Electronic Supplementary Information

Identification of Camphor Derivatives as Novel M2 Ion Channel Inhibitors of Influenza A Virus

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Biological experiments

Patch Clamp Assay.

The inhibitors were tested via patch clamp assay using A/M2 expressed 293Trex cells and membrane currents were recorded as in a previous report (Hu et al., 2010).

Plaque Reduction Assay.

A monolayer of MDCK cells were infected with 0.01 MOI influenza A viruses for 1 h at 37 °C. The inoculums were then removed, and the cells were washed twice with phosphate-buffered saline (PBS). The cells were then overlaid with 1% agar DMEM-containing amantadine or one of the synthesized compounds in the presence of 2 μg/mL trypsin and 0.3% BSA. Two to three days after infection, the monolayers were fixed and stained with 0.1% crystal violet solution.

Viral Inhibition Assay.

MDCK cells were grown to confluence in 96-well microtiter plates, the medium was removed, and the cells were covered with 50 μL of medium containing various amounts of amantadine or one of the synthesized compounds in the presence of 1

mg/mL TPCK and 0.3% BSA. The plates were then incubated at 37 °C for 30 min. Fifty microliters, equal to approximately 0.01 MOI of influenza A viruses were then added to the plates. After incubation in 5% CO_2 at 37 °C for 72 h, 10 μL of CCK-8 reagent were added to each well, and the mixture was incubated for 3 h. The A450 was then measured using an UVstar-Microplates Synergy HT. Datas were analyzed using GraphPad Prism 5.

Cytotoxicity Assays.

MDCK cells were grown as monolayers in 96-well plates after seeding for 18-24 h. The medium was removed and rinsed twice with Hanks' solution and the compounds were serially diluted in 100 μL medium containing 0.3% BSA. After incubating for 72 h at 37 °C in a humidified 5% CO_2 incubator, 5 μL CCK-8 reagent in 50 μL medium was added to each well and the absorbance was measured at 450 nm using a UVstar-Microplates Synergy HT plate reader. The CC_{50} values were calculated by nonlinear regression using GraphPad Prism 5.

Experimental chemistry

General Method

All commercially available compounds and solvents were reagent grade and were used without further treatment unless otherwise noted. Reactions were monitored by TLC using Qing Dao Hai Yang GF_{254} silica gel plates (5 x 10 cm); zones were detected visually under ultraviolet irradiation (254 nm) by either spraying with an ethanol solution of Ninhydrin or by treatment with iodine gas. Compounds were

purified silica gel column chromatography which performed on silica gel (200–300 mesh) from Qing Dao Hai Yang and characterized by ^{1}H NMR, ^{13}C NMR and ESI-MS, NMR spectra were recorded on a Bruker NMR AVANCE 400 (400 MHz) or a Bruker NMR AVANCE 500 (500 MHz), and the NMR reagents $CDCl_3$ and DMSO-d_6 were used as internal standards. Chemical shifts (δ) were recorded in part per million and coupling constants (J) in hertz (Hz). MS data were measured on an Agilent MSD-1200 ESI-MS system.

Detailed synthesis procedure and compound characterization.

(1R,2R,5S)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-one (6). To a solution of pyridinium dichromate (7.3 g, 19.4 mmol) in CH_2Cl_2 (20 mL), the solution was immersed in an ice-water bath. (1R,2R,3R,5S)-(−)-isopinocampheol (2 g, 13 mmol) was added dropwise at 0 ℃ to the well-stirred reaction mixture over a period of 15 minutes. Then the reaction mixture is stirred for 2 h and quenched by addition of Et_2O. The solution was then concentrated and purified by flash silica gel column chromatography to obtain **6** as a colorless liquid. Yield: 80%; ^{1}HNMR (400 MHz, $CDCl_3$) δ 0.81 (s, 3H), 1.12 (s, 1H), 1.14 (d, 3H, J = 7.2 Hz), 1.26 (s, 3H), 1.97–2.02 (m, 1H), 2.04–2.09 (m, 1H), 2.37–2.47 (m, 2H), 2.53–2.61 (m, 2H); ^{13}CNMR (125 MHz, $CDCl_3$) δ 16.69, 21.79, 26.91, 34.26, 38.87, 39.08, 44.62, 44.91, 51.18, 214.88; ESI-MS: calculated for $C_{10}H_{16}O$ ($M+H^+$): 153.24, found: 153.3.

(1R,2R,3R,5S)-2,6,6-trimethylbicyclo[3.1.1]heptane-3-carbonitrile (7). To an ice-cooled solution of TosMIC (1.92 g, 9.85 mmol) in dry Me_2SO (9.7 mL) was

added all at once 3.32 g (29.56 mmol) of solid tert-BuOK. After stirring for 5 min under N_2 0.33 mL of MeOH was added, then 1 g (6.57 mmol) of **6**, and the mixture was stirred over night at rt. The reaction mixture was diluted with water (250 mL), acidified with 2 N HCl, and extracted with PE (bp 40-60 °C). The combined extracts were washed with saturated NaCl solution, dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography on silica gel. Yield: 86%; ^{1}HNMR (400 MHz, $CDCl_3$) δ 0.89 (s, 3H), 1.04 (d, 3H, J = 6.4 Hz), 1.20 (s, 1H), 1.21 (s, 3H), 1.69–1.72 (m, 1H), 1.92–1.96 (m, 1H), 2.03–2.22 (m, 3H), 2.33–2.44 (m, 2H); ^{13}CNMR (125 MHz, $CDCl_3$) δ 19.79, 20.05, 22.49, 26.25, 26.43, 29.15, 35.07, 39.46, 39.52, 46.24, 123.35; ESI-MS: calculated for $C_{11}H_{17}N$ ($M+H^+$): 164.27, found: 164.1.

((1R,2R,3R,5S)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)methanamine (8. HCl). A solution of **7** (0.58 g, 4.7 mmol) in anhydrous THF (5 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (0.54 g, 14.2 mmol) in anhydrous THF (20 mL) at 0 °C. The resulting solution was stirred for 10 h at reflux. The solution was then cooled to 0 °C and filtered following the portionwise addition of $Na_2SO_4 \cdot 10H_2O$ (5.0 g). The collected solids were washed with CH_2Cl_2 (2 x 20 mL). The combined organics were evaporated to dryness and treated with saturated HCl/CH_3OH (20 mL) then evaporated to dryness, and the insoluble material was washed with diethyl ether (3 x 20 mL) to afford the corresponding hydrochloride as a white powder. Yield: 64%; mp 250 °C (dec.); ^{1}HNMR (400 MHz, DMSO-d_6) δ 0.73 (s, 3H), 0.88 (d, 3H, J = 6.0 Hz), 1.18 (s, 3H), 1.27 (d, 1H, J = 10 Hz), 1.45–1.50 (m, 1H), 1.59–1.64 (m, 3H), 1.89–2.05 (m, 3H), 2.67–2.71 (m, 1H), 2.92 (d, 1H, J = 3.8 Hz), 7.95 (br, 3H);

^{13}CNMR (125 MHz, DMSO-d_6) δ 19.66, 19.75, 23.23, 26.48, 29.03, 32.90, 33.38, 42.96, 46.88; ESI-MS: calculated for $C_{11}H_{21}N$ ($M+H^+$): 168.30, found: 168.2. HRMS found: 168.17465.

(1R,2R,3R,5S)-2,6,6-trimethylbicyclo[3.1.1]heptane-3-carboxylic acid (9). **7** (2.3 g, 14.09 mmol) was dissolved in AcOH (28.0 mL), H_2SO_4 (7.0 mL) and H_2O (8.5 mL) was added and the mixture was heated to reflux and reacted overnight. The solution was cooled down to room temperature and 100 mL H_2O was added. The aqueous layer was extracted with diethyl ether (100 mL × 3), the combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. The product was purified by flash column chromatography to give a white solid. Yield: 86%; ^{1}HNMR (400 MHz, $CDCl_3$) δ 0.88 (s, 3H), 0.99 (d, 3H, J = 6.3 Hz), 1.21 (s, 3H), 1.28 (d, 1H, J = 10.3 Hz), 1.67–1.69 (m, 1H), 1.94–2.13 (m, 4H), 2.38–2.42 (m, 2H), 11.69 (br, 1H); ^{13}CNMR (125 MHz, $CDCl_3$) δ 19.55, 20.65, 23.55, 26.74, 28.62, 32.79, 39.72, 40.04, 41.41, 46.95, 182.68; ESI-MS: calculated for $C_{11}H_{18}O_2$ ($M-H^+$): 181.25, found: 181.1.

1-((1R,2R,3R,5S)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)ethanone (10). **9** (2.2 g, 12.07 mmol) in anhydrous Et_2O (50.0 mL) was cooled down to 0 ℃, CH_3Li (1.6M, 16.6 mL) was added dropwise in 30 mins. The resulting mixture was stirred at the same temperature for two more hours and warmed to ambient temperature overnight. Saturated NH_4Cl aqueous solution was added. Then the solution was extracted with diethyl ether (50 mL× 3). The organic layers were combined and dried over anhydrous Na_2SO_4. The product was purified by flash column chromatography as a colorless liquid. Yield: 69%; ^{1}HNMR (400 MHz, $CDCl_3$) δ 0.74 (s, 3H), 0.83 (d,

3H, J = 6.4 Hz), 1.17 (s, 3H), 1.28 (d, 1H, J = 10.2 Hz), 1.62–1.65 (m, 1H), 1.69–1.75 (m, 1H), 1.93–1.97 (m, 1H), 2.06–2.10 (m, 1H), 2.11–2.19 (m, 4H), 2.38–2.52 (m, 2H); ^{13}CNMR (125 MHz, $CDCl_3$) δ 19.54, 20.87, 23.92, 26.66, 28.88, 29.25, 30.22, 39.61, 40.38, 46.73, 49.64, 210.67; ESI-MS: calculated for $C_{12}H_{20}O$ ($M+H^+$): 181.29, found: 181.1.

(E)-1-((1R, 2R, 3R, 5S)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)ethanone oxime (11). A mixture of Hydroxylamine hydrochloride (2.9 g, 41.6 mmol) and Pyridine (20 mL) 80 ℃ was stirred until homogeneous. Then, **10** (1.5g, 8.32 mmol) was added. The reaction mixture was stirred and refluxed for 2 h. Reaction was work-up by pouring in ice water. Then filtrate and yield the product as a white powder. Yield: 86.4%; ^{1}HNMR (400 MHz, $CDCl_3$) δ 0.86 (s, 3H), 0.87 (s, 3H), 1.21 (s, 3H), 1.43 (d, 1H, J = 10 Hz), 1.67–1.75 (m, 2H), 1.93–2.00 (m, 5H), 2.04–2.09 (m, 1H), 2.26–2.29 (m, 2H), 8.72 (br, 1H); ^{13}CNMR (125 MHz, $CDCl_3$) δ 12.42, 19.78, 23.17, 26.96, 29.44, 31.00, 39.94, 40.62, 42.88, 47.22, 160.18; ESI-MS: calculated for $C_{12}H_{21}NO$ ($M+H^+$): 196.31, found: 196.2.

(S)-1-((1R,2R,3R,5S)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)ethanamine (12.HCl). To a solution of $LiAlH_4$ (1g) and 15 mL THF, **11** was added dropwise. The reaction mixture was stirred for 12h at 70 ℃. Reaction was work-up by adding the H_2O and extracted by ethylacetate (3 x 20 mL), washed two times by brine. Combined extract dried by Na_2SO_4. The organics were evaporated to dryness and treated with saturated HCl/CH_3OH (20 mL) then evaporated to dryness, and the insoluble material was washed with diethyl ether (3 x 20 mL) to afford the corresponding hydrochloride

as a white powder. Yield: 69%; mp 219-221 °C (dec.); ^{1}HNMR (400 MHz, DMSO-d_6) δ 0.73 (s, 3H), 0.89 (d, 3H, J = 6.4 Hz), 1.16 (s, 3H), 1.21–1.32 (m, 4H), 1.52–1.65 (m, 3H), 1.82–1.99 (m, 3H), 2.00–2.04 (m, 1H), 3.22–3.26 (m, 1H), 8.04 (br, 3H); ^{13}CNMR (125 MHz, DMSO-d_6) δ 17.92, 20.01, 20.68, 23.31, 26.64, 27.40, 31.36, 38.49, 38.92, 47.74, 50.76; ESI-MS: calculated for $C_{12}H_{23}N$ ($M+H^+$): 182.32, found: 182.1, HRMS found: 182.19046.

(1S,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptane-2-carbonitrile (13). The synthesis of **13** was similar with **7**. The reaction temperature was 45 ℃. Yield: 75%; ^{1}HNMR (400 MHz, $CDCl_3$) δ 0.84 (s, 3H), 0.91 (s, 3H), 0.98 (s, 3H), 1.27–1.33 (m, 1H), 1.44–1.51 (m, 1H), 1.53–1.58 (m, 1H), 1.75–1.83 (m, 2H), 1.86–1.93 (m, 1H), 2.15–2.23 (m, 1H), 2.63–2.68 (m, 1H); ^{13}CNMR (125 MHz, $CDCl_3$) δ 14.15, 18.32, 19.25, 27.72, 31.15, 34.12, 36.00, 44.99, 47.84, 49.51, 122.82; ESI-MS: calculated for $C_{11}H_{17}N$ ($M+H^+$): 164.27, found: 164.1.

((1S,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)methanamine (14.HCl). **14** was synthesized according to the procedure described above for **8**. Yield: 57%; mp 295 °C (dec.); ^{1}HNMR (400 MHz, DMSO-d_6) δ 0.80 (s, 3H), 0.82 (s, 6H), 0.95 (d, 1H, J = 8 Hz), 1.06–1.13 (m, 1H), 1.27–1.37 (m, 2H), 1.60–1.69 (m, 2H), 1.91–1.95 (m, 2H), 2.65–2.68 (m, 1H), 2.84 (br, 1H), 8.05 (br, 3H); ^{13}CNMR (125 MHz, DMSO-d_6) δ 13.96, 18.28, 18.86, 27.73, 28.25, 34.32, 41.29, 41.53, 44.41, 47.16, 48.41; ESI-MS: calculated for $C_{11}H_{21}N$ ($M+H^+$): 168.30, found: 168.1, HRMS found: 168.17480.

(1S,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptane-2-carboxylic acid (15). 15 was synthesized according to the procedure described above for **9**. Yield: 66%; ^{1}HNMR

(400 MHz, $CDCl_3$) δ 0.89 (s, 3H), 0.90 (s, 3H), 1.04 (s, 3H), 1.25–1.32 (m, 1H), 1.40–1.52 (m, 2H), 1.66–1.76 (m, 3H), 1.87–1.95 (m, 1H), 2.67–2.72 (m, 1H), 11.78 (br, 1H); ^{13}CNMR (125 MHz, $CDCl_3$) δ 14.87, 18.81, 19.15, 27.71, 30.49, 31.16, 45.00, 49.74, 49.97, 182.02; ESI-MS: calculated for $C_{11}H_{18}O_2$ ($M\text{-}H^+$): 181.25, found: 181.0.

1-((1S,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)ethanone (16). 16 was synthesized according to the procedure described above for **10**. Yield: 82.7%; ^{1}HNMR (400 MHz, $CDCl_3$) δ 0.74 (d, 1H, J = 7.6 Hz), 0.82 (s, 3H), 0.87 (s, 3H), 1.01 (s, 3H) , 1.16–1.32 (m, 3H), 1.60–1.76 (m, 3H), 2.09 (s, 3H), 2.78–2.82 (m, 1H); ^{13}CNMR (125 MHz, $CDCl_3$) δ 15.78, 18.74, 18.97, 27.68, 29.59, 30.53, 31.72, 44.95, 49.38, 50.38, 58.04, 211.16; ESI-MS: calculated for $C_{12}H_{20}O$ ($M+H^+$): 181.29, found: 181.2.

(E)-1-((1S,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)ethanone oxime (17). 17 was synthesized according to the procedure described above for **11**. Yield: 66.7%; ^{1}HNMR (400 MHz, $CDCl_3$) δ 0.88 (s, 3H), 0.91 (s, 3H), 0.92 (s, 3H), 1.17–1.34 (m, 3H), 1.50–1.60 (m, 2H), 1.64–1.69 (m, 1H), 1.70–1.75 (m, 1H), 2.59 (s, 3H), 2.60–2.64 (m, 1H), 9.37 (br, 1H); ^{13}CNMR (125 MHz, $CDCl_3$) δ 15.52, 16.13, 18.64, 19.49, 28.18, 29.38, 31.04, 45.07, 49.58, 49.63, 50.57, 159.76; ESI-MS: calculated for $C_{12}H_{21}NO$ ($M+H^+$): 196.31, found: 196.1.

(R)-1-((1S,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)ethanamine (18.HCl). 18 was synthesized according to the procedure described above for **12**. Yield: 10%; mp 321 °C (dec.); ^{1}HNMR (400 MHz, DMSO-d_6) δ 0.77-0.79 (m, 1H), 0.81 (s, 3H), 0.83 (s, 3H), 0.91 (s, 3H), 1.05–1.12 (m, 1H), 1.22 (d, 3H, J = 6.3 Hz), 1.28–1.35 (m, 1H), 1.53–1.69 (m, 3H), 1.77–1.82 (m, 1H), 1.90–1.97 (m, 1H), 7.86

(br, 3H); ^{13}CNMR (125 MHz, DMSO-d_6) δ 15.08, 18.19, 18.97, 19.14, 27.98, 28.00, 34.03, 43.49, 46.98, 47.35, 48.95, 49.72; ESI-MS: calculated for $C_{12}H_{23}N$ ($M+H^+$): 182.32, found: 182.2, HRMS found: 182.19023.

(1R,4S,Z)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-one oxime (19). 19 was synthesized according to the procedure described above for **11**. Yield: 82%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.13 (s, 3H), 1.20 (s, 3H), 1.22 (s, 3H), 1.28–1.31 (m, 2H), 1.49–1.54 (m, 2H), 1.61–1.64 (m, 1H), 1.69–1.76 (m, 2H), 9.79 (s, 1H); ^{13}CNMR (125 MHz, DMSO-d_6) δ 17.31, 22.08, 22.79, 24.90, 34.07, 42.62, 43.04, 47.97, 49.25, 169.03; ESI-MS: calculated for $C_{10}H_{17}NO$ ($M+H^+$): 168.26, found: 168.1.

(1R,2R,4S)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-amine (20.HCl). 20 was synthesized according to the procedure described above for **12**. Yield: 10.9%; mp 233-236 °C (dec.); ^{1}HNMR (400 MHz, DMSO-d_6) δ 1.03 (s, 3H), 1.21–1.37 (m, 8H), 1.66–1.93 (m, 5H), 2.59–2.62 (d, 1H, J = 12.1 Hz), 2.90–2.96 (m, 1H), 8.38 (s, 1H), 9.34 (s, 1H); ^{13}CNMR (125 MHz, DMSO-d_6) δ 22.23, 22.44, 24.42, 25.23, 32.41, 37.66, 38.00, 43.95, 50.06, 56.88; ESI-MS: calculated for $C_{10}H_{19}NO$ ($M+H^+$): 154.27, found: 154.1, HRMS found: 154.15926.

Compound **21** (CAS No.: 14370-45-7), **22** (CAS No.: 242-92-4) and **23** (CAS No.: 32511-34-5) were purchased from Sigma-Aldrich and used without further purification. The chemicals are all reagent grade with the purity of more than 97 %.

Docking Studies：

Molecular docking using GLIDE 5.8 software (Schrödinger, New York, NY, USA) was performed to explore the structural features of **18** with the M2 ion channel. The SSNMR structure of M2 was obtained from the RCSB Protein Data Bank (PDB code: 2kqt), and accounted for conformational changes in the transmembrane helices induced upon ligand binding in DMPC bilayers. Hydrogen atoms were added to the protein structure and refined by energy minimization using Protein Preparation Wizard (Schrödinger). A grid file was generated using the "Receptor Grid Generation" module; the whole channel lumen around Amt was considered the grid for docking. The small molecule Amt and **18** were built up in the Maestro interface and prepared by Ligprep using the OPLS_2005 force field. According to their physiological pH and activities at low pH, Amt and **18** were modeled in their protonated form. Ligands were docked in the M2 structure using standard precision (SP) and extra precision (XP) under default settings.

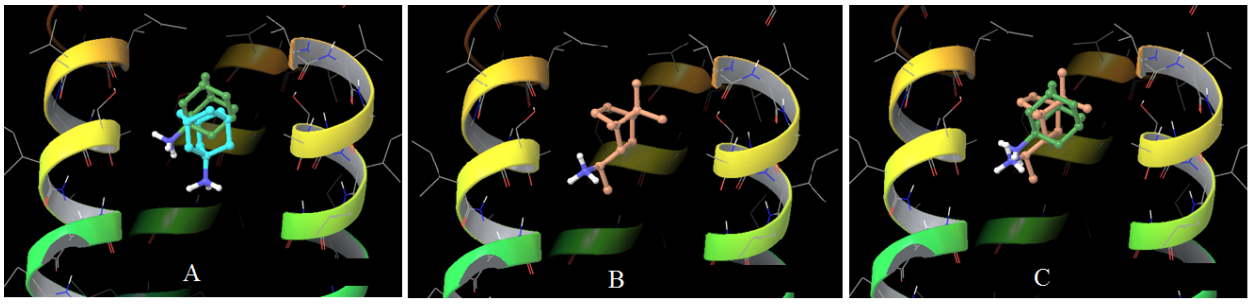
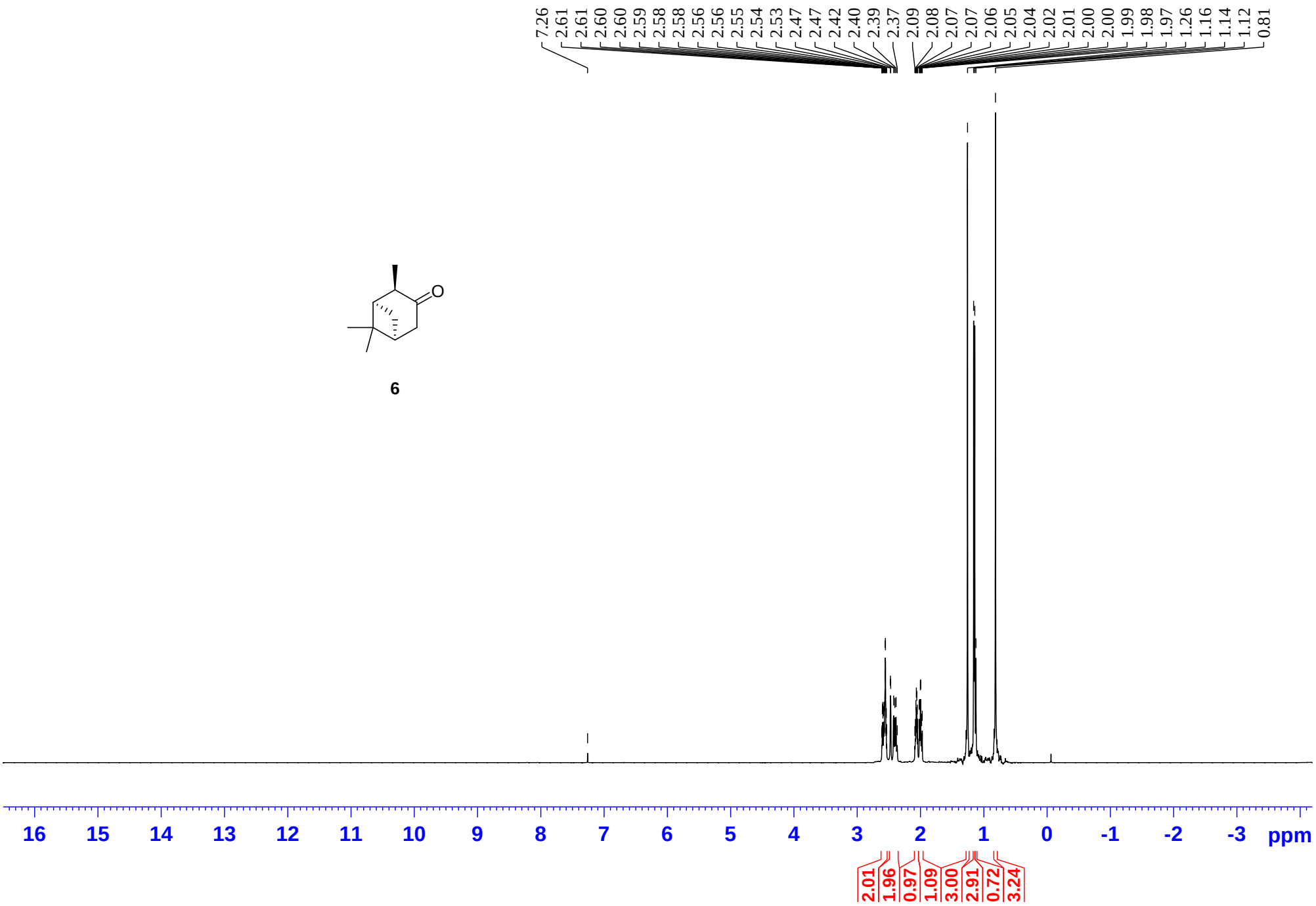


Figure S1. Docking conformation of amantadine and **18**. For the sake of clarity, one of the transmembrane helices is not shown. A: Overlap of molecular dynamic result with NMR results. B: Docking predict mode. C: Overlap of the MD mode of amantadine and predicted mode.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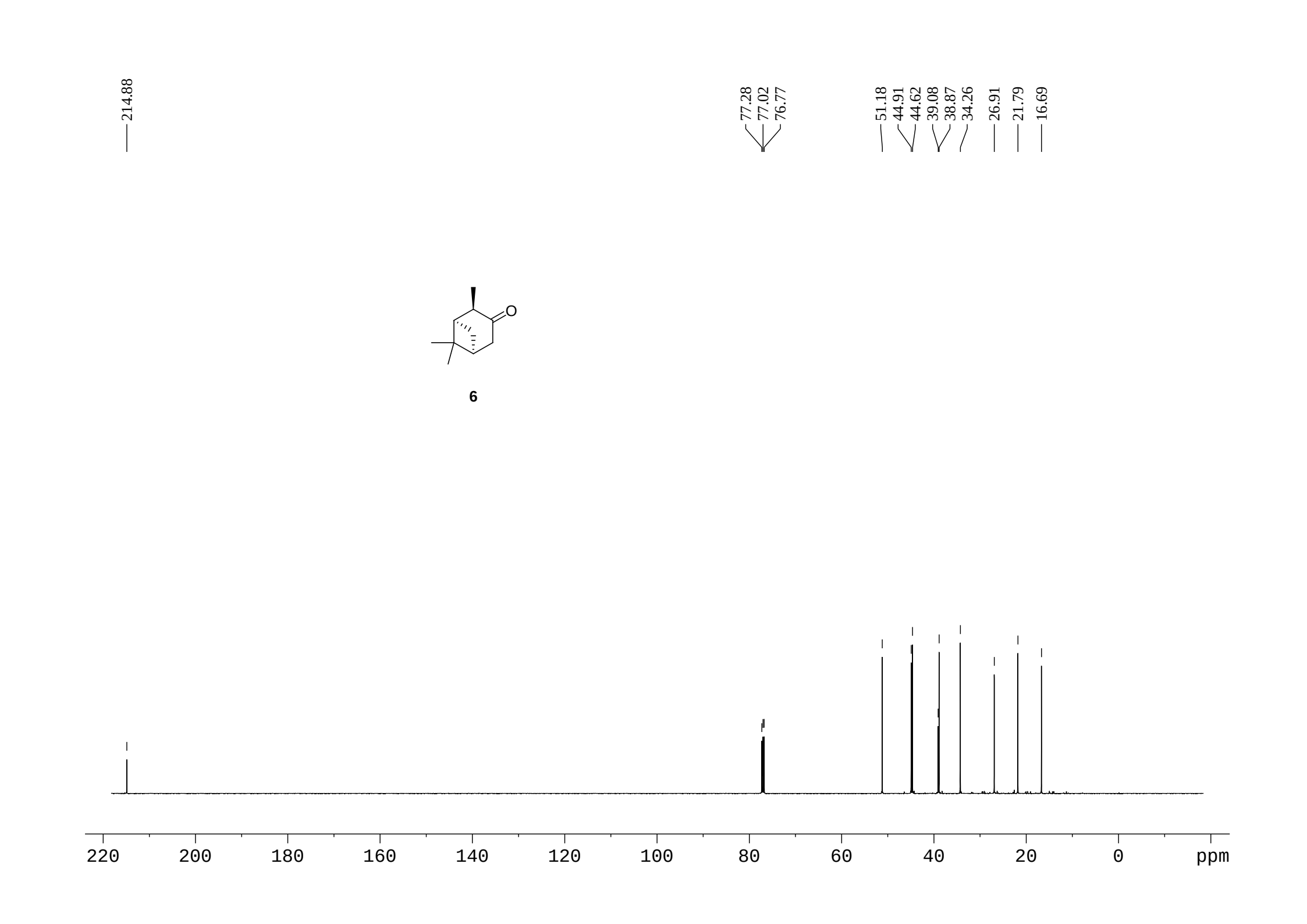
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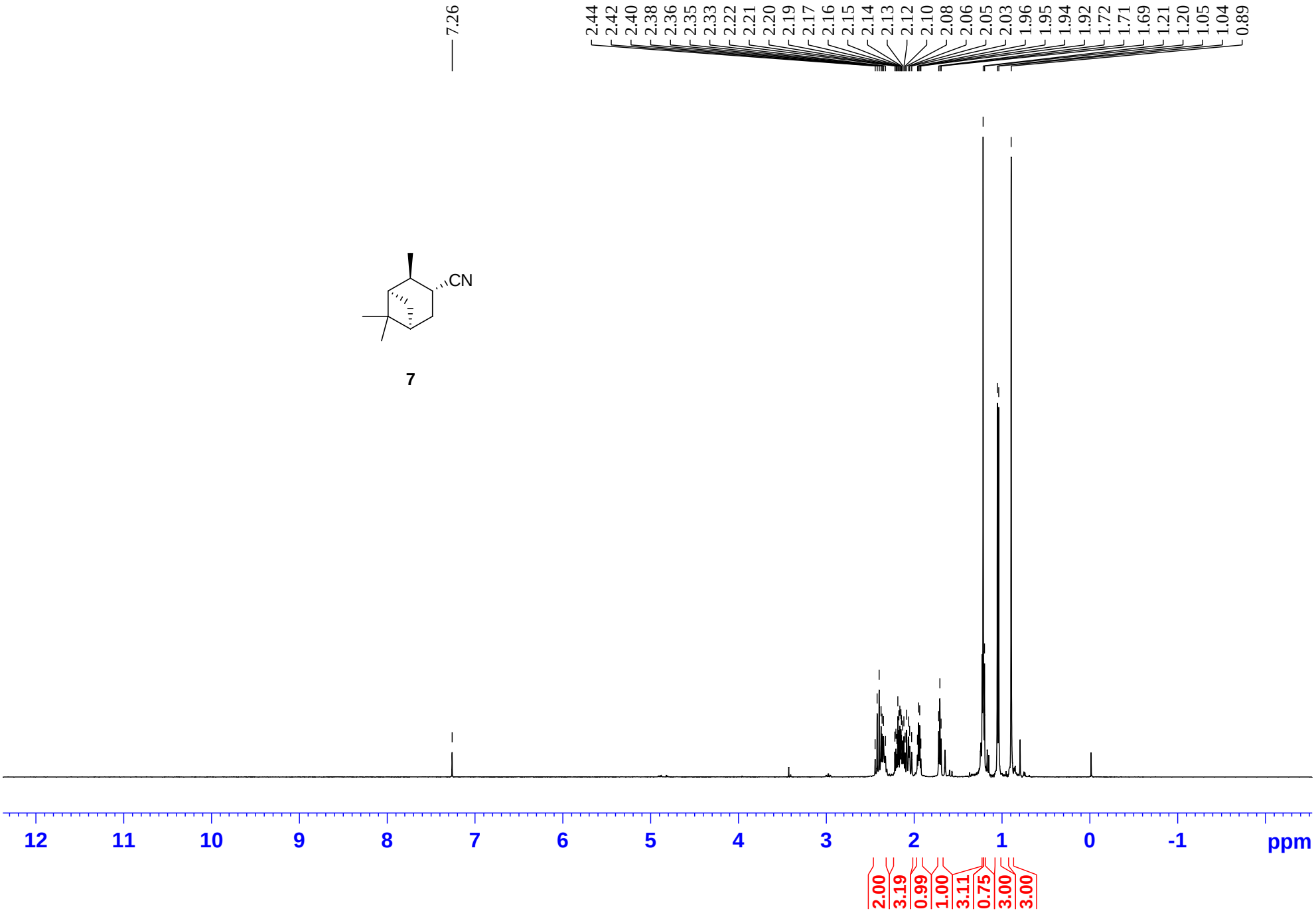
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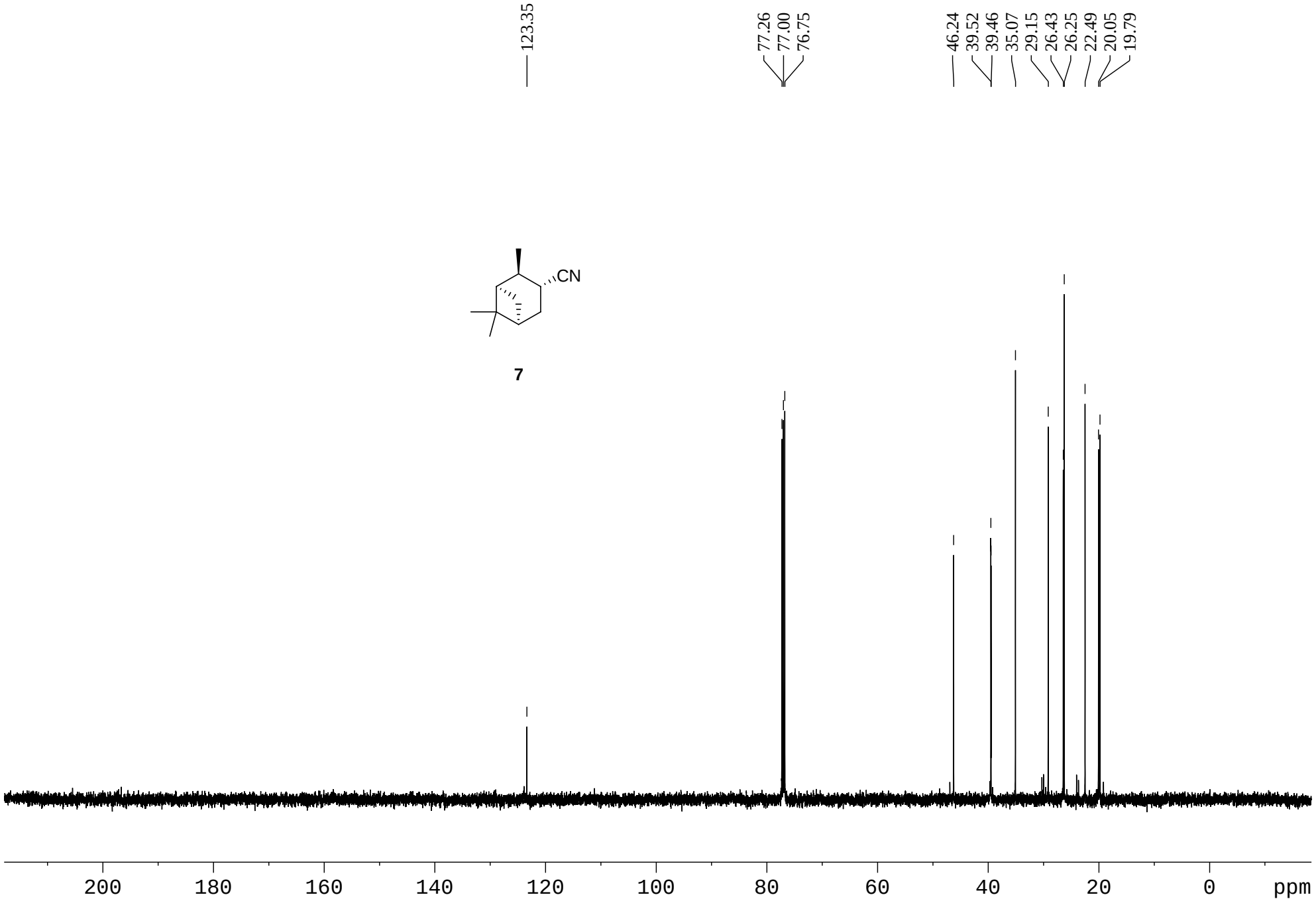
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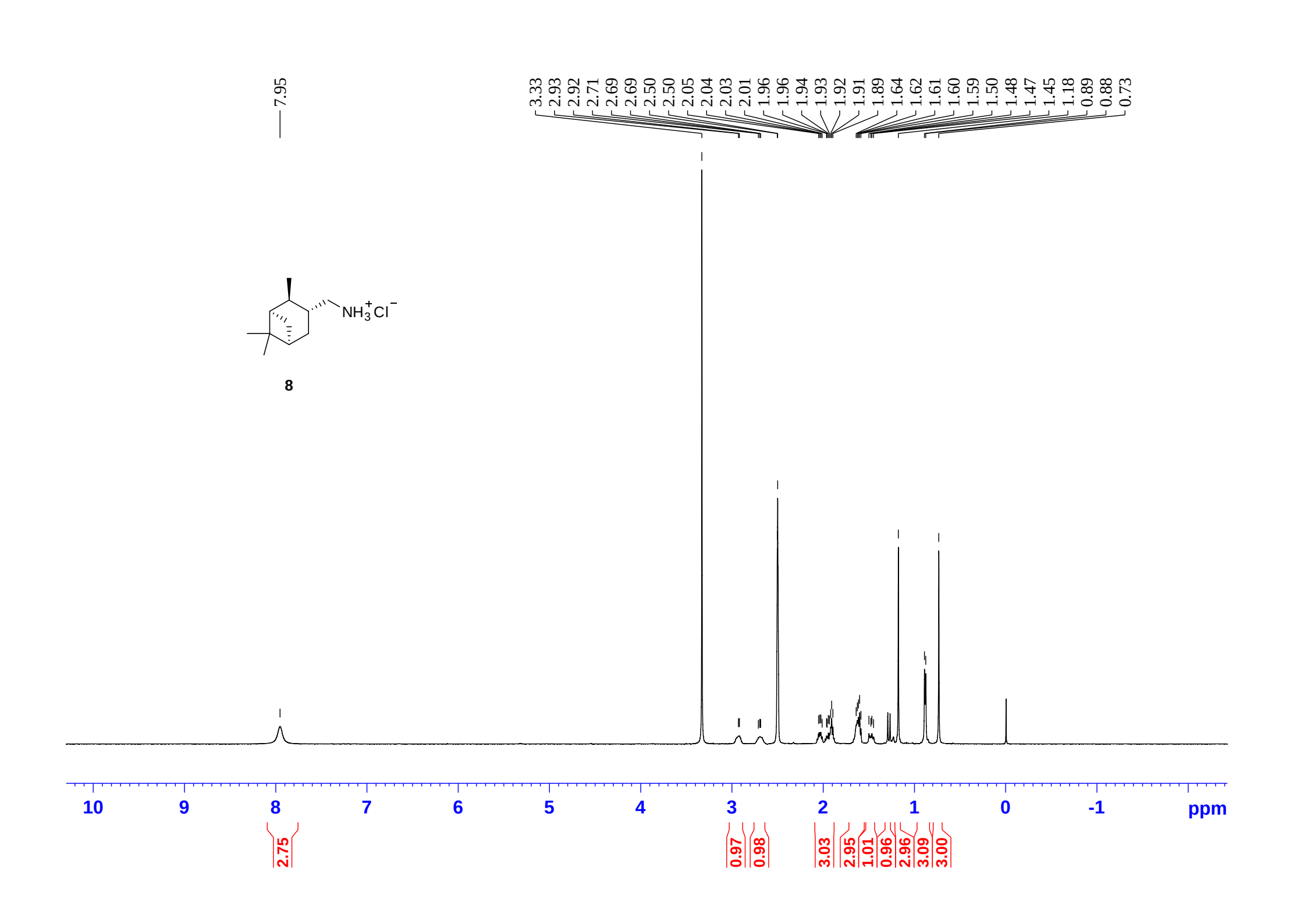
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1.61
1.60
1.59
1.50
1.48
1.47
1.45
1.18
0.89
0.88
0.73
NH3+Cl−
10
9
8
7
6
5
4
3
2
1
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ppm
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0.98
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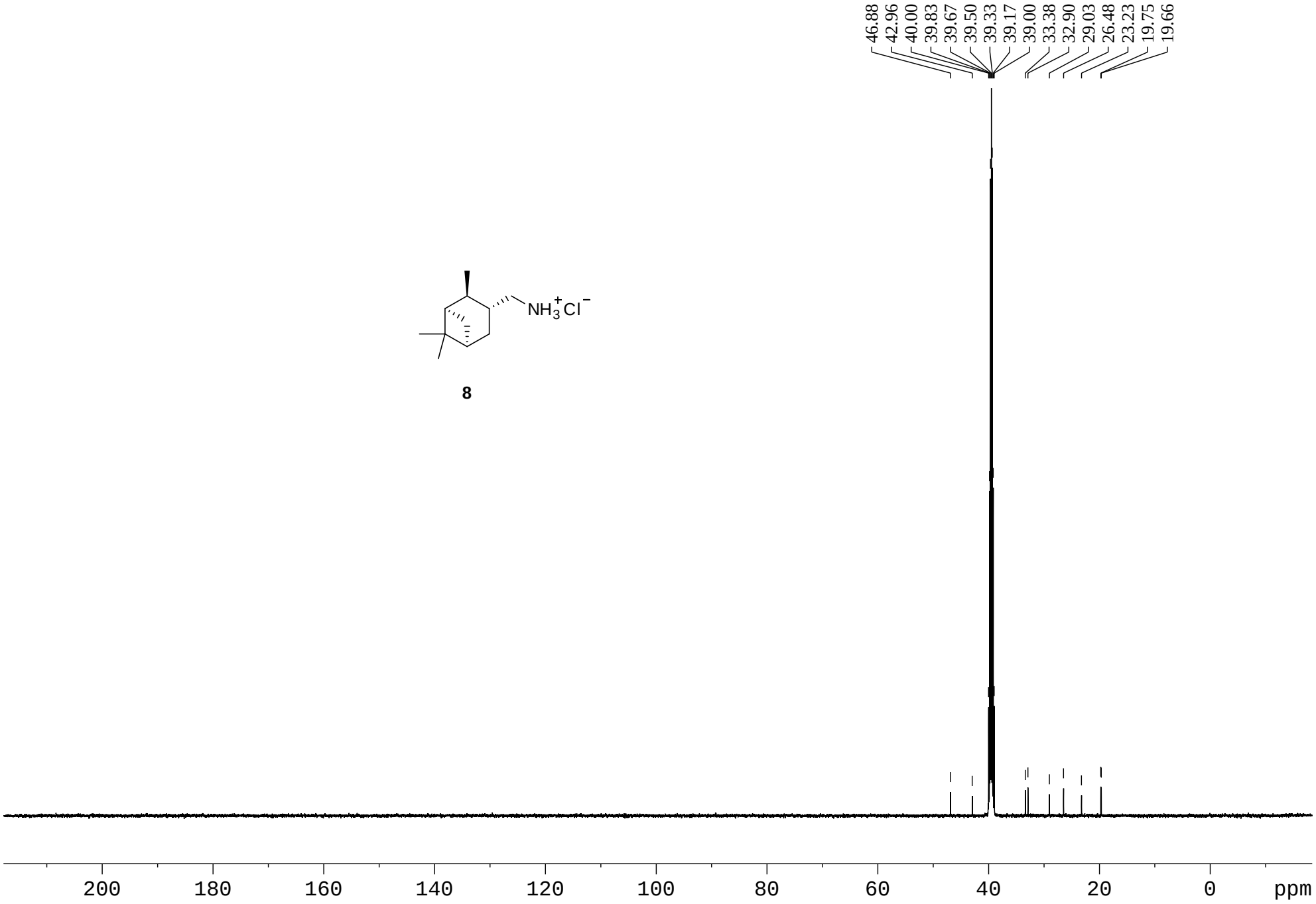
0.96
2.96
3.09
3.00

8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39.33
39.17
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33.38
32.90
29.03
26.48
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NH3+Cl−
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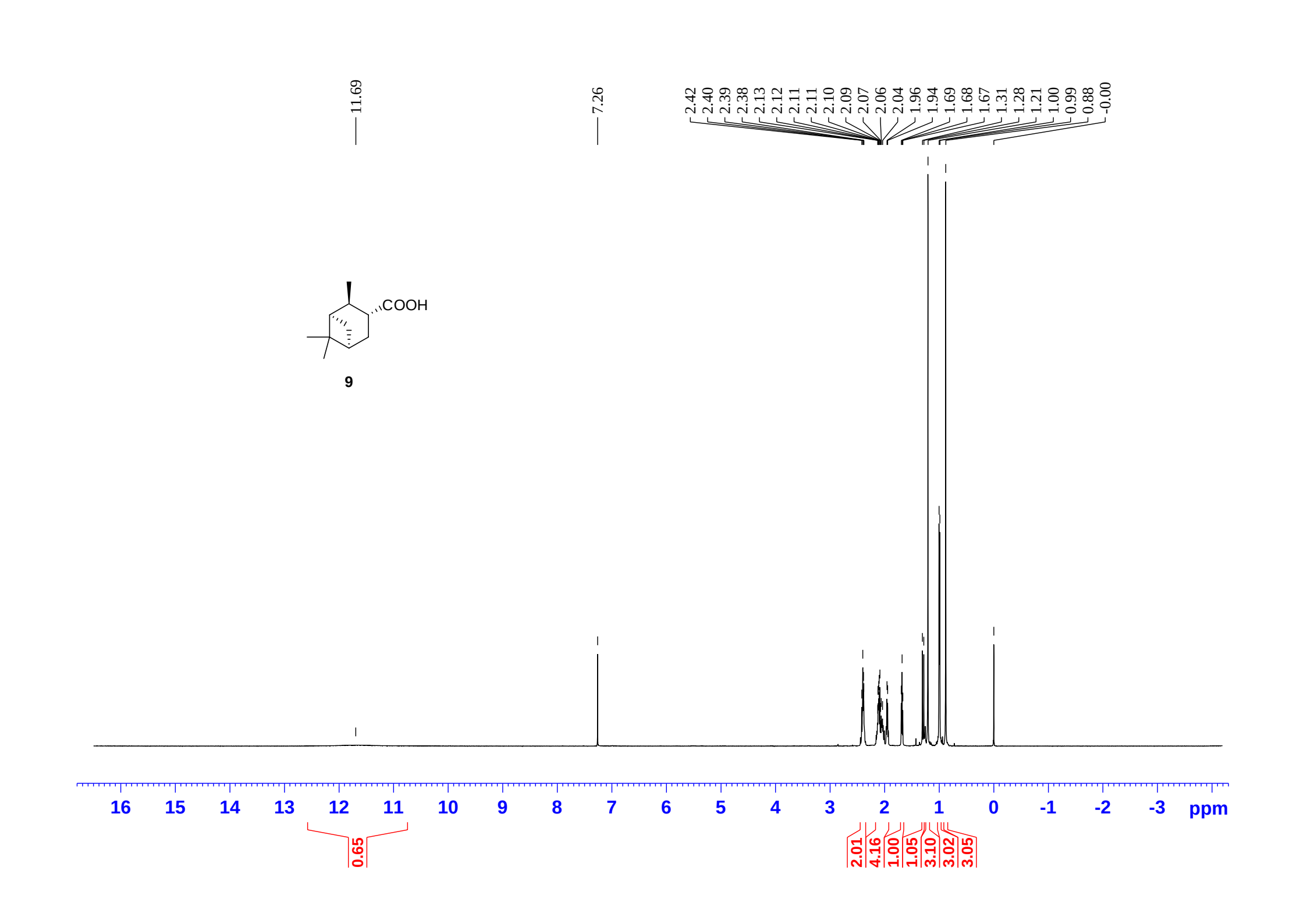
60
40
20
0
ppm

8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2.10
2.09
2.07
2.06
2.04
1.96
1.94
1.69
1.68
1.67
1.31
1.28
1.21
1.00
0.99
0.88
-0.00
COOH
9
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
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-3
ppm
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1.00
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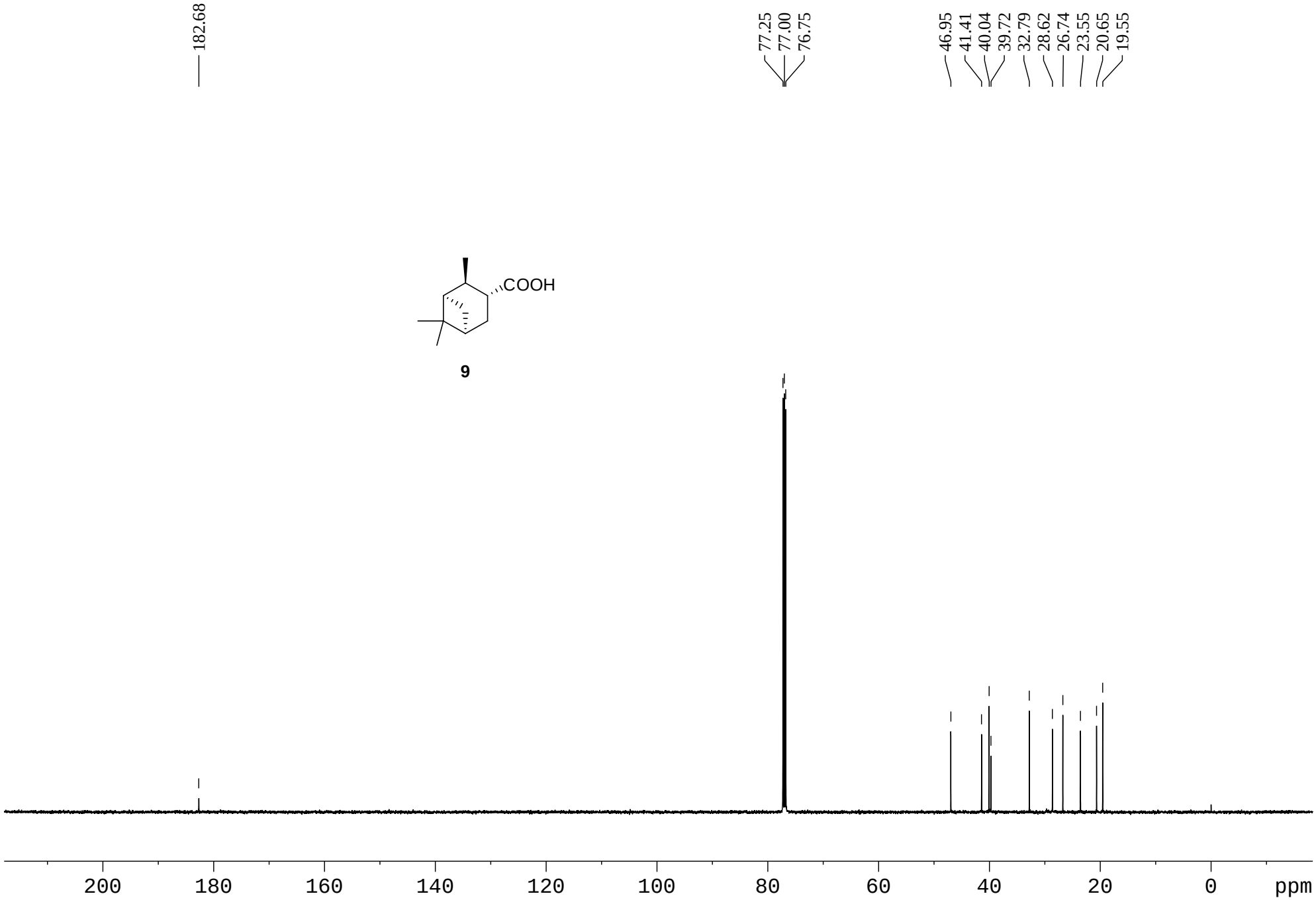
3.02
3.05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26.74
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COOH
9
200
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120
100
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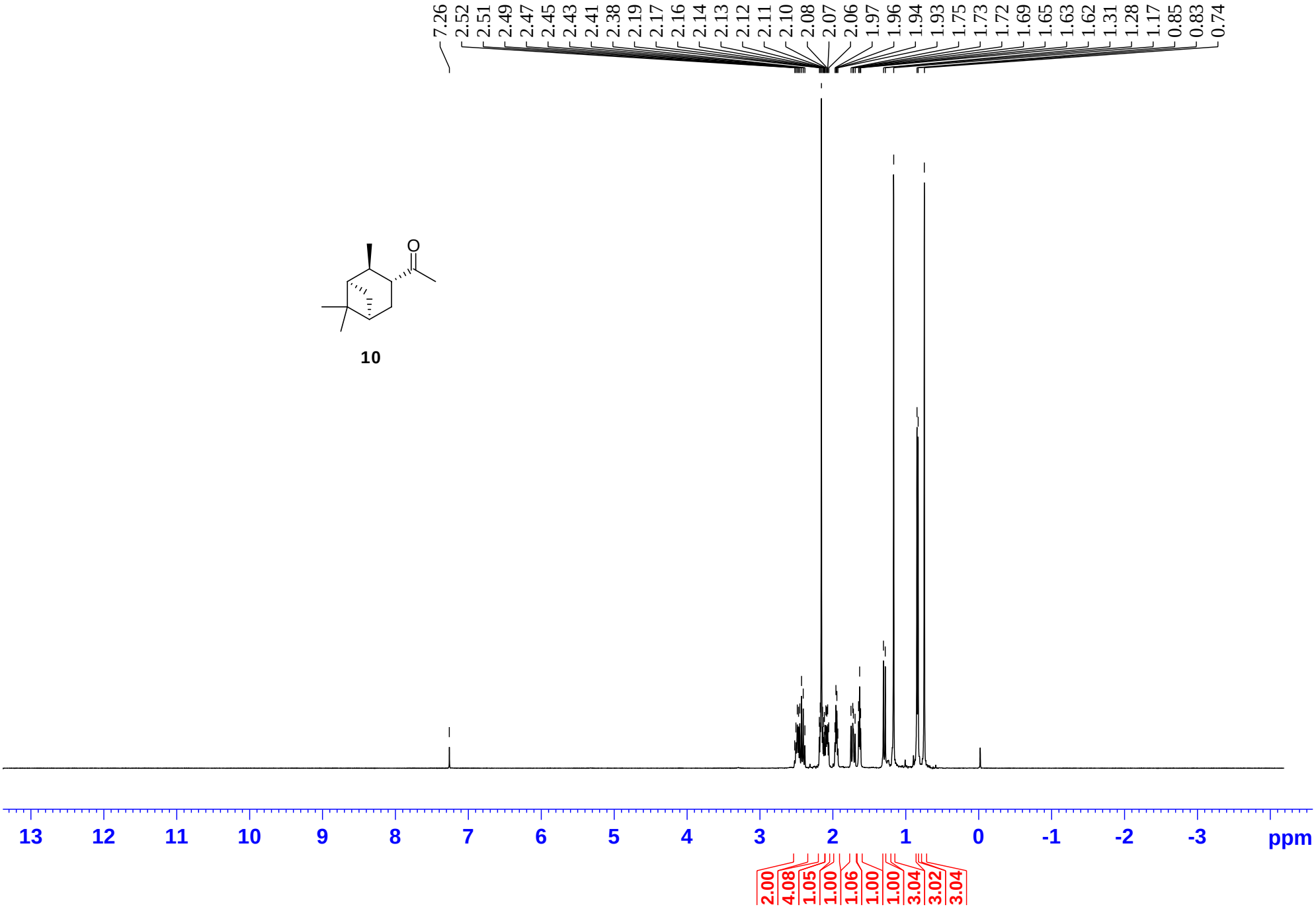
40
20
0
ppm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2.41
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2.19
2.17
2.16
2.14
2.13
2.12
2.11
2.10
2.08
2.07
2.06
1.97
1.96
1.94
1.93
1.75
1.73
1.72
1.69
1.65
1.63
1.62
1.31
1.28
1.17
0.85
0.83
0.74
O
10
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
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1.00
1.00
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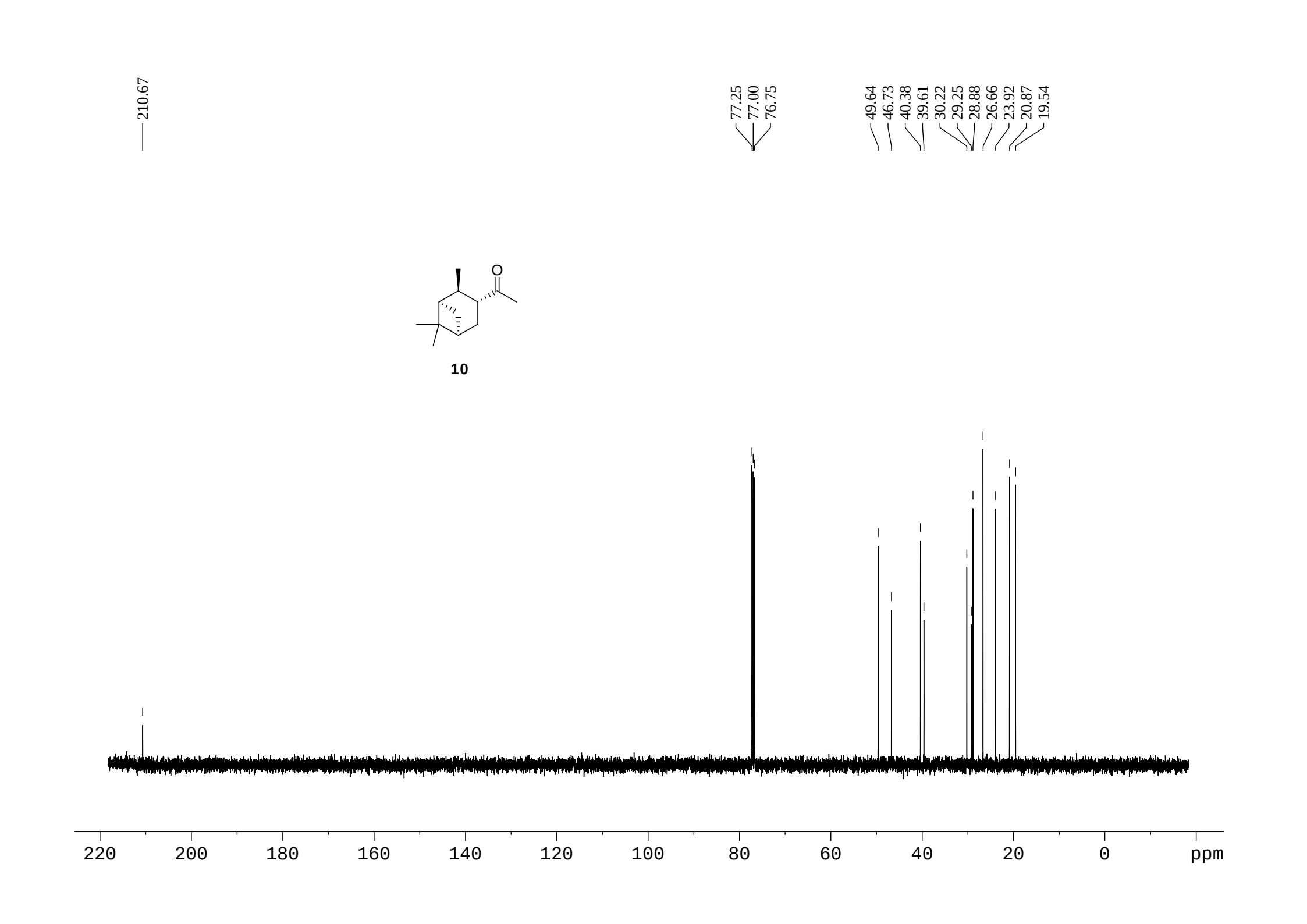
3.02
3.04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39.61
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28.88
26.66
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O
220
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180
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100
80
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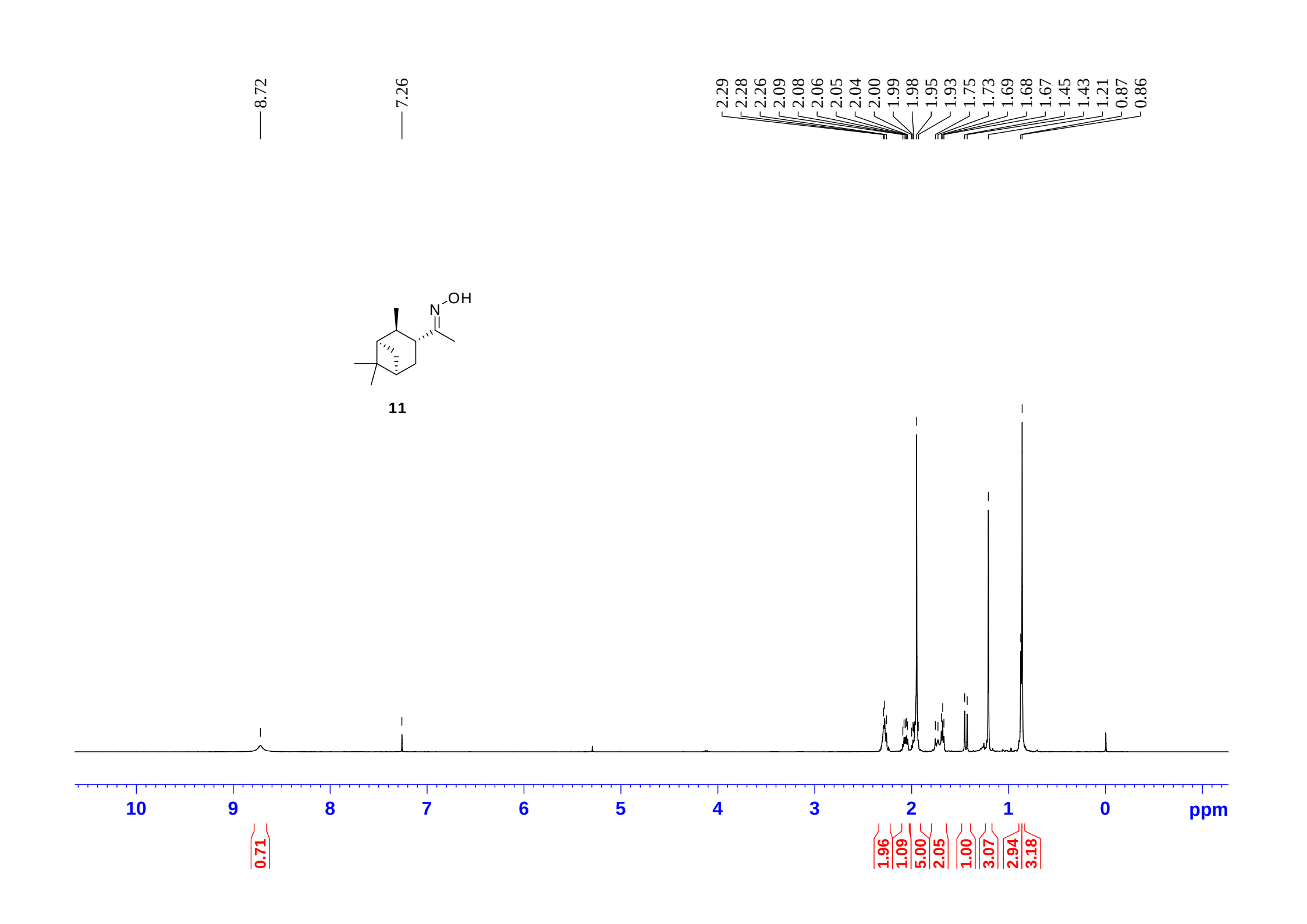
40
20
0
ppm

10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2.29
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2.26
2.09
2.08
2.06
2.05
2.04
2.00
1.99
1.98
1.95
1.93
1.75
1.73
1.69
1.68
1.67
1.45
1.43
1.21
0.87
0.86
N
OH
11
10
9
8
7
6
5
4
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ppm
0.71
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1.09
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2.05
1.00
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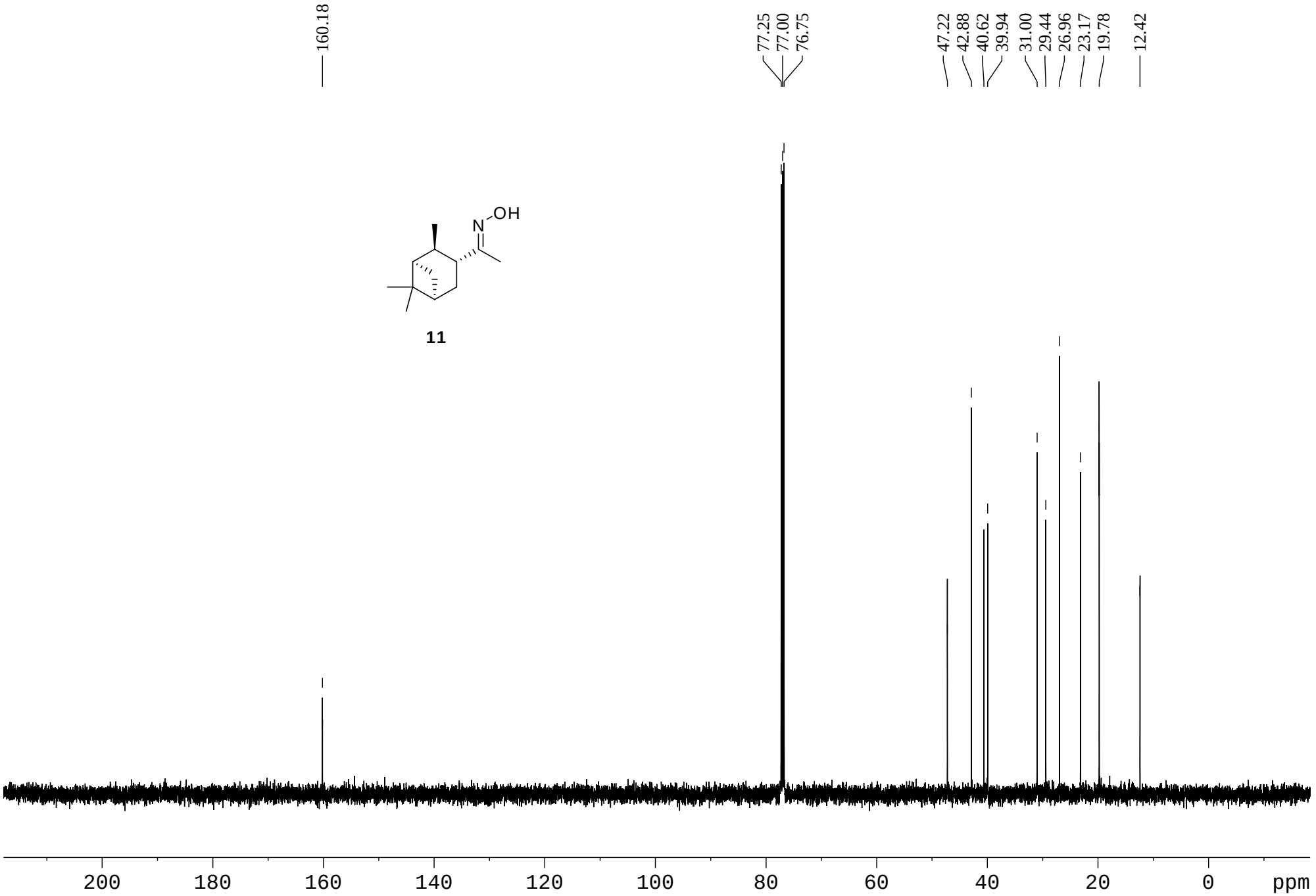
2.94
3.18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40.62
39.94
31.00
29.44
26.96
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19.78
12.42
N
OH
11
200
180
160
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120
100
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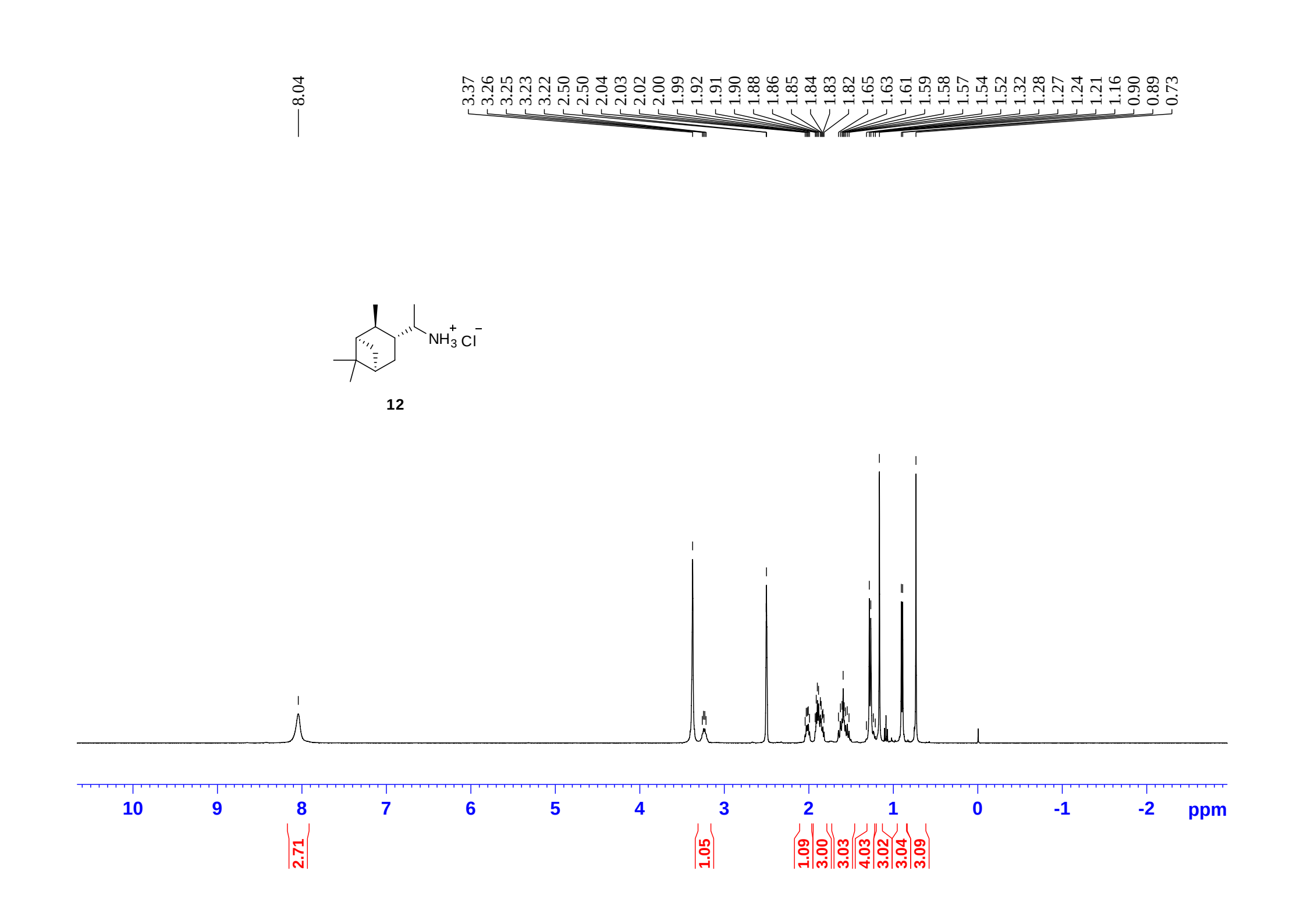
60
40
20
0
ppm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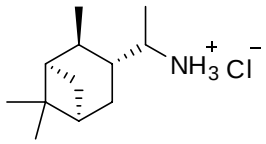
3.37
3.26
3.25
3.23
3.22
2.50
2.50
2.04
2.03
2.02
2.00
1.99
1.92
1.91
1.90
1.88
1.86
1.85
1.84
1.83
1.82
1.65
1.63
1.61
1.59
1.58
1.57
1.54
1.52
1.32
1.28
1.27
1.24
1.21
1.16
0.90
0.89
0.73
NH3 Cl
12
10
9
8
7
6
5
4
3
2
1
0
-1
-2
ppm
2.71
1.05
1.09
3.00
3.03
4.03
3.02
3.04
3.09


NH3 Cl

12

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39.67
39.50
39.33
39.17
39.00
38.92
38.49
31.36
27.40
26.64
23.31
20.68
20.01
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150
140
130
120
110
100
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70
60
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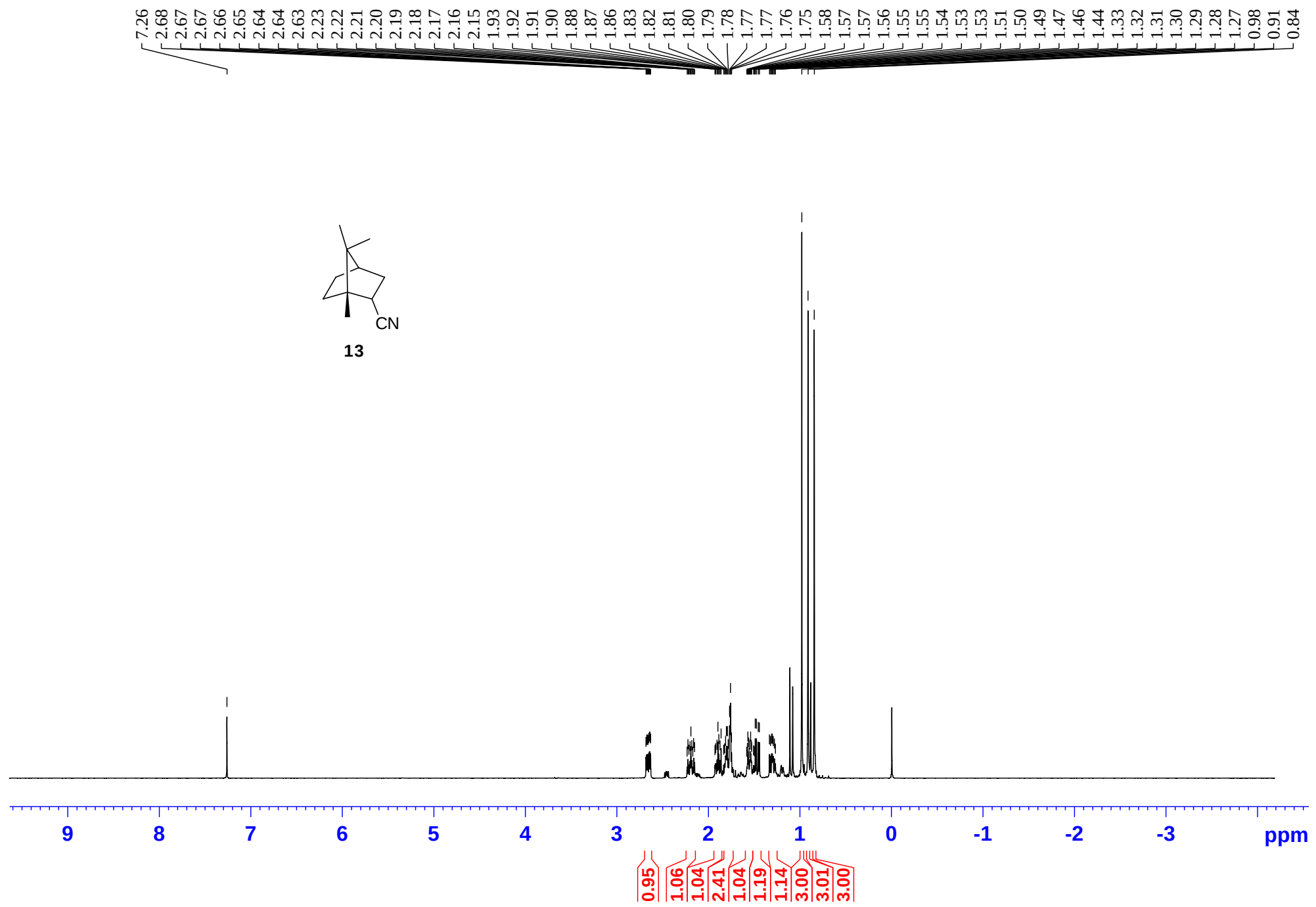
40
30
20
10
ppm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2.67
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2.65
2.64
2.64
2.63
2.23
2.22
2.21
2.20
2.19
2.18
2.17
2.16
2.15
1.93
1.92
1.91
1.90
1.88
1.87
1.86
1.83
1.82
1.81
1.80
1.79
1.78
1.77
1.77
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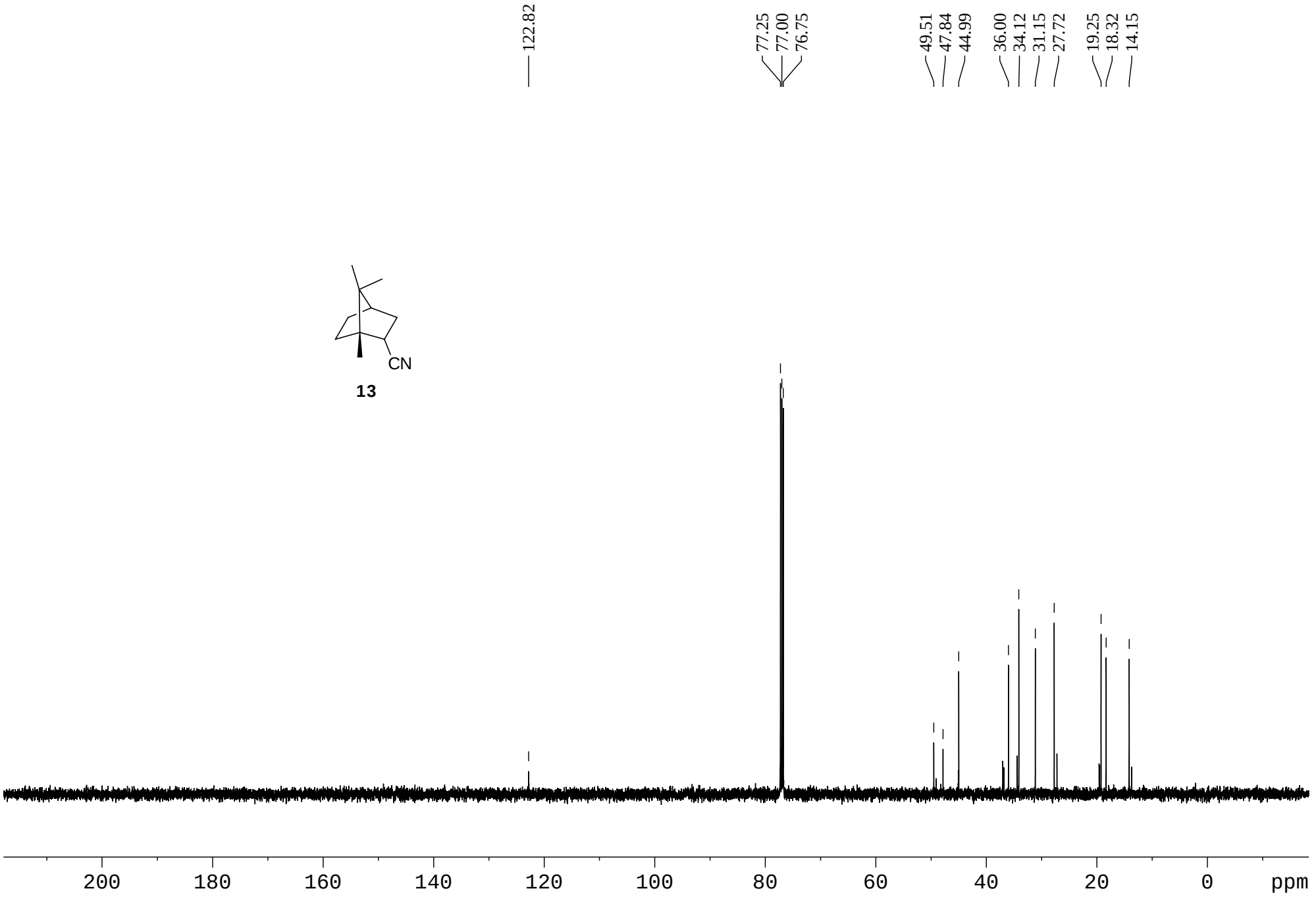
1.55
1.54
1.53
1.53
1.51
1.50
1.49
1.47
1.46
1.44
1.33
1.32
1.31
1.30
1.29
1.28
1.27
0.98
0.91
0.84
CN
13
9
8
7
6
5
4
3
2
1
0
-1
-2
-3
ppm
0.95
1.06
1.04
2.41
1.04
1.19
1.14
3.00
3.01
3.00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44.99
36.00
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31.15
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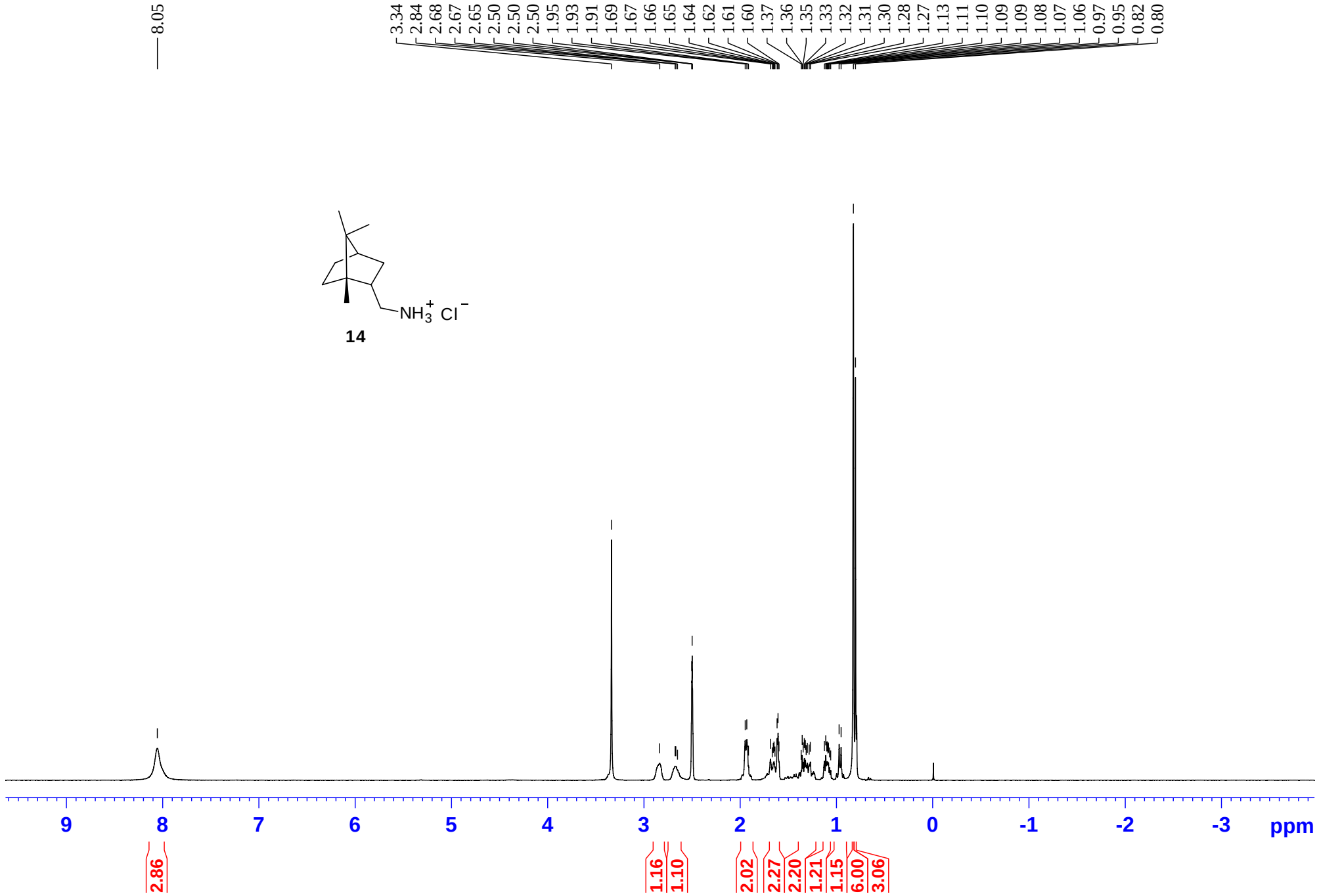
19.25
18.32
14.15
CN
13
200
180
160
140
120
100
80
60
40
20
0
ppm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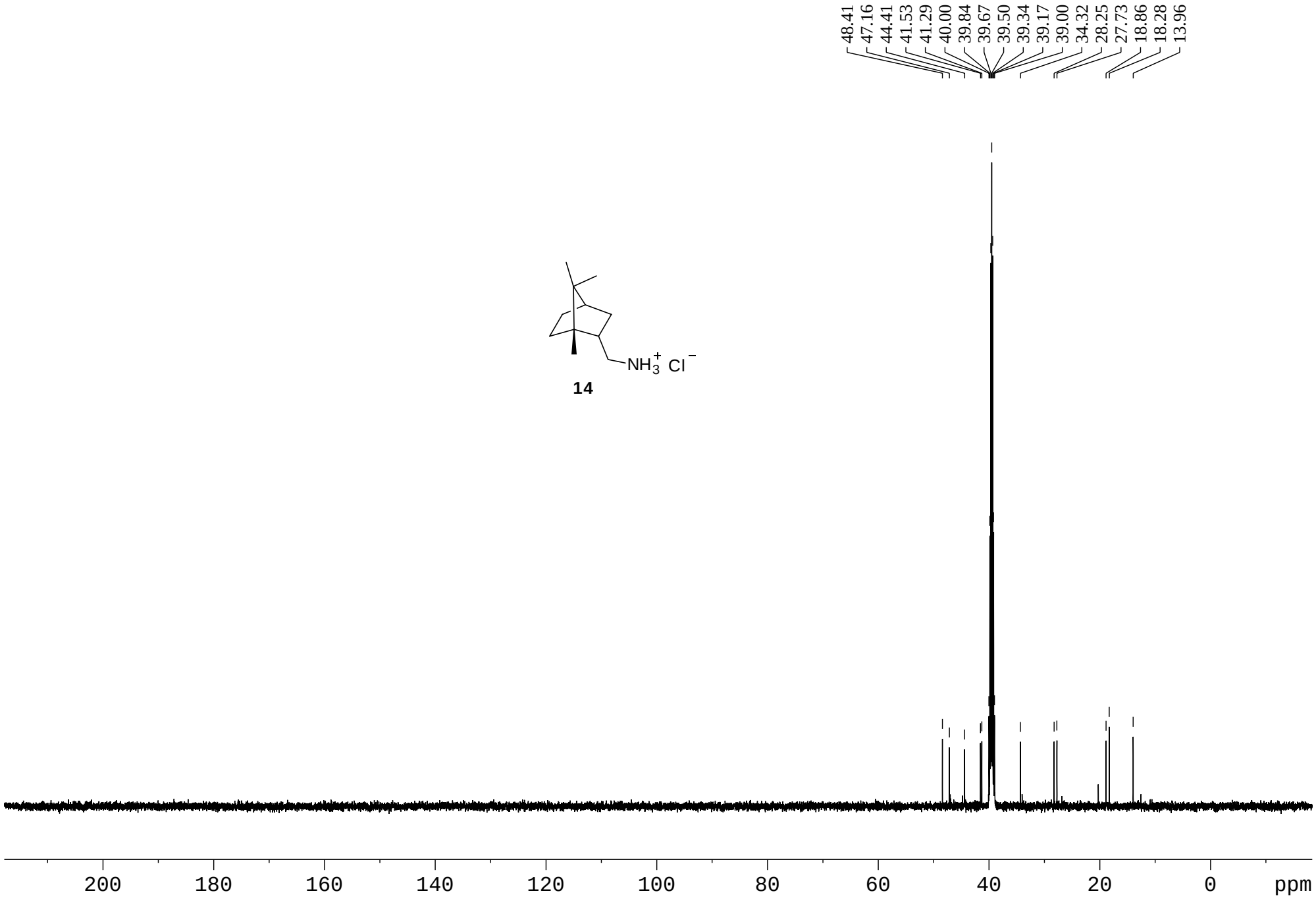
2.65
2.50
2.50
2.50
1.95
1.93
1.91
1.69
1.67
1.66
1.65
1.64
1.62
1.61
1.60
1.37
1.36
1.35
1.33
1.32
1.31
1.30
1.28
1.27
1.13
1.11
1.10
1.09
1.09
1.08
1.07
1.06
0.97
0.95
0.82
0.80
NH3+ Cl−
14
9
8
7
6
5
4
3
2
1
0
-1
-2
-3
ppm
2.86
1.16
1.10
2.02
2.27
2.20
1.21
1.15
6.00
3.06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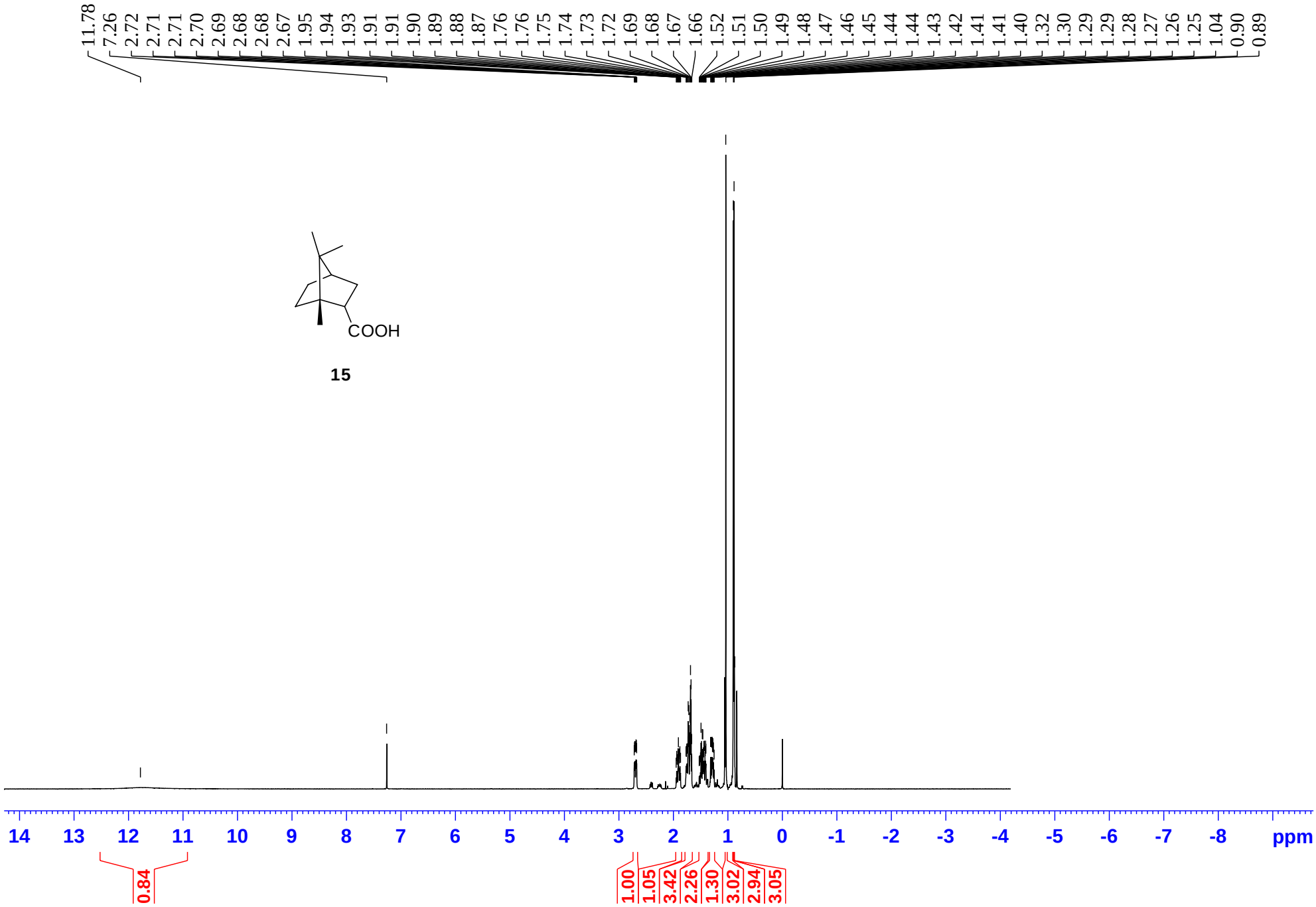
39.67
39.50
39.34
39.17
39.00
34.32
28.25
27.73
18.86
18.28
13.96
NH3+ Cl−
14
200
180
160
140
120
100
80
60
40
20
0
ppm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2.71
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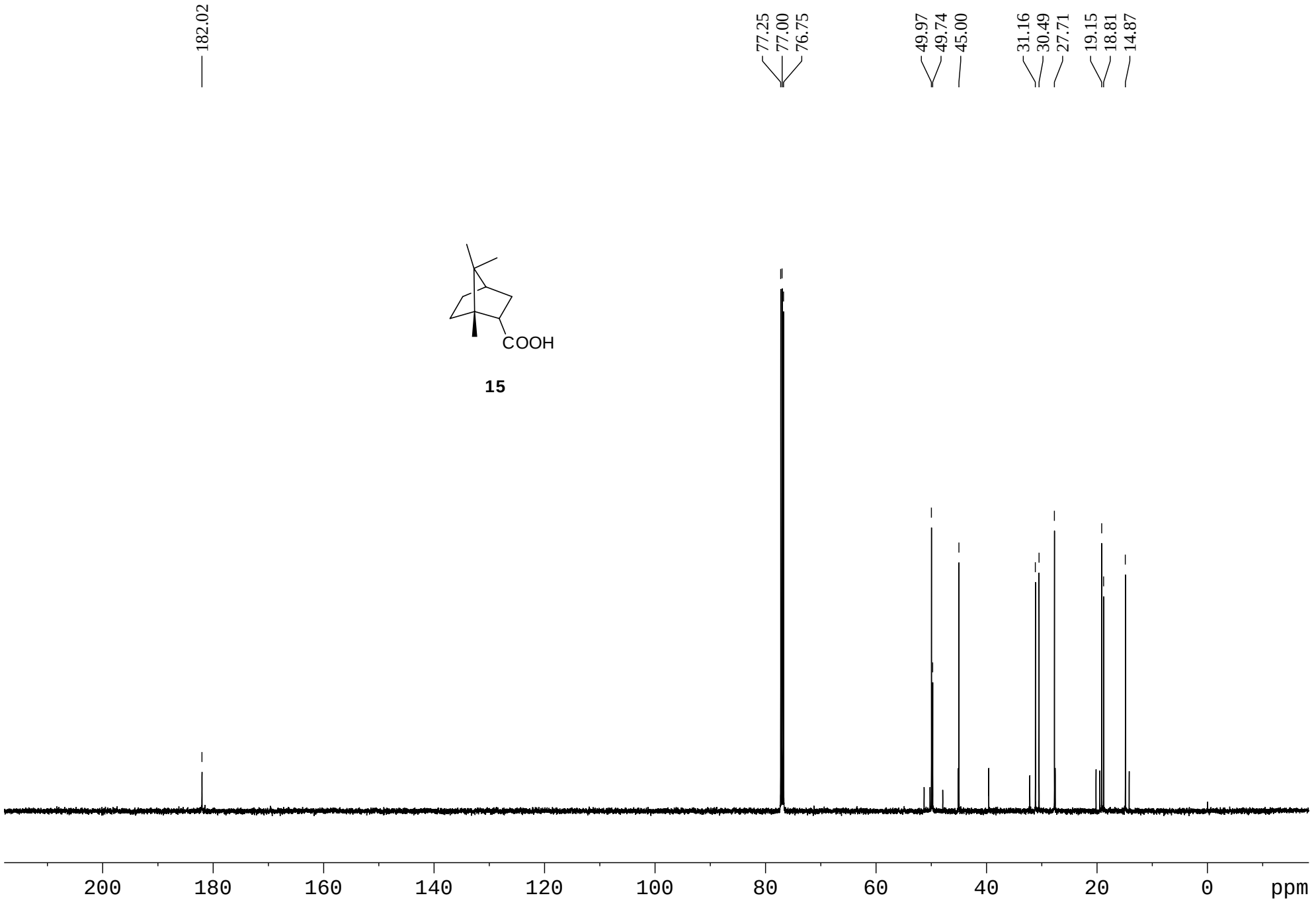
2.68
2.68
2.67
1.95
1.94
1.93
1.91
1.91
1.90
1.89
1.88
1.87
1.76
1.76
1.75
1.74
1.73
1.72
1.69
1.68
1.67
1.66
1.52
1.51
1.50
1.49
1.48
1.47
1.46
1.45
1.44
1.44
1.43
1.42
1.41
1.41
1.40
1.32
1.30
1.29
1.29
1.28
1.27
1.26
1.25
1.04
0.90
0.89
COOH
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
-5
-6
-7
-8
ppm
0.84
1.00
1.05
3.42
2.26
1.30
3.02
2.94
3.05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31.16
30.49
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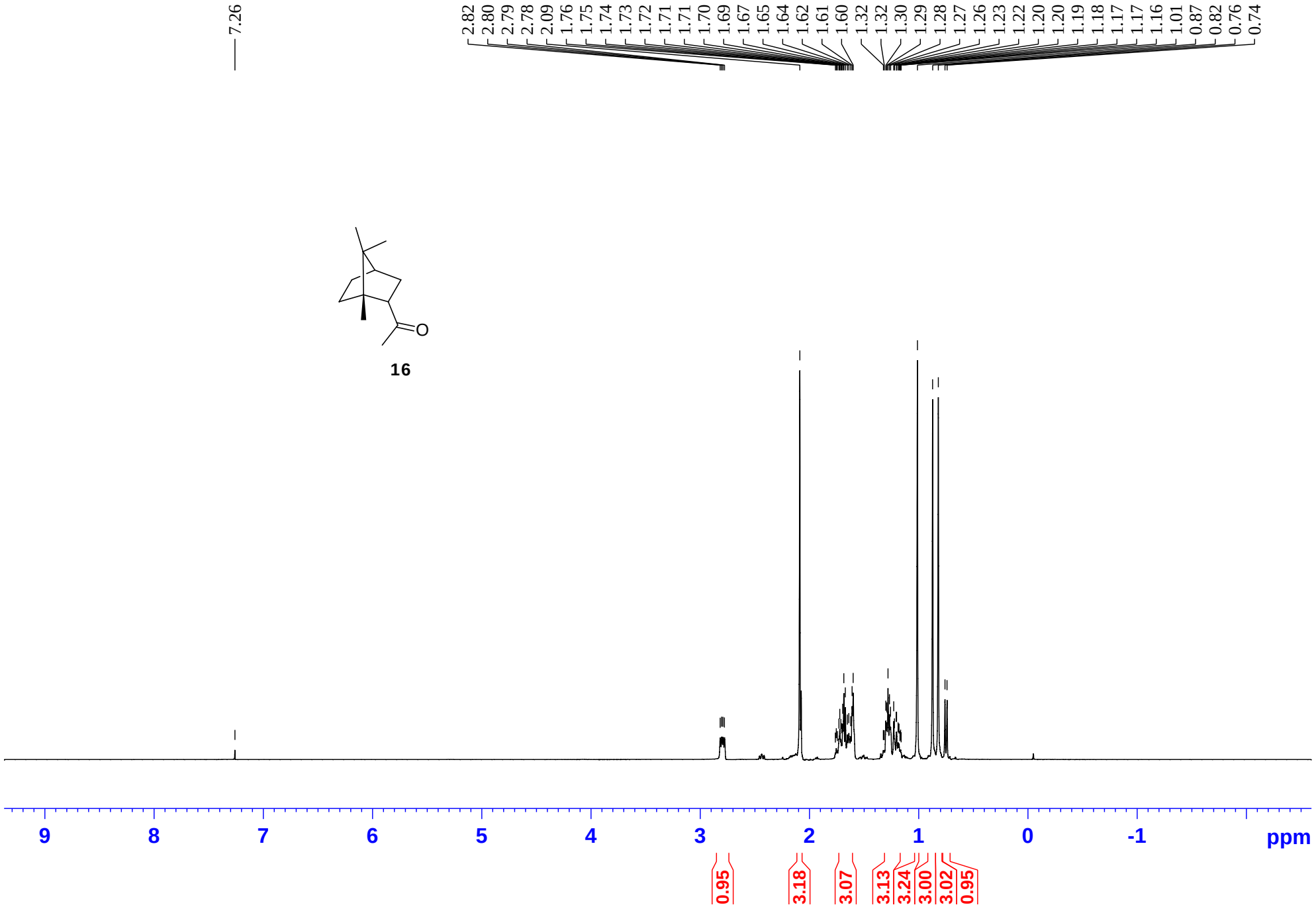
14.87
COOH
200
180
160
140
120
100
80
60
40
20
0
ppm

15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2.09
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1.75
1.74
1.73
1.72
1.71
1.71
1.70
1.69
1.67
1.65
1.64
1.62
1.61
1.60
1.32
1.32
1.30
1.29
1.28
1.27
1.26
1.23
1.22
1.20
1.20
1.19
1.18
1.17
1.17
1.16
1.01
0.87
0.82
0.76
0.74
O
16
9
8
7
6
5
4
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-1
ppm
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3.13
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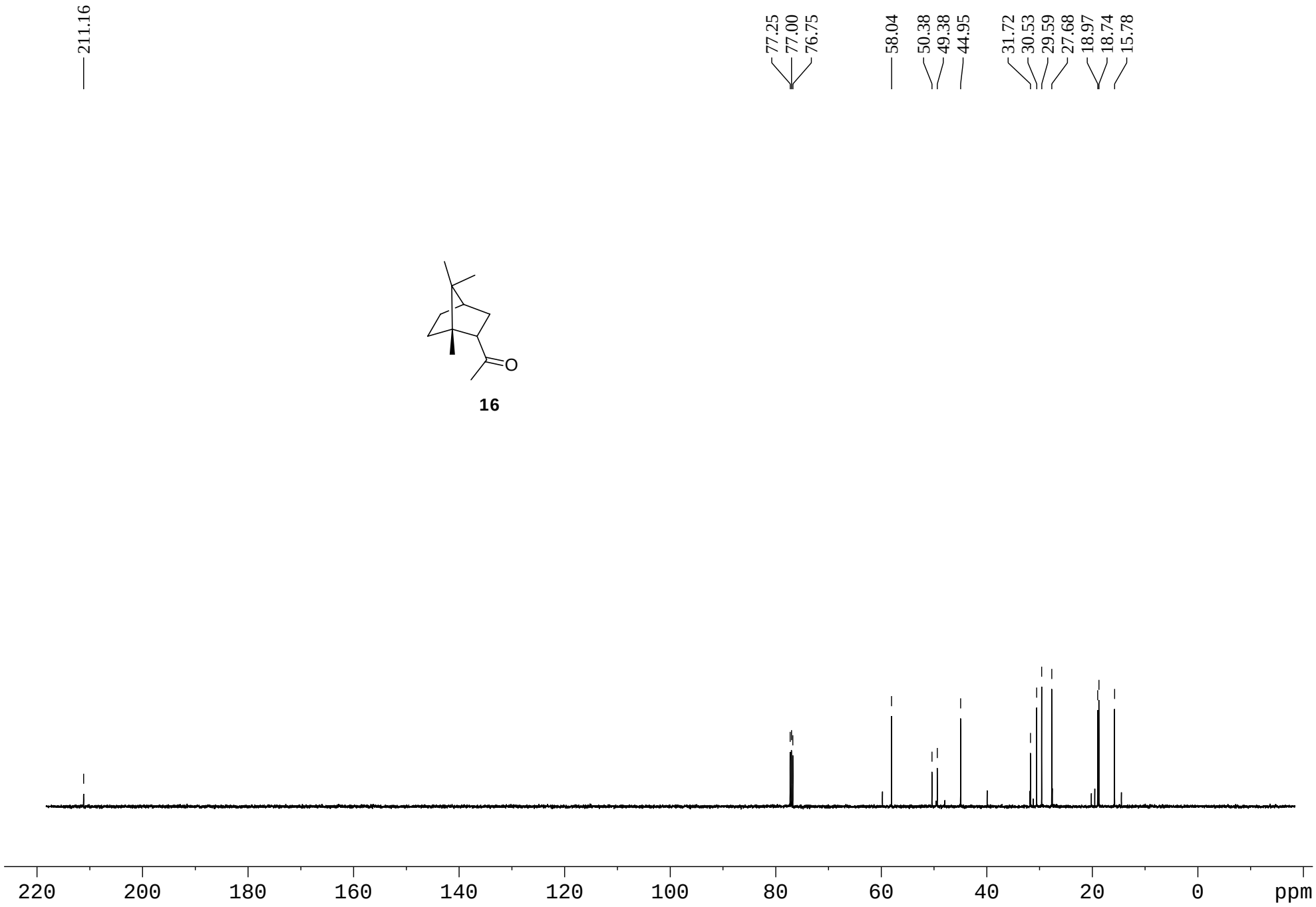
3.02
0.95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49.38
44.95
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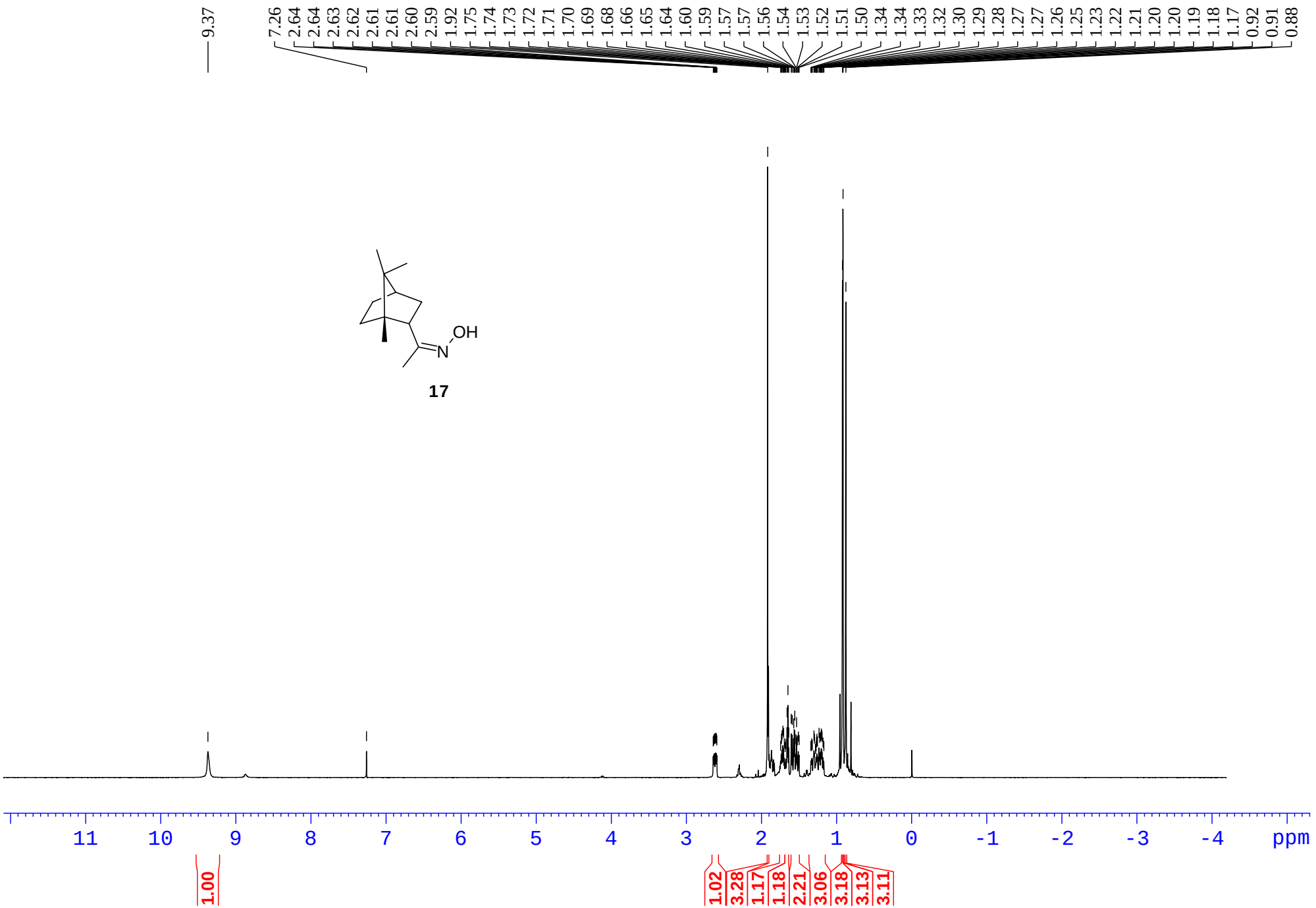
30.53
29.59
27.68
18.97
18.74
15.78
O
220
200
180
160
140
120
100
80
60
40
20
0
ppm

16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2.62
2.61
2.61
2.60
2.59
1.92
1.75
1.74
1.73
1.72
1.71
1.70
1.69
1.68
1.66
1.65
1.64
1.60
1.59
1.57
1.57
1.56
1.54
1.53
1.52
1.51
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1.33
1.32
1.30
1.29
1.28
1.27
1.27
1.26
1.25
1.23
1.22
1.21
1.20
1.20
1.19
1.18
1.17
0.92
0.91
0.88
OH
N
17
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
ppm
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1.02
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2.21
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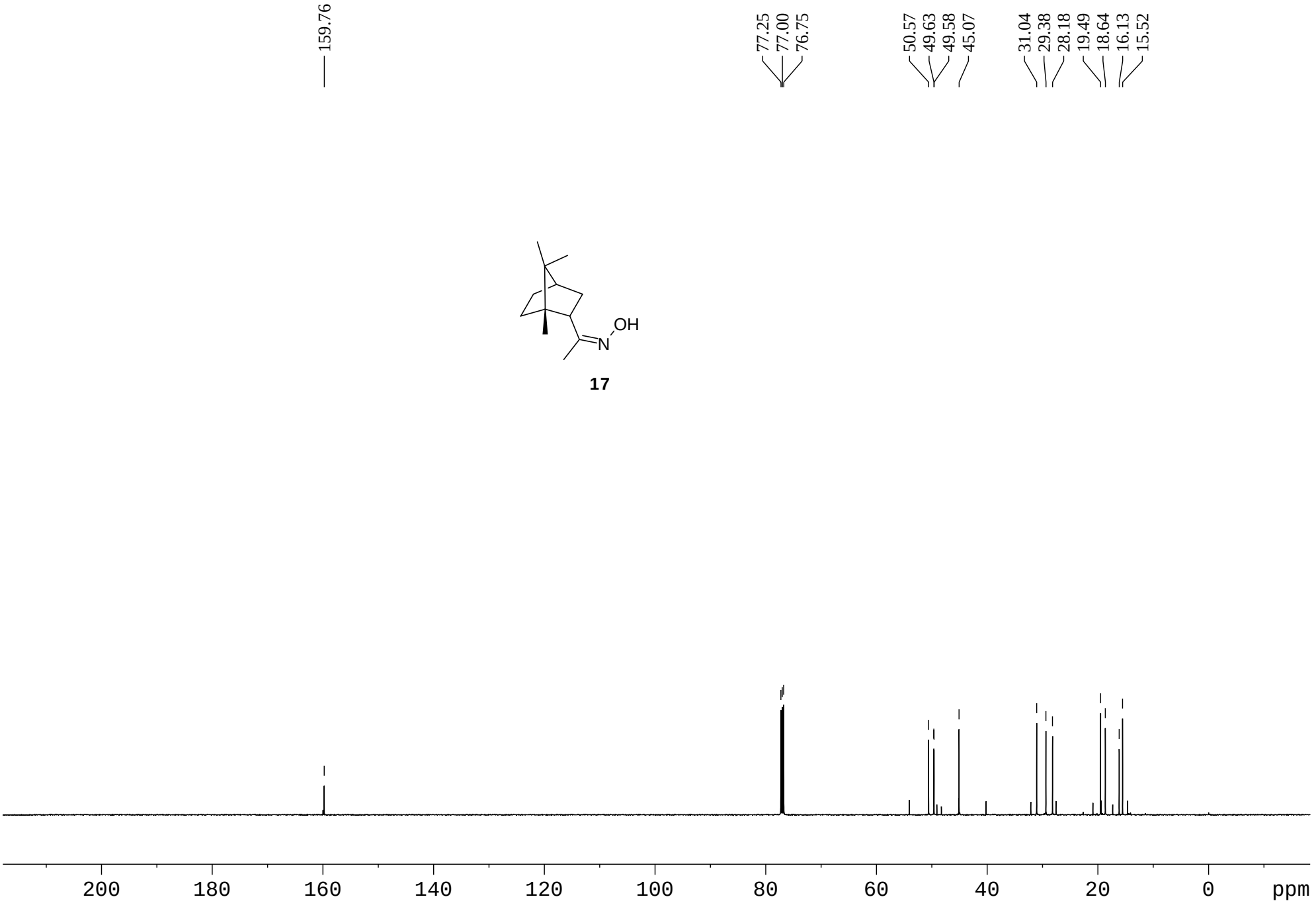
3.13
3.11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49.58
45.07
31.04
29.38
28.18
19.49
18.64
16.13
15.52
OH
N
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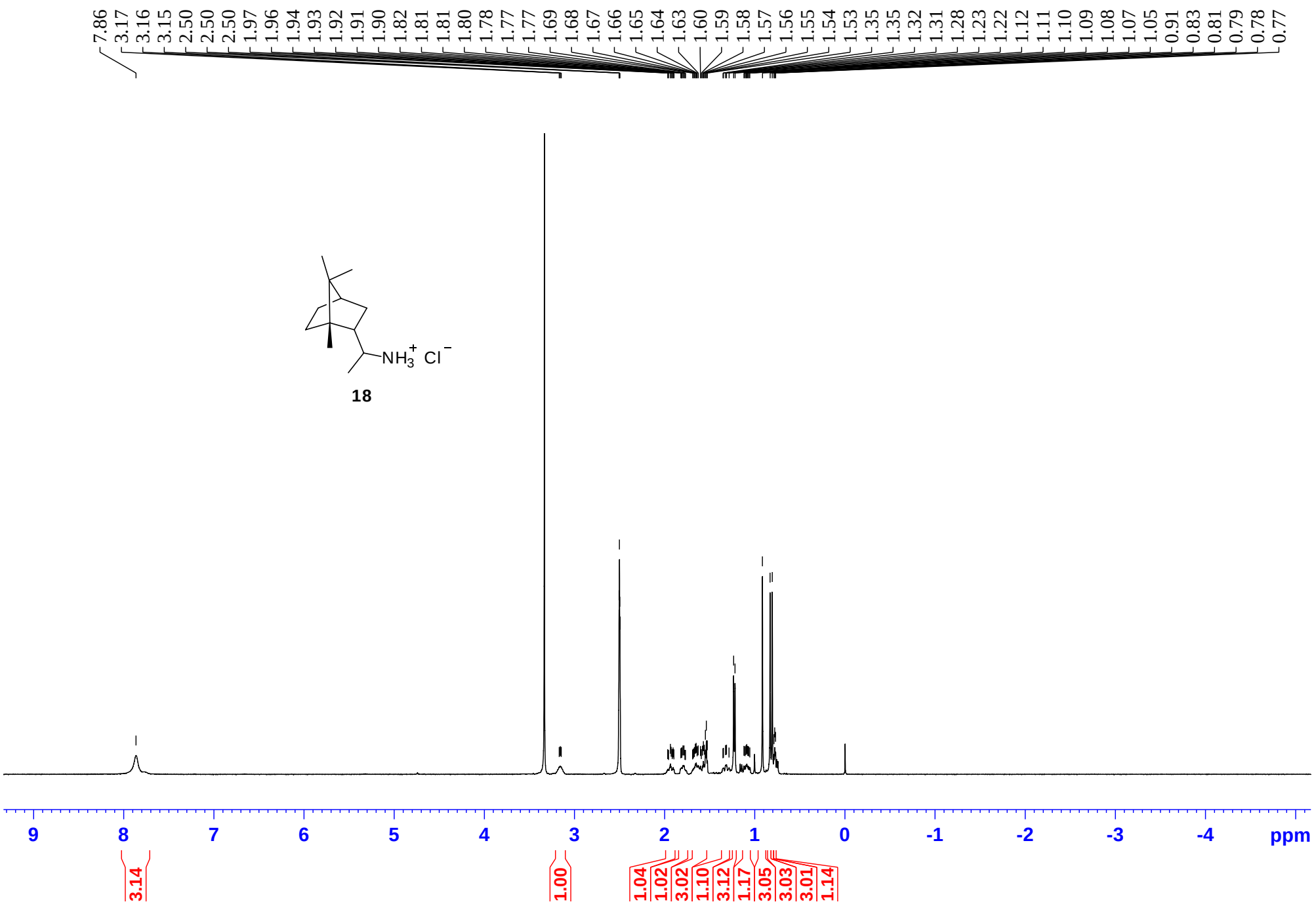
180
160
140
120
100
80
60
40
20
0
ppm

17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2.50
2.50
1.97
1.96
1.94
1.93
1.92
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1.90
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1.81
1.80
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1.68
1.67
1.66
1.65
1.64
1.63
1.60
1.59
1.58
1.57
1.56
1.55
1.54
1.53
1.35
1.35
1.32
1.31
1.28
1.23
1.22
1.12
1.11
1.10
1.09
1.08
1.07
1.05
0.91
0.83
0.81
0.79
0.78
0.77
NH3+ Cl−
18
9
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
ppm
3.14
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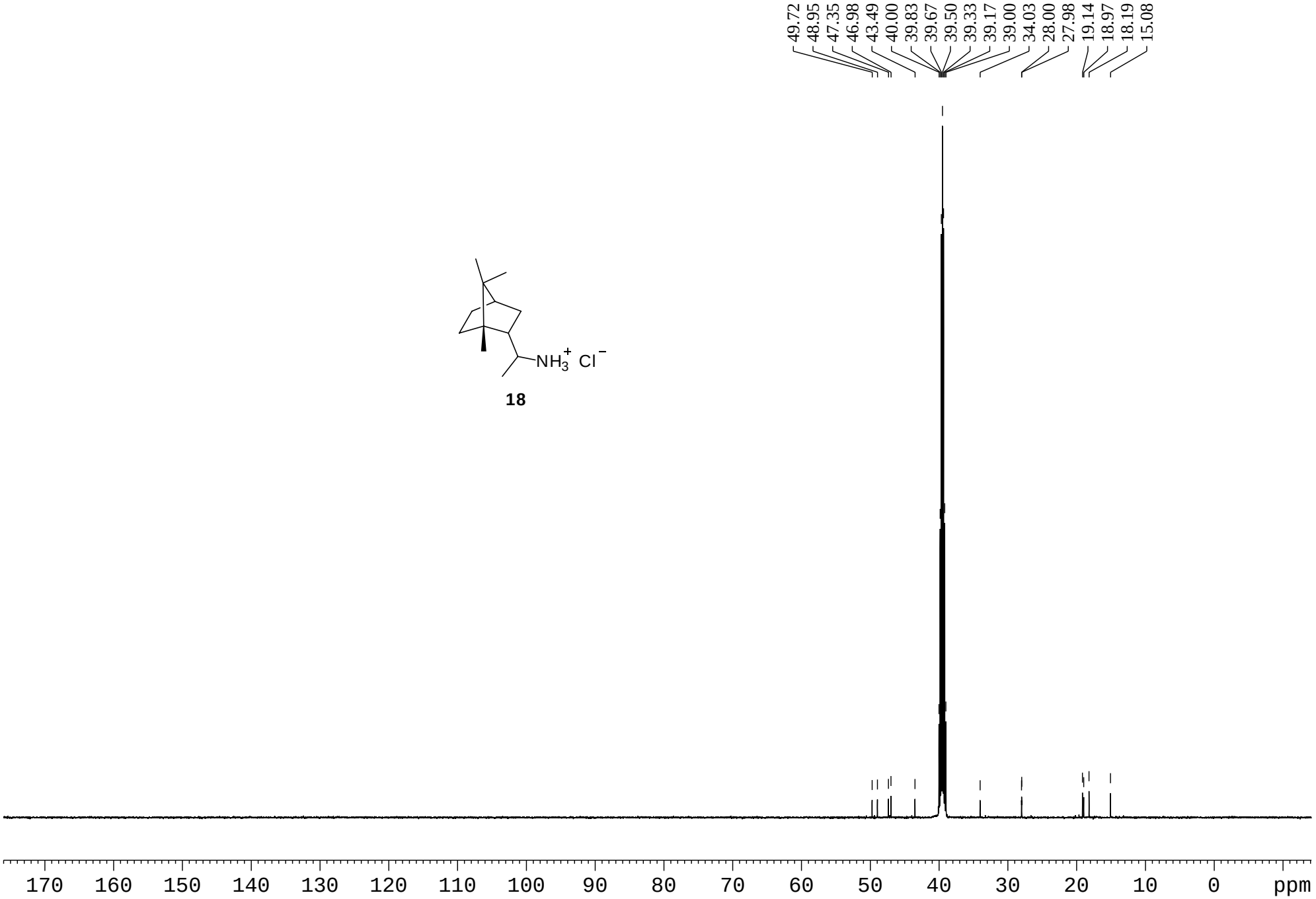
1.02
3.02
1.10
3.12
1.17
3.05
3.03
3.01
1.14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47.35
46.98
43.49
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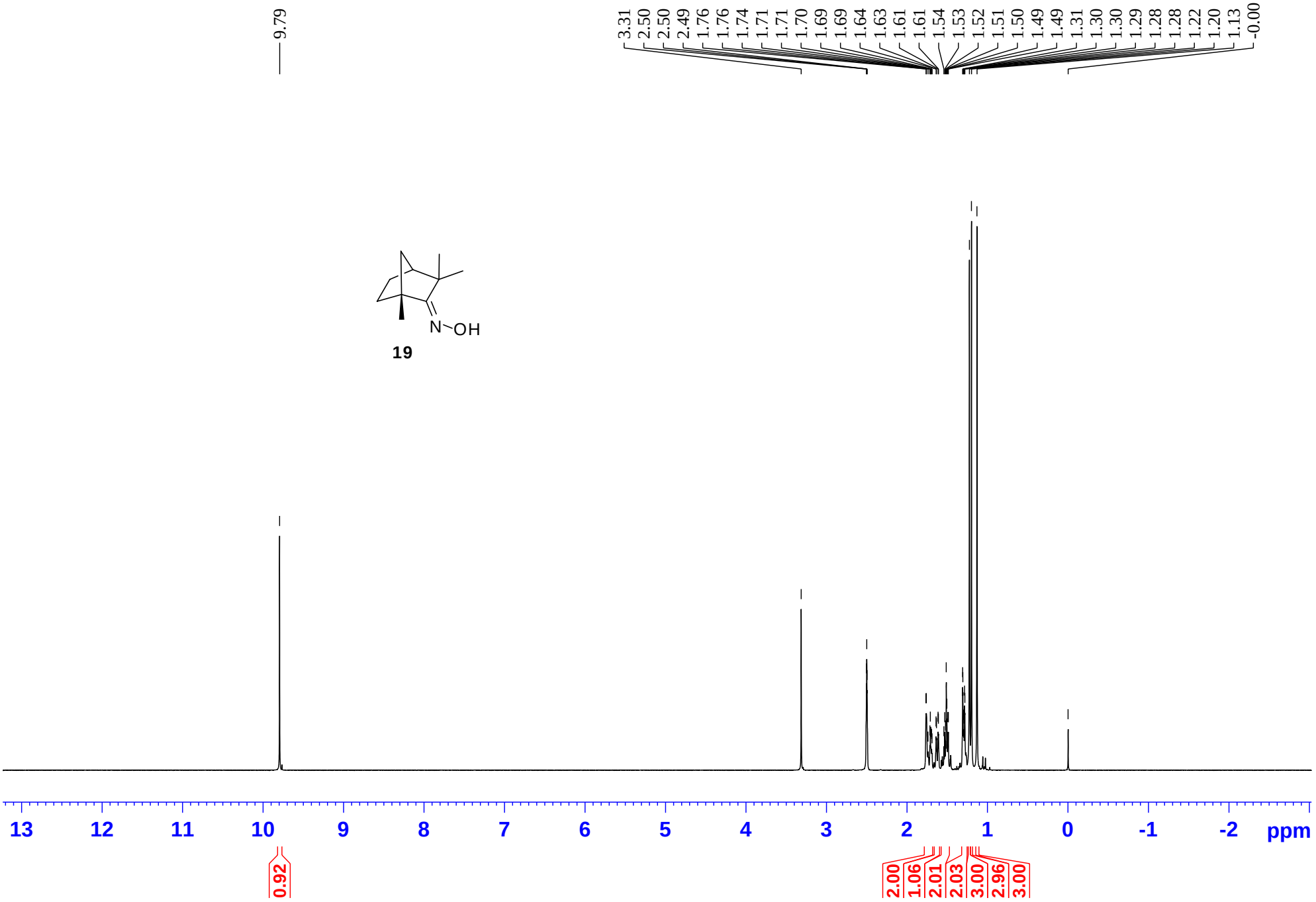
39.67
39.50
39.33
39.17
39.00
34.03
28.00
27.98
19.14
18.97
18.19
15.08
NH3+ Cl−
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

18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1.71
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1.69
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1.64
1.63
1.61
1.61
1.54
1.53
1.52
1.51
1.50
1.49
1.49
1.31
1.30
1.30
1.29
1.28
1.28
1.22
1.20
1.13
-0.00
N
OH
19
13
12
11
10
9
8
7
6
5
4
3
2
1
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-1
-2
ppm
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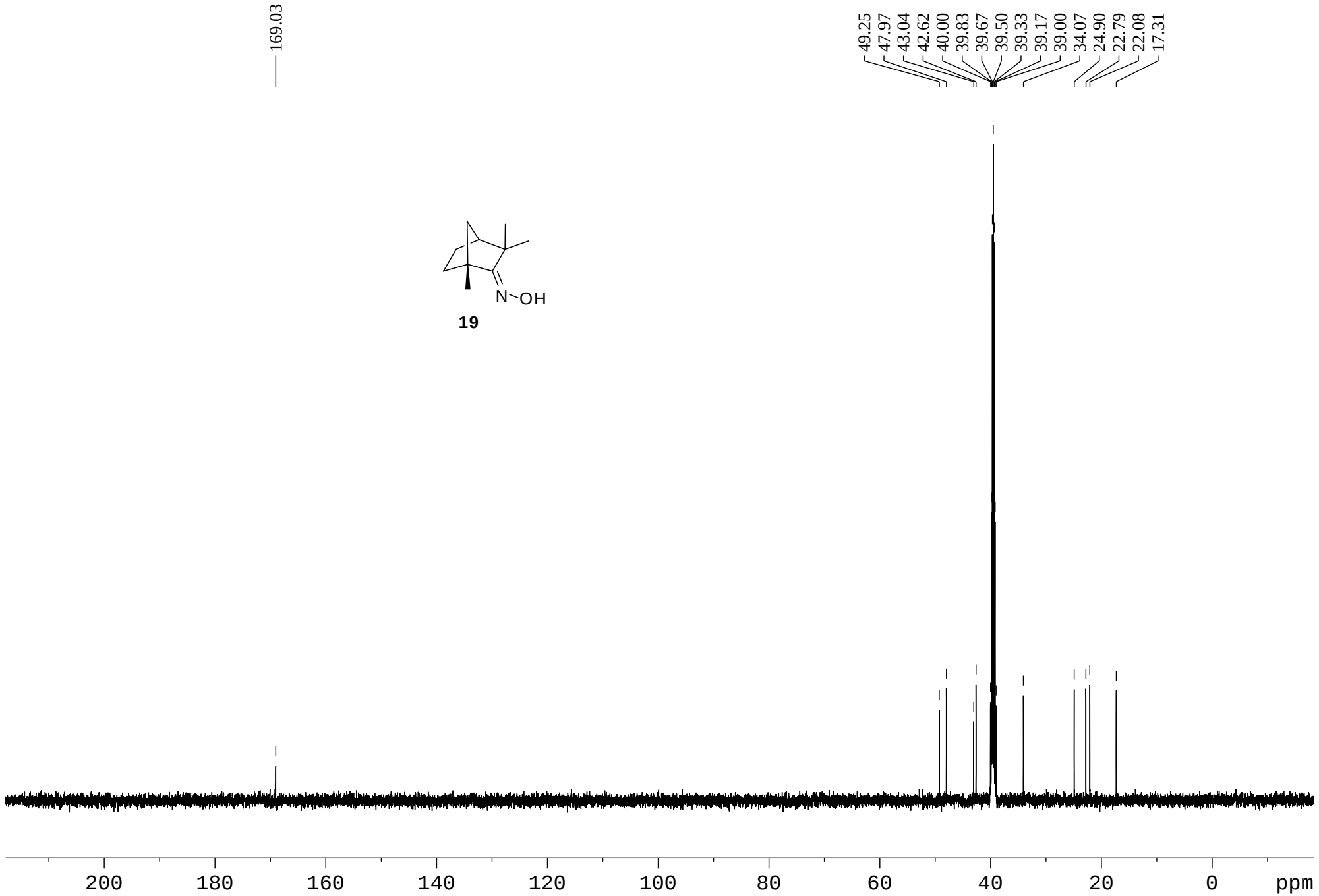
2.00
1.06
2.01
2.03
3.00
2.96
3.00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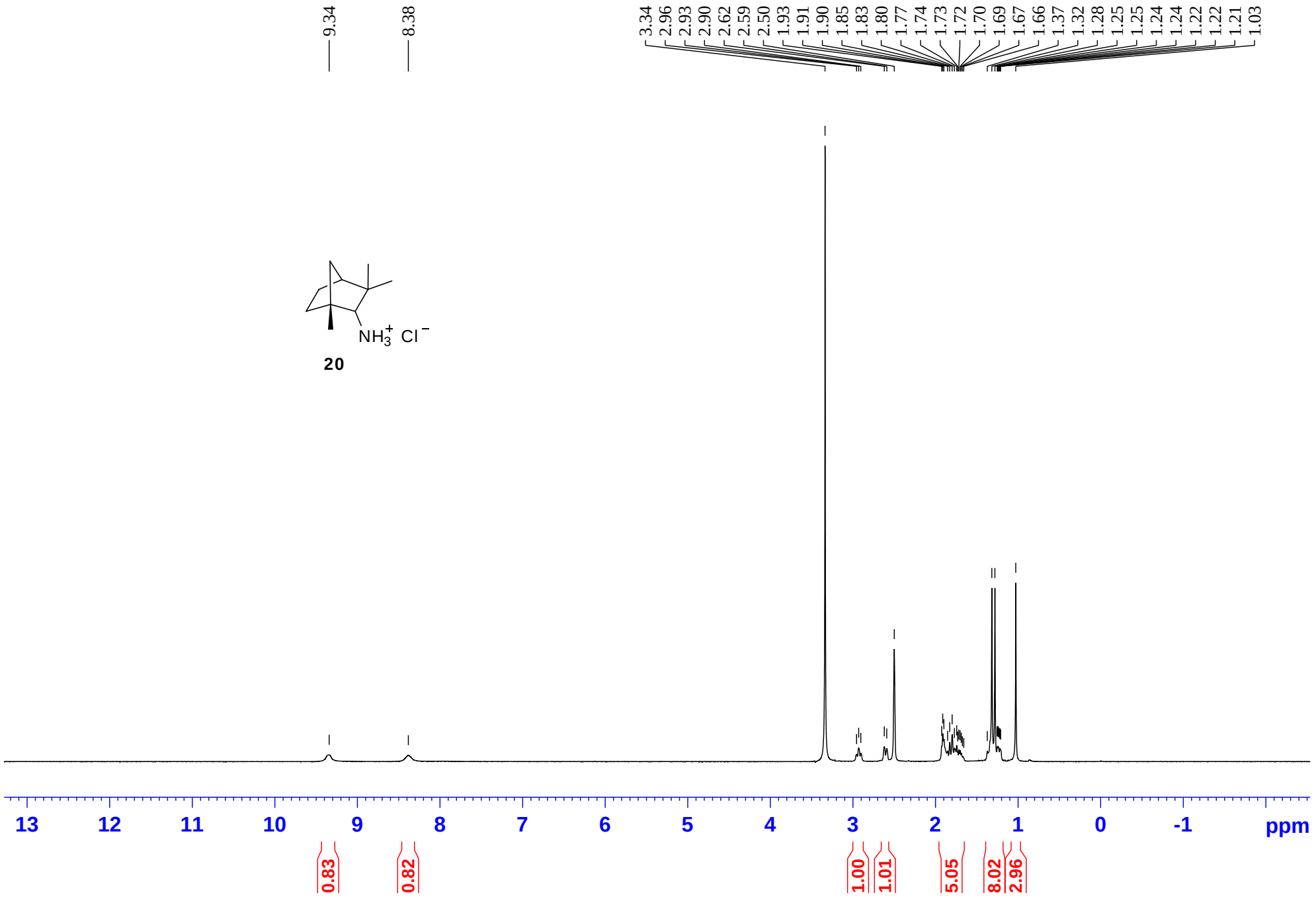
49.25
47.97
43.04
42.62
40.00
39.83
39.67
39.50
39.33
39.17
39.00
34.07
24.90
22.79
22.08
17.31
N
OH
200
180
160
140
120
100
80
60
40
20
0
ppm

19


9.34
8.38
3.34
2.96
2.93
2.90
2.62
2.59
2.50
1.93
1.91
1.90
1.85
1.83
1.80
1.77
1.74
1.73
1.72
1.70
1.69
1.67
1.66
1.37
1.32
1.28
1.25
1.25
1.24
1.24
1.22
1.22
1.21
1.03
NH3+ Cl−
20
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm
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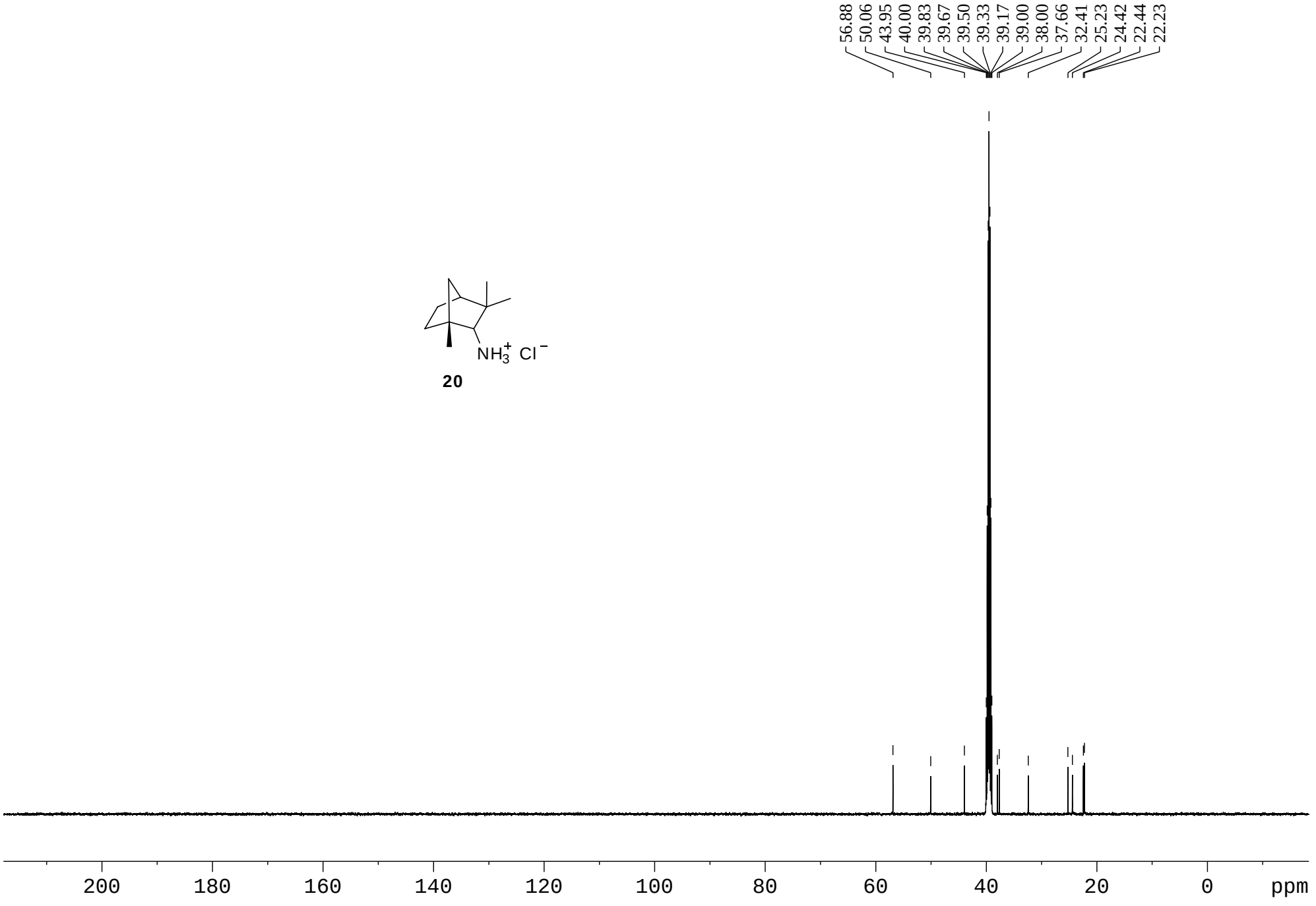
0.82
1.00
1.01
5.05
8.02
2.96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43.95
40.00
39.83
39.67
39.50
39.33
39.17
39.00
38.00
37.66
32.41
25.23
24.42
22.44
22.23
NH3+ Cl−
200
180
160
140
120
100
80
60
40
20
0
ppm

20