A Straightforward Three-component Synthesis of α-Amino esters containing a Phenylalanine or a Phenylglycine Scaffold

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SUPPORTING INFORMATION

Table of Contents

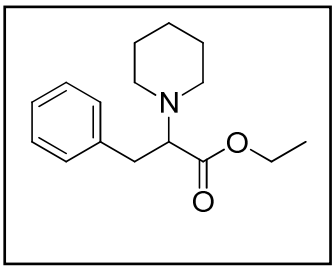
General:

Solvents and reagents were purchased from commercial suppliers and used without further purification. All reactions were monitored by gas chromatography (GC) using a 5 m BP1 column. Melting points (mp) were determined on a capillary melting apparatus and are uncorrected. Infrared spectra were recorded on a FT-IR spectrometer in ATR mode. NMR spectra were recorded in $CDCl_3$, at 400 MHz (^1H), 100 MHz (^{13}C) and 376 MHz (^{19}F). Chemical shifts (δ) are reported in parts per million (ppm) relative to the residual non-deuterated solvent signal. Coupling constant values (*J*) are given in Hertz (Hz) and refer to apparent multiplicities, indicated as follows: s (singlet); br s (broad singlet); d (doublet); t (triplet); q (quartet); m (multiplet); dd (doublet of doublets). Mass spectra were measured on a GC/MS apparatus. Some elemental analyses returned unsatisfactory C% results. Consequently, for consistency, all compounds were characterized by High Resolution Mass Spectrometry (HRMS). This service was provided by an outside facility. The purity of all compounds could be established by the examination of their NMR spectra, included below. Compounds that have been previously described in the literature are linked to relevant bibliographic references. Compounds labeled by asterisk (*) are, to the best of our knowledge, new compounds.

Typical procedure starting from benzyl bromides (Table 1): a dried 100 mL round-bottomed flask was flushed with argon and charged with acetonitrile (40 mL). Zinc dust (2 g, 30 mmol) and trifluoroacetic acid (0.2 mL) were added under vigorous stirring. After 5 min, the amine (10 mmol), ethyl glyoxylate (~50% solution in toluene, 2.6 mL, ~13 mmol) and the benzyl bromide (25 mmol) were added to the solution and allowed to react for 1 h at room temperature. The reaction was quenched with a saturated ammonium chloride solution (150 mL) and the organic products extracted with dichloromethane (2 x 100 mL). After removal of the solvent, a chromatographic purification on neutral alumina using a pentane/diethyl ether mixture as an eluant (90/10→10/90) afforded the pure product. Alternatively, the pure α-amino ester could be obtained from the crude oil by using an acid-base work-up, as detailed in Ref. 1.

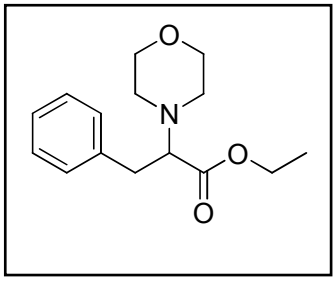
Typical procedure starting from aryl bromides (Table 3): a dried 100 mL round-bottomed flask was flushed with argon and charged with acetonitrile (25 mL). Zinc dust (4 g, 61 mmol), trifluoroacetic acid (0.2 mL) and 1,2-dibromoethane (0.3 mL) were added and the solution was heated under vigorous stirring until gas was evolved. Heating was stopped and the solution allowed to cool for 15 min. The aryl bromide (20 mmol) and cobalt bromide (0.44 g, 2 mmol) were added to the mixture and after 30 min at room temperature, stirring was stopped and the surrounding solution was taken up using a syringe and transferred into another flask containing the amine (5 mmol) and ethyl glyoxylate (~50% solution in toluene, 2.6 mL, ~13 mmol, depolymerized prior to use by 30 min heating at 60°C) in 10 mL acetonitrile. After 1 h at room temperature, the reaction was quenched with a saturated ammonium chloride solution (100 mL) and the organic products extracted with dichloromethane (2 x 100 mL). After removal of the solvent, a chromatographic purification on neutral alumina using a pentane/diethyl ether mixture as an eluant (90/10→10/90) afforded the pure product. Alternatively, the pure α-amino ester could be obtained from the crude oil by using an acid-base work-up, as detailed in Ref. 1.

Ethyl 3-phenyl-2-(piperidin-1-yl)propanoate (1a)[2]:



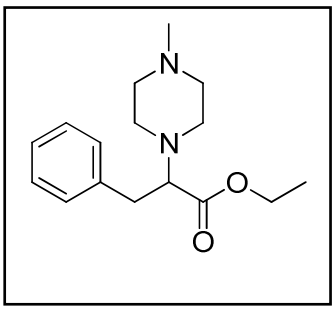
Colorless oil. m = 2.48 g (95%). ATR-FTIR (neat, cm^{-1}): 2933, 1726, 1184, 1148, 1115, 1053, 747, 698. ^{1}H NMR (400 MHz): δ 7.29-7.18 (m, 5H), 4.11-4.03 (m, 2H), 3.41 (dd, *J* = 9.8, *J* = 5.5 Hz, 1H), 3.11-2.94 (m, 2H), 2.77-2.49 (m, 4H), 1.68-1.42 (m, 6H), 1.15 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz): δ 171.4, 138.4, 129.3, 128.2, 126.3, 70.4, 59.9, 51.1, 35.9, 26.5, 24.6, 14.4. MS, m/z (relative intensity): 188 ($[M-CO_2Et]^+$,79), 170 ($[M-PhCH_2]^+$,100), 142 (37), 124 (5), 105 (15), 96 (6). HRMS Calcd. for $C_{16}H_{24}NO_2$ $[M+H]^+$: 262.1807, found: 262.1815.

Ethyl 2-morpholino-3-phenylpropanoate (1b)[3]:



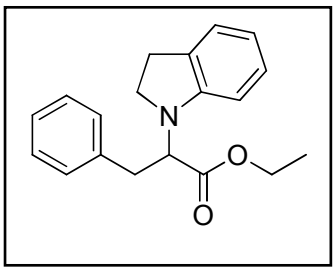
Pale yellow oil. m = 2.19 g (83%). ATR-FTIR (neat, cm^{-1}): 2959, 1725, 1453, 1154, 1115, 748. ^{1}H NMR (400 MHz): δ 7.37-7.15 (m, 5H), 4.18-3.99 (m, 2H), 3.80-3.64 (m, 4H), 3.42 (dd, *J* = 9.3, *J* = 6.0 Hz, 1H), 3.14-2.90 (m, 2H), 2.81-2.58 (m, 4H), 1.16 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz): δ 171.0, 137.9, 129.2, 128.3, 126.5, 69.9, 67.3, 60.3, 50.3, 35.5, 14.4. MS, m/z (relative intensity): 191 (9), 190 (79), 173 (8), 172 ($[M-PhCH_2]^+$, 100), 144 (36), 105 (10), 91 (6). HRMS Calcd. for $C_{15}H_{22}NO_3$ **[**$M+H]^+$: 264.1600, found: 264.1600.

Ethyl 2-(4-methylpiperazin-1-yl)-3-phenylpropanoate (1c)[3]:



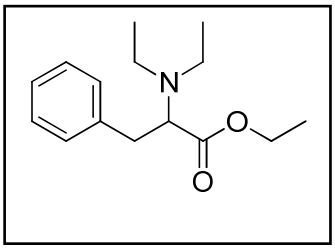
Yellow oil. m = 1.12 g (41%). ATR-FTIR (neat, cm^{-1}): 2936, 2794, 1726, 1454, 1284, 1156, 1142, 1011, 747. ^{1}H NMR (400 MHz): δ 7.22-7.13 (m, 5H), 4.02-3.97 (m, 2H), 3.37 (dd, *J* = 9.4, *J* = 5.8 Hz, 1H), 3.05-2.96 (m, 1H), 2.92-2.86 (m, 1H), 2.76-2.66 (m, 2H), 2.64-2.56 (m, 2H), 2.39 (br s, 3H), 2.22 (s, 3H), 1.08 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz): δ 170.9, 138.1, 129.2, 128.2, 126.3, 69.5, 60.1, 55.4, 49.6, 46.0, 35.6, 14.3. MS, m/z (relative intensity): 276 ($[M]^+$, 5), 203 ($[M-CO_2Et]^+$, 55), 185 ($[M-PhCH_2]^+$, 100), 160 (31), 131 (5), 112 (18), 98 (76), 70 (40), 56 (5). HRMS Calcd. for $C_{16}H_{25}N_2O_2$ $[M+H]^+$: 277.1916, found: 277.1908.

Ethyl 2-(indolin-1-yl)-3-phenylpropanoate (1d)[*]:



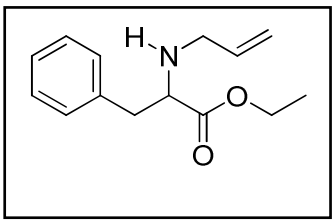
Yellow oil. m = 2.63 g (89%). ATR-FTIR (neat, cm^{-1}): 3027, 1729, 1605, 1488, 1256, 1158, 1024, 742, 698. ^{1}H NMR (400 MHz): δ 7.55-7.22 (m, 5H), 7.21-7.04 (m, 2H), 6.76-6.70 (m, 1H), 6.60-6.56 (m, 1H), 4.50 (t, *J* = 7.7 Hz, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.73 (t, *J* = 8.5 Hz, 2H), 3.41-3.34 (m, 1H), 3.22-3.14 (m, 1H), 3.10-2.99 (m, 2H), 1.17 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz): δ 171.5, 150.5, 137.8, 129.9, 129.0, 128.5, 127.2, 126.7, 124.6, 117.9, 106.9, 60.7, 60.3, 48.6, 35.5, 28.3, 14.2. MS, m/z (relative intensity): 295 ($[M]^+$, 12), 222 ($[M-CO_2Et]^+$, 26), 204 ($[M-PhCH_2]^+$, 100), 176 (52), 130 (51), 105 (8), 91 (12), 77 (4). HRMS Calcd. for $C_{19}H_{21}NO_2Na$ $[M+Na]^+$: 318.1470, found: 318.1478.

Ethyl 2-(diethylamino)-3-phenylpropanoate (1e)[4]:



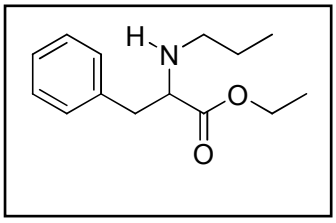
Pale yellow oil. m = 2.33 g (93%). ATR-FTIR (neat, cm^{-1}): 3029, 2970, 1726, 1157, 747, 698. ATR-FTIR (neat, cm^{-1}): 2971, 1726, 1605, 1496, 1454, 1157, 747, 698. ^{1}H NMR: δ 7.20-7.09 (m, 5H), 4.02-3.96 (m, 2H), 3.53 (dd, *J* = 8.4, J = 6.5 Hz, 1H), 2.99 (dd, *J* = 13.4, *J* = 8.9 Hz, 1H), 2.81 (dd, *J* = 13.4, *J* = 6.2 Hz, 1H), 2.77-2.65 (m, 2H), 2.53-2.40 (m, 2H), 1.08 (t, *J* = 7.1 Hz, 3H), 0.81 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR: δ 172.7, 138.8, 128.9, 128.1, 126.2, 65.0, 60.0, 44.5, 36.4, 14.3, 13.8. MS, m/z (relative intensity): 250 ($[M+1]^+$, 2), 177 (14), 176 ($[M-CO_2Et]^+$, 100), 160 (4), 159 (7), 158 ($[M-PhCH_2]^+$, 89), 148 (8), 132 (2), 131 (5), 130 (39), 120 (3), 119 (2), 112 (3), 105 (11), 103 (2), 102 (3), 91 (4), 84 (5), 56 (5). HRMS Calcd. for $C_{15}H_{24}NO_2$ $[M+H]^+$: 250.1807, found: 250.1811.

Ethyl 2-(allylamino)-3-phenylpropanoate (1f)[5]:



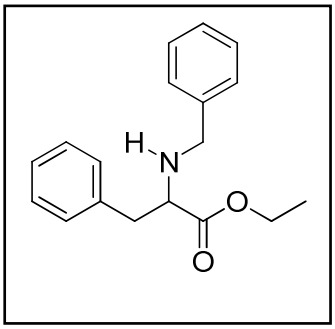
Yellow oil. m = 1.86 g (80%). ATR-FTIR (neat, cm^{-1}): 3228, 3029, 1729, 1418, 1027, 919, 743, 699. ^{1}H NMR (400 MHz): δ 7.22-7.08 (m, 5H), 5.78-5.68 (m, 1H), 5.06-4.97 (m, 2H), 4.01 (q, *J* = 7.1 Hz, 2H), 3.45 (t, *J* = 6.9 Hz, 1H), 3.22-3.16 (m, 1H), 3.03 (dd, *J* = 13.9, *J* = 6.1 Hz, 1H), 2.92-2.82 (m, 2H), 1.61 (br s, 1H), 1.06 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz): δ 174.6, 137.3, 136.2, 129.3, 128.4, 126.7, 116.4, 62.1, 60.6, 50.6, 39.8, 14.2. MS, m/z (relative intensity): 234 ($[M+1]^+$, 4), 160 ($[M-CO_2Et]^+$, 75), 142 ($[M-PhCH_2]^+$, 100), 128 (24), 114 (45), 91 (38), 68 (30). HRMS Calcd. for $C_{14}H_{20}NO_2$ $[M+H]^+$: 234.1494, found: 234.1498.

Ethyl 3-phenyl-2-(propylamino)propanoate (1g)[*]:



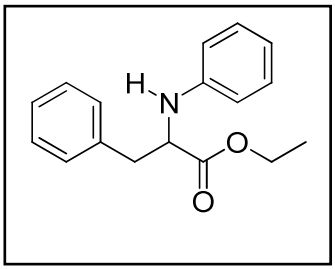
Colorless oil. m = 1.95 g (83%). ATR-FTIR (neat, cm^{-1}): 3230, 2959, 2933, 1730, 1455, 1031, 743, 698. ^{1}H NMR (400 MHz): δ 7.22-7.10 (m, 5H), 4.02 (q, *J* = 7.1 Hz, 2H), 3.42 (t, *J* = 7.1 Hz, 1H), 2.93-2.81 (m, 2H), 2.51-2.34 (m, 2H), 1.53 (br s, 1H), 1.44-1.33 (m, 2H), 1.07 (t, *J* = 7.1 Hz, 3H), 0.79 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz): δ 174.8, 137.4, 129.2, 128.4, 126.6, 63.1, 60.5, 50.0, 39.8, 23.2, 14.2, 11.6. MS, m/z (relative intensity): 236 ($[M+1]^+$, 5), 162 ($[M-CO_2Et]^+$, 100), 144 ($[M-PhCH_2]^+$, 83), 132 (15), 120 (63), 116 (51), 103 (16), 91 (23), 77 (8), 70 (15). HRMS Calcd. for $C_{14}H_{22}NO_2$ $[M+H]^+$: 236.1651, found: 236.1648.

Ethyl 2-(benzylamino)-3-phenylpropanoate (1h)[6]:



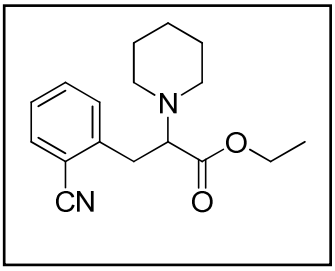
Yellow oil. m = 2.09 g (74%). ATR-FTIR (neat, cm^{-1}): 3333, 3028, 2980, 1728, 1454, 1027, 736, 696. ^{1}H NMR (400 MHz): δ 7.21-7.09 (m, 10H), 4.02 (q, *J* = 7.1 Hz, 2H), 3.74 (d, *J* = 13.2 Hz, 1H), 3.57 (d, *J* = 13.2 Hz, 1H), 3.45 (t, *J* = 6.9 Hz, 1H), 2.88 (d, *J* = 6.9 Hz, 2H), 1.75 (br s, 1H), 1.09 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz): δ 174.68, 139.7, 137.4, 129.3, 128.4, 128.2, 127.0, 126.7, 62.2, 60.6, 52.0, 39.8, 14.2. MS, m/z (relative intensity): 284 ($[M+1]^+$, 1), 210 ($[M-CO_2Et]^+$, 33), 192 ($[M-PhCH_2]^+$, 70), 118 (11), 91 (100), 65 (5). HRMS Calcd. for $C_{18}H_{22}NO_2$ $[M+H]^+$: 284.1651, found: 284.1653.

Ethyl 3-phenyl-2-(phenylamino)propanoate (1i)[7]:



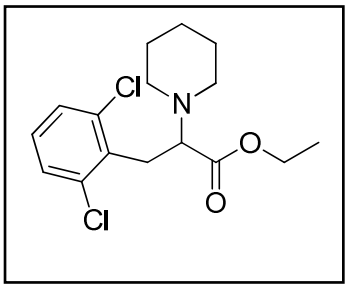
Light brown oil. m = 1.76 g (65%). ATR-FTIR (neat, cm^{-1}): 3391, 3055, 3028, 2981, 1730, 1601, 1506, 1497, 1189, 1027, 746, 692. ^{1}H NMR (400 MHz): δ 7.37-7.21 (m, 7H), 6.80 (t, *J* = 7.3 Hz, 1H), 6.69 (t, *J* = 7.8 Hz, 2H), 4.42 (t, *J* = 6.3 Hz, 1H), 4.21 (s, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.24-3.15 (m, 2H), 1.22 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz): δ 173.2, 146.5, 136.5, 129.4, 128.5, 127.0, 118.5, 113.7, 61.2, 57.8, 38.7, 14.2. MS, m/z (relative intensity): 269 ($[M]^+$, 11), 196 ($[M\text{-}CO_2Et]^+$, 31), 178 ($[M\text{-}PhCH_2]^+$, 100), 150 (12), 132 (7), 118 (52), 104 (74), 77 (18). HRMS Calcd. for $C_{17}H_{19}NO_2$ $[M+Na]^+$: 292.1313, found: 292.1317.

Ethyl 3-(2-cyanophenyl)-2-(piperidin-1-yl)propanoate (1j)[*]:



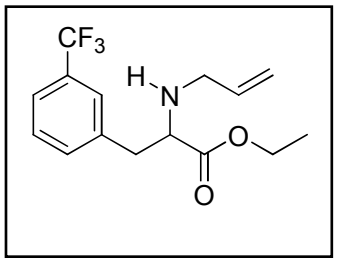
Colorless oil. m = 2.24 g (78%). ATR-FTIR (neat, cm^{-1}): 2936, 2226, 1713, 1450, 1337, 1170, 762. ^{1}H NMR (400 MHz): δ 7.61 (d, *J* = 7.7 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 1H), 7.36-7.27 (m, 2H), 4.18-4.05 (m, 2H), 3.52-3.48 (m, 1H), 3.22-3.20 (m, 2H), 2.77-2.71 (m, 2H), 2.52-2.47 (m, 2H), 1.56-1.51 (m, 4H), 1.44-1.39 (m, 2H), 1.19 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz): δ 170.9, 142.8, 132.8, 132.4, 130.7, 126.9, 118.0, 113.1, 69.0, 60.4, 51.1, 33.7, 26.4, 24.5, 14.4. MS, m/z (relative intensity): 213 ($[M\text{-}CO_2Et]^+$, 100), 184 ($[M\text{-}NCPh]^+$, 16), 170 ($[M\text{-}NCPhCH_2]^+$, 81), 142 (24), 96 (4), 82 (107), 55 (4). HRMS Calcd. for $C_{17}H_{23}N_2O_2$ $[M+H]^+$: 287.1760, found: 287.1748.

Ethyl 3-(2,6-dichlorophenyl)-2-(piperidin-1-yl)propanoate (1k)[*]:



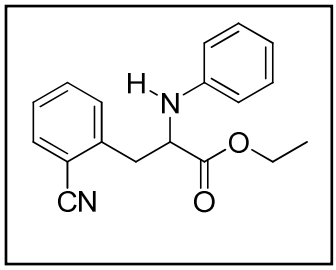
Orange oil. m = 2.87 g (87%). ATR-FTIR (neat, cm^{-1}): 2934, 1727, 1561, 1434, 1180, 1158, 1105, 1034, 767. ^{1}H NMR (400 MHz): δ 7.17 (d, *J* = 8.0 Hz, 2H), 6.98 (t, *J* = 8.0 Hz, 1H), 4.07-4.00 (m, 2H), 3.55 (t, *J* = 7.5 Hz, 1H), 3.29 (dd, *J* = 13.7, *J* = 8.0 Hz, 1H), 3.15 (dd, *J* = 13.7, *J* = 7.1 Hz, 1H), 2.73-2.68 (m, 2H), 2.43-2.39 (m, 2H), 1.46-1.40 (m, 4H), 1.34-1.30 (m, 2H), 1.11 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz): δ 171.6, 136.0, 135.3, 128.1, 127.8, 66.6, 60.1, 51.3, 30.8, 26.4, 24.5, 14.4. MS, m/z (relative intensity): 299 (6), 281 (6), 259 (6), 258 (40), 257 (10), 256 ($[M\text{-}CO_2Et]^+$, 64), 190(5), 175 (9), 173 (6), 171 (11), 170 ($[M\text{-}Cl_2PhCH_2]^+$, 100), 168 (5), 164 (6), 161 (7), 159 (7), 143 (7), 142 (31), 137 (6), 124 (5), 69 (5). HRMS Calcd. for $C_{16}H_{22}Cl_2NO_2$ $[M+H]^+$: 330.1028, found: 330.1020.

Ethyl 2-(allylamino)-3-(3-(trifluoromethyl)phenyl)propanoate (1l)[*]:



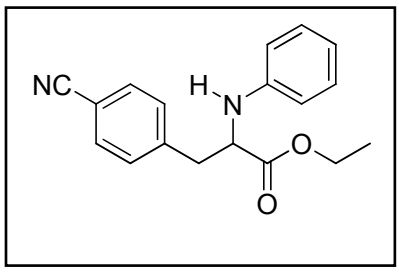
Yellow oil. m = 2.41 g (80%). ATR-FTIR (neat, cm^{-1}): 3350, 2983, 1730, 1326, 1161, 1121, 1026, 702. ^{1}H NMR (400 MHz): δ 7.50-7.38 (m, 4H), 5.86-5.76 (m, 1H), 5.17-5.07 (m, 2H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.53 (t, *J* = 6.9 Hz, 1H), 3.28 (dd, *J* = 13.9, *J* = 5.9 Hz, 1H), 3.13 (dd, *J* = 13.9, *J* = 6.1 Hz, 1H), 3.07-2.94 (m, 2H), 1.78 (br s, 1H), 1.16 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz): δ 174.3, 138.4, 136.0, 132.8, 130.6 (q, *J* = 32.2 Hz), 128.8, 126.0 (q, *J* = 3.8 Hz), 124.1 (q, *J* = 272.3 Hz), 123.5 (q, *J* = 3.8 Hz), 116.6, 61.7, 60.8, 50.6, 39.5, 14.1. ^{19}F NMR (376 MHz) : δ –62.67. MS, m/z (relative intensity): 302 ($[M+1]^+$, 5), 228 ($[M\text{-}CO_2Et]^+$, 88), 208 (14), 191 (10), 159 (22), 142 ($[M\text{-}F_3CPhCH_2]^+$, 100), 114 (40), 91 (7), 68 (24). HRMS Calcd. for $C_{15}H_{19}F_3NO_2$ $[M+H]^+$: 302.1368, found: 302.1365.

Ethyl 3-(2-cyanophenyl)-2-(phenylamino)propanoate (1m)[*]:



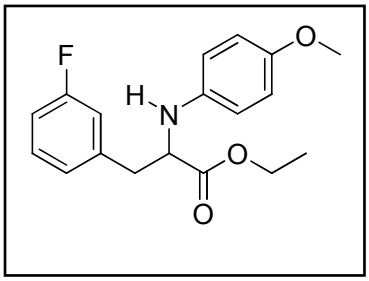
Yellow oil. m = 1.62 g (55%). ATR-FTIR (neat, cm^{-1}): 3372, 2981, 2224, 1731, 1601, 1507, 1184, 1024, 749, 692. ^{1}H NMR (400 MHz): δ 7.56 (dd, *J* = 7.8, *J* = 1.0 Hz, 1H), 7.44 (td, *J* = 7.7, *J* = 1.3 Hz, 1H), 7.31-7.25 (m, 2H), 7.11-7.07 (m, 2H), 6.69-6.65 (m, 1H), 6.57-6.55 (m, 2H), 4.36 (t, *J* = 6.8 Hz, 1H), 4.12-4.02 (m, 2H), 3.33-3.21 (m, 2H), 1.11 (t, *J* = 7.1 Hz 3H). ^{13}C NMR (100 MHz): δ 172.5, 146.1, 140.8, 133.0, 132.8, 130.6, 129.4, 127.5, 118.8, 118.1, 113.7, 113.3, 61.6, 57.4, 37.4, 14.1. MS, m/z (relative intensity): 295 (5), 294 ($[M]^+$, 35), 222 (17), 221 ($[M\text{-}CO_2Et]^+$, 98), 219 (16), 205 (7), 204 (41), 179 (14), 178 ($[M\text{-}NCPhCH_2]^+$, 100), 150 (11), 128 (5), 104 (37), 77 (11). HRMS Calcd. for $C_{18}H_{18}N_2O_2Na$ $[M+Na]^+$: 317.1266, found: 317.1260.

Ethyl 3-(4-cyanophenyl)-2-(phenylamino)propanoate (1n)[*]:



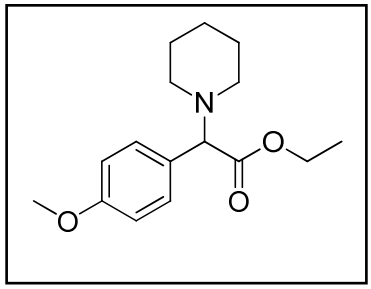
Yellow oil. m = 2.27 g (77%). ATR-FTIR (neat, cm^{-1}): 3348, 3026, 2912, 2228, 1717, 1603, 1520, 1291, 1194, 826, 747, 694. ^{1}H NMR (400 MHz): δ 7.59 (d, *J* = 8.5 Hz, 2H), 7.31-7.27 (m, 2H), 7.23-7.18 (m, 2H), 6.79 (t, *J* = 8.3 Hz, 1H), 6.63 (d, *J* = 8.3 Hz, 2H), 4.40 (t, *J* = 6.1 Hz, 1H), 4.21-4.11 (m, 2H), 3.26-3.14 (m, 2H), 1.21 (t, *J* = 7,1 Hz 3H). ^{13}C NMR (100 MHz): δ 172.4, 145.9, 142.2, 132.2, 130.2, 129.5, 118.9, 113.7, 110.9, 61.5, 57.4, 38.5, 14.2. MS, m/z (relative intensity): 294 ($[M]^+$, 11), 221 ($[M\text{-}CO_2Et]^+$, 34), 178 ($[M\text{-}NCPhCH_2]^+$, 100), 150 (13), 132 (6), 118 (12), 104 (60), 77 ($[C_6H_5]^+$, 15). HRMS Calcd. for $C_{18}H_{18}N_2O_2Na$ $[M+Na]^+$: 317.1266, found: 317.1272.

Ethyl 3-(3-fluorophenyl)-2-(4-methoxyphenylamino)propanoate (1o)[*]:



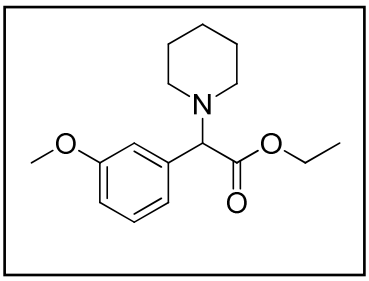
Orange oil. m = 2.13 g (67%). ATR-FTIR (neat, cm^{-1}): 3365, 2936, 2835, 2588, 1733, 1511, 1175, 1139, 1030, 823, 785. ^{1}H NMR (400 MHz): δ 7.26-7.20 (m, 1H), 6.97-6.83 (m, 3H), 6.83-6.73 (m, 4H), 4.29-4.25 (m, 1H), 4.05 (q, *J* = 7.1 Hz, 2H), 3.72 (s, 3H), 3.26-3.10 (m, 2H), 1.09 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz): δ 171.7, 162.7 (d, *J* = 245.9 Hz), 154.6, 138.6 (d, *J* = 7.4 Hz), 137.0, 129.9 (d, *J* = 8.3 Hz), 125.1 (d, *J* = 2.9 Hz), 117.8, 116.3 (d, *J* = 21.3 Hz), 114.9, 113.9 (d, *J* = 21.0 Hz), 61.4, 60.7, 55.6, 37.8, 14.0. ^{19}F NMR (376 MHz): δ –113.30. MS, m/z (relative intensity): 317 ($[M]^+$, 18), 299 (11), 244 ($[M\text{-}CO_2Et]^+$, 15), 226 (7), 208 ($[M\text{-}FPhCH_2]^+$, 100), 162 (12), 134 (95), 109 (5). HRMS Calcd. for $C_{18}H_{21}FNO_3$ $[M+H]^+$: 318.1505, found: 318.1519.

Ethyl 2-(4-methoxyphenyl)-2-(piperidin-1-yl)acetate (2a)[*]:



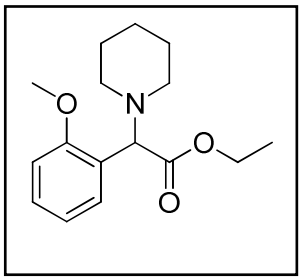
Yellow oil. m = 0.86 g (62%). ATR-FTIR (neat, cm^{-1}): 2633, 1731, 1610, 1510, 1245, 1151, 1067, 835. ^{1}H NMR (400 MHz): δ 7.28 (d, *J* = 8.7 Hz, 2H), 6.79 (d, *J* = 8.7 Hz, 2H), 4.16-4.00 (m, 2H), 3.81 (s, 1H), 3.73 (s, 3H), 2.45-2.20 (m, 4H), 1.55-1.47 (m, 4H), 1.38-1.32 (m, 2H), 1.13 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz): δ 172.1, 159.5, 130.0, 128.3, 113.8, 74.4, 60.7, 55.3, 52.4, 25.8, 24.4, 14.2. MS, m/z (relative intensity): 204 ($[M\text{-}CO_2Et]^+$, 100), 136 (5), 121 (59). HRMS Calcd. for $C_{16}H_{24}NO_3$ $[M+H]^+$: 278.1756, found: 278.1745.

Ethyl 2-(3-methoxyphenyl)-2-(piperidin-1-yl)acetate (2b)[*]:



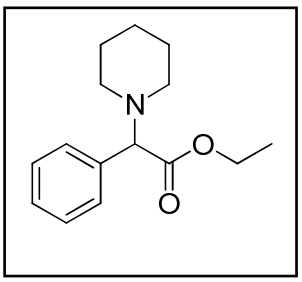
Orange oil. m = 0.84 g (60%). ATR-FTIR (neat, cm^{-1}): 2934, 2835, 2758, 1732, 1254, 1152, 1029, 693. ^{1}H NMR (400 MHz): δ 7.17 (d, *J* = 7.8 Hz, 1H), 7.01 (s, 1H), 6.95 (d, *J* = 7.8 Hz, 1H), 6.79 (dd, *J* = 8.2, *J* = 2.6 Hz, 1H), 4.16-4.04 (m, 3H), 3.75 (s, 3H), 2.51-2.41 (m, 4H), 1.62-1.56 (m, 4H), 1.41-1.36 (m, 2H), 1.14 (t, *J* = 8.2 Hz, 3H). ^{13}C NMR (100 MHz): δ 171.1, 159.8, 136.7, 129.4, 121.5, 114.3, 74.1, 61.0, 55.4, 52.2, 25.3, 24.1, 14.1. MS, m/z (relative intensity): 204 ($[M-CO_2Et]^+$, 100), 121 (14), 91 (2). HRMS Calcd. for $C_{16}H_{24}NO_3$ $[M+H]^+$: 278.1756, found: 278.1750.

Ethyl 2-(2-methoxyphenyl)-2-(piperidin-1-yl)acetate (2c)[*]:



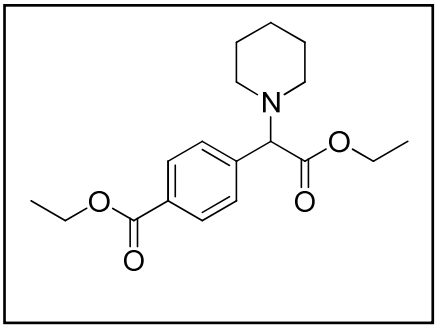
Yellow oil. m = 0.79 g (57%). ATR-FTIR (neat, cm^{-1}): 2933, 2851, 2804, 2757, 1735, 1242, 1180, 1152, 1027, 754. ^{1}H NMR (400 MHz): δ 7.43-7.40 (m, 1H), 7.22-7.18 (m, 1H), 6.90 (td, *J* = 7.5, *J* = 1.0 Hz, 1H), 6.80 (d, *J* = 8.2 Hz, 1H), 4.51 (s, 1H), 4.14-4.03 (m, 2H), 3.74 (s, 3H), 2.43 (br s, 4H), 1.54-1.53 (m, 4H), 1.37-1.33 (m, 2H), 1.13 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz): δ 171.6, 157.6, 129.6, 129.0, 120.6, 110.8, 66.3, 60.5, 55.6, 52.1, 26.0, 24.3, 14.3. MS, m/z (relative intensity): 204 ($[M-CO_2Et]^+$, 100), 188 (8), 172 (2), 121 (10), 91 (3). HRMS Calcd. for $C_{16}H_{24}NO_3[M+H]^+$: 278.1756, found: 278.1748.

Ethyl 2-phenyl-2-(piperidin-1-yl)acetate (2d)[8]:



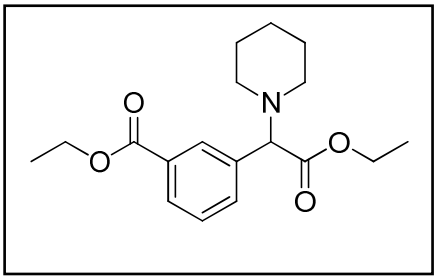
Orange oil. m = 1.09 g (88%). ATR-FTIR (neat, cm^{-1}): 3029, 2933, 2851, 2801, 2758, 1731, 1210, 1150, 1116, 1037, 728, 697. ^{1}H NMR (400 MHz): δ 7.38-7.35 (m, 2H), 7.25-7.19 (m, 3H), 4.13-4.01 (m, 2H), 3.88 (s, 1H), 2.33-2.31 (m, 4H), 1.54-1.49 (m, 4H), 1.38-1.32 (m, 2H), 1.12 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (100 MHz): δ 171.8, 136.4, 128.8, 128.4, 128.1, 75.0, 60.7, 52.4, 25.8, 24.4, 14.2. MS, m/z (relative intensity): 174 ($[M-CO_2Et]^+$, 100), 117 (7), 91 (53). HRMS Calcd. for $C_{15}H_{22}NO_2$ $[M+H]^+$: 248.1651, found: 248.1634.

Ethyl 4-(2-ethoxy-2-oxo-1-(piperidin-1-yl)ethyl)benzoate (2e)[*]:



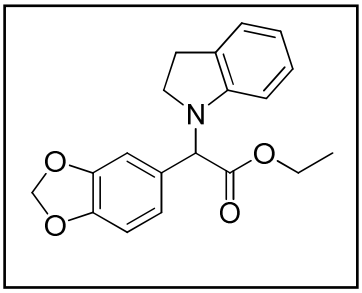
Yellow oil. m = 1.55 g (97%). ATR-FTIR (neat, cm^{-1}): 2980, 2935, 2853, 2805, 2759, 1717, 1272, 1152, 1103, 1022, 775. ^{1}H NMR (400 MHz): δ 7.94 (d, *J* = 8.2 Hz, 2H), 7.46 (d, *J* = 8.2 Hz, 2H), 4.29 (q, *J* = 7.1 Hz, 2H), 4.14-4.03 (m, 2H), 3.97 (s, 1H), 2.33 (br s, 4H), 1.54-1.50 (m, 4H), 1.38-1.30 (m, 5H), 1.14 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz): δ 171.2, 166.4, 141.5, 130.3, 129.7, 128.8, 74.7, 61.0 (2 peaks), 52.4, 25.8, 24.3, 14.4, 14.1. MS, m/z (relative intensity): 246 ($[M-CO_2Et]^+$, 100), 218 (31), 135 (5). HRMS Calcd. for $C_{18}H_{26}NO_4$ $[M+H]^+$: 320.1862, found: 320.1858.

Ethyl 3-(2-ethoxy-2-oxo-1-(piperidin-1-yl)ethyl)benzoate (2f)[*]:



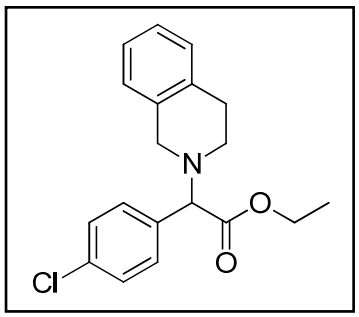
Yellow oil. m = 0.87 g (54%). ATR-FTIR (neat, cm^{-1}): 2980, 2935, 2852, 2805, 2759, 1718, 1153, 1108, 1081, 744. ^{1}H NMR (400 MHz): δ 7.99 (s, 1H), 7.92 (d, *J* = 7.9 Hz, 1H), 7.63 (d, *J* = 7.9 Hz, 1H), 7.35 (t, *J* = 7.9 Hz, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 4.17-3.98 (m, 2H), 3.97 (s, 1H), 2.33 (br s, 4H), 1.56-1.50 (m, 4H), 1.38-1.31 (m, 5H), 1.14 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz): δ 171.4, 166.4, 133.1, 130.7, 130.0, 129.4, 128.6, 74.6, 61.1, 52.3, 25.8, 24.3, 14.4, 14.2. MS, m/z (relative intensity): 246 ($[M\text{-}CO_2Et]^+$, 100), 218 (25). HRMS Calcd. for $C_{18}H_{26}NO_4$ $[M+H]^+$: 320.1862, found: 320.1862.

Ethyl (benzo[1,3]dioxol-5-yl)-(2,3-dihydro-indol-1-yl)-acetate (2g)[*]:



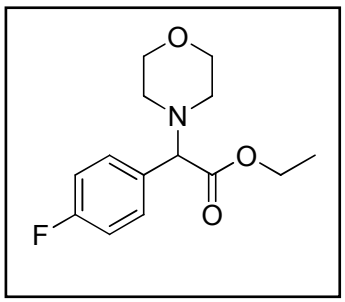
Light brown oil. m = 1.09 g (67%). ATR-FTIR (neat, cm^{-1}): 2979, 1736, 1605, 1503, 1442, 1234, 1173, 1157, 1035, 1025, 933, 743. ^{1}H NMR (400 MHz): δ 6.99-6.92 (m, 2H), 6.84 (s, 1H), 6.77 (d, *J* = 8.1 Hz, 1H), 6.70 (d, *J* = 8.0 Hz, 1H), 6.59 (t, *J* = 7.3 Hz, 1H), 6.34 (d, *J* = 7.8 Hz, 1H), 5.87 (s, 2H), 5.04 (s, 1H), 4.18-4.07 (m, 2H), 3.54 (q, *J* = 8.8 Hz, 1H), 3.12-3.06 (m, 1H), 2.91-2.77 (m, 2H), 1.15 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz): δ 171.3, 150.9, 148.0, 147.7, 130.4, 129.0, 127.2, 124.7, 122.2, 118.4, 109.1, 108.3, 107.0, 101.3, 63.8, 61.1, 50.0, 28.2, 14.3. MS, m/z (relative intensity): 325 (M^+, 13), 253 (15), 252 ($[M\text{-}CO_2Et]^+$, 100), 194 (6), 192 (5), 135 (29), 130 (20), 77 (5). HRMS Calcd. for $C_{19}H_{20}NO_4$ $[M+H]^+$: 326.1392, found: 326.1390.

Ethyl 2-(4-chlorophenyl)-2-(3,4-dihydroisoquinolin-2(1H)-yl)acetate (2h)[*]:



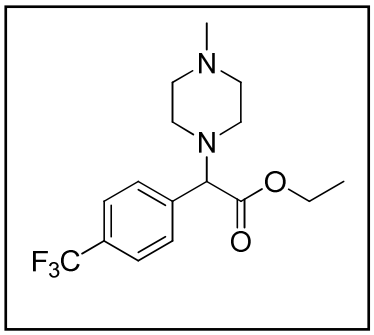
Orange oil. m = 1.09 g (66%). ATR-FTIR (neat, cm^{-1}): 2979, 1732, 1489, 1090, 1015, 744. ^{1}H NMR (400 MHz): 7.39 (d, *J* = 8.5 Hz, 2H), 7.27 (d, *J* = 8.5 Hz, 2H), 7.06-7.01 (m, 3H), 6.87 (d, *J* = 6.9 Hz, 1H), 4.16-4.09 (m, 3H), 3.65-3.55 (m, 2H), 2.82-2.67 (m, 4H), 1.16 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz): 171.2, 134.8, 134.3, 134.2, 134.1, 130.1, 128.9, 128.7, 126.7, 126.3, 125.7, 72.8, 61.2, 53.7, 48.3, 28.8, 14.2. MS, m/z (relative intensity): 256 ($[M\text{-}CO_2Et]^+$, 100), 193 (2), 152 (2), 125 (8), 105 (9), 91 (2). HRMS Calcd. for $C_{19}H_{21}ClNO_2$ $[M+H]^+$: 330.1261, found: 330.1253.

Ethyl 2-(4-fluorophenyl)-2-morpholinoacetate (2i)[*]:



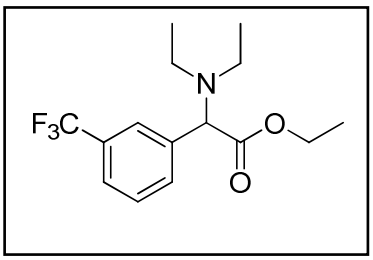
Yellow oil. m = 1.05 g (78%). ATR-FTIR (neat, cm^{-1}): 2957, 2856, 1753, 1507, 1155, 1115, 1029, 808. ^{1}H NMR (400 MHz): δ 7.39-7.35 (m, 2H), 6.99-6.95 (m, 2H), 4.14-4.02 (m, 2H), 3.87 (s, 1H), 3.67-3.65 (m, 4H), 2.38 (br s, 4H), 1.13 (t, *J* =7.2 Hz, 3H). ^{13}C NMR (100 MHz): δ 172.0, 162.8 (d, *J* = 247.4 Hz), 130.5 (d, *J* = 8.1 Hz), 115.6 (d, *J* = 21.5 Hz), 73.7, 66.8, 61.1, 51.5, 14.1. ^{19}F NMR (376 MHz): δ –113.69. MS, m/z (relative intensity): 317 ($[M]^+$, 18), 299 (11), 244 ([M-171.0, 164.0, 161.6, 130.6, 130.5, 115.7-115.5, 73.66.7, 66.1, 51.5, 14.1. ^{19}F NMR (376 MHz): δ –113.51. MS, m/z (relative intensity): 194 ($[M\text{-}CO_2Et]^+$, 100), 123 (13), 109 (15). HRMS Calcd. for $C_{14}H_{19}FNO_3$ $[M+H]^+$: 268.1349, found: 268.1346.

Ethyl 2-(4-methylpiperazin-1-yl)-2-(4-(trifluoromethyl)phenyl)acetate (2j)*:



Yellow oil. m = 0.62 g (37%). ATR-FTIR (neat, cm^{-1}): 2940, 2799, 1735, 1323, 1161, 1122, 1066, 840. ^{1}H NMR (400 MHz): δ 7.55-7.50 (m, 4H), 4.16-4.01 (m, 2H), 3.97 (s, 1H), 2.44 (br s, 8H), 2.24, (s, 3H), 1.14 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz): δ 170.7, 140.1 (q, *J* = 1.3 Hz), 130.6 (q, *J* = 32.4 Hz), 129.1, 125.5 (q, *J* = 3.8 Hz), 124.0 (q, *J* = 273.2 Hz), 73.7, 61.3, 54.8, 50.8, 45.8, 14.1. ^{19}F NMR (376 MHz): δ –62.66. MS, m/z (relative intensity): 330 ($[M]^+$, 17), 257 ($[M\text{-}CO_2Et]^+$, 100), 214 (31), 159 (8), 98 (6), 70 (13). HRMS Calcd. for $C_{16}H_{22}F_3N_2O_2$ $[M+H]^+$: 331.1633, found: 331.1648.

Ethyl 2-(diethylamino)-2-(3-(trifluoromethyl)phenyl)acetate (2k)*:



Yellow oil. m = 1.28 g (84%). ATR-FTIR (neat, cm^{-1}): 2973, 1734, 1447, 1329, 1160, 1123, 1073, 1026, 796, 710, 660. ^{1}H NMR (400 MHz): δ 7.65 (s, 1H), 7.55 (d, *J* = 7.7 Hz, 1H), 7.45 (d, *J* = 7.7 Hz, 1H), 7.35 (t, *J* = 7.7 Hz, 1H), 4.46 (s, 1H), 4.16-4.06 (m, 2H), 2.54 (q, *J* = 7.1 Hz, 4H), 1.14 (t, *J* = 7.1 Hz, 3H), 0.91 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (100 MHz): δ 170.6, 137.8, 131.0, 129.6 (q, *J* = 32.3 Hz), 127.7, 124.4 (q, *J* = 3.8 Hz), 124.1 (q, *J* = 261.4 Hz), 123.6 (q, *J* = 3.8 Hz), 67.7, 59.8, 42.8, 13.1, 11.0. ^{19}F NMR (376 MHz): δ –62.71. MS, m/z (relative intensity): 231 (14), 230 ($[M\text{-}CO_2Et]^+$, 100), 214 (6), 203 (6), 202 (30), 175 (7), 174 (16), 159 (17), 127 (18), 109 (6). HRMS Calcd. for $C_{15}H_{21}F_3NO_2$ $[M+H]^+$: 304.1524, found: 304.1534.

References:

(1) Le Gall, E.; Troupel, M.; Nedelec, J. -Y. *Tetrahedron* **2006**, *62*, 9953-9965.

(2) Katritzky, A. R.; Urogdi, L.; Mayence, A. *Synthesis* **1989**, 323-327.

(3) Hoover, D. J.; Wester, R. T.; Rosati, R. L. Eur. Pat. Appl. (**1988**), EP 266950 A2 19880511.

(4) Rulev, A. Y.; Larina, L. I.; Voronkov, M. G. *Molecules* **2001**, *6*, 892-899

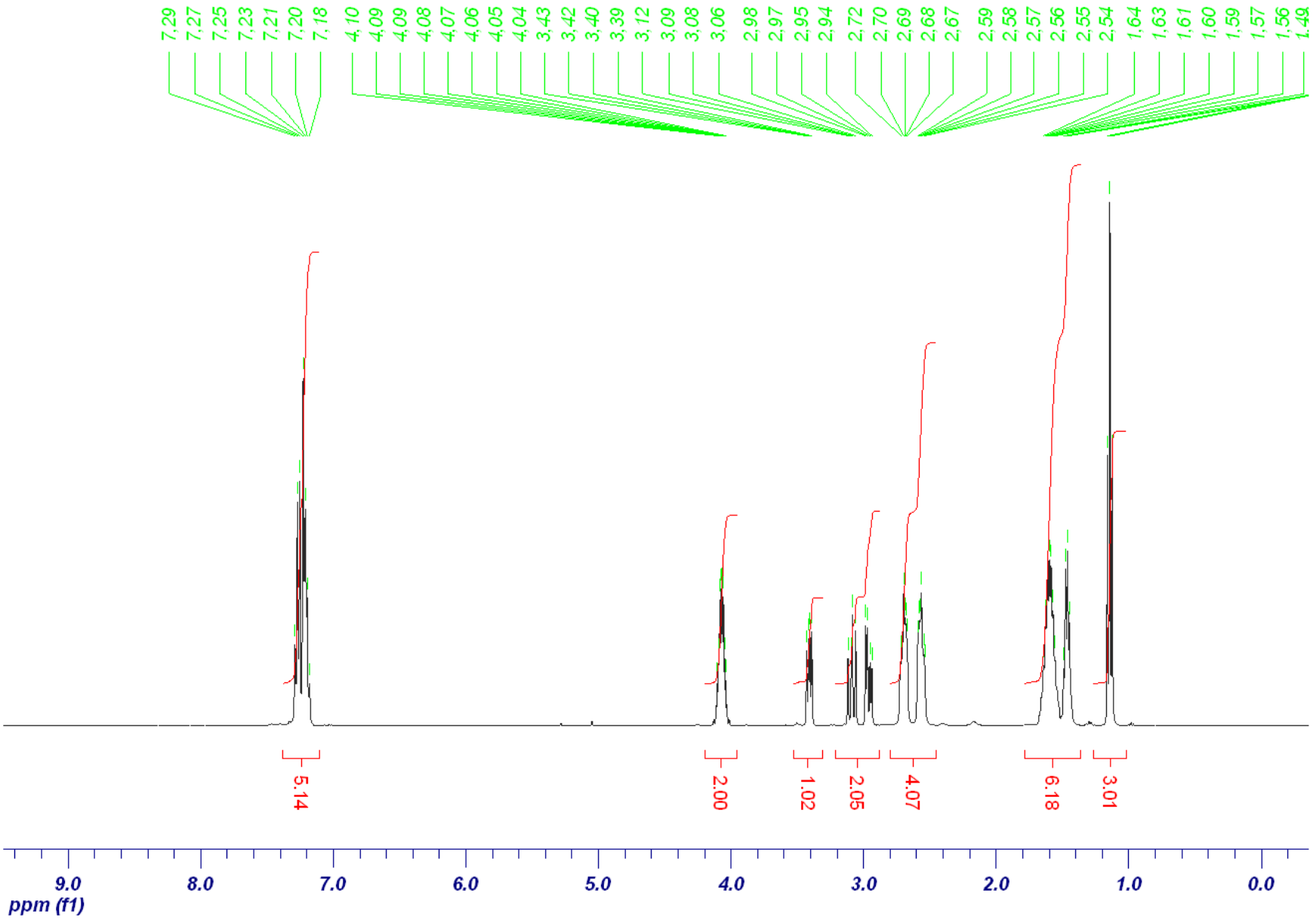
(5) Bernard, J. –M.; Blart, E.; Genet, J. –P.; Lemaire-Audoire, S.; Savignac, M. PCT Int. Appl. (**1994**), WO 9424088 A1 19941027.

(6) Yendapally, R.; Hurdle, J. G.; Carson, E. I.; Lee, R. B.; Lee, R. E. *J. Med. Chem.* **2008**, *51*, 1487-1491.

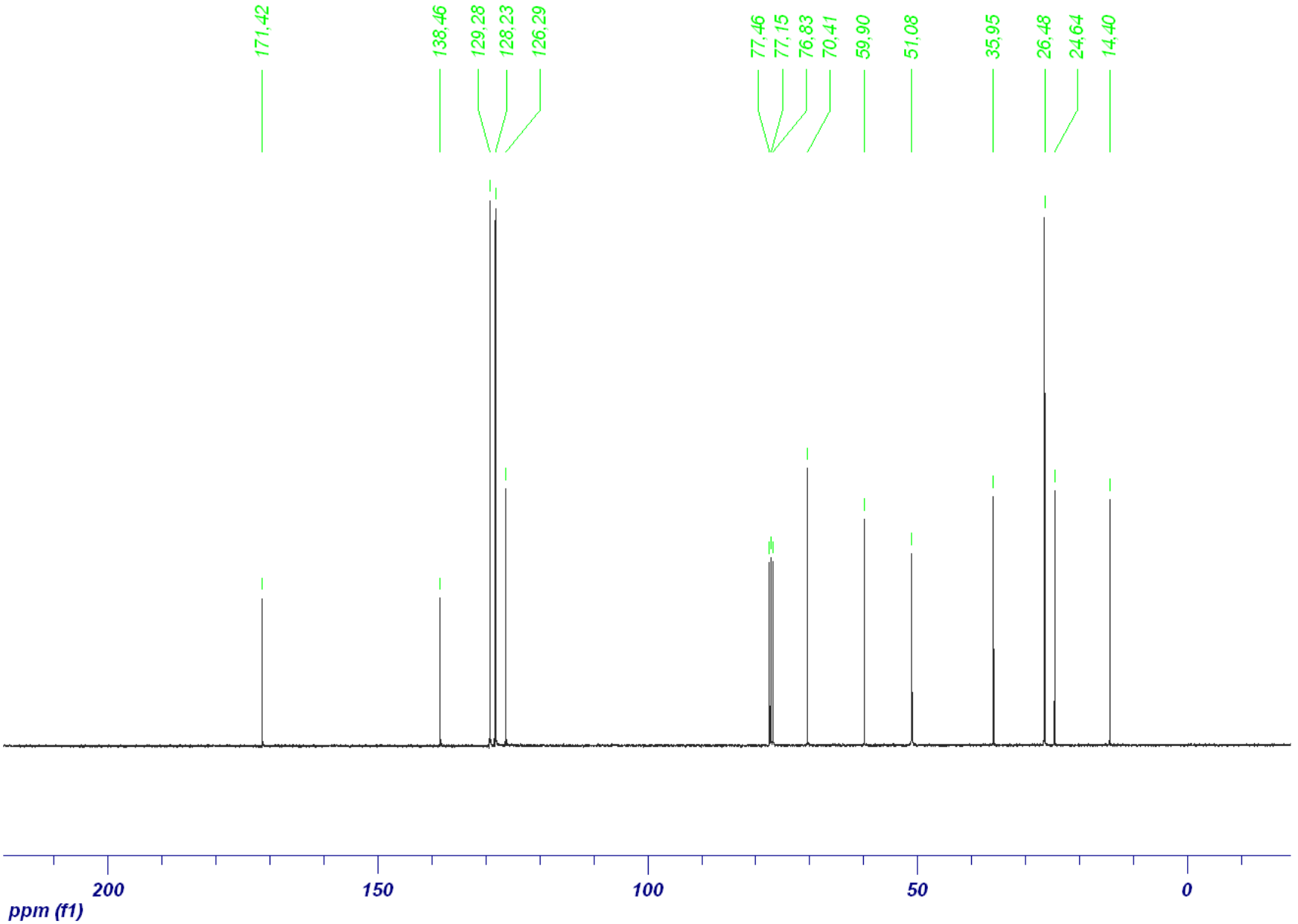
(7) Bachmann, S.; Fielenbach, D.; Jorgensen, K. A. *Org. Biomol. Chem*. **2004**, *2*, 3044-3049

(8) Deng, Q. –H.; Xu, H. –W.; Yuen, A. W. –H.; Xu, Z. –J.; Che, C. –M. *Org. Lett*. **2008**, *10*, 1529-1532.

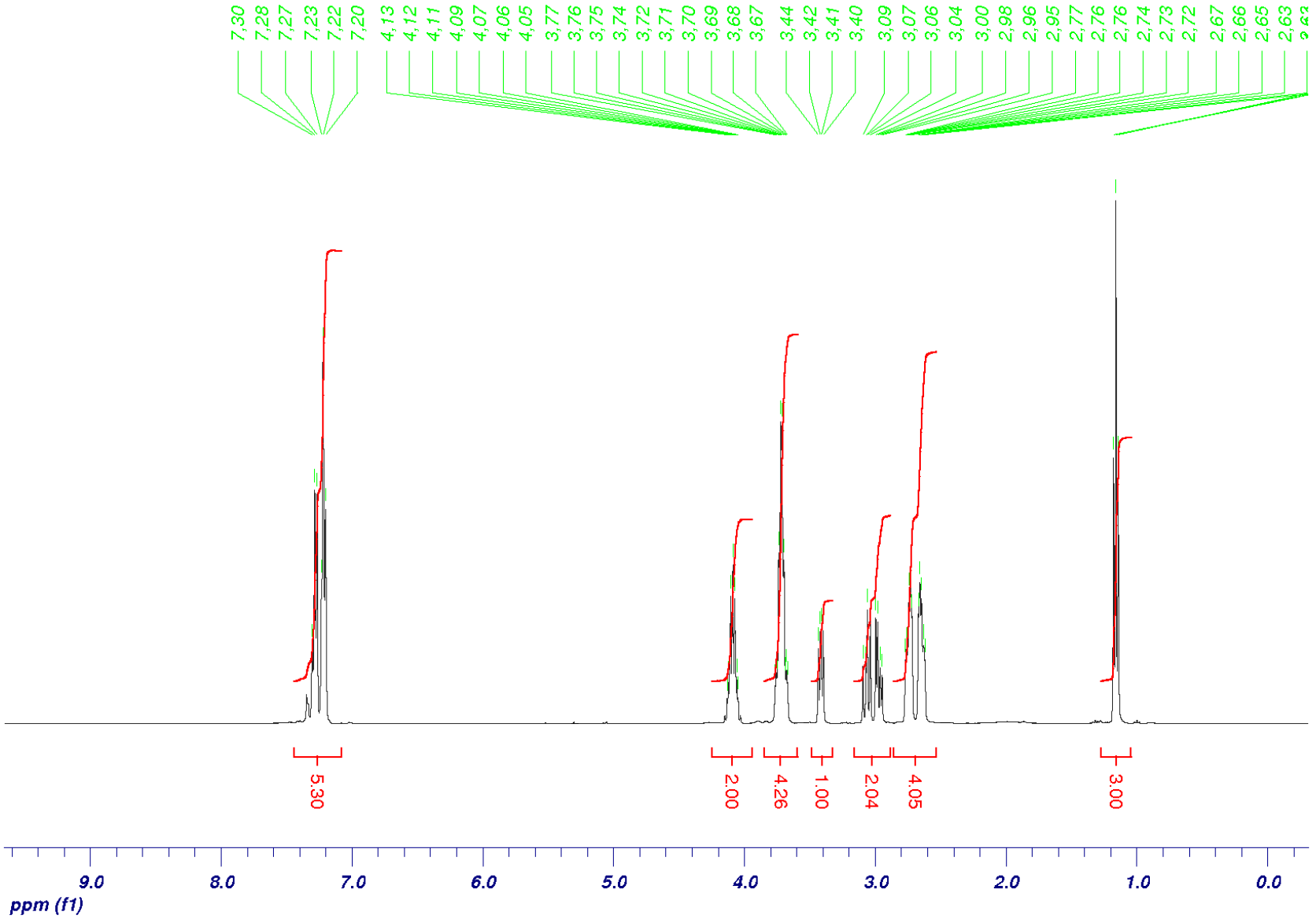
^{1}H NMR spectrum of **1a**



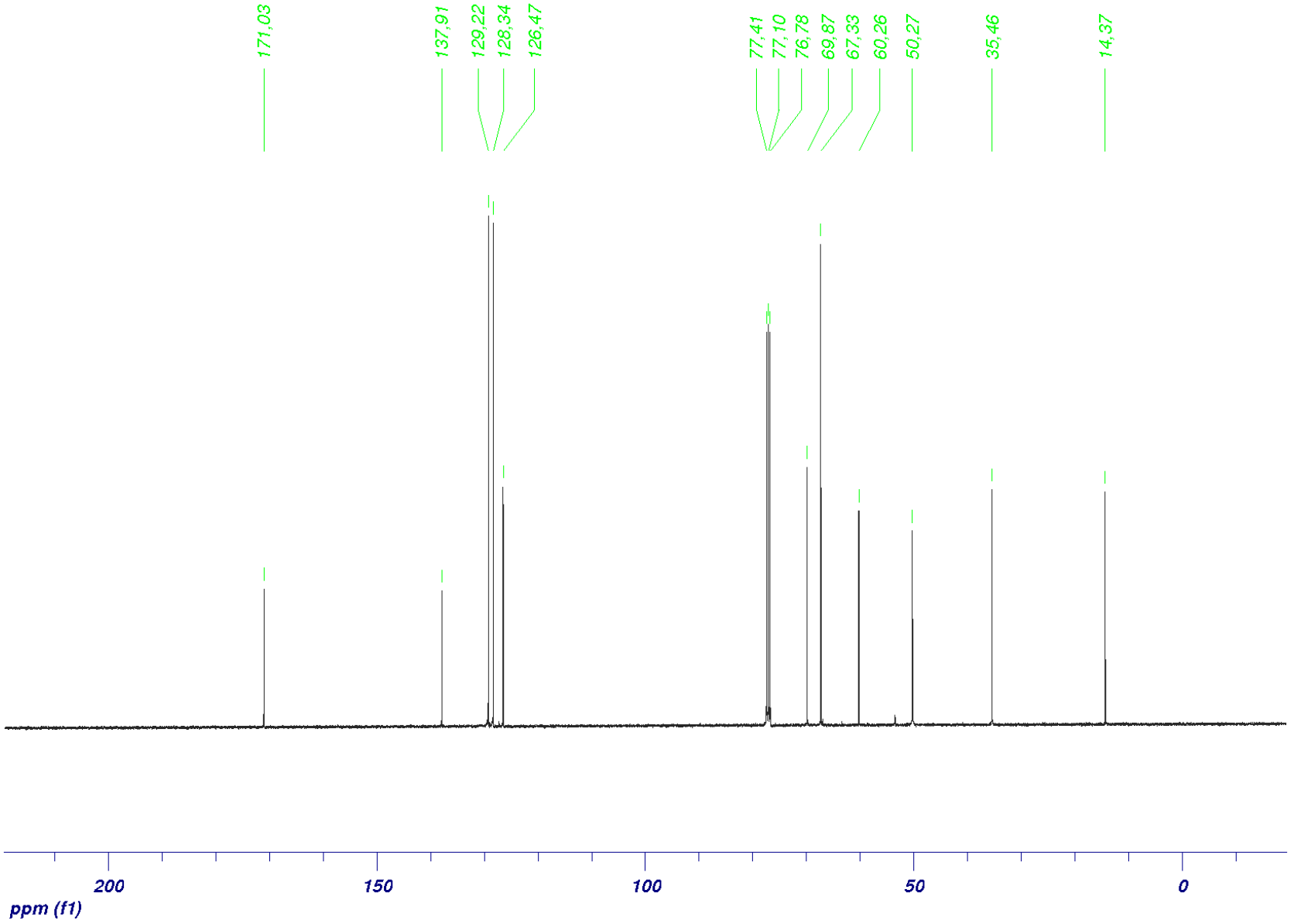
^{13}C NMR spectrum of **1a**



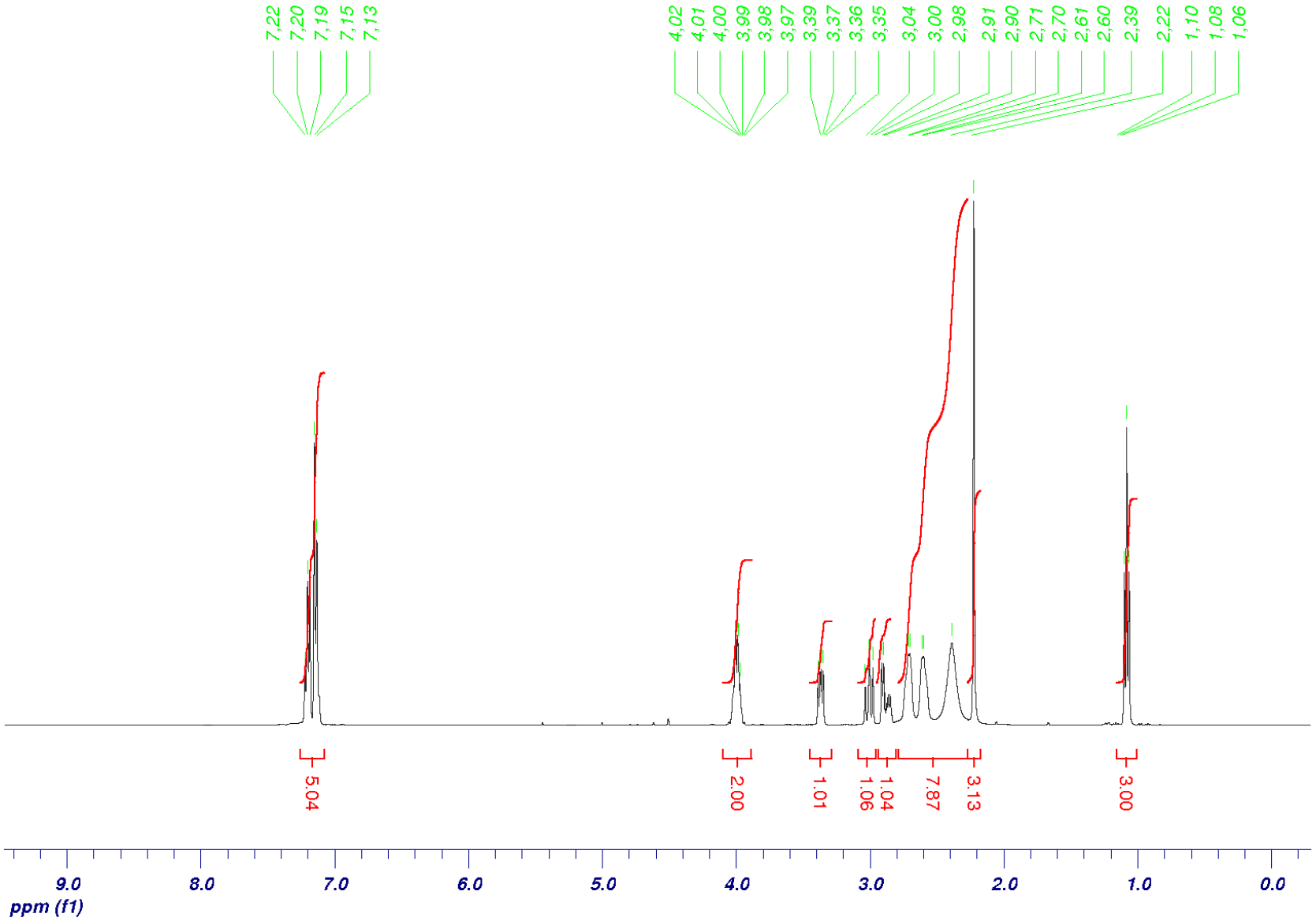
^{1}H NMR spectrum of **1b**



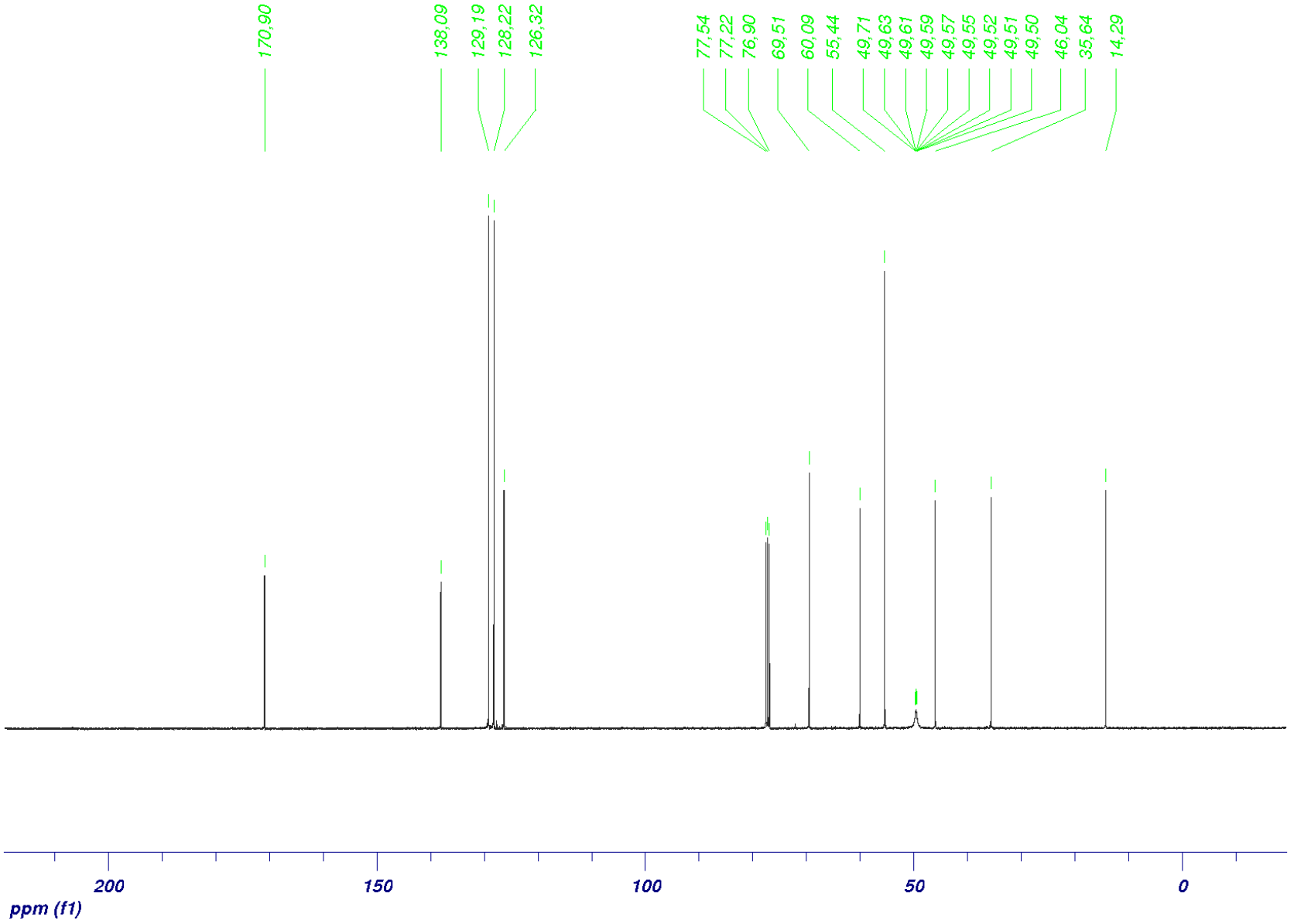
^{13}C NMR spectrum of **1b**



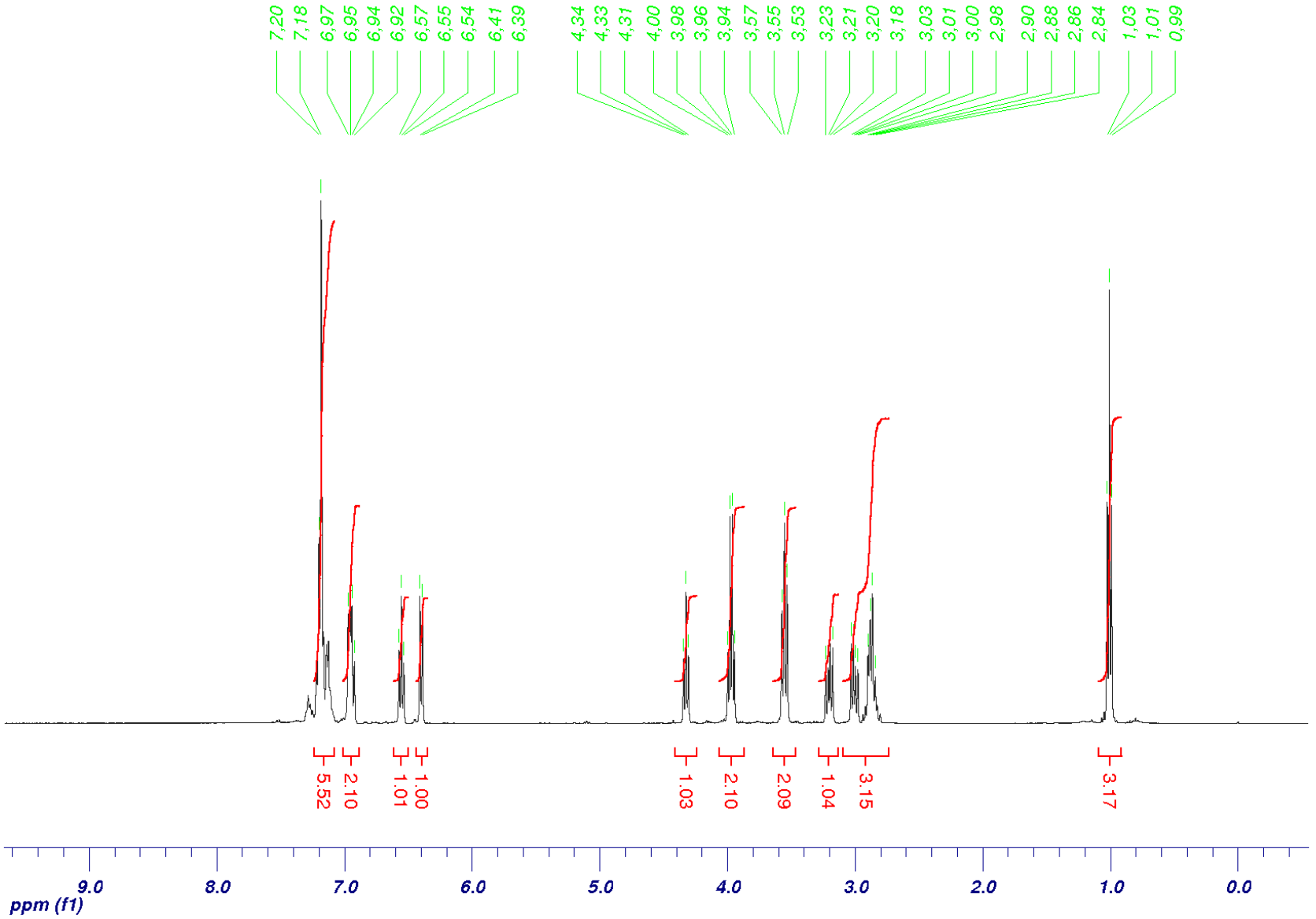
^{1}H NMR spectrum of **1c**



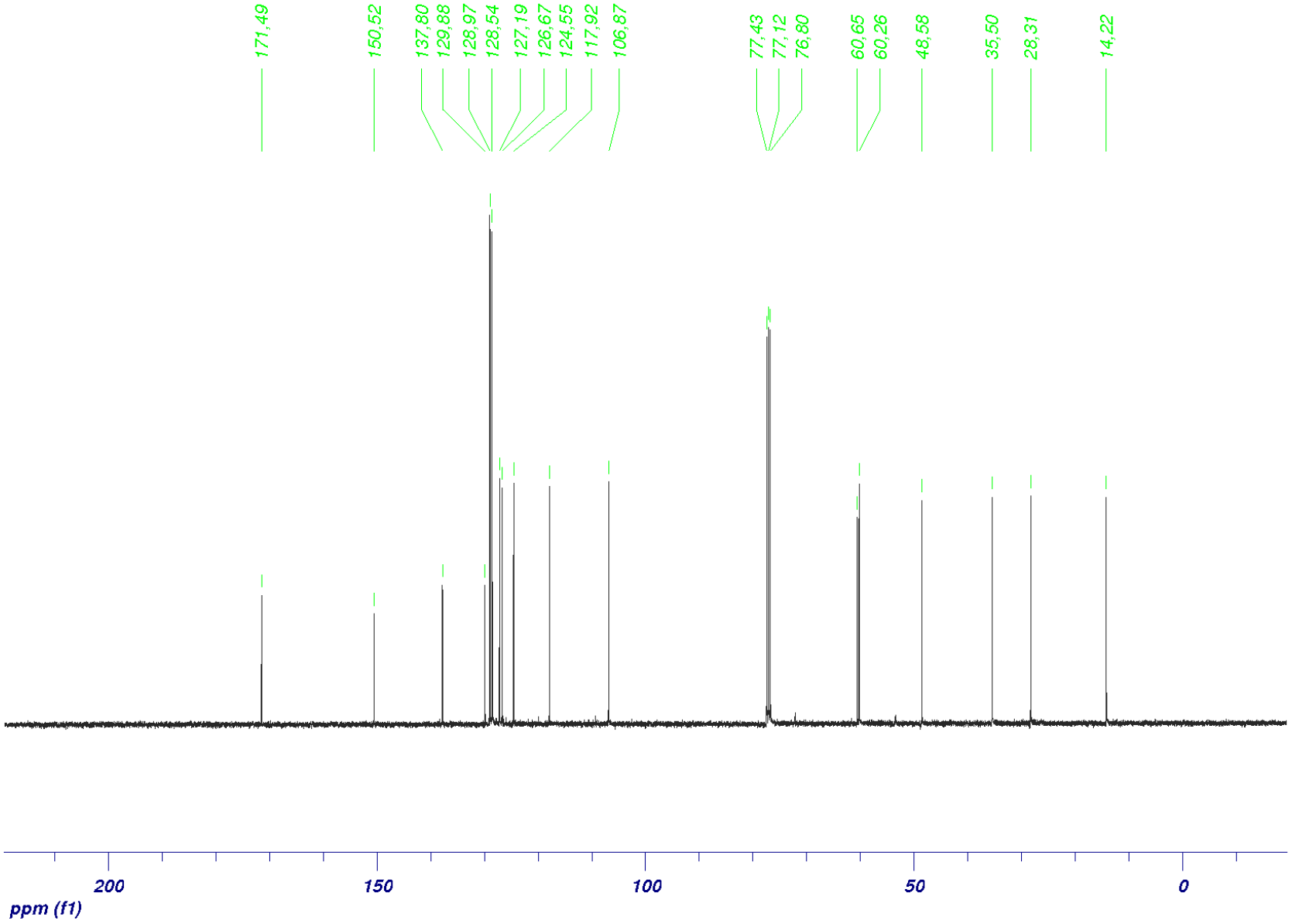
^{13}C NMR spectrum of **1c**



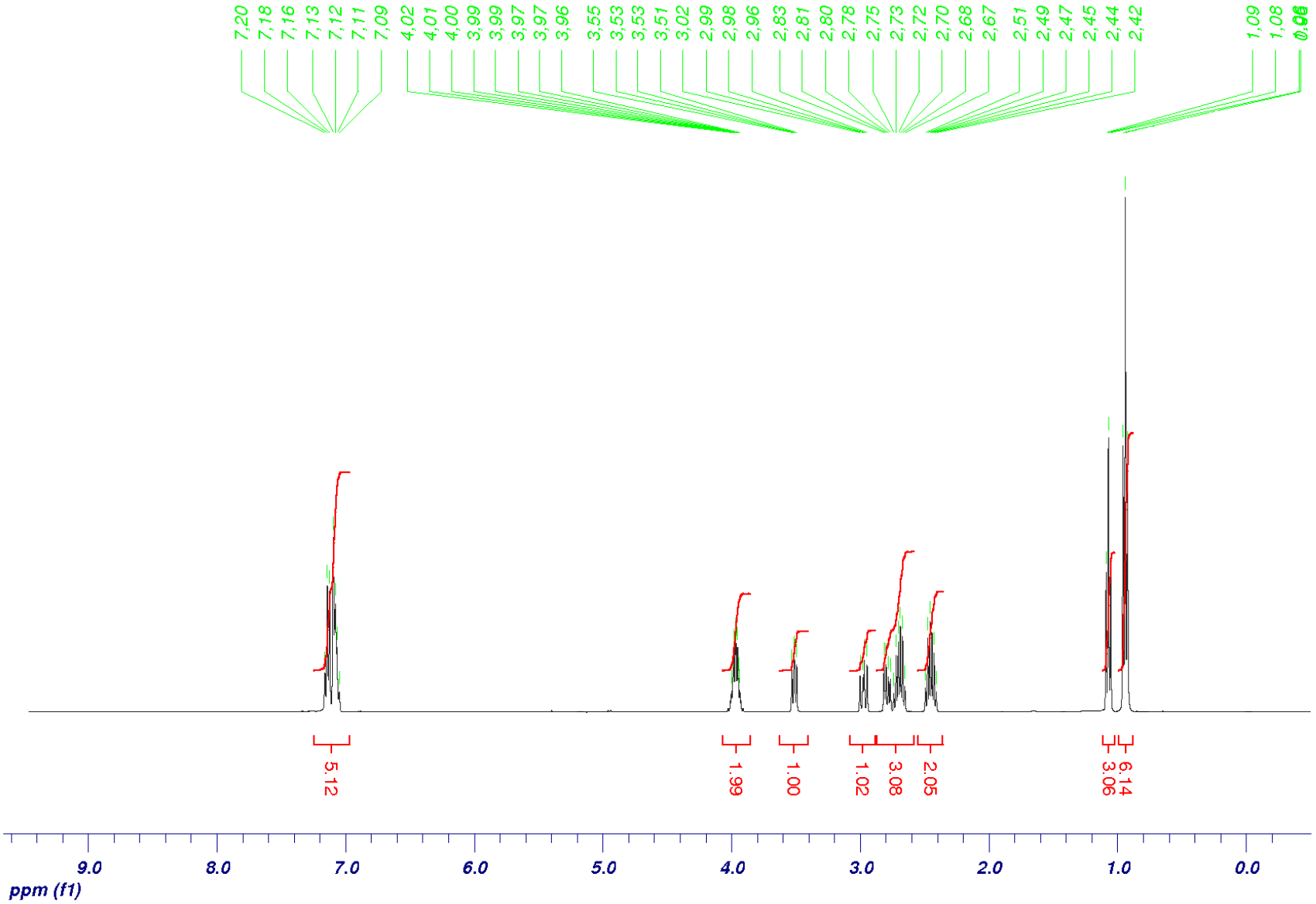
^{1}H NMR spectrum of **1d**



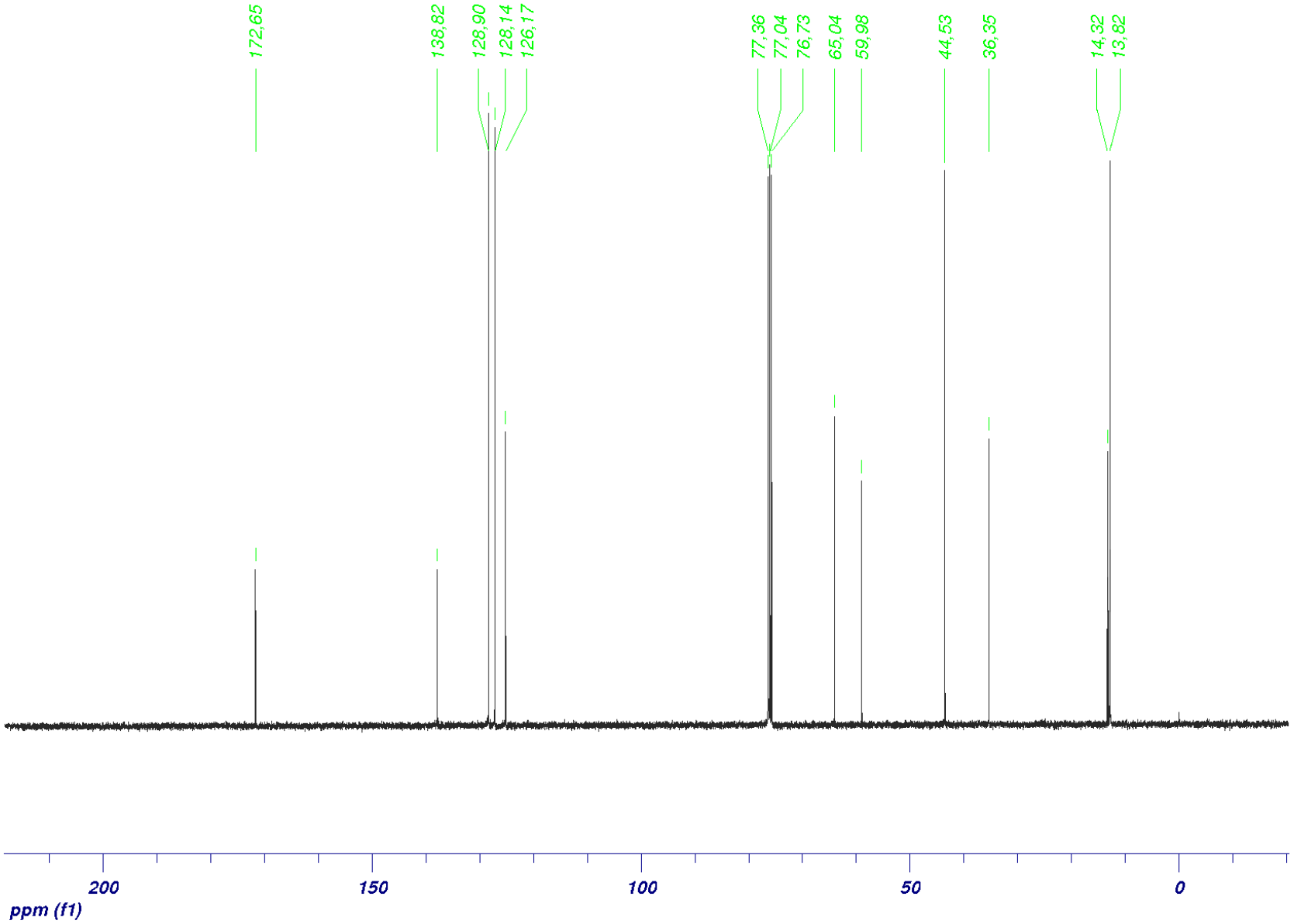
^{13}C NMR spectrum of **1d**



^{1}H NMR spectrum of **1e**



^{13}C NMR spectrum of **1e**



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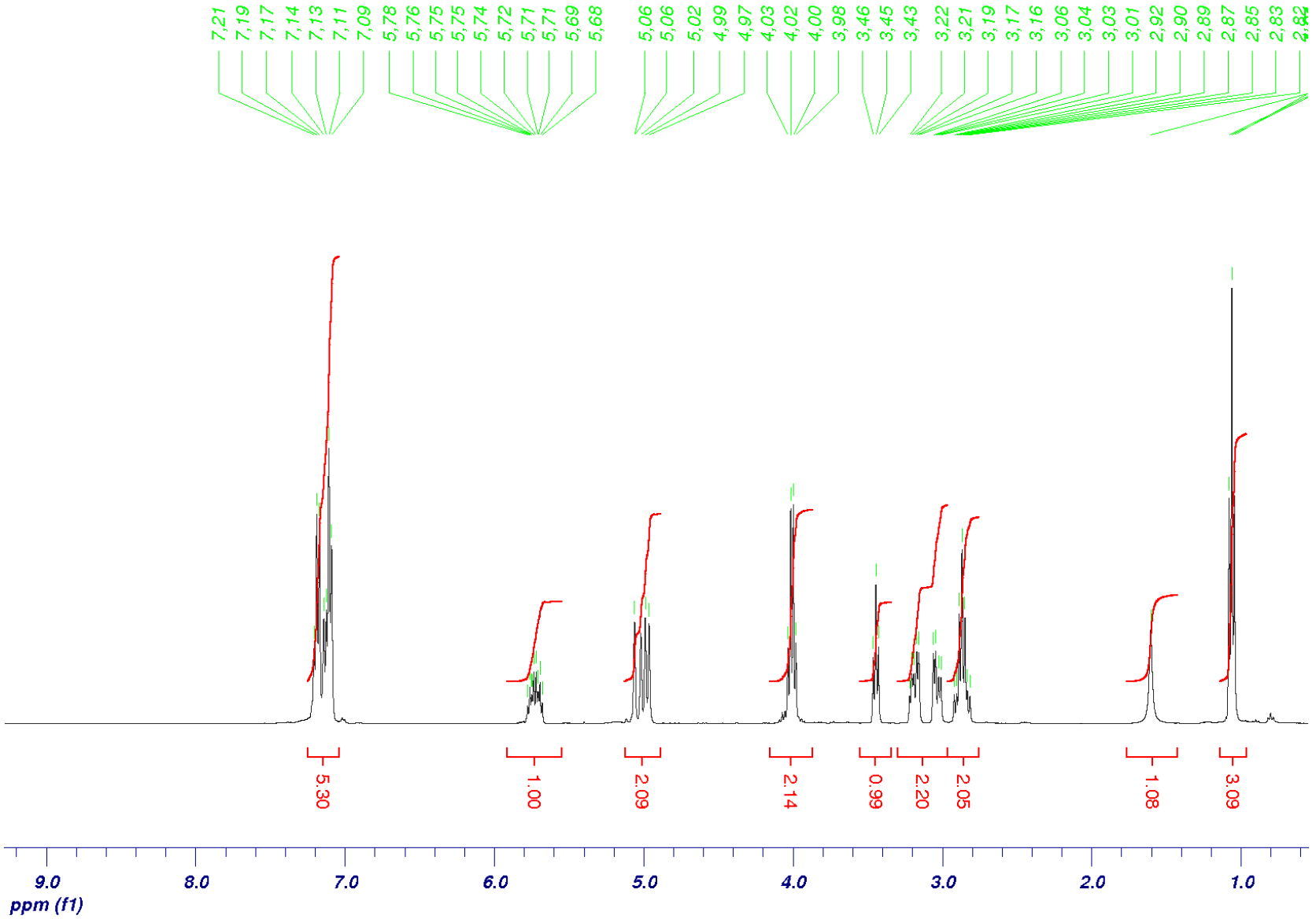
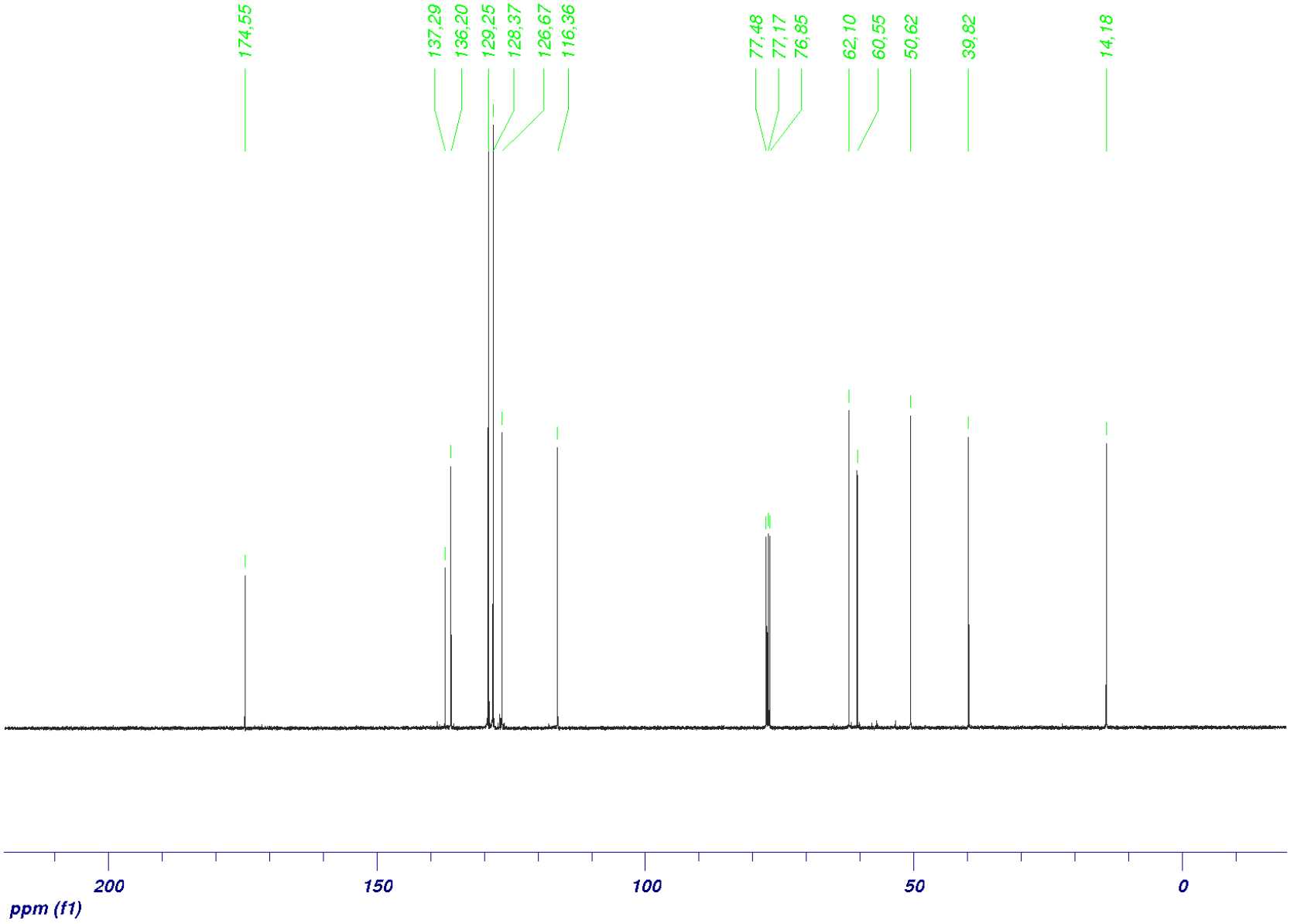
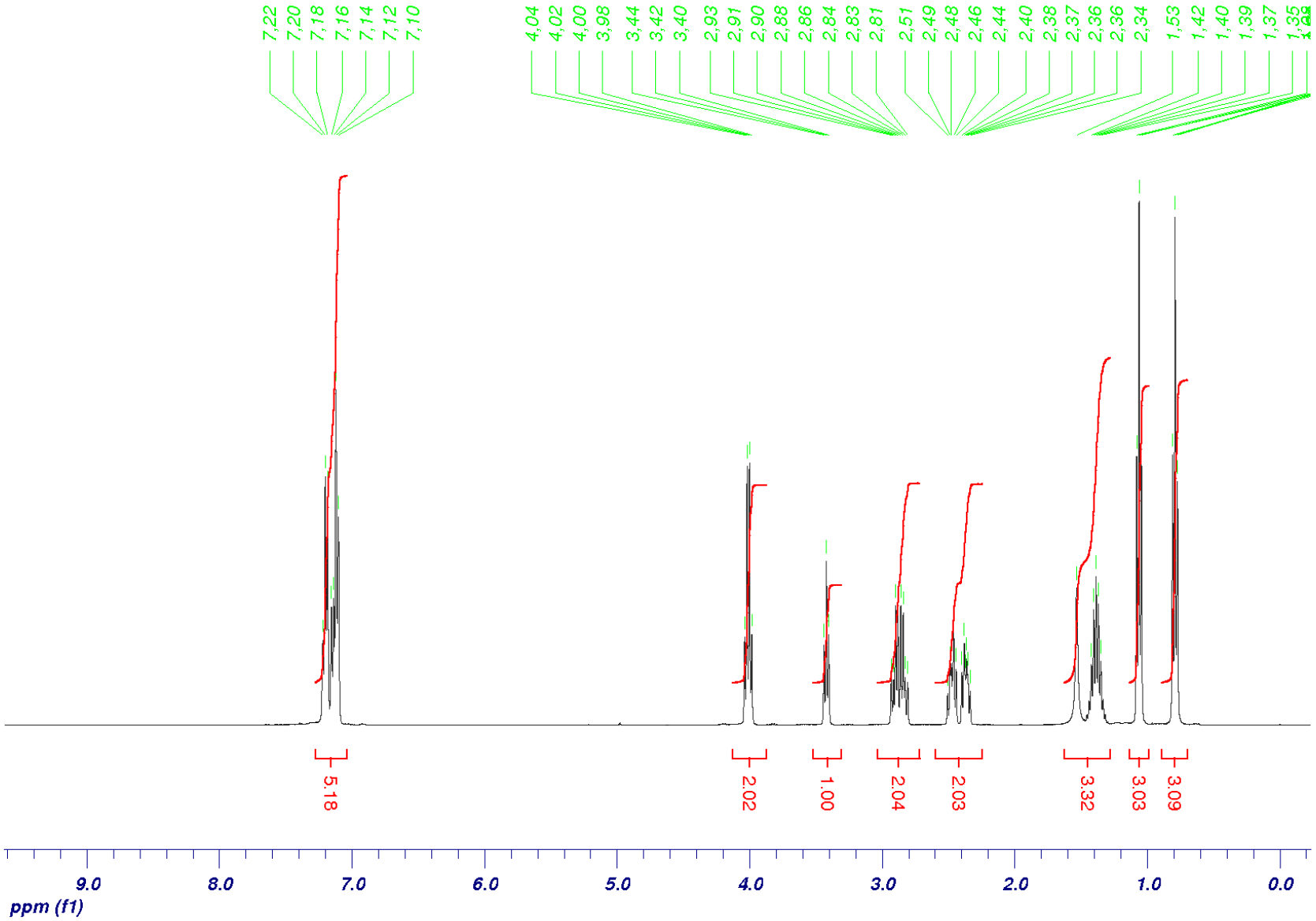


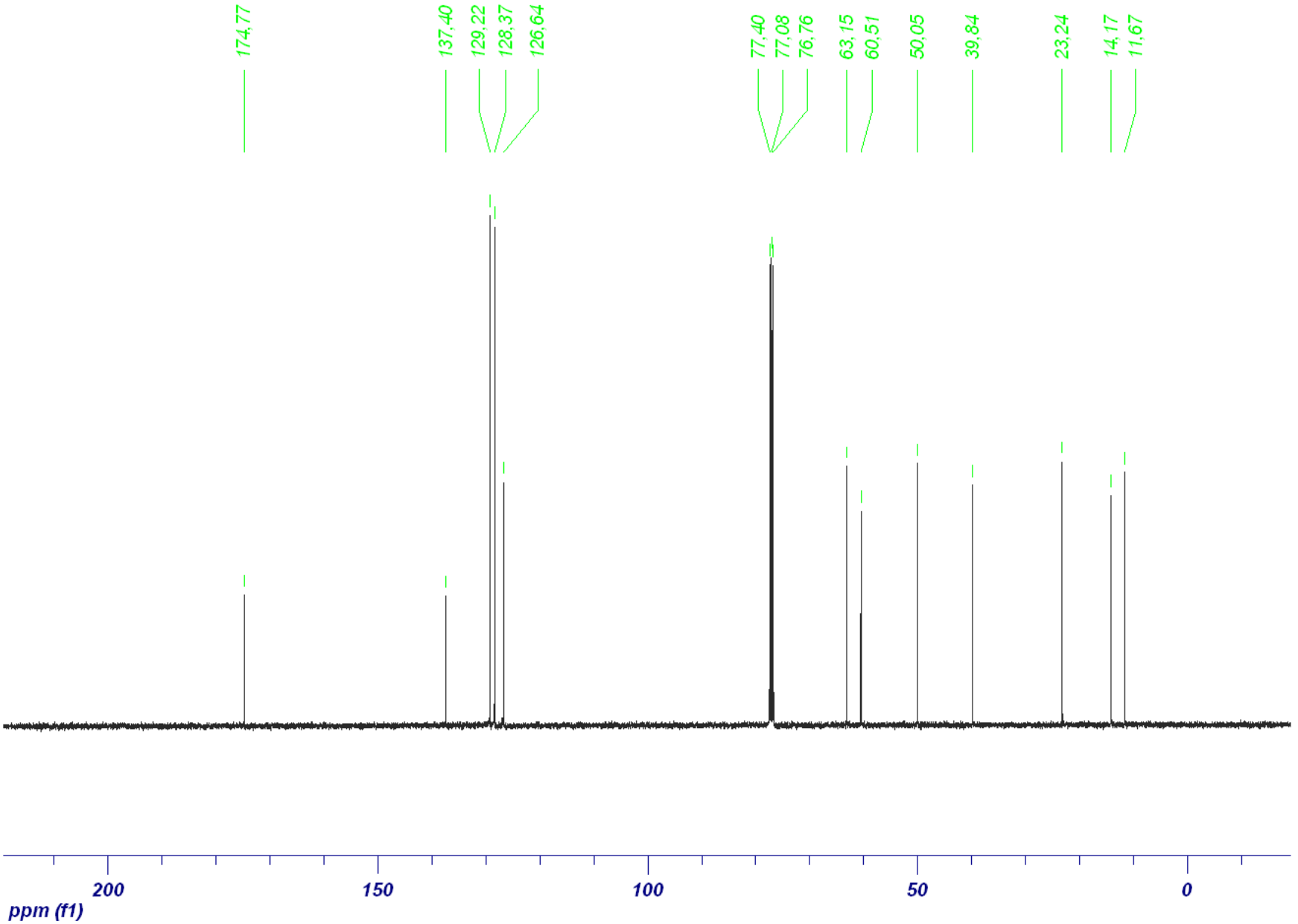
^{13}C NMR spectrum of **1f**



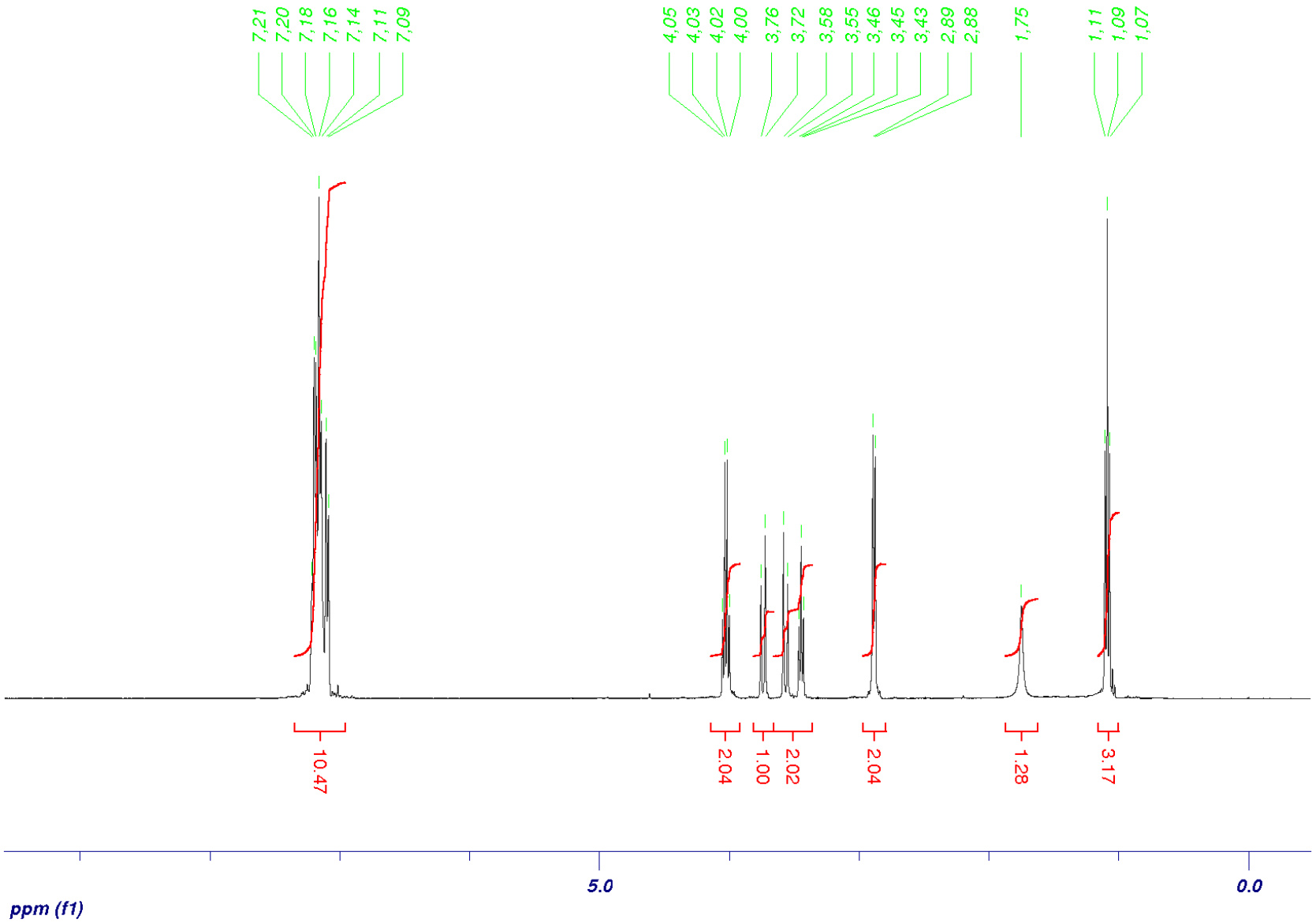
^{1}H NMR spectrum of **1g**



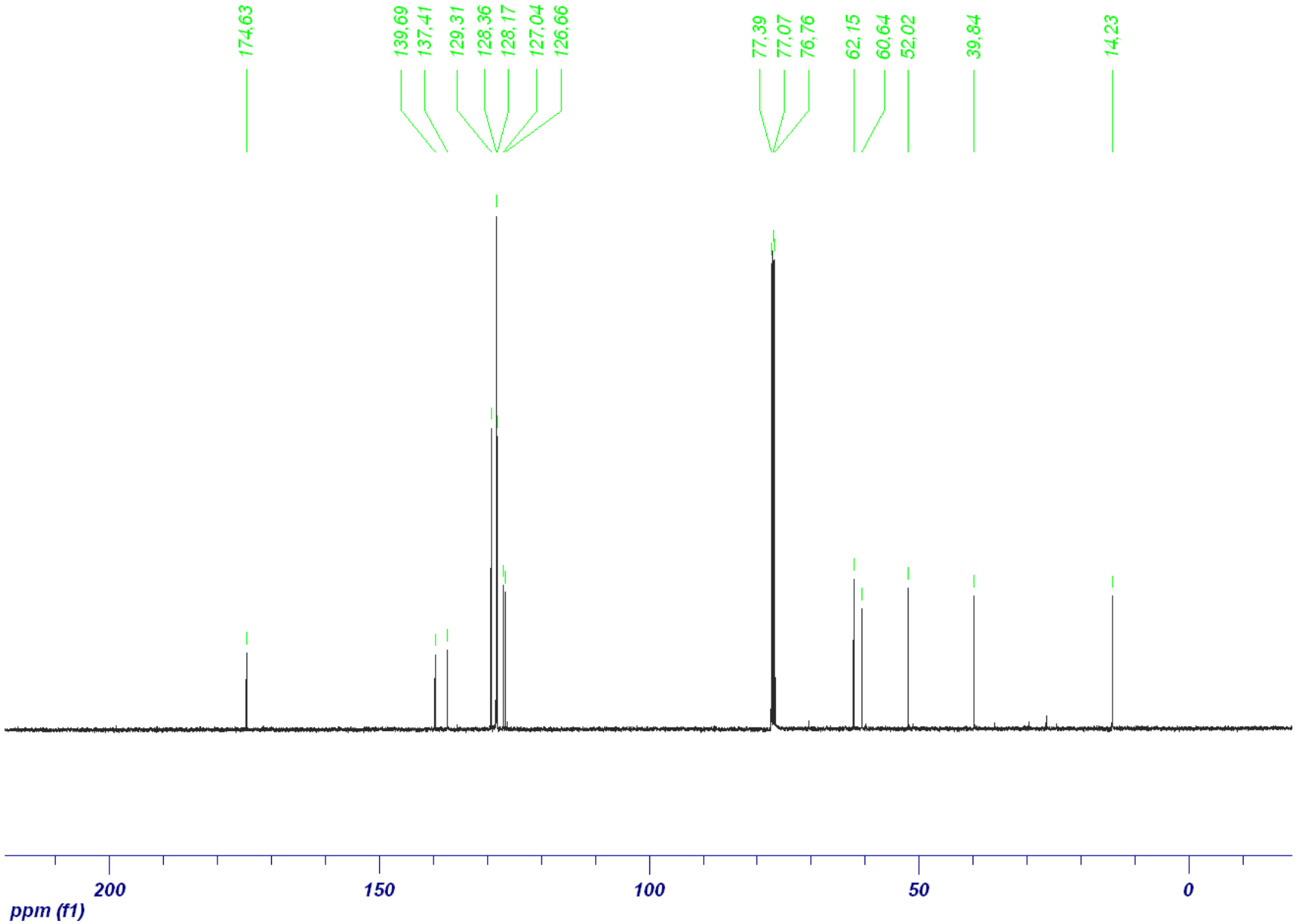
^{13}C NMR spectrum of **1g**



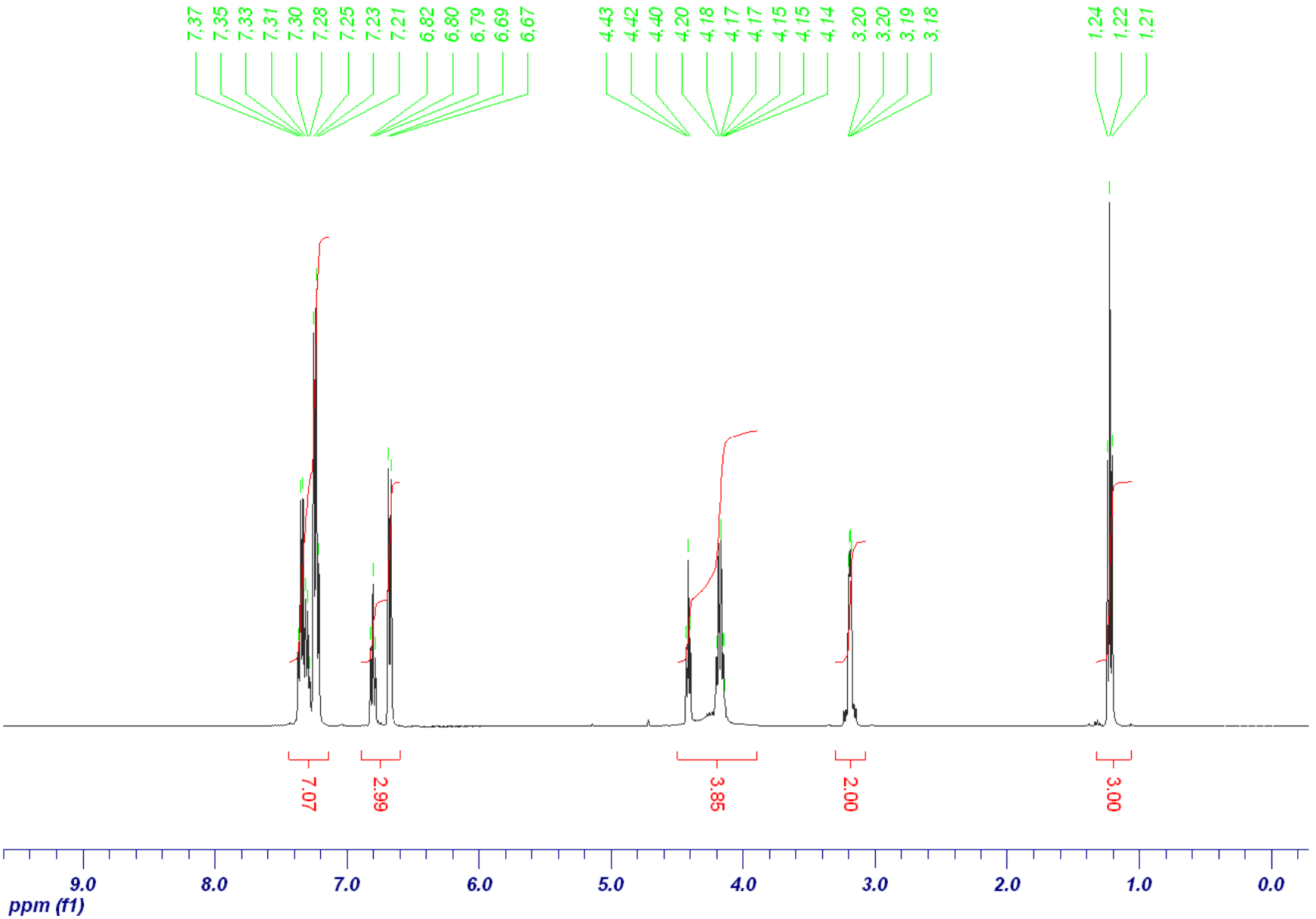
^{1}H NMR spectrum of **1h**



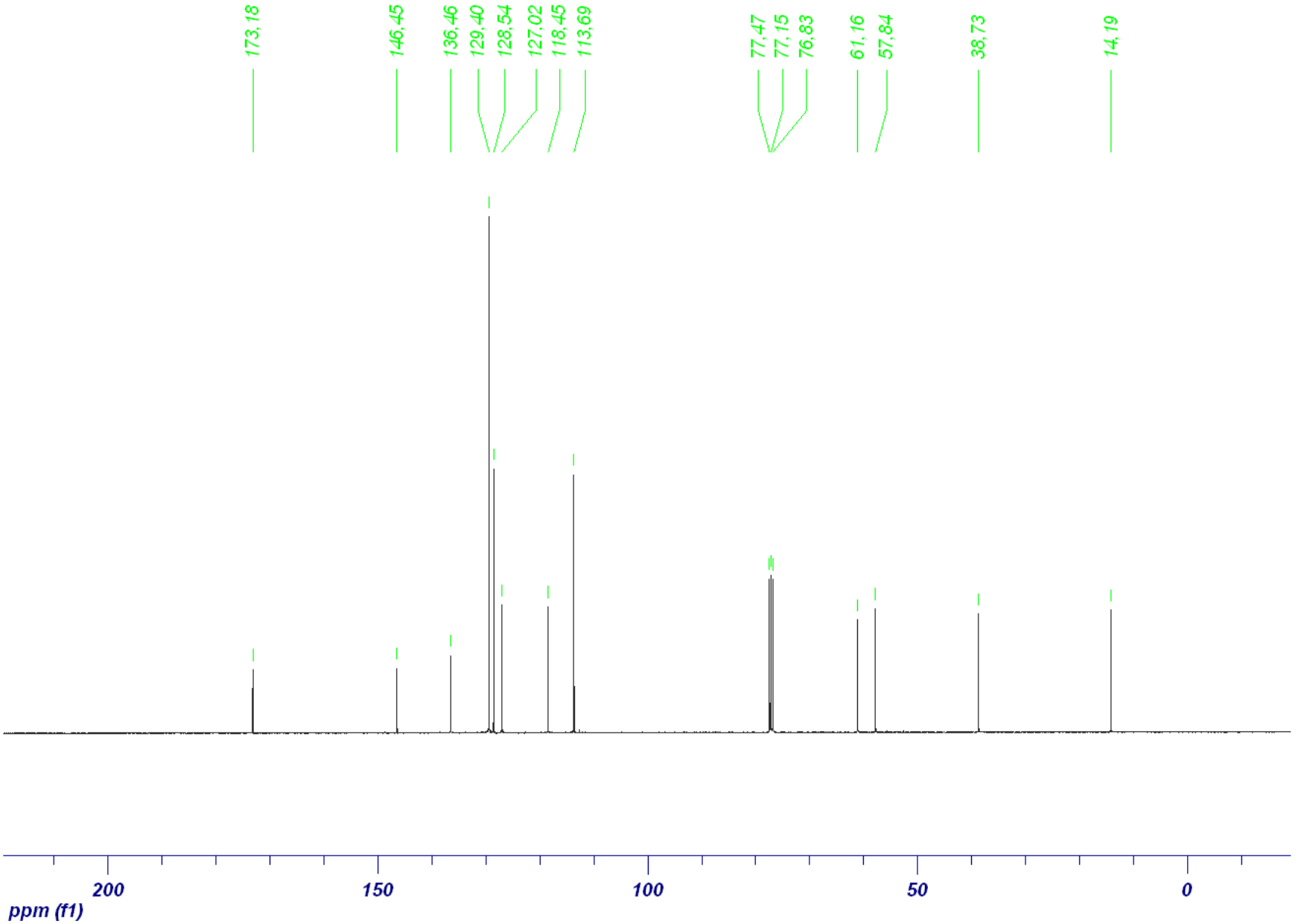
^{13}C NMR spectrum of **1h**



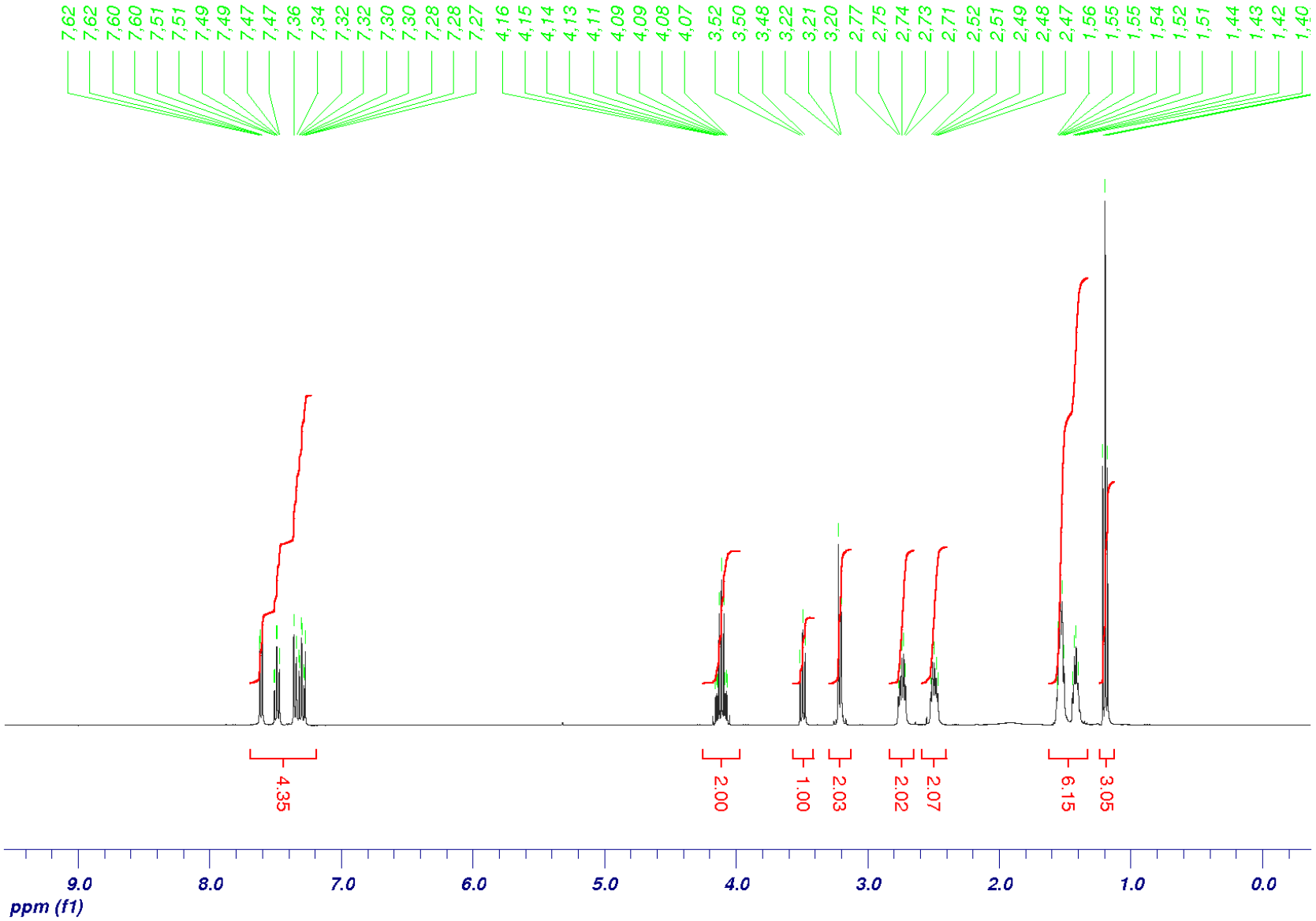
^{1}H NMR spectrum of **1i**



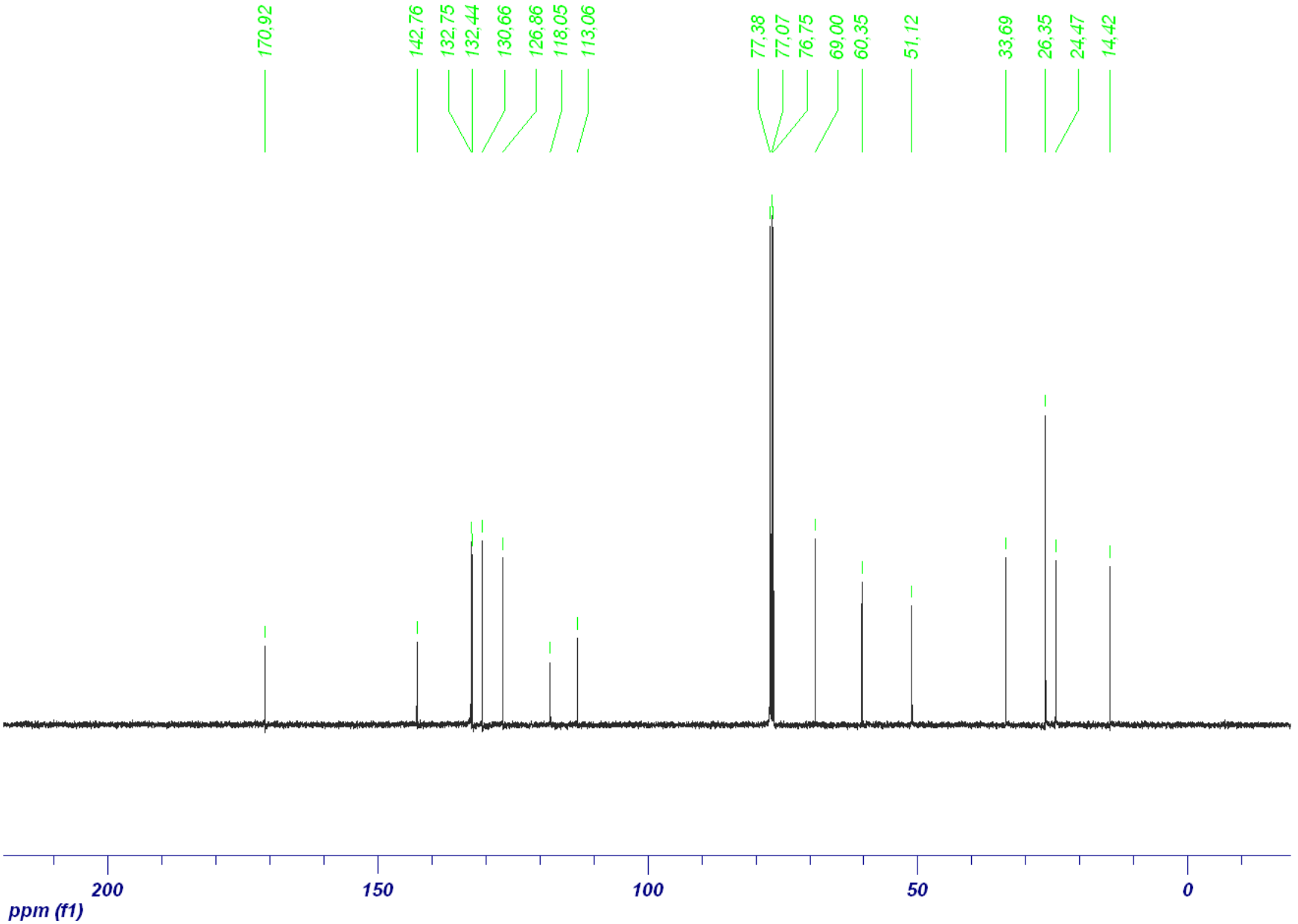
^{13}C NMR spectrum of **1i**



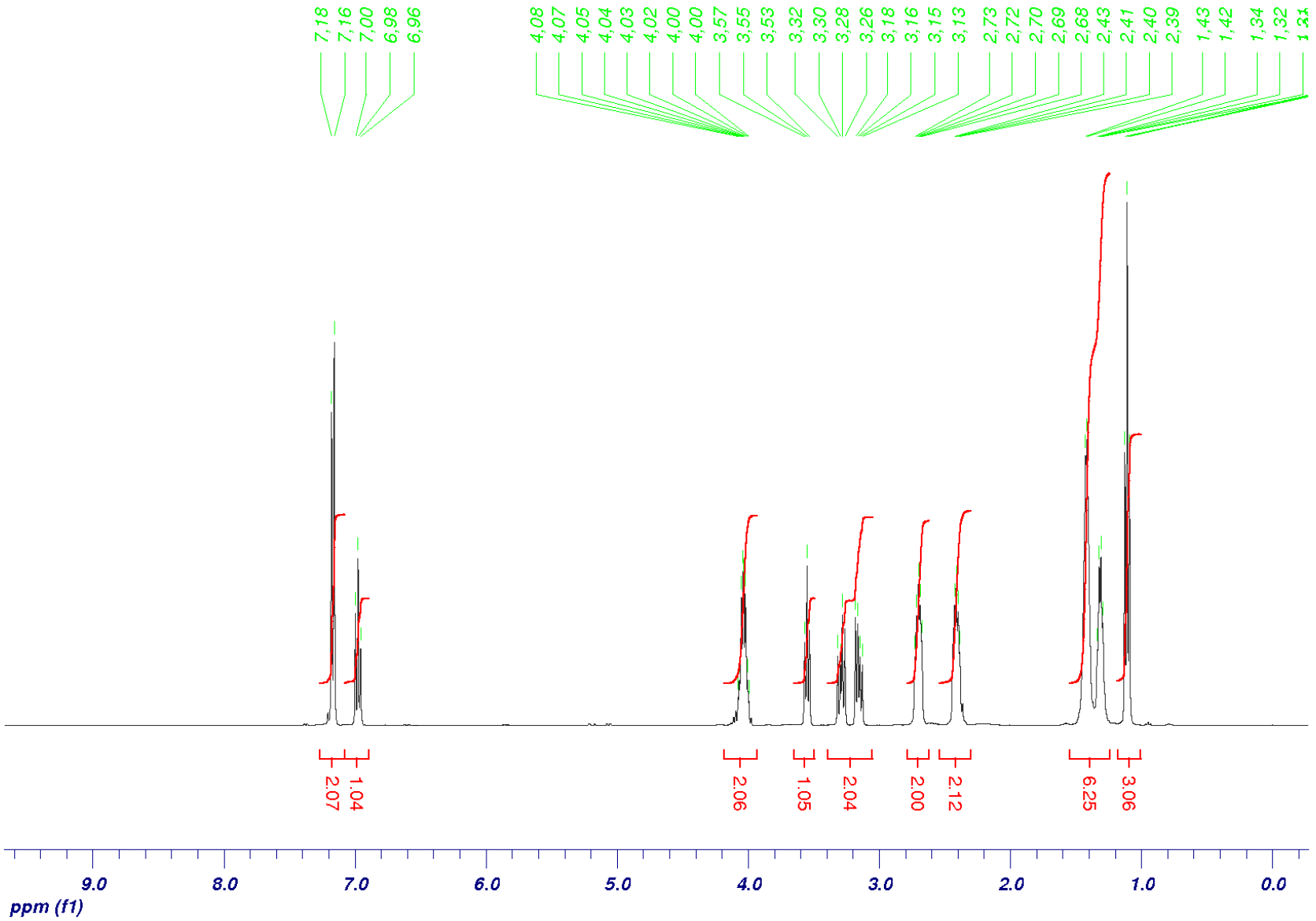
^{1}H NMR spectrum of **1j**



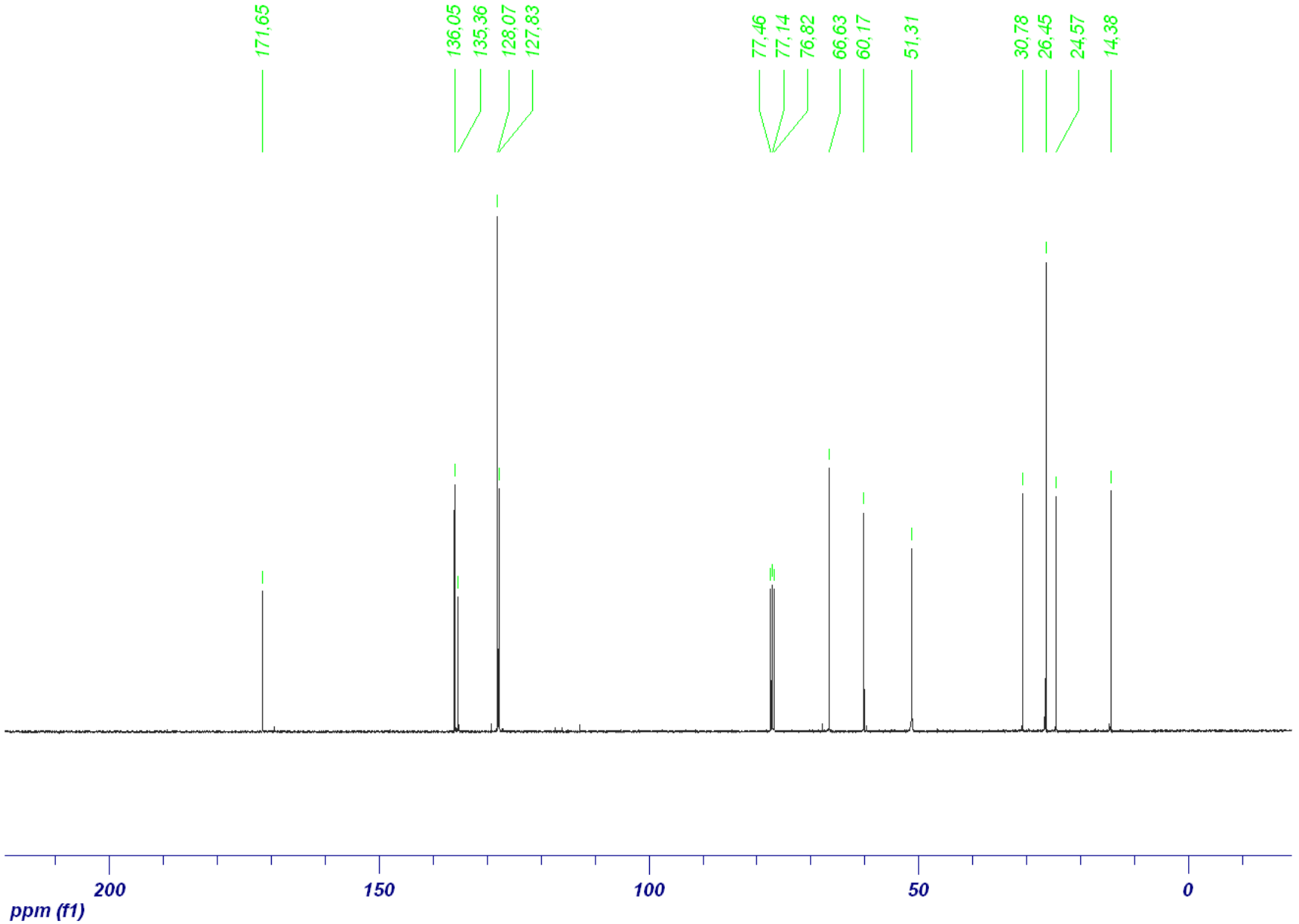
^{13}C NMR spectrum of **1j**



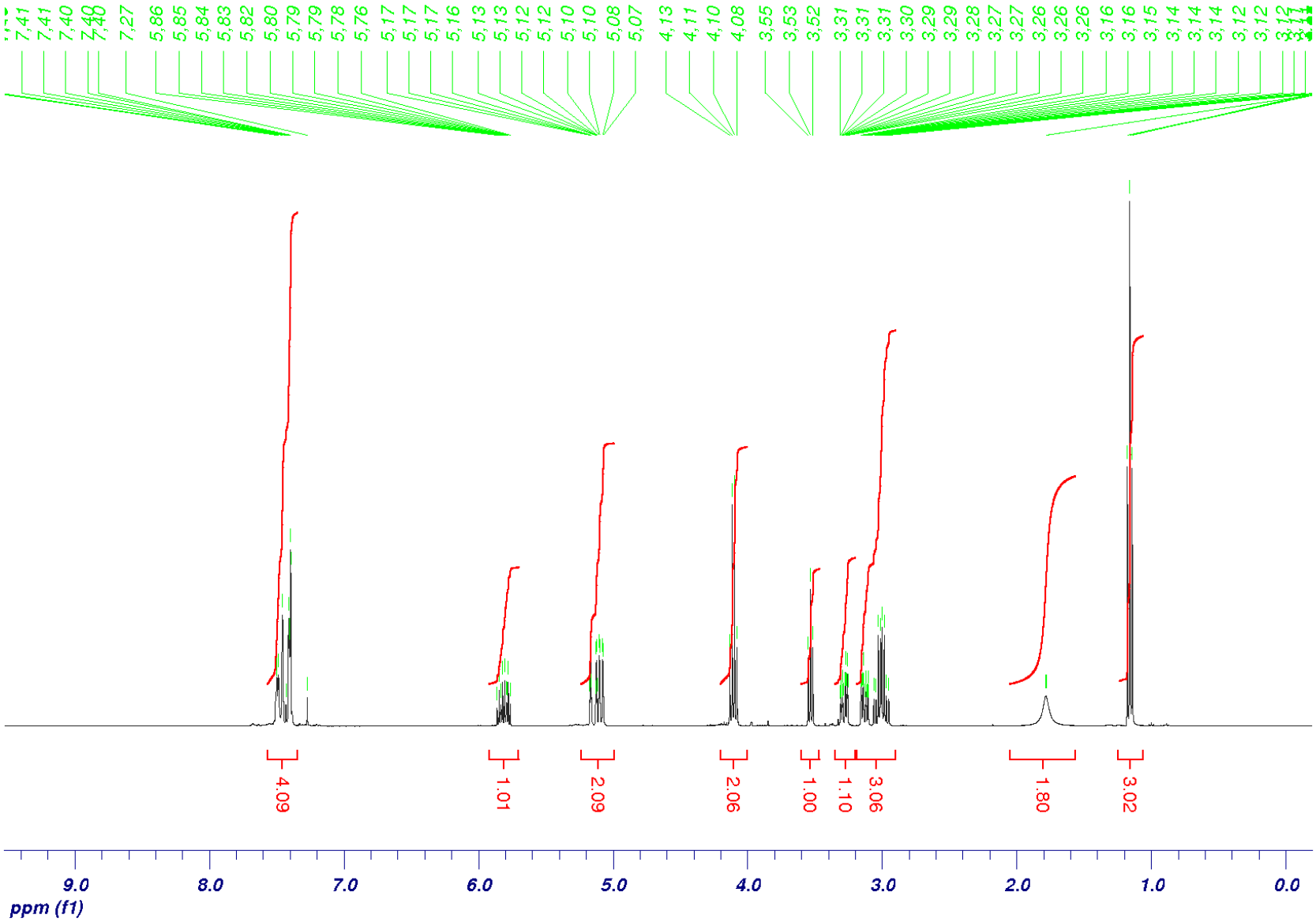
^{1}H NMR spectrum of **1k**



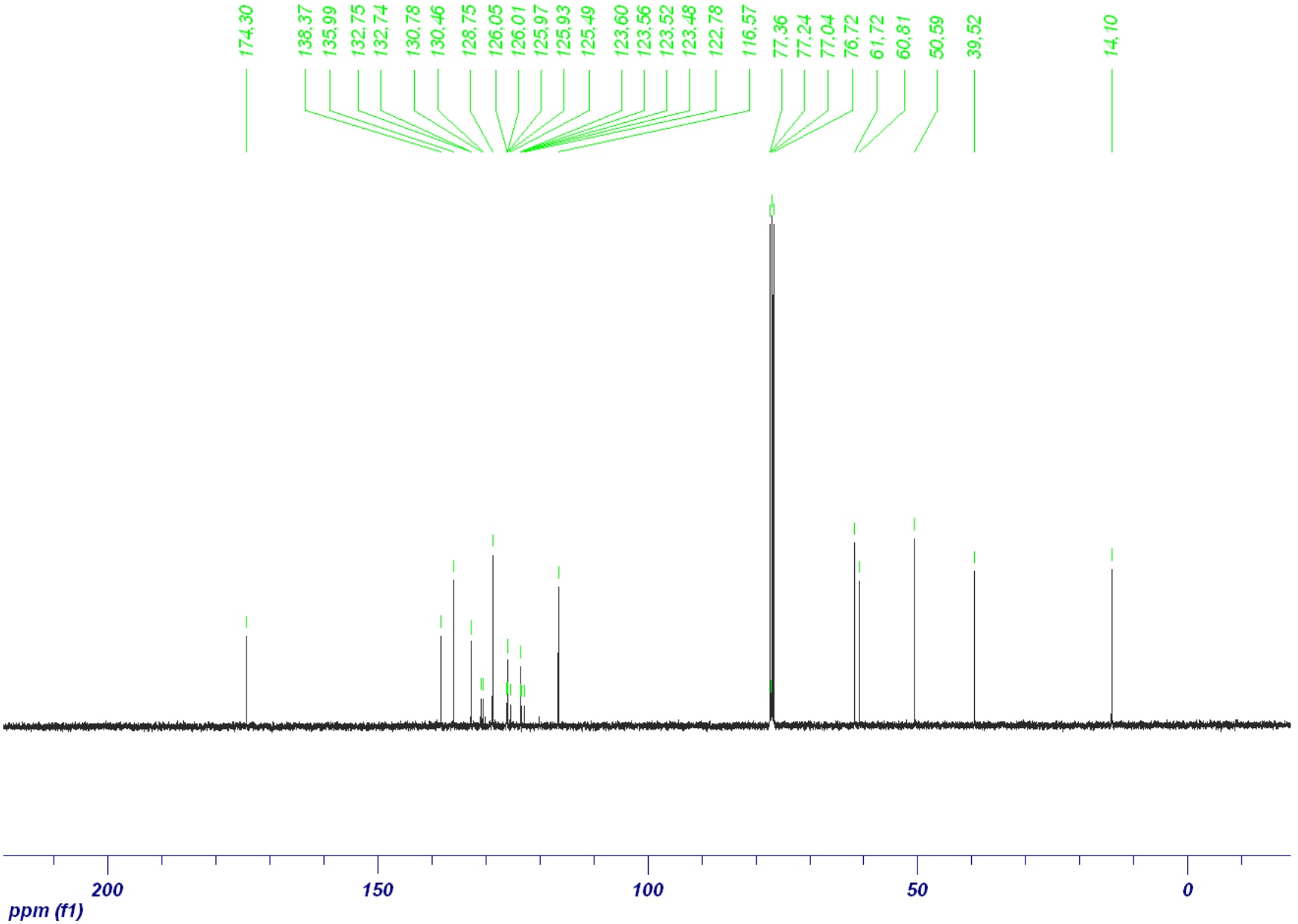
^{13}C NMR spectrum of **1k**



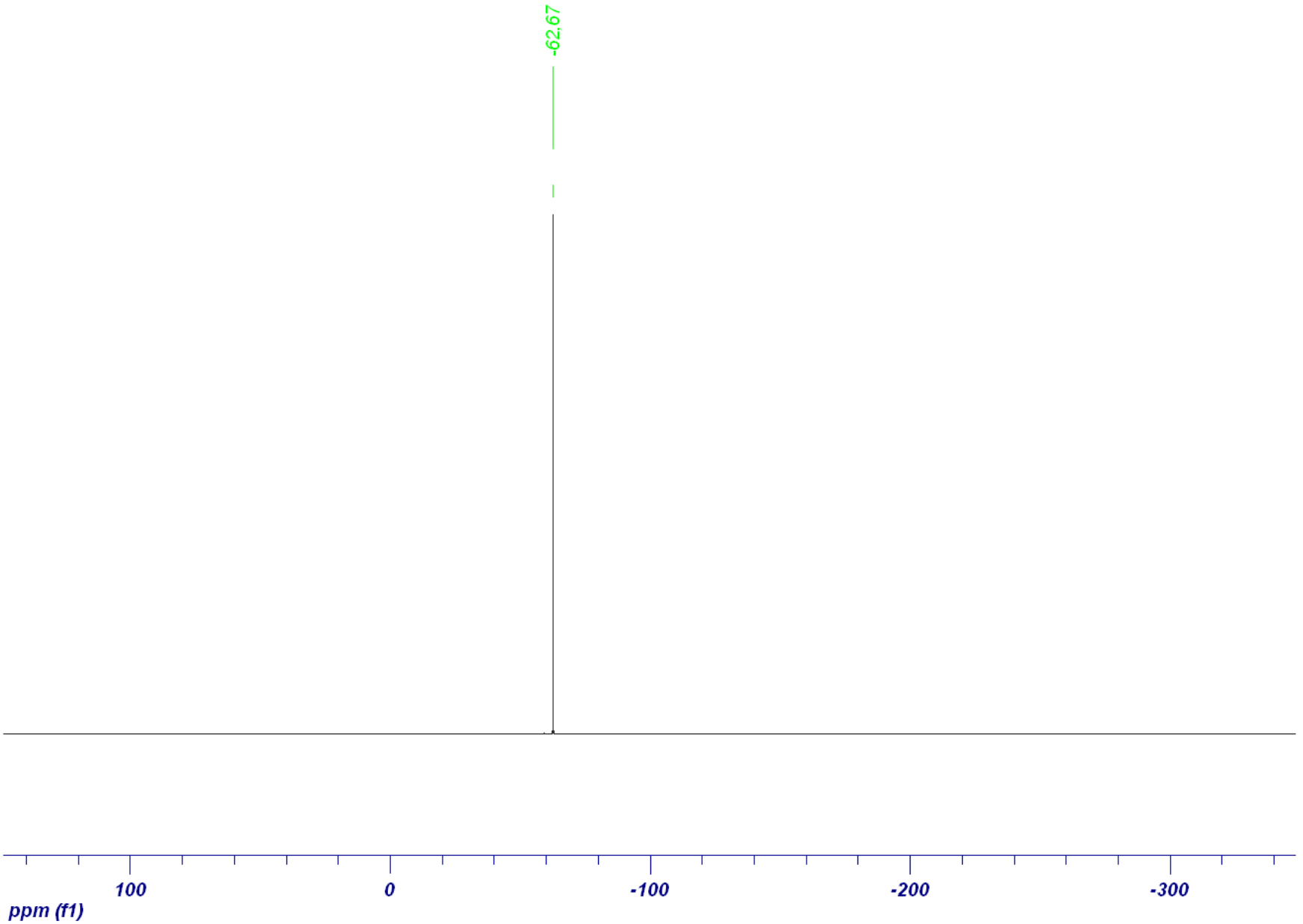
^{1}H NMR spectrum of **1l**



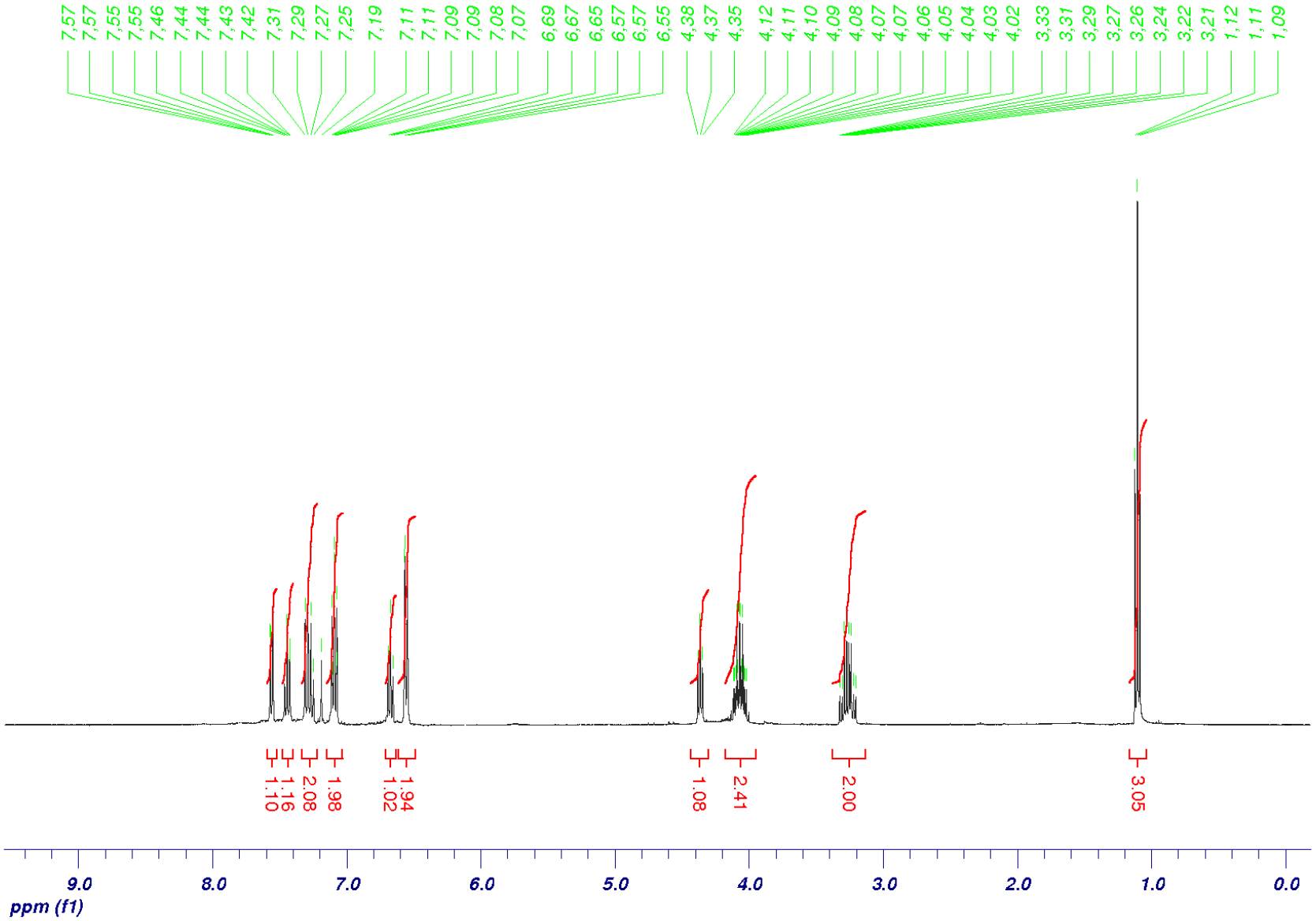
^{13}C NMR spectrum of **1l**



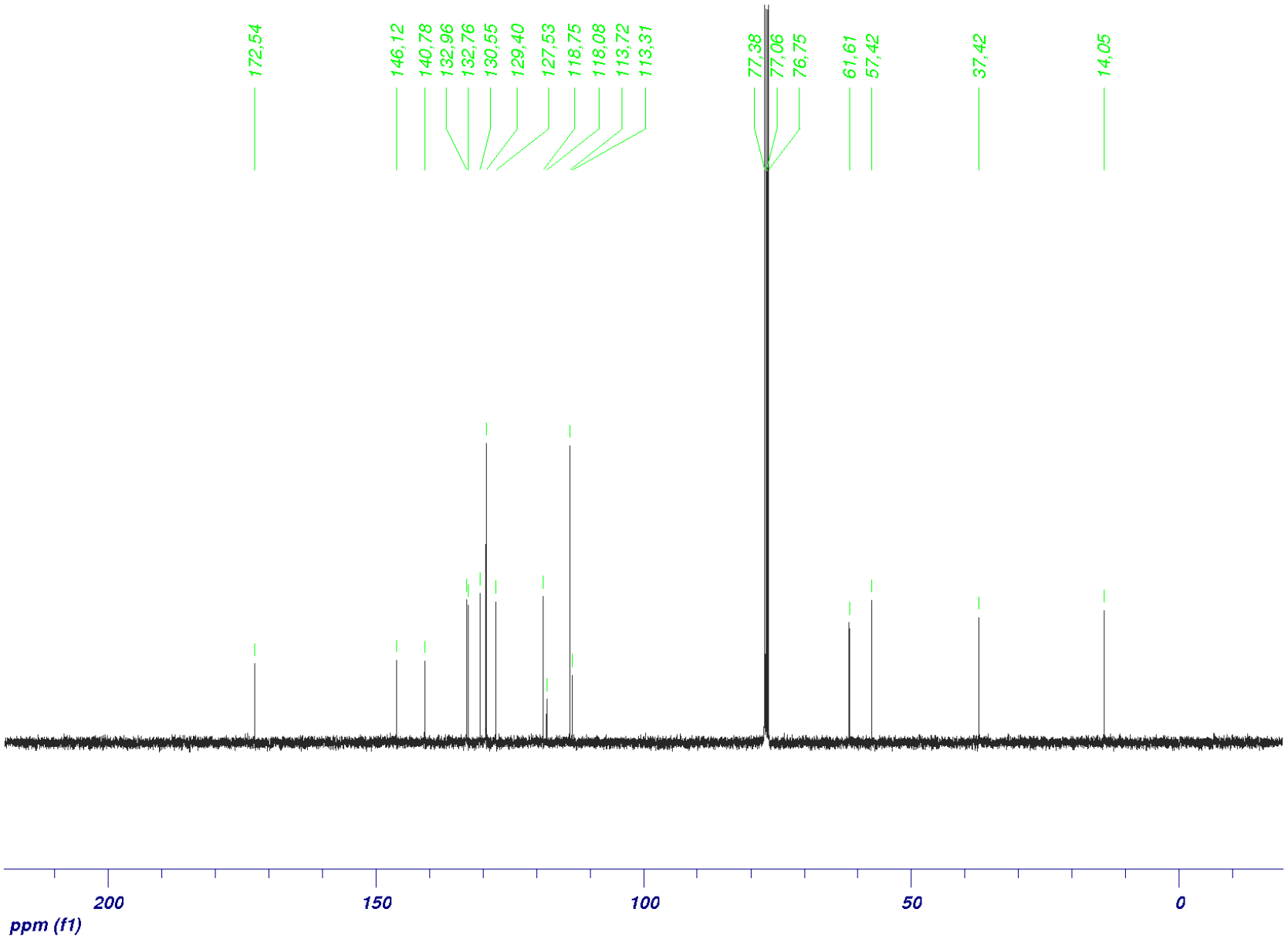
^{19}F NMR spectrum of **1l**



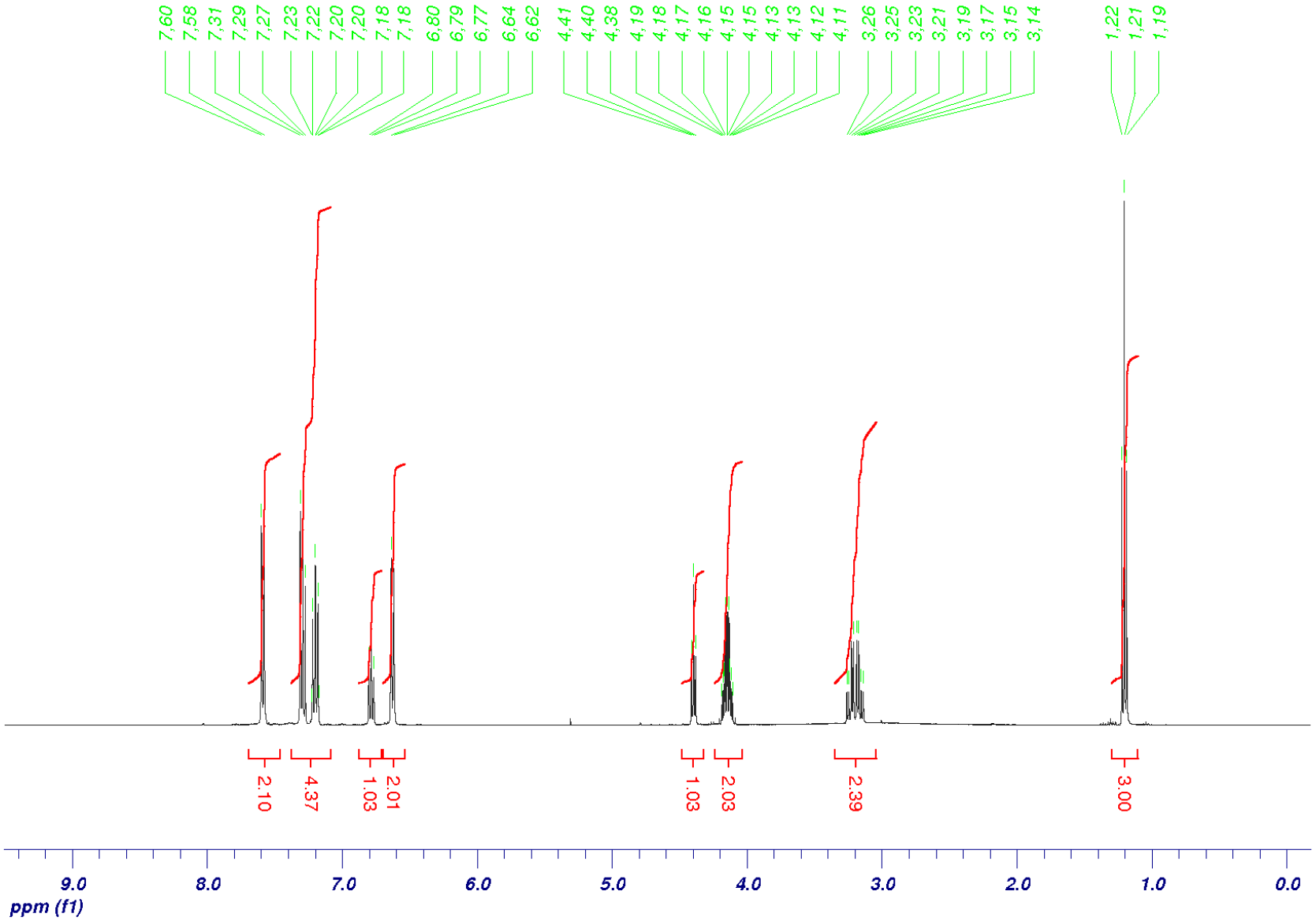
^{1}H NMR spectrum of **1m**



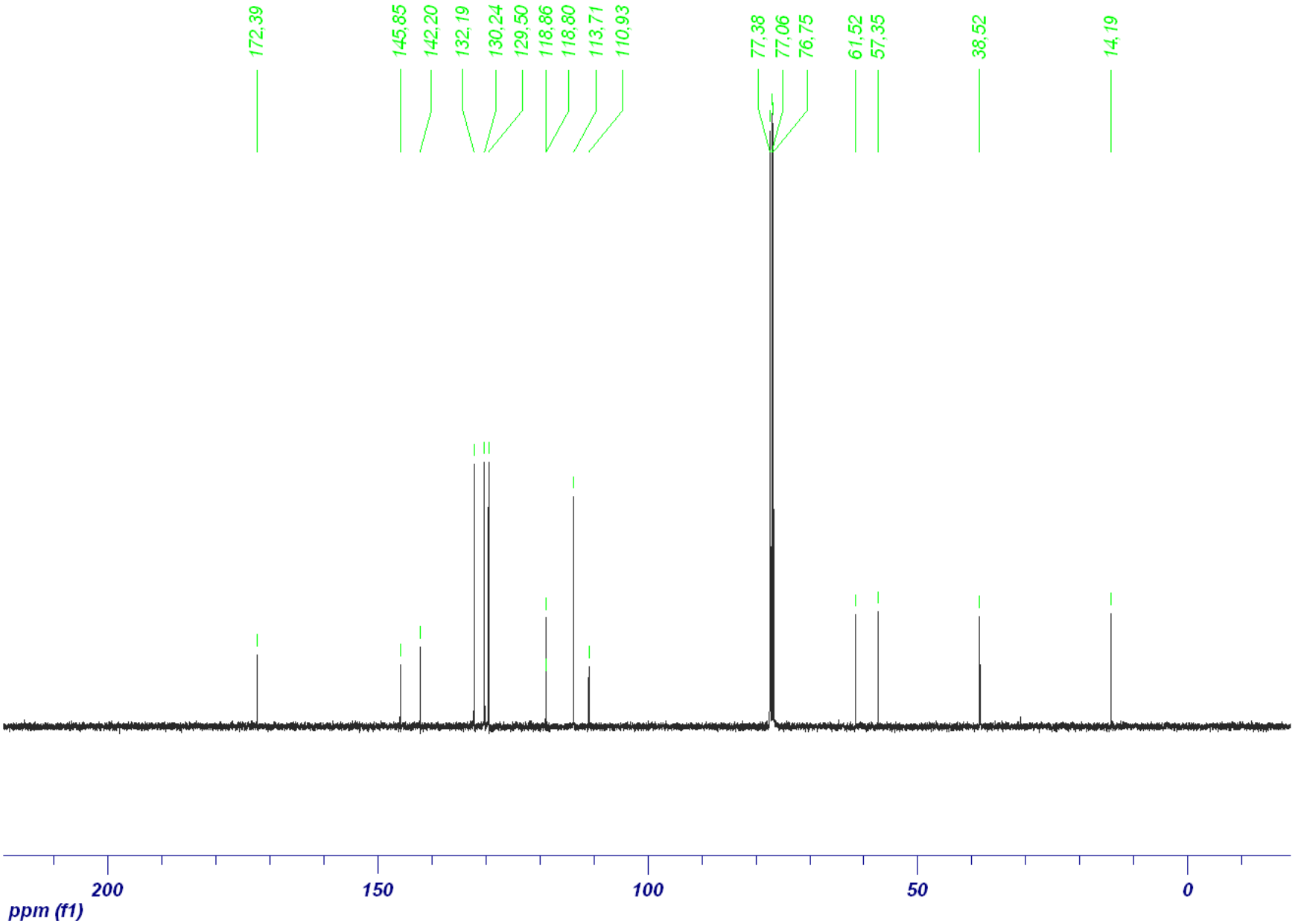
^{13}C NMR spectrum of **1m**



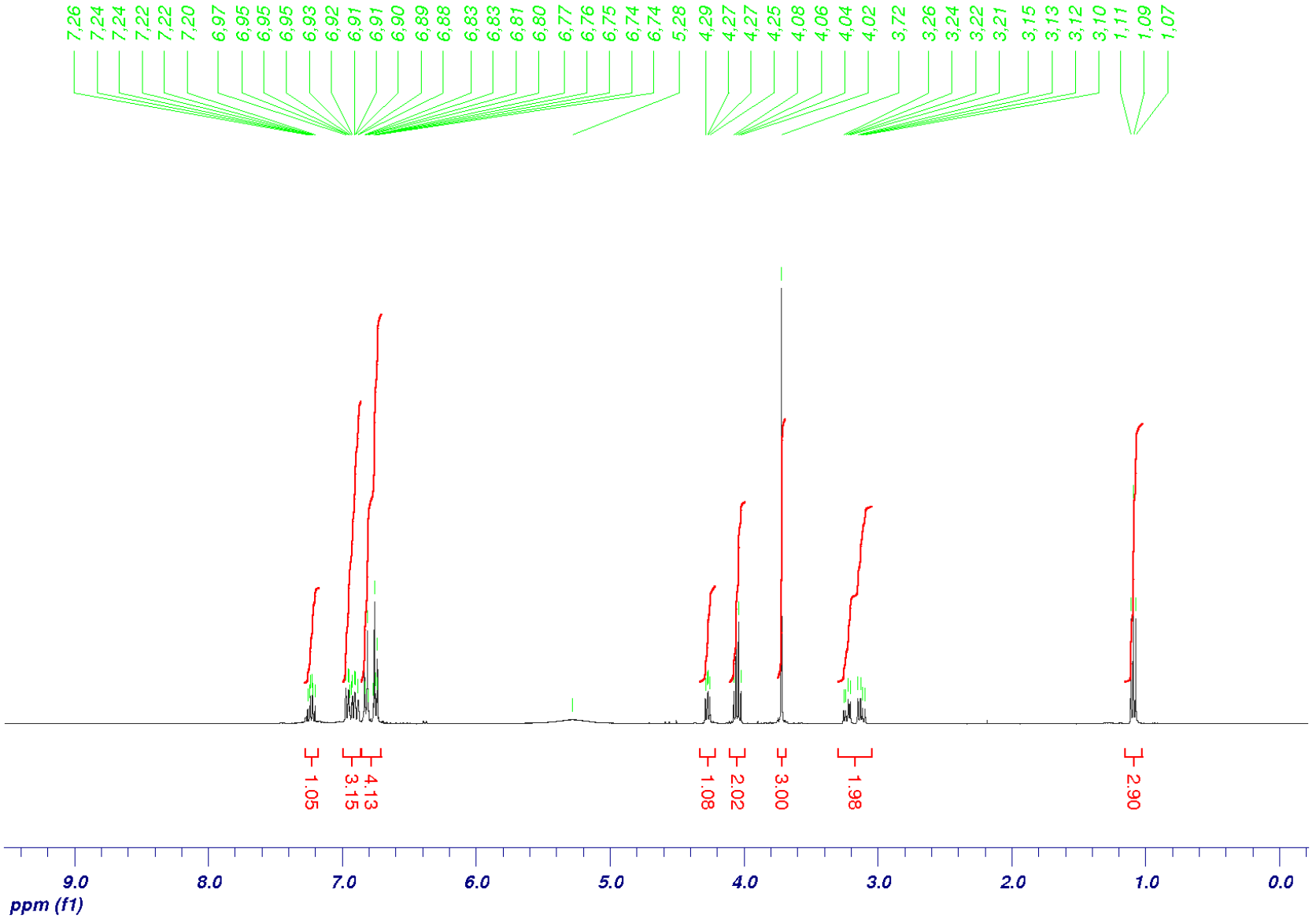
^{1}H NMR spectrum of **1n**



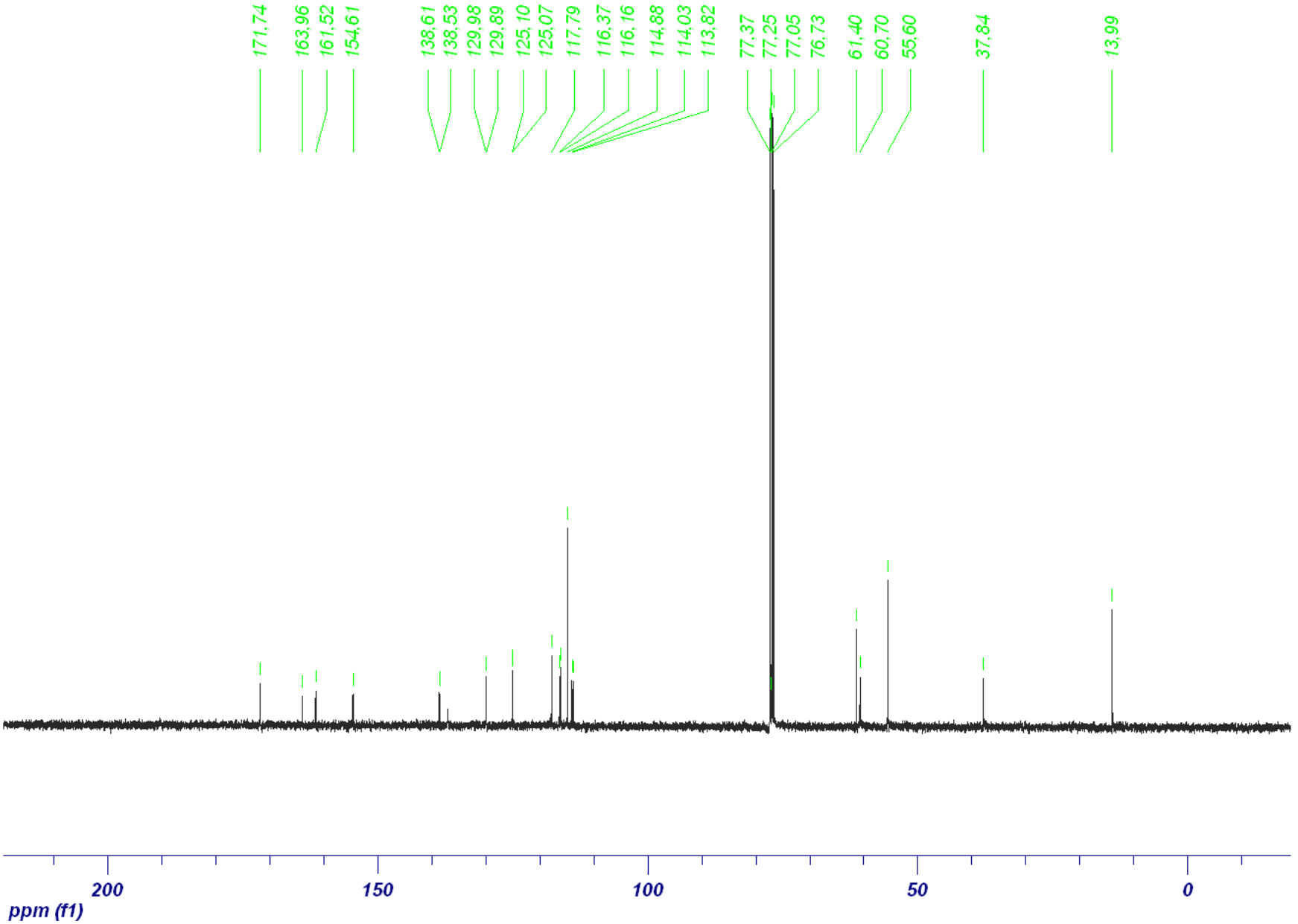
^{13}C NMR spectrum of **1n**



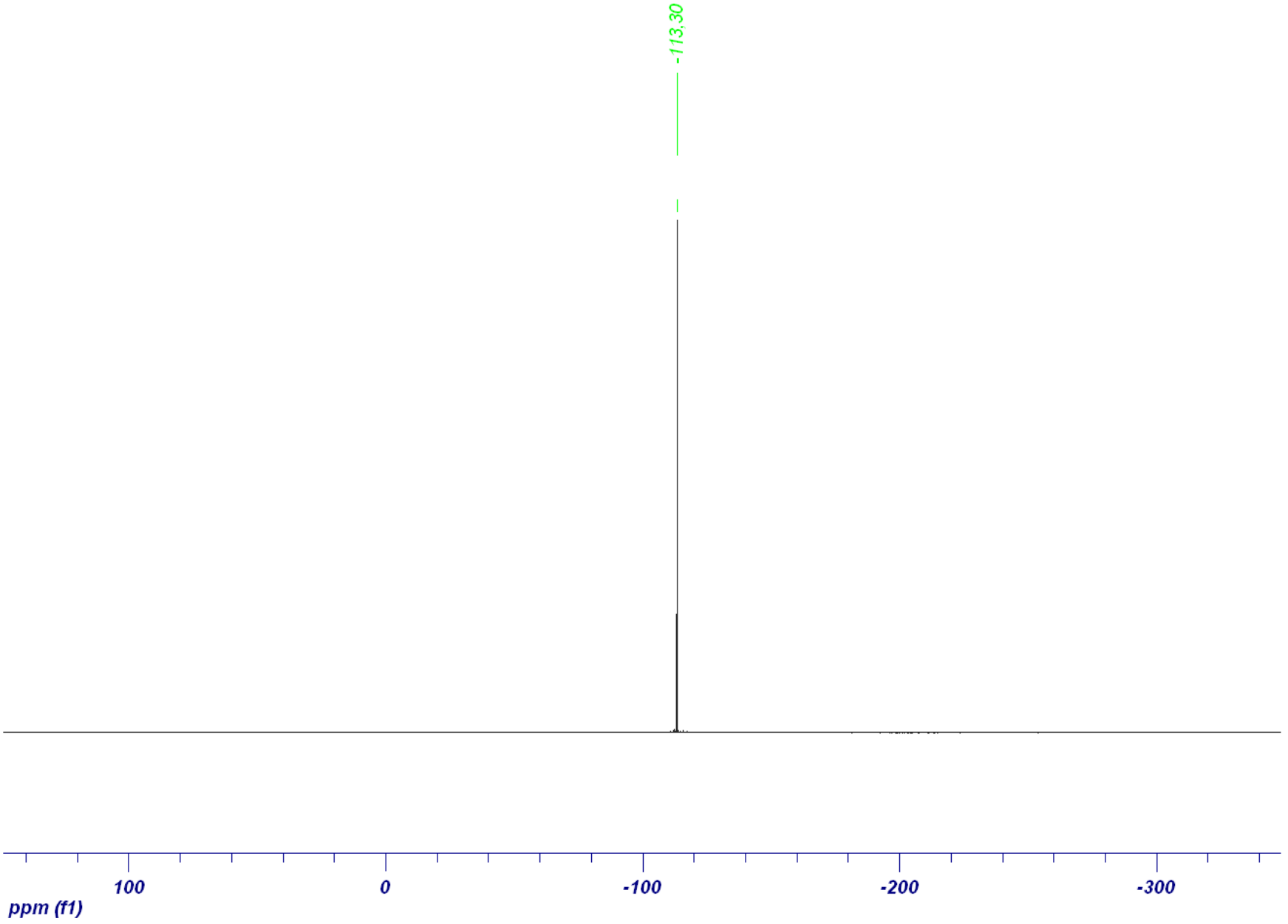
^{1}H NMR spectrum of **1o**



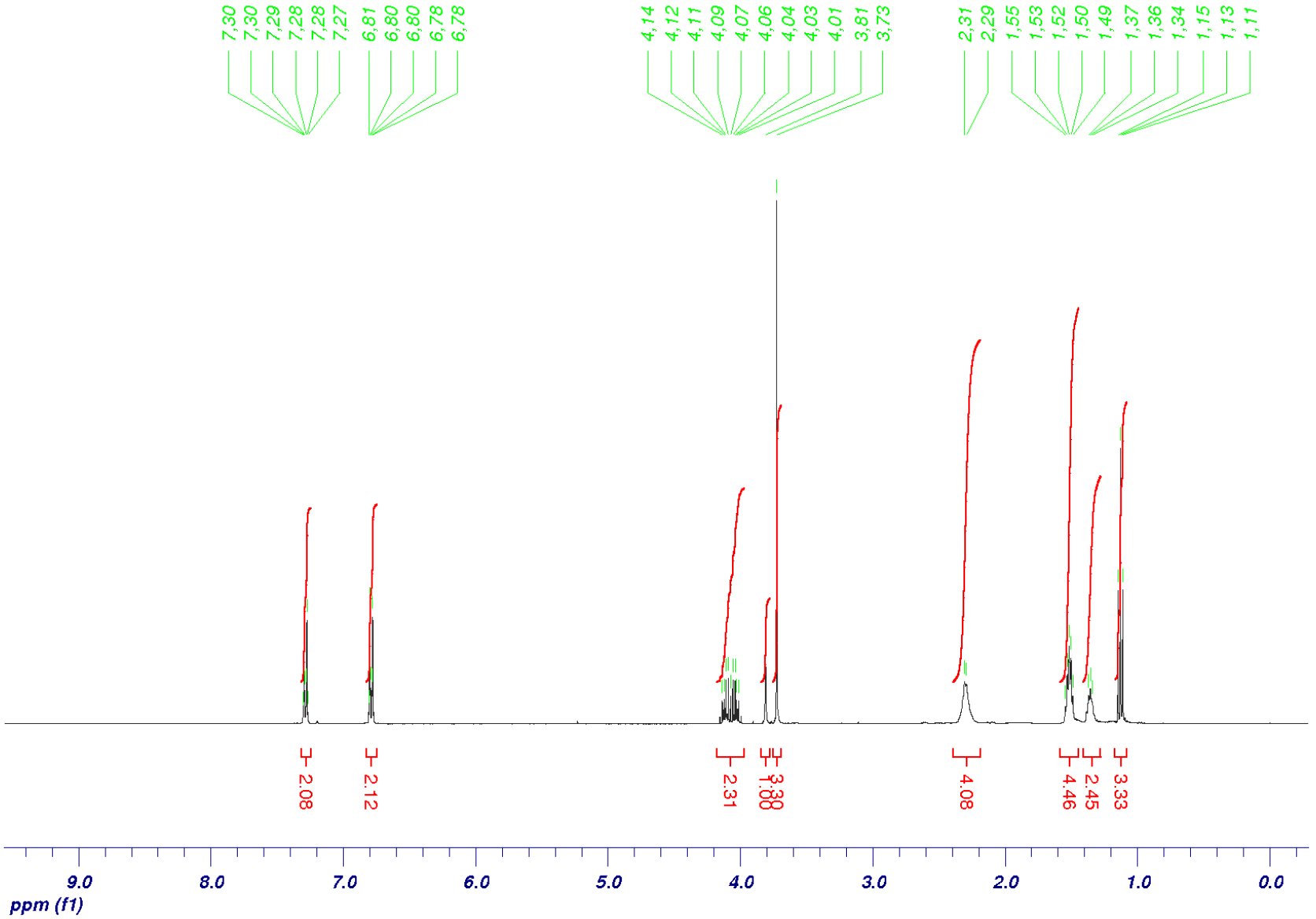
^{13}C NMR spectrum of **1o**



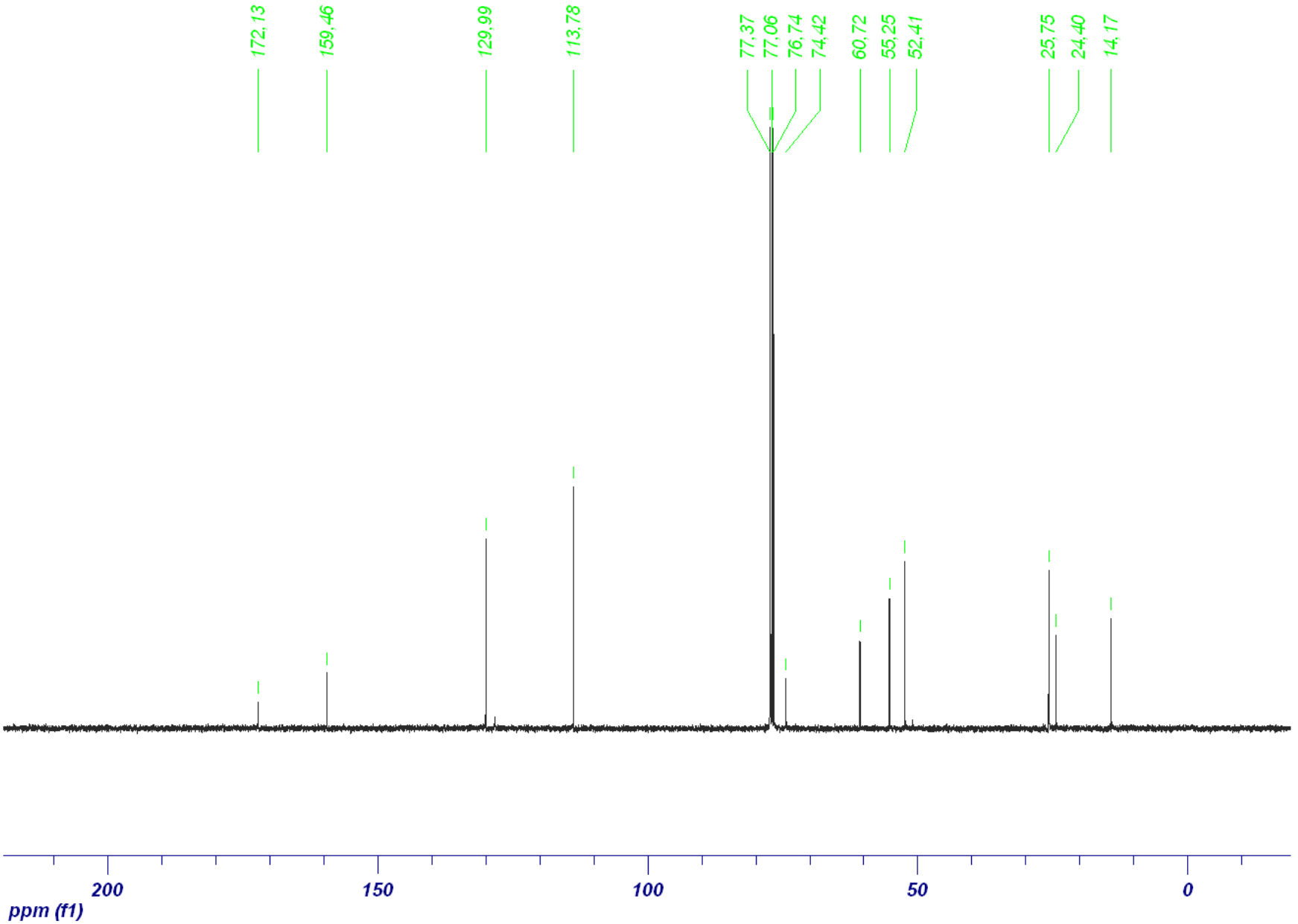
^{19}F NMR spectrum of **1o**



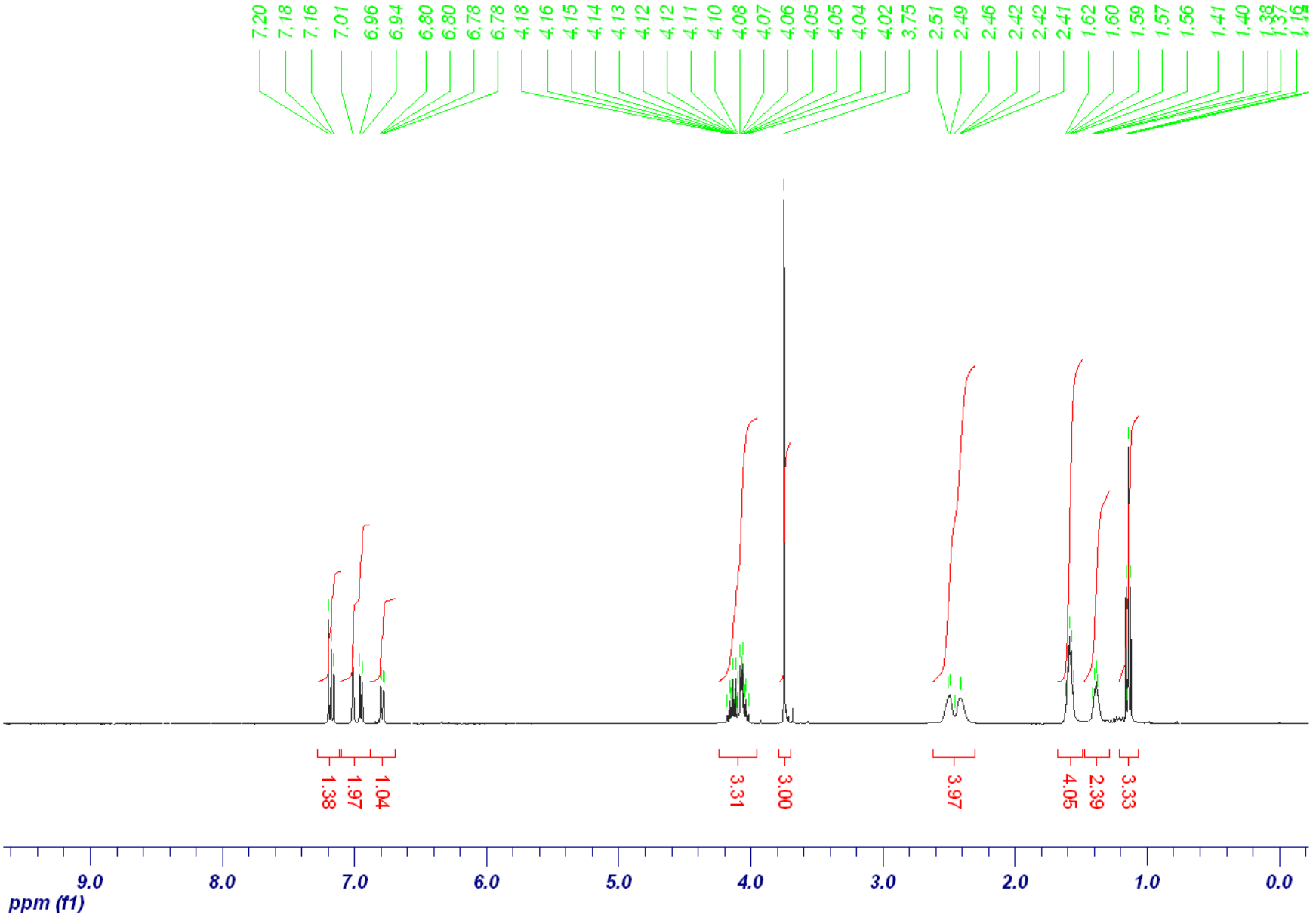
^{1}H NMR spectrum of **2a**



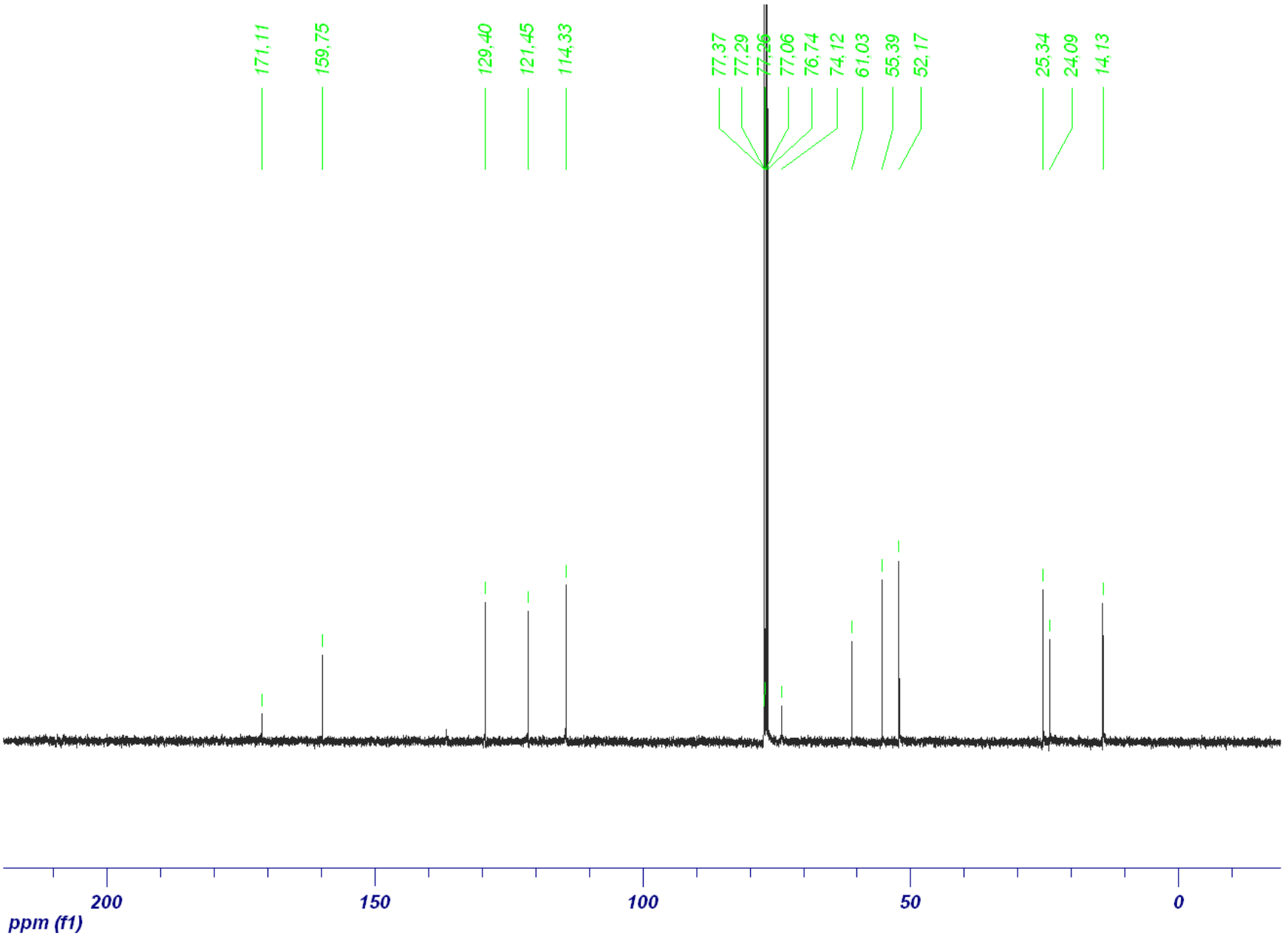
^{13}C NMR spectrum of **2a**



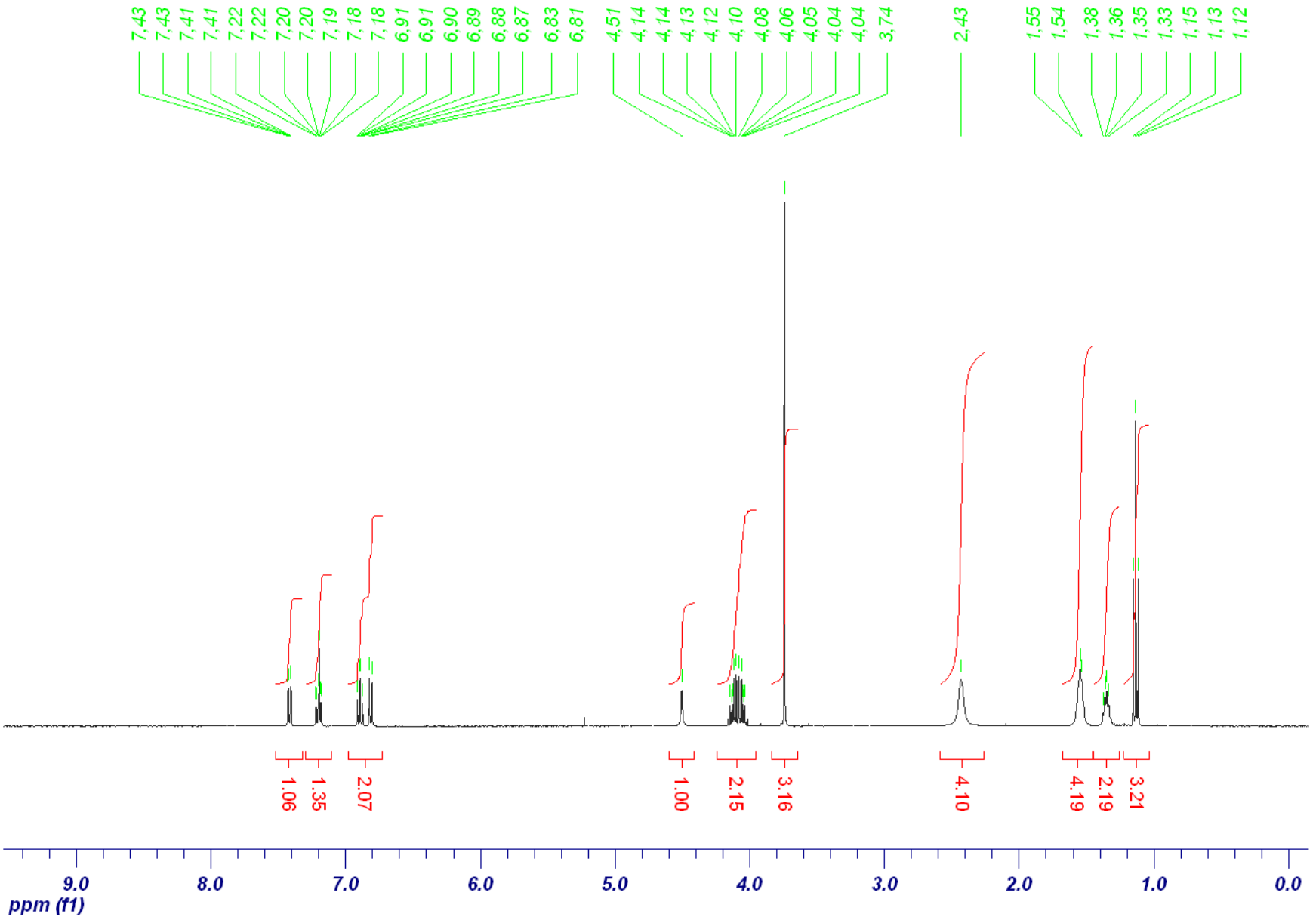
^{1}H NMR spectrum of **2b**



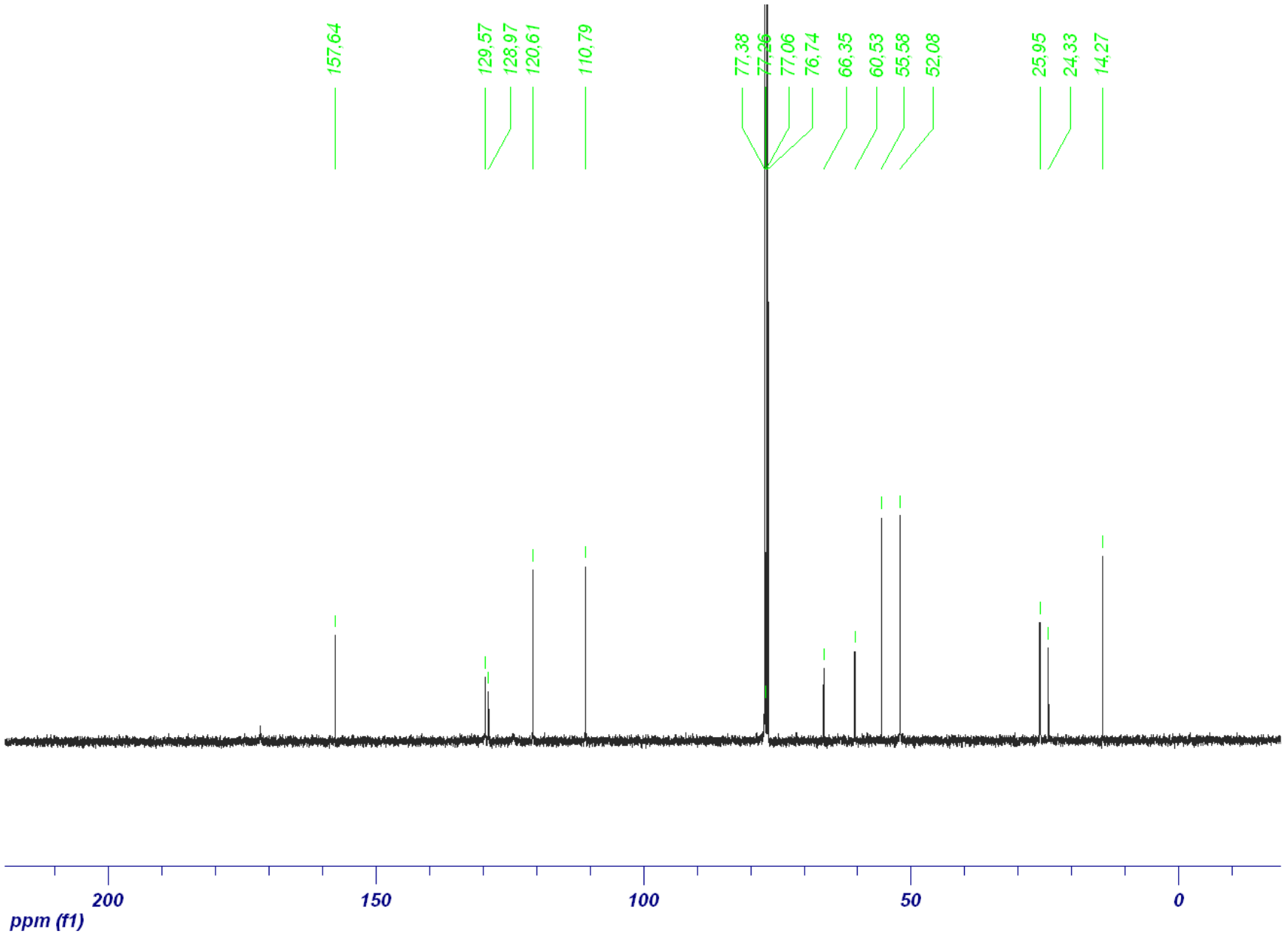
^{13}C NMR spectrum of **2b**



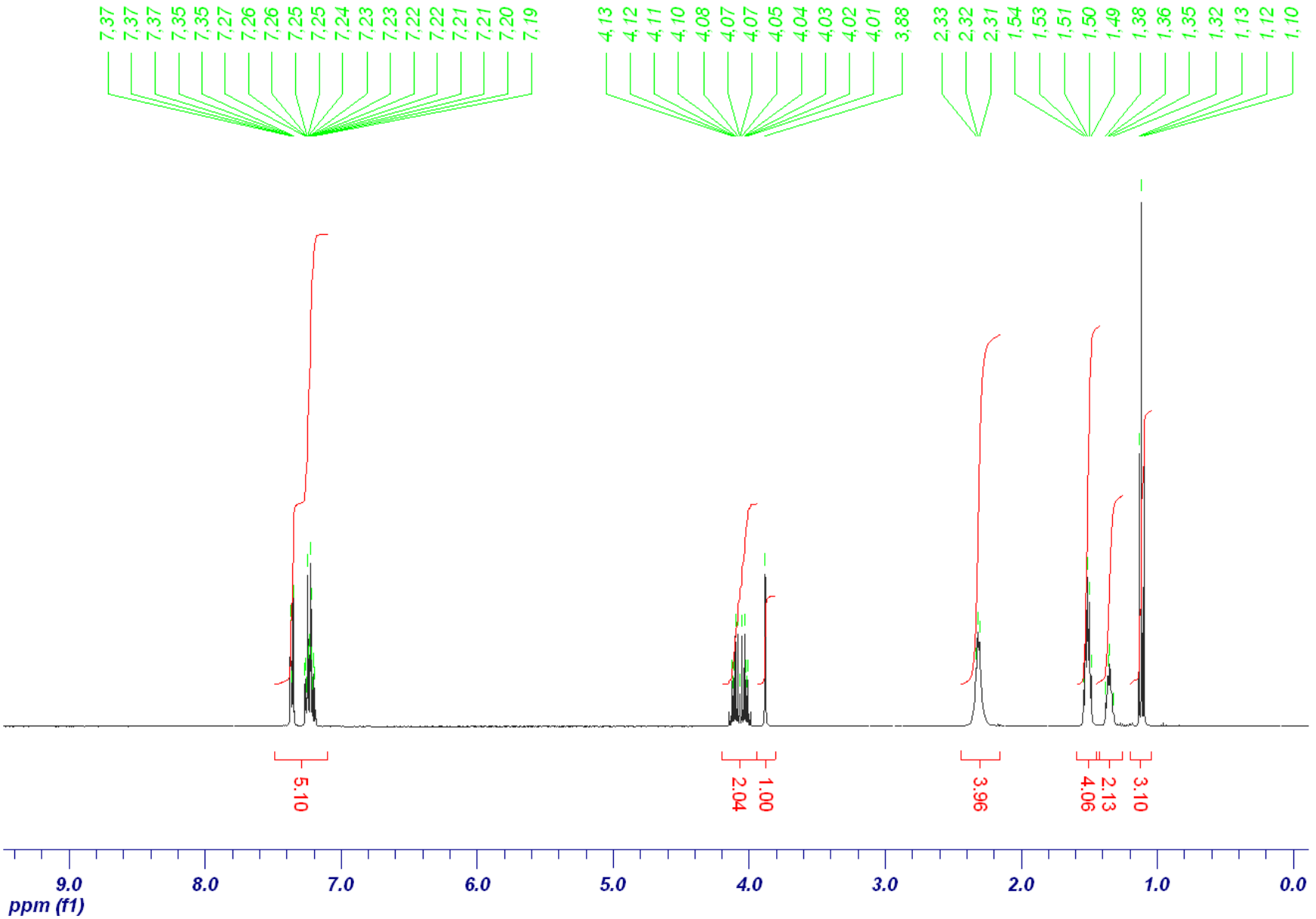
^{1}H NMR spectrum of **2c**



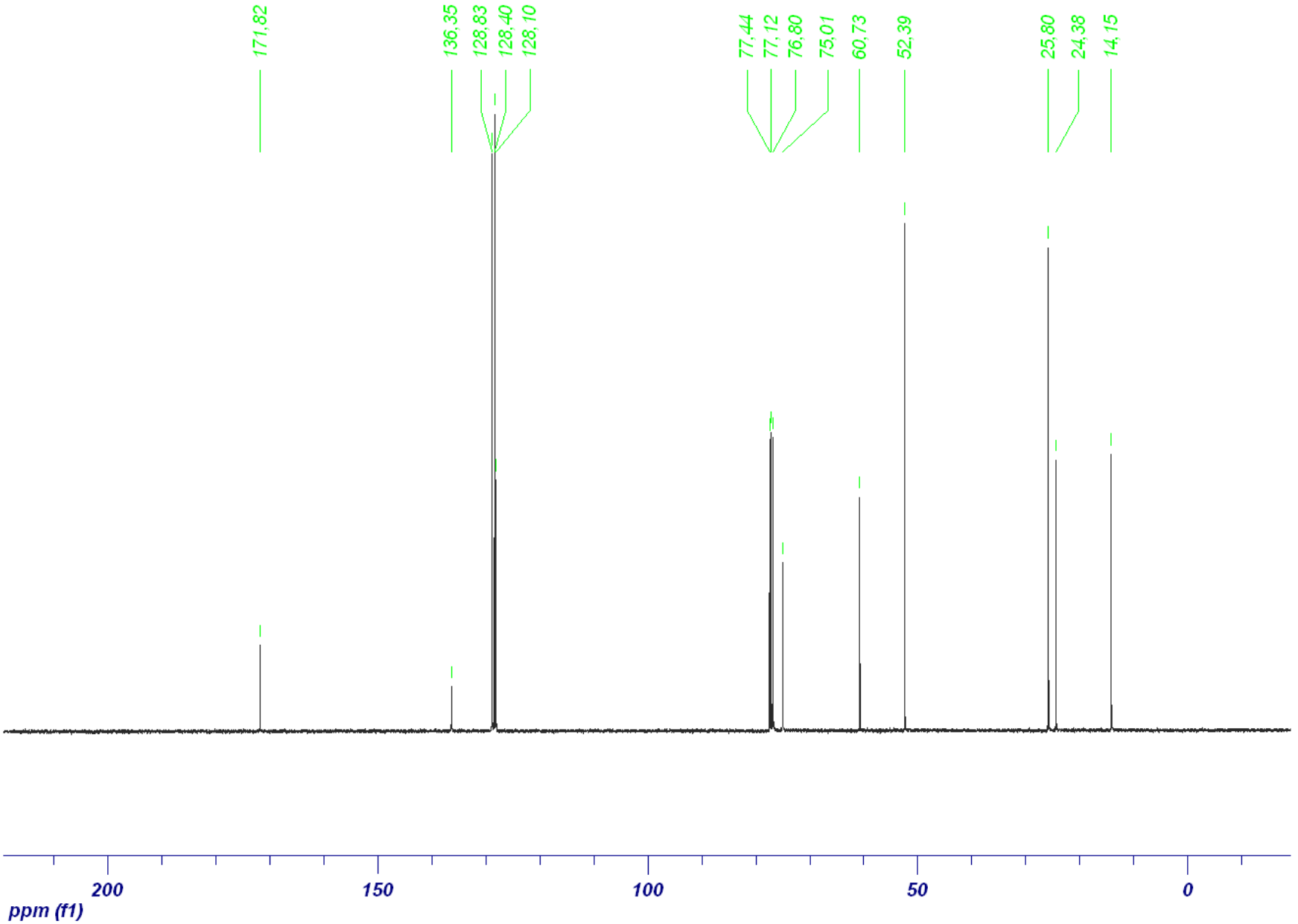
^{13}C NMR spectrum of **2c**



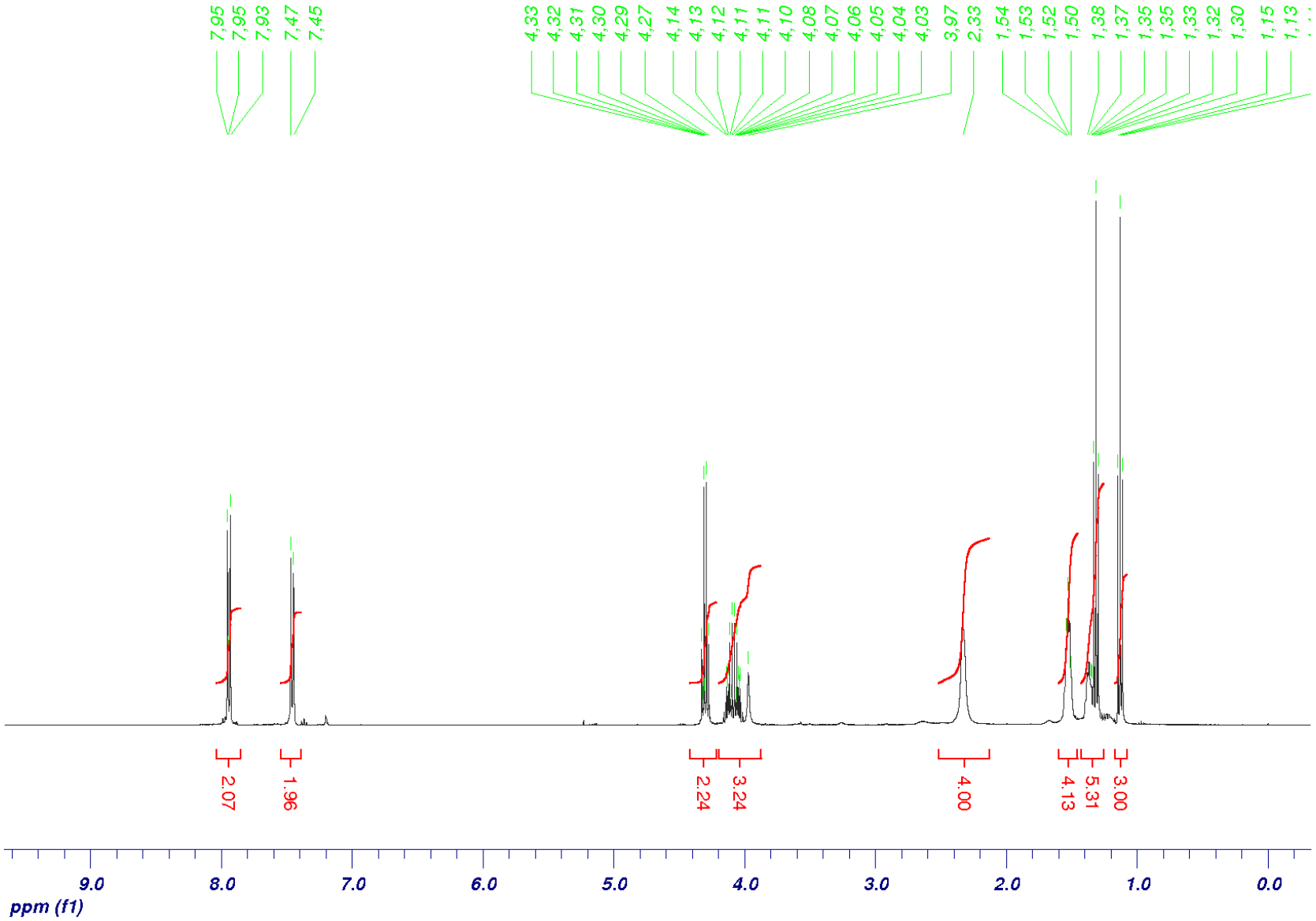
^{1}H NMR spectrum of **2d**



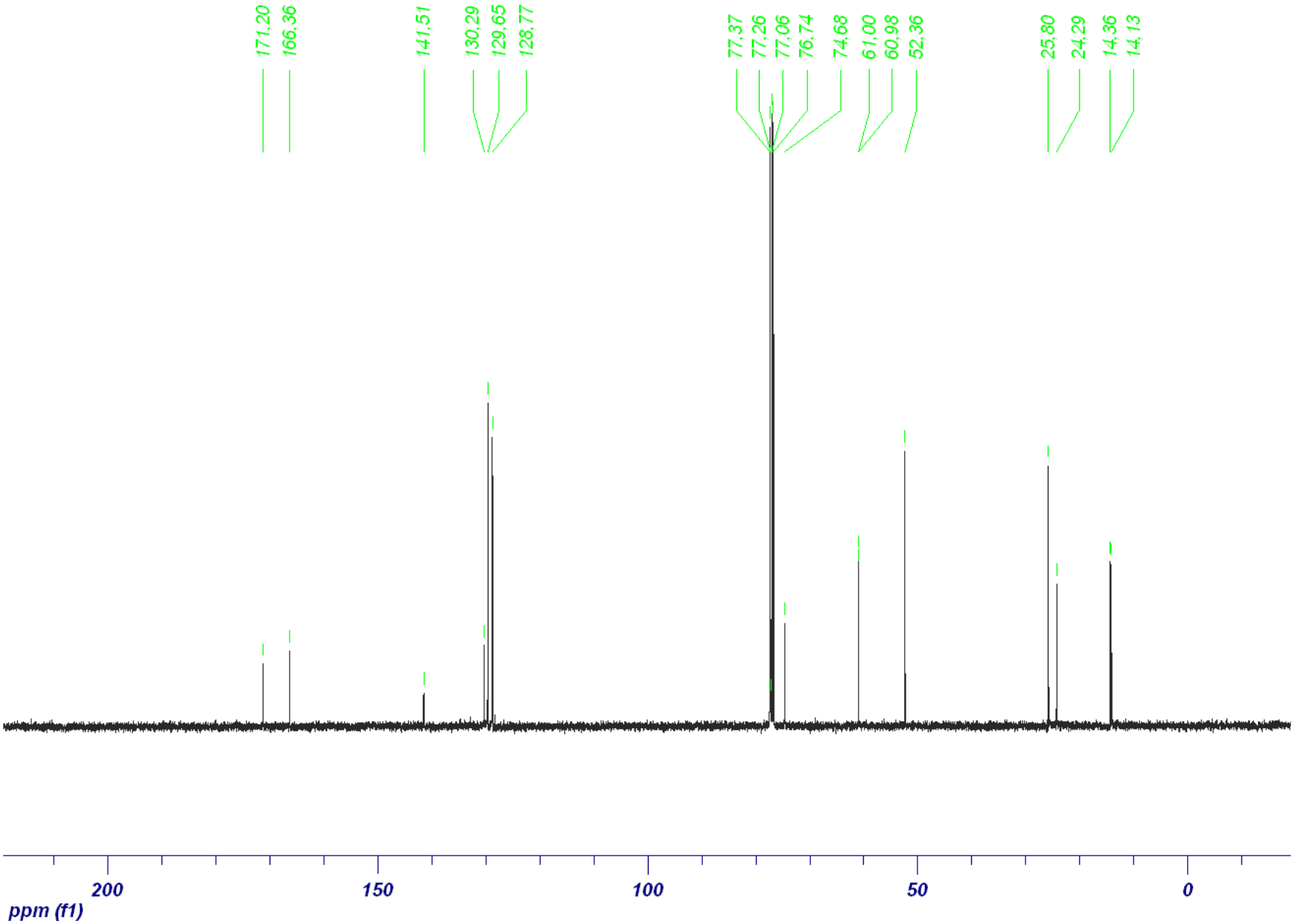
^{13}C NMR spectrum of **2d**



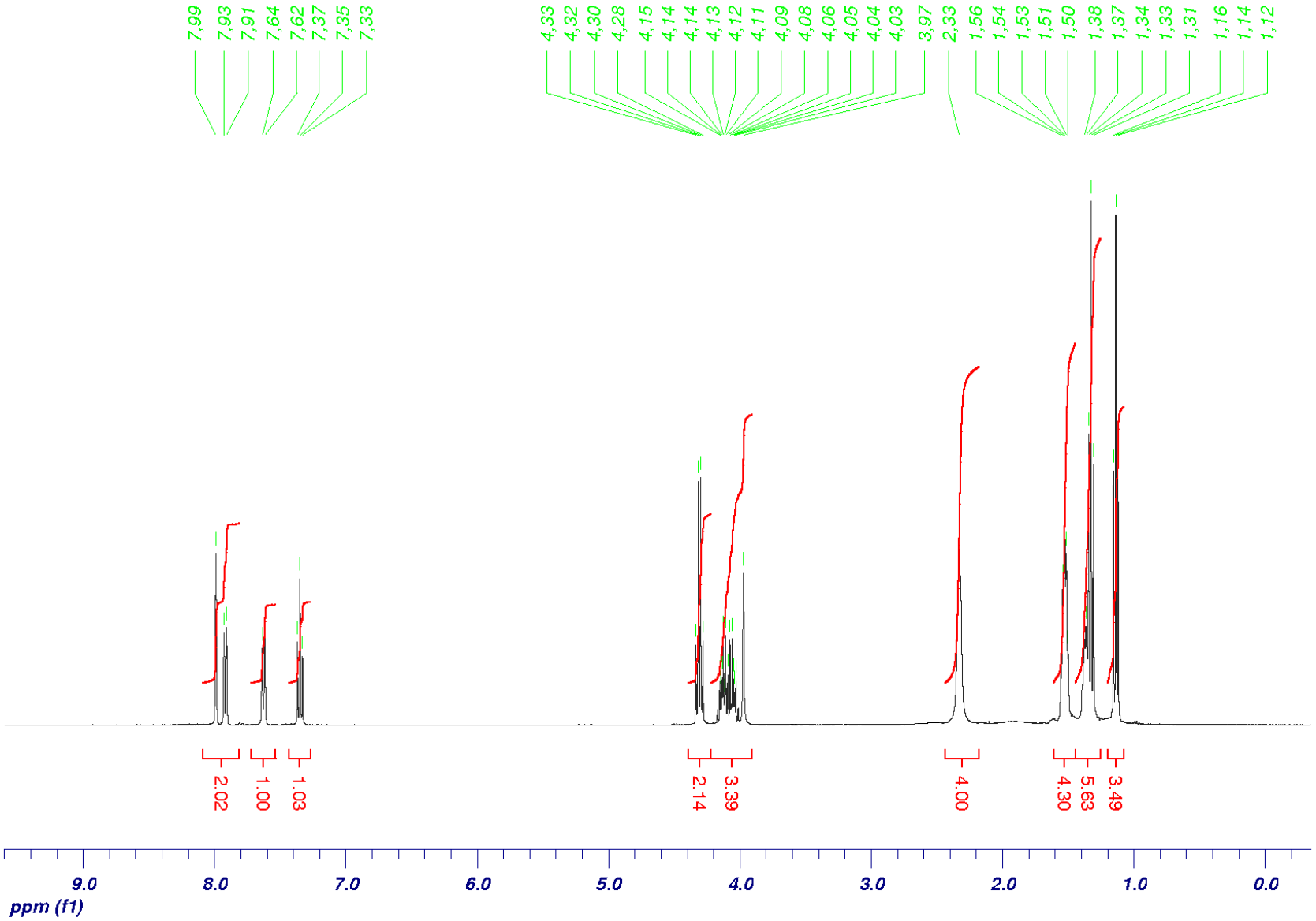
^{1}H NMR spectrum of **2e**



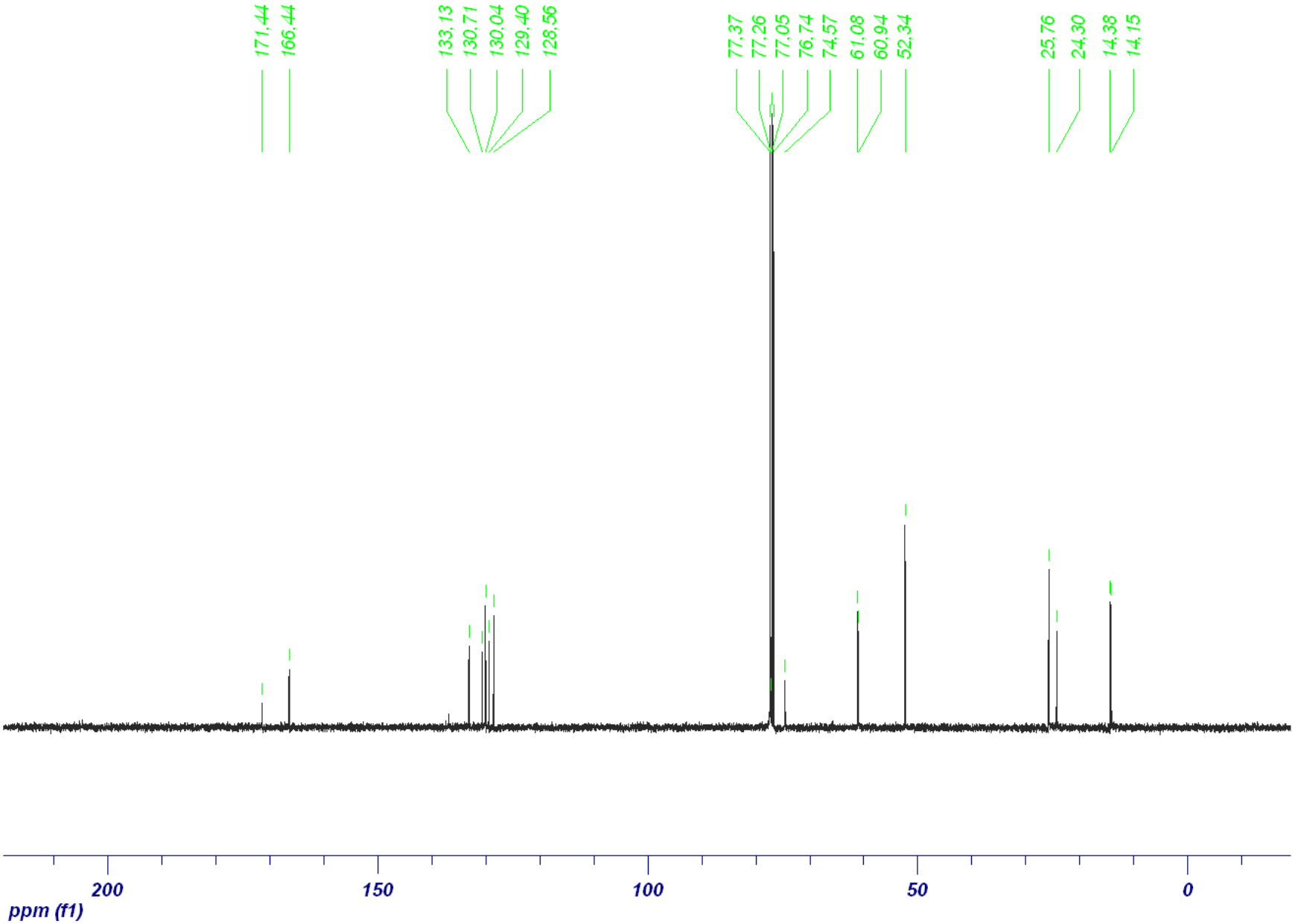
^{13}C NMR spectrum of **2e**



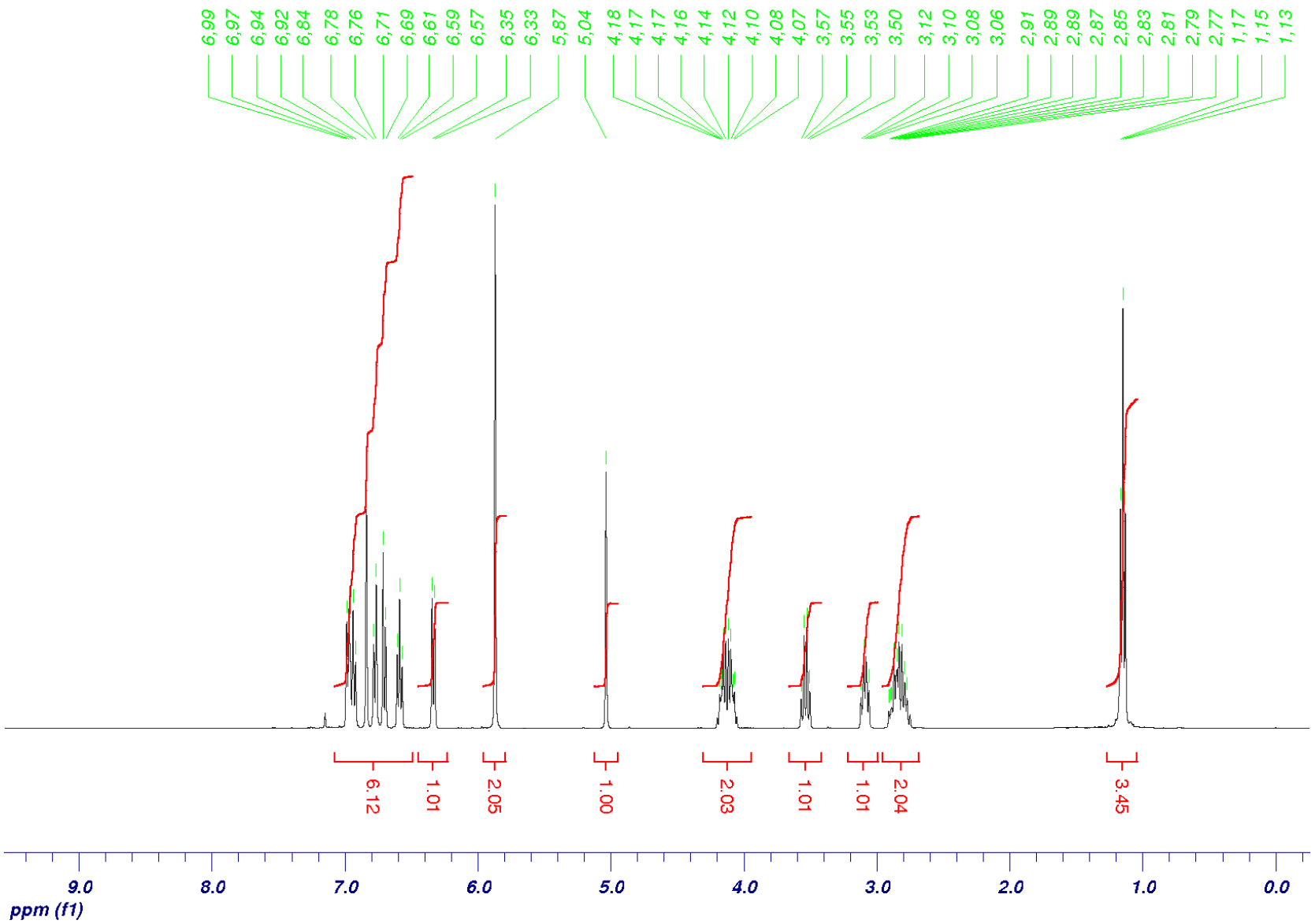
^{1}H NMR spectrum of **2f**



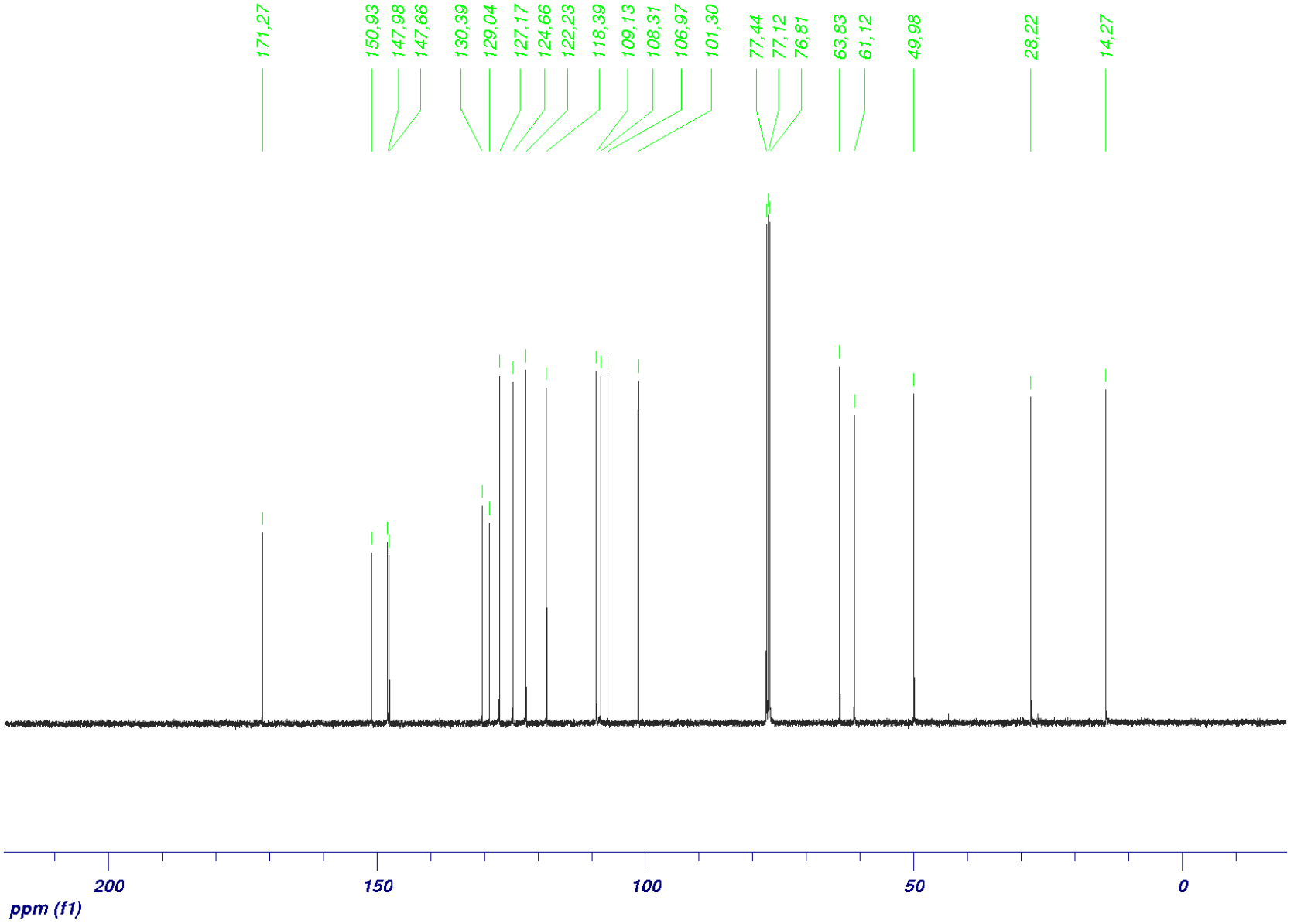
^{13}C NMR spectrum of **2f**



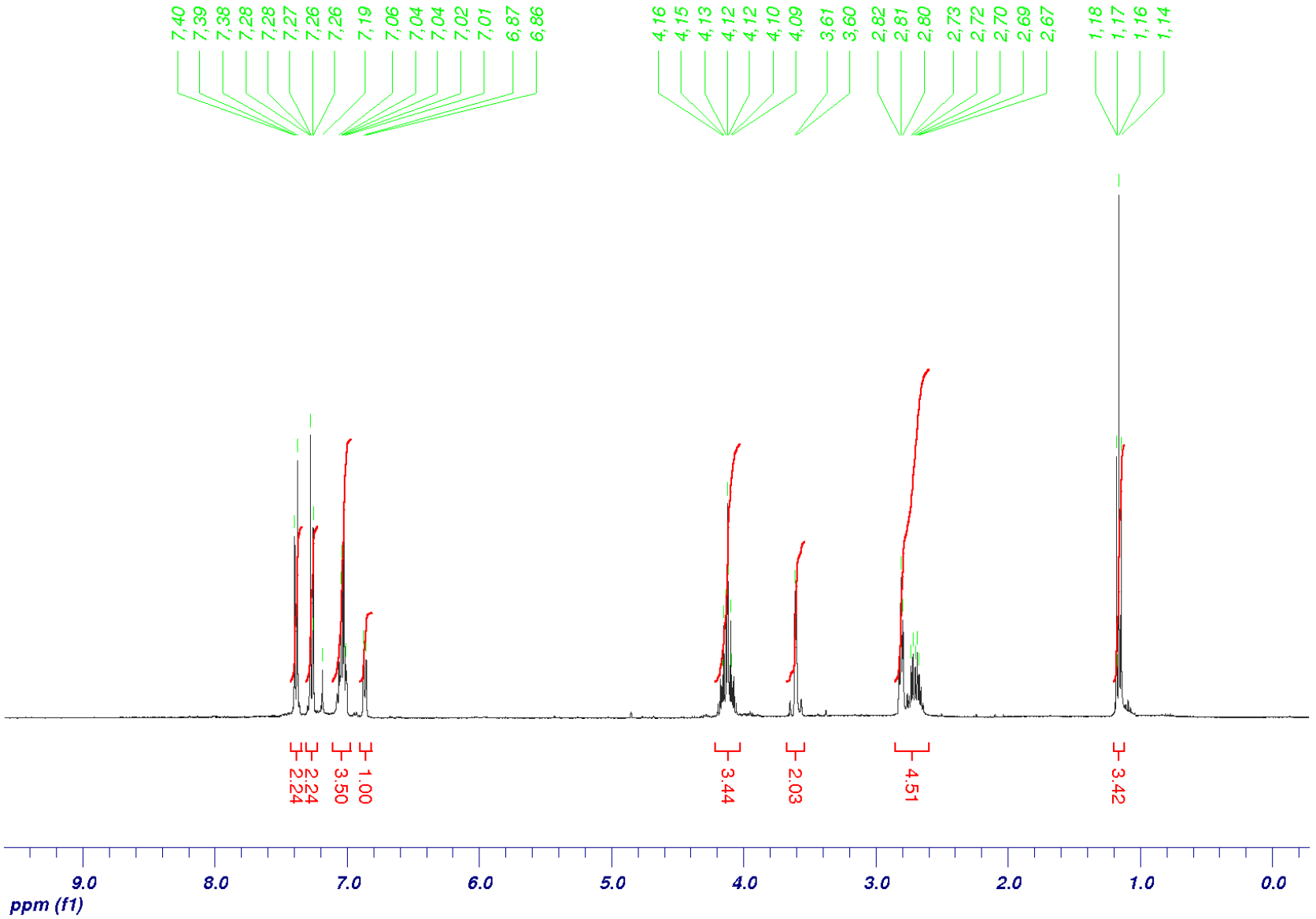
^{1}H NMR spectrum of **2g**



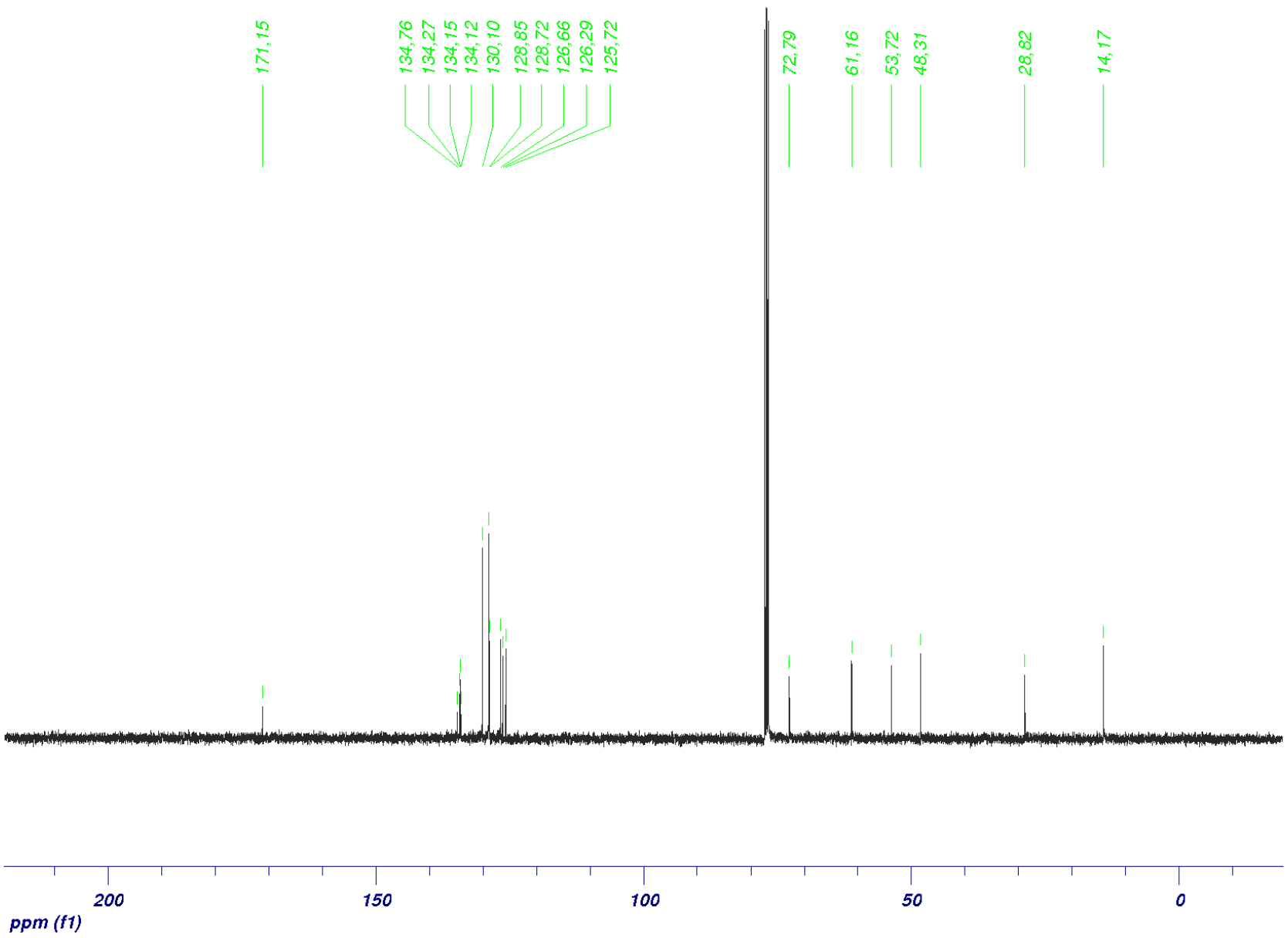
^{13}C NMR spectrum of **2g**



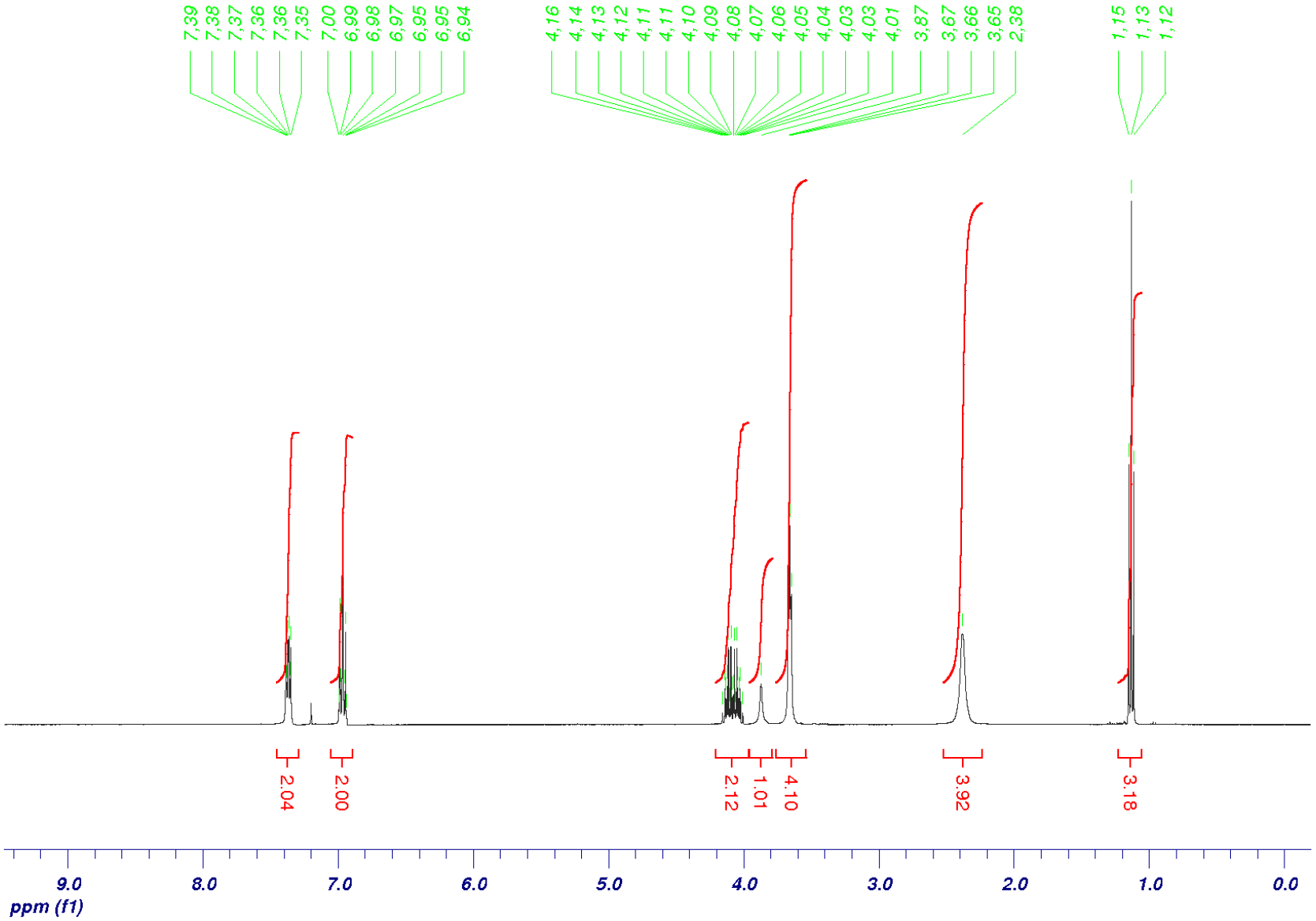
^{1}H NMR spectrum of **2h**



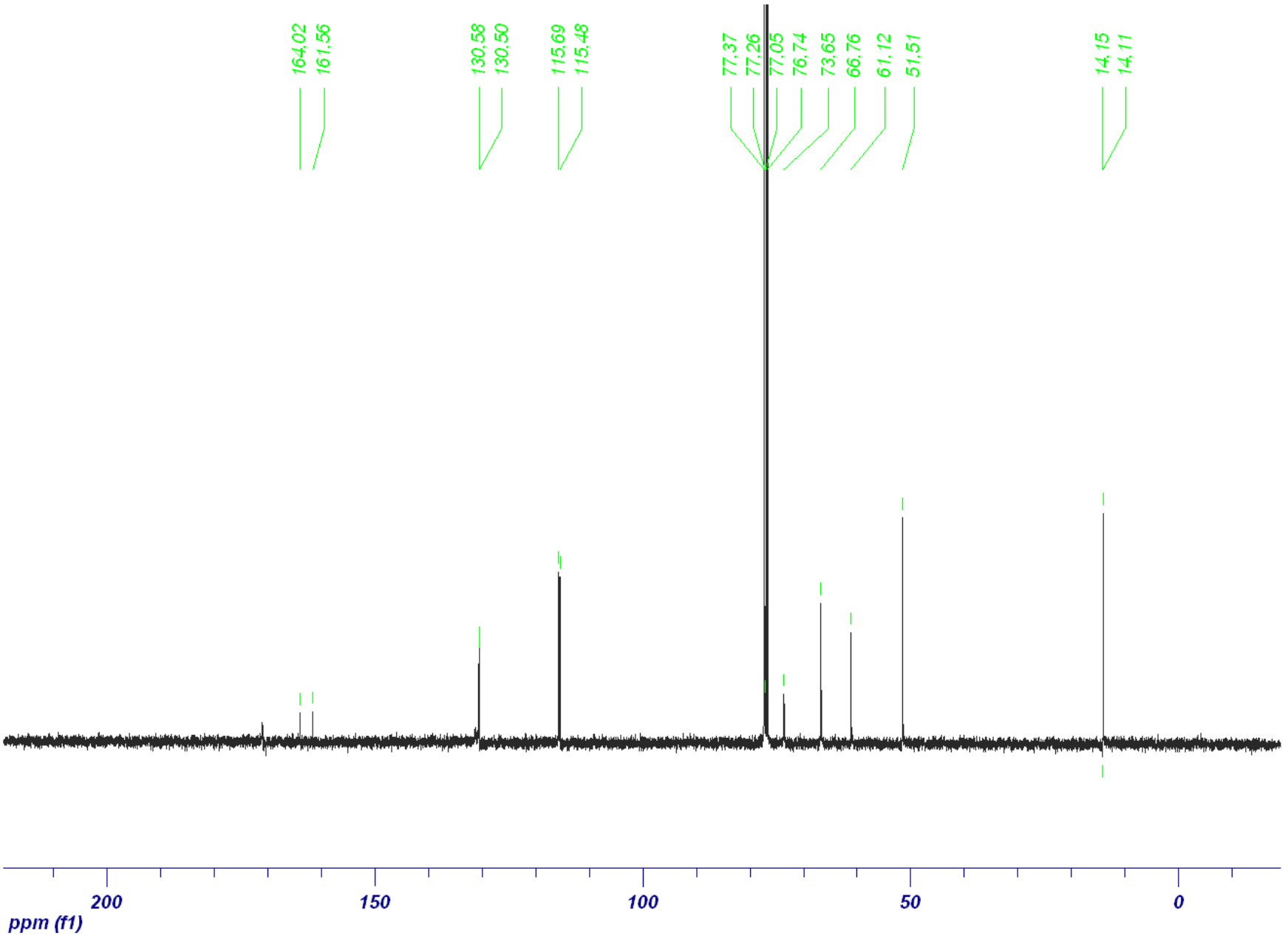
^{13}C NMR spectrum of **2h**



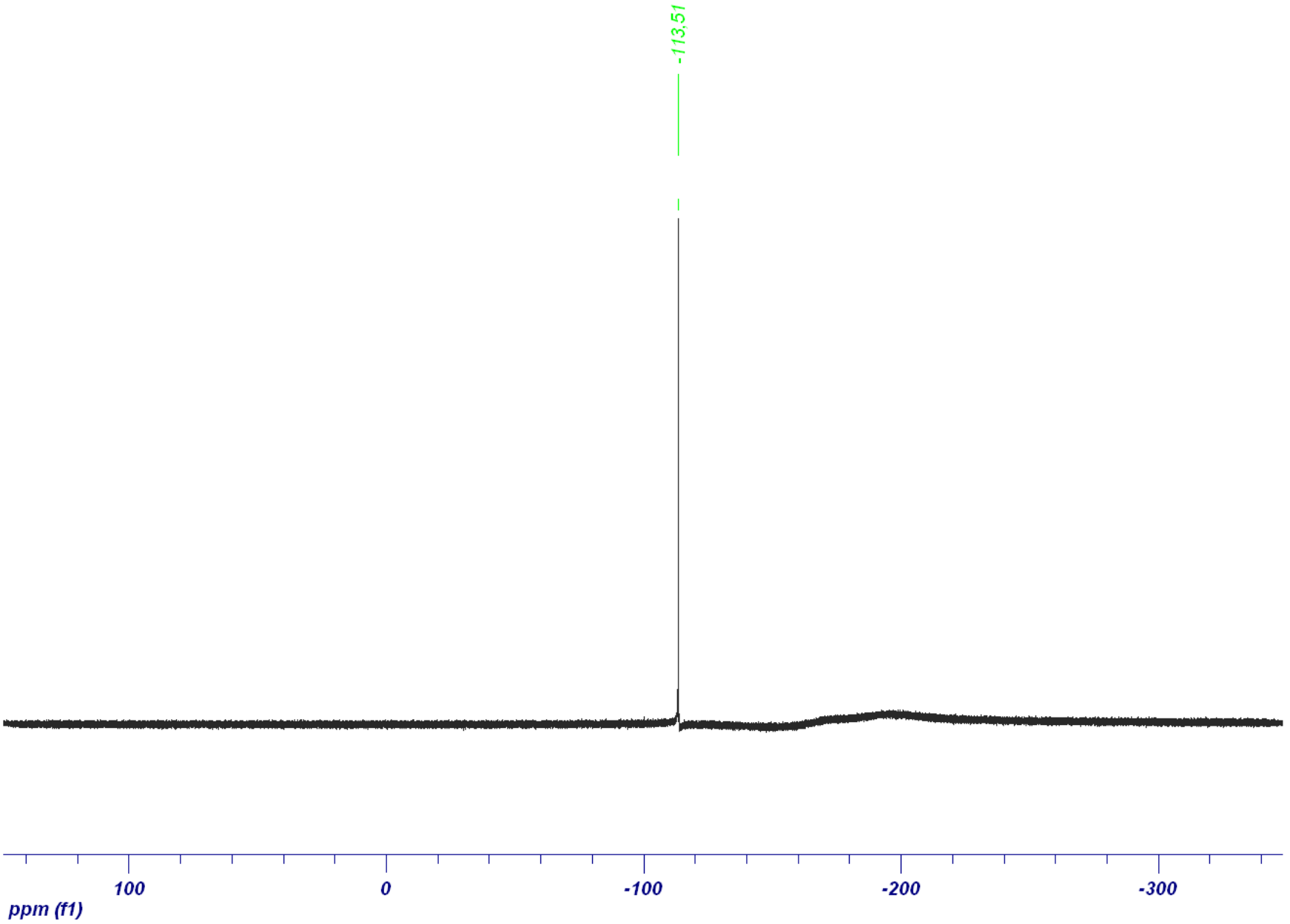
^{1}H NMR spectrum of **2i**



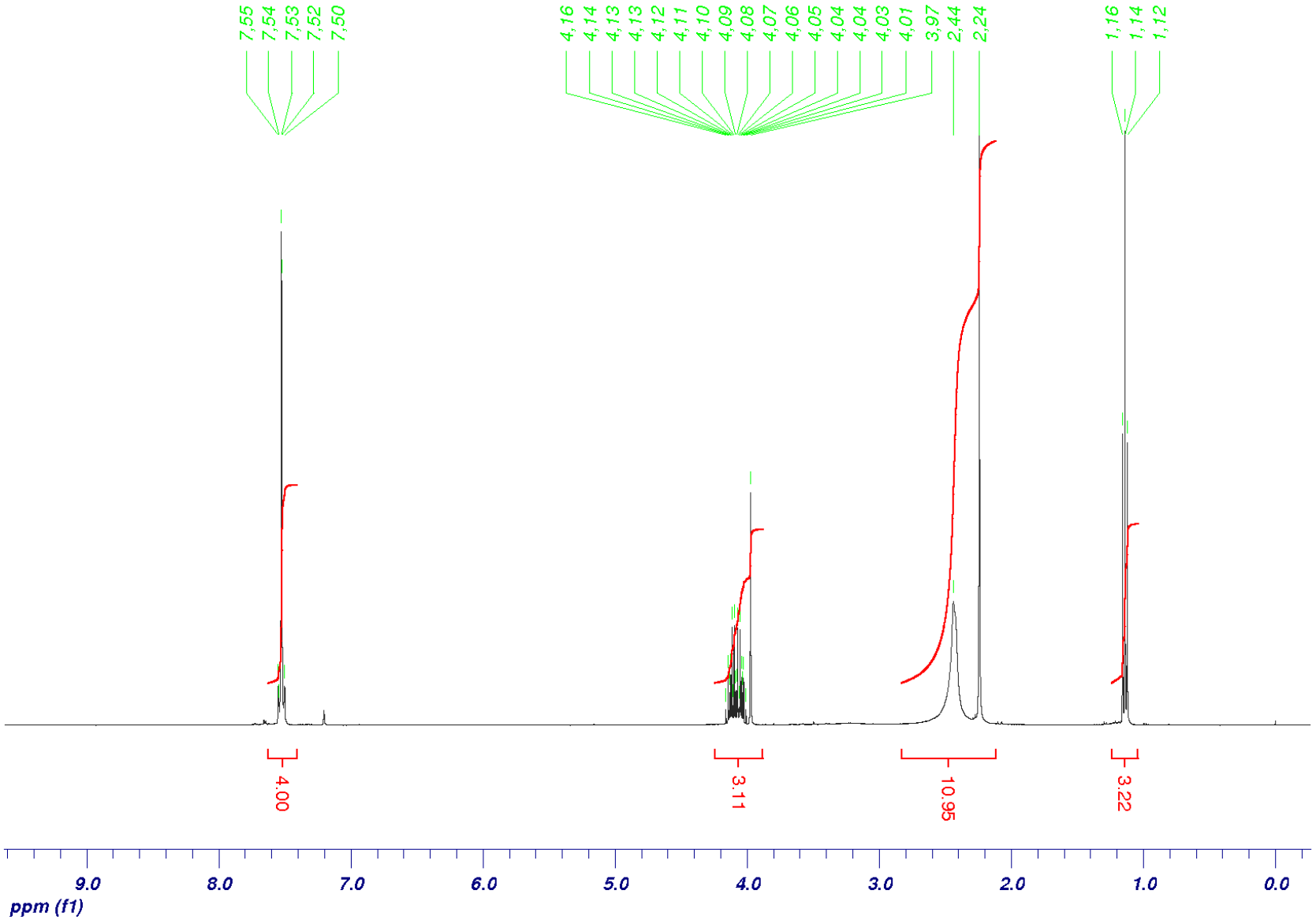
^{13}C NMR spectrum of **2i**



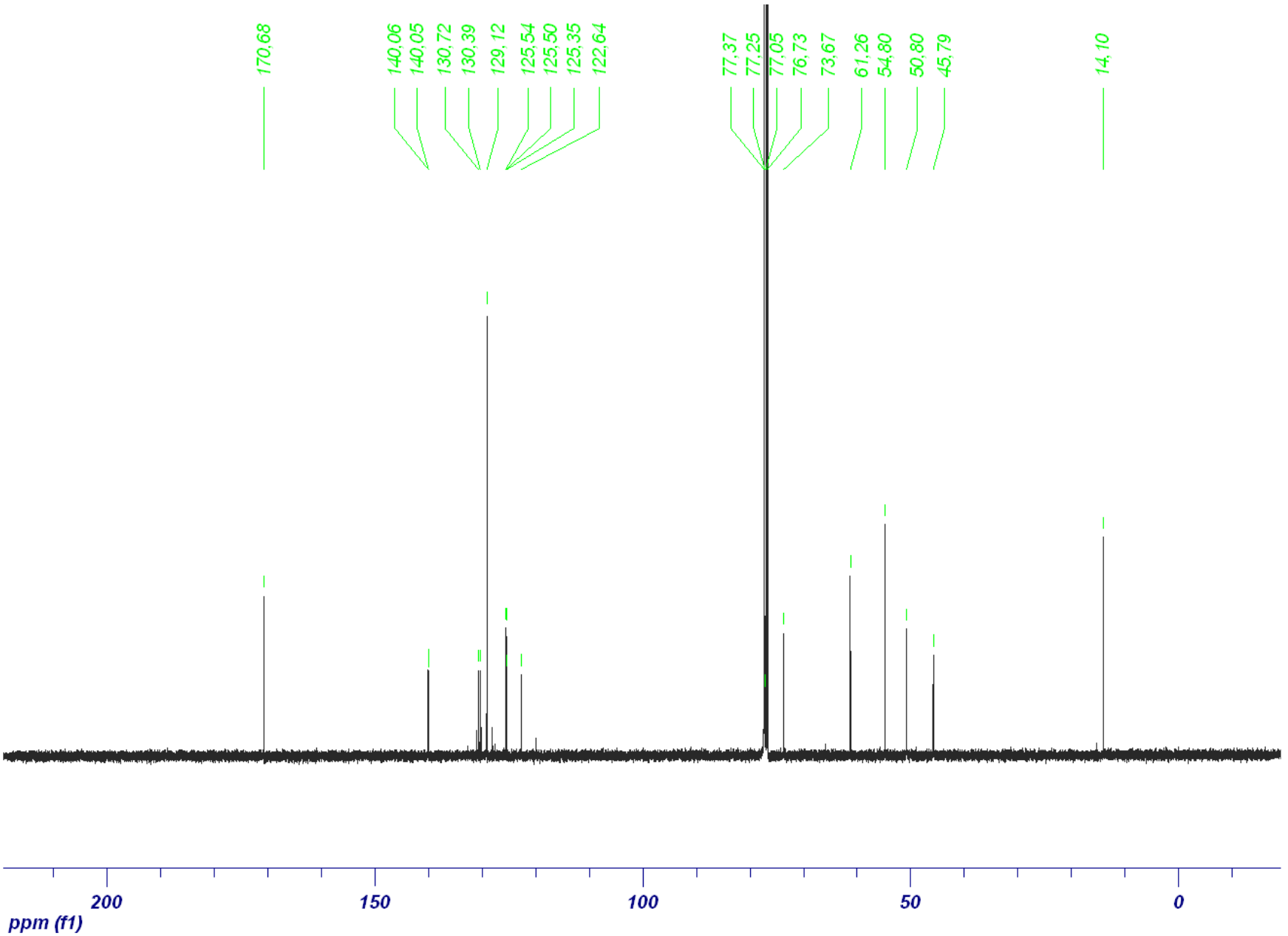
^{19}F NMR spectrum of **2i**



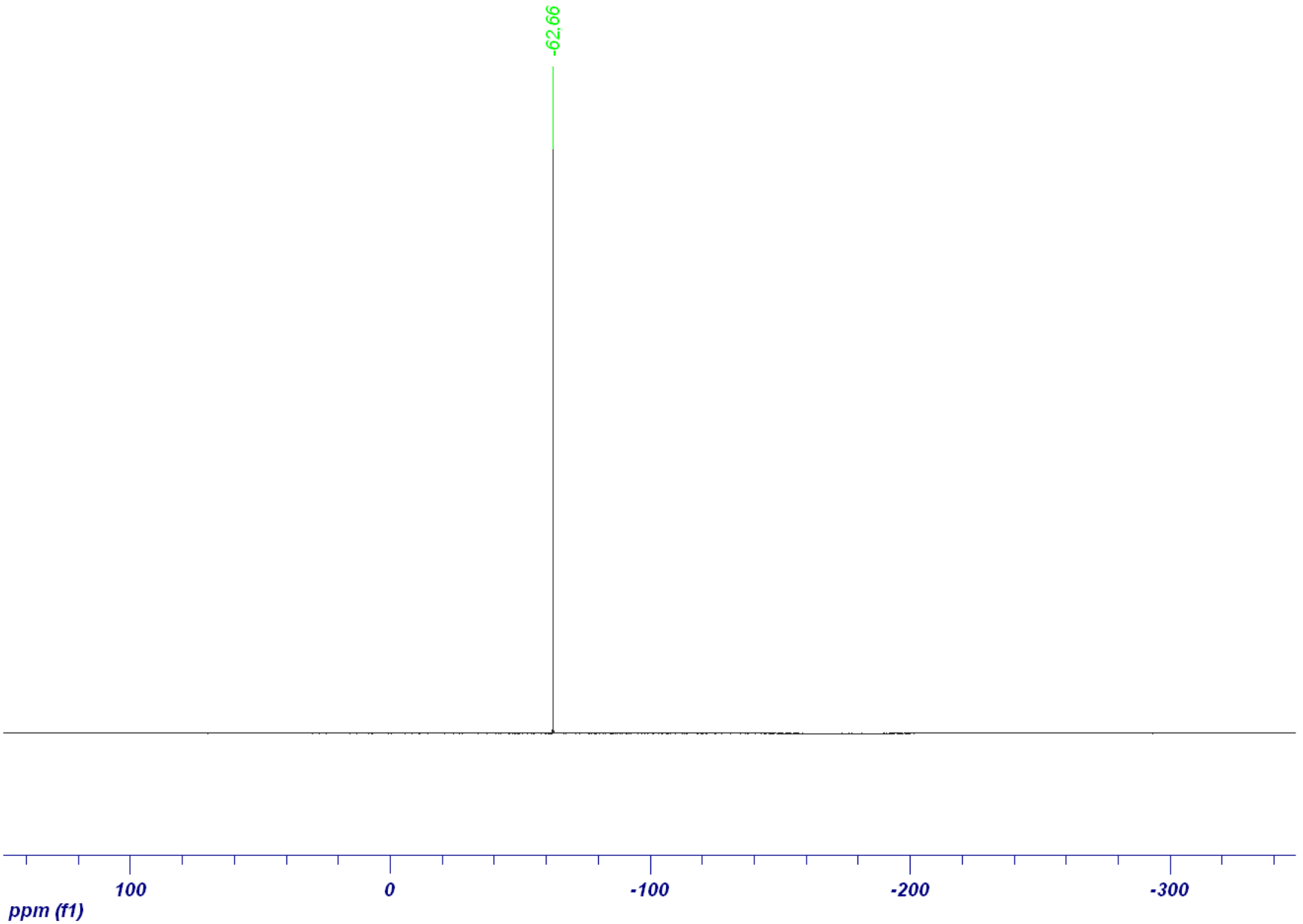
^{1}H NMR spectrum of **2j**



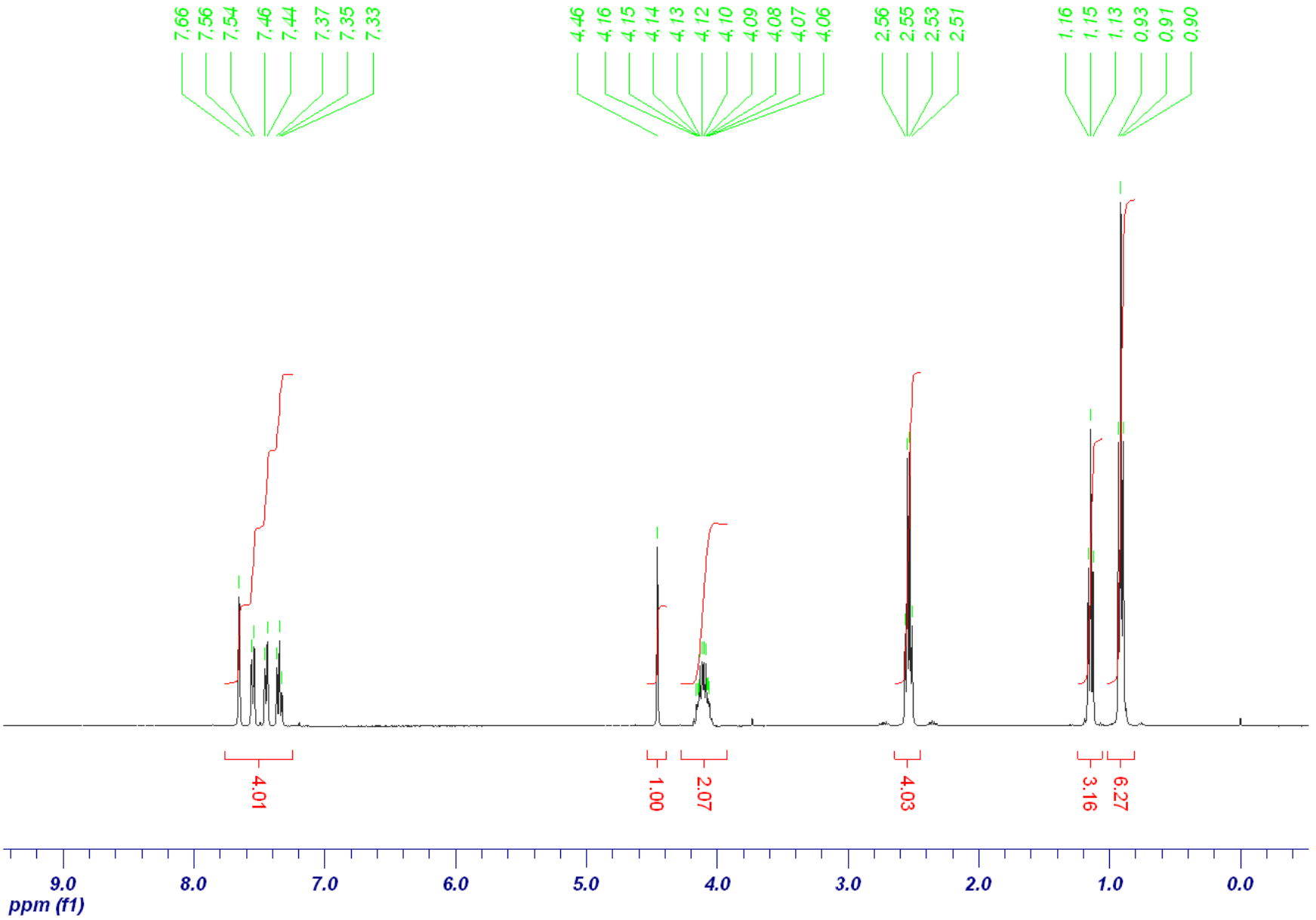
^{13}C NMR spectrum of **2j**



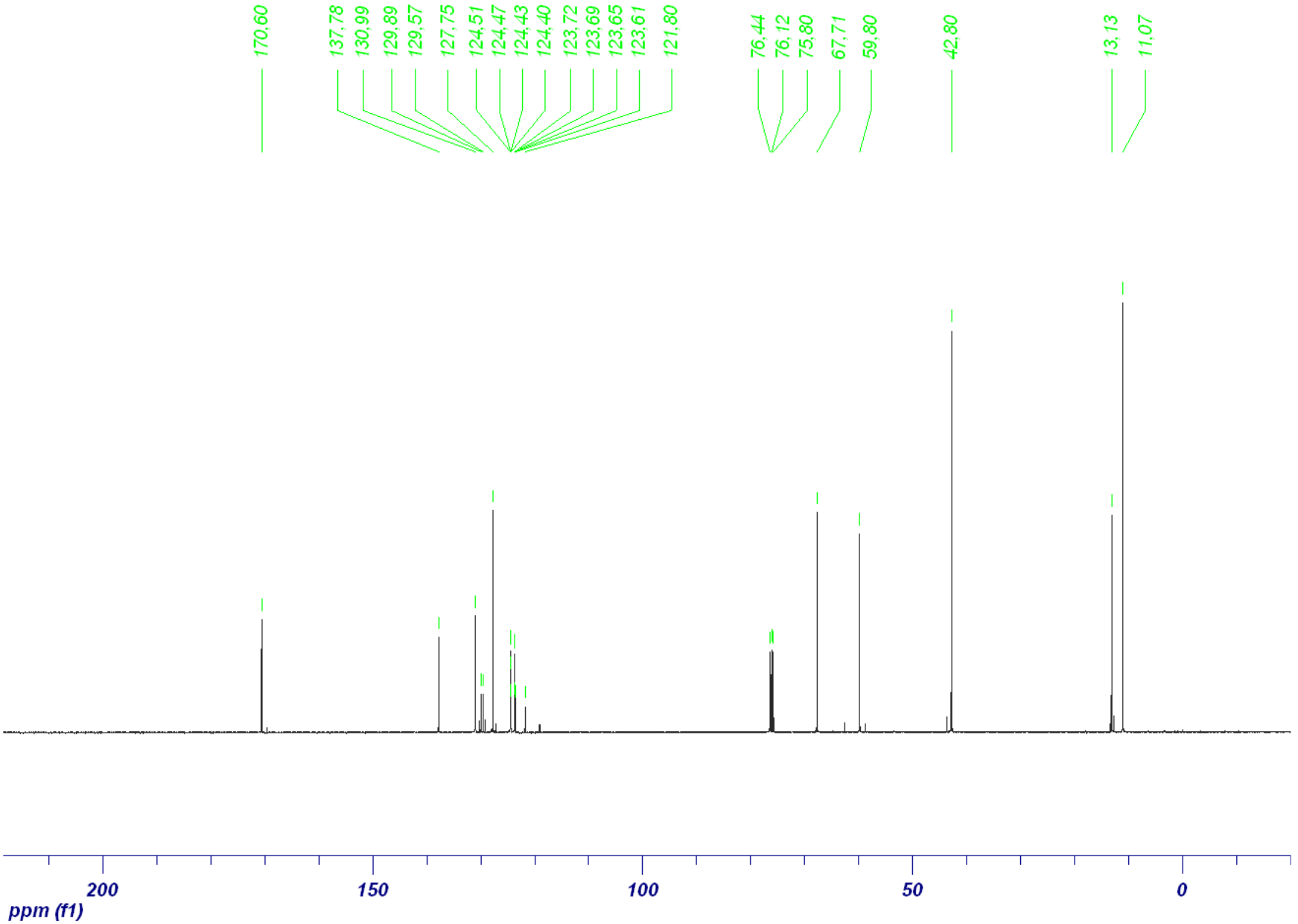
^{19}F NMR spectrum of **2j**



^{1}H NMR spectrum of **2k**



^{13}C NMR spectrum of **2k**



^{19}F NMR spectrum of **2k**