Electronic supplementary materials *Mendeleev Commun.*, 2020, **30**, 156–158

Synthesis of an allosteric modulator of ionotropic glutamate receptors

Mstislav I. Lavrov, Oleg V. Stroganov, Vladimir L. Zamoyski, Vladimir V. Grigoriev, Maxim E. Zapolskiy, Sergey V. Sysolyatin, Valeriy V. Malykhin, Vladimir N. Surmachev and Vladimir A. Palyulin

NMR spectra were recorded on a Bruker Avance 400 NMR spectrometer using $CDCl_3$ for calibration. High-resolution mass spectra were recorded with an Orbitrap Elite Thermo Scientific spectrometer. TLC monitoring was done on Merck Silica gel 60 F_{254} plates, compounds were visualized by I_2 and UV (λ 254 nm). Melting points were measured in the block in an open capillary (REACH Devices RD-MP).

5,7-Dimethyl-1,3-diazaadamantan-6-one **2**. A mixture of 210 mL of isopropyl alcohol, 50 g (0.357 mol) of urotropin, 51.05 mL (0.893 mol) of acetic acid and 37.7 mL (0.357 mol) of diethyl ketone is refluxed at 82 °C with stirring for 2 h. After that, isopropyl alcohol is distilled off. Then hot extraction with heptane is carried out and the extract is cooled to -8 °C. The precipitated crystals are filtered off. Yield 50.43 g (78%), mp 120-122 °C.[18]
^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.9 (s, 6H), 3.06 (d, 4H, *J* 13.6 Hz); 3.31 (d, 4H, *J* 13.6 Hz); 4.14 (s, 2H).

3,7-Bis(chloroacetyl)-1,5-dimethyl-3,7-diazabicyclo[3.3.1]nonan-9-one **3**. A mixture of 133 mL of water and 17.76 g (0.444 mol) of sodium hydroxide is cooled to 1°C with stirring, after which a solution of 20 g (0.111 mol) of 5,7-dimethyl-1,3-diazaadamantan-6-one in 133 mL of methylene chloride is added. Then, while maintaining cooling at 1-3 °C, a solution of 35.5 mL (0.444 mol) of chloroacetyl chloride in 133 mL of methylene chloride is added dropwise over 6 h. Next, another 133 mL of water is added to the reaction mixture. Then methylene chloride is distilled off, and the residue is cooled to room temperature. The precipitate formed is filtered, washed with water and dried in air. Yield 28.54 g (80%), mp 235-237 °C.[19]
^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.1 (s, 6H); 2.87 (d, 2H, *J* 13.7 Hz); 3.43 (d, 2H, *J* 13.7 Hz); 4.04 (d, 2H, *J* 12.9 Hz); 4.07 (d, 2H, *J* 13.7 Hz); 4.34 (d, 2H, *J* 12.9 Hz); 4.96 (d, 2H, *J* 13.7 Hz). ^{13}C NMR (100.4 MHz, $CDCl_3$) δ: 16.5, 41.2, 46.6, 53.7, 57.9, 166.7, 210.3.

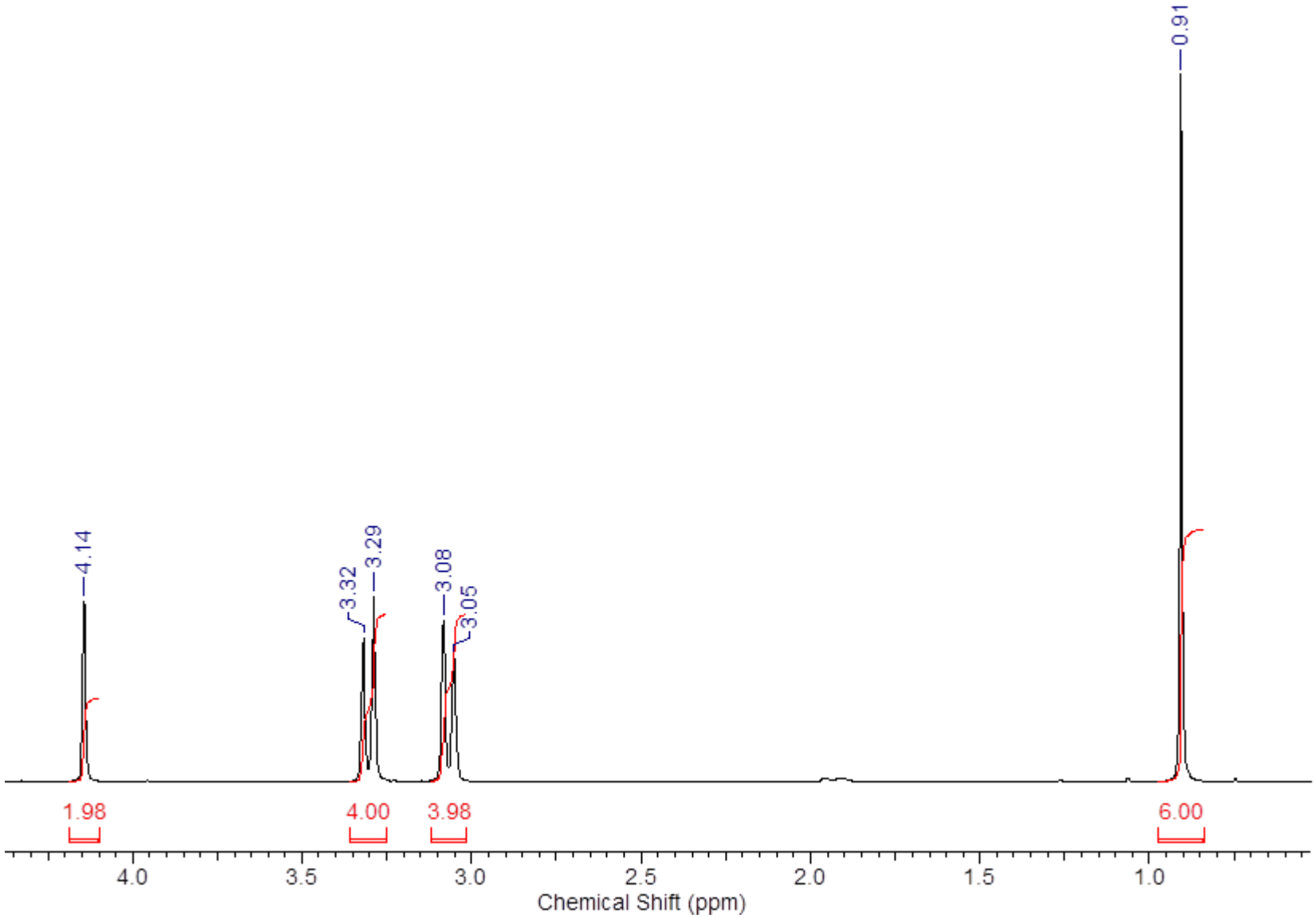
N-*Hydroxy-4-methoxy-3-(chloromethyl)benzylideneamine* **5**. A mixture of 240 mL of ethyl alcohol, 45 g (0.243 mol) of 3-(chloromethyl)-4-methoxybenzaldehyde and 18.74 g (0.269 mol) of hydroxylamine hydrochloride is stirred at room temperature for 15 h. Then the mixture is cooled to 5 °C, 240 mL of water are added, and the stirring is continued for 20 min. The precipitate formed is filtered, washed with water and dried in air. Yield 45.26 g (93%), mp 110-113 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.92 (s, 3H); 4.65 (s, 2H); 6.92 (d, 1H, *J* 8.5 Hz); 7.53 (d, 1H, *J* 8.5 Hz); 7.62 (s, 1H); 8.11 (s, 1H); 8.58 (br. s, 1H). ^{13}C NMR (100.4 MHz, $CDCl_3$) δ: 41.2, 55.9, 111.0, 124.5, 126.5, 129.10, 149.8, 158.9.

N-*Hydroxy-4-methoxy-3-(pyrrolidin-1-ylmethyl)benzylideneamine* **6**. A mixture of 32 mL of methylene chloride, 13 mL (0.16 mol) of pyrrolidine is cooled to 2°C, and 8 g (0.04 mol) of *N*-hydroxy-4-methoxy-3-(chloromethyl)benzylideneamine are added dropwise so that the reaction temperature did not exceed 17°C. The reaction mixture is stirred for 2 h at room temperature, and then 10 mL of water are added. The organic phase is separated and dried over Na_2SO_4. The mixture is then filtered off from the desiccant, and the filter is washed with 10 mL of methylene chloride. Evaporation of solvent from the obtained filtrate yields 8.44 g (90%) of 6, mp 113-115 °C.

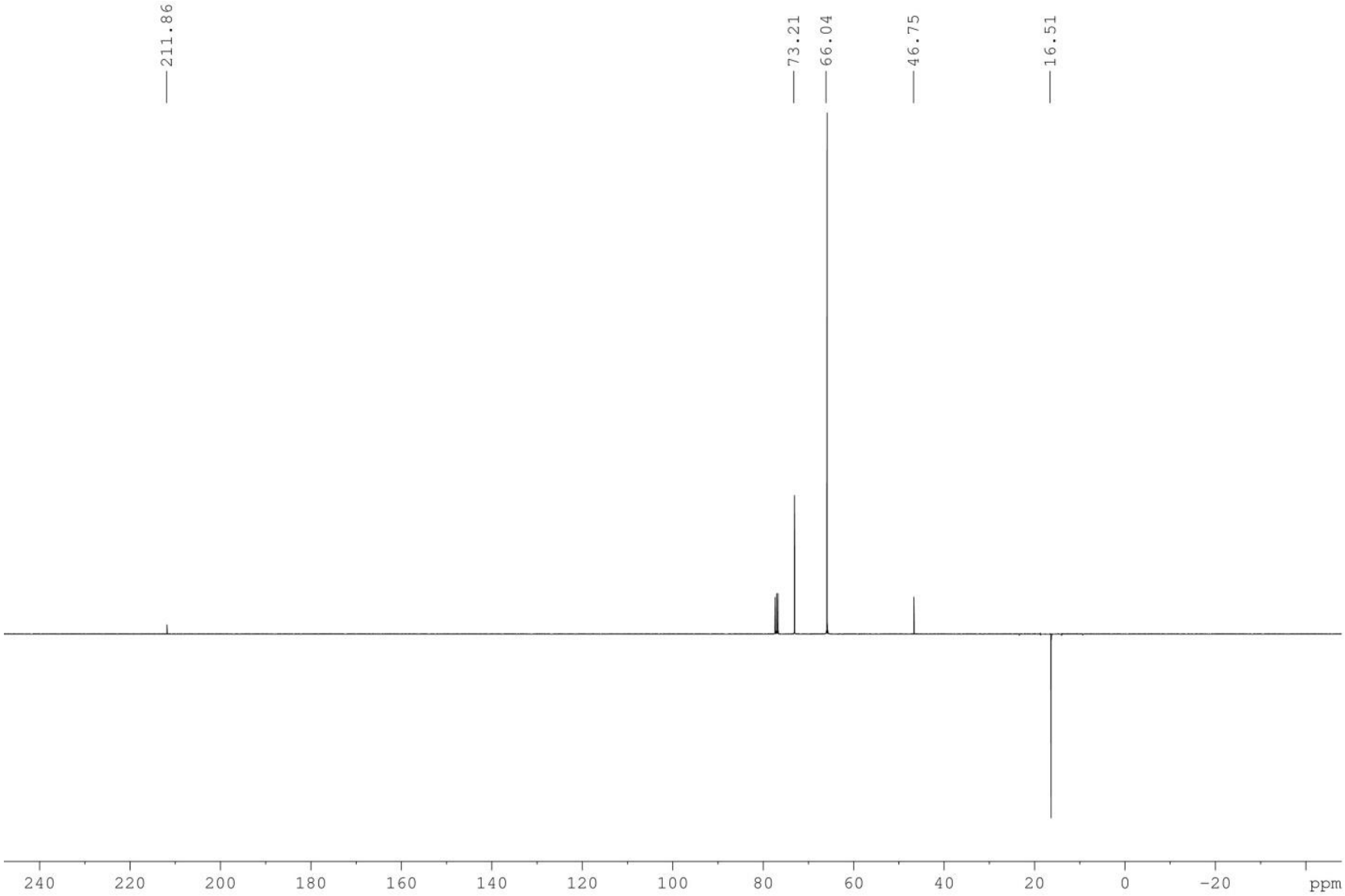
^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.82 (br. s, 4H); 2.67 (br. s, 4H); 3.75 (s, 2H); 3.83 (s, 3H); 6.83 (d, 1H, *J* 8.34 Hz); 7.30 (d.d, 1H, *J* 8.34 Hz, *J* 2.15 Hz); 7.96 (s, 1H); 8.05 (s, 1H). ^{13}C NMR (100.4 MHz, $CDCl_3$) δ: 23.5, 53.3, 54.1, 55.5, 110.2, 125.7, 126.9, 127.7, 129.3, 149.0, 158.6.

4-Methoxy-3-(pyrrolidin-1-ylmethyl)benzylamine **7**. A mixture of 6.6 g (0.028 mol) of *N*-hydroxy-4-methoxy-3-(pyrrolidin-1-ylmethyl)benzylideneamine, 45 mL of methanol, 7.13 g (0.057 mol) of oxalic acid dihydrate and 20 mL of methanol is stirred for 10 min, then 0.82 g of 5 wt.% Pd/C catalyst is added. The reaction mixture is purged with nitrogen and hydrogenated with hydrogen at atmospheric pressure and room temperature for 4.5 h. The hydrogen absorption is 1.4 L. Then the catalyst is filtered and washed on the filter with 5 mL of methanol. The filtrate is diluted with 75 mL of isopropanol and then concentrated *in vacuo* to a volume of 100-110 mL. The residue is cooled to 2 °C, and the precipitate formed is filtered. The oxalate is dissolved in 50 mL of water and made basic with 10% NaOH to pH 9. The aqueous solution is extracted with methylene chloride (3-150 mL). The organic extract is washed with 50 mL of water and dried over Na_2SO_4. The desiccant is filtered and washed on a filter with 30 mL of methylene chloride. The filtrate is evaporated to dryness to yield 4.31 g (70%) of 7 as oil.

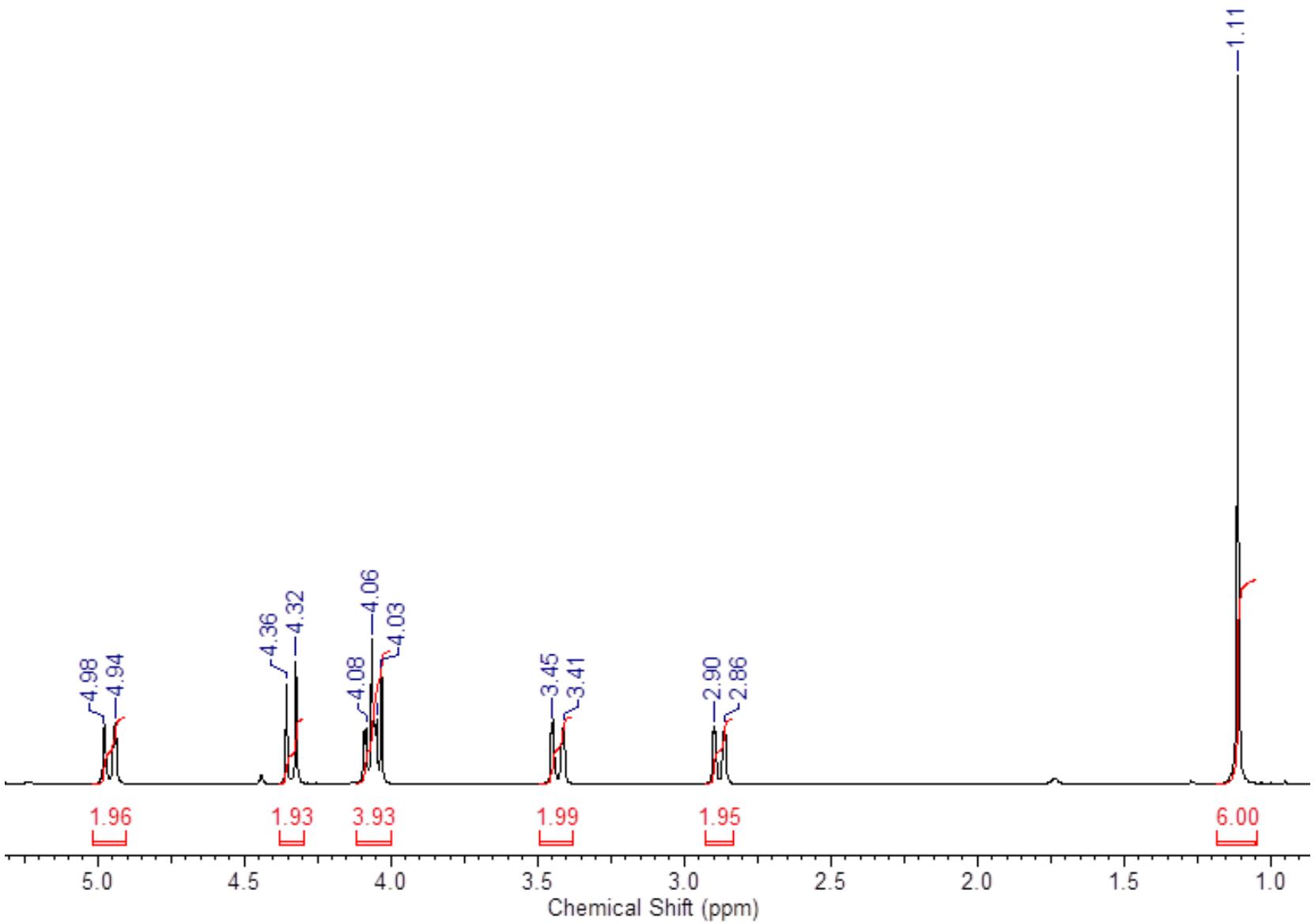
^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.76 (br. s, 4H); 2.50 (br. s, 2H); 2.55 (br. s, 4H); 3.64 (s, 2H); 3.76 (s, 2H); 3.77 (s, 3H); 6.78 (d, 1H, *J* 8.34 Hz); 7.12 (d.d, 1H, *J* 8.34 Hz, *J* 2.15 Hz); 7.26 (s, 1H). ^{13}C NMR (100.4 MHz, $CDCl_3$) δ: 23.5, 46.35, 53.9, 54.3, 55.5, 110.4, 126.3, 127.5, 129.3, 135.3, 156.2.



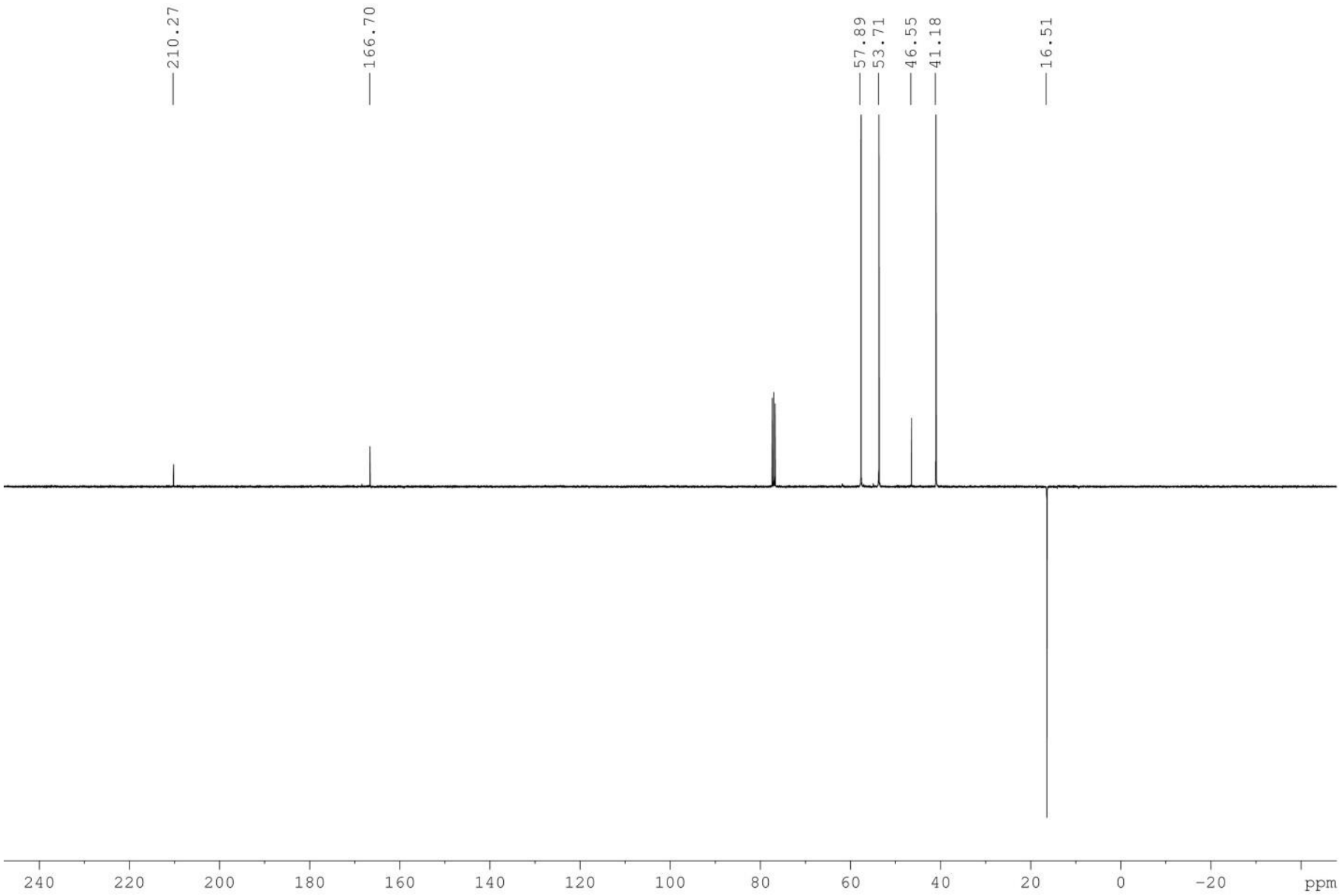
^{1}H NMR spectrum of compound 2



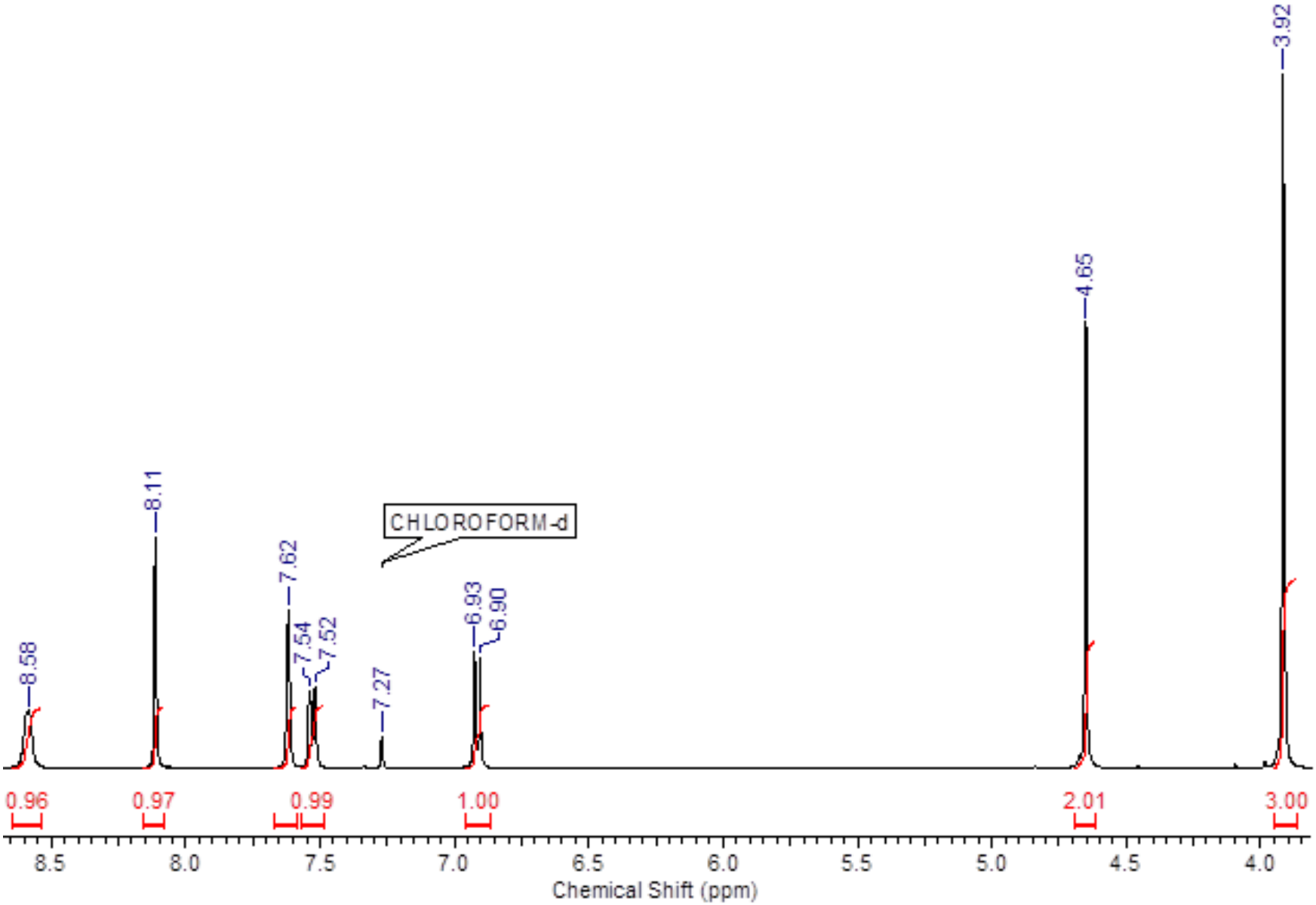
^{13}C NMR spectrum of compound 2



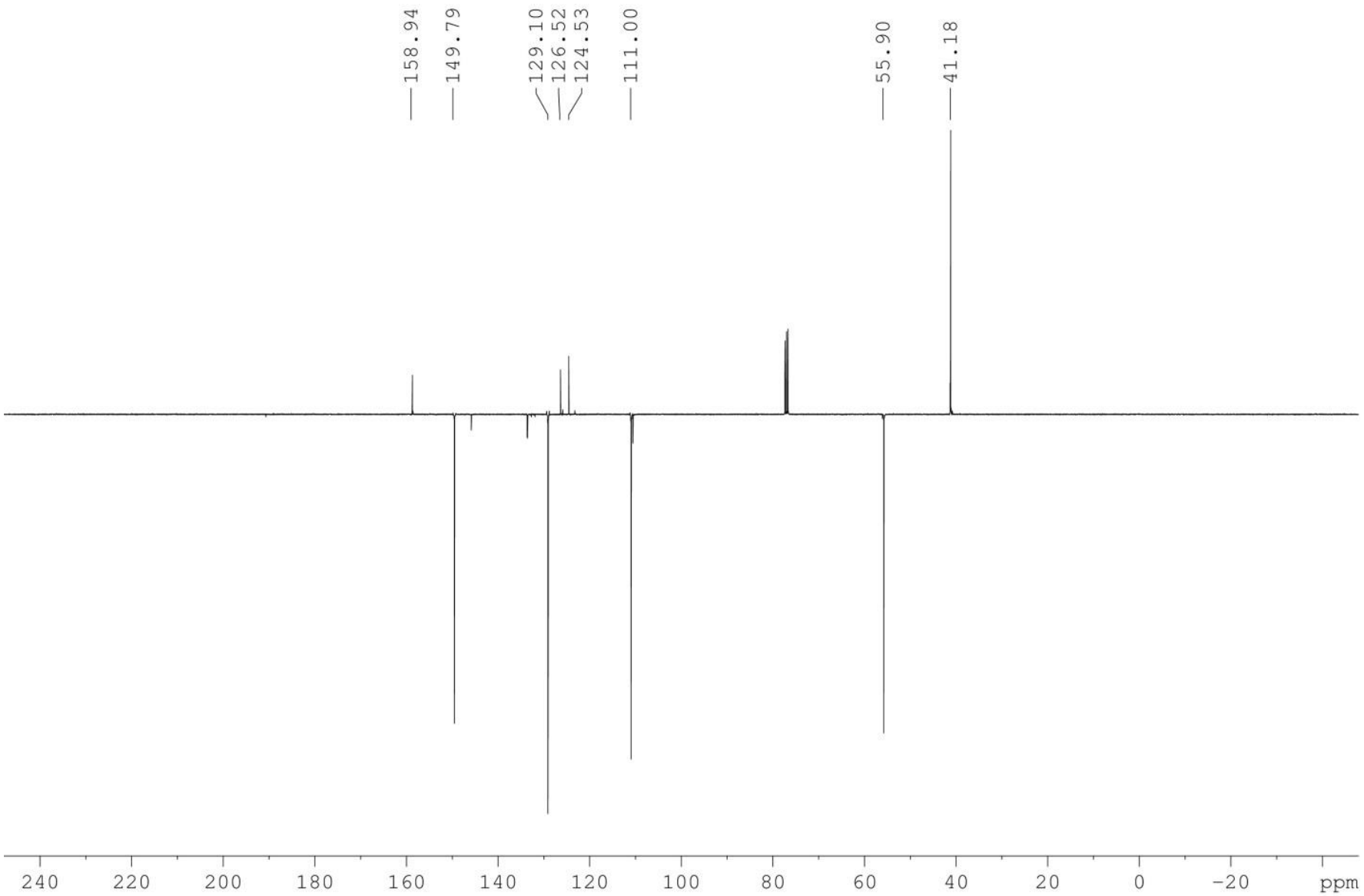
^{1}H NMR spectrum of compound 3



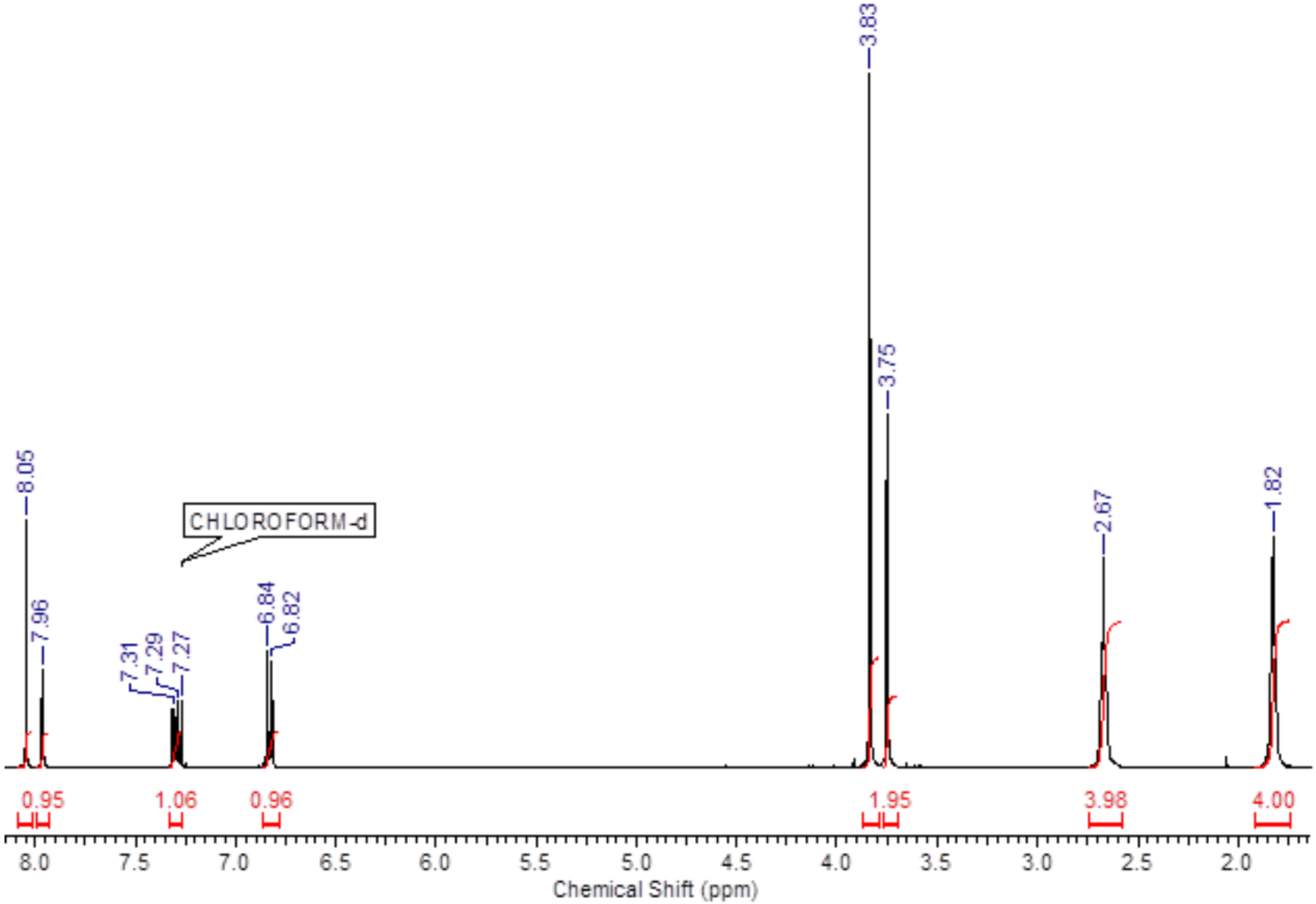
^{13}C NMR spectrum of compound 3



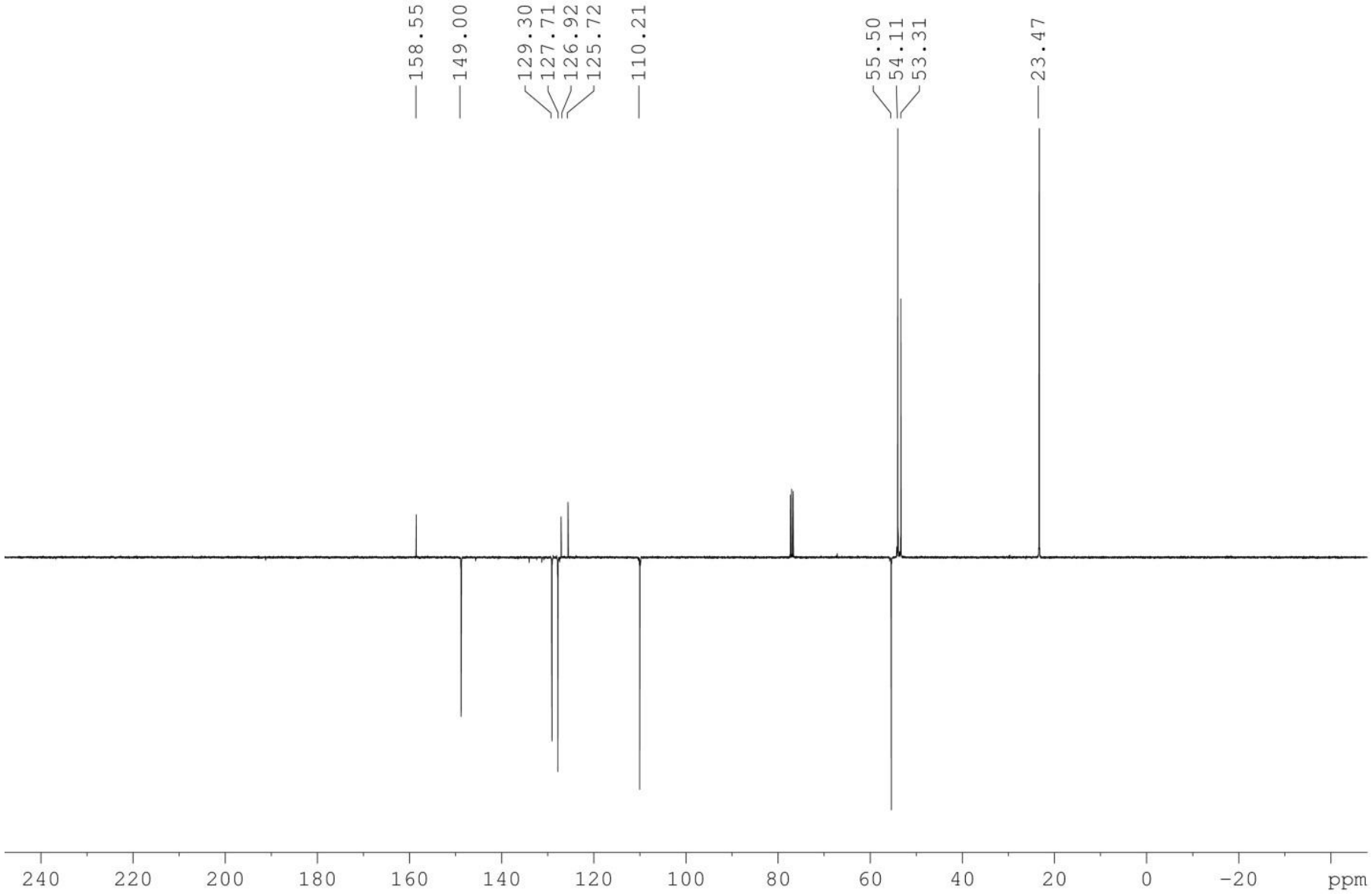
^{1}H NMR spectrum of compound 5



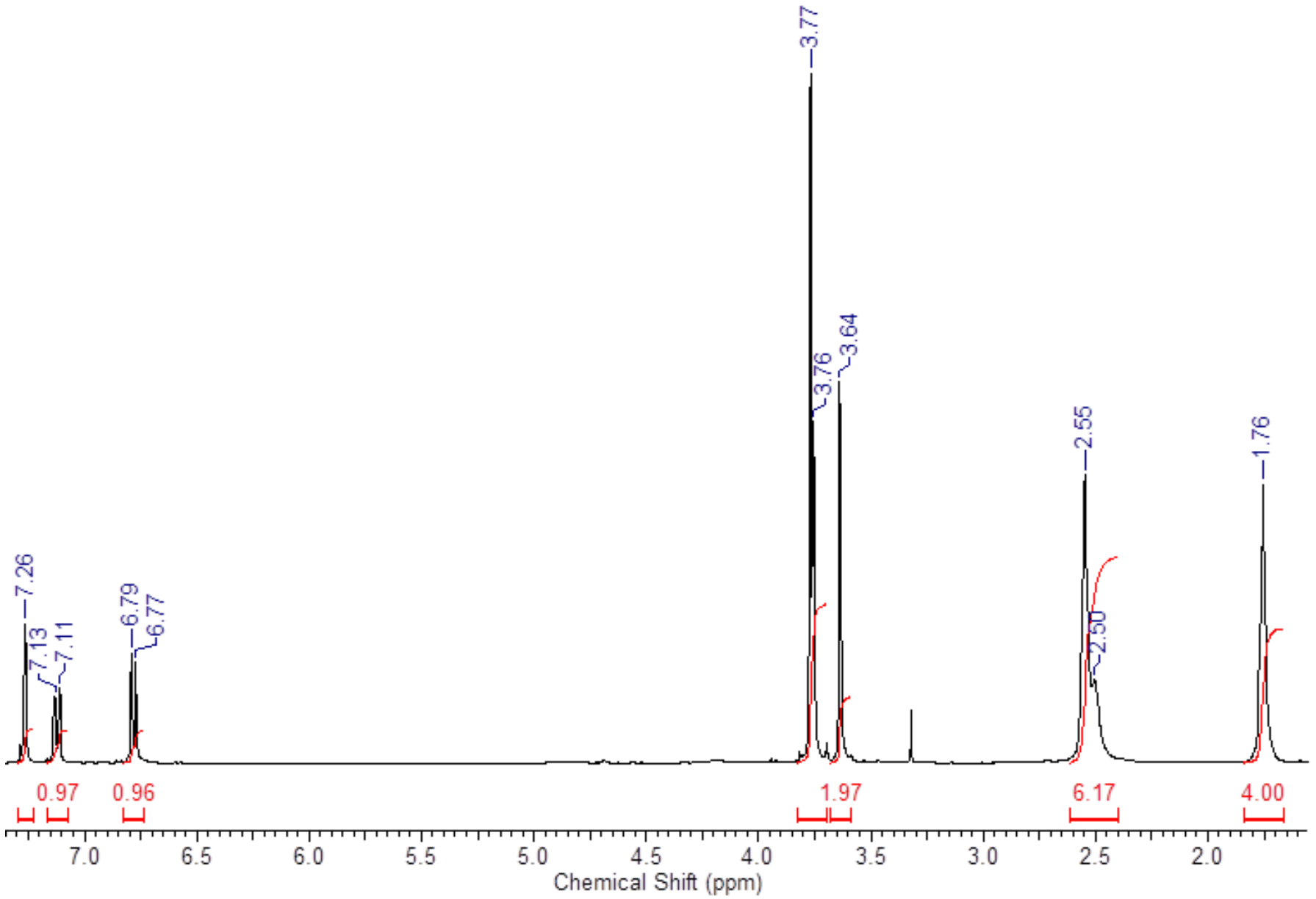
^{13}C NMR spectrum of compound 5


3.83
3.75
8.05
7.96
CHLOROFORM-d
7.31
7.29
7.27
6.84
6.82
2.67
1.82
0.95
1.06
0.96
1.95
3.98
4.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
Chemical Shift (ppm)

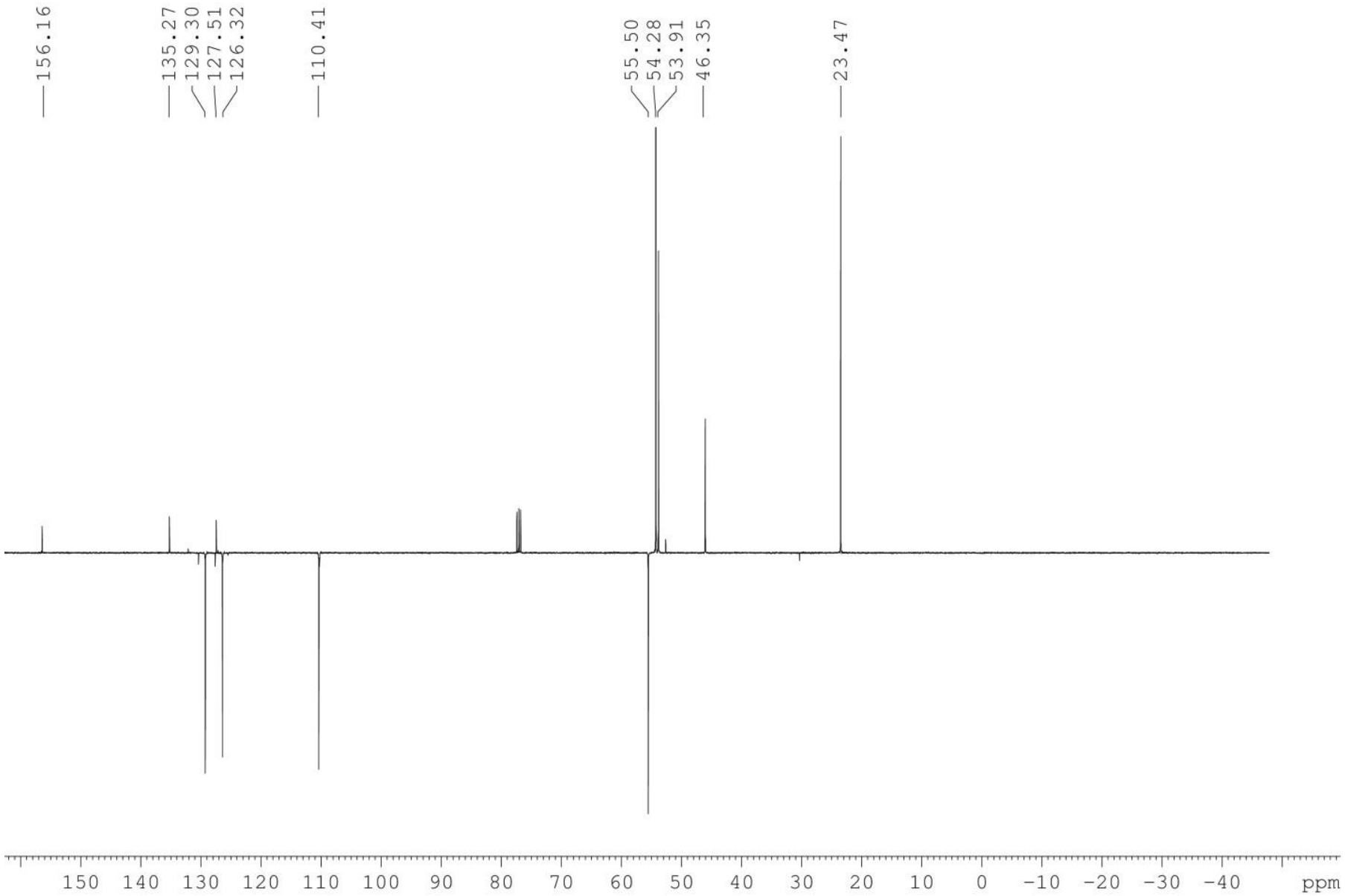
^{1}H NMR spectrum of compound 6



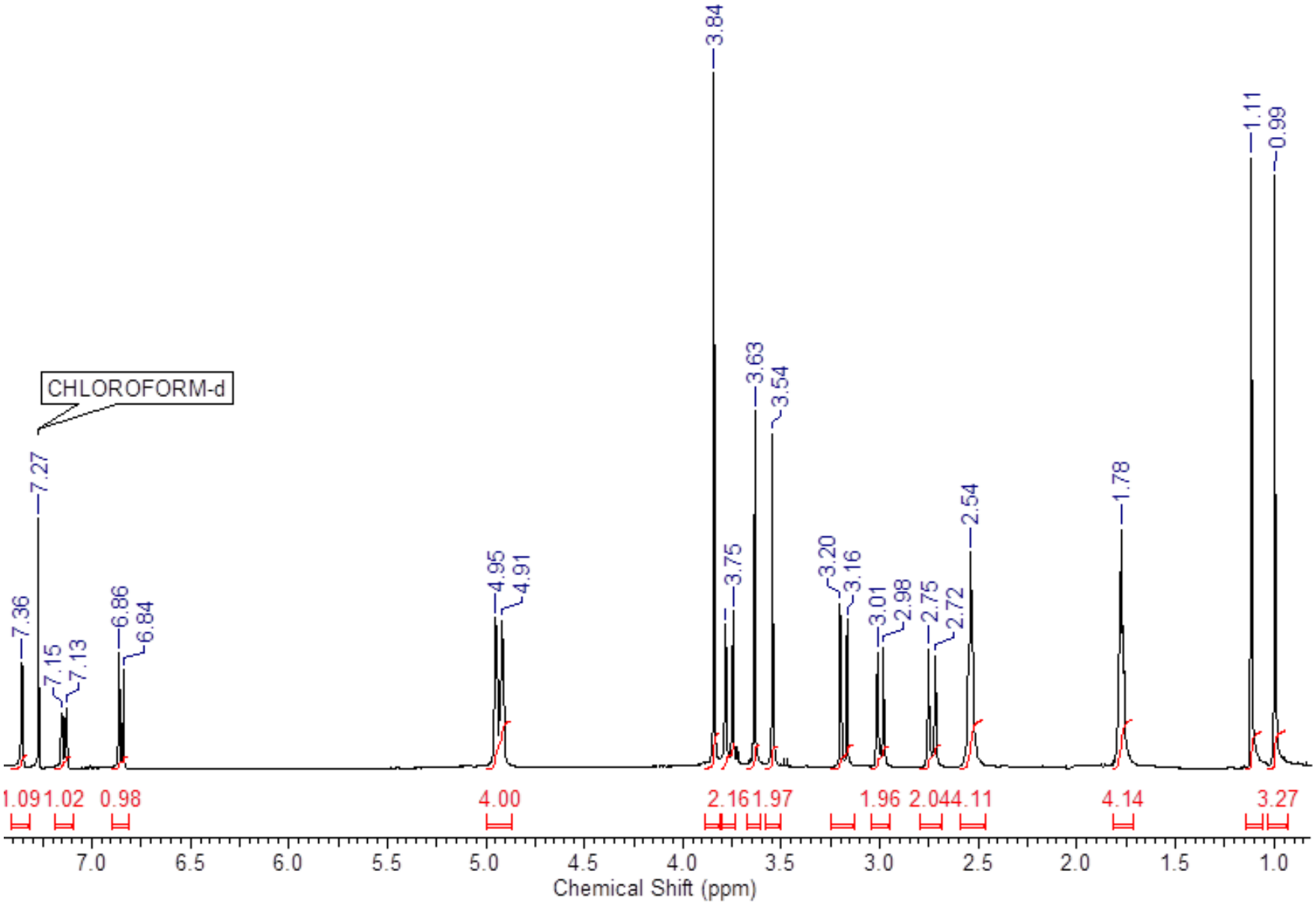
^{13}C NMR spectrum of compound 6



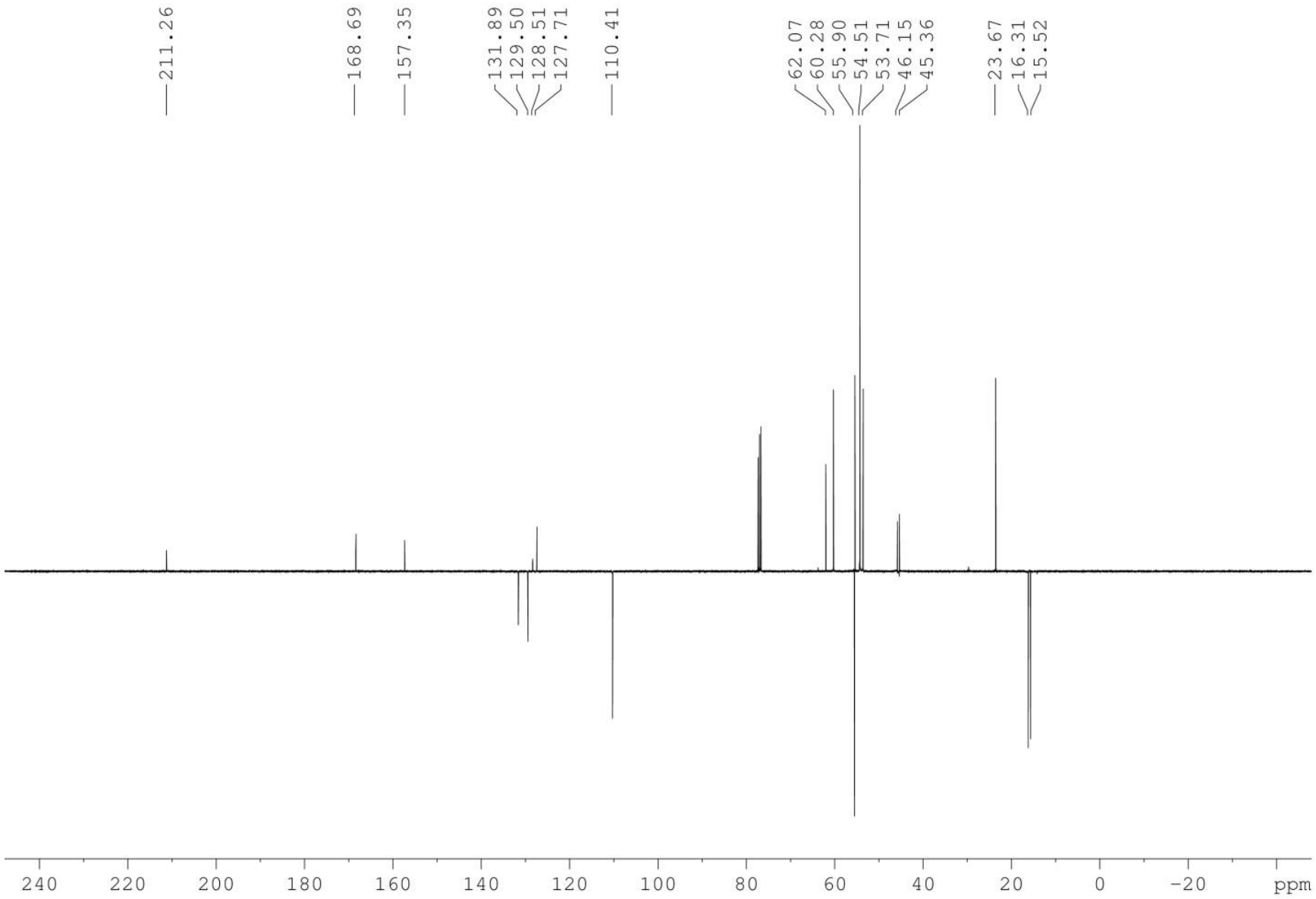
^{1}H NMR spectrum of compound 7



^{13}C NMR spectrum of compound 7



^{1}H NMR spectrum of compound 1



^{13}C NMR spectrum of compound 1