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Enamine-Mediated Mannich Reaction of Cyclic N,O-Acetals and Amido Acetals: the Multigram Synthesis of Pyrrolidine Alkaloid Precursors

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General Information

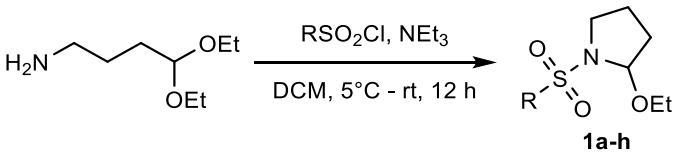
^{1}H spectra were recorded on a Bruker MSL 400 (400 MHz) spectrometer or Bruker Avance 600 (600 MHz) spectrometer. ^{13}C NMR spectra were recorded on a Bruker Avance 600 (151 MHz) spectrometer. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference (proton, $CDCl_3$ δ 7.28, $(CD_3)_2SO$ δ 2.50; carbon, $CDCl_3$ δ 77.7, $(CD_3)_2SO$ δ 40.0). ^{31}P NMR spectra were recorded on a Bruker MSL 400 (162 MHz) spectrometer using 85% H_3PO_4 as an external reference. Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), bs (broad singlet). Coupling constants were reported in Hertz (Hz). The IR spectra were recorded on a Vector 22 Fourier spectrometer by Bruker in the range of 400-4000 cm^{-1}. Crystalline samples were studied as a suspension in vaseline oil. The melting points were determined in glass capillaries on a Stuart SMP 10 instrument and were uncorrected. Elemental analysis of the compounds was carried out on a high-temperature 2-reactor C, H, Nanalyzer of EuroVector brand EA 3000. The halogen content was determined by the Schöniger method. MALDI-TOF mass spectra were recorded on a Bruker ULTRAFLEX III TOF/TOF instrument (with 2,5-dihydroxybenzoic acid matrix). All commercially available reagents were used as received for the reactions without any purification. All solvents were purified and dried according to standard procedures. 1-Sulfonyl-2-ethoxypyrrolidines **1a-h**,[1,2] *N*-(4,4-diethoxybutyl)sulfonylamides **2a,b**,[1,2] di-*o*-tolyl(4,4-diethoxybutyl)phosphoramidate **2c**[3], *N*-(4,4-diethoxybutyl)pyrimidin-2-amine **2d**[4] and 1-(4,4-diethoxybutyl)-3-phenylurea **2e**[5] were synthesized by reported procedures (see below).

The X-ray diffraction data for the crystals were collected on a Bruker SMART Apex II (**2a, 2b, 2e**) and Bruker D8 Venture (**2f, 3b, 3e**) diffractometer equipped with a CCD detector (Mo-Kα, λ = 0.71073 Å, graphite monochromator). Semi-empirical absorption correction was applied by the SADABS program.[6] The structures were solved by direct methods and refined by the full-matrix least squares in the anisotropic approximation for non-hydrogen atoms. The calculations were carried out by the SHELX-2014 program package[7] using Olex2 1.2.[8] The crystallographic parameters and the structure refinement details for all investigated crystals are given in Table S1. Crystallographic data for structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center (2175117-2175122).

Synthesis of starting compounds

2-Ethoxypyrrolidines **1** and *N*-(4,4-diethoxybutyl)sulfonylamides **2** were obtained as described below from the same starting materials, namely, sulfonyl chlorides and 4,4-diethoxybutane-1-amine. The synthetic outcome of this reaction depends on the order of addition of reagents, as has been shown by us earlier.[1,2]

General procedure for the synthesis of 2-ethoxypyrrolidines 1a-h[1,2]

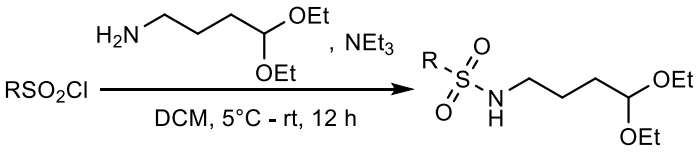


1a-h

R = 4-Me-C_6H_4 (a); Ph (b); 4-Cl-C_6H_4 (c); 2-naphthyl (d); 2-thienyl (e); Et (f), Cl-$(CH_2)_3$- (g); vinyl (h)

A 4,4-diethoxybutane-1-amine (3.4 g, 20 mmol, 1.0 eq.) and triethylamine (3.5 mL, 5.54 g, 25 mmol, 1.25 eq.) were dissolved in dichloromethane (100 mL). The solution was cooled (5–8°C) and a sulfonyl chloride (20 mmol, 1.0 equiv.) was added in portions. Reaction mixture was allowed to stir at room temperature for 12 h, washed with saturated $NaHCO_3$ solution in water (100 mL). Organic layer was separated, dried over $MgSO_4$ and evaporated to give target compounds **1**, which were used without further purification.

General procedure for the synthesis of *N*-(4,4-diethoxybutyl)sulfonylamides 2a,b[1,2]

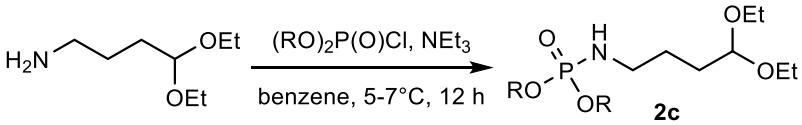


2a,b

R = 4-AcNH-C_6H_4 (a); Me (b)

A sulfonyl chloride (20 mmol, 1.0 eq.) was added in portions to a cooled solution (5–8°C) of triethylamine (3.5 mL, 5.54 g, 25 mmol, 1.25 eq.) in dichloromethane (100 mL). Immediately, a 4,4-diethoxybutane-1-amine (3.4 g, 20 mmol, 1.0 eq.) was added in portions. Reaction mixture was allowed to stir at room temperature for 12 h, washed with saturated $NaHCO_3$ solution in water (100 mL). Organic layer was separated, dried over $MgSO_4$ and evaporated to give target compounds **2**, which were used without further purification.

Procedure for the synthesis of di-*o*-tolyl(4,4-diethoxybutyl)phosphoramidate 2c[3]

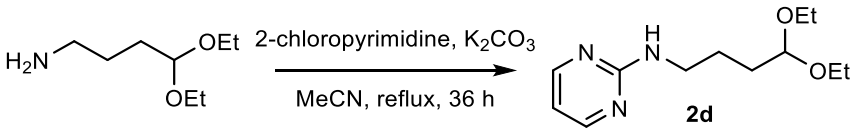


2c

R = 2-Me-C_6H_4

A 4,4-diethoxybutan-1-amine (1.77 g, 11.0 mmol, 1.0 eq.) and and triethylamine (7.66 mL, 5.56 g, 55.0 mmol, 5.0 eq.) were dissolved in dry benzene (30 mL). The solution was cooled (5-7°C) and a di-*o*-tolyl phosphorochloridate (3.26 g, 11.0 mmol, 1.0 eq.) was added dropwise while maintaining temperature at 5-7°C. The reaction mixture was allowed to stir at 5-7°C for additional 12 hours. The precipitate was filtered off. he solvent was removed from the filtrate under reduced pressure to give the compound **2c** as yellowish oil, which was used without further purification. Yield 4.12 g, 89%; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.18 (t, 6H, *J* = 7.1 Hz), 1.56-1.67 (m, 4H), 2.23 (s, 6H), 3.07-3.17 (m, 2H), 3.38-3.49 (m, 2H), 3.54-3.65 (m, 2H), 4.43 (t, 1H, *J*=5.1 Hz), 7.00-7.07 (m, 2H), 7.10-7.19 (m, 4H), 7.36-7.40 (m, 2H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 15.28, 16.31, 26.63, 30.75, 41.66 (d, *J* = 0.9 Hz), 61.24, 102.59, 119.90 (d, *J* = 2.6 Hz), 124.66 (d, *J* = 0.9 Hz), 126.93 (d, *J* = 1.3 Hz), 129.19 (d, *J* = 6.6 Hz), 131.20, 149.55 (d, *J* = 7.2 Hz). ^{31}P NMR ($CDCl_3$, 161.9 MHz): δ -0.61.

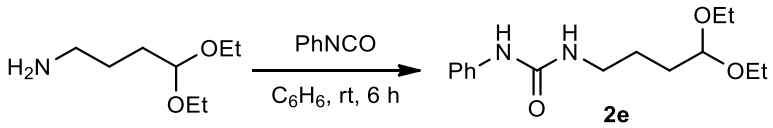
Procedure for the synthesis of *N*-(4,4-diethoxybutyl)pyrimidin-2-amine 2d[4]



2d

A 2-chloropyrimidine (1.0 g, 8.73 mmol, 1.0 eq.) was dissolved in dry acetonitrile (30 mL). 4,4-Diethoxybutyl-1-amine (1.40 g, 8.73 mmol, 1.0 eq.) and potassium carbonate (1.50 g, 10.86 mmol, 1.25 eq.) were added and the reaction mixture was refluxed for 36 h. The inorganic salts were filtered off. The solvent was removed from the filtrate under reduced pressure to give the compound **2d** as yellowish oil, which was used without further purification. Yield 1.69 g, 81%; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.18 (t, 6H, *J* = 7.1 Hz), 1.64-1.72 (m, 4H), 3.40-3.52 (m, 4H), 3.58-3.67 (m, 2H), 4.50 (t, 1H, *J* = 5.5 Hz), 5.68-5.78 (br. s, 1H), 6.48 (t, 1H, *J* = 4.8 Hz), 8.24 (d, 2H, *J* = 4.8 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 15.76, 25.22, 31.57, 41.68, 61.63, 103.18, 110.6, 158.36, 162.93.

Procedure for the synthesis of 1-(4,4-diethoxybutyl)-3-phenylurea 2e[5]



A 4,4-diethoxybutan-1-amine (2.03 g, 12.6 mmol, 1.0 eq) was dissolved in benzene (10 mL). A solution was cooled (5-7°C) and a phenylisocyanate (1.50 g, 12.6 mmol, 1.0 eq.) was added dropwise while maintaining temperature at 5-7°C. Reaction mixture was allowed to stir at room temperature for 6 h. The solvent was removed under reduced pressure and residue dried in vacuum (10 Torr, rt, 3 h) to give 1-(4,4-diethoxybutyl)-3-phenylurea **2e** as yellow oil, which solidified upon storage. The obtained compound was used without further purification.

Synthesis of 2-(2-acylmethylene)pyrrolidines 3

General procedure for the synthesis of compounds 3

To a solution of 2-ethoxypyrrolidine **1** (1.86 mmol, 1.0 equiv) or 4,4-diethoxybutan-1-amine derivative **2** (1.86 mmol, 1.0 equiv) and ketone (18.6 mmol, 10.0 equiv) in dioxane (10mL) *L*-proline (0.21 g, 1.86 mmol, 1.0 equiv), pyridine (0.15 mL, 0.14 g, 1.0 equiv) and trifluoroacetic acid (0.14 mL, 1.86 mmol, 1 equiv) were added. The reaction mixture was refluxed for 15 h, cooled and the solvent was removed under reduced pressure. A distilled water (20 mL) was added to the residue and resulting slurry was stirred at room temperature for 3 h. The precipitate was filtered off and dried in under reduced pressure (10 Torr, 30°C, 5h) to give the target compound **3**.

Characterization data

1-(1-Tosylpyrrolidin-2-yl)propan-2-one (3aa)

White solid; yield 0.49 g, 94%; mp 96-97°C; IR (KBr, cm^{-1}) 1154, 1596, 1717; ^{1}H NMR (DMSO-d_6, 600 MHz): δ 1.33-1.41 (m, 1H), 1.43-1.49 (m, 1H), 1.53-1.61 (m, 1H), 1.65-1.77 (m, 1H), 2.11 (s, 3H), 2.41 (s, 3H), 2.76 (dd, 1H, *J* = 17.2 Hz, *J* = 9.3 Hz), 2.93 (dd, 1H, *J* = 17.1 Hz, *J* = 3.3 Hz), 3.02-3.10 (m, 1H), 3.24-3.35 (m, 1H), 3.76-3.84 (m, 1H), 7.44 (d, 2H, *J* = 7.9 Hz), 7.69 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR (DMSO-d_6, 150 MHz): δ 21.48, 23.78, 30.79, 31.76, 49.20, 50.15, 56.30, 127.76, 130.36, 134.33, 143.91, 207.22; Elemental analysis: calc. for $C_{14}H_{19}NO_3S$; C, 59.76; H, 6.81; N, 4.98; S, 11.40; found C, 59.71; H, 6.75; N, 4.79; S, 11.27.

1-(1-Tosylpyrrolidin-2-yl)butan-2-one (3ab)

White solid; yield 0.44 g, 80%; mp 68-70°C; IR (KBr, cm^{-1}) 1159, 1597, 1711; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.03 (t, 3H, *J* = 7.3 Hz), 1.44-1.57 (m, 2H), 1.71-1.86 (m, 2H), 2.44 (s, 3H), 2.49 (q, 2H, *J* = 7.3 Hz), 2.66 (dd, 1H, *J* = 17.4 Hz, *J* = 9.6 Hz), 3.06-3.14 (m, 1H), 3.20 (dd, 1H, *J* = 17.4 Hz, *J* = 3.4 Hz), 3.39-3.47 (m, 1H), 3.91-3.97 (m, 1H), 7.33 (d, 2H, *J* = 8.4 Hz), 7.72 (d, 2H, *J* = 8.2 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 7.61, 21.49, 23.80, 32.13, 36.52, 49.30, 56.03, 67.07, 127.59, 129.70, 133.94, 143.51, 209.80; Elemental analysis: calc. for $C_{15}H_{21}NO_3S$; C, 60.99; H, 7.17; N, 4.74; S, 10.85; found C, 60.93; H, 6.91; N, 4.97; S, 10.83.

1-(1-Tosylpyrrolidin-2-yl)pentan-2-one (3ac)

White solid; yield 0.39 g, 68%; mp 73-74°C; IR (KBr, cm^{-1}) 1159, 1597, 1711; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 0.93 (t, 3H, *J* = 7.4 Hz), 1.40-1.57 (m, 2H), 1.57 -1.66 (m, 2H), 1.71-1.90 (m, 2H), 2.33-2.42 (m, 2H), 2.43 (s, 3H), 2.65 (dd, 1H, *J* = 17.5 Hz, *J* = 9.6 Hz), 3.05-3.13 (m, 1H), 3.20 (dd, 1H, *J* = 17.5 Hz, *J* = 3.3 Hz), 3.40-3.49 (m, 1H), 3.90-3.98 (m, 1H), 7.32 (d, 2H, *J* = 8.1 Hz), 7.71 (d, 2H, *J* = 8.3 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 13.68, 17.12, 21.49, 23.79, 24.32, 32.12, 45.30, 49.68, 55.98, 127.59, 129.70, 133.94, 143.50, 209.45; Elemental analysis: calc. for $C_{16}H_{23}NO_3S$; C, 62.11; H, 7.49; N, 4.53; S, 10.36; found C, 62.01; H, 7.71; N, 4.51; S, 10.23.

2-(1-Tosylpyrrolidin-2-yl)cyclohexanone (3ad)

White solid; yield 0.28 g, 46%; *dr* =1 : 2 (determined by ^{1}H NMR), mp 101-102°C; IR (KBr, cm^{-1}) 1157, 1597, 1704; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.36-1.47 (m, 2H), 1.56-1.82 (m, 5H), 1.84-1.92 (m, 1H), 1.95-2.04 (m, 1H), 2.06-2.17 (m, 1H), 2.33-2.41 (m, 2H), 2.46 (s, 3H), 3.07-3.18 (m, 1H), 3.21-3.34 (m, 1H), 3.36-3.45 (m, 1H), 4.02-4.12 (m, 1H), 7.31-7.37 (m, 2H), 7.69-7.76 (d, 2H); D^1: ^{13}C NMR ($CDCl_3$, 150 MHz): δ 21.50, 24.61, 24.78, 26.56, 27.32, 28.20, 42.18, 49.82, 55.38, 58.68, 127.73, 129.69, 133.54, 143.51, 212.17; D^2: ^{13}C NMR ($CDCl_3$, 150 MHz): δ 23.84, 25.09, 28.11, 30.50, 31.93, 40.14, 42.93, 48.62, 54.85, 60.19, 127.59, 129.69, 135.14, 143.35, 211.80; Elemental analysis: calc. for $C_{17}H_{23}NO_3S$; C, 63.52; H, 7.21; N, 4.36; O, 14.93; S, 9.98; found C, 63.71; H, 7.37; N, 4.43; S, 9.79.

1-Phenyl-2-(1-tosylpyrrolidin-2-yl)ethanone (3ae)

White solid; yield 0.45 g, 71%; mp 100-101°C; IR (KBr, cm^{-1}) 1156, 1580, 1596, 1682; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.52-1.61 (m, 1H), 1.63-1.72 (m, 1H), 1.78 -1.89 (m, 2H), 2.45 (s, 3H), 3.09-3.20 (m, 2H), 3.48-3.56 (m, 1H), 3.83-3.89 (m, 1H), 4.10-4.20 (m, 1H), 7.34 (d, 2H, *J* = 7.9 Hz), 7.50 (t, 2H, *J* = 7.6 Hz), 7.60 (t, 1H, *J* = 7.3 Hz), 7.75 (d, 2H, *J* = 8.0 Hz), 8.02 (d, 2H, *J* = 7.7 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 21.52, 23.85, 31.92, 46.19, 49.23, 56.72, 127.65, 128.19, 128.69, 129.76, 133.35, 134.03, 136.68, 143.55, 198.55; Elemental analysis: calc. for $C_{19}H_{21}NO_3S$; C, 66.45; H, 6.16; N, 4.08; S, 9.34; found C, 66.39; H, 6.11; N, 3.88; S, 9.12.

2-(1-((4-Methoxyphenyl)sulfonyl)pyrrolidin-2-yl)-1-phenylethanone (3af)

Starting with 1-(4-methoxyphenyl)ethan-1-one (0.28 g, 1.0 eq.), **3af** was synthesized as yellowish oil; yield 0.43 g, 62%; IR (KBr, cm^{-1}) 1576, 1600, 1675; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.51-1.61 (m, 1H), 1.65-1.74 (m, 1H), 1.79-1.90 (m, 2H), 2.45 (s, 3H), 3.04-3.21 (m, 2H), 3.48-3.56 (m, 1H), 3.81 (dd, 1H, *J* = 16.6 Hz, *J* = 3.0 Hz), 3.90 (s, 3H), 4.09-4.18 (m, 1H), 6.98 (d, 2H, *J* = 9.0 Hz), 7.34 (d, 2H, *J* = 8.0 Hz), 7.76 (d, 2H, *J* = 8.3 Hz), 8.02 (d, 2H, *J* = 8.9 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 21.50, 23.82, 31.79, 45.84, 49.20, 55.50, 56.92, 113.69, 113.82, 127.61, 129.73, 130.50, 134.00, 143.51, 163.71, 197.07; Elemental analysis: calc. for $C_{19}H_{21}NO_4S$; C, 63.49; H, 5.89; N, 3.90; S, 8.92; found C, 63.67; H, 5.71; N, 4.12; S, 9.13.

1-(2-Hydroxyphenyl)-2-(1-tosylpyrrolidin-2-yl)ethanone (3ag)

White solid; yield 0.25 g, 38%; mp 167-169°C; IR (KBr, cm^{-1}) 1157, 1582, 1640, 3503; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.55-1.65 (m, 2H), 1.67-1.77 (m, 1H), 1.79-1.96 (m, 2H), 2.46 (s, 3H), 3.06-3.24 (m, 2H), 3.46-3.60 (m, 1H), 3.91 (dd, 1H, *J* = 16.4 Hz, *J* = 2.8 Hz), 4.08-4.19 (m, 1H), 6.95-7.05 (m, 2H), 7.36 (d, 2H, *J* = 8.0 Hz), 7.52 (t, 1H, *J* = 7.5 Hz), 7.76 (d, 2H, *J* = 8.1 Hz), 7.93 (d, 1H, *J* = 8.1 Hz), 12.17 (s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 21.52, 23.82, 31.71, 45.90, 49.17, 56.64, 118.49, 119.21, 119.33, 127.59, 129.79, 130.37, 133.89, 136.66, 143.67, 162.51, 204.68; Elemental analysis: calc. for $C_{19}H_{21}NO_4S$; C, 63.49; H, 5.89; N, 3.90; S, 8.92; found C, 63.33; H, 5.64; N, 3.83; S, 8.99.

1-(3-Acetylphenyl)-2-(1-tosylpyrrolidin-2-yl)ethanone (3ah)

Starting with 1,1'-(1,3-phenylene)bis(ethan-1-one) (0.15 g, 0.5 equiv), **3ah** was synthesized as white solid; yield 0.26 g, 36%; mp 149-152°C; IR (KBr, cm^{-1}) 1158, 1597, 1684; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.51-1.61 (m, 1H), 1.64-1.76 (m, 1H), 1.80-1.93 (m, 2H), 2.46 (s, 3H), 2.70 (s, 3H), 3.08-3.30 (m, 2H), 3.46-3.57 (m, 1H), 3.81-3.94 (m, 1H), 4.09-4.25 (m, 1H), 7.35 (d, 2H, *J* = 7.9 Hz), 7.63 (t, 1H, *J* = 7.6 Hz), 7.76 (d, 2H, *J* = 7.9 Hz), 8.12-8.29 (m, 2H), 8.59 (s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 21.51, 23.87, 26.74, 31.89, 46.35, 49.18, 56.58, 127.61, 128.03, 129.16, 129.78, 132.43, 132.62, 133.91, 136.96, 137.59, 143.64, 197.28, 197.81; Elemental analysis: calc. for $C_{21}H_{23}NO_4S$; C, 65.43; H, 6.01; N, 3.63; S, 8.32; found C, 65.37; H, 5.87; N, 3.80; S, 8.20.

1-(Naphthalen-2-yl)-2-(1-tosylpyrrolidin-2-yl)ethanone (3ai)

Starting with 1-(naphthalen-2-yl)ethan-1-one (0.32 g, 1.0 equiv), **3ai** was synthesized as white solid; yield 0.31 g, 42%; mp 136-137°C; IR (KBr, cm^{-1}) 1159, 1577, 1596, 1679; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.53-1.65 (m, 2H), 1.69-1.78 (m, 1H), 1.82-1.91 (m, 2H), 2.45 (s, 3H), 3.11-3.20 (m, 1H), 3.28 (dd, 1H, *J* = 16.8 Hz, *J* =

10.4 Hz), 3.52-3.59 (m, 1H), 4.02 (dd, 1H, *J* = 16.8 Hz, *J* = 2.8 Hz), 4.16-4.26 (m, 1H), 7.33 (d, 2H, *J* = 8.0 Hz), 7.59 (t, 1H, *J* = 7.6 Hz), 7.64 (t, 1H, *J* = 7.2 Hz), 7.77 (d, 2H, *J* = 7.9 Hz), 7.91 (d, 1H, *J* = 8.0 Hz), 7.93 (d, 1H, *J* = 8.7 Hz), 8.03 (d, 1H, *J* = 8.0 Hz), 8.07 (d, 1H, *J* = 8.1 Hz), 8.62 (s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 21.52, 23.88, 31.89, 46.36, 49.27, 56.94, 123.68, 126.88, 127.66, 127.78, 128.53, 128.63, 129.74, 129.77, 130.32, 132.62, 133.95, 134.04, 135.75, 143.56, 198.50; Elemental analysis: calc. for $C_{23}H_{23}NO_3S$; C, 70.20; H, 5.89; N, 3.56; S, 8.15; found C, 70.34; H, 5.99; N, 3.68; S, 8.03.

1-(Naphthalen-1-yl)-2-(1-tosylpyrrolidin-2-yl)ethanone (3aj)

White solid; yield 0.34 g, 48%; mp 86-87°C; IR (KBr, cm^{-1}) 1158, 1509, 1573, 1596, 1666; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.52-1.63 (m, 1H), 1.69-1.81 (m, 1H), 1.81-1.95 (m, 2H), 2.45 (s, 3H), 3.12-3.19 (m, 1H), 3.24 (dd, 1H, *J* = 16.9 Hz, *J* = 10.2 Hz), 3.48-3.58 (m, 1H), 4.00 (dd, 1H, *J* = 16.9 Hz, *J* = 2.8 Hz), 4.16-4.28 (m, 1H), 7.34 (d, 2H, *J* = 7.9 Hz), 7.53-7.64 (m, 3H), 7.77 (d, 2H, *J* = 8.0 Hz), 7.91 (d, 1H, *J* = 8.0 Hz), 8.04 (d, 1H, *J* = 8.2 Hz), 8.07 (d, 1H, *J* = 7.1 Hz), 8.71 (d, 1H, *J* = 8.6 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 21.52, 23.90, 32.08, 49.23, 56.91, 124.50, 125.71, 126.46, 127.64, 128.07, 128.51, 128.62, 129.75, 130.19, 133.17, 134.02, 134.98, 143.55, 202.38; Elemental analysis: calc. for $C_{23}H_{23}NO_3S$; C, 70.20; H, 5.89; N, 3.56; S, 8.15; found C, 70.44; H, 6.04; N, 3.68; S, 8.24.

3-(1-Tosylpyrrolidin-2-yl)pentane-2,4-dione (3ak)

Yellowish oil; yield 0.32 g, 54%; IR (KBr, cm^{-1}) 1160, 1598, 1702; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.26-1.37 (m, 1H), 1.52-1.63 (m, 1H), 1.75-1.83 (m, 2H), 2.18 (s, 3H), 2.44 (s, 3H), 2.45 (s, 3H), 3.13-3.20 (m, 1H), 3.30-3.37 (m, 1H), 4.07-4.13 (m, 1H), 4.55 (d, 1H, *J* = 5.2 Hz), 7.33 (d, 2H, *J* = 7.9 Hz), 7.70 (d, 2H, *J* = 8.1 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 21.54, 23.82, 28.76, 33.43, 49.43, 59.18, 69.86, 127.75, 129.90, 133.19, 144.07, 202.70, 205.74; Elemental analysis: calc. for $C_{16}H_{21}NO_4S$; C, 59.42; H, 6.54; N, 4.33; S, 9.91; found C, 59.64; H, 6.60; N, 4.43; S, 9.79.

1,3-Bis(1-tosylpyrrolidin-2-yl)propan-2-one (3al)

Starting with acetone (0.067 mL, 0.054 g, 0.5 equiv), **3al** was synthesized as white solid; yield 0.13 g, 14%; *dr* =1 : 1 (determined by ^{1}H NMR); mp 70-74°C; IR (KBr, cm^{-1}) 1159, 1598, 1707; ^{1}H NMR (DMSO-d_6, 600 MHz): δ 1.33-1.42 (m, 2H), 1.46-1.62 (m, 4H), 1.69-1.78 (m, 2H), 2.40 (s, 6H), 2.75-2.84 (m, 2H), 2.89-2.98 (m, 2H), 3.05-4.12 (m, 2H), 3.26-3.35 (m, 2H), 3.76-3.89 (m, 2H), 7.41-7.47 (m, 4H), 7.67-7.73 (m, 4H); **D^1**: ^{13}C NMR (DMSO-d_6, 150 MHz): δ 21.45, 23.78, 31.72, 49.20, 56.20, 66.82, 127.74, 130.34, 134.26, 143.90, 207.55; **D^2**: ^{13}C NMR (DMSO-d_6, 150 MHz): δ 21.45, 24.18, 30.76, 44.96, 56.26, 66.82, 126.95, 130.08, 134.26, 143.90, 207.22; Elemental analysis: calc. for $C_{25}H_{32}N_2O_5S_2$; C, 59.50; H, 6.39; N, 5.55; S, 12.71; found C, 59.25; H, 6.51; N, 5.40; S, 12.51.

3-Hydroxy-5,5-dimethyl-2,6-bis(1-tosylpyrrolidin-2-yl)cyclohex-2-en-1-one (3am)

Starting with 5,5-dimethylcyclohexane-1,3-dione (dimedone) (0.13 g, 0.5 equiv), **3am** was synthesized as white solid; yield 0.55 g, 51%; mp 169-171°C; IR (KBr, cm^{-1}) 1119, 1457, 1612; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.00 (s, 3H), 1.05 (s, 3H), 1.27-1.31 (m, 1H), 1.42-1.57 (m, 4H), 1.64-1.72 (m, 2H), 1.93-2.00 (m, 1H), 2.02-2.08 (m, 1H), 2.21-2.2.24 (m, 2H), 2.44 (s, 3H), 2.47 (s, 3H), 2.53-2.59 (m, 1H), 2.95-3.06 (m, 2H), 3.25-3.31 (m, 1H), 3.34-3.42 (m, 1H), 5.45 (br s, 1H), 5.73 (d, 1H, *J* = 4.4 Hz), 7.31 (d, 2H, *J* = 7.9 Hz), 7.35 (d, 2H, *J* = 8.0 Hz), 7.78 (d, 2H, *J* = 8.0 Hz), 7.82 (d, 2H, *J* = 7.9 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 21.50, 21.56, 26.38, 27.52, 28.28, 28.35, 28.60, 29.70, 30.90, 41.24, 41.97, 42.64, 45.83, 50.69, 85.60, 110.19, 127.13, 127.81, 129.54, 129.63, 136.09, 137.39, 143.12, 143.88, 167.00, 198.12; Elemental analysis: calc. for $C_{30}H_{38}N_2O_6S_2$; C, 61.41; H, 6.53; N, 4.77; S, 10.93; found C, 61.30; H, 6.70; N, 4.96; S, 10.69.

1-(1-(Phenylsulfonyl)pyrrolidin-2-yl)propan-2-one (3an)

Yellowish oil; yield 0.41 g, 83%; IR (KBr, cm^{-1}) 1160, 1585, 1712; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.42-1.52 (m, 1H), 1.54-1.61 (m, 1H), 2.18 (s, 3H), 2.69 (dd, 1H, *J* = 17.7 Hz, *J* = 9.5 Hz), 3.09-3.16 (m, 1H), 3.25 (dd, 1H, *J* =

17.7 Hz, *J* = 3.4 Hz), 3.40-3.51 (m, 1H), 3.90-4.05 (m, 1H), 7.54 (t, 2H, *J* = 7.6 Hz), 7.61 (t, 1H, *J* = 7.3 Hz), 7.84 (d, 2H, *J* = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 23.81, 30.55, 32.13, 49.15, 50.58, 55.98, 127.56, 129.13, 132.76, 136.97, 207.03; Elemental analysis: calc. for $C_{13}H_{17}NO_3S$; C, 58.41; H, 6.41; N, 5.24; S, 11.99; found C, 58.35; H, 6.26; N, 5.37; S, 12.07.

1-(1-((4-Chlorophenyl)sulfonyl)pyrrolidin-2-yl)propan-2-one (3ao)

White solid; yield 0.40 g, 72%; mp 61-62°C; IR (KBr, cm^{-1}) 1158, 1586, 1718; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.38-1.53 (m, 2H), 1.59-1.70 (m, 1H), 1.72-1.82 (m, 1H), 2.11 (s, 3H), 2.77 (dd, 1H, *J* = 17.2 Hz, *J* = 9.3 Hz), 2.93 (dd, 1H, *J* = 17.2 Hz, *J* = 3.8 Hz), 3.04-3.14 (m, 1H), 3.30-3.36 (m, 1H), 3.78-3.88 (m, 1H), 7.71 (d, 2H, *J* = 8.6 Hz), 7.82 (d, 2H, *J* = 8.7 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 23.81, 30.78, 31.77, 49.24, 50.01, 56.46, 129.63, 130.07, 136.10, 138.53, 207.09; Elemental analysis: calc. for $C_{13}H_{16}ClNO_3S$; C, 51.74; H, 5.34; Cl, 11.75; N, 4.64; S, 10.62; found C, 51.69; H, 5.20; Cl, 11.86; N, 4.79; S, 10.50.

1-(1-(Naphthalen-2-ylsulfonyl)pyrrolidin-2-yl)propan-2-one (3ap)

White solid; yield 0.34 g, 58%; mp 67-69°C; IR (KBr, cm^{-1}) 1154, 1590, 1716; ^{1}H NMR (DMSO-d_6, 600 MHz): δ 1.32-1.40 (m, 1H), 1.42-1.49 (m, 1H), 1.52-1.61 (m, 1H), 1.68-1.77 (m, 1H), 2.13 (s, 3H), 2.79 (dd, 1H, *J* = 17.1 Hz, *J* = 9.4 Hz), 2.98 (dd, 1H, *J* = 17.1 Hz, *J* = 3.7 Hz), 3.15-3.24 (m, 1H), 3.34-3.40 (m, 1H), 3.89-3.99 (m, 1H), 7.66-7.75 (m, 2H), 7.83 (dd, 1H, *J* = 8.7 Hz, *J* = 1.9 Hz), 8.06 (d, 1H, *J* = 8.1 Hz), 8.16 (d, 1H, *J* = 8.7 Hz), 8.21 (d, 1H, *J* = 8.0 Hz), 8.49 (d, 2H, *J* = 1.9 Hz); ^{13}C NMR (DMSO-d_6, 150 MHz): δ 23.30, 30.27, 31.21, 48.72, 49.59, 55.91, 122.65, 127.59, 127.77, 128.36, 128.87, 129.32, 129.46, 131.77, 133.93, 134.35, 206.70; Elemental analysis: calc. for $C_{17}H_{19}NO_3S$; C, 64.33; H, 6.03; N, 4.41; S, 10.10; found C, 64.17; H, 6.28; N, 4.51; S, 10.18.

1-(1-(Naphthalen-2-ylsulfonyl)pyrrolidin-2-yl)butan-2-one (3aq)

White solid; yield 0.49 g, 79%; mp 75-80°C; IR (KBr, cm^{-1}) 1134, 1504, 1590, 1712; ^{1}H NMR (DMSO-d_6, 600 MHz): δ 0.91 (t, 3H, *J* = 7.3 Hz), 1.31-1.47 (m, 2H), 1.51-1.60 (m, 1H), 1.66-1.75 (m, 1H), 2.36-2.47 (m, 2H), 2.75 (dd, 1H, *J* = 16.9 Hz, *J* = 9.4 Hz), 2.93 (dd, 1H, *J* = 16.9 Hz, *J* = 3.8 Hz), 3.13-3.23 (m, 1H), 3.32-3.37 (m, 1H), 3.89-3.98 (m, 1H), 7.65-7.72 (m, 2H), 7.81 (dd, 1H, *J* = 8.6 Hz, *J* = 1.9 Hz), 8.05 (d, 1H, *J* = 8.3 Hz), 8.14 (d, 1H, *J* = 8.7 Hz), 8.20 (d, 1H, *J* = 7.9 Hz), 8.46 (d, 2H, *J* = 1.9 Hz); ^{13}C NMR (DMSO-d_6, 150 MHz): δ 8.44, 24.36, 32.28, 36.62, 49.41, 49.77, 57.07, 123.70, 128.63, 128.82, 129.38, 129.91, 130.36, 130.49, 132.81, 135.01, 135.39, 210.15; Elemental analysis: calc. for $C_{18}H_{21}NO_3S$; C, 65.23; H, 6.39; N, 4.23; S, 9.67; found C, 65.02; H, 6.20; N, 4.09; S, 9.82.

1-(1-(Naphthalen-2-ylsulfonyl)pyrrolidin-2-yl)pentan-2-one (3ar)

Yellowish oil; yield 0.53 g, 83%; IR (KBr, cm^{-1}) 1158, 1504, 1591, 1711; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 0.95 (t, 3H, *J* = 7.4 Hz), 1.45-1.51 (m, 1H), 1.52-1.59 (m, 1H), 1.61-1.68 (m, 2H), 1.73-1.85 (m, 2H), 2.37-2.52 (m, 2H), 2.69 (dd, 1H, *J* = 17.4 Hz, *J* = 9.6 Hz), 3.16-3.22 (m, 1H), 3.26 (dd, 1H, *J* = 17.4 Hz, *J* = 3.3 Hz), 3.48-3.53 (m, 1H), 4.06-4.11 (m, 1H), 7.61-7.69 (m, 2H), 7.85 (dd, 1H, *J* = 8.6 Hz, *J* = 1.8 Hz), 7.94 (d, 1H, *J* = 8.0 Hz), 7.99 (d, 1H, *J* = 8.7 Hz), 8.01 (d, 1H, *J* = 8.0 Hz), 8.41 (d, 2H, *J* = 1.7 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 13.73, 17.19, 23.89, 32.18, 45.37, 49.21, 49.73, 56.18, 122.96, 127.54, 127.90, 128.75, 128.90, 129.36, 129.38, 132.24, 134.11, 134.91, 209.39; Elemental analysis: calc. for $C_{19}H_{23}NO_3S$; C, 66.06; H, 6.71; N, 4.05; S, 9.28; found C, 66.18; H, 6.45; N, 4.23; S, 9.02.

2-(1-(Naphthalen-2-ylsulfonyl)pyrrolidin-2-yl)-1-phenylethan-1-one (3as)

White solid; yield 0.19 g, 29%; mp 138-139°C; IR (KBr, cm^{-1}) 1597, 1663, 2867, 2967, 3178; ^{1}H NMR (DMSO-d_6, 600 MHz): δ 1.38-1.48 (m, 1H), 1.51-1.70 (m, 2H), 1.77-1.89 (m, 1H), 3.19-3.28 (m, 1H), 3.36-3.49 (m, 2H), 3.55 (dd, 1H, *J* = 17.1 Hz, *J* = 3.3 Hz), 4.05-4.15 (m, 1H), 7.56 (t, 2H, *J* = 7.5 Hz), 7.64-7.75 (m, 3H), 7.85 (d, 1H, *J* = 8.4 Hz), 8.00 (d, 2H, *J* = 7.5 Hz), 8.07 (d, 1H, *J* = 7.9 Hz), 8.17 (d, 1H, *J* = 8.6 Hz), 8.22 (d, 1H, *J* = 7.9 Hz), 8.50 (s, 1H); ^{13}C NMR (DMSO-d_6, 150 MHz): δ 24.40, 32.36, 46.25, 49.93, 57.53, 123.69, 128.66, 128.84,

128.96, 129.45, 129.78, 129.95, 130.37, 130.56, 132.81, 134.41, 134.91, 135.41, 137.44, 199.16; Elemental analysis: calc. for $C_{22}H_{21}NO_3S$; C, 69.63; H, 5.58; N, 3.69; S, 8.45; found 69.87; H, 5.67; N, 3.51; S, 8.49.

1-(1-((3-Chloropropyl)sulfonyl)pyrrolidin-2-yl)propan-2-one (3at)

Yellowish oil; yield 0.27 g, 54%; IR (KBr, cm^{-1}) 1147, 1712; ^1H NMR ($CDCl_3$, 600 MHz): δ 1.66-1.75 (m, 1H), 1.84-1.98 (m, 2H), 2.15 (s, 3H), 2.17-2.25 (m, 1H), 2.26-2.35 (m, 2H), 2.62 (dd, 1H, *J* = 17.5 Hz, *J* = 9.1 Hz), 3.06-3.18 (m, 3H), 3.32-3.46 (m, 2H), 3.65-3.74 (m, 2H), 4.10-4.18 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 24.28, 26.40, 30.42, 32.37, 43.03, 45.68, 48.75, 50.02, 55.80, 206.75; Elemental analysis: calc. for $C_{10}H_{18}ClNO_3S$; C, 44.85; H, 6.78; Cl, 13.24; N, 5.23; S, 11.97; found C, 44.91; H, 6.82; Cl, 13.29; N, 5.37; S, 12.05.

1-(1-(Ethylsulfonyl)pyrrolidin-2-yl)propan-2-one (3au)

Yellowish oil; yield 0.31 g, 75%; IR (KBr, cm^{-1}) 1144, 1714; ^1H NMR ($CDCl_3$, 600 MHz): δ 1.37 (t, 3H, *J* = 7.4 Hz), 1.64-1.73 (m, 1H), 1.84-1.97 (m, 2H), 2.15 (s, 3H), 2.16-2.26 (m, 1H), 2.61 (dd, 1H, *J* = 17.5 Hz, *J* = 9.2 Hz), 2.93-3.04 (m, 2H), 3.12 (dd, 1H, *J* = 17.5 Hz, *J* = 3.7 Hz), 3.28-3.45 (m, 2H), 4.09-4.18 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 7.83, 24.33, 30.45, 32.34, 43.19, 48.72, 50.16, 55.68, 206.95; Elemental analysis: calc. for $C_9H_{17}NO_3S$; C, 49.29; H, 7.81; N, 6.39; S, 14.62; found C, 49.45; H, 7.95; N, 6.48; S, 14.59.

1-(1-(Thiophen-2-ylsulfonyl)pyrrolidin-2-yl)propan-2-one (3av)

Yellowish oil; yield 0.39 g, 76%; IR (KBr, cm^{-1}) 1155, 1712; ^1H NMR ($CDCl_3$, 600 MHz): δ 1.48-1.64 (m, 2H), 1.77-1.92 (m, 2H), 2.18 (s, 3H), 2.72 (dd, 1H, *J* = 17.7 Hz, *J* = 9.7 Hz), 3.17-3.29 (m, 2H), 3.45-3.51 (m, 1H), 3.92-4.03 (m, 1H), 7.13-7.18 (m, 1H), 7.60-7.63 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 23.85, 30.51, 32.05, 49.37, 50.35, 56.37, 127.51, 131.80, 132.38, 136.78, 206.88; Elemental analysis: calc. for $C_{11}H_{15}NO_3S_2$; C, 48.33; H, 5.53; N, 5.12; S, 23.46; found C, 48.19; H, 5.39; N, 5.22; S, 23.31.

1-(1-(Vinylsulfonyl)pyrrolidin-2-yl)propan-2-one (3aw)

Yellowish oil; yield 0.28 g, 70%; IR (KBr, cm^{-1}) 1149, 1712; ^1H NMR ($CDCl_3$, 600 MHz): δ 1.58-1.68 (m, 1H), 1.73-1.81 (m, 1H), 1.82-1.90 (m, 1H), 2.03-2.10 (m, 1H), 2.12 (s, 3H), 2.63 (dd, 1H, *J* = 17.7 Hz, *J* = 9.5 Hz), 3.09 (dd, 1H, *J* = 17.7 Hz, *J* = 3.4 Hz), 3.31-3.40 (m, 1H), 3.86-3.95 (m, 1H), 6.01 (d, 1H, *J* = 10.0 Hz), 6.22 (d, 1H, *J* = 16.6 Hz), 6.46 (dd, 1H, *J* = 16.6 Hz, *J* = 10.0 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 24.10, 30.44, 32.26, 48.89, 50.28, 55.92, 128.41, 131.33, 206.85; Elemental analysis: calc. for $C_9H_{15}NO_3S$; C, 49.75; H, 6.96; N, 6.45; S, 14.76; found C, 49.87; H, 6.80; N, 6.34; S, 14.98.

***N*-(4-((2-(2-oxopropyl)pyrrolidin-1-yl)sulfonyl)phenyl)acetamide (3ba)**

Starting with sulfonylamide **2a**, compound **3ba** was synthesized by general procedure as white solid; yield 0.41 g, 68%; mp 104-106°C; IR (KBr, cm^{-1}) 1158, 1524, 1589, 1703, (SO2), 3347; ^1H NMR ($CDCl_3$, 600 MHz): δ 1.47-1.59 (m, 2H), 1.72-1.85 (m, 2H), 2.18 (s, 3H), 2.21 (s, 3H), 2.69 (dd, 1H, *J* = 17.6 Hz, *J* = 9.4 Hz), 3.06-3.15 (m, 1H), 3.20 (dd, 1H, *J* = 17.6 Hz, *J* = 3.5 Hz), 3.39-3.47 (m, 1H), 3.89-3.99 (m, 1H), 7.68-7.80 (m, 4H), 8.31 (s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 23.80, 24.58, 30.61, 32.09, 49.18, 50.58, 55.97, 119.42, 128.68, 131.23, 142.55, 169.15, 207.30; Elemental analysis: calc. for $C_{15}H_{20}N_2O_4S$; C, 55.54; H, 6.21; N, 8.64; S, 9.88; found C, 55.49; H, 6.17; N, 8.53; S, 9.76.

***N*-(4-((2-(2-oxobutyl)pyrrolidin-1-yl)sulfonyl)phenyl)acetamide (3bb)**

Starting with sulfonylamide **2a**, compound **3bb** was synthesized by general procedure as white solid; yield 0.28 g, 45%; mp 70-73°C; IR (KBr, cm^{-1}) 1157, 1530, 1592, 1704, 3339; ^1H NMR ($CDCl_3$, 600 MHz): δ 1.07 (t, 3H, *J* = 7.3 Hz), 1.47-1.55 (m, 2H), 1.74-1.82 (m, 2H), 2.21 (s, 3H), 2.40-2.53 (m, 2H), 2.67 (dd, 1H, *J* = 17.4 Hz, *J* = 9.4 Hz), 3.06-3.13 (m, 1H), 3.17 (dd, 1H, *J* = 17.4 Hz, *J* = 3.5 Hz), 3.41-3.48 (m, 1H), 3.92-3.99 (m, 1H), 7.71-7.75 (m, 4H), 8.25 (s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 7.64, 23.82, 24.61, 32.15, 36.61, 49.21, 49.29,

56.12, 119.42, 128.70, 131.31, 142.46, 169.13, 210.07 ; Elemental analysis: calc. for $C_{16}H_{22}N_2O_4S$; C, 56.79; H, 6.55; N, 8.28; S, 9.47; found C, 56.93; H, 6.70; N, 8.37; S, 9.36.

_N_-(4-((2-(2-oxo-2-phenylethyl)pyrrolidin-1-yl)sulfonyl)phenyl)acetamide (3bc)

Starting with sulfonylamide **2a**, compound **3bc** was synthesized by general procedure as white solid; yield 0.23 g, 32%; mp 147-148°C; IR (KBr, cm^{-1}) 1154, 1592, 1517, 1537, 1682, 3317; ^1H NMR (DMSO-d_6, 600 MHz): δ 1.39-1.47 (m, 1H), 1.51-1.59 (m, 1H), 1.62-1.71 (m, 1H), 1.76-1.86 (m, 1H), 2.09 (s, 3H), 3.09-3.16 (m, 1H), 3.35-3.40 (m, 2H), 3.49 (dd, 1H, J = 17.3 Hz, J = 3.4 Hz), 3.94-4.04 (m, 1H), 7.55 (t, 2H, J = 7.8 Hz), 7.66 (t, 1H, J = 7.4 Hz), 7.75 (d, 2H, J = 8.7 Hz), 7.81 (d, 2H, J = 8.8 Hz), 7.99 (d, 2H, J = 7.2 Hz), 10.34 (s, 1H); ^{13}C NMR (DMSO-d_6, 150 MHz): δ 23.86, 24.63, 31.85, 45.79, 49.32, 56.88, 119.24, 128.44, 128.96, 129.26, 130.68, 133.87, 136.96, 143.89, 169.55, 198.70; Elemental analysis: calc. for $C_{20}H_{22}N_2O_4S$; C, 62.16; H, 5.74; N, 7.25; S, 8.30; found C, 62.03; H, 5.69; N, 7.37; S, 8.18.

1-(1-(Methylsulfonyl)pyrrolidin-2-yl)propan-2-one (3bd)

Starting with sulfonylamide **2b**, compound **3bd** was synthesized by general procedure as yellowish oil; yield 0.38 g, 99%; IR (KBr, cm^{-1}) 1149, 1712; ^1H NMR ($CDCl_3$, 600 MHz): δ 1.63-1.71 (m, 1H), 1.78-1.93 (m, 2H), 2.12 (s, 3H), 2.14-2.21 (m, 1H), 2.61 (dd, 1H, J = 17.7 Hz, J = 9.2 Hz), 2.79 (s, 3H), 3.09 (dd, 1H, J = 17.7 Hz, J = 3.7 Hz), 3.19-3.26 (m, 1H), 3.36-3.44 (m, 1H), 3.94-4.04 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 24.09, 30.42, 32.34, 34.04, 49.02, 50.09, 55.95, 206.92; Elemental analysis: calc. for $C_8H_{15}NO_3S$; C, 46.81; H, 7.37; N, 6.82; S, 15.62; found C, 46.97; H, 7.41; N, 6.93; S, 15.59.

Di-_o_-tolyl (2-(2-oxopropyl)pyrrolidin-1-yl)phosphonate (3bf)

Starting with phosphoramidate **2c**, compound **3bf** was synthesized by general procedure as yellowish oil; yield 0.52 g, 72%; IR (KBr, cm^{-1}) 1274, 1586, 1712; ^1H NMR ($CDCl_3$, 600 MHz): δ 1.62-1.71 (m, 1H), 1.82-1.98 (m, 2H), 2.11 (s, 3H), 2.13-2.19 (m, 1H), 2.23 (s, 3H), 2.24 (s, 3H), 2.54 (dd, 1H, J = 16.9 Hz, J = 10.0 Hz), 3.13 (dd, 1H, J = 16.8 Hz, J = 3.0 Hz), 3.31-3.40 (m, 1H), 3.43-3.49 (m, 1H), 4.21-4.32 (m, 1H), 7.01-7.10 (m, 2H), 7.12-7.23 (m, 4H), 7.30-7.41 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 16.31 (d, J = 5.4 Hz), 25.00 (d, J = 8.8 Hz), 30.41, 32.28 (d, J = 9.6 Hz), 47.29 (d, J = 3.8 Hz), 50.01, 55.63 (d, J = 5.4 Hz), 119.77 (d, J = 21.5 Hz), 124.75 (d, J = 14.4 Hz), 126.97 (d, J = 17.3 Hz), 129.18 (d, J = 23.8 Hz), 131.32 (d, J = 5.1 Hz), 149.48 (d, J = 17.9 Hz), 207.08; ^{31}P NMR ($CDCl_3$, 161.9 MHz) δ -2.32; Elemental analysis: calc. for $C_{21}H_{26}NO_4P$; C, 65.11; H, 6.76; N, 3.62; P, 8.00; found C, 65.05; H, 6.71; N, 3.51; P, 8.15.

1-(1-(Pyrimidin-2-yl)pyrrolidin-2-yl)propan-2-one (3bg)

Starting with _N_-(4,4-diethoxybutyl)pyrimidin-2-amine **2d**, compound **3bg** was synthesized by general procedure as yellowish oil; yield 0.19 g, 54%; IR (KBr, cm^{-1}) 1694, 2977; ^1H NMR ($CDCl_3$, 600 MHz): δ 1.53-1.61 (m, 1H), 1.68-1.81 (m, 2H), 1.86-1.92 (m, 1H), 1.95 (s, 3H), 2.22 (dd, 1H, J = 16.1 Hz, J = 9.5 Hz), 2.96 (dd, 1H, J = 16.1 Hz, J = 3.1 Hz), 3.26-3.34 (m, 1H), 3.36-3.42 (m, 1H), 4.21-4.34 (m, 1H), 6.25 (t, 1H, J = 4.7 Hz), 8.07 (d, 1H, J = 4.7 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 23.06, 30.19, 31.02, 46.79, 53.76, 109.18, 157.38, 159.73, 206.51; Elemental analysis: calc. for $C_{11}H_{15}N_3O$; C, 64.37; H, 7.37; N, 20.47; found C, 64.49; H, 7.54; N, 20.32.

X-ray data

Table S1. Crystallographic data for the compounds **3aa,3ab,3ae,3af,3ao,3bc**

Compound	**3aa**	**3ab**	**3ae**	**3af**	**3ao**	**3bc**
Chemical formula	$C_{14}H_{19}NO_3S$	$C_{15}H_{21}NO_3S$	$C_{19}H_{21}NO_3S$	$C_{20}H_{23}NO_4S$	$C_{13}H_{16}ClNO_3S$	$8(C_{20}H_{22}N_2O_4S)$ $4(C_2H_6OS)\cdot H_2O$
M_r	281.36	295.39	343.43	373.45	301.78	3422.16
Crystal system,	Monoclinic	Monoclinic	Monoclinic	Monoclinic,	Monoclinic	Monoclinic
Space group	$P2_1/n$	$P2_1/c$	$P2_1/c$	$P2_1/c$	$P2_1/n$	$C2/c$
Temperature (K)	150	296	150	100	120	100
a, b, c (Å)	a=7.4021(2) b=23.2039(6) c=8.3106(2)	a=13.029(3) b=8.265(2) c=14.612(3)	a=37.3753(9) b=7.6042(3) c=11.9845(5)	a=21.211(9) b=9.495(4) c=9.430(4)	a=7.4433(4) b=23.3631(13) c=8.2238(4)	a=60.154(7) b=7.6235(12) c=41.742(6)
β (°)	103.900(1)	99.696(8)	93.180(1)	100.051(11)	103.848(2)	121.812(4)
V (Å^3)	1385.61(6)	1551.0(6)	3400.9(2)	1870.1(13)	1388.54(13)	16267(4)
Z	4	4	8	4	4	4
μ (mm^{-1})	0.24	0.22	0.21	0.20	0.43	0.25
Absorption correction	Multi-scan					
T_{min}, T_{max}	0.663 / 0.746	0.679 / 0.746	0.690 / 0.746	0.613 / 0.746	0.610 / 0.746	0.548 / 0.746
No. of measured reflections	13417	9811	37024	13697	13717	46657
No. of independent reflections	2714	3024	9057	4520	3684	14232
No. of observed [I > 2σ(I)] reflections	2532	2336	7155	3366	3168	6325
R_{int}	0.032	0.063	0.048	0.042	0.036	0.215
$(\sin\theta/\lambda)_{max}$ (Å^{-1})	0.617	0.617	0.682	0.661	0.682	0.595
R_{int}	0.0316	0.0625	0.0483	0.0420	0.0357	0.2148
R_1/ $wR(F^2)$, [I>2σ]	0.0505 / 0.1189	0.0501 / 0.1178	0.0621 / 0.1260	0.0492 / 0.1003	0.0387 / 0.0895	0.0923 / 0.2245
R_1/ $wR(F^2)$, (all data)	0.0542 / 0.1211	0.0682 / 0.1278	0.0832 / 0.1357	0.0745 / 0.1114	0.0475 / 0.0936	0.2177 / 0.2912
No. of reflections	2714	3024	9057	4520	3684	14232
No. of parameters	172	183	454	237	173	1054
H-atom treatment	H-atom parameters constrained					
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.53 / −0.46	0.44 / −0.41	0.46 / -0.45	0.37 / −0.36	0.67 / -0.62	0.93 / -1.07
CCDC No	2175117	2175118	2175119	2175120	2175121	2175122

The molecular and crystal structure of compounds **3aa,ab,ae,af** and **3ao,bc** were determined by X-ray analysis. The five-membered pyrrolidine cycle has the same envelope conformation with the maximum deviation of the C3 or C4 atoms from the plane (mean deviation is 0.15-0.26Å) in all investigated compounds. The non-rigidity of this fragment leads to disordering of atoms C3 and C4 in crystals of compounds **3ae** and **3ao** and their crystallization with several molecules in the independent part of the unit cell. In general, the molecular structure of the studied compounds in crystals is almost identical, minor

differences are present only in the conformations of the substituent at the C2 atom, what is caused by the mobility of single bonds. The absence of classical hydrogen binding centers in the structure of molecules leads to the fact that the packing of molecules in crystals is formed due the CH…O and CH…π interactions and represents infinite layers or chains connected by van der Waals interactions (Figure S1, Table S2).

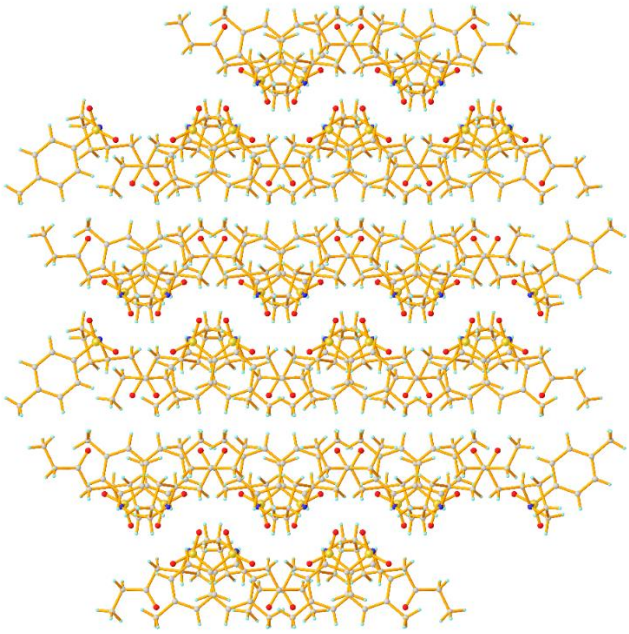


Figure S1 Crystal packing of compounds **3aa,ab,ae,af** and **3ao** on the example of the molecule **3ab**

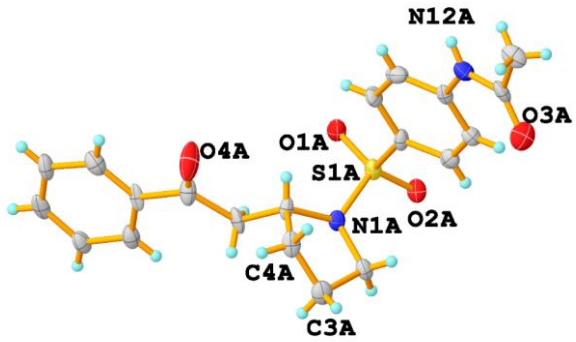


Figure S2 Molecular structure of compound **3bc** on the example of the molecule **A**.
Ellipsoids are given with a 50% probability.

Compound **3bc** crystallizes as a solvate, in which 4 independent molecules of the basic substance, two DMSO molecules and one molecule of water. The substituent of the nitrogen atom is almost flat in all independent molecules. The maximum deviation from the plane is observed in molecule B, the O3B atom diverges from the plane by 0.342 Å (Figure S2). This fragment remains the flattest in molecule C- the maximum deviation of the O3C atom is 0.52 Å. The difference in the conformation of the substituent at the C2 atom is determined by the mobility of the C15 atom, the torsion angle N1C2C15C16 is 158.8(5), 171.2(7), 172.1(7) and 179.8(7) ˚ for A, B, C and D molecules respectively. All molecules in the independent part are binded by classical hydrogen bonds (Table S2, Figure S3), and further packing of molecules in the crystal is formed by weaker interactions CH…O and CH…π interactions(Figure S3).

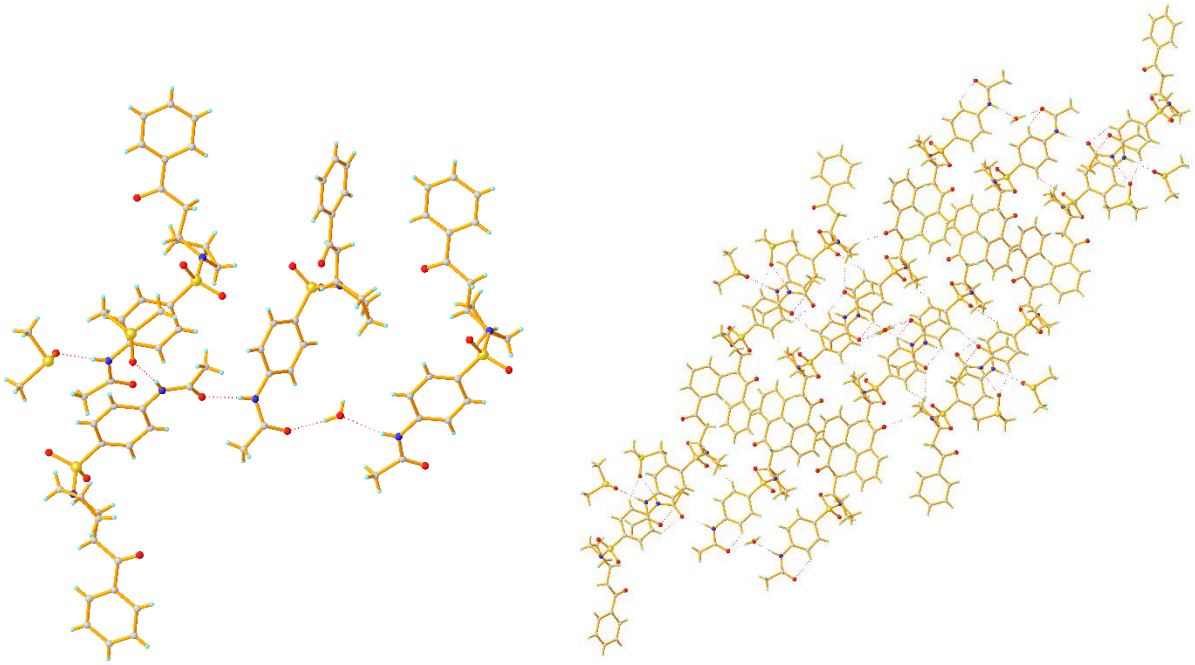


Figure S3 H-bonds and crystal packing of compound **3bc**

Table S2 H-bonds in crystals of investigated compounds

H-bond	Symmetry equivalent	D – H, Å	H...A, Å	D...A, Å	D - H...A, ˚
		3aa			
C7-H7...O1	intramolecular	0.95	2.56	2.920(3)	103
C8-H8...O2	x,y,-1+z	0.95	2.57	3.475(3)	159
C15-H15A...O1	-1/2+x,1/2-y,1/2+z	0.98	2.53	3.486(3)	165
		3ab			
C8-H8...O3	-x,-1/2+y,1/2-z	0.93	2.38	3.281(3)	163
C10-H10...O1	x,-1+y,z	0.93	2.57	3.493(3)	172
C13-H13B...O2	1-x,1/2+y,1/2-z	0.97	2.53	3.368(3)	144
		3ae			
C7B-H7B...O2B	intramolecular	0.95	2.58	2.925(3)	102
C4B-H4BB...O3B	x,1/2-y,1/2+z	0.99	2.46	3.425(7)	163
C11B-H11B...O2B	x,-1/2-y,-1/2+z	0.95	2.46	3.126(3)	127
		3af			
C3-H3B...N1	x,3/2-y,-1/2+z	0.99	2.51	3.496(3)	173
C7-H7...O2	intramolecular	0.95	2.55	2.906(3)	103
C8-H8...O2	x,1/2-y,-1/2+z	0.95	2.43	3.311(3)	154
C13-H13B...O2	intramolecular	0.99	2.50	3.166(3)	125
C21-H21B...O2	x,1/2-y,-1/2+z	0.98	2.47	3.304(3)	143
		3ao			
C7-H7...O1	intramolecular	0.95	2.57	2.9227(19)	102
C8-H8...O2	x,y,1+z	0.95	2.51	3.445(2)	166
		3bc			
N12A-H12A...O1S	intramolecular	0.88	1.92	2.800(12)	177
N12B-H12B...O3D	intramolecular	0.88	1.97	2.850(11)	176
N12C-H12C...O3S	intramolecular	0.88	2.11	2.919(8)	153
N12D-H12D...O2S	intramolecular	0.88	1.98	2.848(10)	167
O3S-H3SD...O3B	intramolecular	0.87	1.94	2.800(8)	169
O3S-H3SE...O3B	1-x,y,3/2-z	0.87	1.99	2.800(8)	154
C4A-H4AA...O4B	x,-1+y,z	0.99	2.44	3.371(13)	157
C5A-H5AA...O3C	1-x,-1+y,3/2-z	0.99	2.36	3.239(9)	147
C5A-H5AB...O1B	intramolecular	0.99	2.55	3.536(12)	172
C7C-H7C...O3A	1-x,1+y,3/2-z	0.95	2.53	3.165(12)	125

H-bond	Symmetry equivalent	D – H, Å	H...A, Å	D...A, Å	D - H...A, ˚
C8A-H8A...O3A	intramolecular	0.95	2.27	2.851(10)	118
C8B-H8B...O3B	intramolecular	0.95	2.31	2.867(9)	117
C8C-H8C...O3C	intramolecular	0.95	2.23	2.848(10)	122
C8D-H8D...O2S	intramolecular	0.95	2.49	3.247(10)	137
C10D-H10D...O3D	intramolecular	0.95	2.24	2.849(13)	121
C5D-H5DA...O1D	intramolecular	0.99	2.55	2.931(10)	103
C11A-H11A...O1A	intramolecular	0.95	2.57	2.923(11)	102
C11B-H11B...O1B	intramolecular	0.95	2.57	2.925(10)	102
C11B-H11B...O2A	intramolecular	0.95	2.43	3.142(11)	131'
C11C-H11C...O1C	intramolecular	0.95	2.57	2.935(10)	103
C11C-H11C...O2B	x,1+y,z	0.95	2.41	3.196(10)	140'
C11D-H11D...O2D	intramolecular	0.95	2.55	2.928(11)	104
C11D-H11D...O2C	1-x,-1+y,3/2-z	0.95	2.49	3.217(11)	133'
C14D-H14D...O3C	1-x,y,3/2-z	0.98	2.52	3.500(13)	174
C15B-H15F...O1B	intramolecular	0.99	2.56	3.197(9)	122
C15C-H15G...O1C	intramolecular	0.99	2.58	3.218(10)	122

Cell Toxicity Assay

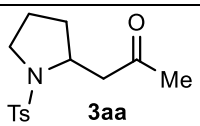
The toxic effect on cells was determined using the colorimetric method of cell proliferation MTT (Thiazolyl Blue Tetrazolium Bromide, Sigma). For this, 10 µl of MTT reagent in Hank's balanced salt solution (HBSS) (final concentration 0.5 mg/ml) was added to each well. The plates were incubated at 37 °C for 2–3 h in an atmosphere humidified with 5 % CO_2. Absorbance was recorded at 540 nm using a microplate reader Invitrologic (Russia). Experiments for all compounds were repeated three times. The M-HeLa clone 11 human, epithelioid cervical carcinoma, strain of HeLa, clone of M-HeLa; human duodenal cancer cell lines (HuTu 80) from the Type Culture Collection of the Institute of Cytology (Russian Academy of Sciences) and Chang liver cell lines (Human liver cells) from N. F. Gamaleya Research Center of Epidemiology and Microbiology were used in the experiments. The cells were cultured on a standard nutrient medium “Igla” produced by the Moscow Institute of Poliomyelitis and Viral Encephalitis. M.P. Chumakov by PanEco company with the addition of 10 % fetal calf serum and 1 % nonessential amino acids (NEAA).

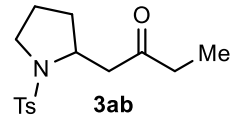
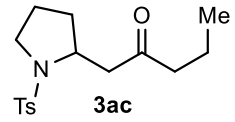
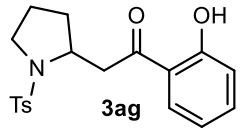
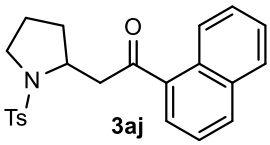
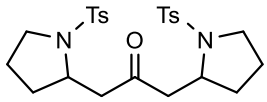
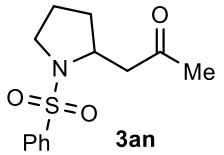
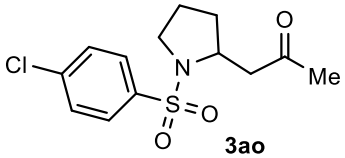
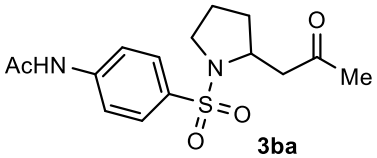
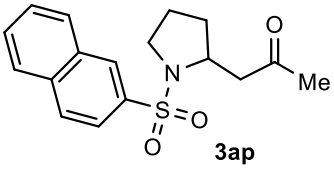
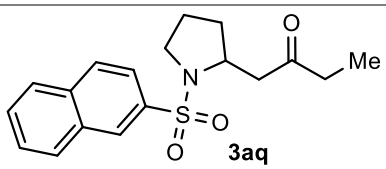
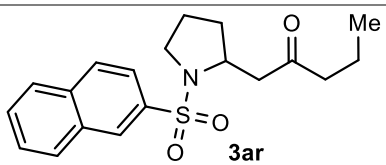
The cells were sown on a 96-well panel from Eppendorf at a concentration of 5×10^3 cells per well in a volume of 100 µl of medium and cultured in a CO_2 incubator at 37 °C. In 48 h after planting the cells, the culture medium was taken into the wells, and 100 µL of solutions of the studied drug in the specified dilutions were added to the wells. Dilutions of the compounds were prepared directly in growth medium supplemented with 5 % DMSO to improve solubility. The cytotoxic effect of the test compounds was determined at concentrations of 1–100 µM.

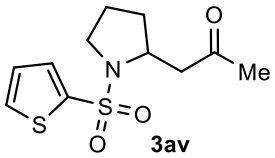
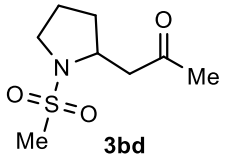
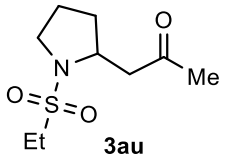
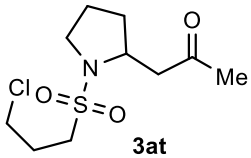
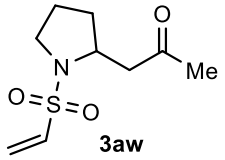
Statistical Analysis

The calculation of the IC_{50}, the concentration of the drug causing inhibition of cell growth by 50 %, was performed using the program: MLA – ‘Quest Graph ™ IC_{50} Calculator.’ AAT Bioquest, Inc, June 25, 2021, https://www.aatbio.com/tools/ic50-calculator. The data in tables and graphs are given as the mean±standard error.

Table S3 Cytotoxic effects of compounds **3** on the cancer and normal human cell lines[a]

Test compounds	IC50 (µM)		
	Cancer cell lines		Normal cell line
	M-HeLa	HuTu 80	Chang liver
 **3aa**	56.3±4.4	86.0±6.8	>100

Test compounds	IC50 (μM)		
	Cancer cell lines		Normal cell line
	M-HeLa	HuTu 80	Chang liver
 **3ab**	52±4.2	90.7±8.2	85.7±7.6
 **3ac**	54.5±4.3	98.3±8.7	90.0±8.4
 **3ag**	56.3±4.3	68.0±5.2	>100
 **3aj**	52.2±4.1	93.6±7.3	100±9.3
 **3al**	37.4±2.9	74.8±5.8	57.7±4.4
 **3an**	71.1±5.7	100±8.6	>100
 **3ao**	57.6±4.6	>100	55.4±4.5
 **3ba**	57.5±4.4	>100	>100
 **3ap**	58.0±4.7	>100	56.9±4.6
 **3aq**	58.2±4.7	60.7±5.3	84.6±7.5
 **3ar**	90.2±8.3	>100	92.3±8.5

Test compounds	IC50 (μM)		
	Cancer cell lines		Normal cell line
	M-HeLa	HuTu 80	Chang liver
 **3av**	61.8±4.6	>100	>100
 **3bd**	56.1±4.3	>100	>100
 **3au**	59.3±5.1	>100	87.9±7.5
 **3at**	57.8±4.5	>100	>100
 **3aw**	51.0±4.2	>100	>100
Tamoxifen	28.0±2.5		46.2±3.5
Doxorubicin		3.0±0.1	3.0±0.1

[a] *Three independent experiments were carried out; the activity was tested at concentrations of 1–100 μM*

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Copies of NMR spectra

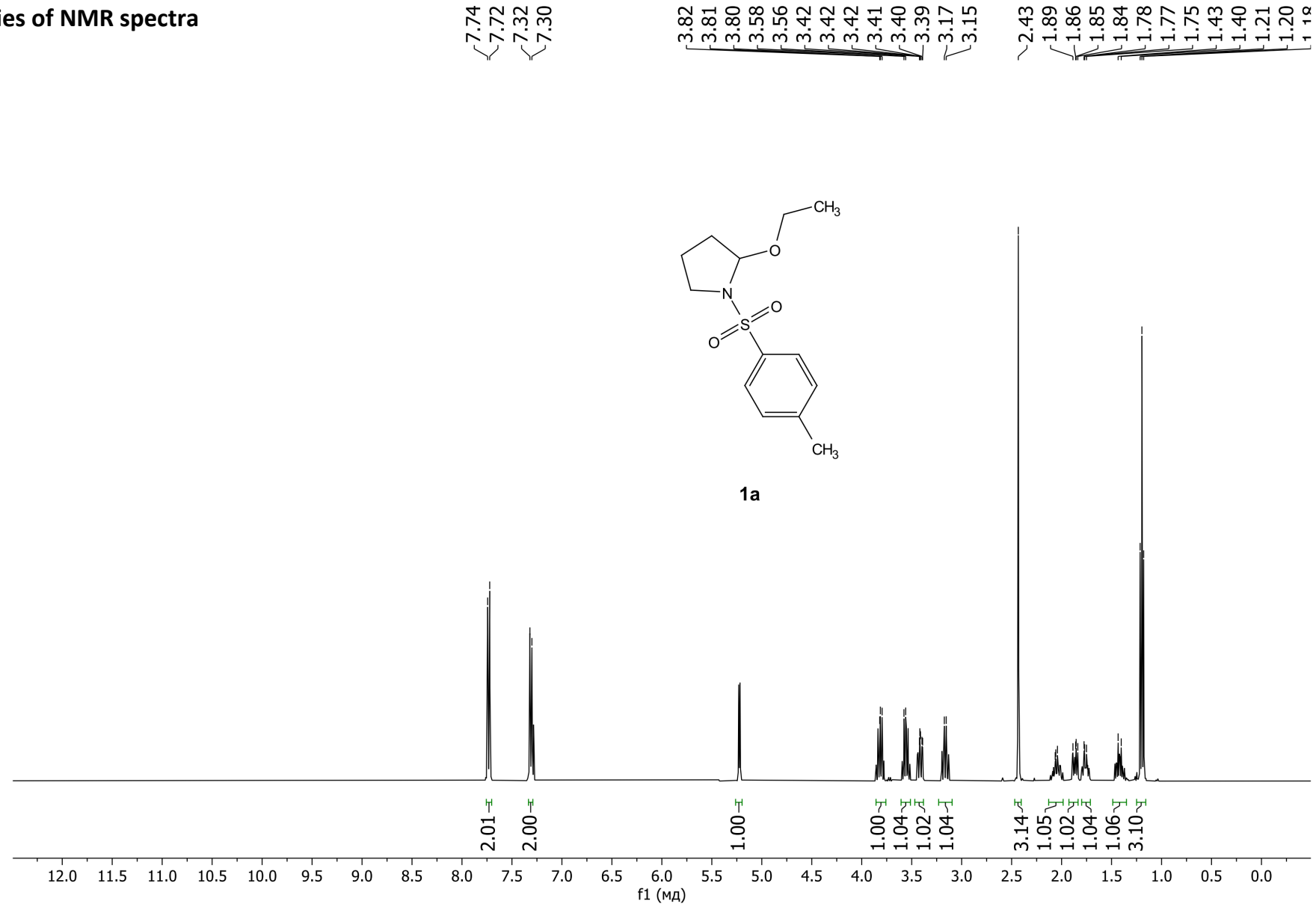

Figure S4. ^{1}H NMR spectrum ($CDCl_3$, 400MHz) of the compound **1a**

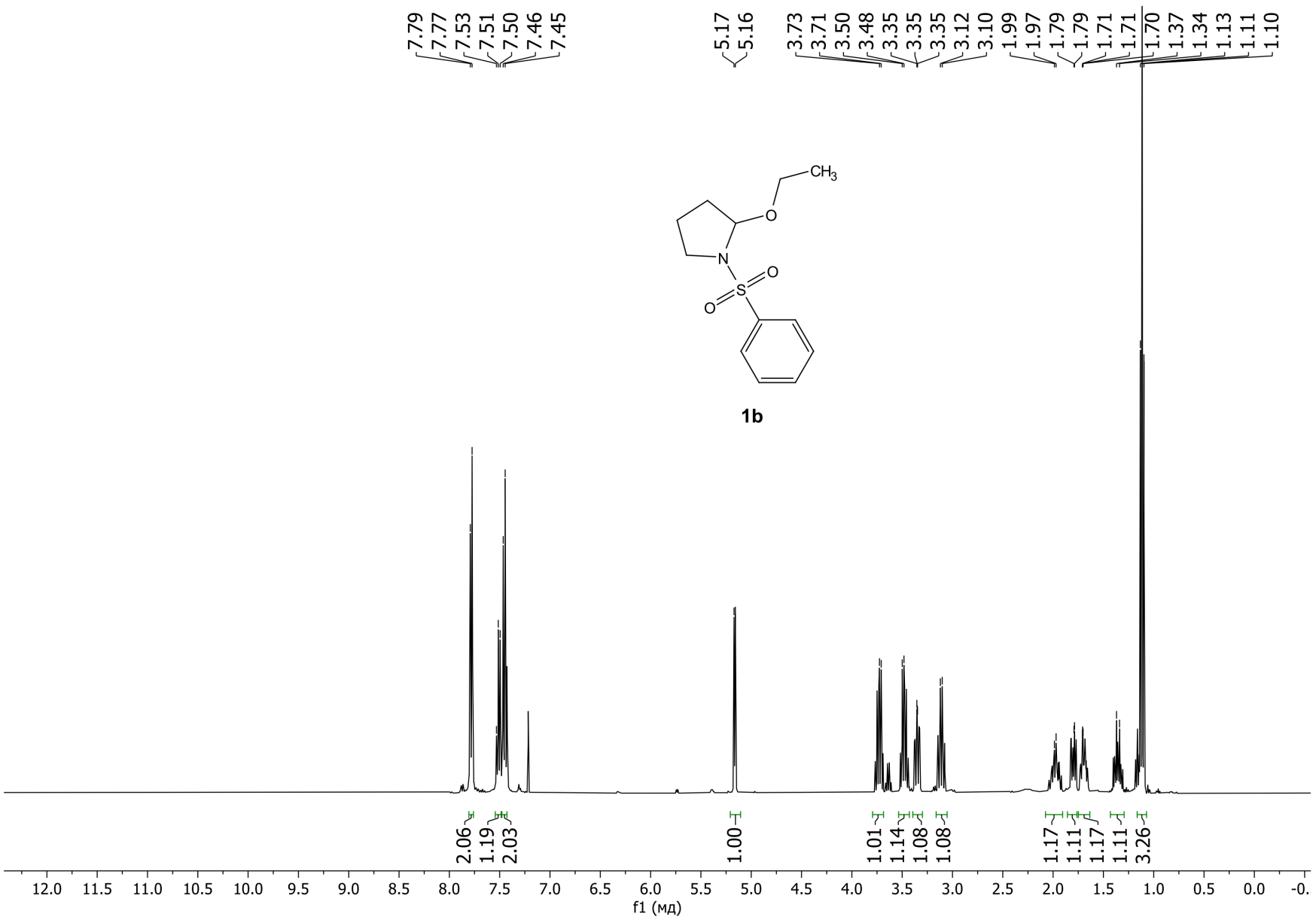

Figure S5. ^{1}H NMR spectrum ($CDCl_3$, 400MHz) of the compound **1b**

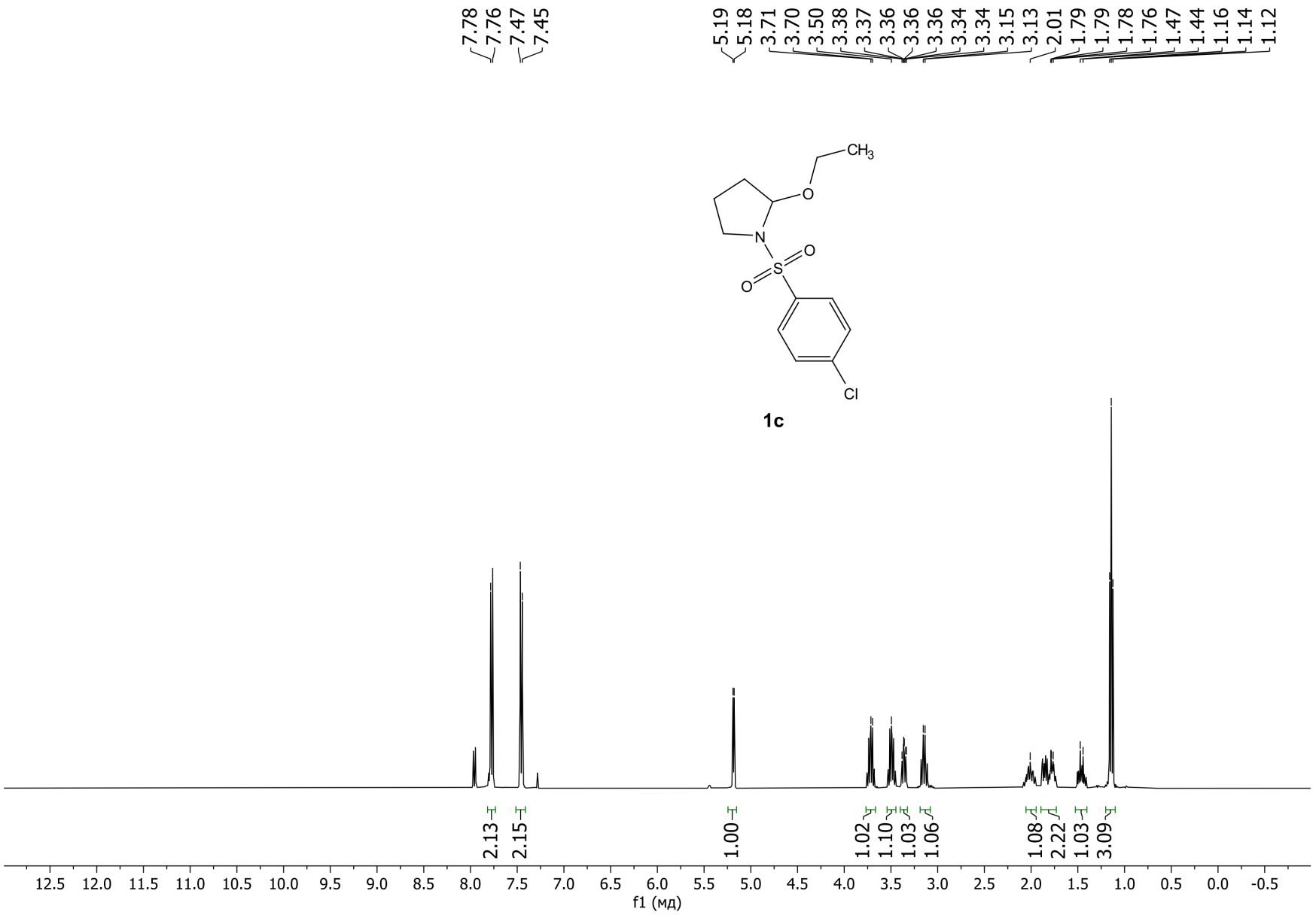

Figure S6. ^{1}H NMR spectrum ($CDCl_3$, 400MHz) of the compound **1c**

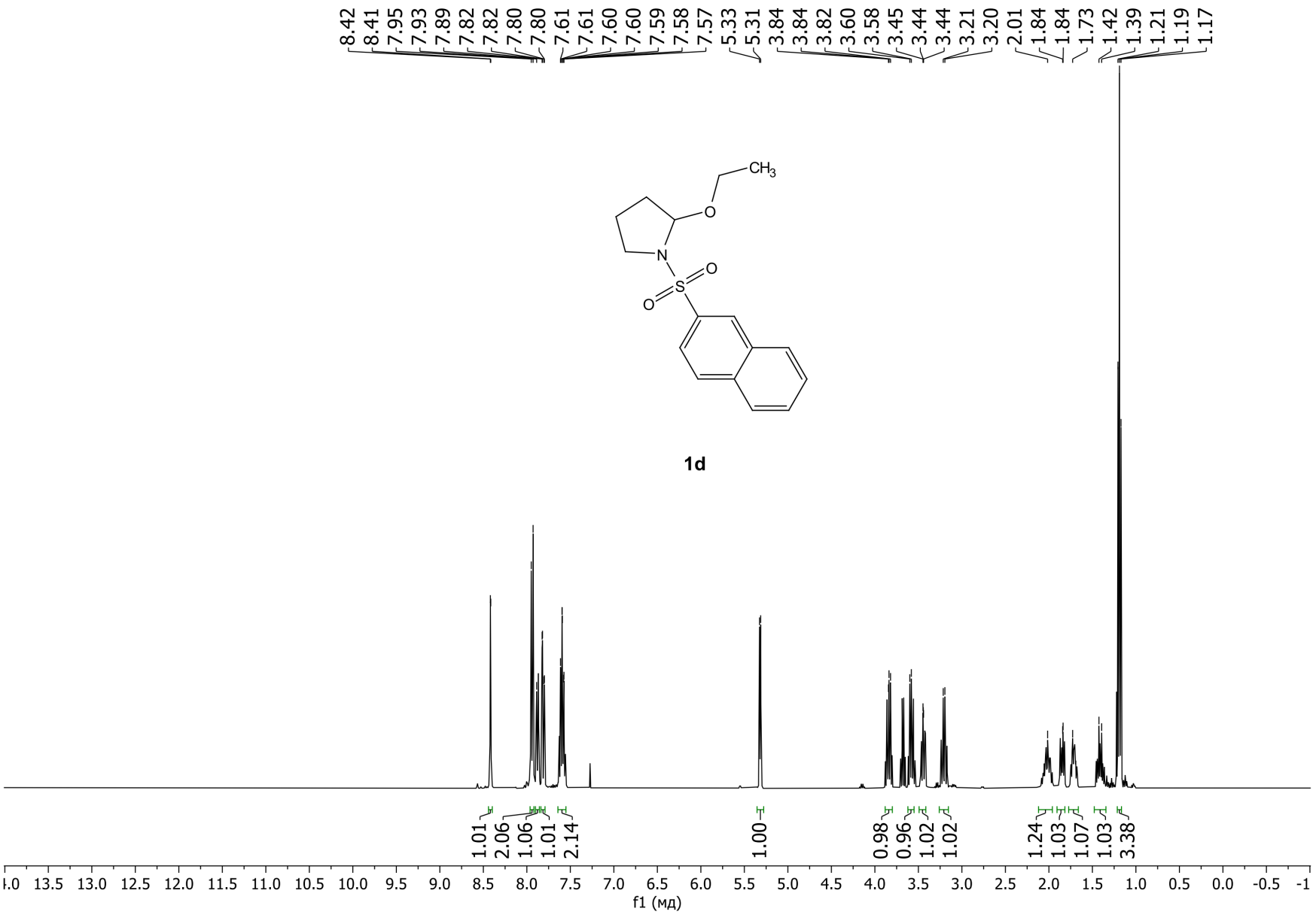

Figure S7. ^{1}H NMR spectrum ($CDCl_3$, 400MHz) of the compound **1d**

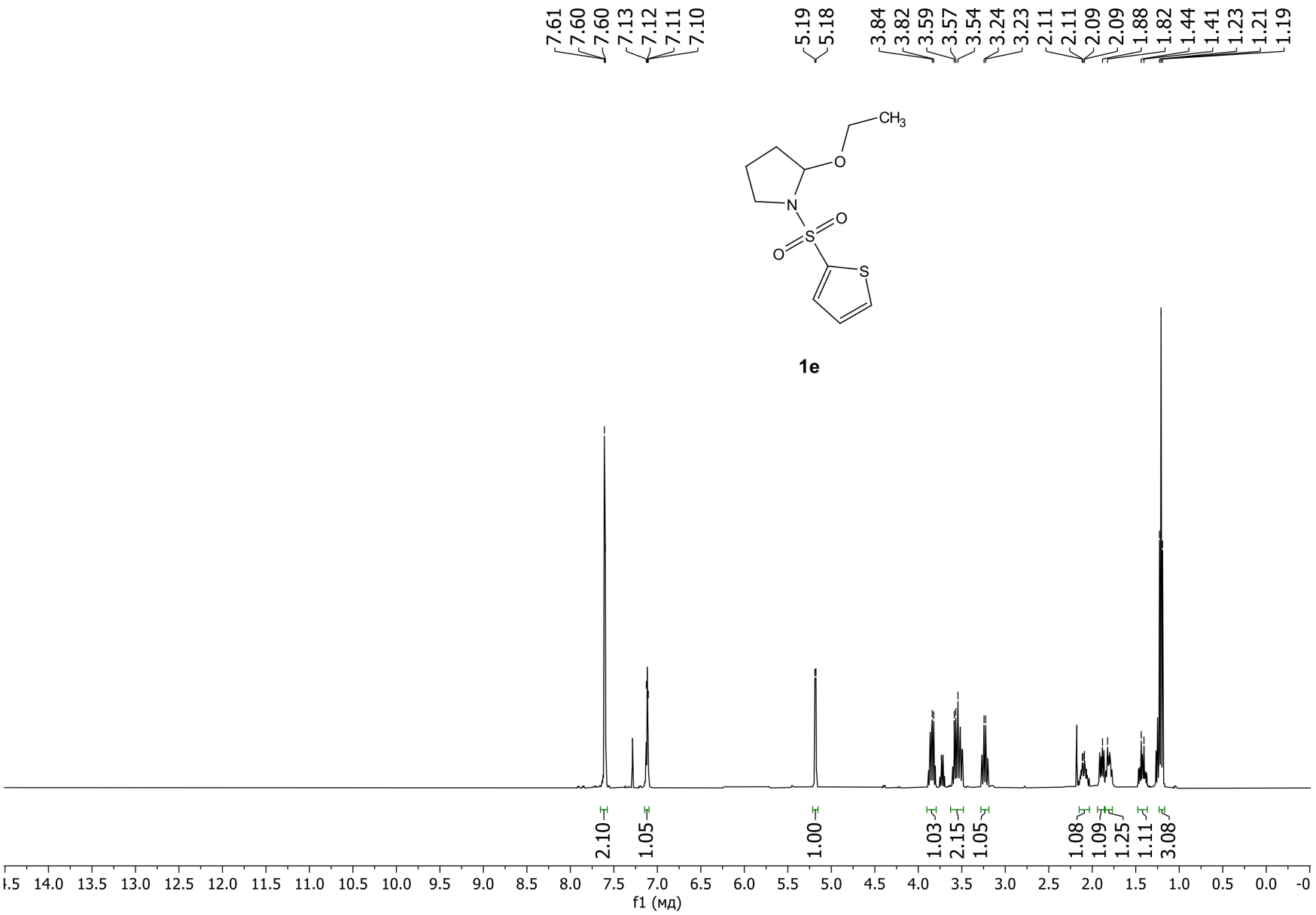

Figure S8. ^{1}H NMR spectrum ($CDCl_3$, 400MHz) of the compound **1e**

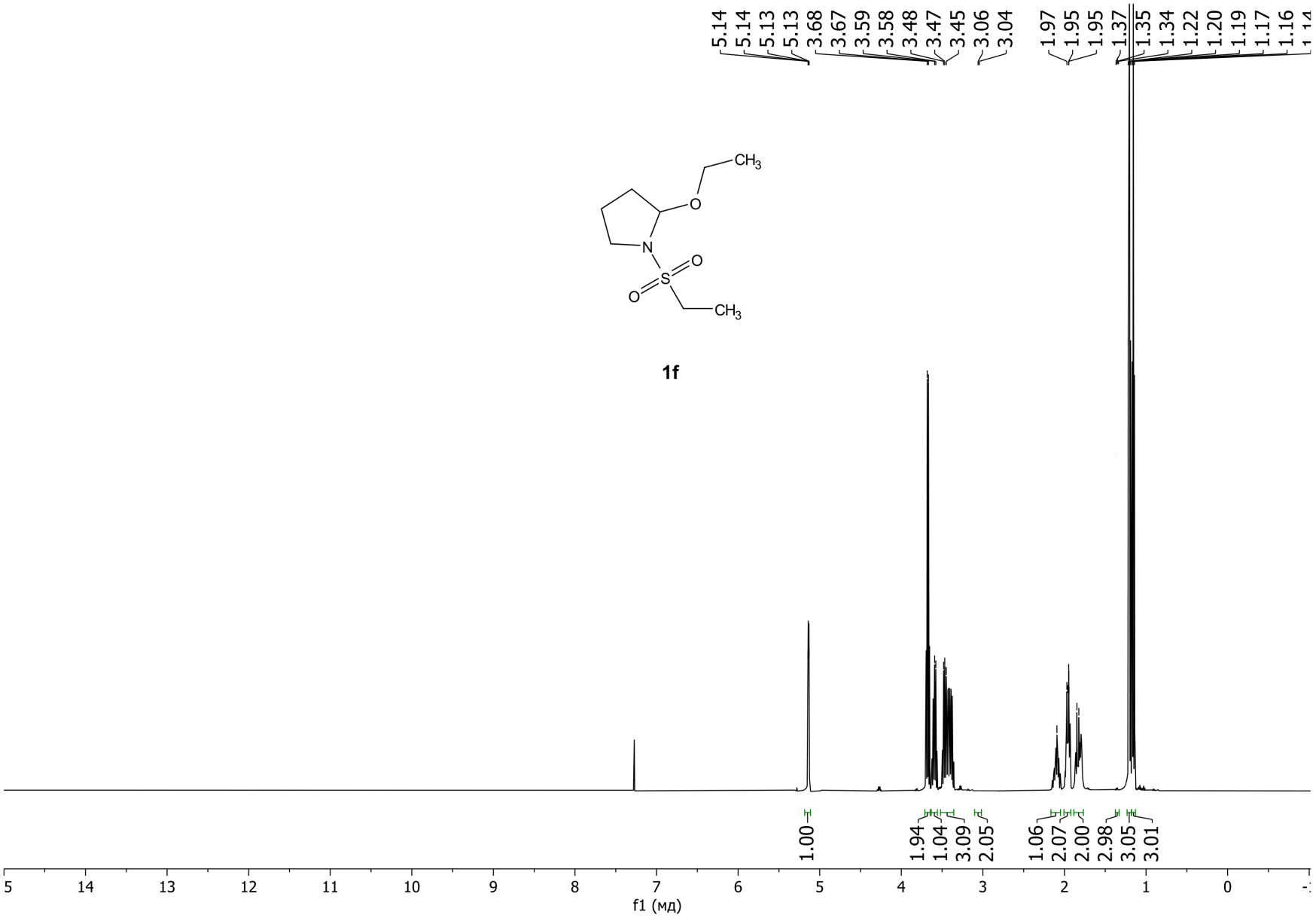

Figure S9. ^{1}H NMR spectrum ($CDCl_3$, 400MHz) of the compound **1f**

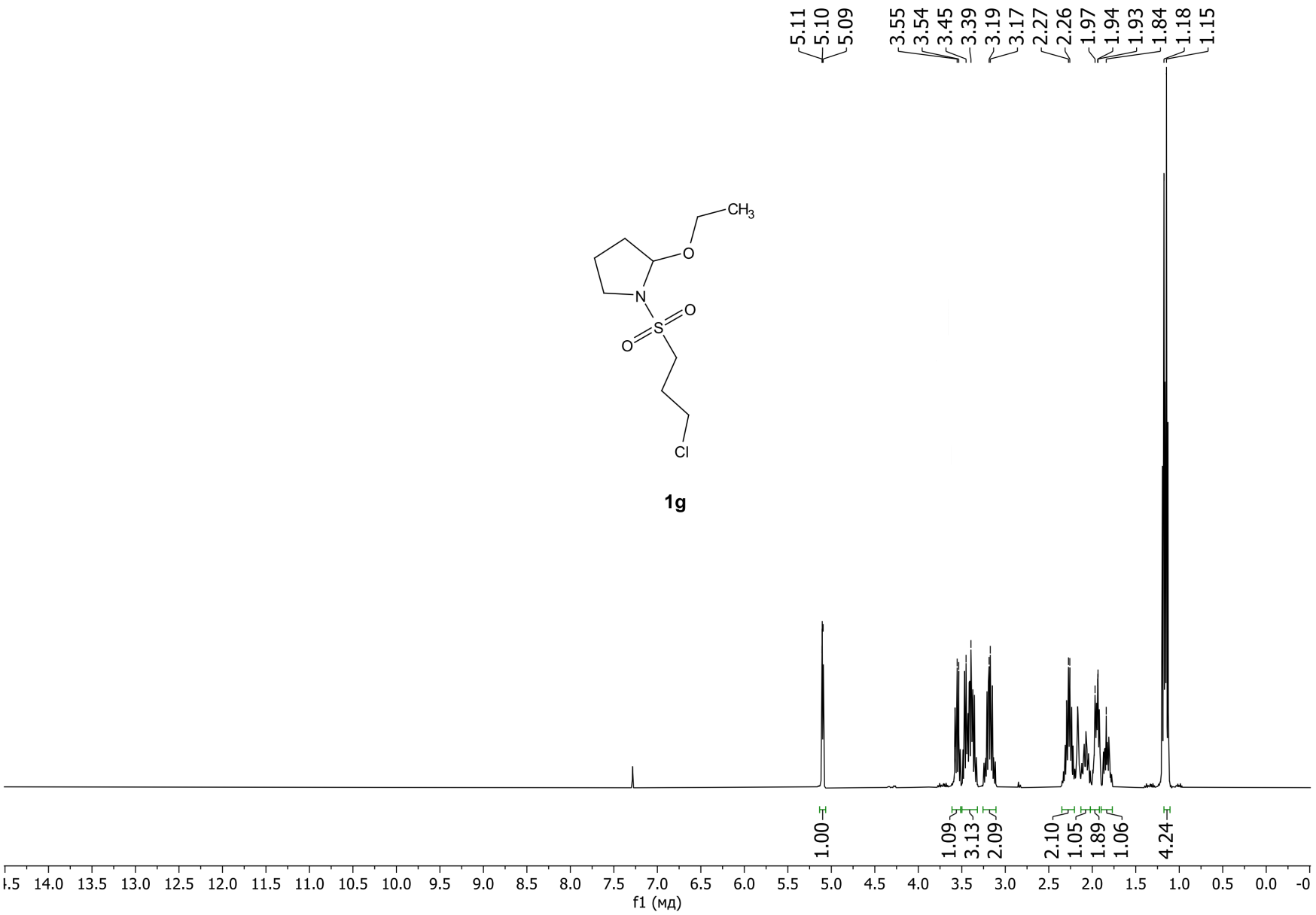

Figure S10. ^{1}H NMR spectrum ($CDCl_3$, 400MHz) of the compound **1g**

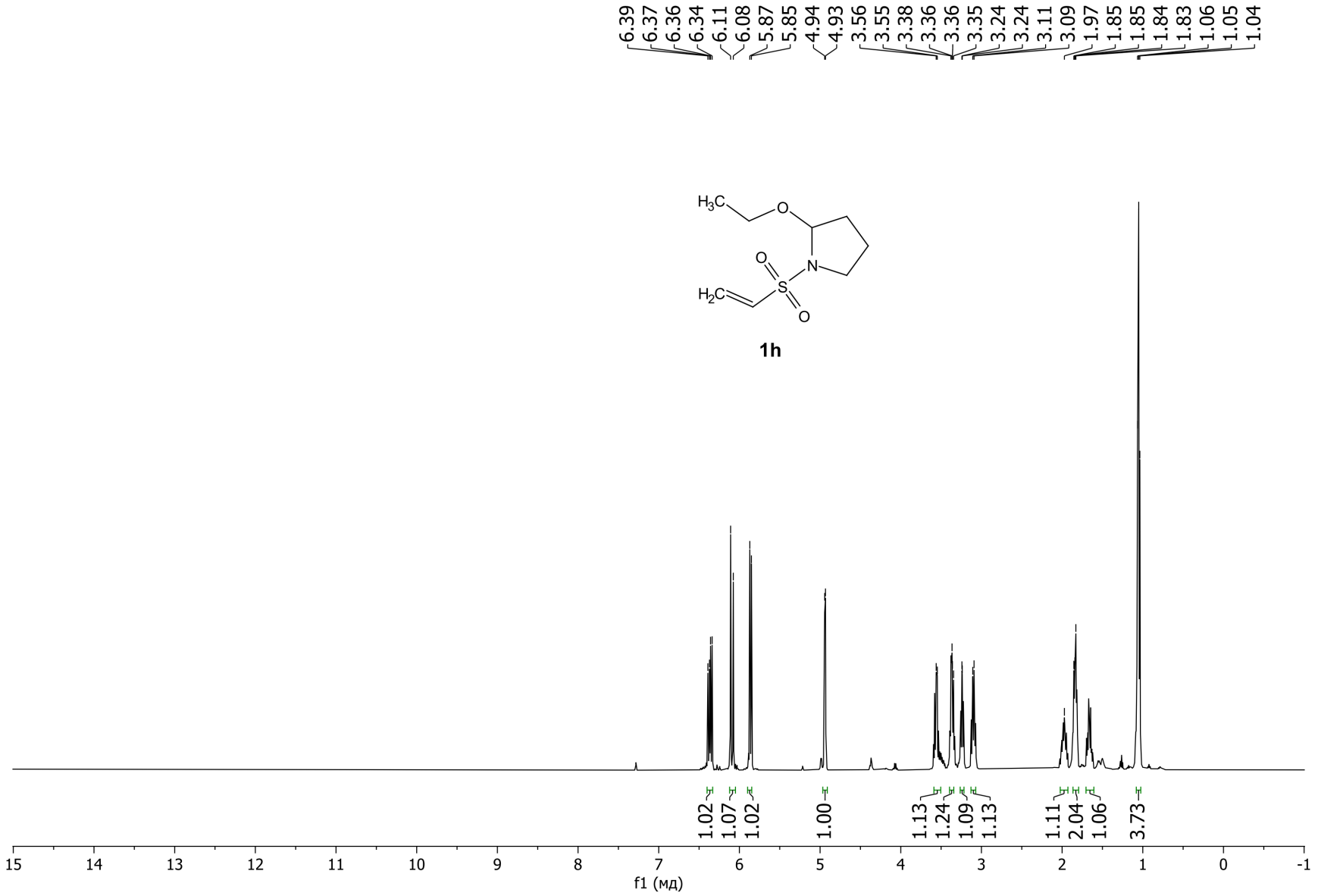

Figure S11. ^{1}H NMR spectrum ($CDCl_3$, 400MHz) of the compound **1h**

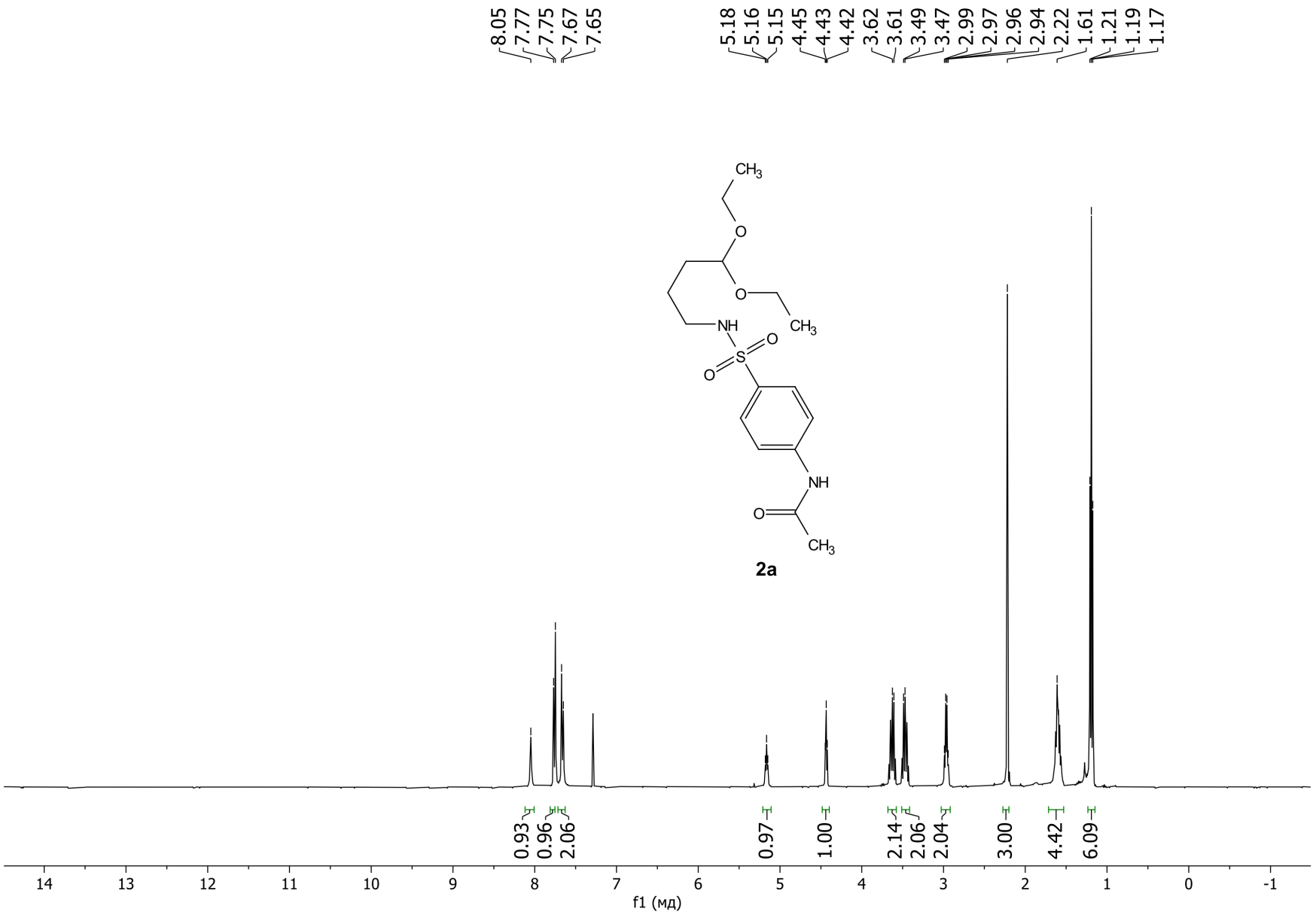

Figure S12. ^{1}H NMR spectrum ($CDCl_3$, 400MHz) of the compound **2a**

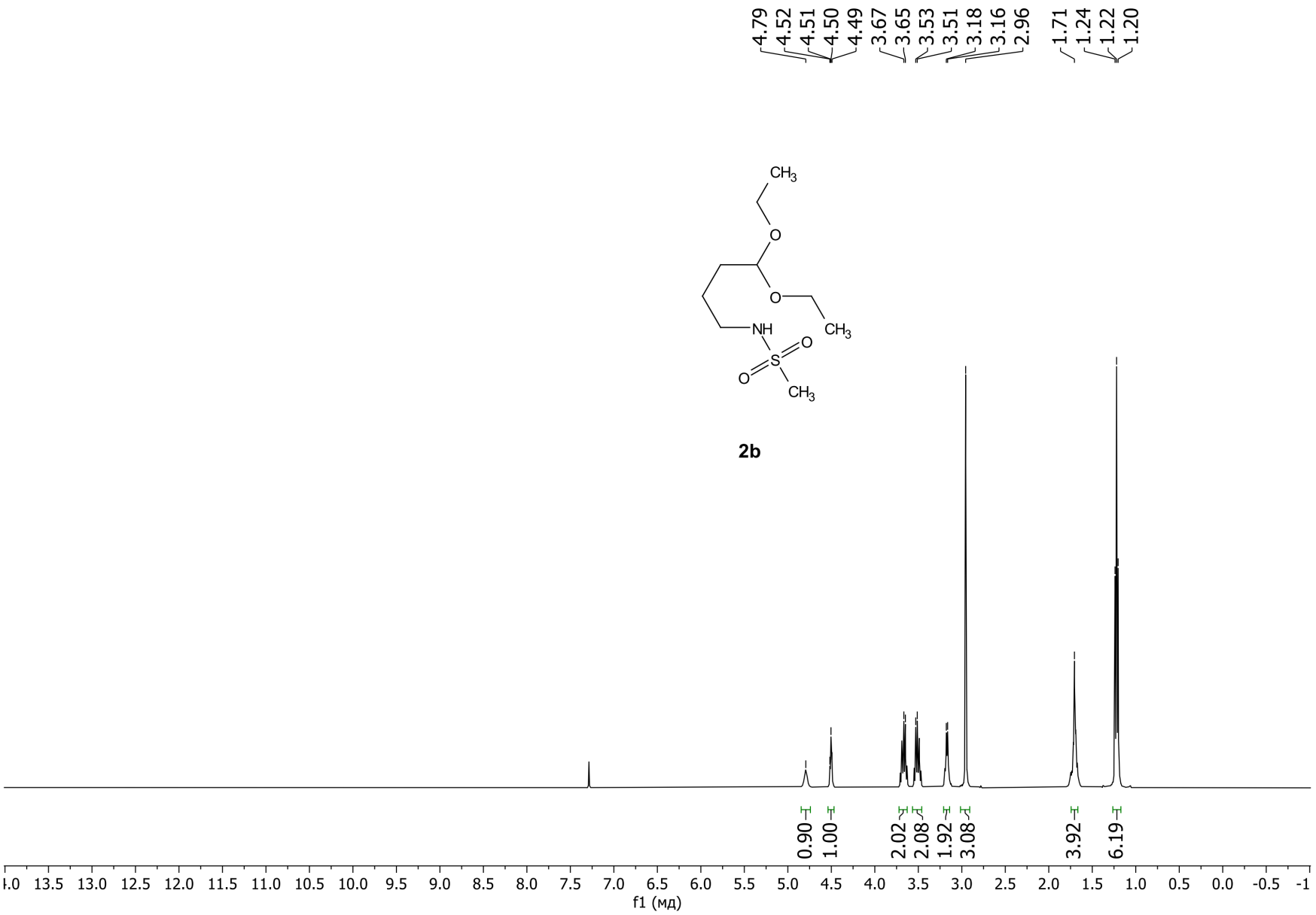

Figure S13. ^{1}H NMR spectrum ($CDCl_3$, 400MHz) of the compound **2b**

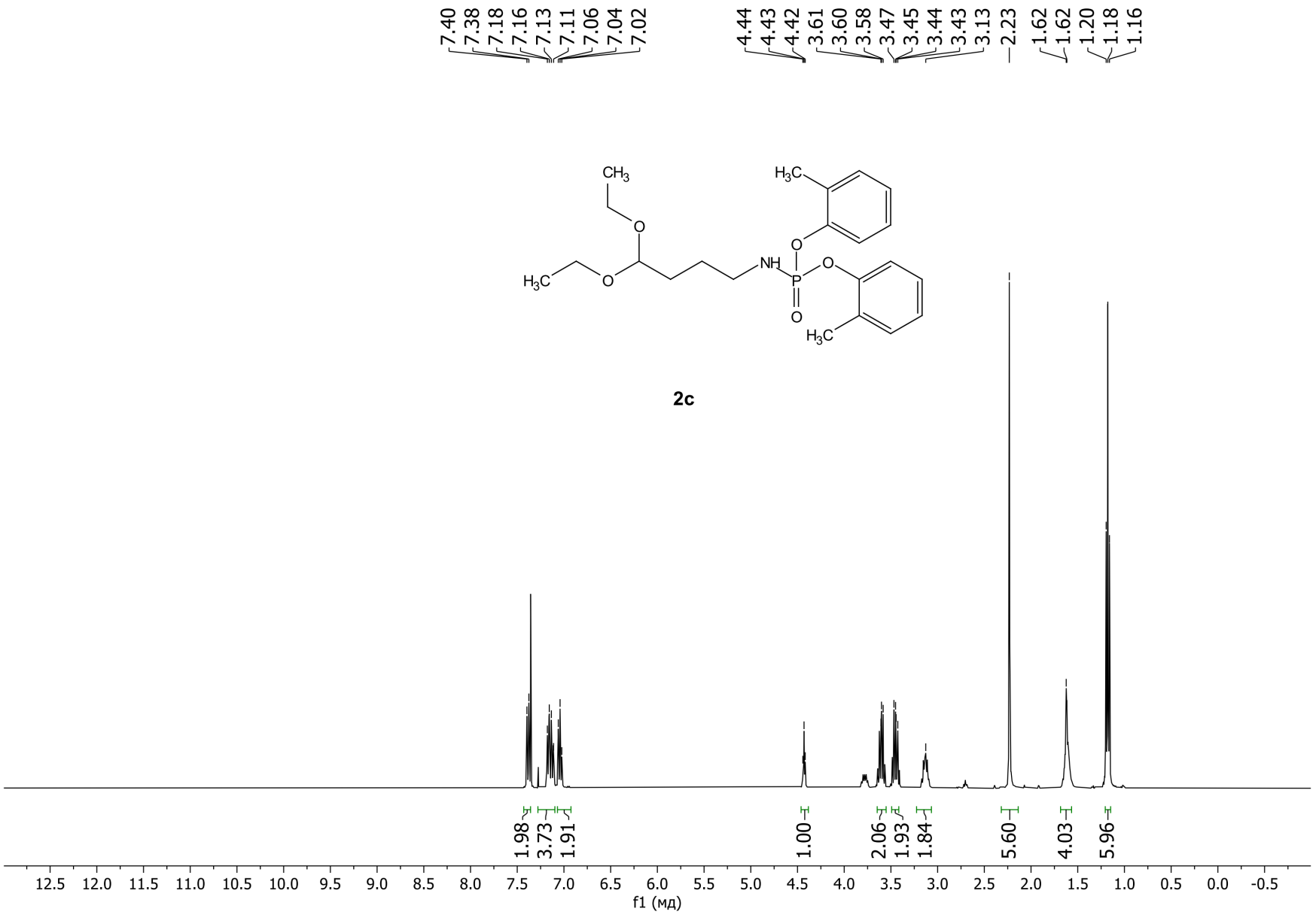

Figure S14. ^{1}H NMR spectrum ($CDCl_3$, 400MHz) of the compound **2c**

2c

Figure S15. NMR ^{31}P spectrum ($CDCl_3$, 162MHz) of the compound **2c**

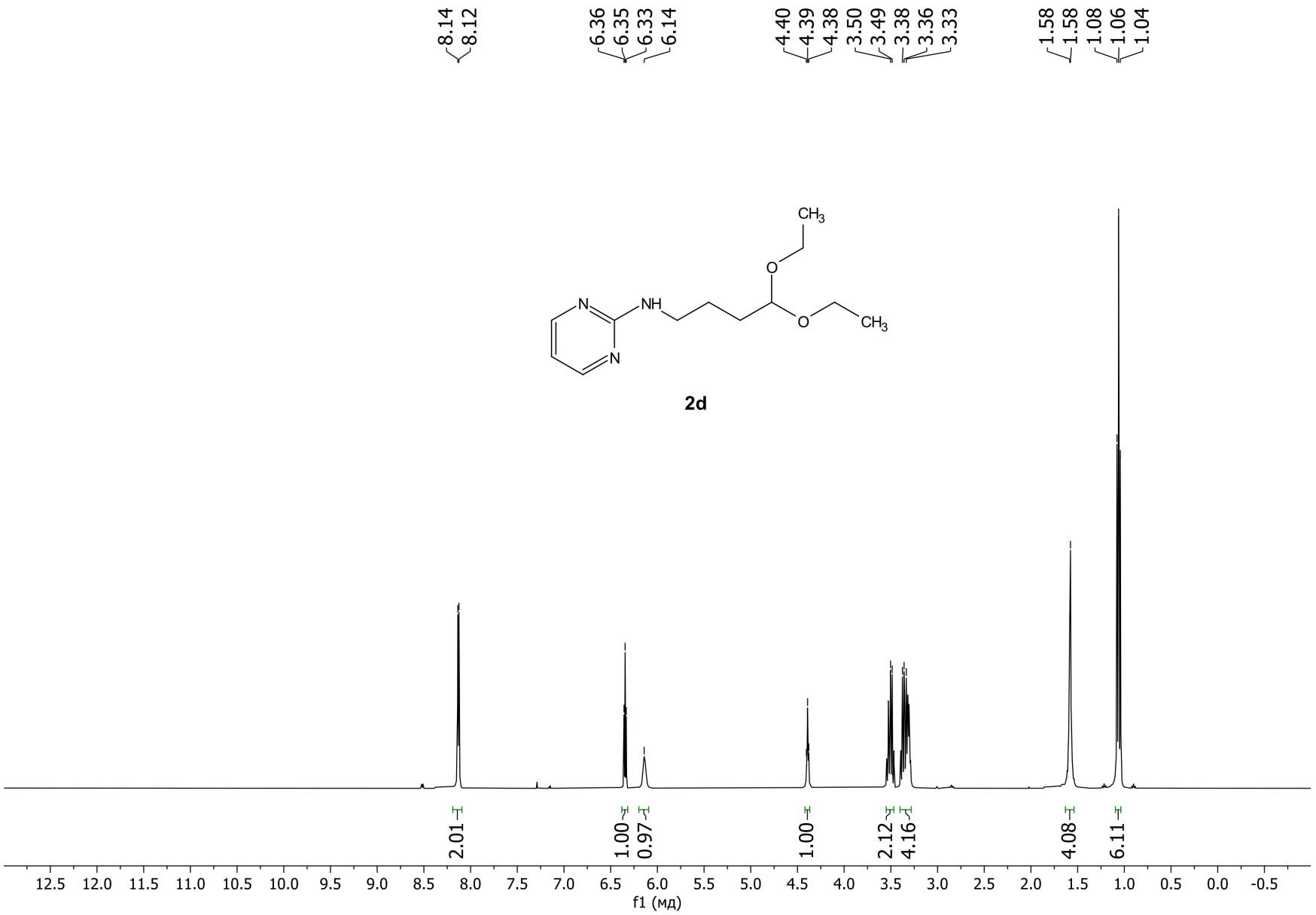

Figure S16. ^{1}H NMR spectrum ($CDCl_3$, 400MHz) of the compound **2d**

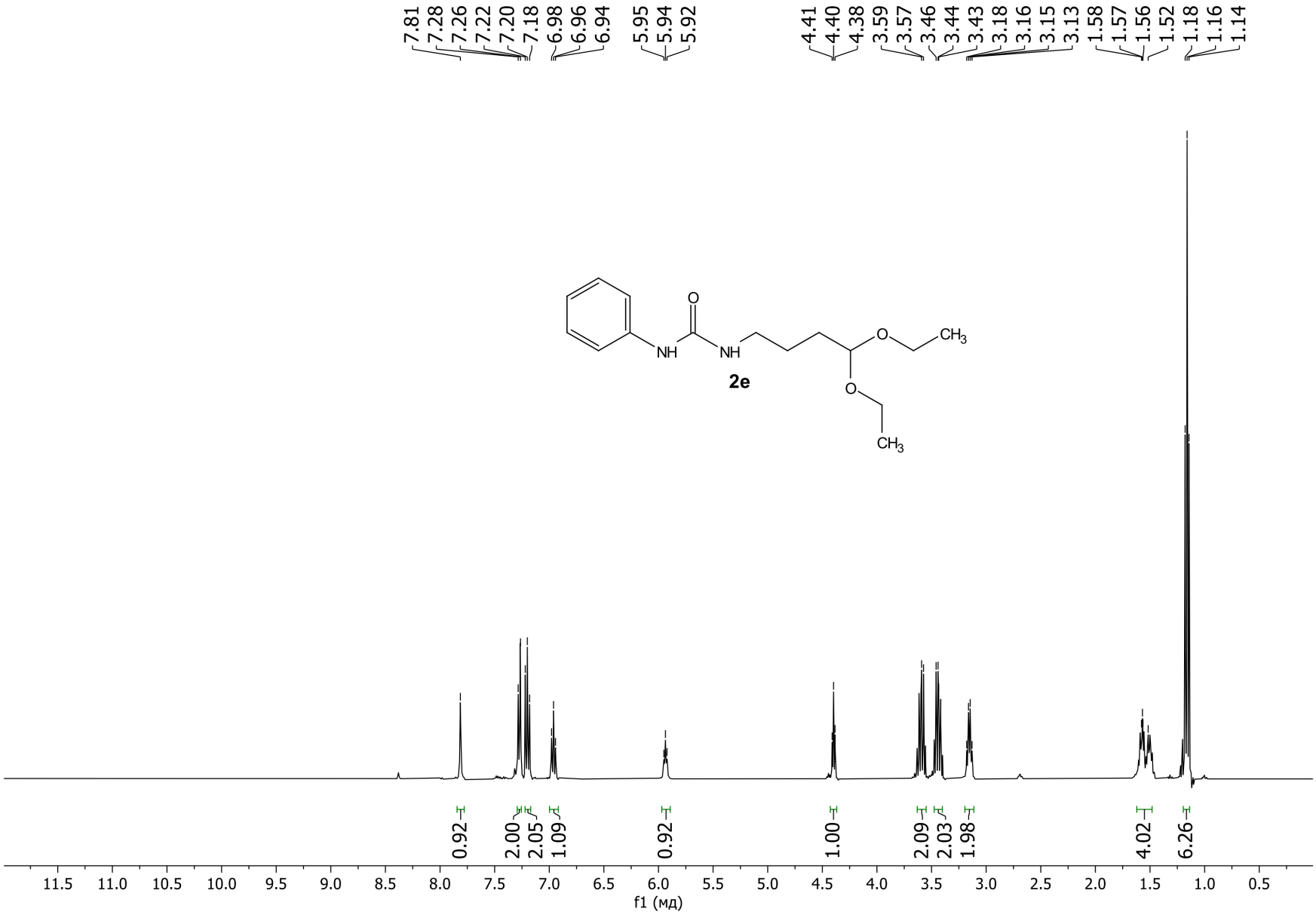

Figure S17. ^{1}H NMR spectrum ($CDCl_3$, 400MHz) of the compound **2e**

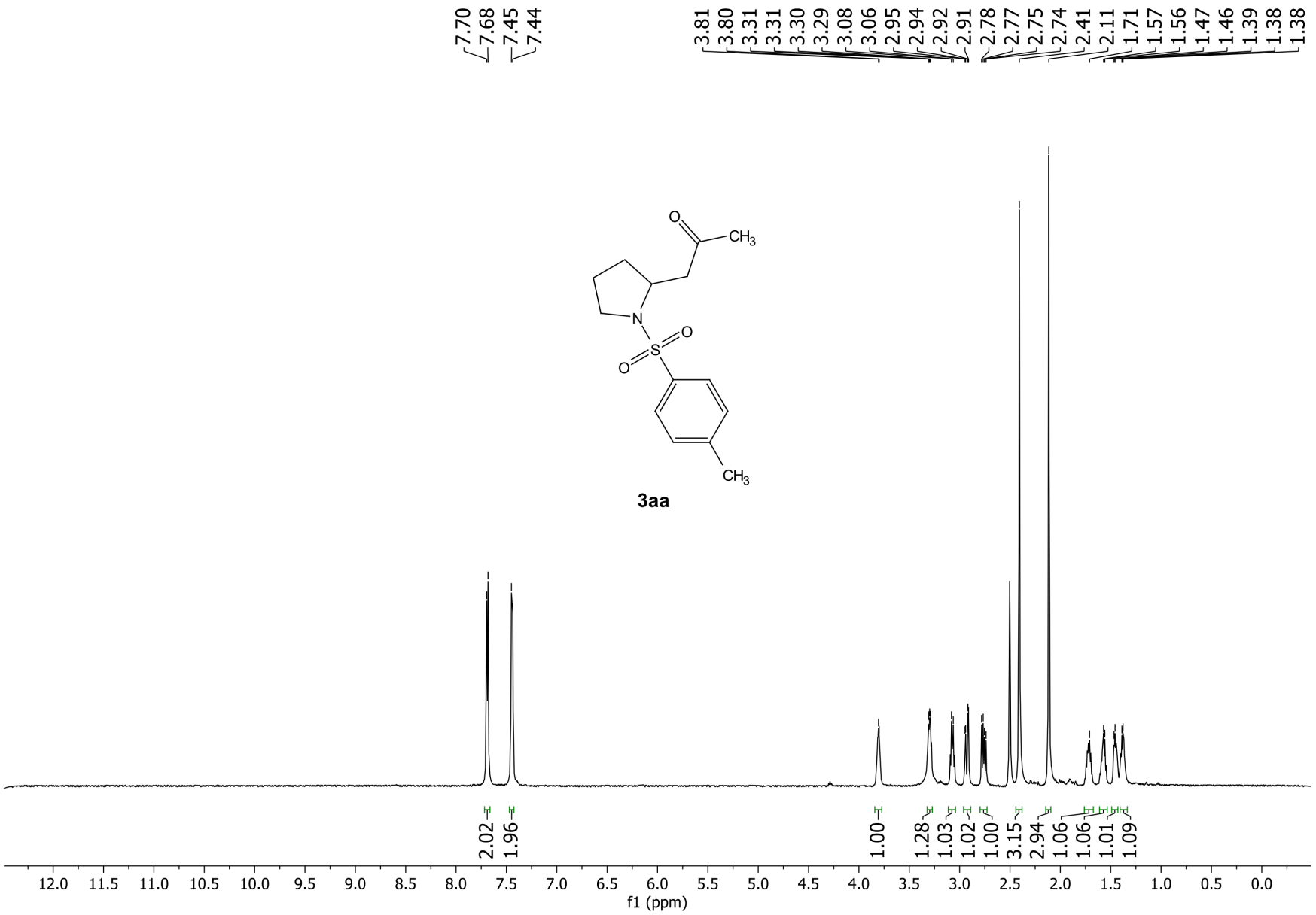

Figure S18. ^{1}H NMR spectrum ($(CD_3)_2SO$, 600MHz) of the compound **3aa**

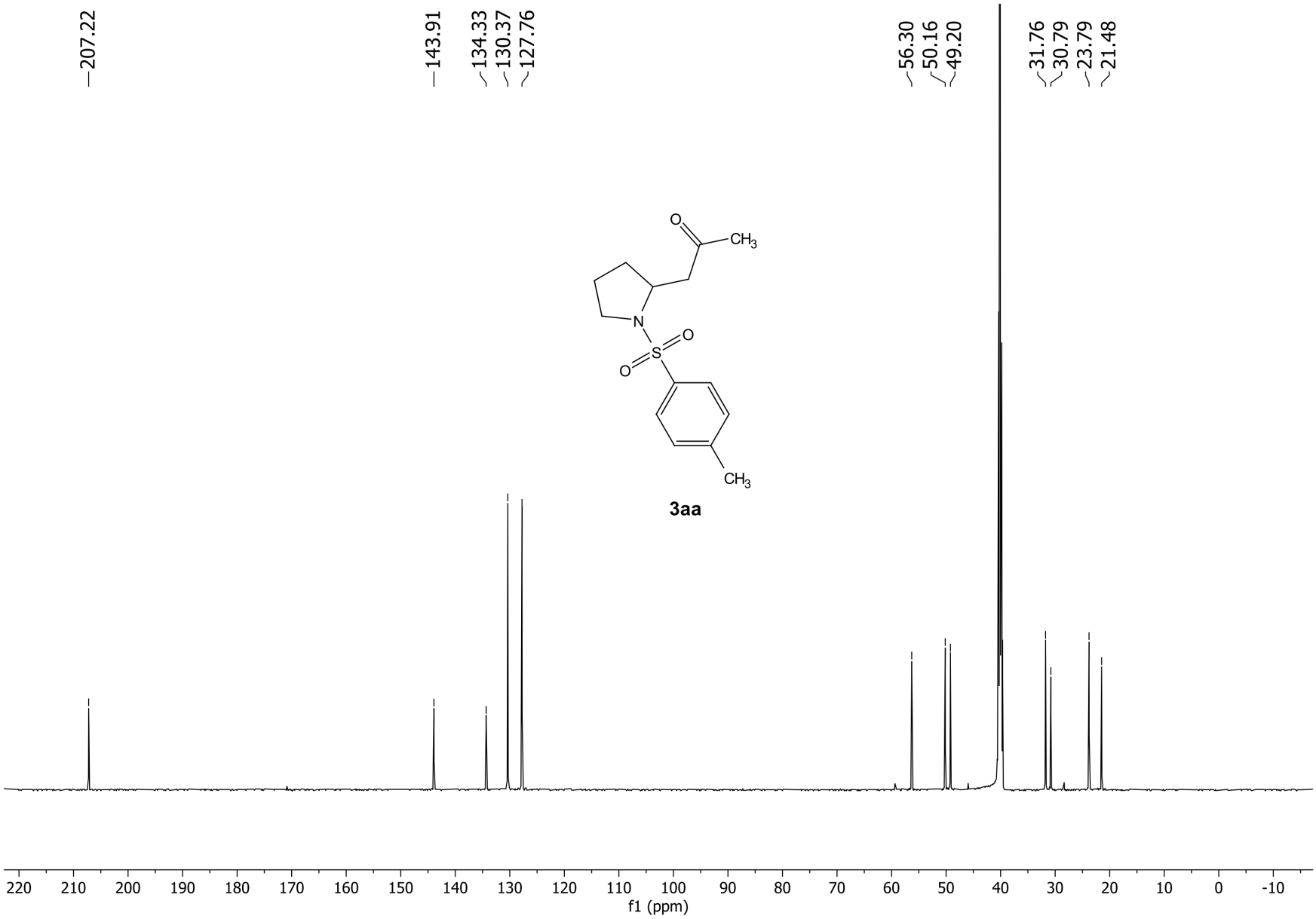

Figure S19. ^{13}C-{1H} NMR spectrum ($(CD_3)_2SO$, 150MHz) of the compound **3aa**

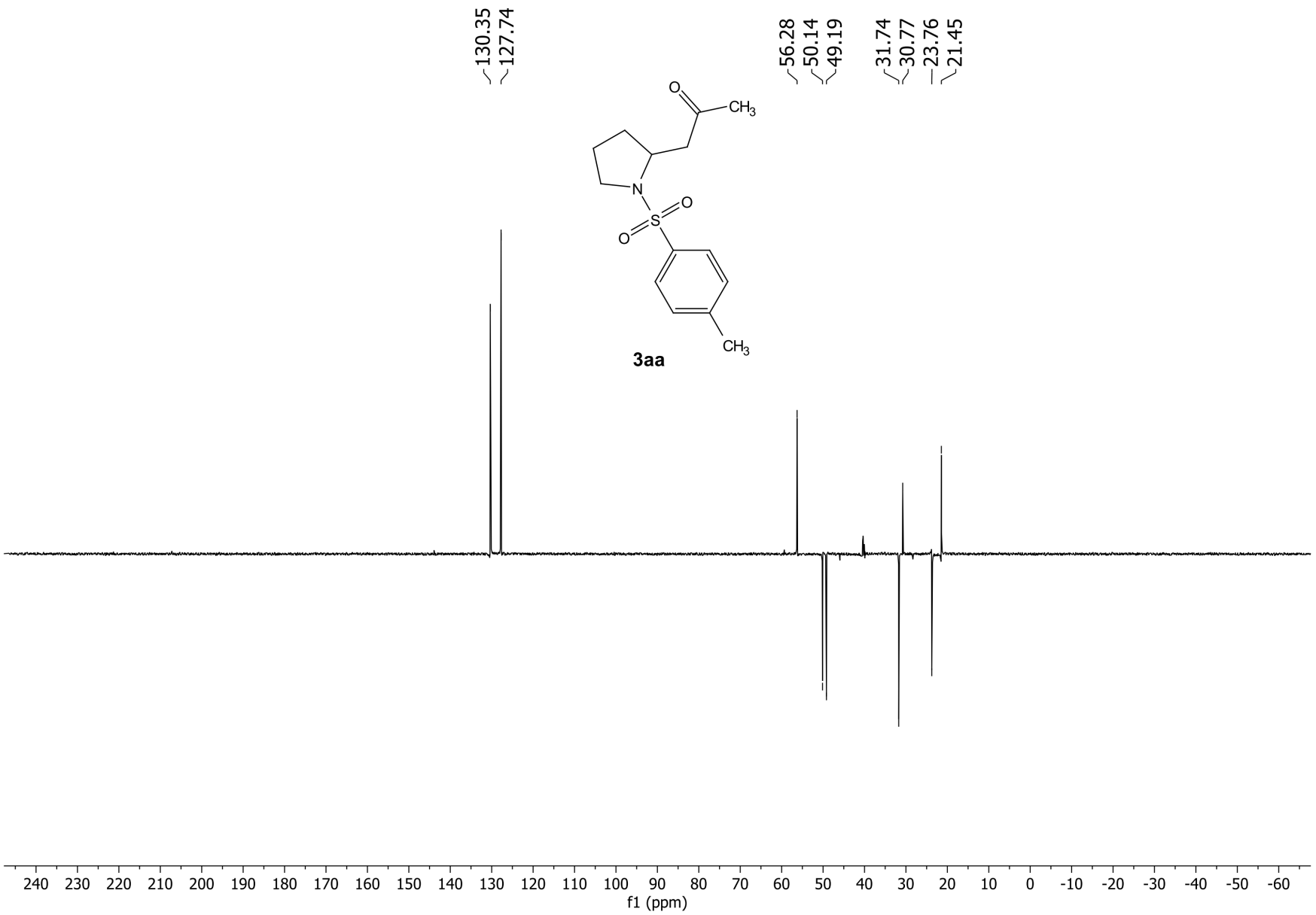

Figure S20. 135° DEPT spectrum ($(CD_3)_2SO$, 150MHz) of the compound **3aa**

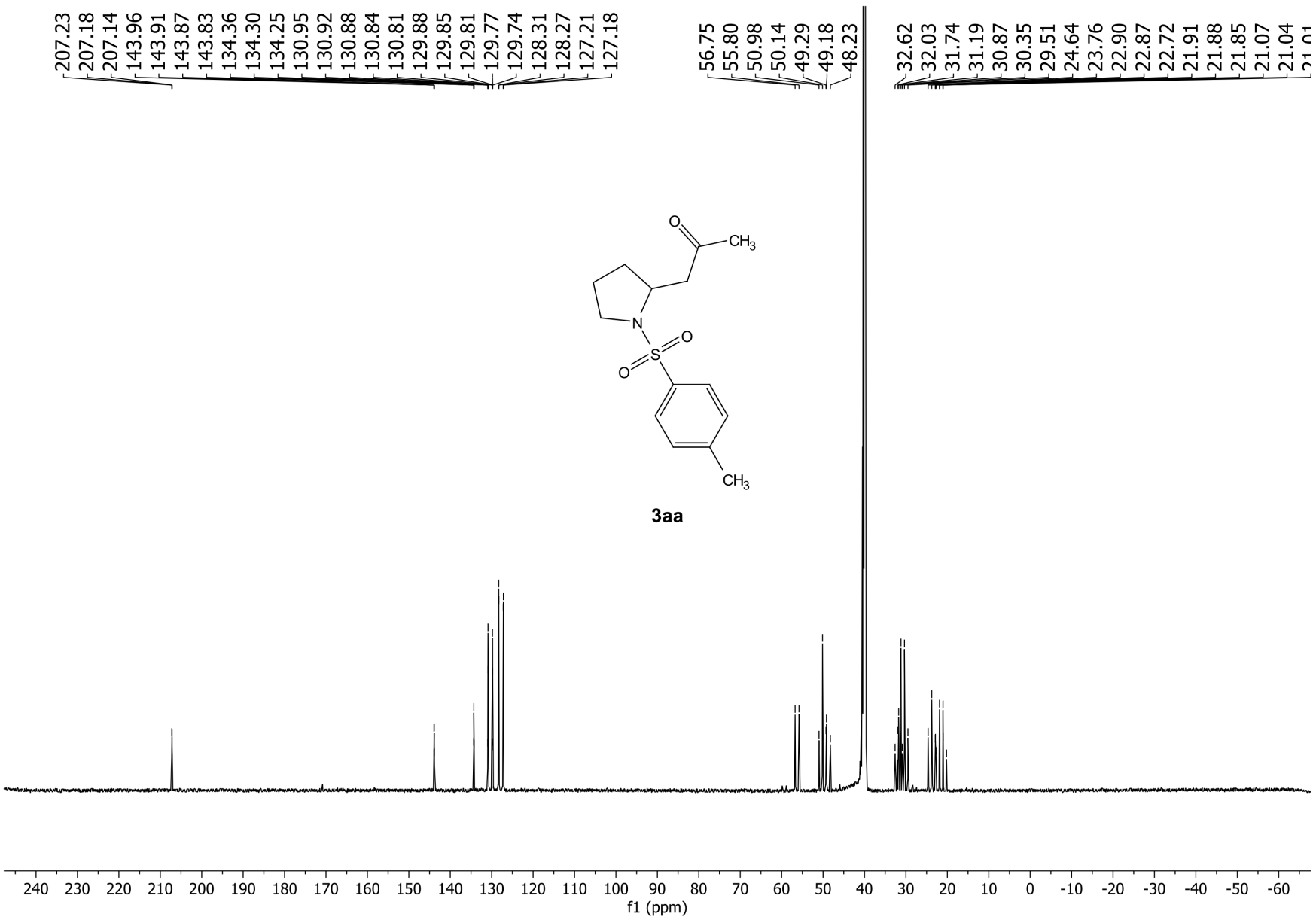

Figure S21. ^{13}C NMR spectrum ($(CD_3)_2SO$, 150MHz) of the compound **3aa**

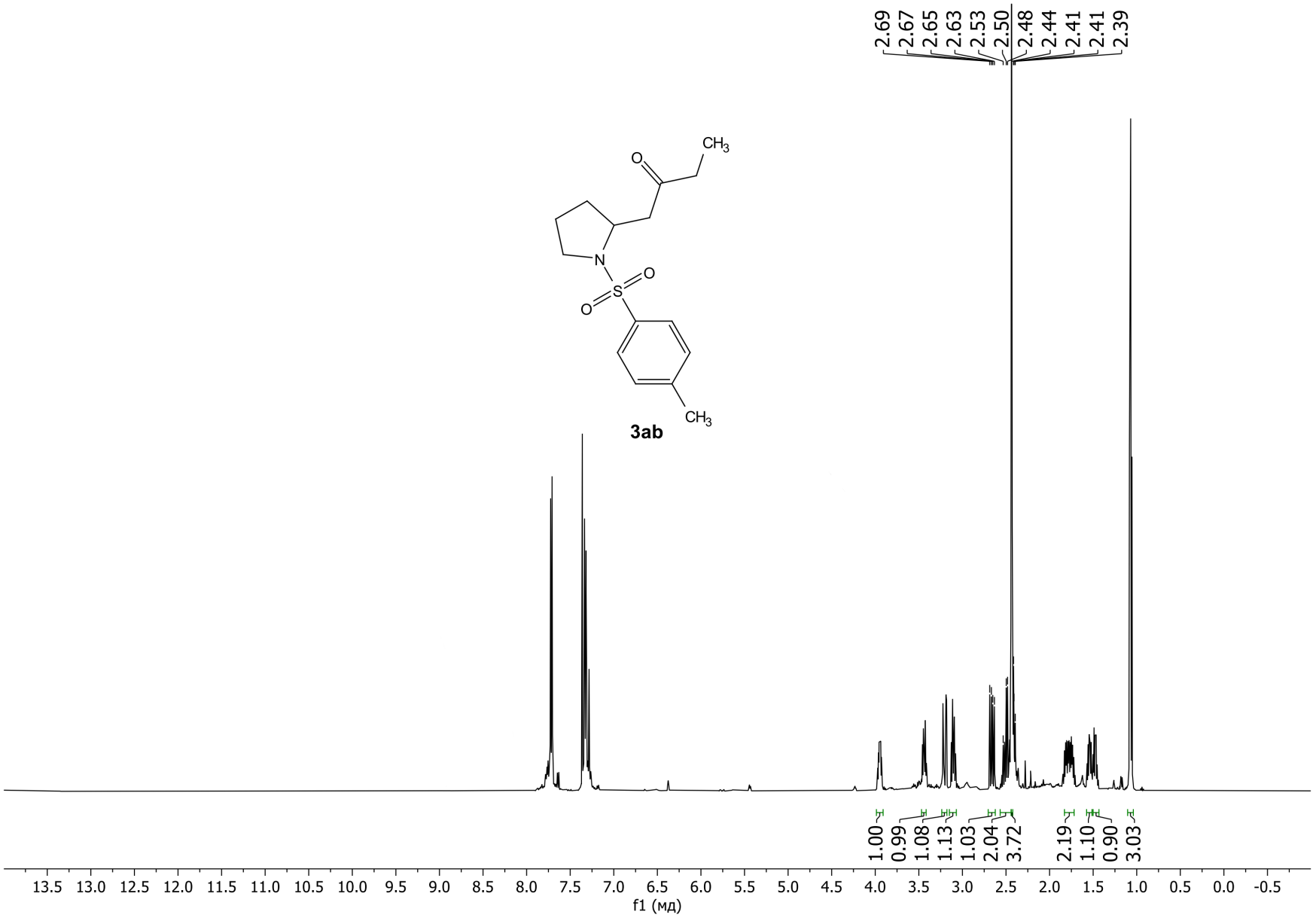

Figure S22. ^{1}H NMR spectrum ($CDCl_3$, 600MHz) of the compound **3ab**

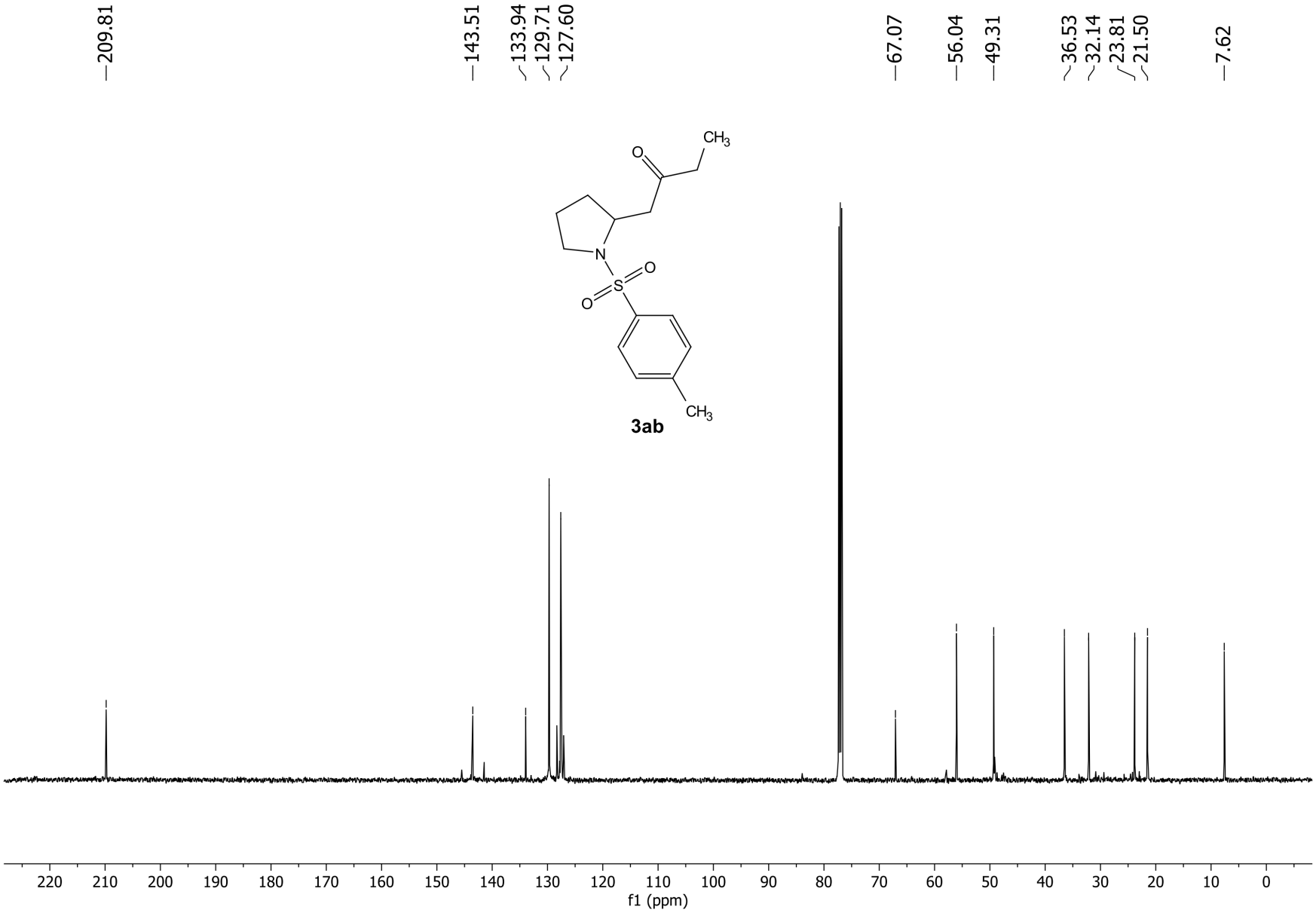

Figure S23. ^{13}C-{1H} NMR spectrum ($CDCl_3$, 150MHz) of the compound **3ab**

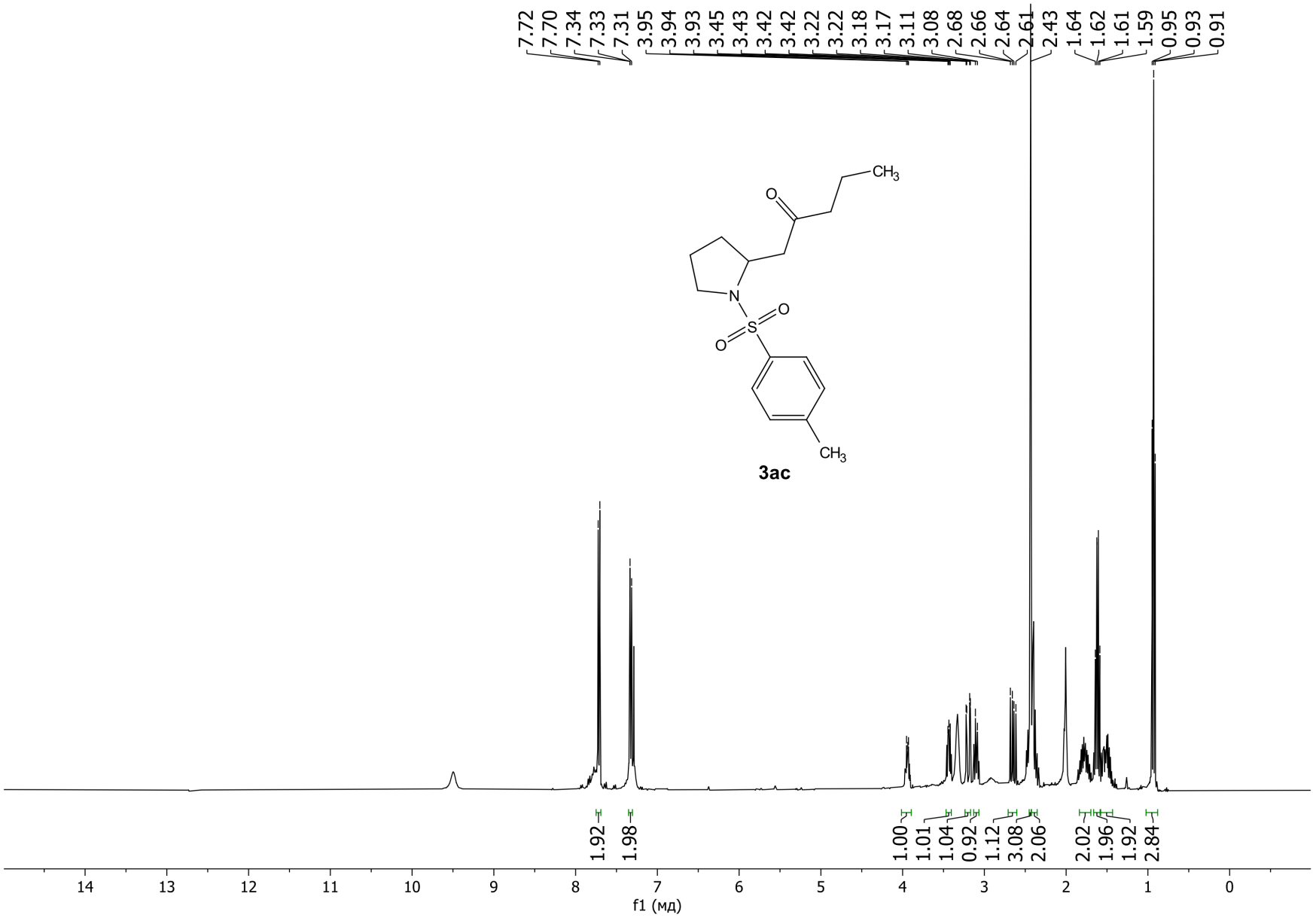

Figure S24. ^{1}H NMR spectrum ($CDCl_3$, 600MHz) of the compound **3ac**

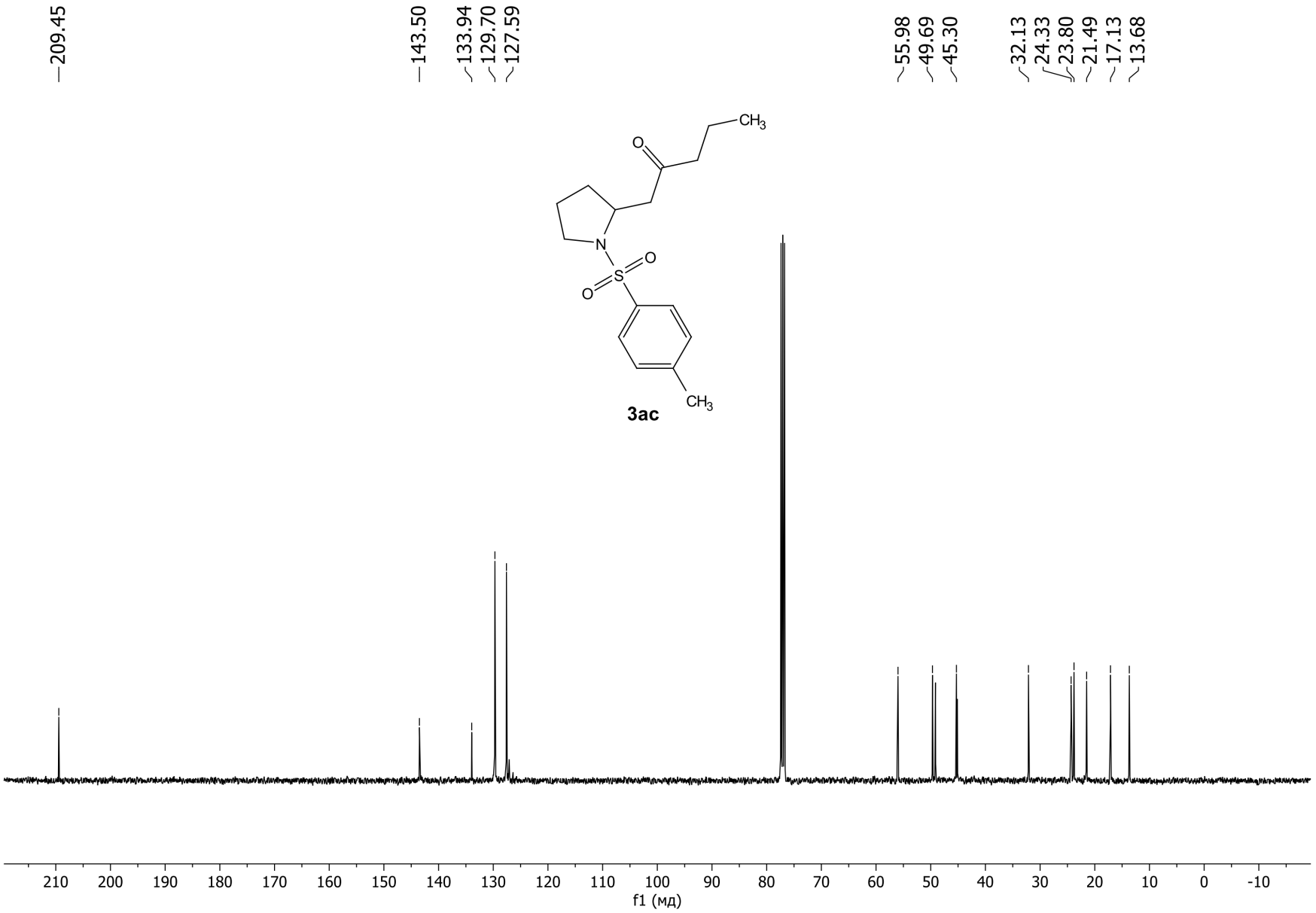

Figure S25. ^{13}C-{1H} NMR spectrum ($CDCl_3$, 150MHz) of the compound **3ac**

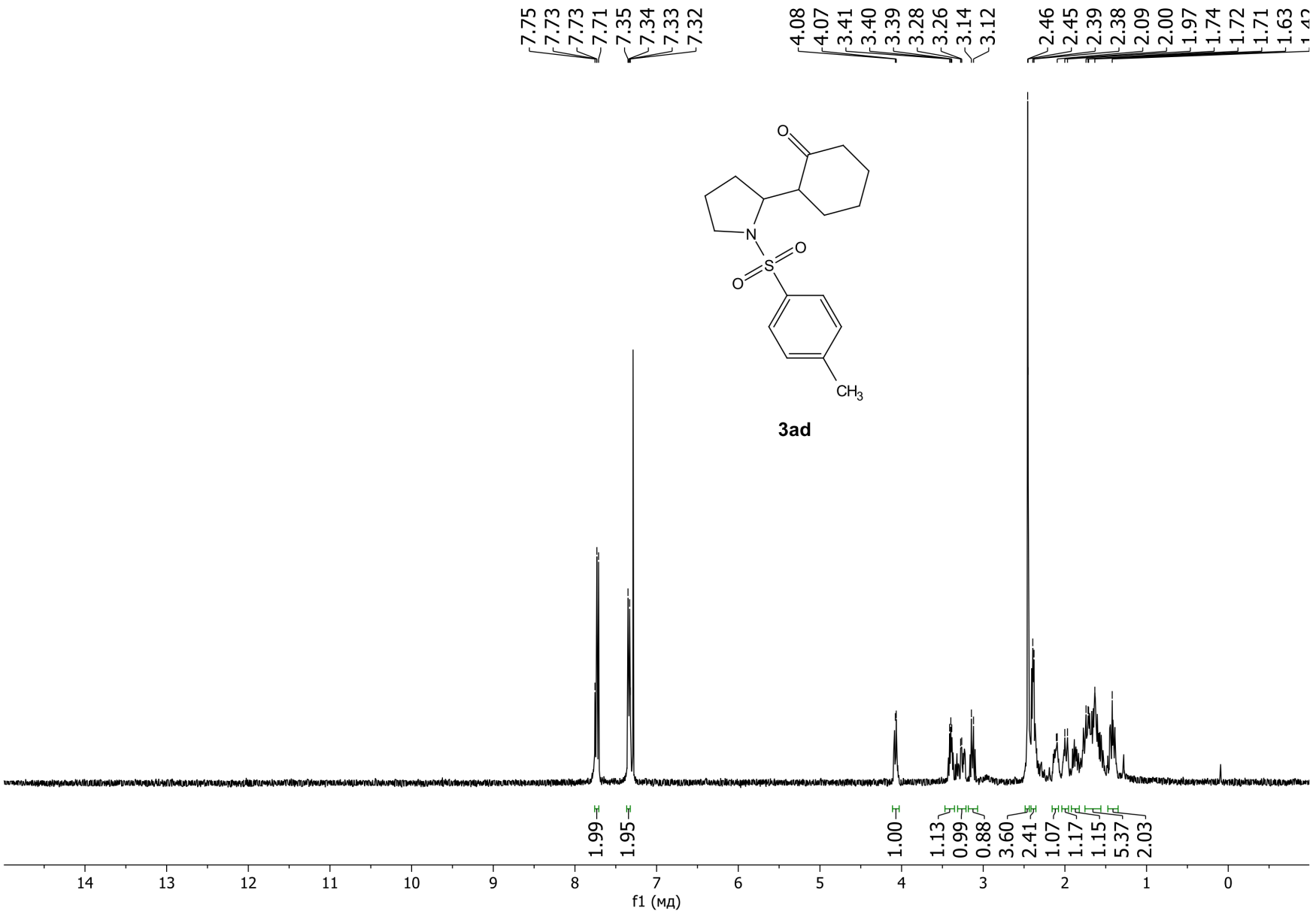

Figure S26. ^{1}H NMR spectrum ($CDCl_3$, 600MHz) of the compound **3ad**

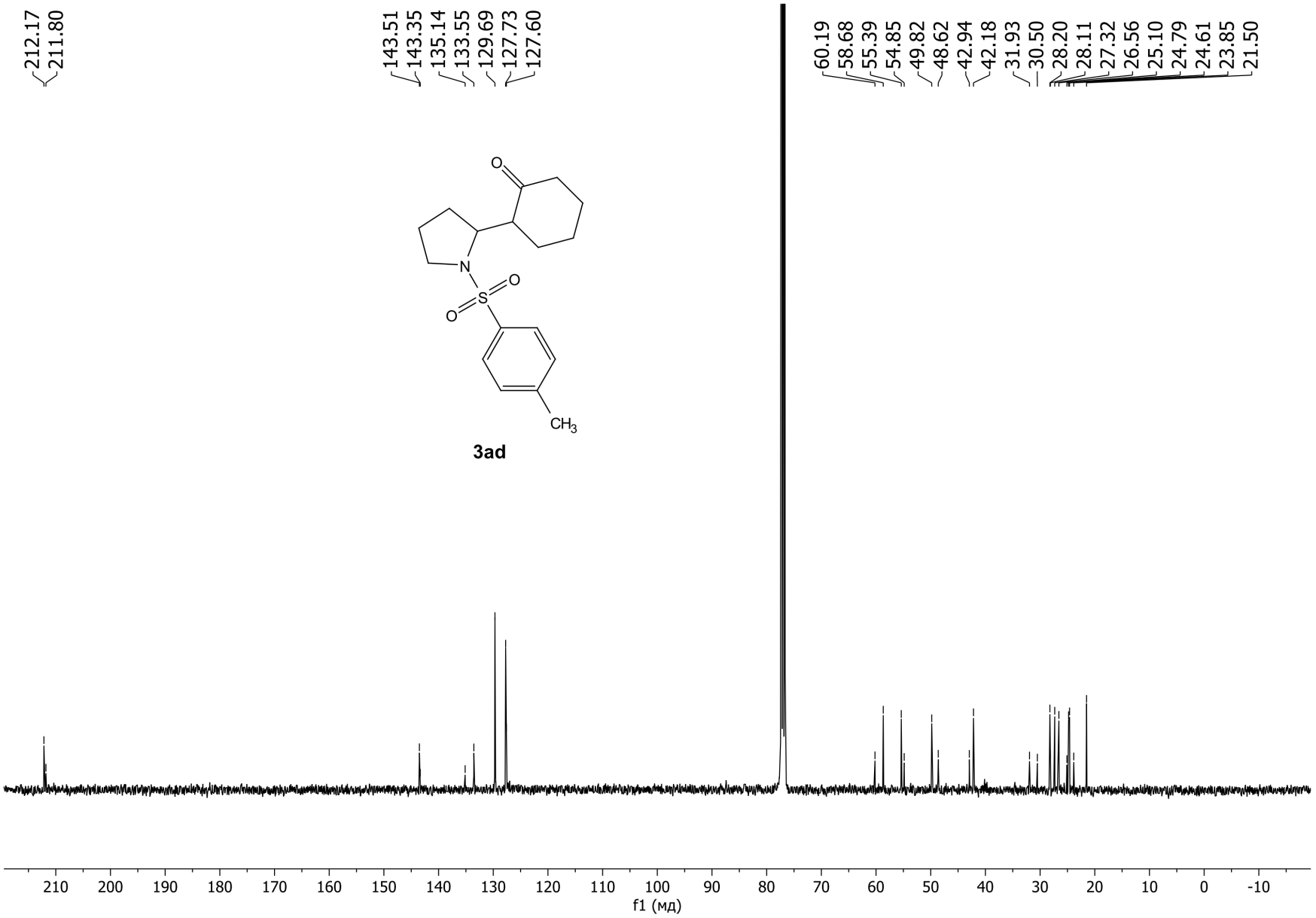

Figure S27. ^{13}C-{1H} NMR spectrum ($CDCl_3$, 150MHz) of the compound **3ad**

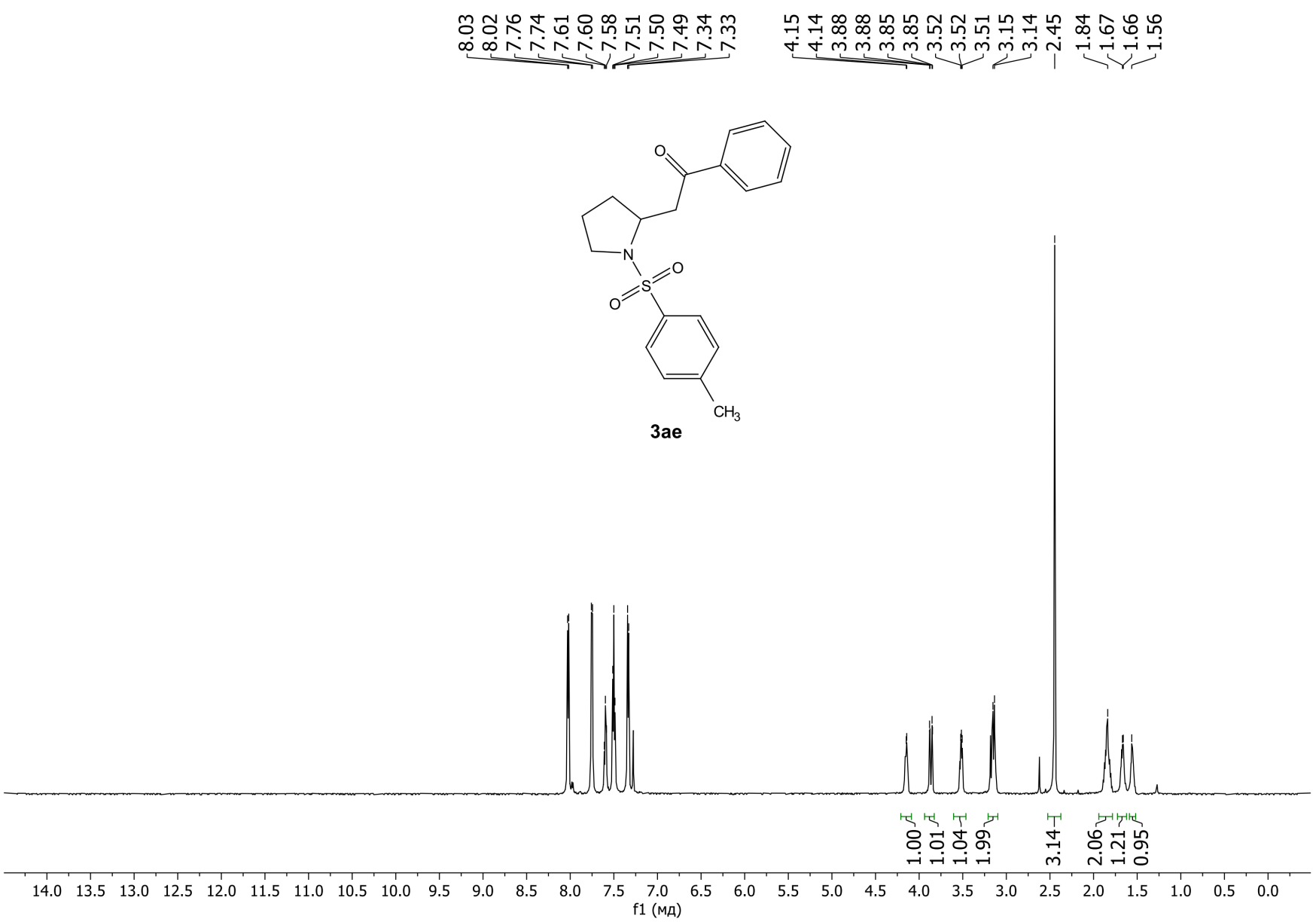

Figure S28. ^{1}H NMR spectrum ($CDCl_3$, 600MHz) of the compound **3ae**

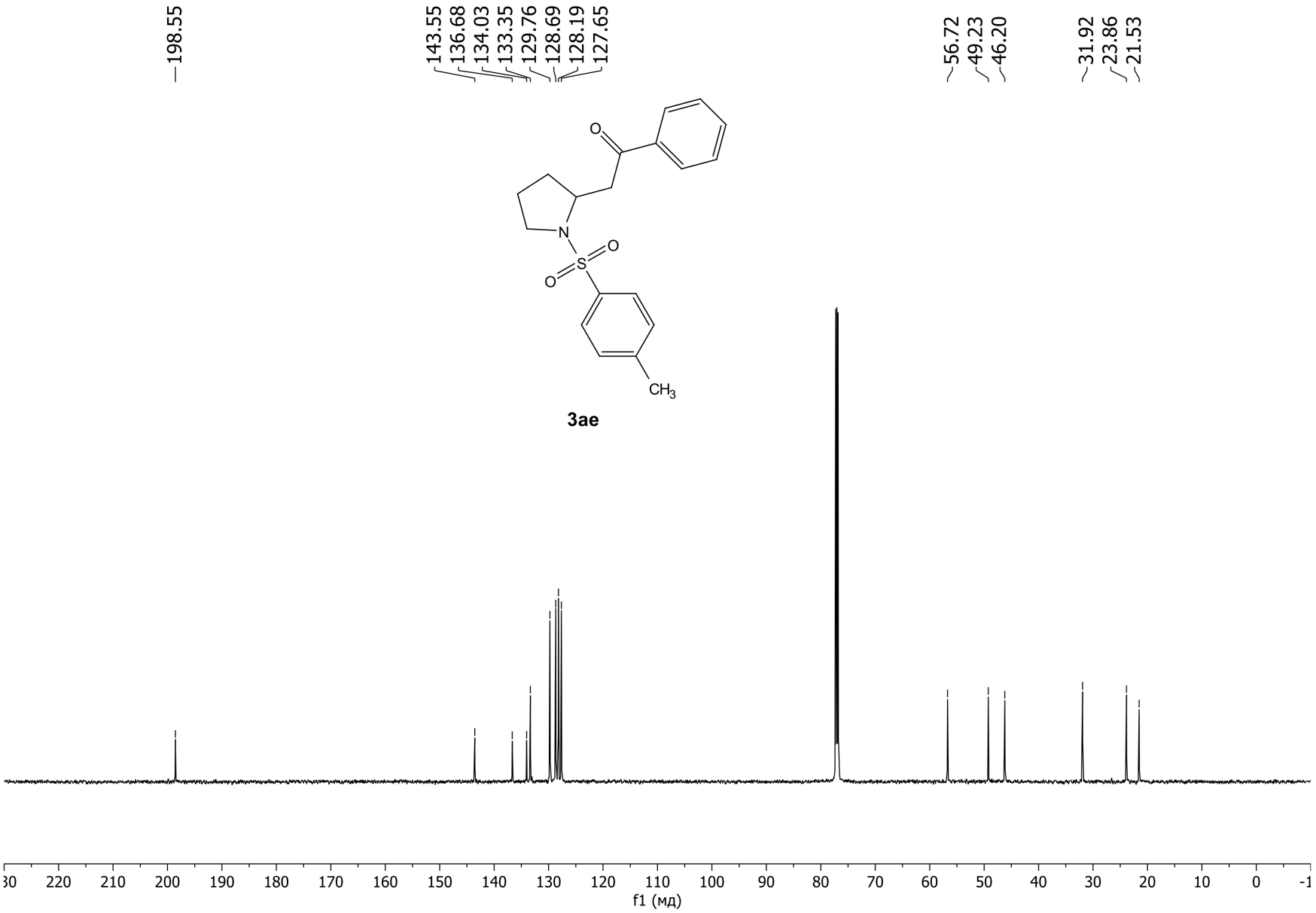

Figure S29. ^{13}C-{1H} NMR spectrum ($CDCl_3$, 150MHz) of the compound **3ae**

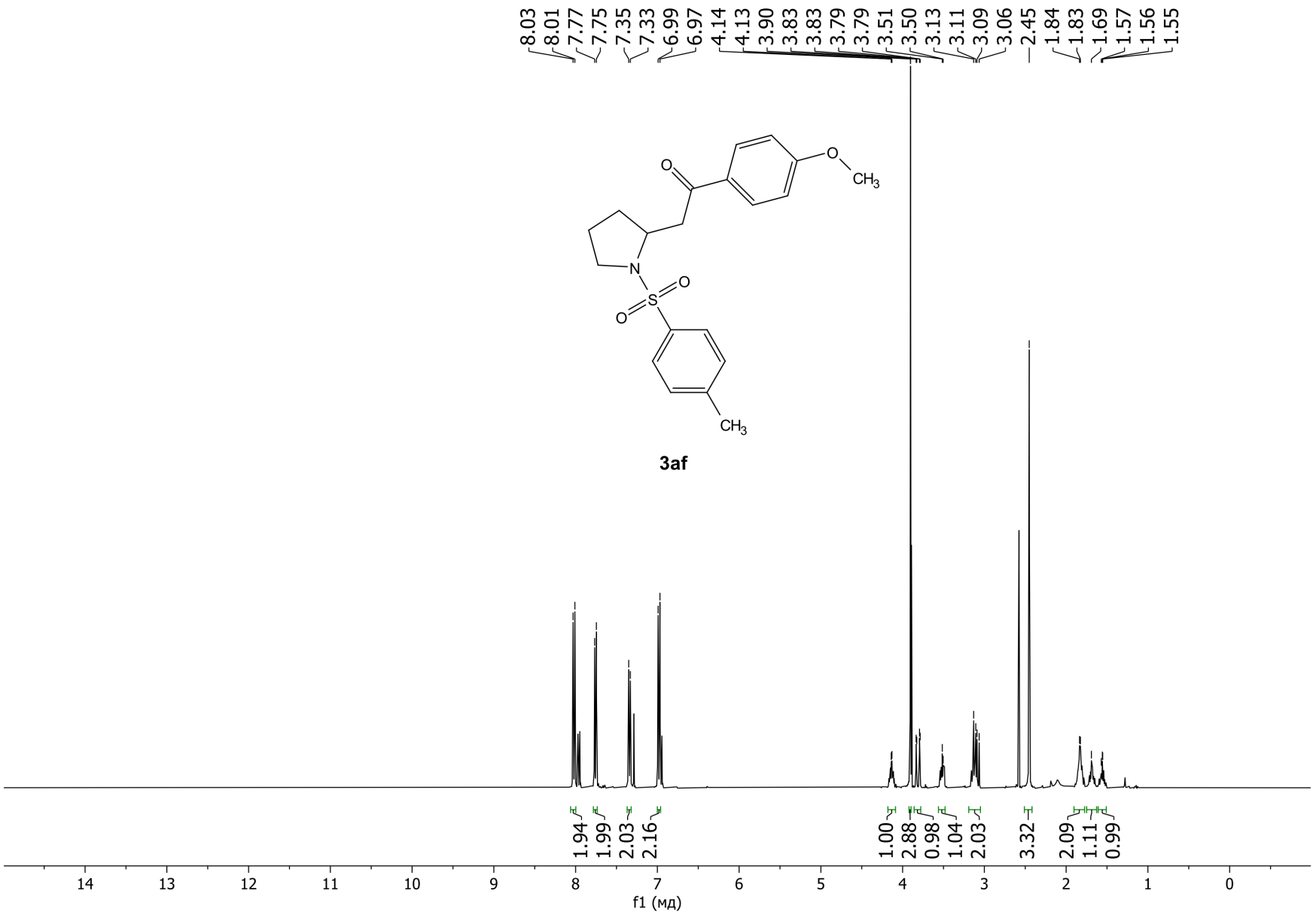

Figure S30. ^{1}H NMR spectrum ($CDCl_3$, 600MHz) of the compound **3af**

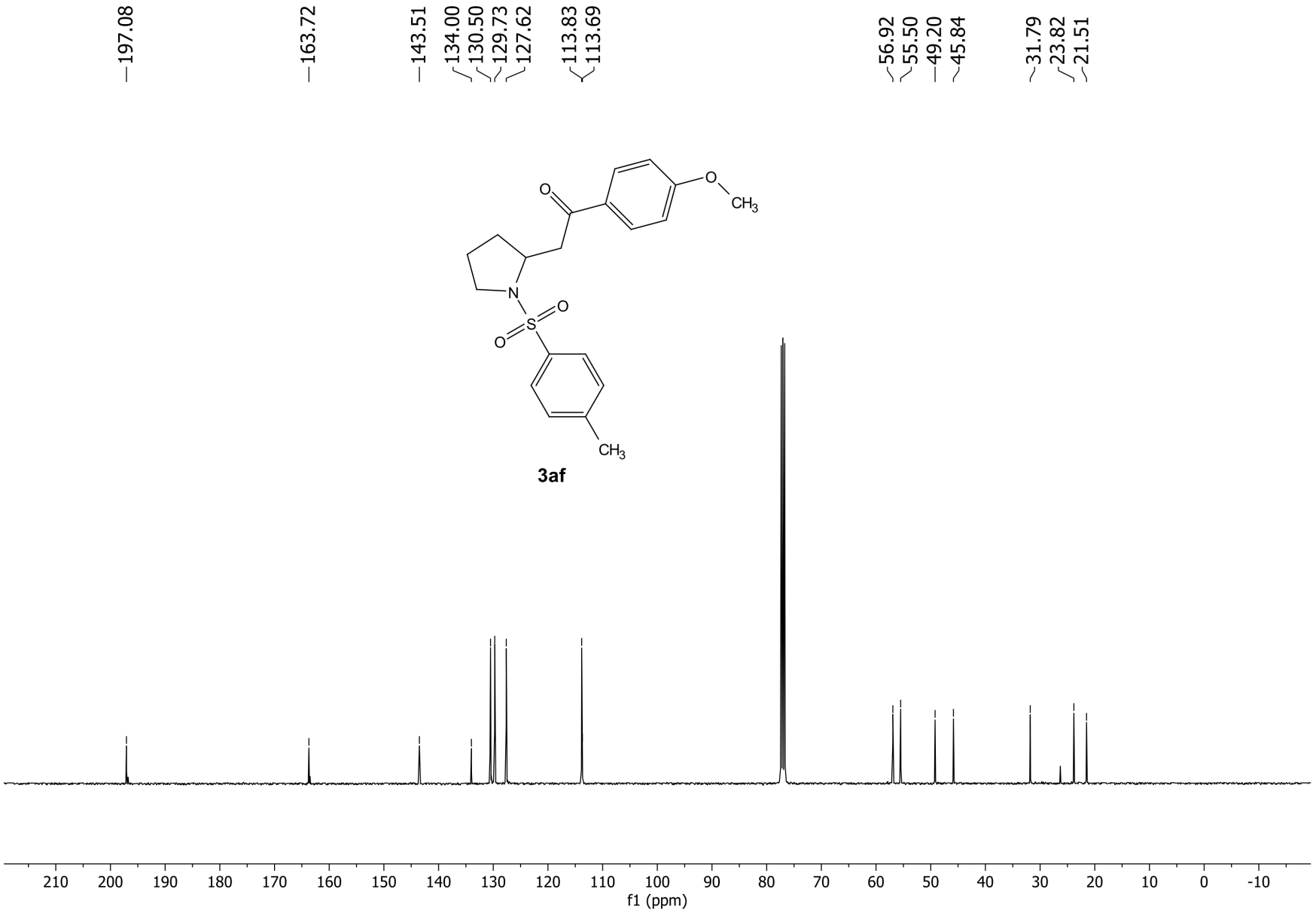

Figure S31. ^{13}C-{1H} NMR spectrum ($CDCl_3$, 150MHz) of the compound **3af**

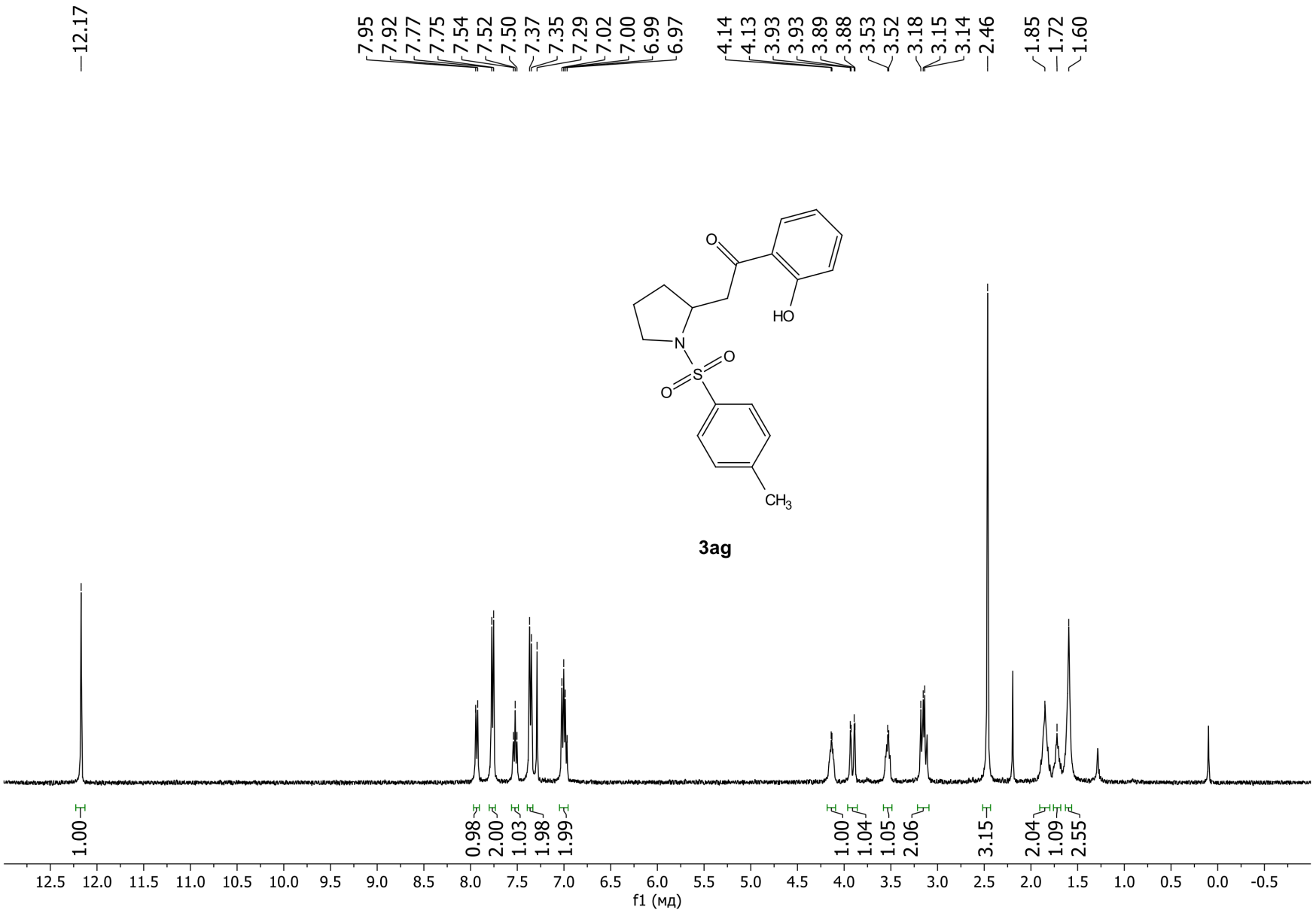

Figure S32. ^{1}H NMR spectrum ($CDCl_3$, 600MHz) of the compound **3ag**

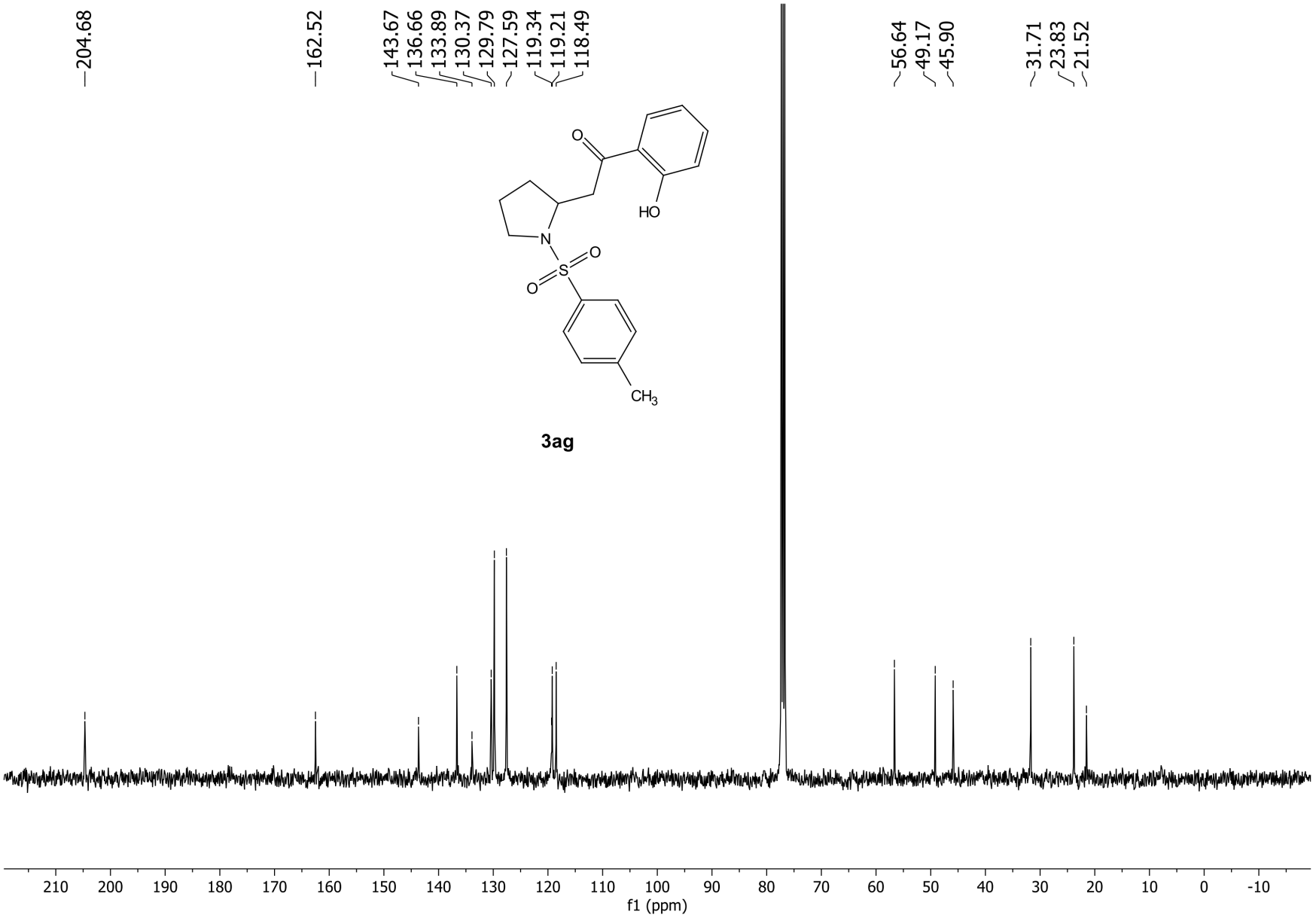

Figure S33. ^{13}C-{1H} NMR spectrum ($CDCl_3$, 150MHz) of the compound **3ag**

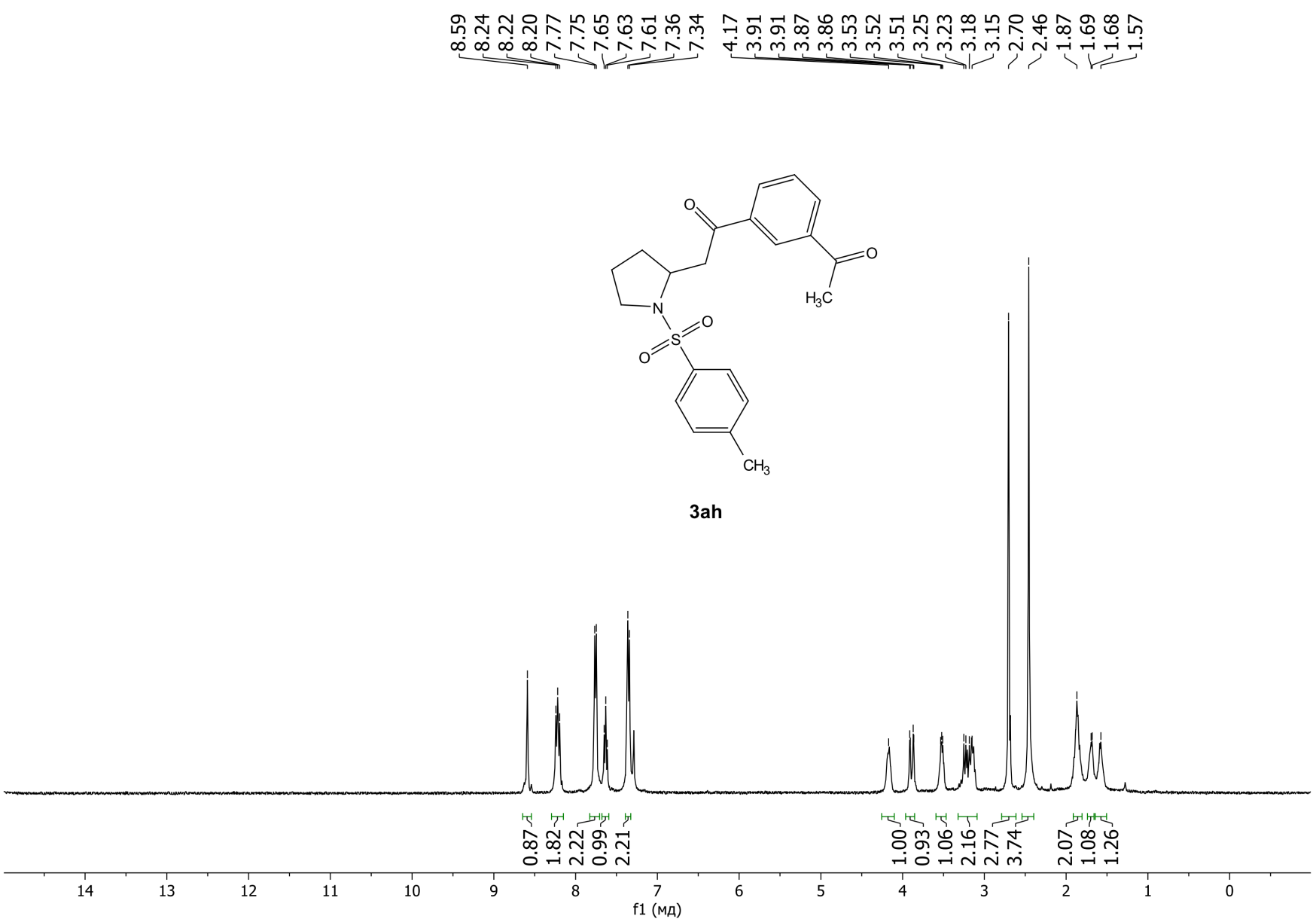

Figure S34. ^{1}H NMR spectrum ($CDCl_3$, 600MHz) of the compound **3ah**

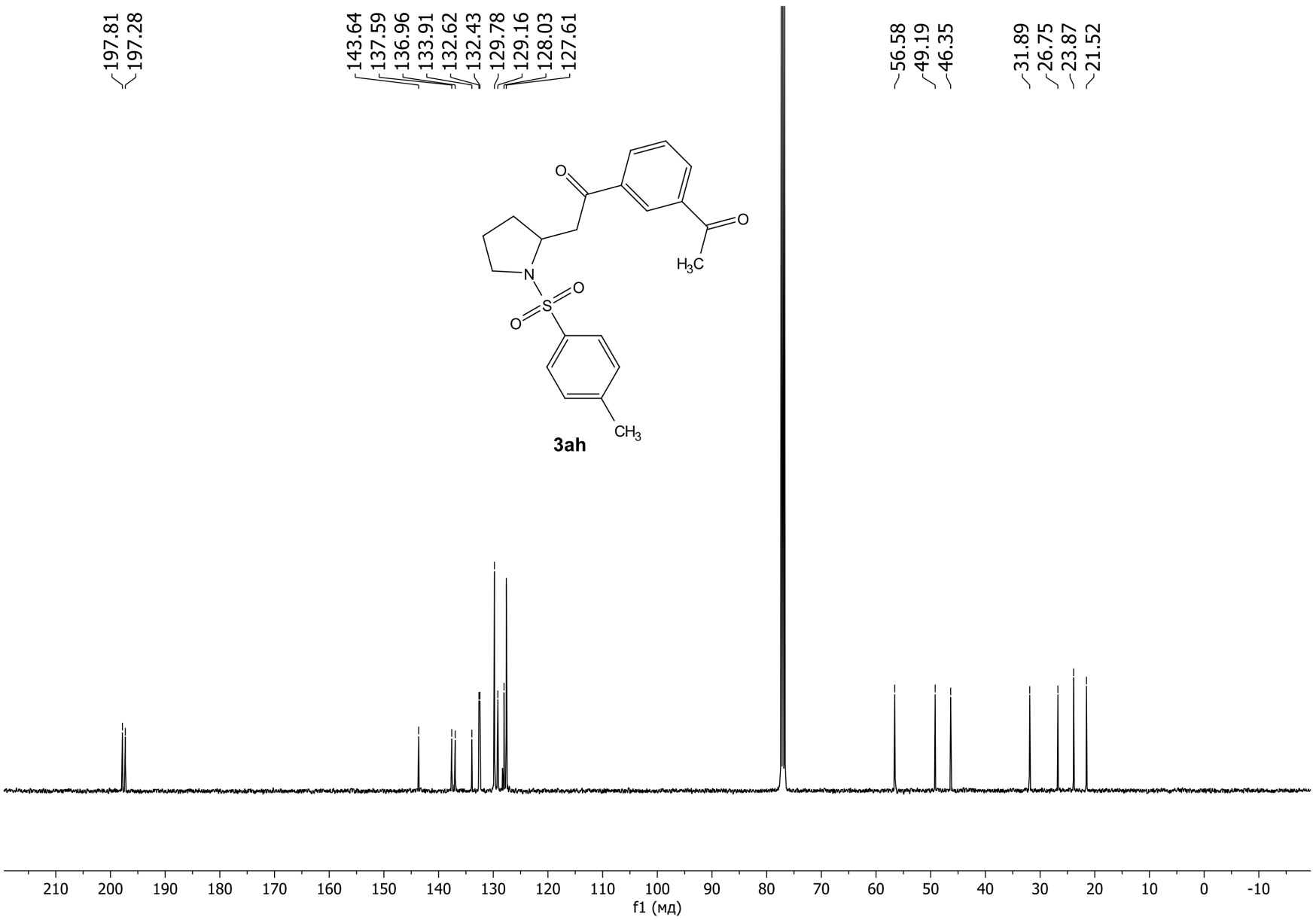

Figure S35. ^{13}C-{1H} NMR spectrum ($CDCl_3$, 150MHz) of the compound **3ah**

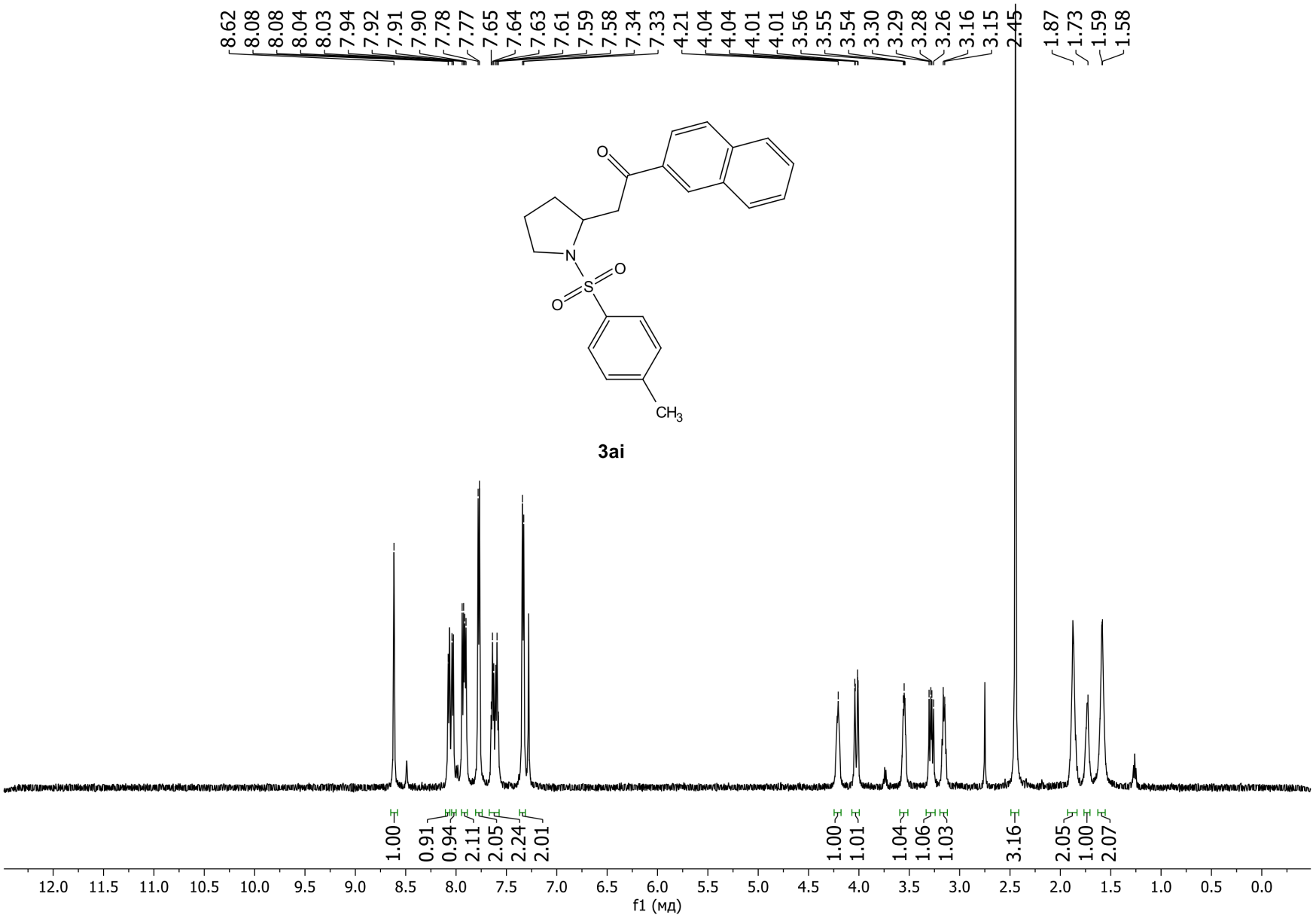

Figure S36. ^{1}H NMR spectrum ($CDCl_3$, 600MHz) of the compound **3ai**

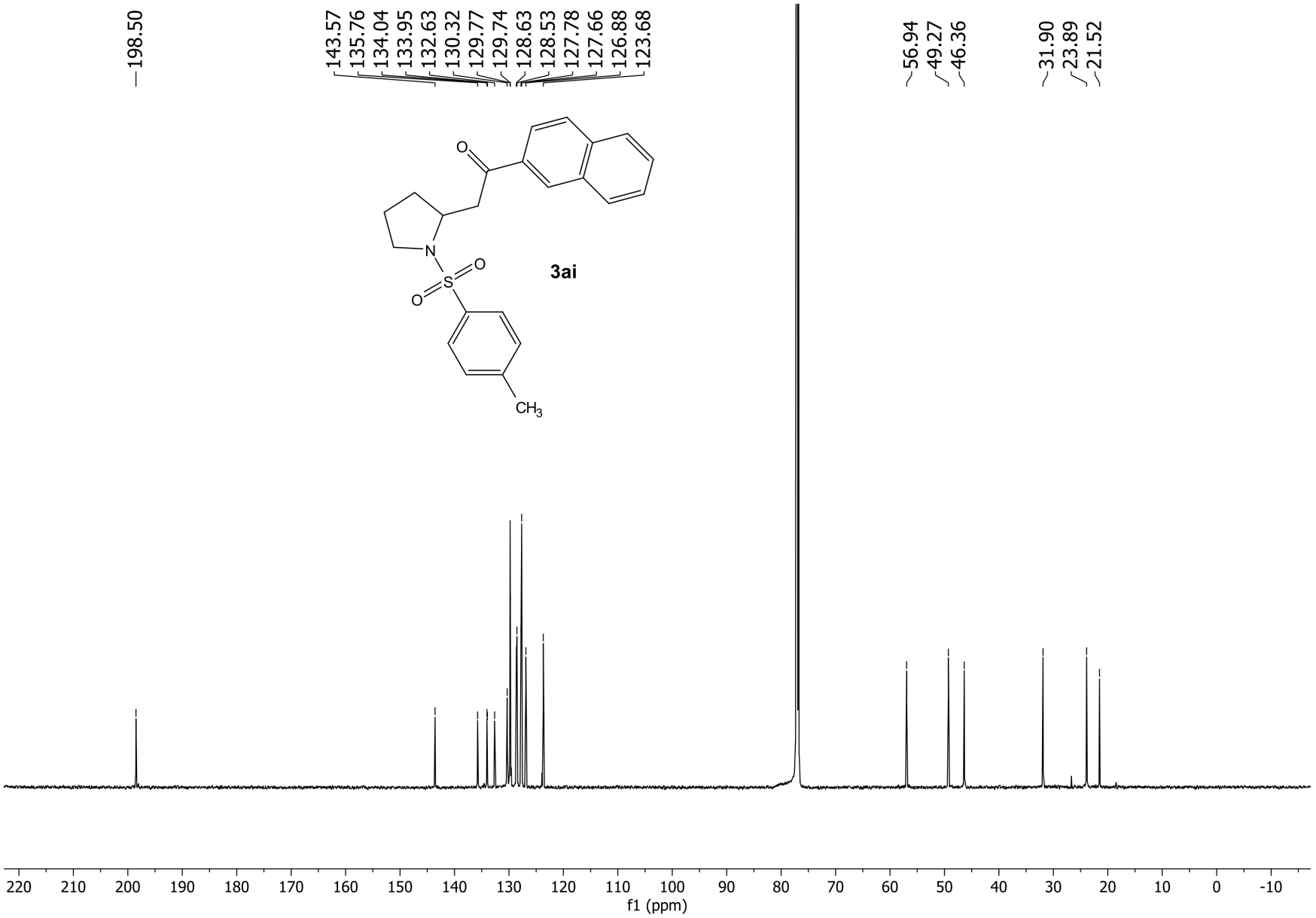

Figure S37. ^{13}C-{1H} NMR spectrum ($CDCl_3$, 150MHz) of the compound **3ai**

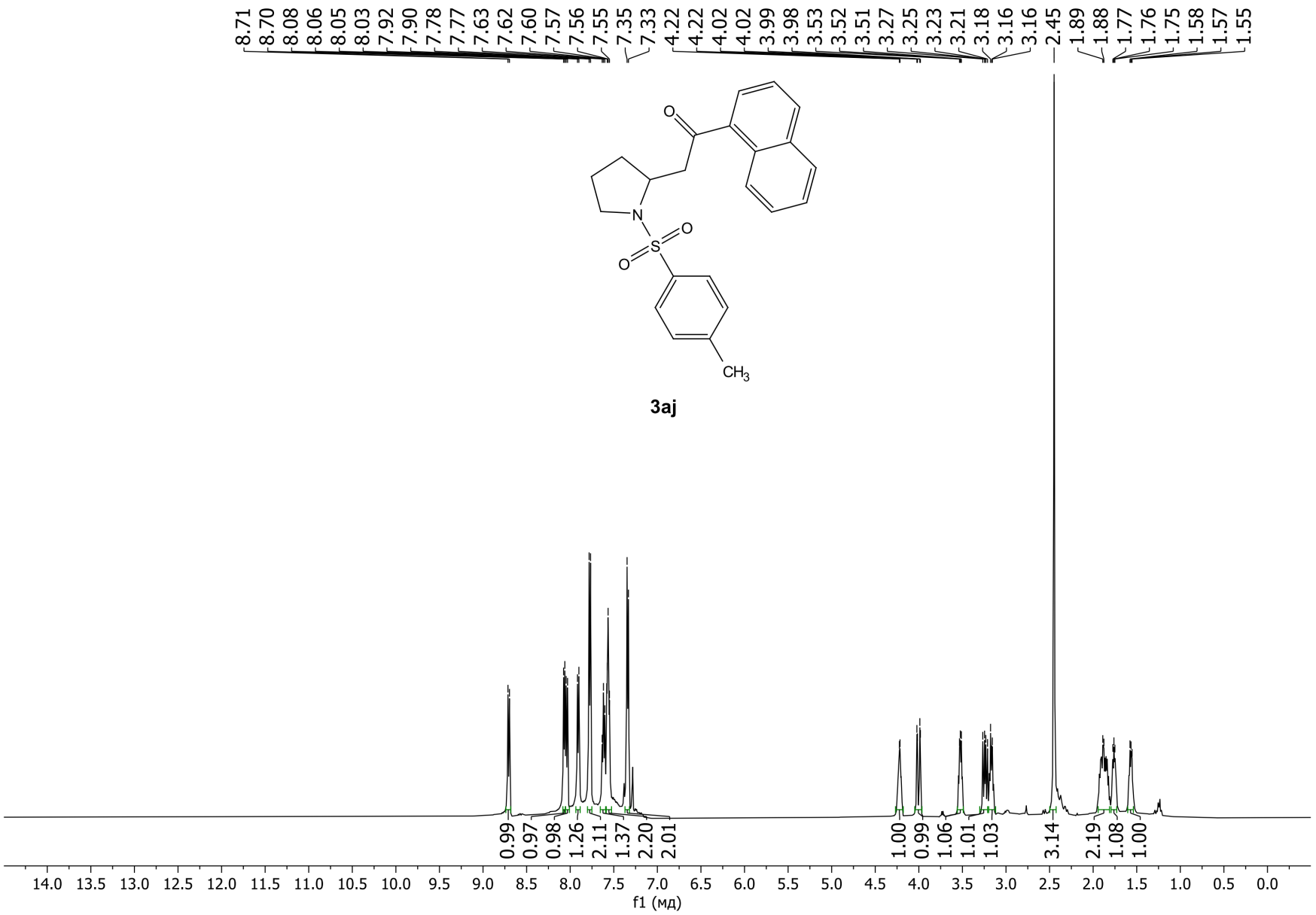

Figure S38. ^{1}H NMR spectrum ($CDCl_3$, 600MHz) of the compound **3aj**

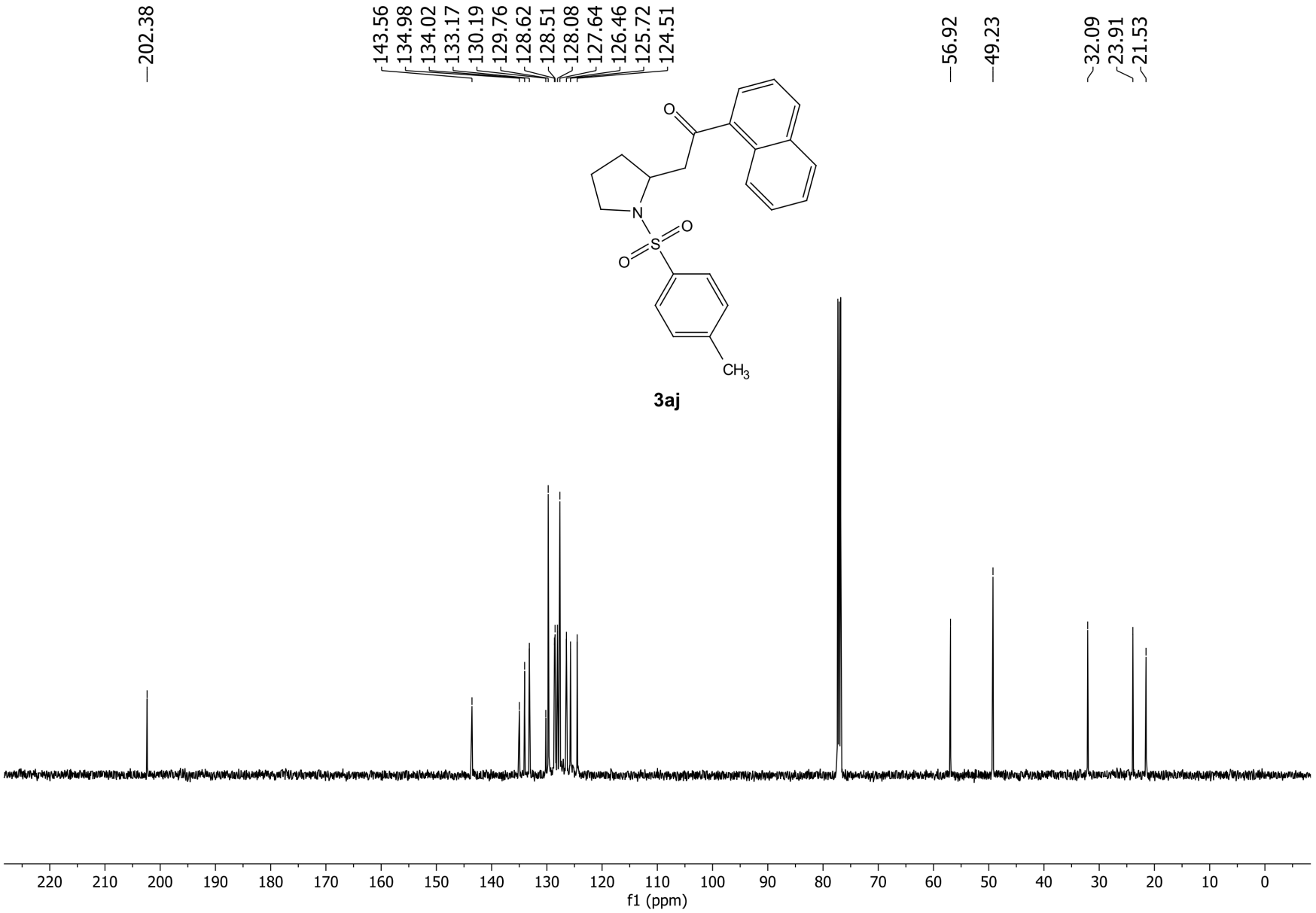

Figure S39. ^{13}C-{1H} NMR spectrum ($CDCl_3$, 150MHz) of the compound **3aj**

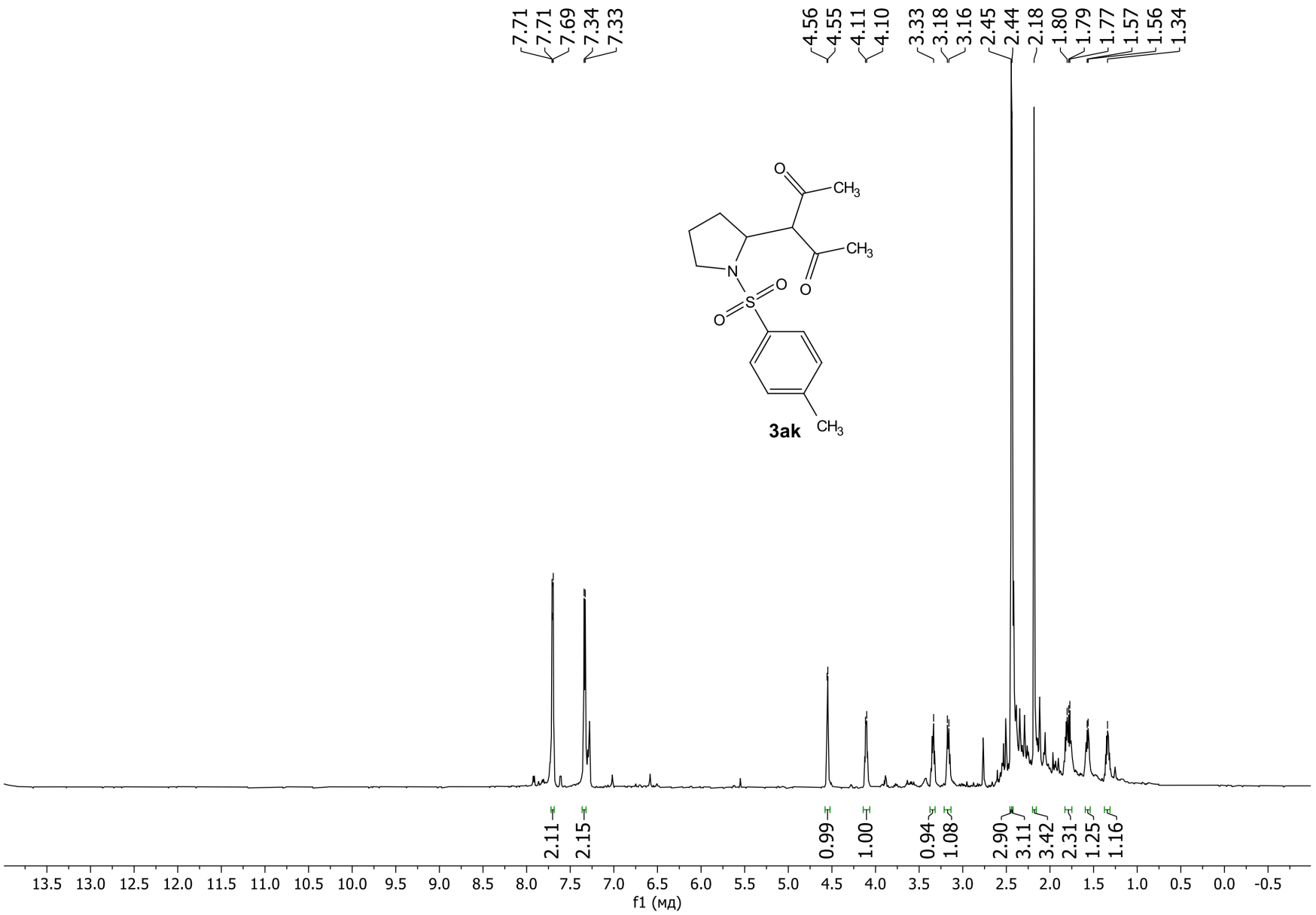

Figure S40. ^{1}H NMR spectrum ($CDCl_3$, 600MHz) of the compound **3ak**

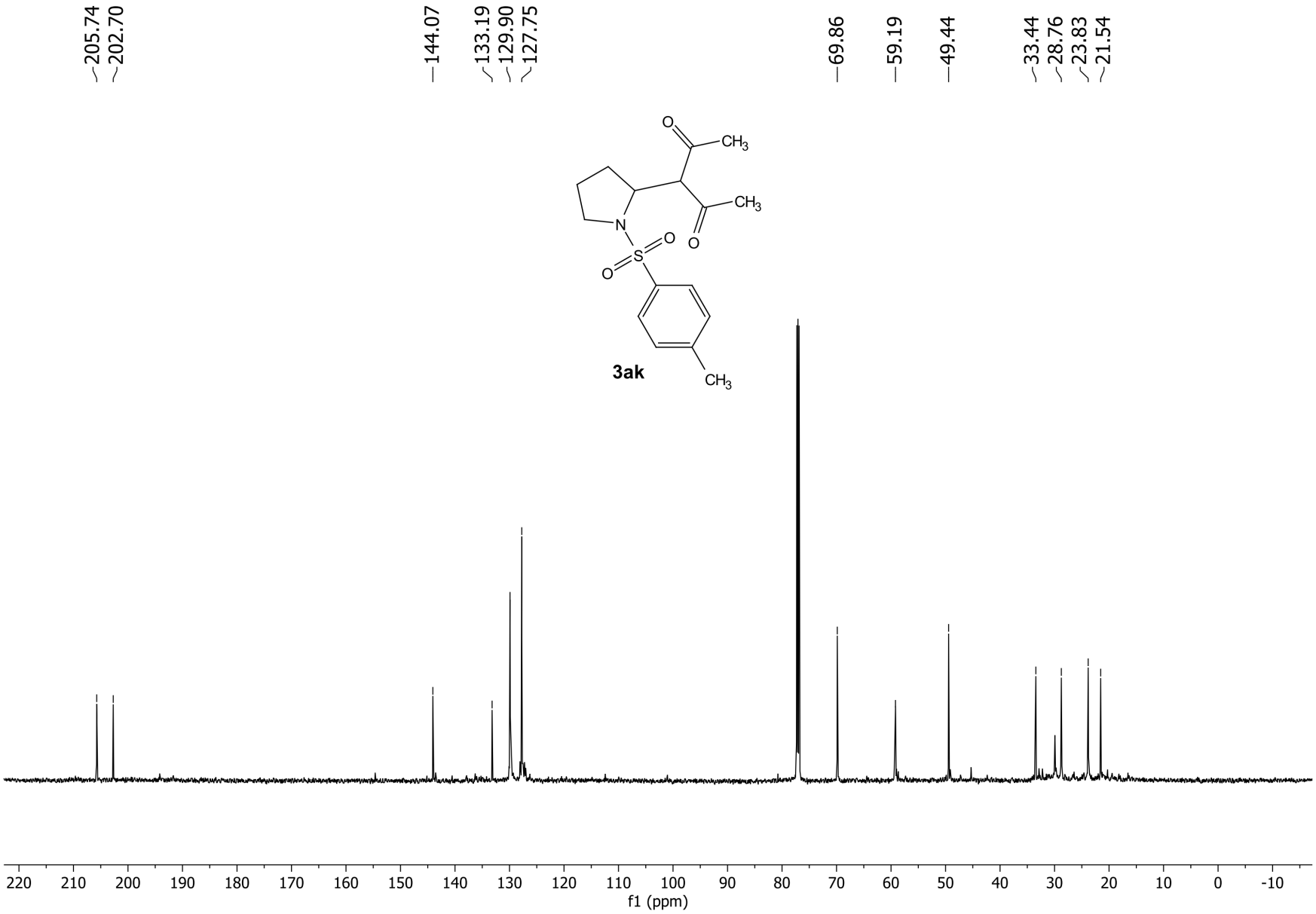

Figure S41. ^{13}C-{1H} NMR spectrum ($CDCl_3$, 150MHz) of the compound **3ak**

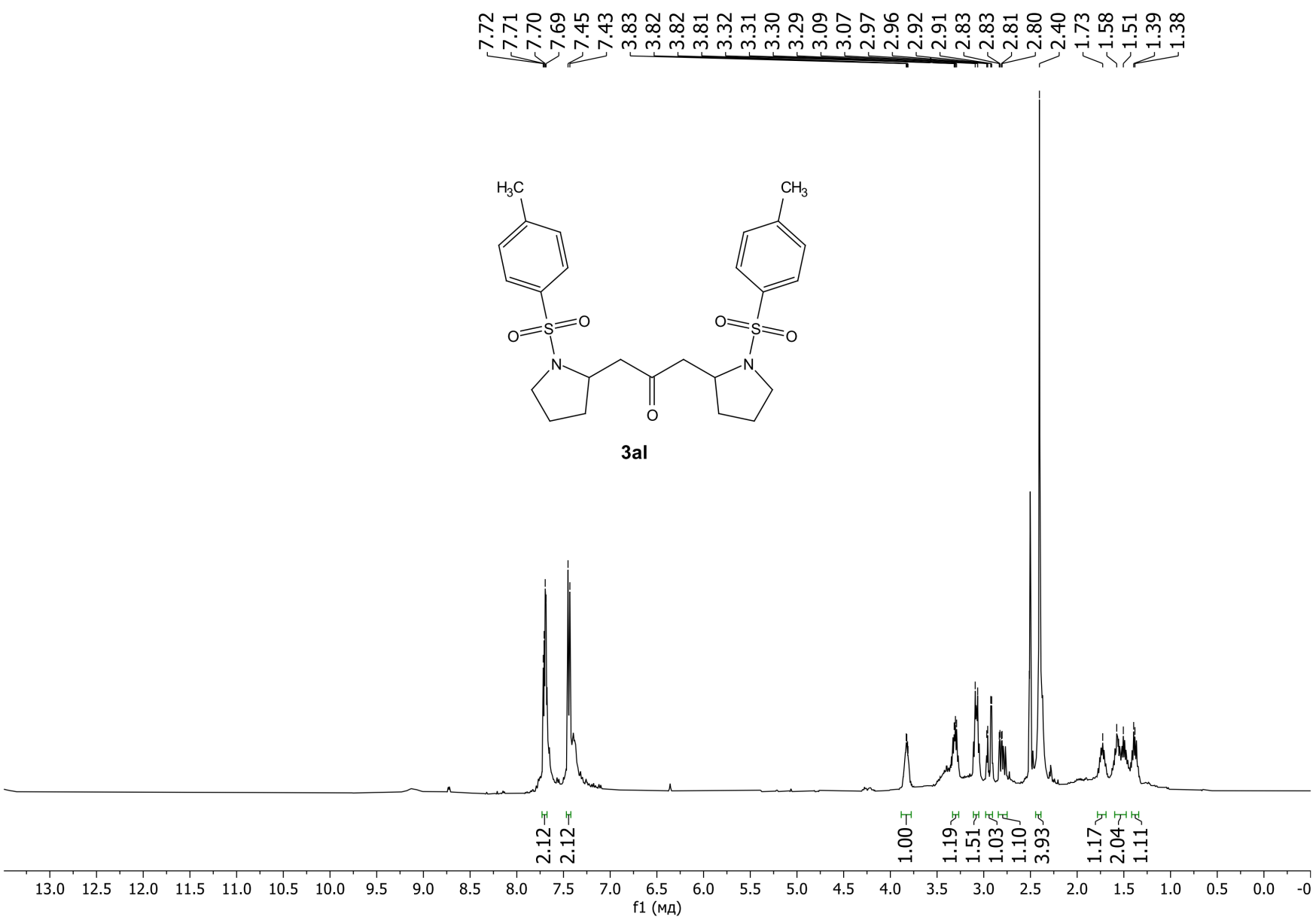

Figure S42. ^{1}H NMR spectrum ($(CD_3)_2SO$, 600MHz) of the compound **3al**

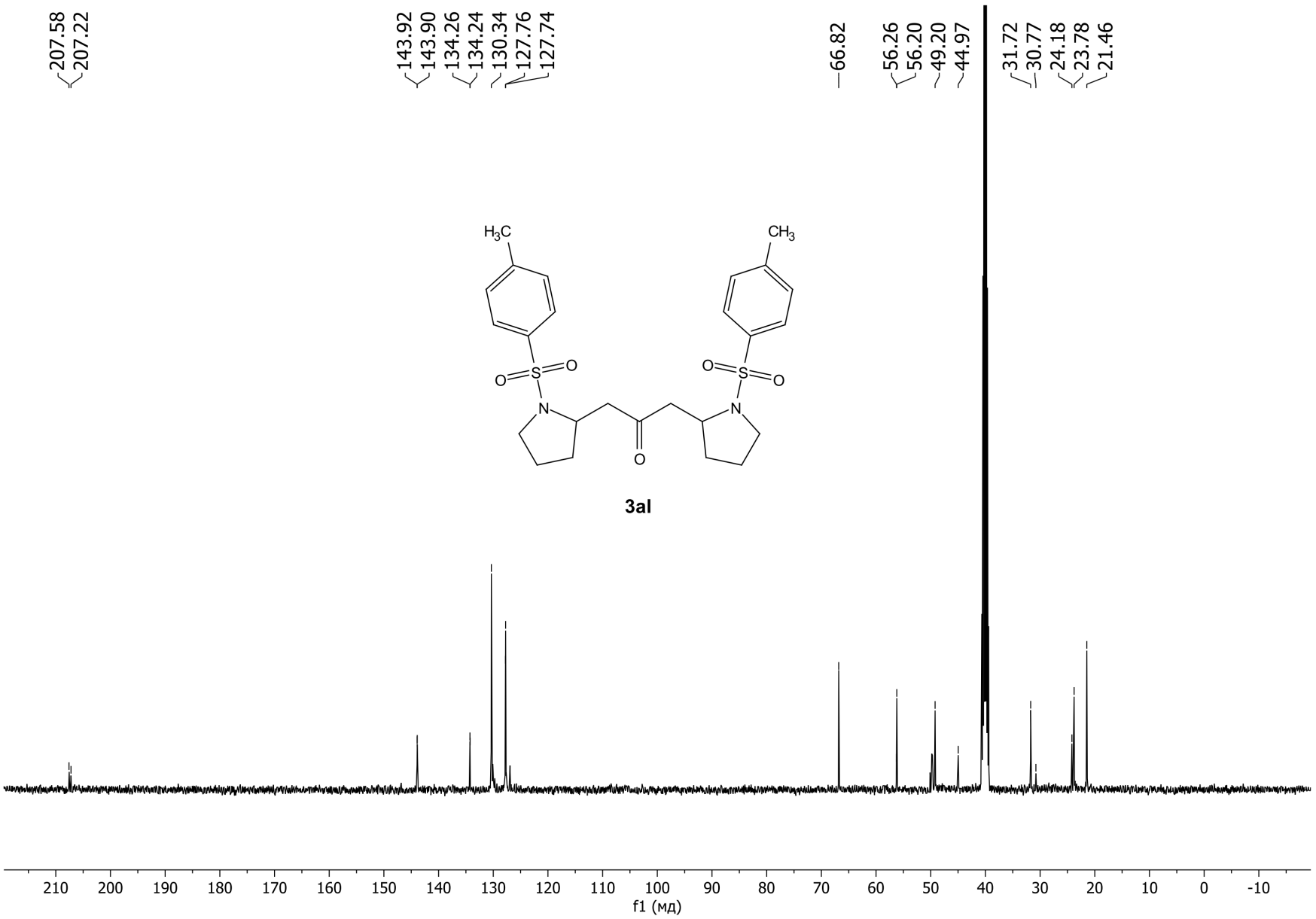

Figure S43. ^{13}C-{1H} NMR spectrum ($(CD_3)_2SO$, 150MHz) of the compound **3al**

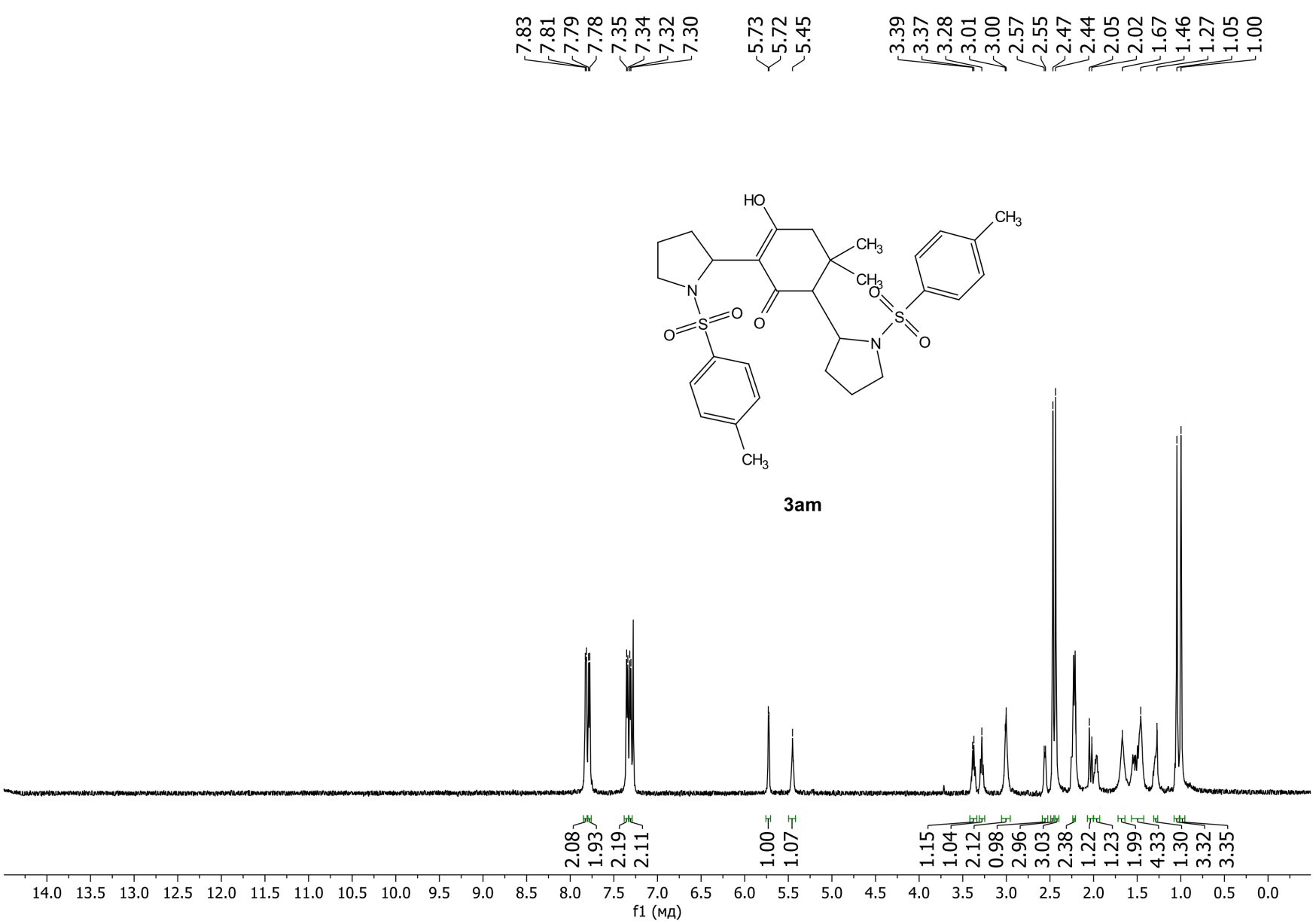

Figure S44. ^{1}H NMR spectrum ($CDCl_3$, 600MHz) of the compound **3am**

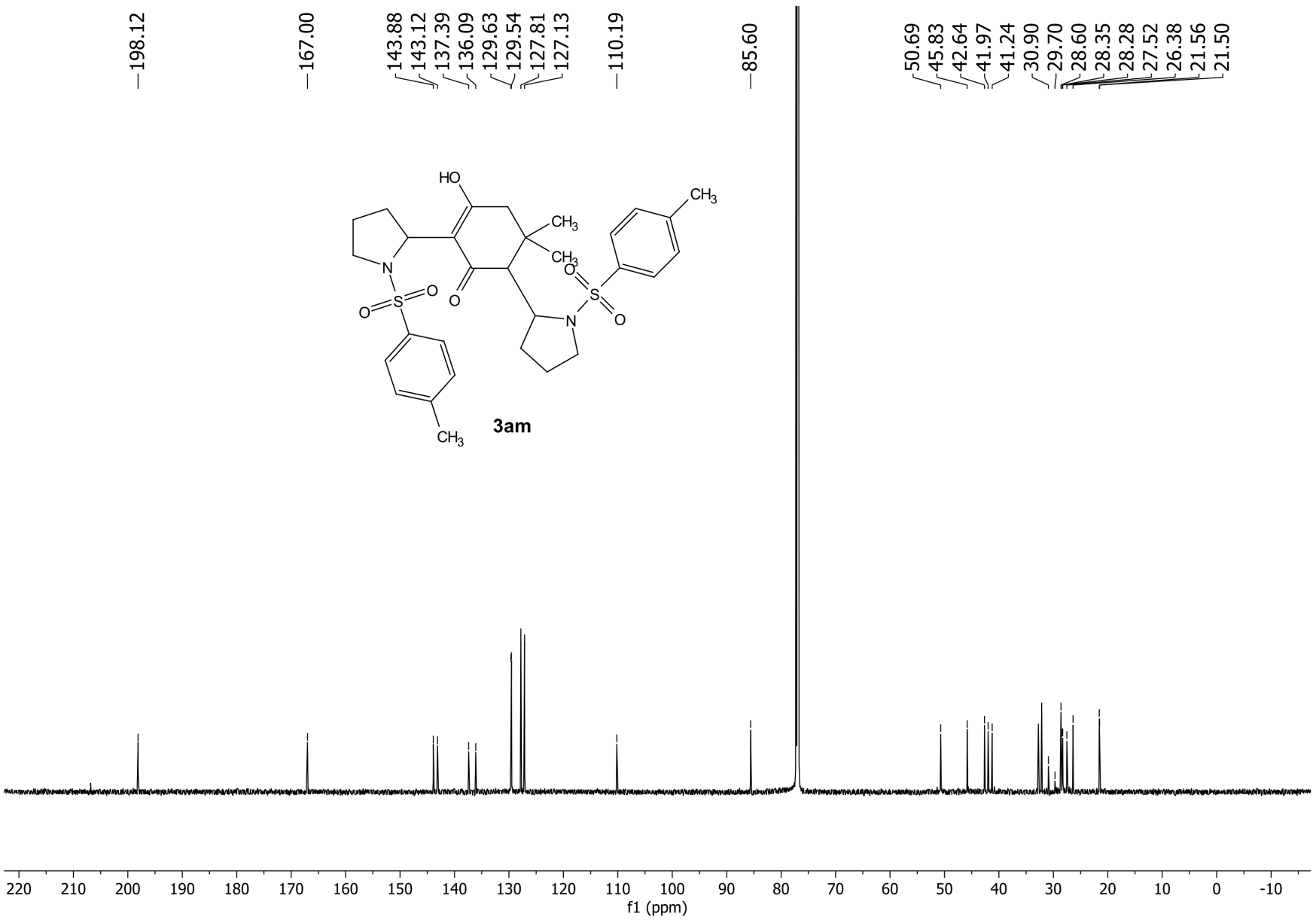

Figure S45. ^{13}C-{1H} NMR spectrum ($CDCl_3$, 150MHz) of the compound **3am**

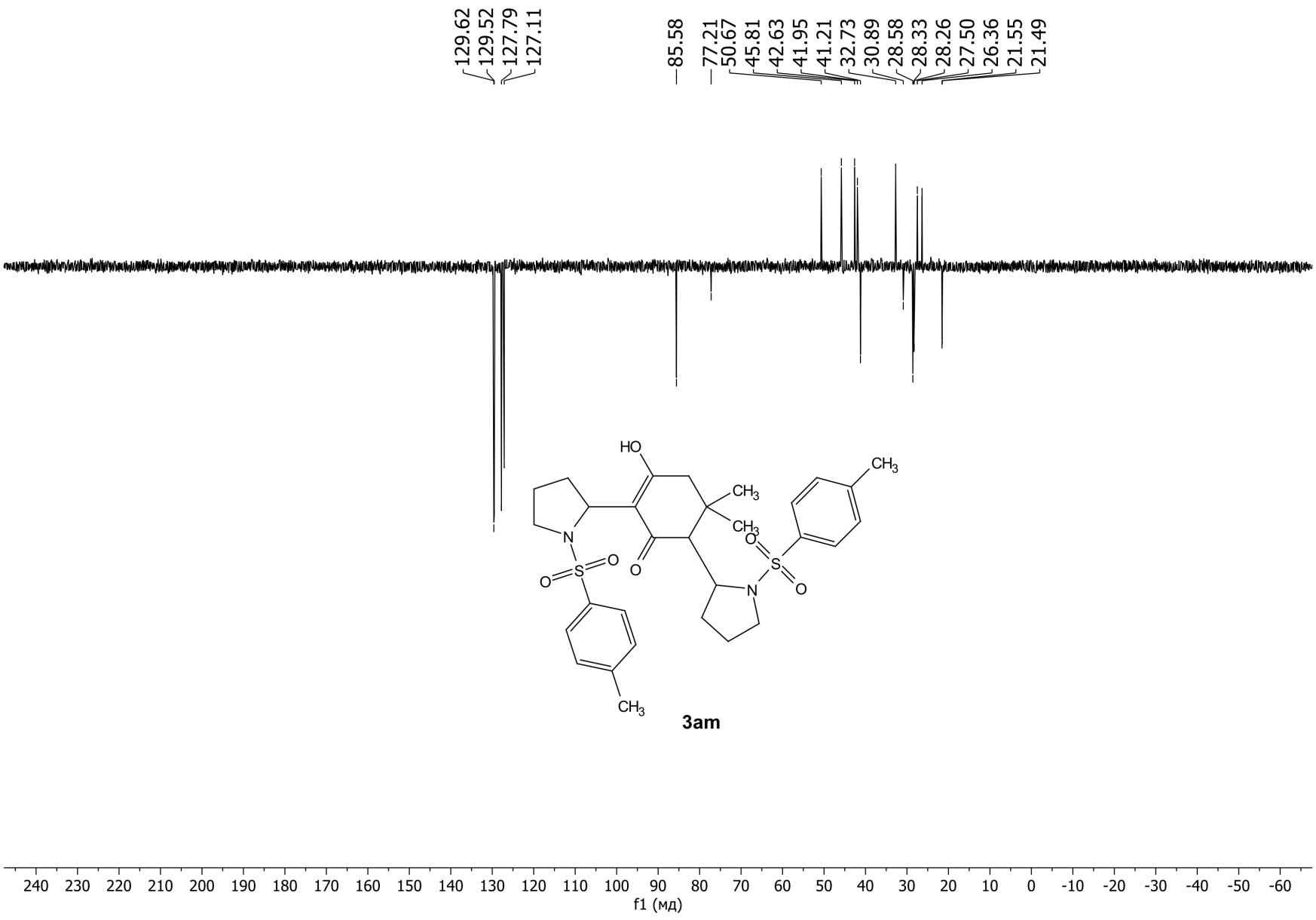

Figure S46. 135° DEPT spectrum ($CDCl_3$, 150MHz) of the compound **3am**

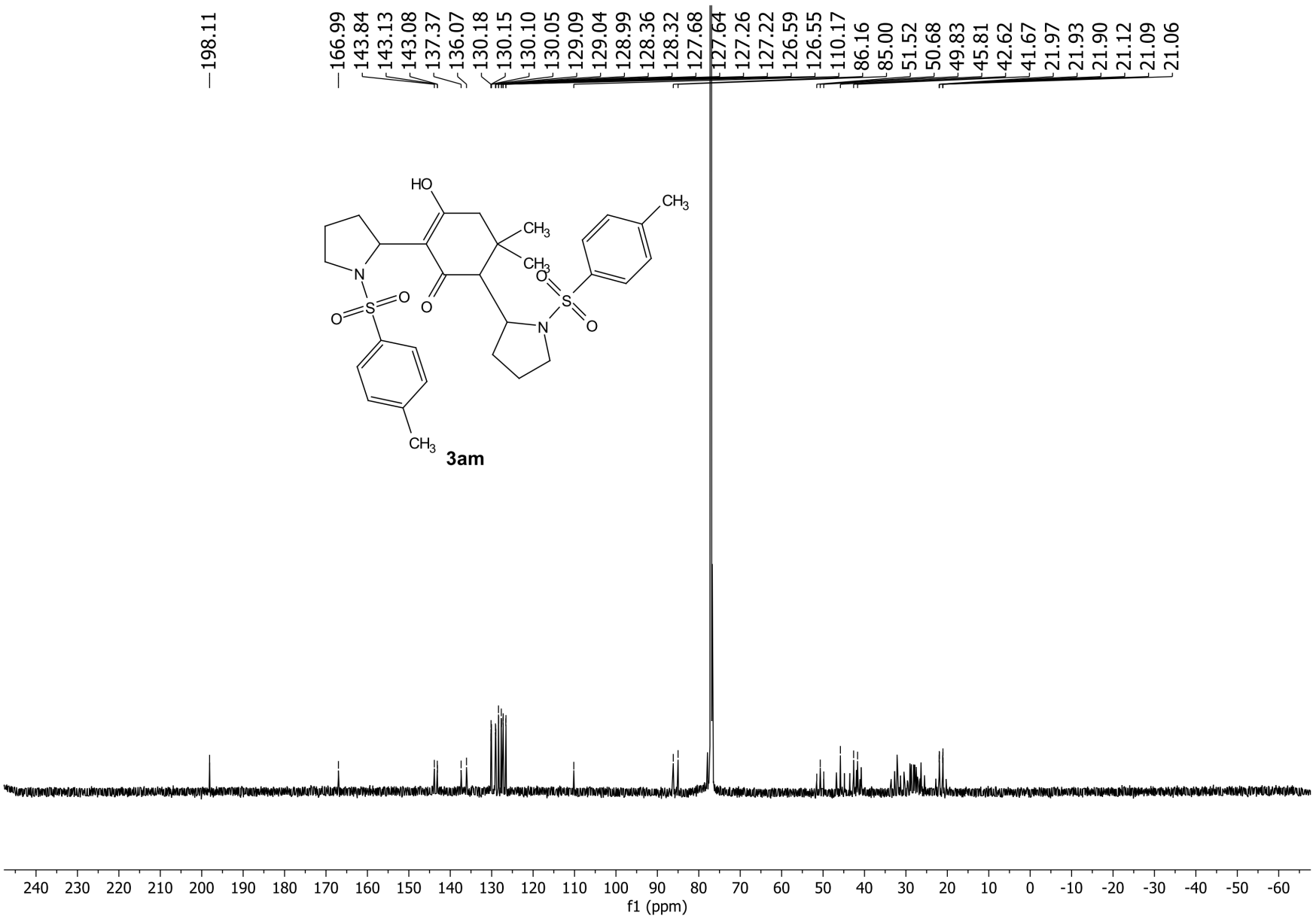

Figure S47. ^{13}C NMR spectrum ($CDCl_3$, 150MHz) of the compound **3am**

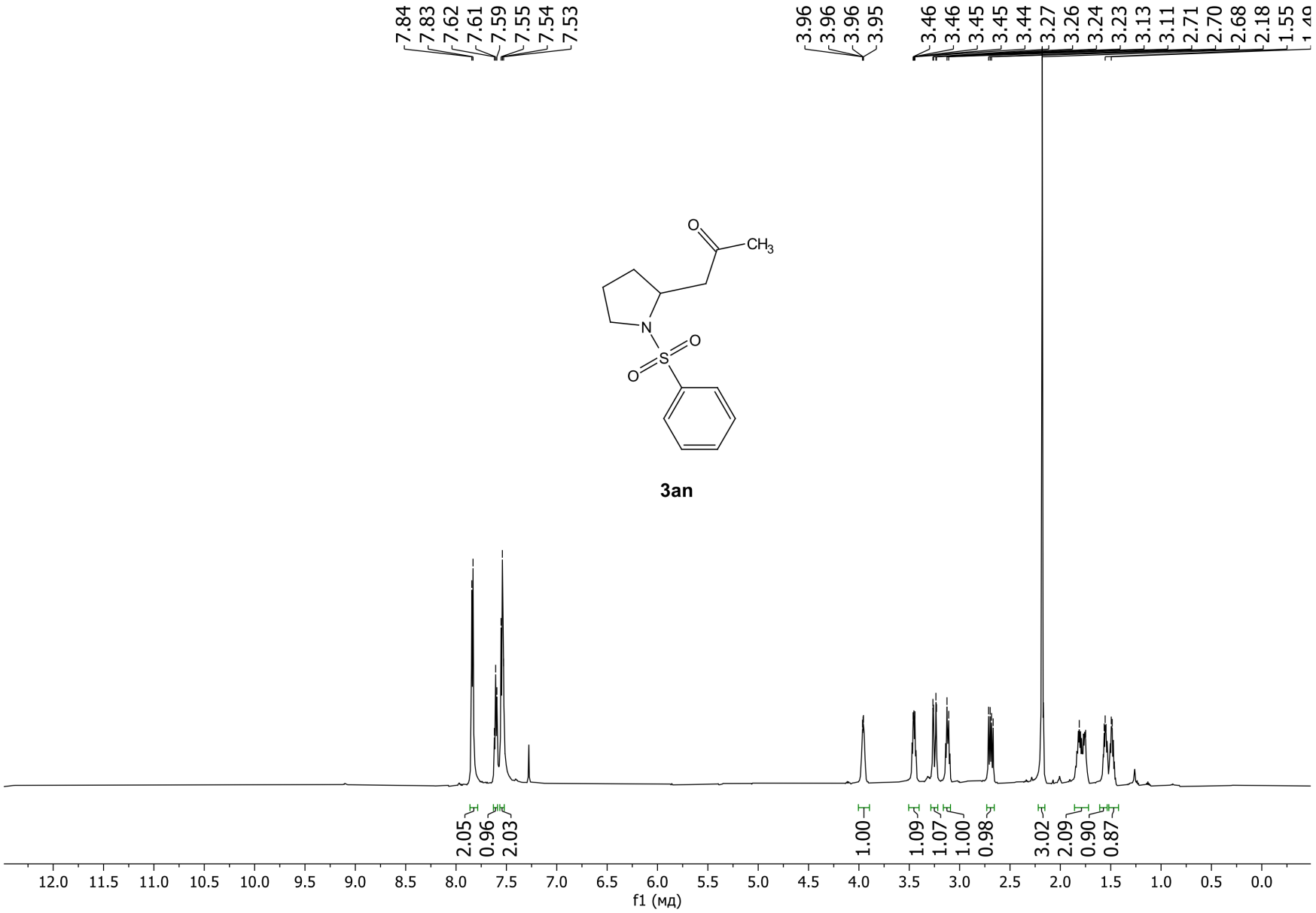

Figure S48. ^{1}H NMR spectrum ($CDCl_3$, 600MHz) of the compound **3an**

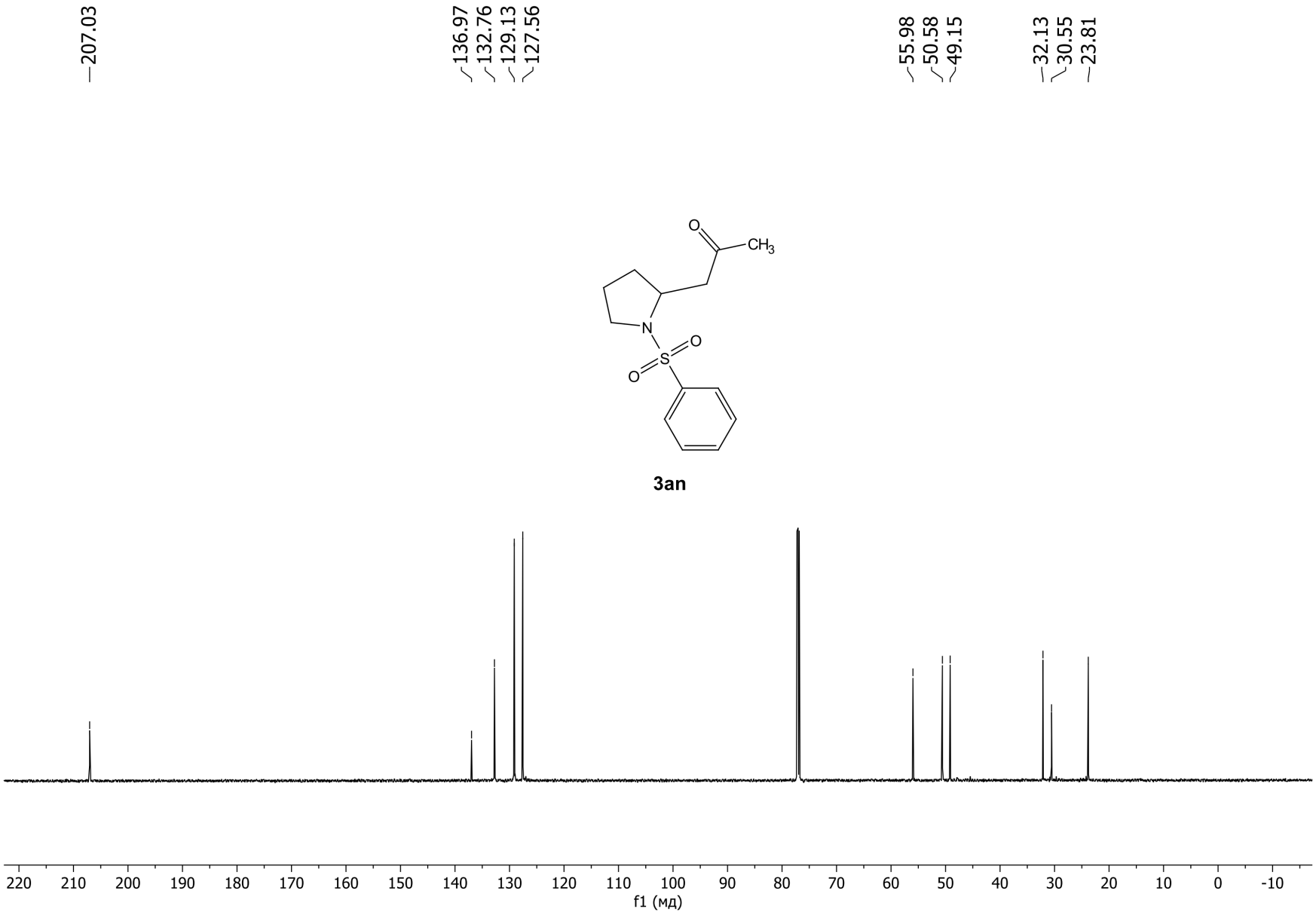

Figure S49. ^{13}C-{1H} NMR spectrum ($CDCl_3$, 150MHz) of the compound **3an**

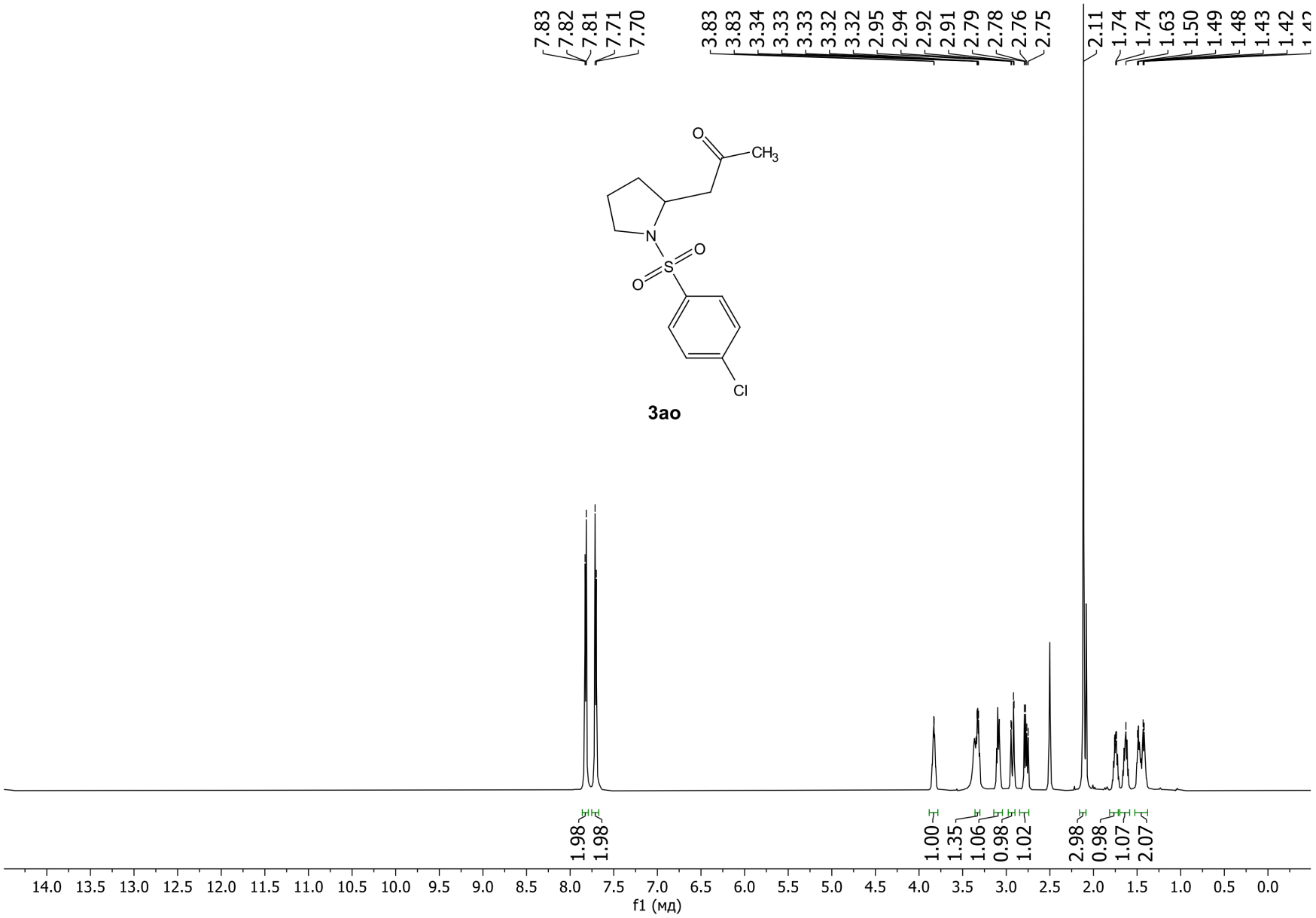

Figure S50. ^{1}H NMR spectrum ($CDCl_3$, 600MHz) of the compound **3ao**

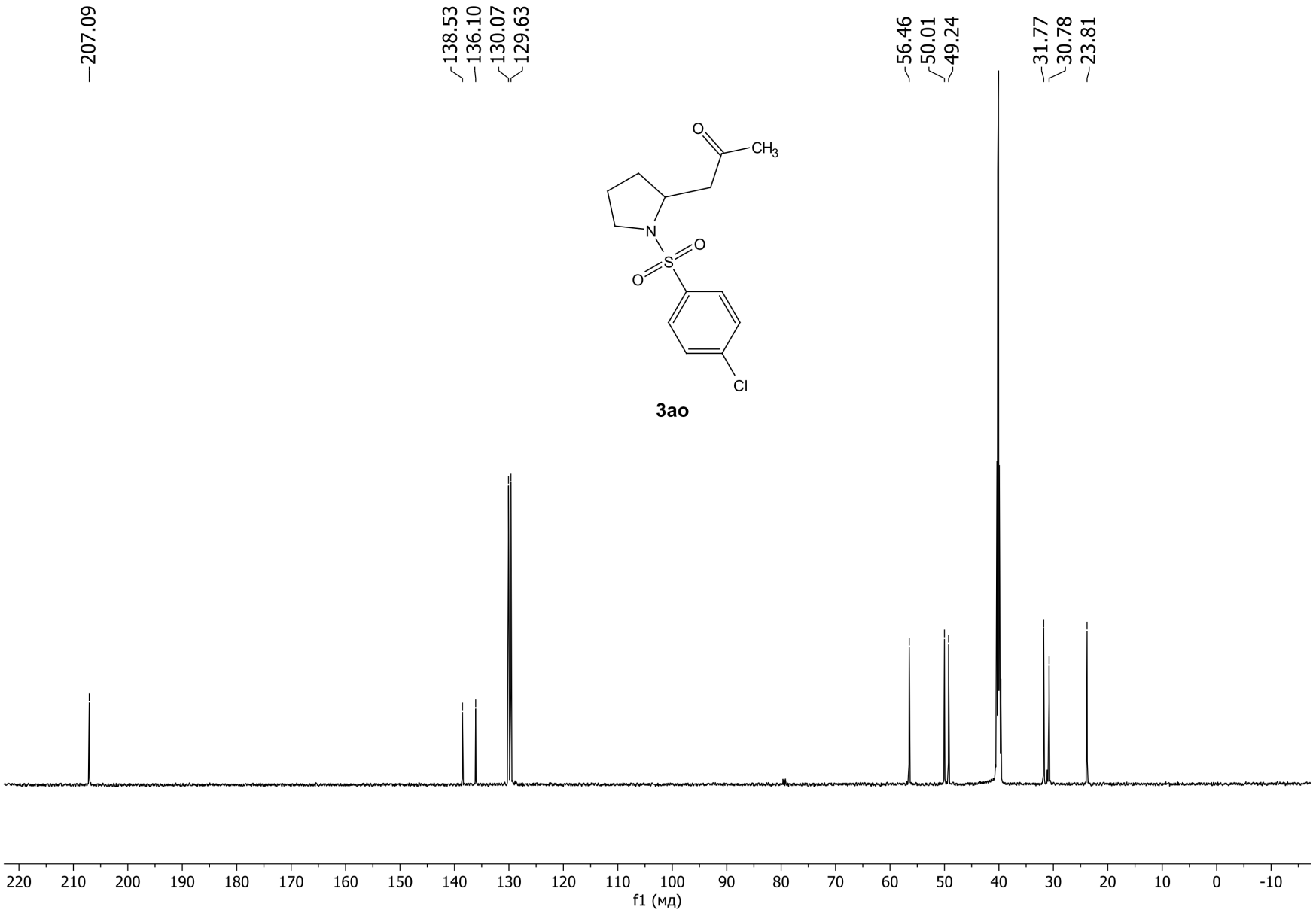

Figure S51. ^{13}C-{1H} NMR spectrum ($CDCl_3$, 150MHz) of the compound **3ao**

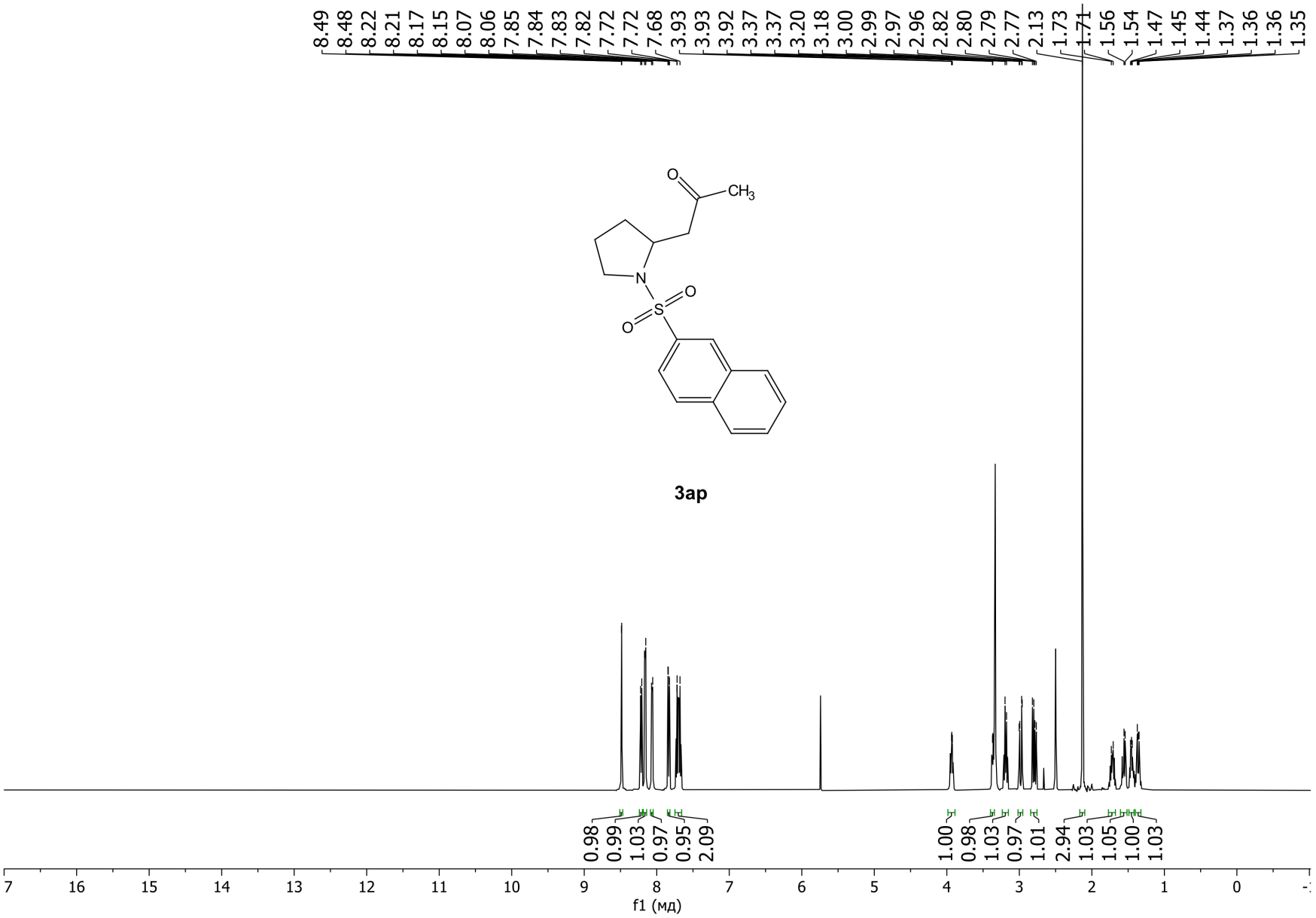

Figure S52. ^{1}H NMR spectrum ($(CD_3)_2SO$, 600MHz) of the compound **3ap**

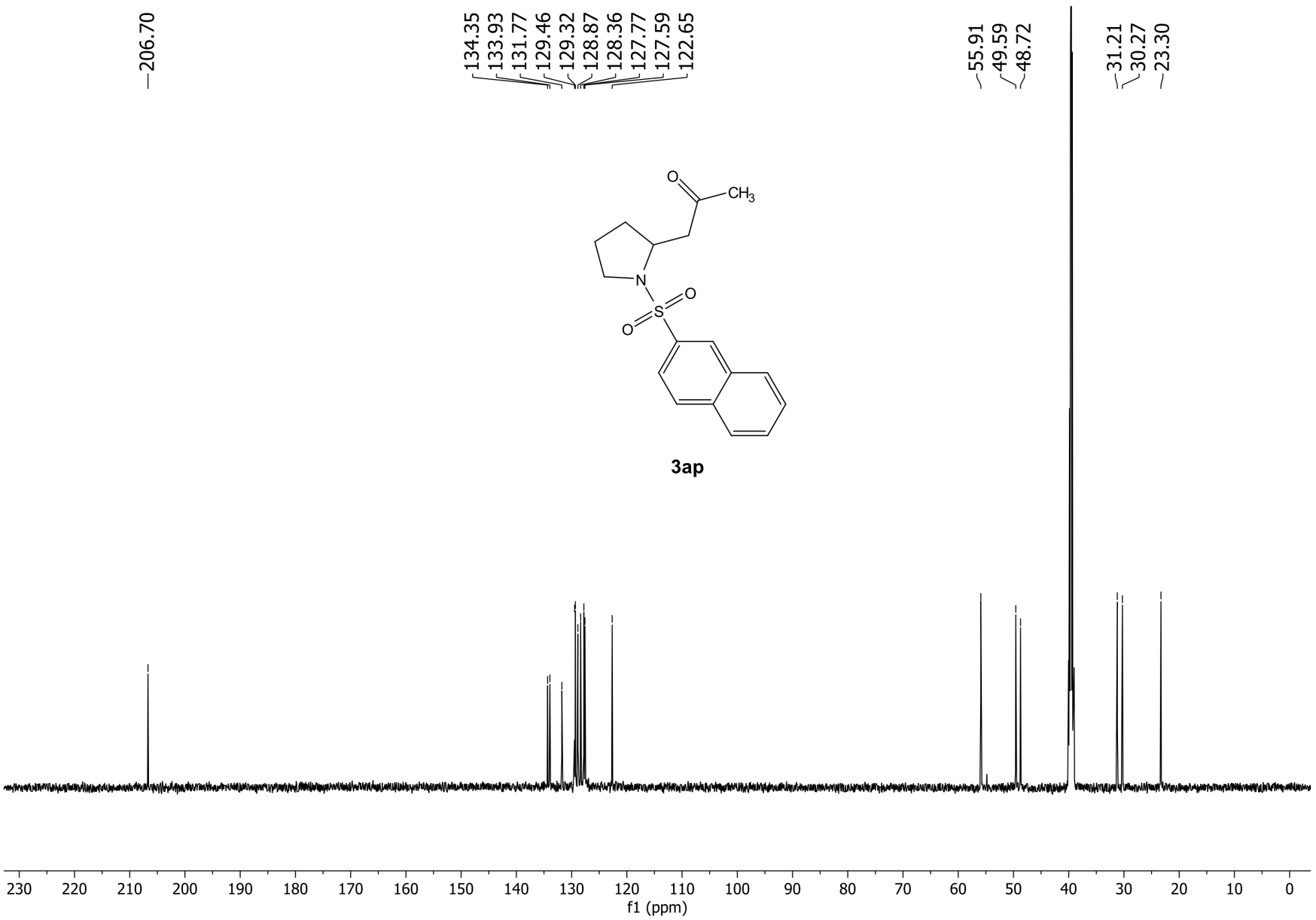

Figure S53. ^{13}C-{1H} NMR spectrum ($(CD_3)_2SO$, 150MHz) of the compound **3ap**

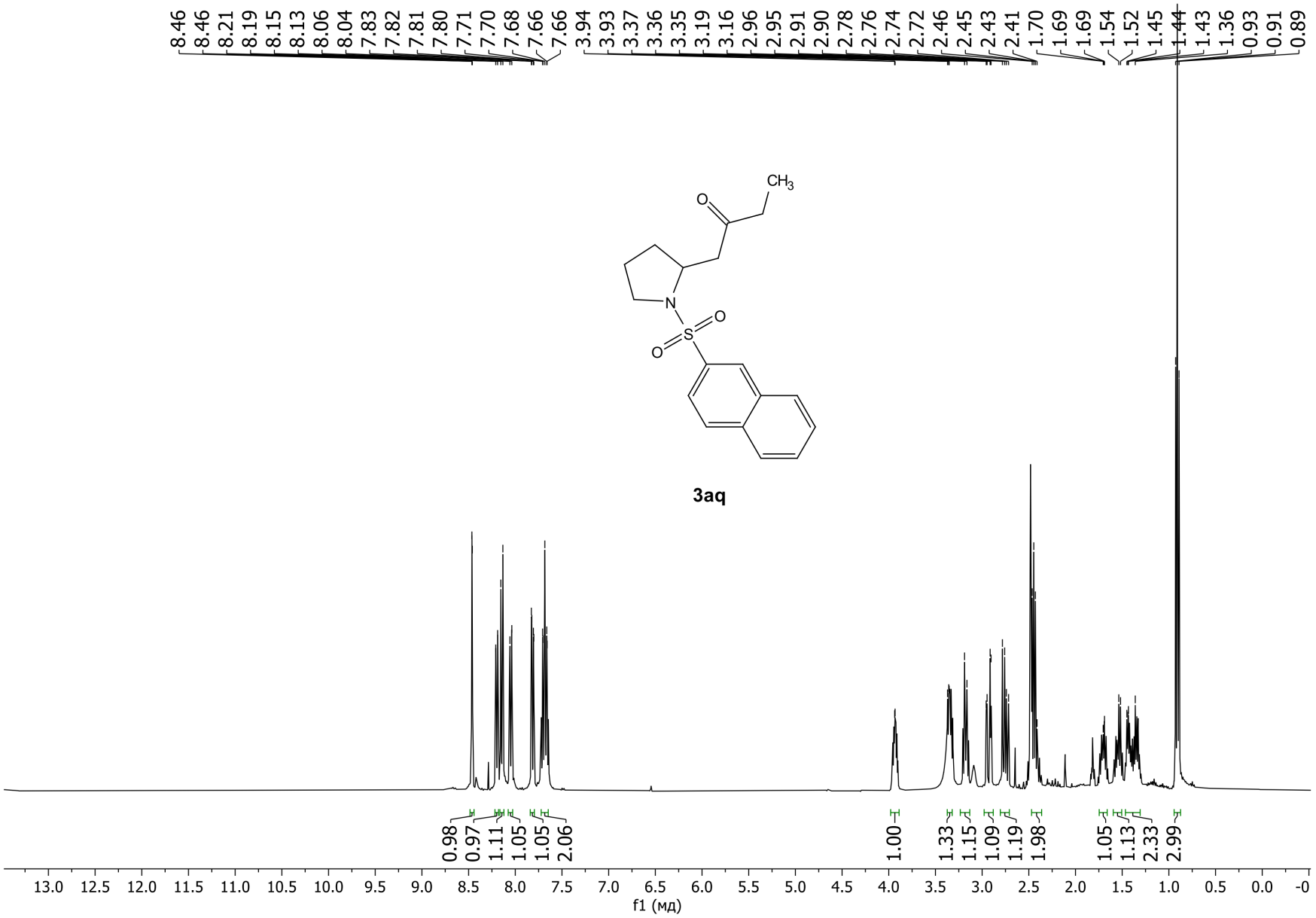

Figure S54. ^{1}H NMR spectrum ($(CD_3)_2SO$, 600MHz) of the compound **3aq**

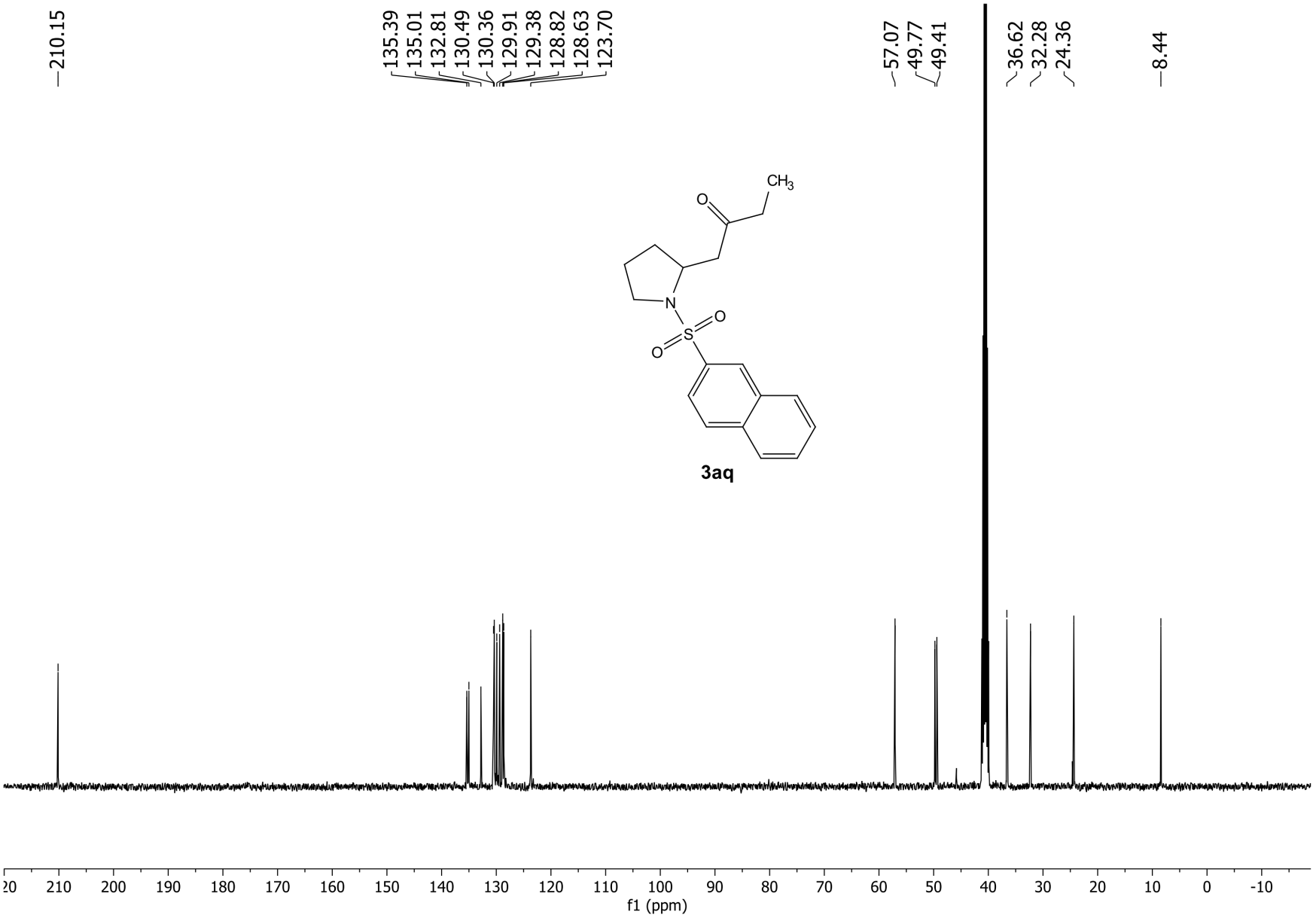

Figure S55. ^{13}C-{1H} NMR spectrum ($(CD_3)_2SO$, 150MHz) of the compound **3aq**

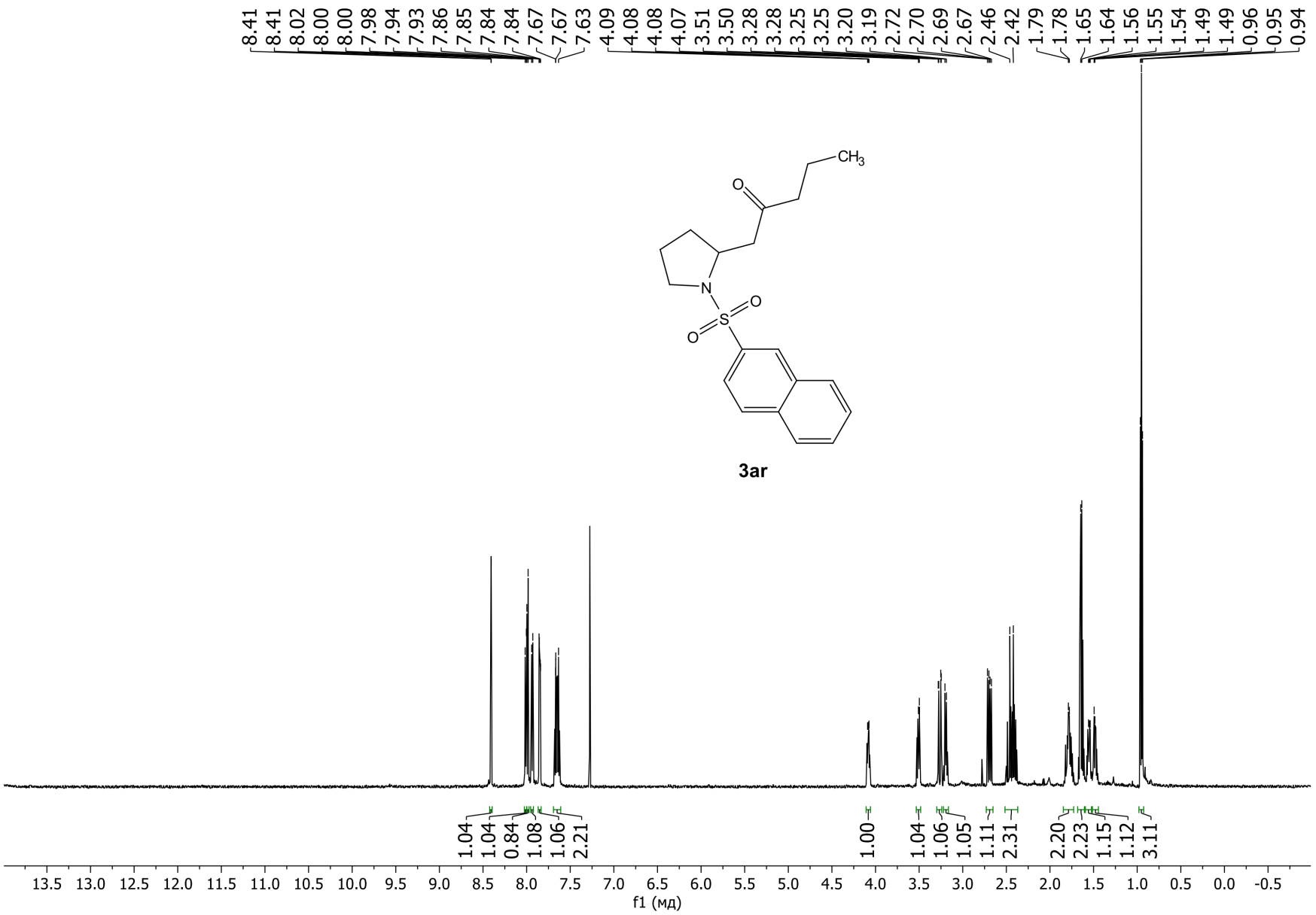

Figure S56. ^{1}H NMR spectrum ($CDCl_3$, 600MHz) of the compound **3ar**

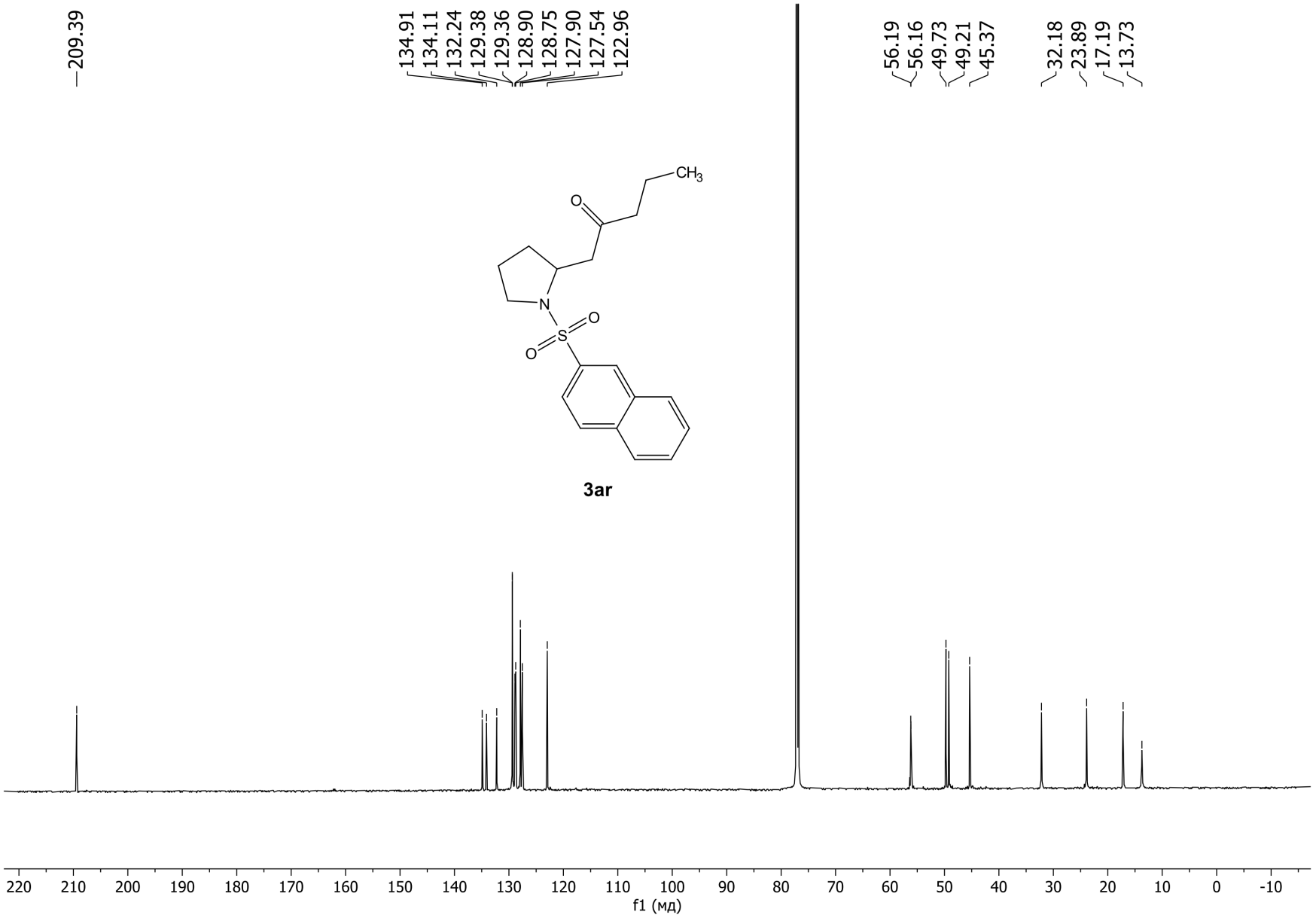

Figure S57. ^{13}C-{1H} NMR spectrum ($CDCl_3$, 150MHz) of the compound **3ar**

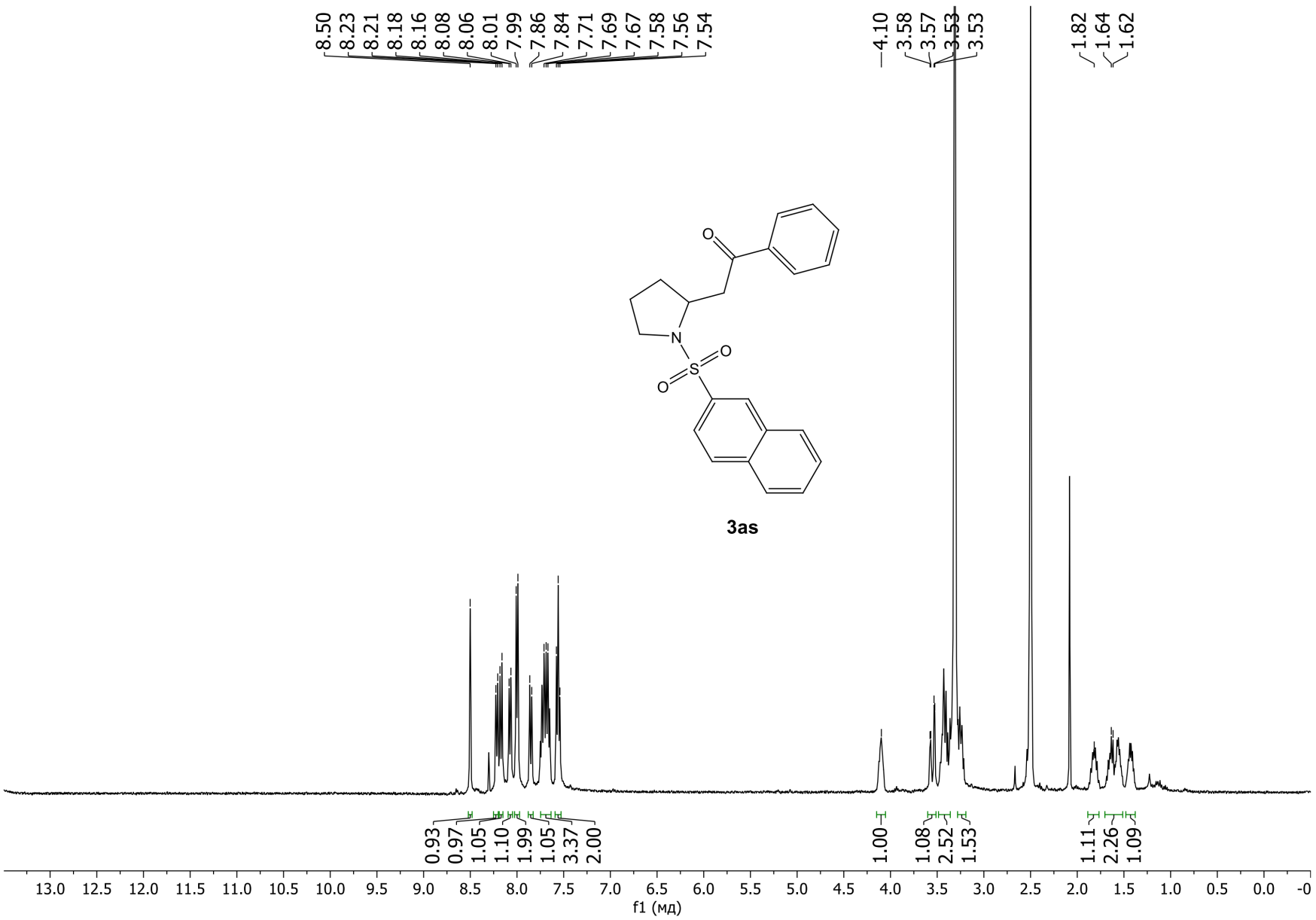

Figure S58. ^{1}H NMR spectrum ($(CD_3)_2SO$, 600MHz) of the compound **3as**

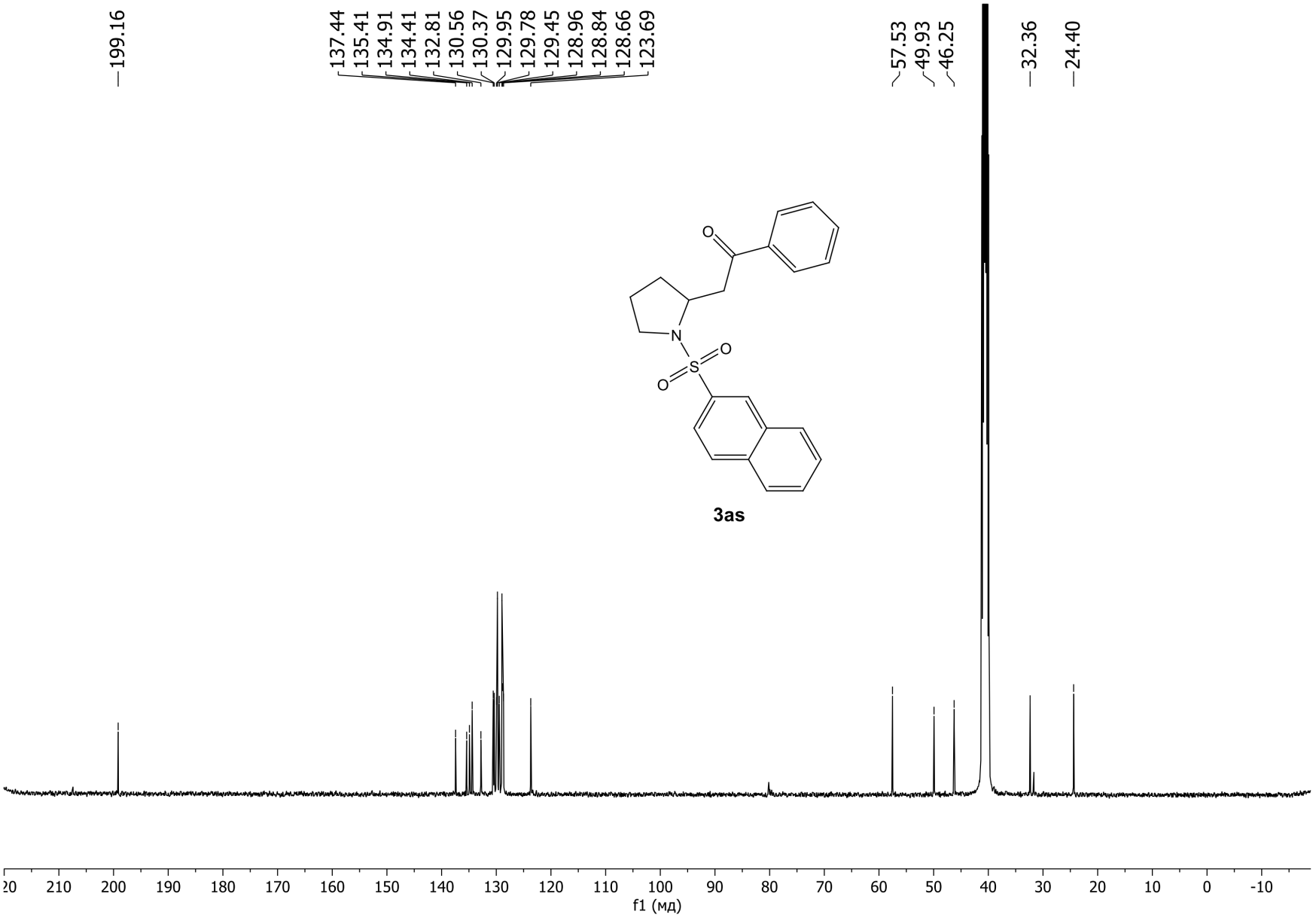

Figure S59. ^{13}C-{1H} NMR spectrum ($(CD_3)_2SO$, 150MHz) of the compound **3as**

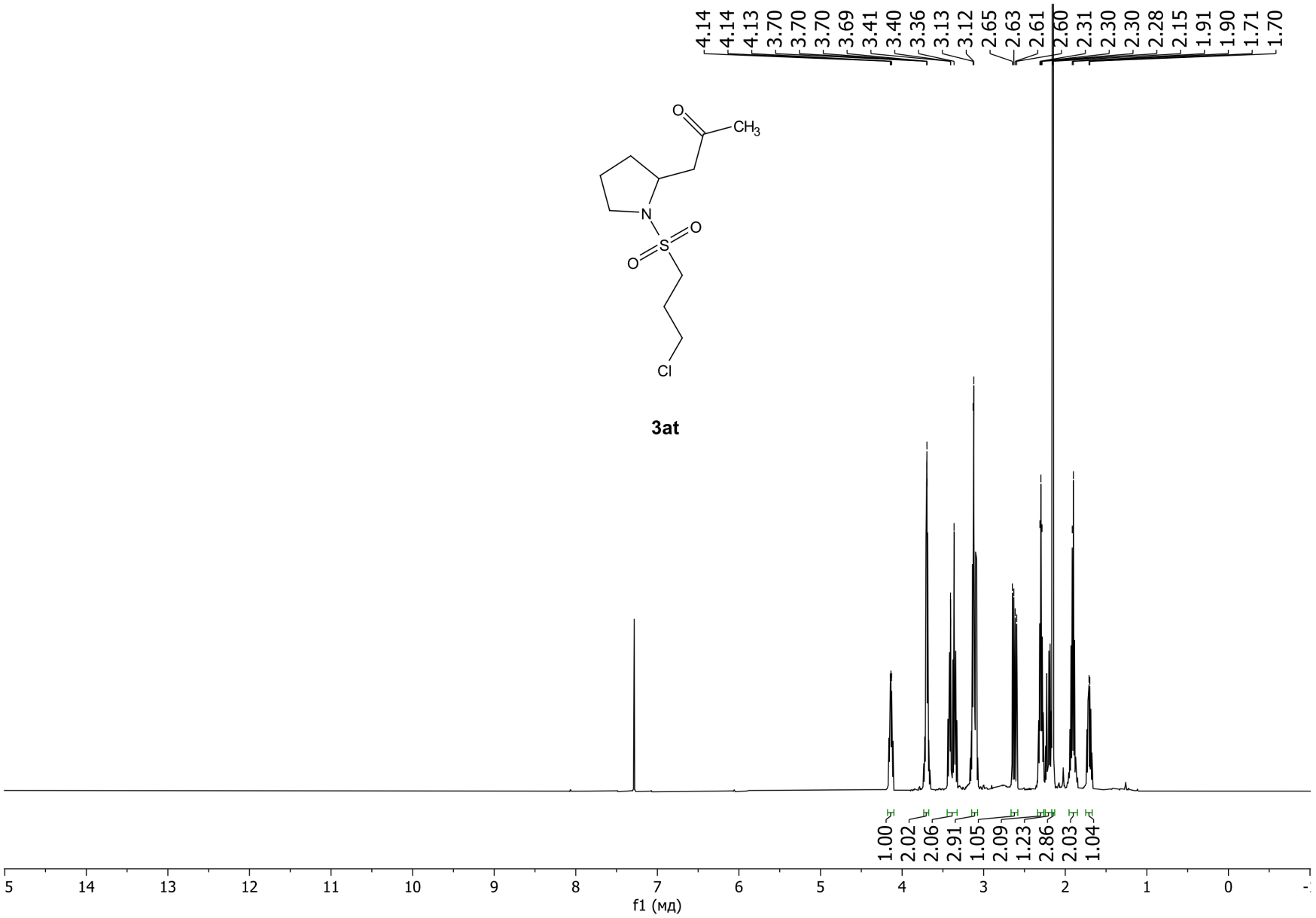

Figure S60. ^{1}H NMR spectrum ($CDCl_3$, 600MHz) of the compound **3at**

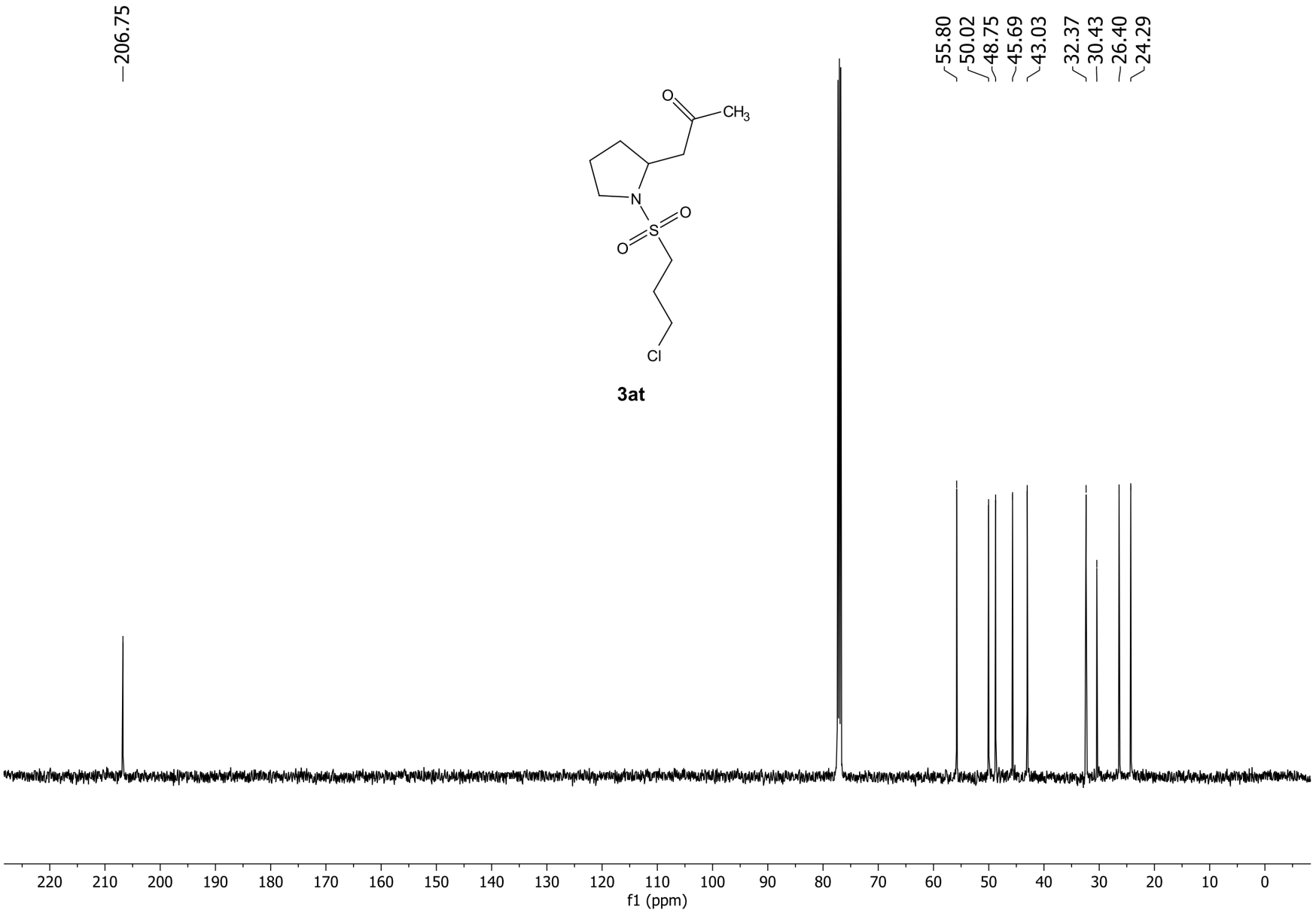

Figure S61. ^{13}C-{1H} NMR spectrum ($CDCl_3$, 150MHz) of the compound **3at**

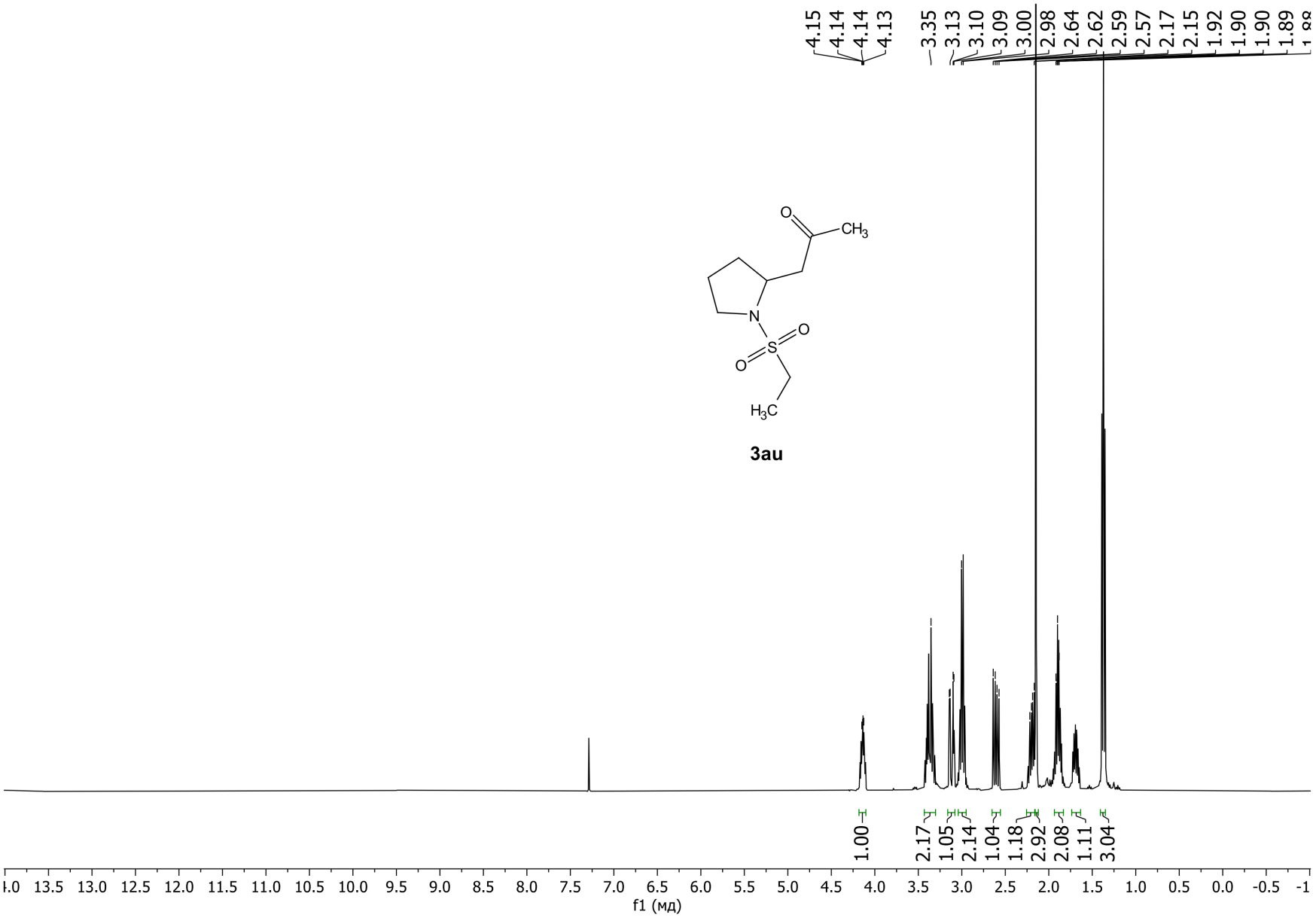

Figure S62. ^{1}H NMR spectrum ($CDCl_3$, 600MHz) of the compound **3au**

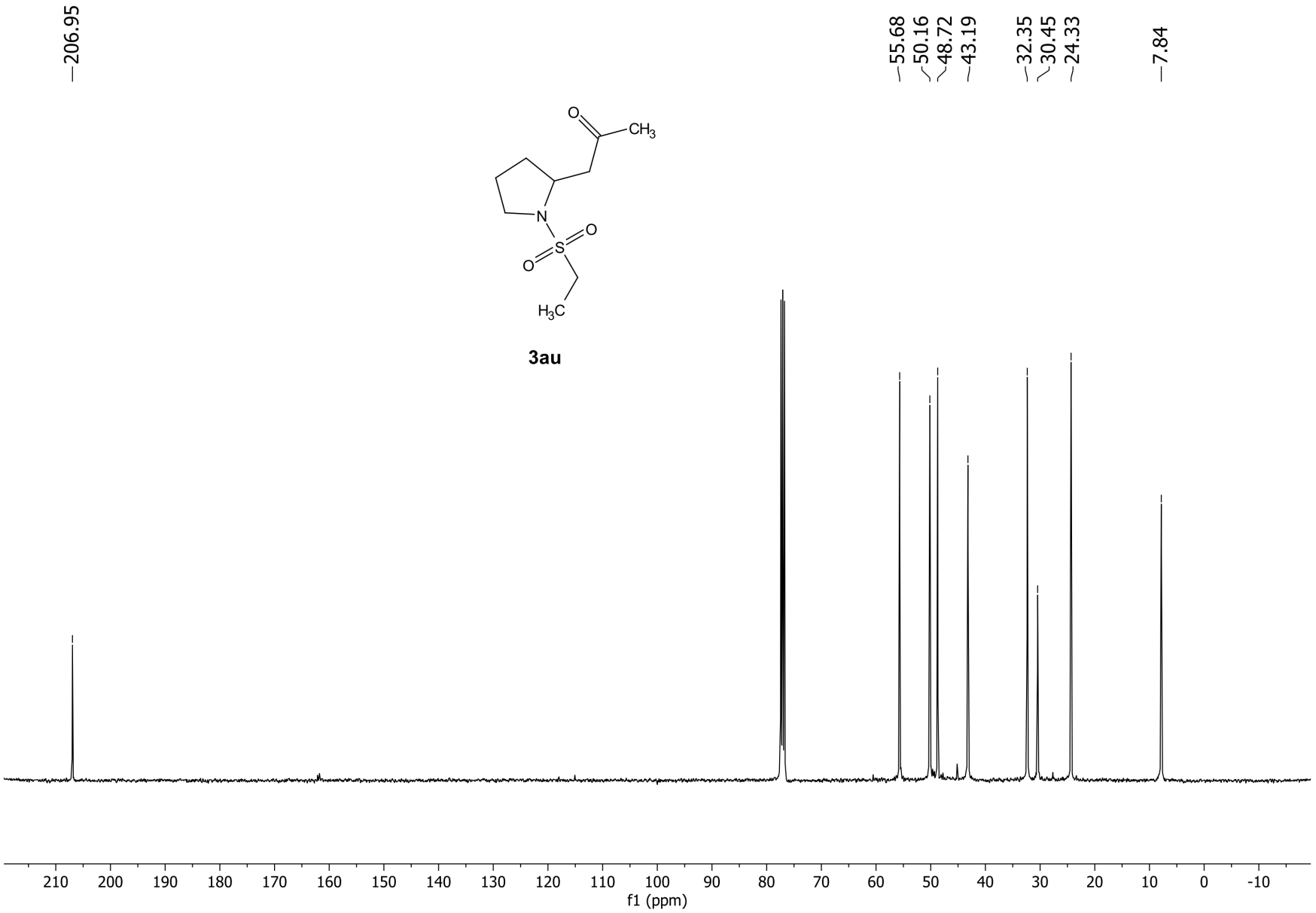

Figure S63. ^{13}C-{1H} NMR spectrum ($CDCl_3$, 150MHz) of the compound **3au**

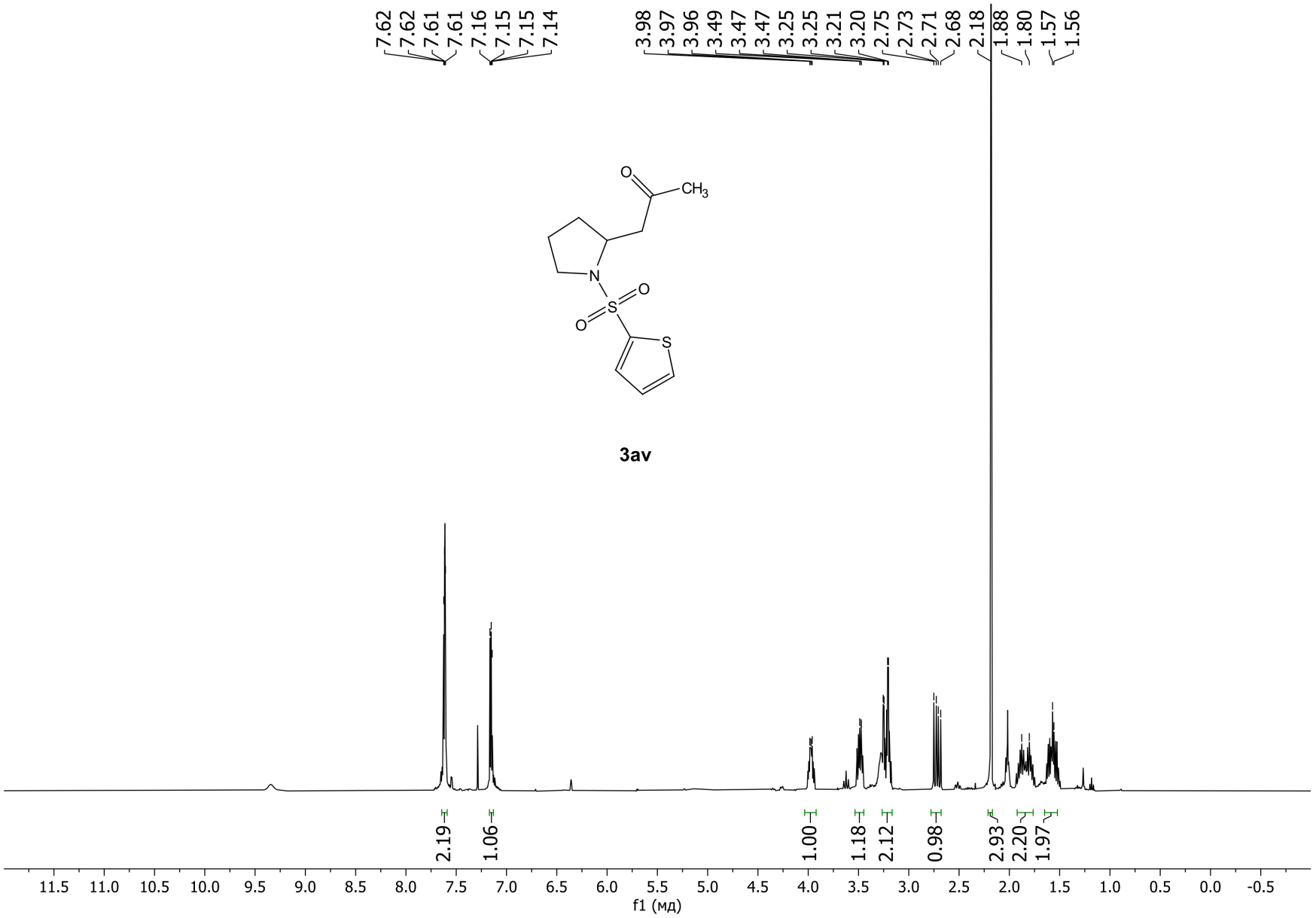

Figure S64. ^{1}H NMR spectrum ($CDCl_3$, 600MHz) of the compound **3av**

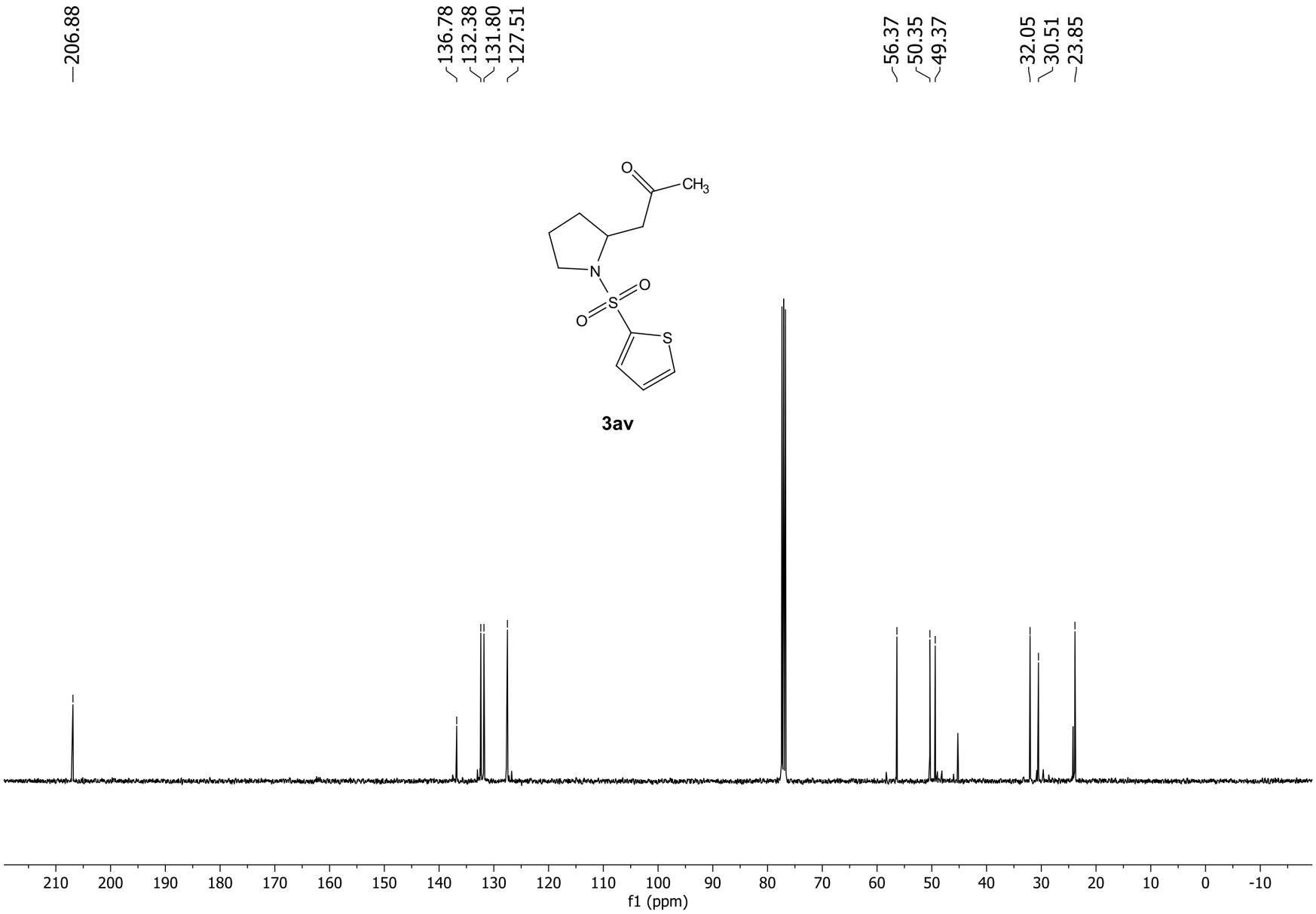

Figure S65. ^{13}C-{1H} NMR spectrum ($CDCl_3$, 150MHz) of the compound **3av**

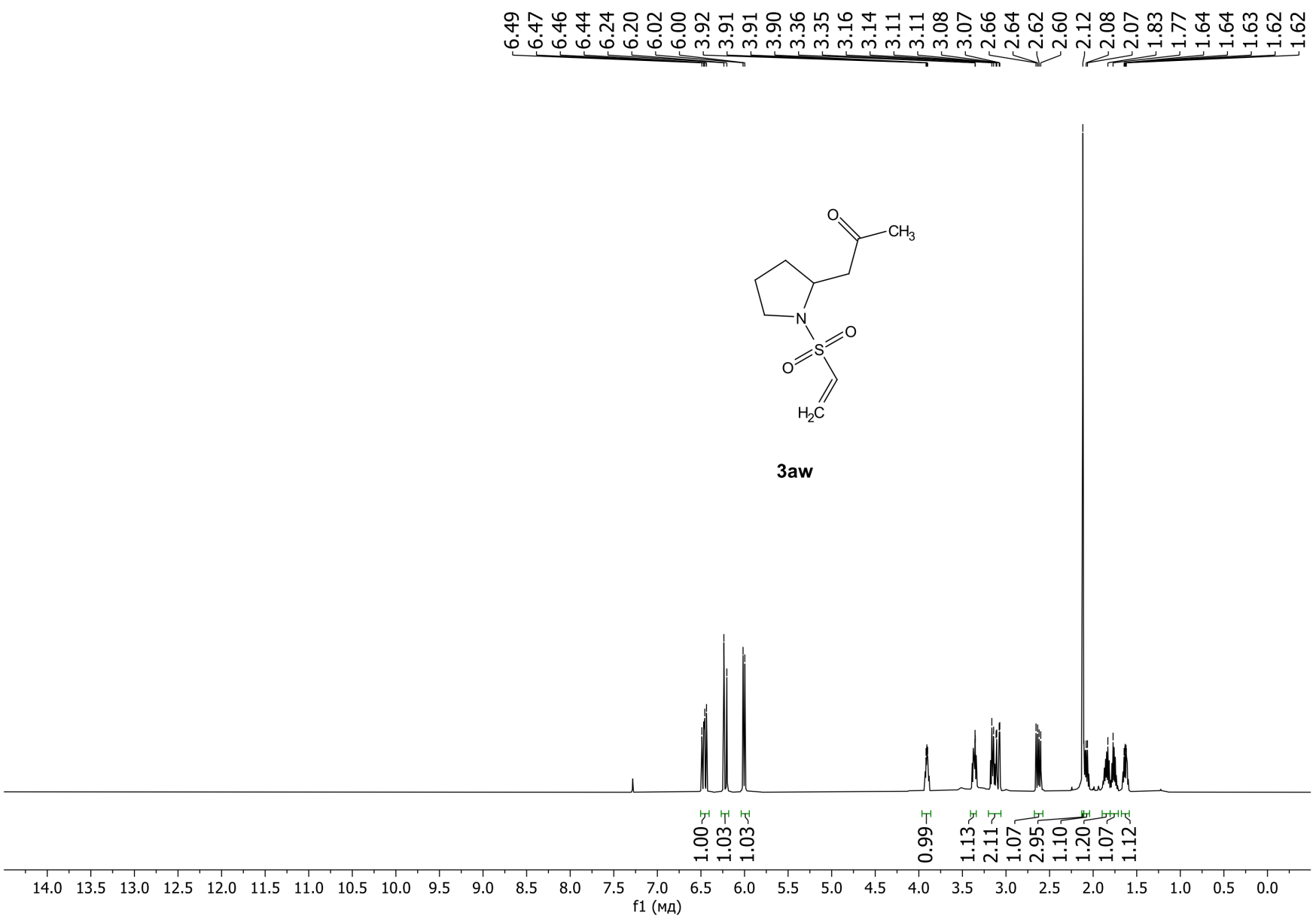

Figure S66. ^{1}H NMR spectrum ($CDCl_3$, 600MHz) of the compound **3aw**

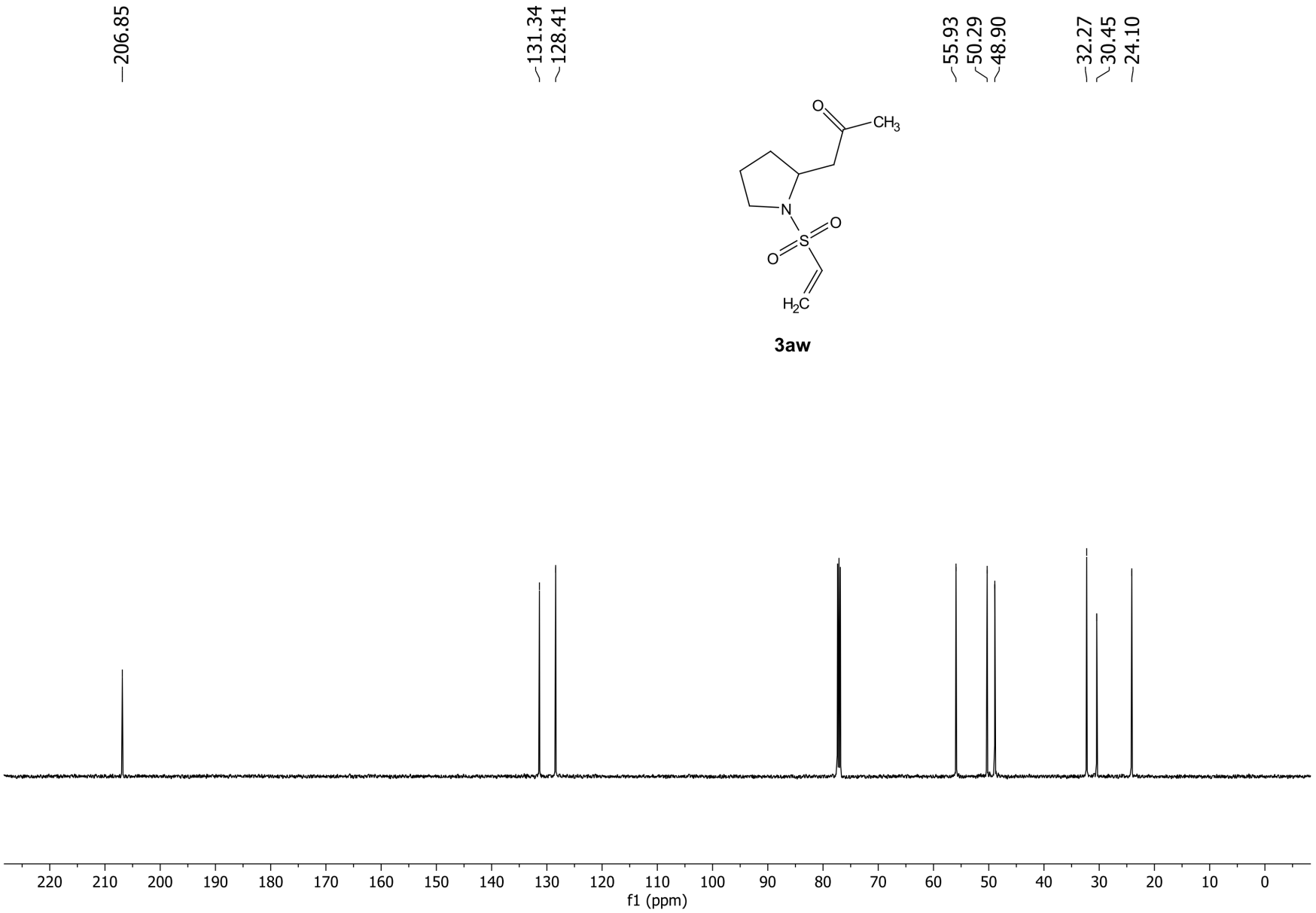

Figure S67. ^{13}C-{1H} NMR spectrum ($CDCl_3$, 150MHz) of the compound **3aw**

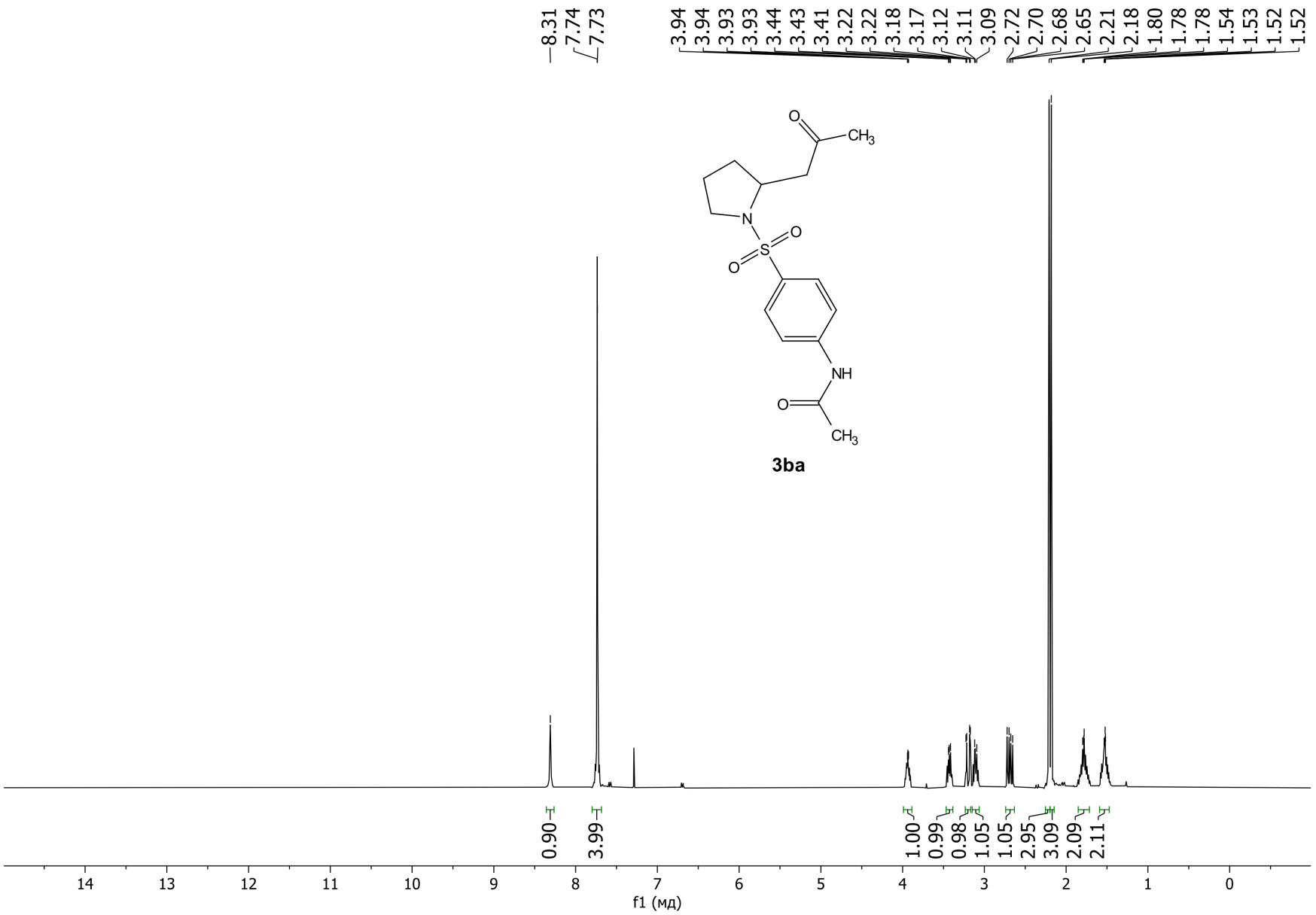

Figure S68. ^{1}H NMR spectrum ($CDCl_3$, 600MHz) of the compound **3ba**

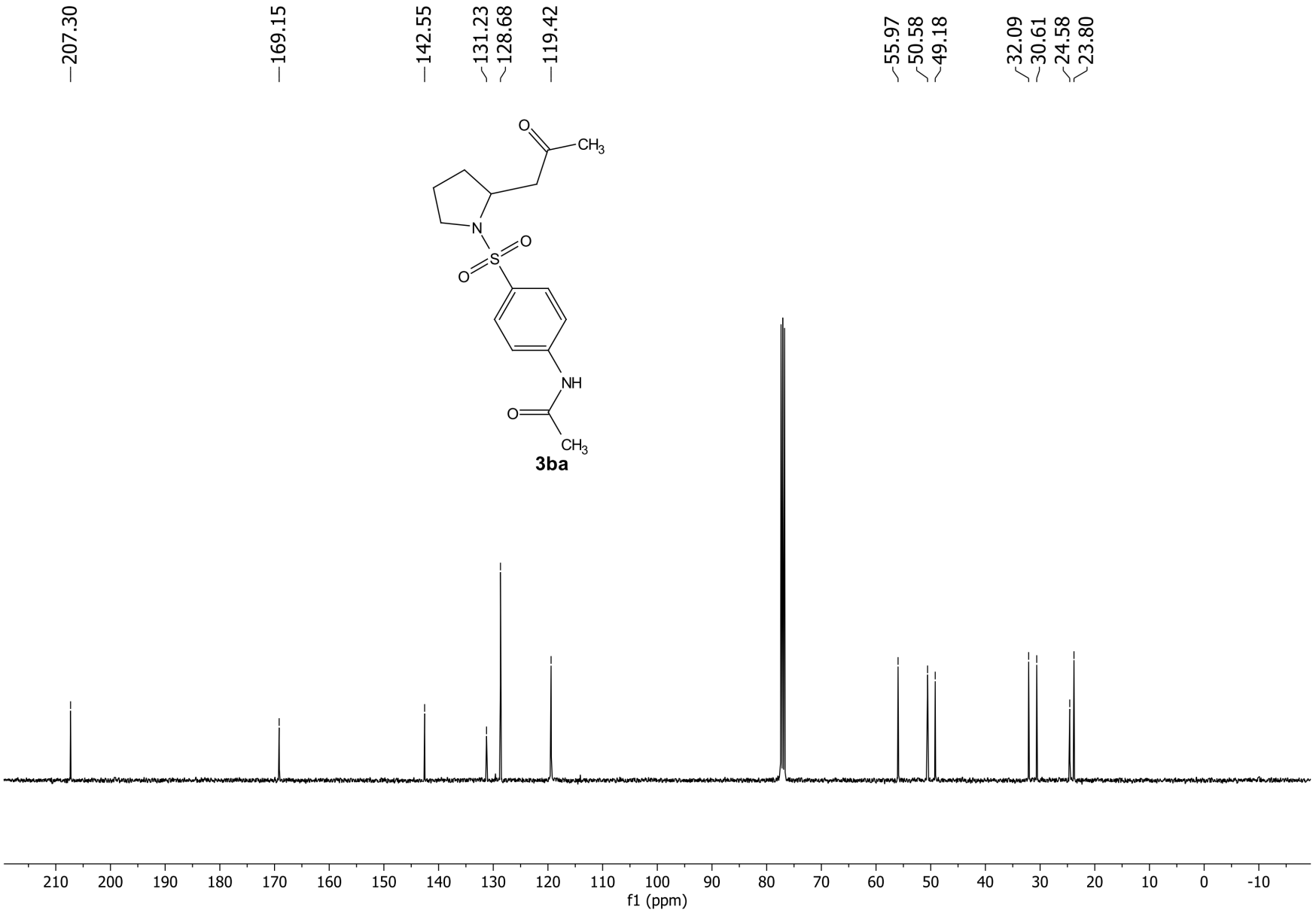

Figure S69. ^{13}C-{1H} NMR spectrum ($CDCl_3$, 150MHz) of the compound **3ba**

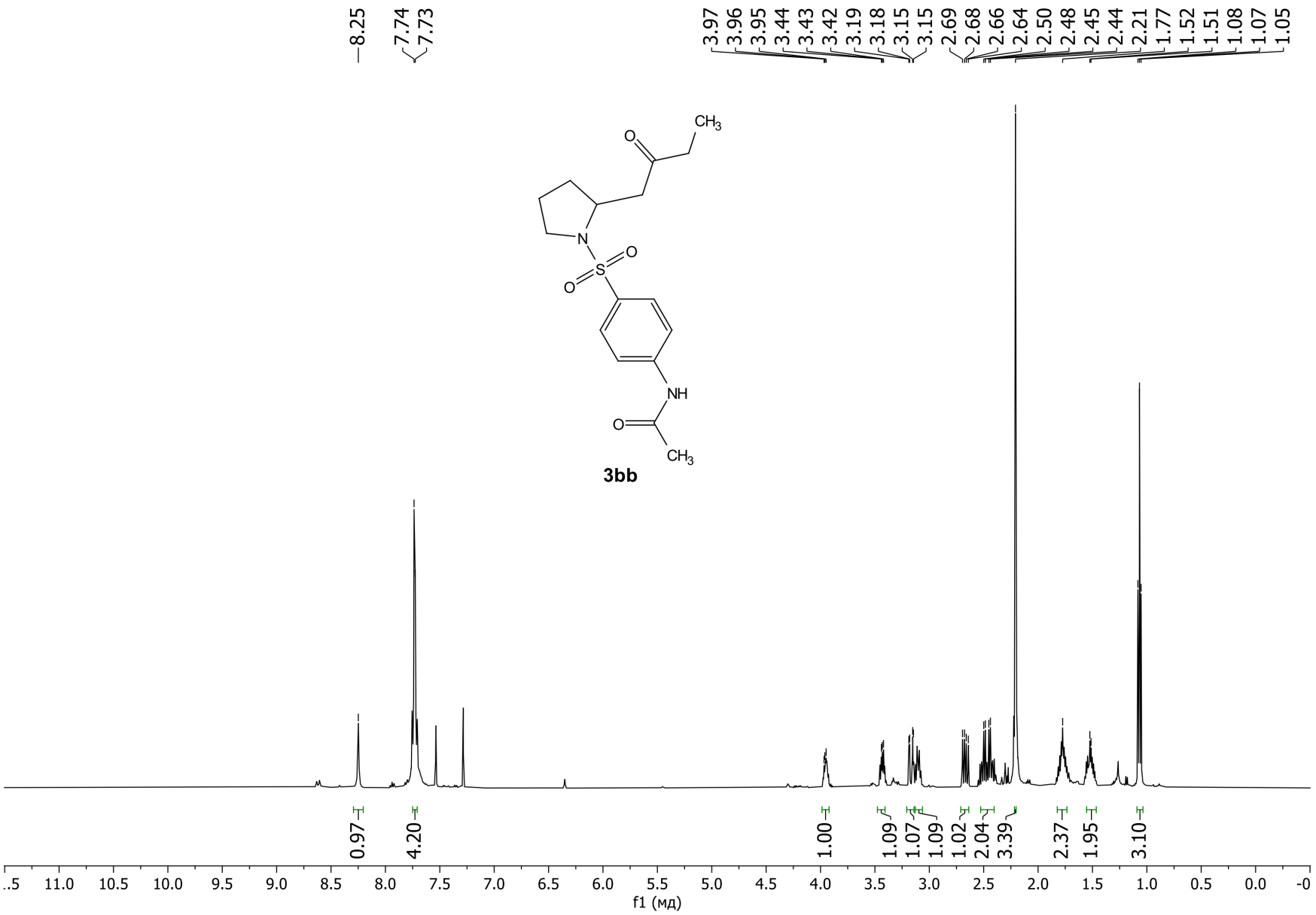

Figure S70. ^{1}H NMR spectrum ($CDCl_3$, 600MHz) of the compound **3bb**

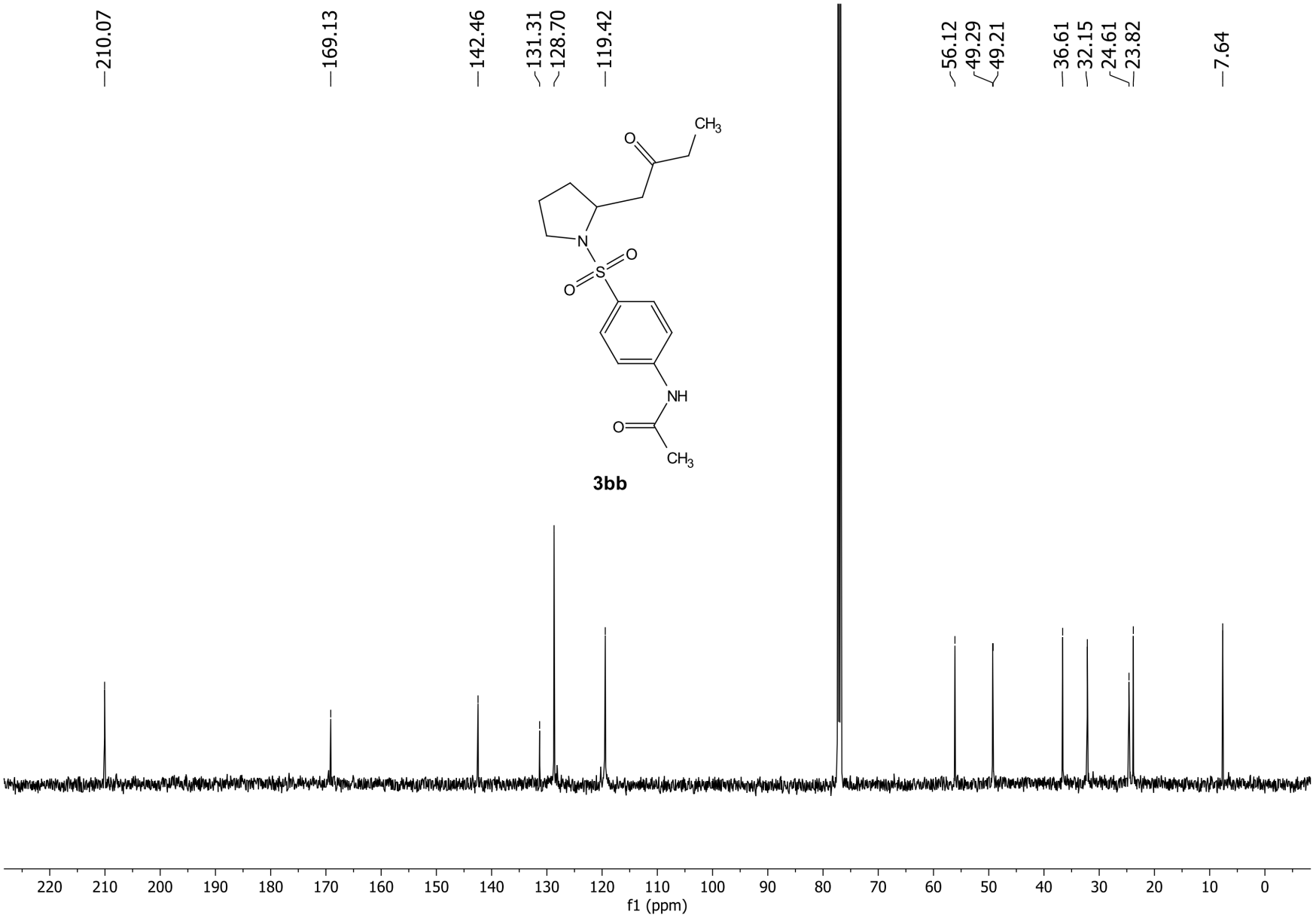

Figure S71. ^{13}C-{1H} NMR spectrum ($CDCl_3$, 150MHz) of the compound **3bb**

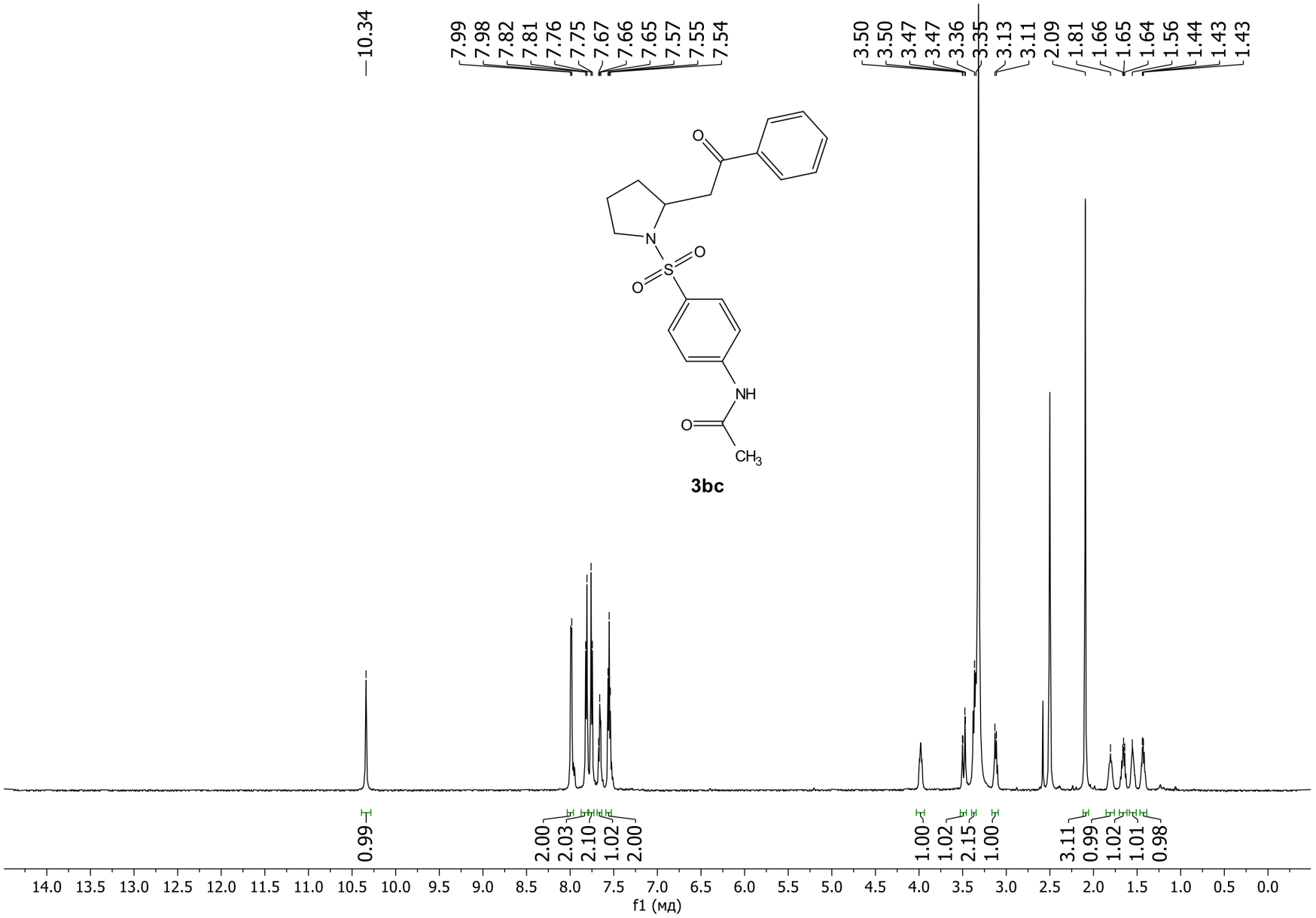

Figure S72. ^{1}H NMR spectrum ($(CD_3)_2SO$, 600MHz) of the compound **3bc**

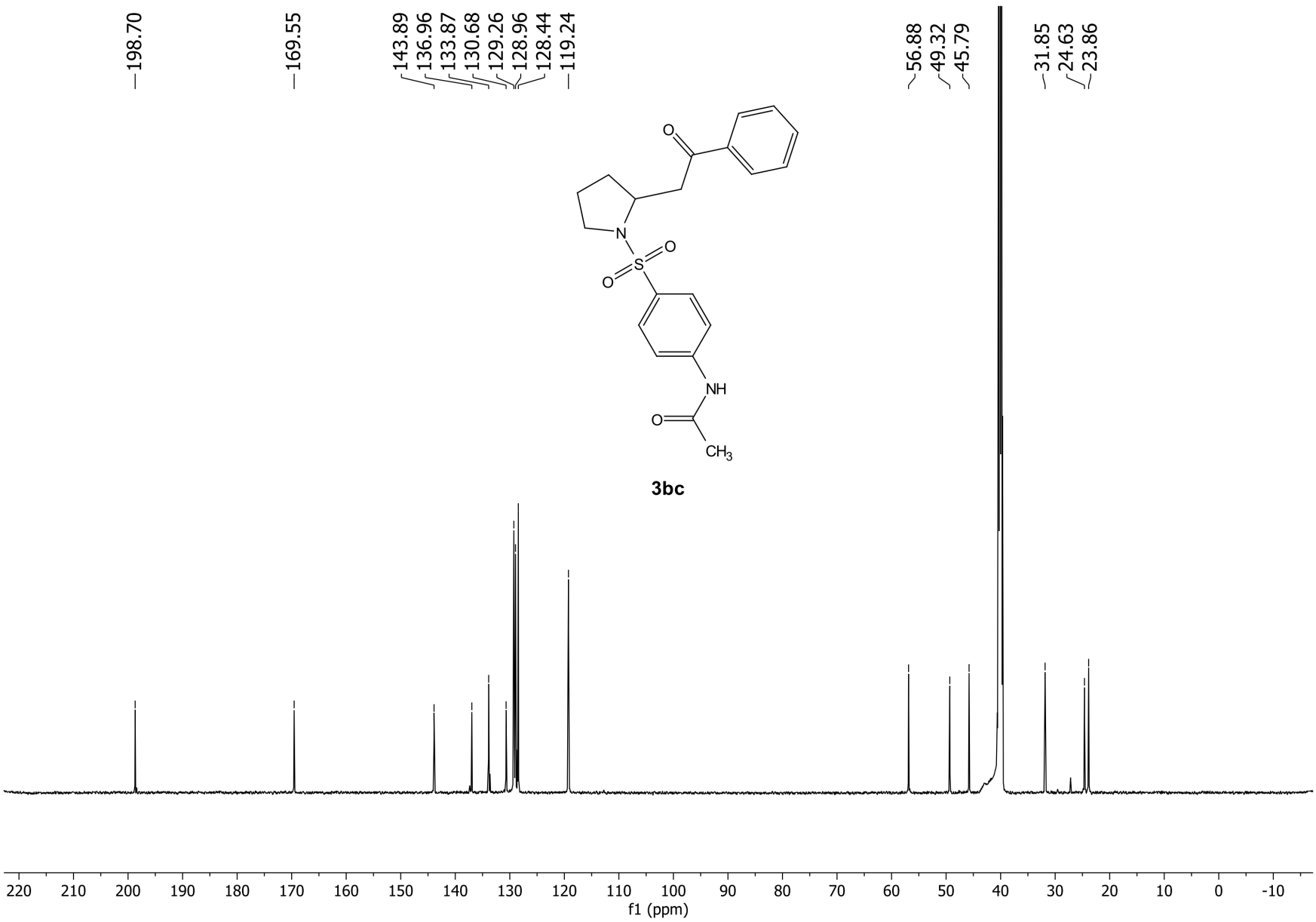

Figure S73. ^{13}C-{1H} NMR spectrum ($(CD_3)_2SO$, 150MHz) of the compound **3bc**

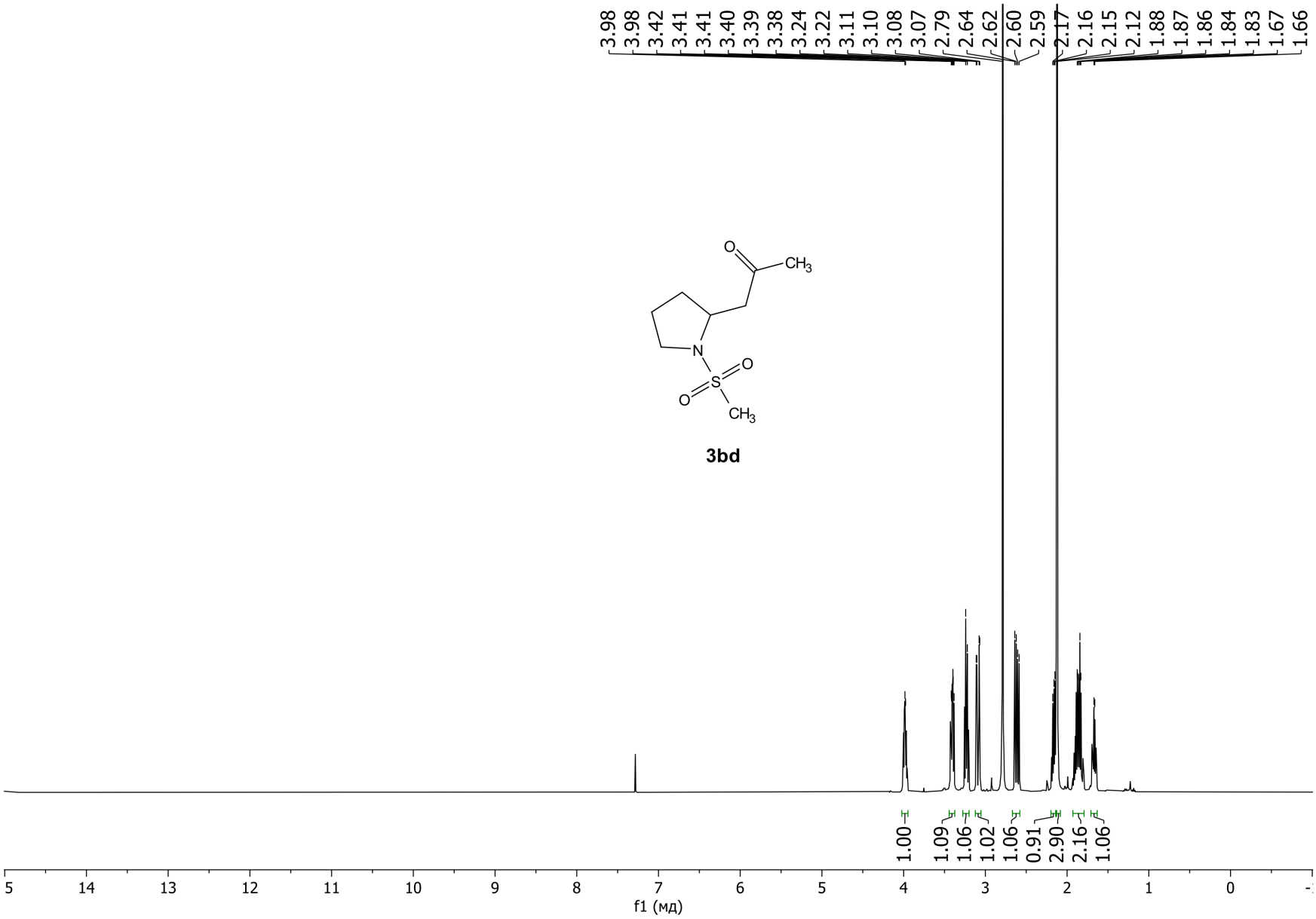

Figure S74. ^{1}H NMR spectrum ($CDCl_3$, 600MHz) of the compound **3bd**

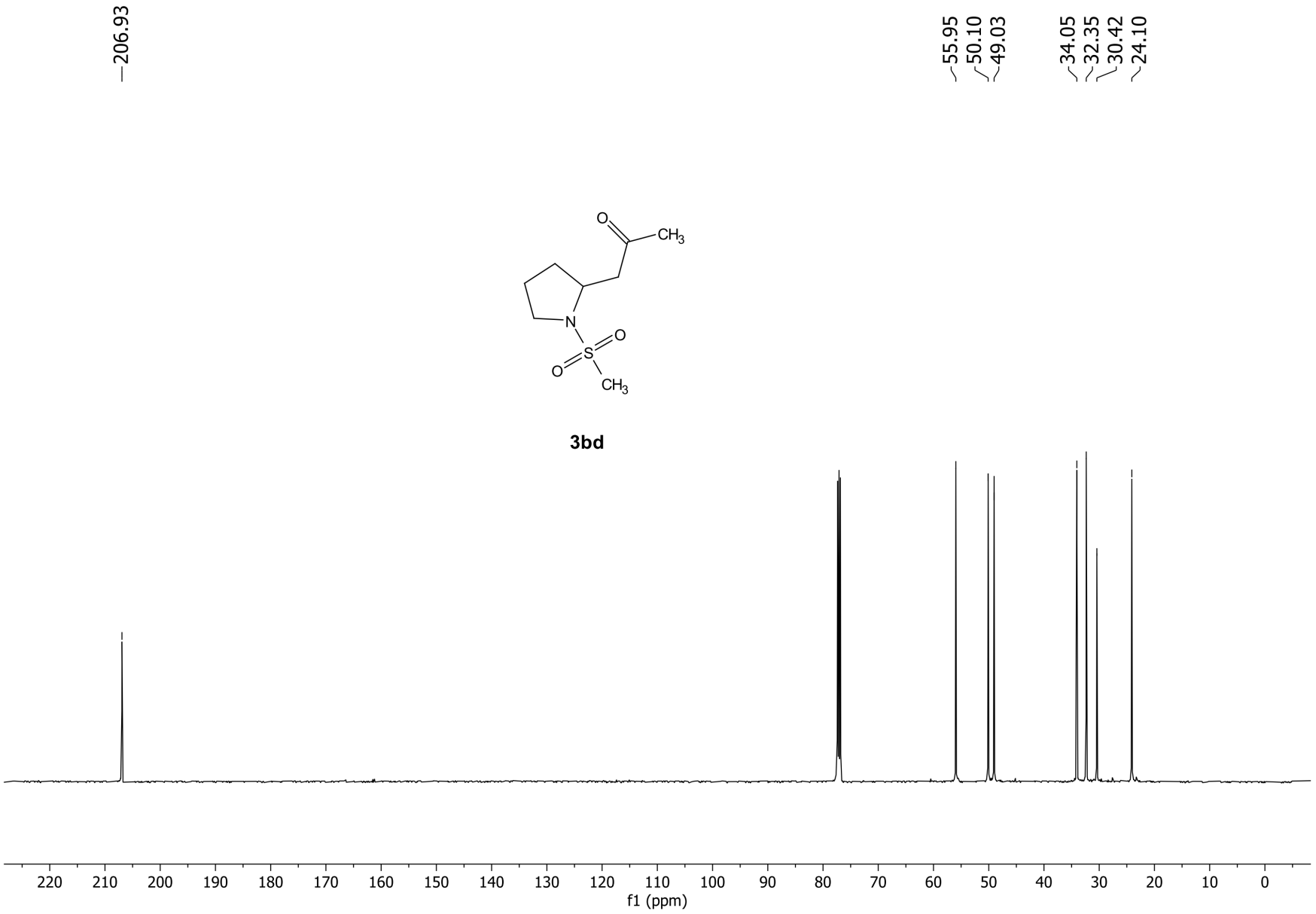

Figure S75. ^{13}C-{1H} NMR spectrum ($CDCl_3$, 150MHz) of the compound **3bd**

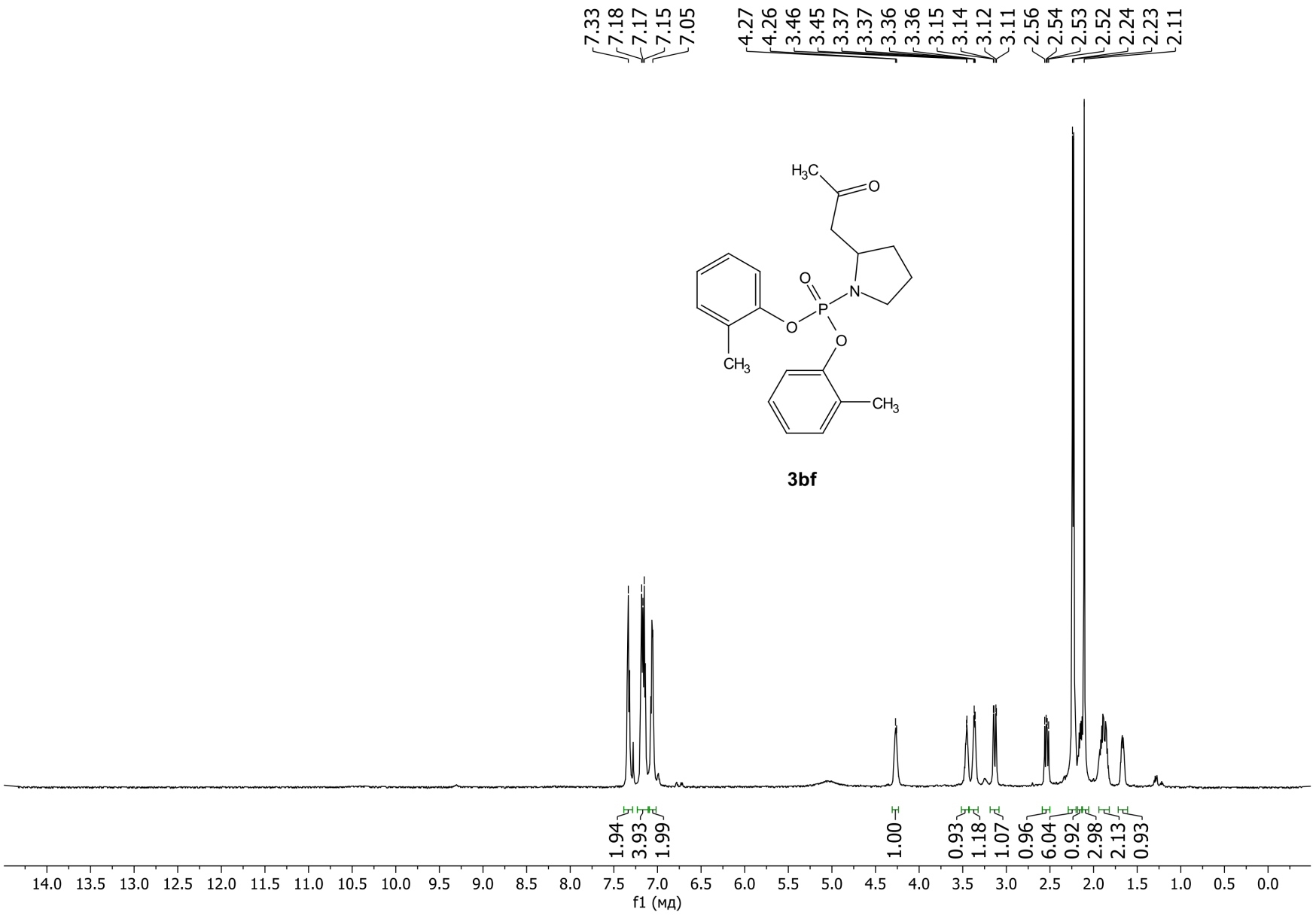

Figure S76. ^{1}H NMR spectrum ($CDCl_3$, 600MHz) of the compound **3bf**

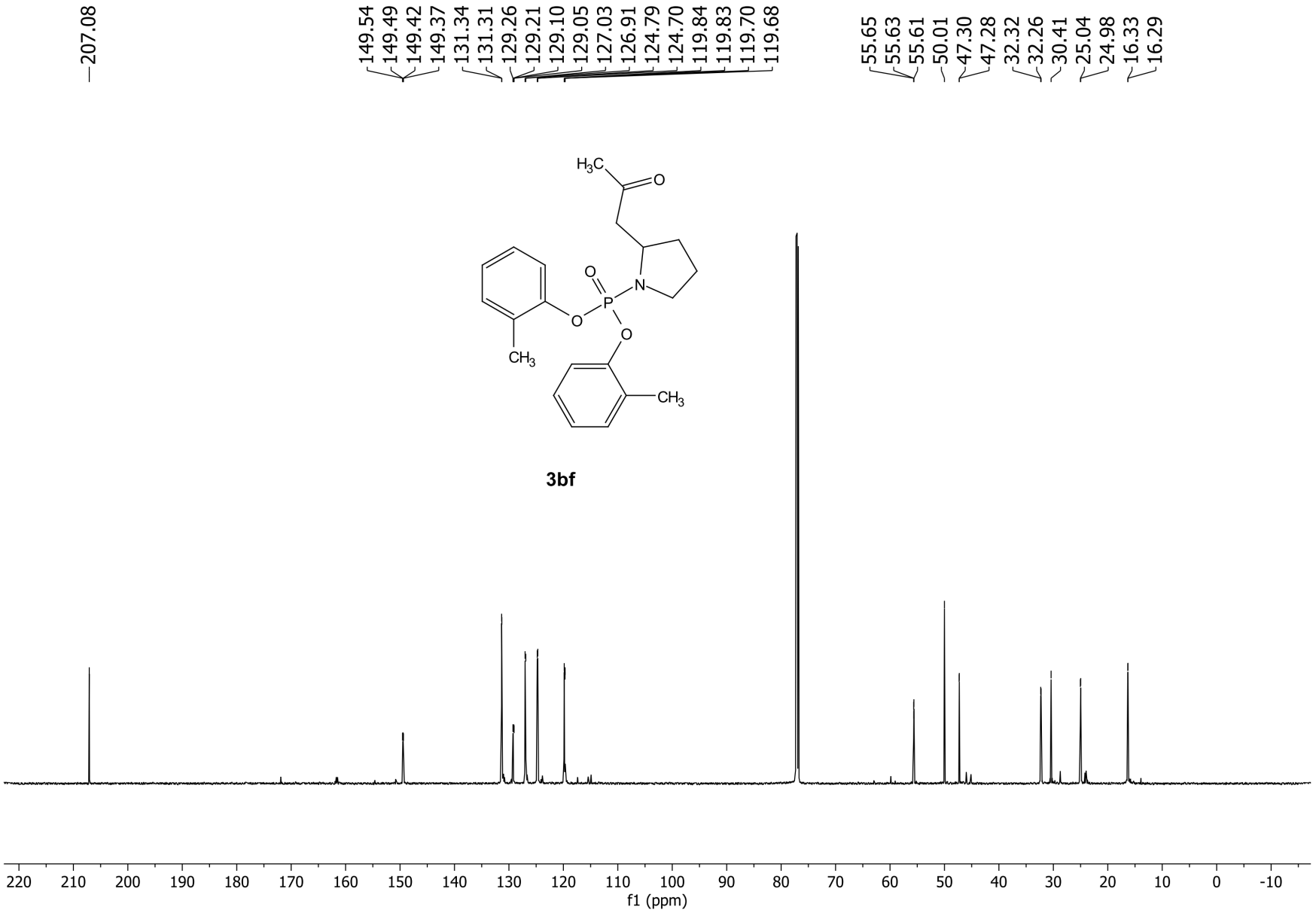

Figure S77. ^{13}C-{1H} NMR spectrum ($CDCl_3$, 150MHz) of the compound **3bf**

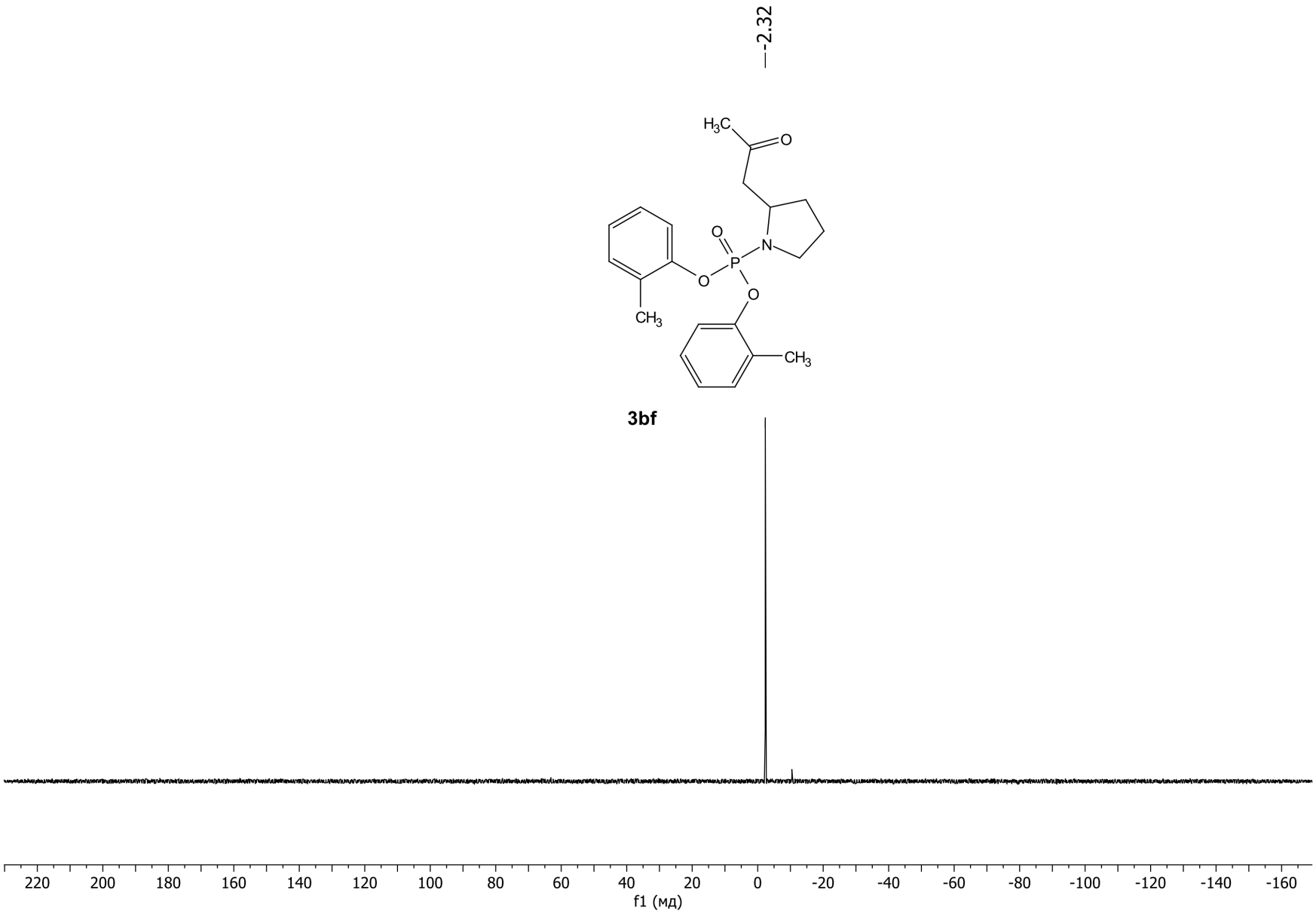

Figure S78. ^{31}P NMR spectrum ($CDCl_3$, 162MHz) of the compound **3bf**

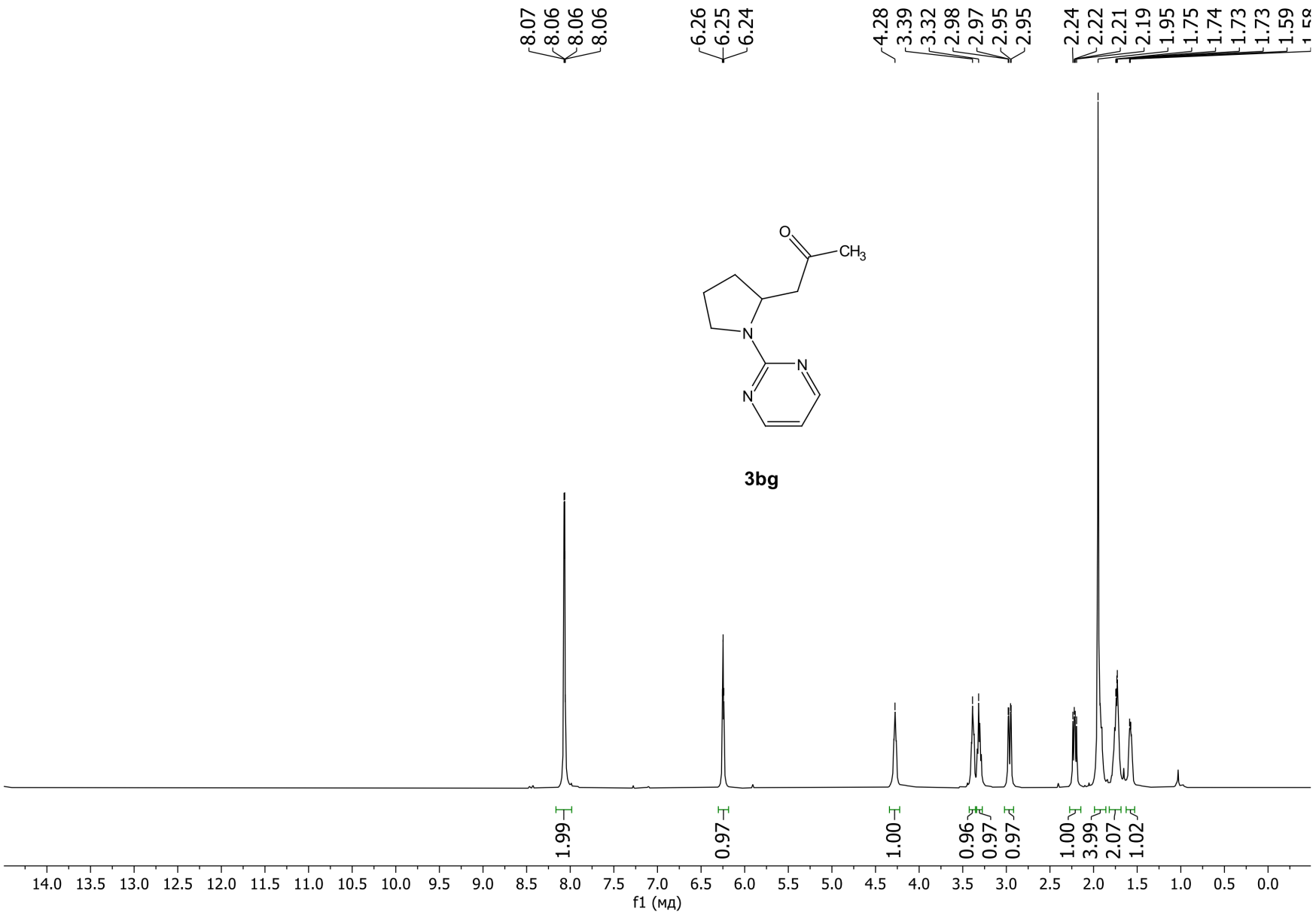

Figure S79. ^{1}H NMR spectrum ($CDCl_3$, 600MHz) of the compound **3bg**

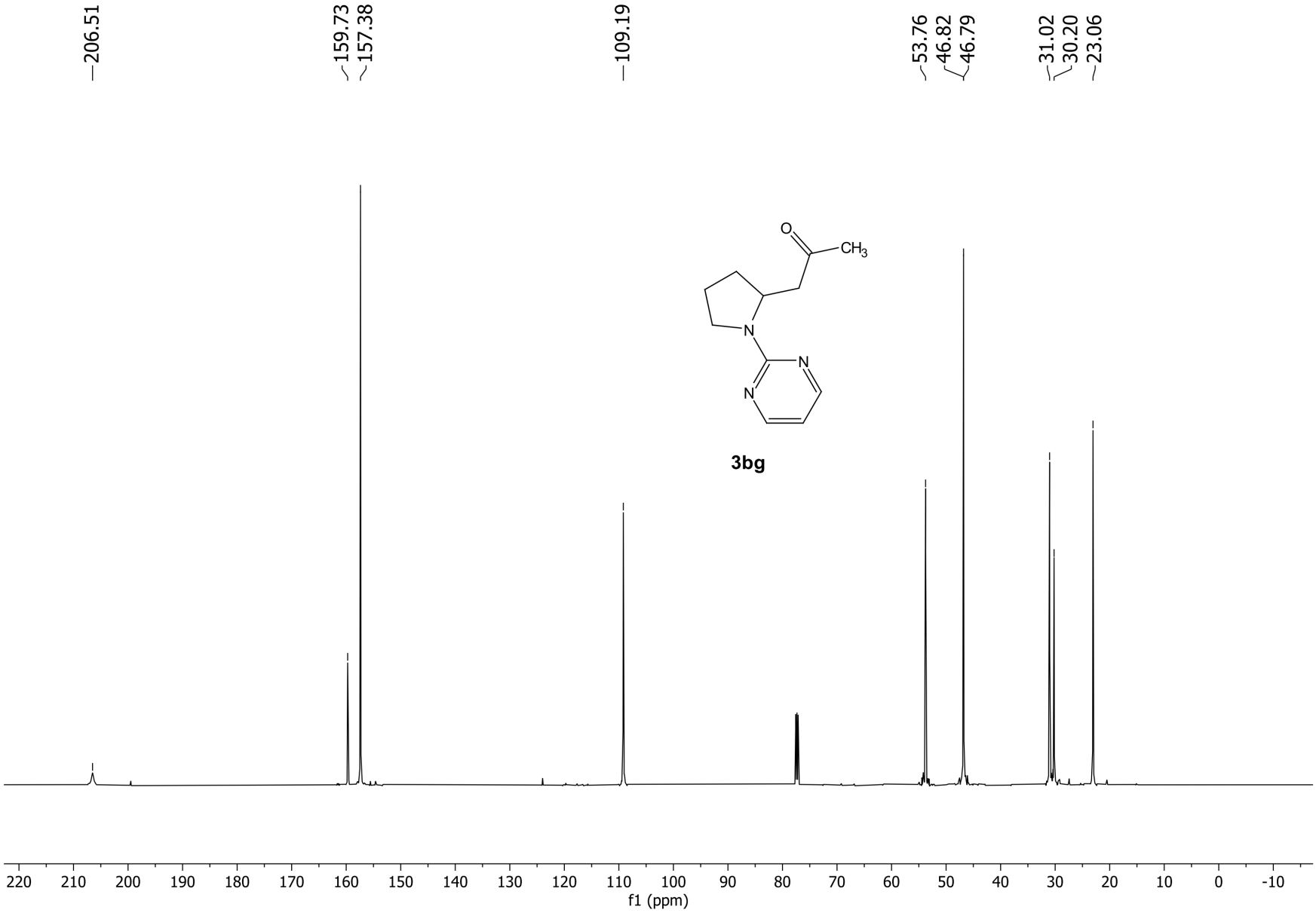

Figure S80. ^{13}C-{1H} NMR spectrum ($CDCl_3$, 150MHz) of the compound **3bg**