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An expedient synthesis of a picolinamide-based betain bearing a 3-sulfonatopropyl substituent

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Experimental Section

The purities of all compounds were assessed by elemental analysis and NMR and found to be ≥ 95%. NMR spectra were recorded on a Bruker Avance II 300 spectrometer at 300 MHz (^{1}H) and 75 MHz (^{13}C) in D_2O in the pulse mode followed by Fourier transformation using Me_4Si as internal standard. Spin multiplicities are designated as s (singlet), d (doublet), t (triplet), q (quartet) or m (multiplet). IR spectra in the solid phase were recorded on a Bruker Tensor-27 instrument with an attenuated total internal reflectance (ATR) module. Refraction parameters were measured using an IRF-454B2M refractometer. Melting points were determined using a Stuart SMP10 instrument. Elemental analyses were carried out at the Laboratory of Organic Microanalysis of INEOS RAS.

General synthetic procedure for compounds.

A solution of 2-picolinic acid **5′** (1.23g, 0.01 mol) or its derivative and 1,3-propanesultone **2** (1.46 g, 0.012 mol) in methanol is stirred at ambient temperature for 7 days or refluxed for 8 hours. Excess solvent is removed in vacuum. The products are isolated by filtration.

3-(2-Carbamoylpyridin-1-ium-1-yl)propane-1-sulfonate (**3**).

a) Ester **6** (0.54 g, 0.002 mol) is stirred with aqueous ammonia (25%, 10 ml) for 7 days, then the mixture is evaporated to dryness. The residue is re-crystallized from ethanol–water (10:1) to afford 0.31 g (64%, Table 1, entry 3) of **3**, m. p. 185–187°C (lit. data: m. p. 187–188°C; *Molecules*, 2022, **27**, 7542).

IR spectrum (solid, ν/cm^{-1}): 1611 s (C=O), 1581 w (C=C$_{py}$), 1228 s, 1160 s, 1037 s (SO_3).

b) A mixture of ethyl picolinate **5** (0.75 g, 0.005 mol), 1,3-propanesultone **2** (0.75 g, 0.006 mol) and acetonitrile (3 ml) is refluxed for 8 hours, then the solvent is removed in vacuum. The residue is stirred with aqueous ammonia (25%, 20 ml) for 5 days, then the mixture is evaporated to dryness. The residue is crystallized under diethyl ether (10 ml) to afford 1.08 g (89%) of **3**, m.p. 185–187°C.

IR spectrum (solid, ν/cm^{-1}): 1613 s (C=O), 1581 w (C=C$_{py}$), 1229 s, 1158 s, 1038 s (SO_3).

c) A mixture of ethyl picolinate **5** (1.5 g, 0.01 mol), 1,3-propanesultone **2** (1.5 g, 0.012 mol) and ethanol (5 ml) is refluxed for 8 hours, and the solvent is removed in vacuum. The mixture is evaporated to dryness, and aqueous ammonia (25%, 50 ml) is added. The mixture was evaporated again. The oily residue was boiled in acetonitrile. The resulting precipitate was filtered and crystallized under ethanol/water mixture (10:1, 10 ml) to afford 0.55 g (23%) of product **3**, m.p. 185–188°C. IR spectrum
(solid, ν/cm^{-1}): 1613 s (C=O), 1580 w (C=C$_{py}$), 1229 s, 1184 s, 1030 s (SO$_3$).

3-(2-Ethoxycarbonylpyridin-1-ium-1-yl)propane-1-sulfonate (***6***)

According to the general procedure, a mixture of ethyl picolinate **5** (1.51 g, 0.01 mol), 1,3-propanesultone **2** (1.50 g, 0.012 mol) and acetonitrile (5 ml) is refluxed for 8 hours. Removal of the solvent in vacuum affords 2.02 g (74%) of **6**, m.p. 189–191°C (from ethanol).

IR spectrum (solid, ν/cm^{-1}): 1735 s (C=O), 1616 w (C=C$_{py}$), 1199 s, 1148 s, 1042 s (SO$_3$).

^{1}H-NMR (300.1 MHz, D$_2$O, δ, ppm, J/Hz): 1.39 (t, 3H, ^3J=7.1, CH$_2$**CH$_3$**), 2.48 (m, 2H, ^3J=7.3, -H$_2$C**CH$_2$**CH$_2$-), 3.04 (t, 2H, ^3J=7.3, -CH$_2$SO$_3$), 4.53 (q, 2H, ^3J=7.1, **CH$_2$**CH$_3$),4.97 (t, 2H, ^3J=7.3, -OCH$_2$-), 8.56 (d, 1H, ^3J=8.0, H3), 8.23 (t, 1H, ^3J=7.9, H4), 8.61 (t, 1H, ^3J=7.9, H5), 9.03 (d, 1H, ^3J=8.0, H6).

^{13}C-NMR (75.5 MHz, D$_2$O, δ, ppm): 13.06, 16.76, 26.23, 26.40, 47.39, 59.18, 65.23, 130.62, 146.98, 147.95, 160.18.

Anal. calcd. for C$_{11}$H$_{15}$NO$_5$S · H$_2$O. Calculated: C, 45.35; H, 5.88; N, 4.80; S, 11.00. Found: C, 45.76; H, 5.61; N, 5.02; S, 11.46.

3-(2-Methoxycarbonylpyridin-1-ium-1-yl)propane-1-sulfonate (***6′***).

According to the general procedure, a mixture of picolinic acid **5′** (1.23 g, 0.01 mol), 1,3-propanesultone **2** (1.50 g, 0.012 mol) and methanol (5 ml) is refluxed for 4 hours. Excess solvent is removed in vacuum. An oily product is isolated (0.5 g).

^{1}H-NMR (300.1 MHz, D$_2$O, δ, ppm, J/Hz): 2.48 (m, 2H, ^3J=7.4, -H$_2$C**CH$_2$**CH$_2$-), 3.19 (t, 2H, ^3J=7.4, -CH$_2$SO$_3$), 5.01 (t, 2H, ^3J=7.4, -OCH$_2$-), 4.07 (s, 3H, C(O)OCH$_3$), 8.24 (d, 1H, ^{3}J=8.1, H3), 8.62 (t, 1H, ^{3}J=8.1, H4), 8.00 (t, 1H, ^{3}J=8.1, H5), 9.12 (d, 1H, ^{3}J=8.1, H6).

^{13}C-NMR (75.5 MHz, D$_2$O, δ, ppm): 23.57, 47.90, 58.17, 66.93, 127.49, 128.11, 145.27, 147.19, 148.22, 162.19.

3-(Pyridin-1-ium-2-carbonyloxy)propane-1-sulfonate (***7***).

According to the general procedure, a mixture of picolinic acid **5′** (1.23 g, 0.01 mol), 1,3-propanesultone **2** (1.50 g, 0.012 mol) and methanol (5 ml) is stirred at ambient temperature for 7 days to afford 0.61 g (25%) of **7**, m.p. 227–230°C (from ethanol–water 10:1).

IR spectrum (solid, ν/cm^{-1}): 1737 s (C=O), 1611 w (C=C$_{py}$), 1208 s, 1138 s, 1027 s (SO$_3$).

^{1}H-NMR (300.1 MHz, D$_2$O, δ, ppm, J/Hz): 2.25 (m, 2H, ^3J=7.3, -H$_2$C**CH$_2$**CH$_2$-), 3.07 (t, 2H, ^3J=7.3, -CH$_2$SO$_3$), 4.61 (t, 2H, ^3J=7.3, -OCH$_2$-), 8.60 (d, 1H, ^3J=8.0, H3), 8.26 (t, 1H, ^3J=7.9, H4), 8.73 (t, 1H, ^3J=7.9, H5), 8.89 (d, 1H, ^3J=8.0, H6).

^{13}C-NMR (75.5 MHz, D$_2$O, δ, ppm): 23.59, 47.60, 66.50, 112.38, 122.42, 127.85, 130.73, 139.84, 143.25, 147.77, 160.18.

Anal. calcd. for C$_9$H$_{11}$NO$_5$S. Calculated: C, 44.075; H, 4.52; N, 5.71; S, 13.07. Found: C, 44.04; H, 4.51; N, 5.30; S, 13.57.

3,3-Dimethyl-1-oxo-2,3-dihydro-1H-imidazo[1,5-a]pyridin-4-ium 3-methoxypropane-1-sulfonate (**8**)

Salt **4** (0.82 g, 0.003 mol) was refluxed for 3 h in 10 ml of acetone (10 ml). Next day, the volatiles were removed in vacuum, the residue was stirred with diethyl ether for 2 h, and the crystals formed were filtered and dried to afford 0.51 g (62%) of unreacted compound **4** are obtained. By evaporation, 0.11 g (11.7%) of compound **8** was isolated, m.p. 170–174°C (methanol–acetone, 1:20). IR spectrum (solid, ν, cm^{-1}): 1729 s (C=O), 1637 w ($C{=}C_{pyridine}$), 1208 s, 1160 s, 1033 s (SO_3). ^{1}H-NMR (300.1 MHz, D_2O, δ, ppm, J/Hz): 1.84 (m, 2H, -$H_2C\mathbf{CH_2}CH_2$-), 1.89 (s, 6H, $2CH_3$), 2.84 (t, 2H, ^3J 7.2, -CH_2SO_3), 3.25 (s, 3H, ^3J=7.2, CH_3O), 3.47 (t, 2H, ^3J=7.2, OCH_2-), 8.42 (d, 1H, ^3J=8.1, H3), 8.31 (t, 1H, ^3J=8.1, H4), 8.76 (t, 1H, ^3J=8.1, H5), 9.31 (d, 1H, ^3J=8.1, H6). ^{13}C-NMR (75.5 MHz, D_2O, δ, ppm): 24.10, 26.48, 47.65, 57.69, 70.57, 84.15, 123.80, 130.93, 138.48, 141.63, 148.03, 158.99.

Anal. calcd. for $C_{13}H_{23.5}N_2O_{6.75}S$ (**2** ·1.75H_2O): C, 44.87; H, 6.80; N, 8.05; S, 9.21. Found: C, 44.89; H, 6.18; N, 8.28; S, 10.53.

X-ray datasets for **6** were collected in Kurchatov Centre for Synchrotron Radiation and Nanotechnology using 'Belok' beamline. The intensities of collected reflections were integrated, merged and empirically corrected for absorption using XDS software [W. Kabsch, *Acta Cryst*., **D66**, 133].

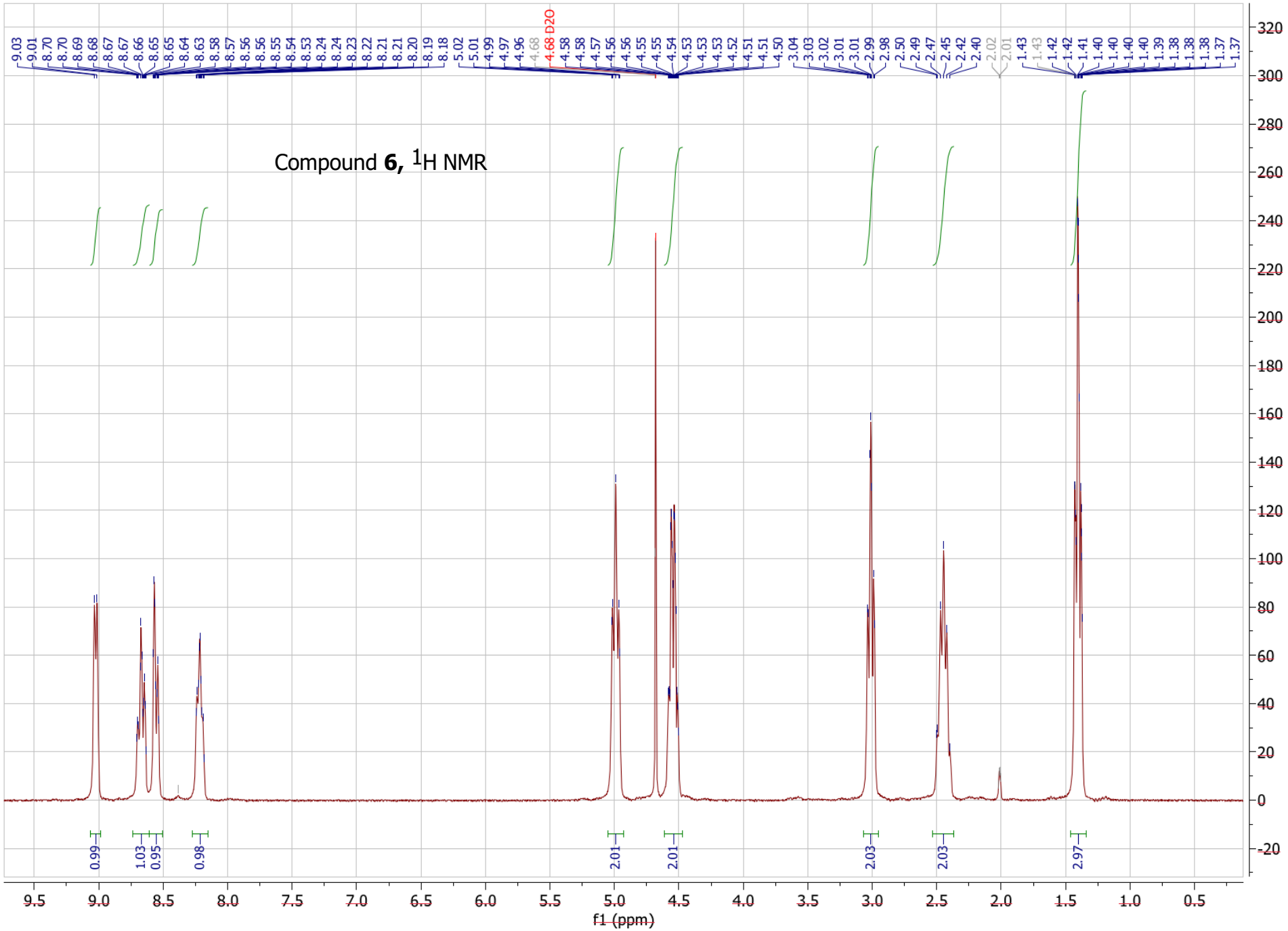
The structures were solved by dual-space algorithm using ShelXT software [G.M. Sheldrick, *Acta Cryst*., 2015, **A71**, 3] and refined in anisotropic approximation for non-hydrogen atoms against F^2(hkl) using ShelXL software [G.M. Sheldrick, *Acta Cryst*., 2015, **C71**, 3]. Hydrogen atoms of methyl, methylene and aromatic fragments were calculated for idealised geometry and refined with constraints. All necessary information concerning X-ray structural study are given in Table 1S. Molecular graphics were drawn using OLEX2 software [O. V. Dolomanov et al, *J. Appl. Cryst.*, 2009, 42, 339].

CCDC 2300128 contains supplementary crystallographic data for **6**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via https://www.ccdc.cam.ac.uk/structures.

Table S1 Crystallographic data for **6**.

Formula moiety	$C_{11}H_{15}NO_5S$, H_2O
Brutto formula	$C_{11}H_{17}NO_6S$
Formula weight	291.31
Diffractometer	Marexperts dtb goniostat
Scan mode	ω scans
Anode [Wavelength, Å]	synchrotron [0.7527]
Crystal Dimensions, mm	0.05 × 0.05 × 0.12
Crystal color	colourless
Crystal system	monoclinic
a, Å	11.644(2)
b, Å	8.1330(16)
c, Å	15.090(3)

α, °	90
β, °	111.40(3)
γ, °	90
Volume, Å^3	1330.5(5)
Density, g cm^{-3}	1.454
Temperature, K	100
T_{min}/T_{max}	0.734/1.000
μ, mm^{-1}	0.308
Space group	$P2_1/n$
Z	4
F(000)	616
Reflections collected	11697
Independent reflections	3404
Reflections ($I > 2\sigma(I)$)	3113
Parameters	177
R_{int}	0.0547
$2\theta_{min} – 2\theta_{max}$, °	6.130 – 61.784
wR_2 (all reflections)	0.1064
$R_1(I > \sigma(I))$	0.0388
GOF	1.038
ρ_{min}/ρ_{max}, eÅ^{-3}	–0.443/0.390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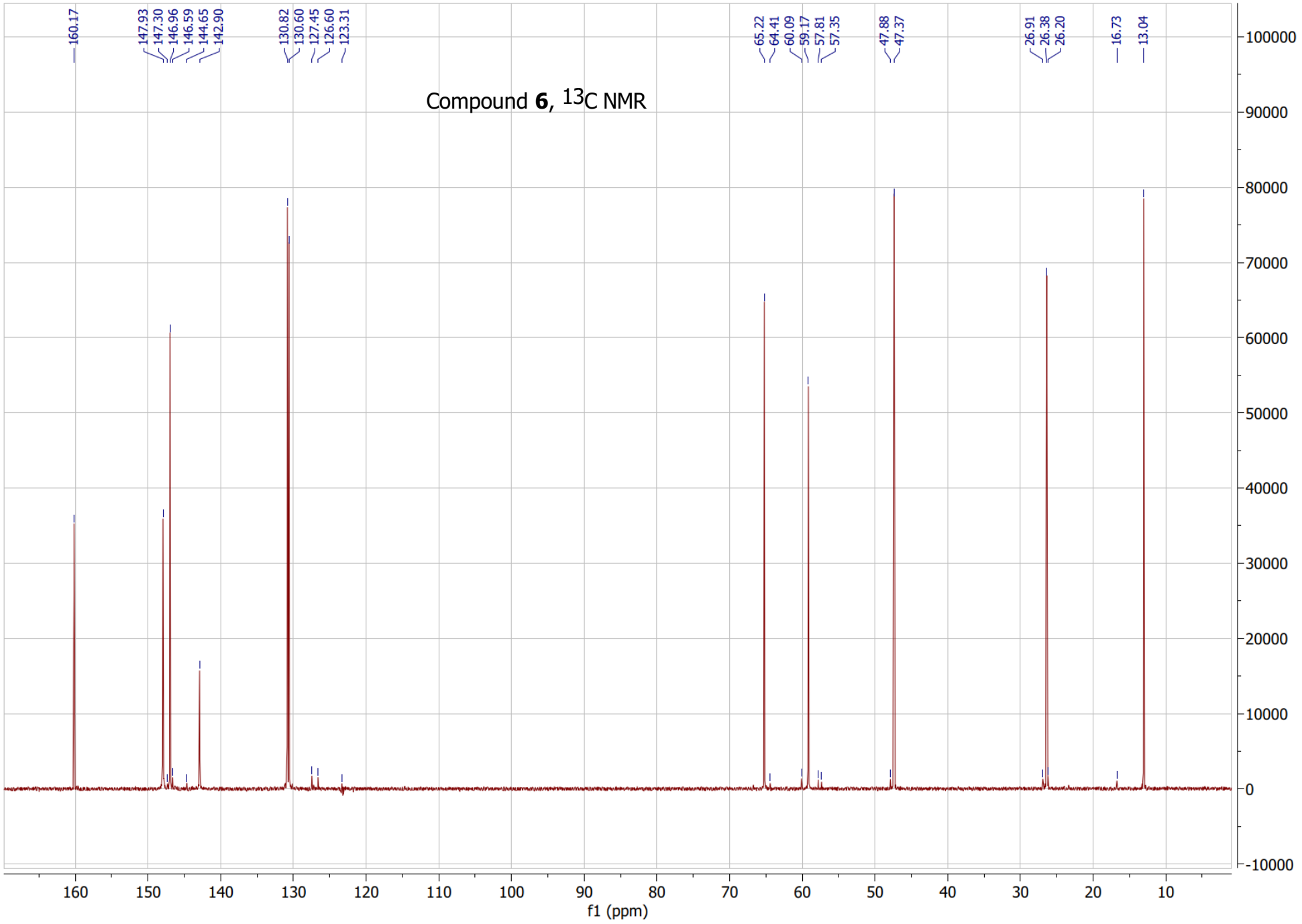
f1 (ppm)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147.30
146.96
146.59
144.65
142.90
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130.60
127.45
126.60
123.31
65.22
64.41
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26.91
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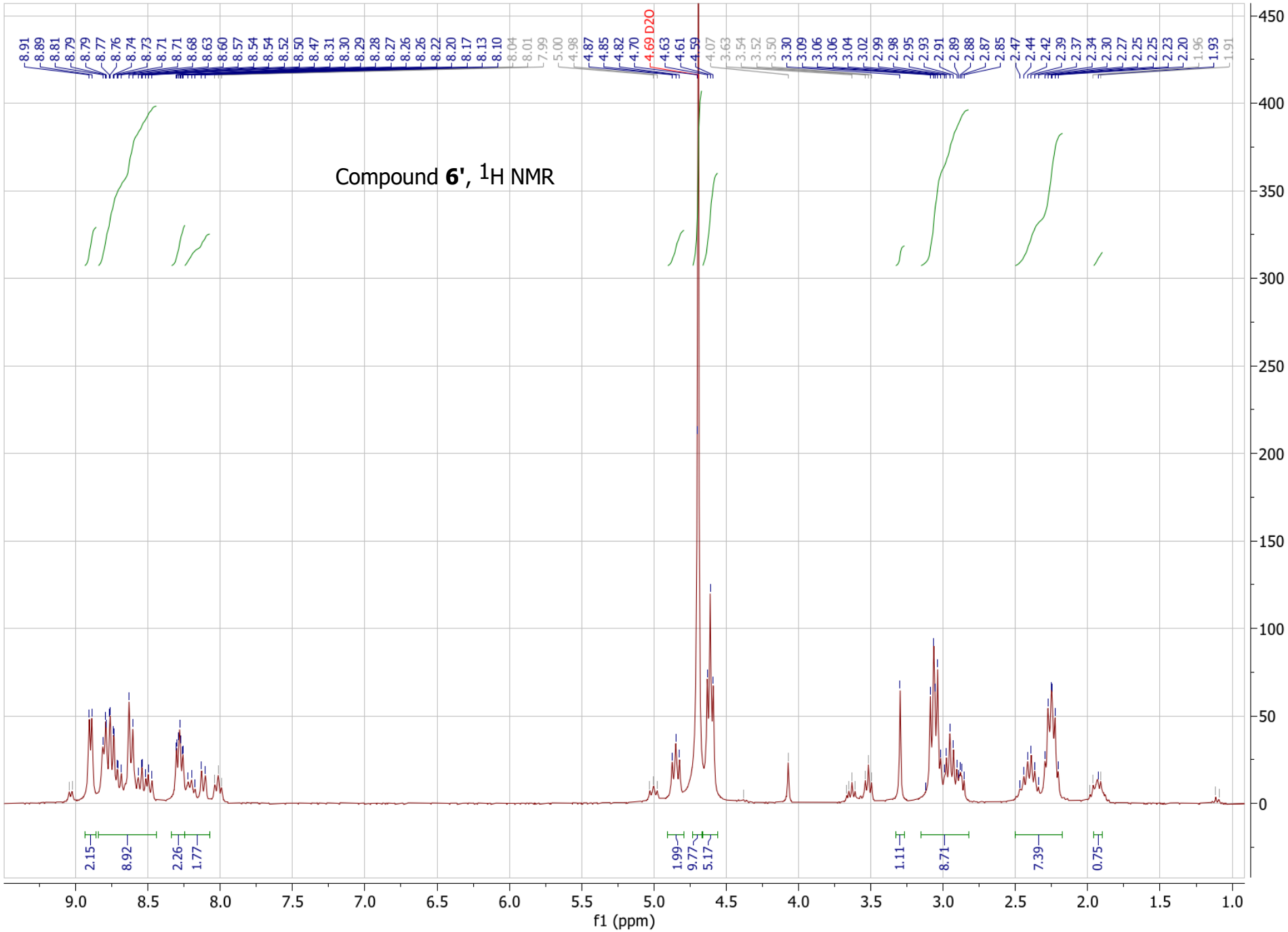
26.20
16.73
13.04
f1 (ppm)


Compound **6'**, ^{1}H NMR
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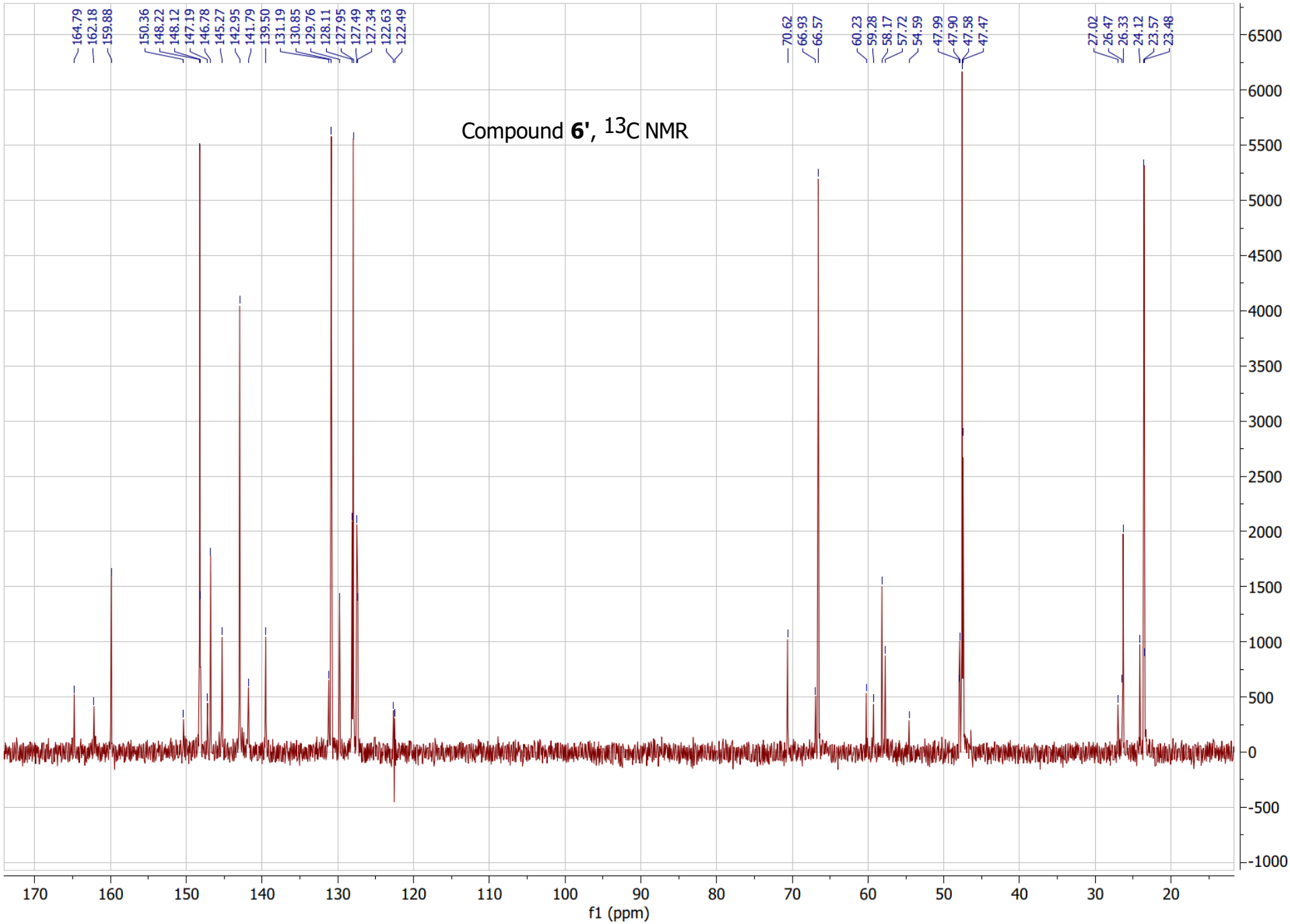
2.15 8.92 2.26 1.77 1.99 9.77 5.17 1.11 8.71 7.39 0.75
f1 (ppm)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127.49
127.34
122.63
122.49
70.62
66.93
66.57
60.23
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58.17
57.72
54.59
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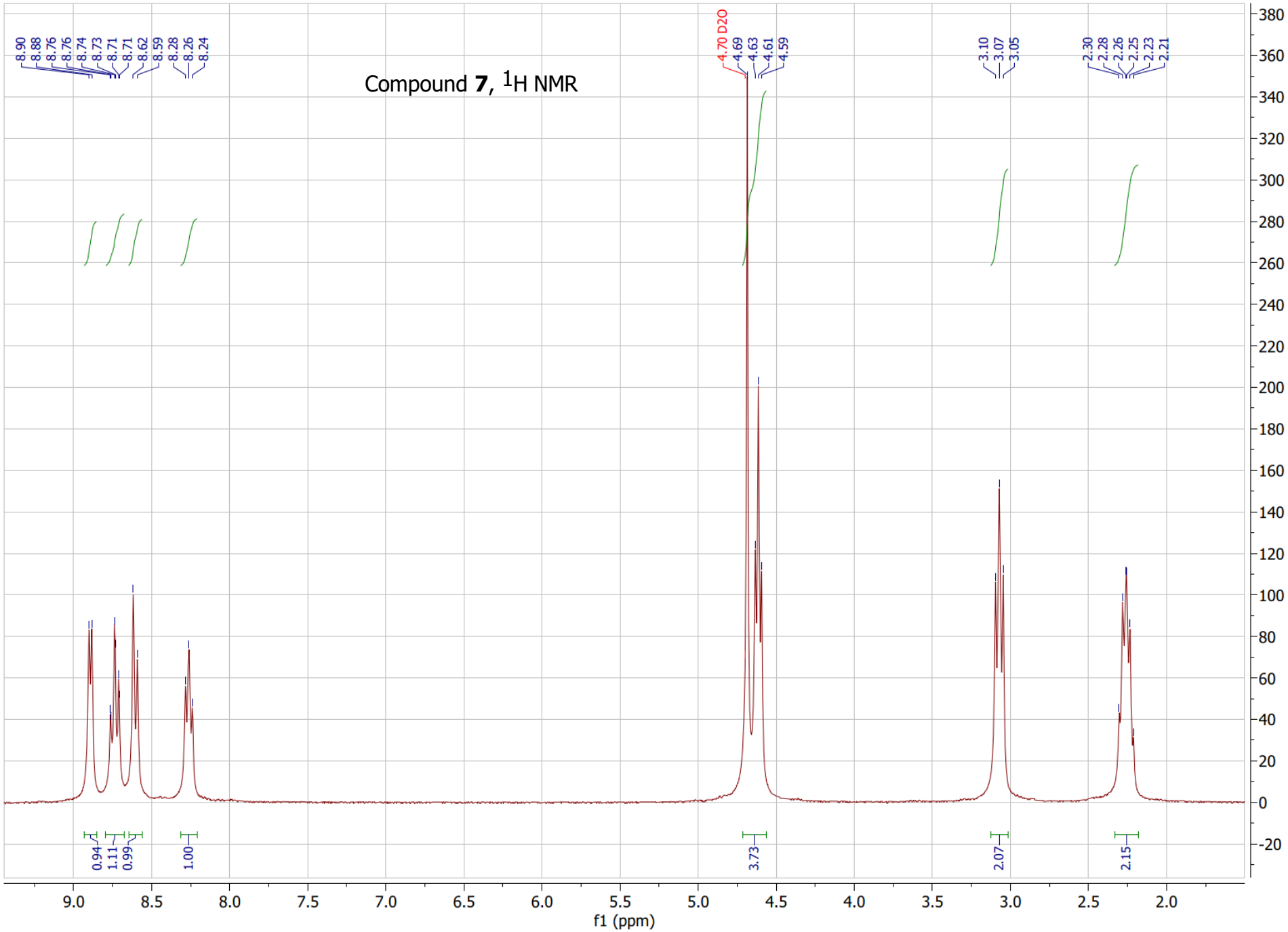
23.48
f1 (ppm)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8.76
8.76
8.74
8.73
8.71
8.71
8.62
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8.26
8.24
4.70 D20
4.69
4.63
4.61
4.59
3.10
3.07
3.05
2.30
2.28
2.26
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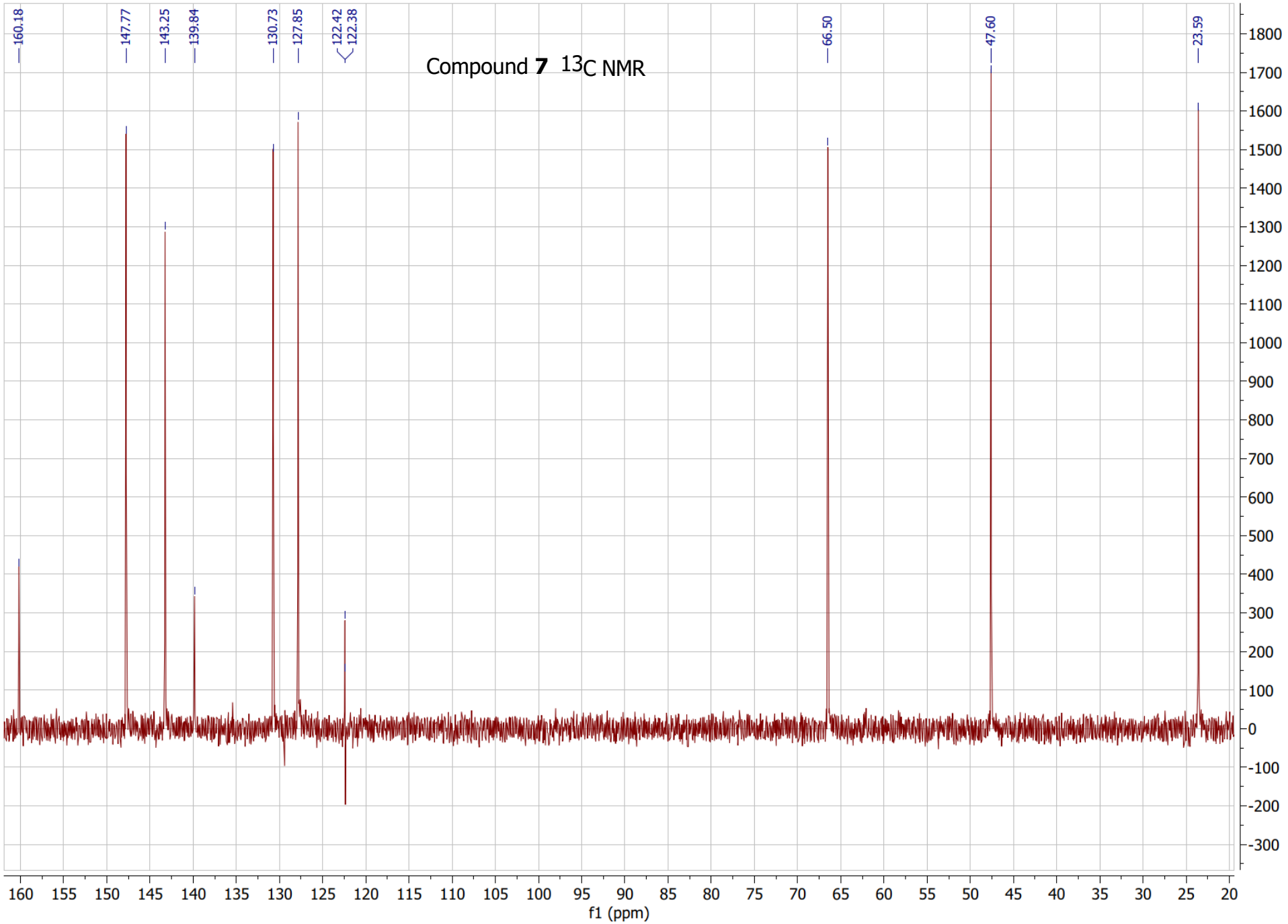
2.07
2.15
f1 (ppm)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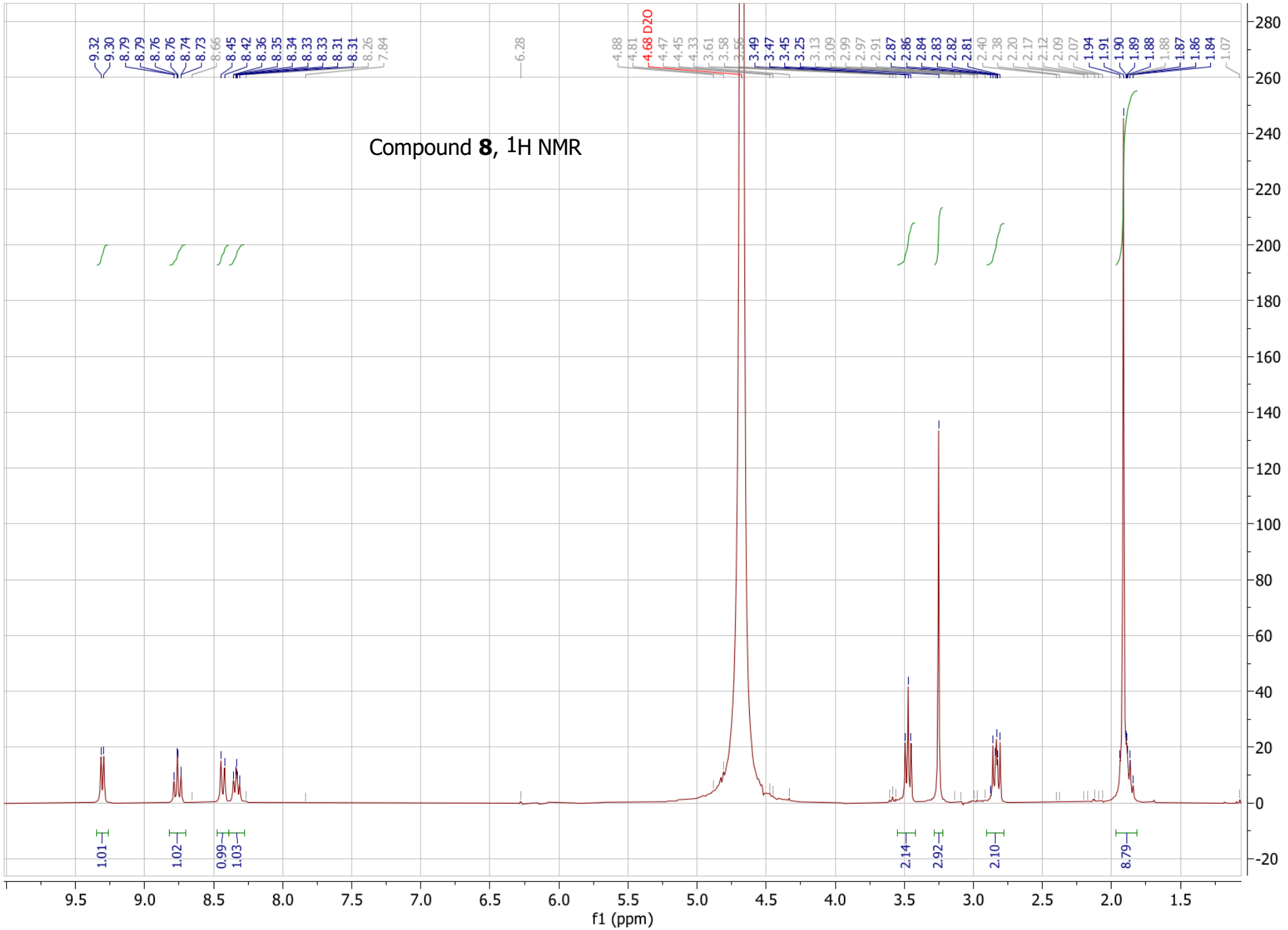
f1 (ppm)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8.73
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8.42
8.36
8.35
8.34
8.33
8.33
8.31
8.31
8.26
7.84
6.28
4.88
4.81
4.68 D2O
4.47
4.45
4.33
3.61
3.58
3.56
3.49
3.47
3.45
3.25
3.13
3.09
2.99
2.97
2.91
2.87
2.86
2.84
2.83
2.82
2.81
2.40
2.38
2.20
2.17
2.12
2.09
2.07
1.94
1.91
1.90
1.89
1.88
1.88
1.87
1.86
1.84
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1.01
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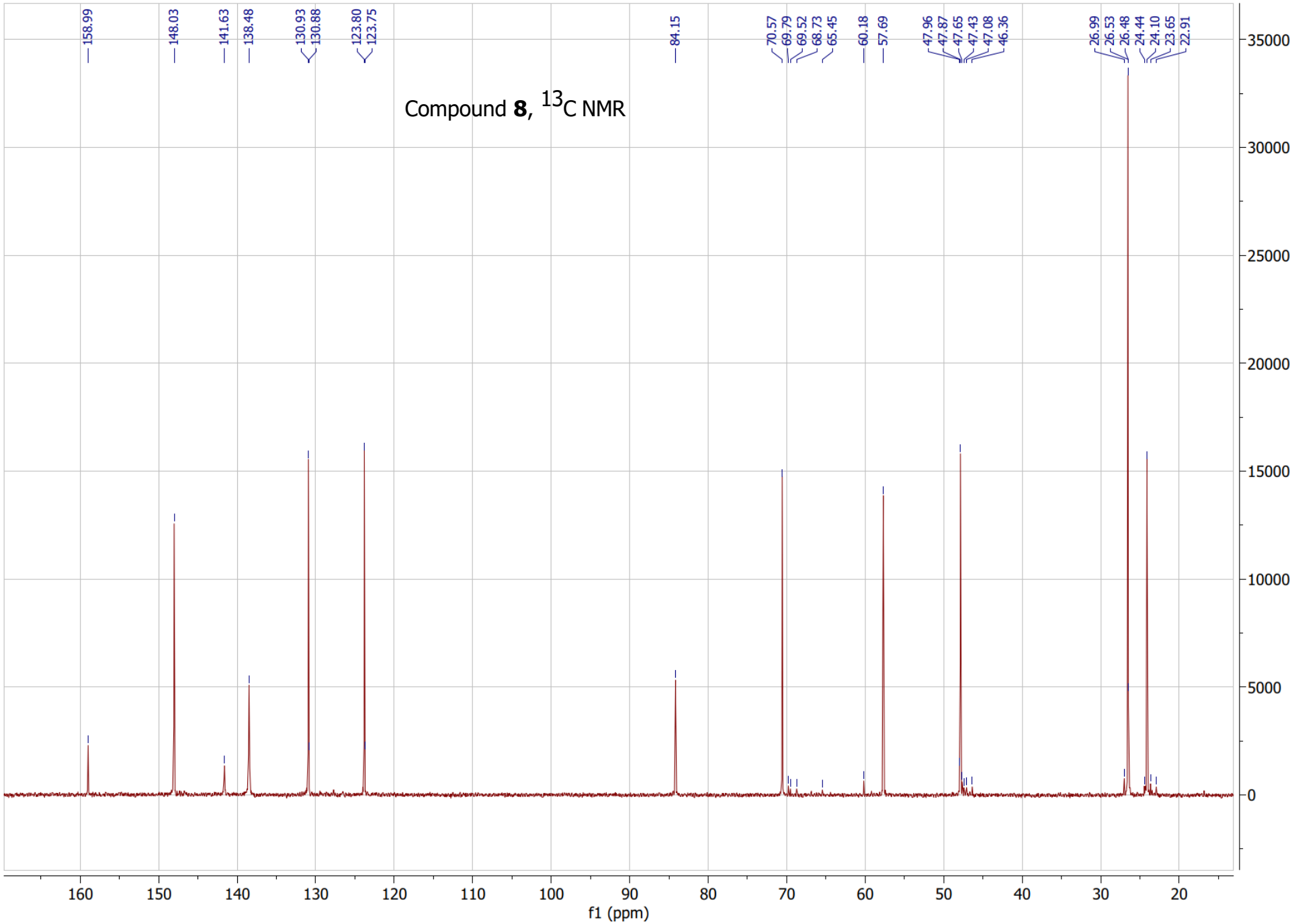
2.10
8.79
f1 (ppm)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141.63
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26.99
26.53
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f1 (ppm)

checkCIF/PLATON report

Structure factors have been supplied for datablock(s) 6

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No syntax errors found. CIF dictionary Interpreting this report

Datablock: 6

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                 Calculated                  Reported
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Hall group       -P 2yn                      -P 2yn
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Sum formula      C11 H17 N O6 S              C11 H17 N O6 S
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Dx,g cm-3        1.454                       1.454
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Mu (mm-1)        0.306                       0.308
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F000'            616.96
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Nref             3532                        3404
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Tmin'            0.964

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Click on the hyperlinks for more details of the test.

Alert level C

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PLAT913_ALERT_3_C Missing # of Very Strong Reflections in FCF ....         16 Note
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Alert level G

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PLAT092_ALERT_4_G Check: Wavelength Given is not Cu,Ga,Mo,Ag,In Ka    0.75270 Ang.
PLAT180_ALERT_4_G Check Cell Rounding: # of Values Ending with 0 =          3 Note
PLAT432_ALERT_2_G Short Inter X...Y Contact  O1       ..C9       .       2.87 Ang.
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PLAT912_ALERT_4_G Missing # of FCF Reflections Above STh/L=  0.600         56 Note
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PLAT978_ALERT_2_G Number C-C Bonds with Positive Residual Density.          8 Info
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   0 ALERT level B = A potentially serious problem, consider carefully
   3 ALERT level C = Check. Ensure it is not caused by an omission or oversight
  15 ALERT level G = General information/check it is not something unexpected

   5 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
   3 ALERT type 2 Indicator that the structure model may be wrong or deficient
   5 ALERT type 3 Indicator that the structure quality may be low
   4 ALERT type 4 Improvement, methodology, query or suggestion
   1 ALERT type 5 Informative message, check
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It is advisable to attempt to resolve as many as possible of the alerts in all categories. Often the minor alerts point to easily fixed oversights, errors and omissions in your CIF or refinement strategy, so attention to these fine details can be worthwhile. In order to resolve some of the more serious problems it may be necessary to carry out additional measurements or structure refinements. However, the purpose of your study may justify the reported deviations and the more serious of these should normally be commented upon in the discussion or experimental section of a paper or in the "special_details" fields of the CIF. checkCIF was carefully designed to identify outliers and unusual parameters, but every test has its limitations and alerts that are not important in a particular case may appear. Conversely, the absence of alerts does not guarantee there are no aspects of the results needing attention. It is up to the individual to critically assess their own results and, if necessary, seek expert advice.

Publication of your CIF in IUCr journals

A basic structural check has been run on your CIF. These basic checks will be run on all CIFs submitted for publication in IUCr journals (*Acta Crystallographica*, *Journal of Applied Crystallography*, *Journal of Synchrotron Radiation*); however, if you intend to submit to *Acta Crystallographica Section C* or *E* or *IUCrData*, you should make sure that full publication checks are run on the final version of your CIF prior to submission.

Publication of your CIF in other journals

Please refer to the *Notes for Authors* of the relevant journal for any special instructions relating to CIF submission.

PLATON version of 10/05/2023; check.def file version of 10/05/2023

Datablock 6 - ellipsoid plot