Supporting Information

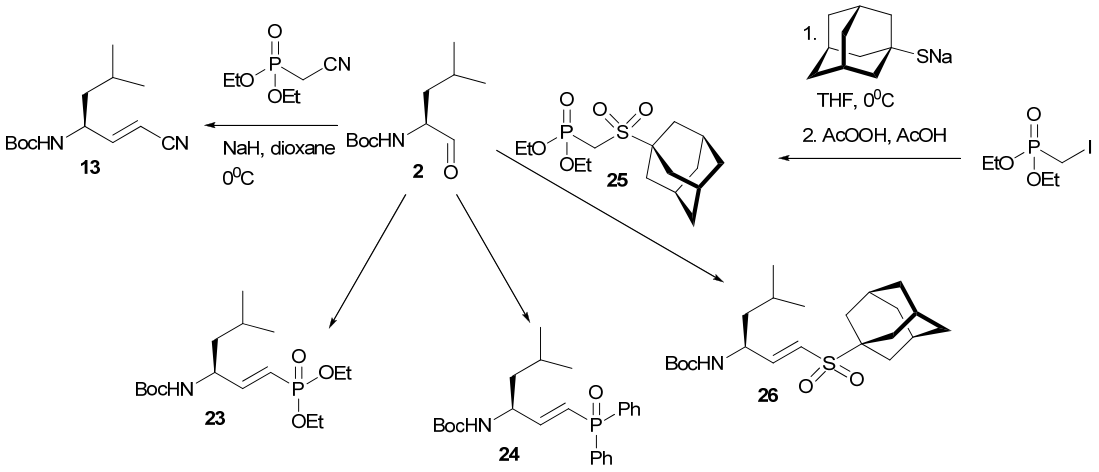
Proteasome Selectivity Towards Michael Acceptor Containing Oligopeptide-based Inhibitors

Wouter A. van der Linden, Paul P. Geurink, Chris Oskam, Gijsbert A. van der Marel, Bogdan I. Florea, Herman S. Overkleeft*

**Leiden Institute of Chemistry and Netherlands Proteomics Centre, P.O. Box 9502, 2300 RA, Leiden, The Netherlands E-mail: h.s.overkleeft@ chem.leidenuniv.nl; Fax: +31-71-5274307; Tel: +31-71-5274342*

General

All reagents were commercial grade and were used as received unless indicated otherwise. Toluene (Tol.) (purum), ethyl acetate (EtOAc) (puriss.), and light petroleum ether (PetEt) (puriss.) were obtained from Riedel-de Haën and were distilled prior to use. Dichloromethane (DCM), dimethyl formamide (DMF), and dioxane (Biosolve) were stored on 4 Å molecular sieves. Tetrahydrofuran (THF) (Biosolve) was distilled from $LiAlH_4$ prior to use. Reactions were conducted under an argon atmosphere. Reactions were monitored by TLC analysis by using DC-fertigfolien (Schleicher & Schuell, F1500, LS254) with detection by UV absorption (254 nm), spraying with 20% H_2SO_4 in ethanol, followed by charring at ~150ºC; by spraying with a solution of $(NH_4)_6Mo_7O_{24}C_4H_2O$ (25 g/L) and $(NH_4)_4Ce(SO_4)_4C_2H_2O$ (10 g/L) in 10% sulfuric acid, followed by charring at ~150ºC; or by spraying with an aqueous solution of $KMnO_4$ (7%) and KOH (2%). Column chromatography was performed on Screening devices (0.040–0.063 nm). LC/MS analysis was performed on a LCQ Advantage Max (Thermo Finnigan) equipped with an Gemini C18 column (Phenomenex). HRMS were recorded on a LTQ Orbitrap (Thermo Finnigan). 1H- and 13C-APT-NMR spectra were recorded on a Jeol JNM-FX-200 (200/50), Bruker DPX-300 (300/75 MHz), Bruker AV-400 (400/100 MHz) equipped with a pulsed field gradient accessory or a Bruker AV-500 (500/125 MHz). Chemical shifts are given in ppm (δ) relative to tetramethylsilane as an internal standard. Coupling constants are given in Hz. All presented 13C-APT spectra are proton decoupled. IR spectra were recorded on a Shimadzu FTIR-8300 spectrometer. Optical rotations were measured on a Propol automatic polarimeter (sodium D line, λ = 589 nm).



(S,E)-4-Boc-amino-6-methylhept-2-enenitrile (13). Diethyl cyanomethylphosphonate (1.39 g, 7.88 mmol, 1.5 equiv.) was dissolved in 30 mL THF at 0ºC. NaH (60% disp. in mineral oil, 0.315 g, 7.88 mmol, 1.5 equiv.) was added and the mixture was stirred for 30 minutes. Boc-leucinal **2** (1.11 g, 5.16 mmol, 1 equiv.) in THF was added, and the mixture was stirred o/n. EA was added, and the mixture was extracted with 1M HCl (2x) and brine. The organic layer was dried with $MgSO_4$ and concentrated. Column chromatography (EA:PE (10-25%)) yielded the title compound (0.52 g, 2.18 mmol, 42%). ^{1}H NMR (200 MHz, $CDCl_3$): δ ppm 6.61 (dd, J_1 = 16.26 Hz, J_2 = 5.12 Hz, 1H), 5.49 (dd, J_1 = 16.06 Hz, J_2 = 1.46 Hz, 1H), 4.45-4.20 (m, 2H), 1.80-1.35 (m, 12H), 0.94 (d, J = 6.58 Hz, 6H). ^{13}C NMR (50.1 MHz, $CDCl_3$): δ ppm 155.44, 154.80, 116.71, 98.53, 79.18, 50.1, 42.37, 27.85, 24.22, 22.82, 21.41.

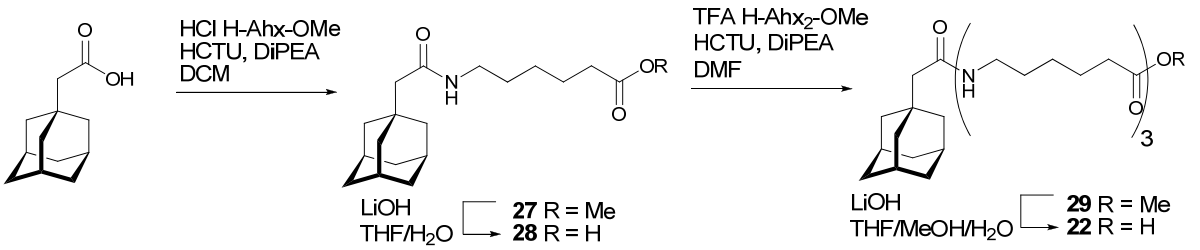
Boc-leucine vinyl diethylphosphonate (23). Tetraethyl methylenediphosphonate (0.9 g, 3.12 mmol, 1.5 equiv.) was dissolved in 10 mL THF at 0ºC. NaH (60% disp in mineral oil, 125 mg, 3.12 mmol, 1.5 equiv.) was added, and the mixture was stirred for 30 minutes at 0ºC. Boc-leucinal **2** (448 mg, 2.08 mmol, 1 equiv.) in THF was added and the resulting mixture was stirred for 3h. 1M HCl and EA were added, and the layers were separated. The organic layer was washed with 1M HCl and brine and was dried with $MgSO_4$ and concentrated. Column chromatography yielded the title compound (596 mg, 1.71 mmol, 82%). ^{1}H NMR (200 MHz, $CDCl_3$): δ ppm 6.66 (ddd, J_1 = 21.91 Hz, J_2 = 17.17 Hz, J_3 = 4.76 Hz, 1H), 5.77 (ddd, J_1 = 17.16 Hz, J_2 = 3.66 Hz, J_3 = 1.46 Hz, 1H), 4.45-4.15 (m, 2H), 4.07 (p, J = 7.68 Hz, 4H), 1.78-1.50 (m, 1H), 1.44 (s, 9H), 1.40-1.25 (m, 8H), 0.93 (d, J = 6.56 Hz, 6H). ^{13}C NMR (50.1 MHz, $CDCl_3$): δ ppm 154.70, 153.08, 152.99, 116.85, 113.13, 78.13, 77.64, 77.00, 76.35,

60.88, 60.77, 50.63, 50.22, 42.53, 27.61, 23.97, 22.03, 21.30, 21.24, 15.49. α_D^{20} -14.5º (c = 1.00, $CHCl_3$).

(S,E)-1-(diphenylphosphinoxide)-3-(Boc-amino)-5-methyl-1-hexene (24). Diethyl methylphosphonate (0.96 g, 6.32 mmol, 1 equiv.) was dissolved in THF and cooled to -78ºC. LiHMDS (12.64 mL 1M sln in THF/EtPh, 2 equiv.) was added and the solution was stirred for 15 min. Chlorodiphenylphosphinoxide (1.5 g, 6.32 mmol, 1 equiv.) was added and the solution was stirred for 1h at -40ºC. Boc-leucinal **2** (1.48 g, 6.3 mmol, 1 equiv.) in THF was added dropwise, and the mixture was stirred for 3h at -40ºC. The reaction was quenched with H_2O, and the resulting mixture was extracted with EA (3x). The combined organic layers were dried with Na_2SO_4 and concentrated. Flash column chromatography (EA:PE 40-80%, 2x)) yielded the title compound (184 mg, 0.29 mmol, 5% isolated yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.78-7.36 (m, 10H), 6.79-6.51 (m, 1H), 6.45-6.32 (m, 1H), 4.98-4.71 (m, 1H), 4.42-4.20 (m, 1H), 1.88-1.13 (m, 12H), 0.98-0.83 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 155.08, 152.01, 133.35, 133.11, 132.30, 132.08, 131.60, 131.21, 131.12, 128.41, 128.29, 121.55, 120.54, 79.32, 51.58, 51.41, 43.19, 28.16, 24.56, 22.61, 21.92.

Diethyl 1-adamantylsulfonylmethylphosphonate (25). 1-adamantylthiol (1.77 g, 10 mmol, 1 equiv.) was dissolved in 50 mL THF at 0ºC. NaH (0.42 g 60% disp. in min. oil, 10.5 mmol, 1.05 equiv.) was added, and the mixture was stirred for 1h. diethyl iodomethylphosphonate (2.78 g, 10 mmol, 1 equiv.) in THF was added, and the mixture was stirred for 1.5 h. The reaction was quenched with 1M HCl, and the mixture was extracted with DCM (2x). The organic layer was dried with $MgSO_4$ and concentrated. The residue was dissolved in 1,4-dioxane and cooled to 0ºC. Peroxyacetic acid (8.4 mL 32% in AcOH (w/w), 40 mmol, 4 equiv.) was added and the mixture was stirred for 2h. Sat. aq. $NaHCO_3$ was added, and the mixture was extracted with EA (2x). The organic layer was dried with $MgSO_4$ and concentrated. The residue was recrystallised from EA:PE to yield the title compound (2.79 g, 7.95 mmol, 79%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 4.31-4.23 (m, 4H), 3.48 (d, *J* = 18.66 Hz, 2H), 2.21 (s, 3H), 2.04 (d, *J* = 2.31 Hz, 6H), 1.80-1.66 (m, 6H), 1.38 (t, *J* = 7.07 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 63.61, 63.54, 42.81, 41.46, 35.60, 34.65, 28.12, 16.29, 16.22.

Boc-leucinyl vinyl-1-adamantylsulfone (26). Diethyl 1-adamantylsulfonylmethylphosphonate **25** (1.9 g, 5.4 mmol, 1.1 equiv.) was dissolved in 50 mL THF at 0ºC. KOtBu (607 mg, 5.4 mmol, 1.1 equiv.) was added and the mixture was stirred for 30 min. Boc-leucinal (1.06 g, 4.92 mmol, 1 equiv.) in THF was added and the mixture was stirred at 0ºC for 1h. Sat. aq. NH_4Cl was added and the mixture was extracted with EA (2x). The organic layer was dired with $MgSO_4$ and concentrated. Column chromatography (EA:PE (5-30%)) and recrystallisation from DCM:PE yielded the title compound (1.22 g, 3.06 mmol, 62%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 6.69 (dd, *J* = 15.04, 5.33 Hz, 1H), 6.33 (d, *J* = 15.11 Hz, 1H), 5.17 (d, *J* = 7.61 Hz, 1H), 4.40-4.29 (m, 1H), 2.14 (s, 3H), 2.01-1.90 (m, 6H), 1.80-1.62 (m, 7H), 1.47-1.41 (m, 11H), 0.96-0.91 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 154.77, 150.76, 122.70, 79.16, 59.40, 49.75, 42.38, 35.45, 34.22, 27.97, 27.75, 24.35, 22.34, 21.73.



AdaAhxOMe (27). To a solution of methyl 6-aminohexanoate HCl salt (0.78 g, 4.30 mmol) and 1-adamantaneacetic acid (0.94 g, 4.73 mmol) in DCM (25 mL) were added HCTU (2.0 g, 4.94 mmol) and DiPEA (2.31 mL, 14 mmol). The mixture was stirred for 3 hours, after which EtOAc (100 mL)

was added followed by extraction of the mixture with 1M HCl (2x), saturated $NaHCO_3$ (2x) and brine. Drying over $MgSO_4$ and concentration of the mixture resulted in crude product, which was further purified by column chromatography (EA:PE (10-100%)). The product (yield: 1.38 g, 4.30 mmol, quant.) was obtained as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 5.60-5.53 (m, 1H), 3.67 (s, 3H), 3.24 (dd, *J* = 13.22, 6.87 Hz, 2H), 2.32 (t, *J* = 7.41, 7.41 Hz, 2H), 1.99-1.94 (m, 3H), 1.91 (s, 2H), 1.73-1.59 (m, 15H), 1.56-1.48 (m, 2H), 1.41-1.31 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 173.95, 170.81, 51.78, 51.42, 42.56, 39.01, 36.70, 33.79, 32.62, 29.33, 28.56, 26.36, 24.39. LC-MS: system B, gradient 10% → 90% ACN/(0.1% TFA/H_2O): R_t (min): 8.71 (ESI-MS (m/z): 322.20 ($M + H^+$)).

Ada-Ahx-OH (28). Methyl ester **27** (2.79 g, 8.68 mmol) was dissolved in THF (35 mL) and cooled to 0°C. An aqueous solution of LiOH (1M, 1.1 eq., 9.54 mmol, 9.54 mL) was added and the reaction was stirred at 0°C for 12 hours after which TLC analysis indicated complete consumption of starting material. Water (50 mL) was added and the mixture was extracted twice with EtOAc. Next, the aqueous layer was acidified with concentrated HCl to pH1 and extracted again with EtOAc (2x). The latter two combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure, which yielded the title compound (yield: 2.63 g, 8.57 mmol, 99%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 10.87 (s, 1H), 5.95 (t, *J* = 5.56, 5.56 Hz, 1H), 3.24 (dd, *J* = 13.16, 6.81 Hz, 2H), 2.34 (t, *J* = 7.34, 7.34 Hz, 2H), 1.99-1.92 (m, 5H), 1.73-1.58 (m, 14H), 1.53 (td, *J* = 14.65, 7.37, 7.37 Hz, 2H), 1.43-1.33 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 177.96, 171.55, 51.49, 42.48, 39.15, 36.62, 33.86, 32.63, 29.11, 28.51, 26.24, 24.20. LC-MS: system B, gradient 10% → 90% ACN/(0.1% TFA/H_2O): R_t (min): 7.49 (ESI-MS (m/z): 308.13 ($M + H^+$)).

Ada-Ahx$_3$-OMe (29). Methyl 6-(6-(tert-butoxycarbonylamino)hexanamido)hexanoate (3.37 g, 9.39 mmol) was dissolved in DCM/TFA (1/1, v/v) and stirred for 30 mintues before being coevoparated with toluene (3x). AdaAhxOH **28** (2.63 g, 8.57 mmol) was dissolved in DMF. HCTU (4.08 g, 9.86 mmol, 1.15 eq) and DiPEA (5.12 mL, 31 mmol, 3.3 equiv.) were added and the mixture was stirred for 10 minutes. Methyl 6-hexanamido)hexanoate TFA salt in DMF was added, and the mixture was stirred for 2h. The mixture was concentrated, dissolved in DCM, washed with 1M HCl (2x), sat. aq. $NaHCO_3$ (4x) and brine. After drying with $MgSO_4$ and concentration, the title compound was obtained as a colorless solid (yield: 4.10 g, 7.49 mmol, 87%) after column purification (MeOH/EtOAc (0-15%)). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 6.42 (t, *J* = 5.67, 5.67 Hz, 1H), 6.38 (t, *J* = 5.61, 5.61 Hz, 1H), 6.13 (t, *J* = 5.60, 5.60 Hz, 1H), 3.66 (s, 3H), 3.25-3.18 (m, 6H), 2.31 (t, *J* = 7.43, 7.43 Hz, 2H), 2.18 (t, *J* = 7.42, 7.42 Hz, 4H), 1.98-1.94 (m, 3H), 1.92 (s, 2H), 1.73-1.58 (m, 18H), 1.56-1.47 (m, 6H), 1.39-1.29 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 173.95, 172.97, 172.92, 171.02, 51.54, 51.37, 42.52, 39.07, 39.00, 36.65, 36.27, 33.75, 32.57, 29.28, 29.15, 28.51, 26.40, 26.38, 26.29, 25.18, 25.15, 24.39. LC-MS: system B, gradient 10% → 90% ACN/(0.1% TFA/H_2O): R_t (min): 7.93 (ESI-MS (m/z): 548.33 ($M + H^+$)).

Ada-Ahx$_3$-OH (22). Methyl ester **29** (4.10 g, 7.49 mmol) was dissolved in THF/MeOH 5:1 (35 mL) and cooled to 0°C. An aqueous solution of LiOH (1M, 1.1 eq., 8.24 mmol, 8.24 mL) was added and the reaction was stirred at RT for 12 hours after which TLC analysis indicated complete consumption of starting material. Water (50 mL) was added and the mixture was extracted twice with EtOAc. Next, the aqueous layer was acidified with concentrated HCl to pH1 and extracted with DCM (3x). The combined DCM layers were dried ($MgSO_4$) and concentrated under reduced pressure, which yielded the title compound (yield: 3.79 g, 7.12 mmol, 95%) as a colorless solid. ^{1}H NMR (400 MHz, MeOD): δ ppm 7.96-7.90 (m, 2H), 7.86-7.79 (m, 1H), 3.19-3.11 (m, 6H), 2.29 (t, *J* = 7.35, 7.35 Hz, 2H), 2.17 (t, *J* = 7.45, 7.45 Hz, 4H), 1.97-1.93 (m, 3H), 1.91 (s, 2H), 1.74 (d, *J* = 12.27 Hz, 3H), 1.69-1.57 (m, 15H), 1.55-1.46 (m, 6H), 1.40-1.28 (m, 6H) . ^{13}C NMR (100 MHz, MeOD): 177.40, 175.97, 173.74, 51.91, 43.79, 40.21, 37.95, 37.02, 34.83, 33.81, 30.24, 30.19, 30.14, 27.68, 27.58, 27.53, 26.74, 25.75 . LC-MS: system B, gradient 10% → 90% ACN/(0.1% TFA/H_2O): R_t (min): 7.21 (ESI-MS (m/z): 534.33 ($M + H^+$)).

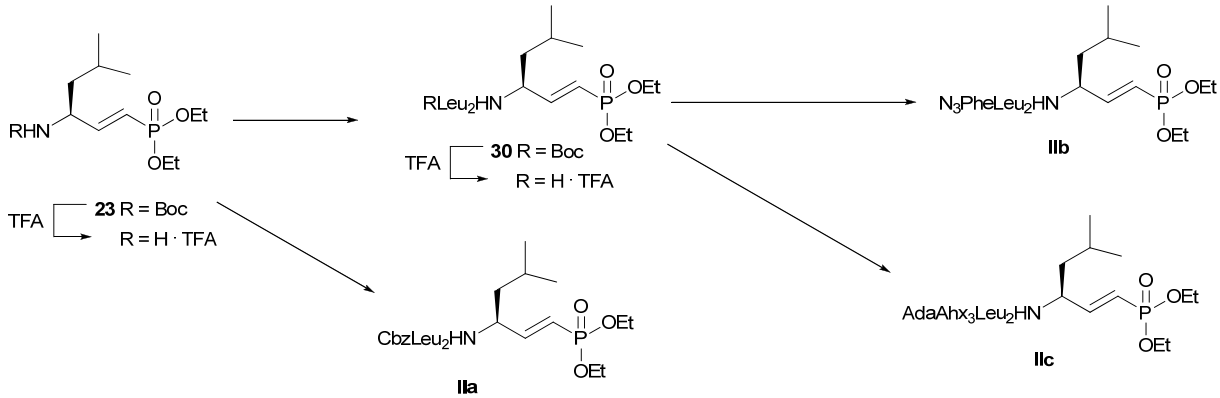
General protocol for azide couplings

The Boc-protected warhead was dissolved in TFA:DCM (1:1, v/v) and stirred for 20 minutes.

Coevaporation with toluene (3x) afforded the warhead TFA-salt, which was used without further purification. The appropriate hydrazide (**16** or **18**) was dissolved in 1:1 DMF:DCM (v/v) and cooled to -30ºC. *t*BuONO (1.1 eq) and HCl (2.8 eq, 4M sln. in 1,4-dioxane) were added, and the mixture was stirred for 3h at -30ºC after which TLC analysis (10% MeOH/DCM, v/v) showed complete consumption of the starting material. The warhead-TFA salt was added to the reaction mixture as a solution in DMF with 1.1 equivalent of DiPEA. A further 3.9 equivalents were added to the reaction mixture, and this mixture was allowed to warm to RT slowly overnight. The mixture was diluted with EA and extracted with H_2O (3x). The organic layer was dried over $MgSO_4$ and purified by flash column chromatograpy.

General protocol for block couplings

The Boc-protected tripeptide was dissolved in TFA:DCM (1:1, v/v) and stirred for 20 minutes. Coevaporation with toluene (3x) afforded the tripeptide TFA-salt, which was used without further purification. The carboxylic acid (1 equivalent **21** or **22**) was dissolved in DCM:DMF (1/1). HBTU (1.1 equiv), DiPEA (3.5 equiv.) were added and the mixture was stirred for 5 min. A solution of the tripeptide TFA salt in DMF was added and the mixture was stirred for 2h before being concentrated. The residue was taken up in DCM, washed with 1M HCl (2x), sat. aq. $NaHCO_3$ (4x), brine, and dried with Na_2SO_4. The residue was purified by flash column chromatograpy.

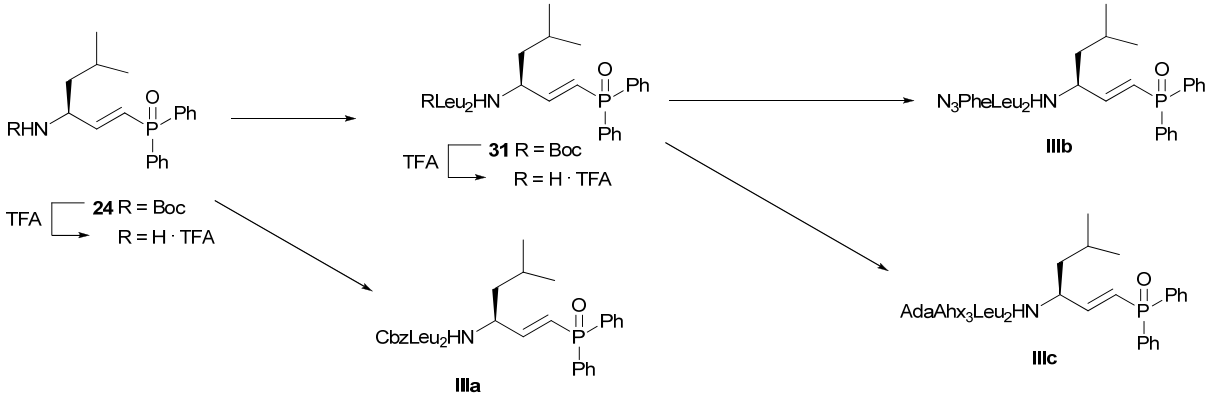


Cbz-Leu$_2$-leucinyl vinyl diethylphosphonate (IIa). Following the general procedure for azide coupling the title compound was obtained from Boc-leucinyl vinyl diethylphosphonate **23** (98 mg, 280 µmol, 1.1 equiv.) and Cbz-Leu$_2$-NHNH$_2$ **16** (100 mg, 254 µmol, 1 equiv). Purification by flash chromatography (MeOH:DCM (0-3%)) gave the title compound **IIa** (71 mg, 117 µmol, 46%). α_D^{20} -50.6º (c = 1.00, $CHCl_3$). IR (film) 3269, 2955, 2870, 1699, 1645, 1539, 1468, 1387, 1367, 1232, 1024, 962 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.85-7.70 (m, 1H), 7.36-7.22 (m, 5H), 6.78-6.62 (m, 2H), 5.85-5.72 (m, 1H), 5.14-4.97 (m, 2H), 4.70-4.54 (m, 2H), 4.45-4.35 (m, 1H), 4.08-3.93 (m, 4H), 1.83-1.68 (m, 1H), 1.66-1.31 (m, 8H), 1.32-1.20 (m, 6H), 0.94-0.77 (m, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 172.36, 171.29, 156.21, 153.02, 152.99, 136.31, 128.17, 127.69, 127.50, 116.21, 114.35, 66.43, 61.65, 61.58, 61.52, 53.24, 51.77, 49.28, 49.06, 42.64, 41.37, 40.74, 24.62, 24.53, 24.41, 24.36, 22.82, 22.73, 22.62, 22.43, 22.17, 22.09, 21.57, 16.11, 16.08, 16.05, 16.02. HRMS: calcd. for $[C_{39}H_{53}N_3O_5P]^+$ 610.36156, found 610.36163.

Boc-Leu$_2$-leucinyl vinyl diethylphosphonate (**30**). Following the general procedure for azide coupling the title compound was obtained from Boc-leucinyl vinyl diethylphosphonate **23** (86 mg, 0.246 mmol, 1.1 equiv.) and Boc-Leu$_2$-NHNH$_2$ **18** (80 mg, 0.224 mmol, 1 equiv). Purification by flash chromatography EA:tol (50-100%) gave the title compound (118 mg, 0.205 mmol, 92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.48-7.40 (m, 1H), 6.72 (ddd, J_1 = 22.2 Hz, J_2 = 17.2 Hz, J_3 = 5.2 Hz, 1H), 5.81 (t, J = 18.5 Hz, 2H), 5.56-5.50 (m, 1H), 4.72-4.63 (m, 1H), 4.55-4.48 (m, 1H), 4.12-4.00 (m, 5H), 1.75-1.20 (m, 25H), 0.95-0.86 (m, 18H).). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 172.68, 171.22, 155.84, 152.60, 152.56, 116.90, 115.05, 80.00, 61.77, 61.72, 61.67, 53.26, 51.82, 49.48, 49.26, 43.14, 40.79, 40.61, 28.21, 24.64, 22.80, 22.70, 22.05, 21.95, 21.87, 16.26, 16.20.

Azido-Phe-Leu$_2$-leucinyl vinyl diethylphosphonate (IIb). Following the general procedure for block coupling, the title compound was obtained from Boc-Leu$_2$-leucinyl vinyl diethylphosphonate **30** (118 mg, 205 μmol) and azido-phenylalanine **21** (44 mg, 230 μmol, 1.1 equiv.). Flash column chromatography (EA:tol (50-100%)) yielded **IIb** (68 mg, 100 μmol, 50%). α_D^{20} -36.8º (c = 1.00, $CHCl_3$). IR (film) 3277, 2957, 2926, 2112, 1641, 1541, 1468, 1387, 1367, 1226, 1163, 1053, 1024, 964 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.33-7.19 (m, 5H), 7.08-6.99 (m, 1H), 6.68 (ddd, *J* = 22.22, 17.15, 5.33 Hz, 1H), 5.77 (t, *J* = 17.2 Hz, 1H), 4.70-4.60 (m, 1H), 4.55-4.45 (m, 2H), 4.25 (dd, *J* = 8.25, 4.15 Hz, 1H), 4.12-3.96 (m, 4H), 3.22 (dd, *J* = 14.17, 3.67 Hz, 1H), 3.04 (dd, *J* = 14.12, 8.27 Hz, 1H), 1.77-1.16 (m, 15H), 1.00-0.78 (m, 18H). ^{13}C NMR (100 MHz, CD_3OD): δ ppm 171.56, 171.05, 168.88, 152.42, 135.94, 129.37, 128.55, 127.14, 117.06, 115.20, 64.64, 61.89, 61.83, 61.76, 51.89, 51.62, 49.56, 49.34, 43.18, 41.03, 40.91, 38.00, 29.64, 24.81, 24.72, 24.48, 22.78, 22.74, 22.54, 22.50, 22.07, 21.99, 16.32, 16.29, 16.26, 16.23. HRMS: calcd. for $[C_{32}H_{54}N_6O_6P]^+$ 649.3837, found 649.38385.

Ada-Ahx$_3$-Leu$_2$-leucinyl vinyl diethylphosphonate (IIc). Following the general procedure for block coupling, the title compound was obtained from Boc-Leu$_2$-leucinyl vinyl diethylphosphonate **30** (122 mg, 212 μmol, 1 equiv.) and Ada-Ahx$_3$-OH **22** (124 mg, 233 μmol, 1.1 equiv.). Flash column chromatography (MeOH:DCM (2-10%)) yielded **IIc** (149 mg, 150 μmol, 71%). α_D^{20} -38.2º (c = 1.00, MeOH). IR (film) 3277, 3072, 2928, 2905, 2868, 1638, 1545, 1452, 1367, 1234, 1053, 1028, 968 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.14-8.03 (m, 3H), 7.96 (t, *J* = 5.14, 5.14 Hz, 2H), 7.89-7.84 (m, 1H), 6.67 (ddd, *J* = 22.07, 17.21, 4.83 Hz, 1H), 5.86-5.74 (m, 1H), 4.64-4.54 (m, 1H), 4.45-4.30 (m, 2H), 4.05 (p, *J* = 7.26, 4H), 3.18-3.11 (m, 6H), 2.25 (t, *J* = 7.28, 2H), 2.17 (t, *J* = 7.40 Hz, 4H), 1.97-1.89 (m, 5H), 1.80-1.25 (m, 45H), 0.98-0.87 (m, 18H). ^{13}C NMR (100 MHz, CD_3OD): δ ppm 176.23, 175.88, 174.85, 174.15, 173.66, 154.79, 154.74, 117.24, 115.37, 63.43, 63.37, 53.50, 53.29, 51.91, 51.05, 50.83, 43.73, 43.49, 41.82, 41.72, 40.29, 40.24, 37.90, 37.02, 36.66, 33.75, 30.21, 30.14, 30.10, 27.64, 27.58, 27.55, 26.71, 26.57, 25.93, 25.88, 25.85, 23.46, 23.38, 22.19, 22.12, 22.03, 16.72, 16.66. HRMS calcd for $[C_{53}H_{96}N_6O_9P]^+$ 991.69709, found 991.698.



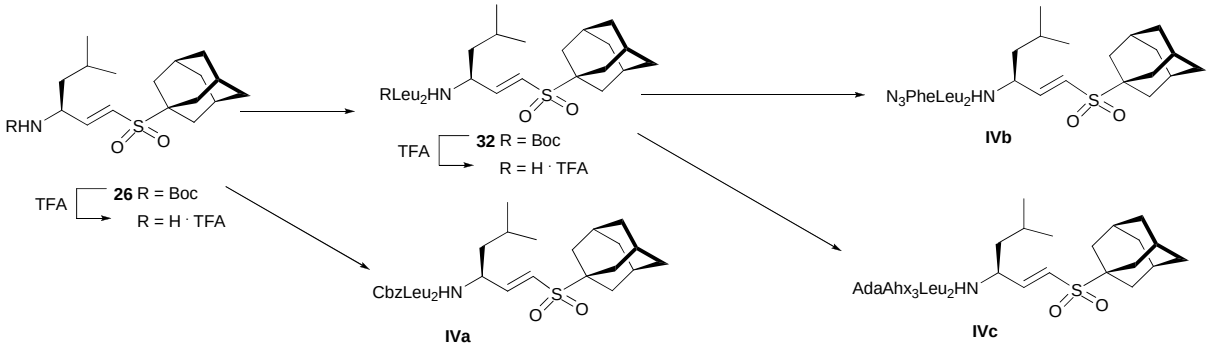
Boc-Leu$_2$-leucinyl vinyl diphenylphosphinoxide (31). Following the general procedure for azide coupling the title compound was obtained from Boc-leucinyl-vinyl diphenylphosphinoxide **24** (380 mg, 0.92 mmol, 1.1 equiv.) and Boc-Leu$_2$-$NHNH_2$ **18** (300 mg, 0.84 mmol, 1 equiv). Purification by flash chromatography EA:tol (30-70%, 3x) gave the title compound (221 mg, 0.345 mmol, 41%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.87-7.33 (m, 10H), 6.81 (d, *J* = 7.14 Hz, 1H), 6.73-6.42 (m, 2H), 5.47 (d, *J* = 5.53 Hz, 1H), 4.83-4.69 (m, 1H), 4.56-4.48 (m, 1H), 4.08-3.98 (m, 1H), 1.83-1.15 (m, 15H), 1.03-0.77 (m, 18H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 172.49, 171.33, 155.89, 151.63, 133.49, 133.01, 132.44, 131.96, 131.60, 131.24, 131.15, 128.49, 128.42, 128.30, 121.26, 120.26, 79.95, 53.46, 51.96, 49.73, 49.56, 43.09, 40.90, 40.75, 28.18, 24.74, 24.67, 24.59, 22.80, 22.70, 22.08, 21.80.

Cbz-Leu$_2$-leucinyl vinyl diphenylphosphinoxide (IIIa). Following the general procedure for azide coupling the title compound was obtained from Boc-leucinyl-vinyl diphenylphosphinoxide **24** (179 mg, 280 μmol, 1.1 equiv.) and Cbz-Leu$_2$-$NHNH_2$ **16** (100 mg, 254 μmol, 1 equiv). Purification by flash chromatography (MeOH:DCM (0-3%)) gave the title compound **IIIa** (79 mg, 117 μmol, 46%).

α_D^{20} -56.8º(c = 1.00, $CHCl_3$). IR (film) 3271, 3059, 2955, 1701, 1645, 1539, 1437, 1387, 1367, 1263, 1236, 1171, 1121, 1105, 1043, 1028, 972 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ ppm 7.75 (d, *J* = 8.59 Hz, 1H), 7.71-7.60 (m, 4H), 7.54-7.24 (m, 11H), 6.90 (d, *J* = 7.88 Hz, 1H), 6.67-6.40 (m, 2H), 6.05 (d, *J* = 7.42 Hz, 1H), 5.12-4.95 (m, 2H), 4.78-4.68 (m, 1H), 4.59-4.51 (m, 1H), 4.22-4.13 (m, 1H), 1.80-1.19 (m, 9H), 0.92-0.72 (m, 18H). HRMS: calcd. for $[C_{39}H_{53}N_3O_5P]^+$ 674.37173, found 674.37195.

Azido-Phe-Leu$_2$-leucinyl vinyl diphenylphosphinoxide (IIIb). Following the general procedure for block coupling, the title compound was obtained from Boc-Leu$_2$-leucinyl vinyl diphenylphosphinoxide **31** (75 mg, 117 µmol) and azido-phenylalanine **21** (22 mg, 120 µmol, 1.1 equiv.). Flash column chromatography (EA:tol (50-100%), 2x) yielded **IIIb** (71 mg, 100 µmol, 85%). α_D^{20} -43.6º (c = 1.00, $CHCl_3$). IR 3281, 3059, 2955, 2928, 2870, 2112, 1641, 1541, 1437, 1387, 1367, 1173, 1121, 1105, 1028, 997 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ ppm 7.86-7.34 (m, 10H), 7.28-7.13 (m, 5H), 7.05 (d, *J* = 8.00 Hz, 1H), 6.60-6.37 (m, 2H), 4.82-4.70 (m, 1H), 4.63-4.54 (m, 1H), 4.49-4.41 (m, 1H), 4.28-4.22 (m, 1H), 3.19-3.10 (m, 1H), 3.04-2.95 (m, 1H), 1.81-1.16 (m, 9H), 0.94-0.71 (m, 18H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 171.39, 171.09, 169.23, 151.88, 136.08, 133.01, 132.38, 131.92, 131.37, 131.27, 131.18, 131.08, 129.29, 128.66, 128.61, 128.54, 128.49, 127.00, 121.51, 120.50, 64.30, 51.95, 51.74, 49.79, 49.62, 43.16, 41.17, 40.59, 37.94, 24.85, 24.80, 24.46, 22.76, 22.70, 22.22, 22.00, 21.91. HRMS: calcd. for $[C_{40}H_{54}N_6O_4P]^+$ 713.39387, found 713.39426.

Ada-Ahx$_3$-Leu$_2$-leucinyl vinyl diphenylphosphinoxide (IIIc). Following the general procedure for block coupling, the title compound was obtained from Boc-Leu$_2$-leucinyl vinyl diphenylphosphinoxide **31** (72 mg, 113 µmol) and Ada-Ahx$_3$-OH **22** (60 mg, 124 µmol, 1.1 equiv.). Flash column chromatography (MeOH:DCM (5-11%)) yielded **IIIc** (101 mg, 96 µmol, 85%). α_D^{20} -41.0º (c = 1.00, MeOH). IR 3277, 2928, 2904, 2849, 1638, 1545, 1437, 1367, 1277, 1171, 1121, 1105 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ ppm 8.14 (d, *J* = 8.26 Hz, 1H), 8.08 (d, *J* = 6.47 Hz, 1H), 8.04 (d, *J* = 7.37 Hz, 1H), 7.99-7.91 (m, 2H), 7.89-7.82 (m, 1H), 7.74-7.47 (m, 10H), 6.73-6.46 (m, 2H), 4.73-4.63 (m, 1H), 4.43-4.35 (m, 1H), 4.34-4.26 (m, 1H), 3.20-3.08 (m, 6H), 2.25 (t, *J* = 7.31, 7.31 Hz, 1H), 2.16 (t, *J* = 7.24, 7.24 Hz, 1H), 1.96-1.89 (m, 5H), 1.79-1.25 (m, 39H), 0.98-0.82 (m, 18H). ^{13}C NMR (100 MHz, CD_3OD): δ ppm 176.41, 175.94, 174.98, 174.31, 173.73, 153.55, 133.90, 133.49, 132.84, 132.72, 132.35, 132.28, 132.25, 132.18, 130.02, 130.00, 129.90, 129.88, 121.76, 120.75, 53.75, 53.46, 51.93, 51.51, 51.34, 43.74, 43.43, 41.75, 41.62, 40.30, 40.25, 37.90, 37.03, 36.65, 33.76, 30.22, 30.12, 27.64, 27.60, 27.55, 26.71, 26.54, 25.98, 25.94, 25.89, 23.45, 23.40, 23.30, 22.14, 22.08, 21.98. HRMS: calcd. for $[C_{61}H_{96}N_6O_7P]^+$ 1055.70726, found 1055.70846.

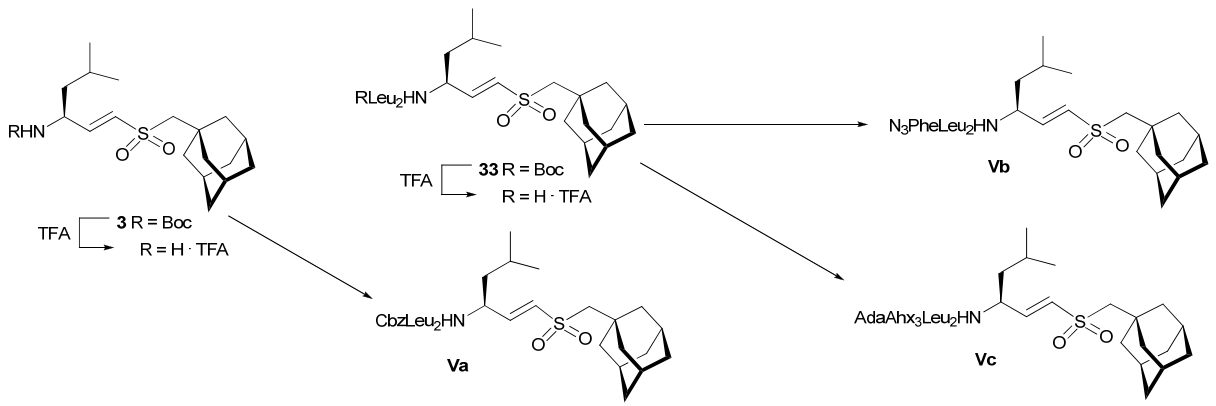


Boc- Leu$_2$-leucinyl vinyl 1-adamantylmethylsulfone (32). Following the general procedure for azide coupling the title compound was obtained from Boc-leucinyl vinyl 1-adamantylsulfone **26** (410 mg, 1 mmol, 1.1 equiv.) and Boc-Leu$_2$-$NHNH_2$ **18 (** 330 mg, 0.91 mmol, 1 equiv). Purification by flash chromatography EA:tol (0-40%) gave the title compound (383 mg, 0.6 mmol, 66%). ^1H NMR (400 MHz, $CDCl_3$): δ ppm 7.36-7.22 (m, 1H), 6.77 (dd, *J* = 15.18, 4.95 Hz, 1H), 6.73-6.71 (m, 1H), 6.42 (d, *J* = 15.11 Hz, 1H), 5.40 (d, *J* = 4.68 Hz, 1H), 4.81-4.71 (m, 1H), 4.47 (dd, *J* = 14.48, 7.85 Hz, 1H), 4.09-4.00 (m, 1H), 2.14 (s, 3H), 2.01-1.91 (m, 6H), 1.78-1.46 (m, 15H), 1.44 (s, 9H), 0.96-0.87 (m, 18H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 172.61, 171.23, 156.05, 150.22, 123.19, 80.19, 59.62, 53.61, 51.97, 48.14, 42.85, 40.75, 40.42, 35.71, 34.44, 28.23, 28.03, 24.87, 24.65, 22.80, 22.62, 22.19, 21.96, 21.82.

Cbz-Leu$_2$-leucinyl vinyl 1-adamantylsulfone (IVa). Following the general procedure for azide coupling the title compound was obtained from Boc-leucinyl vinyl 1-adamantylsulfone **26** (206 mg, 0.5 mmol, 1.1 equiv.) and Cbz-Leu$_2$-NHNH$_2$ **16** (177 mg, 0.45 mmol, 1 equiv). Purification by flash chromatography (EA:tol (0-25%)) gave the title compound (271 mg, 400 µmol, 89%). α_D^{20} -44.4º (c = 1.00, $CHCl_3$). IR (film) 3287, 2957, 2914, 1699, 1645, 1539, 1454, 1263, 1134, 1047, 1028, 976 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.44-7.28 (m, 5H), 6.88 (d, *J* = 6.69 Hz, 1H), 6.76 (dd, *J* = 15.13, 5.06 Hz, 1H), 6.37 (d, *J* = 15.09 Hz, 1H), 5.94 (d, *J* = 6.57 Hz, 1H), 5.14-5.01 (m, 2H), 4.79-4.69 (m, 1H), 4.51 (q, *J* = 7.57 Hz, 1H), 4.19 (dd, *J* = 13.60, 6.89 Hz, 1H), 2.11 (s, 3H), 1.99-1.87 (m, 6H), 1.84-1.33 (m, 15H), 0.93-0.82 (m, 18H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 172.41, 171.28, 156.69, 150.59, 136.25, 128.68, 128.35, 128.01, 123.19, 67.17, 59.86, 54.01, 52.08, 48.37, 42.94, 40.95, 35.89, 34.66, 28.20, 25.15, 24.89, 24.78, 22.97, 22.90, 22.68, 22.44, 22.19, 22.04. HRMS Calcd. for $[C_{37}H_{58}N_3O_6S]^+$ 672.40408, found 672.40442.

Azido-Phe-Leu$_2$-leucinyl vinyl 1-adamantylsulfone (IVb). the general procedure for block coupling, the title compound was obtained from Boc- Leu$_2$-leucinyl vinyl 1-adamantylsulfone **32** (140 mg, 220 µmol, 1 equiv) and azido-phenylalanine **21** (46 mg, 242 µmol, 1.1 equiv.). Flash column chromatography (EA:tol (20-40%)) yielded **IVb** (81 mg, 112 µmol, 52%). α_D^{20} -35.0º (c = 1.00, $CHCl_3$). IR (film) 3287, 2955, 2912, 2112, 1643, 1541, 1456, 1304, 1283, 1259, 1136 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.49 (d, *J* = 8.19 Hz, 1H), 7.38-7.11 (m, 5H), 6.77 (dd, *J* = 15.11, 5.34 Hz, 1H), 6.38 (d, *J* = 15.13 Hz, 1H), 4.82-4.69 (m, 1H), 4.62-4.52 (m, 2H), 4.22 (dd, *J* = 8.26, 4.03 Hz, 1H), 3.19 (dd, *J* = 14.15, 3.83 Hz, 1H), 3.04 (dd, *J* = 14.13, 8.53 Hz, 1H), 2.13 (s, 3H), 1.99-1.88 (m, 6H), 1.84-1.32 (m, 15H), 0.94-0.81 (m, 18H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 171.65, 171.13, 169.03, 150.21, 135.95, 129.29, 128.58, 127.16, 123.33, 64.57, 59.72, 51.92, 51.68, 48.26, 42.87, 41.09, 41.06, 37.89, 35.71, 34.55, 28.04, 24.99, 24.73, 24.53, 22.72, 22.69, 22.24, 22.16, 22.04. HRMS calcd. for $[C_{38}H_{59}N_6O_5S]^+$ 711.42622, found 711.42633.

Ada-Ahx$_3$-Leu$_2$-leucinyl vinyl-1-adamantylsulfone (IVc). Following the general procedure for block coupling, the title compound was obtained from Boc- Leu$_2$-leucinyl vinyl 1-adamantylsulfone **32** (140 mg, 220 µmol, 1 equiv.) and Ada-Ahx$_3$-OH **22** (252 mg, 242 µmol, 1.1 equiv.). Flash column chromatography (EA:MeOH (0-7%)) yielded **IVc** (158 mg, 152 µmol, 69%). α_D^{20} -34.0º (c = 1.00, MeOH). IR (film) 3285, 2910, 2851, 1639, 1541, 1454, 1279, 1134 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.08-7.98 (m, 1H), 7.96-7.87 (m, 2H), 7.84-7.78 (m, 1H), 6.69 (dd, *J* = 15.14, 4.90 Hz, 1H), 6.41 (d, *J* = 15.11 Hz, 1H), 4.67-4.60 (m, 1H), 4.34 (t, *J* = 7.29 Hz, 1H), 4.24 (dd, *J* = 8.46, 6.37 Hz, 1H), 3.19-3.04 (m, 6H), 2.27-2.18 (m, 2H), 2.18-2.04 (m, 7H), 2.00-1.82 (m, 12H), 1.84-1.38 (m, 29H), 1.37-1.22 (m, 6H), 0.97-0.82 (m, 18H). ^{13}C NMR (100 MHz, CD_3OD): δ ppm 176.40, 175.89, 175.81, 175.00, 174.18, 173.68, 152.03, 124.26, 60.82, 53.92, 53.32, 51.93, 51.88, 49.64, 43.74, 43.15, 41.56, 40.31, 40.26, 40.18, 40.13, 37.91, 37.04, 36.99, 36.83, 36.58, 35.64, 33.76, 30.22, 30.13, 29.59, 27.65, 27.62, 27.56, 26.72, 26.53, 26.03, 25.92, 25.89, 23.44, 23.40, 22.11, 22.01, 21.95. HRMS calcd. for $[C_{59}H_{101}N_6O_8S]^+$ 1053.73961, found 1073.74023.



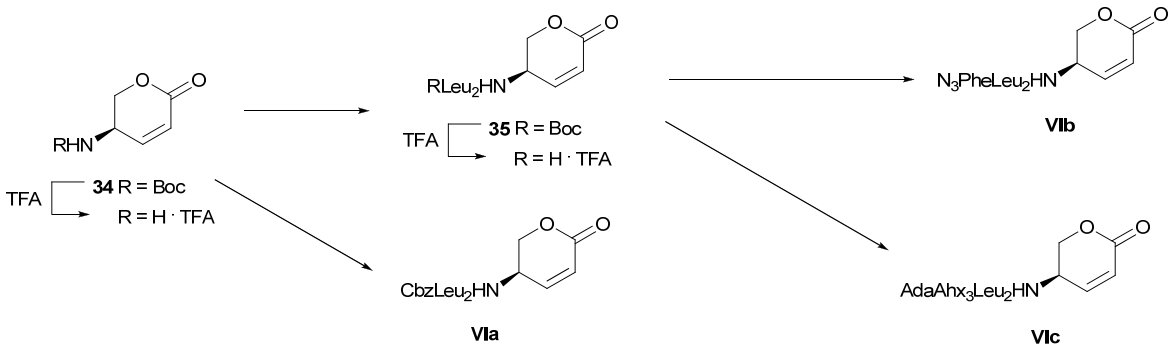
Boc- Leu$_2$-leucinyl vinyl 1-adamantylmethylsulfone (**33**). Following the general procedure for azide coupling the title compound was obtained from Boc-leucinyl vinyl 1-adamantylmethylsulfone **3** (800 mg, 1.88 mmol, 1.1 equiv.) and Boc-Leu$_2$-NHNH$_2$ **18** (610 mg, 1.71 mmol, 1 equiv). Purification by

flash chromatography EA:tol (0-20%) gave the title compound **33** (1.01 g, 1.55 mmol, 91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.38 (d, *J* = 8.32 Hz, 1H), 7.08 (d, *J* = 5.80 Hz, 1H), 6.78 (dd, *J* = 15.06, 5.24 Hz, 1H), 6.52 (d, *J* = 15.03 Hz, 1H), 5.55 (d, *J* = 5.54 Hz, 1H), 4.78-4.69 (m, 1H), 4.52-4.44 (m, 1H), 4.21-4.07 (m, 1H), 2.80 (s, 2H), 2.02-1.97 (m, 3H), 1.84-1.81 (m, 6H), 1.76-1.48 (m, 18H), 1.44 (s, 9H), 0.96-0.86 (m, 18H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 172.76, 171.37, 155.83, 146.35, 130.80, 79.89, 66.90, 53.26, 51.95, 47.60, 42.72, 41.93, 40.48, 36.27, 34.16, 28.19, 24.69, 24.56, 22.76, 22.70, 22.55, 22.12, 21.91.

Cbz-Leu$_2$-leucinyl vinyl 1-adamantylmethylsulfone (Va). Following the general procedure for azide coupling the title compound was obtained from Boc-leucinyl vinyl 1-adamantylmethylsulfone **3** (309 mg, 0.73 mmol, 1.1 equiv.) and Cbz-Leu$_2$-$NHNH_2$ **16** (260 mg, 0.66 mmol, 1 equiv). Purification by flash chromatography (EA:tol (0-25%)) gave the title compound **Va** (365 mg, 530 μmol, 73%). α_D^{20} -50.6º (c = 1.00, $CHCl_3$). IR (film) 3290, 2959, 2907, 1699, 1645, 1539, 1456, 1263, 1240, 1132, 1139, 1028 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.75-7.49 (m, 2H), 7.36-7.25 (m, 5H), 6.76 (dd, *J* = 15.04, 5.19 Hz, 1H), 6.47 (d, *J* = 14.97 Hz, 1H), 6.43-6.29 (m, 1H), 5.14-4.97 (m, 2H), 4.76-4.65 (m, 1H), 4.61-4.52 (m, 1H), 4.41-4.31 (m, 1H), 2.75 (s, 2H), 2.00-1.95 (m, 3H), 1.85-1.22 (m, 21H), 0.94-0.78 (m, 18H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 172.44, 171.37, 156.33, 146.66, 136.24, 130.61, 128.36, 127.94, 127.60, 66.92, 66.71, 53.47, 51.89, 47.62, 42.62, 41.96, 41.32, 40.64, 36.29, 34.20, 28.22, 24.82, 24.53, 22.78, 22.62, 22.56, 22.34, 21.76. HRMS calcd. for $[C_{38}H_{60}N_3O_6S]^+$ 686.41973, found 686.42012.

Azido-Phe-Leu$_2$-leucinyl vinyl 1-adamantylmethylsulfone (Vb). Following the general procedure for block coupling, the title compound was obtained from Boc- Leu$_2$-leucinyl vinyl 1-adamantylmethylsulfone **33** (232 mg, 357 μmol, 1.1 equiv) and azido-phenylalanine **21** (62 mg, 320 μmol, 1 equiv.). Flash column chromatography (EA:tol (0-10-50%)) yielded **Vb** (144 mg, 200 μmol, 62%). α_D^{20} -35.0º (c = 1.00, $CHCl_3$). IR (film) 3277, 2957, 2907, 2851, 2110, 1638, 1541, 1454, 1387, 1313, 1265, 1132, 1119, 968 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.69 (d, *J* = 6.39 Hz, 1H), 7.54 (d, *J* = 8.23 Hz, 1H), 7.48 (d, *J* = 8.11 Hz, 1H), 7.33-7.13 (m, 5H), 6.75 (dd, *J* = 15.07, 5.68 Hz, 1H), 6.44 (d, *J* = 15.02 Hz, 1H), 4.73-4.63 (m, 2H), 4.62-4.54 (m, 1H), 4.24 (dd, *J* = 8.64, 4.16 Hz, 1H), 3.15 (dd, *J* = 14.24, 3.68 Hz, 1H), 3.04 (dd, *J* = 14.23, 8.72 Hz, 1H), 2.77 (s, 2H), 2.02-1.95 (m, 3H), 1.85-1.32 (m, 21H), 0.97-0.80 (m, 18H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 171.72, 171.42, 168.96, 146.10, 135.97, 131.02, 129.23, 128.57, 127.14, 66.88, 64.41, 51.95, 51.54, 47.83, 42.75, 42.02, 41.42, 40.87, 37.84, 36.32, 34.29, 28.26, 24.90, 24.64, 24.55, 22.67, 22.65, 22.46, 22.37, 21.98. HRMS calcd. for $[C_{39}H_{61}N_6O_5S]^+$ 725.44187, found 725.44237.

Ada-Ahx$_3$-Leu$_2$-leucinyl vinyl-1-adamantylmethylsulfone (Vc). Following the general procedure for block coupling, the title compound was obtained from Boc- Leu$_2$-leucinyl vinyl 1-adamantylmethylsulfone **33** (227 mg, 348 μmol, 1.1 equiv.) and Ada-Ahx$_3$-OH **22** (170 mg, 320 μmol, 1.1 equiv.). Flash column chromatography (MeOH:DCM (0-7%)) yielded **Vc** (313 mg, 290 μmol, 92%). α_D^{20} -33.2º (c = 1.00, MeOH). IR (film) 3277, 3080, 2903, 2849, 1636, 1541, 1452, 1367, 1343, 1281, 1117, 1034 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.06 (t, *J* = 7.28, 7.28 Hz, 2H), 7.91 (t, *J* = 4.96, 4.96 Hz, 2H), 7.81 (t, *J* = 4.94, 4.94 Hz, 1H), 6.72 (dd, *J* = 15.10, 5.01 Hz, 1H), 6.56 (d, *J* = 15.11 Hz, 1H), 4.70-4.61 (m, 1H), 4.43-4.29 (m, 2H), 3.21-3.09 (m, 6H), 2.90 (s, 2H), 2.32-2.21 (m, 2H), 2.17 (t, *J* = 7.33, 7.33 Hz, 4H), 2.01-1.23 (m, 61H), 0.99-0.85 (m, 18H). ^{13}C NMR (100 MHz, CD_3OD): δ ppm 176.18, 176.10, 175.74, 175.65, 174.88, 174.80, 174.09, 174.01, 173.52, 147.66, 132.22, 67.65, 53.60, 53.21, 51.87, 49.15, 49.06, 43.66, 43.16, 43.01, 41.56, 41.47, 40.24, 40.19, 37.86, 37.52, 36.99, 36.57, 35.12, 33.69, 30.15, 30.10, 30.03, 29.75, 27.58, 27.54, 27.49, 26.65, 26.50, 25.87, 25.82, 25.76, 23.49, 23.44, 22.18, 22.06, 22.02. HRMS calcd. for $[C_60H_{103}N_6O_8S]^+$ 1067.75526, found 1067.75646.



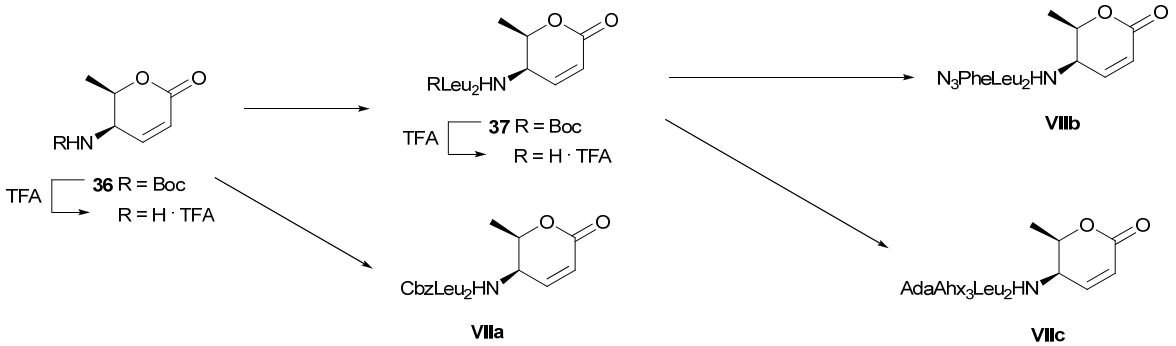
Boc-Leu$_2$- (R)-5-amino-5,6-dihydro-pyran-2-one (35). Following the general procedure for azide coupling the title compound was obtained from (*R)*-5-(Boc-amino)-5,6-dihydro-pyran-2-one **34**[i] (103 mg, 484 µmol, 1.1 equiv.) and Boc-Leu$_2$-NHNH$_2$ **18** (158 m g, 440 µmol, 1 equiv). Purification by flash chromatography (EA:tol (30-60%)) gave the title compound (129 mg, 290 µmol, 67%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.68-7.51 (m, 1H), 6.92-6.84 (m, 2H), 6.08 (d, *J* = 9.67 Hz, 1H), 5.32-5.22 (m, 1H), 4.83-4.71 (m, 1H), 4.51-4.43 (m, 2H), 4.33-4.24 (m, 1H), 4.13-4.03 (m, 1H), 1.78-1.48 (m, 6H), 1.43 (s, 9H), 0.99-0.86 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 172.87, 172.39, 162.76, 155.99, 144.85, 122.45, 80.39, 69.69, 53.58, 51.85, 41.77, 40.61, 28.19, 24.72, 22.85, 21.74.

Cbz-Leu$_2$- (R)-5-amino-5,6-dihydro-pyran-2-one (VIa). Following the general procedure for azide coupling the title compound was obtained from (*R)*-5-(Boc-amino)-5,6-dihydro-pyran-2-one **34**[i] (36 mg, 160 µmol, 1.1 equiv.) and Cbz-Leu$_2$-NHNH$_2$ **16** (59 mg, 150 µmol, 1 equiv). Purification by flash chromatography (EA:tol (20-50%)) gave the title compound **VIa**. α_D^{20} -106.8º (c = 0.94, $CHCl_3$). IR (film) 3288, 2957, 2930, 1717, 1699, 1645, 1533, 1456, 1387, 1261, 1231, 1092, 1040 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.40-7.26 (m, 5H), 6.93 (dd, *J* = 9.74, 4.51 Hz, 1H), 6.10 (dd, *J* = 9.79, 1.05 Hz, 1H), 5.09 (s, 2H), 4.72-4.65 (m, 1H), 4.48 (dd, *J* = 11.56, 4.44 Hz, 1H), 4.38 (dd, *J* = 9.74, 4.96 Hz, 1H), 4.27 (dd, *J* = 11.52, 5.03 Hz, 1H), 4.11 (t, *J* = 7.47 Hz, 1H), 1.77-1.26 (m, 6H), 0.99-0.85 (m, 12H). (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 172.47, 172.20, 162.88, 156.69, 144.16, 135.91, 130.85, 128.55, 128.28, 127.91, 122.85, 69.91, 68.14, 67.31, 54.28, 51.83, 41.57, 40.88, 40.45, 24.88, 24.76, 22.87, 21.73, 21.68. HRMS calcd. for $[C_{25}H_{36}N_3O_6]^+$ 474.25986, found 496.24181.

Azido-Phe-Leu$_2$- (R)-5-amino-5,6-dihydro-pyran-2-one (VIb). Following the general procedure for block coupling, the title compound was obtained from Boc-Leu$_2$- (R)-5-amino-5,6-dihydro-pyran-2-one **35** (44 mg, 100 µmol, 1 equiv) and azido-phenylalanine **21** (21 mg, 110 µmol, 1.1 equiv.). Flash column chromatography (EA:PE (20-70%)) yielded **VIb** (19 mg, 37 µmol, 37%). IR (film) 3279, 2957, 2926, 2112, 1734, 1645, 1541, 1456, 1229, 1094 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.34-7.19 (m, 5H), 6.94 (dd, *J* = 9.76, 4.56 Hz, 1H), 6.11 (d, *J* = 4.56 Hz, 1H), 4.72-4.64 (m, 1H), 4.50 (dd, *J* = 11.53, 4.36 Hz, 1H), 4.41-4.34 (m, 2H), 4.30 (dd, *J* = 11.55, 4.79 Hz, 1H), 3.19 (dd, *J* = 14.00, 4.92 Hz, 1H), 2.98 (dd, *J* = 13.98, 8.48 Hz, 1H), 1.79-1.48 (m, 6H), 1.02-0.83 (m, 12H). ^{13}C NMR (100 MHz, CD_3OD): δ ppm 174.91, 174.33, 171.74, 146.37, 137.87, 130.47, 129.59, 128.04, 123.34, 71.12, 65.51, 53.36, 53.13, 43.16, 41.79, 41.76, 38.67, 25.92, 25.83, 23.45, 23.40, 22.03, 21.97. HRMS calcd for $[C_{26}H_{37}N_6O_5]^+$ 513.28199, found 513.28168.

Ada-Ahx$_3$-Leu$_2$- (R)-5-amino-5,6-dihydro-pyran-2-one (VIc). Following the general procedure for block coupling, the title compound was obtained from Boc-Leu$_2$- (R)-5-amino-5,6-dihydro-pyran-2-one **35** (44 mg, 100 µmol, 1 equiv.) and Ada-Ahx$_3$-OH **22** (57 mg, 110 µmol, 1.1 equiv.). Flash column chromatography (EA:MeOH (0-15%)) yielded **VIc** (76 mg, 89 µmol, 89%). α_D^{20} -54.0º (c = 1.00, MeOH). IR (film) 3285, 2905, 2851, 1732, 1641, 1545, 1439, 1202, 1175, 1134, 1094 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.49 (d, *J* = 7.28 Hz, 1H), 8.11 (d, *J* = 6.68 Hz, 1H), 8.07 (d, *J* = 7.32 Hz, 1H), 8.00-7.92 (m, 2H), 7.90-7.83 (m, 1H), 6.97-6.90 (m, 1H), 6.09 (d, *J* = 9.73 Hz, 1H), 4.74-4.63 (m, 1H), 4.54-4.45 (m, 1H), 4.43-4.24 (m, 3H), 3.22-3.06 (m, 6H), 2.25 (t, *J* = 7.09, 7.09 Hz, 2H), 2.18 (t, *J* = 7.02, 7.02 Hz, 4H), 1.01-0.86 (m, 12H), 1.99-1.89 (m, 5H), 1.81-1.20 (m, 36H). ^{13}C NMR (100 MHz, CD_3OD): δ ppm 176.46, 176.02, 175.93, 175.08, 174.84, 174.75, 173.80, 146.64,

123.18, 71.00, 55.82, 53.55, 53.15, 51.96, 43.77, 43.33, 43.24, 41.84, 41.63, 40.32, 40.27, 40.19, 40.14, 37.93, 37.06, 37.01, 36.68, 33.79, 30.23, 30.17, 30.12, 27.66, 27.57, 26.72, 26.59, 25.93, 25.90, 23.51, 23.43, 22.02, 21.93. HRMS calcd. for $[C_{47}H_{79}N_6O_8]^+$ 855.59539, found 855.59589.



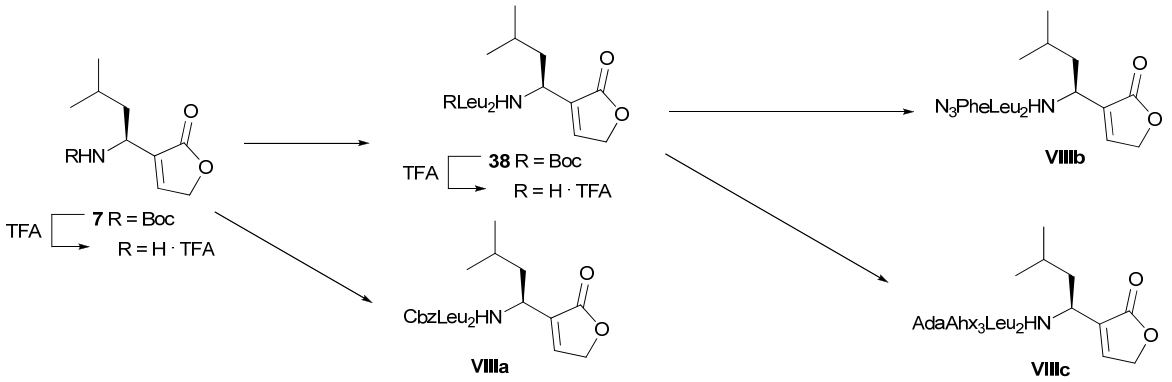
Boc-Leu$_2$-(5R, 6R)-5-amino-6-methyl-5,6-dihydropyran-2-one (37). Following the general procedure for azide coupling the title compound was obtained from (5R, 6R)-5-(Boc-amino)-6-methyl-5,6-dihydropyran-2-one **36**[ii] (112 mg, 495 µmol, 1.1 equiv.) and Boc-Leu$_2$-NHNH$_2$ **18** (161 m g, 450 µmol, 1 equiv). Purification by flash chromatography (EA:tol (30-60%)) gave the title compound **37** (168 mg, 370 µmol, 82%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.52 (d, *J* = 5.55 Hz, 1H), 7.12-7.00 (m, 1H), 6.85 (dd, *J* = 9.59, 5.77 Hz, 1H), 6.12 (d, *J* = 9.63 Hz, 1H), 5.28 (d, *J* = 6.31 Hz, 1H), 4.72-4.64 (m, 2H), 4.50-4.42 (m, 1H), 4.13-4.02 (m, 1H), 1.71-1.44 (m, 6H), 1.43 (s, 9H), 1.31 (d, *J* = 6.27 Hz, 3H), 0.97-0.87 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 172.87, 172.71, 164.00, 155.84, 143.31, 122.73, 80.24, 75.98, 53.05, 51.94, 43.65, 40.83, 40.68, 28.14, 24.65, 22.86, 22.71, 21.88, 21.68, 15.98.

Cbz-Leu$_2$- (5R, 6R)-5-amino-6-methyl-5,6-dihydropyran-2-one (VIIa). Following the general procedure for azide coupling the title compound was obtained from (5R, 6R)-5-(Boc-amino)-6-methyl-5,6-dihydropyran-2-one **36**[ii] (36 mg, 160 µmol, 1.1 equiv.) and Cbz-Leu$_2$-NHNH$_2$ **16** (59 mg, 150 µmol, 1 equiv). Purification by flash chromatography (EA:tol (25-60%)) gave the title compound **VIIa** (13 mg, 27 µmol, 18%). α_D^{20} -278.8º (c = 0.16, $CHCl_3$). IR (film) 2957, 1734, 1717, 1699, 1684, 1668, 1639, 1558, 1541, 1506, 1456, 1387, 1250, 1067 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.42-7.29 (m, 5H), 7.04 (d, *J* = 8.49 Hz, 1H), 6.83 (dd, *J* = 9.46, 6.03 Hz, 1H), 6.38 (d, *J* = 6.79 Hz, 1H), 6.15 (d, *J* = 9.54 Hz, 1H), 5.22 (d, *J* = 3.99 Hz, 1H), 5.19-5.03 (m, 2H), 4.71-4.60 (m, 2H), 4.48-4.38 (m, 1H), 4.11-4.03 (m, 1H), 1.83-1.39 (m, 6H), 1.28 (d, *J* = 6.26 Hz, 3H), 0.99-0.84 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 172.37, 143.02, 128.57, 128.34, 128.19, 123.17, 78.36, 75.97, 70.12, 67.59, 54.38, 52.23, 43.75, 40.73, 40.67, 31.42, 24.99, 24.83, 23.00, 22.88, 21.74, 21.51, 16.23. HRMS calcd. for $[C_{26}H_{38}N_3O_6]^+$ 488.27551, found 488.27512.

Azido-Phe-Leu$_2$- (5R, 6R)-5-amino-6-methyl-5,6-dihydropyran-2-one (VIIb). Following the general procedure for block coupling, the title compound was obtained from Boc-Leu$_2$-(5R, 6R)-5-amino-6-methyl-5,6-dihydropyran-2-one **37** (32 mg, 70 µmol, 1 equiv) and azido-phenylalanine **21** (15 mg, 77 µmol, 1.1 equiv.). Flash column chromatography (EA:PE (20-65%)) yielded **VIIb** (22 mg, 42 µmol, 60%). 3281, 2955, 2926, 2870, 2112, 1736, 1639, 1533, 1456, 1387, 1251, 1069 cm^{-1}.
^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.35-7.20 (m, 5H), 6.92 (dd, *J* = 9.60, 6.12 Hz, 1H), 6.15 (d, *J* = 9.63 Hz, 1H), 4.78-4.68 (m, 1H), 4.63 (dd, *J* = 5.92, 3.31 Hz, 1H), 4.44-4.35 (m, 2H), 4.16 (dd, *J* = 8.38, 4.96 Hz, 1H), 3.19 (dd, *J* = 14.02, 4.93 Hz, 1H), 2.98 (dd, *J* = 13.98, 8.46 Hz, 1H), 1.74-1.22 (m, 9H), 1.00-0.83 (m, 12H). ^{13}C NMR (100 MHz, CD_3OD): δ ppm 174.19, 144.85, 133.33, 130.49, 129.58, 128.03, 123.70, 77.58, 65.55, 53.25, 45.21, 41.91, 41.78, 38.70, 25.94, 25.82, 23.42, 23.35, 22.13, 22.04, 16.73. HRMS calcd. for $[C_{27}H_{39}N_6O_5]^+$ 527.29764, found 527.29736.

Ada-Ahx$_3$-Leu$_2$- 5R, 6R)-5-amino-6-methyl-5,6-dihydropyran-2-one (VIIc). Following the general procedure for block coupling, the title compound was obtained from Boc-Leu$_2$-(5R, 6R)-5-amino-6-methyl-5,6-dihydropyran-2-one **37** (41 mg, 90 µmol, 1 equiv.) and Ada-Ahx$_3$-OH **22** (51 mg, 100 µmol, 1.1 equiv.). Flash column chromatography (EA:MeOH (0-15%)) yielded **VIIc** (31 mg, 35

μmol, 40%). α_D^{20} -100º (c = 0.4, MeOH). IR (film) 3285, 2905, 2851, 1734, 1639, 1541, 1456, 1369, 1257, 1204, 1069 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ ppm 8.42 (d, *J* = 8.28 Hz, 1H), 8.10 (d, *J* = 6.55 Hz, 1H), 8.06 (d, *J* = 6.41 Hz, 1H), 7.99-7.91 (m, 2H), 7.89-7.83 (m, 1H), 6.95-6.87 (m, 1H), 6.14 (d, *J* = 9.39 Hz, 1H), 4.77-4.67 (m, 1H), 4.67-4.59 (m, 1H), 4.45-4.31 (m, 2H), 4.15-4.05 (m, 1H), 3.21-3.10 (m, 6H), 2.29-2.12 (m, 6H), 1.99-1.89 (m, 5H), 1.80-1.18 (m, 41H), 0.98-0.87 (m, 12H). ^{13}C NMR (100 MHz, CD_3OD): δ ppm 176.28, 176.04, 175.08, 174.93, 174.85, 173.83, 144.87, 123.67, 77.55, 53.28, 53.19, 51.97, 45.20, 43.79, 41.87, 41.79, 40.34, 40.29, 37.94, 37.07, 36.72, 33.81, 30.25, 30.19, 30.13, 27.67, 27.59, 26.74, 26.63, 25.93, 23.46, 23.39, 22.11, 22.01, 16.73. HRMS calcd. for $[C_{48}H_{81}N_6O_8]^+$ 869.61104, found 869.61133.

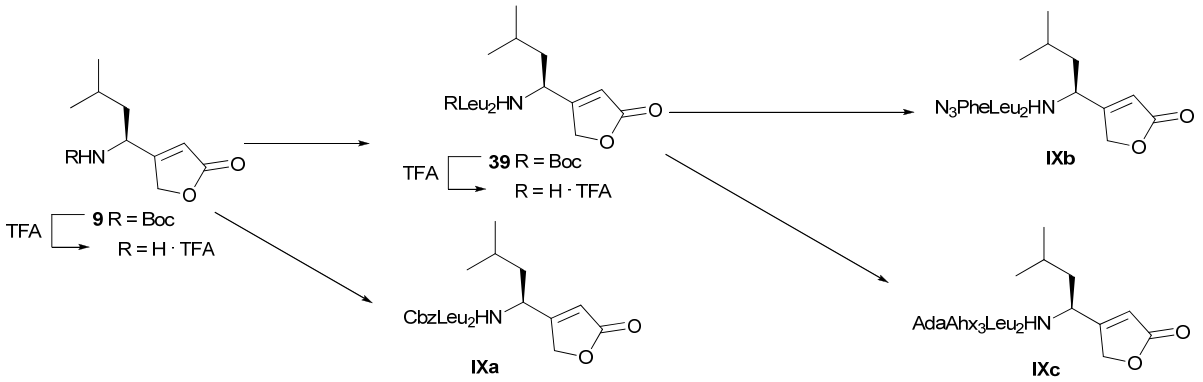


Boc-Leu$_2$- 3-leucinylfuran-2(5H)-one (38). Following the general procedure for azide coupling the title compound was obtained from Boc-3-leucinylfuran-2(5H)-one **7** (71 mg, 264 μmol, 1.1 equiv.) and Boc-Leu$_2$-$NHNH_2$ **18** (86 mg, 240 μmol, 1 equiv). Purification by flash chromatography (EA:tol (30-70%)) gave the title compound (47 mg, 95 μmol, 40%). ^1H NMR (400 MHz, $CDCl_3$ δ ppm 7.38-7.35 (m, 1H), 7.01 (d, *J* = 8.29 Hz, 1H), 6.65 (d, *J* = 7.30 Hz, 1H), 5.11-5.02 (m, 1H), 4.94-4.82 (m, 1H), 4.82-4.75 (m, 2H), 4.43-4.34 (m, 1H), 4.11-4.02 (m, 1H), 1.75-1.40 (m, 18H), 1.02-0.80 (m, 18H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 172.73, 171.32, 156.10, 145.85, 134.29, 80.52, 70.24, 53.63, 52.19, 44.78, 41.65, 40.56, 28.21, 24.78, 22.93, 22.79, 21.76, 21.70, 21.54.

Cbz-Leu$_2$- 3-leucinylfuran-2(5H)-one (VIIIa). Following the general procedure for azide coupling the title compound was obtained from Boc-3-leucinylfuran-2(5H)-one **7** (56 mg, 208 μmol, 1.1 equiv.) and Cbz-Leu$_2$-$NHNH_2$ **16** (79 mg, 200 μmol, 1 equiv). Purification by flash chromatography (EA:tol (20-50%)) gave the title compound **VIIIa** (91 mg, 172 μmol, 86%). α_D^{20} -76.8º (c = 1.00, $CHCl_3$). IR (film) 3346, 3329, 2957, 2870, 1738, 1697, 1672, 1647, 1541, 1506, 1456, 1387, 1367, 1269, 1209, 1070, 1040 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3/CD_3OD$, 1/1): δ ppm 7.72 (d, *J* = 8.27 Hz, 1H), 7.43-7.28 (m, 6H) , 5.11 (q, *J* = 12.32, 12.28, 12.28 Hz, 2H), 4.45-4.41 (m, 3H), 4.40-4.35 (m, 1H), 4.15 (dd, *J* = 8.19, 6.69 Hz, 1H), 1.75-1.43 (m, 9H), 1.02-0.82 (m, 18H). ^{13}C NMR (100 MHz, $CDCl_3/CD_3OD$, 1/1): δ ppm 173.37, 172.96, 171.98, 156.70, 146.27, 135.73, 134.03, 128.08, 127.75, 127.32, 70.26, 66.56, 53.65, 51.68, 44.31, 41.23, 40.55, 39.76, 24.38, 24.26, 22.41, 22.32, 22.28, 21.05, 20.96, 20.82. HRMS calcd for $[C_{29}H_{44}N_3O_6]^+$ 530.32246, found 530.32230.

Azido-Phe-Leu$_2$-3-leucinylfuran-2(5H)-one (VIIIb). Following the general procedure for block coupling, the title compound was obtained from Boc-Leu$_2$- 3-leucinylfuran-2(5H)-one **38** (24.6 mg, 50 μmol, 1 equiv) and azido-phenylalanine **21** (12 mg, 64 μmol, 1.3 equiv.). Flash column chromatography (MeOH:DCM (0-2.5%)) yielded **VIIIb** (14 mg, 25 μmol, 50%). IR (film) 3277, 2957, 2932, 2110, 1749, 1639, 1541, 1457, 1387, 1340, 1287, 1207, 1067, 1049 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$ δ ppm 7.36-7.21 (m, 5H), 6.98 (d, *J* = 8.58 Hz, 1H), 6.80 (d, *J* = 7.55 Hz, 1H), 6.58 (d, *J* = 7.89 Hz, 1H), 4.90 (dd, *J* = 15.58, 8.09 Hz, 1H), 4.82-4.77 (m, 2H), 4.47-4.32 (m, 2H), 4.27 (dd, *J* = 7.72, 4.09 Hz, 1H), 3.29 (dd, *J* = 14.09, 3.94 Hz, 1H), 3.07 (dd, *J* = 14.13, 7.76 Hz, 1H), 1.80-1.20 (m, 9H), 0.95-0.81 (m, 18H). HRMS calcd for $[C_{30}H_{45}N_6O_5]^+$ 569.34459, found 569.34450.

Ada-Ahx$_3$-Leu$_2$- 3-leucinylfuran-2(5H)-one (VIIIc). Following the general procedure for block coupling, the title compound was obtained from Boc-Leu$_2$- 3-leucinylfuran-2(5H)-one **38** (23 mg, 46 µmol, 1 equiv.) and Ada-Ahx$_3$-OH **22** (27 mg, 51 µmol, 1.1 equiv.). Flash column chromatography (MeOH:DCM (3-8%)) yielded **VIIIc** (40 mg, 44 µmol, 95%). α_D^{20} -35.2º (c = 0.66, MeOH). IR (film) 3275, 2905, 1747, 1636, 1541, 1456, 1340, 1205, 1067, 1045 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD δ ppm 8.23-8.07 (m, 4H), 7.97 (t, *J* = 4.76 Hz, 1H), 7.50-7.47 (m, 1H), 4.87-4.82 (m, 2H), 4.80-4.70 (m, 1H), 4.41-4.26 (m, 2H), 3.22-3.09 (m, 6H), 2.28 (t, *J* = 7.38 Hz, 2H), 2.20 (t, *J* = 7.32 Hz, 4H), 1.98-1.88 (m, 5H), 1.79-1.23 (m, 39H), 0.99-0.84 (m, 18H). ^{13}C NMR (100 MHz, CD_3OD): δ ppm 176.67, 176.18, 176.15, 176.09, 175.25, 174.99, 174.27, 173.87, 149.49, 148.79, 135.42, 72.18, 53.92, 53.50, 51.94, 51.88, 49.86, 45.53, 43.71, 42.92, 41.60, 41.42, 40.32, 40.19, 40.13, 40.00, 37.86, 37.01, 36.70, 36.65, 33.79, 30.11, 30.01, 29.97, 27.51, 27.47, 27.32, 26.58, 26.51, 25.90, 25.88, 25.86, 23.59, 23.43, 23.41, 22.01, 21.90, 21.85. HRMS calcd for $[C_{51}H_{87}N_6O_8]^+$ 911.65799, found 911.65872.



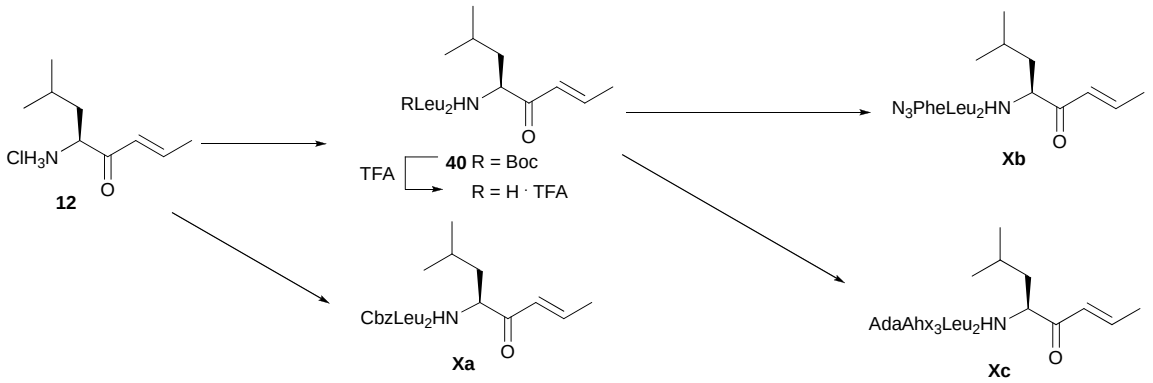
Boc-Leu$_2$-4-leucinyl-furan-2(5H)-one (39). Following the general procedure for azide coupling the title compound was obtained from Boc-4-leucinyl-furan-2(5H)-one **9** (124 mg, 0.46 mmol, 1.1 equiv.) and Boc-Leu$_2$-NHNH$_2$ **18** (149 mg, 0.42 mmol, 1 equiv). Purification by flash chromatography EA:tol (20-50%) gave the title compound (118 mg, 0.24 mmol, 57%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 6.62-6.58 (m, 1H), 5.92 (s, 1H), 5.13-5.08 (m, 1H), 4.96-4.74 (m, 3H), 4.58-4.50 (m, 1H), 4.03-3.95 (m, 1H), 1.70-1.40 (m, 18H), 1.05-0.96 (m, 18H).

Cbz-Leu$_2$-4-leucinyl-furan-2(5H)-one (IXa). Following the general procedure for azide coupling the title compound was obtained from Boc-4-leucinyl-furan-2(5H)-one **9** (77 mg, 286 µmol, 1.1 equiv.) and Cbz-Leu$_2$-NHNH$_2$ **16** (102 mg, 260 µmol, 1 equiv). Purification by flash chromatography (EA:tol (30-70%)) gave the title compound (112 mg, 211 µmol, 81%). α_D^{20} -80.2º (c = 1.00, $CHCl_3$). IR (film) 3269, 2957, 2934, 2870, 1782, 1751, 1699, 1668, 1641, 1539, 1471, 1456, 1387, 1369, 1261, 1238, 1153, 1120, 1030 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$ δ ppm 7.41 (d, *J* = 8.16 Hz, 1H), 7.36-7.24 (m, 5H), 6.13 (d, *J* = 4.81 Hz, 1H), 5.92-5.89 (m, 1H), 5.15-4.97 (m, 2H), 4.88-4.66 (m, 3H), 4.43 (dd, *J* = 14.23, 7.30 Hz, 1H), 4.25-4.17 (m, 1H), 1.86-1.31 (m, 9H), 0.95-0.81 (m, 18H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 173.74, 172.69, 172.05, 171.63, 156.78, 135.81, 128.53, 128.25, 127.59, 115.17, 71.61, 66.96, 54.24, 52.22, 45.81, 41.82, 41.07, 40.06, 24.92, 24.67, 24.44, 23.19, 22.69, 22.57, 21.96, 21.86, 21.16. HRMS calcd. for $[C_{29}H_{44}N_3O_6]^+$ 530.32246, found 530.32224.

Azido-Phe-Leu$_2$-4-leucinyl-furan-2(5H)-one (**IXb).** Following the general procedure for block coupling, the title compound was obtained from Boc-Leu$_2$-4-leucinyl-furan-2(5H)-one **39** (59 mg, 120 µmol) and azido-phenylalanine **21** (26 mg, 130 µmol, 1.1 equiv.). Flash column chromatography (EA:tol (30-60%) yielded **IXb** (31 mg, 55 µmol, 45%). α_D^{20} -61.6º (c = 0.38, $CHCl_3$). IR (film) 3273, 2957, 2932, 2872, 2110, 1782, 1753, 1638, 1541, 1465, 1437, 1387, 1369, 1248, 1223, 1153, 1032 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.36-7.20 (m, 5H), 7.06-7.02 (m, 1H), 6.82-6.78 (m, 1H), 6.75-6.71 (m, 1H), 5.94-5.92 (m, 1H), 4.88-4.73 (m, 3H), 4.42-4.35 (m, 1H), 4.33-4.25 (m, 2H), 3.27 (dd, J_1 = 14.1 Hz, J_2 = 4.2 Hz, 1H), 3.08 (dd, J_1 = 14.1 Hz, J_2 = 7.5 Hz, 1H), 1.80-1.30 (m, 9H), 0.98-0.80 (m, 18H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 171.77, 171.66, 171.11, 169.34, 135.41, 129.39, 128.71, 127.40, 115.44, 71.59, 64.91, 52.34, 52.07, 45.94, 42.02, 40.60, 39.97, 38.05, 24.95, 24.64,

24.59, 23.16, 22.76, 22.72, 21.90, 21.87, 21.34. HRMS: calcd. for $[C_{30}H_{45}N_6O_5]^+$ 569.34459, found 569.34443.

Ada-Ahx$_3$-Leu$_2$-4-leucinyl-furan-2(5H)-one (IXc). Following the general procedure for block coupling, the title compound was obtained from Boc-Leu$_2$-4-leucinyl-furan-2(5H)-one **39** (59 mg, 120 µmol) and Ada-Ahx$_3$-OH **22** (69 mg, 130 µmol, 1.1 equiv.). Flash column chromatography (MeOH:DCM (0-7%) yielded **IXc** (87 mg, 96 µmol, 80%). α_D^{20} -54.0º (c = 1.00, MeOH). IR (film) 3285, 2928, 2903, 2870, 1780, 1747, 1638, 1541, 1439, 1367, 1277, 1242, 1155, 1032 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD): δ ppm 7.85 (t, *J* = 5.2 Hz, 1H), 7.95 (t, *J* = 5.4 Hz, 2H), 5.95 (d, *J* = 1.5 Hz, 1H), 4.91-4.84 (m, 3H), 4.38-4.27 (m, 2H), 3.18-3.11 (m, 6H), 2.28-2.22 (m, 2H), 2.17 (t, *J* = 7.5 Hz, 4H), 1.96-1.92 (m, 3H), 1.92-1.90 (m, 2H), 1.83-1.44 (m, 33H), 1.39-1.29 (m, 6H), 0.98-0.88 (m, 18H). ^{13}C NMR (100 MHz, CD_3OD): δ ppm 176.41, 175.95, 175.86, 175.06, 174.52, 174.27, 173.73, 115.72, 73.25, 53.65, 53.35, 51.94, 47.29, 43.75, 42.60, 41.62, 41.40, 40.31, 40.26, 40.18, 37.91, 37.04, 36.99, 36.62, 33.77, 30.22, 30.14, 27.65, 27.60, 27.56, 26.72, 26.54, 25.97, 25.90, 25.71, 23.70, 23.40, 22.11, 21.93, 21.49. HRMS: calcd. for $[C_{51}H_{87}N_6O_8]^+$ 911.65799, found 911.65874.



Cbz-Leu$_2$-(S,E)-5-amino-7-methyloct-2-en-4-one (Xa). Following the general procedure for azide coupling the title compound was obtained from (E,S)-1-isobutyl-2-oxo-pent-3-enyl-amine HCl salt **12** (38 mg, 200 µmol, 1.1 equiv.) and Cbz-Leu$_2$-NHNH$_2$ **16** (71 mg, 180 µmol, 1 equiv). Purification by flash chromatography (EA:tol (0-25%)) gave the title compound (62 mg, 120 µmol, 67%). α_D^{20} -45.5º (c = 0.8, $CHCl_3$). IR (film) 3263, 2955, 2936, 2870, 1699, 1663, 1641, 1539, 1466, 1437, 1387, 1367, 1286, 1261, 1234, 1121, 1045, 1028, 970 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.35-7.25 (m, 5H), 7.21 (d, *J* = 8.27 Hz, 1H), 6.20 (dd, *J* = 15.65, 1.56 Hz, 1H), 5.82 (d, *J* = 1.56 Hz, 1H), 5.16-5.01 (m, 2H), 4.88 (dt, *J* = 9.25, 9.17, 4.10 Hz, 1H), 4.59 (dd, *J* = 15.15, 7.54 Hz, 1H), 4.35-4.26 (m, 1H), 1.90 (dd, *J* = 6.86, 1.46 Hz, 3H), 1.76-1.35 (m, 9H), 0.94-0.82 (m, 18H), 7.06-6.95 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 197.92, 172.09, 171.48, 156.19, 144.83, 136.34, 128.67, 128.40, 127.98, 127.84, 66.81, 54.21, 53.36, 51.66, 41.59, 41.19, 40.84, 24.78, 24.66, 24.57, 23.25, 22.72, 22.45, 22.19, 21.82, 18.41. HRMS calcd. for $[C_{29}H_{46}N_3O_5]^+$ 516.3432, found 516.34294.

Boc-Leu$_2$-(S,E)-5-amino-7-methyloct-2-en-4-one (40). Following the general procedure for azide coupling the title compound was obtained from (E,S)-1-isobutyl-2-oxo-pent-3-enyl-amine HCl salt **12** (100 mg, 520 µmol, 1.1 equiv.) and Boc-Leu$_2$-NHNH$_2$ **18** (170 mg, 470 µmol, 1 equiv). Purification by flash chromatography (EA:tol (0-25%)) gave the title compound (119 mg, 250 µmol, 48%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.02 (dq, *J* = 15.51, 6.87 Hz, 1H), 6.85 (d, *J* = 7.39 Hz, 1H), 6.68 (d, *J* = 7.85 Hz, 1H), 6.21 (dd, *J* = 15.64, 1.66 Hz, 1H), 5.07 (d, *J* = 6.64 Hz, 1H), 4.89-4.82 (m, 1H), 4.54-4.45 (m, 1H), 4.17-4.07 (m, 1H), 1.93 (dd, *J* = 6.88, 1.60 Hz, 3H), 1.73-1.34 (m, 18H), 0.99-0.85 (m, 18H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 197.79, 172.47, 171.49, 155.68, 144.85, 128.56, 54.37, 52.99, 51.65, 41.18, 40.97, 28.24, 24.80, 24.67, 24.58, 23.24, 22.80, 22.06, 21.85, 18.44.

Azido-Phe-Leu$_3$-(S,E)-5-amino-7-methyloct-2-en-4-one (Xb). Following the general procedure for block coupling, the title compound was obtained from Boc-Leu$_2$-(S,E)-5-amino-7-methyloct-2-en-4-one **40** (40 mg, 83 µmol, 1 equiv) and azido-phenylalanine **21** (23 mg, 120 µmol, 1.45 equiv.). Flash

column chromatography (MeOH:DCM (0-4%)) yielded **Xb** (36 mg, 66 µmol, 79%). α_D^{20} -31.7º (c = 0.46, $CHCl_3$). IR (film) 3273, 2955, 2930, 2870, 2110, 1638, 1541, 1456, 1437, 1387, 1367, 1255, 1221, 1152, 970 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ ppm 7.33-7.18 (m, 5H), 7.00 (dq, *J* = 20.73, 6.87 Hz, 1H), 6.28 (dd, *J* = 15.61, 1.66 Hz, 1H), 4.70 (dd, *J* = 9.12, 5.42 Hz, 1H), 4.47-4.41 (m, 1H), 4.14 (dd, *J* = 8.49, 5.00 Hz, 1H), 3.18 (dd, *J* = 14.03, 4.98 Hz, 1H), 2.97 (dd, *J* = 14.03, 8.51 Hz, 1H), 1.91 (dd, *J* = 6.87, 1.60 Hz, 3H), 1.74-1.45 (m, 9H), 1.00-0.85 (m, 18H). ^{13}C NMR (100 MHz, CD_3OD): δ ppm 199.71, 174.31, 174.06, 145.97, 137.86, 130.44, 129.59, 129.37, 128.04, 65.49, 56.27, 53.10, 52.99, 42.06, 41.90, 40.91, 38.69, 25.97, 25.83, 23.68, 23.42, 23.33, 22.32, 22.14, 21.93, 18.54. HRMS calcd. for $[C_{30}H_{47}N_6O_4]^+$ 555.36533, found 555.36519.

Ada-Ahx$_3$-Leu$_2$-(S,E)-5-amino-7-methyloct-2-en-4-one (Xc). Following the general procedure for block coupling, the title compound was obtained from Boc-Leu$_2$-(S,E)-5-amino-7-methyloct-2-en-4-one **40** (59 mg, 122 µmol, 1 equiv.) and Ada-Ahx$_3$-OH **22** (72 mg, 135 µmol, 1.1 equiv.). Flash column chromatography (MeOH:DCM (2-8%)) yielded **Xc** (88 mg, 98 µmol, 80%). α_D^{20} -44.0º (c = 1.00, MeOH). IR (film) 3281, 2928, 2905, 2868, 1636, 1545, 1439, 1367, 1276, 1171, 1067, 972 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ ppm 8.22 (d, *J* = 7.90 Hz, 1H), 8.08 (t, *J* = 6.69, 6.69 Hz, 2H), 7.95 (t, *J* = 5.01, 5.01 Hz, 2H), 7.88-7.82 (m, 1H), 7.04-6.94 (m, 1H), 6.32-6.26 (m, 1H), 4.68 (dd, *J* = 14.25, 8.13 Hz, 2H), 4.49-4.34 (m, 2H), 3.19-3.09 (m, 6H), 2.23 (t, *J* = 7.37, 7.37 Hz, 2H), 2.17 (t, *J* = 7.41, 7.41 Hz, 1H), 1.98-1.88 (m, 5H), 1.78-1.43 (m, 36H), 1.39-1.27 (m, 6H), 0.97-0.87 (m, 18H). ^{13}C NMR (100 MHz, CD_3OD): δ ppm 199.63, 176.09, 175.95, 174.78, 174.46, 173.74, 145.86, 129.25, 56.38, 53.17, 52.99, 51.93, 43.74, 41.92, 41.85, 40.85, 40.31, 40.25, 37.90, 37.03, 36.98, 36.68, 33.76, 30.21, 30.13, 27.64, 27.56, 26.71, 26.61, 25.91, 25.78, 23.69, 23.45, 23.40, 22.22, 22.06, 21.90, 18.56. HRMS calcd. for $[C_{51}H_{89}N_6O_7]^+$ 897.67873, found 897.67942.

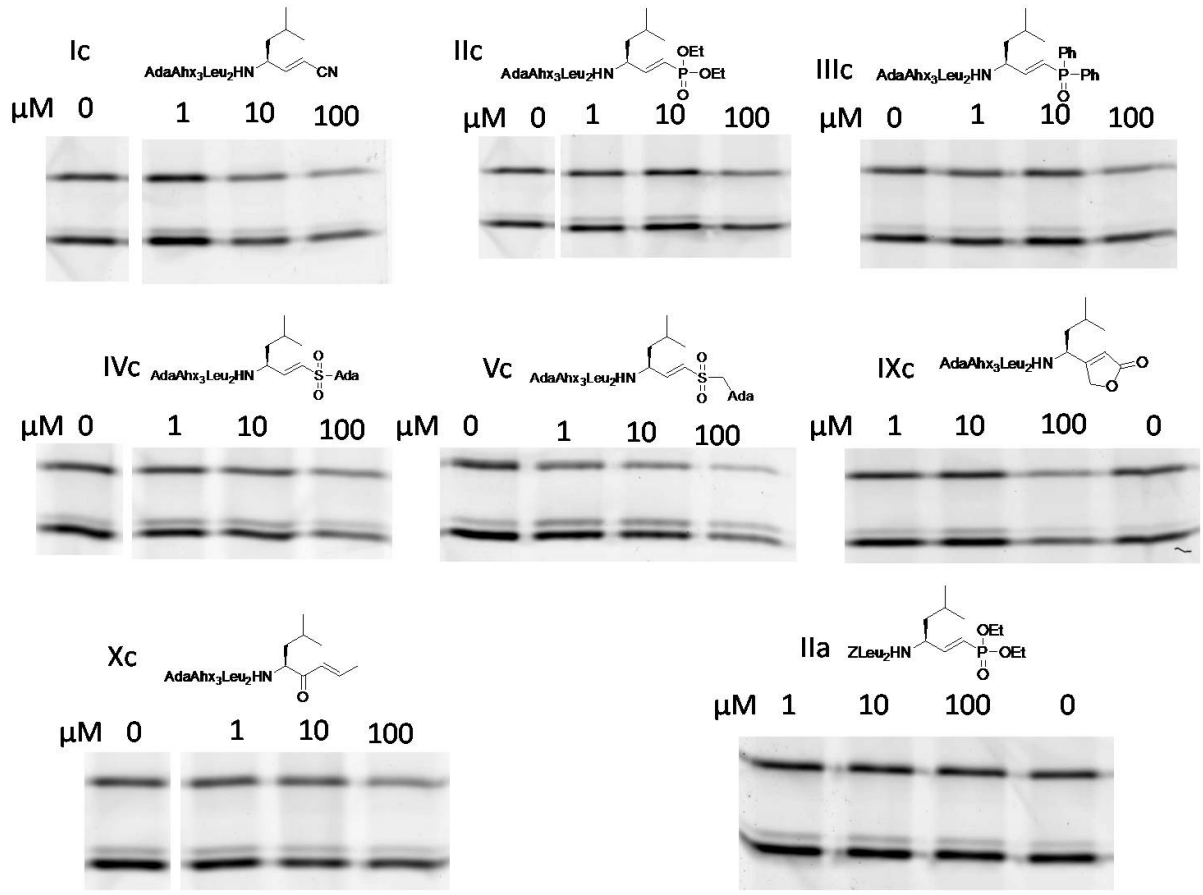


Figure S1: Competition assay of indicated inhibitors at indicated final concentration in HEK293T cells, 37ºC 1h, then MV151 (0.5 µM final conc.) 1h, 37ºC. Inhibitor **IIa** included as measure of no activity.

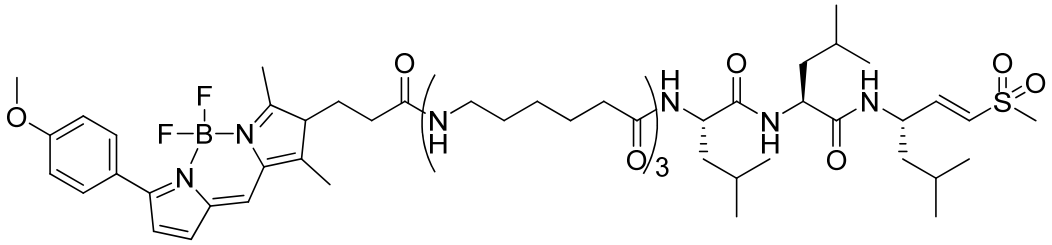
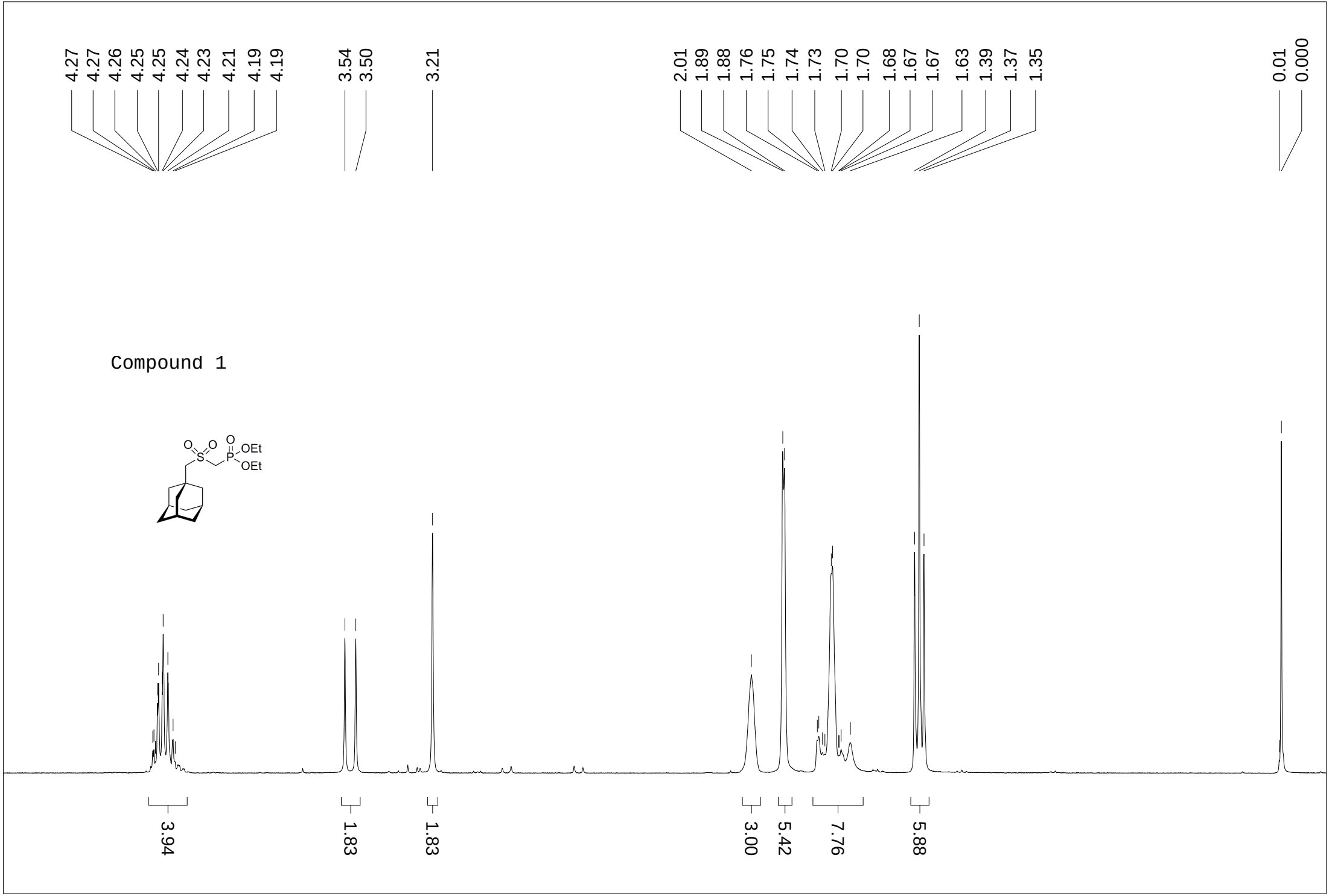
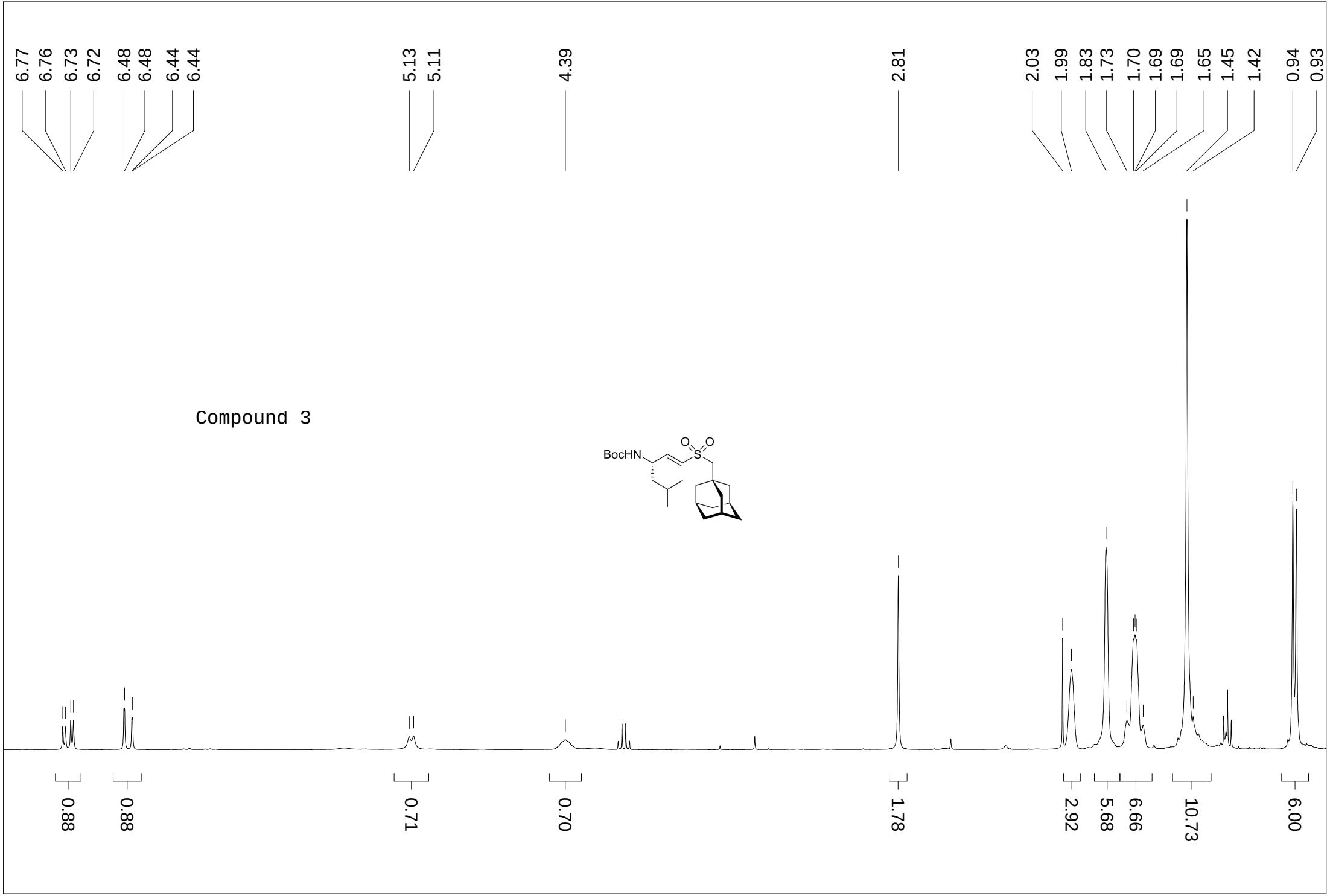


Figure S2: Fluorescent proteasome probe MV151 used in competition assays

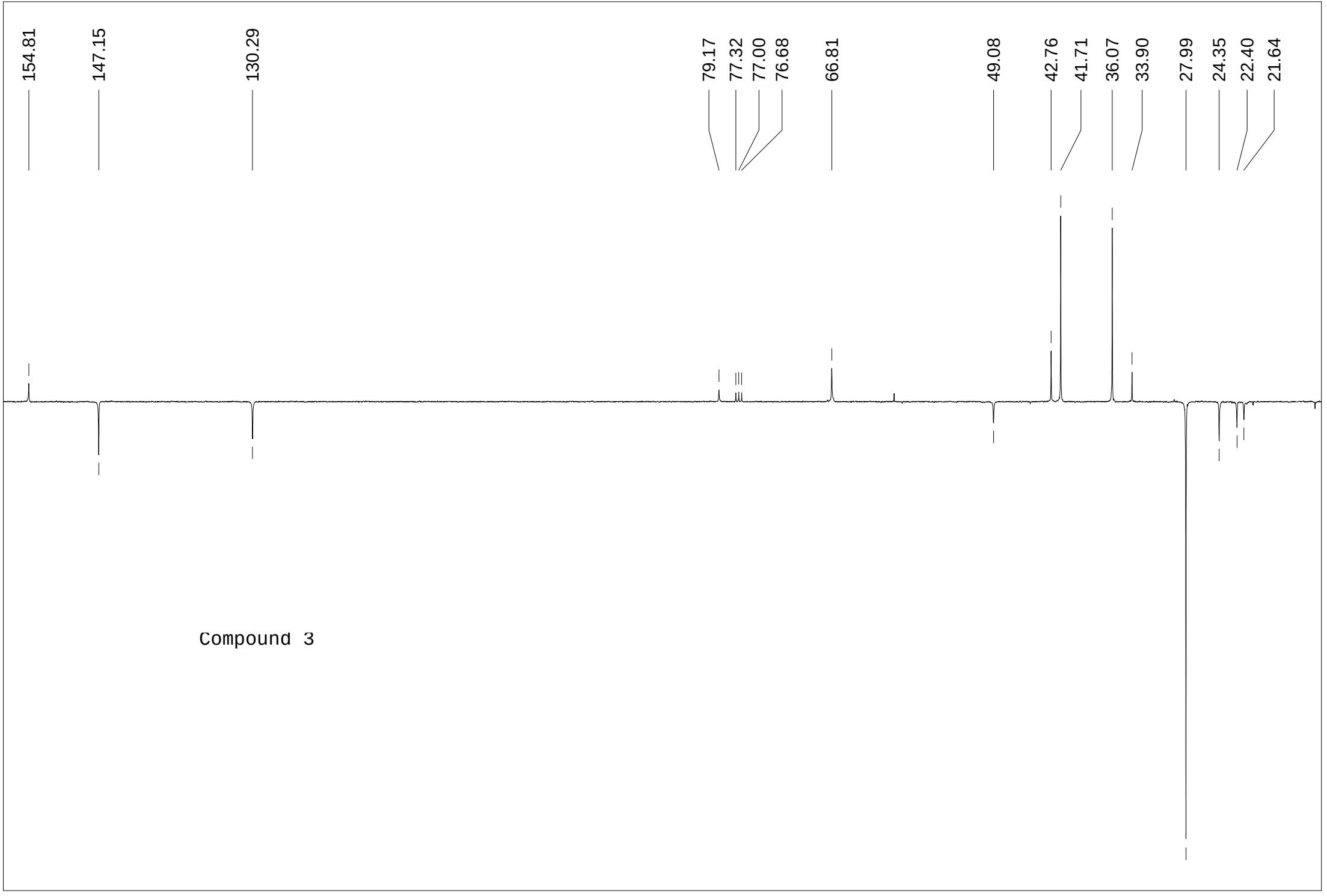
---

[i] M. G. B. Drew, R. J. Harrison, J. Mann, A. J. Tench, R.J. Young, *Tetrahedron*, **1999**, *55*, 1163-1172
[ii] A.M.P. Koskinen, L. A. Otsomaa, *Tetrahedron,* **1997**, *53*, 6473-6484

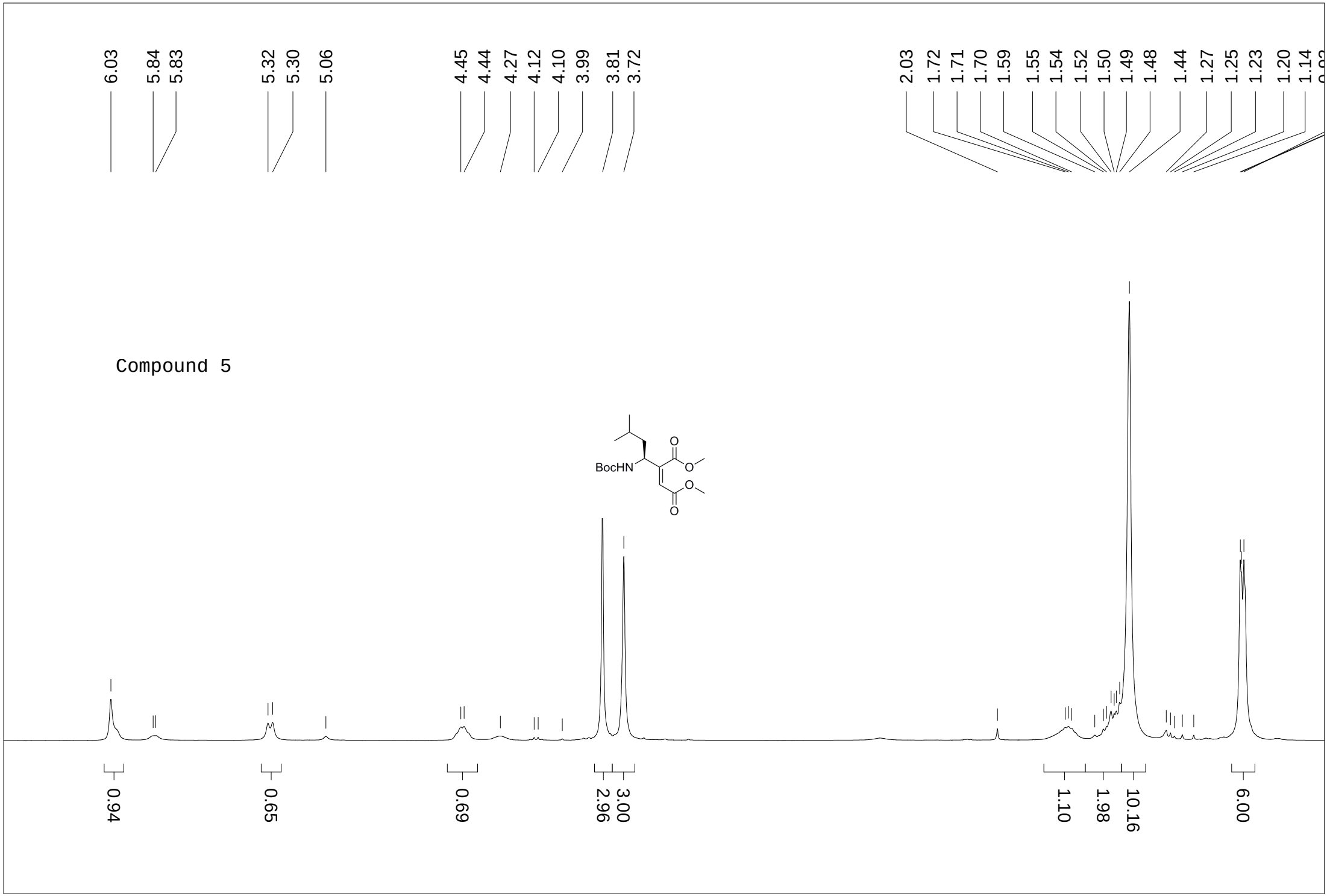

4.27
4.27
4.26
4.25
4.25
4.24
4.23
4.21
4.19
4.19
3.54
3.50
3.21
2.01
1.89
1.88
1.76
1.75
1.74
1.73
1.70
1.70
1.68
1.67
1.67
1.63
1.39
1.37
1.35
0.01
0.000
Compound 1
O
S
O
O
P
OEt
OEt
3.94
1.83
1.83
3.00
5.42
7.76
5.88
ppm (f1)

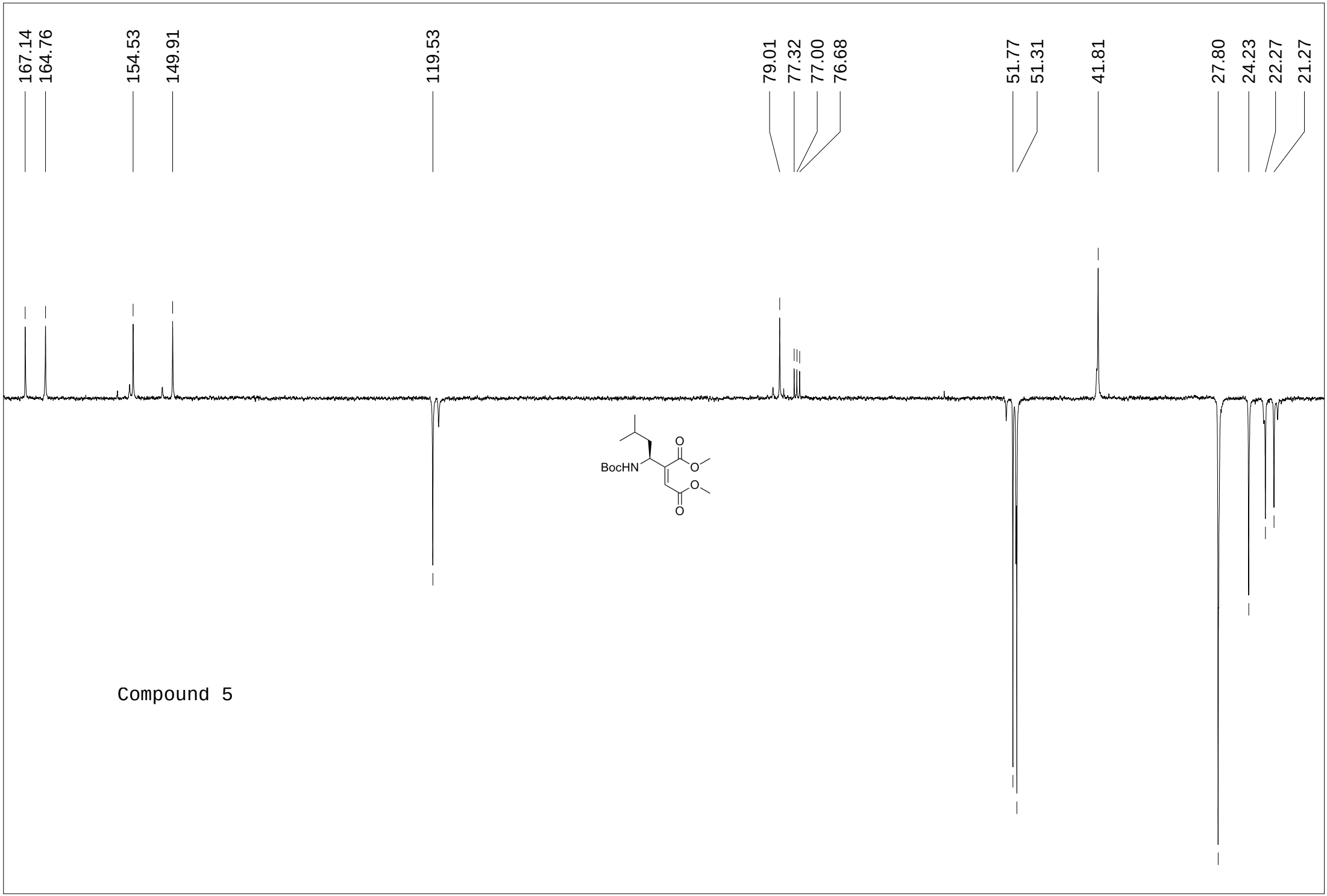

6.77
6.76
6.73
6.72
6.48
6.48
6.44
6.44
5.13
5.11
4.39
2.81
2.03
1.99
1.83
1.73
1.70
1.69
1.69
1.65
1.45
1.42
0.94
0.93
Compound 3
BocHN
O
O
S
0.88
0.88
0.71
0.70
1.78
2.92
5.68
6.66
10.73
6.00

ppm (f1)

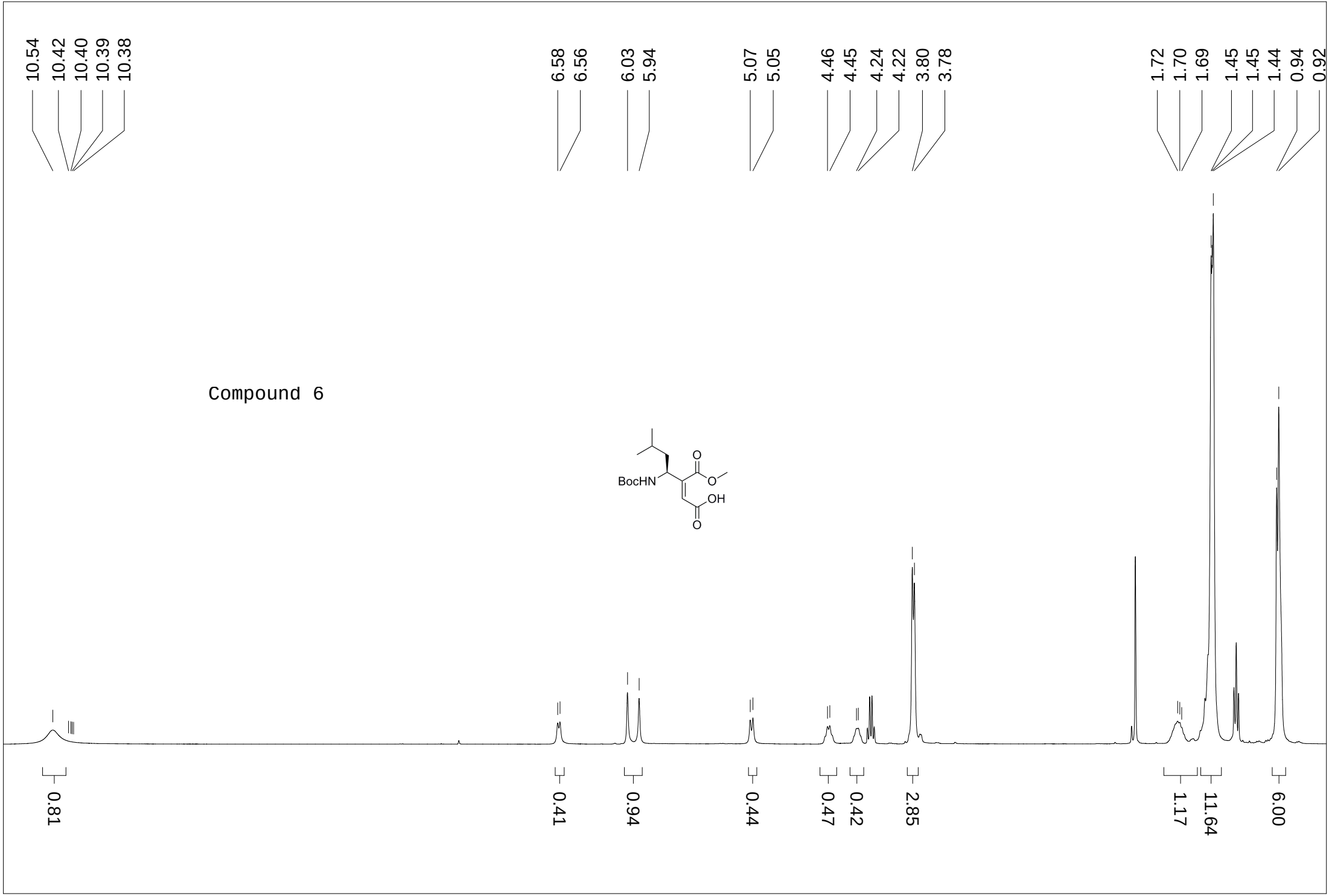

154.81
147.15
130.29
79.17
77.32
77.00
76.68
66.81
49.08
42.76
41.71
36.07
33.90
27.99
24.35
22.40
21.64
Compound 3

ppm (f1)

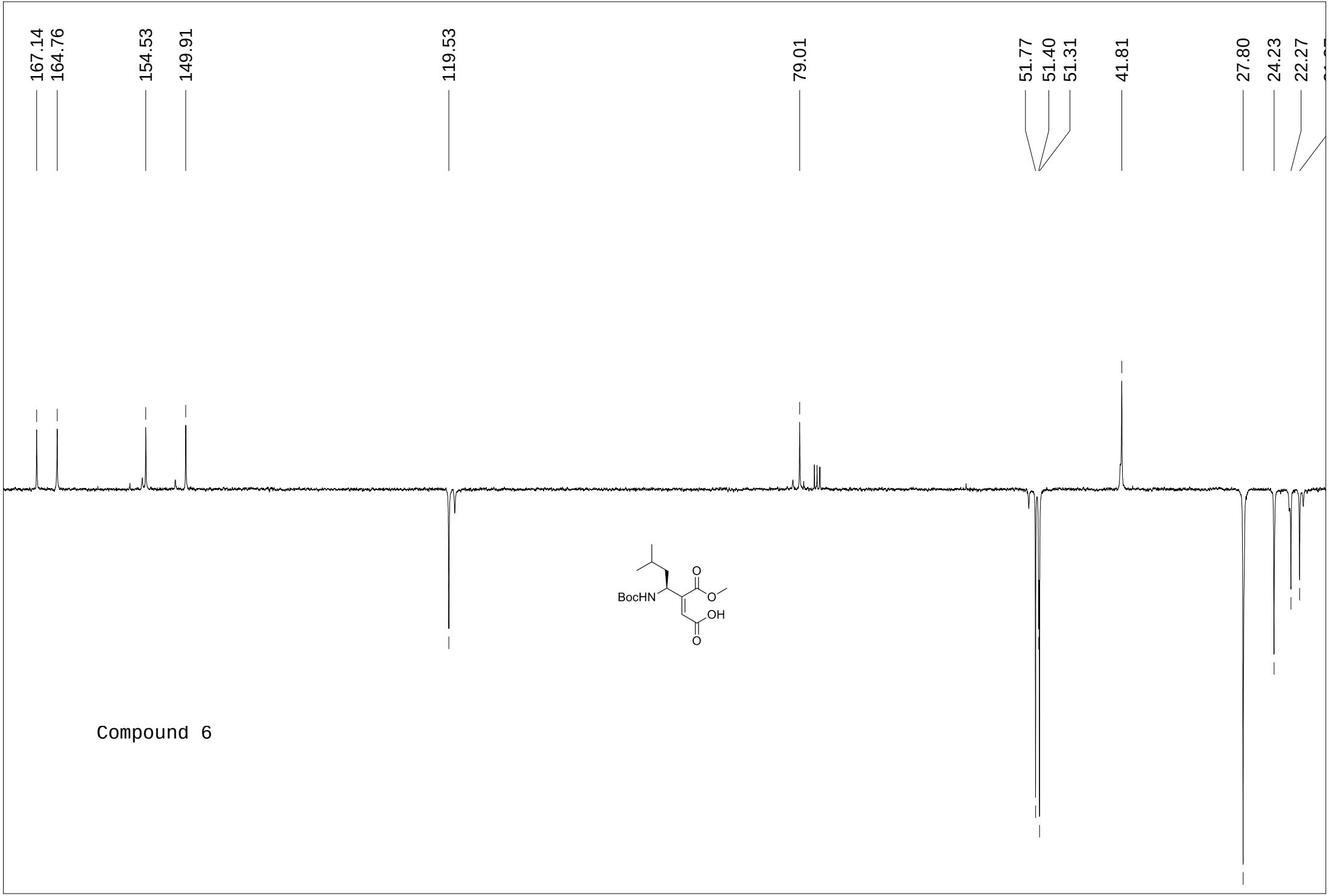

6.03
5.84
5.83
5.32
5.30
5.06
4.45
4.44
4.27
4.12
4.10
3.99
3.81
3.72
2.03
1.72
1.71
1.70
1.59
1.55
1.54
1.52
1.50
1.49
1.48
1.44
1.27
1.25
1.23
1.20
1.14
Compound 5
BocHN
O
O
O
O
0.94
0.95
0.69
2.96
3.00
1.10
1.98
10.16
6.00
ppm (f1)


167.14
164.76
154.53
149.91
119.53
79.01
77.32
77.00
76.68
51.77
51.31
41.81
27.80
24.23
22.27
21.27
BocHN
O
O
O
O
Compound 5

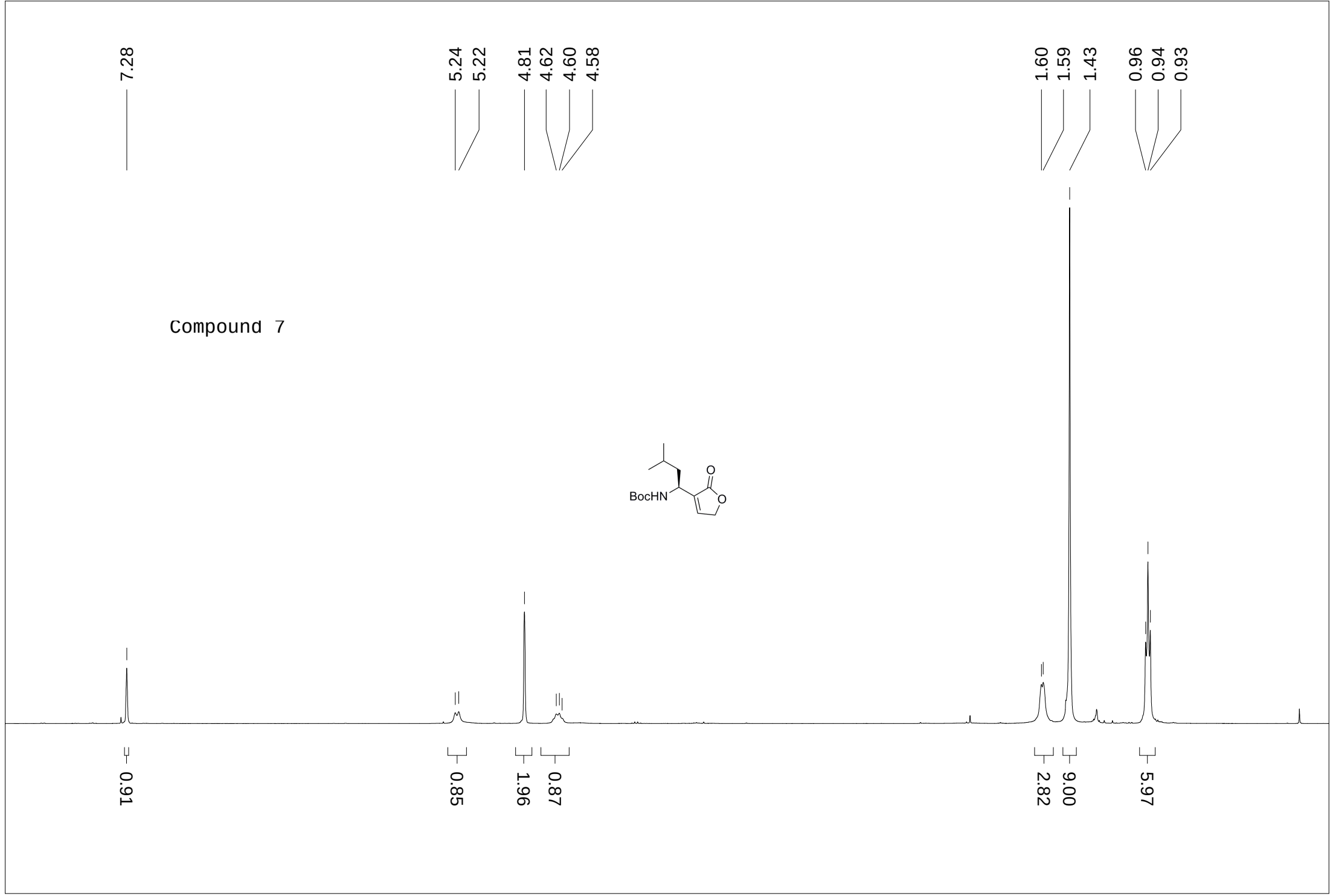
ppm (f1)

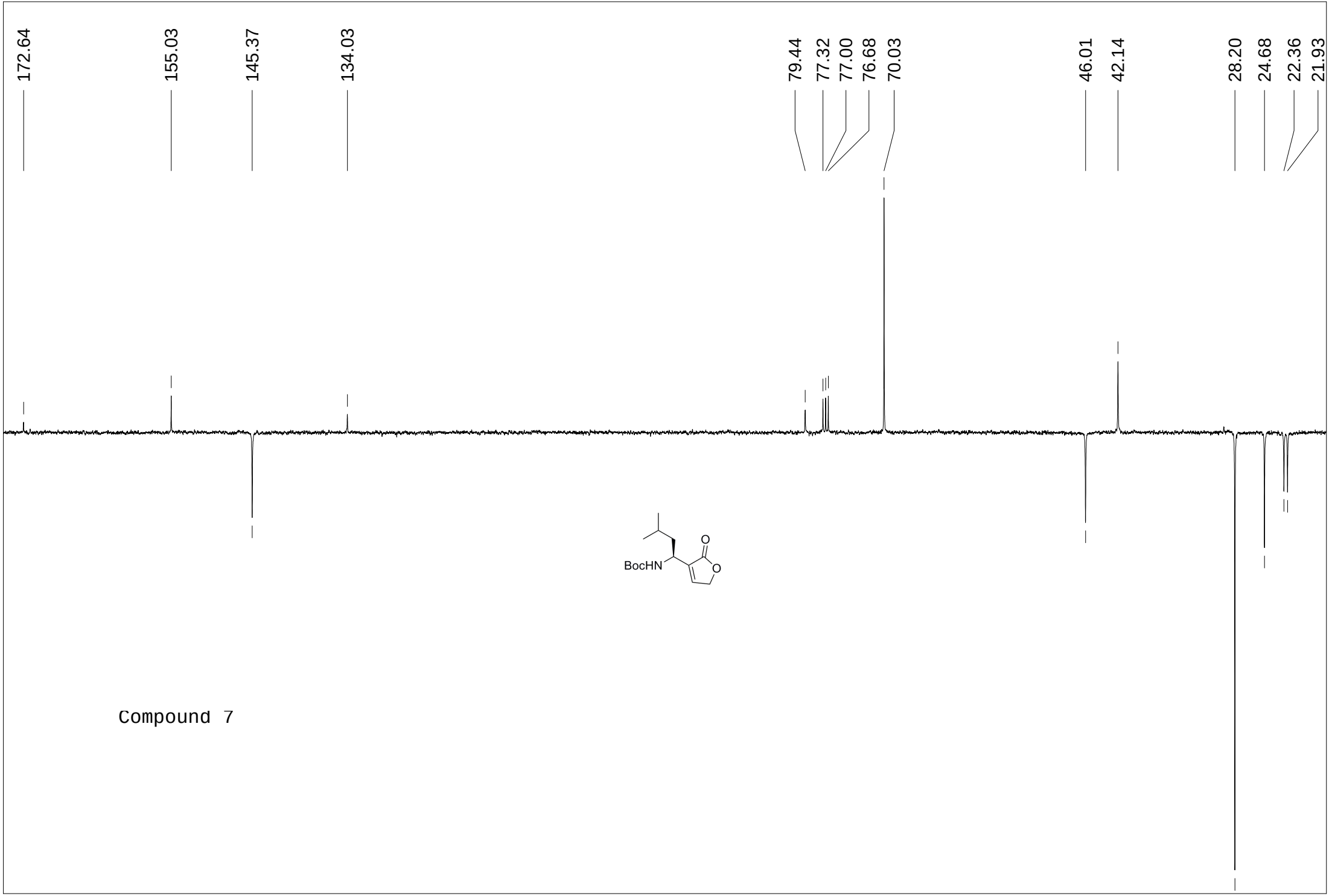

10.54
10.42
10.40
10.39
10.38
6.58
6.56
6.03
5.94
5.07
5.05
4.46
4.45
4.24
4.22
3.80
3.78
1.72
1.70
1.69
1.45
1.45
1.44
0.94
0.92
Compound 6
BocHN
O
O
OH
O
0.81
0.41
0.94
0.44
0.47
0.42
2.85
1.17
11.64
6.00

ppm (f1)


167.14
164.76
154.53
149.91
119.53
79.01
51.77
51.40
51.31
41.81
27.80
24.23
22.27
BocHN
O
O
OH
O
Compound 6

ppm (f1)

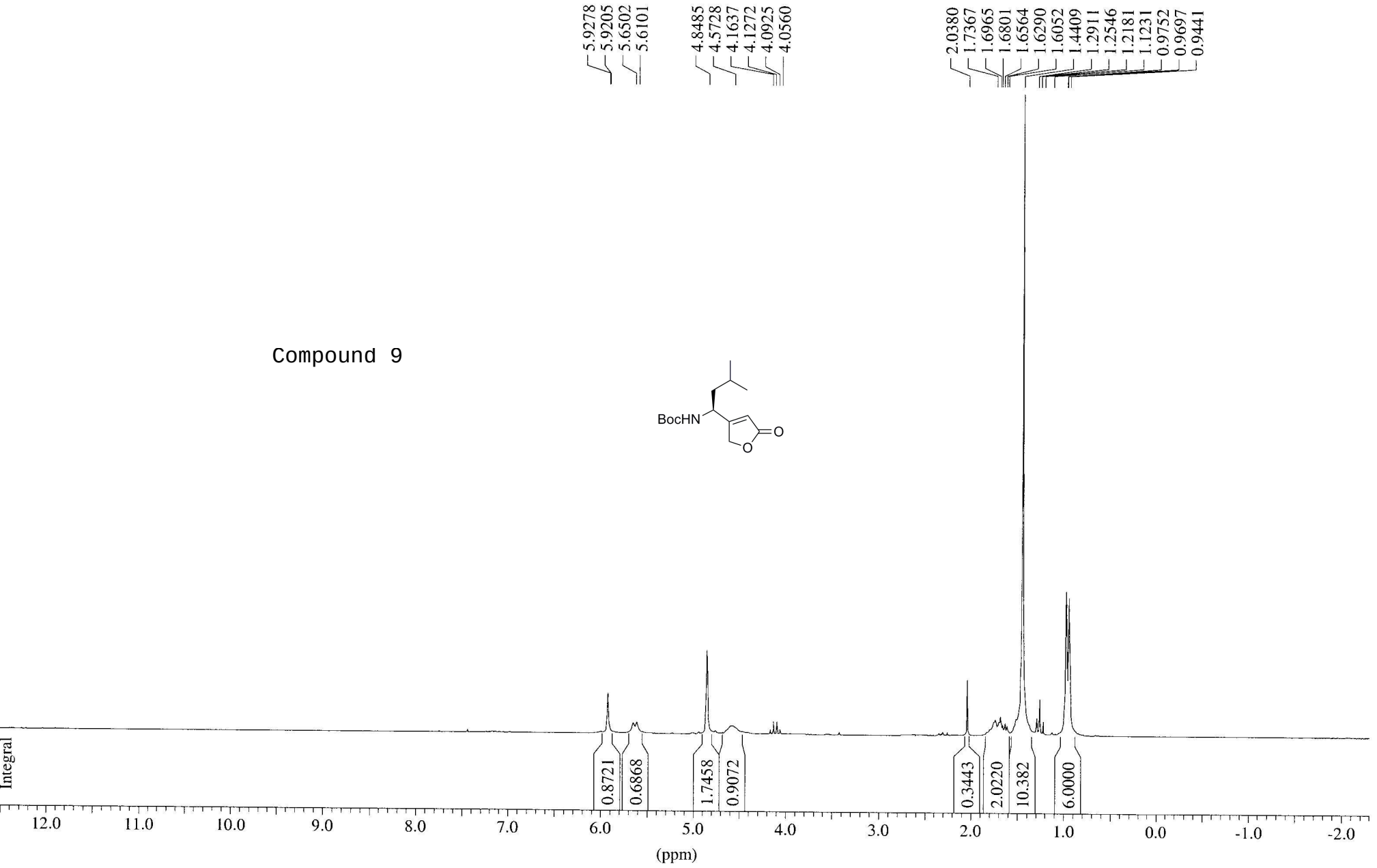

7.28
5.24
5.22
4.81
4.62
4.60
4.58
1.60
1.59
1.43
0.96
0.94
0.93
Compound 7
BocHN
O
O
0.91
0.85
1.96
0.87
2.82
9.00
5.97
ppm (f1)


172.64
155.03
145.37
134.03
79.44
77.32
77.00
76.68
70.03
46.01
42.14
28.20
24.68
22.36
21.93
BocHN
O
O
Compound 7

ppm (f1)

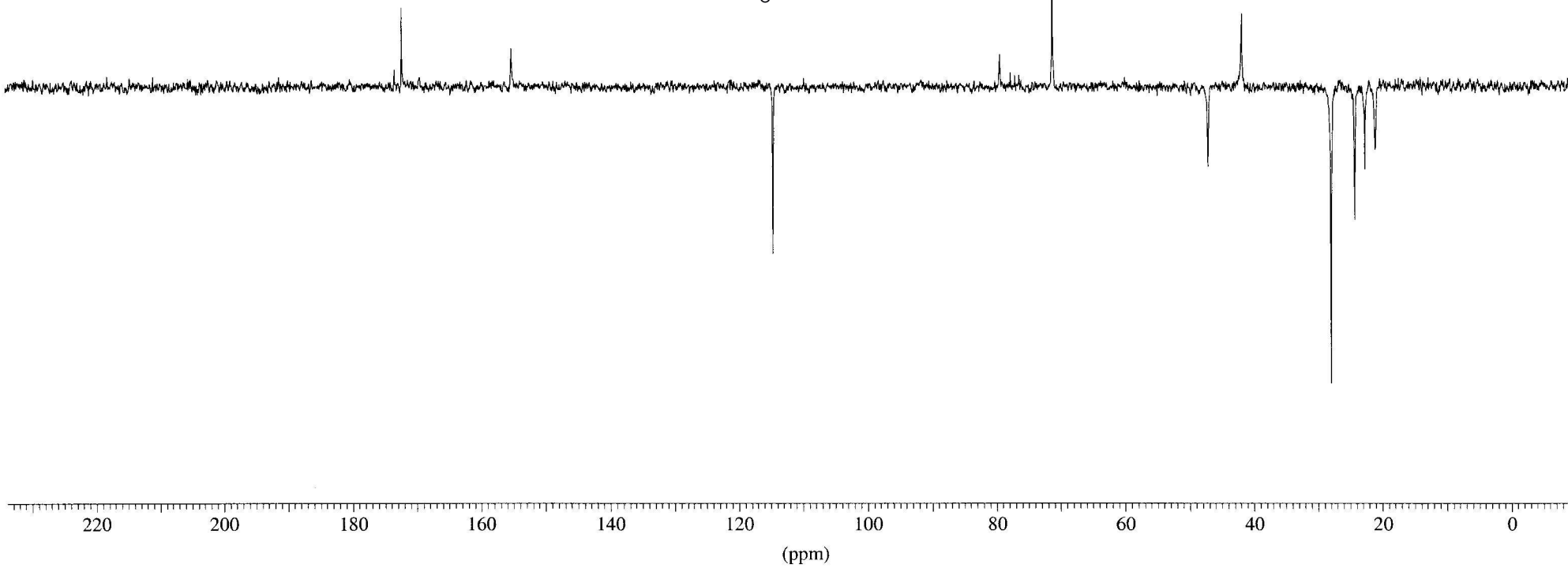
NMR WL102IV

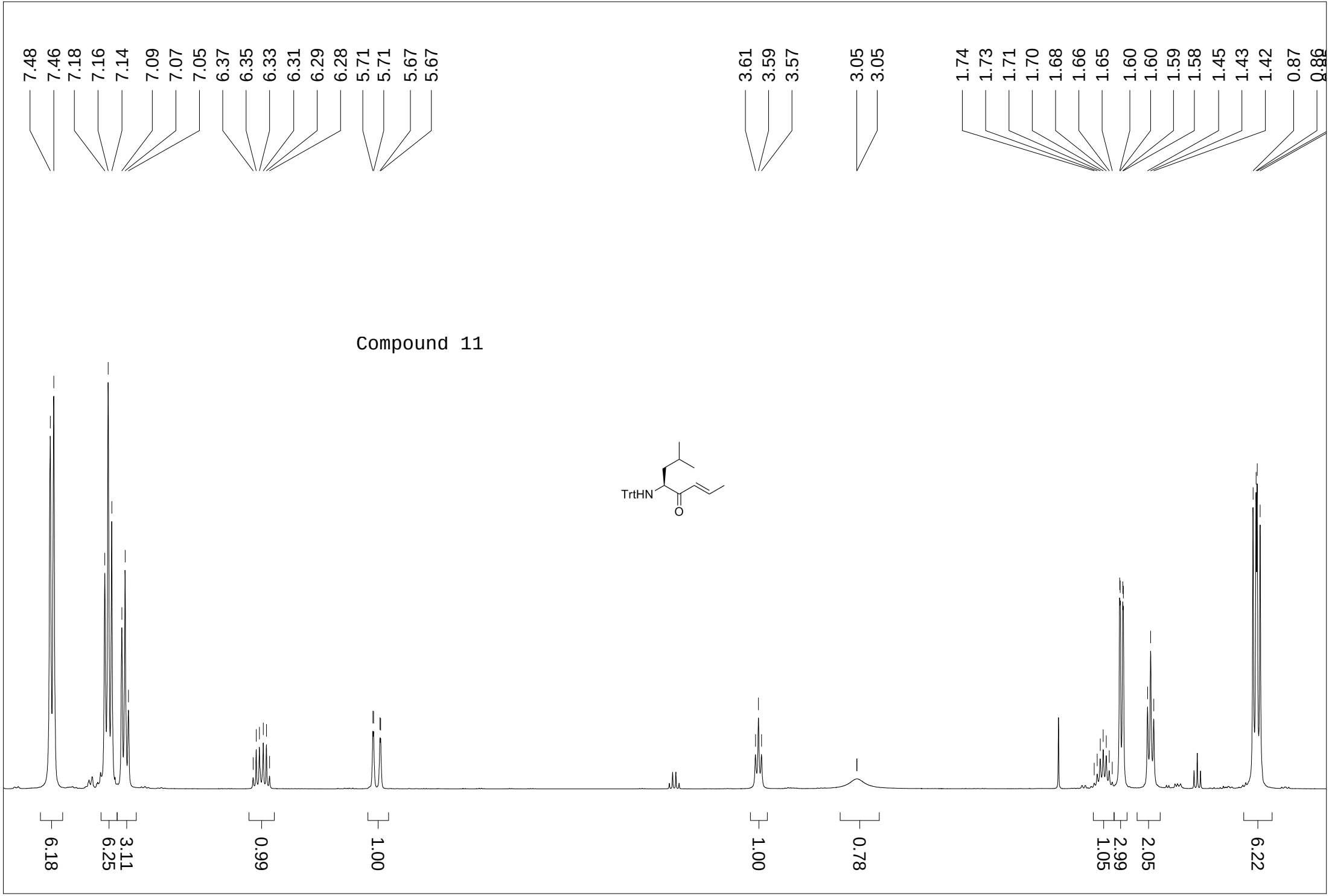
Compound 9

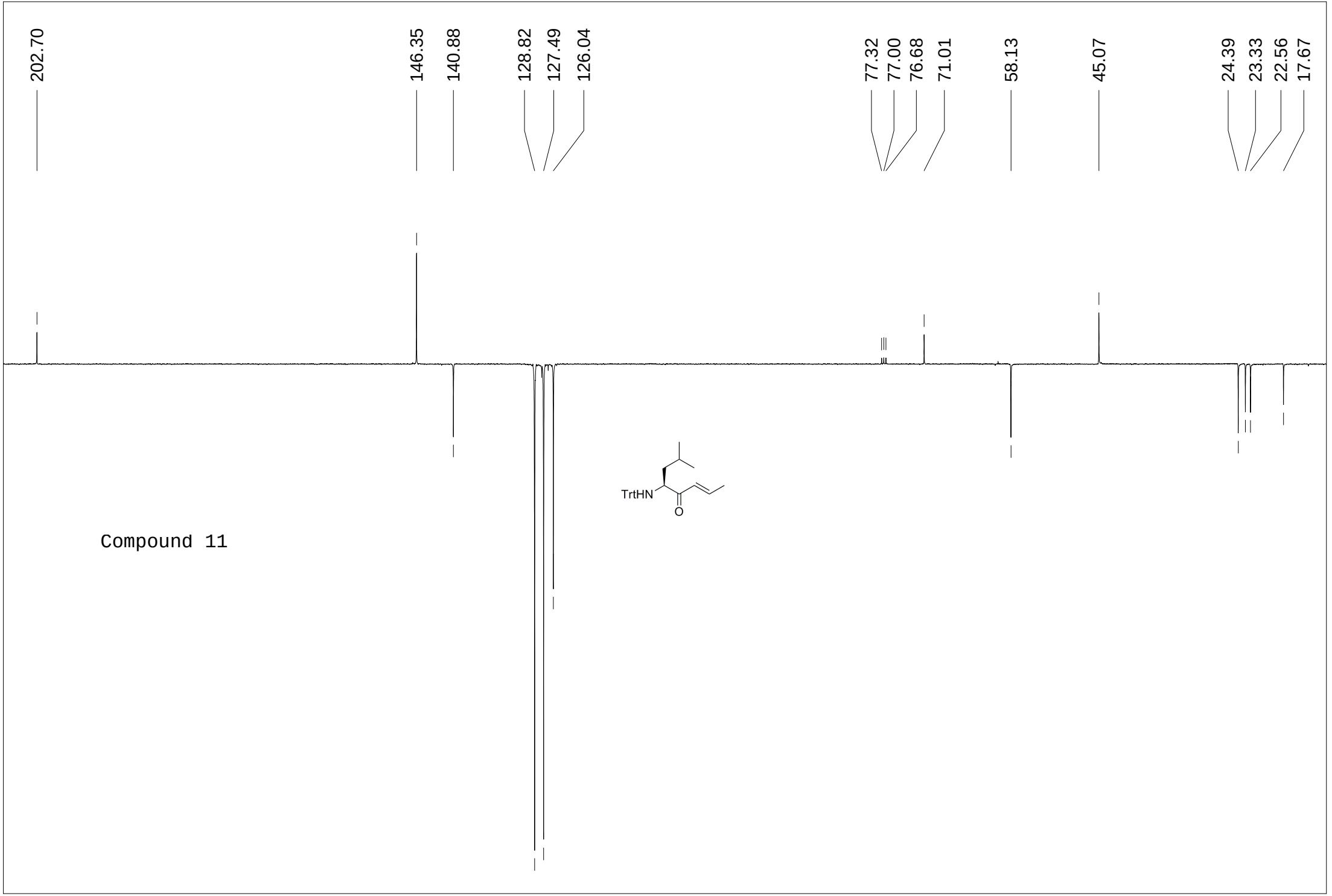


173.3429
172.2209
155.1782
114.5425
79.3957
77.6672
77.0000
76.3632
71.2079
47.1298
41.8532
27.8733
24.2040
22.5967
21.0198

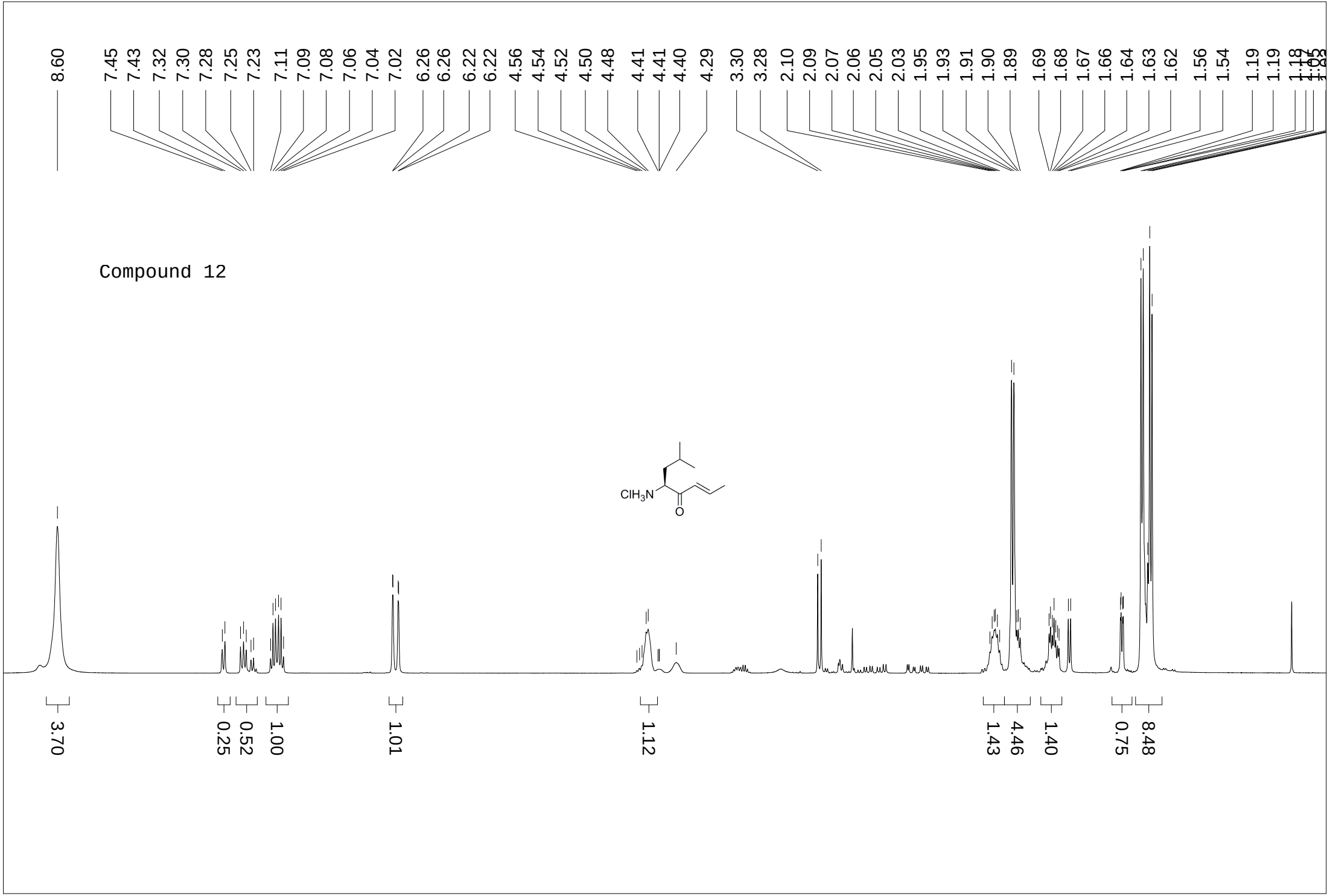
Compound 9

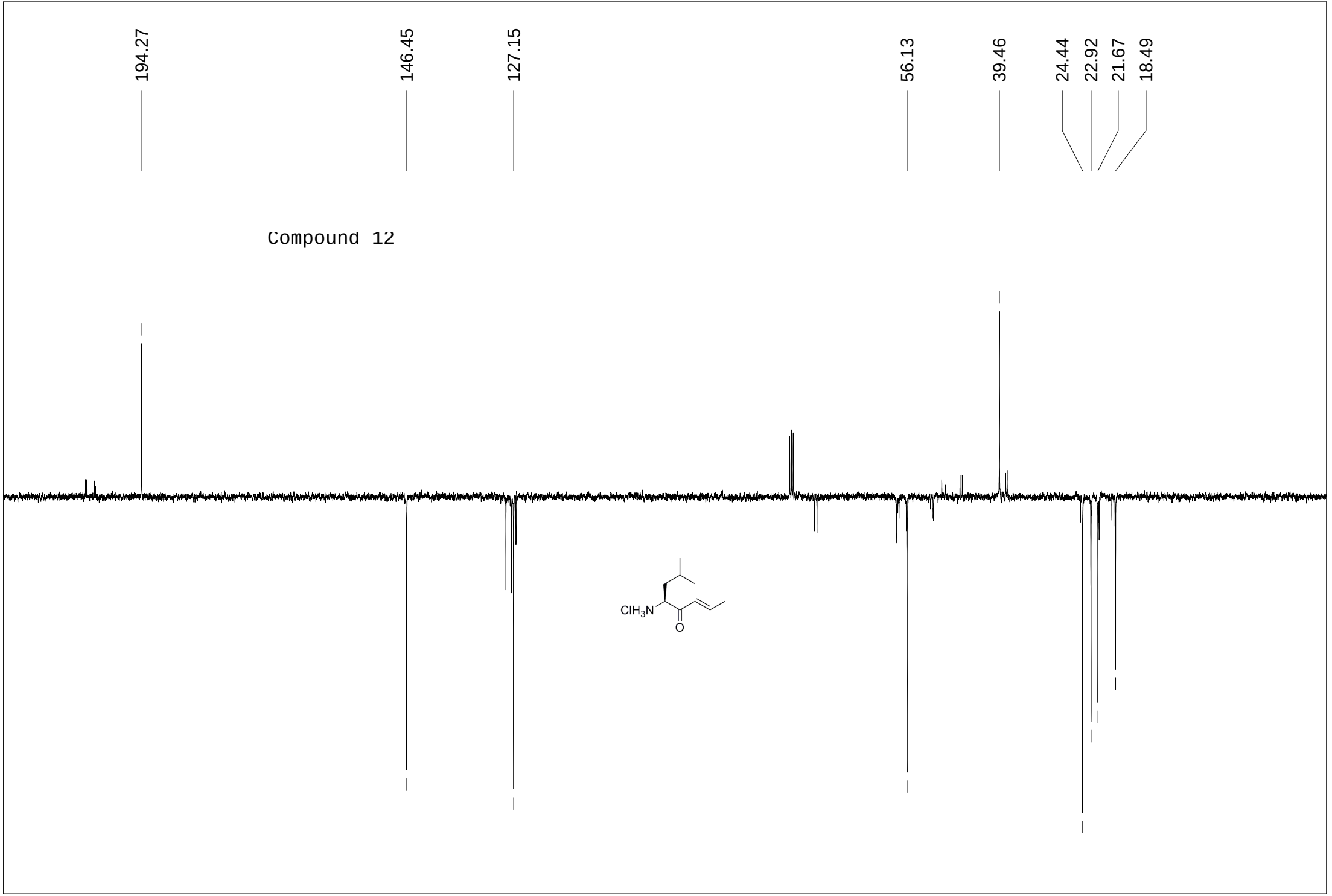



7.48
7.46
7.18
7.16
7.14
7.09
7.07
7.05
6.37
6.35
6.33
6.31
6.29
6.28
5.71
5.71
5.67
5.67
3.61
3.59
3.57
3.05
3.05
1.74
1.73
1.71
1.70
1.68
1.66
1.65
1.60
1.60
1.59
1.58
1.45
1.43
1.42
0.87
Compound 11
TrtHN
O
6.18
6.25
3.11
0.99
1.00
1.00
0.78
1.05
2.99
2.05
6.22
ppm (f1)

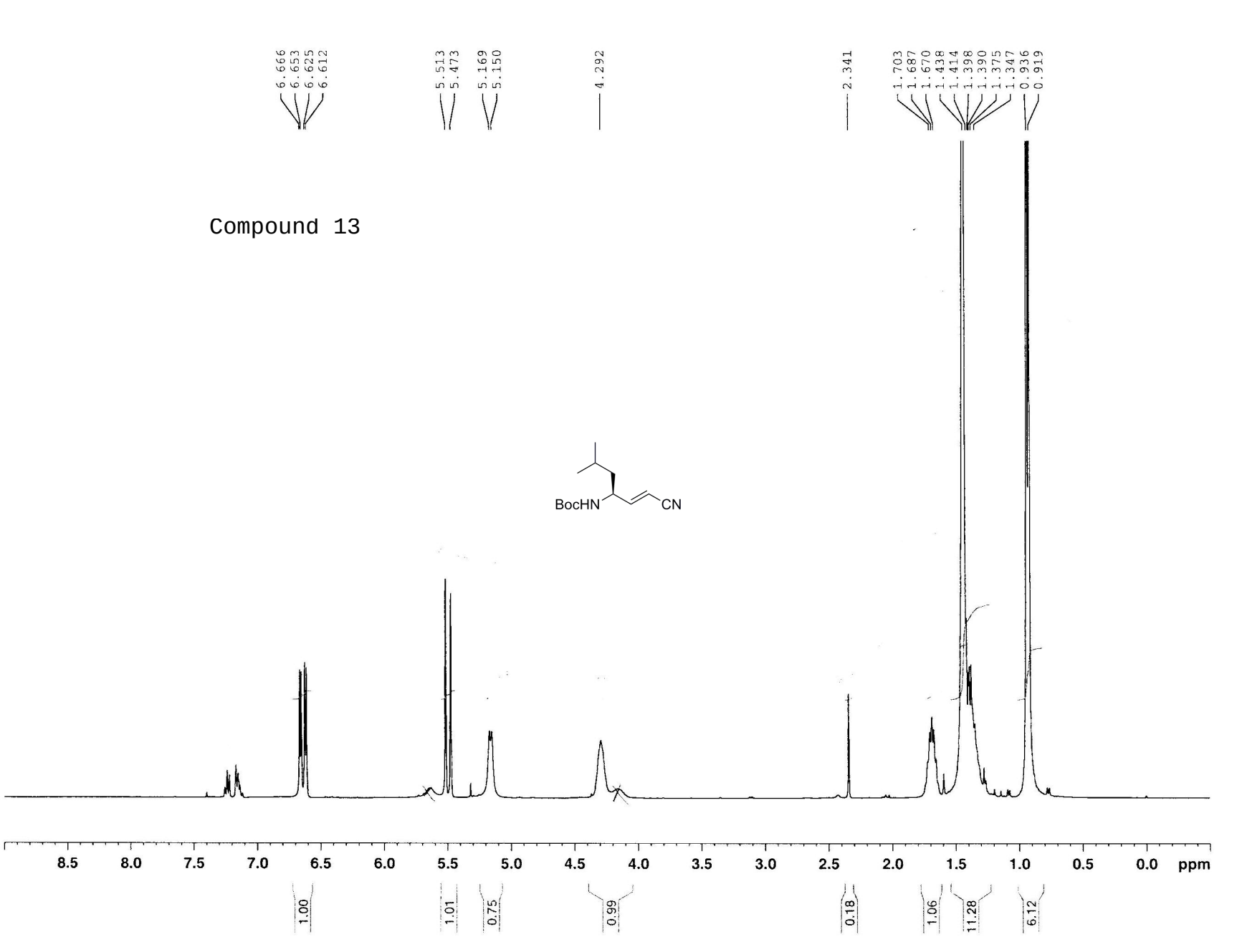

202.70
146.35
140.88
128.82
127.49
126.04
77.32
77.00
76.68
71.01
58.13
45.07
24.39
23.33
22.56
17.67
TrtHN
O
Compound 11

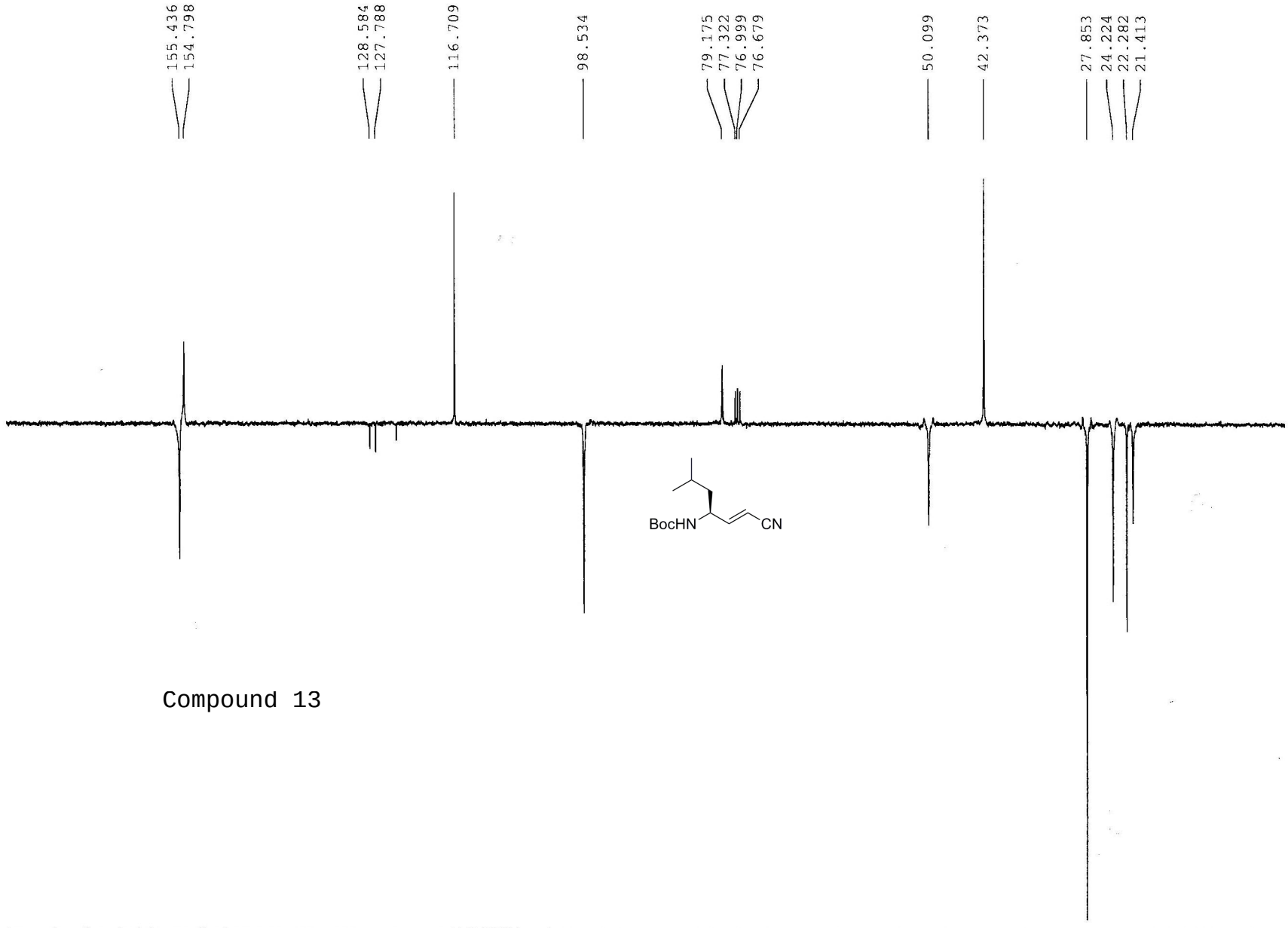
ppm (f1)

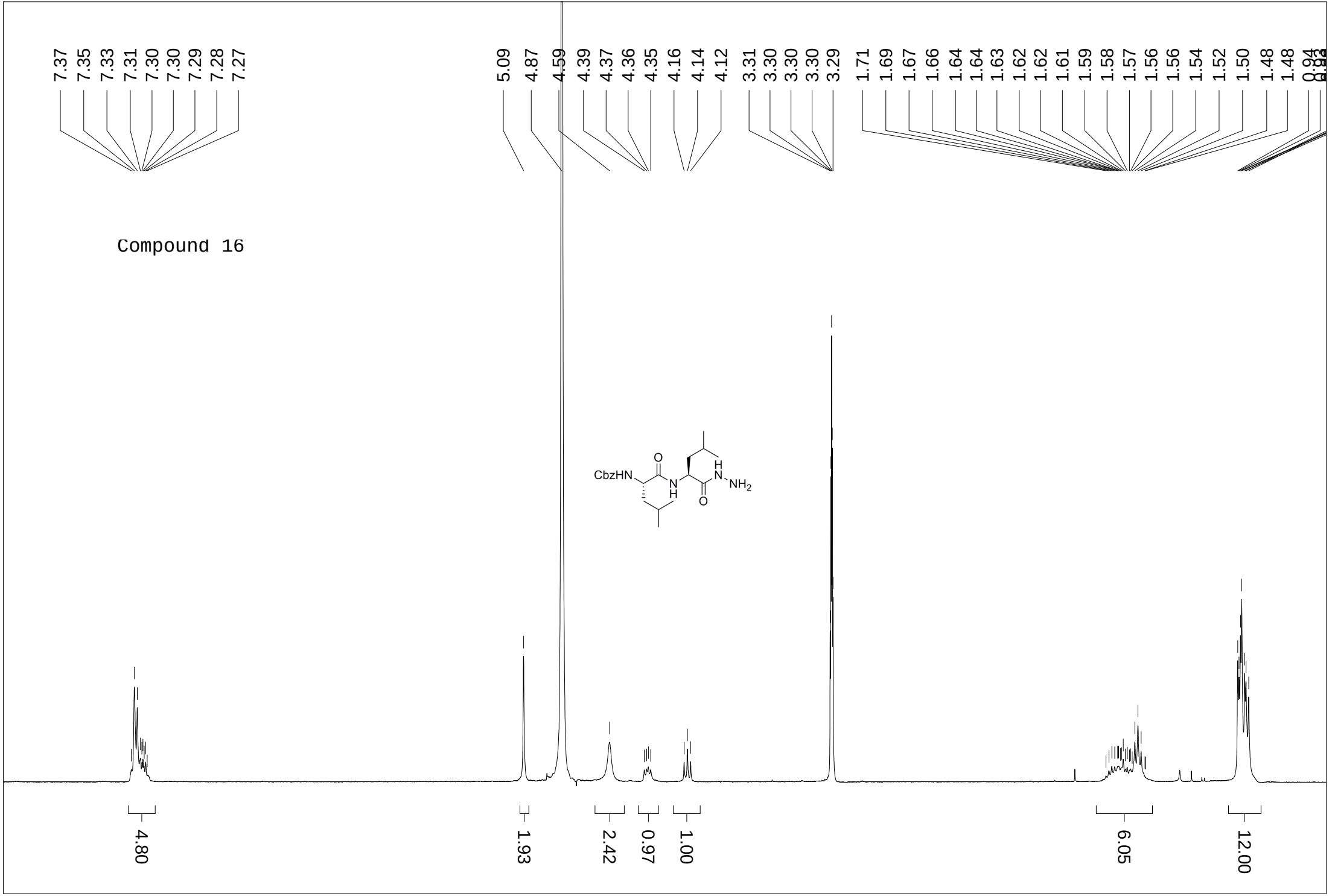

8.60
7.45
7.43
7.32
7.30
7.28
7.25
7.23
7.11
7.09
7.08
7.06
7.04
7.02
6.26
6.26
6.22
6.22
4.56
4.54
4.52
4.50
4.48
4.41
4.41
4.40
4.29
3.30
3.28
2.10
2.09
2.07
2.06
2.05
2.03
1.95
1.93
1.91
1.90
1.89
1.69
1.68
1.67
1.66
1.64
1.63
1.62
1.56
1.54
1.19
1.19
Compound 12
ClH3N
O
3.70
0.25
0.52
1.00
1.01
1.12
1.43
4.46
1.40
0.75
8.48
ppm (f1)

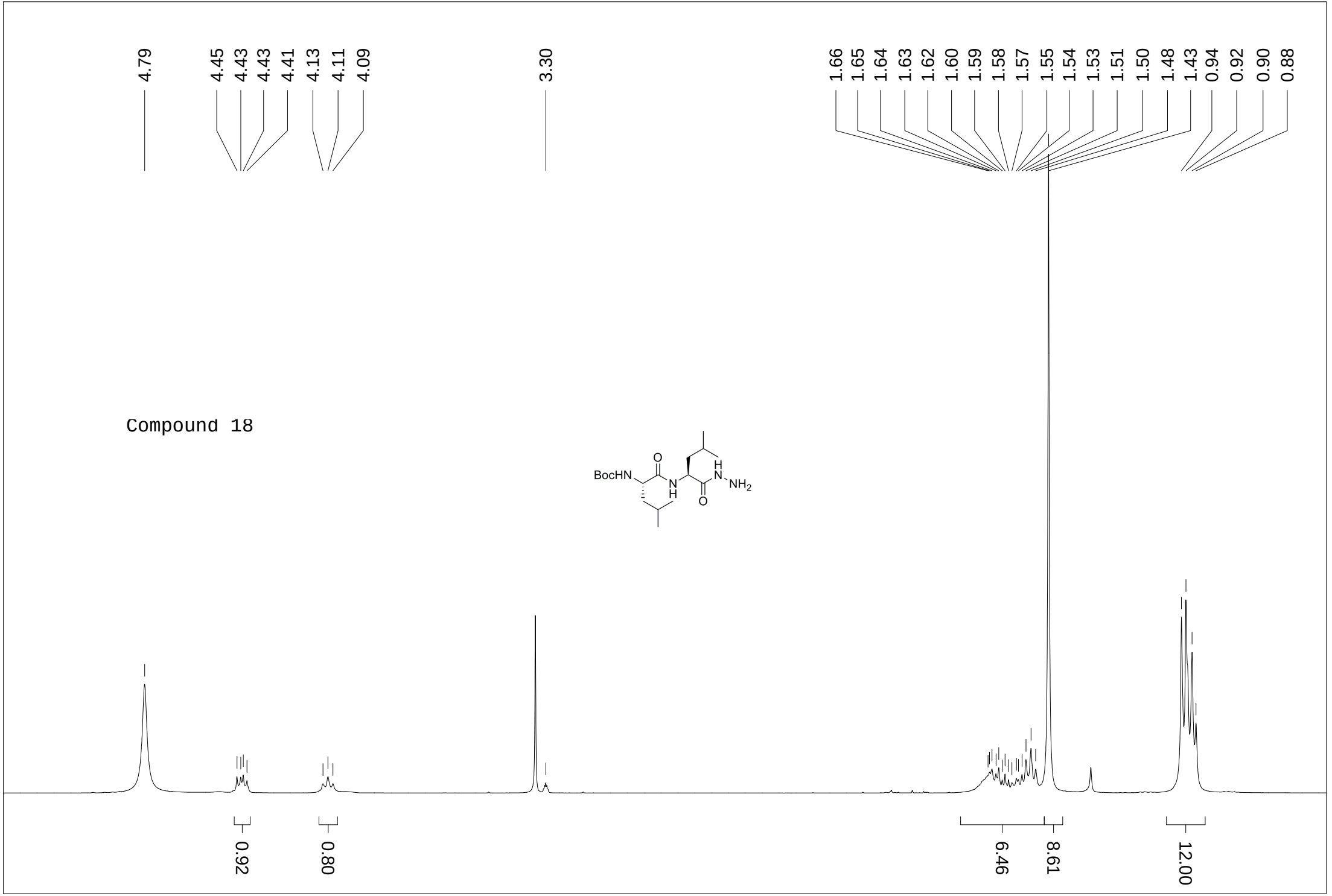

194.27
146.45
127.15
56.13
39.46
24.44
22.92
21.67
18.49
Compound 12
ClH3N
O

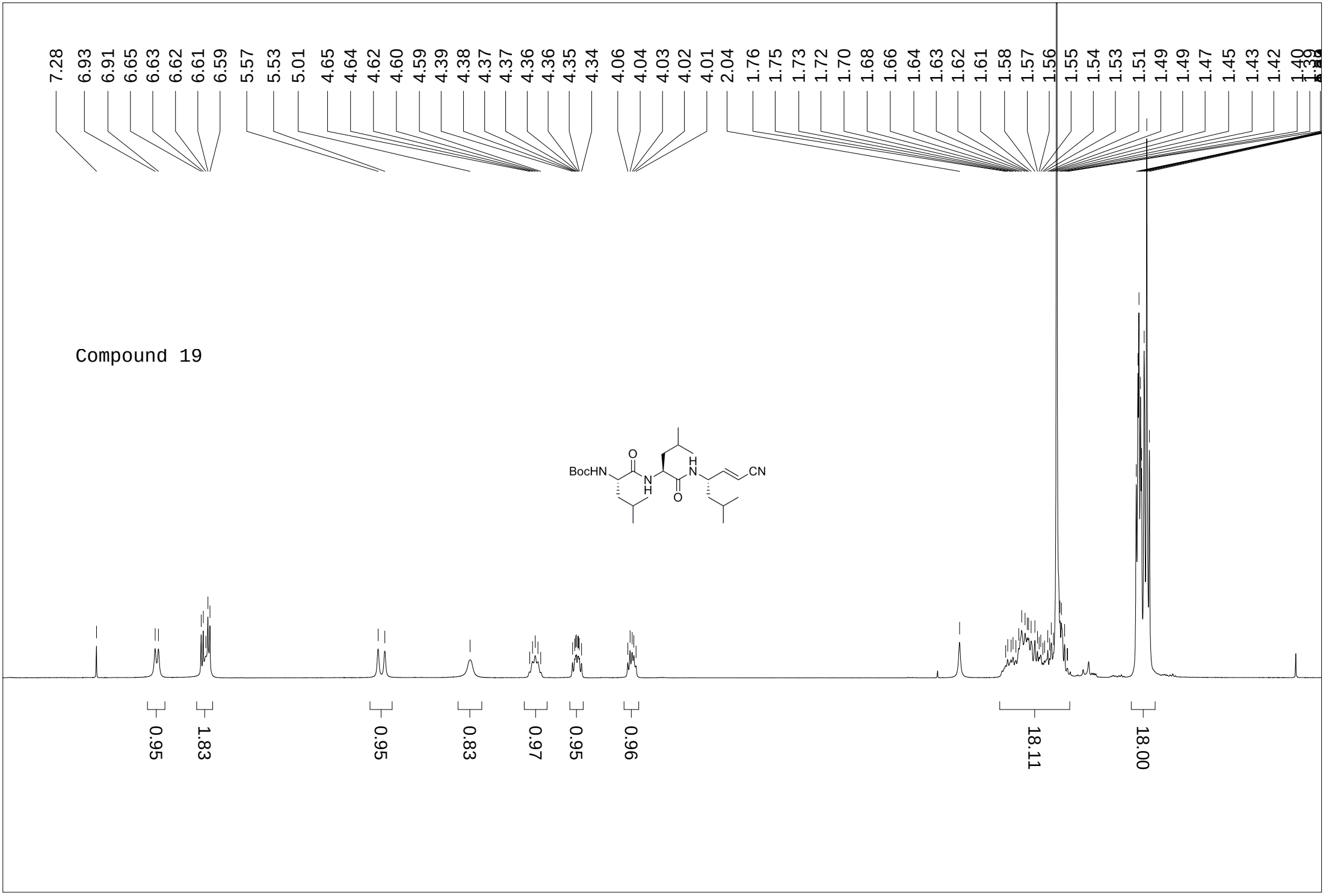
ppm (f1)

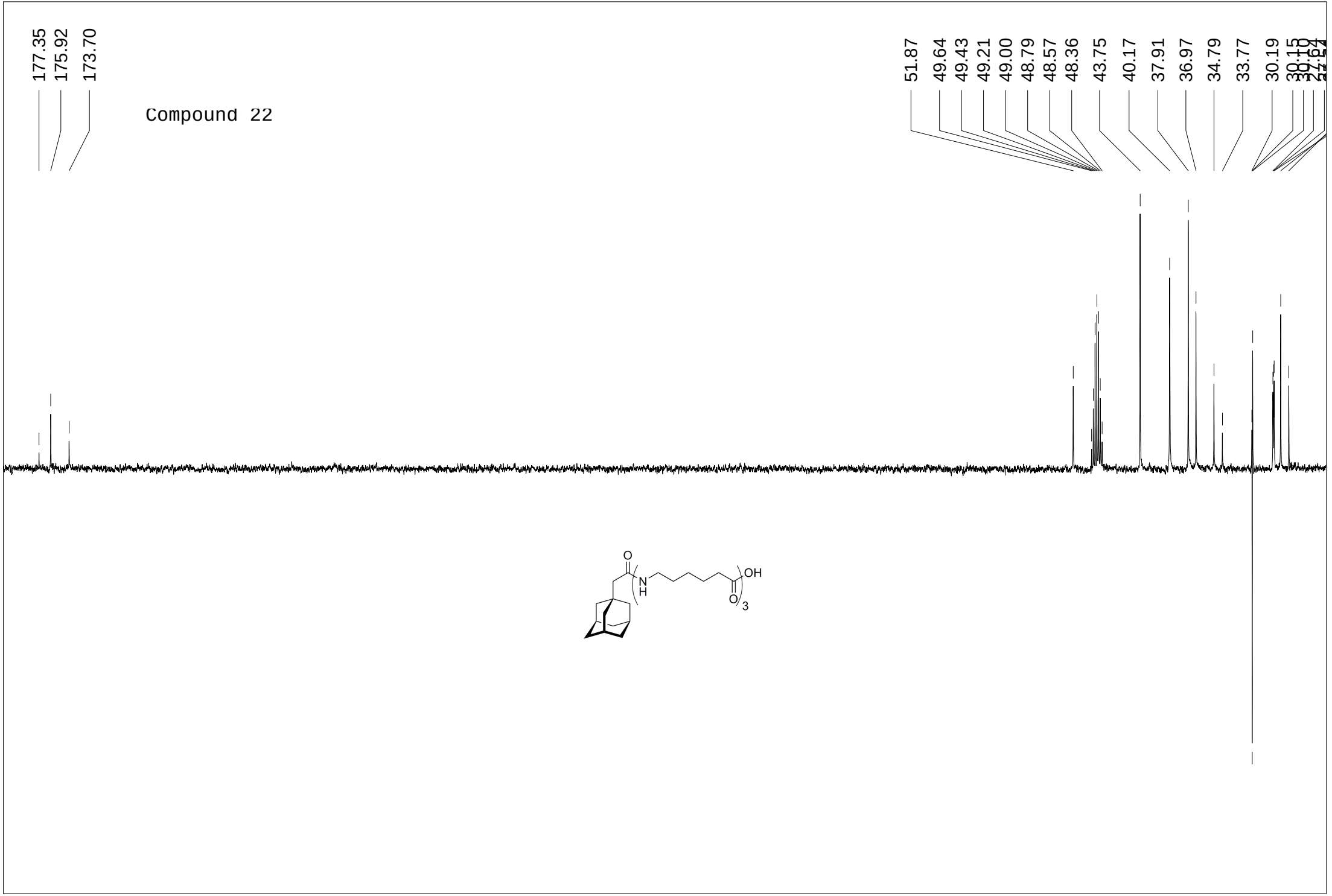

6.666
6.653
6.625
6.612
5.513
5.473
5.169
5.150
4.292
2.341
1.703
1.687
1.670
1.438
1.414
1.398
1.390
1.375
1.347
0.936
0.919
Compound 13
BocHN
CN
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.00
1.01
0.75
0.99
0.18
1.06
11.28
6.12


155.436
154.798
128.584
127.788
116.709
98.534
79.175
77.322
76.999
76.679
50.099
42.373
27.853
24.224
22.282
21.413
BocHN
CN
Compound 13
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

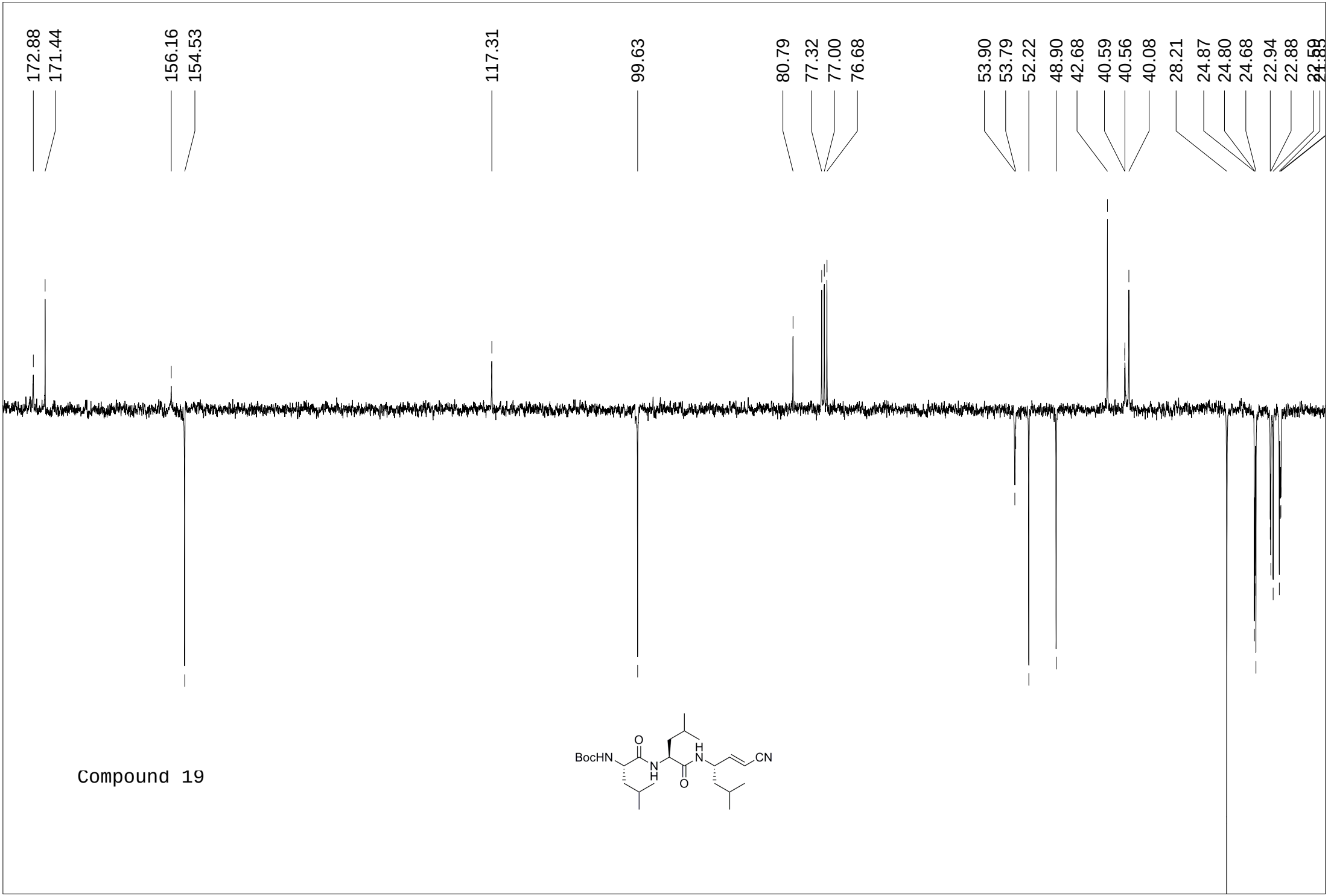

7.37
7.35
7.33
7.31
7.30
7.30
7.29
7.28
7.27
5.09
4.87
4.59
4.39
4.37
4.36
4.35
4.16
4.14
4.12
3.31
3.30
3.30
3.30
3.29
1.71
1.69
1.67
1.66
1.64
1.64
1.63
1.62
1.62
1.61
1.59
1.58
1.57
1.56
1.56
1.54
1.52
1.50
1.48
1.48
Compound 16
CbzHN
O
N
H
O
N
H
NH2
4.80
1.93
2.42
0.97
1.00
6.05
12.00
ppm (f1)


4.79
4.45
4.43
4.43
4.41
4.13
4.11
4.09
3.30
1.66
1.65
1.64
1.63
1.62
1.60
1.59
1.58
1.57
1.55
1.54
1.53
1.51
1.50
1.48
1.43
0.94
0.92
0.90
0.88
Compound 18
BocHN
O
N
H
H
N
NH2
O
0.92
0.80
6.46
8.61
12.00
ppm (f1)

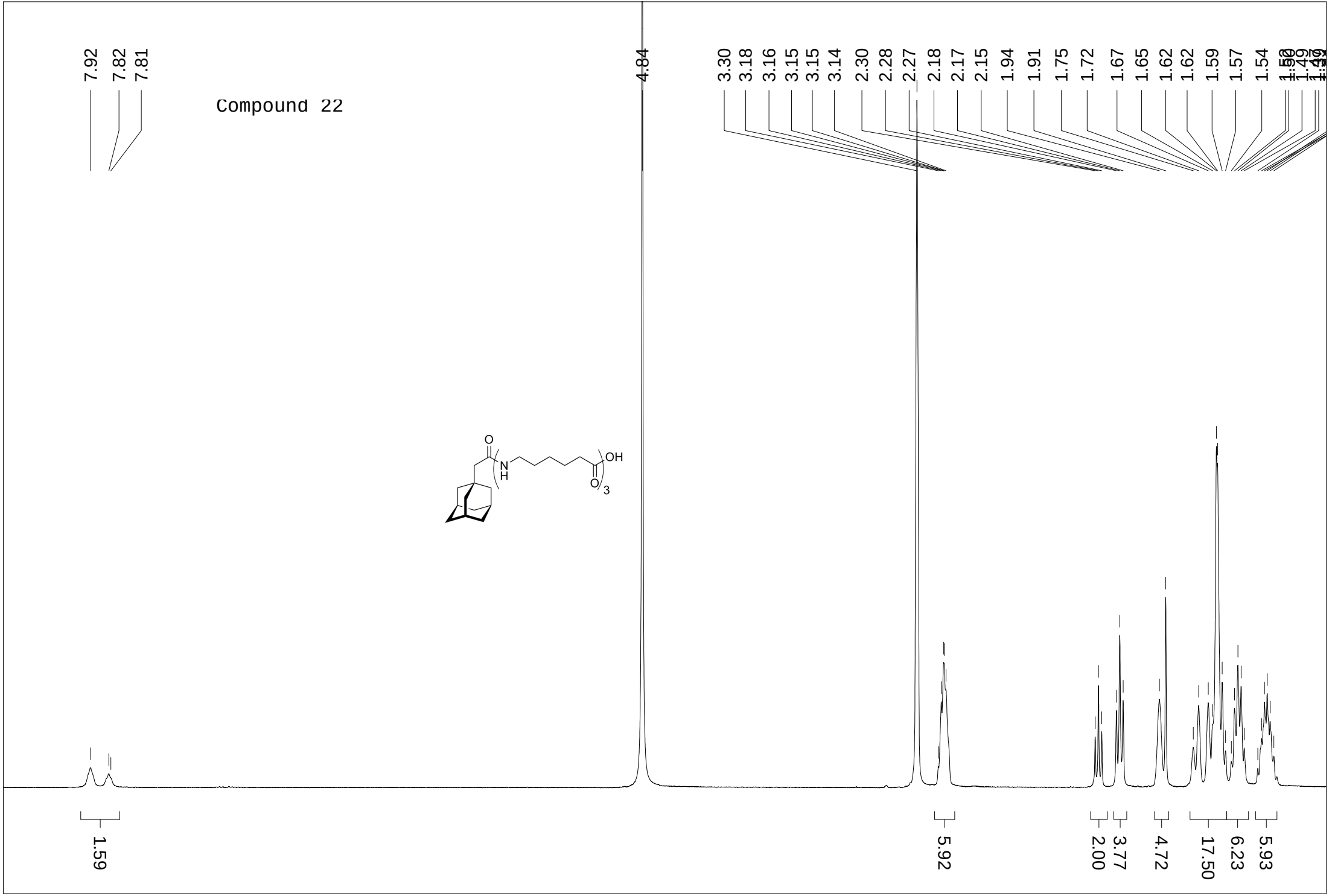

7.28
6.93
6.91
6.65
6.63
6.62
6.61
6.59
5.57
5.53
5.01
4.65
4.64
4.62
4.60
4.59
4.39
4.38
4.37
4.37
4.36
4.36
4.35
4.34
4.06
4.04
4.03
4.02
4.01
2.04
1.76
1.75
1.73
1.72
1.70
1.68
1.66
1.64
1.63
1.62
1.61
1.58
1.57
1.56
1.55
1.54
1.53
1.51
1.49
1.49
1.47
1.45
1.43
1.42
1.40
Compound 19
BocHN
O
N
H
O
N
H
CN
0.95
1.83
0.95
0.83
0.97
0.95
0.96
18.11
18.00
ppm (f1)


177.35
175.92
173.70
Compound 22
51.87
49.64
49.43
49.21
49.00
48.79
48.57
48.36
43.75
40.17
37.91
36.97
34.79
33.77
30.19
O
N
H
OH
O
3

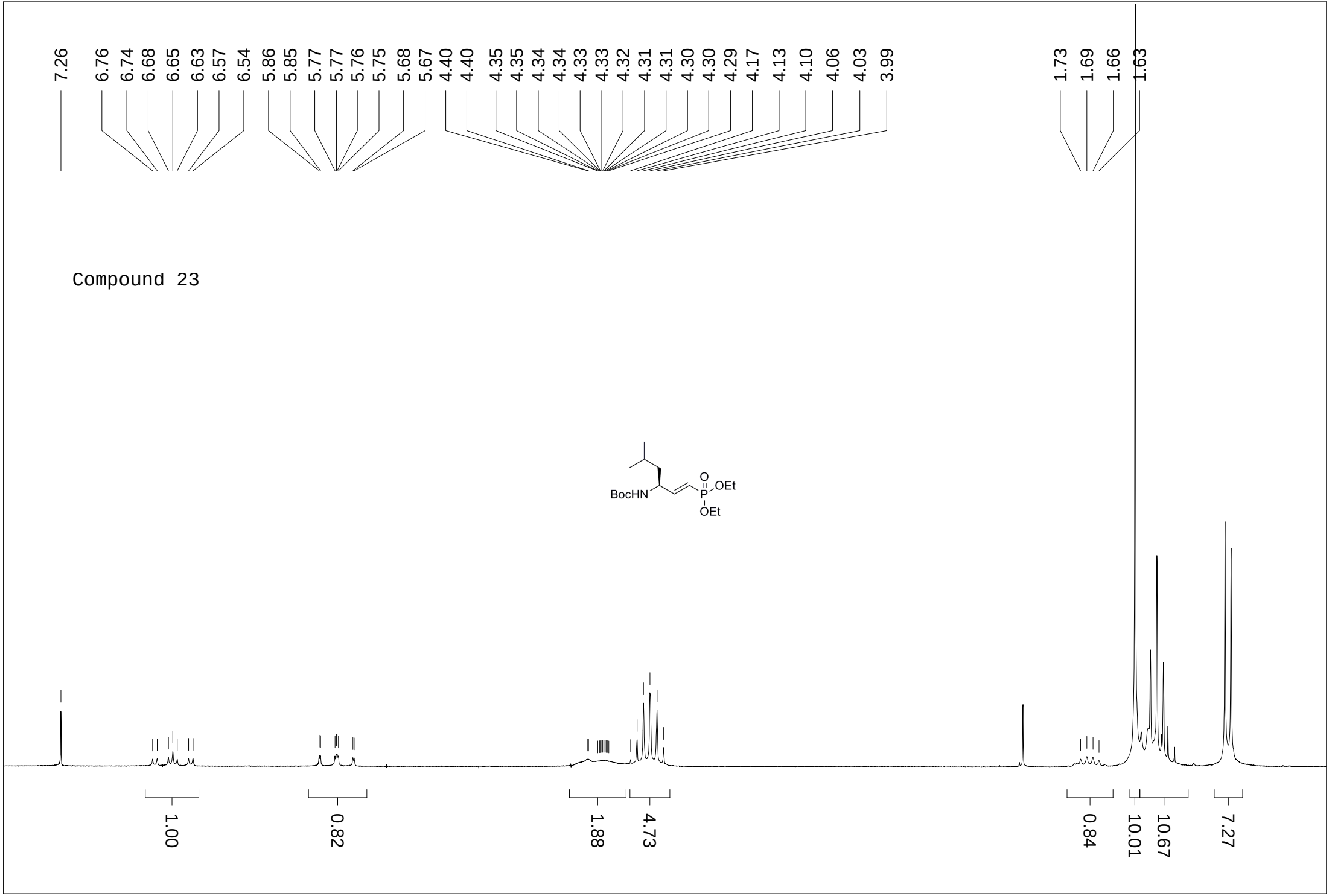
ppm (f1)

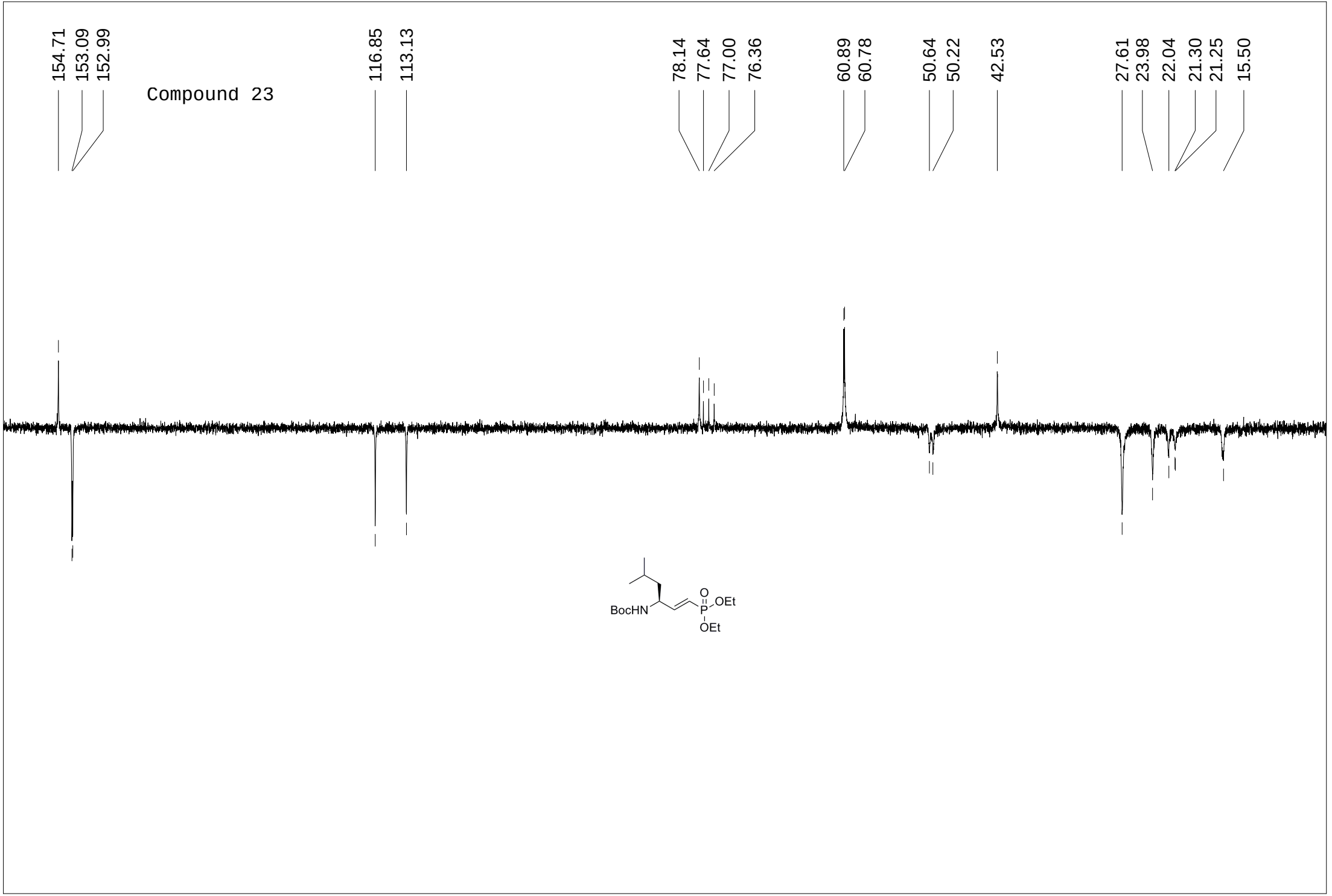

172.88
171.44
156.16
154.53
117.31
99.63
80.79
77.32
77.00
76.68
53.90
53.79
52.22
48.90
42.68
40.59
40.56
40.08
28.21
24.87
24.80
24.68
22.94
22.88
BocHN
O
N
H
O
H
N
CN
Compound 19

ppm (f1)

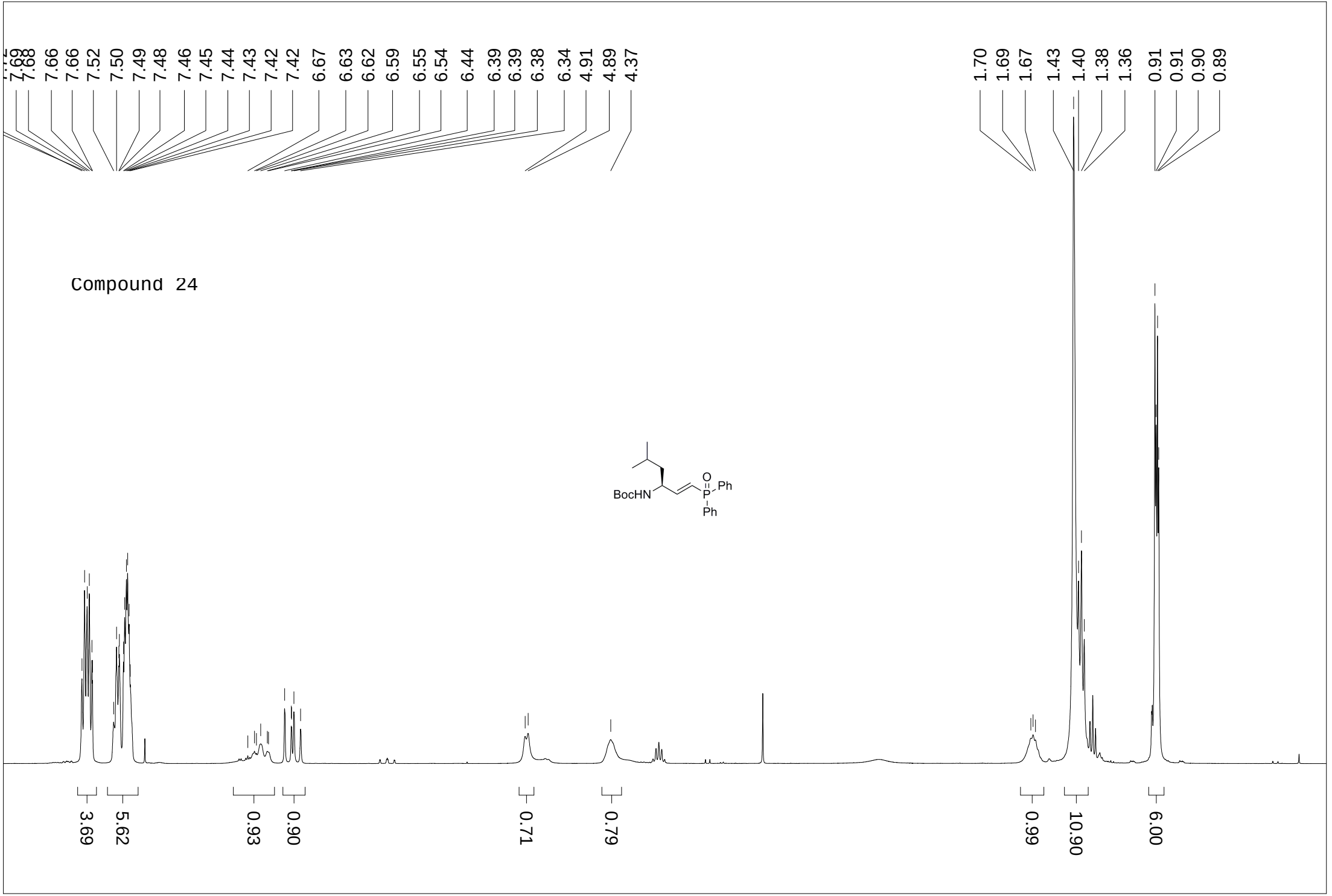

Compound 22
7.92
7.82
7.81
4.84
3.30
3.18
3.16
3.15
3.15
3.14
2.30
2.28
2.27
2.18
2.17
2.15
1.94
1.91
1.75
1.72
1.67
1.65
1.62
1.62
1.59
1.57
1.54
O
N
H
OH
O
3
1.59
5.92
2.00
3.77
4.72
17.50
6.23
5.93

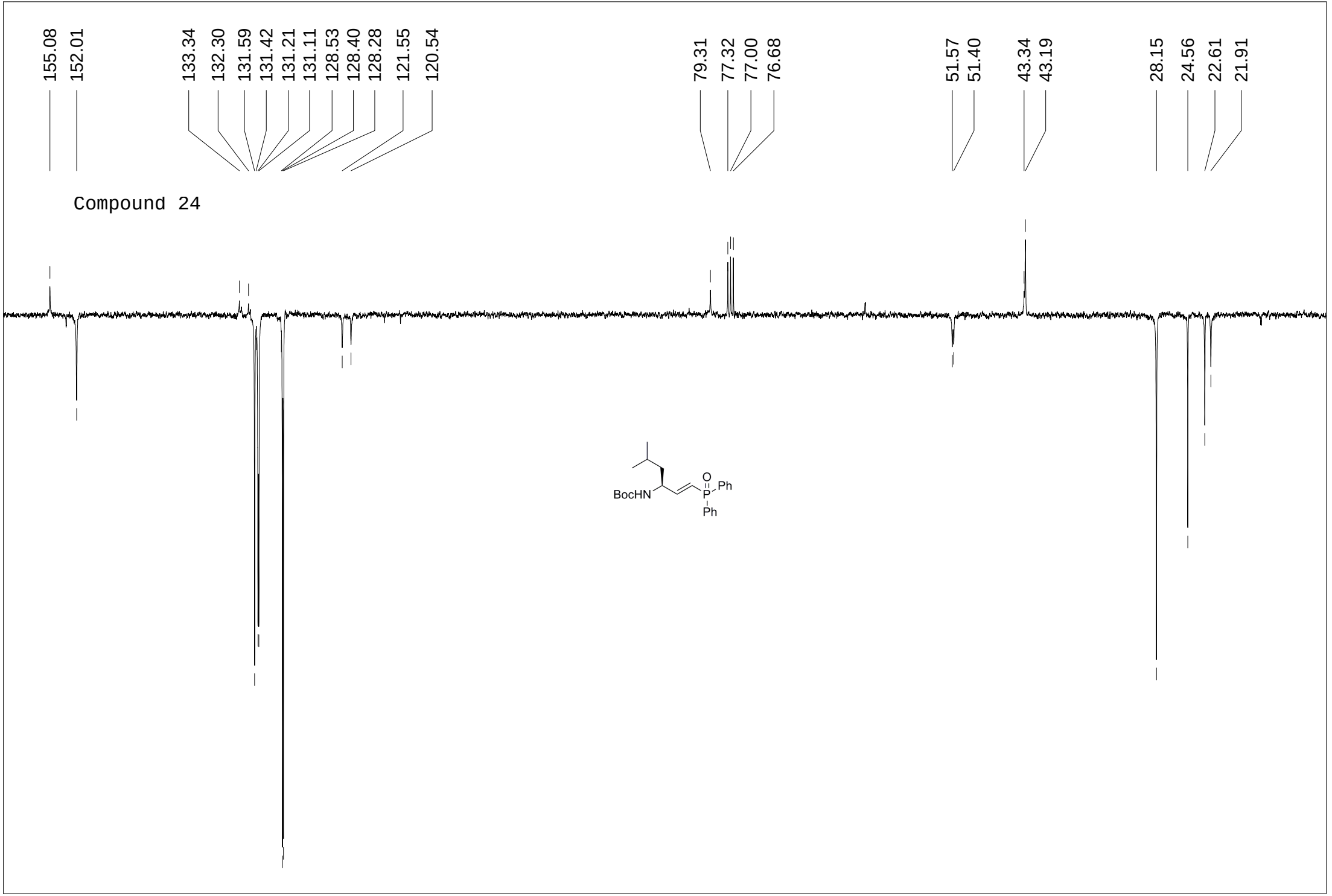
ppm (f1)


7.26
6.76
6.74
6.68
6.65
6.63
6.57
6.54
5.86
5.85
5.77
5.77
5.76
5.75
5.68
5.67
4.40
4.40
4.35
4.35
4.34
4.34
4.33
4.33
4.32
4.31
4.31
4.30
4.30
4.29
4.17
4.13
4.10
4.06
4.03
3.99
1.73
1.69
1.66
1.63
Compound 23
BocHN
O
P
OEt
OEt
1.00
0.82
1.88
4.73
0.84
10.01
10.67
7.27
ppm (f1)


154.71
153.09
152.99
Compound 23
116.85
113.13
78.14
77.64
77.00
76.36
60.89
60.78
50.64
50.22
42.53
27.61
23.98
22.04
21.30
21.25
15.50
BocHN
O
OEt
P
OEt

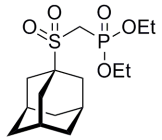
ppm (f1)


7.69
7.68
7.66
7.66
7.52
7.50
7.49
7.48
7.46
7.45
7.44
7.43
7.42
7.42
6.67
6.63
6.62
6.59
6.55
6.54
6.44
6.39
6.39
6.38
6.34
4.91
4.89
4.37
1.70
1.69
1.67
1.43
1.40
1.38
1.36
0.91
0.91
0.90
0.89
Compound 24
BocHN
O
P
Ph
Ph
3.69
5.62
0.93
0.90
0.71
0.79
0.99
10.90
6.00
ppm (f1)


155.08
152.01
133.34
132.30
131.59
131.42
131.21
131.11
128.53
128.40
128.28
121.55
120.54
79.31
77.32
77.00
76.68
51.57
51.40
43.34
43.19
28.15
24.56
22.61
21.91
Compound 24
BocHN
O
P
Ph
Ph

ppm (f1)

Compound 25



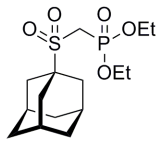
4.31 4.29 4.27 4.25 4.24 3.51 3.46 2.21 2.05 2.04 1.78 1.75 1.72 1.68 1.40 1.38 1.36

3.97 2.04 3.07 6.05 6.20 6.00

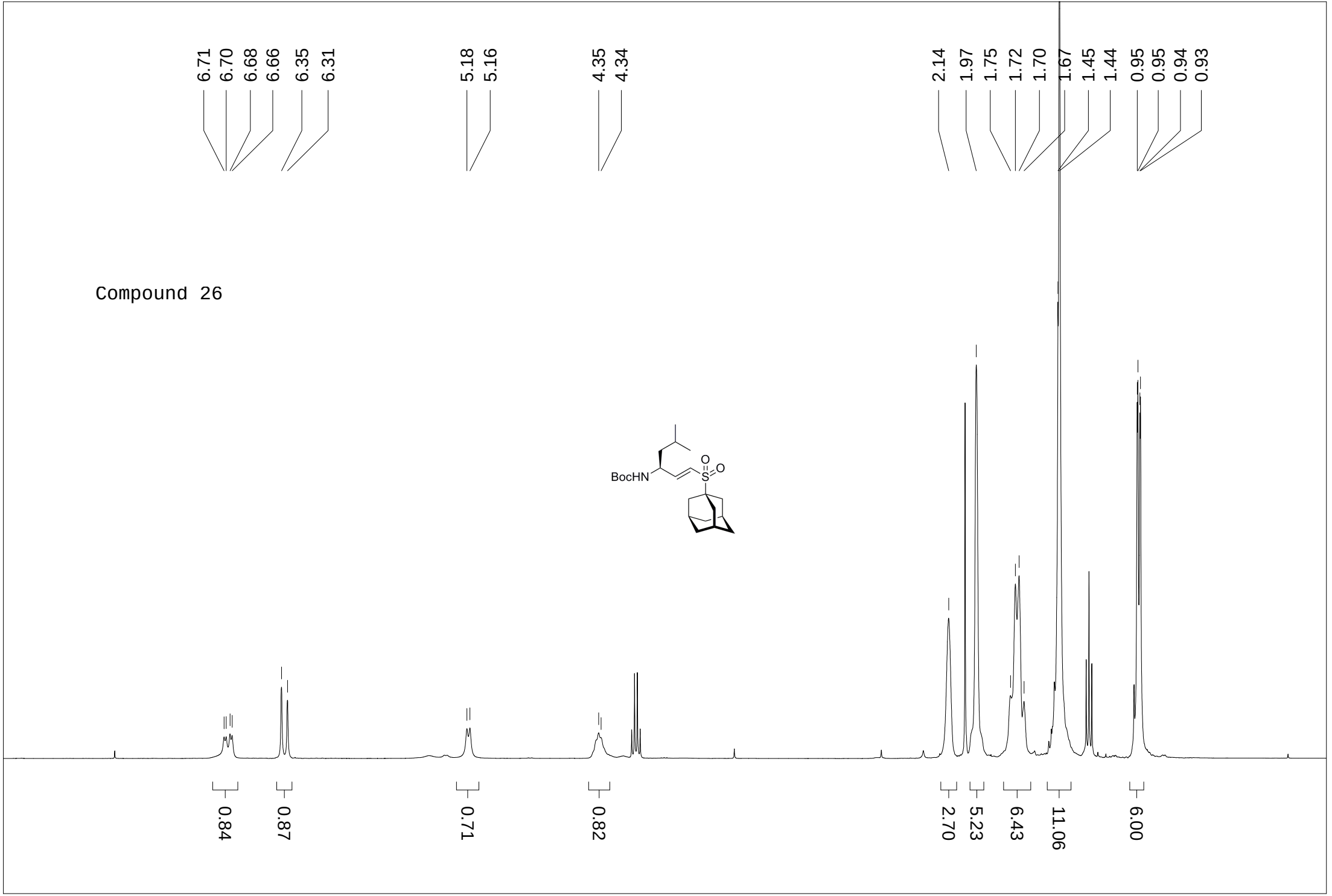
ppm (f1)

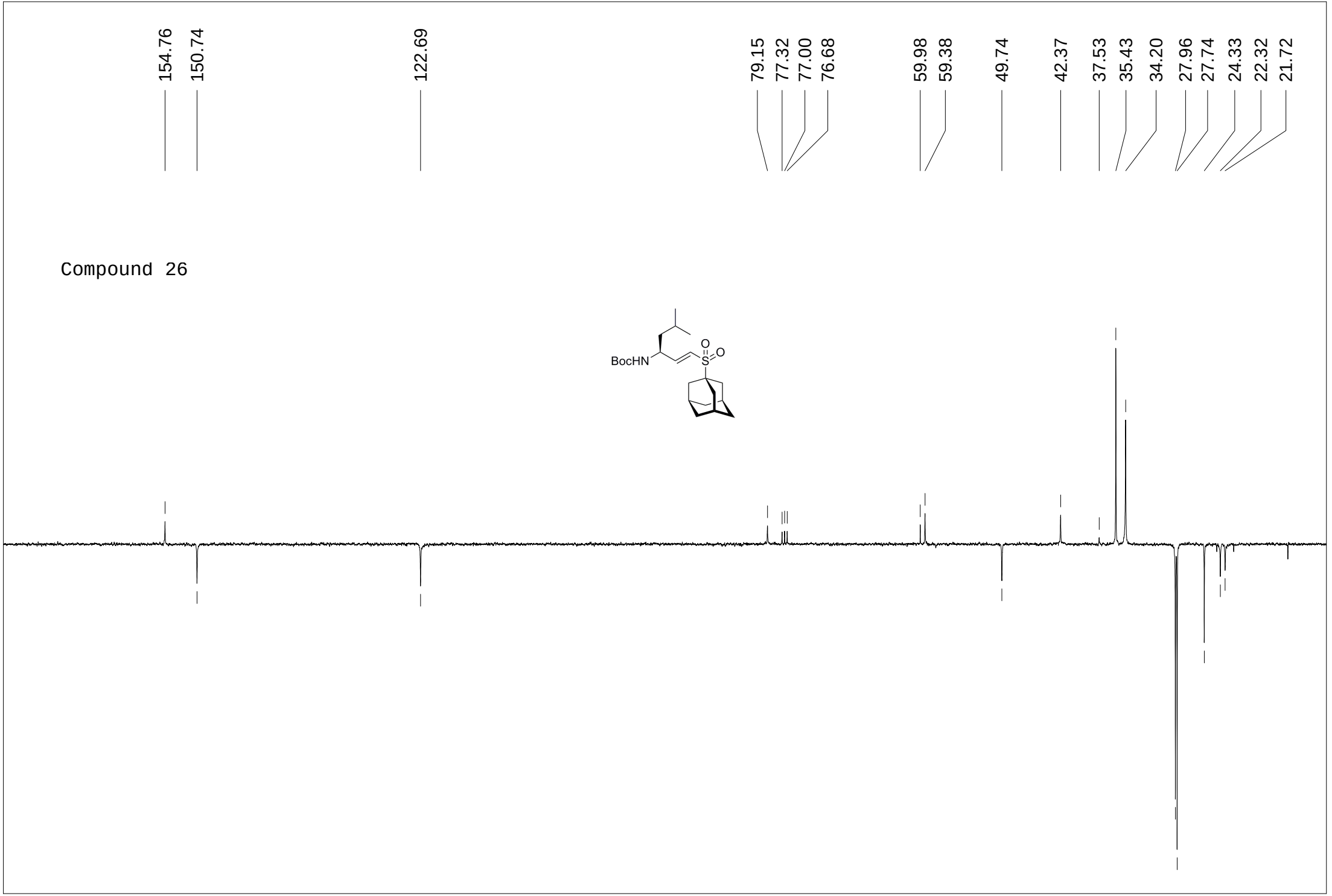
Compound 25

77.32
77.00
76.68
63.62
63.56
42.83
41.47
35.61
34.66
28.13
16.30
16.24

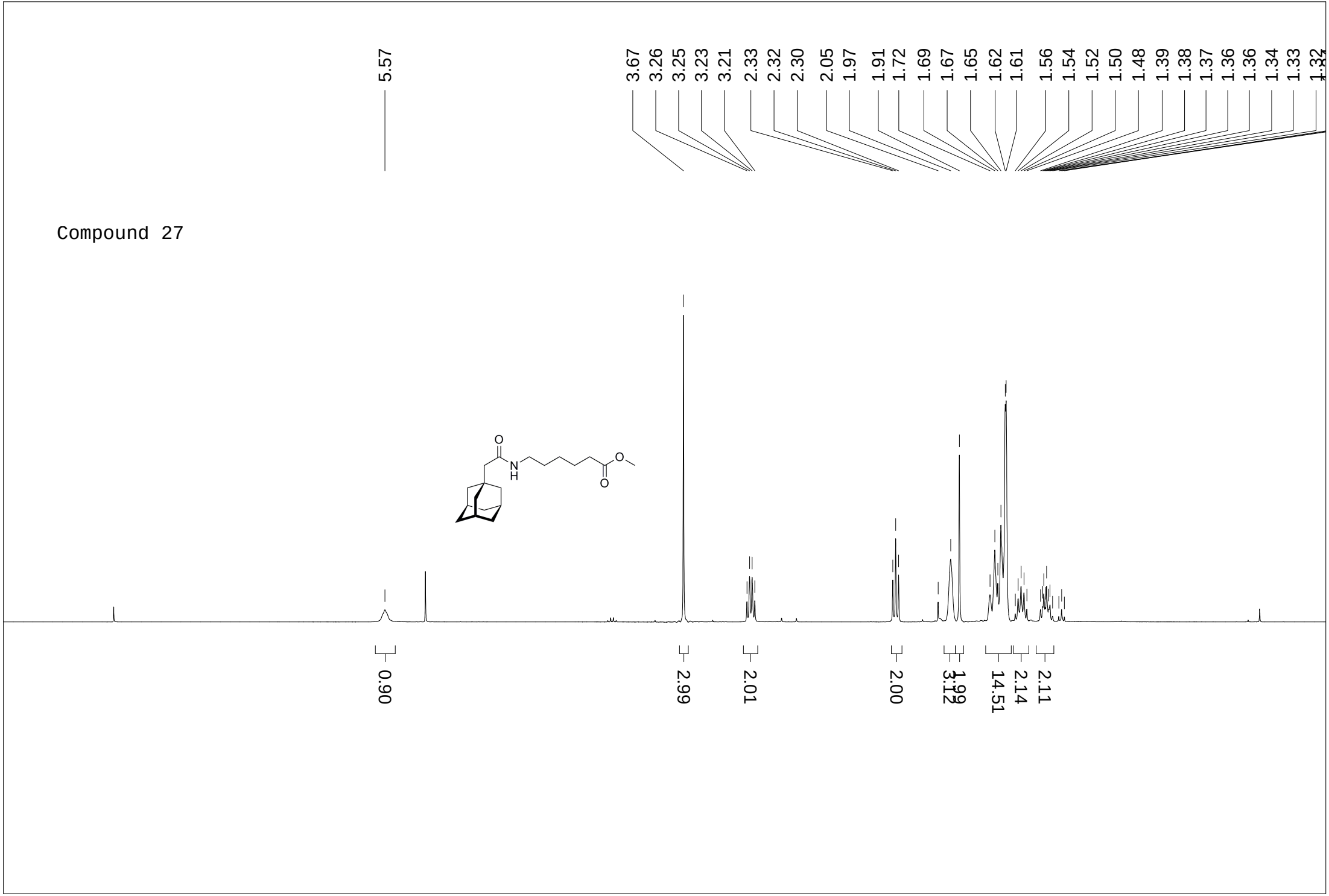


ppm (f1)

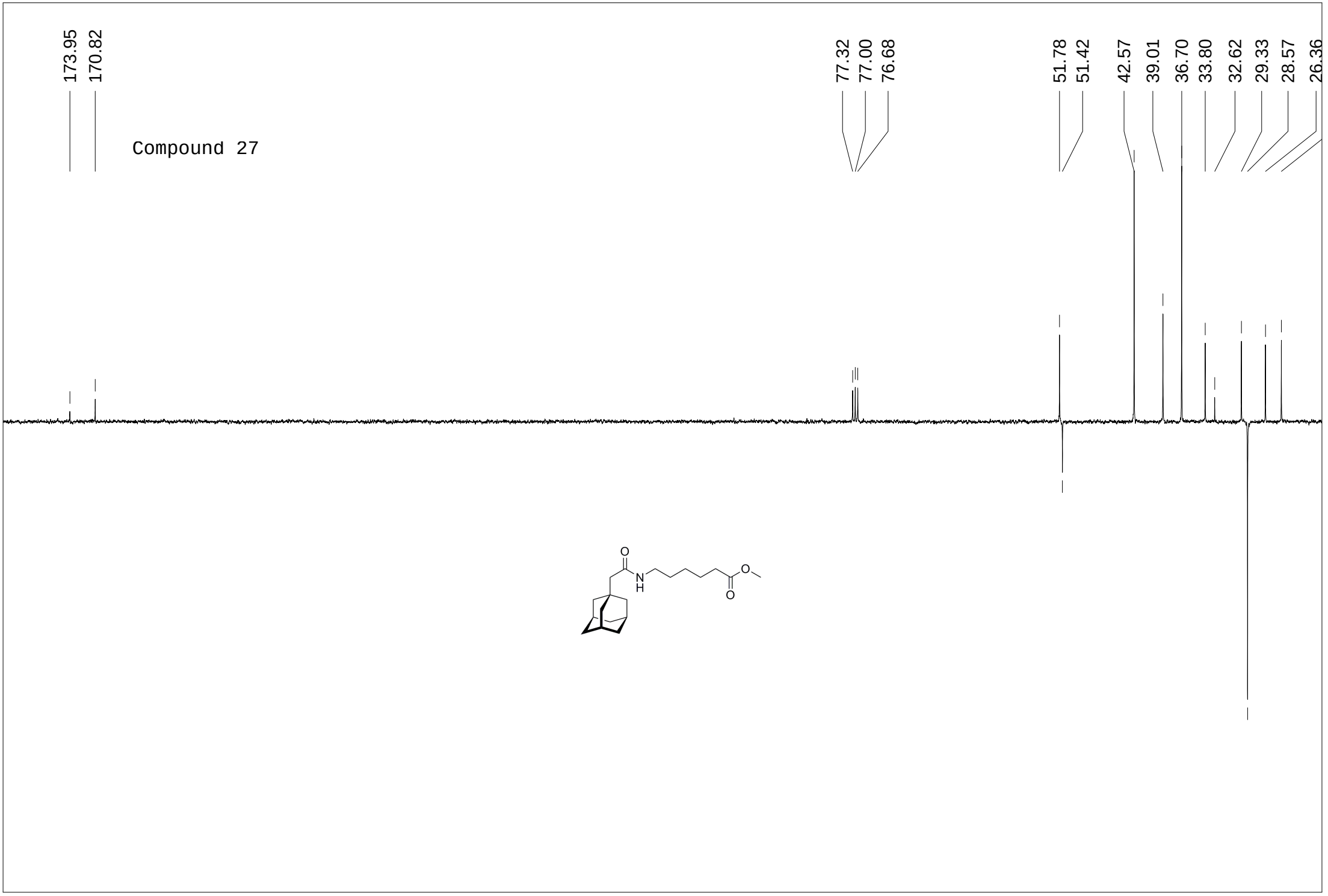

6.71
6.70
6.68
6.66
6.35
6.31
5.18
5.16
4.35
4.34
2.14
1.97
1.75
1.72
1.70
1.67
1.45
1.44
0.95
0.95
0.94
0.93
Compound 26
BocHN
O
S
O
0.84
0.87
0.71
0.82
2.70
5.23
6.43
11.06
6.00
ppm (f1)


154.76
150.74
122.69
79.15
77.32
77.00
76.68
59.98
59.38
49.74
42.37
37.53
35.43
34.20
27.96
27.74
24.33
22.32
21.72
Compound 26
BocHN
O
S
O

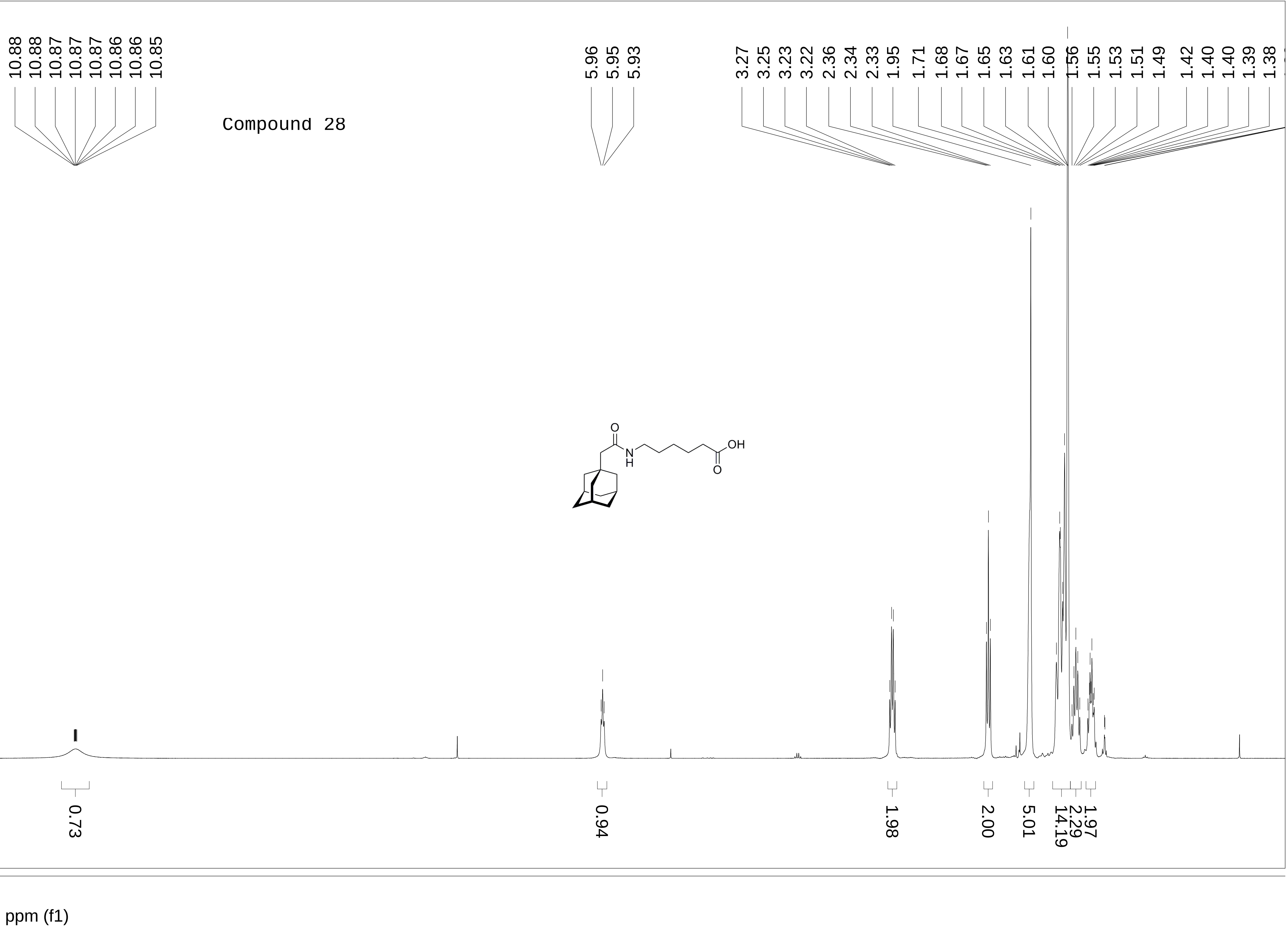
ppm (f1)

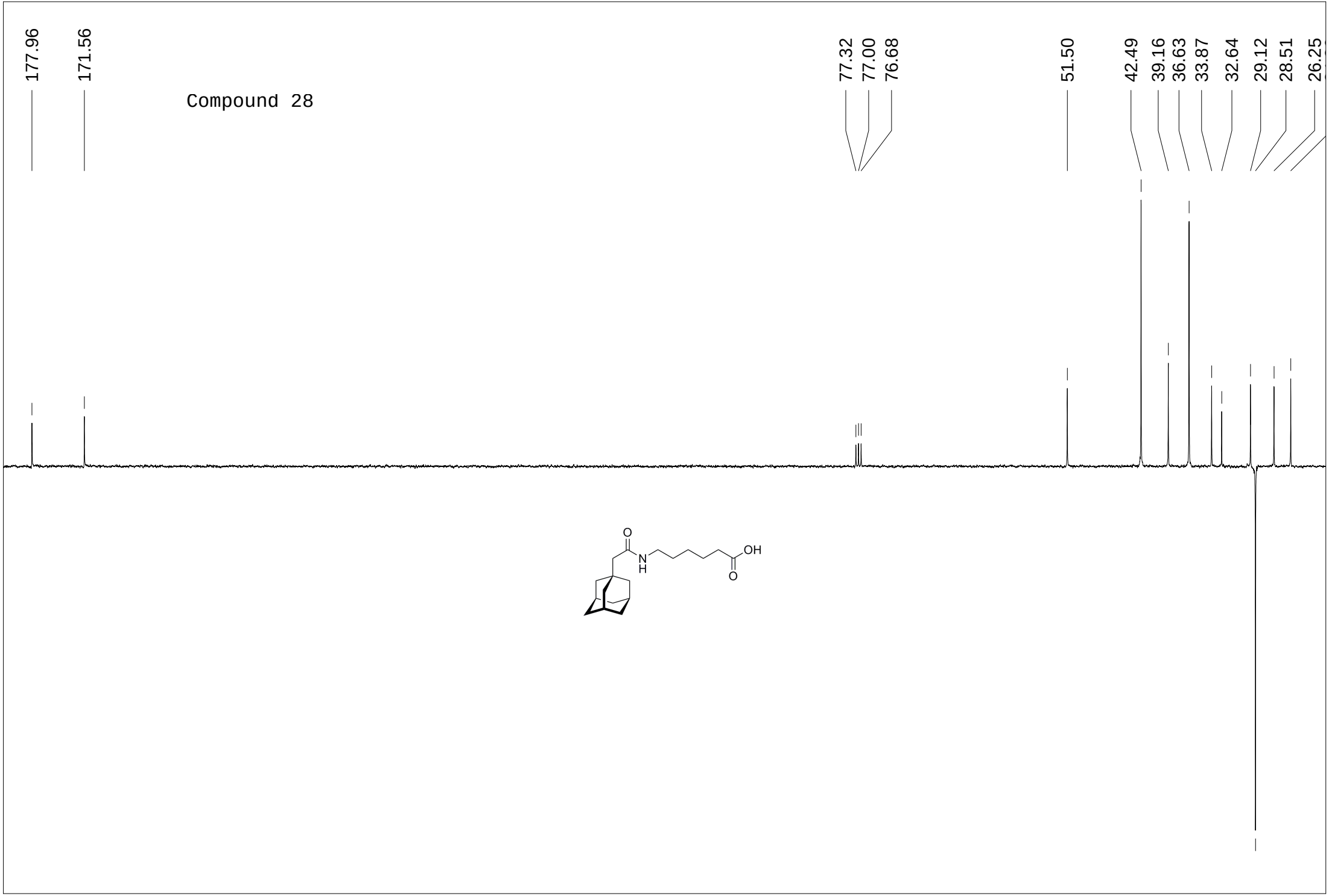

5.57
3.67
3.26
3.25
3.23
3.21
2.33
2.32
2.30
2.05
1.97
1.91
1.72
1.69
1.67
1.65
1.62
1.61
1.56
1.54
1.52
1.50
1.48
1.39
1.38
1.37
1.36
1.36
1.34
1.33
1.32
Compound 27
O
N
H
O
O
0.90
2.99
2.01
2.00
3.12
1.99
14.51
2.14
2.11

ppm (f1)

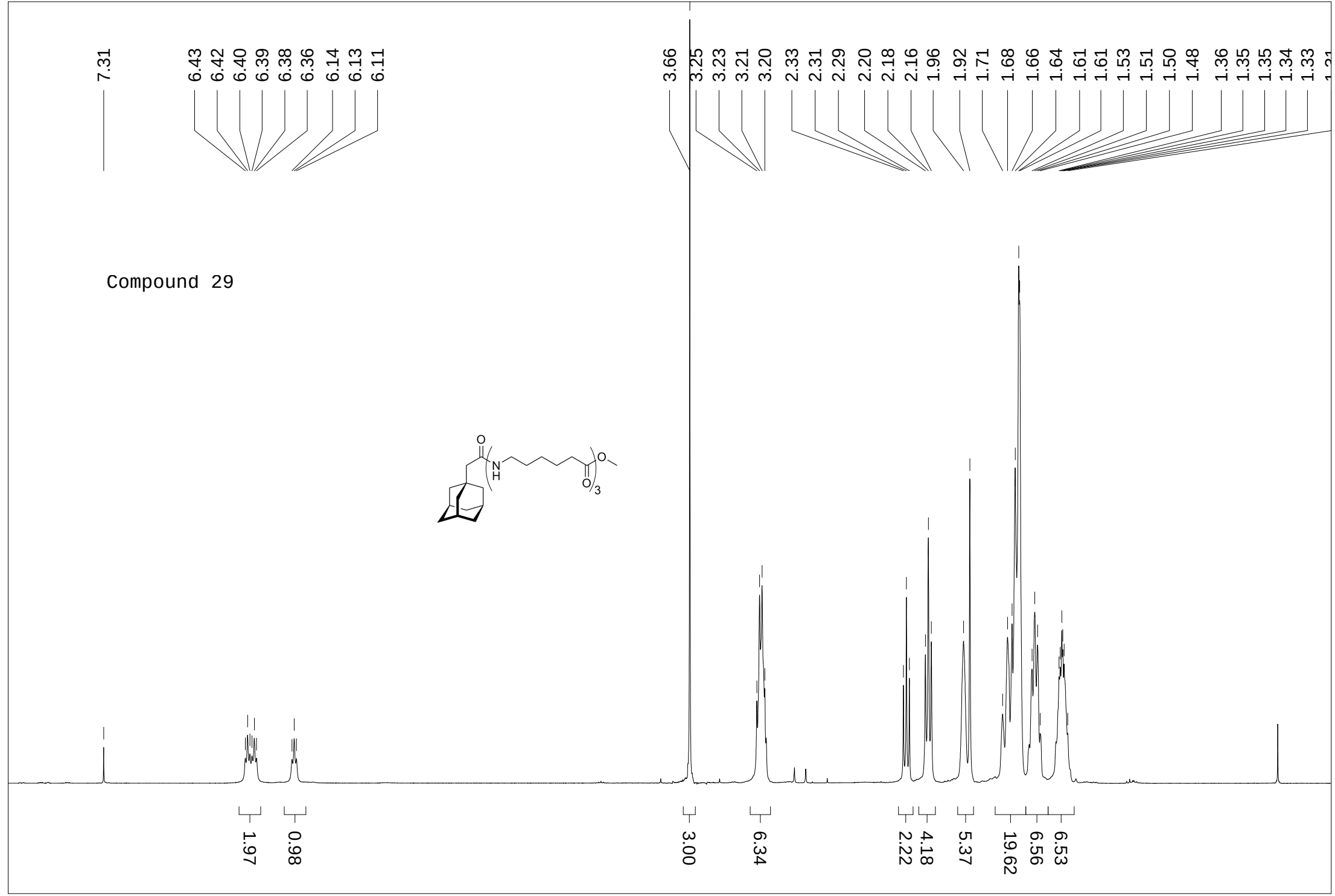

173.95
170.82
77.32
77.00
76.68
51.78
51.42
42.57
39.01
36.70
33.80
32.62
29.33
28.57
26.36
Compound 27
O
N
H
O
O

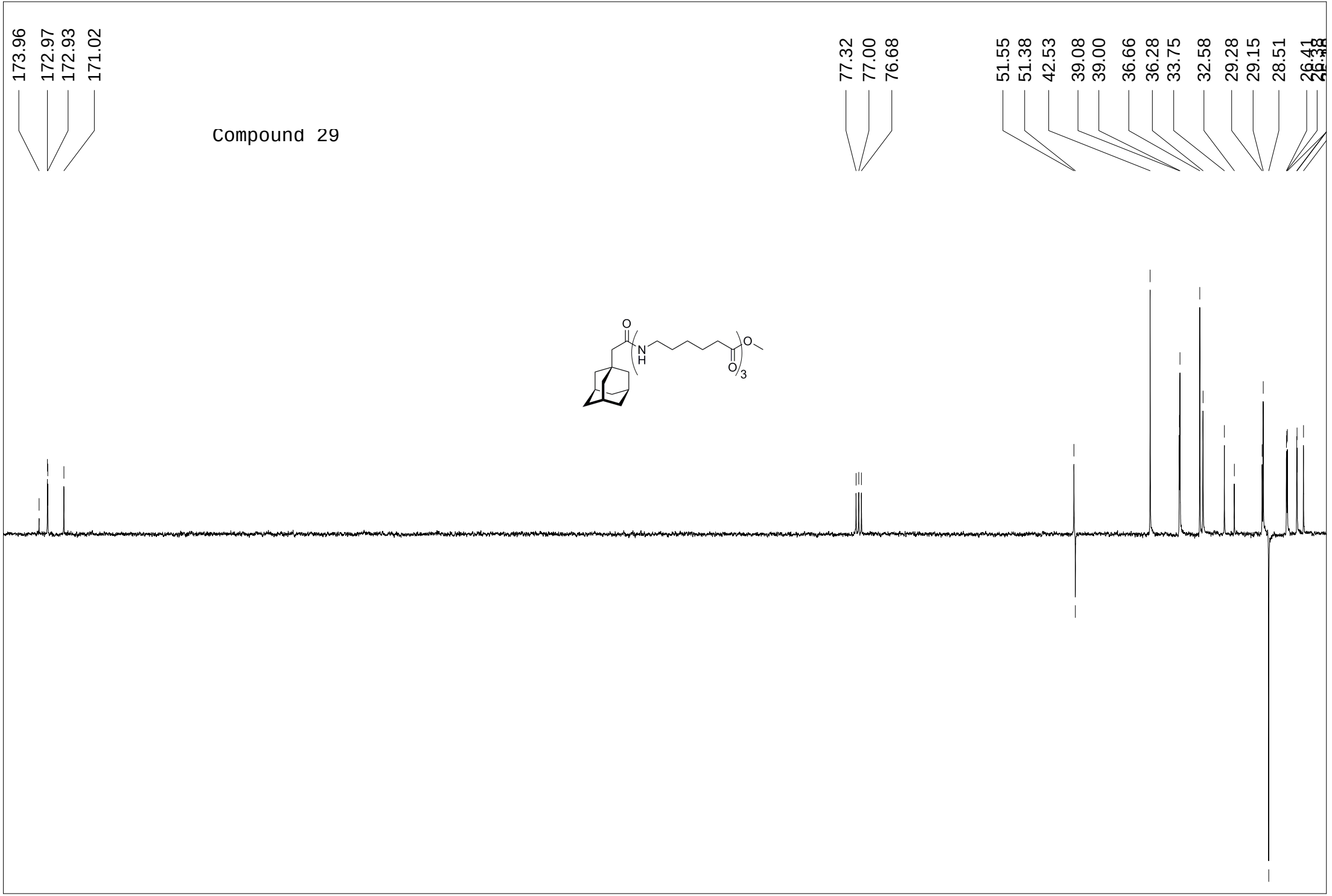
ppm (f1)


10.88
10.88
10.87
10.87
10.87
10.86
10.86
10.85
Compound 28
5.96
5.95
5.93
3.27
3.25
3.23
3.22
2.36
2.34
2.33
1.95
1.71
1.68
1.67
1.65
1.63
1.61
1.60
1.56
1.55
1.53
1.51
1.49
1.42
1.40
1.40
1.39
1.38
O
N
H
OH
O
0.73
0.94
1.98
2.00
5.01
14.19
2.29
1.97
ppm (f1)

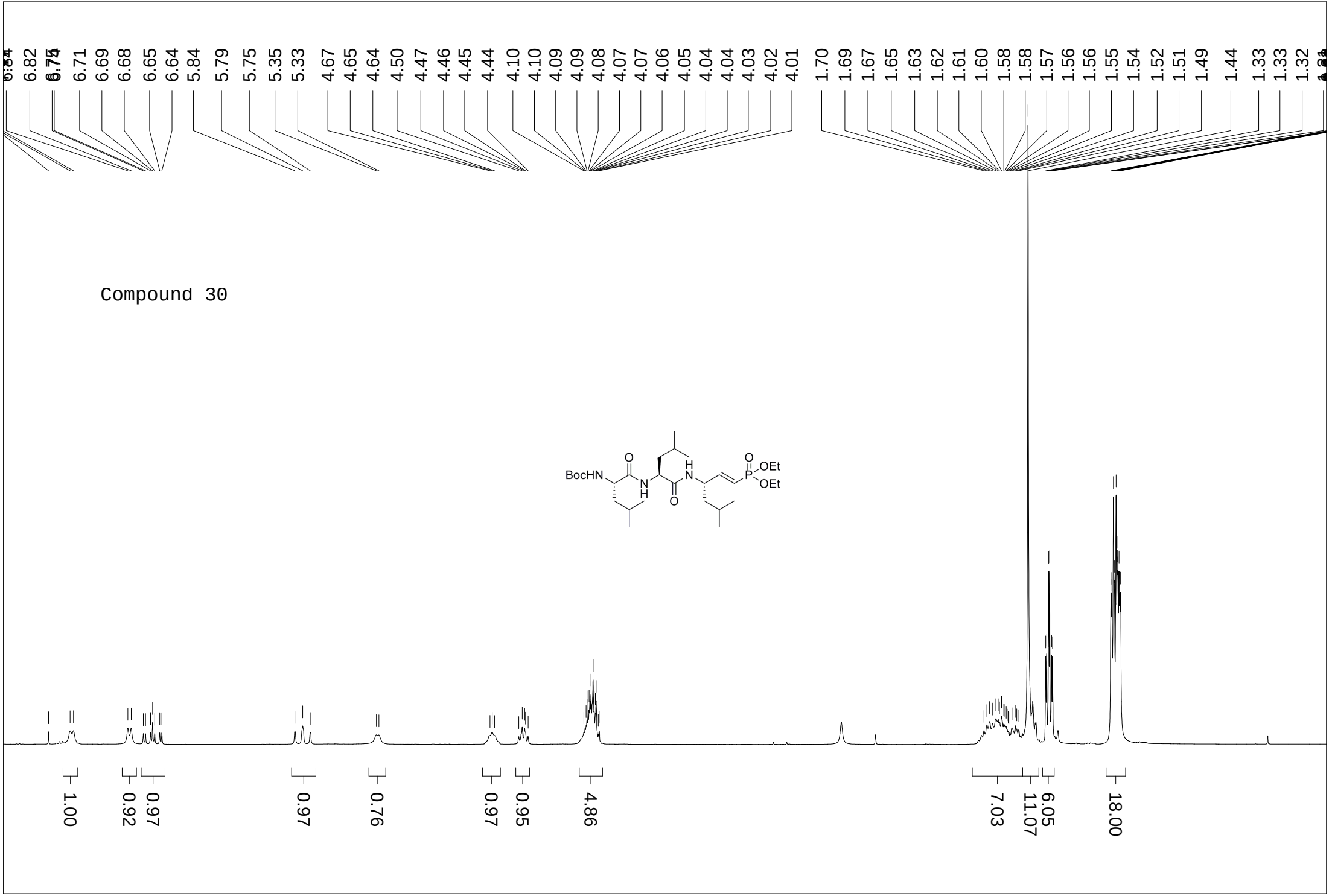

177.96
171.56
77.32
77.00
76.68
51.50
42.49
39.16
36.63
33.87
32.64
29.12
28.51
26.25
Compound 28
O
N
H
OH
O

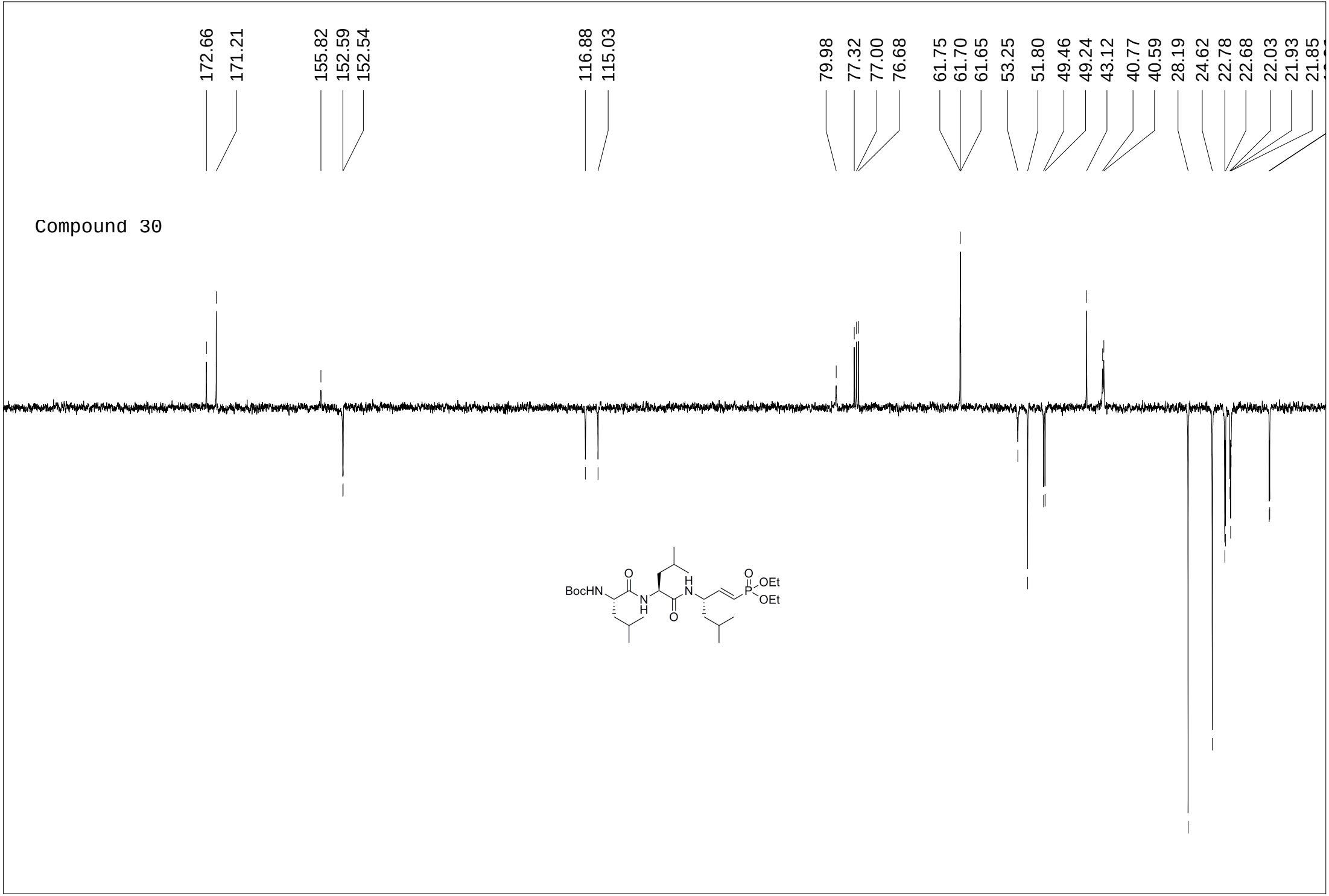
ppm (f1)


7.31
6.43
6.42
6.40
6.39
6.38
6.36
6.14
6.13
6.11
3.66
3.25
3.23
3.21
3.20
2.33
2.31
2.29
2.20
2.18
2.16
1.96
1.92
1.71
1.68
1.66
1.64
1.61
1.61
1.53
1.51
1.50
1.48
1.36
1.35
1.35
1.34
1.33
Compound 29
O
N
H
O
O
3
1.97
0.98
3.00
6.34
2.22
4.18
5.37
19.62
6.56
6.53
ppm (f1)


173.96
172.97
172.93
171.02
77.32
77.00
76.68
51.55
51.38
42.53
39.08
39.00
36.66
36.28
33.75
32.58
29.28
29.15
28.51
Compound 29
O
N
H
O
O
3

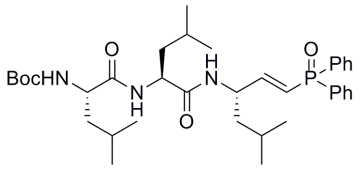
ppm (f1)


6.82
6.71
6.69
6.68
6.65
6.64
5.84
5.79
5.75
5.35
5.33
4.67
4.65
4.64
4.50
4.47
4.46
4.45
4.44
4.10
4.10
4.09
4.09
4.08
4.07
4.07
4.06
4.05
4.04
4.04
4.03
4.02
4.01
1.70
1.69
1.67
1.65
1.63
1.62
1.61
1.60
1.58
1.58
1.57
1.56
1.56
1.55
1.54
1.52
1.51
1.49
1.44
1.33
1.33
1.32
Compound 30
BocHN
OEt
OEt
1.00
0.92
0.97
0.97
0.76
0.97
0.95
4.86
7.03
11.07
6.05
18.00
ppm (f1)


172.66
171.21
155.82
152.59
152.54
116.88
115.03
79.98
77.32
77.00
76.68
61.75
61.70
61.65
53.25
51.80
49.46
49.24
43.12
40.77
40.59
28.19
24.62
22.78
22.68
22.03
21.93
21.85
Compound 30
BocHN
O
N
H
O
H
N
O
P
OEt
OEt

ppm (f1)

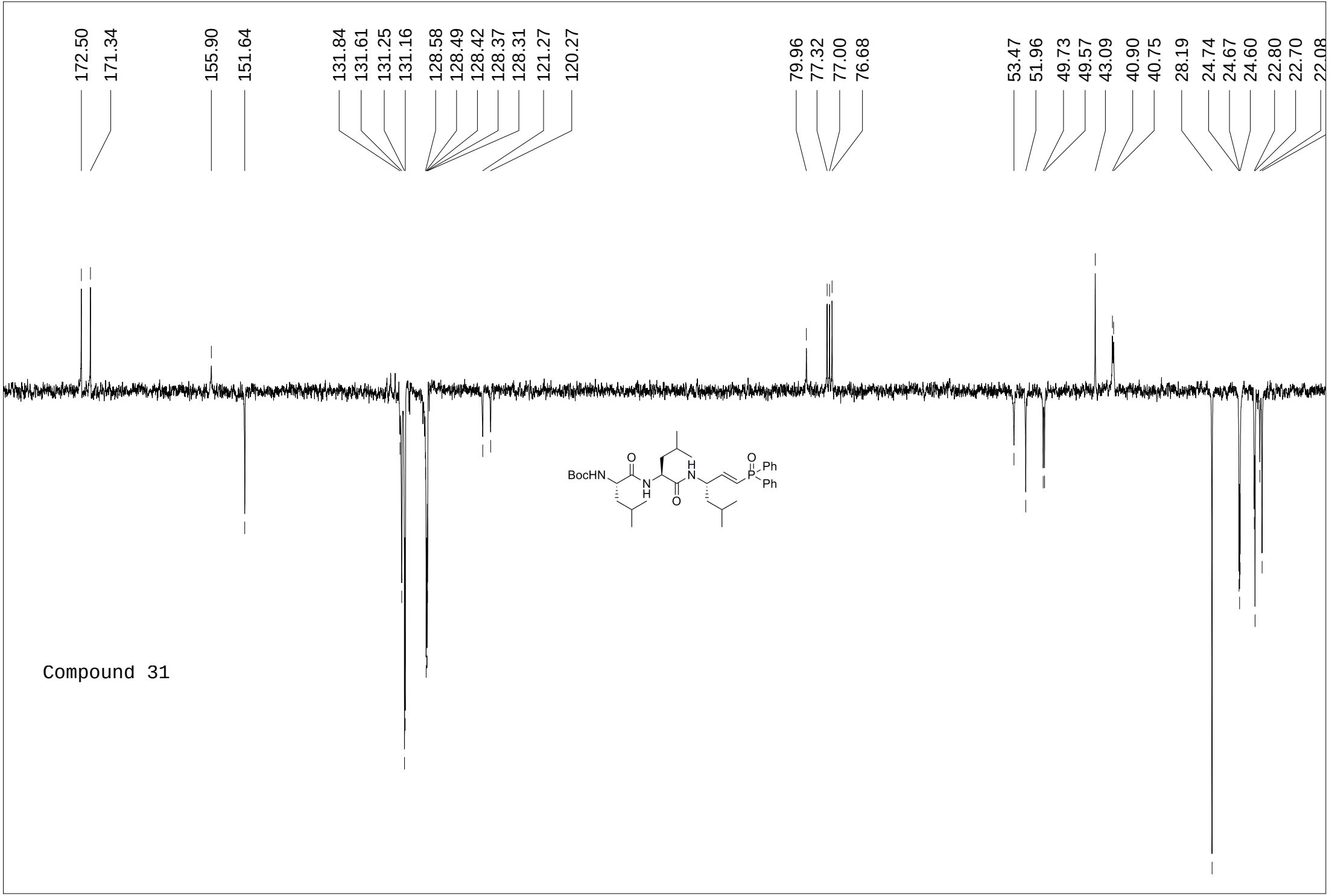
Compound 31



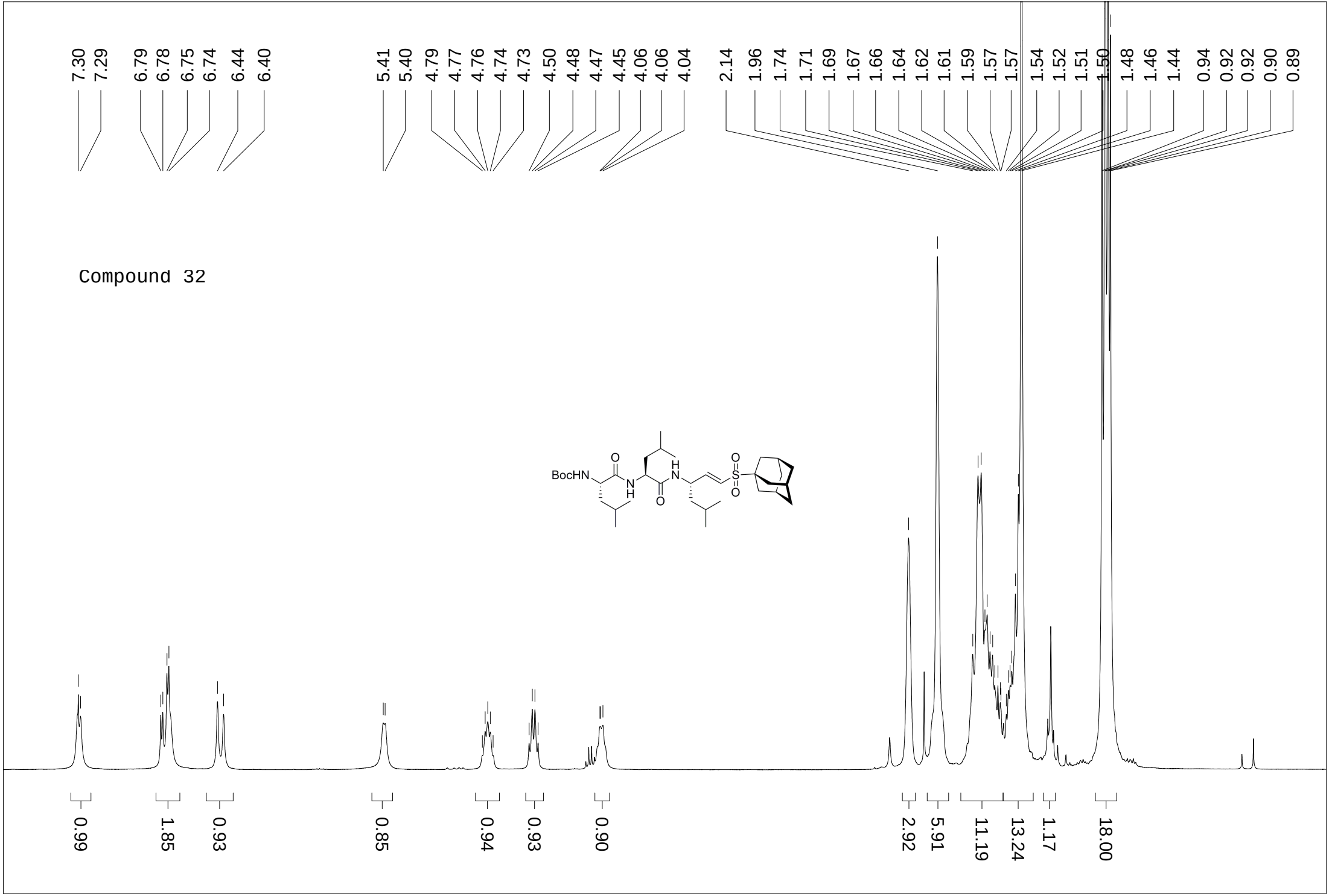
7.65 7.60 7.58 7.54 7.54 7.48 7.45 7.43 7.41 7.39 7.30 7.27 7.25 7.23 7.18 7.16 6.82 6.80 6.70 6.65 6.60 6.55 6.49 6.45 5.48 5.46 4.75 4.53 4.51 4.04 4.02 2.75 2.73 2.71 2.69 2.65 2.65 2.58 2.35 2.25 2.24 2.09 2.07 2.05 2.04 1.72 1.71 1.69 1.62 1.60 1.59 1.57 1.56 1.54 1.51

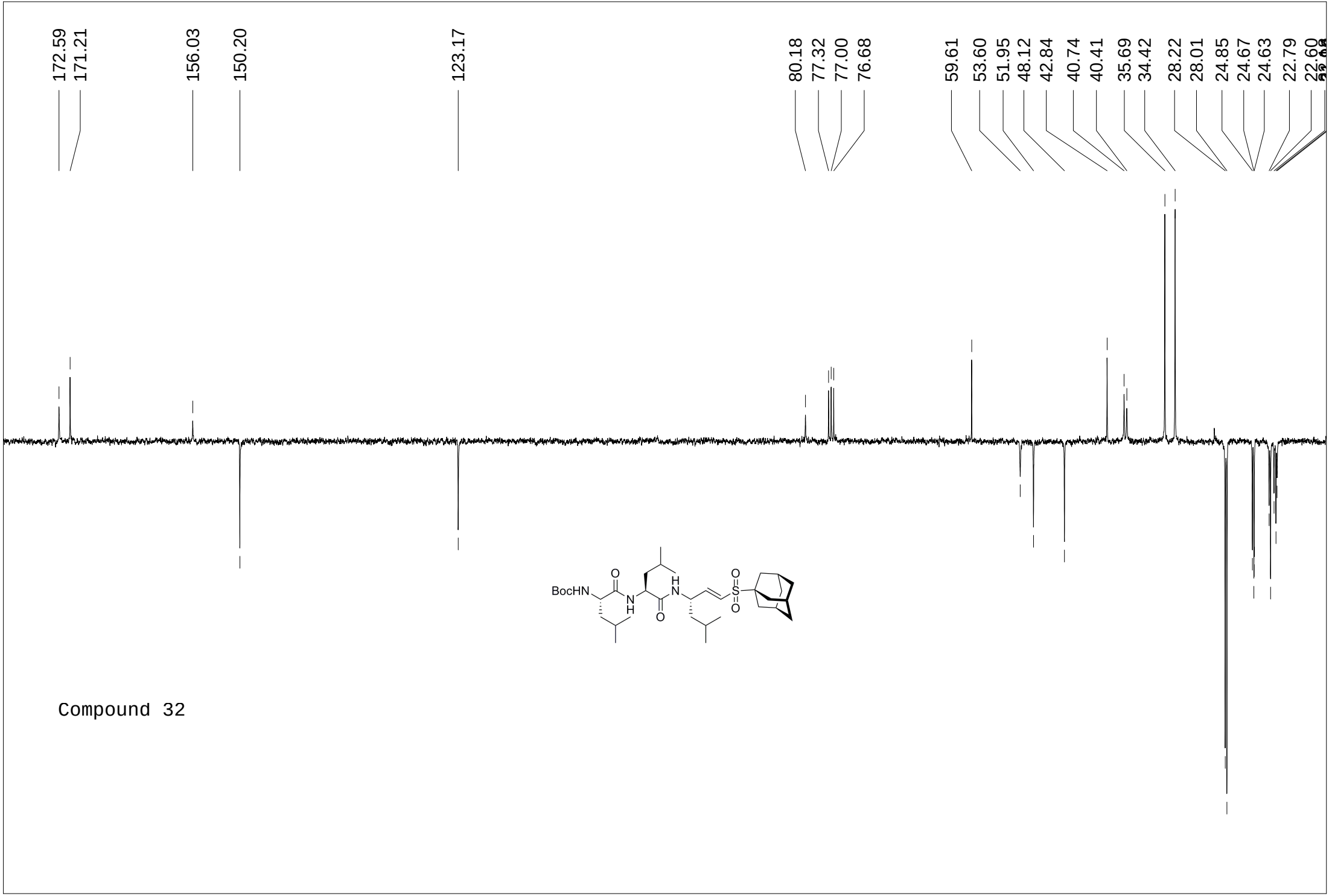
11.00 1.03 0.92 1.89 0.86 0.86 0.90 1.14 18.22 1.29 18.00

ppm (f1)


172.50
171.34
155.90
151.64
131.84
131.61
131.25
131.16
128.58
128.49
128.42
128.37
128.31
121.27
120.27
79.96
77.32
77.00
76.68
53.47
51.96
49.73
49.57
43.09
40.90
40.75
28.19
24.74
24.67
24.60
22.80
22.70
22.08
BocHN
O
N
H
O
H
N
O
P
Ph
Ph
Compound 31

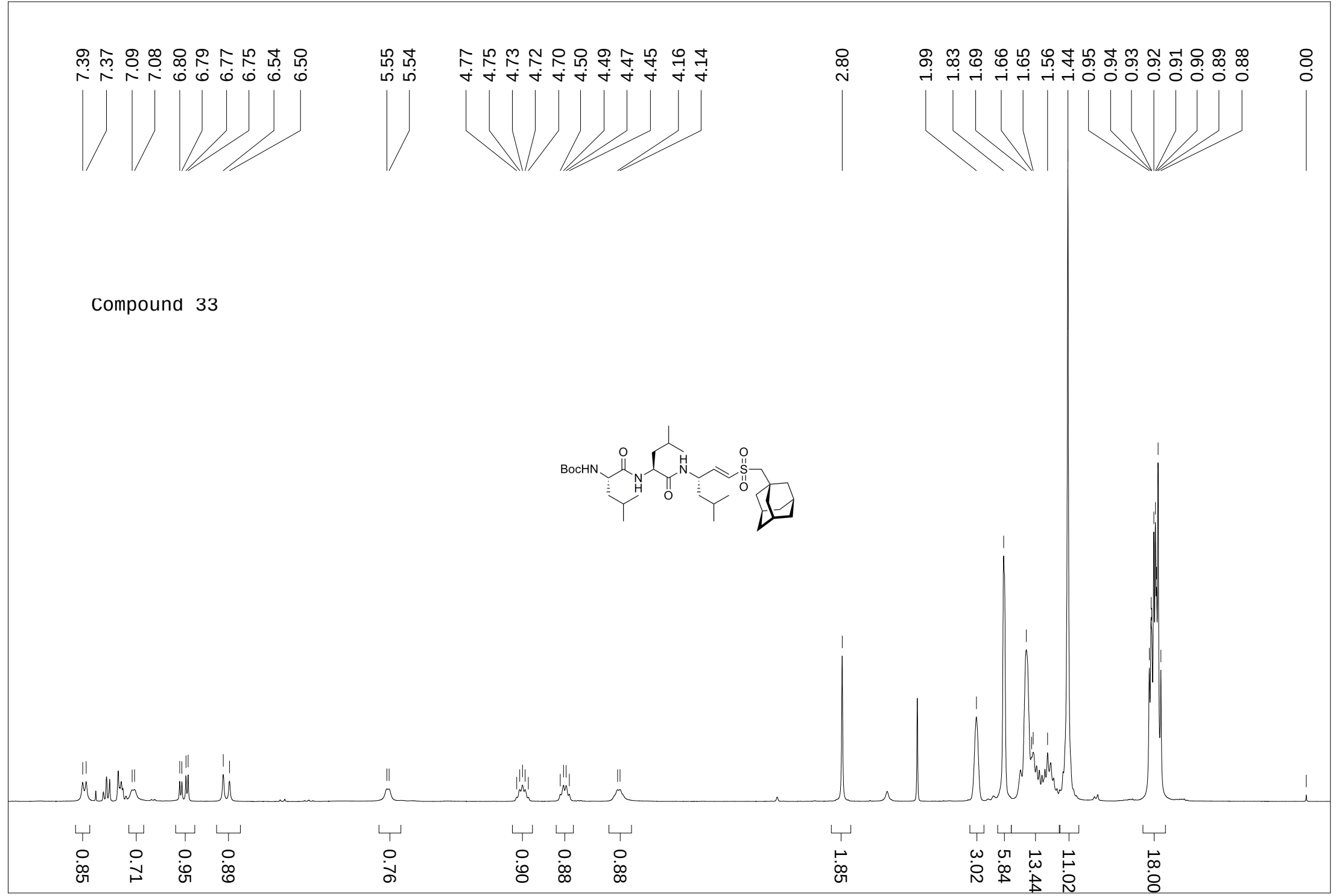
ppm (f1)

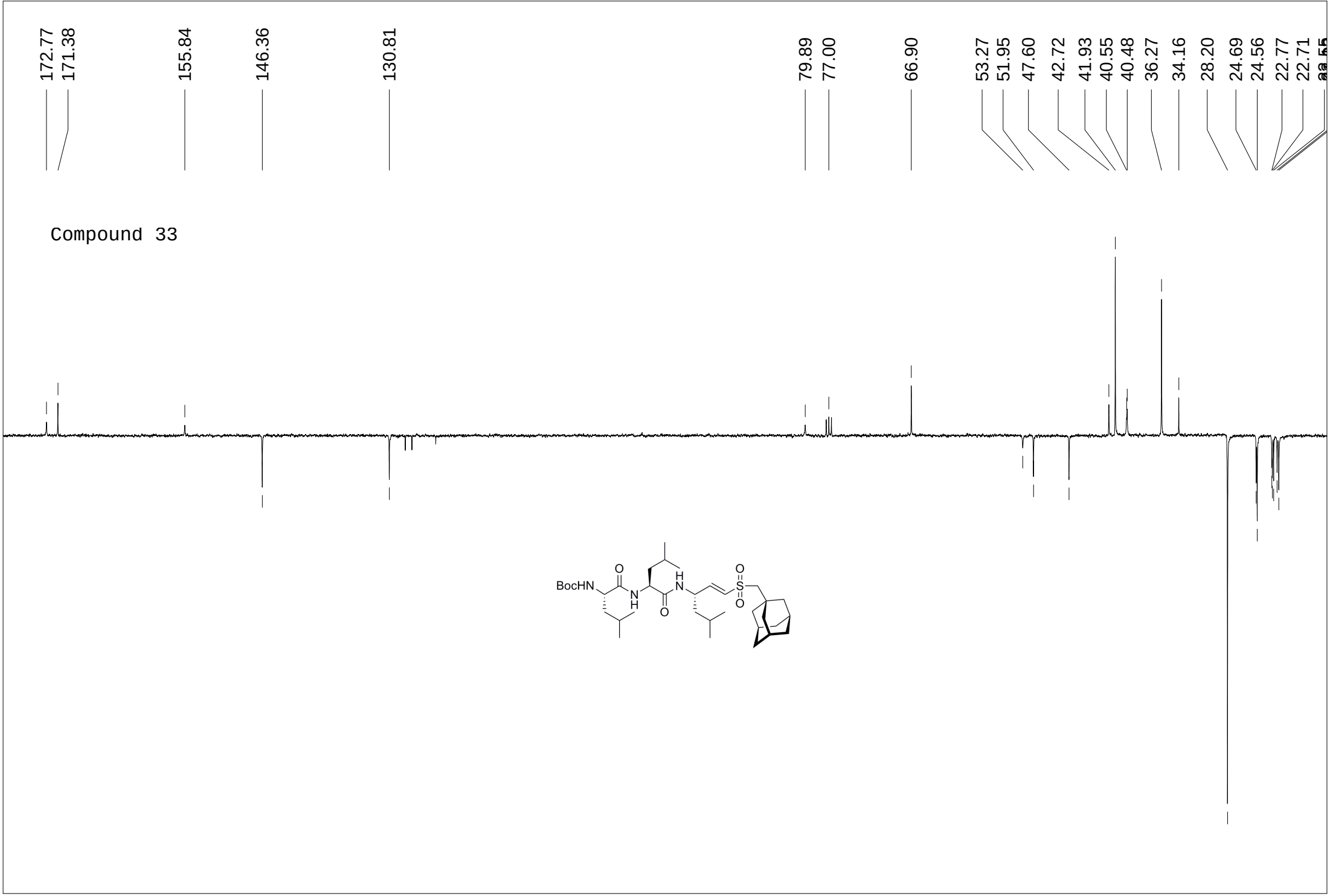

7.30
7.29
6.79
6.78
6.75
6.74
6.44
6.40
5.41
5.40
4.79
4.77
4.76
4.74
4.73
4.50
4.48
4.47
4.45
4.06
4.06
4.04
2.14
1.96
1.74
1.71
1.69
1.67
1.66
1.64
1.62
1.61
1.59
1.57
1.57
1.54
1.52
1.51
1.50
1.48
1.46
1.44
0.94
0.92
0.92
0.90
0.89
Compound 32
BocHN
0.99
1.85
0.93
0.85
0.94
0.93
0.90
2.92
5.91
11.19
13.24
1.17
18.00
ppm (f1)



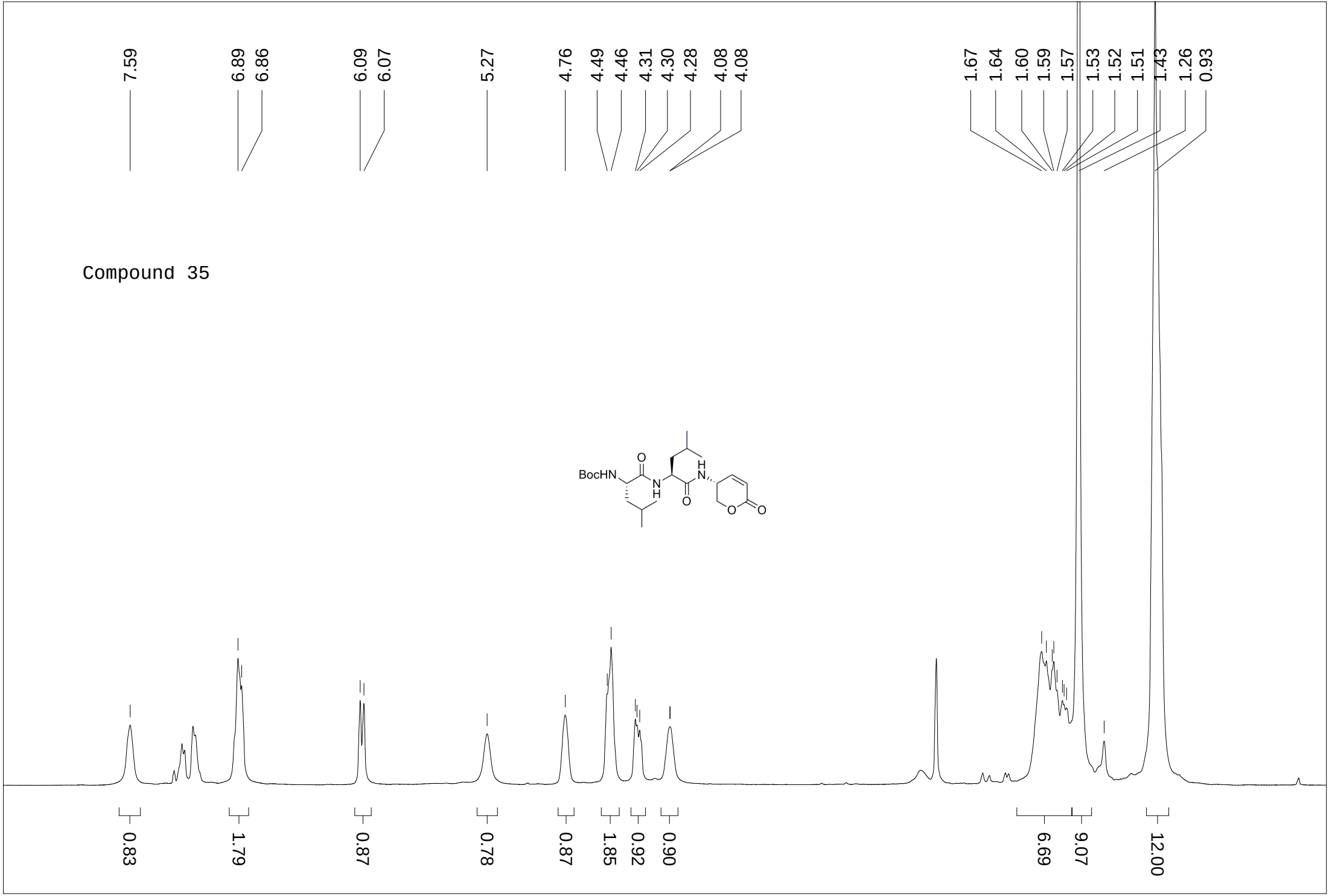
Compound 32

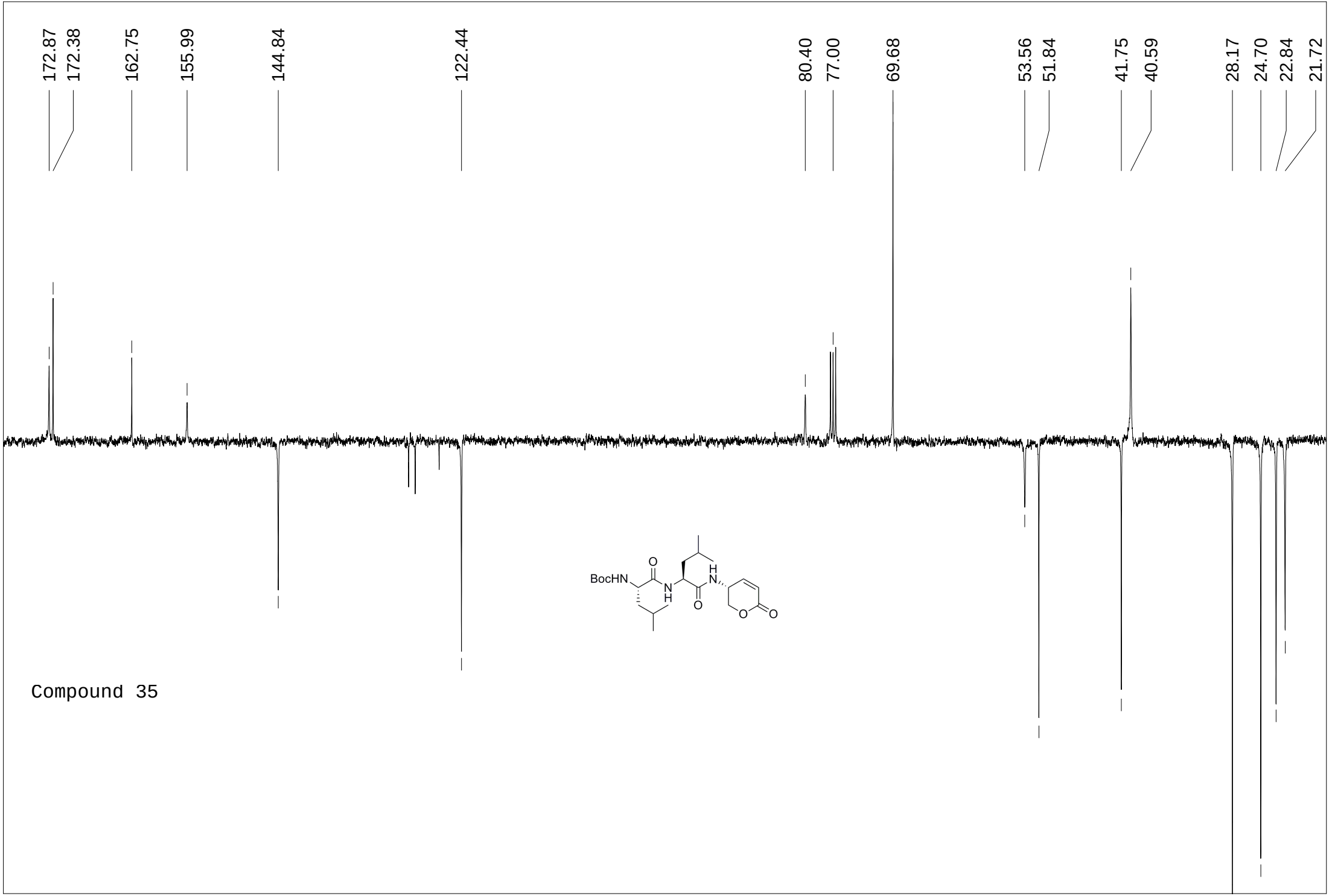
ppm (f1)


7.39
7.37
7.09
7.08
6.80
6.79
6.77
6.75
6.54
6.50
5.55
5.54
4.77
4.75
4.73
4.72
4.70
4.50
4.49
4.47
4.45
4.16
4.14
2.80
1.99
1.83
1.69
1.66
1.65
1.56
1.44
0.95
0.94
0.93
0.92
0.91
0.90
0.89
0.88
0.00
Compound 33
BocHN
0.85
0.71
0.95
0.89
0.76
0.90
0.88
0.88
1.85
3.02
5.84
13.44
11.02
18.00
ppm (f1)

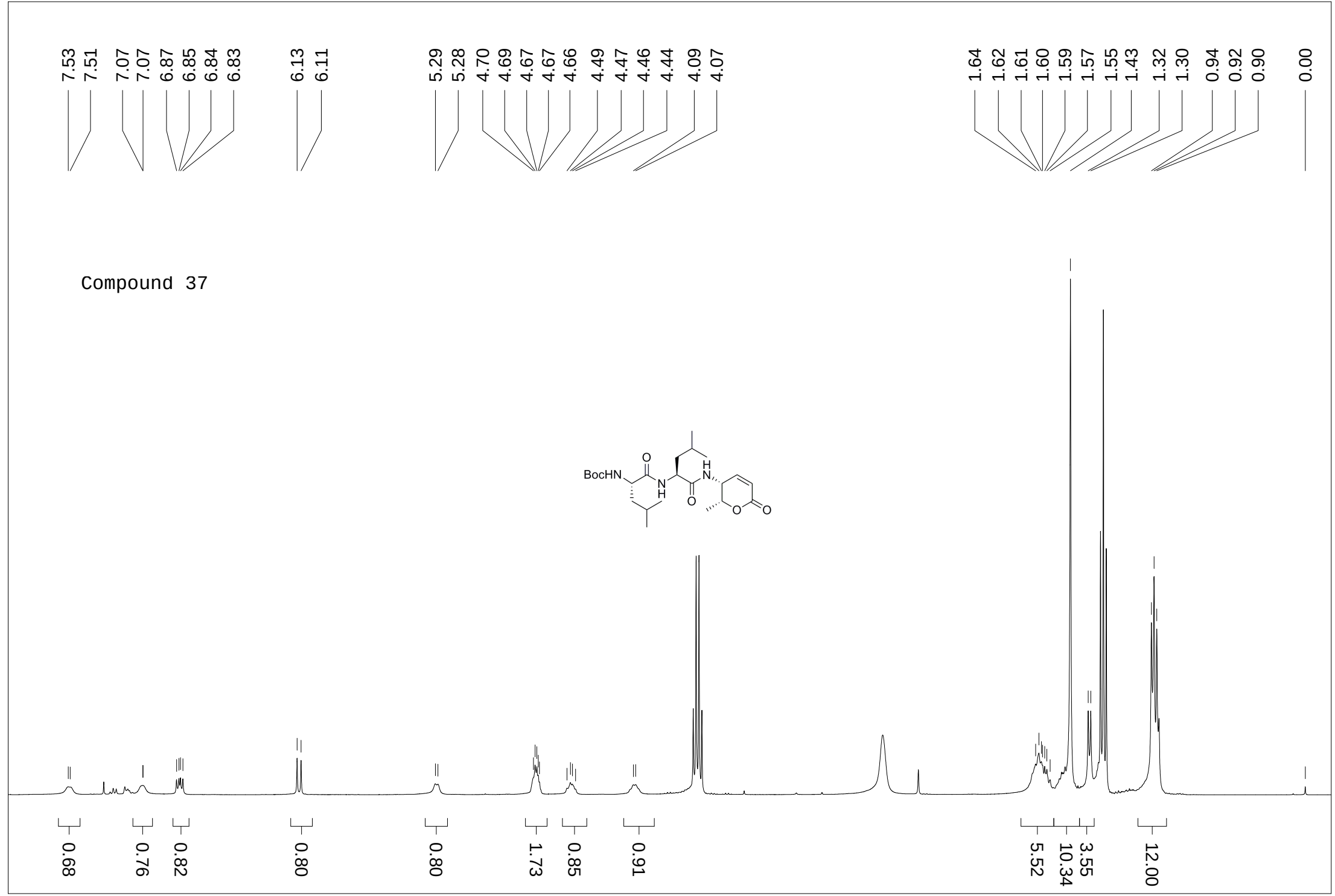

172.77
171.38
155.84
146.36
130.81
79.89
77.00
66.90
53.27
51.95
47.60
42.72
41.93
40.55
40.48
36.27
34.16
28.20
24.69
24.56
22.77
22.71
Compound 33
BocHN
O
N
H
O
H
N
O
S
O
O

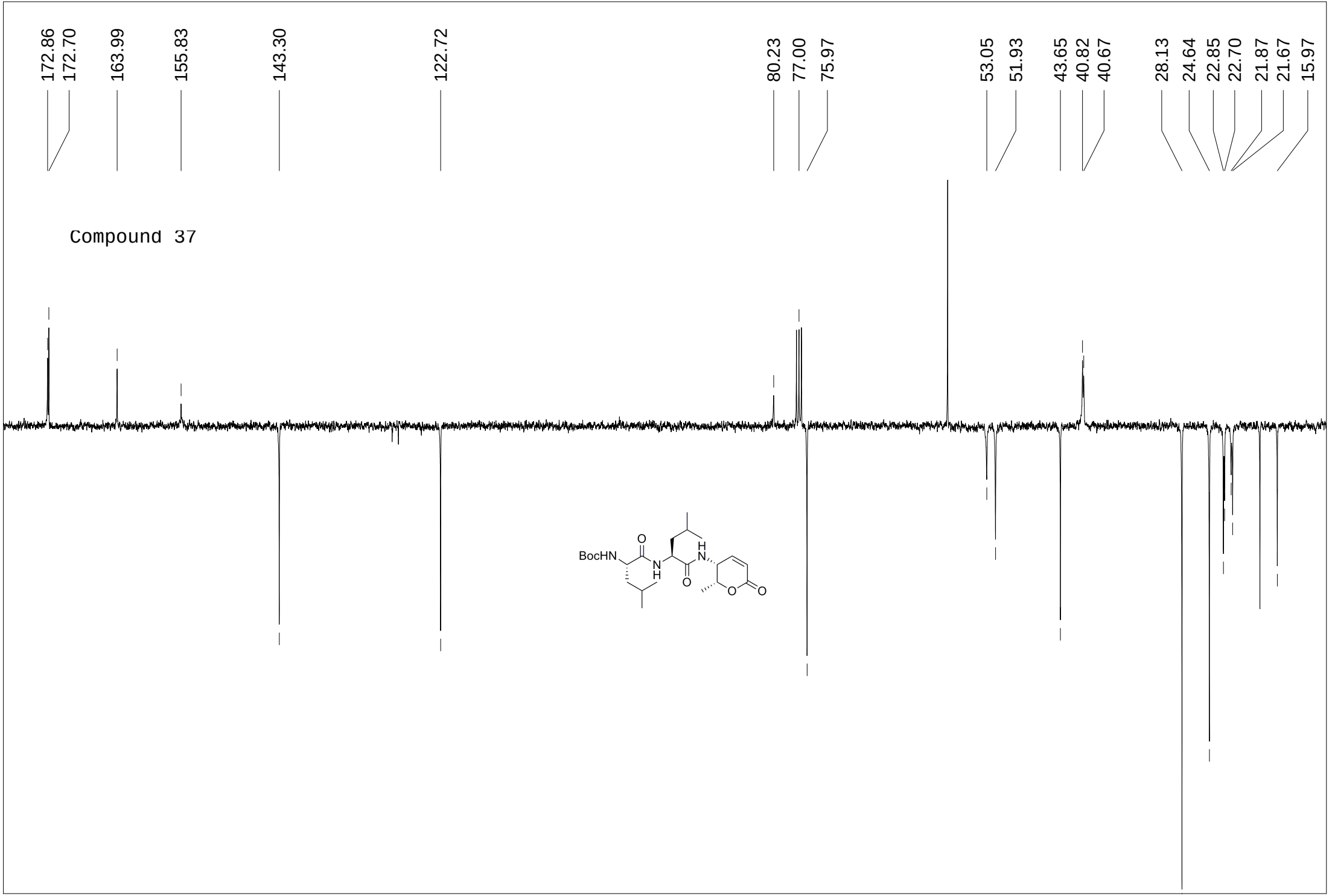
ppm (f1)


7.59
6.89
6.86
6.09
6.07
5.27
4.76
4.49
4.46
4.31
4.30
4.28
4.08
4.08
1.67
1.64
1.60
1.59
1.57
1.53
1.52
1.51
1.43
1.26
0.93
Compound 35
BocHN
0.83
1.79
0.87
0.78
0.87
1.85
0.92
0.90
6.69
9.07
12.00
ppm (f1)

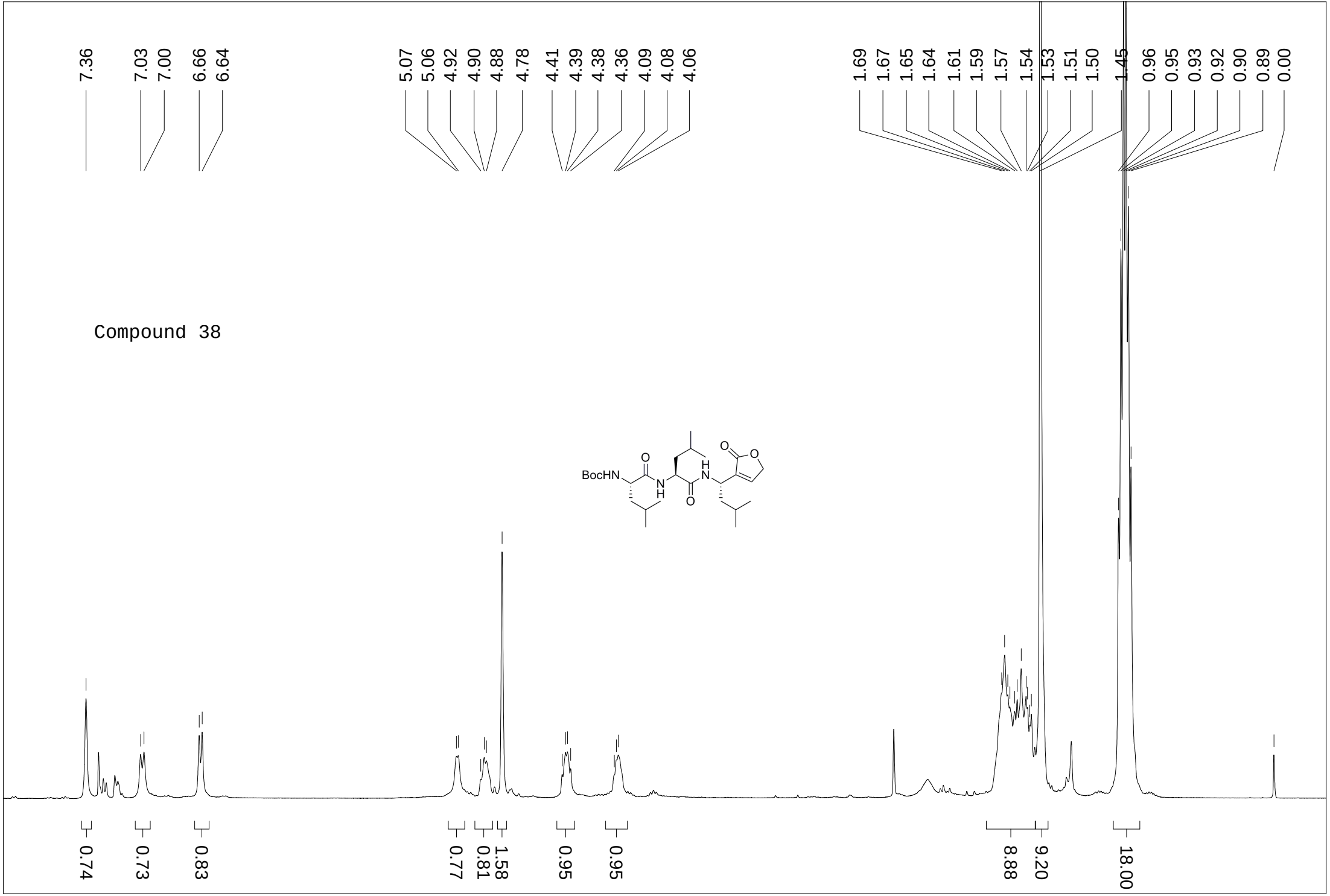

172.87
172.38
162.75
155.99
144.84
122.44
80.40
77.00
69.68
53.56
51.84
41.75
40.59
28.17
24.70
22.84
21.72
BocHN
O
N
H
H
N
O
O
O
Compound 35

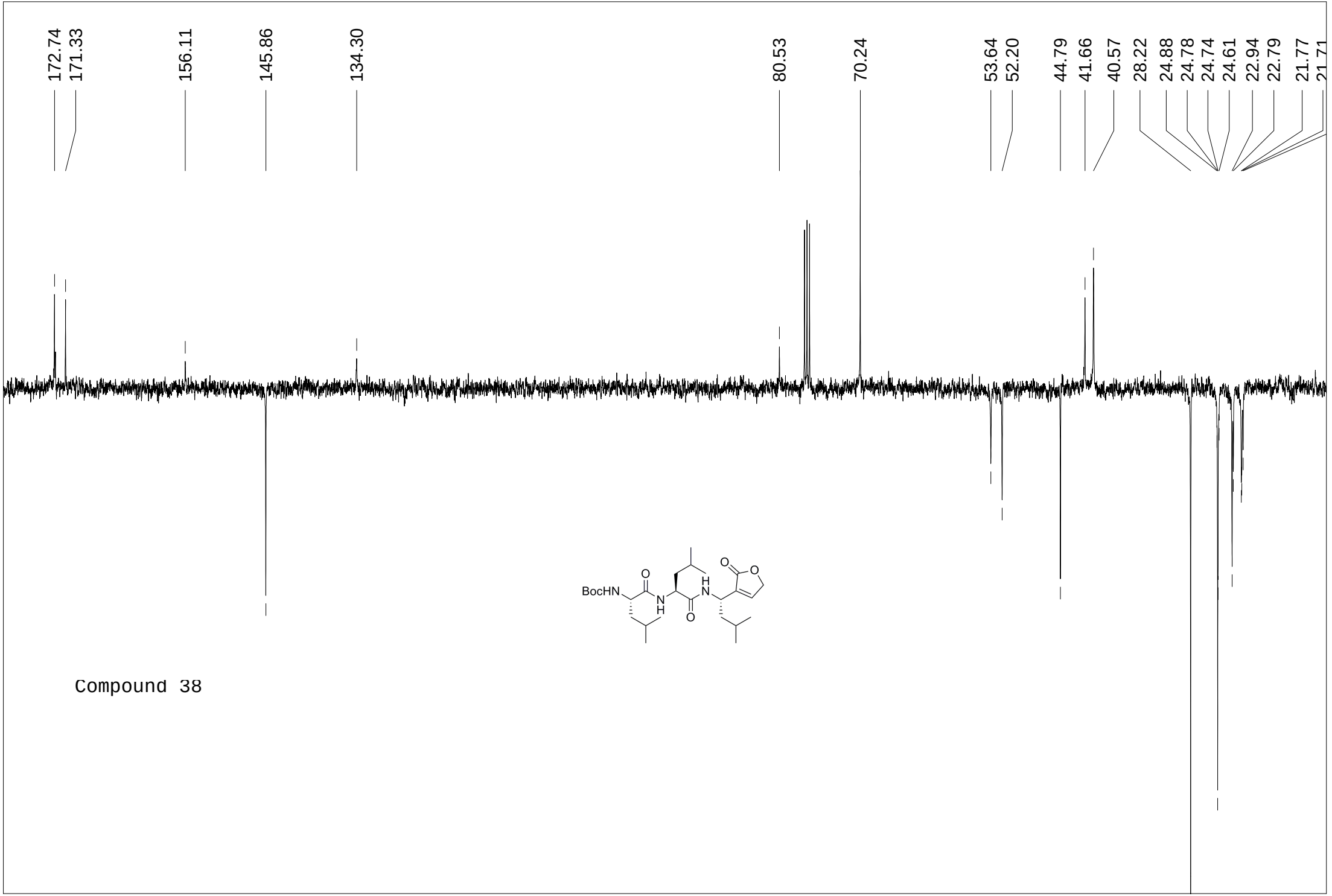
ppm (f1)

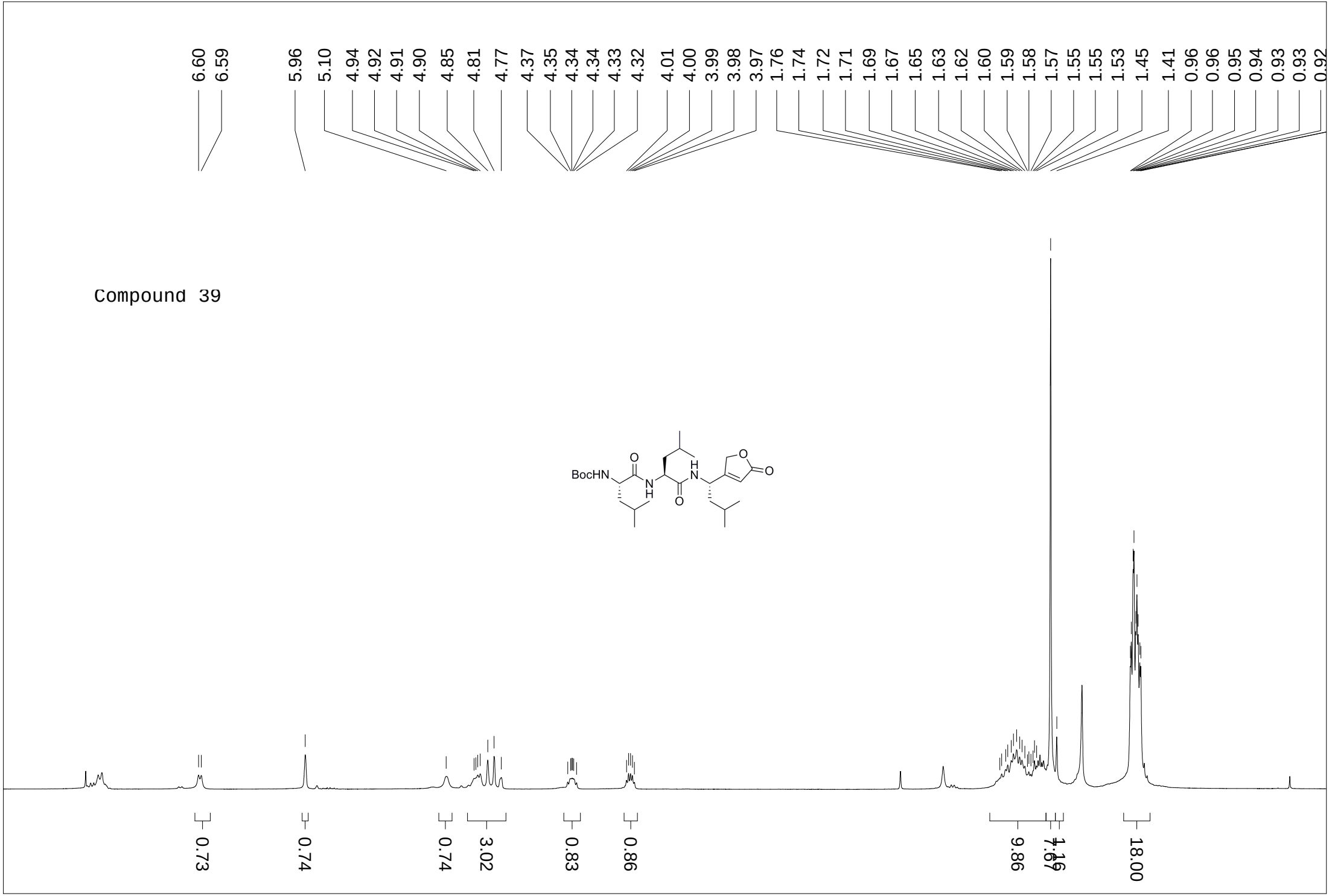

7.53
7.51
7.07
7.07
6.87
6.85
6.84
6.83
6.13
6.11
5.29
5.28
4.70
4.69
4.67
4.67
4.66
4.49
4.47
4.46
4.44
4.09
4.07
1.64
1.62
1.61
1.60
1.59
1.57
1.55
1.43
1.32
1.30
0.94
0.92
0.90
0.00
Compound 37
BocHN
0.68
0.76
0.82
0.80
0.80
1.73
0.85
0.91
5.52
10.34
3.55
12.00
ppm (f1)

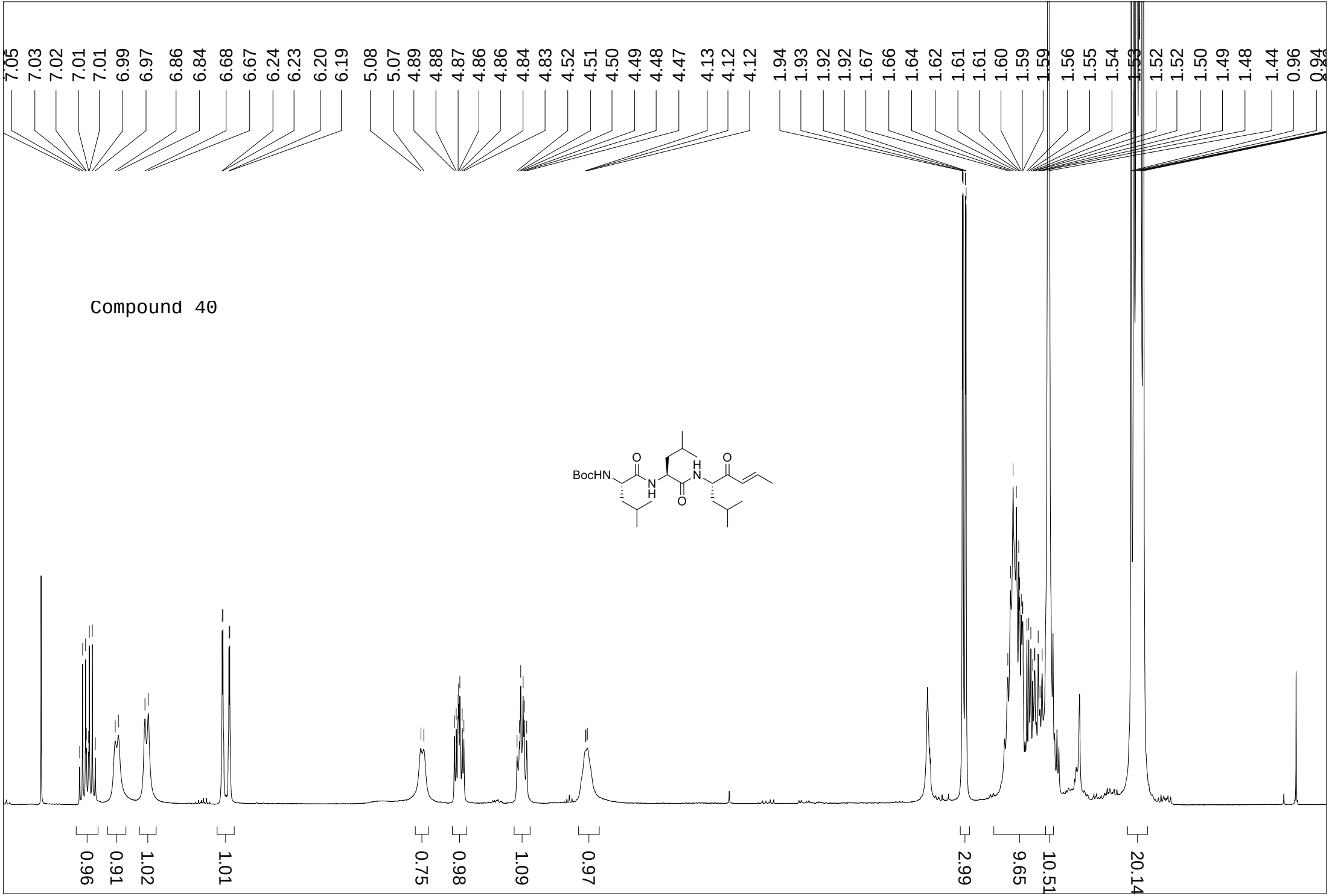

172.86
172.70
163.99
155.83
143.30
122.72
80.23
77.00
75.97
53.05
51.93
43.65
40.82
40.67
28.13
24.64
22.85
22.70
21.87
21.67
15.97
Compound 37
BocHN
O
N
H
O
H
N
O
O

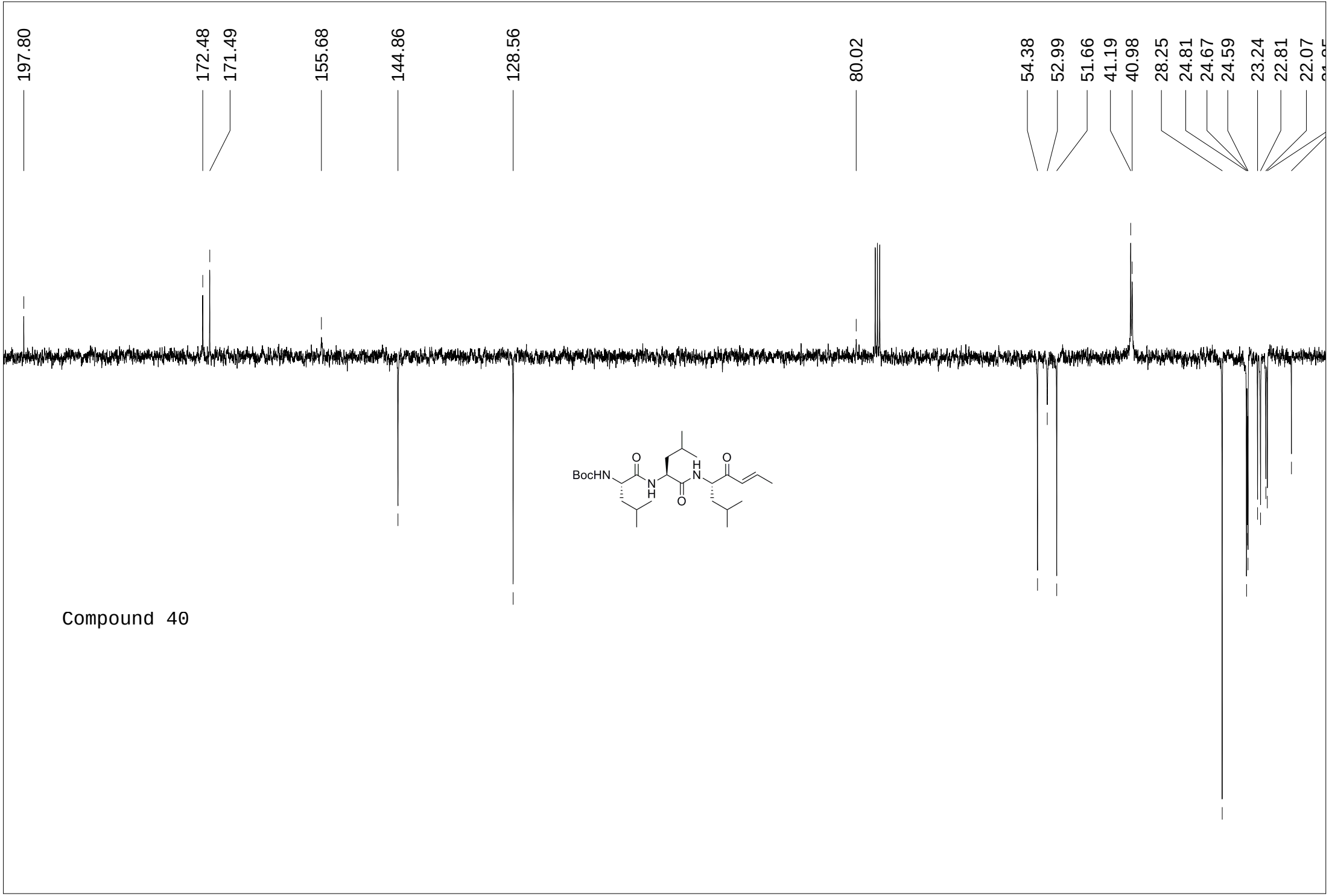
ppm (f1)


7.36
7.03
7.00
6.66
6.64
5.07
5.06
4.92
4.90
4.88
4.78
4.41
4.39
4.38
4.36
4.09
4.08
4.06
1.69
1.67
1.65
1.64
1.61
1.59
1.57
1.54
1.53
1.51
1.50
1.45
0.96
0.95
0.93
0.92
0.90
0.89
0.00
Compound 38
BocHN
0.74
0.73
0.83
0.77
0.81
1.58
0.95
0.95
8.88
9.20
18.00
ppm (f1)

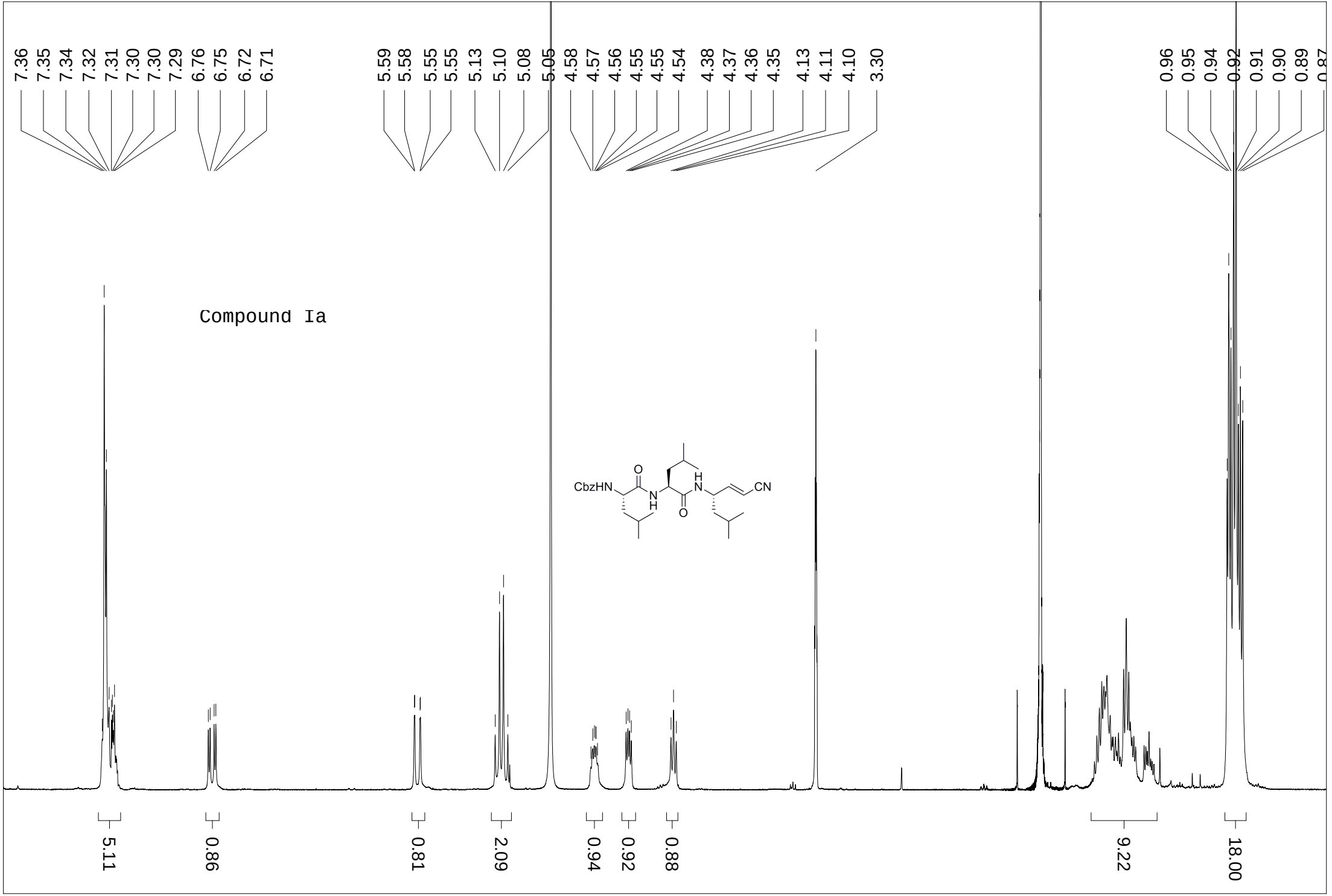

172.74
171.33
156.11
145.86
134.30
80.53
70.24
53.64
52.20
44.79
41.66
40.57
28.22
24.88
24.78
24.74
24.61
22.94
22.79
21.77
21.71
BocHN
O
N
H
O
H
N
O
O
Compound 38
ppm (f1)

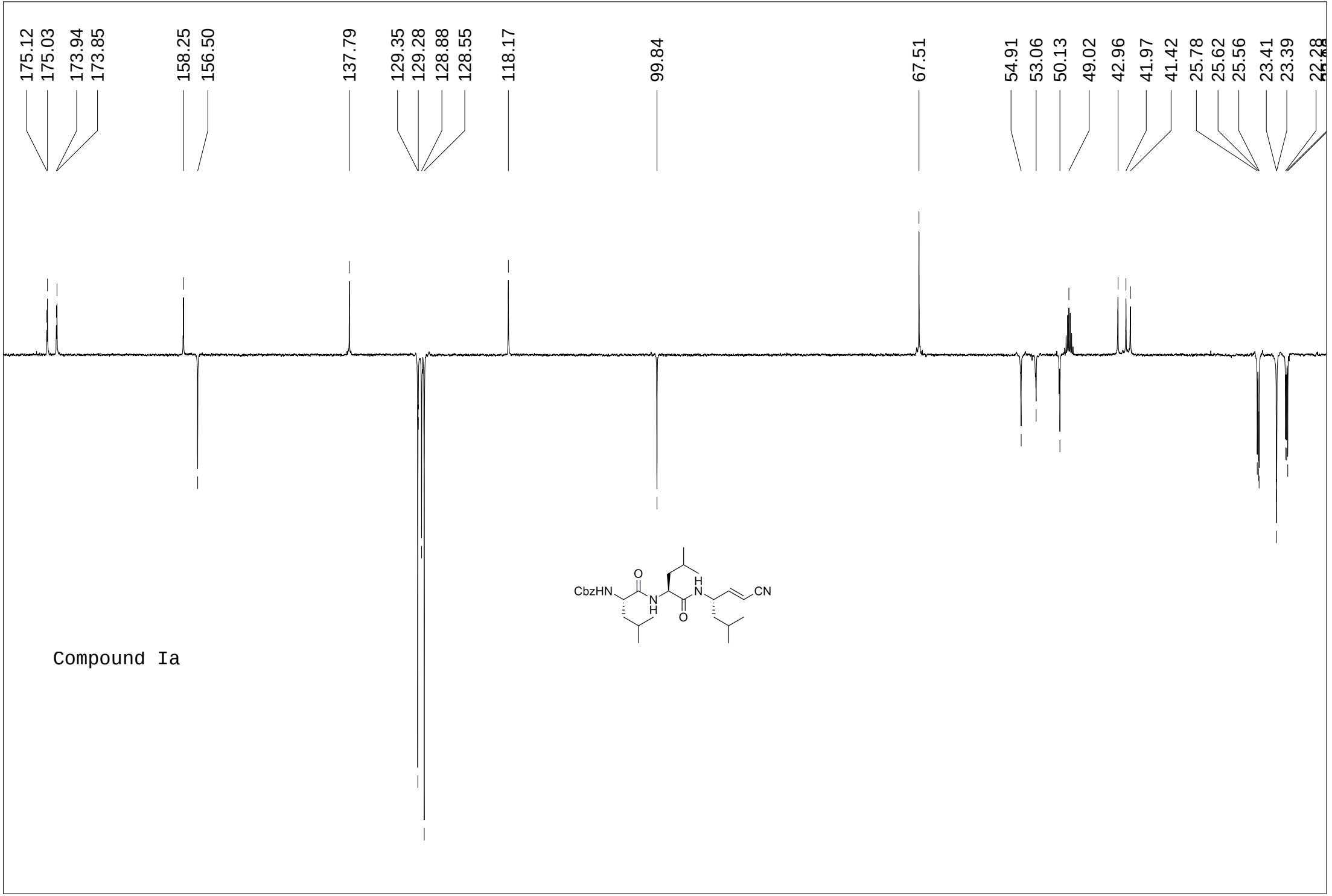

6.60
6.59
5.96
5.10
4.94
4.92
4.91
4.90
4.85
4.81
4.77
4.37
4.35
4.34
4.34
4.33
4.32
4.01
4.00
3.99
3.98
3.97
1.76
1.74
1.72
1.71
1.69
1.67
1.65
1.63
1.62
1.60
1.59
1.58
1.57
1.55
1.55
1.53
1.45
1.41
0.96
0.96
0.95
0.94
0.93
0.93
0.92
Compound 39
BocHN
O
N
H
O
N
H
O
O
0.73
0.74
0.74
3.02
0.83
0.86
9.86
7.87
1.16
18.00
ppm (f1)


7.05
7.03
7.02
7.01
7.01
6.99
6.97
6.86
6.84
6.68
6.67
6.24
6.23
6.20
6.19
5.08
5.07
4.89
4.88
4.87
4.86
4.86
4.84
4.83
4.52
4.51
4.50
4.49
4.48
4.47
4.13
4.12
4.12
1.94
1.93
1.92
1.92
1.67
1.66
1.64
1.62
1.61
1.61
1.60
1.59
1.59
1.56
1.55
1.54
1.53
1.52
1.52
1.50
1.49
1.48
1.44
0.96
0.94
Compound 40
BocHN
0.96
0.91
1.02
1.01
0.75
0.98
1.09
0.97
2.99
9.65
10.51
20.14
ppm (f1)

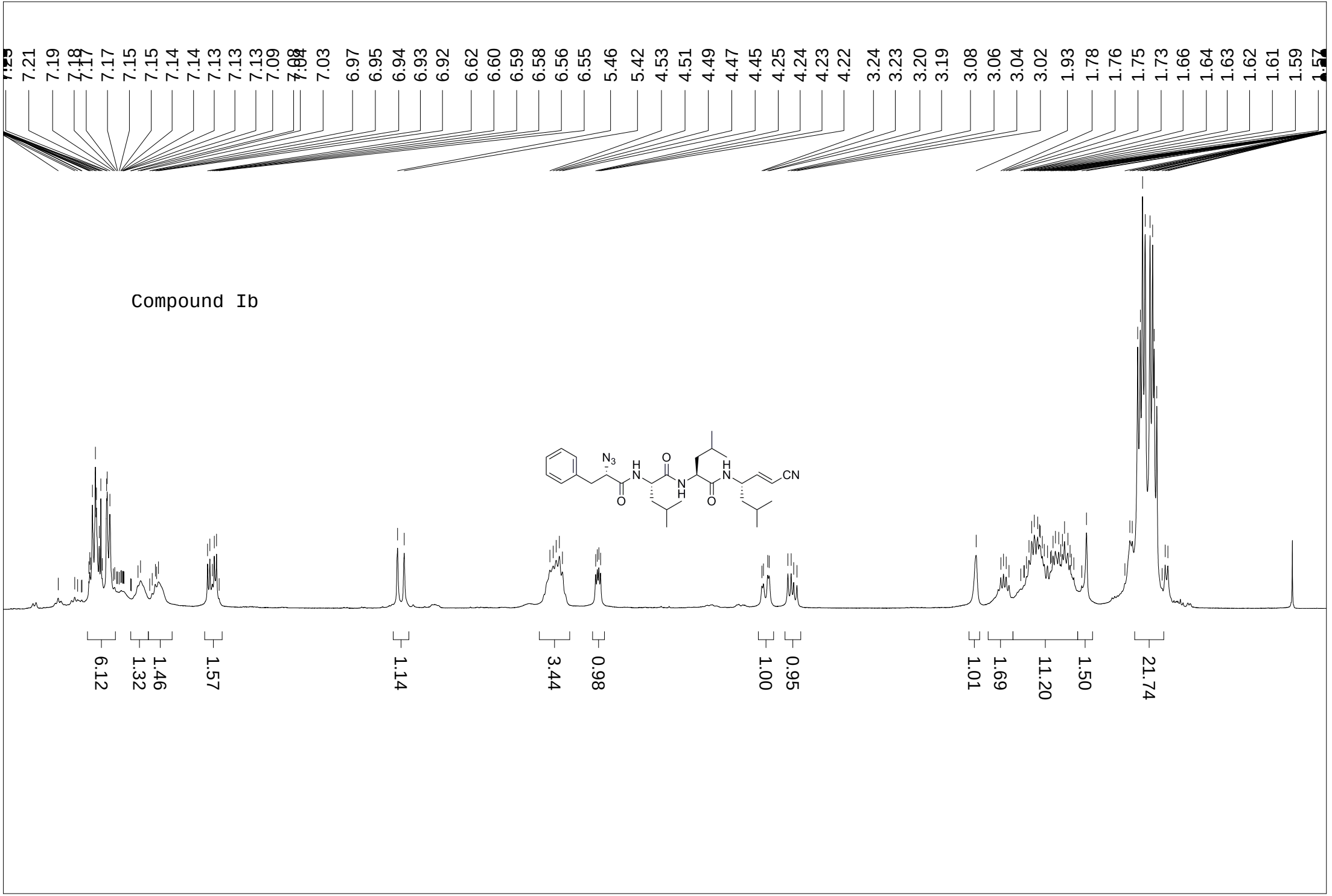

197.80
172.48
171.49
155.68
144.86
128.56
80.02
54.38
52.99
51.66
41.19
40.98
28.25
24.81
24.67
24.59
23.24
22.81
22.07
BocHN
O
N
H
O
H
N
O
Compound 40

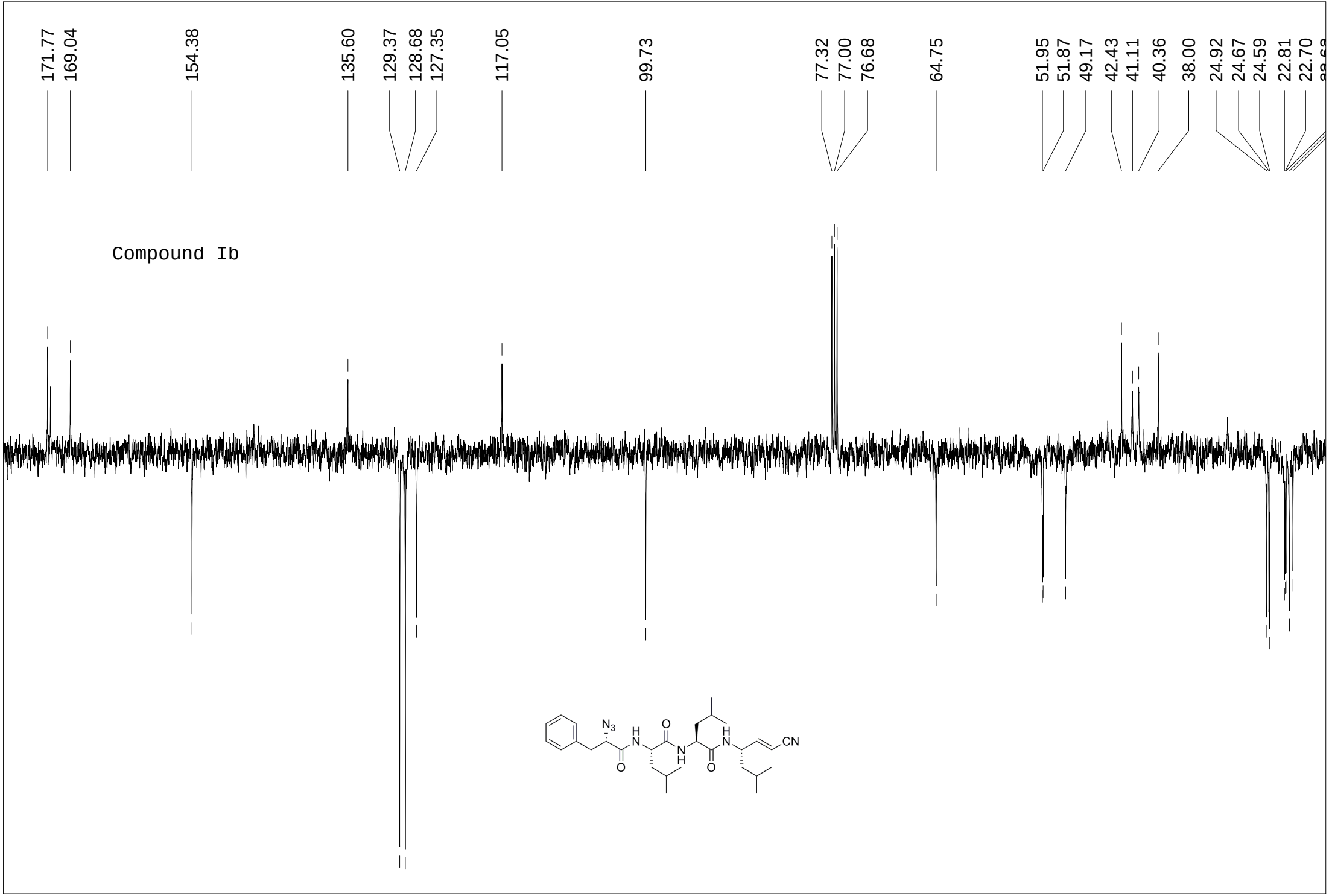
ppm (f1)


7.36
7.35
7.34
7.32
7.31
7.30
7.30
7.29
6.76
6.75
6.72
6.71
5.59
5.58
5.55
5.55
5.13
5.10
5.08
5.05
4.58
4.57
4.56
4.55
4.55
4.54
4.38
4.37
4.36
4.35
4.13
4.11
4.10
3.30
0.96
0.95
0.94
0.92
0.91
0.90
0.89
0.87
Compound Ia
CbzHN
O
N
H
O
H
N
CN
5.11
0.86
0.81
2.09
0.94
0.92
0.88
9.22
18.00
ppm (f1)

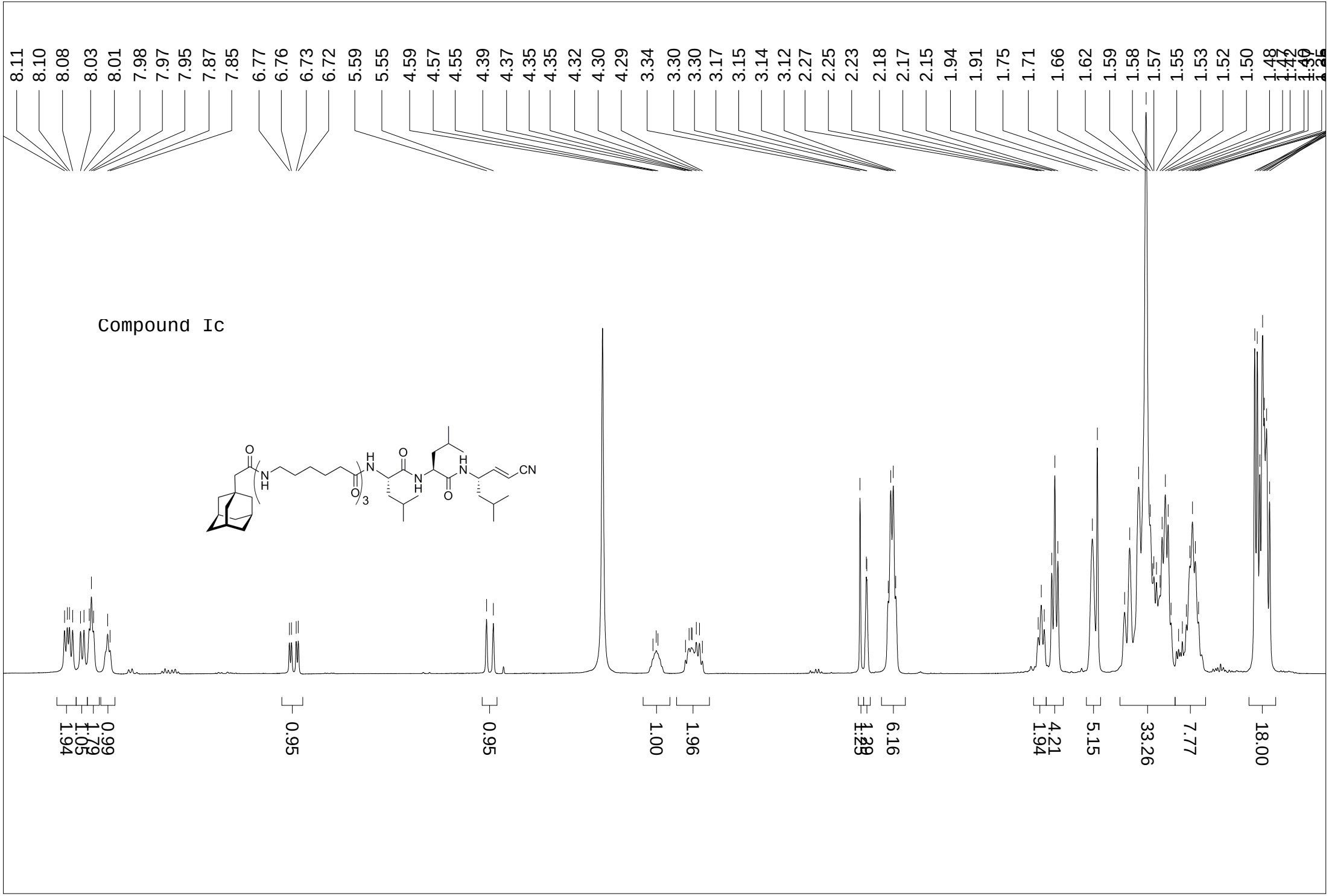

175.12
175.03
173.94
173.85
158.25
156.50
137.79
129.35
129.28
128.88
128.55
118.17
99.84
67.51
54.91
53.06
50.13
49.02
42.96
41.97
41.42
25.78
25.62
25.56
23.41
23.39
CbzHN
O
N
H
H
N
O
CN
Compound Ia

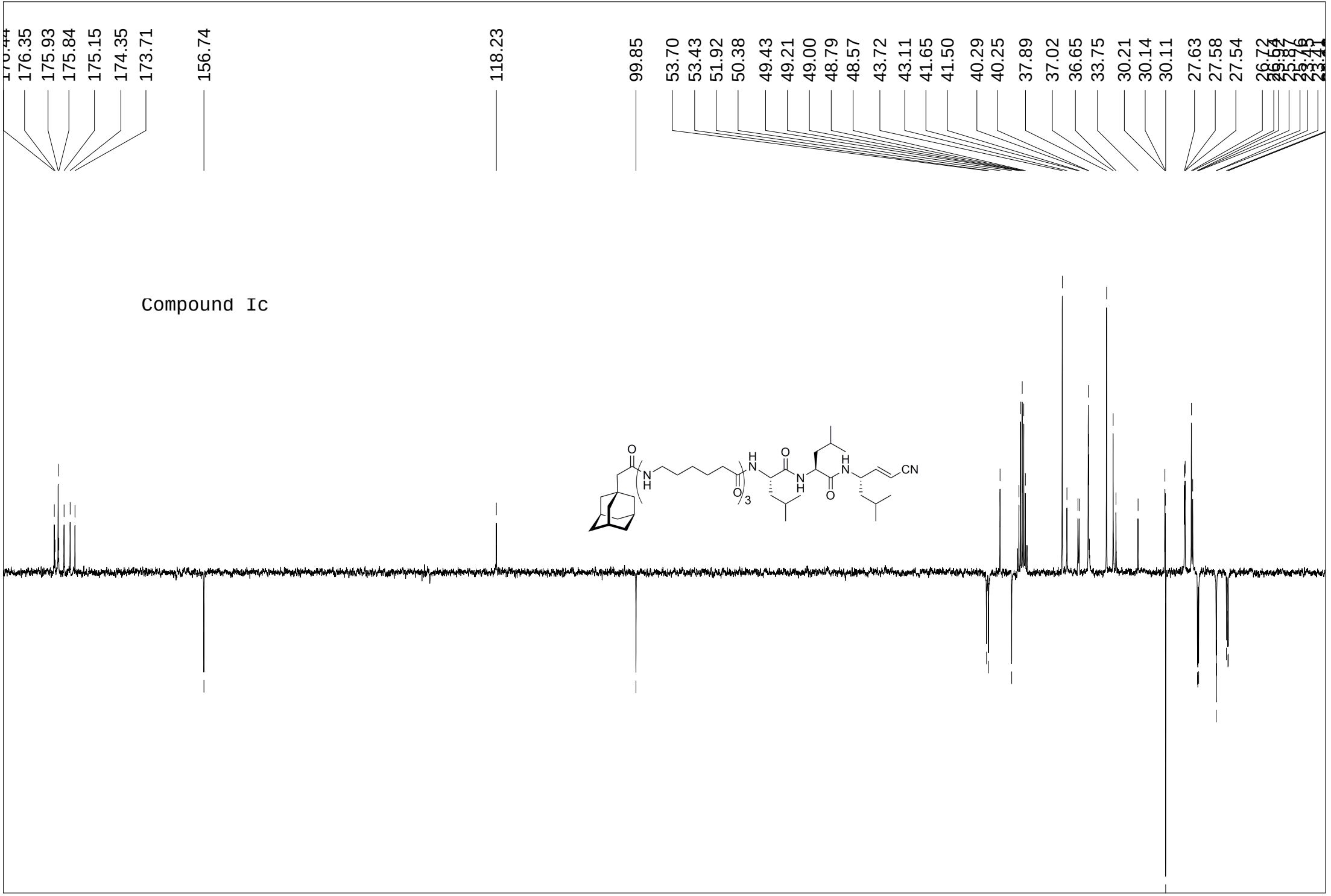
ppm (f1)

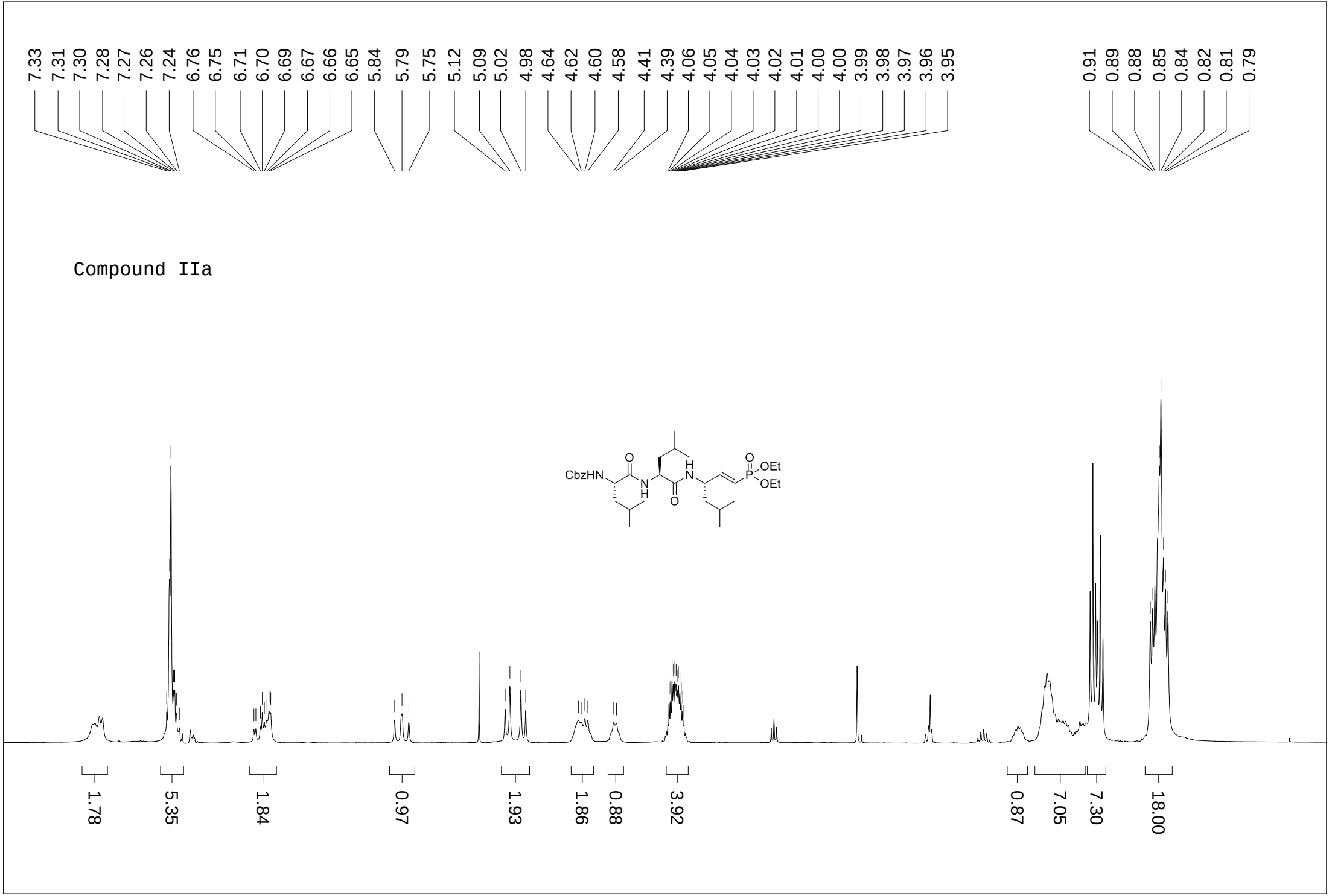

7.21
7.19
7.18
7.17
7.17
7.15
7.15
7.14
7.14
7.13
7.13
7.13
7.09
7.03
6.97
6.95
6.94
6.93
6.92
6.62
6.60
6.59
6.58
6.56
6.55
5.46
5.42
4.53
4.51
4.49
4.47
4.45
4.25
4.24
4.23
4.22
3.24
3.23
3.20
3.19
3.08
3.06
3.04
3.02
1.93
1.78
1.76
1.75
1.73
1.66
1.64
1.63
1.62
1.61
1.59
Compound Ib
6.12
1.32
1.46
1.57
1.14
3.44
0.98
1.00
0.95
1.01
1.69
11.20
1.50
21.74
ppm (f1)

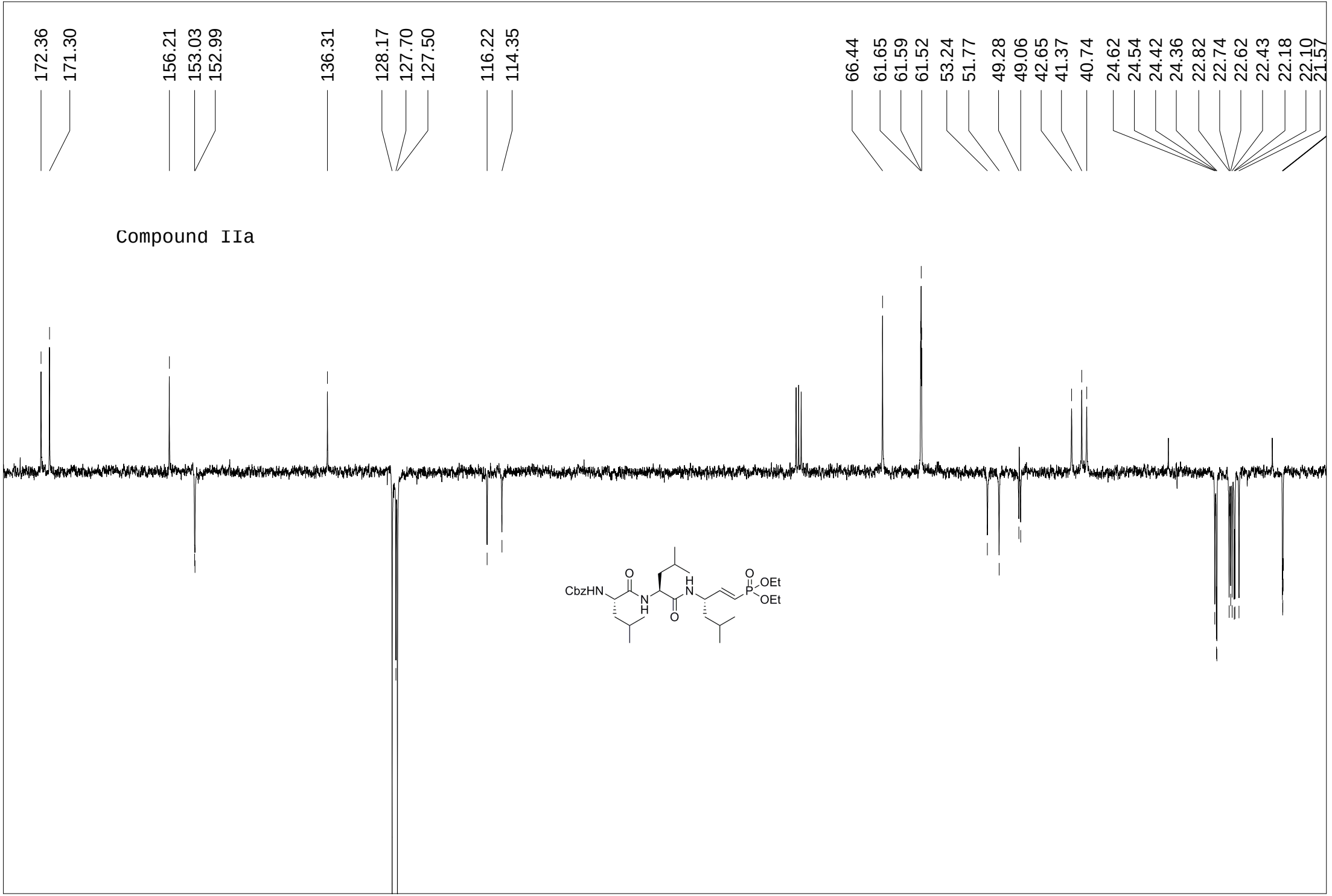

171.77
169.04
154.38
135.60
129.37
128.68
127.35
117.05
99.73
77.32
77.00
76.68
64.75
51.95
51.87
49.17
42.43
41.11
40.36
38.00
24.92
24.67
24.59
22.81
22.70
Compound Ib
N3
H
N
O
O
N
H
H
N
CN
O

ppm (f1)

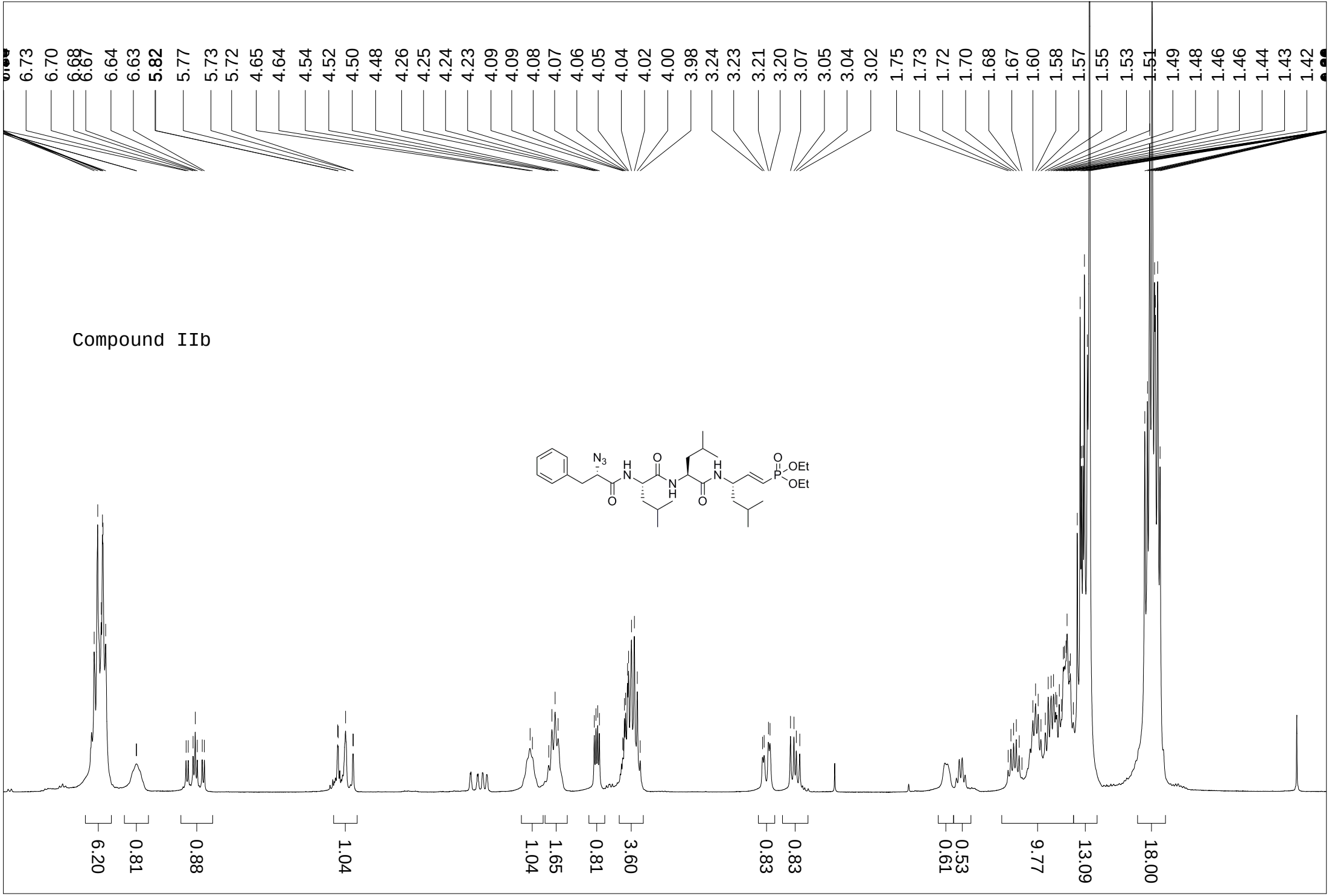

8.11
8.10
8.08
8.03
8.01
7.98
7.97
7.95
7.87
7.85
6.77
6.76
6.73
6.72
5.59
5.55
4.59
4.57
4.55
4.39
4.37
4.35
4.35
4.32
4.30
4.29
3.34
3.30
3.30
3.17
3.15
3.14
3.12
2.27
2.25
2.23
2.18
2.17
2.15
1.94
1.91
1.75
1.71
1.66
1.62
1.59
1.58
1.57
1.55
1.53
1.52
1.50
Compound Ic
CN
1.94
1.05
1.09
0.99
0.95
0.95
1.00
1.96
6.16
4.21
1.94
5.15
33.26
7.77
18.00
ppm (f1)


176.35
175.93
175.84
175.15
174.35
173.71
156.74
118.23
99.85
53.70
53.43
51.92
50.38
49.43
49.21
49.00
48.79
48.57
43.72
43.11
41.65
41.50
40.29
40.25
37.89
37.02
36.65
33.75
30.21
30.14
30.11
27.63
27.58
27.54
Compound Ic
CN
ppm (f1)

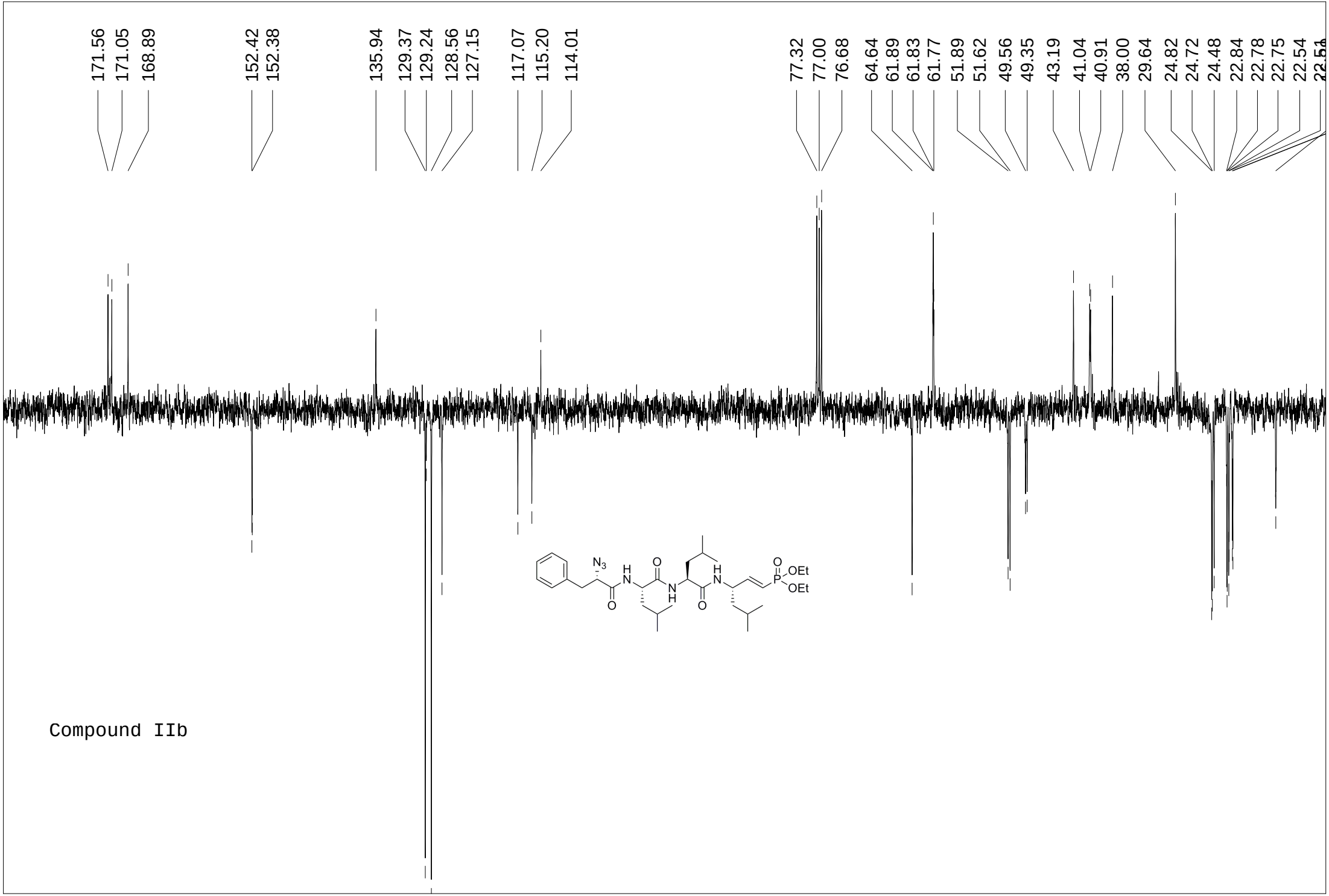

7.33
7.31
7.30
7.28
7.27
7.26
7.24
6.76
6.75
6.71
6.70
6.69
6.67
6.66
6.65
5.84
5.79
5.75
5.12
5.09
5.02
4.98
4.64
4.62
4.60
4.58
4.41
4.39
4.06
4.05
4.04
4.03
4.02
4.01
4.00
4.00
3.99
3.98
3.97
3.96
3.95
0.91
0.89
0.88
0.85
0.84
0.82
0.81
0.79
Compound IIa
CbzHN
O
N
H
O
N
H
O
P
OEt
OEt
1.78
5.35
1.84
0.97
1.93
1.86
0.88
3.92
0.87
7.05
7.30
18.00
ppm (f1)

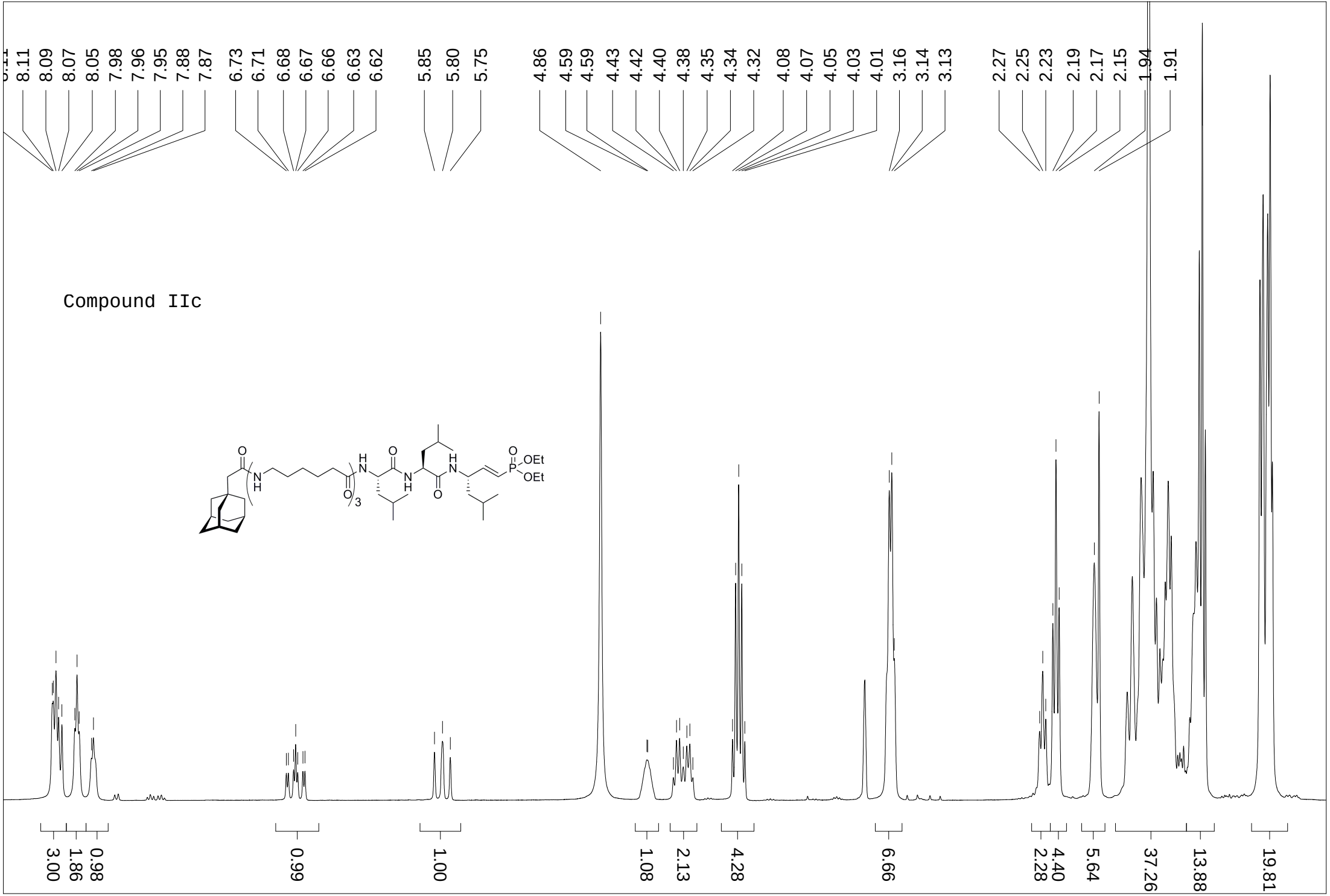

172.36
171.30
156.21
153.03
152.99
136.31
128.17
127.70
127.50
116.22
114.35
66.44
61.65
61.59
61.52
53.24
51.77
49.28
49.06
42.65
41.37
40.74
24.62
24.54
24.42
24.36
22.82
22.74
22.62
22.43
22.18
22.10
21.57
Compound IIa
CbzHN
O
N
H
O
H
N
O
P
OEt
OEt

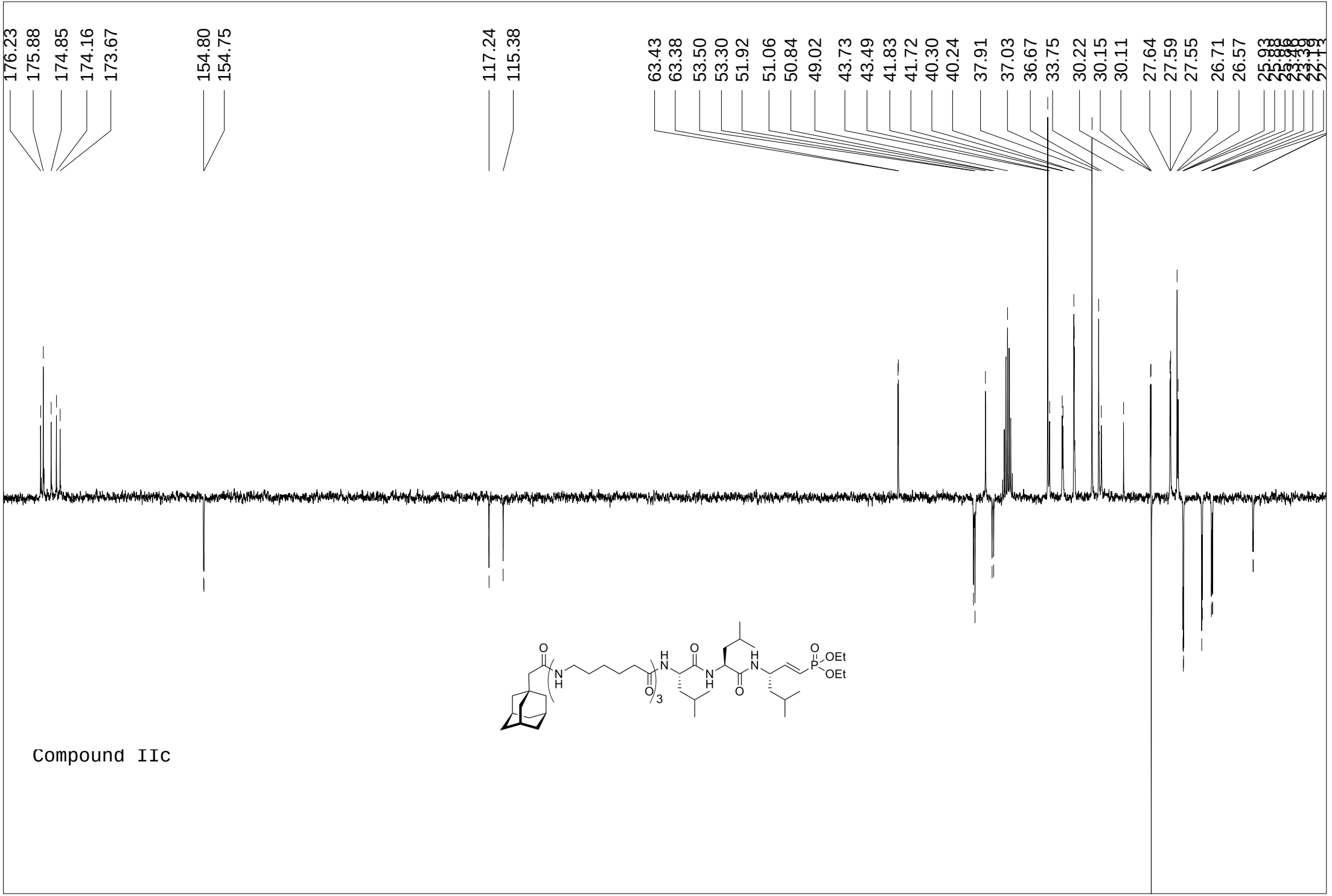
ppm (f1)


6.73
6.70
6.68
6.67
6.64
6.63
5.82
5.77
5.73
5.72
4.65
4.64
4.54
4.52
4.50
4.48
4.26
4.25
4.24
4.23
4.09
4.09
4.08
4.07
4.06
4.05
4.04
4.02
4.00
3.98
3.24
3.23
3.21
3.20
3.07
3.05
3.04
3.02
1.75
1.73
1.72
1.70
1.68
1.67
1.60
1.58
1.57
1.55
1.53
1.51
1.49
1.48
1.46
1.46
1.44
1.43
1.42
Compound IIb
N3
OEt
OEt
6.20
0.81
0.88
1.04
1.04
1.65
0.81
3.60
0.83
0.83
0.61
0.53
9.77
13.09
18.00

ppm (f1)

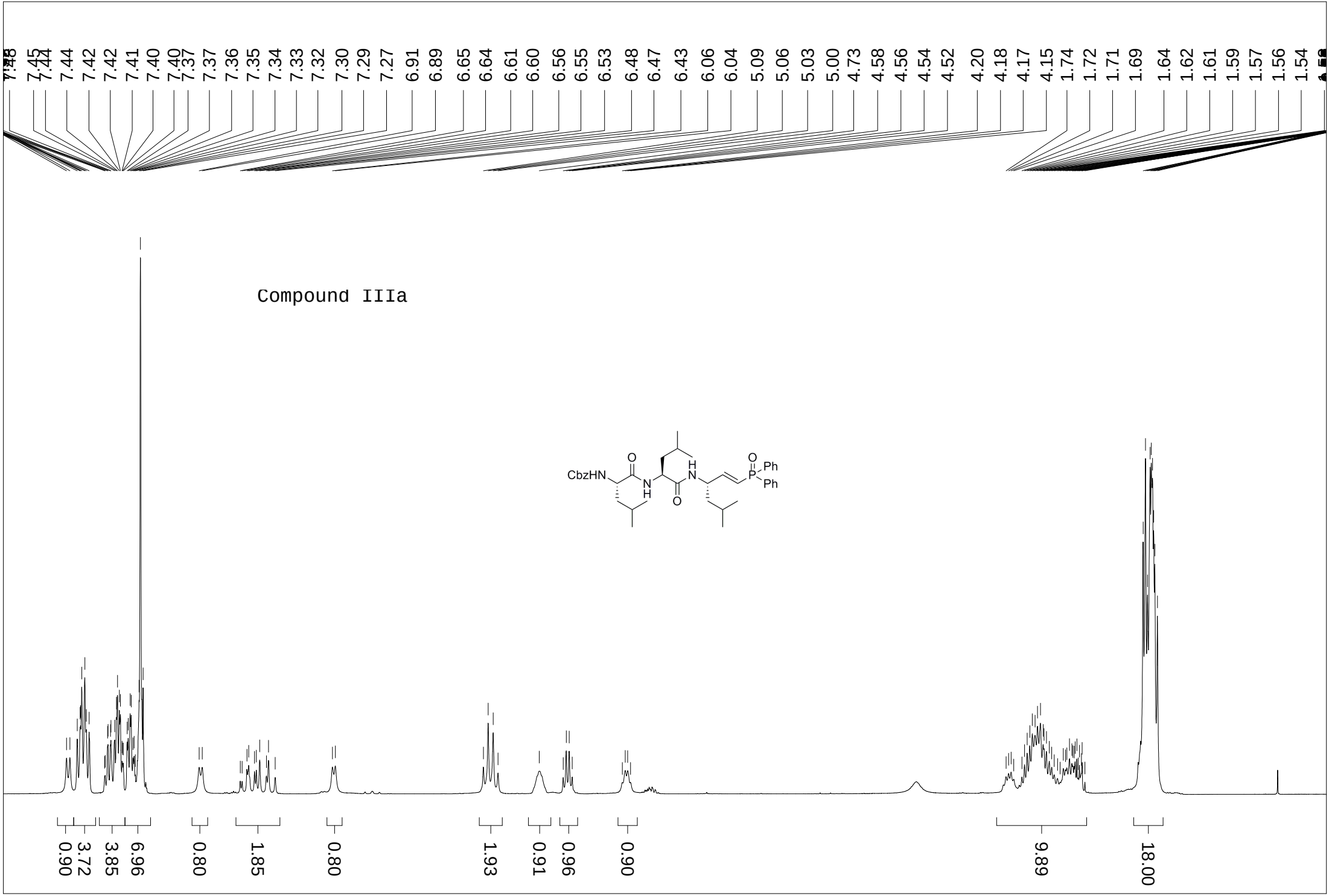

171.56
171.05
168.89
152.42
152.38
135.94
129.37
129.24
128.56
127.15
117.07
115.20
114.01
77.32
77.00
76.68
64.64
61.89
61.83
61.77
51.89
51.62
49.56
49.35
43.19
41.04
40.91
38.00
29.64
24.82
24.72
24.48
22.84
22.78
22.75
22.54
N3
OEt
OEt
Compound IIb
ppm (f1)

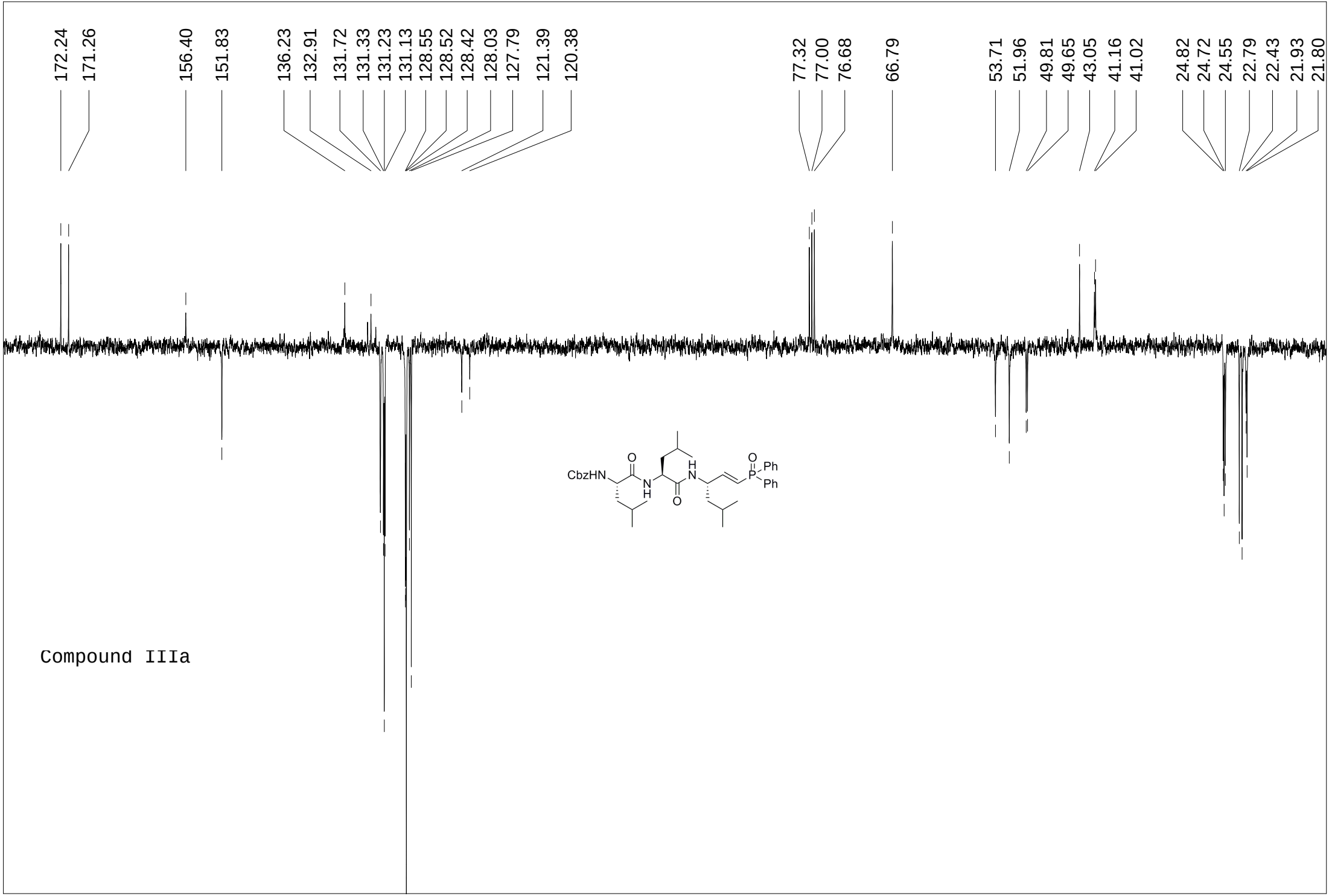

8.11
8.09
8.07
8.05
7.98
7.96
7.95
7.88
7.87
6.73
6.71
6.68
6.67
6.66
6.63
6.62
5.85
5.80
5.75
4.86
4.59
4.59
4.43
4.42
4.40
4.38
4.35
4.34
4.32
4.08
4.07
4.05
4.03
4.01
3.16
3.14
3.13
2.27
2.25
2.23
2.19
2.17
2.15
1.94
1.91
Compound IIc
3.00
1.86
0.98
0.99
1.00
1.08
2.13
4.28
6.66
2.28
4.40
5.64
37.26
13.88
19.81
ppm (f1)

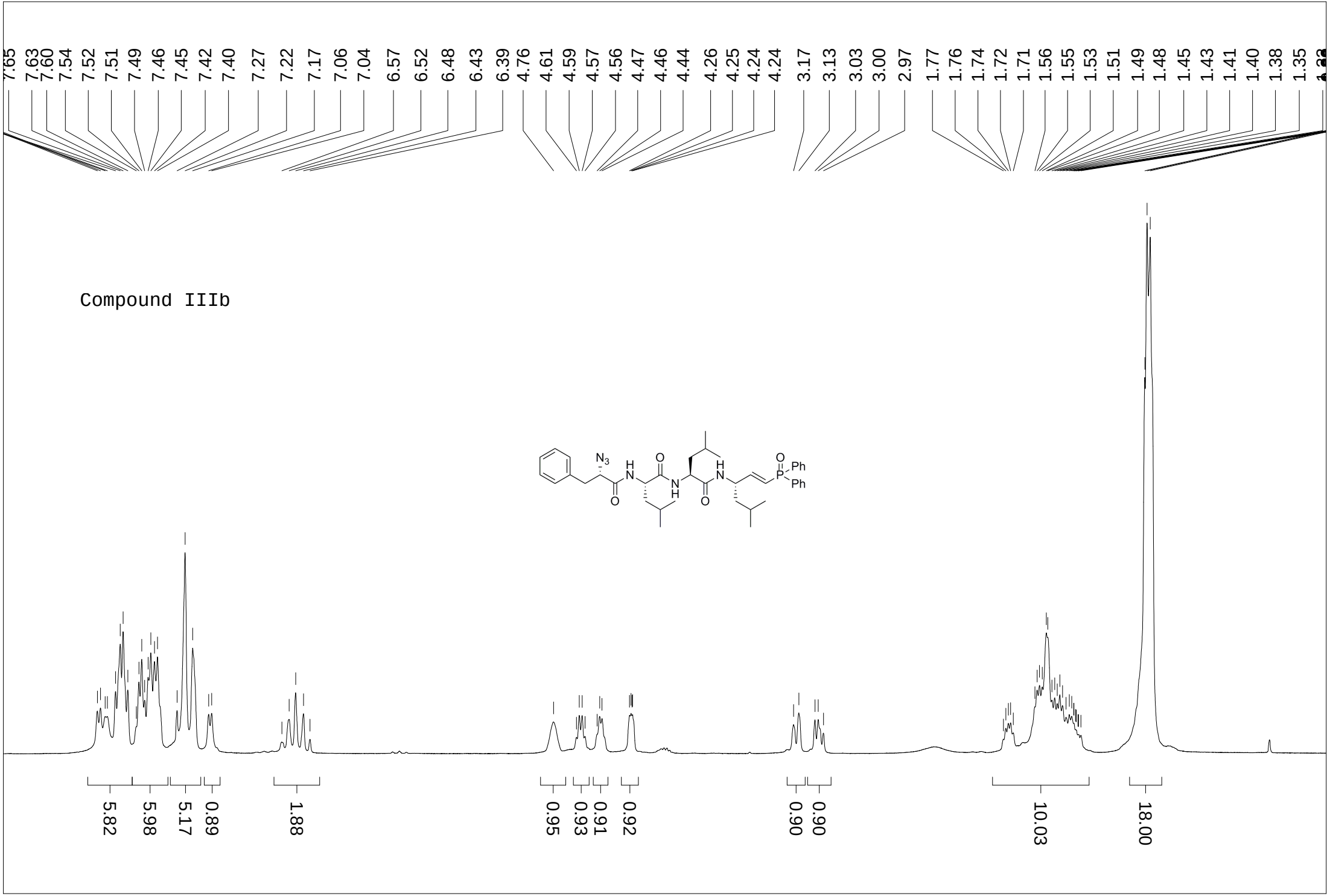


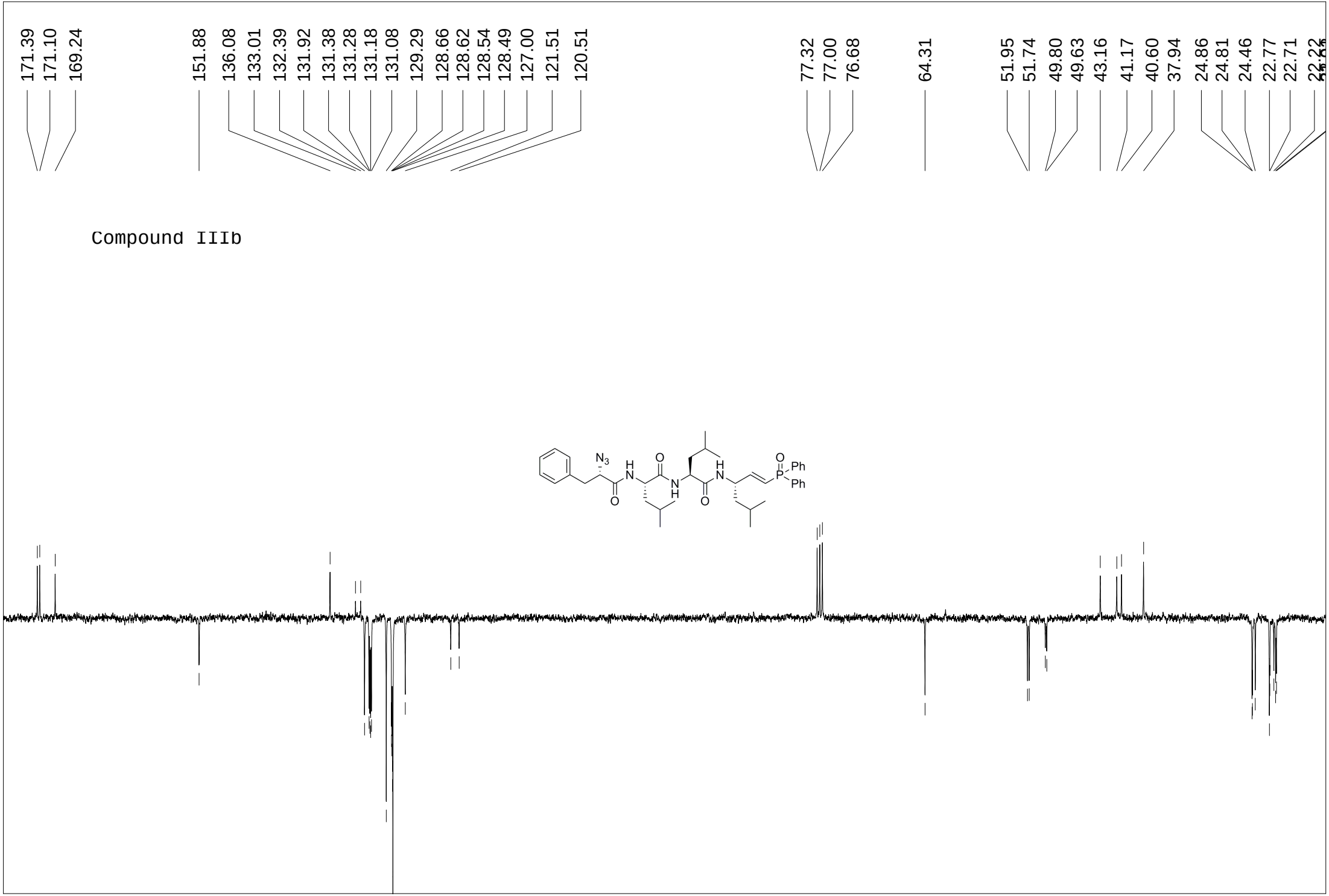
Compound IIc

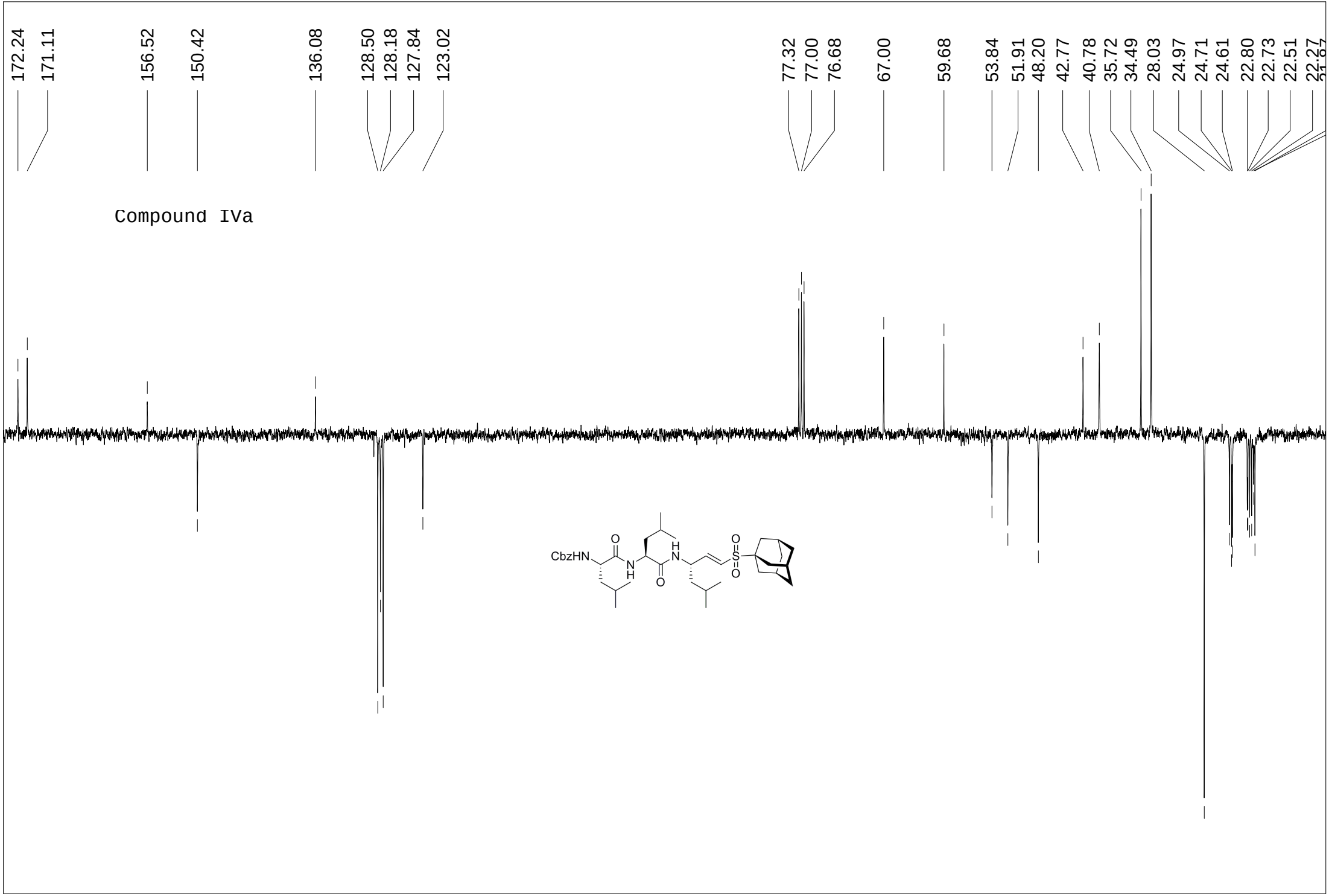
ppm (f1)


7.48
7.45
7.44
7.44
7.42
7.42
7.41
7.40
7.40
7.37
7.37
7.36
7.35
7.34
7.33
7.32
7.30
7.29
7.27
6.91
6.89
6.65
6.64
6.61
6.60
6.56
6.55
6.53
6.48
6.47
6.43
6.06
6.04
5.09
5.06
5.03
5.00
4.73
4.58
4.56
4.54
4.52
4.20
4.18
4.17
4.15
1.74
1.72
1.71
1.69
1.64
1.62
1.61
1.59
1.57
1.56
1.54
Compound IIIa
CbzHN
O
N
H
O
N
H
O
O
P
Ph
Ph
0.90
3.72
3.85
6.96
0.80
1.85
0.80
1.93
0.91
0.96
0.90
9.89
18.00
ppm (f1)

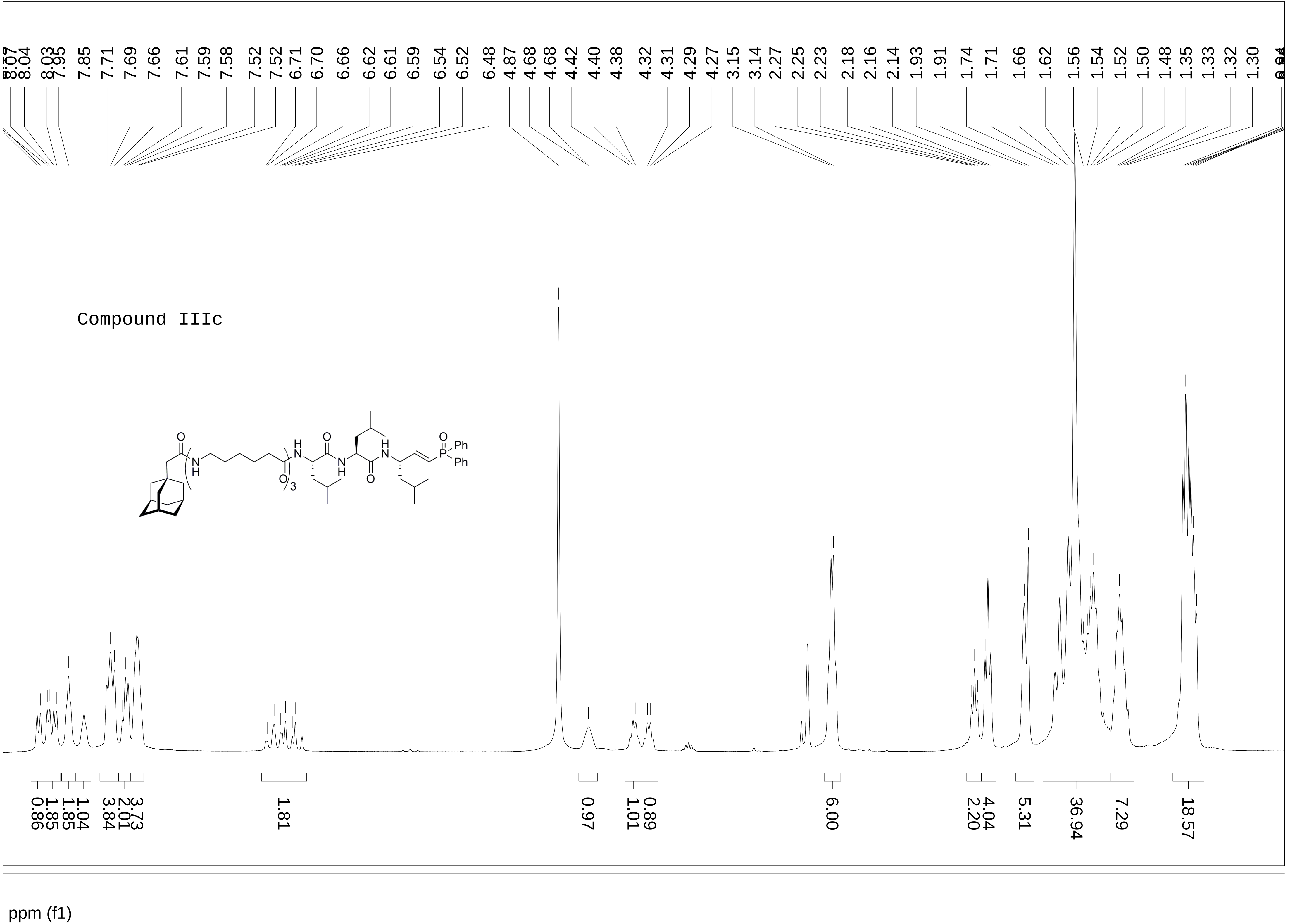

172.24
171.26
156.40
151.83
136.23
132.91
131.72
131.33
131.23
131.13
128.55
128.52
128.42
128.03
127.79
121.39
120.38
77.32
77.00
76.68
66.79
53.71
51.96
49.81
49.65
43.05
41.16
41.02
24.82
24.72
24.55
22.79
22.43
21.93
21.80
CbzHN
O
N
H
O
H
N
O
P
Ph
Ph
Compound IIIa
ppm (f1)


7.65
7.63
7.60
7.54
7.52
7.51
7.49
7.46
7.45
7.42
7.40
7.27
7.22
7.17
7.06
7.04
6.57
6.52
6.48
6.43
6.39
4.76
4.61
4.59
4.57
4.56
4.47
4.46
4.44
4.26
4.25
4.24
4.24
3.17
3.13
3.03
3.00
2.97
1.77
1.76
1.74
1.72
1.71
1.56
1.55
1.53
1.51
1.49
1.48
1.45
1.43
1.41
1.40
1.38
1.35
Compound IIIb
5.82
5.98
5.17
0.89
1.88
0.95
0.93
0.91
0.92
0.90
0.90
10.03
18.00
ppm (f1)

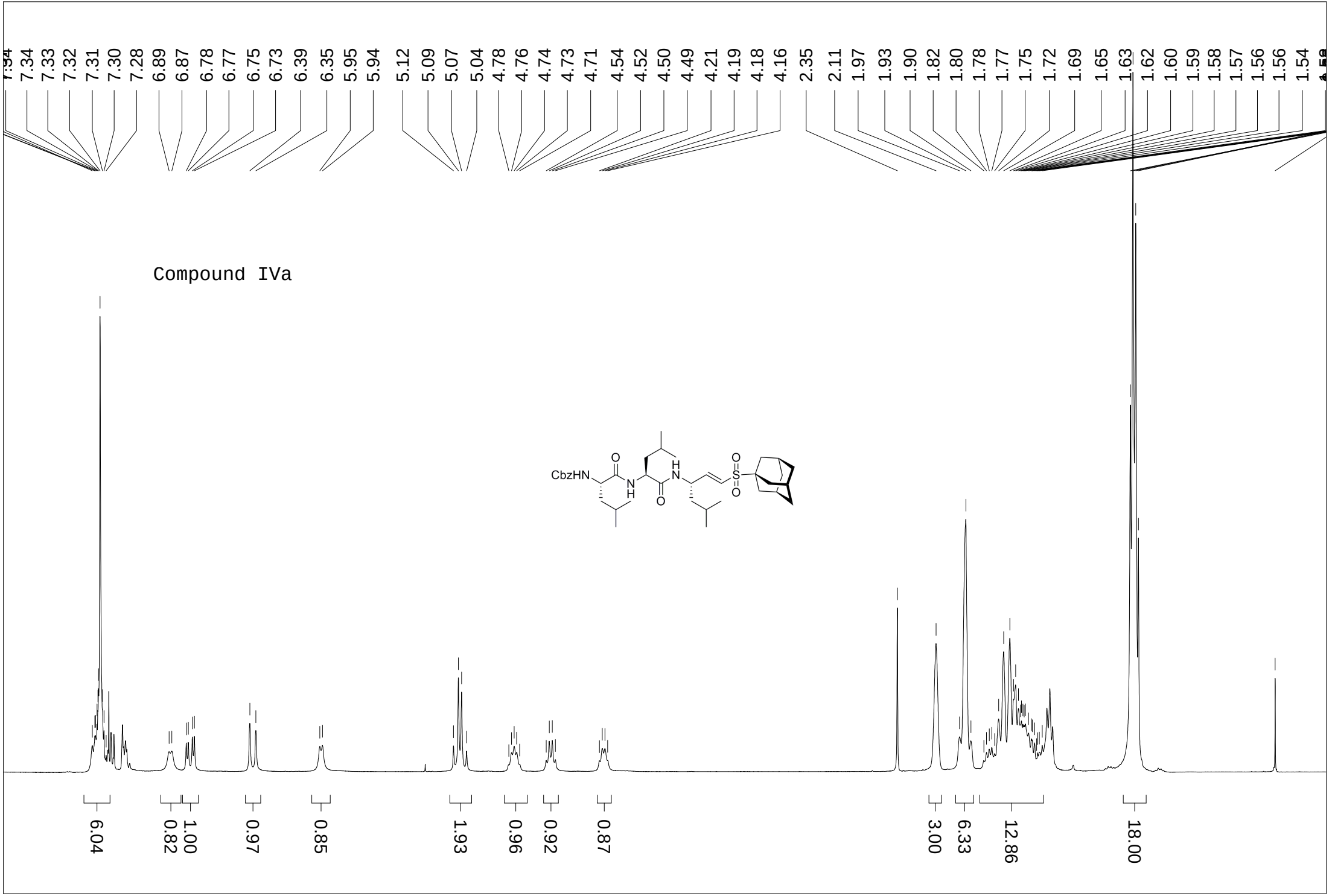

171.39
171.10
169.24
151.88
136.08
133.01
132.39
131.92
131.38
131.28
131.18
131.08
129.29
128.66
128.62
128.54
128.49
127.00
121.51
120.51
77.32
77.00
76.68
64.31
51.95
51.74
49.80
49.63
43.16
41.17
40.60
37.94
24.86
24.81
24.46
22.77
22.71
Compound IIIb
ppm (f1)


172.24
171.11
156.52
150.42
136.08
128.50
128.18
127.84
123.02
77.32
77.00
76.68
67.00
59.68
53.84
51.91
48.20
42.77
40.78
35.72
34.49
28.03
24.97
24.71
24.61
22.80
22.73
22.51
Compound IVa
CbzHN
O
N
H
H
N
O
O
S
O

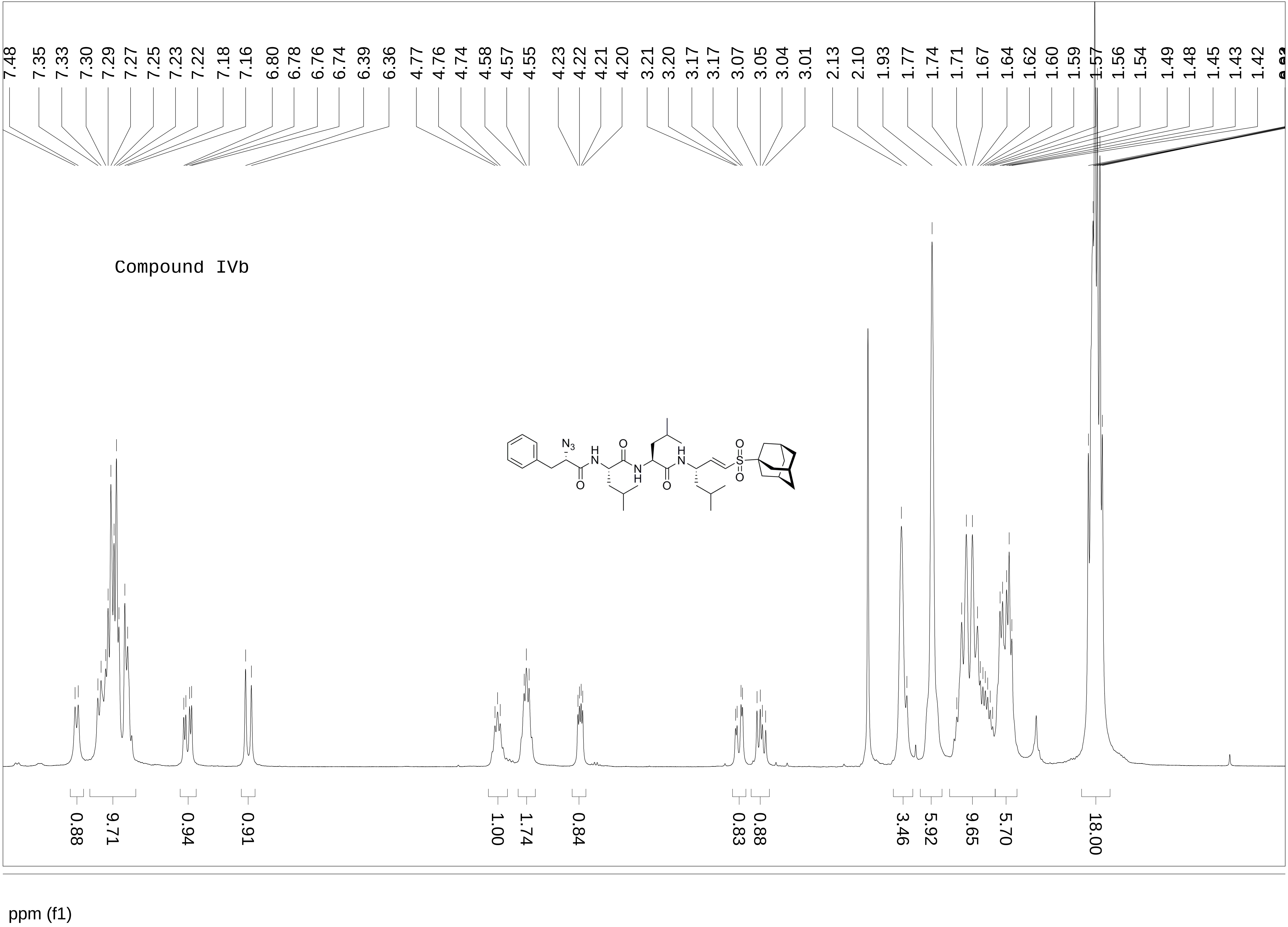
ppm (f1)

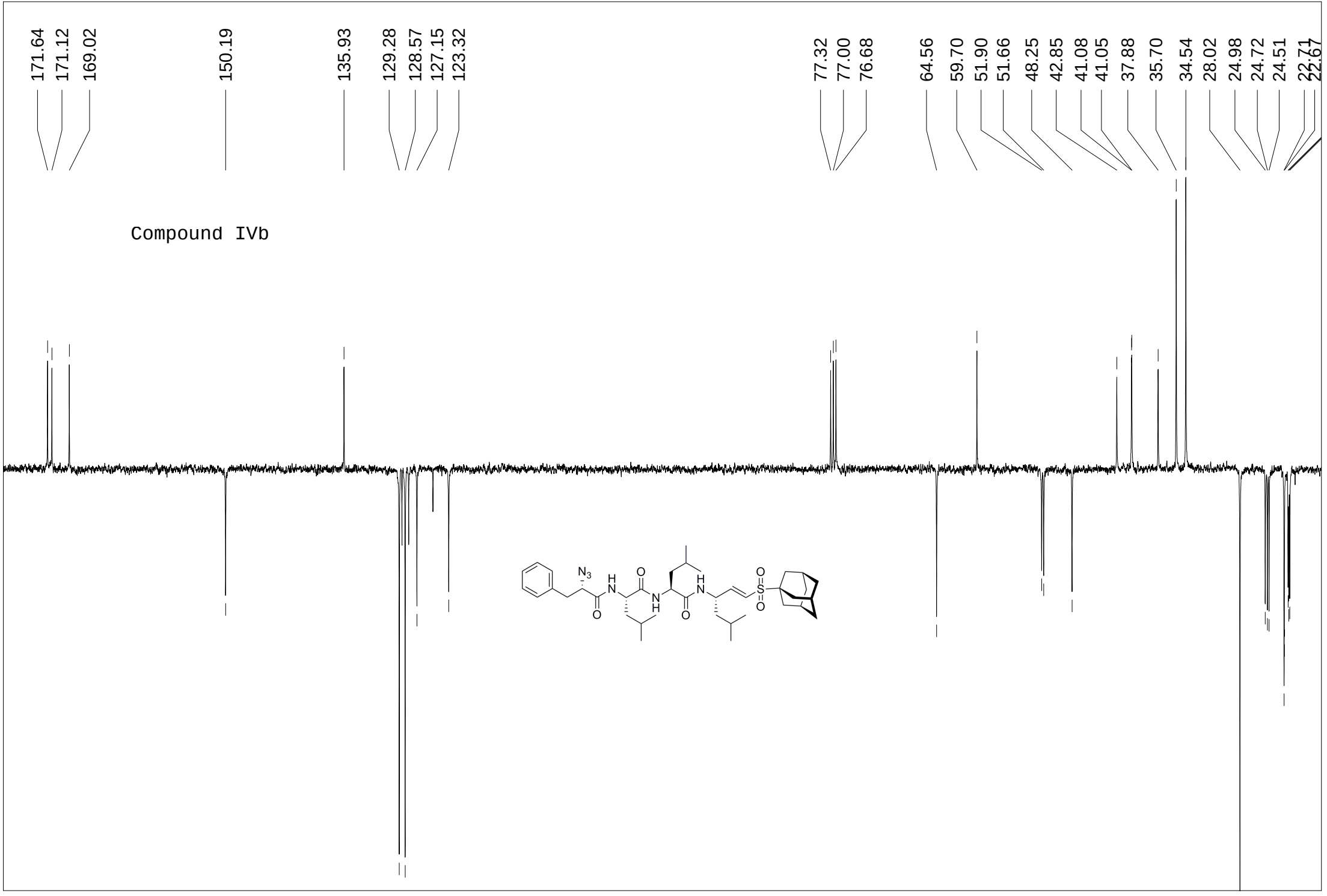


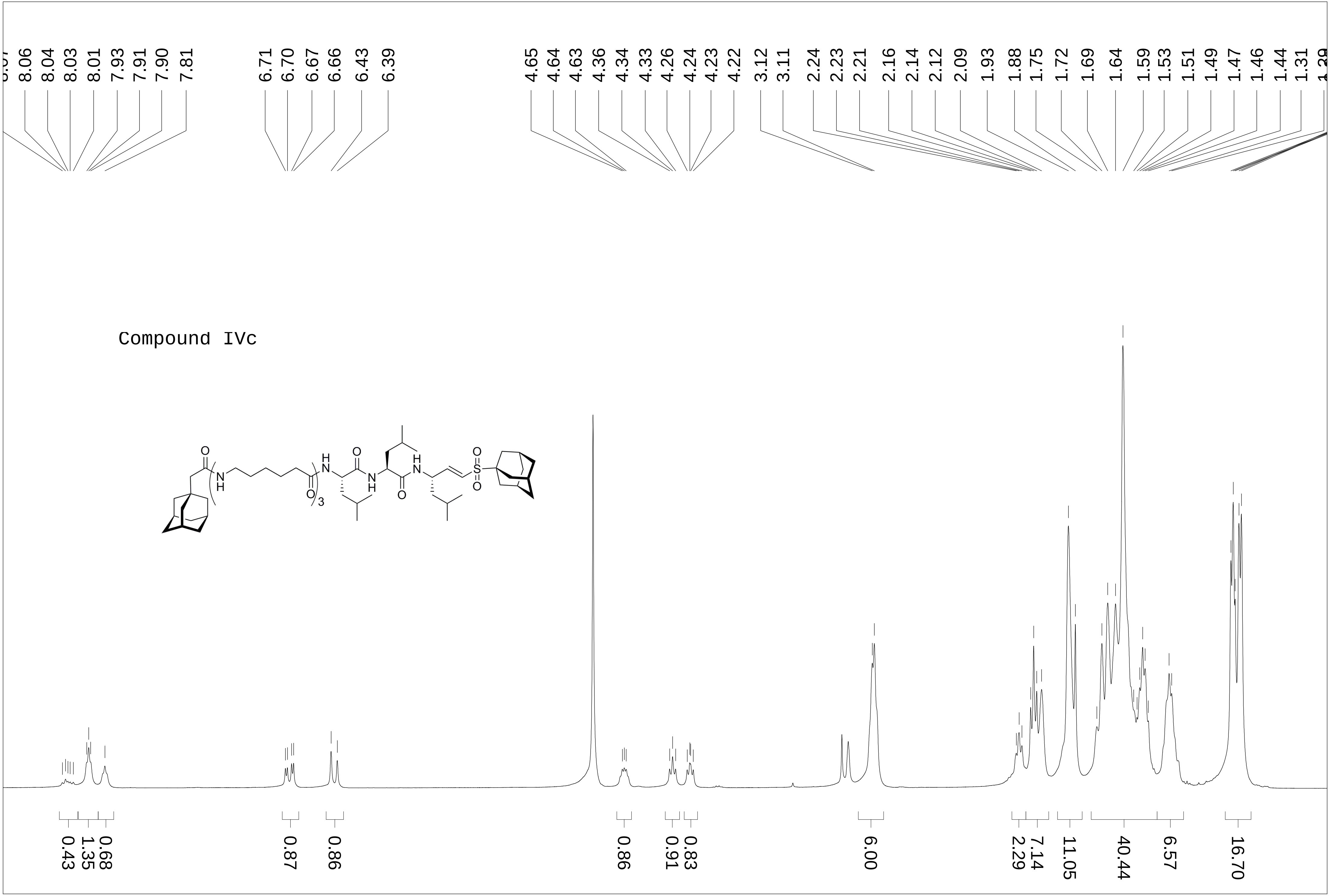
Compound IIIc
8.04 8.03 7.95 7.85 7.71 7.69 7.66 7.61 7.59 7.58 7.52 7.52 6.71 6.70 6.66 6.62 6.61 6.59 6.54 6.52 6.48 4.87 4.68 4.68 4.42 4.40 4.38 4.32 4.31 4.29 4.27 3.15 3.14 2.27 2.25 2.23 2.18 2.16 2.14 1.93 1.91 1.74 1.71 1.66 1.62 1.56 1.54 1.52 1.50 1.48 1.35 1.33 1.32 1.30
O
N
H
O
3
H
N
O
N
H
O
H
N
O
P
Ph
Ph
0.86 1.85 1.85 1.04 3.84 2.01 3.73 1.81 0.97 1.01 0.89 6.00 2.20 4.04 5.31 36.94 7.29 18.57
ppm (f1)


7.34
7.33
7.32
7.31
7.30
7.28
6.89
6.87
6.78
6.77
6.75
6.73
6.39
6.35
5.95
5.94
5.12
5.09
5.07
5.04
4.78
4.76
4.74
4.73
4.71
4.54
4.52
4.50
4.49
4.21
4.19
4.18
4.16
2.35
2.11
1.97
1.93
1.90
1.82
1.80
1.78
1.77
1.75
1.72
1.69
1.65
1.63
1.62
1.60
1.59
1.58
1.57
1.56
1.56
1.54
Compound IVa
CbzHN
O
N
H
O
N
H
O
S
O
O
6.04
0.82
1.00
0.97
0.85
1.93
0.96
0.92
0.87
3.00
6.33
12.86
18.00

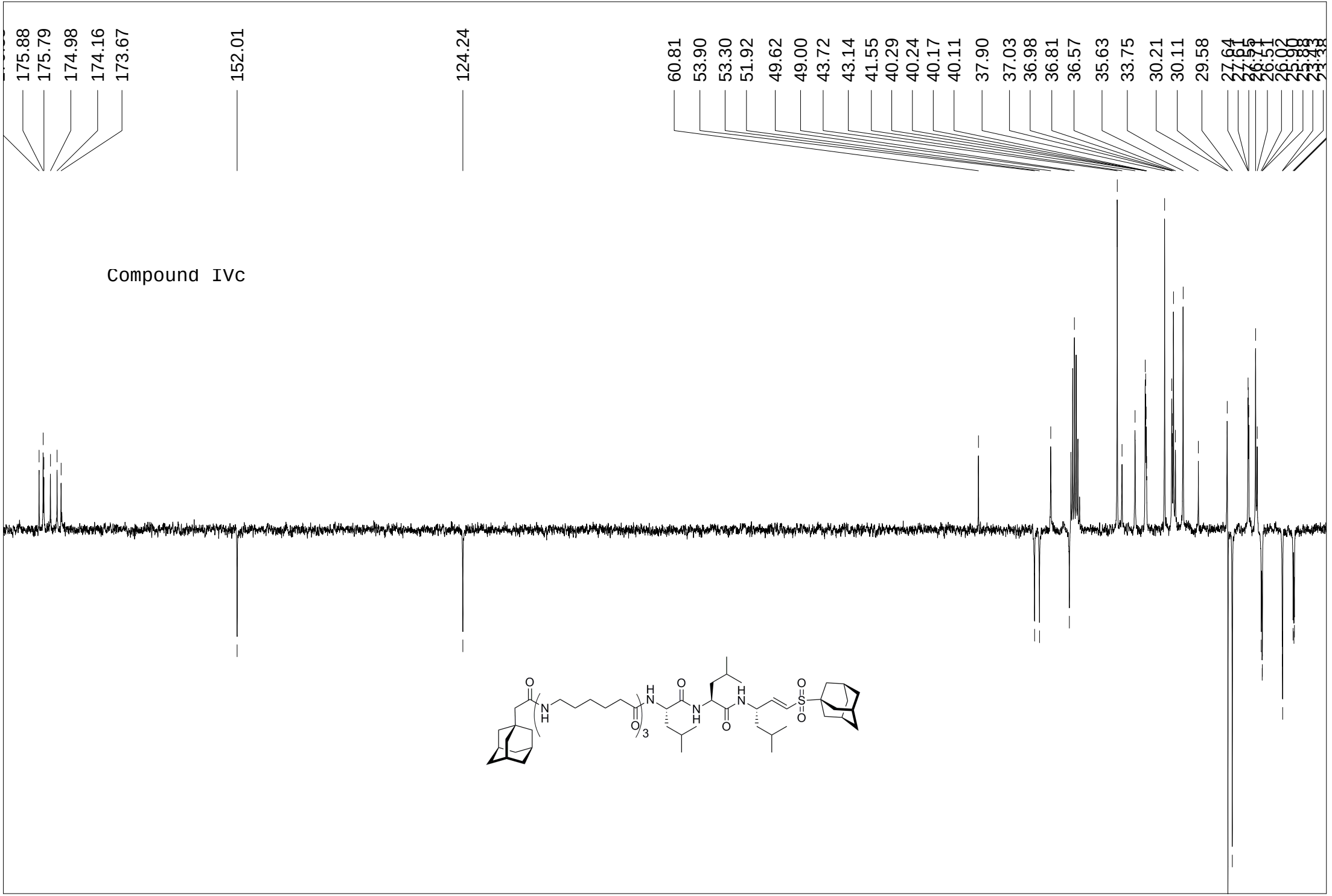
ppm (f1)

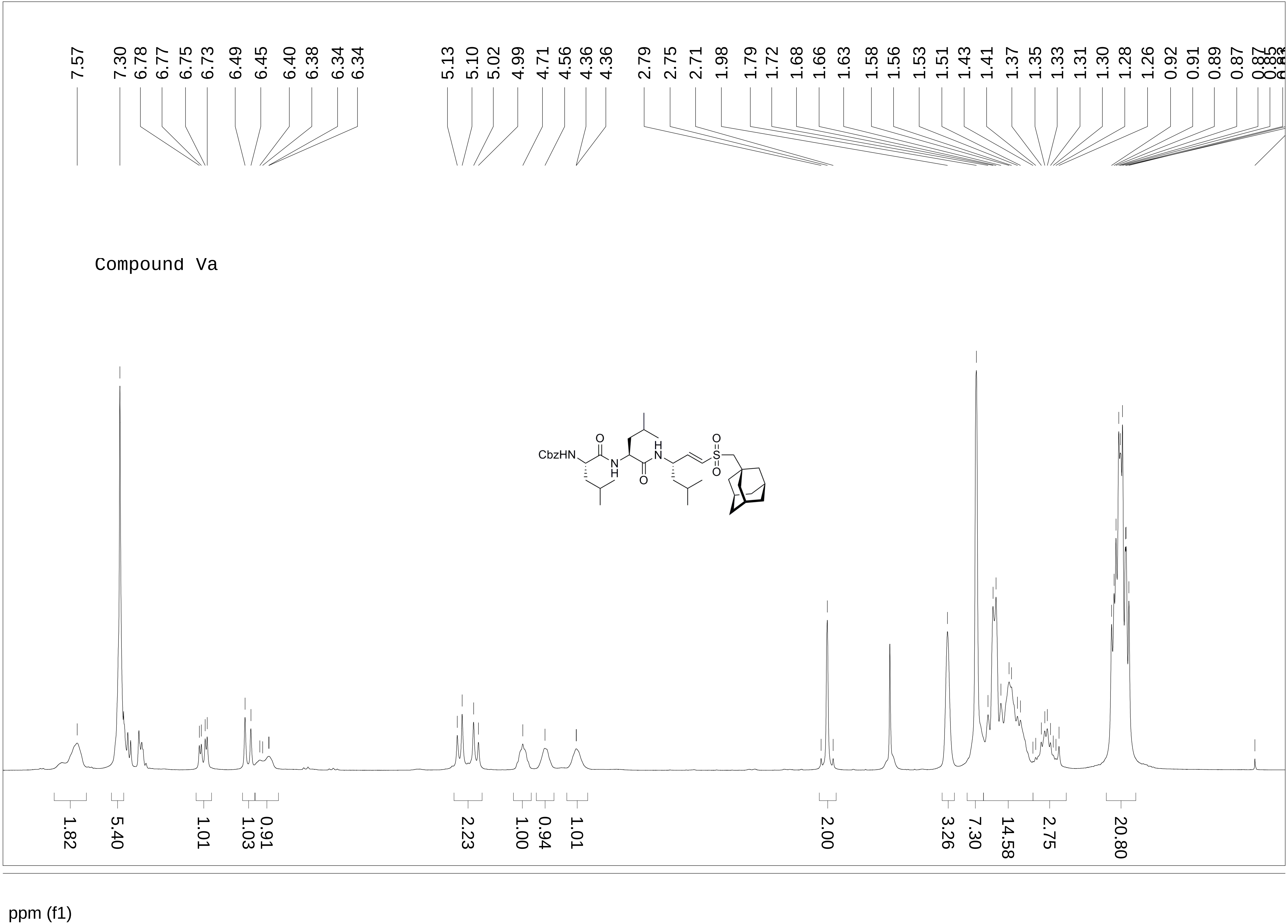

Compound IVb
7.48
7.35
7.33
7.30
7.29
7.27
7.25
7.23
7.22
7.18
7.16
6.80
6.78
6.76
6.74
6.39
6.36
4.77
4.76
4.74
4.58
4.57
4.55
4.23
4.22
4.21
4.20
3.21
3.20
3.17
3.17
3.07
3.05
3.04
3.01
2.13
2.10
1.93
1.77
1.74
1.71
1.67
1.64
1.62
1.60
1.59
1.57
1.56
1.54
1.49
1.48
1.45
1.43
1.42
0.88
9.71
0.94
0.91
1.00
1.74
0.84
0.83
0.88
3.46
5.92
9.65
5.70
18.00
ppm (f1)

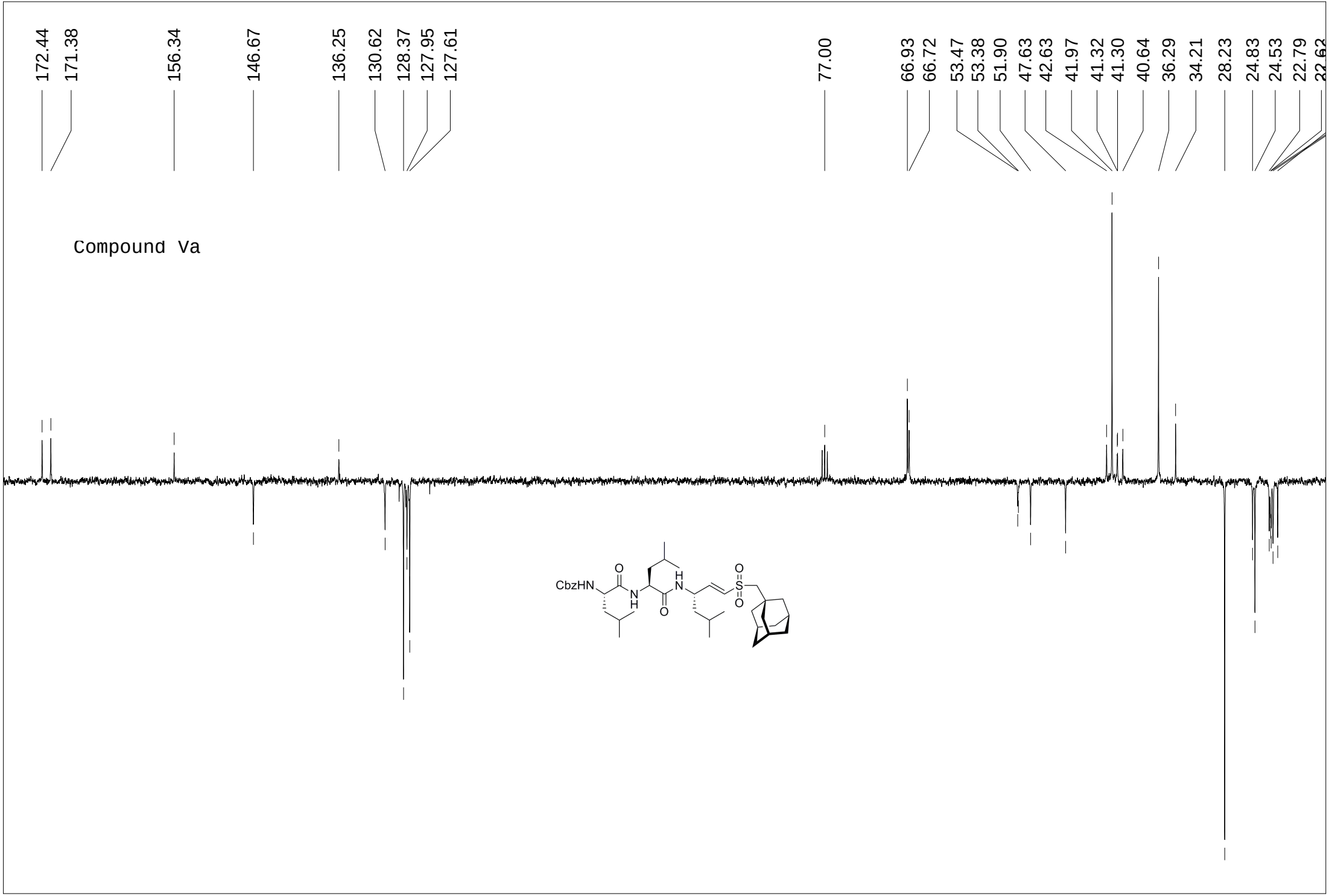

171.64
171.12
169.02
150.19
135.93
129.28
128.57
127.15
123.32
77.32
77.00
76.68
64.56
59.70
51.90
51.66
48.25
42.85
41.08
41.05
37.88
35.70
34.54
28.02
24.98
24.72
24.51
22.71
22.67
Compound IVb
ppm (f1)


8.06
8.04
8.03
8.01
7.93
7.91
7.90
7.81
6.71
6.70
6.67
6.66
6.43
6.39
4.65
4.64
4.63
4.36
4.34
4.33
4.26
4.24
4.23
4.22
3.12
3.11
2.24
2.23
2.21
2.16
2.14
2.12
2.09
1.93
1.88
1.75
1.72
1.69
1.64
1.59
1.53
1.51
1.49
1.47
1.46
1.44
1.31
Compound IVc
0.43
1.35
0.68
0.87
0.86
0.86
0.91
0.83
6.00
2.29
7.14
11.05
40.44
6.57
16.70

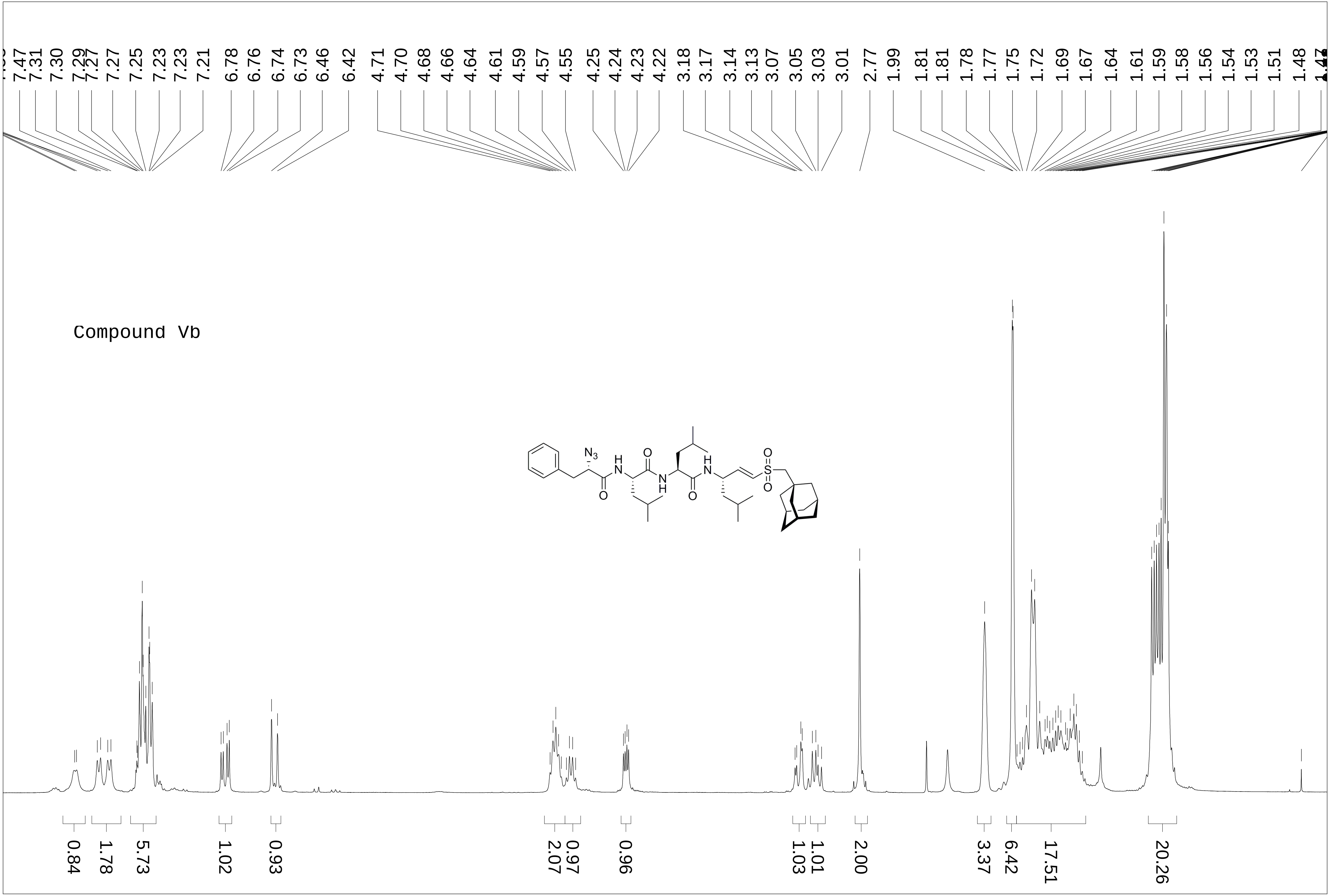
ppm (f1)


175.88
175.79
174.98
174.16
173.67
152.01
124.24
60.81
53.90
53.30
51.92
49.62
49.00
43.72
43.14
41.55
40.29
40.24
40.17
40.11
37.90
37.03
36.98
36.81
36.57
35.63
33.75
30.21
30.11
29.58
Compound IVc
ppm (f1)

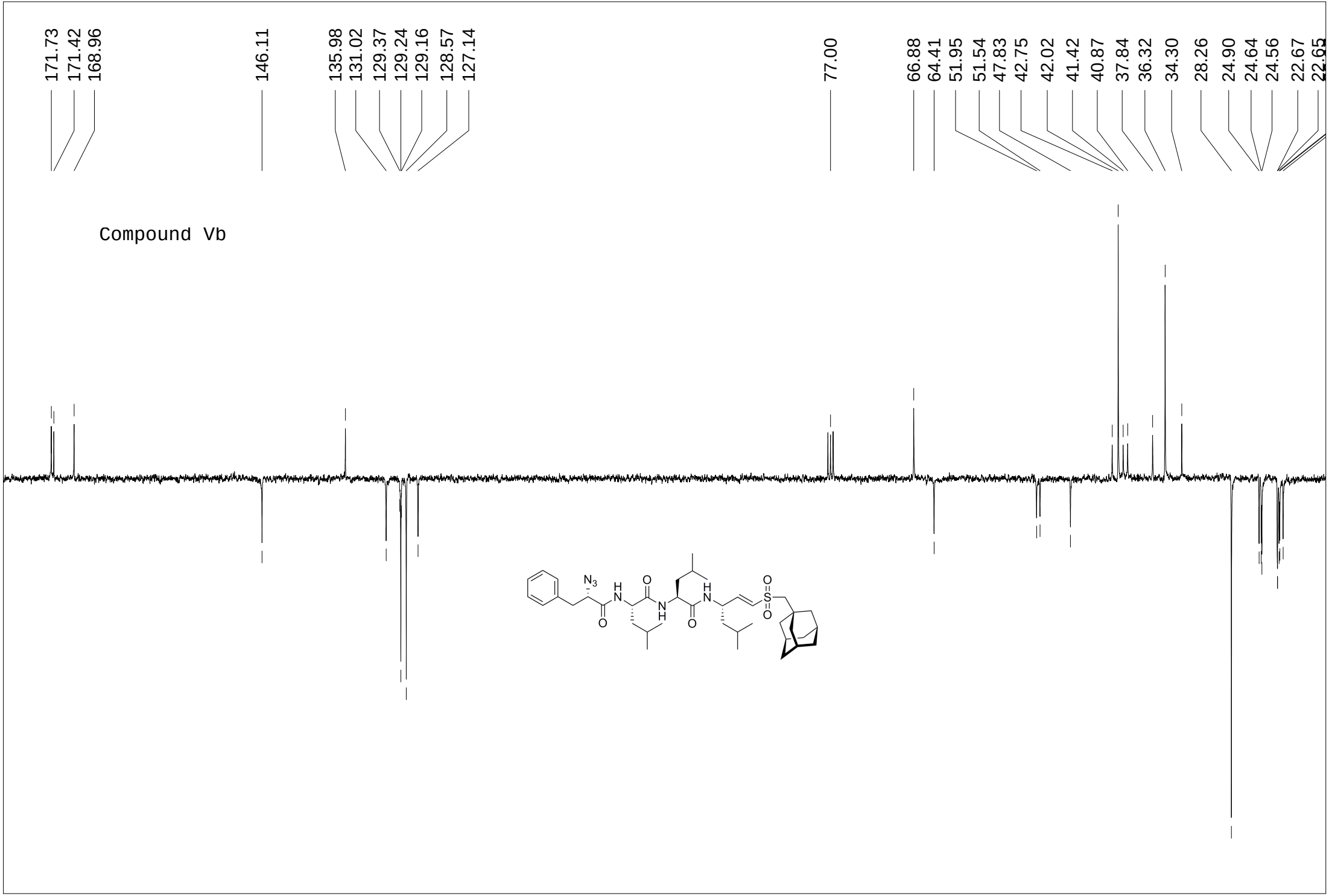

7.57
7.30
6.78
6.77
6.75
6.73
6.49
6.45
6.40
6.38
6.34
6.34
5.13
5.10
5.02
4.99
4.71
4.56
4.36
4.36
2.79
2.75
2.71
1.98
1.79
1.72
1.68
1.66
1.63
1.58
1.56
1.53
1.51
1.43
1.41
1.37
1.35
1.33
1.31
1.30
1.28
1.26
0.92
0.91
0.89
0.87
0.87
0.85
Compound Va
CbzHN
O
N
H
O
H
N
O
S
O
1.82
5.40
1.01
1.03
0.91
2.23
1.00
0.94
1.01
2.00
3.26
7.30
14.58
2.75
20.80
ppm (f1)

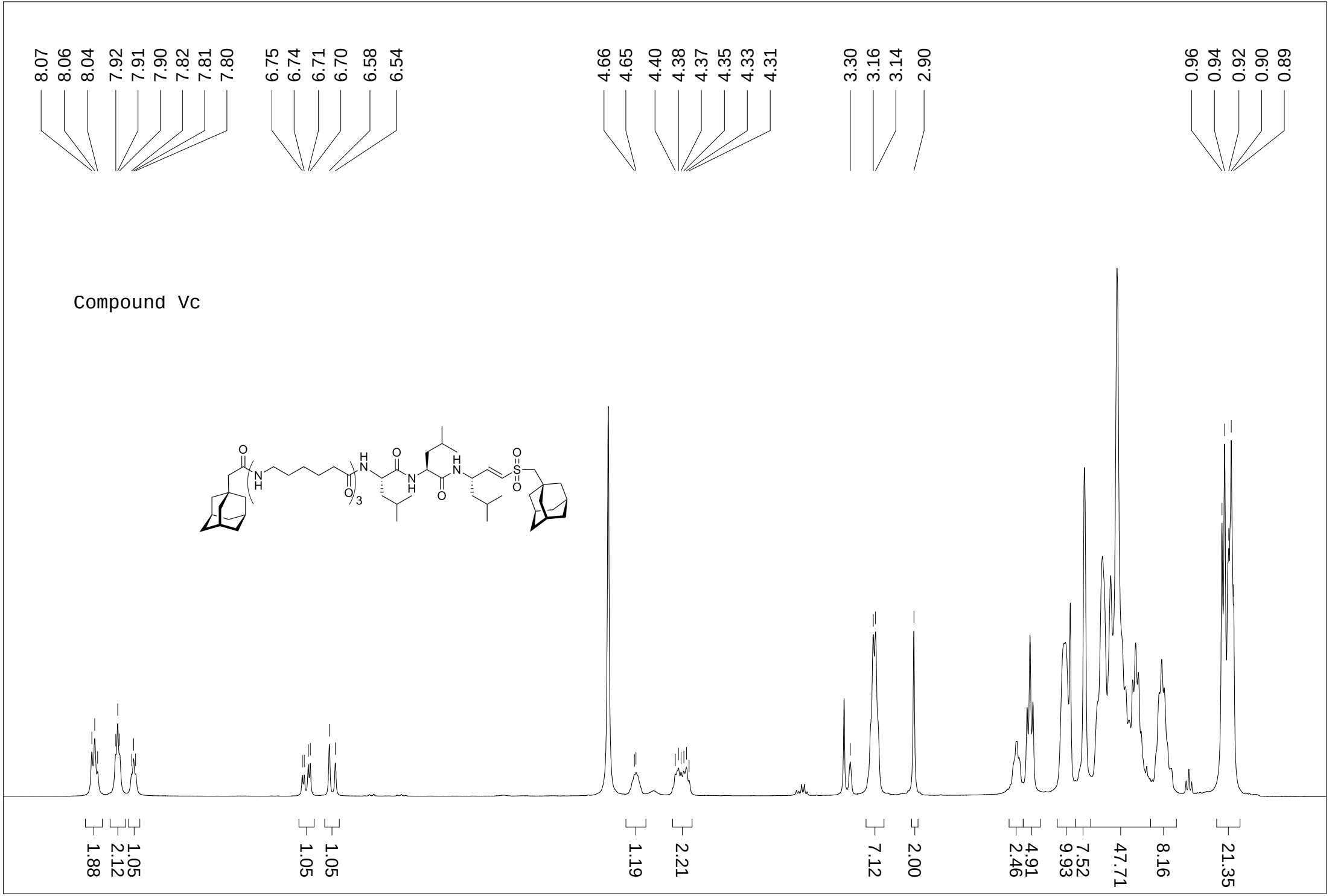

172.44
171.38
156.34
146.67
136.25
130.62
128.37
127.95
127.61
77.00
66.93
66.72
53.47
53.38
51.90
47.63
42.63
41.97
41.32
41.30
40.64
36.29
34.21
28.23
24.83
24.53
22.79
Compound Va
CbzHN
O
N
H
O
H
N
O
S
O

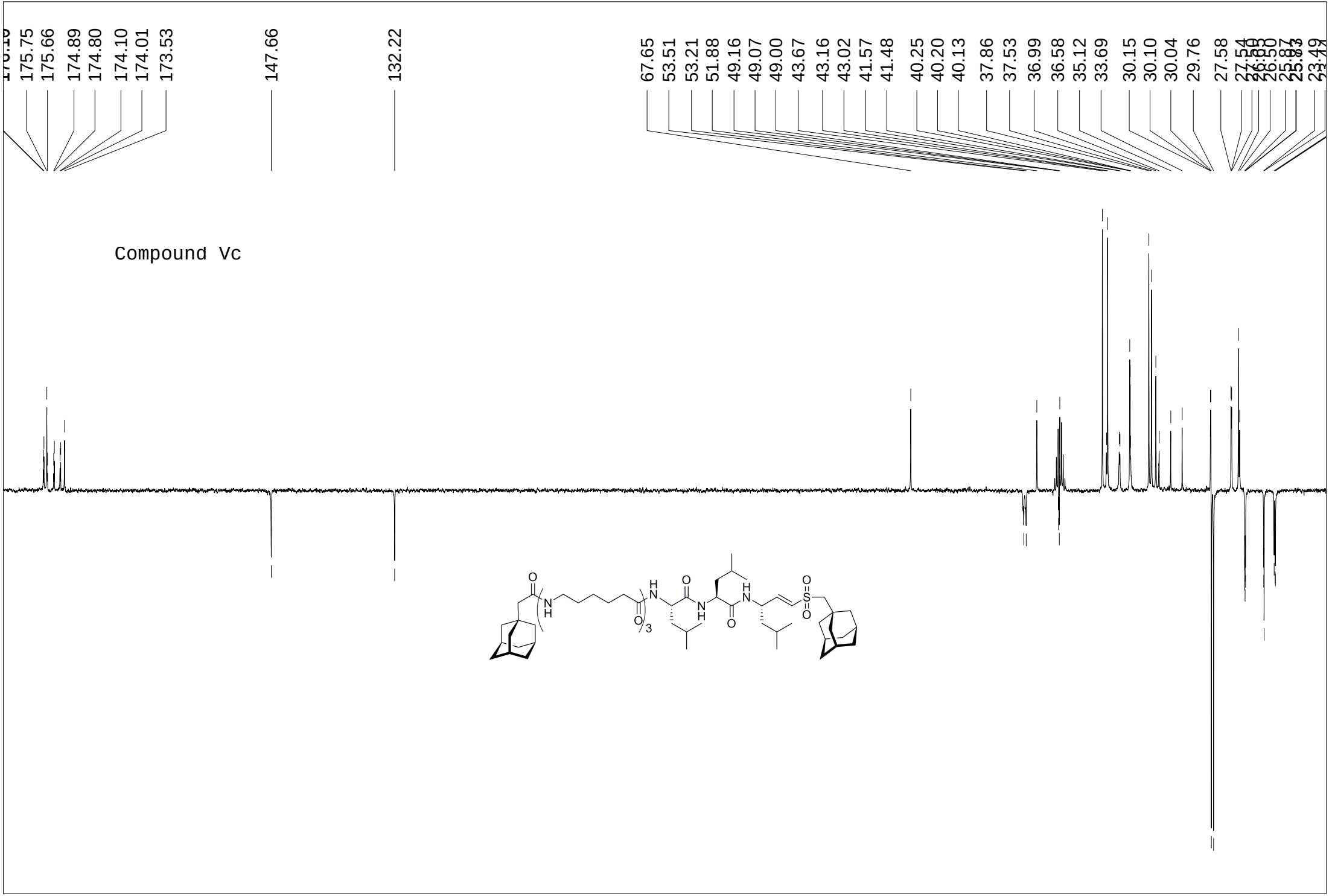
ppm (f1)

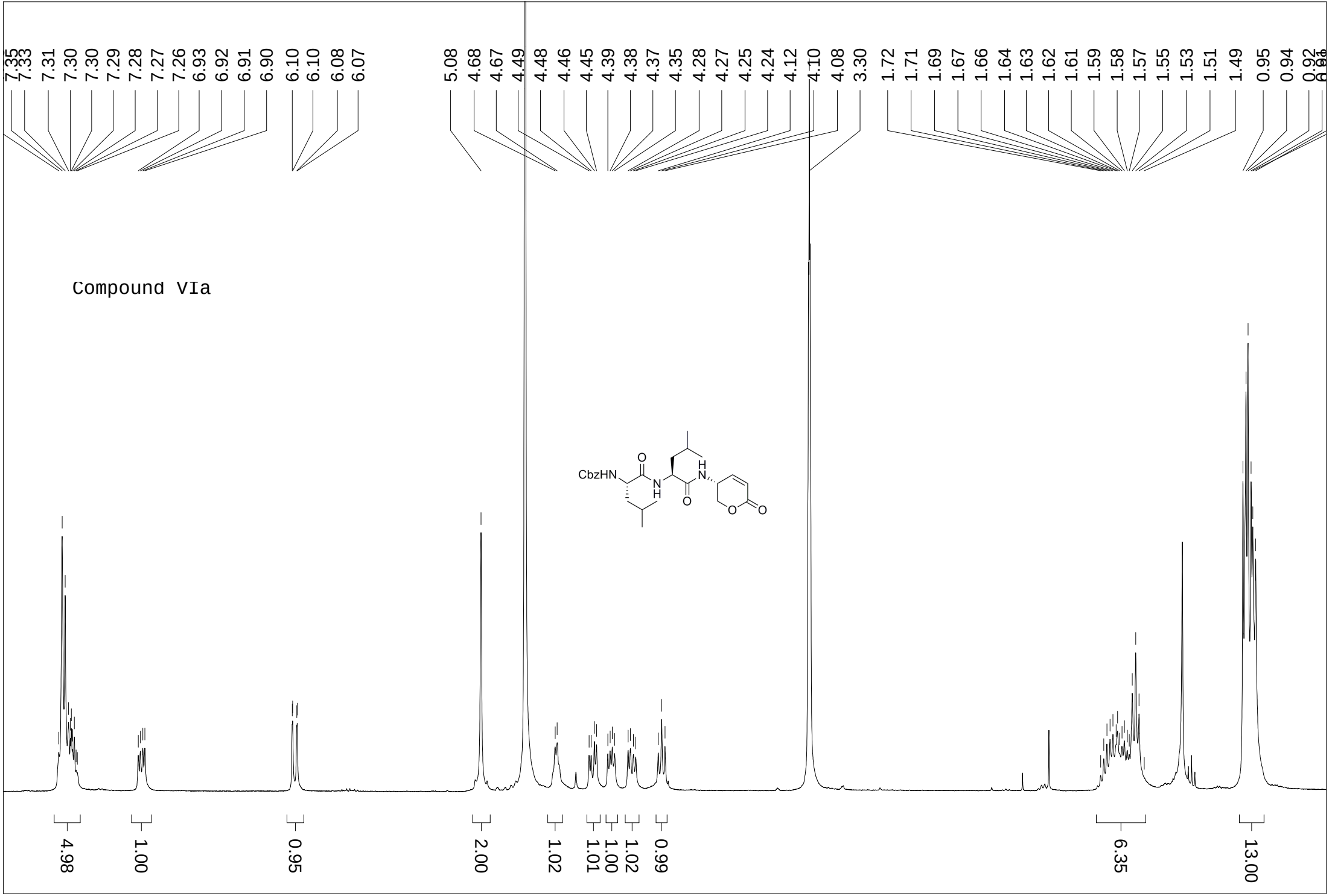

Compound Vb
7.47 7.31 7.30 7.29 7.27 7.27 7.25 7.23 7.23 7.21 6.78 6.76 6.74 6.73 6.46 6.42 4.71 4.70 4.68 4.66 4.64 4.61 4.59 4.57 4.55 4.25 4.24 4.23 4.22 3.18 3.17 3.14 3.13 3.07 3.05 3.03 3.01 2.77 1.99 1.81 1.81 1.78 1.77 1.75 1.72 1.69 1.67 1.64 1.61 1.59 1.58 1.56 1.54 1.53 1.51 1.48
0.84 1.78 5.73 1.02 0.93 2.07 0.97 0.96 1.03 1.01 2.00 3.37 6.42 17.51 20.26
N3
H
N
O
O
N
H
H
N
O
S
O
O

ppm (f1)

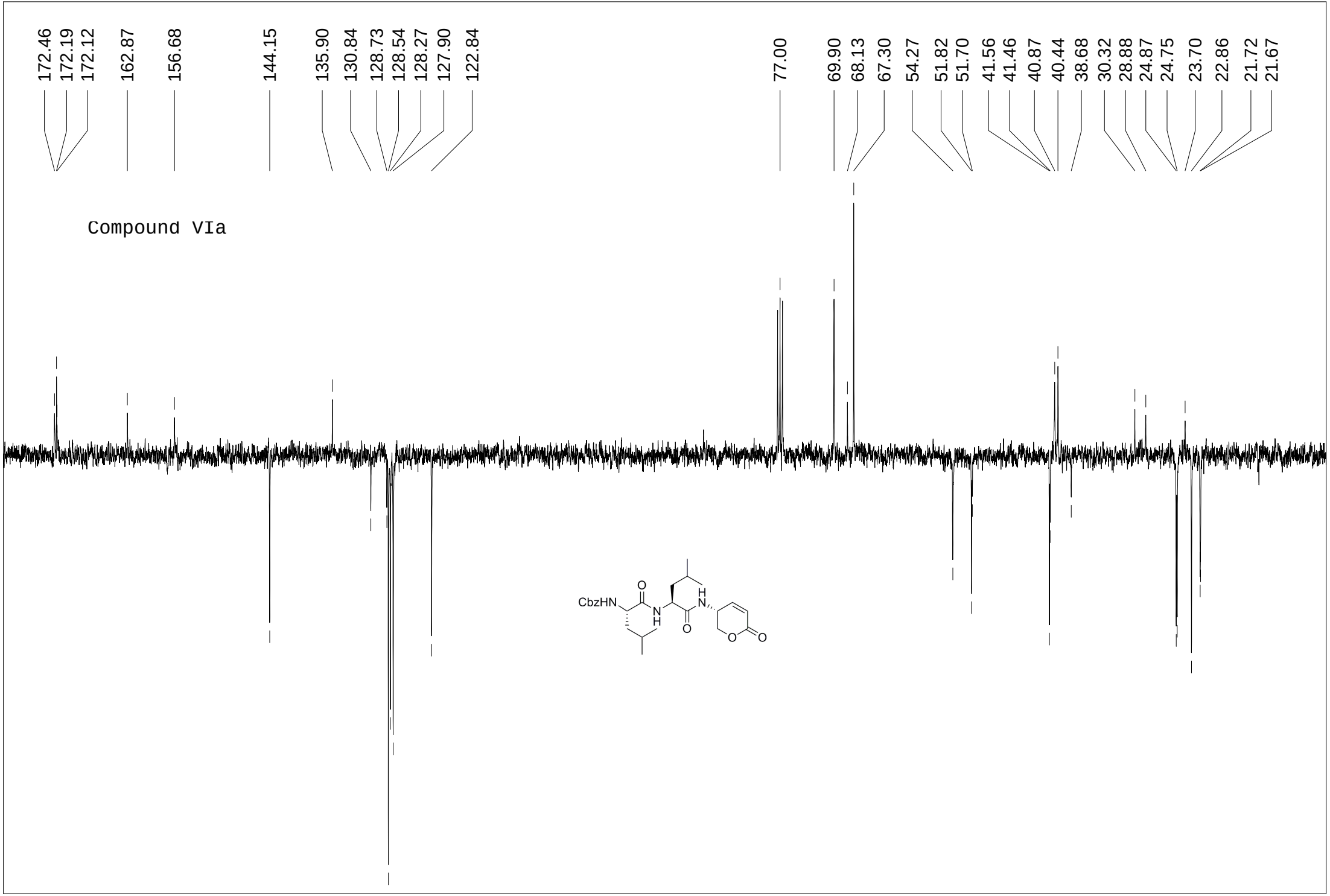

171.73
171.42
168.96
146.11
135.98
131.02
129.37
129.24
129.16
128.57
127.14
77.00
66.88
64.41
51.95
51.54
47.83
42.75
42.02
41.42
40.87
37.84
36.32
34.30
28.26
24.90
24.64
24.56
22.67
22.65
Compound Vb
ppm (f1)


8.07
8.06
8.04
7.92
7.91
7.90
7.82
7.81
7.80
6.75
6.74
6.71
6.70
6.58
6.54
4.66
4.65
4.40
4.38
4.37
4.35
4.33
4.31
3.30
3.16
3.14
2.90
0.96
0.94
0.92
0.90
0.89
Compound Vc
1.88
2.12
1.05
1.05
1.05
1.19
2.21
7.12
2.00
2.46
4.91
9.93
7.52
47.71
8.16
21.35
ppm (f1)

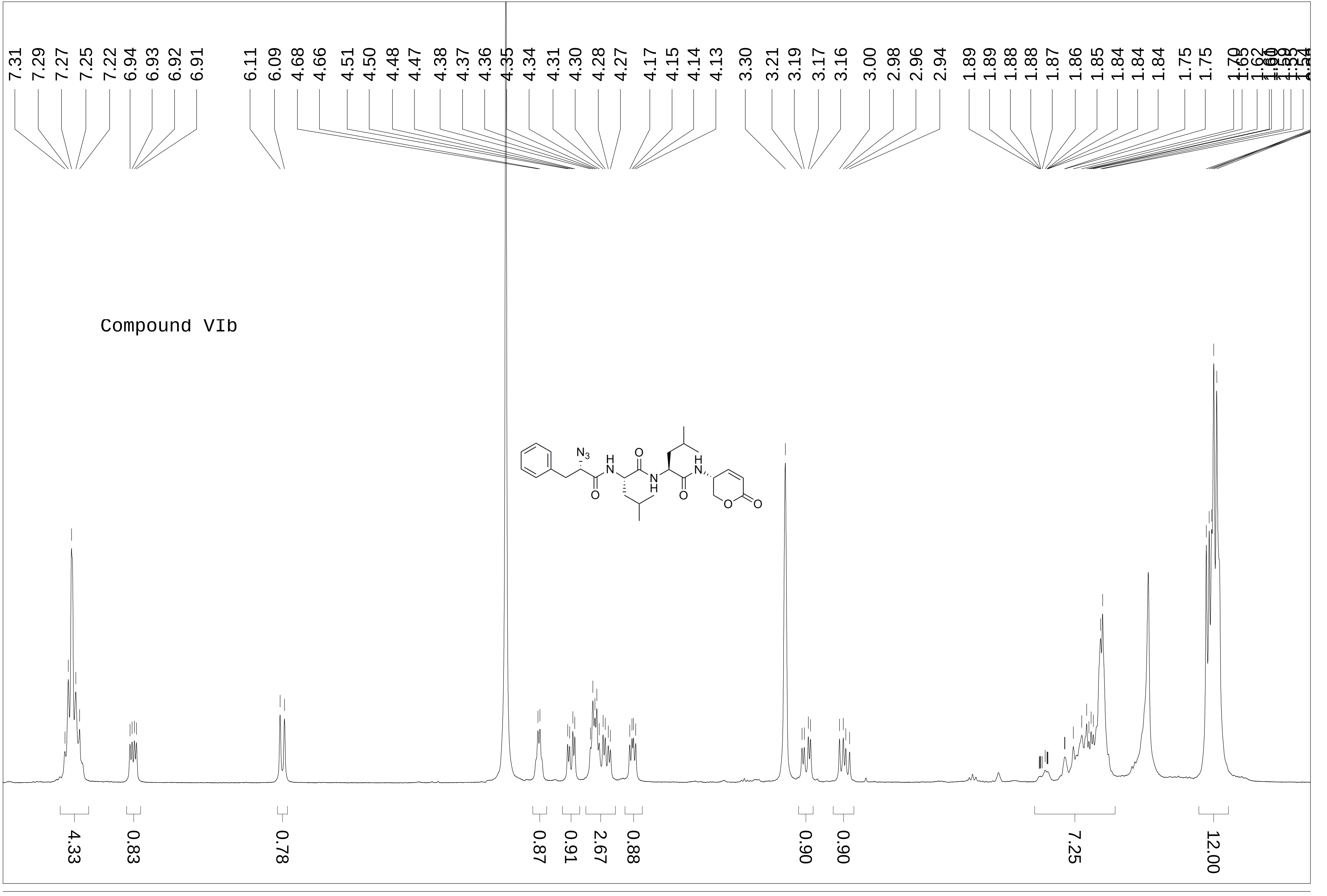

175.75
175.66
174.89
174.80
174.10
174.01
173.53
147.66
132.22
67.65
53.51
53.21
51.88
49.16
49.07
49.00
43.67
43.16
43.02
41.57
41.48
40.25
40.20
40.13
37.86
37.53
36.99
36.58
35.12
33.69
30.15
30.10
30.04
29.76
27.58
Compound Vc
ppm (f1)


7.35
7.33
7.31
7.30
7.30
7.29
7.28
7.27
7.26
6.93
6.92
6.91
6.90
6.10
6.10
6.08
6.07
5.08
4.68
4.67
4.49
4.48
4.46
4.45
4.39
4.38
4.37
4.35
4.28
4.27
4.25
4.24
4.12
4.10
4.08
3.30
1.72
1.71
1.69
1.67
1.66
1.64
1.63
1.62
1.61
1.59
1.58
1.57
1.55
1.53
1.51
1.49
0.95
0.94
0.92
Compound VIa
CbzHN
O
N
H
O
N
H
O
O
O
4.98
1.00
0.95
2.00
1.02
1.01
1.00
1.02
0.99
6.35
13.00

ppm (f1)

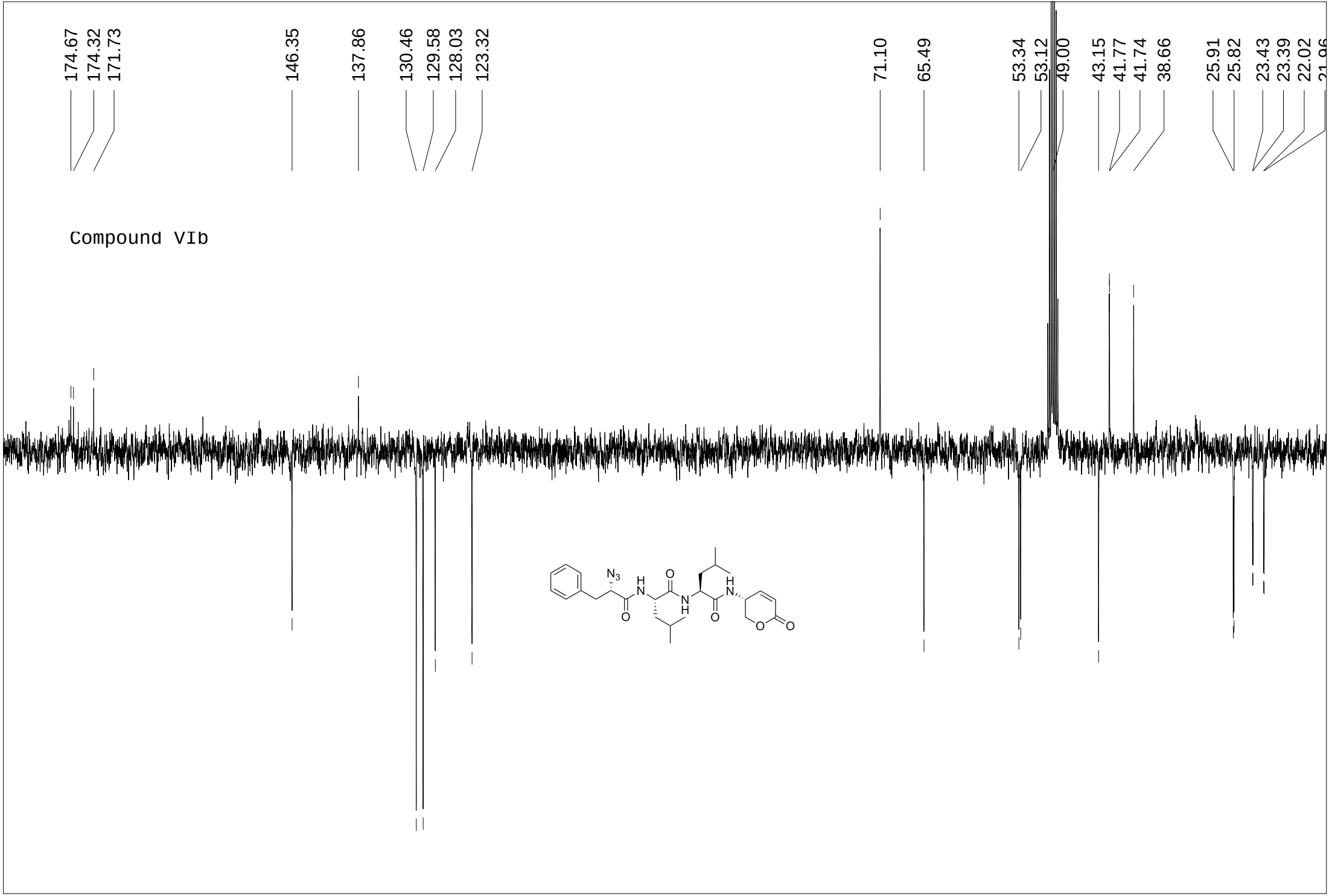

172.46
172.19
172.12
162.87
156.68
144.15
135.90
130.84
128.73
128.54
128.27
127.90
122.84
77.00
69.90
68.13
67.30
54.27
51.82
51.70
41.56
41.46
40.87
40.44
38.68
30.32
28.88
24.87
24.75
23.70
22.86
21.72
21.67
Compound VIa
CbzHN
O
N
H
N
H
O
O
O

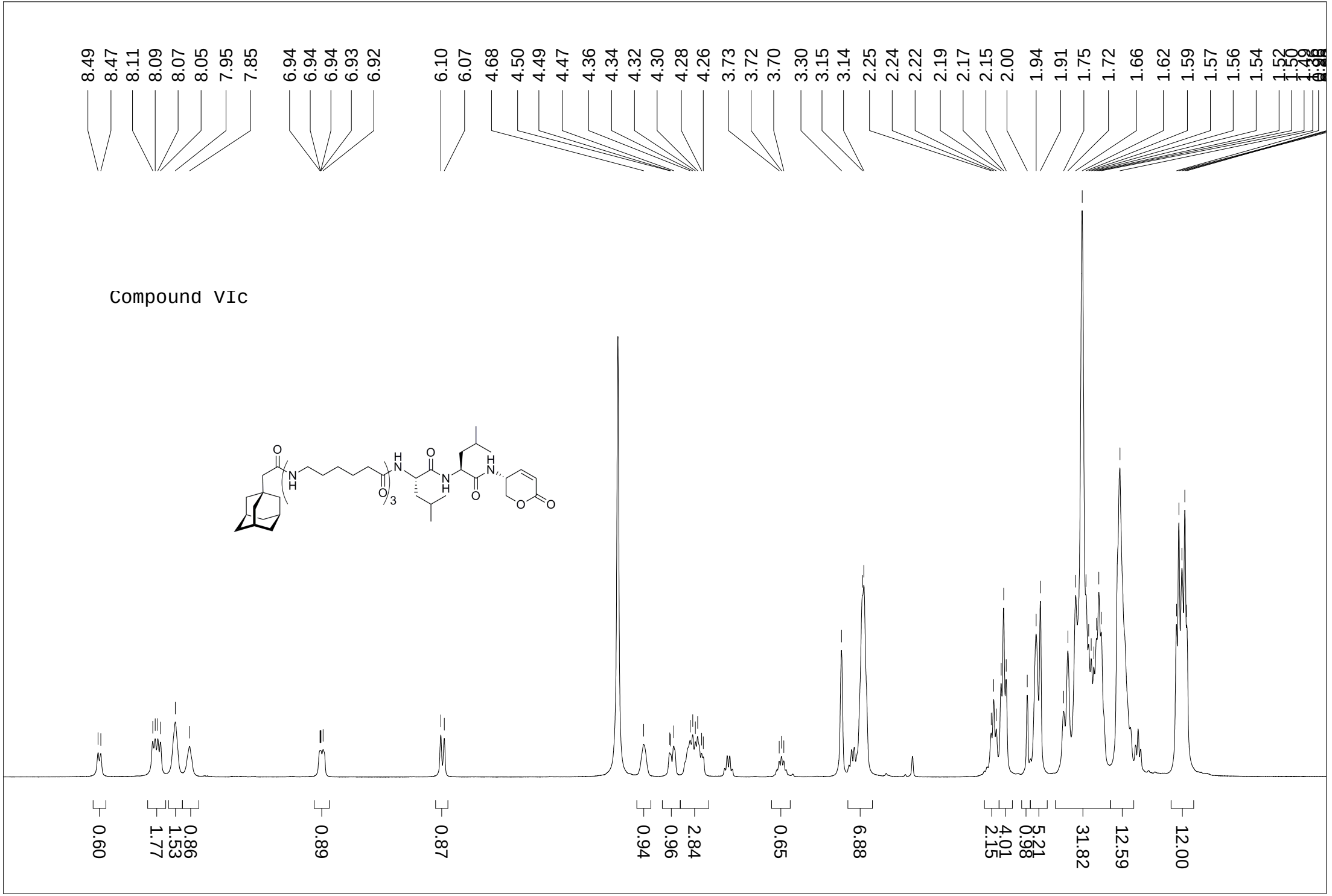
ppm (f1)

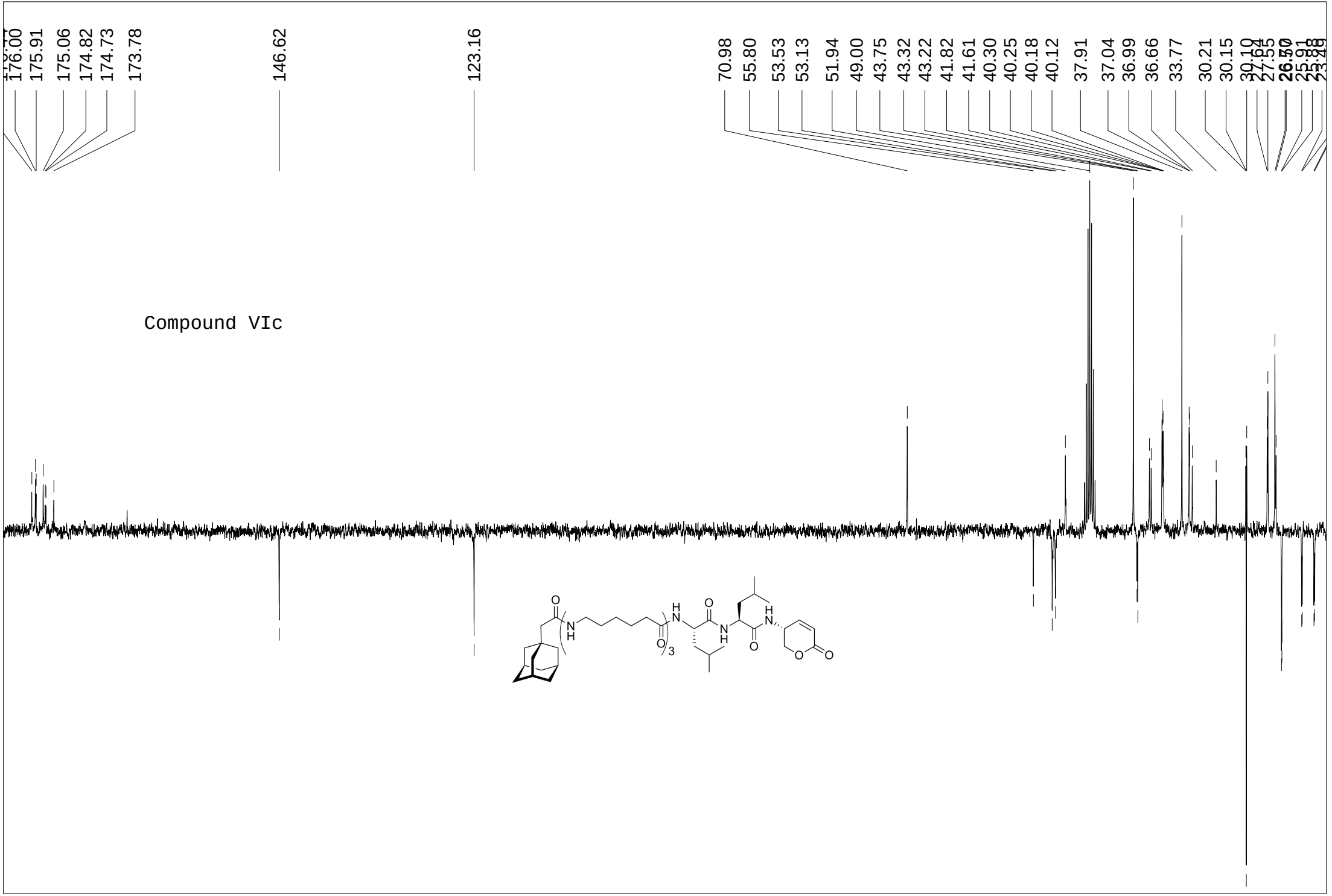


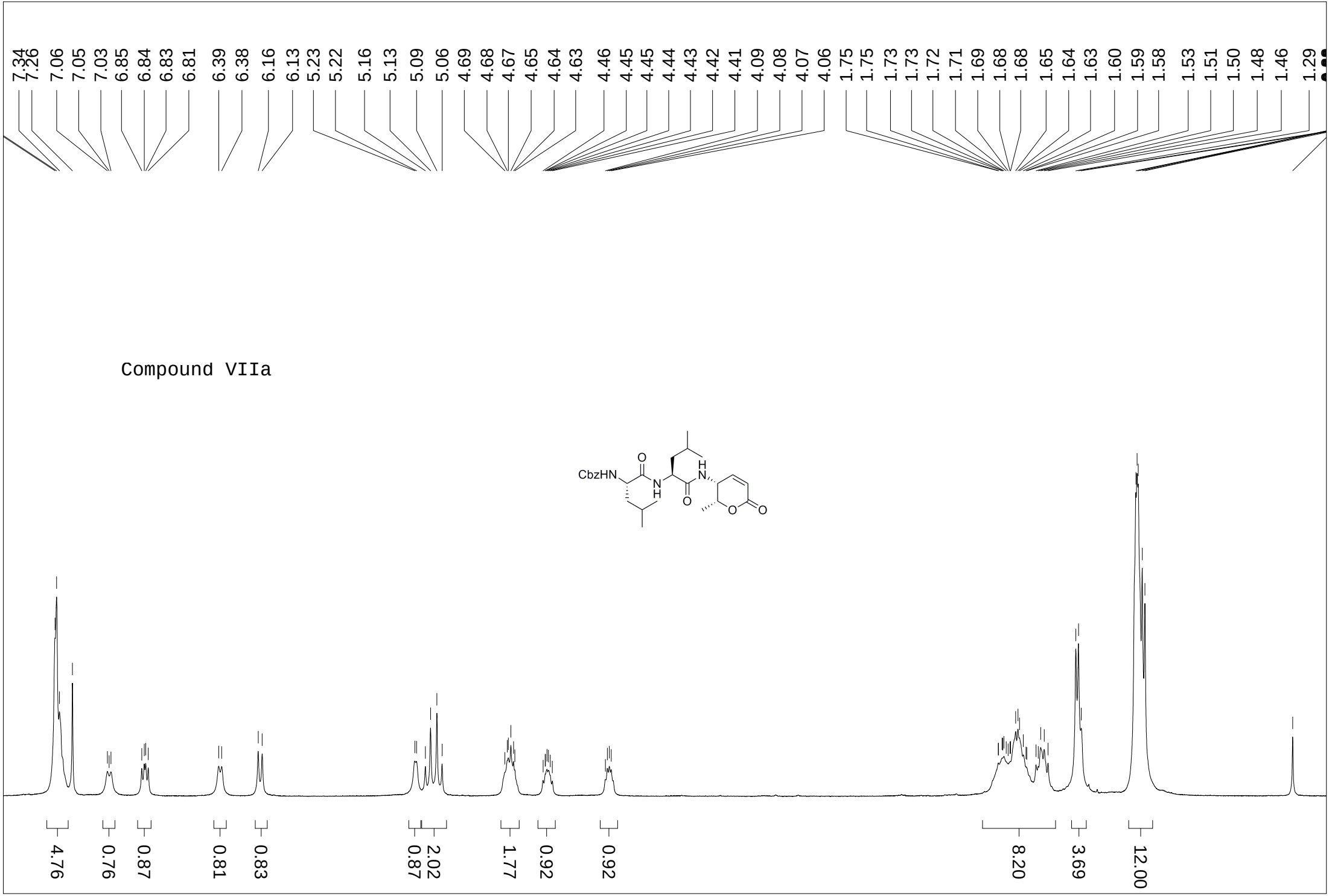
Compound VIb
7.31 7.29 7.27 7.25 7.22 6.94 6.93 6.92 6.91 6.11 6.09 4.68 4.66 4.51 4.50 4.48 4.47 4.38 4.37 4.36 4.35 4.34 4.31 4.30 4.28 4.27 4.17 4.15 4.14 4.13 3.30 3.21 3.19 3.17 3.16 3.00 2.98 2.96 2.94 1.89 1.89 1.88 1.88 1.87 1.86 1.85 1.84 1.84 1.84 1.75 1.75 1.70 1.65 1.62
4.33 0.83 0.78 0.87 0.91 2.67 0.88 0.90 0.90 7.25 12.00

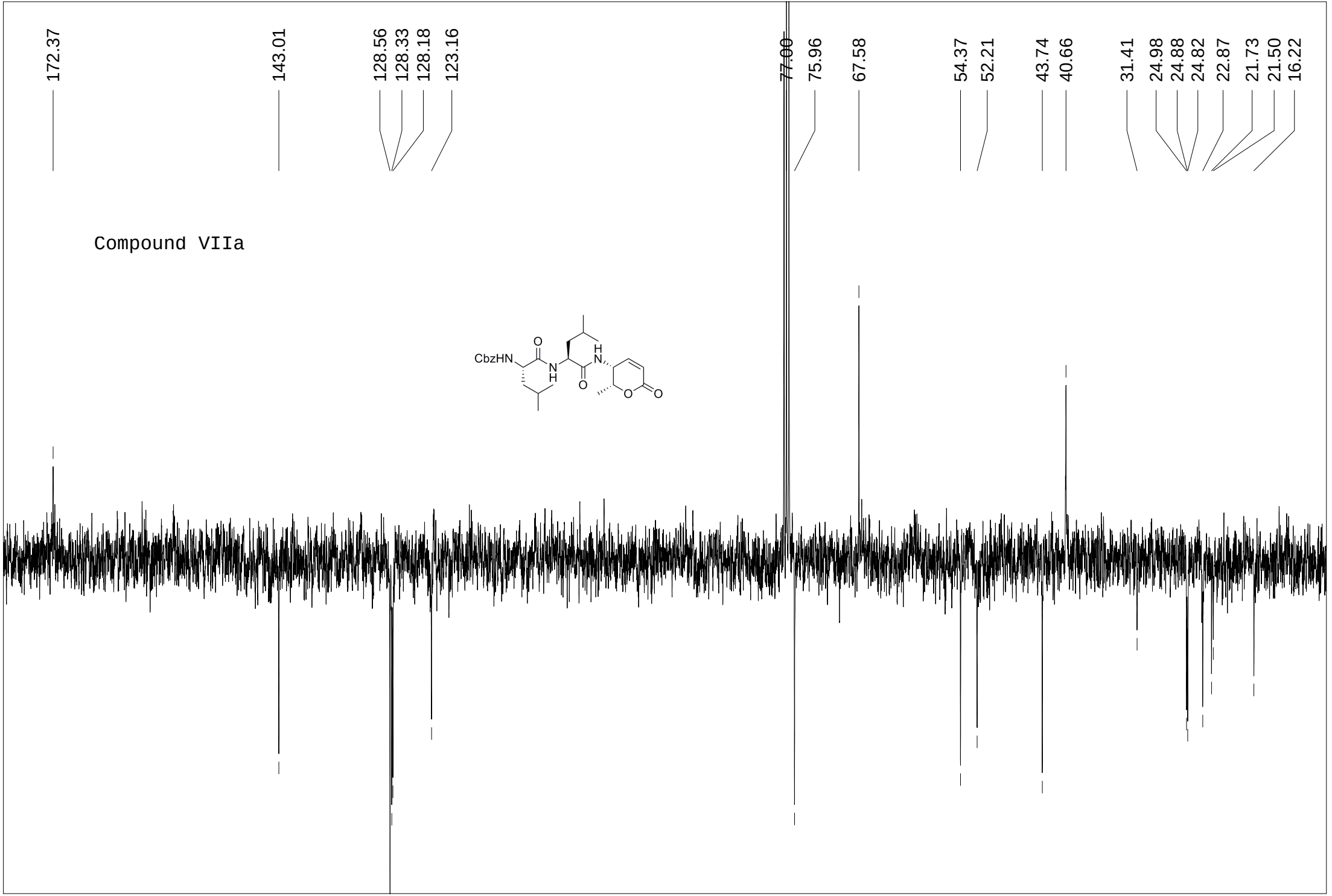
ppm (f1)

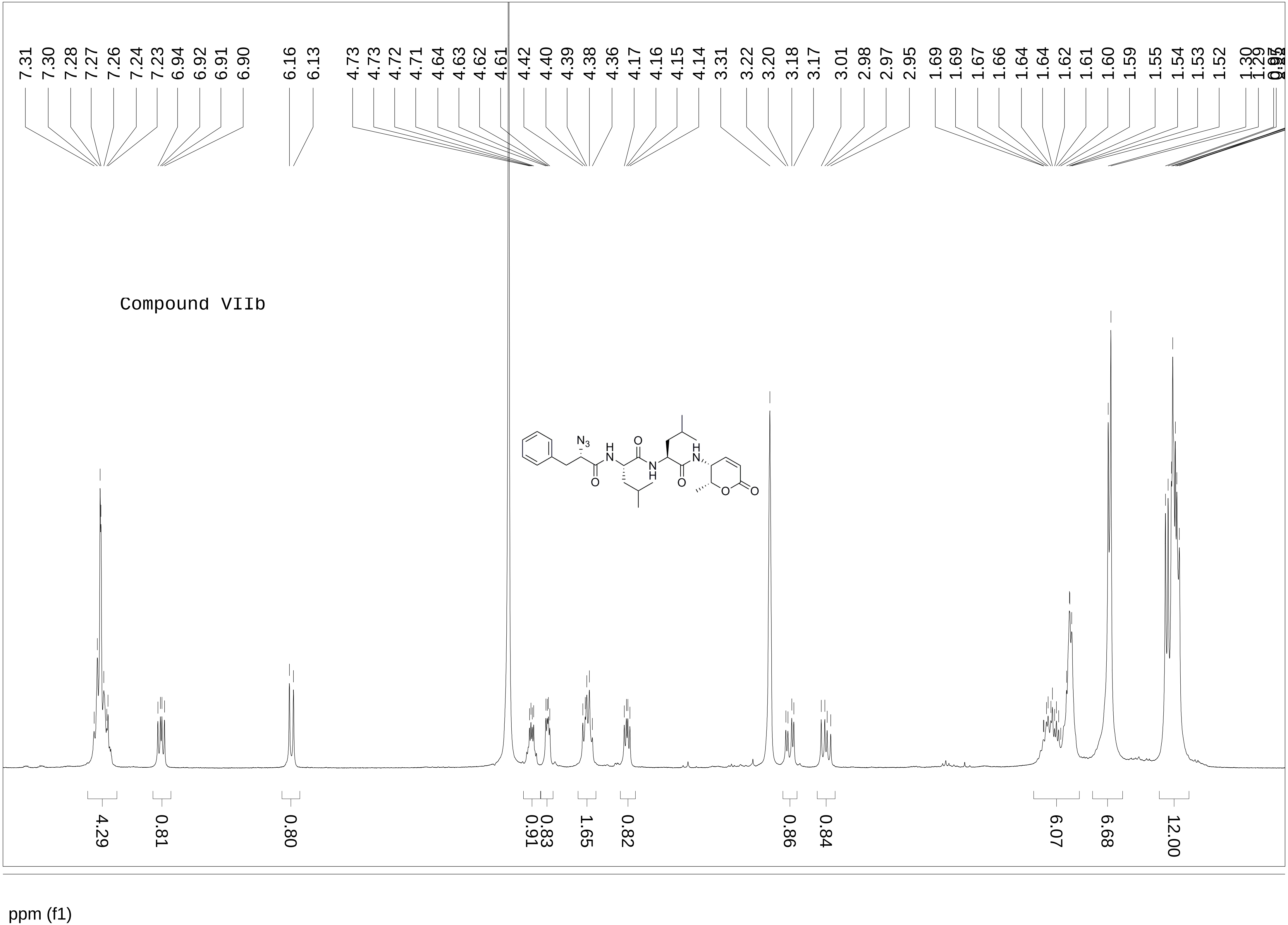

174.67
174.32
171.73
146.35
137.86
130.46
129.58
128.03
123.32
71.10
65.49
53.34
53.12
49.00
43.15
41.77
41.74
38.66
25.91
25.82
23.43
23.39
22.02
Compound VIb
ppm (f1)


8.49
8.47
8.11
8.09
8.07
8.05
7.95
7.85
6.94
6.94
6.94
6.93
6.92
6.10
6.07
4.68
4.50
4.49
4.47
4.36
4.34
4.32
4.30
4.28
4.26
3.73
3.72
3.70
3.30
3.15
3.14
2.25
2.24
2.22
2.19
2.17
2.15
2.00
1.94
1.91
1.75
1.72
1.66
1.62
1.59
1.57
1.56
1.54
1.52
Compound VIc
0.60
1.77
1.53
0.86
0.89
0.87
0.94
0.96
2.84
0.65
6.88
2.15
4.01
0.98
5.21
31.82
12.59
12.00
ppm (f1)

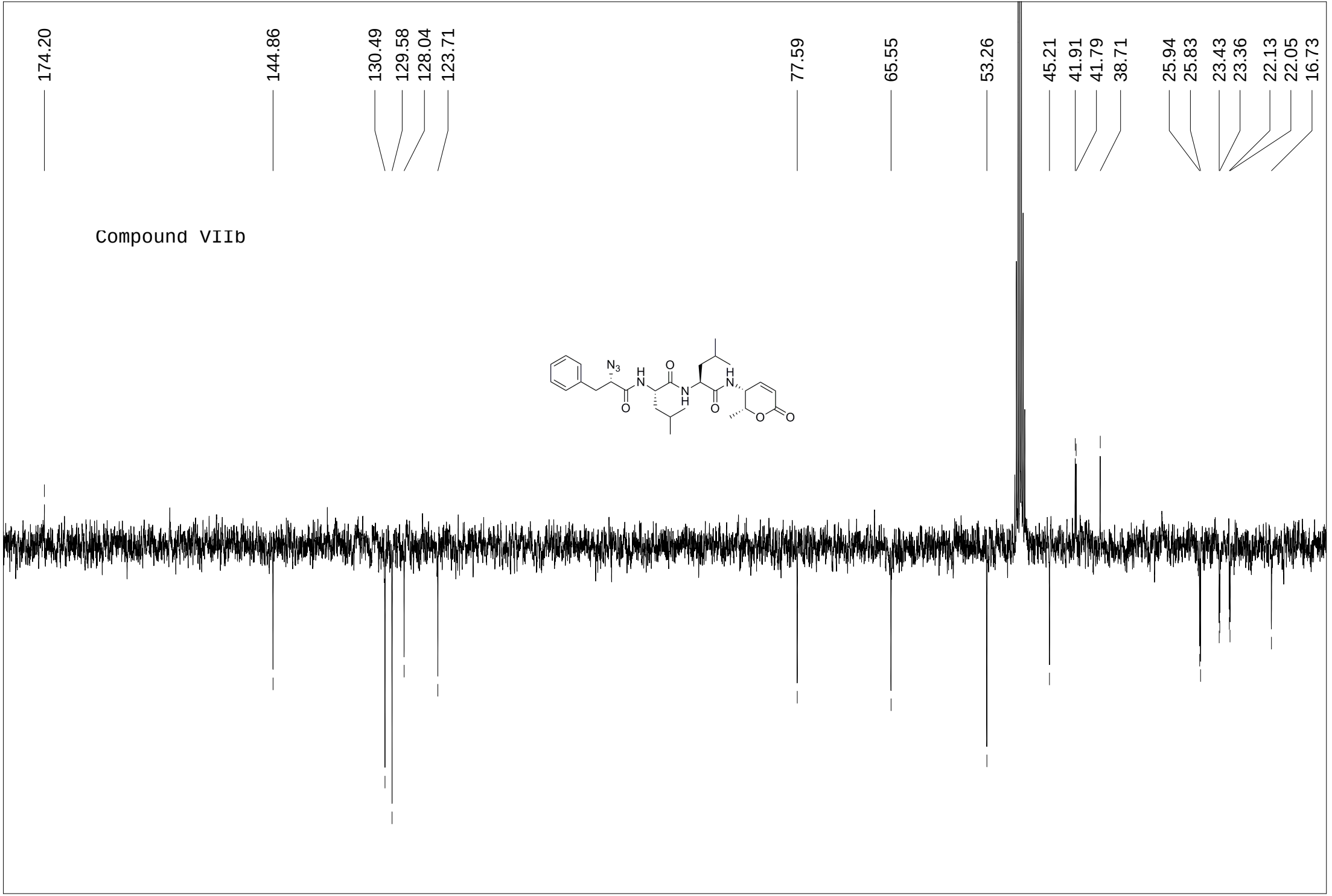

176.00
175.91
175.06
174.82
174.73
173.78
146.62
123.16
70.98
55.80
53.53
53.13
51.94
49.00
43.75
43.32
43.22
41.82
41.61
40.30
40.25
40.18
40.12
37.91
37.04
36.99
36.66
33.77
30.21
30.15
Compound VIc
ppm (f1)

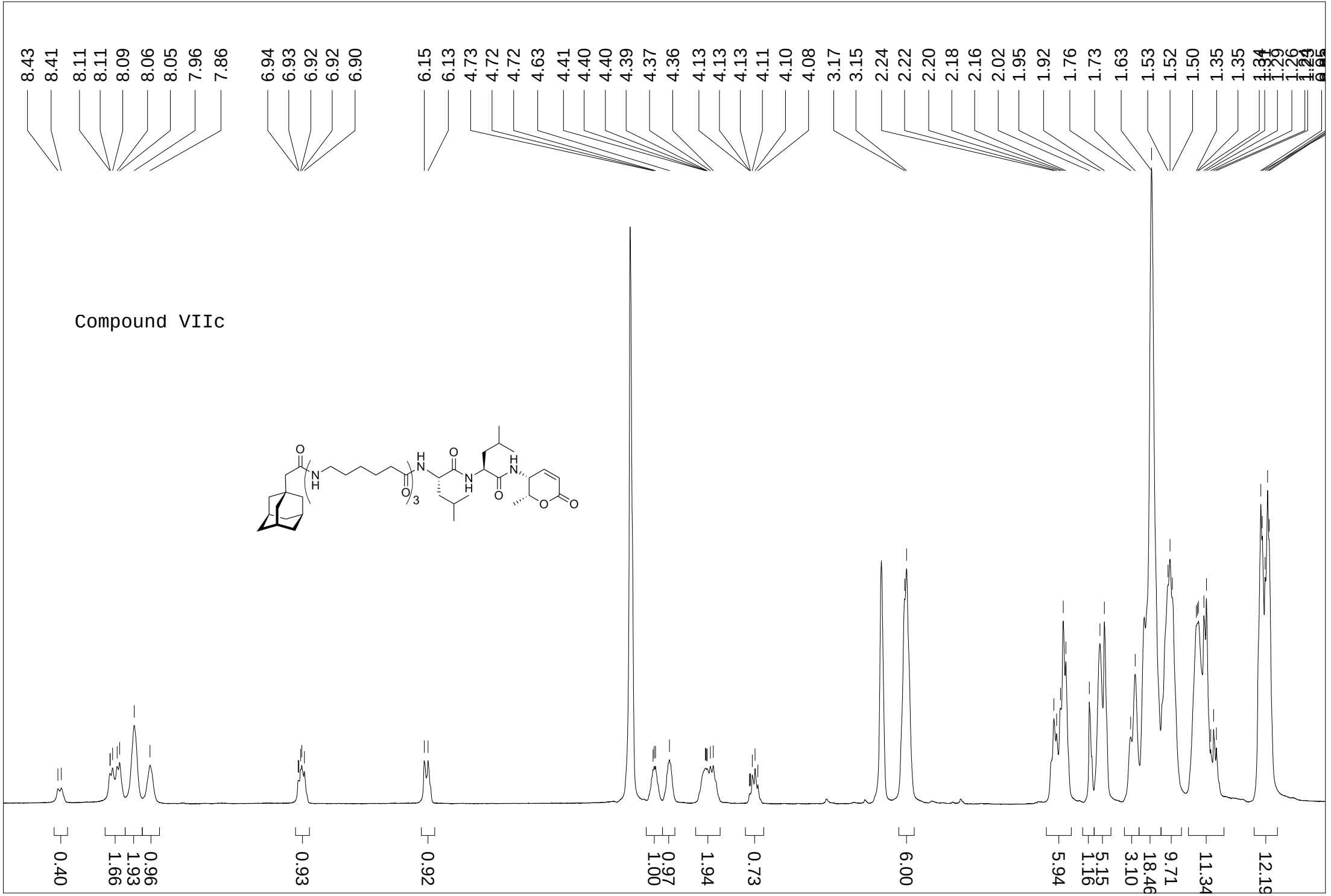

7.34
7.26
7.06
7.05
7.03
6.85
6.84
6.83
6.81
6.39
6.38
6.16
6.13
5.23
5.22
5.16
5.13
5.09
5.06
4.69
4.68
4.67
4.65
4.64
4.63
4.46
4.45
4.45
4.44
4.43
4.42
4.41
4.09
4.08
4.07
4.06
1.75
1.75
1.73
1.73
1.72
1.71
1.69
1.68
1.68
1.65
1.64
1.63
1.60
1.59
1.58
1.53
1.51
1.50
1.48
1.46
1.29
Compound VIIa
CbzHN
O
N
H
O
N
H
O
O
O
4.76
0.76
0.87
0.81
0.83
0.87
2.02
1.77
0.92
0.92
8.20
3.69
12.00
ppm (f1)

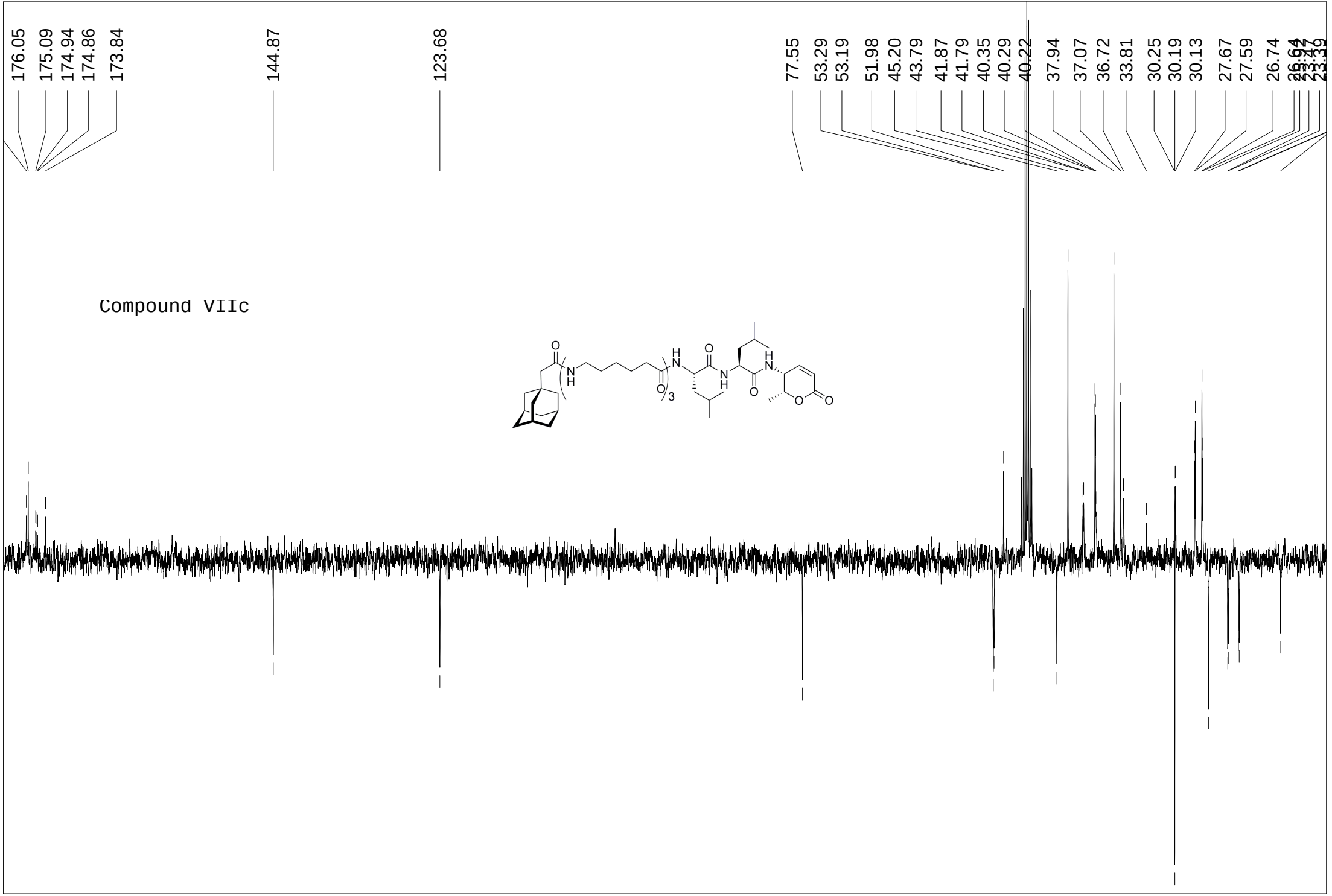

172.37
143.01
128.56
128.33
128.18
123.16
77.00
75.96
67.58
54.37
52.21
43.74
40.66
31.41
24.98
24.88
24.82
22.87
21.73
21.50
16.22
Compound VIIa
CbzHN
O
N
H
O
N
H
O
O
O
ppm (f1)

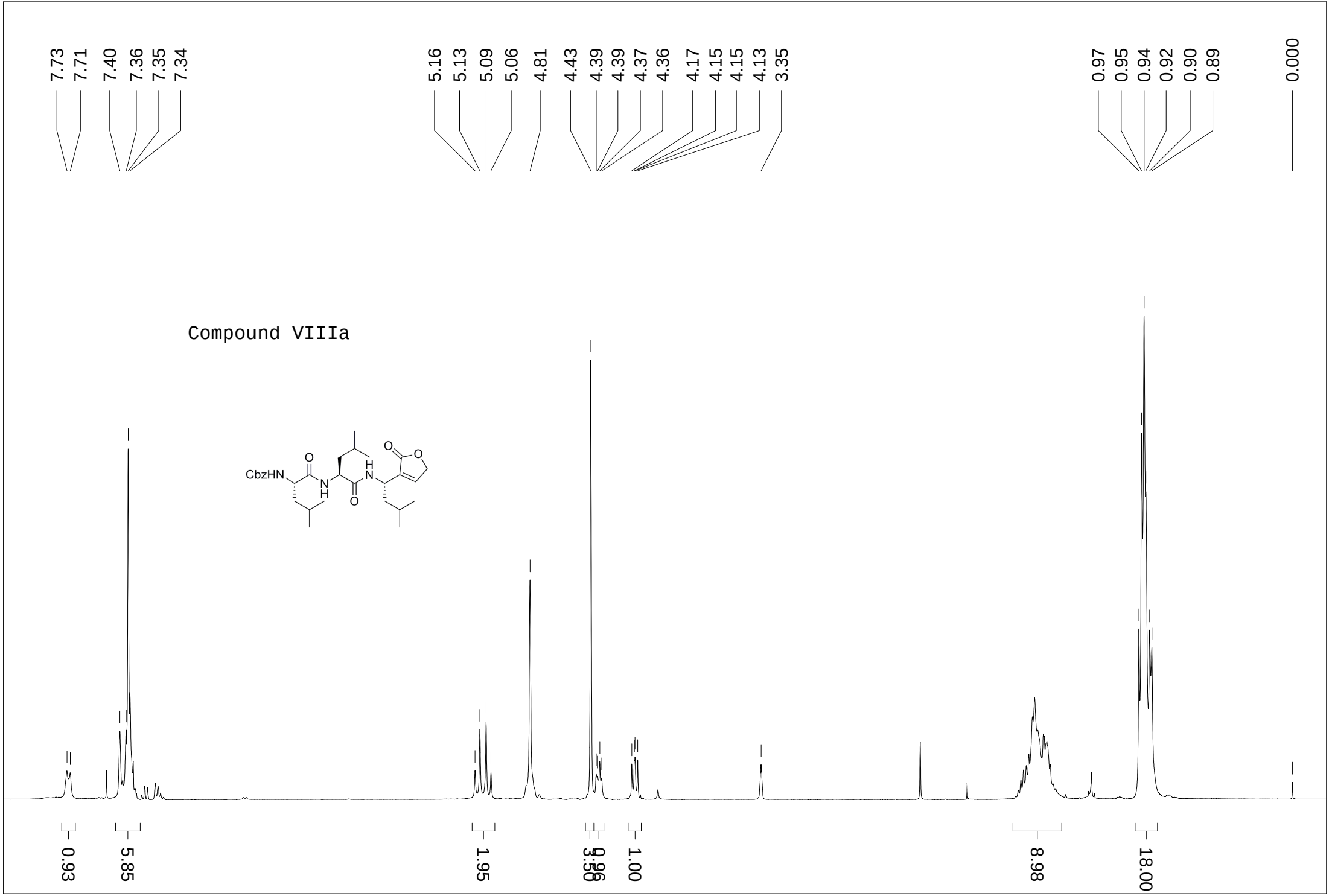


7.31
7.30
7.28
7.27
7.26
7.24
7.23
6.94
6.92
6.91
6.90
6.16
6.13
4.73
4.73
4.72
4.71
4.64
4.63
4.62
4.61
4.42
4.40
4.39
4.38
4.36
4.17
4.16
4.15
4.14
3.31
3.22
3.20
3.18
3.17
3.01
2.98
2.97
2.95
1.69
1.69
1.67
1.66
1.64
1.64
1.62
1.61
1.60
1.59
1.55
1.54
1.53
1.52
1.30
1.29
Compound VIIb
N_3
H
N
O
4.29
0.81
0.80
0.91
0.83
1.65
0.82
0.86
0.84
6.07
6.68
12.00
ppm (f1)

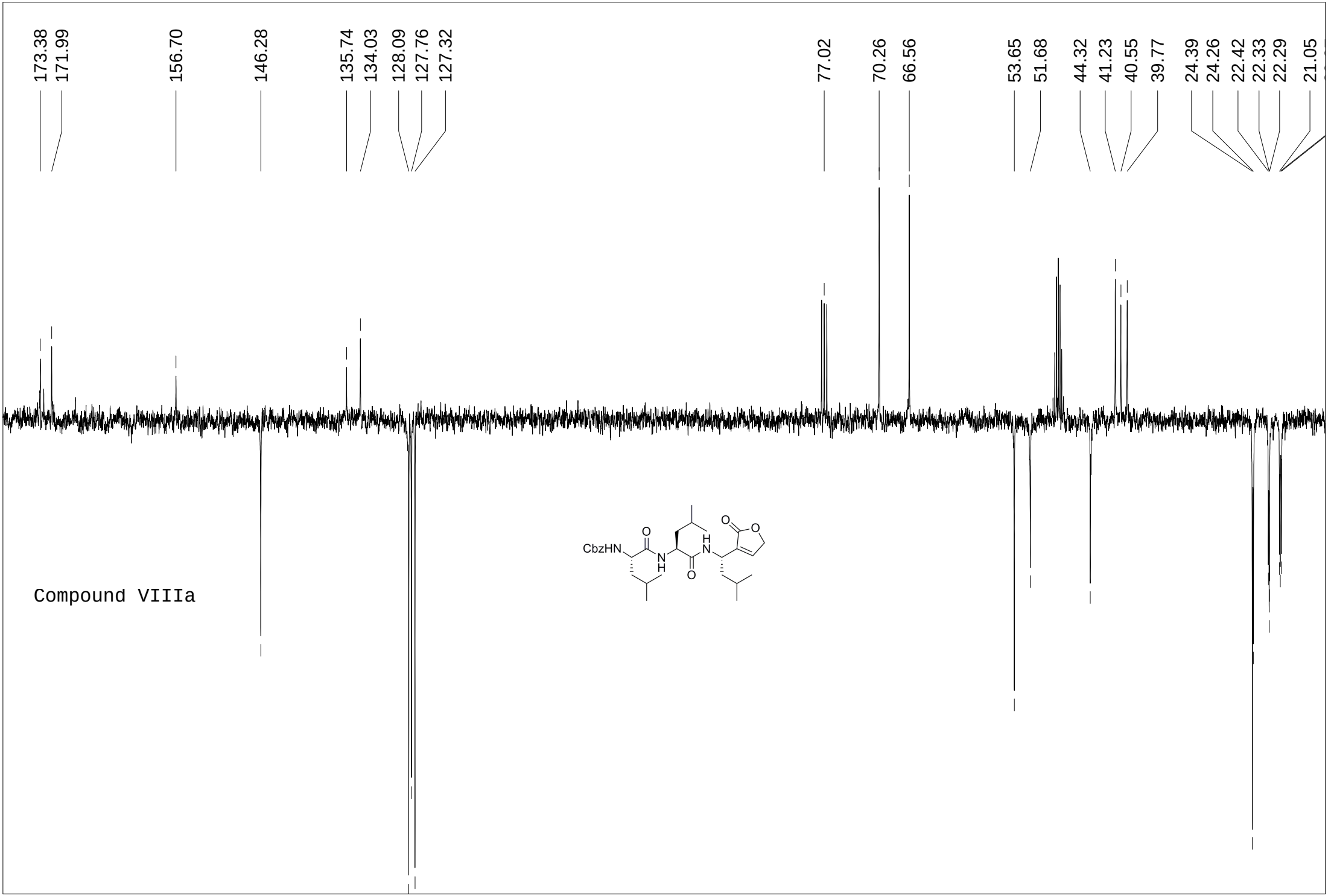

174.20
144.86
130.49
129.58
128.04
123.71
77.59
65.55
53.26
45.21
41.91
41.79
38.71
25.94
25.83
23.43
23.36
22.13
22.05
16.73
Compound VIIb
ppm (f1)


8.43
8.41
8.11
8.11
8.09
8.06
8.05
7.96
7.86
6.94
6.93
6.92
6.92
6.90
6.15
6.13
4.73
4.72
4.72
4.63
4.41
4.40
4.40
4.39
4.37
4.36
4.13
4.13
4.13
4.11
4.10
4.08
3.17
3.15
2.24
2.22
2.20
2.18
2.16
2.02
1.95
1.92
1.76
1.73
1.63
1.53
1.52
1.50
1.35
1.35
Compound VIIc
0.40
1.66
1.93
0.96
0.93
0.92
0.97
1.00
1.94
0.73
6.00
5.94
5.15
1.16
3.10
18.46
9.71
11.34
12.19
ppm (f1)

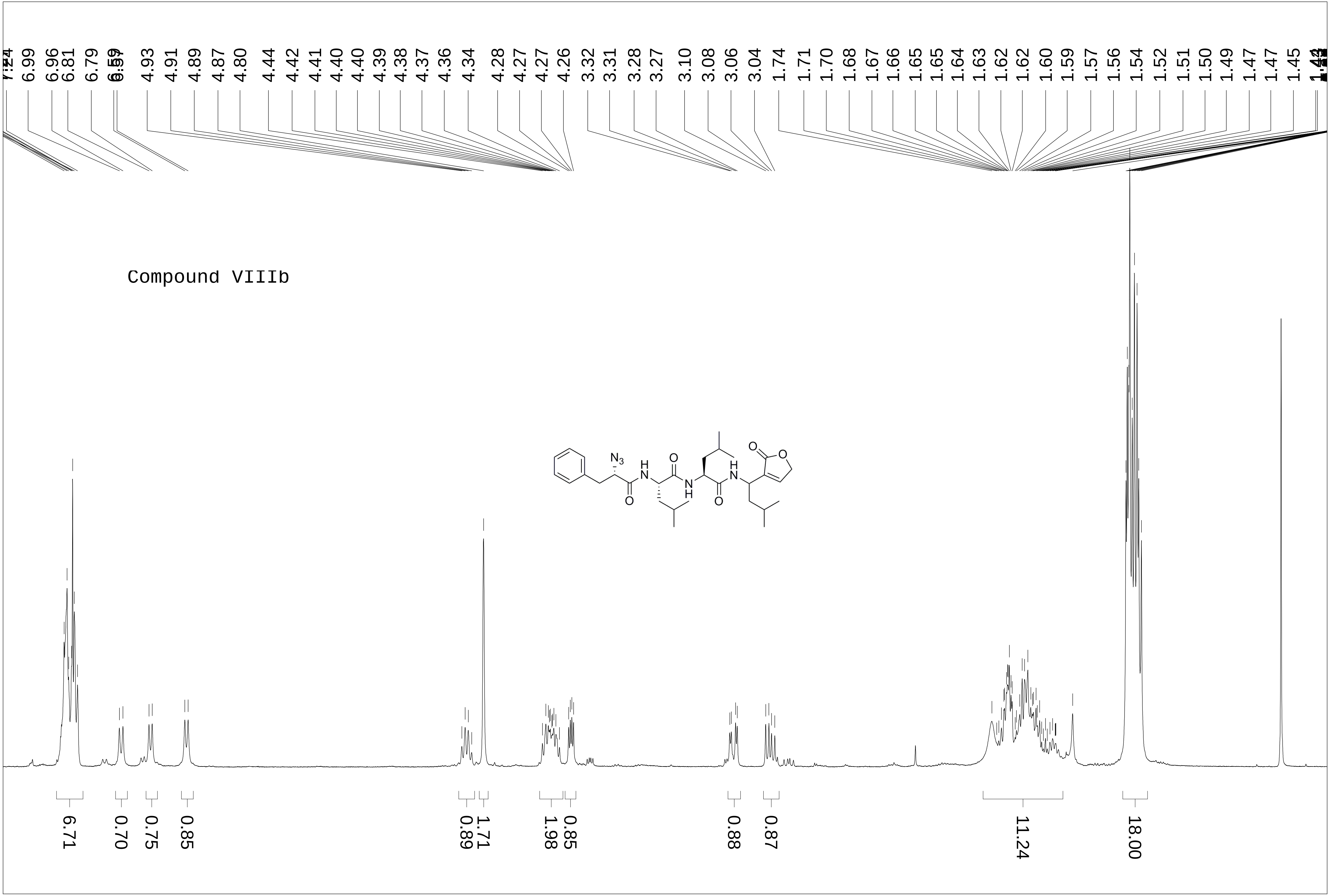

176.05
175.09
174.94
174.86
173.84
144.87
123.68
77.55
53.29
53.19
51.98
45.20
43.79
41.87
41.79
40.35
40.29
40.22
37.94
37.07
36.72
33.81
30.25
30.19
30.13
27.67
27.59
26.74
Compound VIIc
ppm (f1)


7.73
7.71
7.40
7.36
7.35
7.34
5.16
5.13
5.09
5.06
4.81
4.43
4.39
4.39
4.37
4.36
4.17
4.15
4.15
4.13
3.35
0.97
0.95
0.94
0.92
0.90
0.89
0.000
Compound VIIIa
CbzHN
0.93
5.85
1.95
3.30
0.96
1.00
8.98
18.00

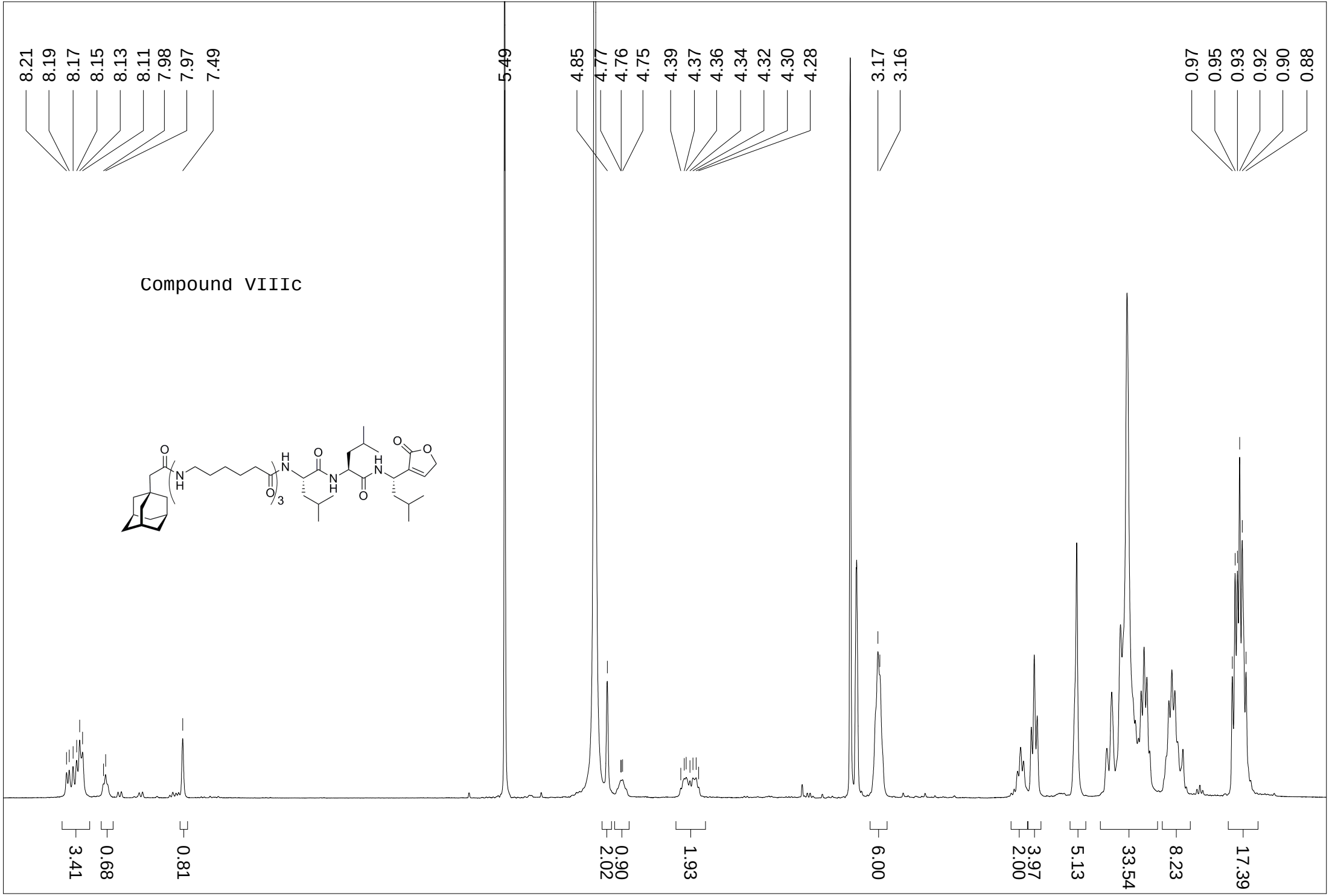
ppm (f1)


173.38
171.99
156.70
146.28
135.74
134.03
128.09
127.76
127.32
77.02
70.26
66.56
53.65
51.68
44.32
41.23
40.55
39.77
24.39
24.26
22.42
22.33
22.29
21.05
Compound VIIIa
CbzHN
O
N
H
O
H
N
O
O
O

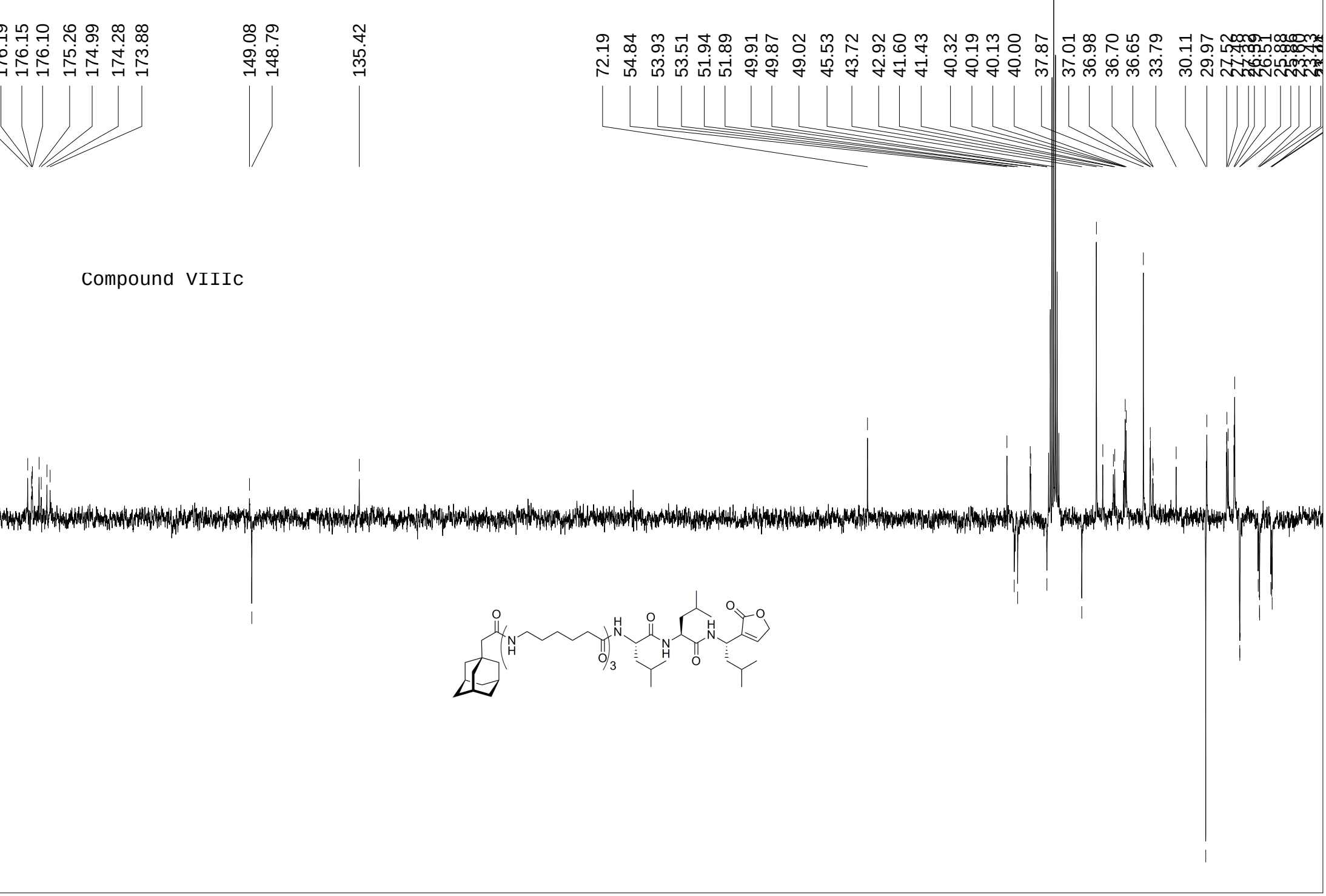
ppm (f1)


Compound VIIIb
N3
H
N
O
O
N
H
H
N
O
O
O
6.99
6.96
6.81
6.79
4.93
4.91
4.89
4.87
4.80
4.44
4.42
4.41
4.40
4.40
4.39
4.38
4.37
4.36
4.34
4.28
4.27
4.27
4.26
3.32
3.31
3.28
3.27
3.10
3.08
3.06
3.04
1.74
1.71
1.70
1.68
1.67
1.66
1.65
1.65
1.64
1.63
1.62
1.62
1.60
1.59
1.57
1.56
1.54
1.52
1.51
1.50
1.49
1.47
1.47
1.45
6.71
0.70
0.75
0.85
0.89
1.71
1.98
0.85
0.88
0.87
11.24
18.00

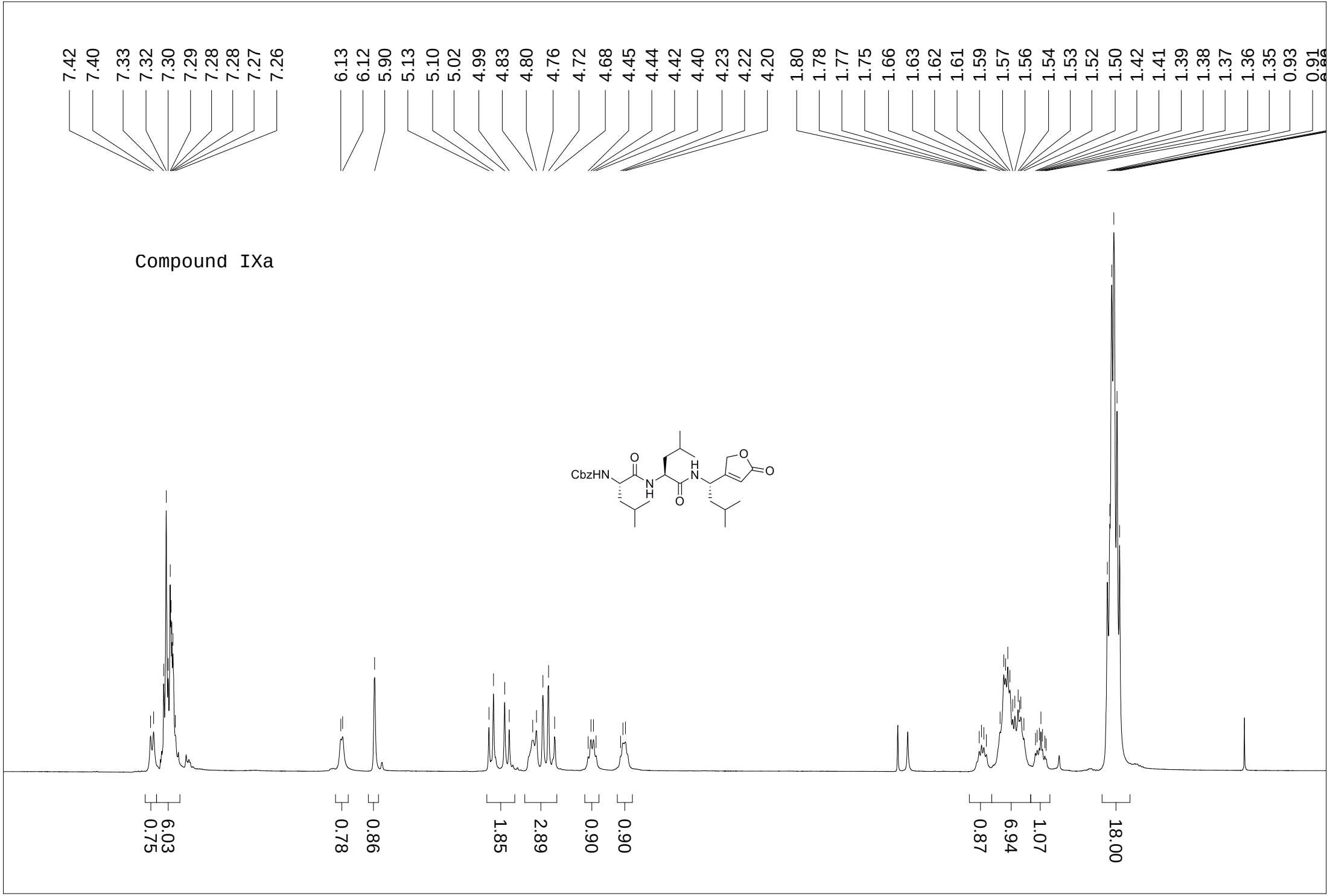
ppm (f1)

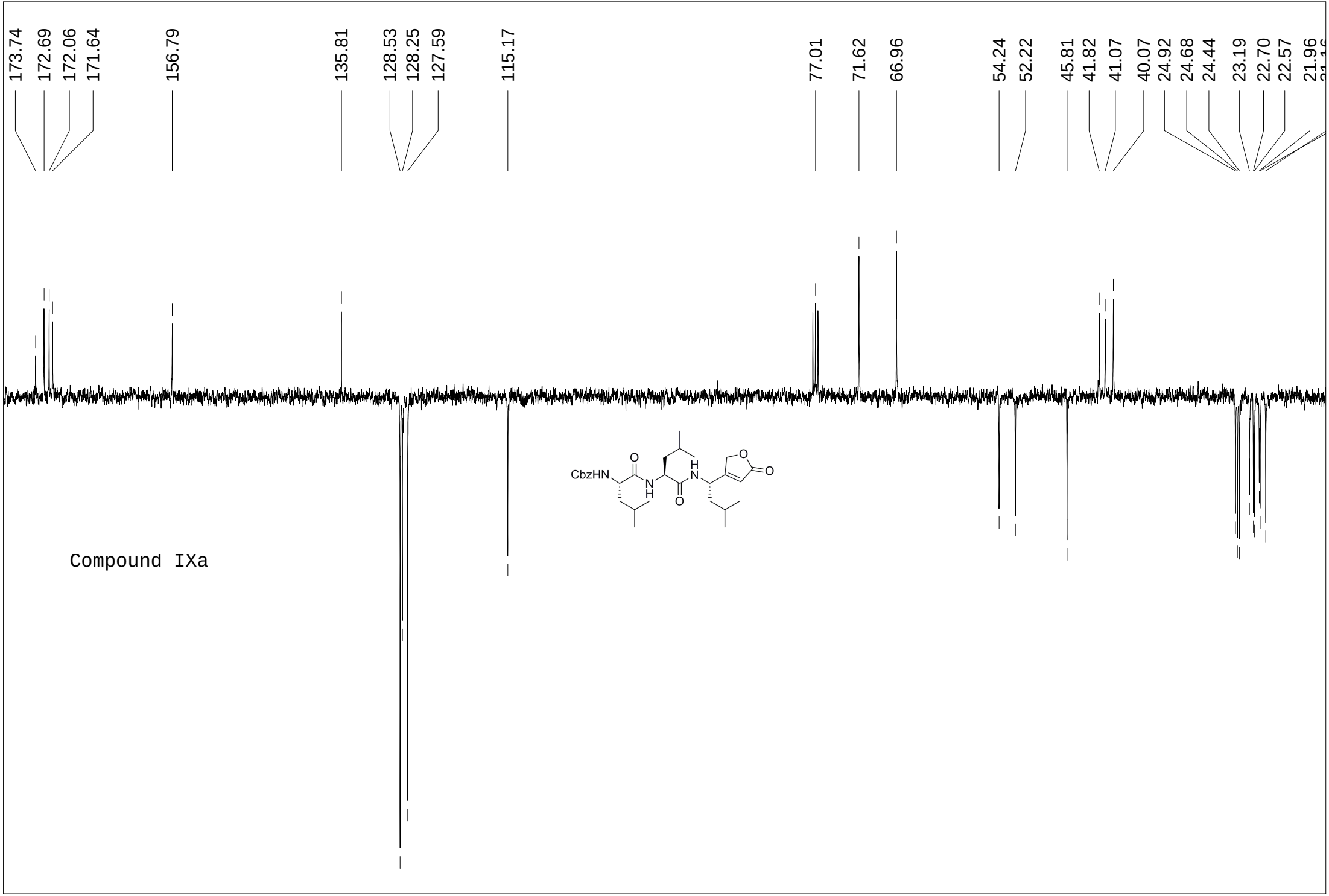

8.21
8.19
8.17
8.15
8.13
8.11
7.98
7.97
7.49
5.49
4.85
4.77
4.76
4.75
4.39
4.37
4.36
4.34
4.32
4.30
4.28
3.17
3.16
0.97
0.95
0.93
0.92
0.90
0.88
Compound VIIIc
3.41
0.68
0.81
2.02
0.90
1.93
6.00
2.00
3.97
5.13
33.54
8.23
17.39

ppm (f1)

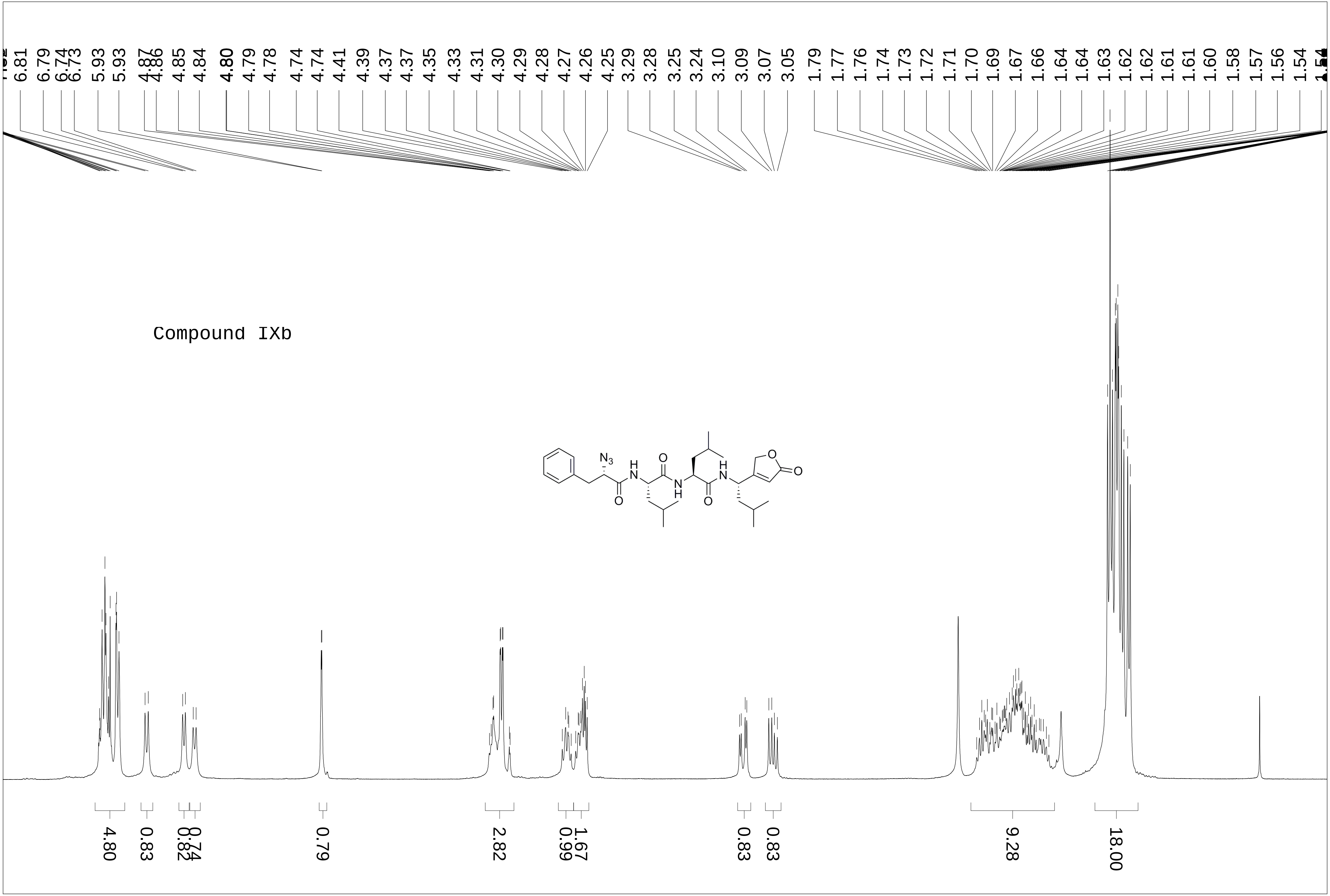

176.19
176.15
176.10
175.26
174.99
174.28
173.88
149.08
148.79
135.42
72.19
54.84
53.93
53.51
51.94
51.89
49.91
49.87
49.02
45.53
43.72
42.92
41.60
41.43
40.32
40.19
40.13
40.00
37.87
37.01
36.98
36.70
36.65
33.79
30.11
29.97
27.52
Compound VIIIc
O
N
H
O
3
H
N
O
N
H
O
H
N
O
O

ppm (f1)

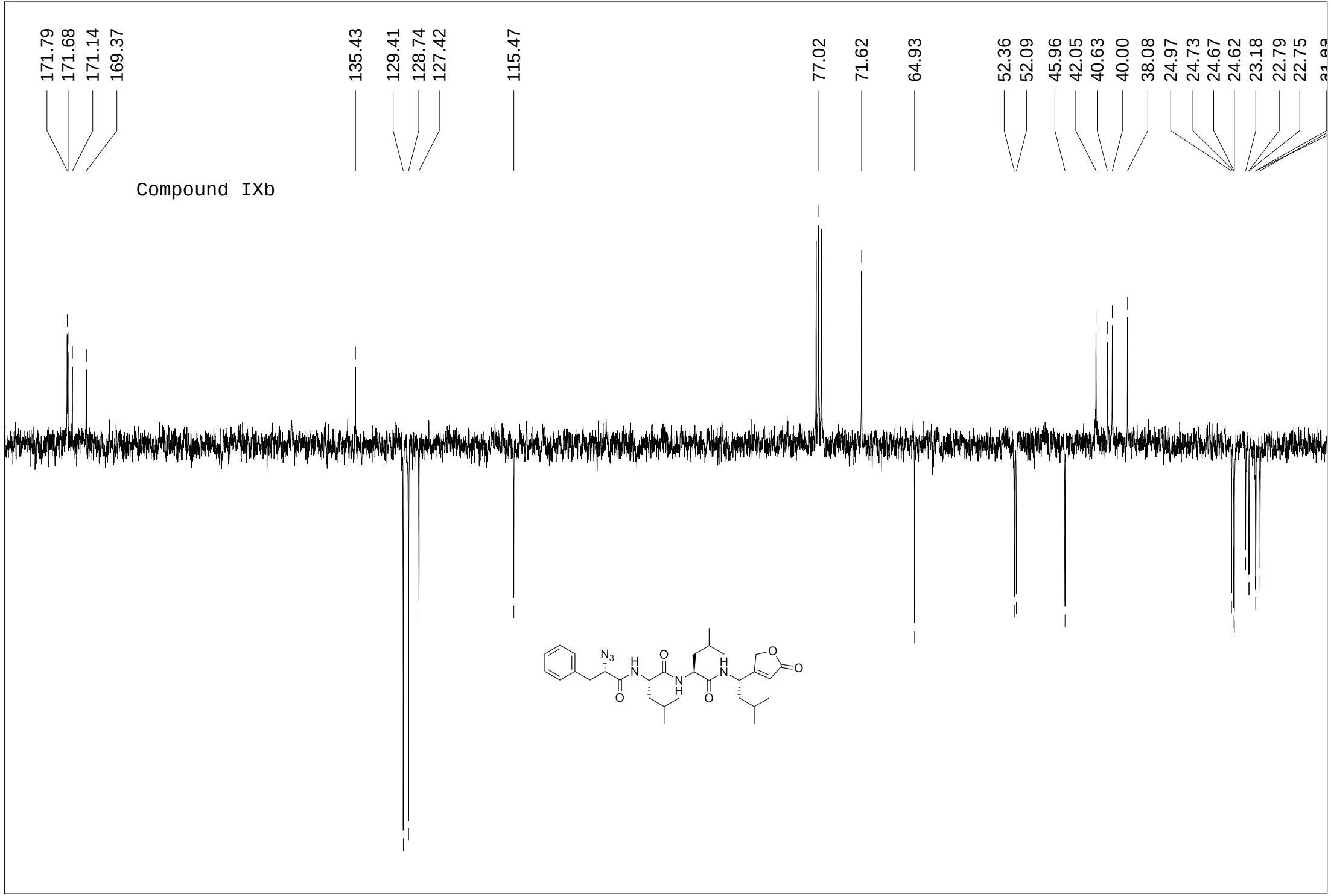

7.42
7.40
7.33
7.32
7.30
7.29
7.28
7.28
7.27
7.26
6.13
6.12
5.90
5.13
5.10
5.02
4.99
4.83
4.80
4.76
4.72
4.68
4.45
4.44
4.42
4.40
4.23
4.22
4.20
1.80
1.78
1.77
1.75
1.66
1.63
1.62
1.61
1.59
1.57
1.56
1.54
1.53
1.52
1.50
1.42
1.41
1.39
1.38
1.37
1.36
1.35
0.93
0.91
Compound IXa
CbzHN
O
N
H
O
N
H
O
O
0.75
6.03
0.78
0.86
1.85
2.89
0.90
0.90
0.87
6.94
1.07
18.00
ppm (f1)

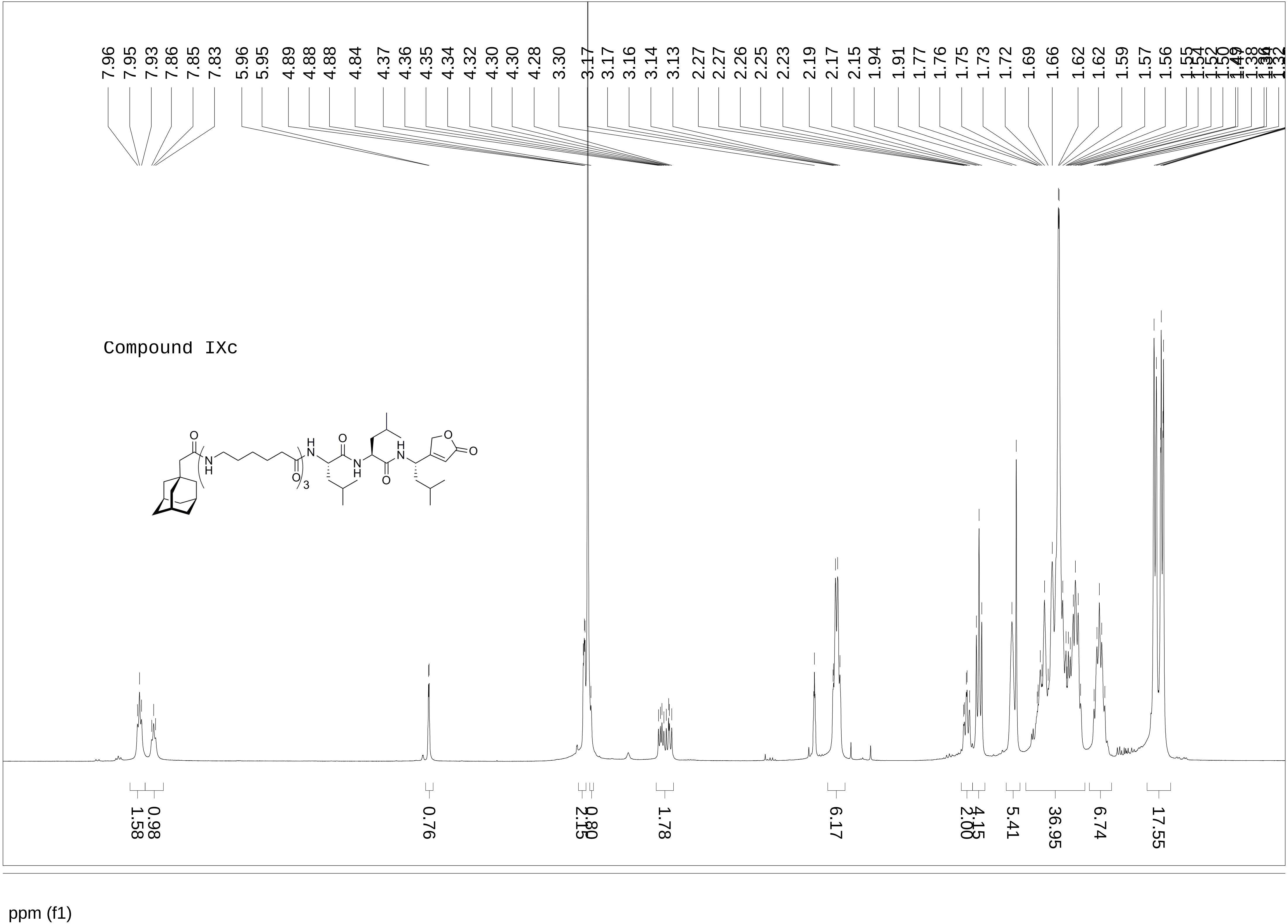

173.74
172.69
172.06
171.64
156.79
135.81
128.53
128.25
127.59
115.17
77.01
71.62
66.96
54.24
52.22
45.81
41.82
41.07
40.07
24.92
24.68
24.44
23.19
22.70
22.57
21.96
CbzHN
O
N
H
O
H
N
O
O
Compound IXa

ppm (f1)

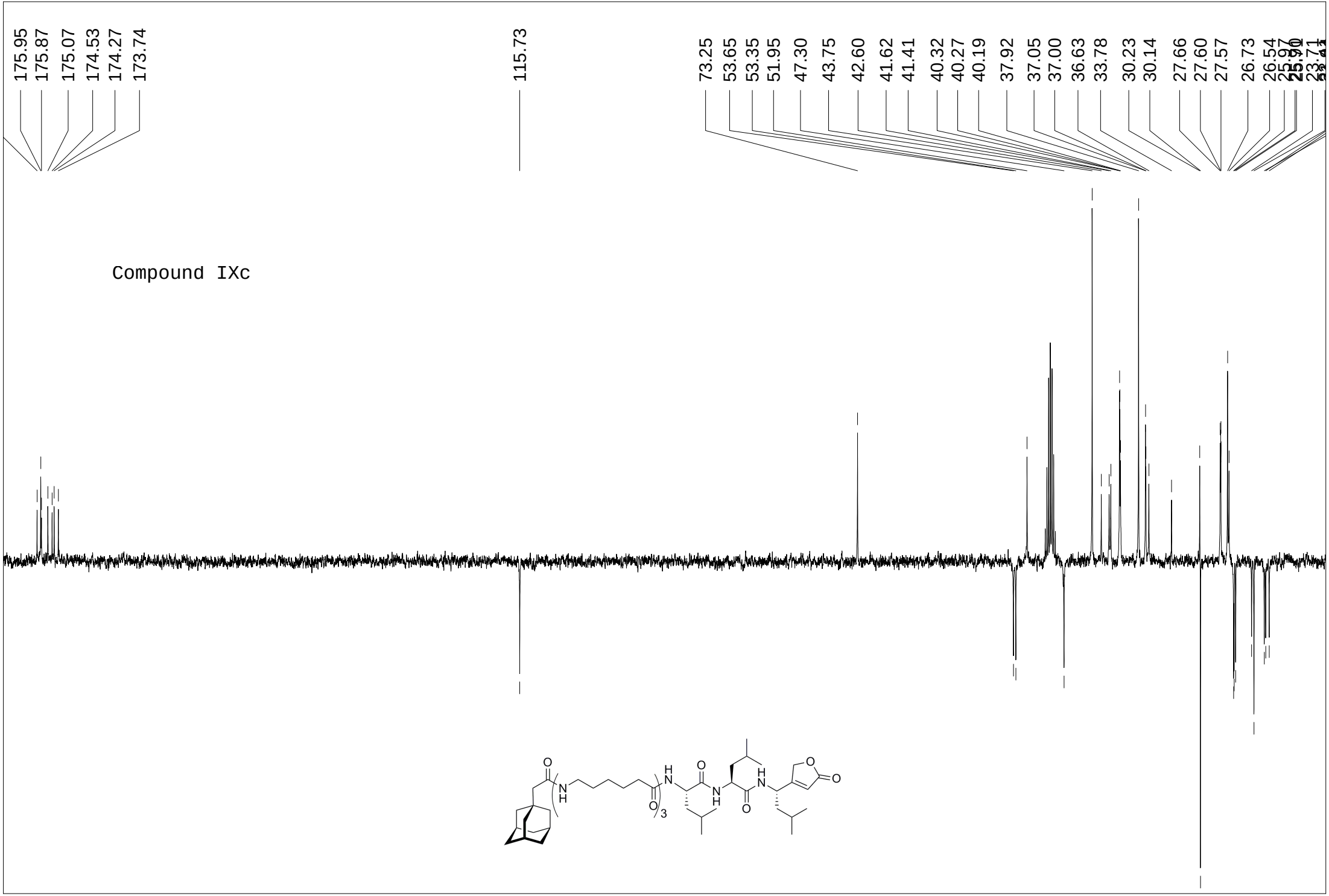

6.81
6.79
6.74
6.73
5.93
5.93
4.87
4.86
4.85
4.84
4.80
4.79
4.78
4.74
4.74
4.41
4.39
4.37
4.37
4.35
4.33
4.31
4.30
4.29
4.28
4.27
4.26
4.25
3.29
3.28
3.25
3.24
3.10
3.09
3.07
3.05
1.79
1.77
1.76
1.74
1.73
1.72
1.71
1.70
1.69
1.67
1.66
1.64
1.64
1.63
1.62
1.62
1.61
1.61
1.60
1.58
1.57
1.56
1.54
Compound IXb
N3
H
N
O
O
N
H
O
H
N
O
O
O
4.80
0.83
0.82
0.74
0.79
2.82
0.99
1.67
0.83
0.83
9.28
18.00

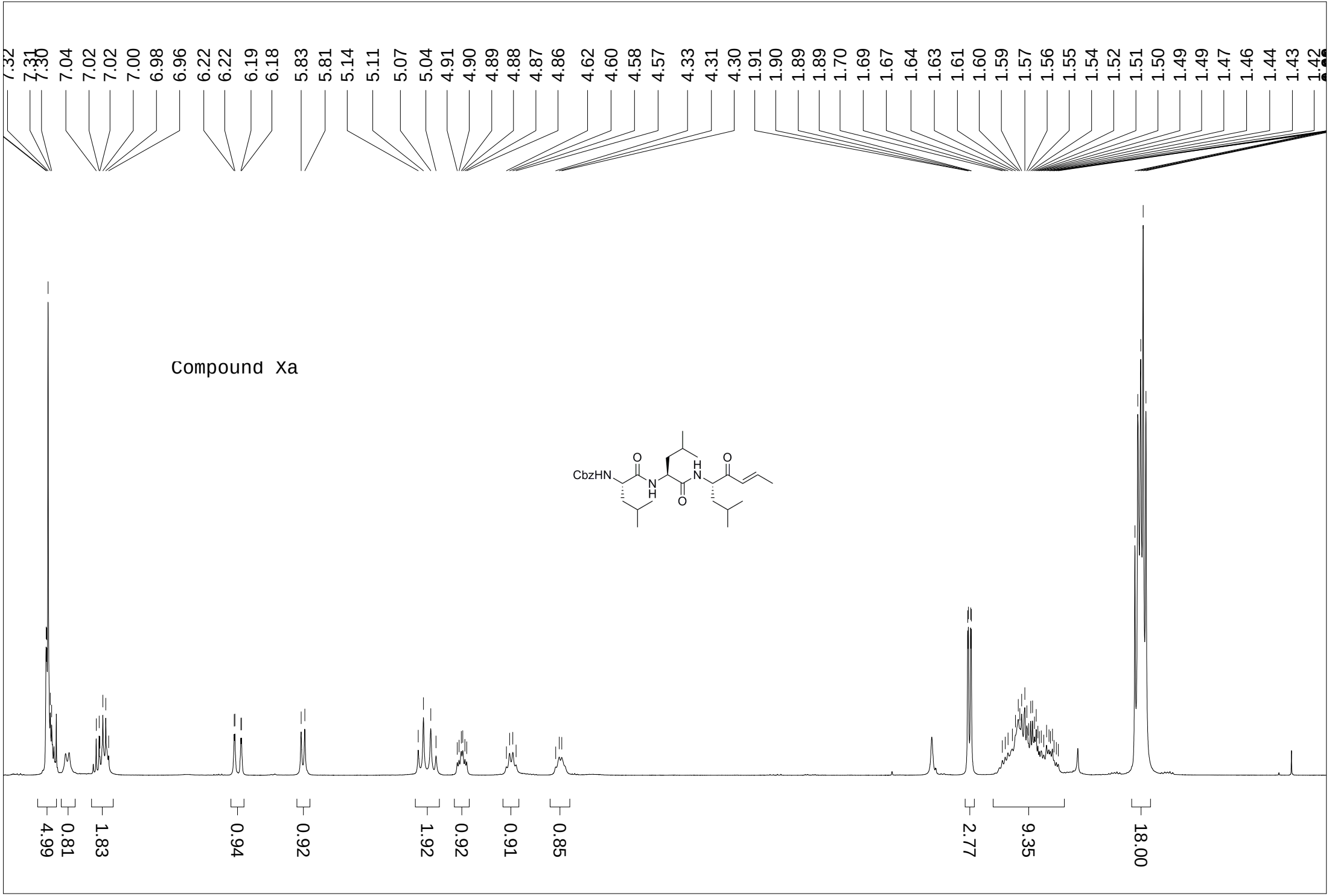
ppm (f1)

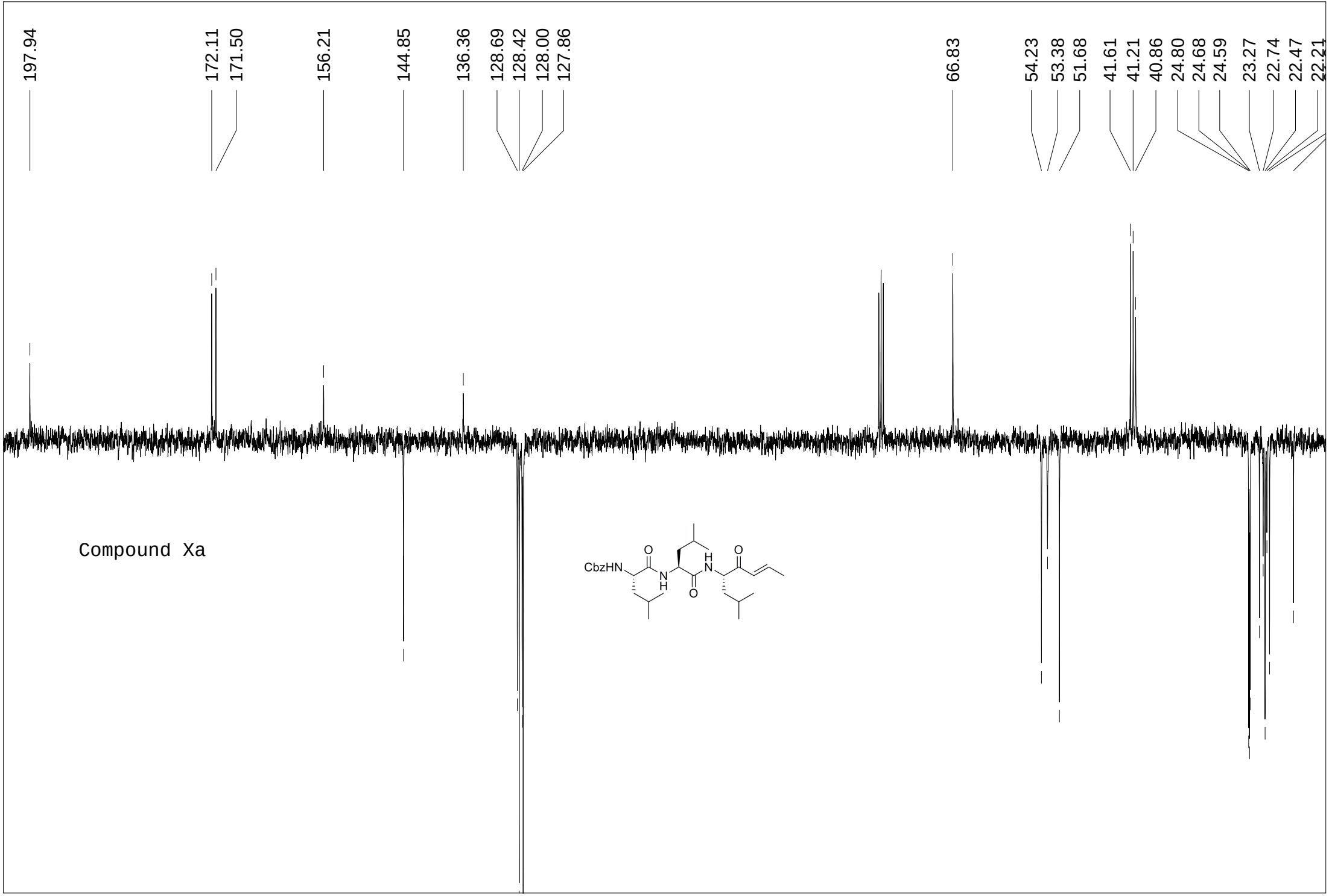

171.79
171.68
171.14
169.37
135.43
129.41
128.74
127.42
115.47
77.02
71.62
64.93
52.36
52.09
45.96
42.05
40.63
40.00
38.08
24.97
24.73
24.67
24.62
23.18
22.79
22.75
Compound IXb
ppm (f1)

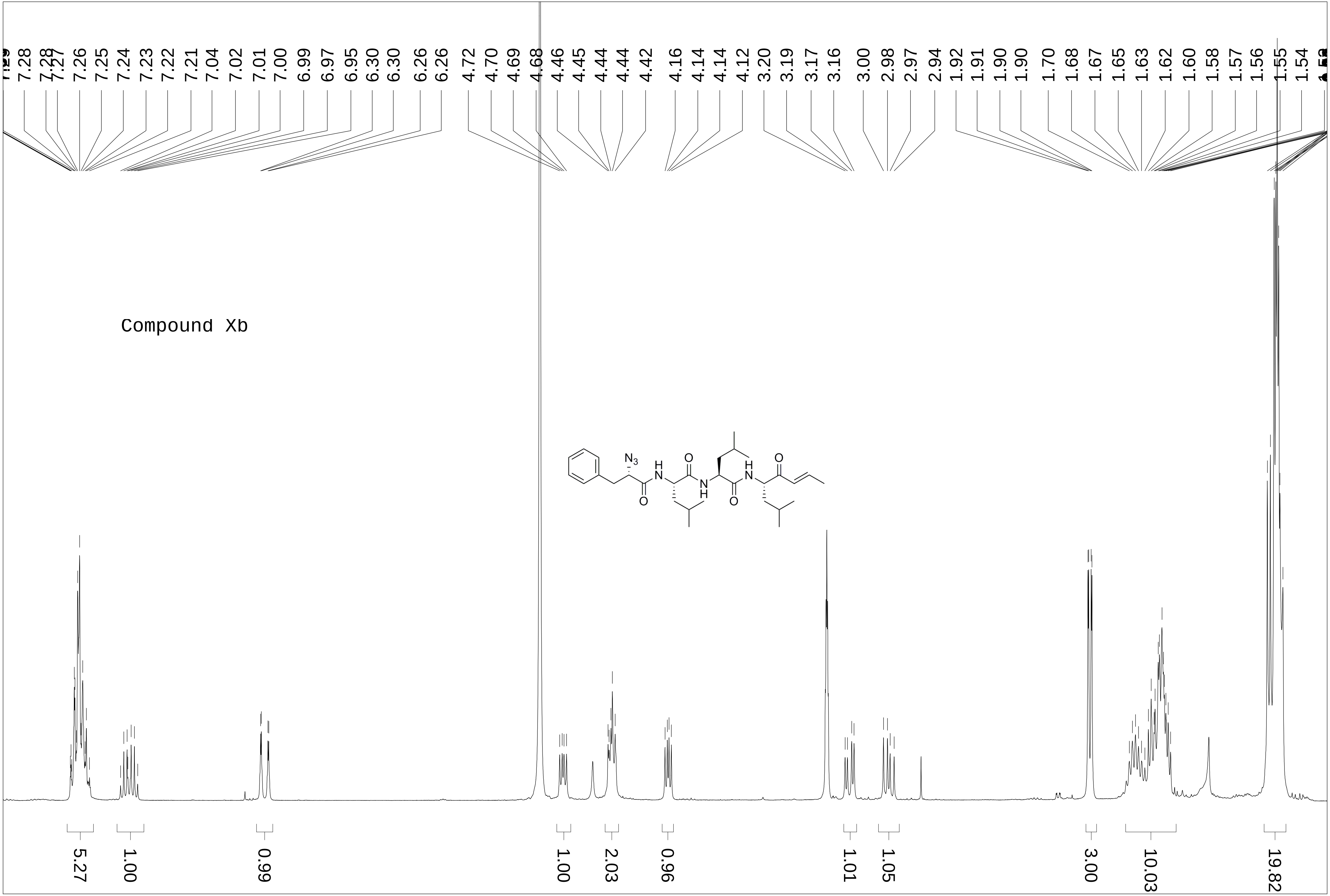


7.96 7.95 7.93 7.86 7.85 7.83 5.96 5.95 4.89 4.88 4.88 4.84 4.37 4.36 4.35 4.34 4.32 4.30 4.30 4.28 3.30 3.17 3.17 3.16 3.14 3.13 2.27 2.27 2.26 2.25 2.23 2.19 2.17 2.15 1.94 1.91 1.77 1.76 1.75 1.73 1.72 1.69 1.66 1.62 1.62 1.59 1.57 1.56 1.55 1.54 1.52 1.50 1.49 1.38
Compound IXc
1.58 0.98 0.76 2.15 2.80 1.78 6.17 2.00 4.15 5.41 36.95 6.74 17.55
ppm (f1)

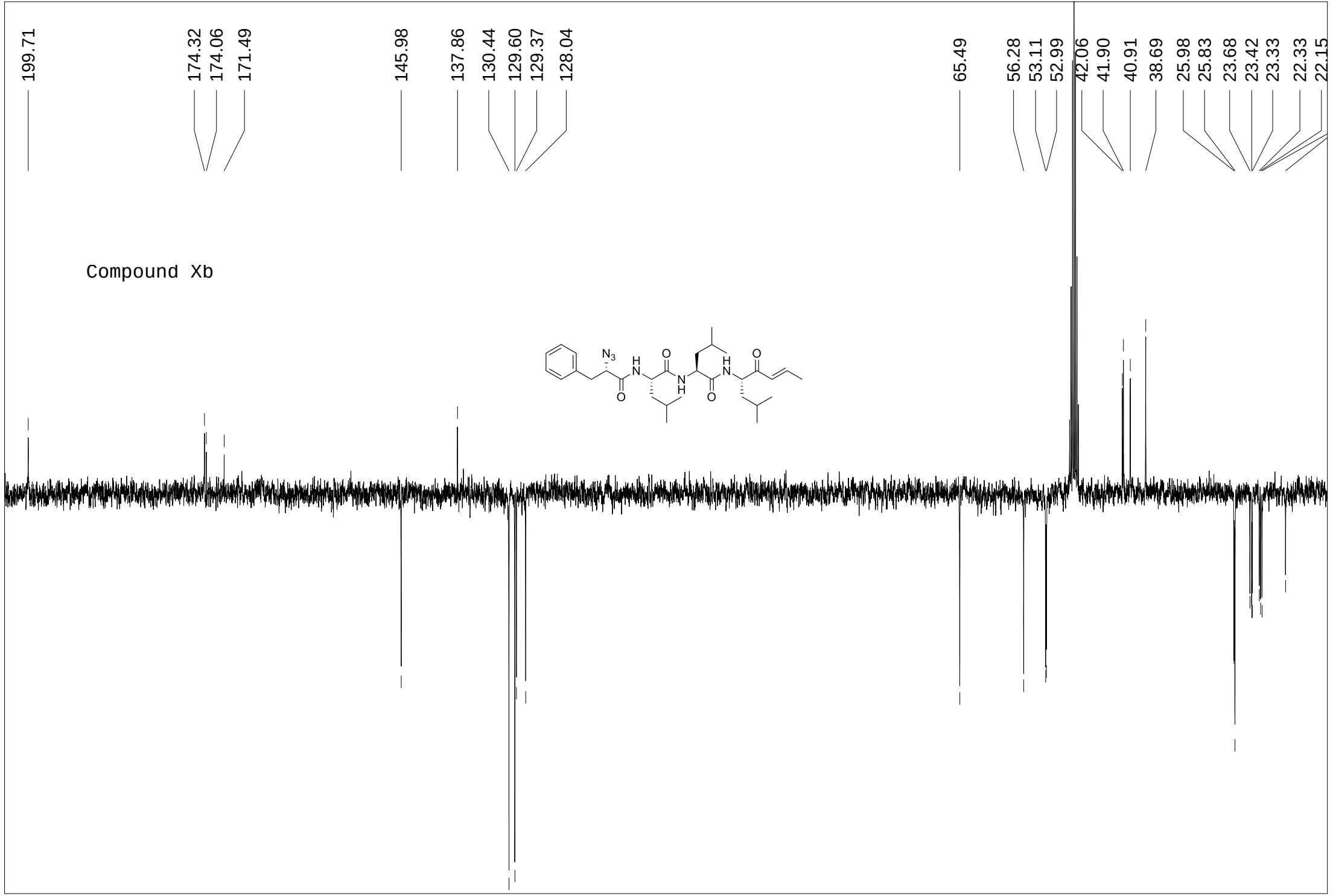

175.95
175.87
175.07
174.53
174.27
173.74
115.73
73.25
53.65
53.35
51.95
47.30
43.75
42.60
41.62
41.41
40.32
40.27
40.19
37.92
37.05
37.00
36.63
33.78
30.23
30.14
27.66
27.60
27.57
26.73
26.54
Compound IXc
ppm (f1)

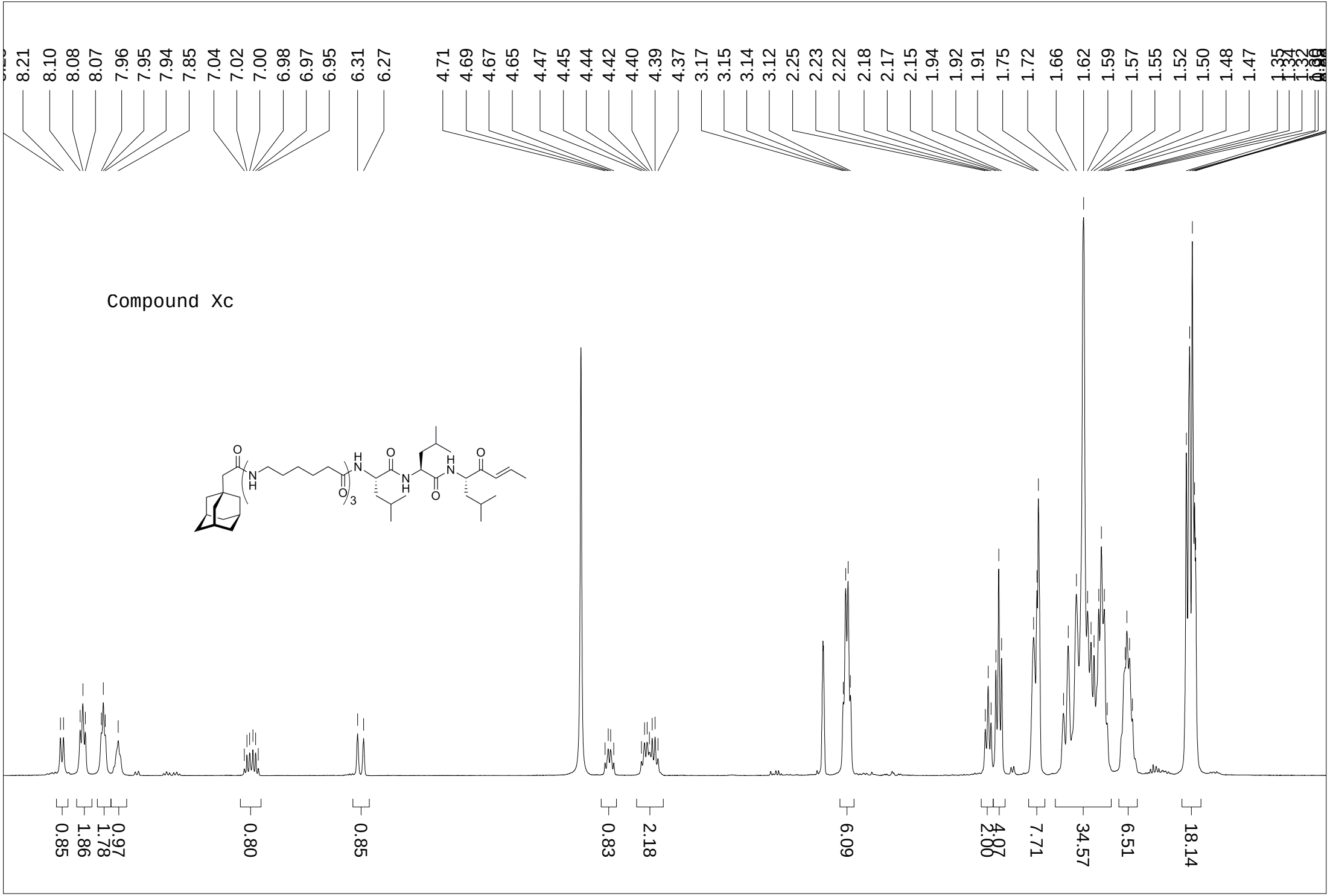

7.32
7.31
7.30
7.04
7.02
7.02
7.00
6.98
6.96
6.22
6.22
6.19
6.18
5.83
5.81
5.14
5.11
5.07
5.04
4.91
4.90
4.89
4.88
4.87
4.86
4.62
4.60
4.58
4.57
4.33
4.31
4.30
1.91
1.90
1.89
1.89
1.70
1.69
1.67
1.64
1.63
1.61
1.60
1.59
1.57
1.56
1.55
1.54
1.52
1.51
1.50
1.49
1.49
1.47
1.46
1.44
1.43
1.42
Compound Xa
CbzHN
O
N
H
O
N
H
O
4.99
0.81
1.83
0.94
0.92
1.92
0.92
0.91
0.85
2.77
9.35
18.00
ppm (f1)


197.94
172.11
171.50
156.21
144.85
136.36
128.69
128.42
128.00
127.86
66.83
54.23
53.38
51.68
41.61
41.21
40.86
24.80
24.68
24.59
23.27
22.74
22.47
22.21
Compound Xa
CbzHN
O
N
H
O
N
H
O
ppm (f1)

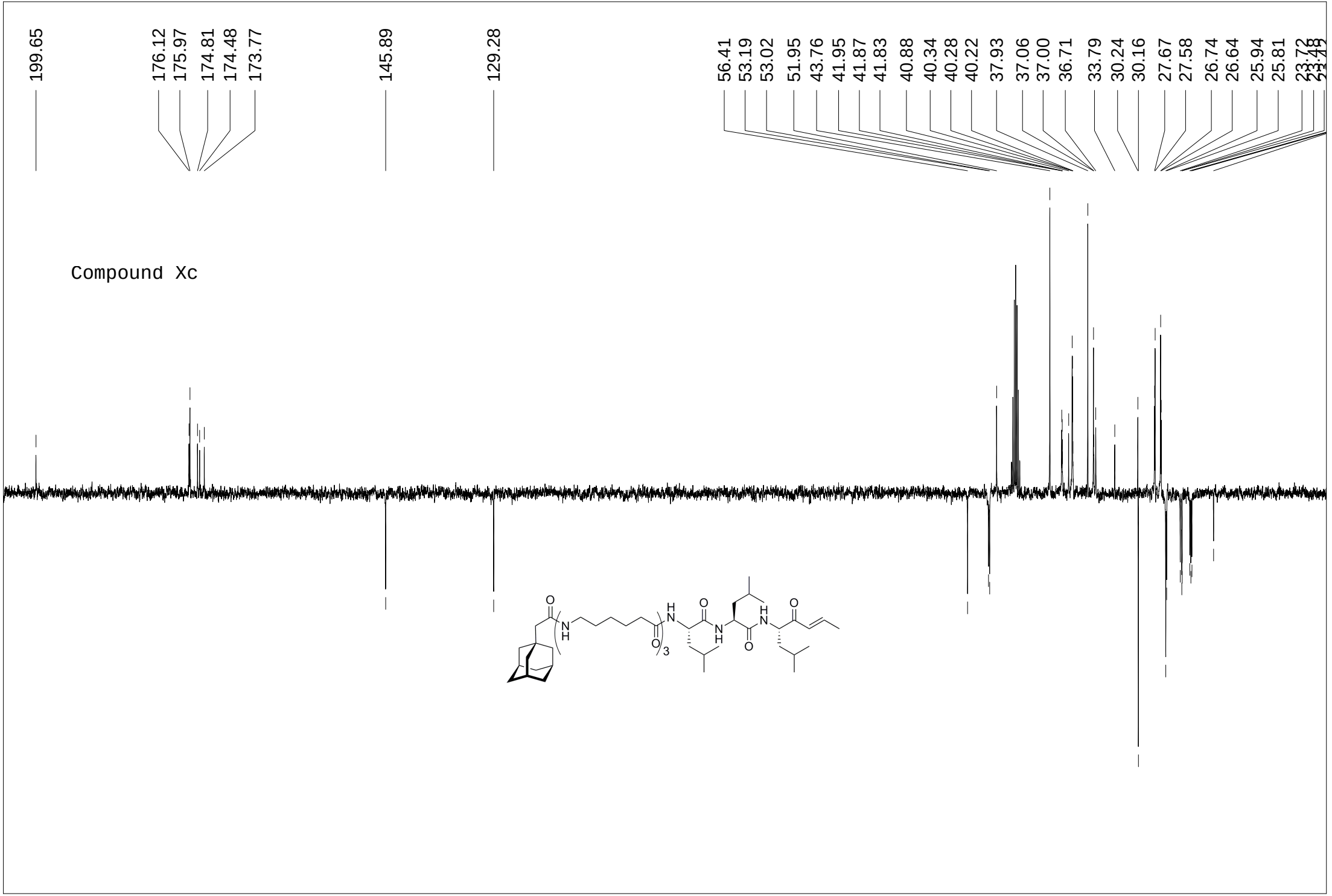

Compound Xb
N3
H
N
O
7.28
7.28
7.27
7.26
7.25
7.24
7.23
7.22
7.21
7.04
7.02
7.01
7.00
6.99
6.97
6.95
6.30
6.30
6.26
6.26
4.72
4.70
4.69
4.68
4.46
4.45
4.44
4.44
4.42
4.16
4.14
4.14
4.12
3.20
3.19
3.17
3.16
3.00
2.98
2.97
2.94
1.92
1.91
1.90
1.90
1.70
1.68
1.67
1.65
1.63
1.62
1.60
1.58
1.57
1.56
1.55
1.54
5.27
1.00
0.99
1.00
2.03
0.96
1.01
1.05
3.00
10.03
19.82

ppm (f1)


199.71
174.32
174.06
171.49
145.98
137.86
130.44
129.60
129.37
128.04
65.49
56.28
53.11
52.99
42.06
41.90
40.91
38.69
25.98
25.83
23.68
23.42
23.33
22.33
22.15
Compound Xb
ppm (f1)


8.21
8.10
8.08
8.07
7.96
7.95
7.94
7.85
7.04
7.02
7.00
6.98
6.97
6.95
6.31
6.27
4.71
4.69
4.67
4.65
4.47
4.45
4.44
4.42
4.40
4.39
4.37
3.17
3.15
3.14
3.12
2.25
2.23
2.22
2.18
2.17
2.15
1.94
1.92
1.91
1.75
1.72
1.66
1.62
1.59
1.57
1.55
1.52
1.50
1.48
1.47
Compound Xc
0.85
1.86
1.78
0.97
0.80
0.85
0.83
2.18
6.09
2.00
4.07
7.71
34.57
6.51
18.14

ppm (f1)


199.65
176.12
175.97
174.81
174.48
173.77
145.89
129.28
56.41
53.19
53.02
51.95
43.76
41.95
41.87
41.83
40.88
40.34
40.28
40.22
37.93
37.06
37.00
36.71
33.79
30.24
30.16
27.67
27.58
26.74
26.64
25.94
25.81
Compound Xc
ppm (f1)