
23	C	2.3692370	-0.2002820	-0.7967390
24	C	-4.9335970	-0.6298600	-0.7618320
25	H	-5.8594300	-0.7997400	-1.3068960
26	C	4.7673400	-0.4930880	-0.8231380
27	C	3.5737850	-0.2858880	-1.4908400
28	H	3.5669290	-0.1833360	-2.5758700
29	C	-4.6274220	0.6361850	-0.2876430
30	H	-5.3101080	1.4647040	-0.4621160
31	C	-3.4441390	0.8493570	0.4084530
32	H	-3.1970830	1.8463170	0.7732480
33	H	-1.2335570	-0.6428440	2.2591260
34	H	5.7010310	-0.7761240	1.0962140
35	H	5.6999810	-0.5547580	-1.3791140

## Compound 19

Row	Symbol	X(Å)	Y(Å)	Z(Å)
1	C	-0.7351170	-0.4728570	-0.8362890
2	N	-0.0755220	0.7863220	-0.5509790
3	C	-0.2456920	1.1611630	0.8454550
4	C	-1.7003150	1.5151970	1.0762150
5	C	-2.6249620	0.4547930	0.5518750
6	C	-3.9529950	0.3981040	0.9682140
7	C	-4.8174570	-0.5641730	0.4765760
8	C	-4.3561120	-1.4945370	-0.4465950
9	C	-3.0384150	-1.4460760	-0.8660040
10	C	-2.1669090	-0.4762710	-0.3781270
11	C	1.2981290	0.8252880	-1.0452130
12	C	2.2802150	-0.1010570	-0.3472920
13	C	2.4733940	-1.3874250	-0.8431550
14	C	3.3096460	-2.2801710	-0.1893690
15	C	3.9658270	-1.8918370	0.9692770
16	C	3.7873280	-0.6081490	1.4655470
17	C	2.9505750	0.2826900	0.8105820
18	H	-0.2083210	-1.3266730	-0.3589470
19	H	-0.6931040	-0.6521370	-1.9212210
20	H	0.3870850	2.0293750	1.0647780
21	H	0.0715420	0.3450990	1.5251880
22	H	-4.3087370	1.1293140	1.6943840
23	H	-5.8513670	-0.5920170	0.8129820
24	H	-5.0264250	-2.2549430	-0.8408330
25	H	-2.6722400	-2.1731510	-1.5916590
26	H	1.2502390	0.5298720	-2.1055170
27	H	1.9690460	-1.6894500	-1.7610780
28	H	3.4547510	-3.2801160	-0.5915640
29	H	4.6257680	-2.5878610	1.4816800
30	H	4.3108690	-0.2943450	2.3655390
31	H	2.8348980	1.2951850	1.1941020
32	H	-1.9124900	2.4677720	0.5696050
33	H	-1.8822310	1.6819980	2.1464200
34	C	1.7681880	2.2127390	-1.0271000
35	N	2.1439160	3.3004720	-0.9906540

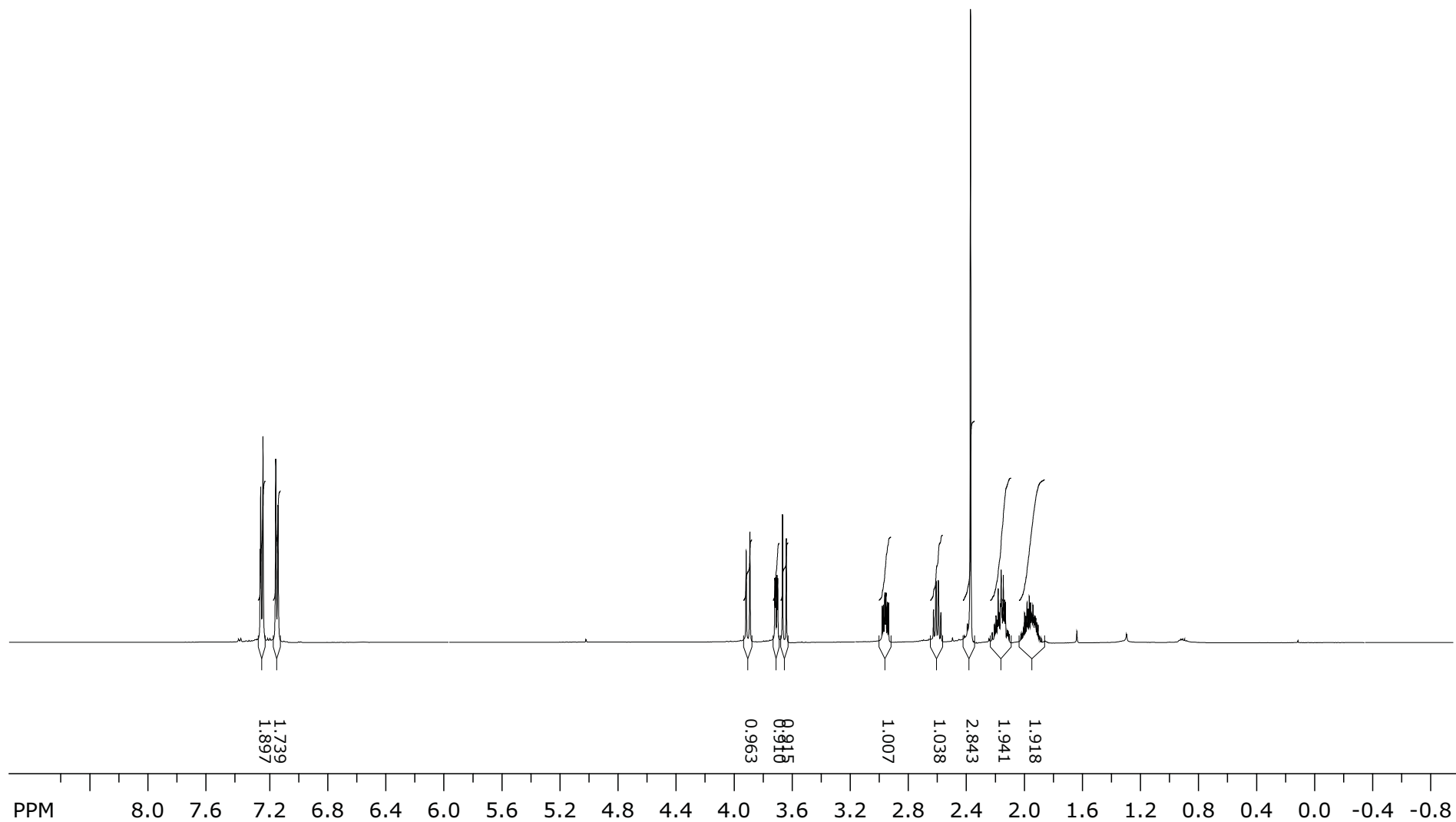
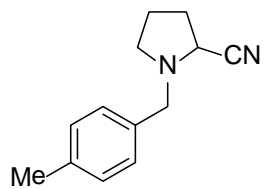
## Compound 20

Row	Symbol	X(Å)	Y(Å)	Z(Å)
1	C	-4.3389760	-1.2623700	-0.5612650
2	C	-3.4531820	-2.1761870	-0.0031090
3	C	-3.9261550	0.0345740	-0.8098790
4	H	-4.6210070	0.7531750	-1.2442290
5	C	-2.1638160	-1.7779990	0.2994430
6	H	-1.4631760	-2.4840460	0.7455150
7	C	-2.6297310	0.4479640	-0.5088060
8	C	-1.7479130	-0.4743600	0.0458960
9	C	-2.1831140	1.8517120	-0.7971390
10	H	-2.9878420	2.5598490	-0.5596470
11	H	-1.9857350	1.9518550	-1.8744630
12	C	-0.9255510	2.2116710	-0.0354970
13	H	-0.5084000	3.1524600	-0.4130990
14	H	-1.1470480	2.3711910	1.0392390
15	C	-0.3373420	-0.0703880	0.4192670
16	H	0.3555550	-0.8623050	0.0962250
17	C	-0.2222980	0.0088360	1.8939560
18	N	-0.0939720	0.1248350	3.0338520
19	N	0.0715170	1.1679110	-0.2216890
20	C	1.4101730	1.5988650	0.1648350
21	H	1.4567080	1.8790760	1.2351970
22	C	2.4537420	0.5628200	-0.1376950
23	C	2.6442960	0.1340330	-1.4501680
24	H	2.0241210	0.5571170	-2.2393290
25	C	3.5976940	-0.8262270	-1.7450570
26	H	3.7397010	-1.1522910	-2.7732180
27	C	4.3744290	-1.3718220	-0.7293080
28	H	5.1239440	-2.1253560	-0.9605650
29	C	4.1880720	-0.9549400	0.5793480
30	H	4.7879400	-1.3822710	1.3796920
31	C	3.2290790	0.0063300	0.8730350
32	H	3.0710100	0.3238560	1.9033650
33	H	1.6214340	2.5141830	-0.4055380
34	H	-5.3564980	-1.5640860	-0.7991730
35	H	-3.7699650	-3.1966890	0.1977540

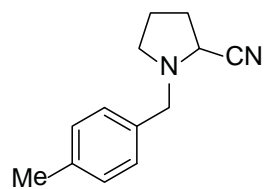
## References:

- (1) Suresh, A. S.; Sandhu, J. S. *Synth. Commun.* **2008**, *38*, 3655.
- (2) Saravanan, P.; Anand, V. R.; Singh, V. K. *Tetrahedron Lett.* **1998**, *39*, 3823.
- (3) Loh, T.-P.; Xu, K.-C.; Ho, D. S.-C.; Sim, K.-Y. *Synlett* **1998**, 369.
- (4) Gassman, P. G.; Talley, J. J. *Tetrahedron Lett.* **1978**, *19*, 3773.
- (5) Das, D.; Richers, M. T.; Ma, L.; Seidel, D. *Org. Lett.* **2011**, *13*, 6584.
- (6) Suginome, M.; Yamamoto, A.; Ito, Y. *Chem. Commun.* **2002**, *13*, 1392.
- (7) (a) Gall, E. L.; Hurvois, J.-P.; Sinbandhit, S. *Eur. J. Org. Chem.* **1999**, 2645; (b) Bahde, R. J.; Rychnovsky, S. D. *Org. Lett.* **2008**, *10*, 4017.
- (8) Han, J.; Xu, B.; Hammond, G. B. *Org. Lett.* **2011**, *13*, 3450.
- (9) Harcourt, D. N.; Waigh, R. D. *J. Chem. Soc. C*, **1971**, 967.
- (10) (a) Shi, J.; Manolikakes, G.; Yeh, C. H.; Guerrero, C. A.; Shenvi, R. A.; Shigehisa, H.; Baran, P. *S. J. Am. Chem. Soc.* **2011**, *133*, 8014; (b) Beaumont, D.; Waigh, R. D.; Sunbhanich, M.; Nott, M. W. *J. Med. Chem.* **1983**, *26*, 507.
- (11) Gaussian 09, Revision A.02, Frisch, M. J. *et al.*, Gaussian, Incorporated, Wallingford, CT 2009.
- (12) Parr, R. G.; Yang, W. *Density-Functional Theory of Atoms and Molecules*, Oxford Univ. Press, Oxford, 1989.
- (13) Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215.
- (14) (a) Petersson, G. A.; Allaham, M. A. *J. Chem. Phys.* **1991**, *94*, 6081. (b) Petersson, G. A.; Bennett, A.; Tensfeldt, T. G.; Allaham, M. A.; Shirley, W. A.; Mantzaris, J. *J. Chem. Phys.* **1988**, *89*, 2193.

<sup>1</sup>H NMR of of **5b** in CDCl<sub>3</sub>



$^{13}\text{C}$  NMR of of **5b** in  $\text{CDCl}_3$



128.7761  
129.1328  
134.5130  
137.0997

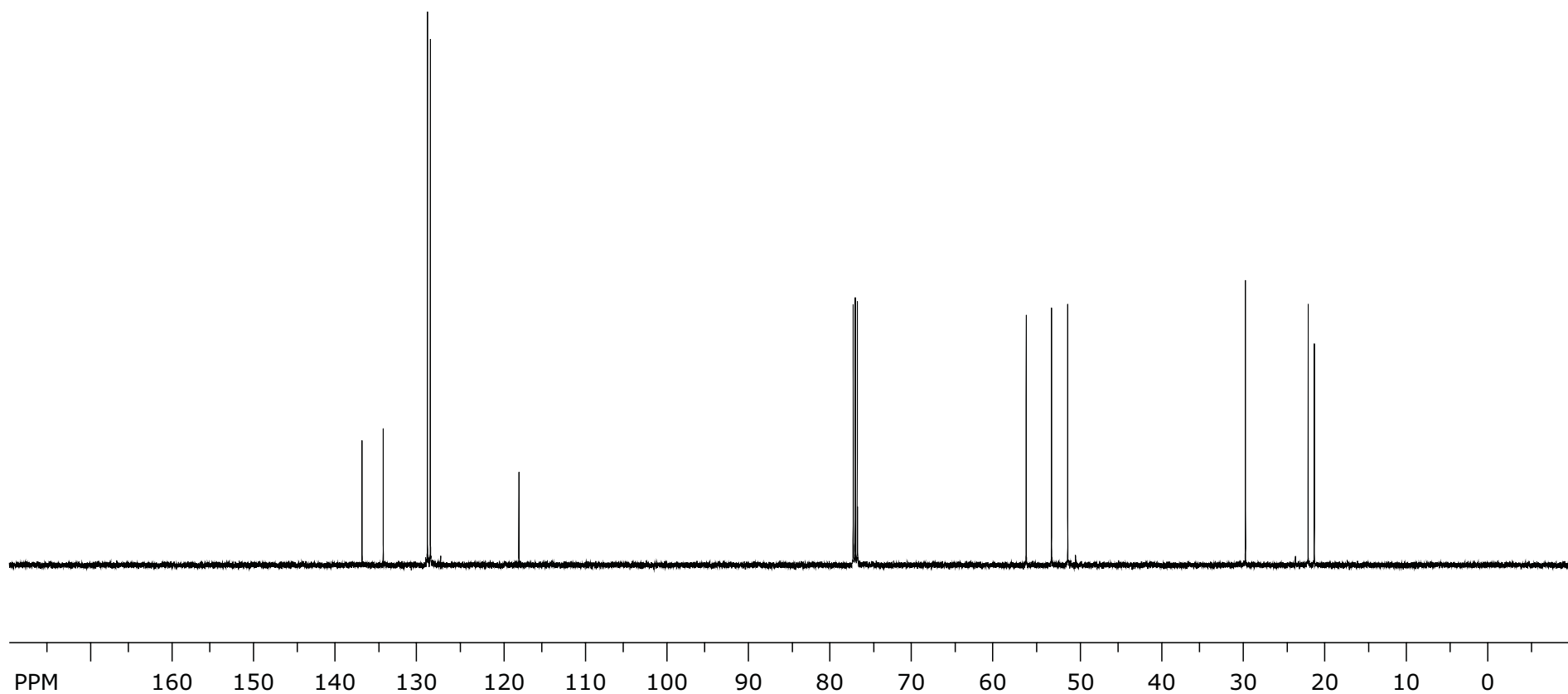
117.9780

76.7457  
77.0000  
77.2544

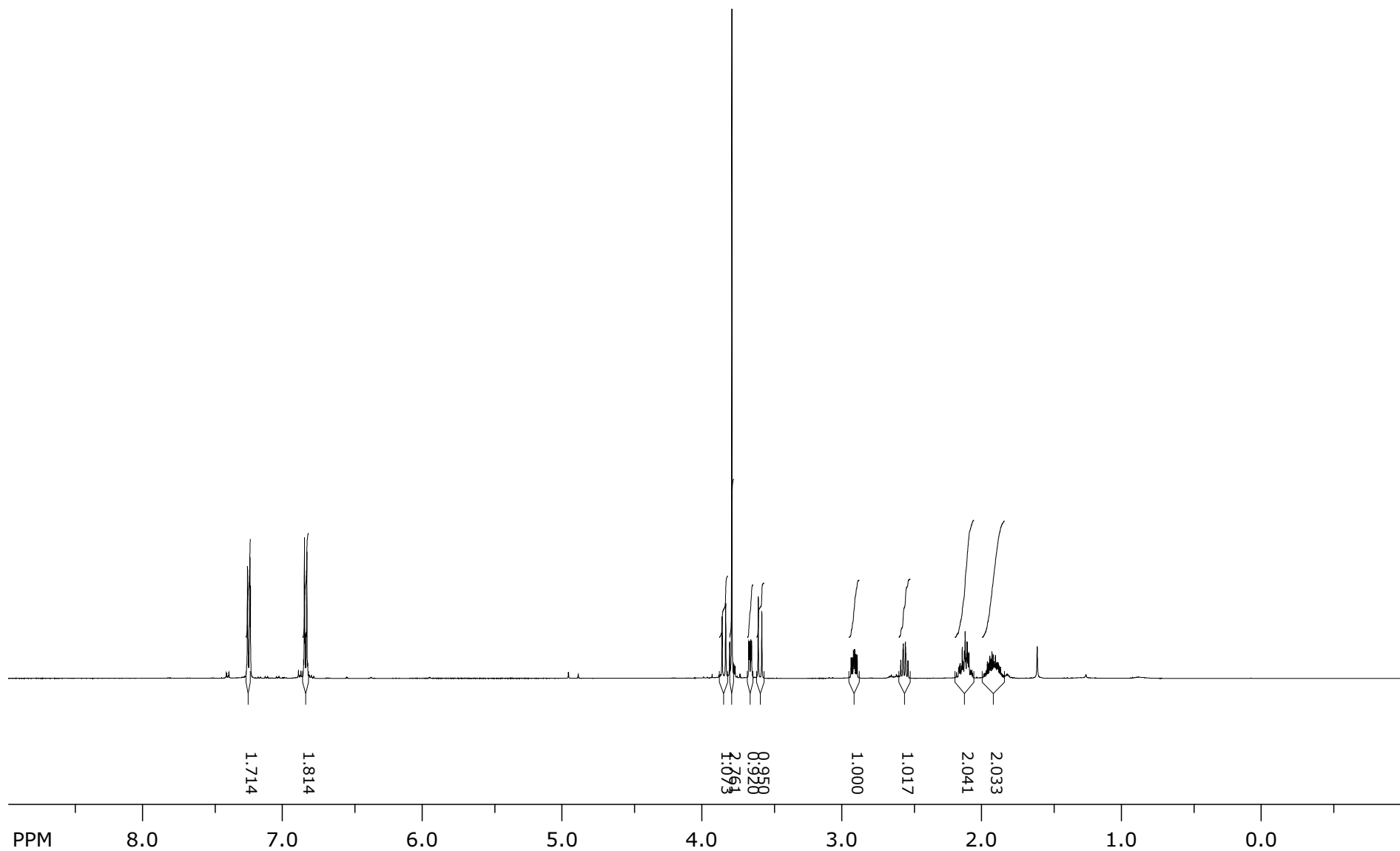
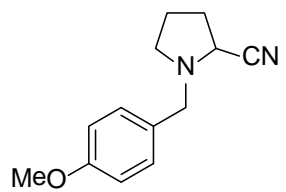
51.1188  
53.0958  
56.1798

29.4735

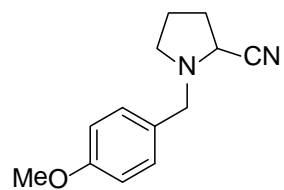
21.0808  
21.8323



<sup>1</sup>H NMR of of **5c** in CDCl<sub>3</sub>



$^{13}\text{C}$  NMR of **5c** in  $\text{CDCl}_3$



158.8925

129.5723  
129.9180

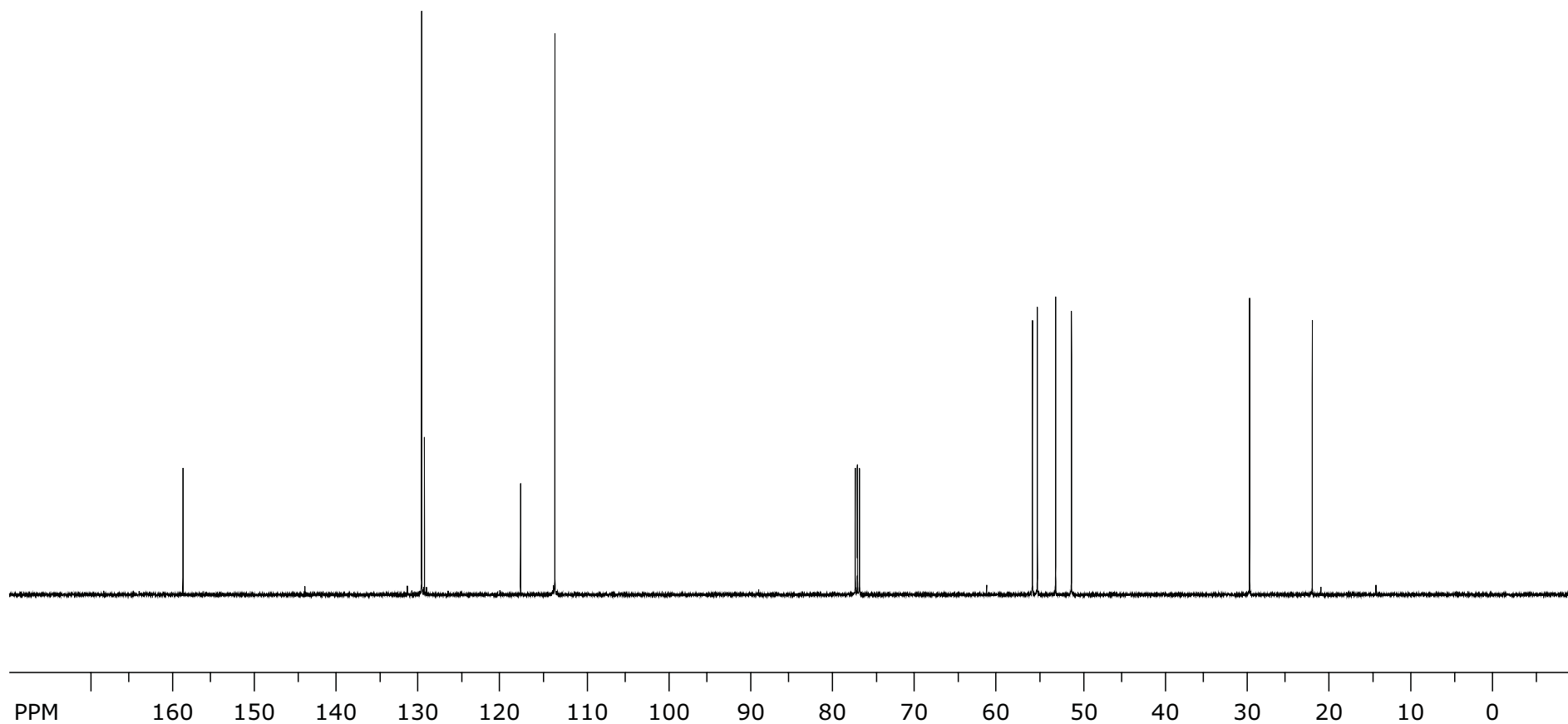
113.7348  
117.8941

76.7453  
77.0000  
77.2546

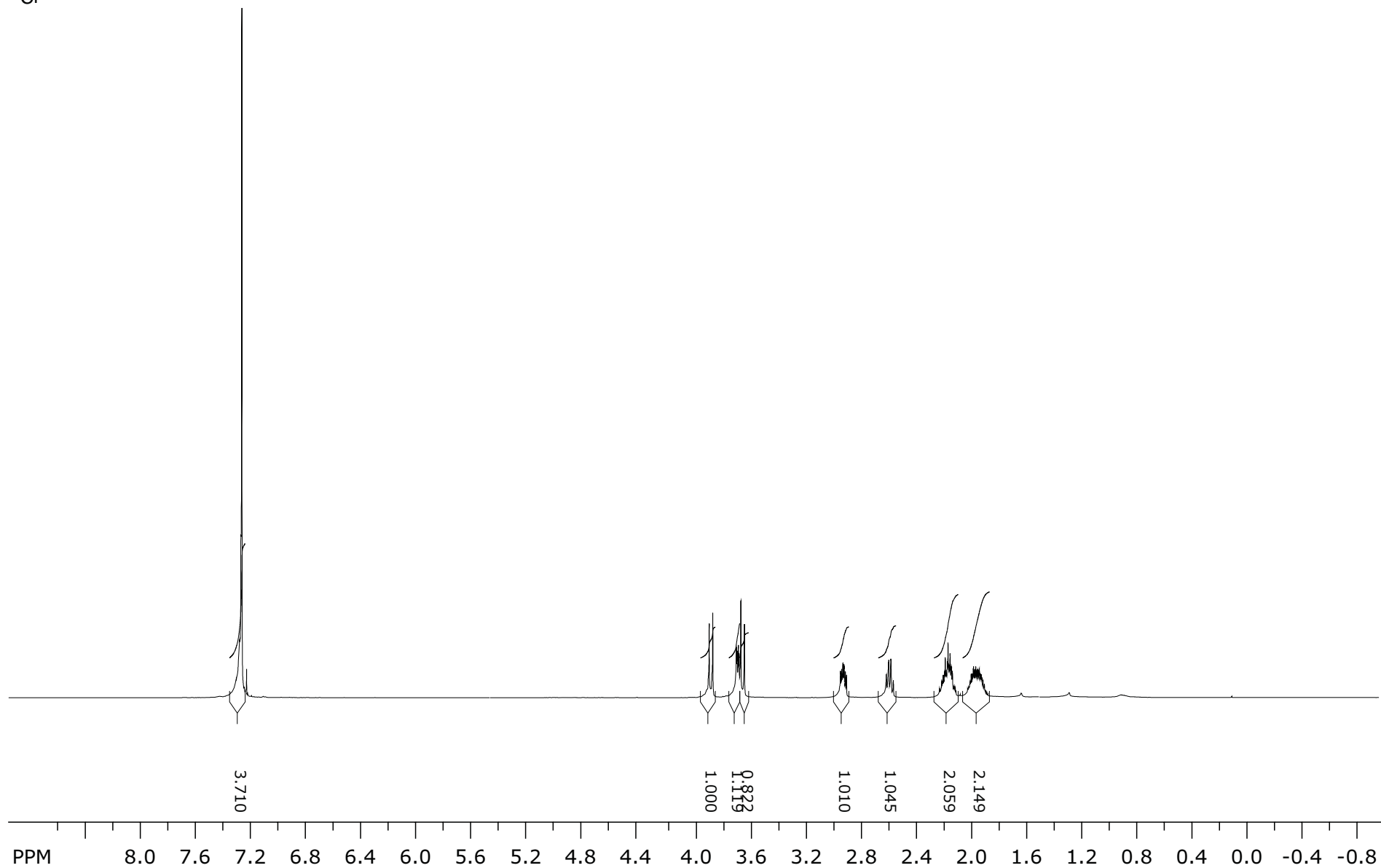
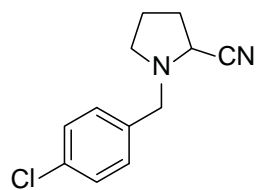
50.9973  
52.9184  
55.1384  
55.7416

29.3670

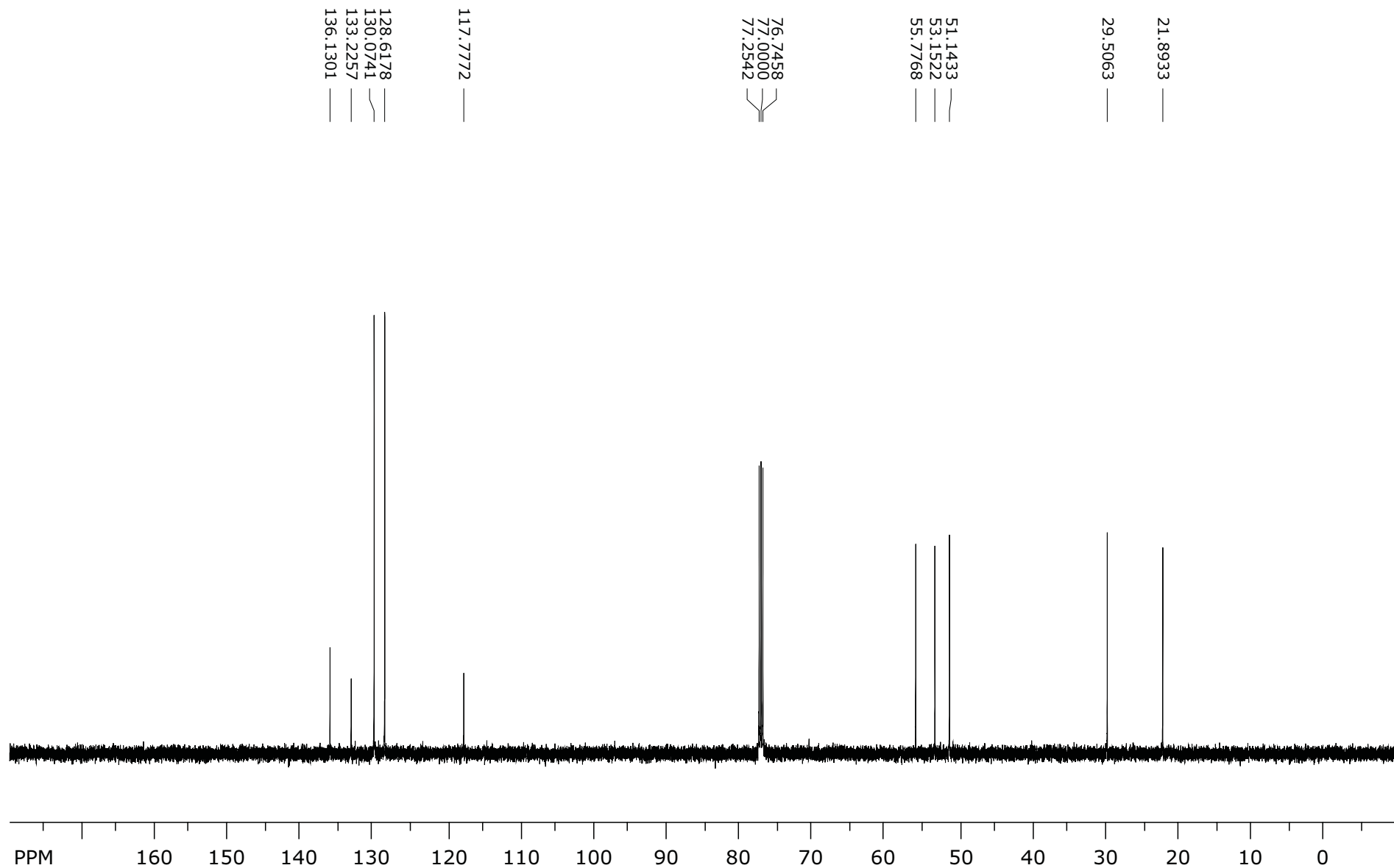
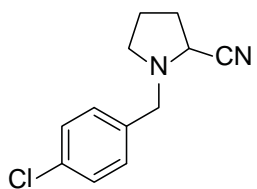
21.7535



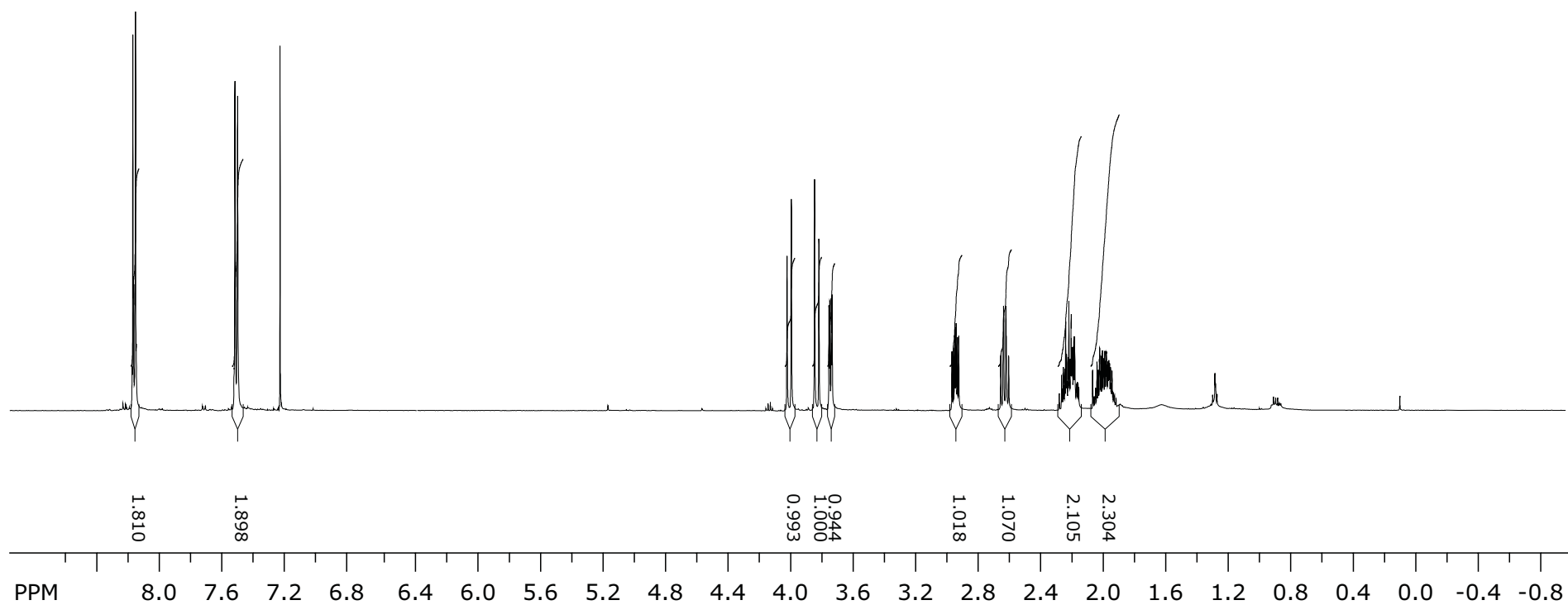
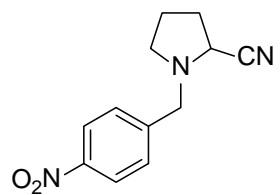
<sup>1</sup>H NMR of of **5d** in CDCl<sub>3</sub>



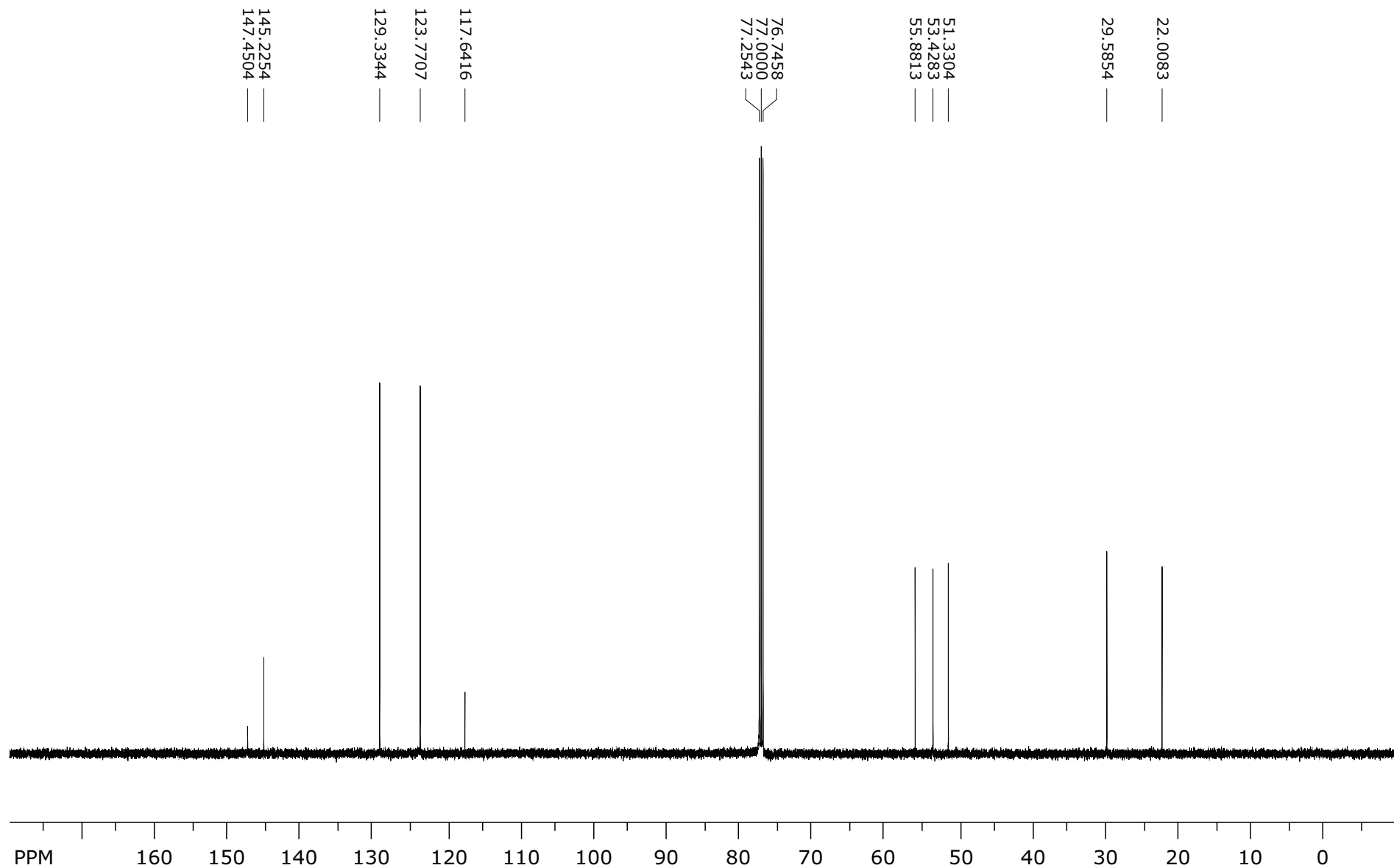
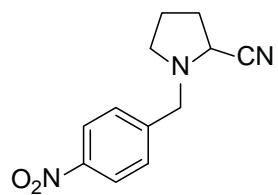
$^{13}\text{C}$  NMR of **5d** in  $\text{CDCl}_3$



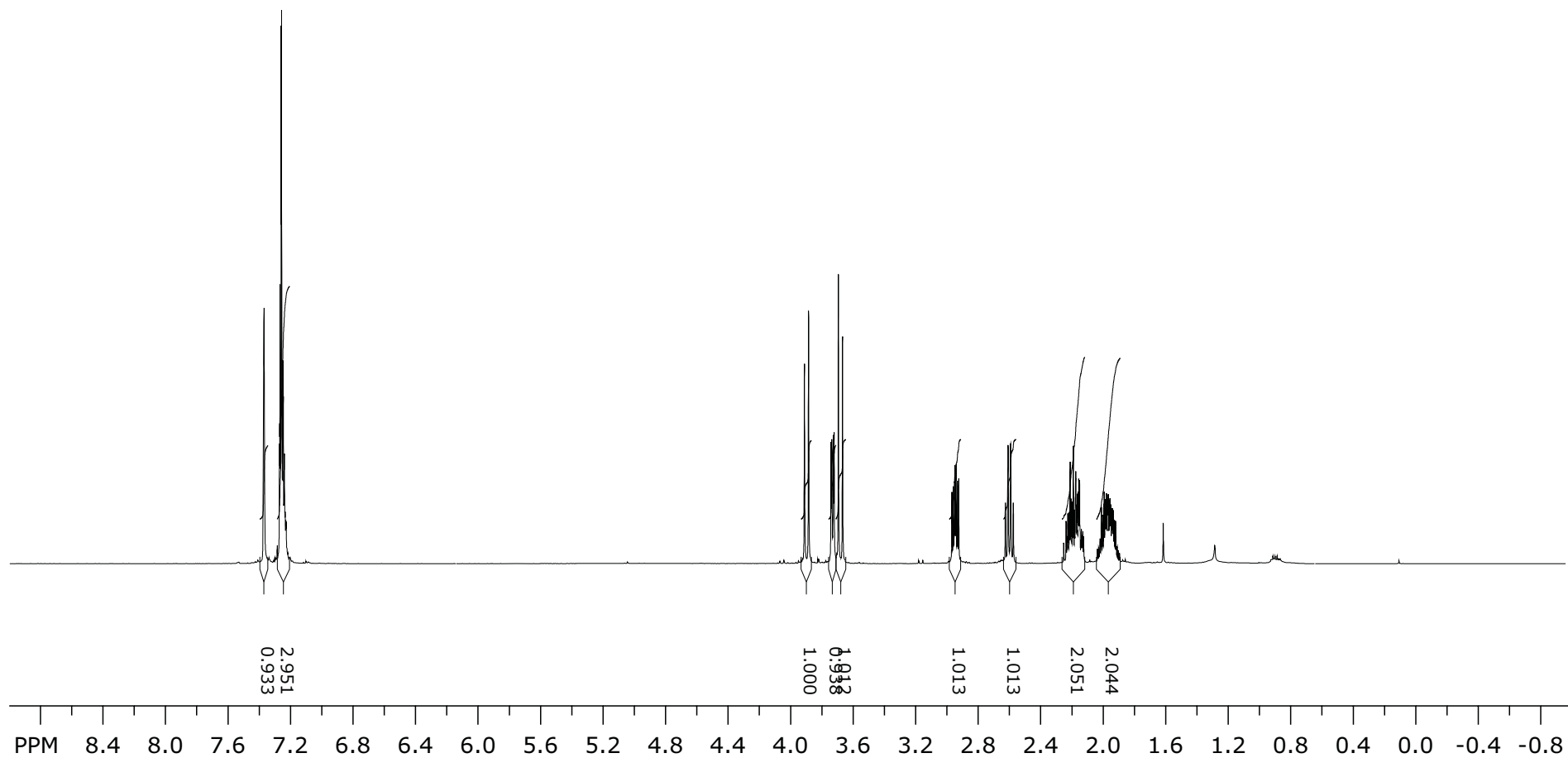
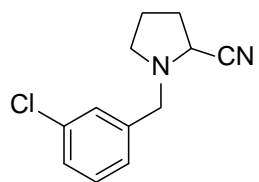
<sup>1</sup>H NMR of of **5e** in CDCl<sub>3</sub>



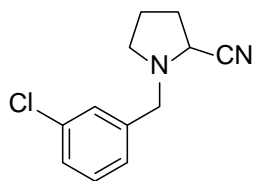
$^{13}\text{C}$  NMR of **5e** in  $\text{CDCl}_3$



$^1\text{H}$  NMR of of **5f** in  $\text{CDCl}_3$



<sup>13</sup>C NMR of **5f** in CDCl<sub>3</sub>

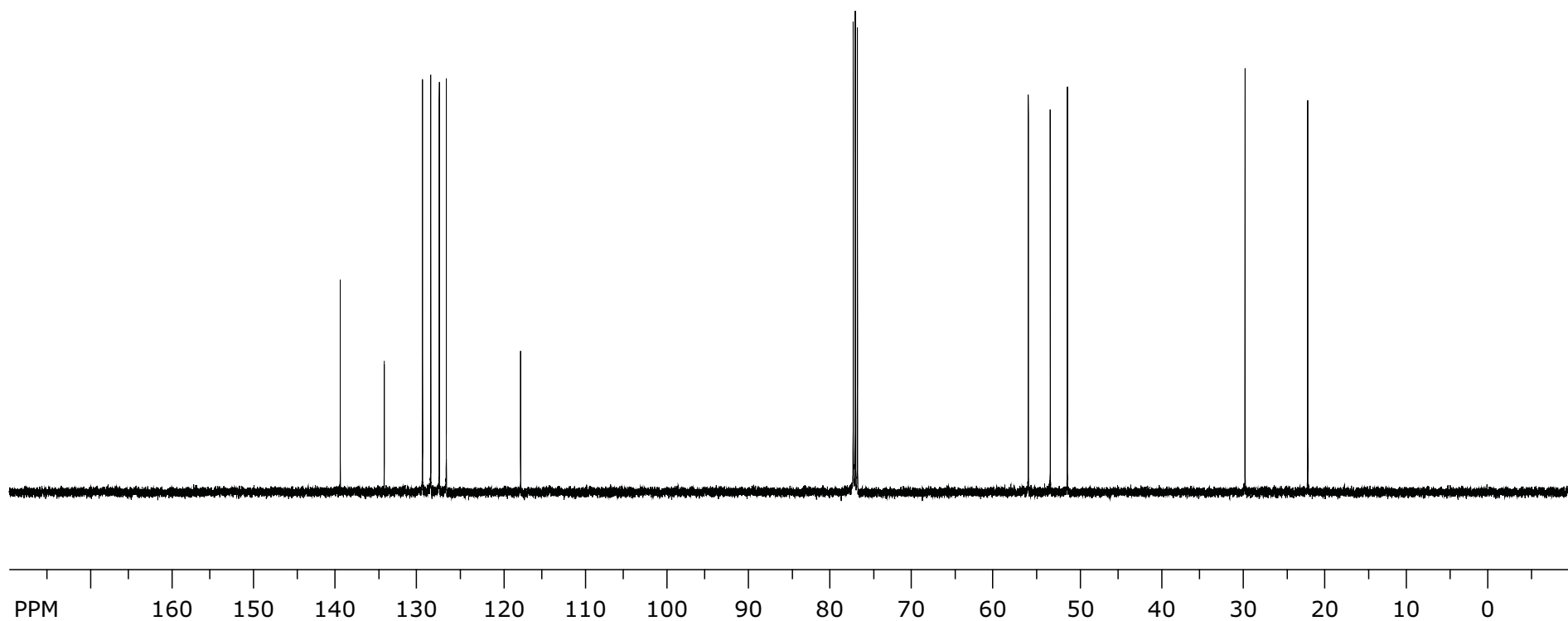


126.8277  
127.6854  
128.7256  
129.7322  
134.3936  
139.7472  
117.7802

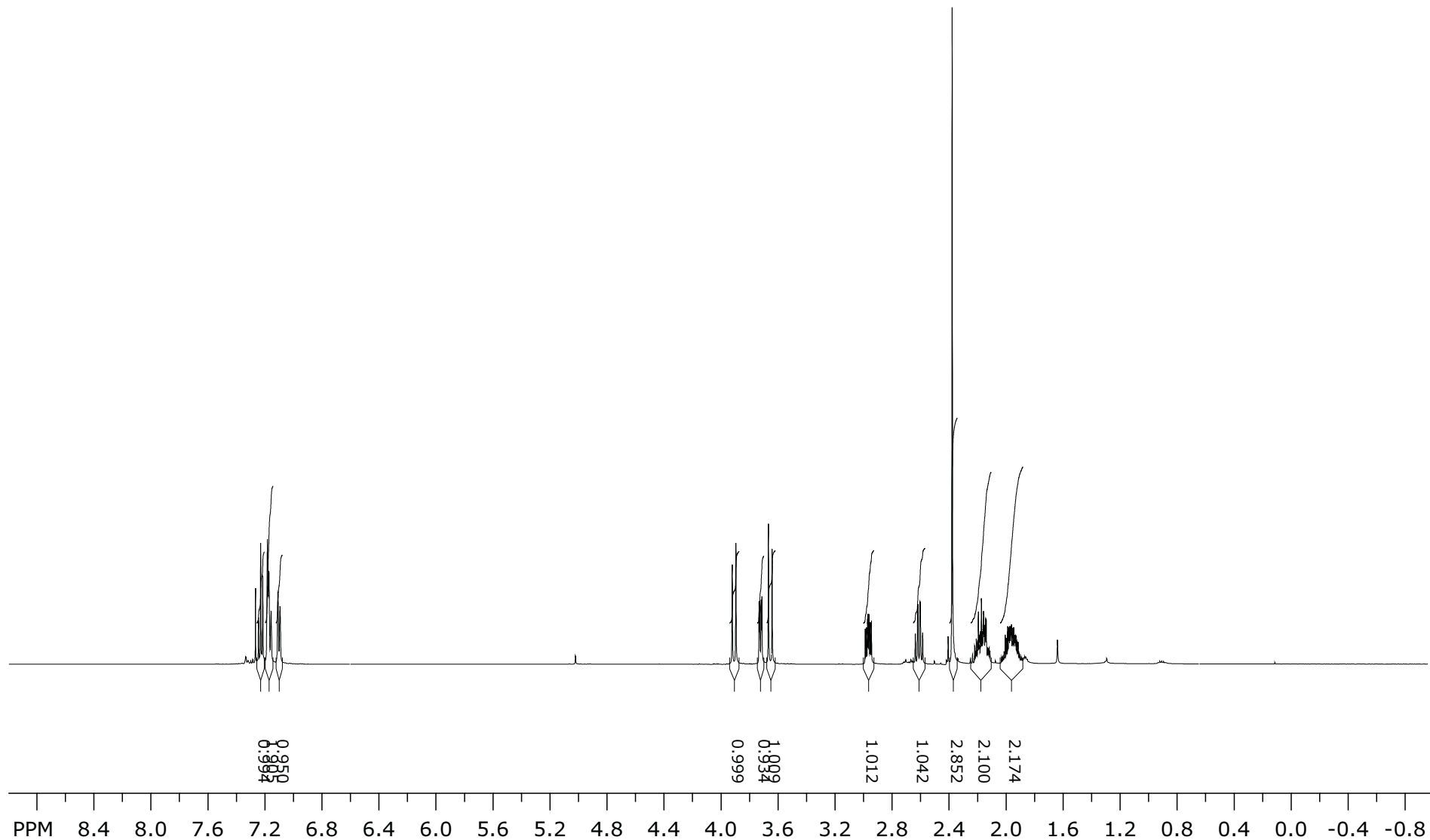
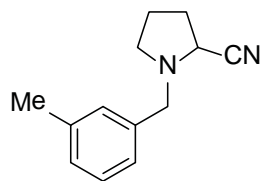
76.7456  
77.0000  
77.2542

51.1661  
53.2493  
55.9263

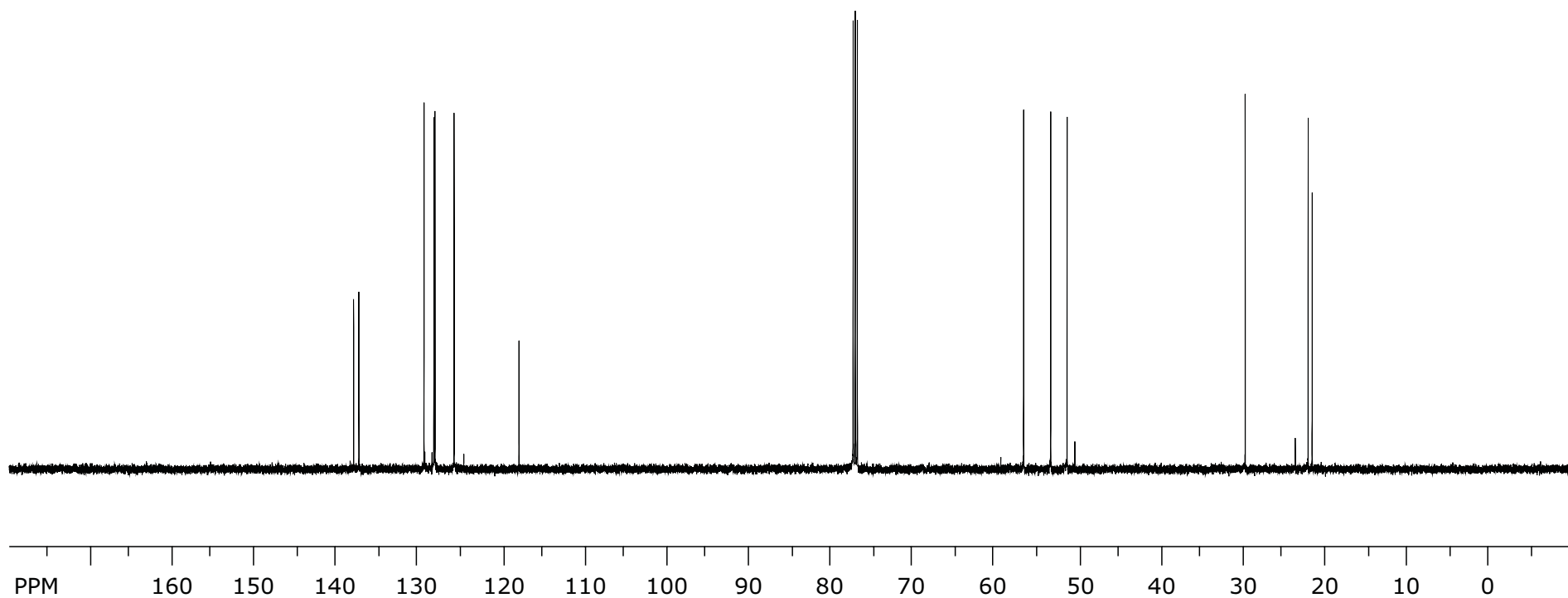
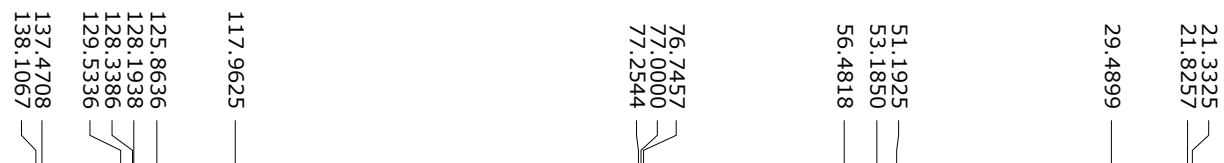
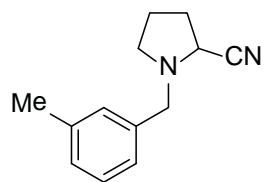
29.5276  
21.8909



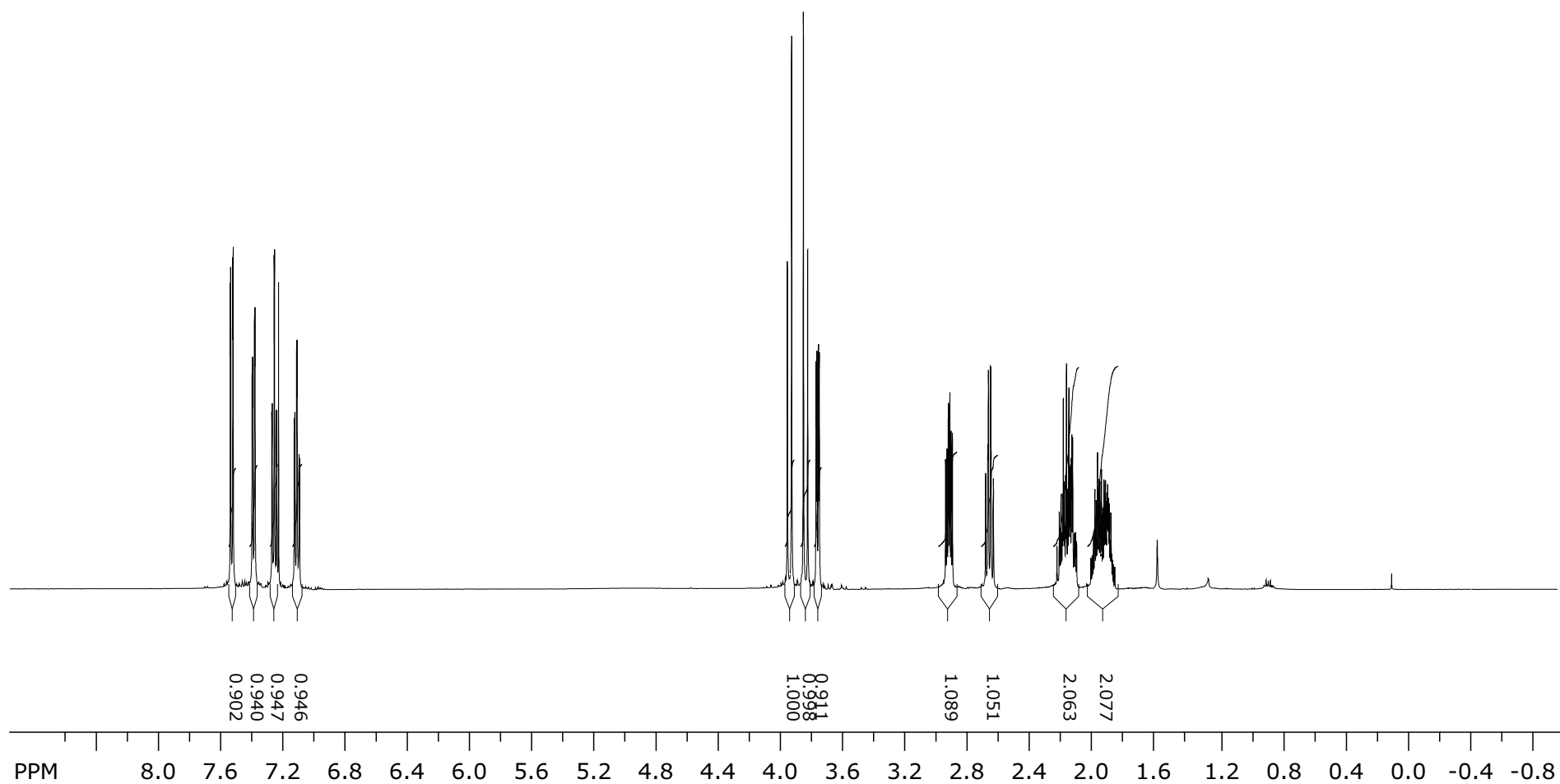
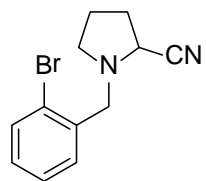
$^1\text{H}$  NMR of of **5g** in  $\text{CDCl}_3$



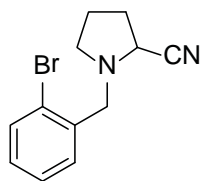
<sup>13</sup>C NMR of **5g** in CDCl<sub>3</sub>



<sup>1</sup>H NMR of of **5h** in CDCl<sub>3</sub>



$^{13}\text{C}$  NMR of **5h** in  $\text{CDCl}_3$



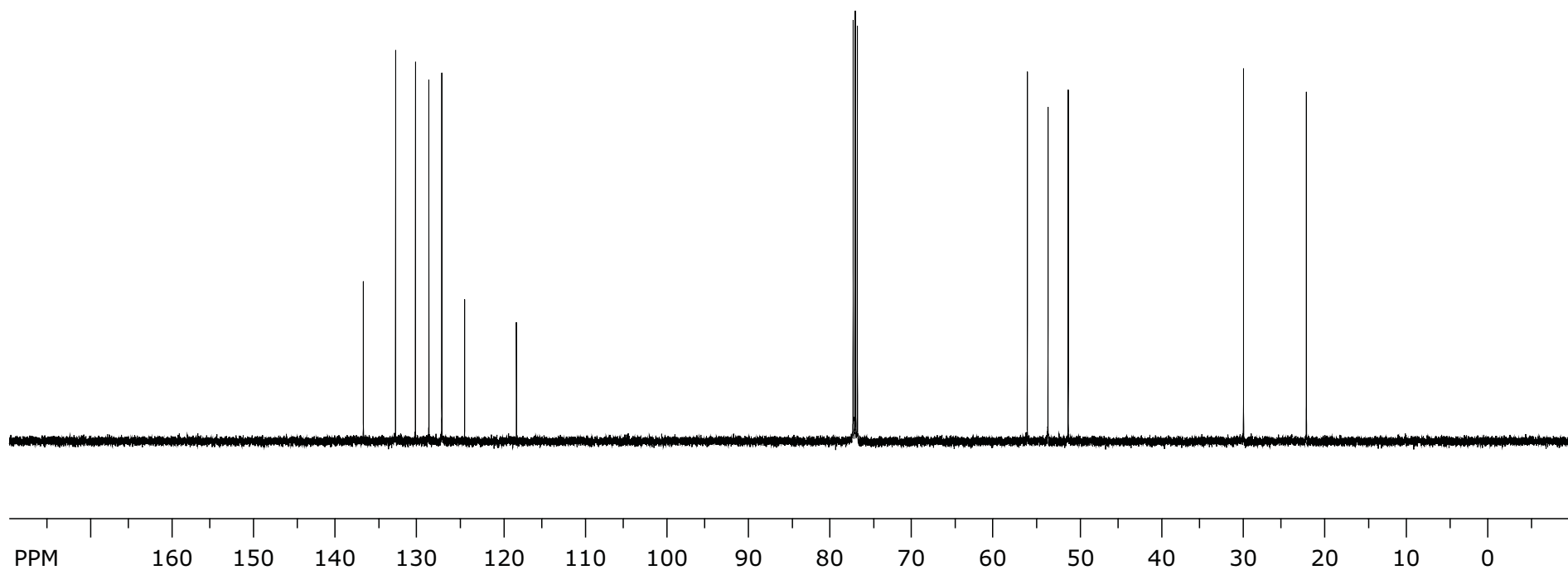
124.5874  
127.3661  
128.9415  
130.5794  
132.9980  
136.9287  
118.2776

76.7456  
77.0000  
77.2542

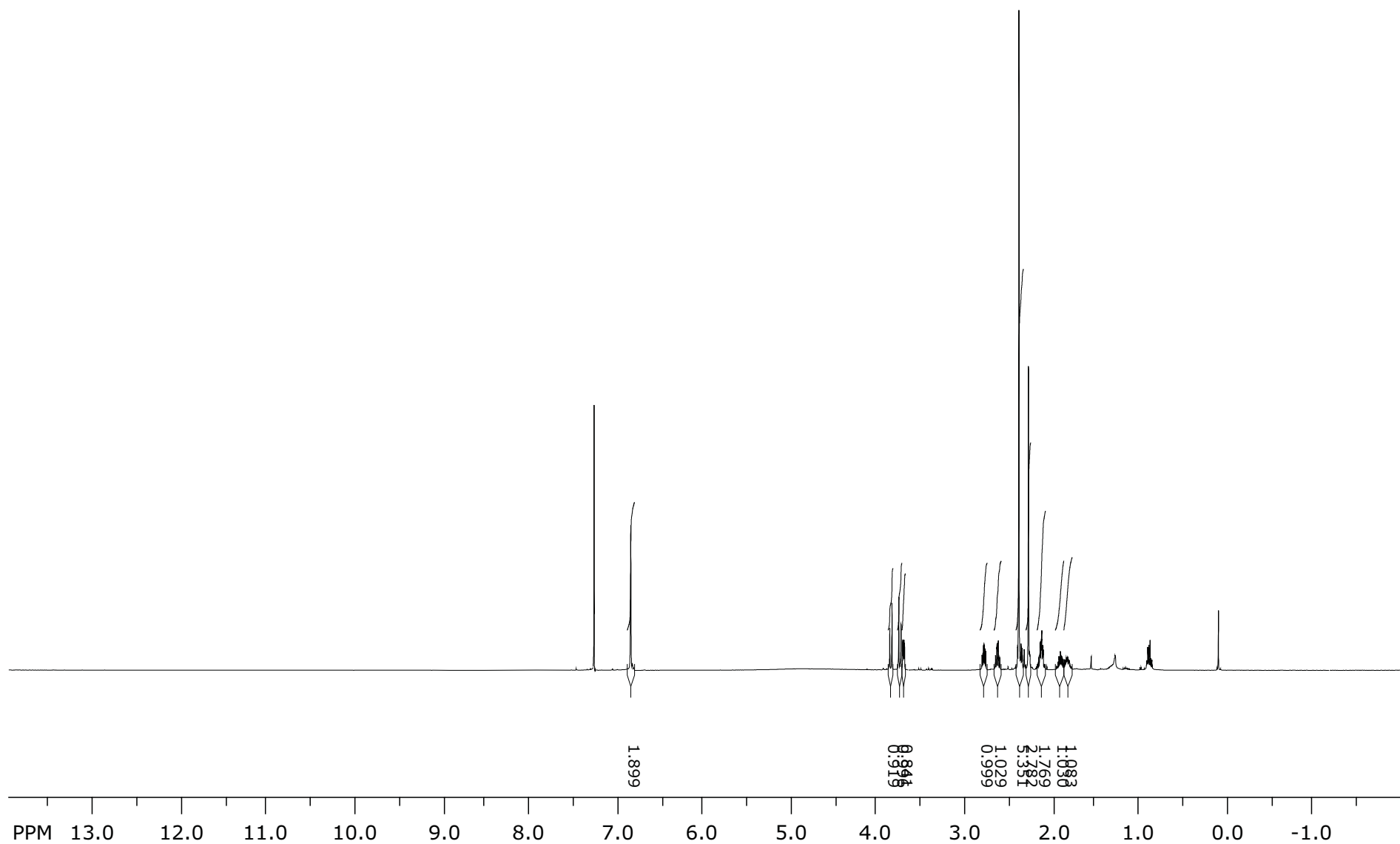
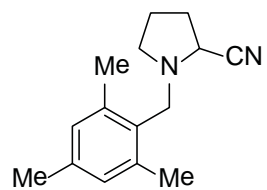
51.0584  
53.5176  
56.0379

29.6992

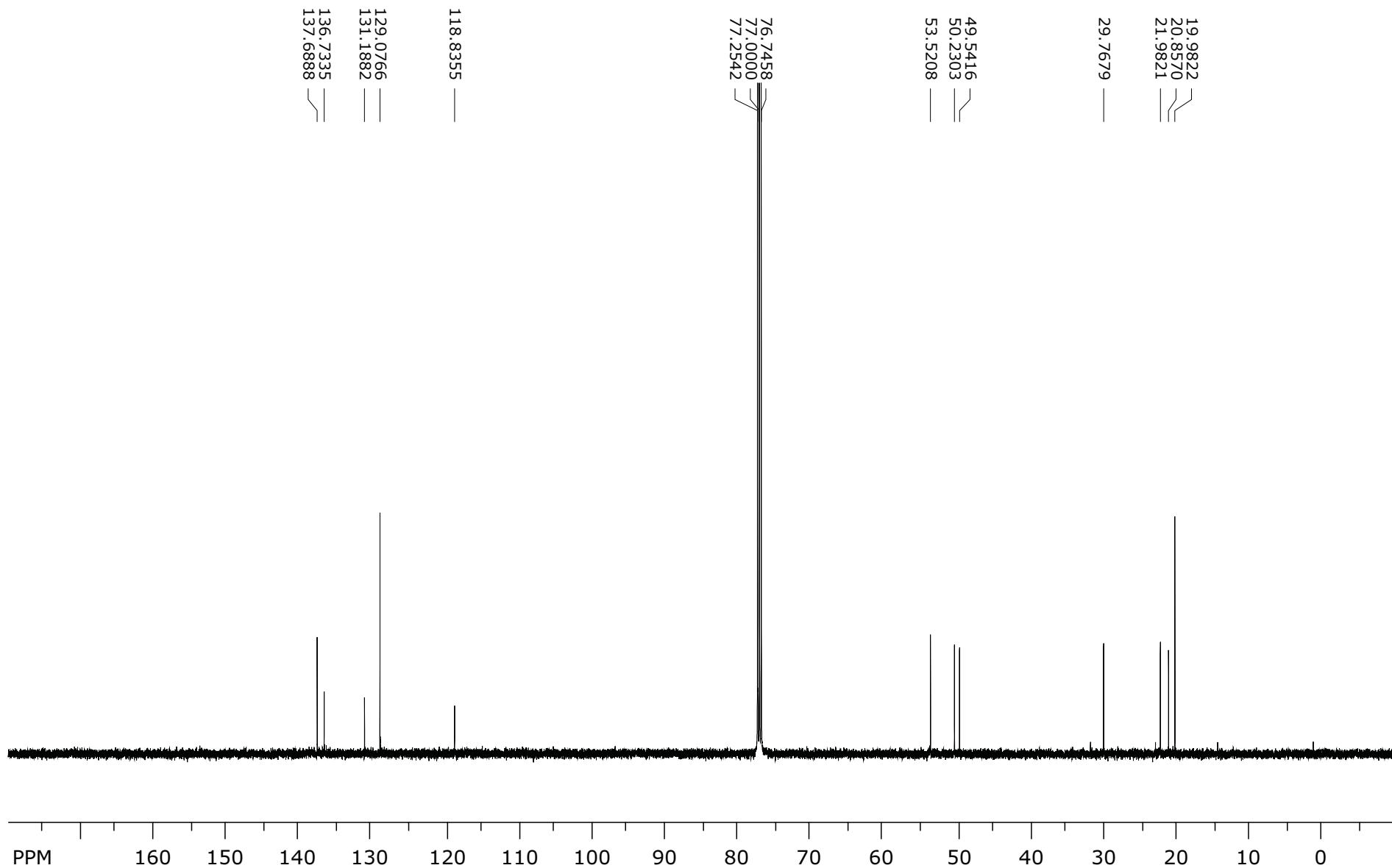
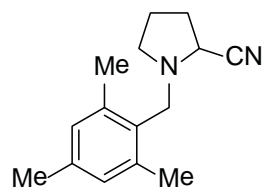
22.0417



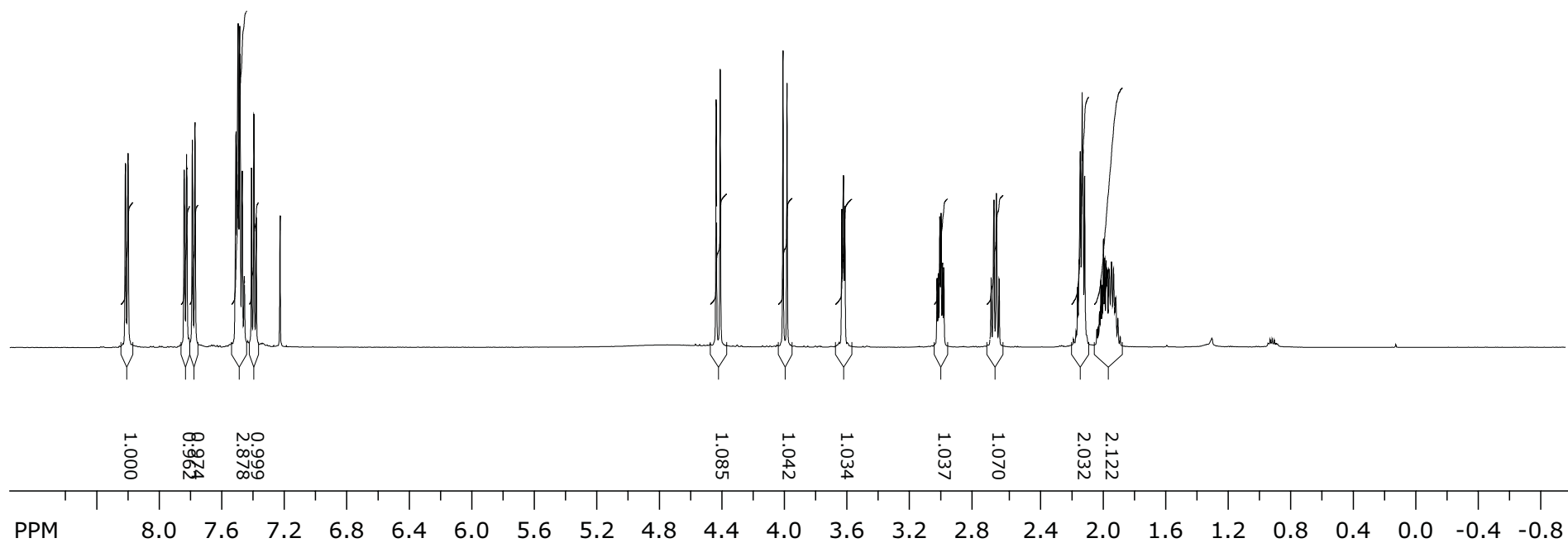
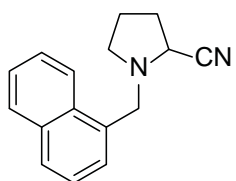
<sup>1</sup>H NMR of of **5i** in CDCl<sub>3</sub>



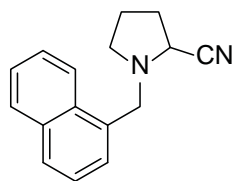
<sup>13</sup>C NMR of **5i** in CDCl<sub>3</sub>



$^1\text{H}$  NMR of of **5j** in  $\text{CDCl}_3$



<sup>13</sup>C NMR of **5j** in CDCl<sub>3</sub>



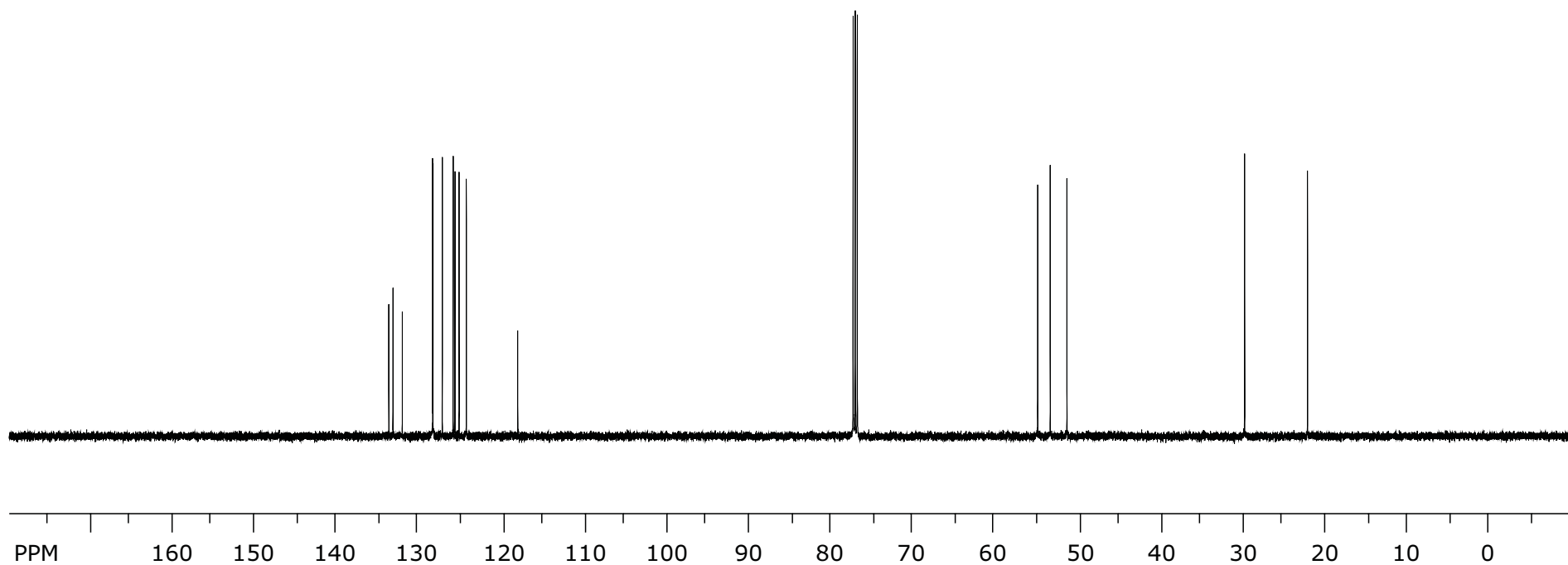
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124.3765  
125.2562  
125.7584  
125.9780  
127.3011  
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128.4759  
132.1802  
133.3092  
133.8132

76.7457  
77.0000  
77.2544

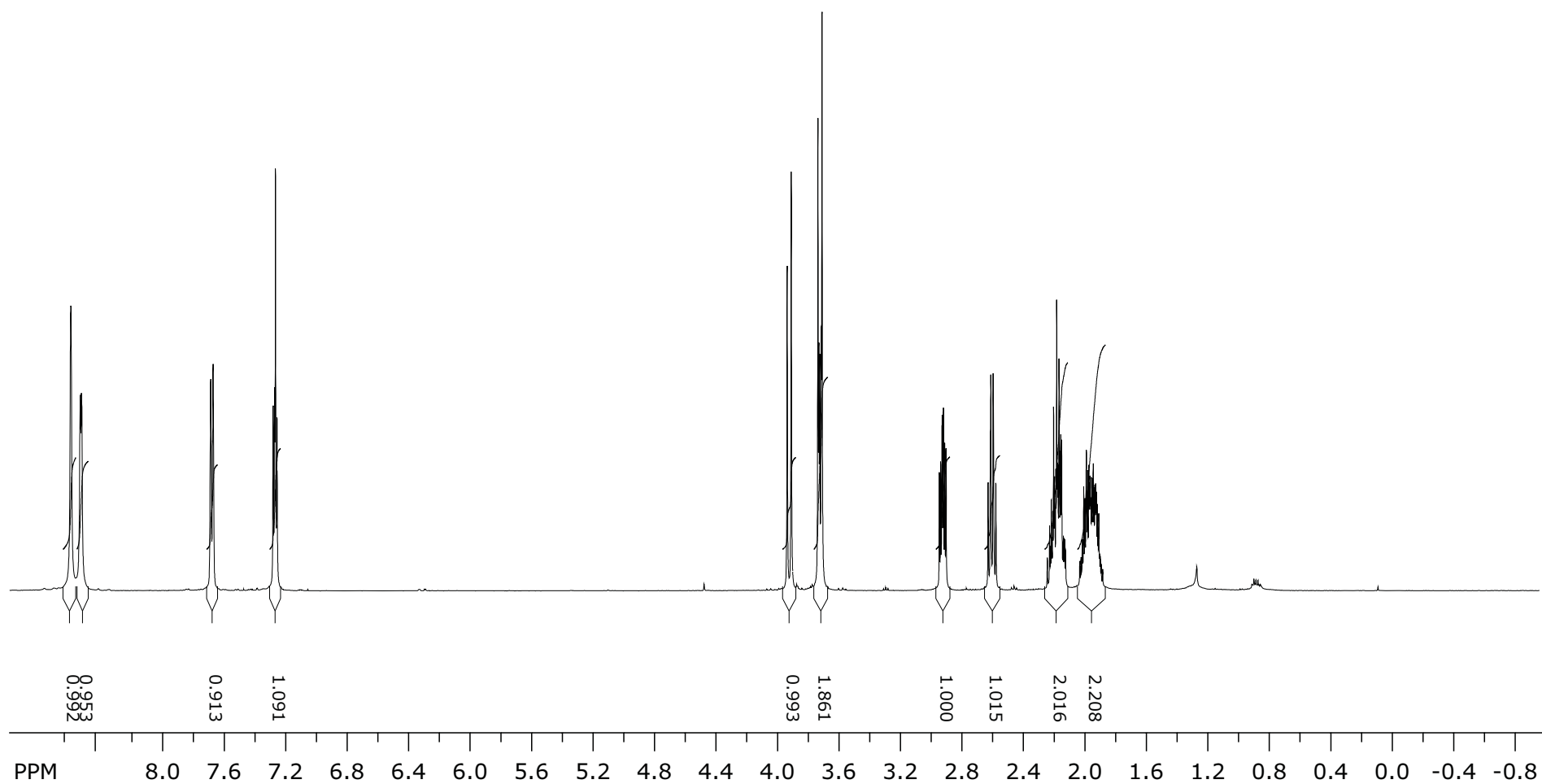
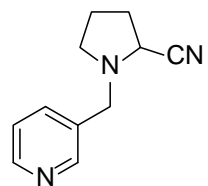
51.2078  
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29.5577

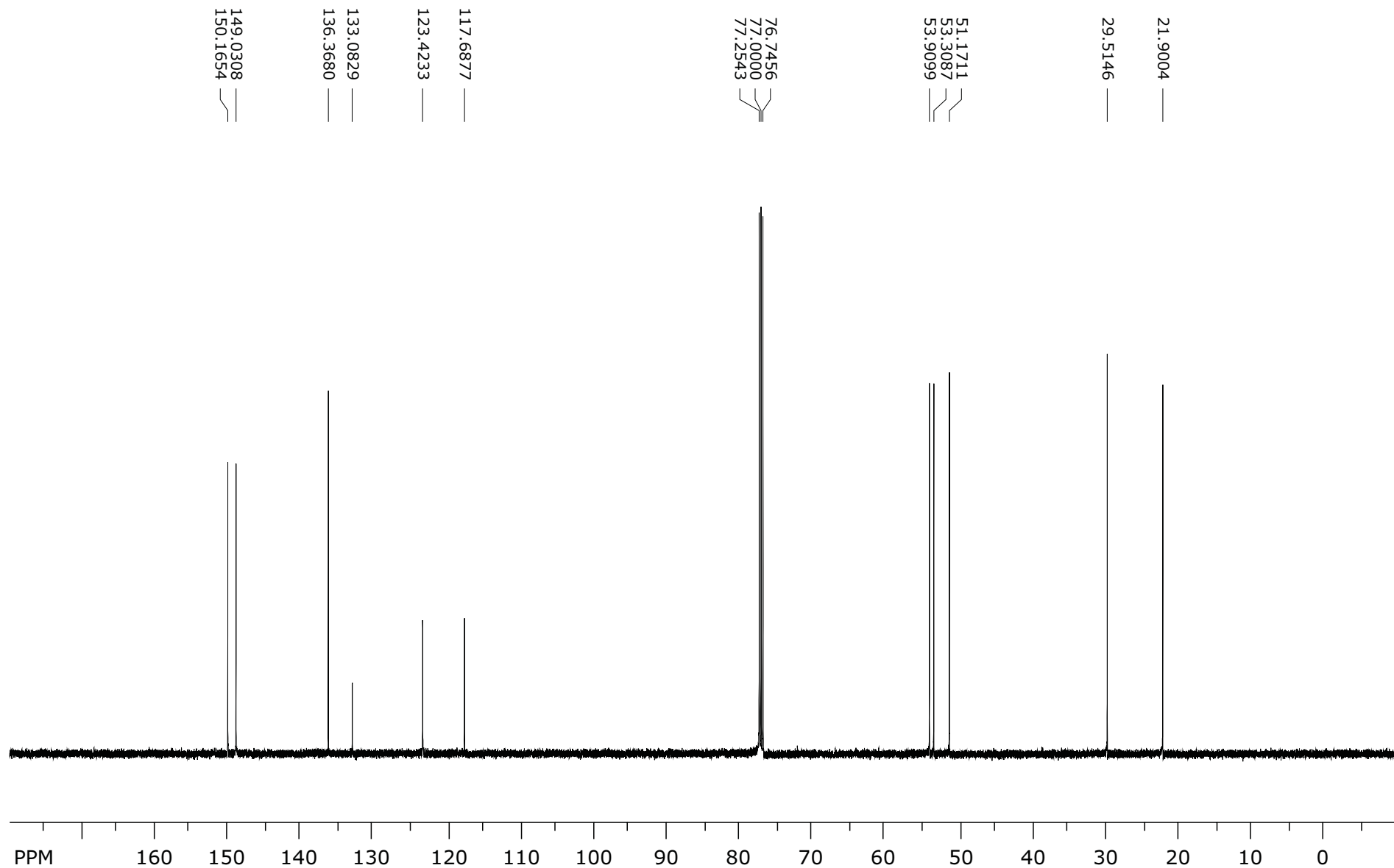
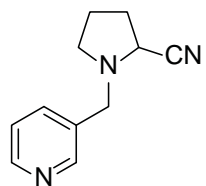
21.8943



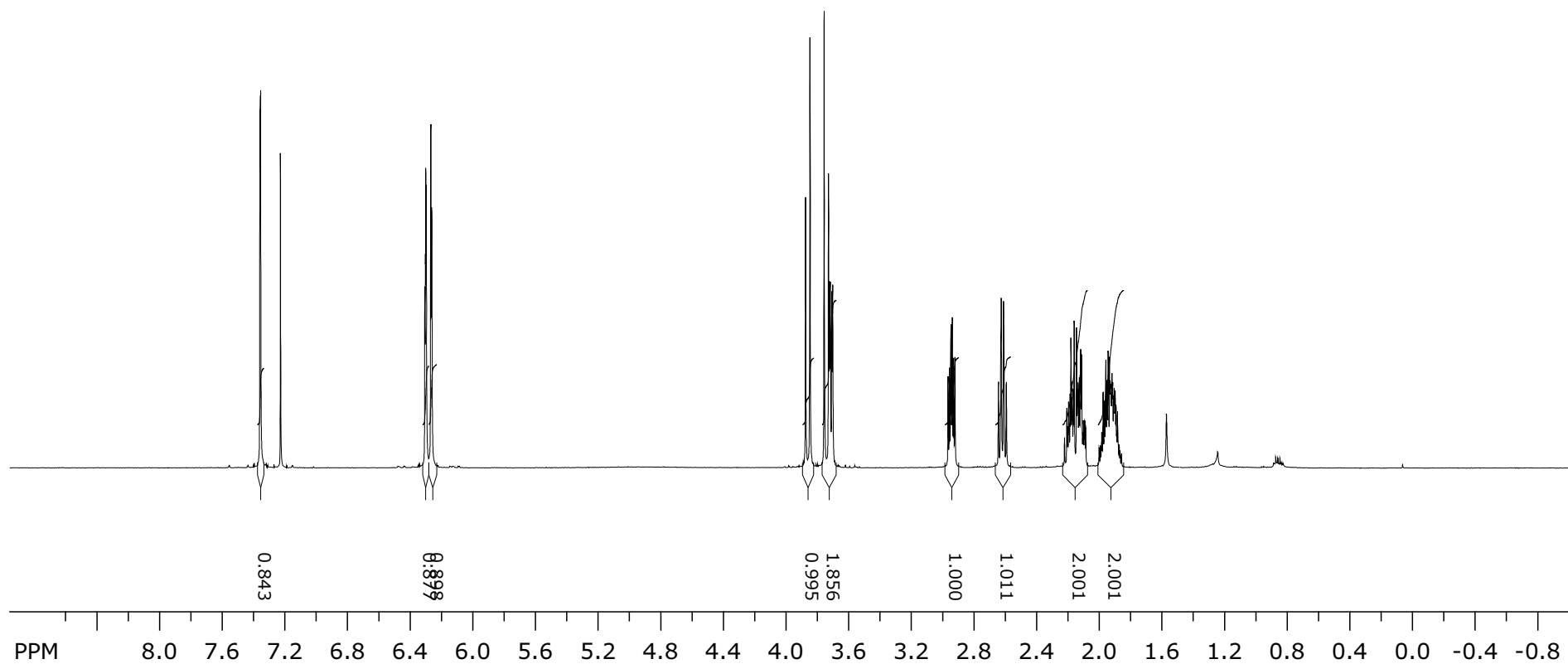
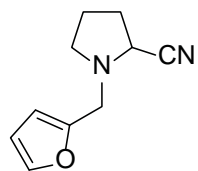
<sup>1</sup>H NMR of of **5k** in CDCl<sub>3</sub>



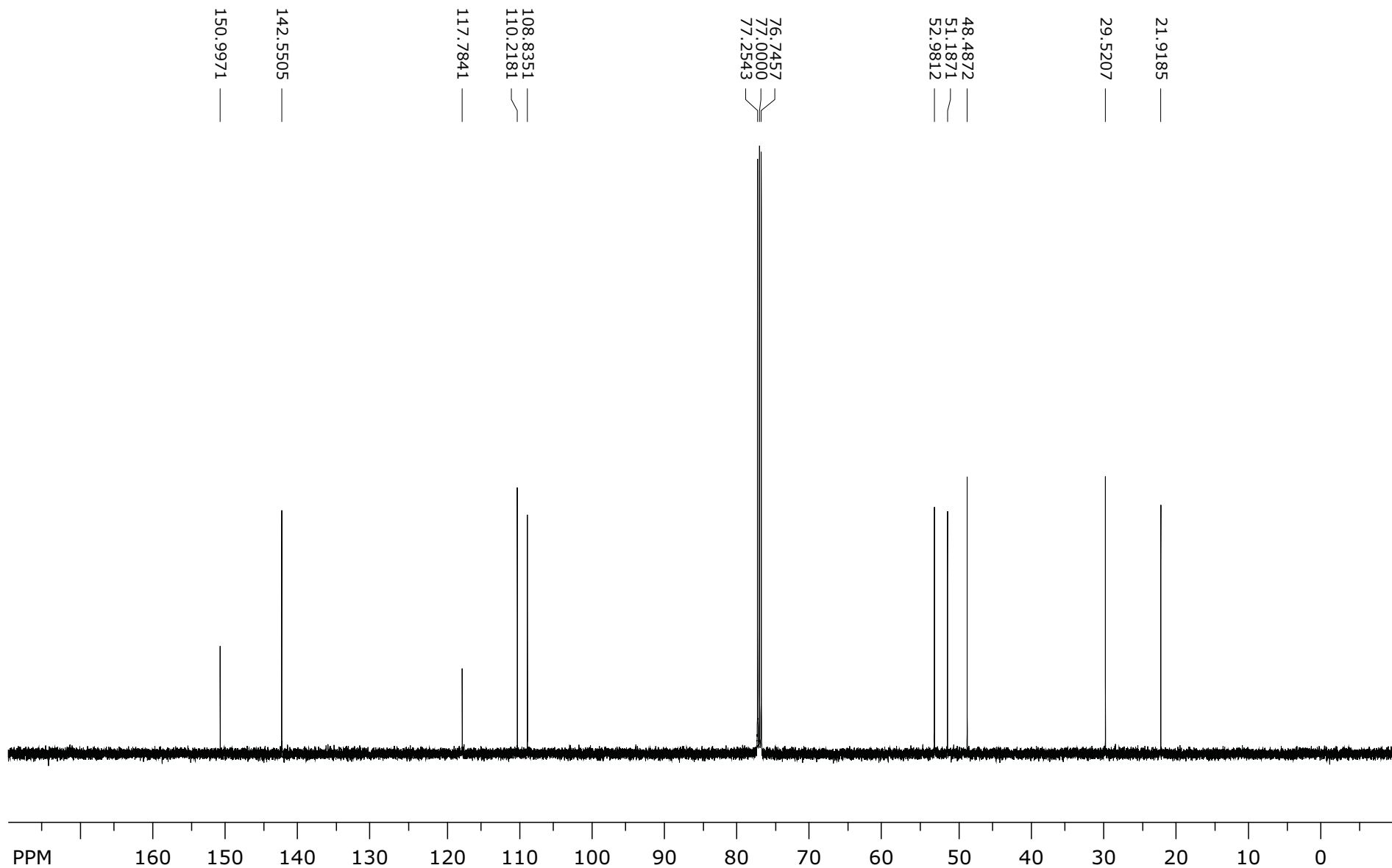
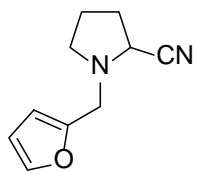
<sup>13</sup>C NMR of **5k** in CDCl<sub>3</sub>



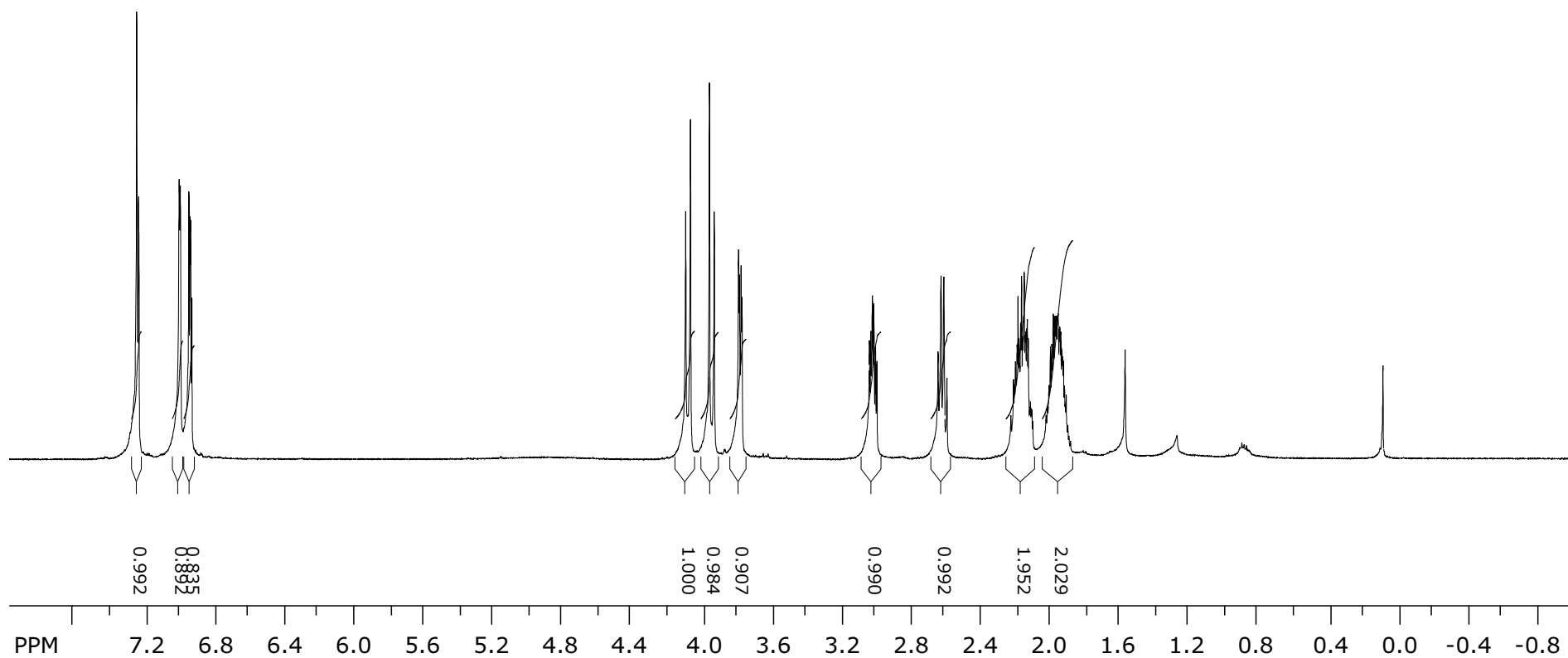
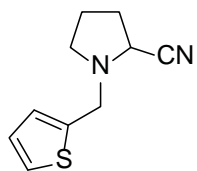
<sup>1</sup>H NMR of of **5I** in CDCl<sub>3</sub>



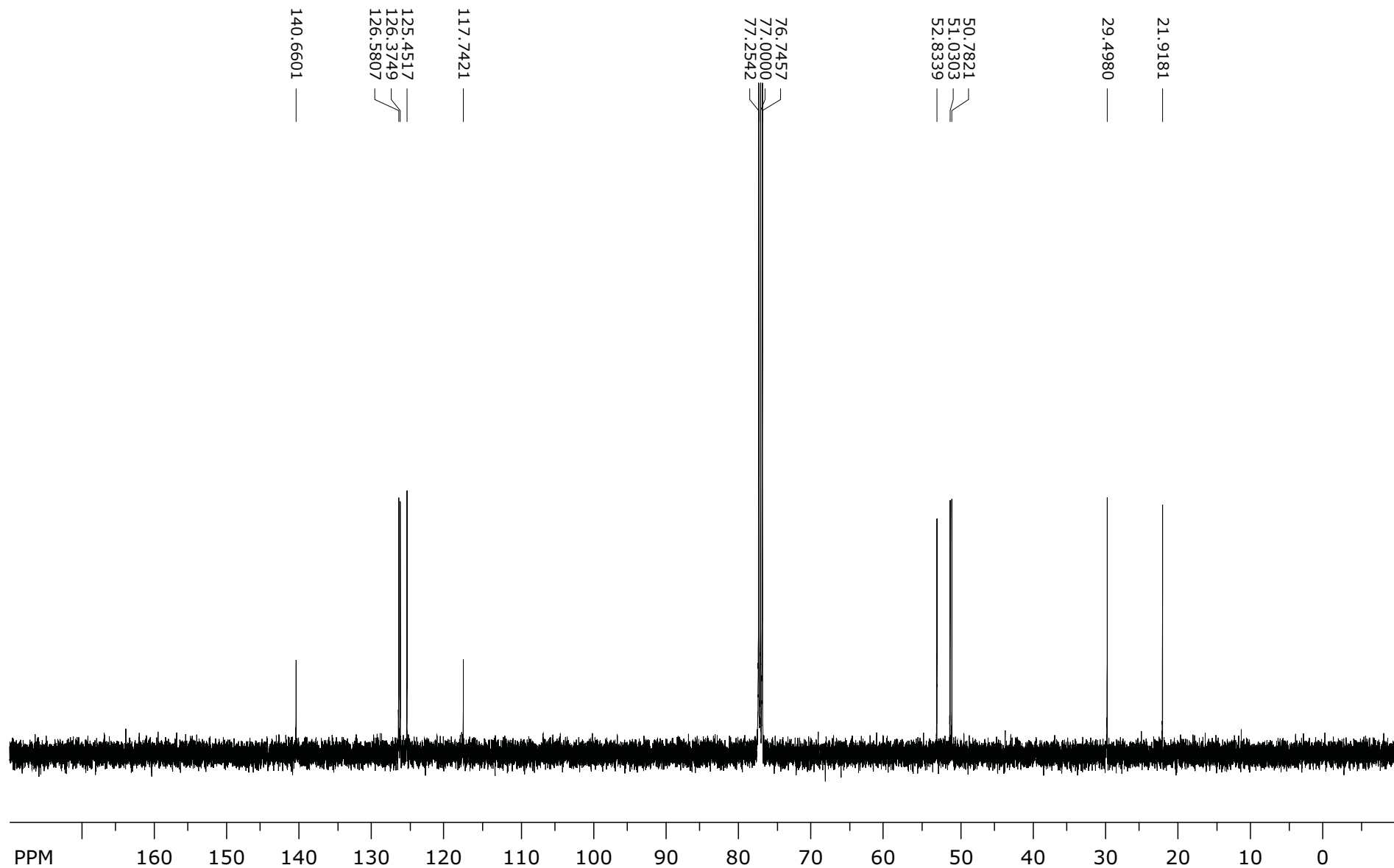
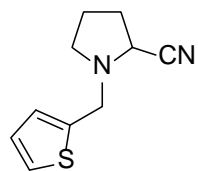
<sup>13</sup>C NMR of **5I** in CDCl<sub>3</sub>



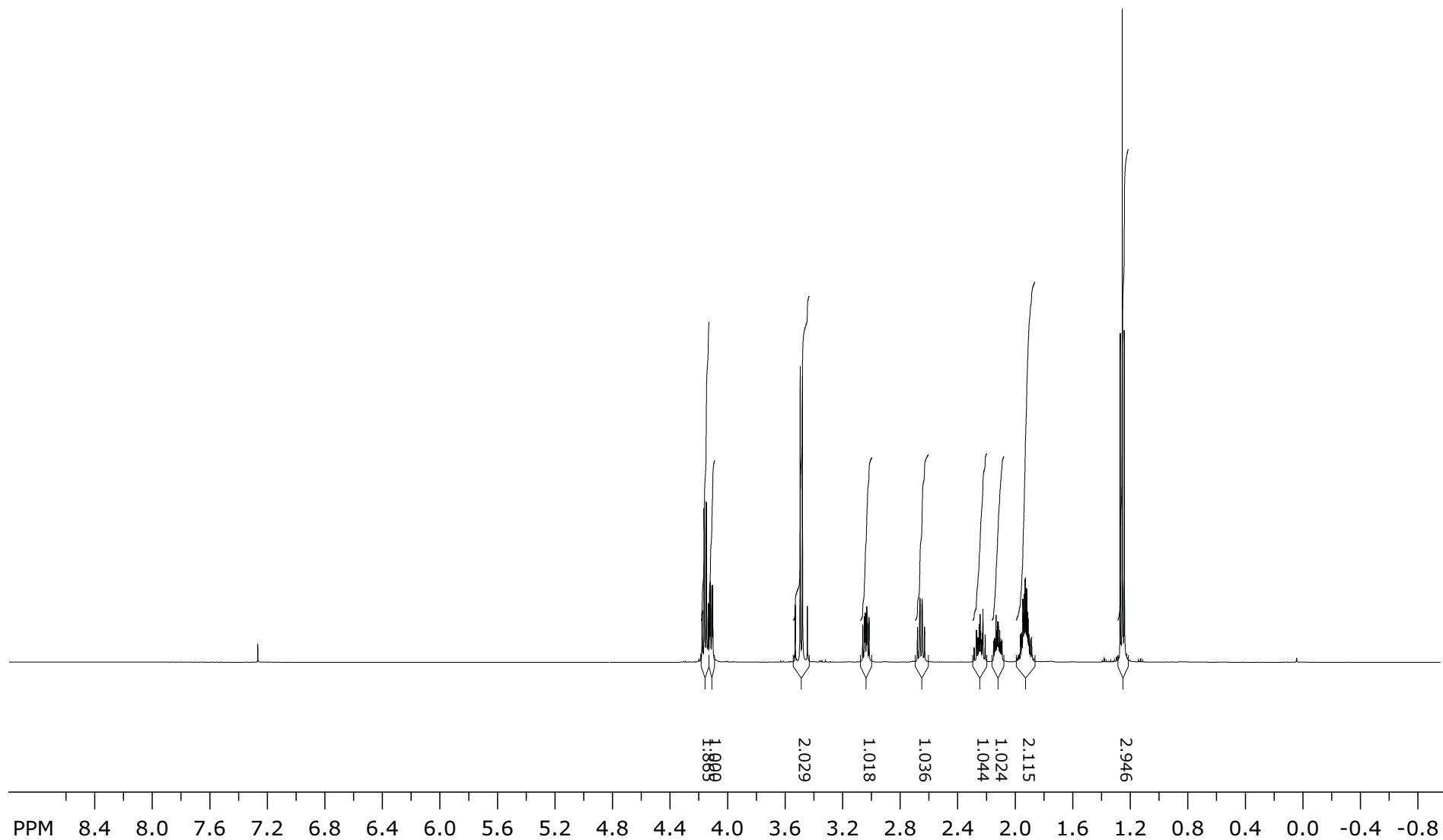
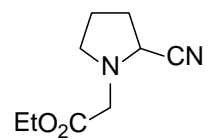
$^1\text{H}$  NMR of **5m** in  $\text{CDCl}_3$



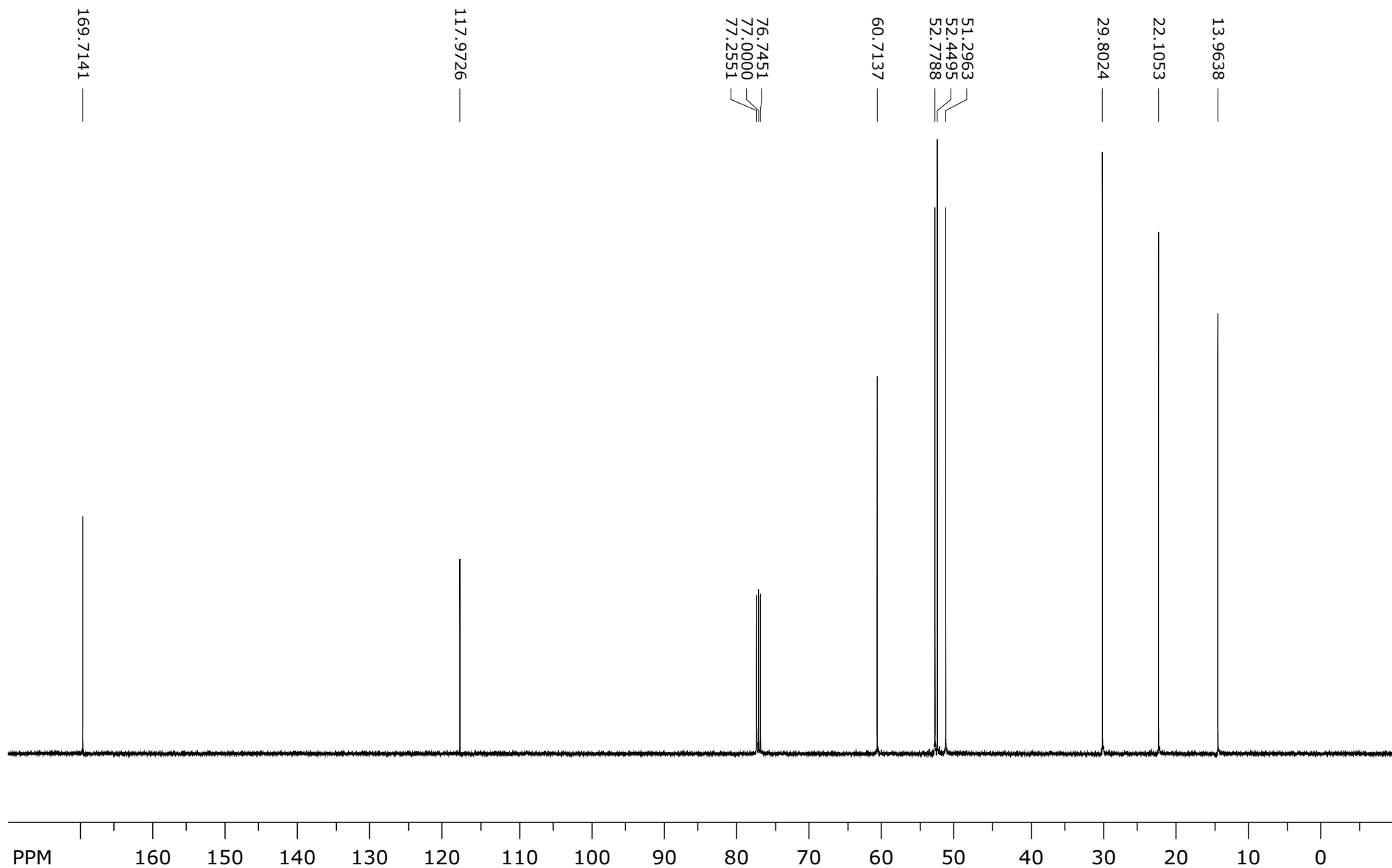
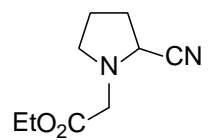
<sup>13</sup>C NMR of **5m** in CDCl<sub>3</sub>



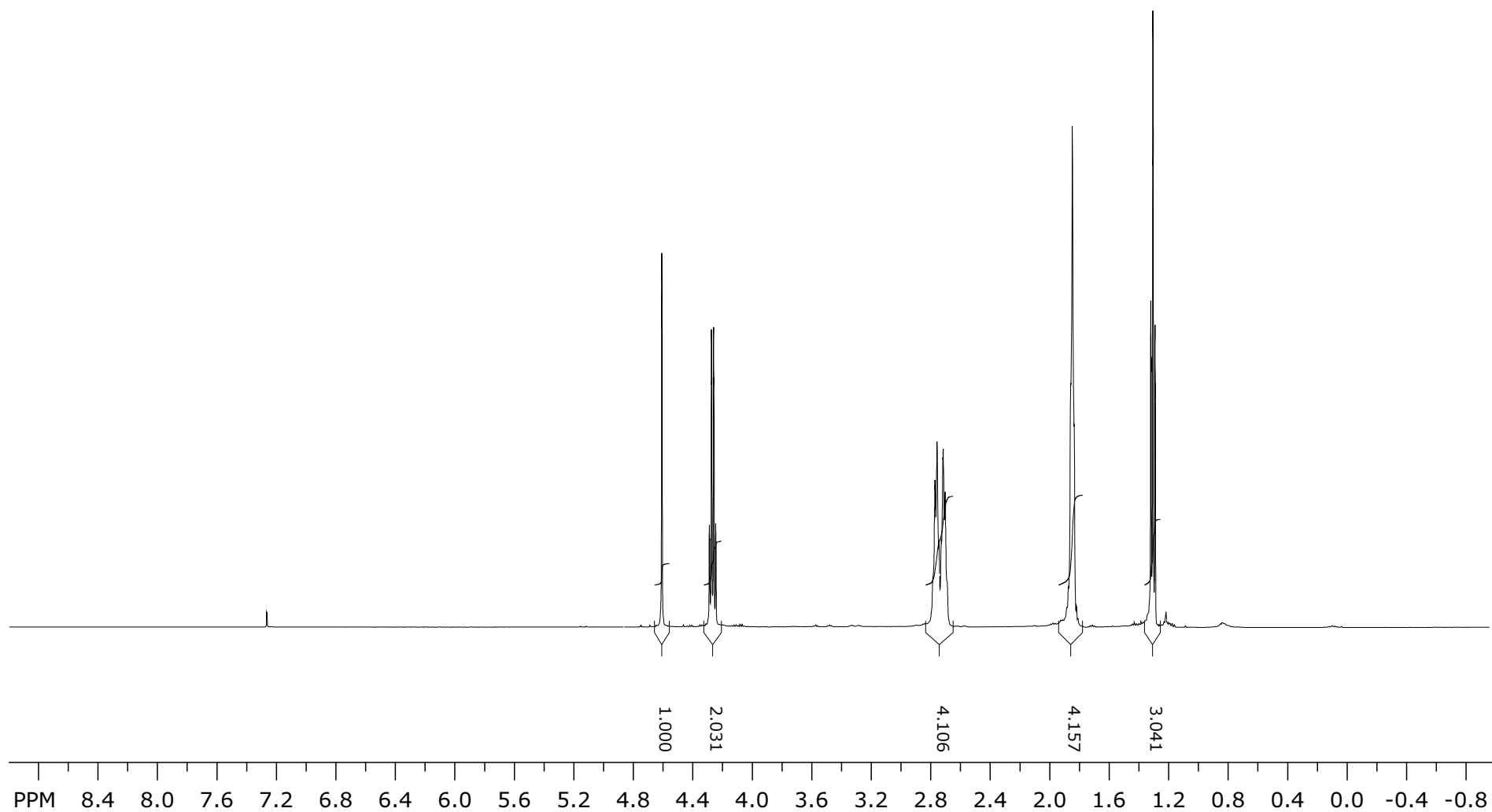
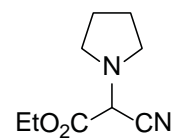
$^1\text{H}$  NMR of of **5n** in  $\text{CDCl}_3$



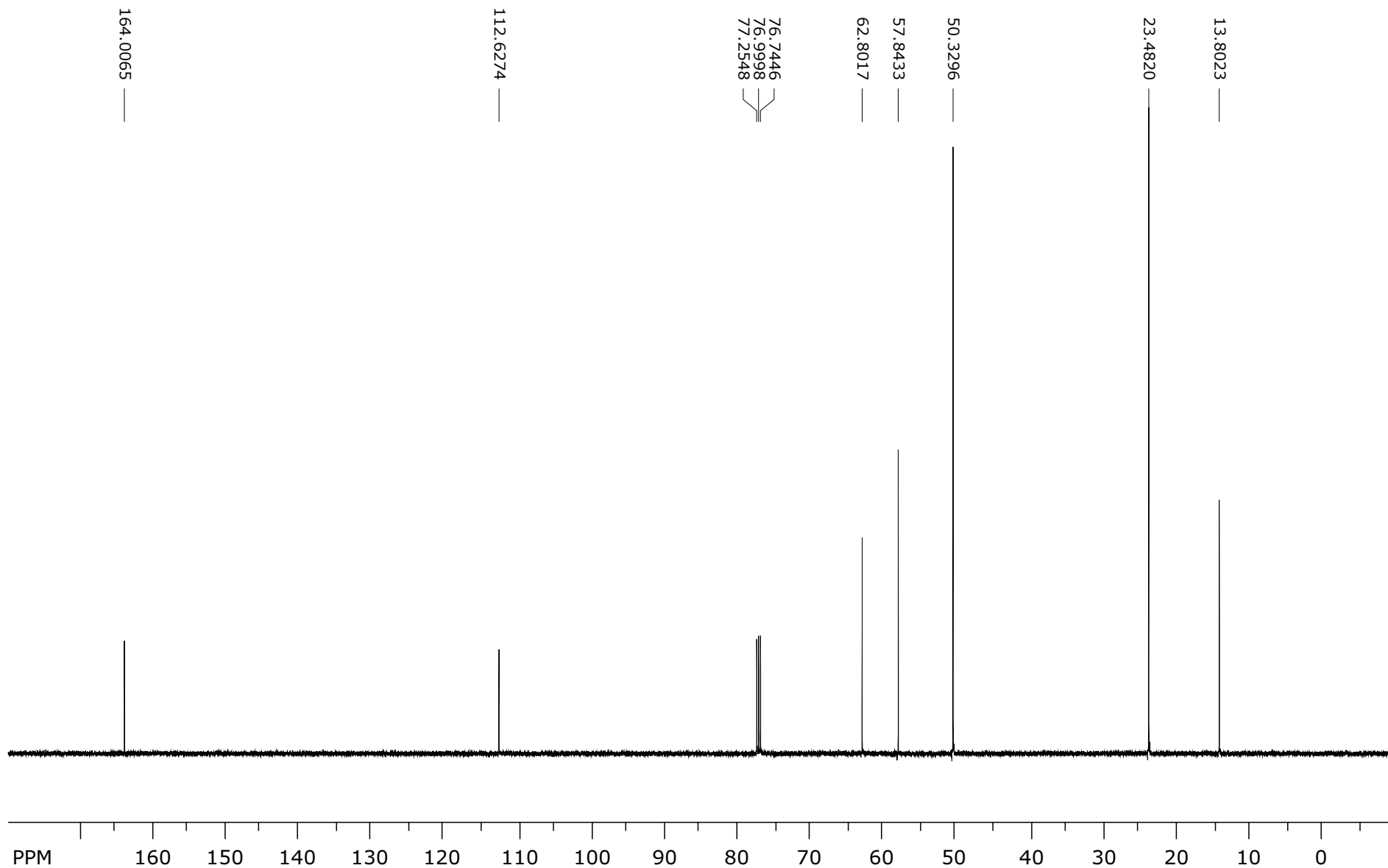
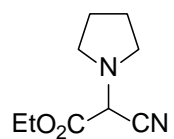
$^{13}\text{C}$  NMR of **5n** in  $\text{CDCl}_3$



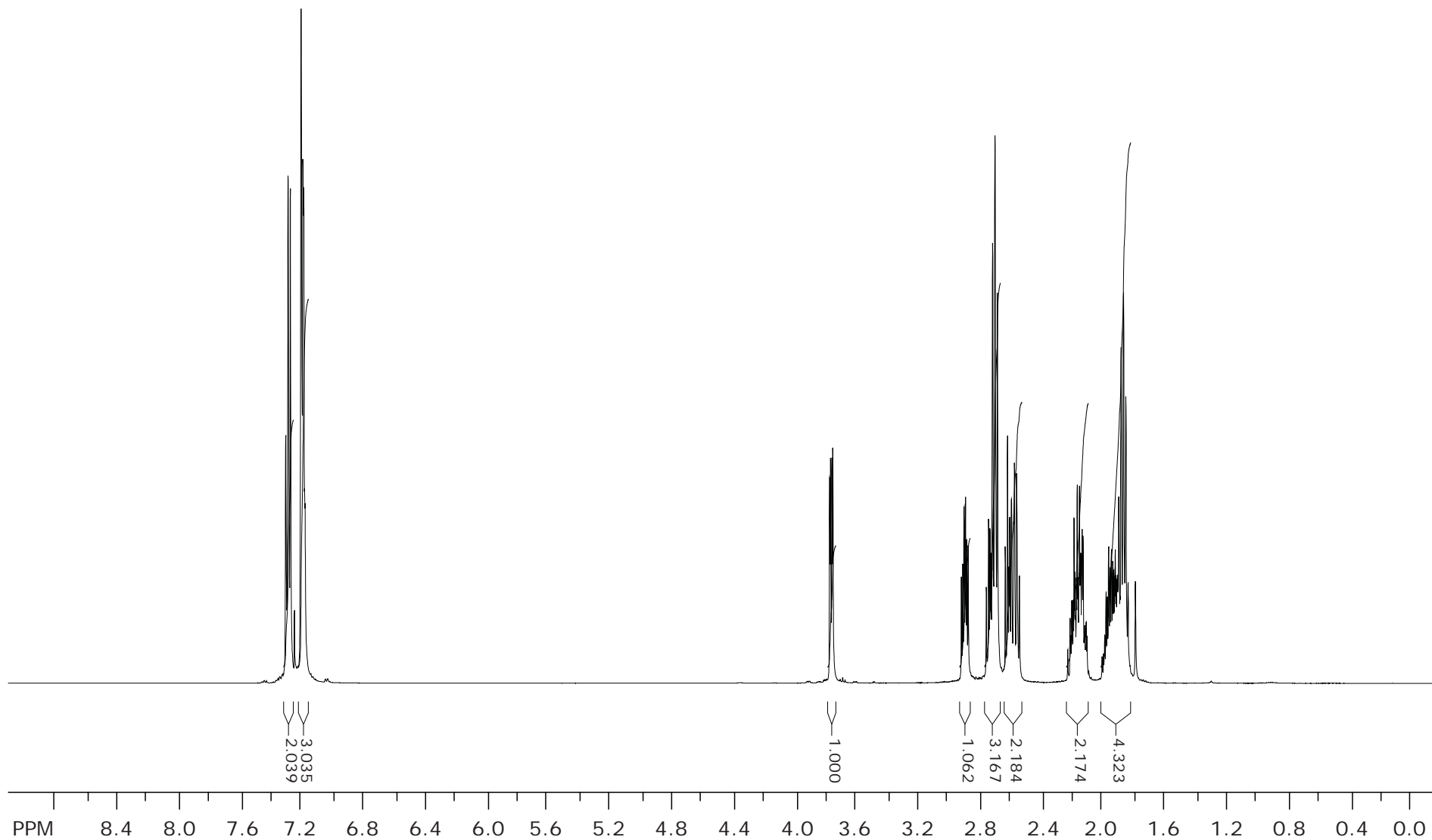
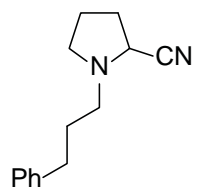
$^1\text{H}$  NMR of of **6n** in  $\text{CDCl}_3$



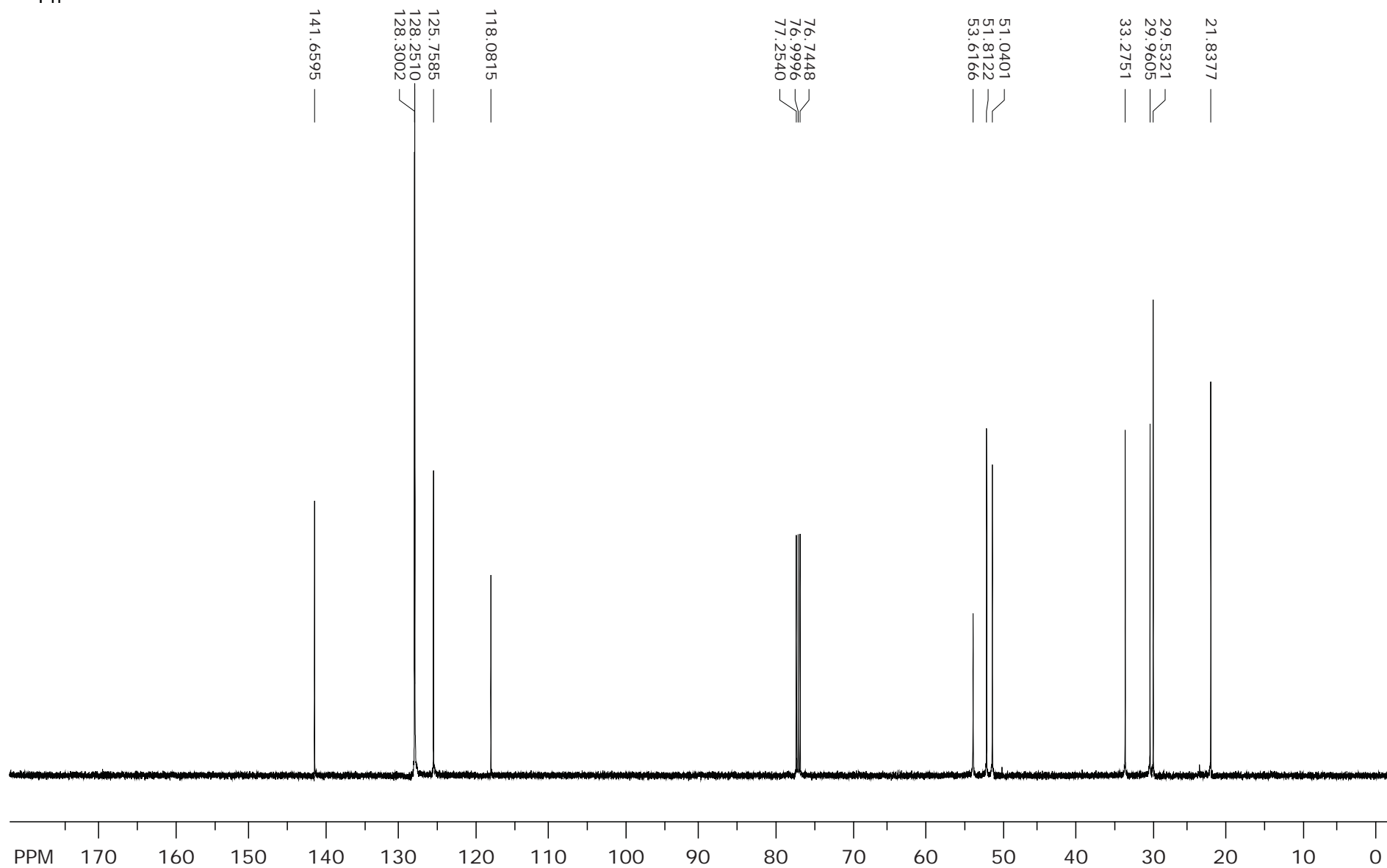
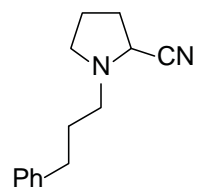
$^{13}\text{C}$  NMR of **6n** in  $\text{CDCl}_3$



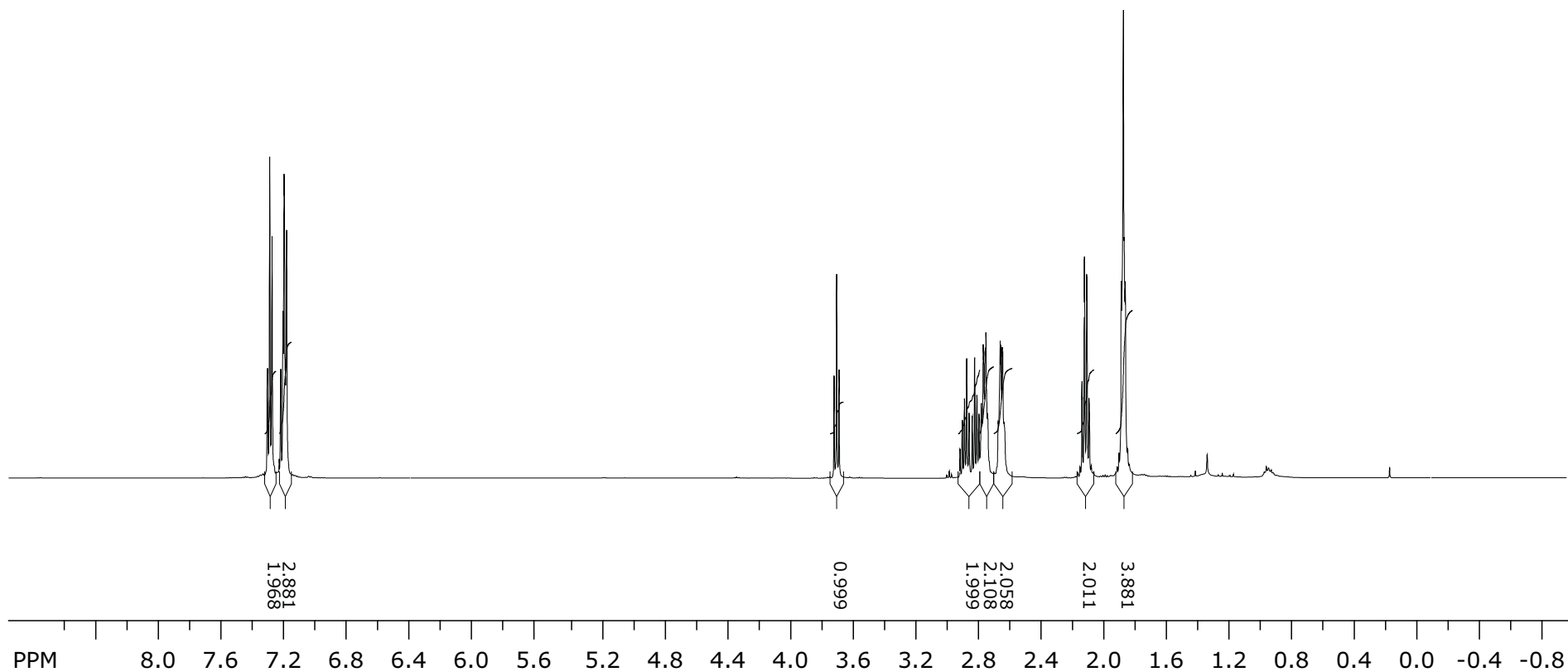
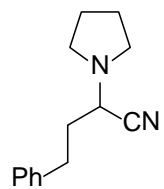
$^1\text{H}$  NMR of of **5o** in  $\text{CDCl}_3$



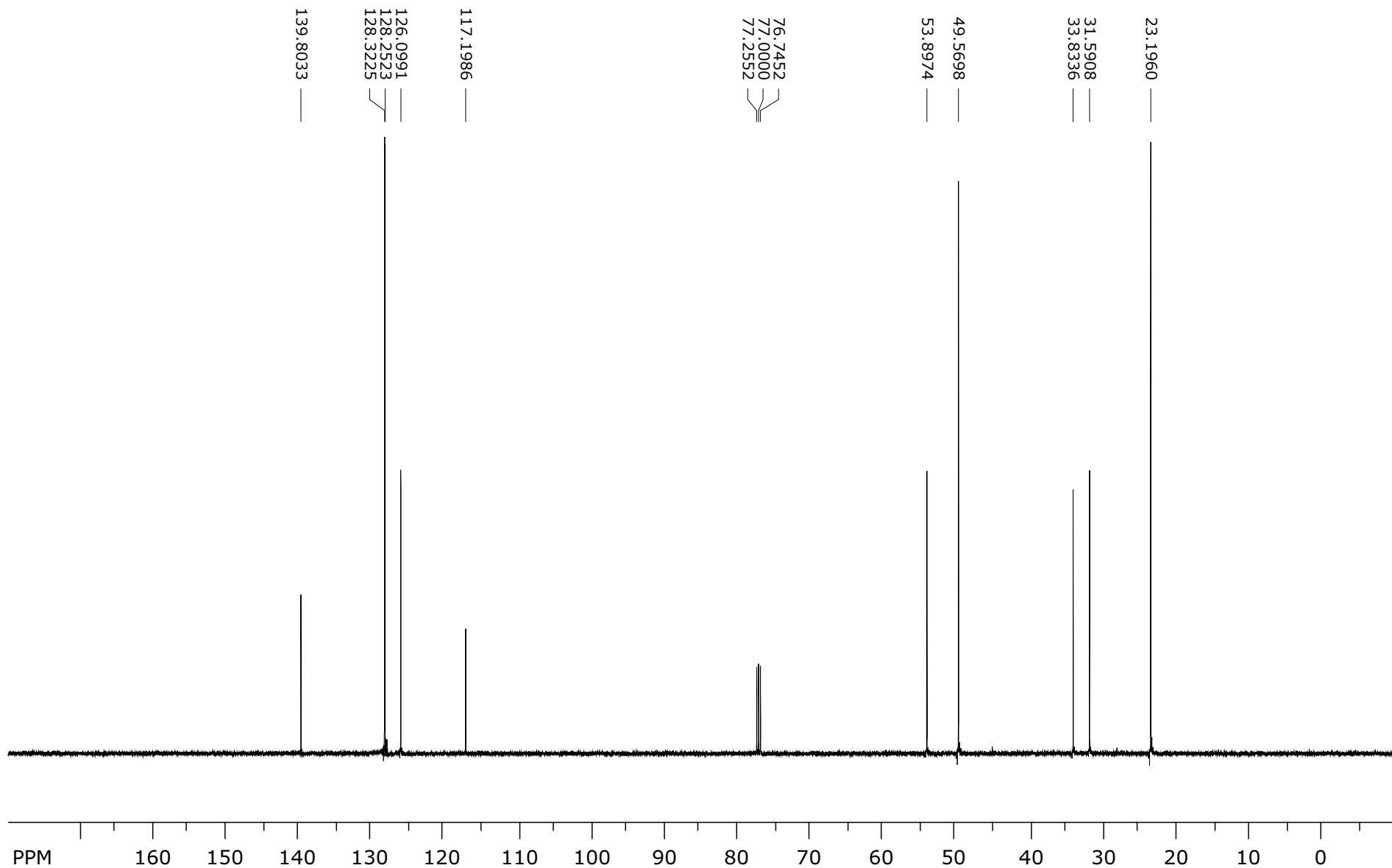
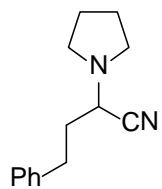
$^{13}\text{C}$  NMR of **5o** in  $\text{CDCl}_3$



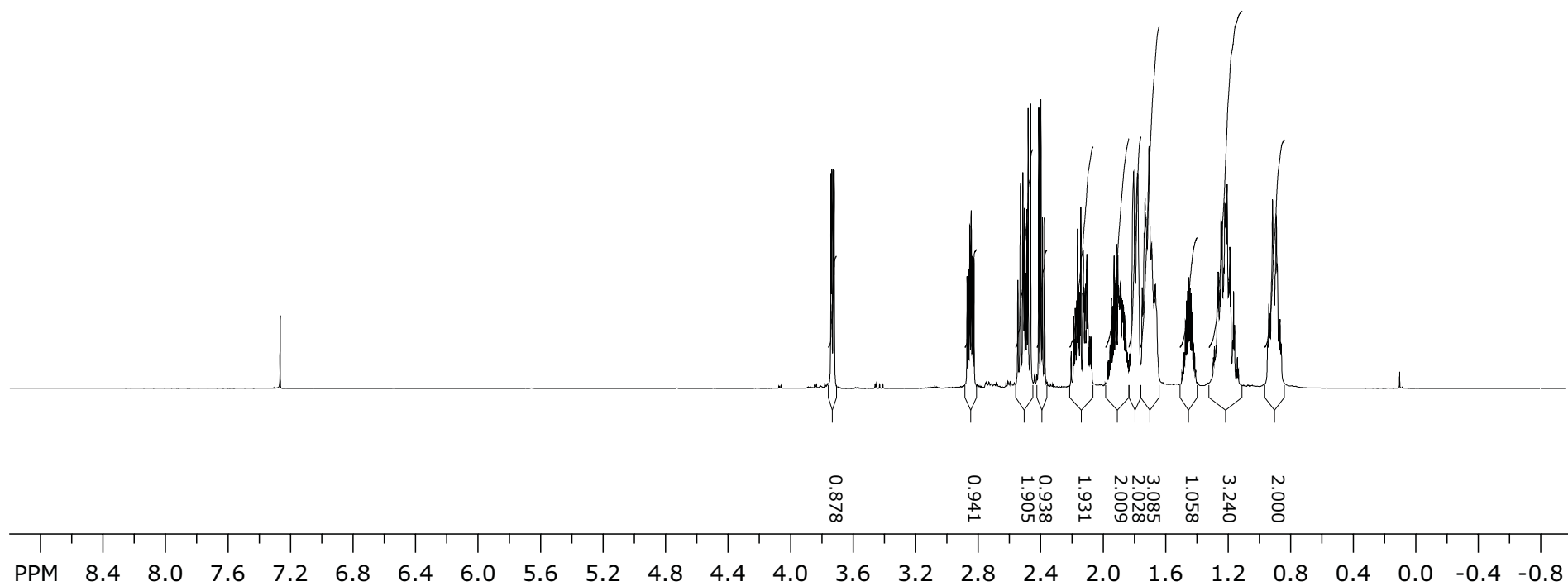
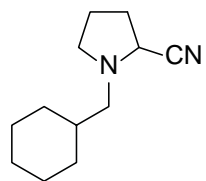
<sup>1</sup>H NMR of of **60** in CDCl<sub>3</sub>



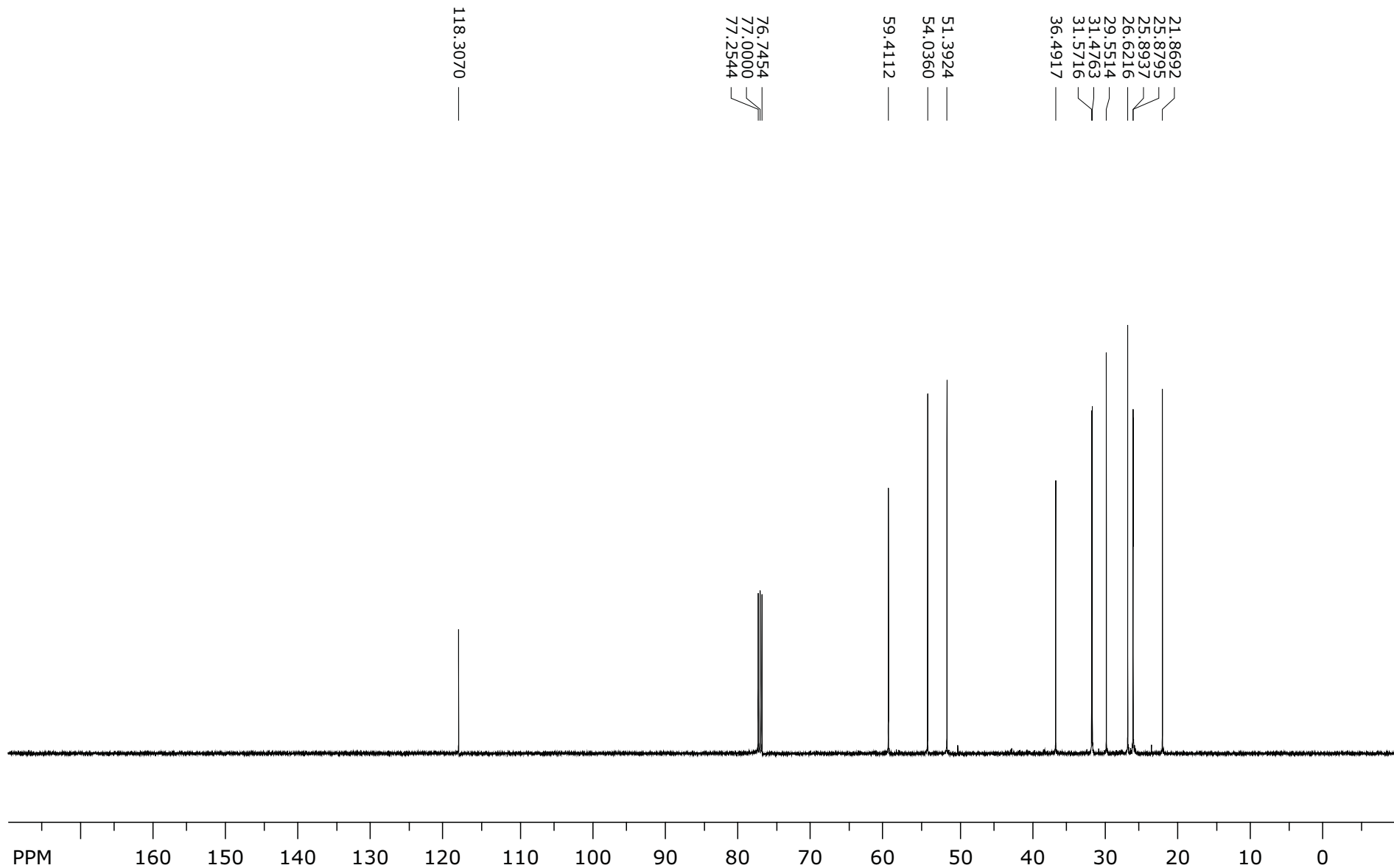
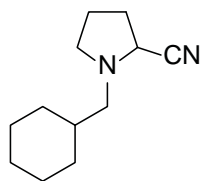
<sup>13</sup>C NMR of **6o** in CDCl<sub>3</sub>



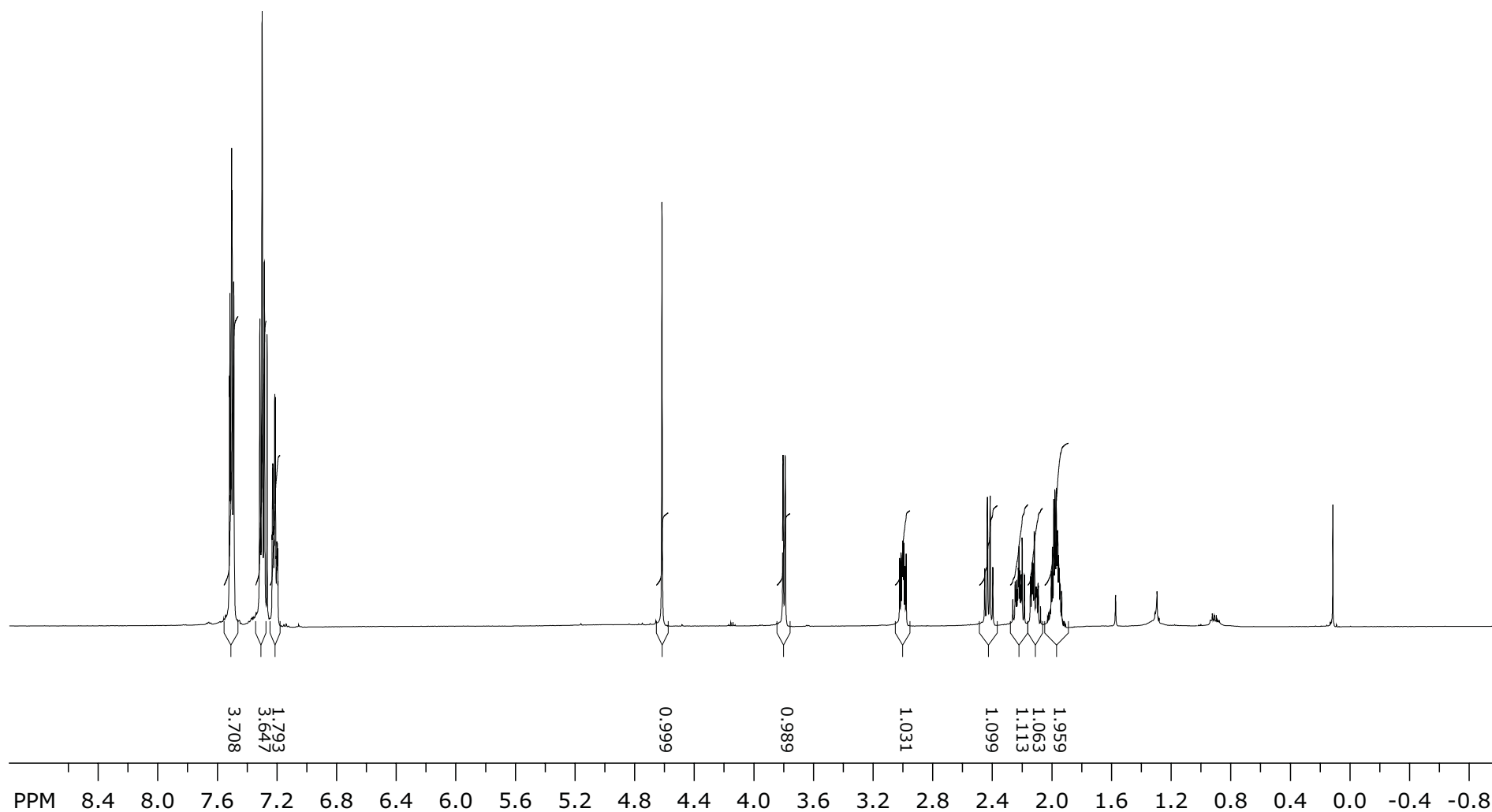
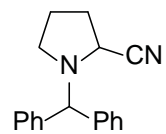
$^1\text{H}$  NMR of of **5p** in  $\text{CDCl}_3$



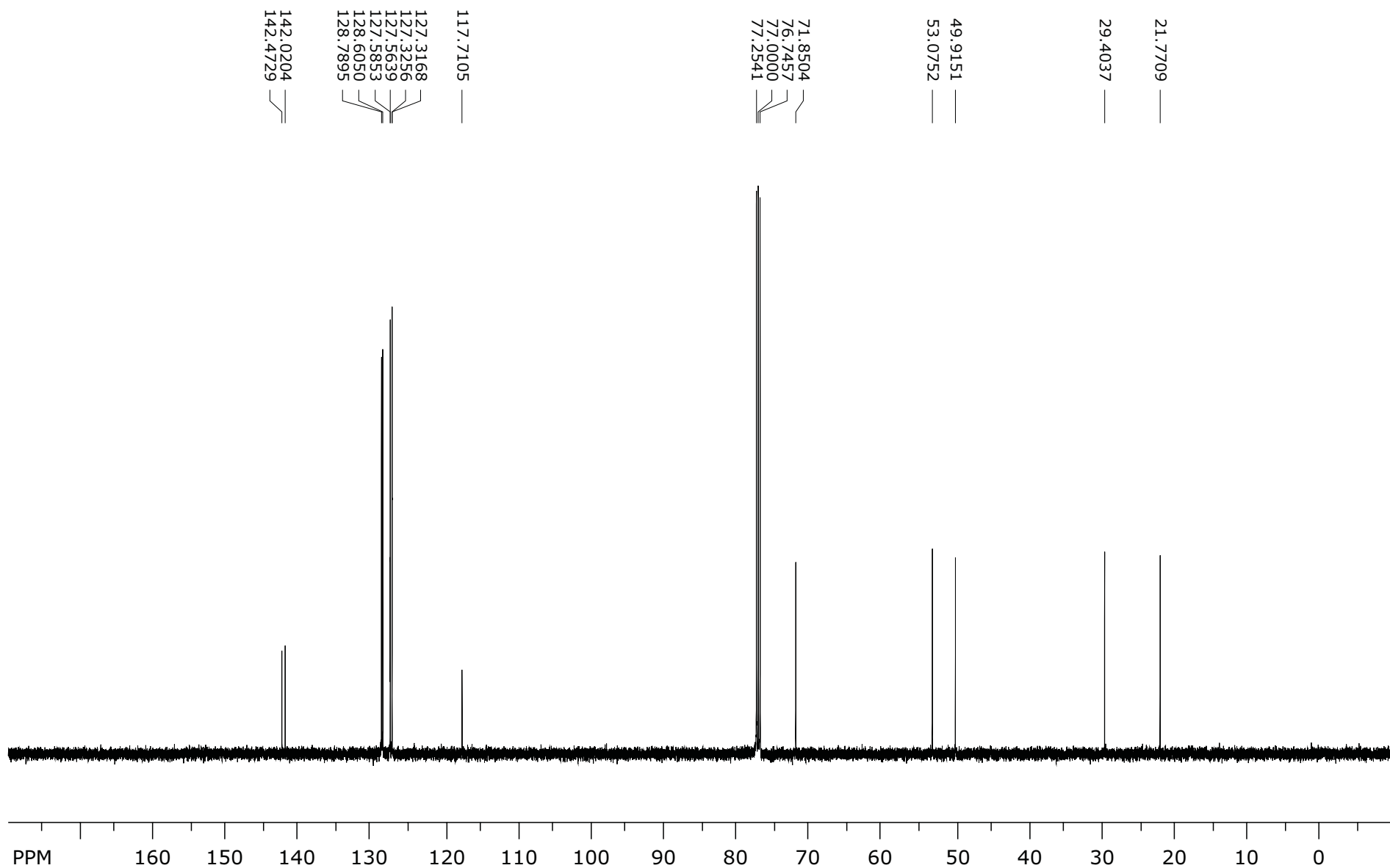
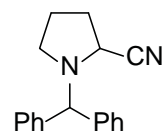
$^{13}\text{C}$  NMR of **5p** in  $\text{CDCl}_3$



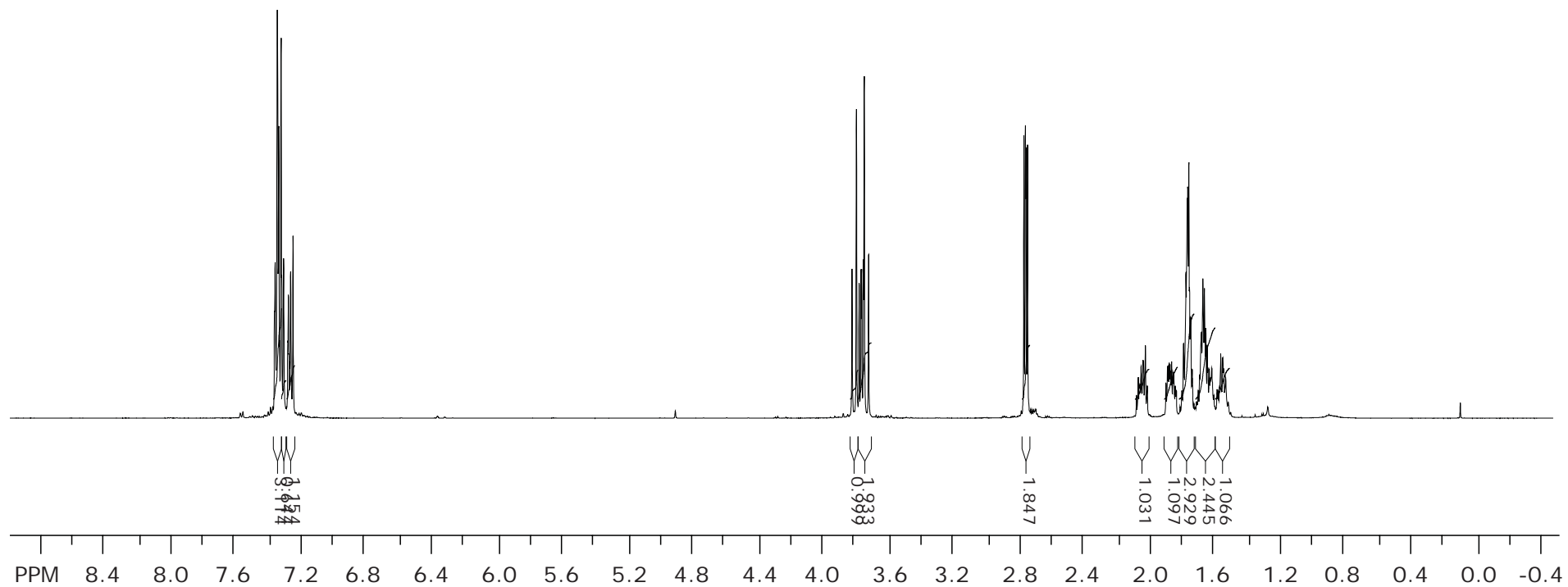
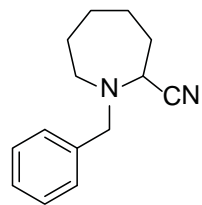
$^1\text{H}$  NMR of **5q** in  $\text{CDCl}_3$



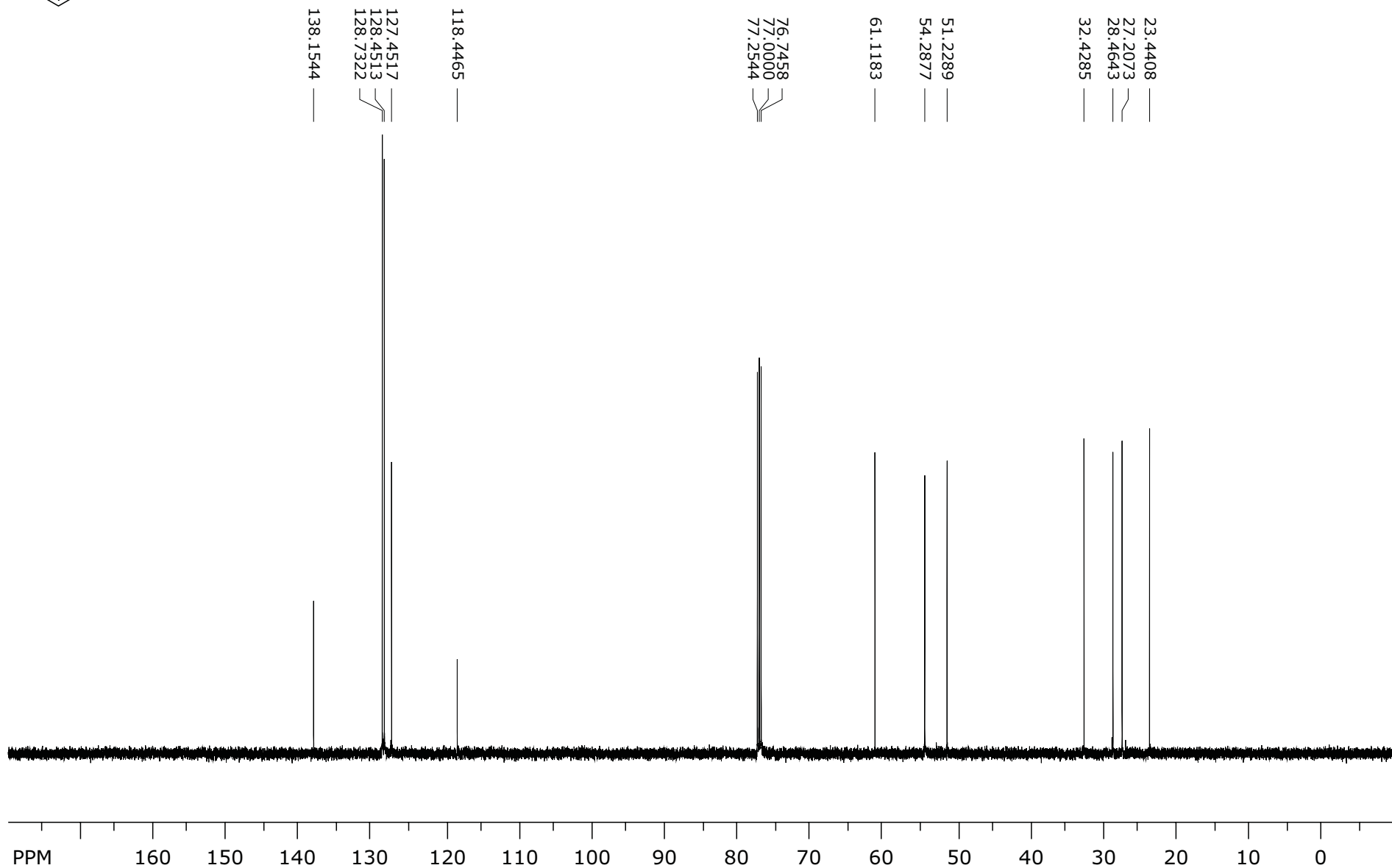
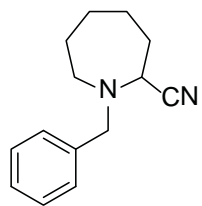
<sup>13</sup>C NMR of **5q** in CDCl<sub>3</sub>



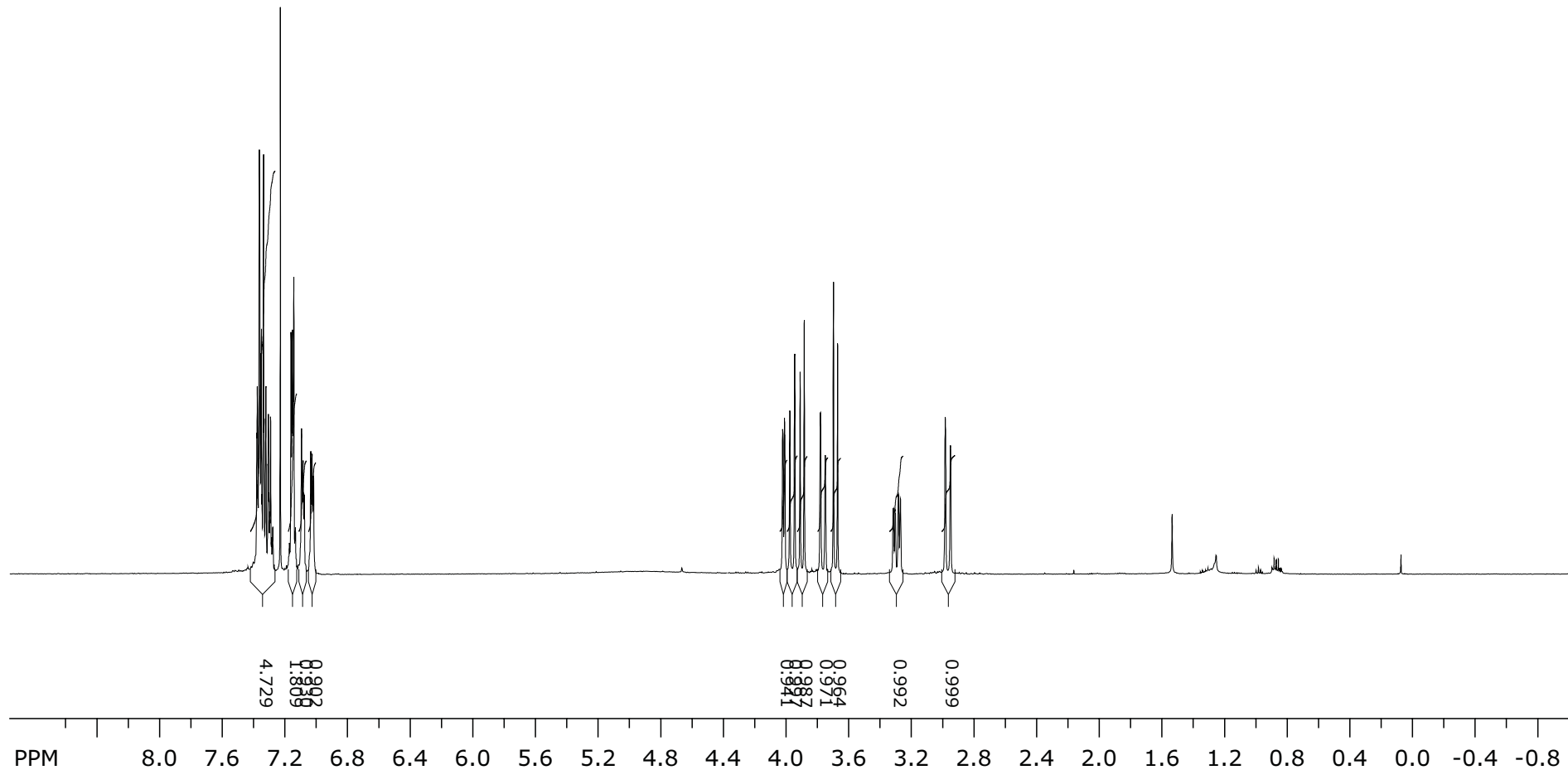
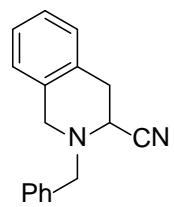
<sup>1</sup>H NMR of of **16** in CDCl<sub>3</sub>



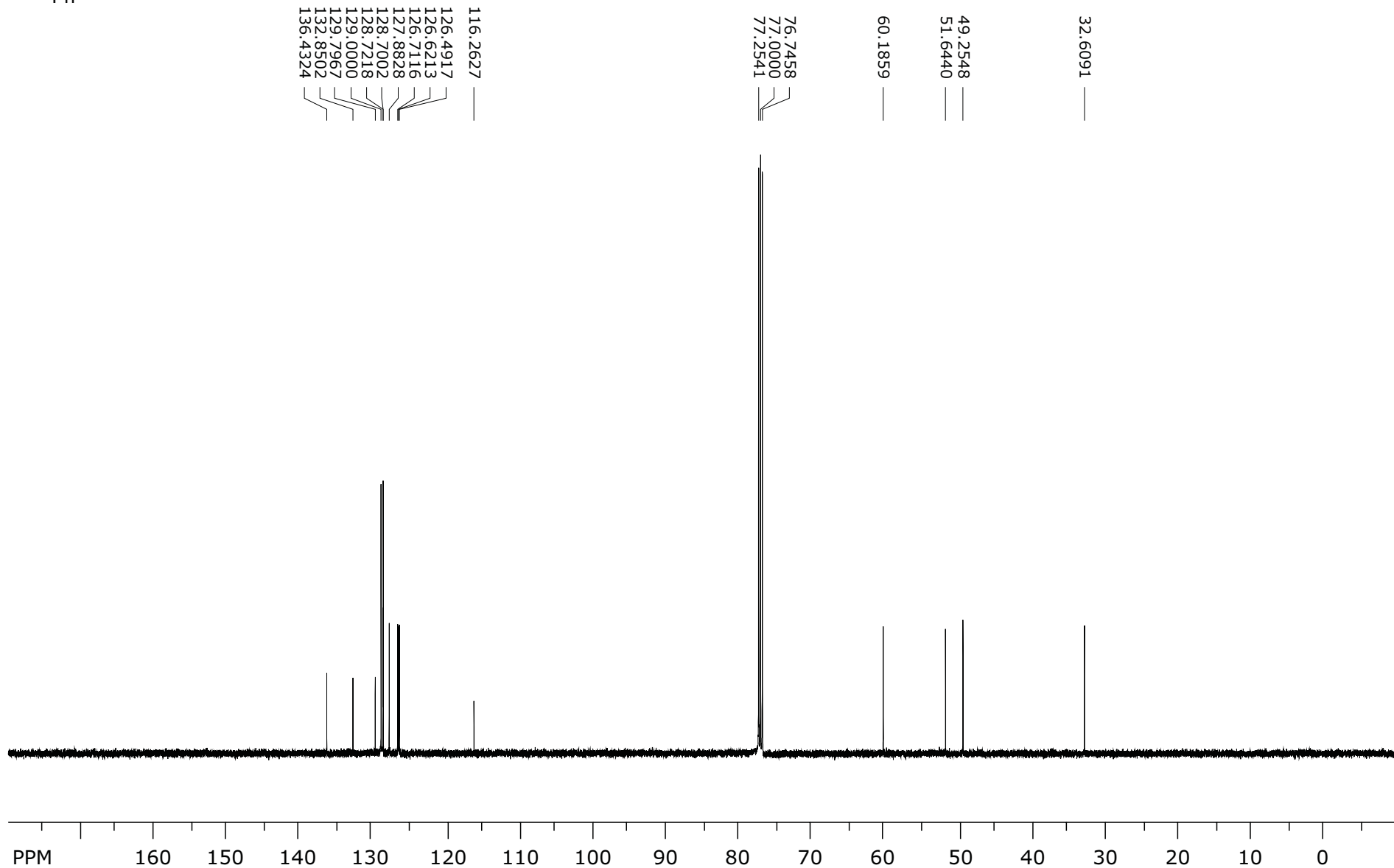
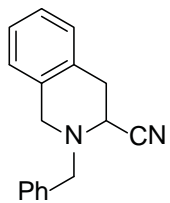
<sup>13</sup>C NMR of **16** in CDCl<sub>3</sub>



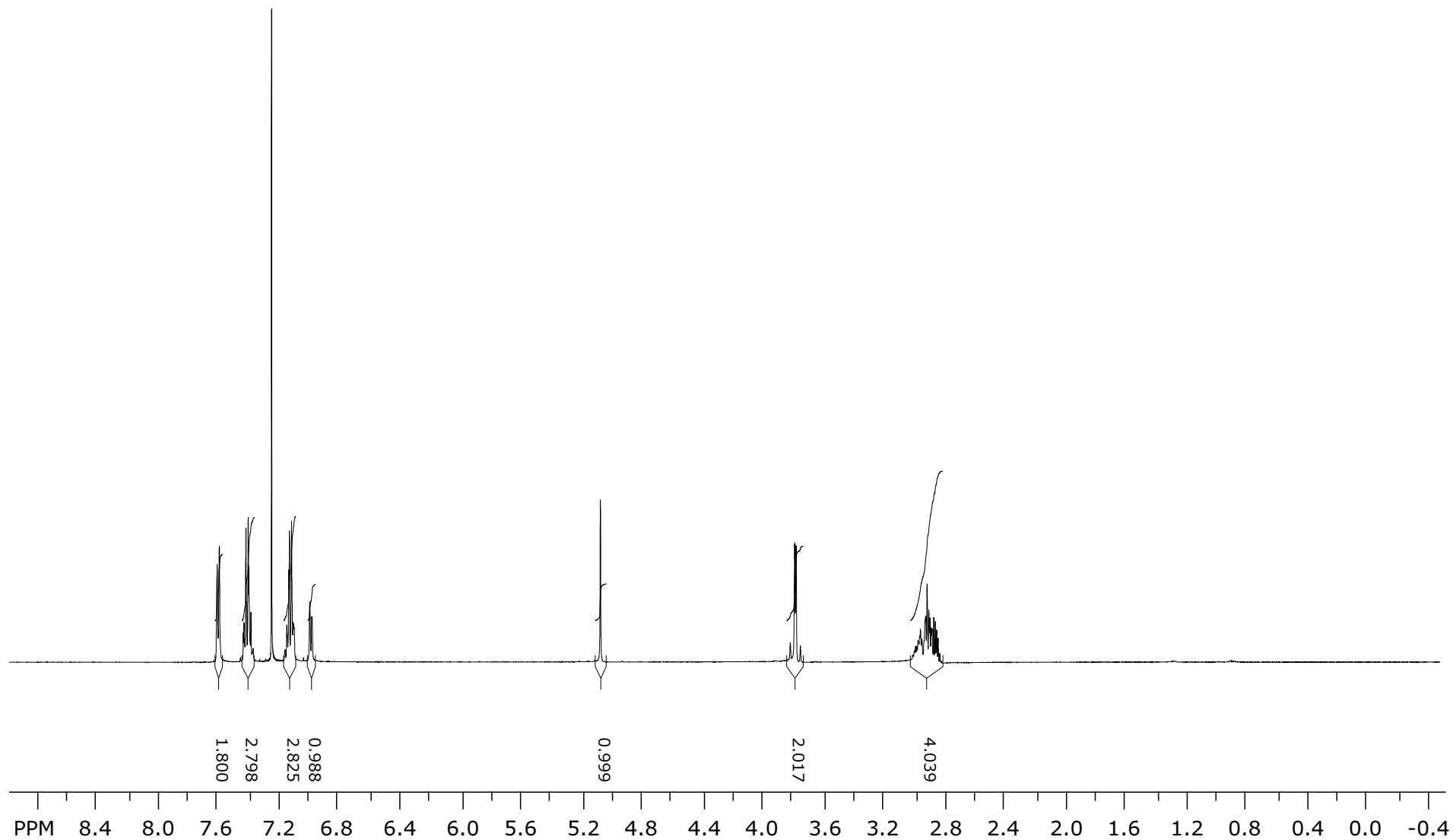
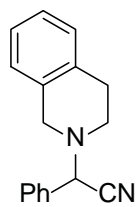
<sup>1</sup>H NMR of of **18** in CDCl<sub>3</sub>



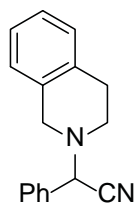
<sup>13</sup>C NMR of **18** in CDCl<sub>3</sub>



$^1\text{H}$  NMR of of **19** in  $\text{CDCl}_3$



<sup>13</sup>C NMR of **19** in CDCl<sub>3</sub>



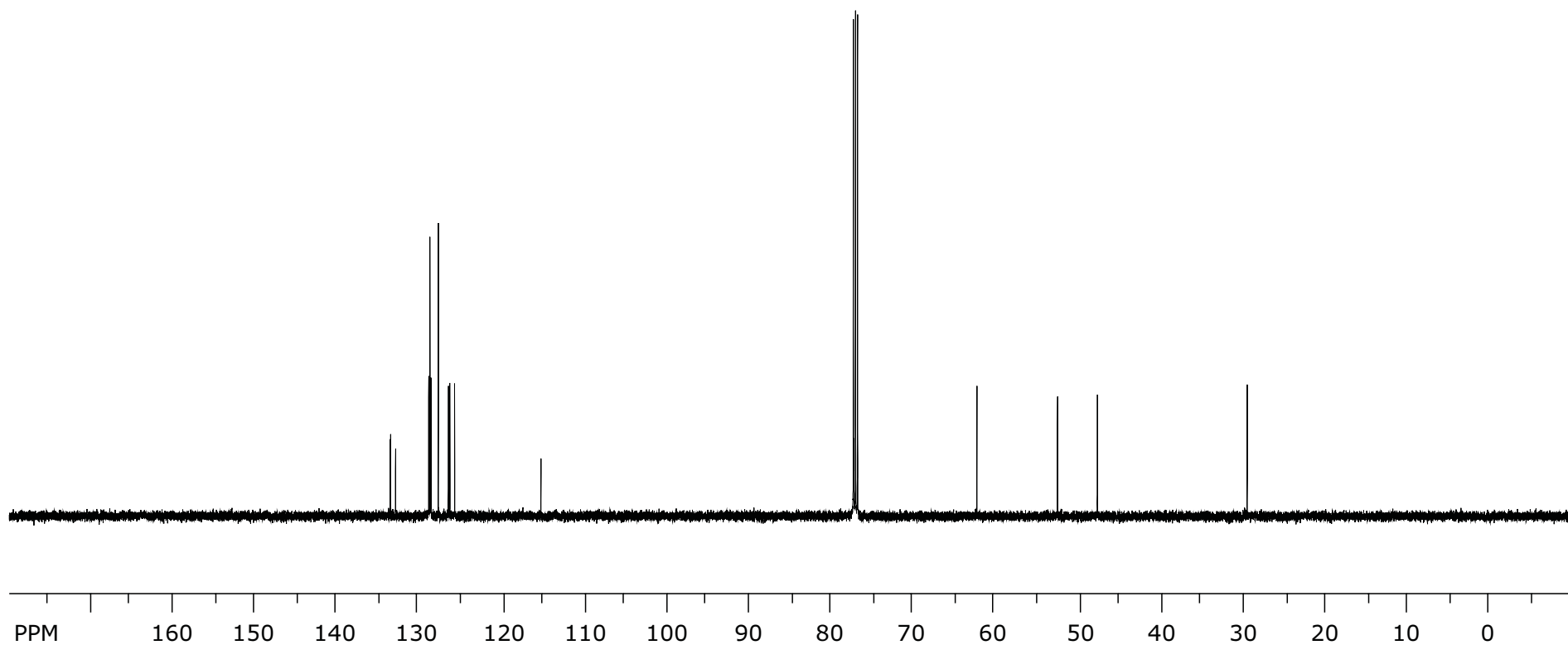
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126.5904  
127.8194  
128.7142  
128.8393  
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133.0299  
133.6268  
133.6656  
115.3224

76.7456  
77.0000  
77.2541

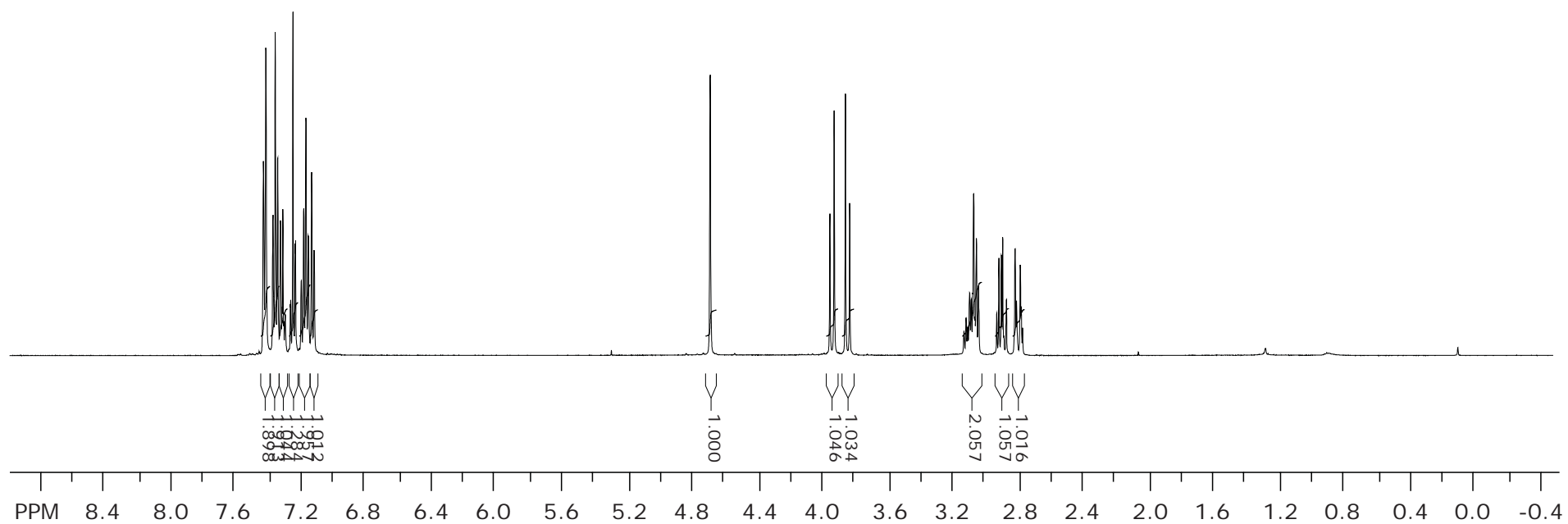
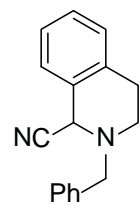
62.2051

47.5305  
52.3859

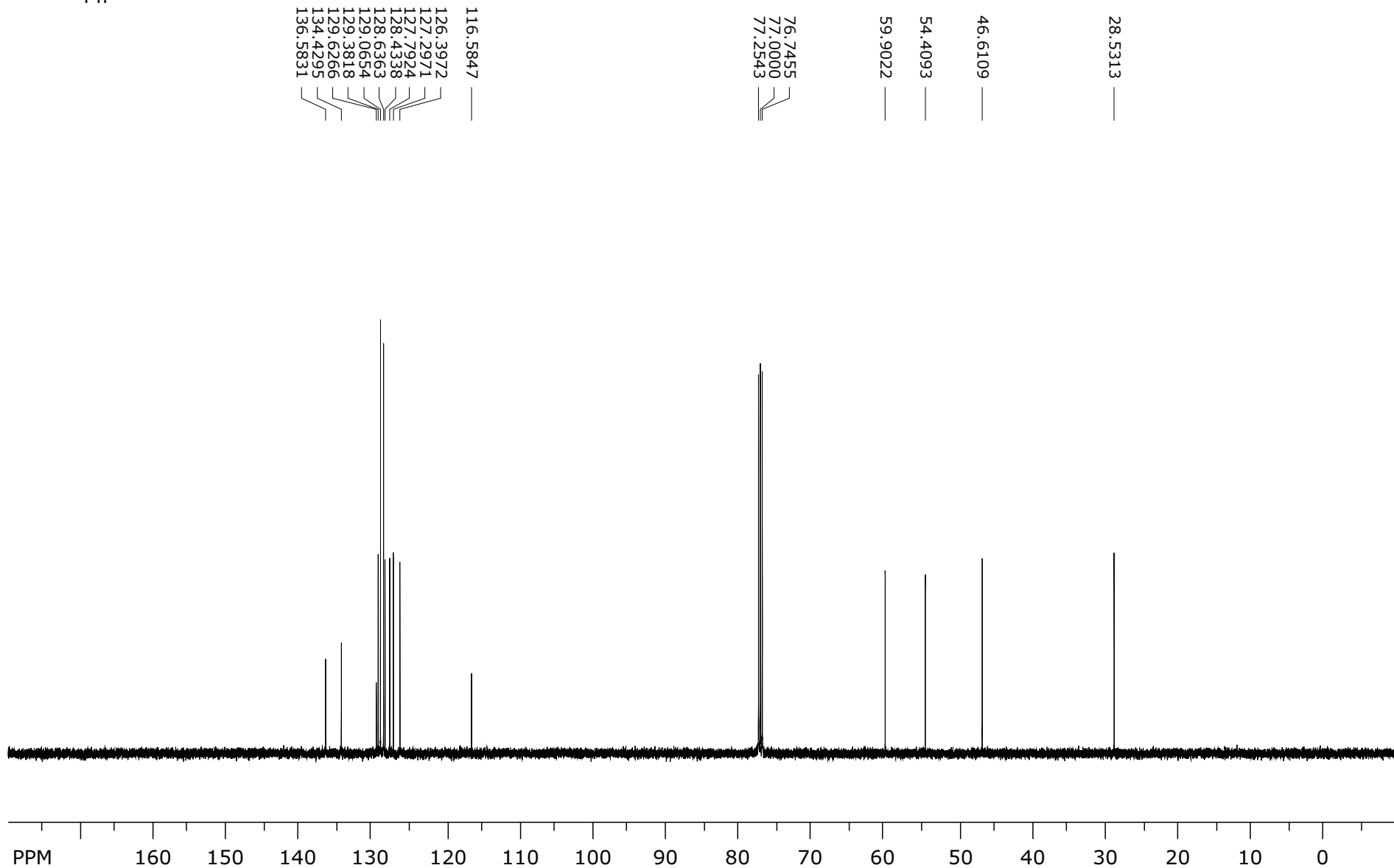
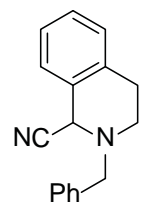
29.2772



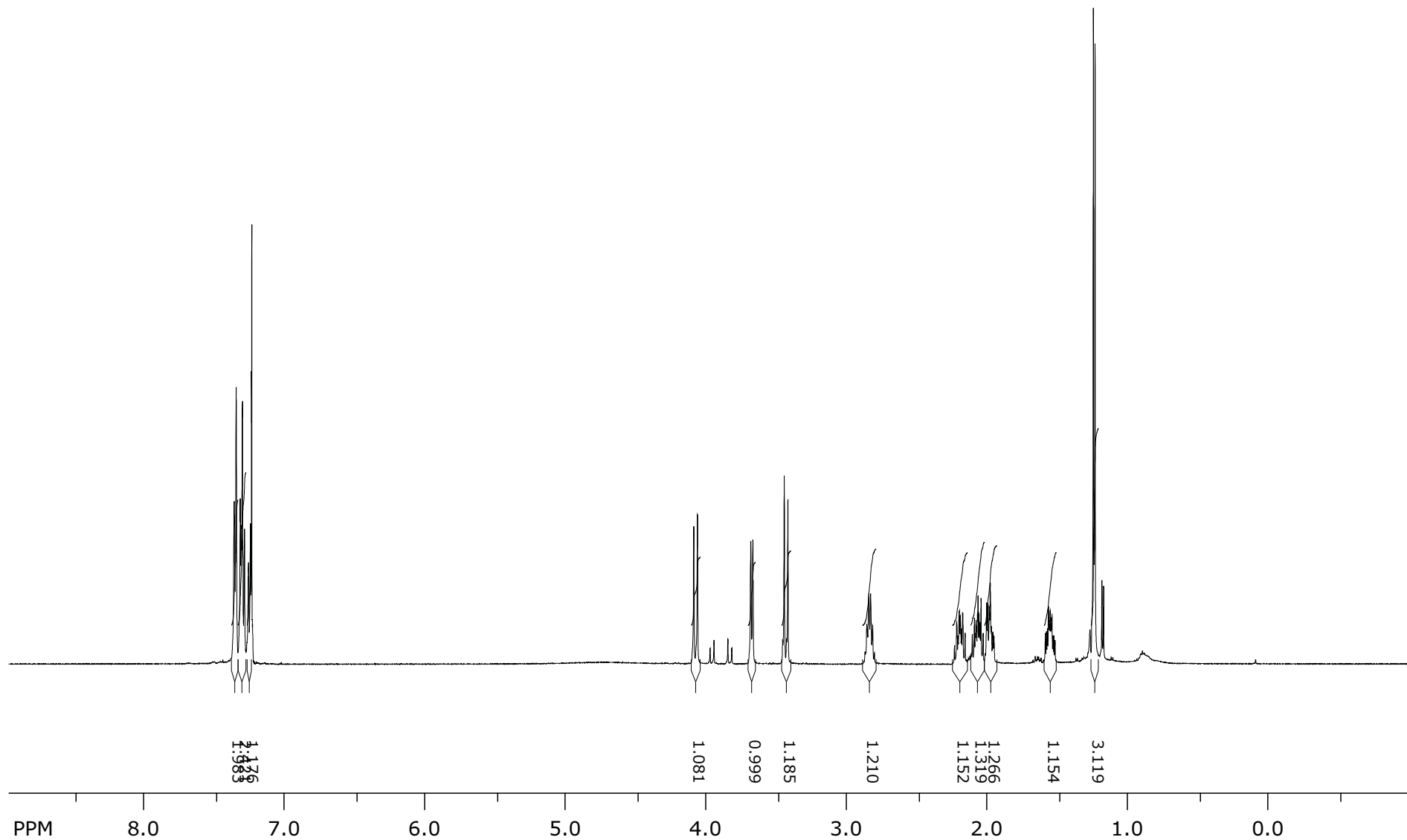
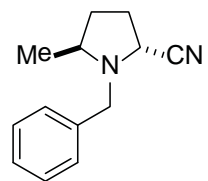
$^1\text{H}$  NMR of **20** in  $\text{CDCl}_3$



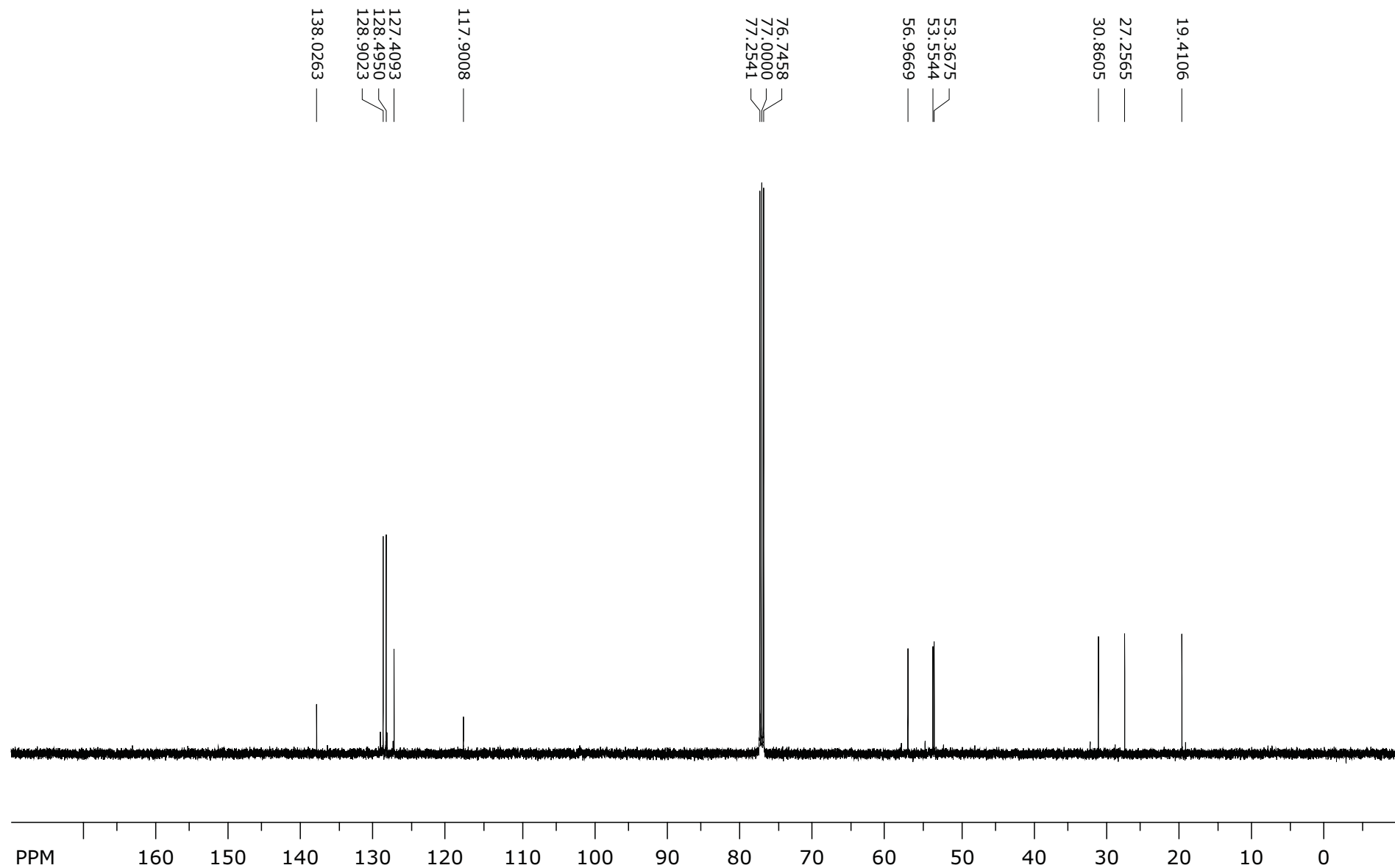
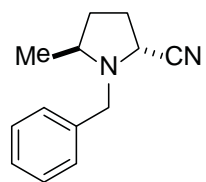
<sup>13</sup>C NMR of **20** in CDCl<sub>3</sub>



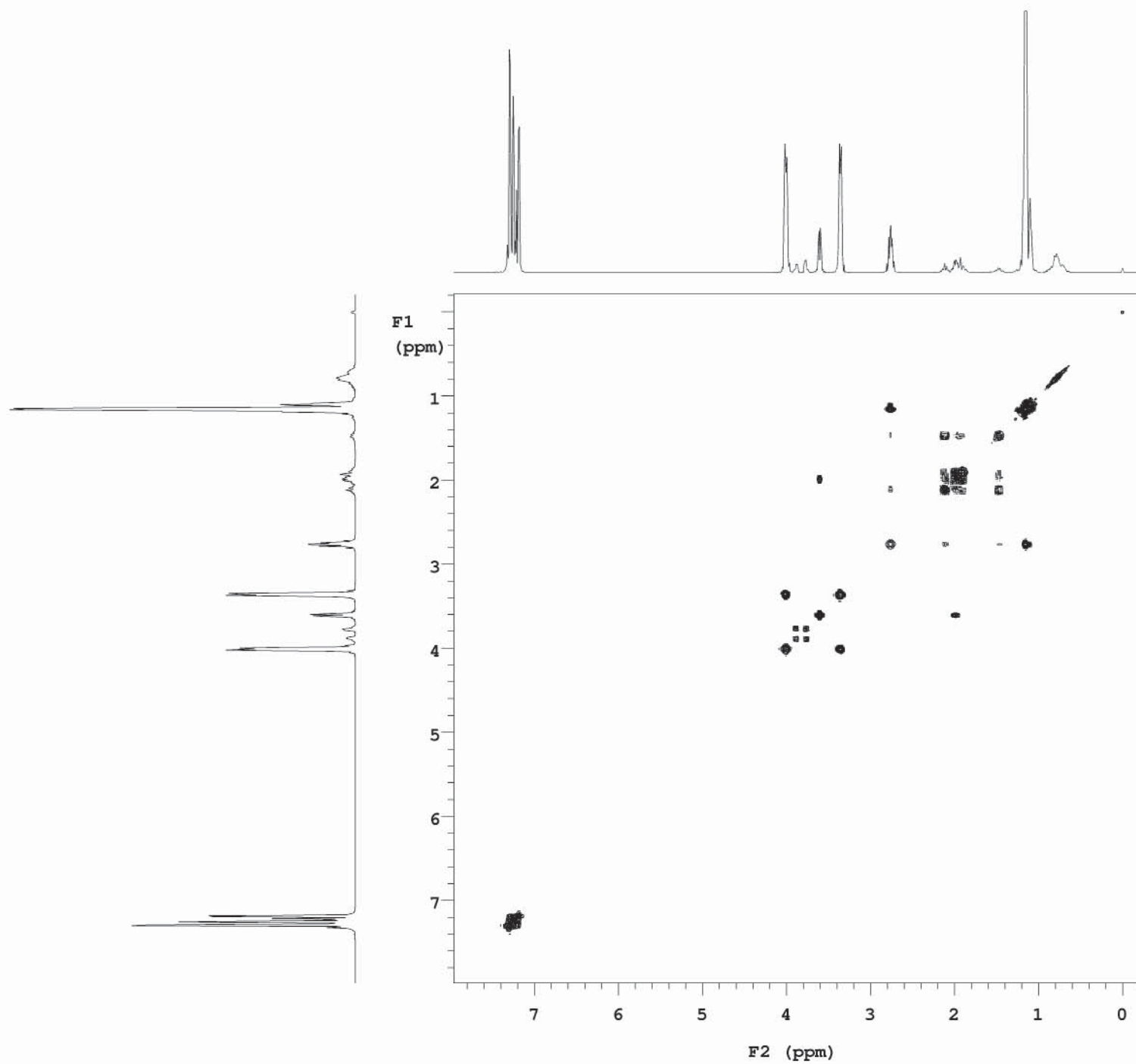
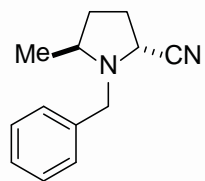
<sup>1</sup>H NMR of of **21** in CDCl<sub>3</sub>



<sup>13</sup>C NMR of **21** in CDCl<sub>3</sub>



GCOSY of **21** in CDCl<sub>3</sub>



NOESY of **21** in  $\text{CDCl}_3$

